Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value

Evidence Report

April 7, 2017

Prepared for

NOTICE: On April 14, 2017, the FDA issued a complete response letter for baricitinib indicating that the FDA is unable to approve the application in its current form and requires additional data to determine the most appropriate doses and to further characterize safety concerns across treatment arms.

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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and health industry manufacturers. For a complete list of funders, visit http://www.icer-review.org/about/support/. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org

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The New England CEPAC is an independent committee of medical evidence experts from across New England, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about New England CEPAC is available at http://icer-review.org/programs/new-england-cepac/.

Expert Review

In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers and other stakeholders. In addition, the Arthritis Foundation worked with ICER to deploy surveys of the Foundation's membership on access to care issues, patient experience per type of treatment received, and other concerns. The results of these surveys are summarized in the report. The following experts provided input and data that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers. Conflict of Interest disclosures are included in Appendix H of the report.

For a complete list of stakeholders from whom we requested input, please visit:
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Table of Contents

List of Acronyms Used in this Report

ABT	Abatacept
ACPA	Anticitrullinated Protein Antibody
ACR	American College of Rheumatology
ADA	Adalimumab
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ARHP	Association of Rheumatology Health Professionals
BAR	Baricitinib
CADTH	Canadian Agency for Drugs and Technologies in Health
CCP	Cyclic Citrullinated Peptide
CDAI	Clinical Disease Activity Index
cDMARD	Conventional Disease-Modifying Anti-Rheumatic Drugs
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
CORRONA	Consortium of Rheumatology Researchers of North America
CRP	C-reactive Protein
CTZ	Certolizumab pegol
DAS28	Disease Activity Score with 28-Joint Counts
DIC	Deviance Information Criterion
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
DREAM	Dutch Rheumatoid Arthritis Monitoring
EQ-5D	EuroQol-5 domain
ESR	Erythrocyte Sedimentation Rate
ETN	Etanercept
EULAR	European League Against Rheumatism
GOL	Golimumab
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index
ICER	Incremental Cost-Effectiveness Ratio
IFAA	International Foundation for Autoimmune Arthritis
IFX	Infliximab
iv	Intravenous
JAK	Janus Kinase
JIA	Juvenile Idiopathic Arthritis
MCID	Minimum Clinically Important Difference
MCS	Mental Component Score
MDHAQ	Multi-Dimensional Health Assessment Questionnaire
mTSS	Modified Total Sharp Score
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
PAS	Patient Activity Scale
PCS	Physical Component Score
PML	Progressive Multifocal Leukoencephalopathy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMIS	Patient-Reported Outcomes Measurement Information System
QALY	Quality-Adjusted Life Year
RA	Rheumatoid Arthritis
RAPID-3	Routine Assessment of Patient Index Data
RCT	Randomized Controlled Trial

RF	Rheumatoid Factor
RISE	Rheumatology Informatics System for Effectiveness
RTX	Rituximab
SAE	Serious Adverse Event
SAR	Sarilumab
sc	Subcutaneous
SDAI	Simplified Disease Activity Index
SF-36	Short Form-36
SMD	Standardized Mean Difference
TB	Tuberculosis
TCZ	Tocilizumab
TIMs	Targeted Immune Modulators
TNF	Tumor Necrosis Factor
TOF	Tofacitinib
TRD	Total Residual Deviance
USPSTF	U.S. Preventive Services Task Force
VAS	Visual Analog Scale
WAC	Wholesale Acquisition Cost

Executive Summary

Background

Rheumatoid arthritis (RA) is the most common chronic inflammatory arthritis in adults, affecting between 1.3 and 1.8 million Americans.[1,2] It is a disease of unknown but immunologically mediated origin. RA is more common in women and may occur at any age, with peak incidence occurring at ages 50-60 years.[3] RA is typically characterized by morning stiffness and symmetrical joint swelling of the feet, hands, and knees, although any joint (and in some cases, internal organs and skin) may be involved.[3] RA is considered a clinical syndrome that, if not controlled, leads to permanent joint damage and deformity in some individuals.[4] The course of RA may also occasionally be complicated by skin, eye, heart, lung, hematologic, and other extra-articular manifestations.[3]

Over its course, the management of RA involves patient education, psychosocial support and therapy, physical and occupational therapy, medications, and joint surgery as required. The medications used are distinguished by whether they treat symptoms only versus those that target mechanisms of tissue damage, collectively referred to as disease-modifying anti-rheumatic drugs (DMARDs). Conventional DMARDs include older systemic agents with broad immunomodulatory effects such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine. More recently, a number of biologic and non-biologic agents targeted at mediators of inflammation in RA known collectively as "targeted immune modulators" (TIMs) have come into widespread use. Historically, RA was associated with both progressive disability and a shortened lifespan, but improvements in earlier diagnosis as well as aggressive use of TIMs have greatly improved survival and other key outcomes in the past 20 years.[5] This review focuses on the comparative clinical effectiveness, potential harms, and comparative value of the major TIMs used in the treatment of moderately-to-severely active RA despite prior conventional DMARD treatment, as well as two agents (baricitinib and sarilumab) currently under regulatory review for this indication.

The Topic in Context

Despite advances in treatment, RA remains a remarkably complex disease to diagnose and manage. There are multiple phenotypic and genotypic variations in the pathogenesis of the disease that affect both the course of RA and the outcome of therapy.[6] Some patients may have milder disease that never progresses to significant joint damage or functional impairment regardless of treatment received, while others experience a highly aggressive course that may require multiple attempts at treatment before the disease is brought under control. Similarly, both initial response to a given treatment and the durability of that response may vary even within phenotypically-similar populations; some individuals may have initial response with a short-lived remission, others may have a more robust initial and subsequent response, and still others may have inadequate response

to many TIMs before finding an appropriate treatment. The patient-physician relationship is therefore key to monitoring and managing ongoing therapy.

While earlier treatment focused on symptom management, actual and prolonged remission of symptoms is now a realistic goal for many patients. In 2012, the American College of Rheumatology (ACR) recommended several disease activity measures be used for routine clinical practice (see "Definitions" below), each with criteria to define remission of symptoms.[7] In addition, the College published treatment guidelines for RA in 2015 that strongly recommended a "treat-to-target" approach for both early and established disease.[8] Briefly, this approach involves (a) a goal of clinical remission, or alternatively, low disease activity as early as possible in the disease course; (b) adjustments in therapy at least every three months to reach the target; (c) strict and regular monitoring for disease activity, as frequently as monthly for patients with moderate to high activity; (d) separate monitoring for structural damage and functional impairment; and (e) discussion of all elements with the patient in a shared decision-making framework.[9]

Despite the evolution of diagnosis and treatment in RA, challenges remain in the management of the disease. For one, there is a general shortage of rheumatologists in the US, making the referral process protracted. The current situation is also unlikely to improve in the near future; a workforce study conducted by the ACR and the Association of Rheumatology Health Professionals (ARHP) projects a 31% decline in U.S. rheumatologists by 2030 due to aging of the workforce and an insufficient number of trainees to meet future demand.[10] In addition, early symptoms are similar across multiple forms of inflammatory arthritis, which also may prolong diagnosis. According to a recent patient survey conducted by the International Foundation for Autoimmune Arthritis, the average time from the onset of RA symptoms to formal diagnosis was 2.6 years.[11] Clinicians must also separately monitor patients for signs of increased disease activity and structural damage, as disease activity indices appear to be predictive of functional decline, but evidence is mixed on whether measures of radiographic joint damage are correlated with functional indices.[12]

Targeted Immune Modulator Therapies for RA

The TIMs of interest for this review are summarized in Table ES1. Through a variety of mechanisms, the TIMs are intended to modulate or inhibit signaling pathways, auto-reactive processes, or excess production of proteins, all of which are components of the inflammatory cascade in RA. The outcomes of near-term interest are remission in disease activity or reduction to very low levels, as well as slowing of progression of joint erosion or narrowing of the space between joints as assessed on radiography. Longer-term outcomes of interest include improvements in daily function as well as reductions in requirements for joint replacement surgery and/or assistive devices.

Table ES1. Targeted Immune Modulators: Dosage Forms and Administration Schedules

TIM	Recommended Dose (mg)	Route of Administration	FDA approval	WAC in February 2017*
Adalimumab (Humira®, AbbVie) ***TNFα inhibitor***	40 mg every other week; some patients not receiving MTX may benefit from taking 40 mg every week	Subcutaneous, self-injection or administered by healthcare professional	12/31/2002	$2,221 per 40 mg syringe
Certolizumab pegol (Cimzia®, UCB) ***TNFα inhibitor***	With or without concomitant MTX, 400 mg at Weeks 0, 2, and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks	Subcutaneous, self-injection or administered by healthcare professional	5/13/2009	$3,680 for 2 200 mg/1mL syringes or 2 200 mg vials of lyophilized powder
Etanercept (Enbrel®, Amgen) ***TNFα inhibitor***	50 mg once weekly with or without MTX	Subcutaneous, self-injection or administered by healthcare professional	11/2/1998	$1,111 per 0.98 mL of a 50 mg/mL syringe
Golimumab (Simponi®/Simponi Aria®, Janssen) ***TNFα inhibitor***	In combination with MTX, 50 mg sc injection once a month or 2 mg/kg iv infusion at weeks 0 and 4, then every 8 weeks	Subcutaneous, self-injection or administered by healthcare professional; Intravenous	4/24/2009 (sc); 07/19/2013 (iv)	$4,150 per 50 mg syringe (sc) or $1,592 per 50 mg (iv)
Infliximab (Remicade®, Janssen Biotech) ***TNFα inhibitor***	In combination with MTX, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks; may increase dose up to 10 mg/kg or treat as often as every 4 weeks	Intravenous	11/10/1999	$1,168 per 100 mg
Abatacept (Orencia®, Bristol Myers-Squibb) ***T-cell inhibitor***	Use as monotherapy or with DMARDs other than TNFα inhibitors; iv infusion dosed by weight [<60 kg 500 mg, 60-100 kg 750 mg, >100 kg 1000 mg], at weeks 0, 2, and 4, then every 4 weeks or 125 mg sc injection once weekly	Subcutaneous or Intravenous	12/27/2005 (iv); 07/31/2011 (sc)	$957 per 125 mg (sc) or $987 per 250 mg (iv)
Rituximab (Rituxan®, Genentech/Biogen) ***CD20-directed cytolytic B-cell antibody***	In combination with MTX, two-1000 mg iv infusions separated by 2 weeks every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks	Intravenous	2/28/2006	$835 per 10 mg/1 mL vial ($8352 per 1000 mg dose)

TIM	Recommended Dose (mg)	Route of Administration	FDA approval	WAC in February 2017*
Sarilumab (Kevzara™, Sanofi/Regeneron) ***IL-6 inhibitor***	150 mg-200 mg every 2 weeks‡	Subcutaneous Injection	Expected mid 2017	
Tocilizumab (Actemra®, Genentech) ***IL-6 inhibitor***	In combination with DMARDs or as monotherapy, start with 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response; 16 2mg subcutaneous injection every other week, increased to every week based on clinical response (or if patient weighs ≥100 kg)	Subcutaneous or Intravenous	1/8/2010 (iv) 10/22/2013 (sc)	$898 per syringe (sc) or $95 per 20 mg (iv)
Baricitinib (Olumiant™, Eli Lilly) ***JAK inhibitor***	2 mg -4 mg once daily‡	Oral	Expected 4/19/2017	
Tofacitinib (Xeljanz®, Pfizer) ***JAK inhibitor***	5mg twice daily with or without conventional DMARDs or 11 mg once-daily (extended-release form)	Oral	11/16/2012	$63 per tablet ($127 for extended release)

* Price reflects the wholesale acquisition price listed on Red Book Online (Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com/. Accessed February 24th, 2017); ǂ dosage at which investigational agents have been evaluated in clinical trials

All TIMs are associated with an increased risk of serious infection (including reactivation of tuberculosis in previously-infected individuals). While early reports of lymphomas in patients receiving TNFα inhibitors were a cause of concern, subsequent observational studies have shown lymphoma risks to be more closely aligned with the disease than with treatment.[13,14] While all patients with RA are at increased risk of herpes zoster ("shingles") infection, it is a particular concern with JAK inhibition. Rituximab and TNFα inhibitors have also been associated with Hepatitis B reactivation, while abatacept is associated with higher rates of respiratory complications in patients with Chronic Obstructive Pulmonary Disease (COPD). Other rare but serious adverse effects include progressive multifocal leukoencephalopathy (PML) with rituximab; worsening heart failure, demyelinating disease, and lupus-like syndromes with TNFα inhibitors; and bowel perforation with IL-6 and JAK inhibitors.

In addition to concerns regarding costs associated with dose increases, TIMs have also received considerable attention for rising prices in recent years. List prices for the two TIMs with the leading market share in RA, adalimumab and etanercept, have risen 70-80% in the last three years, to approximately $4,000 per month.[15] These prices do not consider discounts, rebates, or payment assistance programs provided by manufacturers. However, even after discounts and rebates, TIM

costs remain substantial. A recent examination of both list and net price changes from 2009-2015 found that percentage increases in net prices for adalimumab and etanercept were close to or even exceeded increases in list price, and both prices increased at rates 12-15 times higher than general inflation over the same time period.[16] In fact, adalimumab, etanercept, infliximab, and rituximab were #1, 3, 4, and 5 in global sales among the top 20 prescription drugs; while these figures were across all therapeutic indications, RA represents a substantial proportion of these sales.[17]

Insights Gained from Patients and Patient Groups

We received valuable input from individual patients and patient advocacy groups. A complete discussion of the insights from these conversations is presented in the full report, but several important themes are summarized below.

- Health-system challenges with RA are present from the very beginning. Diagnosis is often delayed, due in large part to a shortage of available rheumatologists in many areas of the US. Even after diagnosis, coordination of care across providers and settings is problematic, particularly for patients who self-administer medication and therefore do not get the opportunity to discuss multiple aspects of their care at an infusion clinic.
- Perhaps in part because of coordination of care challenges, patients stressed the importance of involving family, informal caregivers, and others as a critical component for successful management of the disease.
- It is not uncommon for patients to cycle through various therapies before finding a treatment option to which they both respond to and tolerate. We also received input that "fail-first" or step-therapy insurance policies often require patients to follow a specific sequence of TIM therapies, most commonly requiring a trial of methotrexate followed by multiple attempts with TNFα inhibitors.
- Because of the cyclical nature of the disease and its treatment, patients fear restrictions on access to certain types of drugs, as well as more general restrictions (e.g., stopping and re-starting therapy, requirements to repeat step therapy after switching health plans, etc.).
- The financial burden of RA treatment on patients and their families is also substantial and are not limited to out-of-pocket costs alone. Issues with coordination of care, navigation of insurance requirements by both patient and provider, lost time at work or school, and other challenges contribute to patient and family burden.
- Additional quantitative, patient-centric measures of treatment success are warranted, as many of the recent developments in defining disease remission and treatment response focus primarily on disease activity and not enough on symptom control, activities of daily living, and management of treatment-related side effects.
- "Point-in-time" measures often fail to capture the lability of RA—the disease's burden varies over time, as does the patient's ability to accommodate to the realities of the condition.

- The Arthritis Foundation also deployed two online surveys as part of their engagement in this process to document the RA patient experience (complete details available in the full report). The first survey included nearly 1,600 patients with primarily longstanding disease; 41% of the sample had been diagnosed 15 or more years ago. High levels of comorbidity were reported, as well as profound lifestyle impacts during periods when the disease was not well-controlled—nearly two-thirds required medication for pain and/or mental health concerns, and 20% were forced to leave work or school. In addition, one-third of patients reported difficulties in accessing their medication of choice.
- The second survey compared the experiences of patients who had received TIM therapy with a cohort of patients who had remained on conventional DMARDs. While comparisons were descriptive in nature only, conventional DMARD patients reported higher rates of joint damage, major surgery, and hospitalization or emergency-room visits related to their RA.

Comparative Clinical Effectiveness

To inform our analysis of the comparative clinical effectiveness of TIMs for moderately-to-severely active RA despite prior conventional DMARD therapy, we abstracted evidence from available clinical studies of these agents, whether in published or abstract/presentation form. In total, we included 132 reports of 67 RCTs and 17 observational studies. The 67 RCTs provided data on more than 28,000 patients. Of these RCTs, 60 focused on TIM combination therapy with methotrexate or other conventional DMARDs, five focused exclusively on TIM monotherapy, and two included both combination and monotherapy. We identified a total of 19 RCTs that involved head-to-head comparisons. Of these, eight involved comparisons of one TIM to another, and 11 were comparisons of a biosimilar form of a TIM to the originator product (biosimilar studies are summarized in Appendix C, and not a primary focus of the report). The majority of RCTs were determined to be of good quality, based on comparable study arms at baseline, use of validated outcome measures, and high levels of study retention. Most observational studies were considered of fair quality, due primarily to differences in patient populations at baseline.

Data were analyzed both descriptively and using techniques of network meta-analysis (NMA). Outcomes in the NMA included 20%, 50%, and 70% symptom response using ACR criteria, as well as radiographic progression (as assessed by the "Sharp" score) in a more limited dataset (see Appendix C for further details). Measures of disease activity were variably employed, and so are described in descriptive fashion only.

Clinical Benefits

All TIMs produced statistically- and clinically-superior improvements in symptom response, disease activity, radiographic progression, and other important outcomes when compared to conventional

DMARD therapy alone. This was true regardless of whether TIMs were used in combination with conventional DMARDs or as monotherapy, or whether they were studied in patients naïve to prior TIM treatment or in populations that had received prior TIMs (i.e., "TIM-experienced"). A more complete description of these findings is available in Section 4.3 of the report as well as in Appendix C.

The most frequent comparator in head-to-head studies was adalimumab, one of the longstanding TNFα inhibitors available for RA. Capsule summaries of head-to-head findings can be found below; results are also presented in tabular detail on pages 52-54 of the full report.

- ***Rituximab***: No studies comparing rituximab to another TIM of interest were identified.

- ***Abatacept:*** Abatacept combination therapy was similar to adalimumab combination therapy and infliximab combination therapy in rates of remission achieved, ACR response, and improvement in HAQ-DI and other patient reported outcomes; there was no statistical difference between abatacept and adalimumab in slowing radiographic progression.

- ***IL-6 Inhibitors***

    - ***Tocilizumab:*** In one head-to-head trial, tocilizumab monotherapy was found to be superior to adalimumab monotherapy in rates of clinical remission achieved and ACR response across all levels; tocilizumab did not differ from adalimumab in HAQ-DI improvement and most other patient reported outcomes.

    - ***Sarilumab:*** In one head-to-head trial, sarilumab monotherapy was shown to be superior to adalimumab monotherapy in rates of clinical remission achieved, ACR response across all levels, and improvement in HAQ-DI and other patient reported outcomes.

- ***JAK Inhibitors***

    - ***Tofacitinib:*** In one head-to-head trial, tofacitinib combination therapy was not statistically different from adalimumab combination therapy in rates of remission achieved, ACR response, and improvement in HAQ-DI after six months of follow-up.

    - ***Baricitinib:*** In a single head-to-head trial, baricitinib combination therapy was superior to combination therapy with adalimumab in ACR response across all levels, as well as improvement in HAQ-DI and other patient reported outcomes; there was no difference between baricitinib combination therapy and adalimumab combination therapy in rates of clinical remission achieved.

- ***TNFα Inhibitors***

    - ***Adalimumab:*** Adalimumab monotherapy was inferior to monotherapy with tocilizumab and sarilumab in rates of clinical remission achieved and ACR responses across all levels; adalimumab also resulted in significantly less improvement in HAQ-DI compared with sarilumab. Adalimumab combination therapy was inferior to baricitinib combination therapy in ACR response across all levels, as well as on improvement in HAQ-DI, but the two were similar in rates of clinical remission achieved. In all other head-to-head trials of combination therapy, adalimumab was similar to abatacept, etanercept, tofacitinib, and certolizumab pegol in rates of remission achieved, ACR response across all levels, and improvement in HAQ-DI; there was also no statistical difference between abatacept and adalimumab in slowing radiographic progression.

    - ***Certolizumab Pegol:*** Evidence from one head-to-head trial of certolizumab pegol plus methotrexate versus adalimumab plus methotrexate found no differences between agents in disease activity, ACR response, or HAQ-DI.

    - ***Etanercept:*** One head-to-head trial of etanercept and adalimumab (primarily in combination with concomitant conventional DMARDs) reported similar changes in disease activity and quality of life; observational data suggest no difference in remission or ACR response between etanercept and adalimumab.

    - ***Golimumab:*** No studies comparing golimumab to another TIM of interest were identified.

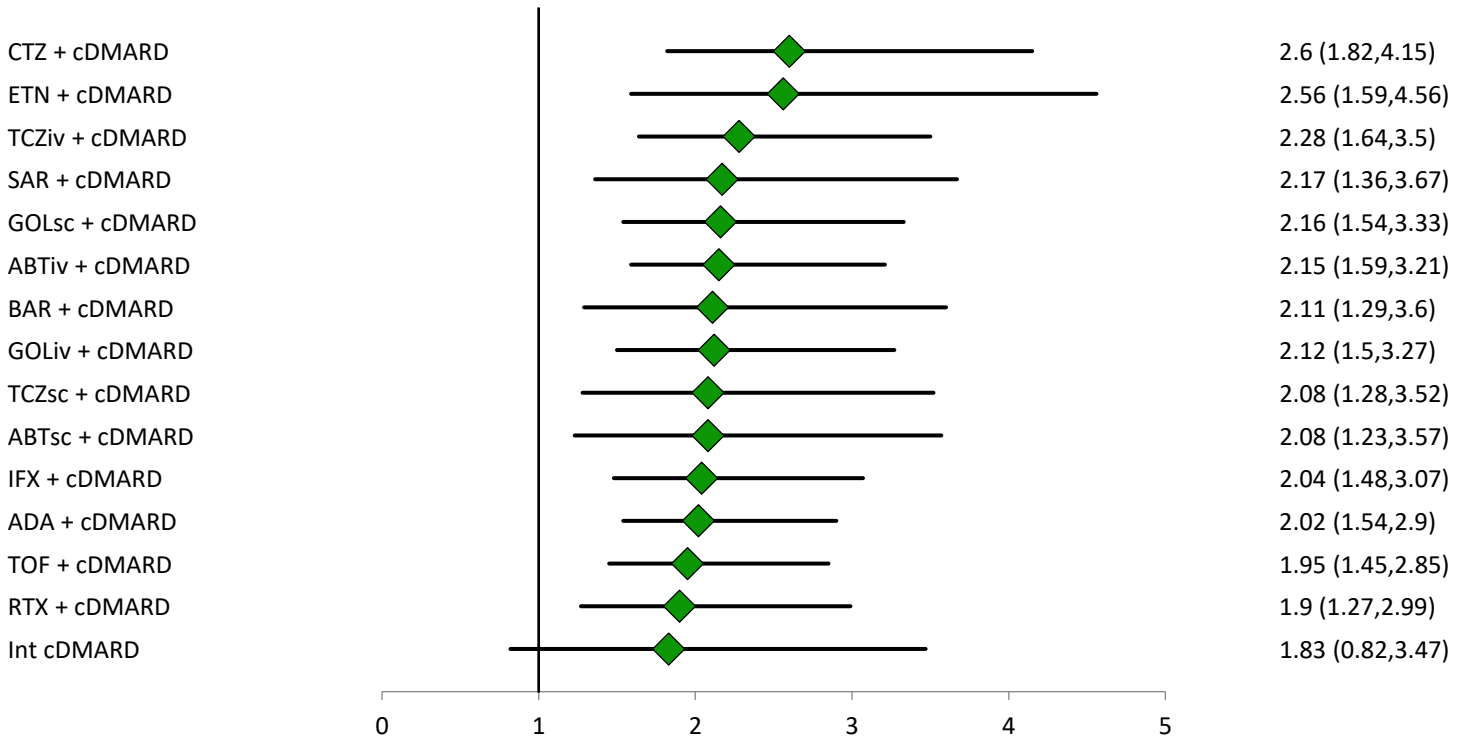
    - ***Infliximab:*** Similar improvements in disease activity, ACR response, and HAQ-DI were observed with both infliximab and abatacept combination therapy in a single head-to-head trial.

Network Meta-Analyses

A detailed discussion of our NMA methods can be found in Appendix C. We used NMAs to assess differences in ACR response between TIMs, by combining both direct (i.e., head-to-head) and indirect (comparison to conventional DMARDs) evidence. The discussion below focuses on the larger NMA, comprised of studies conducted in TIM-naïve or mixed populations (i.e., ≤20% TIM-experienced). Results for TIM-experienced patients can be found in the full report.

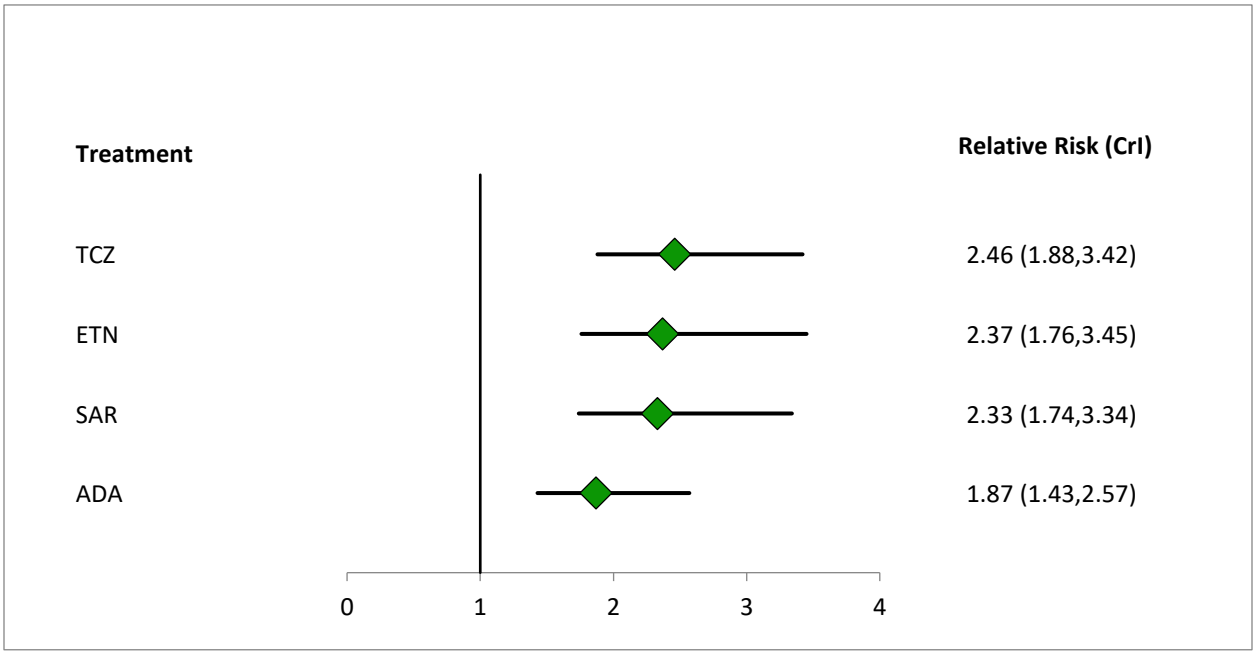
A forest plot of the results for ACR20 or better response for combination therapy and monotherapy regimens in TIM-naïve/mixed populations can be found in Figures ES1 and ES2 respectively. The pattern of findings was similar to that observed in the individual studies. All TIMs were between two and three times more likely to achieve ACR20 or better response when used in combination with conventional DMARDs in comparison to conventional DMARDs alone (Figure ES1). However, there were wide and overlapping estimates of the credible intervals around the estimates for each TIM combination; as a result, none of the comparisons between TIMs differed statistically.

Figure ES1. Relative Risk (Likelihood) of Patients Achieving ACR20 or Better with Combination Therapy Versus Conventional DMARDs Alone TIM-Naïve/Mixed Population



Similarly, in monotherapy comparisons, tocilizumab, etanercept, and sarilumab all produced significantly greater likelihoods of achieving ACR response in comparison to conventional DMARDs alone. However, tocilizumab and sarilumab also produced significantly greater likelihoods of achieving ACR20 or better response than adalimumab, echoing the findings of head-to-head trials.

Figure ES2. Relative Risk (Likelihood) of Patients Achieving ACR20 or Better with Monotherapy Versus Conventional DMARDs Alone, TIM-Naïve/Mixed Population



Standardized mean differences (SMD) were used in analyses of Sharp score to control for variation in scoring methods used; findings for the TIM-naïve/mixed population are presented in league table format in Appendix C, Figure C10. Both monotherapy regimens with data available (tocilizumab and etanercept) produced significant improvements in Sharp score relative to conventional DMARDs, as denoted by credible intervals that did not cross zero. These two TIMS did not differ when indirectly compared, however. Among combination regimens, all produced significant relative improvements versus conventional DMARDs except for tofacitinib, subcutaneous golimumab, and certolizumab pegol, which had credible intervals that included zero.

Harms

Data on adverse events, discontinuations due to adverse events, as well as specific adverse events of interest observed in clinical trials with conventional DMARD controls are presented as weighted averages (i.e., according to total sample size across trials) in Table ES2. Of note, these represent events as recorded before treatment-arm crossover was permitted. Limited data from longer-term trials are available and are summarized in Table 11 of the full report. The most frequently reported

adverse events were mild infections (upper respiratory tract infection, bronchitis, nasopharyngitis), injection site reactions and infusion related reactions. The overall incidence of serious infections, deaths, and all serious adverse events were comparable between treatments, including conventional DMARD therapy. As noted in the table, however, adverse-event rates for tofacitinib were calculated over a 12-week pre-crossover period, versus 24-28 weeks for the other TIMs.

The rates of serious infection, serious adverse events and discontinuation due to adverse events were generally comparable in the head-to-head trials comparing sarilumab, tocilizumab, etanercept, and baricitinib with adalimumab[18-21] (see Appendix C, Table C17). In the AMPLE trial, however, abatacept had a lower rate of discontinuation due to adverse events at year 2 compared with adalimumab (9.5% vs. 3.8%, estimate of difference: −5.7 [95% CI −9.5 to −1.9).[22] In a separate trial comparing infliximab with abatacept, the incidence of serious adverse events and discontinuation due to AEs were numerically lower with abatacept compared with infliximab (SAEs: 9.6 vs 18.2%; discontinuations due to AEs: 3.2 vs 7.3%, respectively), although statistical significance was not tested.[23] There was no evidence of material differences in the rates of malignancies or death between treatment groups across trials.

Table ES2. Adverse Events During the Conventional DMARD Controlled Period

Estimate (%)	Targeted immune modulators plus conventional DMARD											Conventional DMARD + Placebo
	RTX	ABT	TCZ	SAR	TOF†	BAR	ADA	CTZ	ETN	GOL	IFX	
Total (N)[1]	170	217	1,819	184	454	943	780	299	446	704	594	4,683
Any AE	76	79.7	70.7	65.2	50.2	72.1	77.3	74	68.7	54	73.5	64.5
Serious AEs	9	6	6.8	5.4	3.1	5.8	4.2	7.9	3.6	4.2	8.9	5.5
D/C due to AEs	2	0.9	5	9.2	4.3	2.5	2.9	4.8	3.1	3.6	4.8	2.7
Any infection	36	32.8	37.4	30.4	NR	38.2	41.9	30	43.7	44.1	14	29.5
Serious infection	1	1.3	2.9	1.6	NR	1.8	0.9	1.8	1.8	1	2.5	1.5
Tuberculosis	0	0	0	0	NR	0	0.5	0	0	NR	0	0
Injection site reaction		NR	10.1	8.2	N/A	N/A	16.4	2.5	20.8	3.7	N/A	5
Infusion related reaction	25	5.1	NR	N/A	N/A	N/A	N/A	N/A	N/A	3.3	6.2	4.9
Malignancy	0.5	0.6	0.9	NR	NR	0.5	0.3	0	0	0.3	0.8	0.4
Death	NR	0	0.4	0	0.6	0.3	0.2	0	0.5	0	0	0.2

NOTE: Serious AEs include specific listed events (e.g., serious infection, malignancy) as well as other events deemed life-threatening or requiring hospitalization by study investigators

* Values are weighted averages of the percentage of patients with event across key trials; color scheme identifies drugs of the same class.

1-Maximum contributing to the weighted average.; not every study contributes to all adverse events therefore, N contributing may be less in some AEs.

†Assessment period was between week 24 and 28 for all studies except for TOF that was at week 12; AE=adverse event; D/C=discontinuation

Controversies and Uncertainties

Across the 67 RCTs identified for this review, only eight were based on head-to-head comparisons of the TIMs of interest (excluding biosimilar studies). As such, our network meta-analyses of ACR response and Sharp score are largely driven by indirect evidence; however, our findings are relatively consonant with the results of head-to-head studies as well as with our assessment of relative differences in ACR response in comparison to conventional DMARD therapy, and our NMA findings are also comparable to other recent assessments of the evidence.[24-26] Given the longstanding availability of certain types of TIM therapy, there are a large number of observational studies that compare clinical effectiveness, safety, and other measures across drugs. Drawing comparisons across these studies is challenging, however, given differences in datasets as well as attendant selection, information, and other biases attendant in quasi-experimental research.

Even data coming from RCTs poses challenges, however. For one, patients were eligible for rescue therapy and/or treatment-arm crossover 12-24 weeks after randomization, which may not reflect the timing of treatment-switch decisions in typical practice and will limit conclusions regarding the long-term effects of initial treatment. Extending trial-based analyses to longer timepoints requires imputation in many instances, which affects the level of confidence in the results no matter how responsibly it is done. In addition, key outcome measures such as disease activity scores, remission criteria, and modified Sharp score have undergone substantial revision and modification over the years, are employed variably in clinical trials, and not measured in others, making cross-trial comparisons problematic. We attempted to control for variation in our NMA of Sharp score by presenting results as standardized mean differences, but note that this has been infrequently attempted to date. Finally, while comparisons of TIM combination therapy or monotherapy to conventional DMARDs alone provides important information on the incremental benefits of TIMs, such a comparison does not inform considerations of treatment sequencing. This compounds the already significant challenges with extrapolating RCT-based evidence to real-world settings that are common to all chronic therapies. The best approaches to address these concerns include head-to-head trials and pragmatic trials of treatment sequencing, both of which are currently in short supply.

Because TNFα inhibitors have the longest-standing evidence base of the TIMs of interest for this review, much of the early research in treatment sequencing involved assessments of switches between agents in this class for efficacy or safety reasons (commonly referred to as "cycling"). Now that other classes of agents are available, there is interest in evaluating the effectiveness of switches between versus within classes. The pragmatic Rotation or Change (ROC) trial recently addressed this question[27] by randomizing 300 patients with inadequate response to an initial TNFα inhibitor to receive a different TNFα inhibitor or to switch to a non-TNF biologic agent (tocilizumab, abatacept, or rituximab) at investigator discretion. The proportion of patients with low disease

activity on the DAS28-ESR was statistically-significantly greater in the non-TNF group vs. the second TNFα-inhibitor group at both weeks 24 (45% vs. 28%, p=.004) and 52 (41% vs. 23%, p=.003). Results from earlier observational studies and systematic reviews of trials in TNF-experienced patients echoed these findings.[28-30]

In the US setting, the potential for even observational study of different treatment sequences is complicated by payer formulary and benefit design. As described earlier in this report and highlighted further in Section 3, most private payers require initial TIM therapy and sometimes second TIM therapy to be within the TNFα-inhibitor class. Many payers also stipulate that etanercept and adalimumab hold preferred status as the first TIM of choice.

The course of RA may feature multiple periods of remission and flares of symptoms due to the complex and heterogeneous nature of the disease. TIM therapies are chronic, and the long-term effects of prolonged immunomodulation – both clinical benefits and potential harms -- are not well-understood for all therapies, particularly for newer classes of TIMs. Evidence is beginning to emerge on the question of whether TIM doses can be modulated or therapy suspended in patients with evidence of durable remission, but early results are limited and mixed. In addition, as noted in the Topic in Context section, the decision to initiate TIM treatment may in part be due to a missed opportunity to optimize conventional DMARD therapy; such challenges are common to other chronic diseases such as diabetes and heart failure as well.

Finally, while the introduction of TIMs has transformed clinical practice in RA and improved the quality of life and functional capacity of many patients, there are still unanswered questions, including the relationship between levels of disease activity and radiographic evidence of joint damage, whether there are patient or clinical factors that predict response to specific therapies, and the totality of the disease's impact on patients, families, and caregivers. As noted in the Topic in Context section, patient groups do not feel that the current tools for patient-reported outcomes sufficiently capture their experience, but to date no new instruments have been accepted into common use in clinical trials.

Summary

Using the ICER evidence rating matrix, our evidence ratings for selected comparisons of interest are provided in Table ES3 for patients with moderately-to-severely active RA who have had an inadequate response to prior conventional DMARD therapy. As described previously, findings of studies using conventional DMARDs as the control indicate clinically- and statistically-significant improvements in most important disease measures for all TIMs whether delivered as monotherapy or combination therapy, so all FDA-approved TIMs would receive a letter grade of "A" (high certainty of substantial net health benefit) relative to conventional DMARD therapy alone. However, the evidence on long-term effectiveness and safety of the two investigational TIMs

(baricitinib and sarilumab) is still emerging, so we judge the comparative clinical effectiveness of these two agents to have moderate certainty of an incremental or better net health benefit ("B+").

Table ES3. Evidence Ratings for Comparative Clinical Effectiveness: Selected Comparisons

Regimen Type/Comparison	Intervention	Comparator	Rating
Vs. Conventional DMARDs			
Mono- or Combination Therapy	Sarilumab	Conventional DMARDs	B+
	Baricitinib	Conventional DMARDs	B+
	All other TIMs	Conventional DMARDs	A
Head-to-Head Comparisons			
Monotherapy	Sarilumab	Adalimumab	B+
	Tocilizumab	Adalimumab	B+
Combination Therapy	Baricitinib	Adalimumab	C+
	Tofacitinib	Adalimumab	C
	Abatacept (sc)	Adalimumab	C
	Certolizumab pegol	Adalimumab	C
	Abatacept (iv)	Infliximab	B+
	Etanercept	Adalimumab	C
All Other Head-to-Head Comparisons	---	---	I

TIM Monotherapy

The presence of direct comparative data allowed us to be reasonably confident about the relative net health benefit for some between-agent comparisons. Among monotherapy regimens, sarilumab and tocilizumab (iv form) have been compared to adalimumab for impact on both disease activity and ACR response. Both agents produced statistically significantly higher rates of response, improvement in disease activity, and remission, as well as improvement in pain, fatigue, and quality of life, leading to moderate certainty of an incremental or better net health benefit for these agents relative to adalimumab ("B+"). Certainty was moderate because only a single trial was available for each comparison.

TIM Combination Therapy with Conventional DMARDs

Single RCTs have also evaluated combination therapy regimens with methotrexate plus baricitinib, tofacitinib, abatacept (subcutaneous form), or certolizumab pegol in comparison to adalimumab+ methotrexate. In the RA-BEAM study, baricitinib + methotrexate was associated with a statistically-significantly but modestly higher rate of ACR20 response (74% vs. 66% for adalimumab + methotrexate), and no differences were observed in remission rates. Rates of serious harm or discontinuation due to adverse events were also similar, so we judge the evidence for combination therapy with baricitinib vs. adalimumab to represent a comparable or better net health benefit ("C+"). There were no significant differences in clinical outcomes between combination regimens using tofacitinib, abatacept sc, or certolizumab pegol versus adalimumab combination therapy; the addition of indirect evidence through the NMA also yielded no statistical differences between these TIMs. We therefore assign a net health benefit rating of "C" for all three comparisons.

An additional study (RED SEA) compared adalimumab and etanercept in addition to existing conventional DMARD therapy, but was a noninferiority study focused primarily on continuation of therapy after one year and did not measure ACR response; in addition, disease activity measures did not statistically differ between arms. Given these findings, and bolstered by NMA results that showed no statistical differences between treatment arms, we consider the two agents to provide comparable net health benefits ("C").

Finally, the IV form of abatacept was compared to infliximab, both in combination with methotrexate, in a single trial (ATTEST). The proportion of patients achieving an ACR20 or better response was statistically-significantly greater with abatacept (72% vs. 56%), but neither changes in disease activity nor rates of remission differed between groups. However, rates of serious adverse events, discontinuation due to adverse events, and infusion reactions were lower with abatacept vs. infliximab, leading to a judgment of incremental or better net health benefit ("B+").

There is much greater uncertainty in assessing the relative comparative clinical effectiveness of TIMs that have never been compared head to head in a randomized setting. Observational studies might fill in these gaps, but findings have been inconsistent and design and population biases preclude any definitive conclusions. Finally, as presented earlier, our network meta-analysis produced variable estimates of ACR response and radiographic progression; for example, non-response rates ranged from 29-48% across the TIM combination therapy regimens. However, credible intervals were wide and included 0 for nearly all comparisons between TIMs. As a result, we judge there to be insufficient evidence ("I") to differentiate the remaining TIM comparisons, including intra-class comparisons of the remaining TNFα inhibitors, IL-6 inhibitors, and JAK inhibitors.

Other Benefits or Disadvantages

Among the TIMs of focus in our analysis, two (baricitinib and tofacitinib) are oral agents, which may provide a benefit to individuals without ready access to infusion centers and those who prefer oral treatment to self-injection (assuming the treatments are clinically comparable for a given patient). In addition, self-injected and infused products are administered at different frequencies that may be more or less convenient for patients given their specific circumstances. Also, because of RA's heterogeneous nature and likelihood that multiple TIMs will be required for many patients, as well as emerging evidence suggesting that switching to an alternative class of agent rather than "cycling" within class may provide clinical benefit, the availability of five distinct classes of TIMs for the treatment of moderately-to-severely active RA with inadequate response to conventional DMARDs is an important consideration. Finally, the ability of each TIM to address key patient-centric concerns such as rapid improvement in function and work capacity, other downstream clinical benefits such as reduced need for joint replacement, and reduced caregiver burden are critically important issues, although we note that the current evidence to distinguish the TIMs on these measures is sparse.

Long-Term Cost-Effectiveness

We developed a sequential treatment cohort model that assessed the cost-effectiveness of each of the TIMs detailed above relative to conventional DMARDs, as well as against the TIM market leader, adalimumab. Model parameters were estimated from the network meta-analysis described earlier, as well as from the published literature. The primary outcomes of the model included discounted lifetime total payer costs, life years, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios, using a payer/health-system perspective. Quality of life was estimated based on the correlation between ACR response and radiographic progression with function and disability based on the Health Assessment Questionnaire (HAQ).

The sequential treatment cohort model simulated a hypothetical homogeneous cohort of patients from the initiation of a TIM until death; a lifetime time horizon was used to reflect the chronic nature of RA. The model was developed in Microsoft Excel®. Patients could discontinue a TIM due to lack of effectiveness and/or adverse events. Patients discontinued treatment due to lack of effectiveness if they received an ACR score less than 20 (defined as non-responders) in the first treatment cycle. Thus, ACR scores >20 were considered treatment responders. A cycle length of six months was used to reflect the time needed to evaluate a treatment's effectiveness.[31] Patients discontinued treatment beyond the first six months only due to the occurrence of adverse events. Upon therapy withdrawal, the model simulated the patient switching therapy up to three different times: first to a TIM within the same class as the initial therapy, then to a TIM in a different class,

and finally to a palliative care state involving conventional DMARDs alone. Patients remaining on TIMs could experience quality-of-life improvements from level of ACR response as well as continued reductions in radiographic progression, while those on conventional DMARDs experienced continued degradation of quality of life. Further details on model structure, data inputs, and key assumptions can be found in Section 6 of the full report.

Model Parameters

The economic evaluation was primarily from a health-system perspective, and thus focused on direct medical and pharmacy costs. A separate scenario analysis was conducted to extend the perspective to a modified societal one that included indirect costs due to potential productivity gains or losses.[114] All future costs and outcomes were discounted 3% per year.

The model was informed by several key assumptions, which are detailed below.

- Patients can discontinue treatment for two reasons: (1) lack of effectiveness, and (2) occurrence of an adverse event.
- A treatment was administered for at least six months before a decision to discontinue was allowed in the model.
- After three different TIM failures, a patient reverts to conventional DMARD palliative care and stays with that therapy for the rest of his/her life.
- Each TIM is used in combination with methotrexate for the base-case combination therapy results. For subsequent lines of treatment, all relevant TIM therapies in the market basket were averaged and weighted equally.
- Those patients who had an ACR score less than 20 were assumed to be non-responders to TIM therapy.[110] These patients discontinue due to lack of effectiveness after the first TIM treatment cycle (six months).
- Responders experienced a constant probability of discontinuation due to adverse events for each TIM treatment for cycles two and above.[110]
- The cost calculations for intravenously administered therapies accounted for vial wastage (i.e., no vial sharing was allowed).
- The conventional DMARD comparator assumes the continued treatment costs of methotrexate and the clinical outcomes consistent with the clinical review over the remaining lifetime of the cohort. This comparator represents the long-term costs and outcomes in an environment without TIM treatment.

Base Case Results

Table ES4 presents the drug cost, total payer cost, average HAQ, life years gained, and QALYs gained over the lifetime horizon for each treatment pathway for TIMs added on to conventional DMARD. Total payer costs included the drug costs (drug costs, administration costs if any, and monitoring costs) as well as other payer-related costs that may differ by treatment including: hospitalization costs and serious adverse event-related costs. The results indicate that a lower HAQ score corresponded to a higher QALY gain, as expected. The base-case results indicate that treatment with TIMs over a lifetime horizon leads to substantial QALY improvements, ranging from 1.88 (tofacitinib) to 2.43 (etanercept) as compared to conventional DMARD therapy. Note that data for the two investigational agents (sarilumab and baricitinib) are limited to clinical outcomes only, as no price is available.

Table ES4. Results for the Base-Case for TIMs Added on to Conventional DMARDs

Treatment 1	Drug Cost	Total Cost	Average HAQ	Life Years	QALYs
rituximab	$366,768	$464,864	1.25	16.79	12.70
abatacept (iv)	$367,724	$466,733	1.22	16.82	12.78
abatacept (sc)	$452,292	$566,053	1.18	16.87	12.90
tocilizumab (iv)	$369,876	$470,205	1.19	16.85	12.88
tocilizumab (sc)	$329,324	$424,674	1.21	16.83	12.81
sarilumab	-	-	1.21	16.83	12.81
tofacitinib	$467,784	$579,140	1.28	16.75	12.57
baricitinib	-	-	1.25	16.78	12.67
adalimumab	$425,929	$530,720	1.25	16.78	12.68
certolizumab pegol	$417,742	$522,473	1.20	16.84	12.86
etanercept	$470,007	$583,449	1.12	16.94	13.12
golimumab (sc)	$408,413	$512,875	1.25	16.79	12.69
golimumab (iv)	$386,971	$488,380	1.23	16.81	12.75
infliximab	$381,243	$480,448	1.24	16.79	12.73
cDMARD	$18,209	$67,819	1.78	16.16	10.69

Three FDA-approved TIMs (adalimumab, etanercept, tocilizumab iv) had data for monotherapy administration, and thus, treatment with these TIMs as monotherapy (i.e., not in conjunction with conventional DMARDs) was modeled. Table ES5 presents the drug cost, total payer cost, average HAQ, life years gained, and QALYs gained over the lifetime horizon for each treatment pathway for TIMs as monotherapy. Results indicate that treatment with TIMs over a lifetime horizon leads to QALY improvements ranging from 2.20 (adalimumab) to 2.60 (tocilizumab iv) as compared to conventional DMARD therapy (conventional DMARD resulted in a lifetime discounted QALY of 10.75 for the monotherapy simulation).

Table ES5. Results for TIMs as Monotherapy

Treatment 1	Drug Cost	Total Cost	Average HAQ	Life Years	QALYs
tocilizumab (iv)	$384,441	$489,541	1.05	17.03	13.35
sarilumab	-	-	1.07	17.00	13.28
adalimumab	$449,224	$562,748	1.17	16.89	12.95
etanercept	$469,981	$584,952	1.11	16.95	13.16
cDMARD*	$18,235	$67,525	1.76	16.18	10.75

*cDMARD costs and outcomes were slightly different as compared to the combination findings in Table ES4 given the different ACR clinical findings for cDMARD in the monotherapy network meta-analysis as compared to the combination therapy network meta-analysis.

Table ES6 presents the discounted lifetime incremental cost-effectiveness ratios for each of the TIMs as compared to conventional DMARDs and to the TIM market leader, adalimumab. When comparing the TIMs to conventional DMARD therapy, the incremental comparisons showed that tocilizumab sc produced the lowest ratios. Tofacitinib produced the highest cost-effectiveness ratios compared to conventional DMARD therapy. Importantly, however, the cost-effectiveness of all TIMs in combination with conventional DMARDs relative to conventional DMARDs alone exceeded commonly-cited thresholds for cost-effectiveness of $50,000 - $150,000 per QALY gained.

When comparing the TIMs to the market leader adalimumab, eight TIMs were dominant, meaning they were less costly and more effective than adalimumab. Two other TIMs (abatacept sc and etanercept) were more costly but also more effective than adalimumab, with estimated cost-effectiveness ratios of $163,000 and $119,000 per QALY respectively. The final TIM (tofacitinib) was dominated by adalimumab, indicating that it was more costly and less effective. Importantly, however, we note that deterministic point estimates, particularly for QALY gains, are both subject to uncertainty and differ modestly between most of the TIM regimens evaluated. Indeed, findings

from probabilistic sensitivity analyses suggest a high degree of overlap in QALY estimates in pairwise TIM comparisons (Appendix D), consistent with our findings in the evidence review.

Table ES6. Incremental Cost-Effectiveness Ratios for the Base Case, for TIMs Added on to Conventional DMARDs

Treatment 1	ICER (cost per QALY gained) Comparator: cDMARD	ICER (cost per QALY gained) Comparator: adalimumab
rituximab	$198,056	Less costly, More effective
abatacept (iv)	$191,317	Less costly, More effective
abatacept (sc)	$225,853	$163,376
tocilizumab (iv)	$183,949	Less costly, More effective
tocilizumab (sc)	$168,660	Less costly, More effective
tofacitinib	$271,749	More costly, Less effective
adalimumab	$232,644	Reference
certolizumab pegol	$209,736	Less costly, More effective
etanercept	$212,021	$119,233
golimumab (sc)	$222,380	Less costly, More effective
golimumab (iv)	$204,212	Less costly, More effective
infliximab	$202,824	Less costly, More effective

For the three monotherapy regimens (tocilizumab iv, etanercept, adalimumab), cost-effectiveness was similar or improved as monotherapy but still exceeded commonly-cited cost-effectiveness thresholds (see full report for further description and tabular results). Tocilizumab monotherapy was less costly and more effective than adalimumab, while etanercept was more costly, generating a cost-effectiveness ratio of approximately $103,000 per QALY gained.

Sensitivity Analysis Results

One-way and probabilistic sensitivity analyses were conducted to assess variation and uncertainty in model inputs. The one-way sensitivity analyses identified model inputs with the most influence over the incremental cost-effectiveness ratio (see Appendix D for full results). Influential inputs often included the HAQ degradation (annual) for conventional DMARD, TIM adverse event discontinuation rate, baseline HAQ score, mTSS score, HAQ improvement over time due to mTSS changes over time, hospital days per HAQ level, and the level of HAQ improvement associated with certain ACR scores. Across all drugs, only one input, the annual HAQ degradation for conventional

DMARD, resulted in an incremental cost-effectiveness ratio lower than $150,000 per QALY gained from the base-case payer perspective, and this was only seen for tocilizumab.

A probabilistic sensitivity analysis was also conducted to assess variation in all parameters for each TIM compared to cDMARD (see Appendix D for further details). Tocilizumab (sc and iv) had the greatest number (10-27%) of iterations beneath a threshold of $150,000 per QALY gained; no other TIM had more than 4% of iterations below this threshold. Comparative results suggest that the TIMs with favorable deterministic ICERs as compared to adalimumab (either ICER < 150,000/QALY OR less costly and more effective), were also highly likely (>90% likely) to be cost-effective compared to adalimumab at a willingness to pay of $150,000/QALY.

Scenario Analyses Results

Because there is not one standard treatment pathway in RA, the sequential treatment pathway was varied in scenario analyses. The first scenario analysis changed the fourth treatment strategy from palliative care in the base-case to a market basket of all TIMs. Findings were similar to those of the base case. A second scenario analysis explored a sequential treatment pathway that modeled only one switch. Results were relatively consistent with the first scenario analysis and seemed to move all ICER findings closer to that of the average TIM versus conventional DMARD.

Additionally, to account for indirect costs due to absenteeism and unemployment (and the potential for reductions in each), the perspective was extended to a modified societal one. Compared to the health care system perspective, the cost-effectiveness ratios for a modified societal perspective were lower, and results were lower than $150,000 per QALY for both the iv and sc formulations of tocilizumab.

Other scenario analyses focused on results for regimens used in TIM-experienced patients and findings using shorter time horizons (1-3 years). Results exceeded $150,000 per QALY in all instances, and worsened as the time horizon became shorter.

Threshold Analyses Results

Table ES7 presents the results of the threshold analysis of the base-case using a lifetime horizon and health care system perspective. Each TIM in combination with conventional DMARD therapy was compared to conventional DMARD alone. The table presents the WAC per unit, net price per unit and discount needed to obtain the commonly cited cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY gained. The estimated net price was higher than the $150,000 threshold price for all TIMs, indicating that larger discounts from current WAC would be required to achieve even the higher end of the cost-effectiveness threshold range.

Table ES7. Threshold Analysis Results

	WAC per unit	Net price per unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Discount from WAC to reach thresholds
Rituximab (100mg)	$835.22	$709.94	$198.78	$369.17	$539.55	35% to 76%
Abatacept iv (250mg)	$987.03	$690.92	$193.46	$366.19	$538.92	45% to 80%
Abatacept sc (125mg)	$957.14	$813.57	$203.39	$374.24	$545.09	43% to 79%
Tocilizumab iv 20mg	$94.87	$75.89	$21.25	$41.74	$61.48	35% to 78%
Tocilizumab sc (162mg)	$898.31	$718.65	$237.15	$438.38	$639.60	29% to 74%
Sarilumab*	----------		$237.15	$445.56	$646.78	-
Tofacitinib (5mg)	$63.26	$60.10	$13.22	$23.44	$34.26	46% to 79%
Baricitinib*	----------		$13.82	$24.64	$36.06	-
Adalimumab (40mg)	$2,220.62	$1,554.43	$373.06	$699.49	$1,010.38	55% to 83%
Certolizumab pegol (200mg)	$1,839.94	$1,287.95	$347.75	$643.98	$927.33	50% to 81%
Etanercept (50mg)	$1,110.5	$777.35	$209.88	$380.90	$559.69	50% to 81%
Golimumab sc (50mg)	$4,150.38	$2,905.27	$726.32	$1,365.48	$1,975.58	52% to 82%
Golimumab iv (50mg)	$1,592.09	$1,114.46	$300.91	$557.23	$824.70	48% to 81%
Infliximab (100mg)	$1,167.82	$817.47	$220.72	$416.91	$604.93	48% to 81%

*WAC prices for the two investigational drugs were not available as of the date of this report.

Value-based Benchmark Prices

Our value-based benchmark prices for the two investigational agents as well as their in-class counterparts are provided in Table ES8. The value-based benchmark price for a drug is defined as the price that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY

gained. For all TIMs, the discounts required to achieve both threshold prices are greater than the current discounts from WAC, which are lowest (at 5%) for tofacitinib and highest (at 30%) for the TNFα inhibitors as well as abatacept iv. Tocilizumab sc could achieve a $150,000 cost per QALY with a 29% discount, but the best available estimate of current discount levels for tocilizumab is approximately 20%.

Table ES8. Value-based Benchmark Prices for RA Targeted Immune Modulators

	WAC per unit*	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Discount from WAC to reach thresholds*	Average Net Price Within Benchmark Range?
Rituximab (100mg)	$835.22	$369.17	$539.55	35% to 56%	No
Abatacept iv (250mg)	$987.03	$366.19	$538.92	45% to 63%	No
Abatacept sc (125mg)	$957.14	$374.24	$545.09	43% to 61%	No
Tocilizumab iv 20mg	$94.87	$41.74	$61.48	35% to 56%	No
Tocilizumab sc (162mg)	$898.31	$438.38	$639.60	29% to 51%	No
Sarilumab*	----------	$445.56	$646.78	-	N/A
Tofacitinib (5mg)	$63.26	$23.44	$34.26	46% to 63%	No
Baricitinib*	----------	$24.64	$36.06	-	N/A
Adalimumab (40mg)	$2,220.62	$699.49	$1,010.38	55% to 69%	No
Certolizumab pegol (200mg)	$1,839.94	$643.98	$927.33	50% to 65%	No
Etanercept (50mg)	$1,110.5	$380.90	$559.69	50% to 66%	No
Golimumab sc (50mg)	$4,150.38	$1,365.48	$1,975.58	52% to 67%	No
Golimumab iv (50mg)	$1,592.09	$557.23	$824.70	48% to 65%	No
Infliximab (100mg)	$1,167.82	$416.91	$604.93	48% to 64%	No

*WAC as of February 24th, 2017

Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of two new treatments for moderate-to-severe RA patients: sarilumab (including monotherapy) and baricitinib

(for both of which FDA approval is pending). We did not include other therapies modeled above in this potential budget impact analysis, given their established presence in the market.

Potential budget impact was defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to see a more realistic impact on the number of patients treated with the new therapies.

The potential budget impact analysis included the entire candidate population for treatment, which consisted of adults with moderate-to-severe RA who have previously failed treatment with conventional DMARDs. To estimate the size of the potential candidate population for treatment with sarilumab or baricitinib, we first determined the estimated prevalence of RA in the US, which has been reported as 0.6%.[32] Based on our review of the literature, we assumed that 50% of these patients were moderate-to-severe cases, and 50% of this subset had failed initial treatment with conventional DMARDs. Applying these proportions to the projected 2016 US population resulted in an estimate of approximately 486,000 patients in the US over a five-year period.

Based on input from clinical experts and payers, we assumed that sarilumab would take market share from tocilizumab (the other drug in its class) and adalimumab (a head-to-head comparator in clinical trials); similarly, baricitinib would take market share from tofacitinib and adalimumab. In both cases, we assumed that 70% of new users on the drug would come from patients using the other drug in its class, and 30% would come from adalimumab. We tested the potential budget impact of the two new drugs by assuming different unit price points for each (including monotherapy for sarilumab) - namely price to reach cost-effectiveness thresholds of $50,000/QALY, $100,000/QALY and $150,000/QALY, against the calculated discounted WAC for existing drugs.

Table ES9 below illustrates the per-patient budget impact calculations in more detail, based on the prices to reach $150,000 per QALY for sarilumab ($647 per syringe) and baricitinib ($36 per tablet), and the discounted WAC price of the TIMs they would be displacing. Note that no data matching our study entry criteria are available for baricitinib monotherapy, so budget impact was not calculated.

Table ES9. Illustration of Per-Patient Budget Impact Calculation over Five-year Time Horizon

Drugs	Combination therapy	Monotherapy
	Avg. Annual Per-Patient Budget Impact	Avg. Annual Per-Patient Budget Impact
Sarilumab	$24,812	$25,324
Adalimumab + Tocilizumab*	$31,185	$33,445
Net	-$6,373**	-$8,121**
Baricitinib	$27,077	N/A
Adalimumab + Tofacitinib*	$42,450	N/A
Net	-$15,373**	N/A

*Weighted in the ratio 30:70 for adalimumab:tocilizumab and adalimumab:tofacitinib

†For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

**Indicates cost-saving

When treating the eligible cohort with sarilumab combination therapy, the average potential budgetary impact (adjusted for differing periods of drug utilization and associated cost-offsets over a five-year period) results in cost savings at all three cost-effectiveness threshold prices for the drug, ranging from approximately -$18,400 per patient using the price ($647) to achieve $150,000 per QALY to -$60,800 using the price ($237) to achieve a $50,000 per QALY cost-effectiveness threshold.

Treating the eligible cohort with sarilumab monotherapy also resulted in cost savings across the three cost-effectiveness thresholds ranging from approximately -$23,400 per patient using the price ($647) to achieve $150,000 per QALY to approximately -$64,600 using the price ($237) to achieve the $50,000 per QALY threshold over a five-year time-horizon.

Finally, when treating eligible patients with baricitinib combination therapy, the potential budgetary impact over five years resulted in cost savings ranging from approximately -$45,200 using the price

($36) to achieve a cost-effectiveness threshold of $150,000 per QALY to approximately -$90,300 using the price ($14) to achieve $50,000 per QALY.

Summary and Comment

The base-case findings from our analysis suggest that all TIMs provide substantial clinical benefit in comparison to conventional DMARDs alone; however, their additional costs translate into cost-effectiveness estimates that exceed commonly-cited thresholds, ranging from approximately $170,000 to $270,000 per QALY gained. The deterministic findings suggest that all add-on TIMs were in a relatively small cluster with respect to QALYs gained. Compared to the market leader adalimumab, most TIMs in combination with conventional DMARD were more favorable (i.e., had deterministic findings with lower costs and higher QALYs), except for abatacept sc, tofacitinib, and etanercept. Assuming a willingness-to-pay threshold of $150,000/QALY, etanercept plus conventional DMARDs was found to be cost-effective as a first-line TIM, while abatacept sc in combination with conventional DMARDs was estimated to exceed $150,000/QALY, and tofacitinib was estimated to have higher costs and fewer QALYs gained.

The base-case results were generally robust to the sensitivity analyses. In one-way sensitivity analyses of deterministic results, annual HAQ degradation was the most influential parameter, with estimated cost-effectiveness going below $150,000/QALY for abatacept iv, tocilizumab iv, and tocilizumab sc. In probabilistic sensitivity analysis, tocilizumab iv and tocilizumab sc versus conventional DMARD therapy (the TIMs with the lowest cost-effectiveness ratio) fell below a threshold of $150,000 per QALY gained in 10% and 27% of iterations, respectively; for all other TIMs, that fraction was 4% or less. The probabilistic sensitivity analysis suggested TIMs with favorable deterministic ICERs as compared to adalimumab (either ICER < $150,000/QALY or less costly and more effective), were also highly likely (>90% likely) to be cost-effective compared to adalimumab at a cost-effectiveness threshold of $150,000/QALY.

Additionally, multiple scenario analyses were conducted to assess the impact of certain model assumptions and parameters on the results and conclusions. When adding in productivity effects, tocilizumab iv and sc fell below the cost-effectiveness threshold of $150,000/QALY gained, but results for other TIMs remained above this threshold.

Limitations to the present study are described in detail in the full report, and include assumptions regarding reduced effectiveness of later-line treatment based on data from only one class of TIMs (TNFα inhibitors), assuming all TIMs have equal opportunity for first-line use, considering only a single homogenous cohort of patients for treatment, and assuming no effects on TIM adherence other than initial switching due to non-response and subsequent switching for adverse events only.

Finally, results from our budget impact analyses suggest that baricitinib and sarilumab would decrease costs over the TIMs they would displace (i.e., the other agent in class and adalimumab) if

priced to cost $150,000 per QALY or less. We note, however, that because these two agents are investigational their prices (and consequent cost-effectiveness ratios) are currently unknown.

Conclusions

In summary, our analyses indicate that all the TIMs of interest in this evaluation substantially improved health outcomes compared to conventional DMARDs alone. However, their additional cost led to cost-effectiveness estimates that were well above commonly cited thresholds for cost-effectiveness, and the discounts required to achieve these thresholds are greater than estimated current discounts from WAC. Compared to the market leader adalimumab, most TIMs in combination with conventional DMARDs were more favorable (i.e., had deterministic findings with lower costs and higher QALYs).

Public Deliberation and Evidence Votes

At the March 24, 2017 meeting, the New England CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of targeted immune modulators for the treatment of rheumatoid arthritis. The New England CEPAC Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of treatment options for rheumatoid arthritis. The results of the votes are presented below. More detail on the voting results is provided in Section 10 of the full report.

Comparative Effectiveness of Targeted Immune Modulators as Monotherapy:

1. Is the evidence adequate to demonstrate that the net health benefit of tocilizumab monotherapy is superior to that provided by adalimumab monotherapy?

Yes: 11	No: 0

2. Is the evidence adequate to demonstrate that the net health benefit of sarilumab monotherapy is superior to that provided by adalimumab monotherapy?

Yes: 11	No: 0

3. Is the evidence adequate to distinguish the net health benefit between tocilizumab monotherapy and sarilumab monotherapy?

Yes: 0	***No: 11***

4. Is the evidence adequate to demonstrate that the net health benefit of tofacitinib monotherapy is superior to that provided by adalimumab monotherapy?

Yes: 0	***No: 11***

5. Is the evidence adequate to demonstrate that the net health benefit of baricitinib monotherapy is superior to that provided by adalimumab monotherapy?

Yes: 0	***No: 11***

6. Is the evidence adequate to distinguish the net health benefit between tofacitinib monotherapy and baricitinib monotherapy?

Yes: 0	***No: 11***

Comparative Effectiveness of Targeted Immune Modulators in Combination With cDMARDs:

7. Is the evidence adequate to demonstrate that the net health benefit of tocilizumab + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes: 1	***No: 10***

8. Is the evidence adequate to demonstrate that the net health benefit of sarilumab + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes: 0	***No: 11***

9. Is the evidence adequate to distinguish the net health benefit between tocilizumab + cDMARD therapy and sarilumab + cDMARD therapy?

Yes: 0	***No: 11***

10. Is the evidence adequate to demonstrate that the net health benefit of tofacitinib +cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes: 0	***No: 11***

11. Is the evidence adequate to demonstrate that the net health benefit of baricitinib + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes: 6	No: 5

12. Is the evidence adequate to distinguish the net health benefit between tofacitinib + cDMARD therapy and baricitinib + cDMARD therapy?

Yes: 0	***No: 11***

Comparative Value of Targeted Immune Modulators (TIM):

13. **Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money for tocilizumab monotherapy in comparison to adalimumab monotherapy?**

Low: 0	Intermediate: 4	***High: 7***

**Remaining votes on value not taken due to clinical effectiveness votes finding insufficient evidence to show net health benefit.*

Key Policy Implications and Recommendations

The New England CEPAC engaged in a moderated discussion with a Policy Roundtable of subject-matter experts about how best to apply evidence on targeted immunomodulators for plaque psoriasis in policy and practice. The Roundtable included a patient and patient advocate, clinical experts, drug manufacturer representatives, and public and private payer representatives. Many of the Roundtable themes focused on price negotiations which are based on manufacturer rebates and concessions and drive coverage policies for payers.

The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. Below are the top-line policy implications; for more informatioSn please see Section 10.4 in the full report.

Payers and Pharmacy Benefit Managers

1. Consider including in prior authorization processes the requirement that conventional DMARD therapy dosing be optimized before initiating TIM therapy.
2. If step therapy protocols require patients to fail one or two TNFα inhibitors before switching to another TIM, develop a quick and transparent exception process for specific situations.
3. Payers should reach out to providers to learn from their experience with prior authorization in order to streamline and improve the process.
4. Allow patients who are stable on effective treatment to remain on therapy when they change insurers.
5. Reconsider step therapy if pricing becomes better aligned with clinical value.
6. Negotiate better rebates and share savings with patients.
7. Increase transparency around the role of discounting and rebate practice in formulary design.
8. Design innovative risk-sharing payment agreements, including pay-for-performance contracts with manufacturers, value-based contracting with accountable care organizations, and indication-specific pricing.

Providers, Clinical Societies, and Payers

9. Develop clinical guidelines and coverage policies that closely align with the evidence on outcomes of patients stratified by prognostic factors, allowing for earlier use of TIM therapy in patients with poor prognostic factors.

Clinical Societies and Manufacturers

10. Establish standardized assessments to allow for rigorous direct and indirect comparisons of evidence across studies and therapeutic alternatives.

Public Policy Decision Makers

11. In a dysfunctional market system, in order to protect patients today and improve their future access to innovative therapies, policy makers may need to consider some form of regulatory intervention to ensure that drug prices and price increases do not continue their current upward trajectory, taking them further from reasonable alignment with the added benefits to patients.

1. Background

1.1 Introduction

Background

Rheumatoid arthritis (RA) is the most common chronic inflammatory arthritis in adults, affecting between 1.3 and 1.8 million Americans.[1,2] It is a disease of unknown but immunologically mediated origin. RA is more common in women and may occur at any age, with peak incidence occurring at ages 50-60 years.[3] RA is typically characterized by morning stiffness and symmetrical joint swelling of the feet, hands, and knees, although any joint (and in some cases, internal organs and skin) may be involved.[3] RA is considered a clinical syndrome that, if not controlled, leads to permanent joint damage and deformity in some individuals.[4] The course of RA may also occasionally be complicated by skin, eye, heart, lung, hematologic, and other extra-articular manifestations.[3]

Over its course, the management of RA involves patient education, psychosocial support and therapy, physical and occupational therapy, medications, and joint surgery as required. The medications used are distinguished by whether they treat symptoms only versus those that target mechanisms of tissue damage, collectively referred to as disease-modifying anti-rheumatic drugs (DMARDs). Conventional DMARDs include older systemic agents with broad immunomodulatory effects such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine. More recently, a number of biologic and non-biologic agents targeted at mediators of inflammation in RA known collectively as "targeted immune modulators" (TIMs) have come into widespread use. Historically, RA was associated with both progressive disability and a shortened lifespan, but improvements in earlier diagnosis as well as aggressive use of TIMs have greatly improved survival and other key outcomes in the past 20 years.[5]

Methotrexate is the most widely used conventional DMARD and is considered the "anchor drug" because of its effectiveness and relative tolerability as well as its potential to enhance the effectiveness of TIMs.[3] However, only about 50% of patients treated with methotrexate alone will experience sufficient reduction in disease activity or symptoms. Over the past two decades, the introduction of TIMs has transformed the clinical course of disease for many RA patients. Uncertainty remains, however, regarding the relative effectiveness and value of the different types of TIMs and the most effective sequence of TIM therapy. This review focuses on the comparative clinical effectiveness, potential harms, and comparative value of the major TIMs used in the treatment of RA as well as several currently under regulatory review for this indication.

Scope of the Assessment

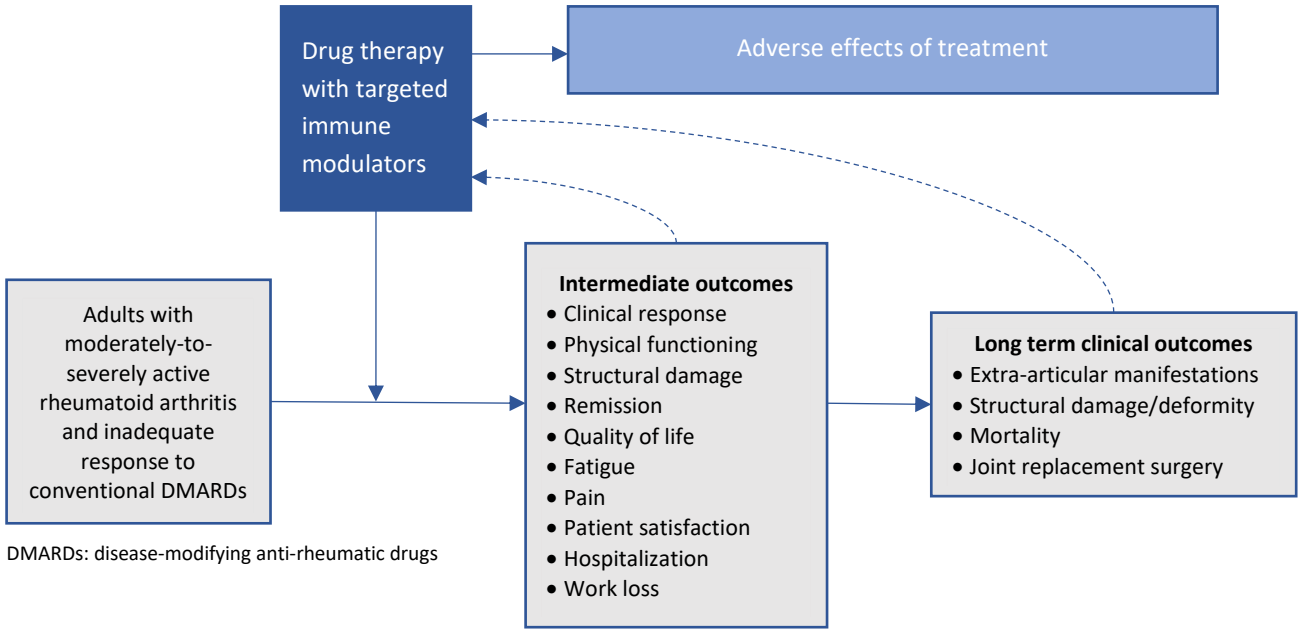
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework.[33] We conducted a systematic literature review using best practices for search strategy development and article retrieval. Data and evidence from randomized controlled trials, systematic reviews, and comparative cohort studies were assembled and reviewed; the focus in cohort studies was primarily on long-term outcomes and uncommon adverse events. Our evidence review included input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Wherever possible, we sought head-to-head studies of these interventions. We also included studies with an active comparison to conventional DMARDs as well as placebo-controlled studies. In addition, we combined direct and indirect evidence in network meta-analyses (NMAs) of selected outcomes. In these analyses, we explored methods to account for differences in trial populations using regression-based adjustment for control arm response rates as well as a variety of sensitivity analyses.[26,34]

Analytic Framework

The general analytic framework for assessment of targeted immune modulators for moderately-to-severely active RA is depicted in Figure 1.

Figure 1. Analytic Framework: Targeted Immune Modulators for Moderately-to-Severely Active Rheumatoid Arthritis



DMARDs: disease-modifying anti-rheumatic drugs

Populations

The population of focus for the review included adults ages 18 and older with moderately-to-severely active rheumatoid arthritis and inadequate response to or intolerance of conventional DMARDs. Classification of disease severity and treatment response were based on investigator assessment; in other words, we did not restrict study selection based on the use of specific tools for such assessments. Studies focusing exclusively on milder disease or on populations first initiating conventional DMARD therapy were excluded.

Studies of children, adolescents, or adults with a history of pediatric forms inflammatory arthritis were excluded. Feedback from patient groups and clinicians suggested that the clinical presentation and disease trajectory of these patients differs substantially from those with the adult onset form of RA.[35]

We also sought evidence on key subpopulations and/or data stratifications of interest. Among those suggested by stakeholders during the open input period were: (a) evaluation of both TIM-naïve patients *and* those with inadequate response to or intolerance of initial TIM therapy; (b) use of TIMs as monotherapy and in combination with conventional DMARDs; (c) route of administration (i.e., oral vs. self-injected vs. infused); and (d) setting of care (e.g., hospital-based vs. ambulatory infusion centers). Feedback received during the public comment period indicated additional subpopulations or stratifications of interest, including (e) presence of comorbidities (e.g.,

cardiovascular, psychiatric, malignancy); (f) both "early" (i.e., within 2 years of symptom onset) and established RA; (g) seropositivity for prognostic markers such as anti-cyclic citrullinated peptide (CCP) antibodies; (h) geography, in particular U.S.-based versus non-U.S. settings; and (i) study funding (i.e., industry-sponsored vs. other funding sources).

Interventions

While guidelines from relevant clinical societies recommend use of TIMs in patients who have not received adequate benefit from conventional DMARD therapy, the most appropriate sequence of use for specific populations remains unclear. For this reason, we considered a comprehensive list of TIMs with FDA indications for RA as well as two investigational therapies presently undergoing FDA review. However, we note that multiple stakeholders indicated that, while the IL-1 inhibitor anakinra is frequently used for pediatric forms of inflammatory arthritis, it is rarely used for adult RA in the U.S., so we removed this agent from consideration. Interventions of interest are listed by class below.

- TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab)
- CD20-directed cytolytic antibody (rituximab)
- T-cell receptor signaling inhibitor (abatacept)
- IL-6 inhibitors (tocilizumab, sarilumab [investigational])
- JAK inhibitors (tofacitinib, baricitinib [investigational])

We sought evidence for all agents listed above, including biosimilar forms as data permitted. We note, however, that the evidence on biosimilars is presented separately, given differences in study design and intent (e.g., non-inferiority vs. superiority, focus on pharmacokinetics) relative to clinical studies of the originator products.

Comparators

Most clinical trials of TIMs have been conducted in patients without adequate response to initial therapy with conventional DMARDs, yet involved comparisons to conventional agents nonetheless for purposes of regulatory approval. We examined studies comparing TIMs to conventional DMARD monotherapy or combination therapy (including triple therapy with the conventional DMARDs methotrexate, sulfasalazine, and hydroxychloroquine) to assess performance versus historical standard treatments, but also evaluated head-to-head studies between TIMs to evaluate for more contemporary comparisons. Conventional DMARDs were included regardless of treatment delivery mechanism (e.g., oral vs. injectable methotrexate).

Finally, while studies with an active comparator arm were preferred, we also included placebo-controlled trials as necessary to complete network meta-analyses of the effects of treatment on key measures of effectiveness that combined direct and indirect evidence.

Outcomes

This review examined key clinical outcomes associated with RA, as noted below:

- Mortality
- Standardized criteria for RA treatment response (e.g., ACR20, ACR50, and ACR70, area-under-the-curve analysis)
- Measures of disease activity, remission, and remission loss (e.g., DAS28, CDAI, SDAI)
- Radiographic evidence of structural damage
- Disease-specific and general health-related quality of life (e.g., HAQ-DI, SF-36)
- Pain (e.g., visual analog scales)
- Other patient-reported outcomes (e.g., patient satisfaction, fatigue, morning joint stiffness)
- Productivity loss and caregiver burden
- Requirements for joint replacement or other surgical intervention
- Utilization of healthcare resources (e.g., hospitalization, rehabilitation, assisted living)
- Cardiovascular events
- Treatment-related adverse events (e.g., serious infection, malignancy, liver abnormalities)
- Costs and cost-effectiveness of TIMs

Based on stakeholder feedback, we also assessed the impact of dose increases, dose decreases, and drug cessation during periods of sustained control or remission on long-term outcomes, as well as the effects of dose levels on clinical outcomes and the rates of serious adverse events. Where available, we also sought information on the clinical rationale for dose adjustments.

Timing

Evidence on intervention effectiveness was derived from studies of at least six months' duration, while information on potential harms was obtained from studies of at least three months' follow-up.

Settings

All settings were considered, including home and other outpatient settings, as well as ambulatory and hospital-based infusion centers.

2. The Topic in Context

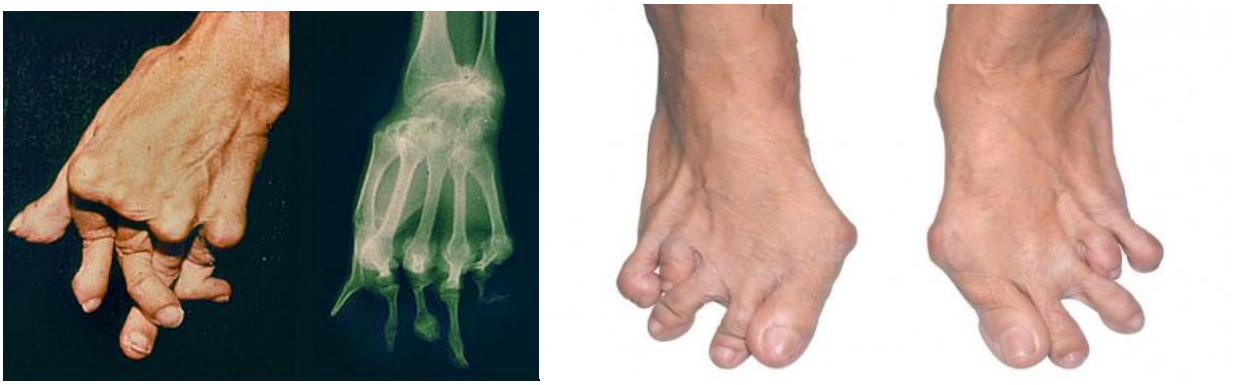
2.1 Overview

In summarizing the contextual considerations for appraisal of a health care intervention, we seek to highlight the four following specific issues:

- Is there a particularly high burden/severity of illness?
- Do other acceptable treatments exist?
- Are other, equally or more effective treatments nearing introduction into practice?
- Would other societal values accord substantially more or less priority to providing access to this treatment for this patient population?

As described in the Background section, the clinical course of RA historically featured increasing disease activity and joint damage. The images below show the deformities can result from longstanding and severely active RA, although these are generally seen in the clinical care of patients first diagnosed prior to aggressive use of conventional DMARDs and TIMs.

Figure 2. Advanced Rheumatoid Arthritis



Sources: https://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-symptoms/
http://www.thehealthsite.com/diseases-conditions/how-rheumatoid-arthritis-affects-the-foot-and-ankle-b1016/

Following the introduction of targeted immune modulator therapy beginning in the late 1990s, there are multiple signs that the clinical course of RA has been transformed. Data from a series of cross-sectional surveys conducted at rheumatology clinics in the UK between 1996-2014 found marked declines in measures of disease activity and improvement in the frequency of remission.[36]

There is also evidence that the introduction of TIMs has had beneficial effects on longer-term clinical outcomes. For example, the annual frequency of major joint replacement surgery among patients with RA declined by nearly one-third following the introduction of the first TIMs in the late 1990s, while the frequency of such surgery increased for all other indications.[37] In addition, the prevalence of specific extra-articular manifestations such as rheumatoid carditis and Felty's syndrome has markedly declined in the biologic era.[38] Finally, there is also evidence from several cohort studies and registries indicating that excess mortality risks in RA have modulated over time, although mortality rates remain higher than those of the general population.[39,40]

Despite these advances, RA remains a remarkably complex disease to diagnose and manage. There are multiple phenotypic and genotypic variations in the pathogenesis of the disease that affect both the course of RA and the outcome of therapy.[6] Some patients may have milder disease that never progresses to significant joint damage or functional impairment regardless of treatment received, while others experience a highly aggressive course that may require multiple attempts at treatment before the disease is brought under control. Similarly, both initial response to a given treatment and the durability of that response may vary even within phenotypically-similar populations; some individuals may have initial response with a short-lived remission, others may have a more robust initial and subsequent response, and still others may have inadequate response to many TIMs before finding an appropriate treatment. The patient-physician relationship is therefore key to monitoring and managing ongoing therapy.

Attempts to identify and risk-stratify patients who might benefit most from treatment have been longstanding. Classification criteria were first proposed in 1956 to identify RA before end-stage joint damage and major disability occurred.[41] The criteria were revised in 1987 and over the next several decades, studies suggested the benefits of early, aggressive, combination therapy in slowing joint damage and the number of treatment options expanded.

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed new criteria to facilitate the study of subjects with RA in its earliest stages. The resultant criteria of 2010 (Appendix E) added new predictive biomarkers such as anti-citrullinated protein antibody (ACPA) and C-reactive protein.[4] Current recommendations suggest risk stratification based on clinical presentation, biomarker data, and radiographic findings to guide treatment selection. For example, patients with poor prognostic markers would likely receive aggressive TIM therapy at diagnosis, while those with milder presentation may begin with a trial of conventional DMARD therapy.[42] While these criteria are now in widespread use, their evolution over time makes comparisons of 20+ years of clinical study challenging.

While earlier treatment focused on symptom management, actual and prolonged remission of symptoms is now a realistic goal for many patients. In 2012, the ACR recommended several disease activity measures be used for routine clinical practice (see "Definitions" below), each with criteria to

define remission of symptoms.[7] In addition, the College published treatment guidelines for RA in 2015 that strongly recommended a "treat-to-target" approach for both early and established disease.[8] Briefly, this approach involves (a) a goal of clinical remission, or alternatively, low disease activity as early as possible in the disease course; (b) adjustments in therapy at least every three months to reach the target; (c) strict and regular monitoring for disease activity, as frequently as monthly for patients with moderate to high activity; (d) separate monitoring for structural damage and functional impairment; and (e) discussion of all elements with the patient in a shared decision-making framework.[9] It was acknowledged, however, that these recommendations were made based on a low-moderate strength of evidence, as most Phase III clinical trials of TIMs have focused on general measures of symptom improvement such as ACR response criteria (i.e., ACR20/50/70) rather than remission targets.

Despite the evolution of diagnosis and treatment in RA, challenges remain in the management of the disease. For one, there is a general shortage of rheumatologists in the US, making the referral process protracted. The current situation is also unlikely to improve in the near future; a workforce study conducted by the ACR and the Association of Rheumatology Health Professionals (ARHP) projects a 31% decline in U.S. rheumatologists by 2030 due to aging of the workforce and an insufficient number of trainees to meet future demand.[10] In addition, early symptoms are similar across multiple forms of inflammatory arthritis, which also may prolong diagnosis. According to a recent patient survey conducted by the International Foundation for Autoimmune Arthritis, the average time from the onset of RA symptoms to formal diagnosis was 2.6 years.[11] Clinicians must also separately monitor patients for signs of increased disease activity and structural damage, as disease activity indices appear to be predictive of functional decline, but evidence is mixed on whether measures of radiographic joint damage are correlated with functional indices.[12]

We received additional input from a variety of clinical experts, clinical organizations, and drug manufacturers that added further nuance to published recommendations. The ACR response criteria were felt to be difficult to interpret across studies, as determination of improvement is clinician-directed and somewhat subjective; the response criteria are also rarely used in clinical practice given the switch to disease activity measures. An additional limitation is a general lack of head-to-head randomized controlled trials (RCTs) comparing treatments within or across classes. As a result, clinicians reported an increasing dependence on published findings and/or data releases from long-term registry studies to us, including the ongoing Consortium of Rheumatology Researchers of North America (CORRONA) studies (http://www.corrona.org/registries/rheumatoid-arthritis) and the ACR's Rheumatology Informatics System for Effectiveness (RISE) registry (http://www.rheumatology.org/I-Am-A/Rheumatologist/Registries/RISE/RISE-for-Research).

Clinicians largely agreed with a focus on treat-to-target approaches and aggressive treatment where warranted, for several reasons. First, a shorter time to achieve treatment success correlates with

better patient retention in treatment. In addition, periods of remission, relapse, and refractory disease are now a given for many RA patients, so close monitoring is of benefit if and when the effectiveness of current treatment wanes. Clinicians also felt that managing disease activity and drug side effects were their primary day-to-day concerns, along with periodic surveillance for joint damage.

2.2 Treatments for Rheumatoid Arthritis

Conventional DMARDs and Other Systemic Agents

Conventional DMARD treatments may be used alone or in combination (either with each other or more commonly, with TIMs).[43] Steroids are also used to control inflammation. The most common agents are described below:

- ***Methotrexate*** is an antimetabolite that interferes with folate synthesis on rapidly dividing cells. Low-dose methotrexate is recommended as the first-line use agent for RA. In addition, it can be used with many TIMs and such combination treatment produces results generally superior to TIM monotherapy. However, methotrexate may be associated with potential hepatotoxicity, requires regular laboratory monitoring and folic acid supplementation, interacts with multiple types of other drugs, and should not be used in patients with significant liver or kidney disease, or in couples planning on conceiving. Methotrexate is generally given weekly (either orally or subcutaneously); many patients also describe a post-dose fatigue ("methotrexate fog") that can last for several days.

  Either nuisance or severe side effects may contribute to early discontinuation of methotrexate. In addition, recent research indicates that early discontinuation may also be associated with physician prescribing practices, namely an incomplete trial of methotrexate, use of sub-optimal doses, and/or failure to switch to subcutaneous administration.[44] Several RCTs and observational studies have shown better bioavailability, treatment response, and adherence to subcutaneous versus oral methotrexate, although most of these studies were sponsored by manufacturers of injectable methotrexate formulations.[45,46,47,48] Regardless of form, emerging data suggest that methotrexate dosing is lower than that recommended by current guidance in many patients. [49,50,51]

- ***Sulfasalazine*** is a sulfa drug that combines salicylate (the active ingredient in aspirin) with sulfapyridine, an antibiotic. Daily oral use has been shown to have beneficial effects in reducing joint inflammation in RA, particularly in the earlier and milder stages of the disease. Common side effects include nausea and abdominal discomfort; sulfasalazine can

also increase sensitivity to sunlight and/or cause skin discoloration. Rarely, sulfasalazine can cause liver function abnormalities and neutropenia. Finally, potentially severe reactions can occur in patients with allergies to sulfa drugs, and as with methotrexate, drug interactions are common.

- ***Hydroxychloroquine*** (Plaquenil®, Concordia) is an oral anti-malarial medication that is often used in early milder forms of RA as well as in combination with other DMARDs. It likely has a variety of beneficial mechanisms of action, including but not limited to inhibition of toll-like receptor signaling and alteration of a number of cell proliferative effects dependent on an acidic pH. Hydroxychloroquine also appears to have a favorable effect on cardiovascular risk by lowering total, low density, and very low density cholesterol and inhibiting platelet aggregation without prolonging bleeding time. The most common side effects are gastrointestinal, including abdominal cramps that often resolve if the drug is withheld for several days and then resumed as a night time dose. Approximately 10% of patients develop skin rashes and hair loss can occur. Hyperpigmentation of skin and mucosal membranes are seen infrequently. Ocular side effects, including reversible corneal deposits are uncommon and irreversible retinopathy is rare when dose is limited to < 5 mg/kg/day and appropriately timed funduscopic evaluations are performed.

- ***Leflunomide*** (Arava®, Sanofi-Aventis) is an oral isoxazole derivative and pyrimidine synthesis inhibitor that works by inhibiting dihydroorotate dehydrogenase and is often used in those who are intolerant or fail to respond to methotrexate. It is occasionally combined with methotrexate in individuals who are not candidates for TIMs or triple conventional DMARD therapy. A previously recommended loading dose of 100 mg/day for three days is now rarely used. The most common side effects occurring in 10-15 % of patients include diarrhea, nausea, abnormal LFTs, alopecia, and skin rash. Far less commonly, hypertension, neuropathy, and cytopenias including agranulocytosis have been reported. The drug is contraindicated in pregnancy and in patients with pre-existing liver disease. Due to the drug's enterohepatic recirculation, active metabolites may persist for up to two years and therefore may require elimination with a bile acid resin binder such as cholestyramine prior to attempted conception.

- ***Steroids,*** most commonly prednisone or equivalent, are recommended for reducing inflammation in RA when disease activity cannot be controlled with a combination of TIMs and conventional DMARDs or as short-term (<3 months) treatment when patients experience a flare of RA symptoms. Steroids can be given using multiple routes of administration, including orally, as an intramuscular injection, intravenously, or as an intra-articular injection for local joint flares. Long-term management of RA with intermediate to

high dose steroids is not recommended; the health effects of such use are well-documented, and include increased susceptibility to infection, thinning of skin, hirsutism, weight gain, hypertension, diabetes, cataracts, osteoporosis, cardiovascular complications, and serious infections.

Targeted Immune Modulators

The targeted immune modulators of interest for this review are described in the sections that follow, and summarized in Table 1.[52]

1) ***TNFα inhibitors:*** **adalimumab (Humira®, AbbVie), certolizumab pegol (Cimzia®, UCB), etanercept (Enbrel®, Amgen), golimumab (Simponi® and Simponi Aria®, Janssen), infliximab (Remicade®, Janssen Biotech):** These are the longest-tenured TIMs on the market, with the first approved in 1998. They work by blocking or reducing the activity of tumor necrosis factor alpha (TNFα), which occurs in excess in RA and other joint diseases, and is a major driver of synovial inflammation.

2) ***CD20-directed cytolytic B-cell antibody:*** **rituximab (Rituxan®, Genentech/Biogen):** Rituximab is indicated for use in patients who have failed at least one prior TNFα therapy. B-cells play multiple roles in RA, including presentation of antigen to T-cells, activating them and magnifying autoreactive T-cell responses in RA; generation of autoantibodies that perpetuate the inflammatory cascade; and production of pro-inflammatory cytokines including TNFα, interleukin (IL)-1, and IL-6.

3) ***T-cell inhibitor:*** **abatacept (Orencia®, Bristol Myers-Squibb):** Abatacept prevents the CD28 protein from binding to its counter-receptor, CD80/CD86, which in turn reduces the activity of T cells. In addition to T-cell inhibition, abatacept has been found to reduce TNFα, IL-6, and other RA inflammatory markers in clinical trials.

4) ***IL-6 inhibitors:*** **tocilizumab (Actemra®, Genentech), sarilumab (Kevzara™, Sanofi/Regeneron):** The cytokine IL-6 activates T cells, B cells, macrophages, and osteoclasts, and is a pivotal mediator of the hepatic acute phase response to inflammation. IL-6 inhibitors bind to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and have been shown to inhibit IL-6-mediated signaling through these receptors. Sarilumab's manufacturers received FDA notification of a delay in a decision on the agent (from October 2016 to an undetermined timepoint) due to manufacturing deficiencies observed during a routine plant inspection.[53]

5) ***JAK inhibitors:*** **tofacitinib (Xeljanz®, Pfizer), baricitinib (Olumiant™, Eli Lilly):** While the TIMs listed above are biologic agents or other large molecules requiring subcutaneous injection or intravenous infusion, JAK inhibitors are oral agents. They work by inhibiting the Janus kinase enzymes, which mediate intracellular signaling pathways involved in the production of inflammatory cytokines, including IL-2, -4, -7, -9, -15, and -21. In January, the manufacturer of baricitinib announced that the FDA had extended the review period for the drug by three months, to April 2017, to allow time for the company to respond to FDA requests for additional data.[54]

All TIMs are associated with an increased risk of serious infection (including reactivation of tuberculosis in previously-infected individuals). While early reports of lymphomas in patients receiving TNFα inhibitors were a cause of concern, subsequent observational studies have shown lymphoma risks to be more closely aligned with the disease than with treatment.[13,14] While all patients with RA are at increased risk of herpes zoster ("shingles") infection, it is a particular concern with JAK inhibition. Rituximab and TNFα inhibitors have also been associated with Hepatitis B reactivation, while abatacept is associated with higher rates of respiratory complications in patients with COPD. Other rare but serious adverse effects include progressive multifocal leukoencephalopathy (PML) with rituximab; worsening heart failure, demyelinating disease, and lupus-like syndromes with TNFα inhibitors; and bowel perforation with IL-6 and JAK inhibitors.

2.3 Other Aspects of Treatment

Dosing Forms, Schedule, and Changes

As listed in Table 1, the TIMs are available in a variety of dosage forms and administration schedules. With the exceptions of the oral agents tofacitinib and baricitinib, all are delivered via subcutaneous injection or intravenous infusion. Abatacept, golimumab, and tocilizumab are available in both forms. As shown in Table 1, agents differ with respect to use of a "loading dose" and frequency of administration during the maintenance period.

For some of the TIMs, dosing adjustments are frequent in clinical practice. Infliximab (3-10 mg/kg) and tocilizumab (4-8 mg/kg) allow for flexible dosage strength in their labeling, and several other agents allow for modifications to the frequency of administration. Increases in dose and reductions in the interval between doses have been reported for these agents, as well as for adalimumab (intensification from every-other-week to weekly dosing). Moreover, despite recommendations for some TIMs to be used with methotrexate (see Table 1 below), in clinical practice, methotrexate may

not be used in conjunction with a TIM because it was poorly tolerated. This has not prevented use of TIM monotherapy.

The shift to a treat-to-target approach and concern about the rising costs of RA medications (see below) have led to increased experimentation with dose-tapering or drug-cessation strategies. Some clinical groups have argued that, for patients with a durable remission of symptoms (generally considered to be 12 months or longer), attempts can be made to reduce the TIM dose or eliminate the drug altogether, with careful monitoring for flares. Several studies have been conducted to assess the effectiveness of dose-sparing strategies with selected TIMs; results are summarized in the full report.[55]

Table 1. Targeted Immune Modulators: Dosage Forms and Administration Schedules

TIM	Recommended Dose (mg)	Route of Administration	FDA approval	WAC in February 2017*
Adalimumab (Humira®, AbbVie) ***TNFα inhibitor***	40 mg every other week; some patients not receiving MTX may benefit from taking 40 mg every week	Subcutaneous, self-injection or administered by healthcare professional	12/31/2002	$2,221 per 40 mg syringe
Certolizumab pegol (Cimzia®, UCB) ***TNFα inhibitor***	With or without concomitant MTX, 400 mg at Weeks 0, 2, and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks	Subcutaneous, self-injection or administered by healthcare professional	5/13/2009	$3,680 for 2 200 mg/1mL syringes or 2 200 mg vials of lyophilized powder
Etanercept (Enbrel®, Amgen) ***TNFα inhibitor***	50 mg once weekly with or without MTX	Subcutaneous, self-injection or administered by healthcare professional	11/2/1998	$1,111 per 0.98 mL of a 50 mg/mL syringe
Golimumab (Simponi®/Simponi Aria®, Janssen) ***TNFα inhibitor***	In combination with MTX, 50 mg sc injection once a month or 2 mg/kg iv infusion at weeks 0 and 4, then every 8 weeks	Subcutaneous, self-injection or administered by healthcare professional; or Intravenous	4/24/2009 (sc); 07/19/2013 (iv)	$4,150 per 50 mg syringe (sc) or $1,592 per 50 mg (iv)
Infliximab (Remicade®, Janssen Biotech) ***TNFα inhibitor***	In combination with MTX, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks; may increase dose up to 10 mg/kg or treat as often as every 4 weeks	Intravenous	11/10/1999	$1,168 per 100 mg

TIM	Recommended Dose (mg)	Route of Administration	FDA approval	WAC in February 2017*
Abatacept (Orencia®, Bristol Myers-Squibb) ***T-cell inhibitor***	Use as monotherapy or with DMARDs other than TNFα inhibitors; iv infusion dosed by weight [<60 kg 500 mg, 60-100 kg 750 mg, >100 kg 1000 mg], at weeks 0, 2, and 4, then every 4 weeks or 125 mg sc injection once weekly	Subcutaneous or Intravenous	12/27/2005 (iv); 07/31/2011 (sc)	$957 per 125 mg (sc) or $987 per 250 mg (iv)
Rituximab (Rituxan®, Genentech/Biogen) ***CD20-directed cytolytic B-cell antibody***	In combination with MTX, two-1000 mg iv infusions separated by 2 weeks every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks	Intravenous	2/28/2006	$835 per 10 mg/1mL vial ($8352 per 1000 mg dose)
Sarilumab (Kevzara™, Sanofi/Regeneron) ***IL-6 inhibitor***	150-200 mg every 2 weeks‡	Subcutaneous Injection	Expected mid 2017	
Tocilizumab (Actemra®, Genentech) ***IL-6 inhibitor***	In combination with DMARDs or as monotherapy, start with 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response; 16 2mg subcutaneous injection every other week, increased to every week based on clinical response (or if patient weighs ≥100 kg)	Subcutaneous or Intravenous	1/8/2010 (iv) 10/22/2013 (sc)	$898 per syringe (sc) or $95 per 20 mg (iv)
Baricitinib (Olumiant™, Eli Lilly) ***JAK inhibitor***	2-4 mg once daily‡	Oral	Expected 4/19/2017	
Tofacitinib (Xeljanz®, Pfizer) ***JAK inhibitor***	5 mg twice daily with or without conventional DMARDs or 11 mg once-daily (extended-release form)	Oral	11/16/2012	$63 per tablet ($127 for extended release)

*‡ Price reflects the wholesale acquisition price listed on Red Book Online (Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com/. Accessed February 24, 2017); ‡ dosage at which investigational agents have been evaluated in clinical trials

Drug Costs

In addition to concerns regarding costs associated with dose increases, TIMs have also received considerable attention for rising prices in recent years. List prices for the two TIMs with the leading market share in RA, adalimumab and etanercept, have risen 70-80% in the last three years, to approximately $4,000 per month.[15] These prices do not consider discounts, rebates, or payment assistance programs provided by manufacturers. However, even after discounts and rebates, TIM

costs remain substantial. A recent examination of both list and net price changes from 2009-2015 found that percentage increases in net prices for adalimumab and etanercept were close to or even exceeded increases in list price, and both prices increased at rates 12-15 times higher than general inflation over the same time period.[16] In fact, adalimumab, etanercept, infliximab, and rituximab were #1, 3, 4, and 5 in global sales among the top 20 prescription drugs; while these figures were across all therapeutic indications, RA represents a substantial proportion of these sales.[17]

As a result, out-of-pocket expenses for patients – especially Medicare patients - have also risen dramatically. The Centers for Medicare and Medicaid Services 2015 Drug Spending Dashboard[56] reports annual out-of-pocket payments for selected drugs, six of which have indications for RA. As shown in Table 2, patient payments average approximately $1,600 per year for self-administered drugs received as a Part D benefit, but approach $4,500 annually for infused agents. In addition, some Medicare beneficiaries only have partial-year Part D coverage or forego such coverage entirely, making most of the TIMs out of their financial reach. It should be noted, however, that the extent to which any gaps in Part B/D coverage are addressed by manufacturer-sponsored programs or other supplemental drug coverage is unknown.

Table 2. Estimated Annual Out-Of-Pocket Payments for Medicare Beneficiaries Receiving Selected RA Medications (2015)

Medication	Type of Benefit	Average Annual Out-of-Pocket Expense
Adalimumab	Part D	$1,588
Etanercept	Part D	$1,590
Certolizumab pegol	Part B	$3,581
Infliximab	Part B	$4,280
Rituximab	Part B	$4,367
Abatacept	Part B	$4,369

Source: Medicare 2015 Drug Spending Dashboard (https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Dashboard/2015-Medicare-Drug-Spending/medicare-drug-spending-dashboard-2015-data.html)

This information was echoed in a recent survey conducted by the Arthritis Foundation, in which nearly half of survey respondents (n=6,256) indicated that out-of-pocket costs for medications is the greatest challenge they face, and nearly 40% sought copayment assistance from manufacturers or other sources, or switched to a more affordable medication.[57] While this survey was conducted among individuals with any form of arthritis, 51% of respondents reported that they had RA. It should also be noted that the majority of respondents had employer-based health insurance; financial challenges would likely be more pressing for patients enrolled in public programs or on the individual market.

Biosimilars

One circumstance with the potential to affect drug costs is the development of biosimilar agents. The FDA has already approved three biosimilars to the TNFα inhibitors adalimumab (adalimumab-atto, Amjevita™, Amgen), etanercept (etanercept-szzs, Erelzi™, Sandoz), and infliximab (infliximab-dyyb, Inflectra™, Celltrion). Inflectra is now on the market, at a WAC price ($946 per 100 mg) that is a 15% discount from the WAC price of originator infliximab.[58] However, many of the long-term price and competitive implications of biosimilars are unknown given the emerging nature of this market. Findings from a recent systematic review suggest that the performance of biosimilar TNFα inhibitors is functionally equivalent to that of the originator products based on head-to-head studies focused on patient-centric outcomes.[59]

Treatment Sequencing

There is little study or guidance on the optimal sequence of treatments in patients over their entire course with moderate-to-severe RA. Guidelines consider combination conventional DMARD therapy (including triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine) to be a low-cost alternative to TIMs in patients with inadequate response to a single conventional DMARD; however, data are mixed on the performance of these regimens relative to TIMs as well as levels of adherence to treatment, and are currently a subject of intense debate.

Most clinical guidelines consider the TIMs to be equivalent, and suggest that initial changes due to lack of efficacy remain in the same class. However, recent evidence suggests that switches to a different class of TIM may be more efficacious.[27] Many payers have created coverage policies that force a particular sequence of treatment. In addition to standard elements of step-therapy protocols, such as matching clinical trial entry criteria and integrating uncertainty on safety for newer versus established agents, it is also possible that these sequences are informed by medications carrying the largest negotiated discounts and/or rebates rather than compelling clinical evidence. Specifically, the companies producing adalimumab and etanercept have negotiated first-line use and preferred status in RA and their other indications (e.g., psoriasis, psoriatic arthritis, Crohn's disease), limiting the potential for other drugs with a narrower indication set to compete.[60] Further details on public and private payer coverage policies can be found in Section 3.

Updates to clinical guidance on treatment are at various stages of study and consensus. Elements under study include testing methotrexate polyglutamate in patients without adequate clinical response to ensure that therapeutic levels of methotrexate are circulating in the blood (and adjusting dose or switching treatment accordingly), considering dose tapering in individuals who appear to be in continued and durable remission, and allowing greater switching flexibility at first treatment failure.

2.4 Insights Gained from Discussions with Patients and Patient Groups

We received valuable input from individual patients and patient advocacy groups throughout the scoping and evidence development process. Patients and patient organizations advised us that health-system challenges with RA are present from the very beginning. Diagnosis is often delayed, due in large part to a shortage of available rheumatologists in many areas of the US. Even after diagnosis, coordination of care across providers and settings is problematic, particularly for patients who self-administer medication and therefore do not get the opportunity to discuss multiple aspects of their care at an infusion clinic. Perhaps in part because of coordination of care challenges, patients stressed the importance of involving family, informal caregivers, and others as a critical component for successful management of the disease.

Regarding treatment, we were advised that it is not uncommon for patients to cycle through various therapies before finding a treatment option to which they both respond to and tolerate; this mirrored the input received from clinicians. We also received input that "fail-first" or step-therapy insurance policies often require patients to follow a specific sequence of TIM therapies, most commonly requiring a trial of methotrexate followed by multiple attempts with TNFα inhibitors. Because of the cyclical nature of the disease and its treatment, patients fear restrictions on access to certain types of drugs, as well as more general restrictions (e.g., stopping and re-starting therapy, requirements to repeat step therapy after switching health plans, etc.).

The financial burden of RA treatment on patients and their families is also substantial. Patients did mention that manufacturers have increased their recent activity around coupons and other copayment assistance programs, but that the financial problems associated with their care remain significant and are not limited to out-of-pocket costs alone. Issues with coordination of care, navigation of insurance requirements by both patient and provider, lost time at work or school, and other challenges contribute to patient and family burden.

Patient organizations advised us that clinical trials are often lacking robust information on patient-centric outcomes, and suggested a focus on recently-developed measures such as those described in the federally-funded Patient-Reported Outcomes Measurement Information System (PROMIS) toolkit (http://www.healthmeasures.net/explore-measurement-systems/promis). We revised our list of possible outcomes considerably based on this feedback. However, patients also felt that much work remains to be done on quantitative, patient-centric measures of treatment success, as many of the recent developments in defining disease remission and treatment response focus primarily on disease activity and not enough on symptom control, activities of daily living, and management of treatment-related side effects. Patients also told us that "point-in-time" measures often fail to capture the lability of RA—the disease's burden varies over time, as does the patient's ability to accommodate to the realities of the condition.

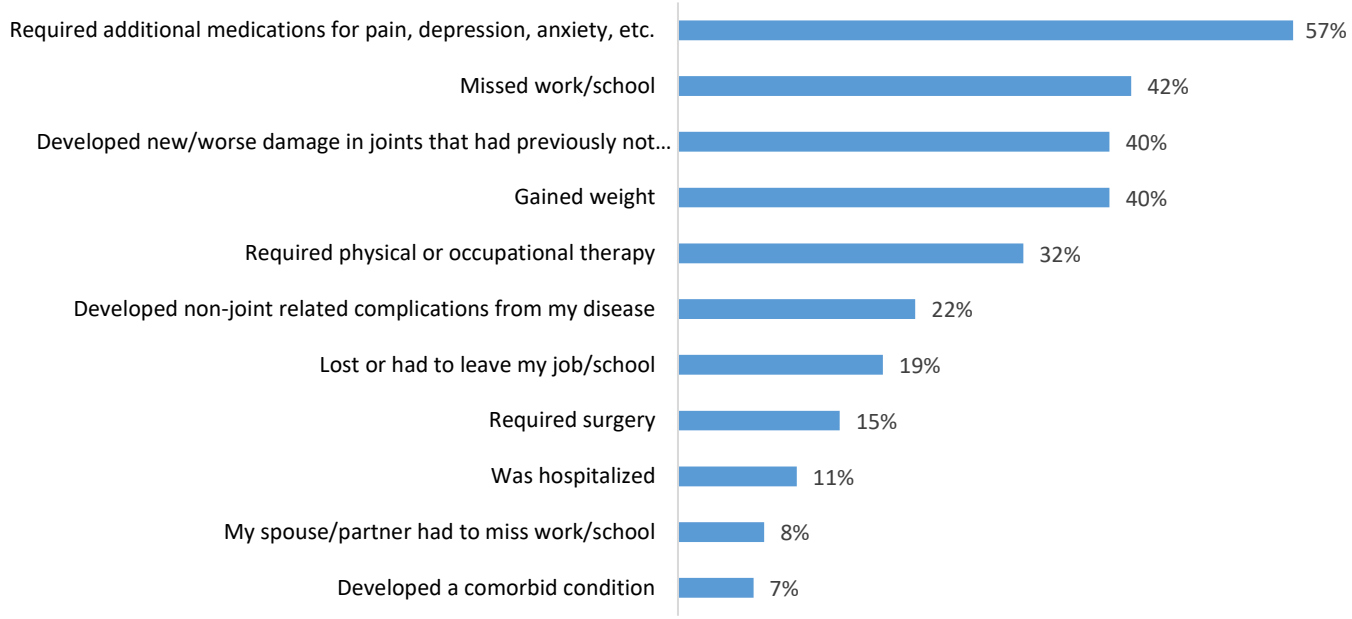
Arthritis Foundation Surveys

Patient Experiences

As part of their engagement with ICER, the Arthritis Foundation, the leading patient advocacy group for patients with RA and other forms of arthritis, deployed an online survey during the first two weeks of November 2016 to gather information about the RA patient experience. Over 3,000 responses were recorded; a total of 1,582 individuals confirmed that they had been diagnosed with rheumatoid arthritis. The population was comparable to the demographic profile in other US-based RA cohort studies. Eighty-eight percent of RA patients were female, 83% were white (10% were African American or Hispanic), and more than half of the sample were age 55 or older (mean 59.5). Most respondents reported insurance coverage with a commercial carrier (58%) or Medicare (41%).

Experience with RA was generally longstanding—41% of the sample had been diagnosed 15 or more years ago.[61] The clinical picture for many was complex, with over one-quarter of patients also diagnosed with obesity or depression, and over 10% prevalence of comorbid cancer, heart disease, and diabetes. In addition to clinical complications, RA also has profound lifestyle impacts during periods of greater disease activity. Figure 2 presents impacts experienced during periods when RA was not well-controlled. Nearly 60% of patients required additional medications for pain or mental health concerns, 42% missed some work or school, and nearly one in five had to discontinue work or school because of their condition.

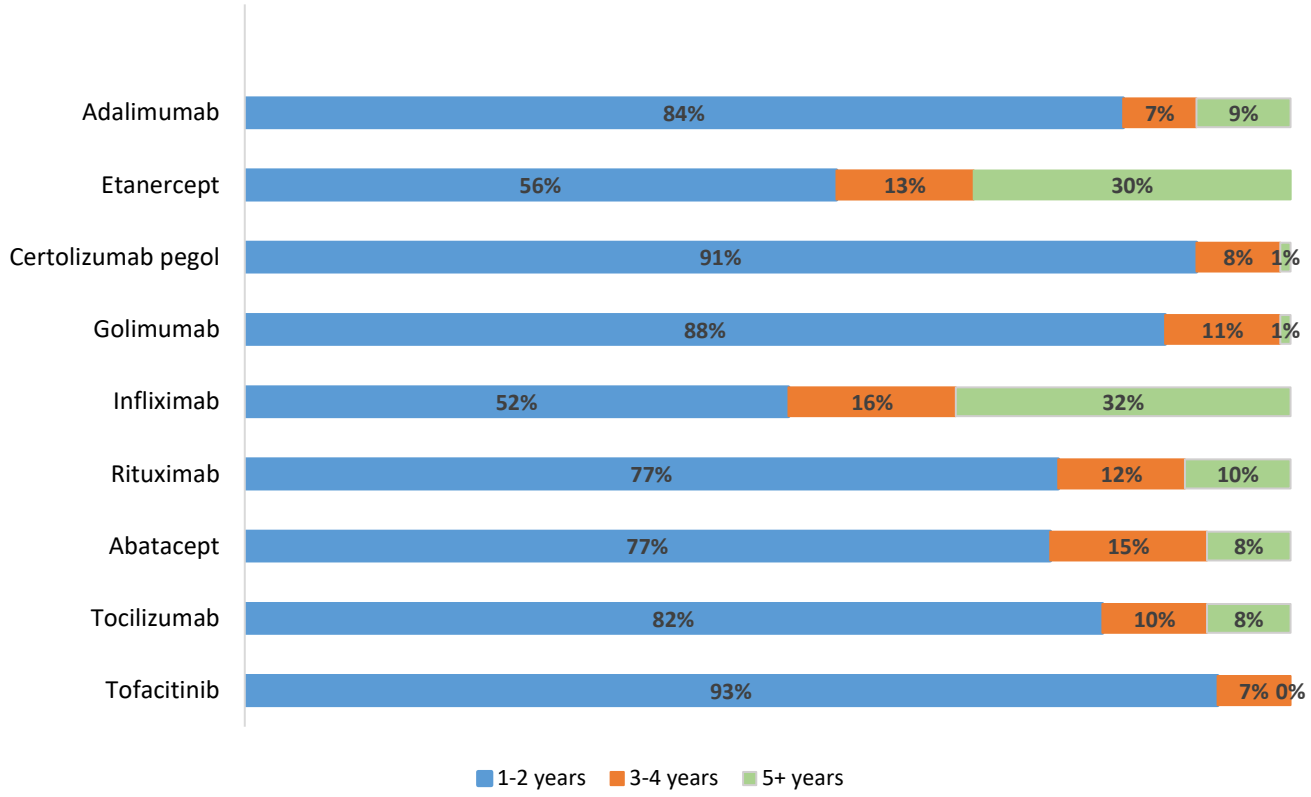
Figure 3. Reported Impacts of Rheumatoid Arthritis During Periods When Disease Was Not Well-Controlled



Source: Arthritis Foundation Survey of Rheumatoid Arthritis Patient Treatment Experiences, November 17, 2016

The survey also indicated that most patients have received multiple TIMs during the course of their disease, without clearly discernible patterns regarding treatment sequence. In addition, changes in medication generally happen relatively early. As shown in Figure 3, while the proportions vary by TIM, 50-93% of patients are on the same therapy for only 1-2 years, and relatively small percentages of patients have a course of treatment that is 5 years or longer. The agents with the greatest proportions of long-duration users were the earliest TIMs approved for RA in the late 1990s (etanercept and infliximab), which may be at least in part a reflection of their time on market rather than any durability advantage they hold over other TIMs.

Figure 4. Duration of Therapy, by Type of Targeted Immune Modulator Therapy



Source: Arthritis Foundation Survey of Rheumatoid Arthritis Patient Treatment Experiences, November 17, 2016

Finally, those surveyed reported few difficulties with accessing treatment facilities or scheduling regular doctor visits, which was surprising given the reported dearth of available rheumatologists. This may be a reflection on the surveyed population (e.g., covered by employer-sponsored health insurance). However, reflecting our conversations with individual patients and patient groups, one-third of patients reported problems with access to their medication of choice and restarting a medication they had been using if they stopped for some reason, and over 40% reported problems with care coordination across providers and settings.

Outcomes of Biologic-Naïve versus Biologic-Experienced Patients

The Arthritis Foundation deployed a second survey to assess outcomes of care in RA patients who had been treated with conventional DMARDs only for at least five years (n=222) as well as those who had received at least one TIM during this time period (n=337).[62] While findings are descriptive in nature only (i.e., not adjusted for clinical or demographic differences between groups), they echo

those of cross-sectional and other observational studies that have documented the clinical effects of the introduction of TIMs. For example, while substantial proportions of both groups reported that they had experienced some level of joint damage, the proportion was statistically-significantly greater in the TIM-naïve group (90% vs. 65%, p<.0001). Similarly, the proportion reporting at least one joint replacement or other major orthopedic surgery (e.g., spinal fusion) was nearly three times greater among TIM-naïve patients (56% vs. 19%, p<.0001. Finally, while disease impacts were pronounced in both patient subsets, greater percentages of biologic-naïve patients reported hospitalization or ER visits due to their condition/symptoms as well as receipt of disability benefits at some point.

2.5 Definitions

- ***ACR Classification Criteria (2010):*** Scoring algorithm for determination of definite RA based (a) number and level of joints involved; (b) diagnostic serology testing; (c) testing for acute-phase reactants; and (d) duration of symptoms.

- ***ACR Response Criteria:*** Known as ACR20, 50, or 70, represents at least 20%, 50%, or 70% improvement in tender/swollen joint counts as well as at least these levels of improvement in at least three of the following five criteria:
  a) Patient global assessment
  b) Physician global assessment
  c) Pain
  d) Disability/function
  e) Acute-phase reactant values

  Historically, ACR20 was the primary endpoint in most clinical trials of RA treatments. With the advent of greater efficacy from treatment with TIMs, the ACR50 and ACR70 are also commonly included as secondary endpoints. With the shift toward treat-to-target approaches, however, measures of disease activity and/or remission are now commonly used (see below).

- ***Acute-phase reactants:*** These are blood-based biomarkers for systemic inflammation characteristic of RA and other autoimmune diseases, typically C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

- ***Anticitrullinated protein antibody (ACPA):*** A blood test that measures the level of autoantibodies against cyclic citrullinated peptides, which are produced in excess in patients

with RA. The test has been used to establish risk for RA as well as to assess disease severity and/or prognosis.

- ***Disease activity measures:*** Multiple measures of disease activity, generally divided into patient-driven, patient/provider composite, and patient/provider/laboratory composite tools. All instruments differentiate low, moderate, and high disease activity:

  - Patient-driven tools
    - **Patient Activity Scale (PAS):** Scored 0-10 on a continuous scale based on questionnaire items regarding disability (HAQ, see below)), pain, and global assessment (visual analog scales [VAS]). A second version (PAS-II) has been developed using the same format but with a different disability measure (HAQ-II)

    - **Routine Assessment of Patient Index Data (RAPID-3):** Scored 0-10 on a continuous scale based on pain and global assessment VAS scales and disability measured via the MDHAQ

  - Patient/provider composite tool
    - **Clinical Disease Activity Index (CDAI):** Scored on a 0-76 continuous scale based on tender and/or swollen joint counts (up to 28 each), as well as patient and provider global VAS scores

  - Patient/provider/laboratory composite tools:
    - **Disease Activity Score with 28-Joint Counts (DAS28):** Scored on a 0-9.4 continuous scale based on tender and/or swollen joint counts (up to 28 each), ESR or CRP findings, and patient global VAS score

    - **Simplified Disease Activity Index (SDAI):** Scored on a 0-86 continuous scale based on tender and/or swollen joint counts (up to 28 each), CRP findings, provider global and patient global VAS score

- ***Health Assessment Questionnaire (HAQ):*** A 20-item RA-specific patient questionnaire designed to measure ability to perform activities of daily living in multiple domains: dressing, standing, eating, walking, hygiene, reach, grip, other activities, and requirements for assistance from devices or other persons for any of these. Also available in an abbreviated 10-item format (HAQ-II) as well as in an expanded multi-dimensional format (MDHAQ) that includes complex activities and psychological status.

- ***Patient-Reported Outcomes Measurement Information System (PROMIS):*** A relatively new set of person-centered measures that monitors physical, mental, and social health. Early tool development has focused on neurological diseases and sickle cell anemia, and initial validation of general health questionnaires has been conducted in RA samples.[63] Instruments are not yet widely used in clinical trials, however.

- ***Remission:*** Most commonly defined based on a zero or minimal score on measures of disease activity (see above), with upper limits ranging from 0.25-1.0 on the 10-point patient-driven scales to 2.6-3.3 on the patient/provider/laboratory composite tools.

- ***Rheumatoid Factor (RF):*** A blood test that measures for the presence of an immunoglobulin (most commonly IgM, but can be IgG and/or IgA) that binds to IgG. The test is positive in approximately 80% of patients with RA but is not diagnostic of the disease, as a positive RF can also be seen in other autoimmune and chronic inflammatory diseases as well as in some otherwise healthy older individuals.

- ***Sharp Score:*** The most widely-accepted method used to measure radiographic joint damage in RA. Multiple modifications are used, but all focus on both erosion and narrowing of the spaces between joints. The most common modifications include the van der Heijde method, which focuses on 43 areas of the hands and feet (score range: 0-448), and that of Genant, which examines 39 hand/foot areas (score range: 0-290).

3. Summary of Coverage Policies and Clinical Guidelines

To understand the insurance landscape for therapies for moderate to severe rheumatoid arthritis, we reviewed publicly available 2017 coverage policies and formularies for the six New England state Medicaid programs, Centers for Medicare and Medicaid Services (CMS) and 12 major Silver-level plans on individual marketplaces across New England.

All public and private carriers in New England managed the 11 drugs in this review through both step therapy and prior authorization. As a general sequence in step therapy protocols for private plans, patients were required to first try one conventional DMARD, usually methotrexate, before treatment with one or two TNFα inhibitors; treatment with other TIMs is only allowed as a third step in most of these algorithms (see Table 3). Adalimumab and etanercept were preferred in all but one plan surveyed. 25% of plans required step therapy with both etanercept and adalimumab before further treatment—and on average, just over half of the plans surveyed required step therapy with two TNFα inhibitors before moving to non-TNF agents. All TIMs were considered in the highest tier for cost- sharing purposes.

Table 3. Drug Management and Step Therapy Requirements* (requirements by % of plans surveyed)

	Preferred drug status?	DMARDs required before use:	# of TNFs required before use:		Adalimumab & Etanercept required before use	Not listed/ non-formulary
			1	2		
TNF Inhibitors						
adalimumab	100%	92%	8%	0%	N/A	0%
certolizumab pegol	42%	92%	17%	58%	25%	0%
etanercept	92%	92%	0%	0%	N/A	0%
golimumab	58%	92%	17%	42%	25%	0%
infliximab	58%	83%	0%	42%	17%	8%
CD20- directed cytolytic antibodies						
rituximab	8%	58%	33%	42%	17%	25%
T-cell inhibitors						
abatacept	0%	92%	33%	67%	22%	0%
IL-6 inhibitors						
tocilizumab	17%	83%	17%	58%	25%	8%
JAK inhibitors						
tofacitinib	25%	75%	0%	50%	17%	17%

**all agents require prior authorization*

In nearly a quarter of the plans surveyed, rituximab was either not listed or explicitly considered a medical benefit. For patients with rheumatoid arthritis, rituximab is only FDA-approved for those who have failed one or more TNFα inhibitors. In our survey, 42% of plans required patients to fail two TNFα inhibitors before receiving rituximab.

An October 2016 review of 10 of the largest private payers nationwide examined 94 TIM coverage policies in relationship to ACR and FDA guidance.[64] Over two-thirds of the payment policies surveyed were more restrictive than the FDA-labeled indications, and one-third were more restrictive than ACR guidelines. As with our own review, the study concluded that there is substantial variation in coverage policy by payer and medication.

Medicaid

As with the private carriers, all but one of the New England Medicaid programs (Massachusetts) identify etanercept and adalimumab as preferred agents. Maine and Rhode Island do not require prior authorization for etanercept or adalimumab, but require prior authorization for all other agents. New Hampshire Medicaid has the most restrictive policy, requiring use of two conventional DMARDs and failure of both etanercept and adalimumab before allowing coverage for other TIMs. Connecticut and Vermont both require failure of one conventional DMARD and one TNFα inhibitor before providing payment for other agents. Massachusetts requires an inadequate response or adverse reaction to conventional DMARDs **or** a biologic DMARD before allowing treatment with tocilizumab or tofacitinib.

Clinical Guidelines

American College of Rheumatology (ACR)[8]
http://www.rheumatology.org/Portals/0/Files/ACR%202015%20RA%20Guideline.pdf

The American College of Rheumatology Guidelines were updated in 2015. Upon failure of conventional DMARD monotherapy in patients with early disease (<6 months from diagnosis), the guidelines recommended conventional DMARD combination therapy, a TNFα inhibitor, or non-TNFα therapy with or without methotrexate. In this instance, recommendations were for TNFα inhibitors over tofacitinib due to the paucity of long-term safety data as well as cost considerations.

Recommendations were similar for patients with established disease, although tofacitinib is considered a viable alternative in patients with inadequate response to a single conventional DMARD; in patients without response to initial TIM or combination DMARD therapy, however, other non-TNFα therapies were preferred over tofacitinib.

In general, the ACR recommended combining TIM therapy with methotrexate for improved response. There was some acknowledgement of evidence of tocilizumab's superiority as a monotherapy over TNFα inhibitors after failed conventional DMARD treatment, although there was no consensus among the panel. ACR recommended continued treatment for patients with disease in remission. They also recommended continuation of current dosing, rather than tapering or discontinuing upon disease stabilization.

National Institutes for Health and Care Excellence (NICE)[65]
https://www.nice.org.uk/guidance/cg79?unlid=10194813432016226224059

The NICE guidelines on treating adults with rheumatoid arthritis were l updated in 2016. All but one of the therapies in our review have been recommended by NICE for treatment of moderate-to-severe rheumatoid arthritis. Guidelines on tofacitinib are expected in January 2018 (see project documents here).

If conventional DMARD therapy has failed for a patient, NICE recommends combining methotrexate therapy with at least one TNFα therapy, before treatment with other TIMs. For those patients who cannot take methotrexate because it is contraindicated, NICE recommends monotherapy with adalimumab, etanercept, certolizumab pegol or tocilizumab. NICE recommends continuing treatment if there is a moderate response after six months of therapy, and switching therapy if a patient has no response after six months.

***The European League Against Rheumatism*[42,66]**
http://ard.bmj.com/content/early/2017/03/06/annrheumdis-2016-210715

The European League Against Rheumatism (EULAR) Recommendations were most recently updated in March 2017. A focused recommendation on treating early arthritis was released in December 2016.

If there is no disease response to initial methotrexate monotherapy (or other conventional DMARDs if methotrexate is contraindicated) at three months, or treatment target is not achieved by six months, EULAR recommends risk stratification. If factors indicating unfavorable prognosis are absent, EULAR encourages continuing switching to or adding another conventional DMARD. If these factors are present, EULAR recommends combination therapy of methotrexate with a TIM. Current practice suggests use of a biologic TIM because of the long-term data available versus JAK inhibitors, although JAK inhibitors and IL-6 inhibitors are felt to have some advantages in patients who cannot use conventional DMARDs as co-medication. If a TIM+conventional DMARD strategy is unsuccessful, EULAR recommends switching to any other TIM, although the organization considers the efficacy and safety to be unknown for use of another TIM after insufficient response to a JAK inhibitor as well as use of another IL-6 inhibitor after failure of initial IL-6 inhibitor therapy.

In contrast to the ACR, EULAR recommends consideration of tapering treatment whenever possible in patients who have achieved stable disease remission.

Patient-Based Recommendations

***Patient Panel (Coordinated by the American College of Rheumatology)*[67]**
http://www.rheumatology.org/Portals/0/Files/When%20Patients%20Write%20the%20Guidelines.pdf

In January 2015, the ACR convened a panel of 10 patients to develop recommendations for treating rheumatoid arthritis. The patient panel voted on recommendations after several days of training led by ACR on how to evaluate evidence. The patient panel recommended combination therapy with two conventional DMARDs after monotherapy non-response. Unlike the ACR professional panel, the patients were more inclined to consider triple conventional DMARD therapy when appropriate. Upon treatment failure of conventional DMARD mono- or combination therapy, these patients recommended a treatment plan that included all TIMs. In contrast to the ACR panel, patients also recommended tofacitinib as an option in early RA. While physicians were cautious about the long-term safety of tofacitinib and preferred methotrexate because of its strong track record, patients thought that the side effects of methotrexate were worse than that of tofacitinib and felt that the evidence demonstrated superior outcomes for tofacitinib. Still, patients preferred TNFα treatment over tofacitinib in therapy sequencing.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative clinical effectiveness of targeted immune modulators for patients with moderately-to-severely active RA who experienced an inadequate response to previous methotrexate or other conventional DMARD therapy, we abstracted evidence from available clinical studies, whether in published, unpublished, or abstract form. The drugs and regimens of interest are included in Table 1.

As described in the Background section, we focused on evidence of the comparative clinical effectiveness of TIMs in the target population (i.e., moderate-to-severe disease with inadequate response to or intolerance of conventional DMARDs); we also included evidence from studies evaluating combination therapy (TIM + conventional DMARD) or TIM monotherapy in comparison to single or combination therapy with conventional DMARDs. Note that, while combination conventional DMARD therapy (including triple therapy) is included as a comparator in our scope, it was not a focus of our review given the paucity of available randomized comparisons.

Our review focused on key clinical outcomes common to RA trials, as well as patient-reported outcomes, healthcare system utilization, and work loss where evidence was available.

- Clinical benefits
    - Trial outcomes
        - ACR20/50/70 response
        - Disease activity (DAS28, SDAI, CDAI)
        - Radiographic progression (modified total Sharp score)
        - Function (HAQ-DI)
    - Patient-reported outcomes
        - Health-related quality of life (e.g., Short Form [SF]-36)
        - Pain
        - Fatigue
- Non-clinical benefits
    - Healthcare system utilization and associated costs
    - Productivity
- Harms
    - Treatment-related adverse events (e.g., deaths, rates of infection, malignancies)
    - Treatment tolerability (e.g., discontinuation due to adverse events)

4.2 Methods

We included evidence from randomized controlled trials (RCTs), comparative observational studies, and high-quality systematic reviews. We excluded single-arm studies as well as early clinical studies focused on very short-term tolerability; Phase II studies were included if they reported on outcomes of interest and met other specified selection criteria. We required studies to include minimum total sample sizes of 100 and 1,000 for RCTs and observational studies respectively. Our sample set was further limited to studies with at least six months' duration of follow-up for adequate surveillance of outcomes. However, long-term extension studies that evaluated outcomes more than three years after comparator-arm crossover was allowed were excluded, given challenges with attributing study findings to initial treatment.

Study comparisons must have been between active agents: we excluded trials in which the only comparator was placebo without background methotrexate or another conventional DMARD, as well as studies that pooled individual agents into a single treatment arm (e.g., TNFα inhibitors). We also excluded studies that only compared combination therapy (TIM + conventional DMARD) to monotherapy with the same TIM, but we did include data on both TIM monotherapy and combination therapy from trials with a third arm that represented conventional DMARD therapy alone. We excluded studies that only compared two different methods of administration (e.g., intravenous vs. subcutaneous) of the same agent. Biosimilar studies were included if they involved comparisons between the biosimilar and originator molecule and focused on the outcomes of interest; studies examining only pharmacodynamics or pharmacokinetics were excluded. Finally, because two of the TIMs have been studied using multiple dosage strengths and are not yet FDA-approved, we focused attention on the dosage most likely to be in the label based on clinical expert input (baricitinib 4 mg and sarilumab 200 mg).

In recognition of the evolving evidence base for RA, we supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). We excluded abstracts that reported data available in peer-reviewed publications as well as abstracts on therapies that have been on the market in the United States for at least three years.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on targeted immune modulators for moderately-to-severely active RA followed established methods in systematic review research.[68] We conducted the review in accordance with the Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[33] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix A, Table A1.

The evidence base for many of the agents included in our scope is relatively long-standing, and several recent systematic reviews and health technology assessments have evaluated the comparative clinical effectiveness of these therapies.[24,25,69] Rather than conduct a *de novo* literature search, we reviewed these systematic reviews for studies published prior to 2010 that met our inclusion criteria.

The timeframe was intended to build upon and update that of a comprehensively scoped report from the Agency for Healthcare Research and Quality (AHRQ).[69] Our search spanned the period from January 2010 to September 2, 2016 and focused on MEDLINE®-, Embase®-, and Cochrane-indexed articles. We limited each search to studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items.

To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses. We included several articles published after our initial search data when the data appeared to inform this report. Further details on the search algorithms, methods for study selection, data extraction, quality assessment, assessment for publication bias, and our approach to meta-analyses are available in Appendices A and C.

Data Synthesis and Statistical Analyses

Evidence tables were generated based on the data abstracted above and are presented descriptively in the sections that follow (see Appendix F). In addition, because the treatments of interest have usually not been directly compared, we developed quantitative, indirect comparisons among all agents using a Bayesian network meta-analysis (NMA) for both ACR and Sharp score outcomes. Consistent with prior published methods,[70] ACR20/50/70 response outcomes from clinical trials were tabulated to create numbers of patients in mutually exclusive categories (i.e., <20, 20-49, 50-69, ≥70); these data were analyzed using a random-effects, multinomial likelihood model to generate proportions of patients in each category. An adjusted model was specified with a covariate for conventional DMARD response rates as a possible control for between-study heterogeneity and general confounding. Model residuals (i.e., deviance information criterion [DIC] and total residual deviance) were evaluated to determine whether conventional DMARD response represented an important effect modifier.

The Sharp score data were analyzed based on the mean change from baseline to week 52. A fixed-effects model was used due to the small number of eligible trials and high degree of single-study connections. To aggregate and synthesize the multiple modifications of Sharp score into a common

metric, the standardized mean difference (SMD) method was calculated to accommodate the various Sharp score modifications and adaptions that have been reported across trials. As described further in Section 6, SMD data were also retransformed to estimates of absolute Sharp score change on the Van der Heijde scale relative to conventional DMARDs to support the comparative value analysis.

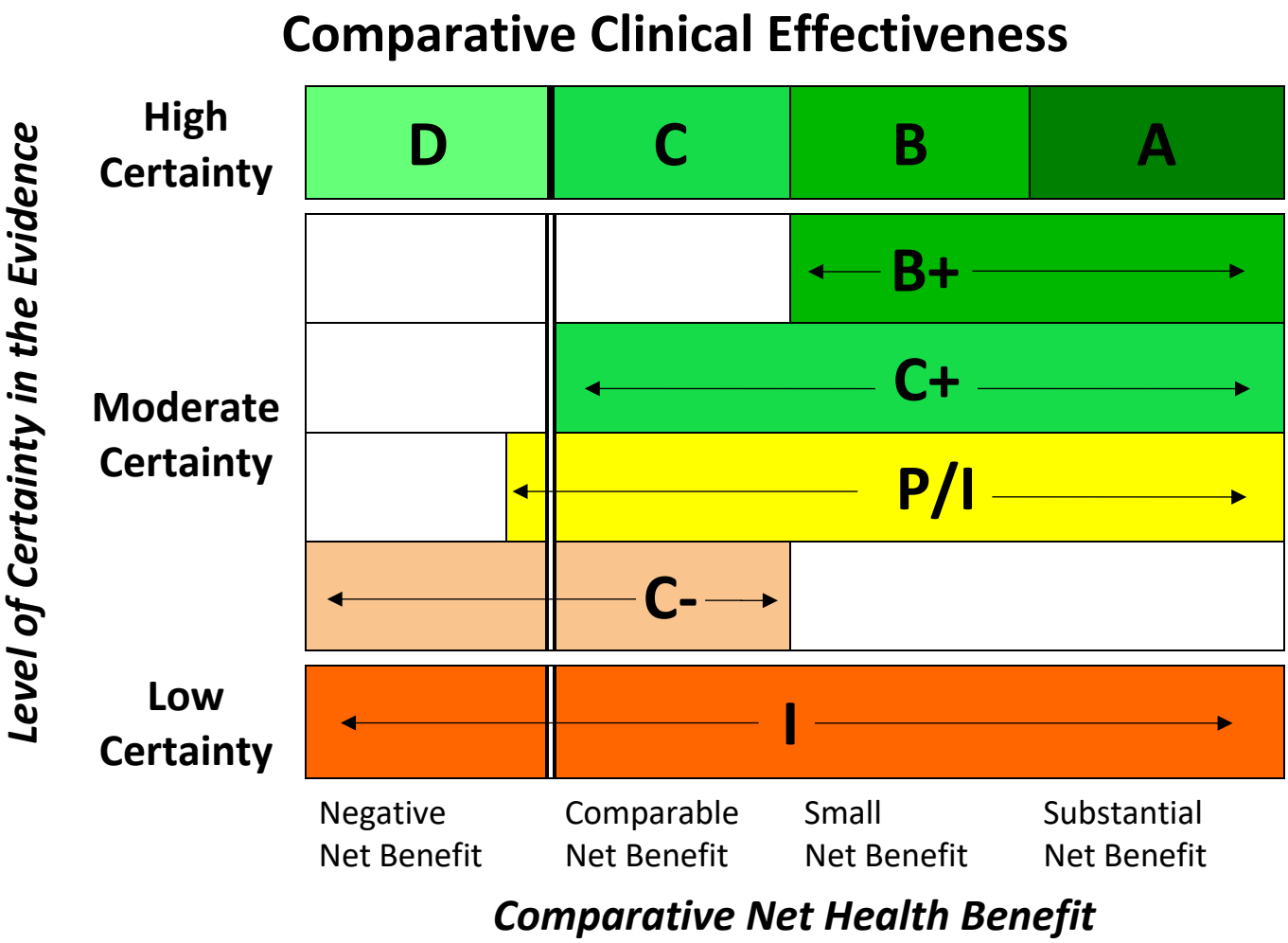
All statistical analyses were run within a Bayesian framework with WinBUGS 1.4.3. Criteria for trial selection, statistical methods and WinBUGS code are detailed in Appendix C.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 2) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

f) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
g) The level of **certainty** in the best point estimate of net health benefit.[71]

Figure 5. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable"*- High certainty of a comparable net health benefit*
D = "Negative"*- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Study Selection

Our literature search identified 4,042 potentially relevant references (see Appendix A, Figure A1), of which 118 met our inclusion criteria. These citations were comprised of 96 publications and 22 conference abstracts/posters. In addition, we reviewed three high quality systematic reviews for studies published prior to 2010 that met our inclusion criteria and identified 31 publications from 18 additional studies.[24,25,69] In total, we included 132 reports of 67 RCTs and 17 observational studies. Primary reasons for study exclusion included the use of regimens or dosing schedules not approved by the FDA, study populations that included patients who were naïve to methotrexate and/or other conventional DMARDs, and smaller sample sizes (<100 for RCTs or <1,000 for observational studies). Additional details of the included references are described in Appendix F.

The 67 RCTs provided data on more than 28,000 patient enrollments. Of these RCTs, 60 focused on TIM combination therapy with methotrexate or other conventional DMARDs, five focused exclusively on TIM monotherapy, and two included both combination and monotherapy. The majority (n=61) of the RCTs focused on populations that were primarily (80% or more) TIM-naïve, or exclusively so. We identified six RCTs conducted only in patients with prior use of one or more TIMs.

We identified a total of 19 RCTs that involved head-to-head comparisons. Of these, eight involved comparisons of one TIM to another, and eleven were comparisons of a biosimilar form of a TIM to the originator product. The remainder of the trials included comparisons to conventional DMARD therapy alone.

Biosimilar trials were identified for adalimumab, etanercept, infliximab, and rituximab. Details of these studies are presented in Appendix C. We do not discuss results in detail in this report, however, as findings uniformly demonstrated non-inferiority of the biosimilar to the originator product in all studies.

Quality of Individual Studies

We rated all 67 trials to be of good (83%) or fair (18%) quality using criteria from the U.S. Preventive Services Task Force (USPSTF).[72] Trials of good quality had study arms that were comparable at baseline, employed valid instruments to evaluate outcomes, and did not demonstrate differential attrition. Fair quality studies typically used a modified intent-to-treat or per-protocol analysis, or reported slight imbalances in baseline characteristics. Of the 17 observational studies, two were judged to be good, eleven fair, and four poor quality. We did not assign a quality rating to references that were obtained from grey literature sources (e.g., conference proceedings).

Most of the trials permitted use of rescue medication as early as three months following randomization, and treatment-arm crossover was generally allowed at six months. While these trials had good internal validity during the pre-crossover period, extrapolation to longer-term effects poses challenges. In addition, because some measures (e.g., radiographic progression) are relatively insensitive to short-term changes, these required imputations due to crossover effects or missing data.

Outcome-Specific Considerations

Our discussion of results is focused on the major clinical and functional outcomes of the available studies, including measures of disease activity and remission, ACR response, radiographic progression, and function or disability. Specific considerations regarding these measures are described below.

Disease Activity Score [DAS28]-ESR was the most frequent measure of disease activity across all trials, reported in about 80% of the trials that included disease activity measures. Other types of disease activity measures reported less frequently included: DAS28-CRP, Clinical Disease Activity Index [CDAI] and Simplified Disease Activity Index [SDAI]. Most studies used remission rates as one of the study endpoints, defined as DAS28 score ≤2.6, SDAI score ≤3.3, or CDAI score ≤2.8. Given the multiplicity of measures as well as their evolution over time, we opted to describe our findings in descriptive fashion only rather than conduct a network meta-analysis.

As noted in the Topic in Context section of this report, the American College of Rheumatology response criteria represent at least 20%, 50%, or 70% improvement in the core measures of RA activity. The primary endpoint in the majority of RCTs included in our analysis set was ACR20. However, ACR20 is generally considered minimal improvement, while ACR50/70 are regarded to be more clinically significant levels of response.[73] We present findings for all levels of response and note where results are similar or inconsistent across these levels.

Structural damage is most commonly assessed using the Sharp score. The Sharp score sums measures of both joint erosion and joint space narrowing across several joints in the hands, wrists, and feet.[a] The score has been modified and adapted over time, with iterations from Van der Heijde[74,75] and Genant[76] appearing most commonly in our review.

However, within the studies included in our review, the Genant and Van der Heijde methods were not applied consistently. Maximum possible scores were frequently not specified by trial investigators, and across the studies that did provide detail on the maximum achievable score, there was considerable variation (e.g., total scores using the Van der Heijde method ranged from

[a] The Van der Heijde modified Sharp score includes an analysis of several joints in the feet, although other approaches focus solely on the hands

380 to 448).[77,78] Consequently, there is substantial uncertainty in the degree of comparability of results between studies. Furthermore, because radiographic progression occurs gradually over time, this outcome is most frequently reported after at least 12 months of follow-up. Trials that permit early escape and/or crossover must extrapolate how much joint damage would likely occur had the patient continued with the initial treatment. These imputations are often based on a very short duration of observation (e.g., 16 weeks) and may underestimate the true progression that patients would experience had no adjustment to their therapy occurred. Missing or post-rescue therapy data were typically imputed using linear extrapolation of data from baseline and post-baseline radiographic assessment timepoints. Finally, we note that, in addition to issues of multiple methods and variants to assess radiographic progression, all such measures rely on clinician interpretation of radiographic data.

The HAQ-DI, a patient completed disability assessment, was the most widely reported measure of function in most the studies we identified. HAQ-DI Score ranges from 0 to 3, with higher scores indicating greater disability. In many published trials, a change of 0.22 in the HAQ-DI score,[79] or a more stringent 0.3,[80] is considered a minimum clinically important difference (MCID).

4.3 Results

Because our study entry criteria involved patient populations with an inadequate response to conventional DMARD therapy, it is unsurprising that the results of conventional DMARD-controlled studies consistently favored TIMs for all major outcomes. These findings are summarized across all TIMs in the report, but are presented by TIM in Appendix F. As noted above, our focus of attention in the report is on the four major clinical outcomes of the trials (disease activity/remission, ACR response, radiographic progression, and function/disability) as well as harms. A summary discussion of other outcomes (e.g., pain, fatigue, quality of life) can be found in Appendix C.

Findings from head-to-head studies are organized by TIM in the sections that follow. For each TIM, we describe results according to their use as monotherapy as well as in combination with conventional DMARDs. We also characterize the findings (as available) in primarily or exclusively TIM-naïve patients as well as those with prior TIM use, and describe any available findings in key subgroups.

Comparisons to Conventional DMARD Therapy

TIM-Naïve/Mixed Populations

All 11 TIMs generated superior improvements in disease activity, remission, and ACR response relative to conventional DMARD therapy alone in TIM-naïve/mixed populations. Incremental improvements were more modest for the JAK inhibitors and rituximab than other TIMs, and findings were limited for TIM monotherapy. Radiographic progression was also statistically-significantly reduced with most TIMs in comparison to conventional DMARDs, but differences in measures used made comparisons across studies difficult. Improvements in function and disability were statistically superior for all TIMs, and data were available that indicated greater proportions of patients receiving TIMs met clinically-important thresholds for HAQ-DI change except certolizumab pegol, etanercept, and tofacitinib (which did not report these data).

Findings for the four major clinical outcomes of interest can be found in Appendix C Tables C1, C3, C5 & C7. Appendix C summarizes results for other important outcomes, including patient-reported data on pain, fatigue, and health-related quality of life as well as work productivity and healthcare resource use.

A total of 49 RCTs compared combination therapy with TIMs and conventional DMARD therapy with conventional DMARDs alone in TIM-naïve or mixed populations. The proportions of patients achieving remission, measured primarily using the DAS28-ESR at 24 weeks, were substantially greater in the TIM groups relative to conventional DMARDs alone (Appendix C, Table C1). Results achieved statistical significance for all TIMs except abatacept and infliximab (statistical testing was not performed). Numbers needed to treat to achieve remission over 24 weeks were approximately 10 or less for all TIMs except tofacitinib (17-20), baricitinib (17), and rituximab (14).

An additional four RCTs compared TIM monotherapy with conventional DMARDs alone on remission measures. Findings showed statistically-significantly higher rates of remission for etanercept and tocilizumab.

The percentages of patients achieving ACR response at 24 weeks was also statistically-significantly greater for TIMs in combination with conventional DMARDs versus conventional DMARDs alone in 33 available RCTs (Appendix C Table C3). This was true not only for ACR20 response (the primary endpoint in most studies), but for ACR50 and 70 as well. As with measures of remission, incremental differences in response were more modest for the JAK inhibitors and rituximab. For example, the incremental percentage of patients achieving ACR20 response ranged from 21-27% for the JAK inhibitors and rituximab, but averaged >30% for all other TIMs.

We also identified five studies of monotherapy, two of tocilizumab and three of etanercept; [81-85] both trials of tocilizumab and two of the three etanercept trials[81,82] demonstrated substantial and statistically-significantly greater percentages of patients achieving ACR response across all thresholds.

A total of 17 RCTs evaluated radiographic progression using a variety of modifications of Sharp score (Appendix C, Table C5). As noted previously, the use of multiple modifications and variations makes even descriptive comparisons of incremental benefit problematic across studies. Fifteen of these included TIM combination therapy versus conventional DMARDs alone, and statistically-significantly reduced progression was demonstrated in the TIM arm for all except golimumab and tofacitinib. Findings for etanercept were mixed; in a comparison with methotrexate monotherapy, improvement in Sharp score was demonstrated for the etanercept combination arm versus a worsening with methotrexate alone.[86] No significant differences were observed between etanercept-methotrexate therapy and triple conventional DMARD therapy in another study, but this trial employed a non-inferiority design.[77]

An additional three monotherapy RCTs (two of etanercept and one of tocilizumab) showed statistically-significantly reduced radiographic progression in the TIM arm relative to methotrexate or other conventional DMARD therapy.

A total of 17 trials of combination TIM+conventional DMARD therapy evaluated the change from baseline on the HAQ-DI in relation to previously-published minimum clinically-important differences (i.e., changes from baseline of either 0.22 or 0.3). Statistically-significantly greater proportions of patients achieved these thresholds in the TIM combination groups versus conventional DMARDs alone for all agents except certolizumab pegol, etanercept, and tofacitinib, where we found no trials that employed the thresholds in this manner.

In four trials examining TIM monotherapy, etanercept and tocilizumab achieved a statistically-significantly greater mean improvement in HAQ-DI score relative to conventional DMARD therapy.[81 84,85]

About other outcomes, all TIMs showed superior improvements in pain, fatigue, and health-related quality of life in comparison to conventional DMARDs (Appendix C). Trial-based data on work productivity and healthcare resource use were more limited and findings were mixed.

TIM-Experienced Populations

Data from TIM-experienced populations were limited. Five of the 11 TIMs have been studied in this setting, all as combination therapy versus conventional DMARDs alone. Abatacept, baricitinib, rituximab, sarilumab, and tocilizumab all produced statistically- and clinically-significant improvements in ACR response and HAQ improvement versus conventional DMARDs alone.

RCT evidence was limited in patients with inadequate response to one or more TIMs. A total of six studies were identified, all of combination therapy with conventional DMARDs versus conventional

DMARDs alone (see Appendix C, Table C1, C2 & C5). Two studies examined the clinical impact of sarilumab combination therapy; one was a published RCT of 546 patients receiving one of two doses of sarilumab or placebo with background conventional DMARDs, [88] and the other was a conference paper describing a subgroup analysis of TIM-experienced patients (N=327) from a similarly-designed RCT of nearly 1,200 individuals.[89] In both analyses, sarilumab 150 and 200 mg combination therapy produced statistically-significantly greater levels of ACR20/50/70 response at 24 weeks; improvements in disease activity and HAQ-DI were also observed.

Single RCTs were also available for combination therapy involving abatacept (iv form), baricitinib, tocilizumab, and rituximab. In all studies, TIM combination therapy resulted in statistically- and clinically-significant improvements in ACR response and HAQ-DI in comparison to conventional DMARDs alone.[90-93] Findings were more limited with regard to disease activity and radiographic progression, but improvements in these measures as well as health-related quality of life were also noted in individual studies.[90,93] [91,92]

Head-to-Head Studies of TIMs

Head-to-head studies are described for each TIM in the sections that follow. All were conducted in TIM-naïve or mixed populations only. Key results of these studies are summarized in Tables 4-7 beginning on page 52.

Rituximab

We did not identify any head-to-head studies comparing rituximab to any of the TIMs of interest.

Abatacept

Abatacept combination therapy was similar to adalimumab combination therapy and infliximab combination therapy in rates of remission achieved, ACR response, and improvement in HAQ-DI and other patient reported outcomes; there was no statistical difference between abatacept and adalimumab in slowing radiographic progression.

We identified two head-to-head trials (AMPLE & ATTEST) comparing combination abatacept+methotrexate with TNFα inhibitors infliximab and adalimumab combination therapy in primarily TIM-naïve patients.[23,94] We did not identify any head-to-head studies comparing abatacept monotherapy to at TIM of interest.

Disease Activity and Remission

In the ATTEST trial, combination therapy of intravenous abatacept+methotrexate did not produce a statistically significant difference in the proportion of patients achieving DAS28-ESR clinical

remission and low disease activity when compared with infliximab+methotrexate at week 24. At week 52, although the proportion of patient on intravenous abatacept (plus methotrexate) achieving low disease activity was higher compared with infliximab combination therapy (35.3% versus 22.4%, estimate of difference (95% CI) =12.9 (2.1, 23.7)), patients achieving clinical remission did not reach clinical significance. Subcutaneous abatacept+methotrexate was also similar to adalimumab+methotrexate in proportion of patients achieving DAS28-ESR clinical remission and low disease activity at week 52; differences in other measures of remission as well as mean changes from baseline were also non-significant (see Table 4).[23,94]

ACR20/50/70

In the non-inferiority AMPLE trial, investigators did not detect discernible differences between subcutaneous abatacept+methotrexate and adalimumab+methotrexate in the proportion of patients achieving ACR20, 50, or 70 at year 1.[94] Although ACR20 response was significantly higher for intravenous abatacept (plus methotrexate) than infliximab combination therapy (72.4 vs 55.8%) at year 1 of the ATTEST trial, ACR50 and 70 did not reach statistical significance.[23]

Radiographic Progression

Radiographic progression was reported in the AMPLE trial of subcutaneous abatacept+methotrexate versus adalimumab+methotrexate.[22] Both treatment arms experienced a similar change in Sharp score at years 1 and 2; at year 2, for example, the mean change in Sharp score was 1.1 in the abatacept group vs. 0.9 in the adalimumab group). Patients exhibited little radiographic progression from the start of the study, with 84.8% and 88.6% showing no progression at Year 1 in the abatacept and adalimumab groups, respectively (statistical significance not reported) (see Table 6).

HAQ-DI

In the two head-to-head RCTs, abatacept+methotrexate arm did not differ from TNFα inhibitor adalimumab+methotrexate arm (at 1 year) and TNFα inhibitor infliximab+methotrexate arm (at 6 months) in achieving an improvement greater or equal to the minimum clinically important difference threshold of 0.3 in HAQ-DI.[23,94] There was also no statistically significant difference between the mean HAQ-DI change from baseline between abatacept+methotrexate and adalimumab+methotrexate (see Table 7).[94]

Other Patient-Reported Outcomes

In the ATTEST trial of combination abatacept (intravenous) or infliximab therapy, slightly greater improvements were observed with abatacept after one year of follow-up with the physical component score (PCS) of the SF-36 (difference of 1.93; 95% CI 0.02 to 3.84) while both treatment arms had similar changes in the mental component score (MCS).[23]

Relative to adalimumab combination therapy, abatacept plus methotrexate-treated patients experienced similar improvements in both pain and fatigue.[94]

IL-6 Inhibitors: Tocilizumab

In one head-to-head trial, tocilizumab monotherapy (8 mg/kg) was found to be superior to adalimumab monotherapy in rates of clinical remission achieved and ACR response across all levels; tocilizumab did not differ from adalimumab in HAQ-DI improvement and most other patient reported outcomes.

We identified one head-to-head trial that compared tocilizumab infusion monotherapy to TNFα inhibitor adalimumab monotherapy in TIM-naïve patients.[19] It should be noted, however, that this trial employed a starting dose of 8 mg/kg for tocilizumab, rather than the FDA-approved starting dose of 4 mg/kg. We did not identify any head-to-head combination studies.

Disease Activity and Remission

In the head-to-head that compared tocilizumab monotherapy to TNFα inhibitor adalimumab monotherapy, tocilizumab was found to be superior to adalimumab in achieving low disease activity at week 24 (51.5% vs. 19.8%, p<0.0001), as well as clinical remission (39.9% vs. 10.5%, p<.0001), using the DAS28-ESR disease activity measure; differences in DAS28-ESR mean changes from baseline were also significant (-3.3 vs. -1.8, p<0.0001). Similar findings were observed using CDAI and SDAI disease activity measures.[19]

ACR20/50/70

Relative to adalimumab monotherapy, a significantly greater proportion of TIM-naïve patients achieved ACR20, 50, and 70 with single agent intravenous tocilizumab in the ADACTA trial. The proportion of patients achieving ACR20 was 65% with tocilizumab (vs. 49% with adalimumab; p=0.0038); a similar relative difference was observed at the 50% and 70% response levels.[19]

Radiographic Progression

We did not identify any studies of tocilizumab in comparison to another TIM that reported on radiographic progression.

HAQ-DI

There was no difference observed between tocilizumab monotherapy and adalimumab monotherapy in the mean HAQ-DI change from baseline at 24 weeks.[19]

Other Patient-Reported Outcomes

Comparisons of tocilizumab to adalimumab monotherapy in the ADACTA trial revealed statistically greater improvement in the mental component summary (MCS) score of the SF-36 at 24 weeks with

tocilizumab (7.9 vs. 5.0 for adalimumab; p=0.0497), but similar improvements in the PCS as well as in measures of fatigue.[19]

IL-6 Inhibitors: Sarilumab

In one head-to-head trial, sarilumab monotherapy was shown to be superior to adalimumab monotherapy in rates of clinical remission achieved, ACR response across all levels, and improvement in HAQ-DI and other patient reported outcomes.

We identified one head-to-head trial that compared sarilumab monotherapy to adalimumab monotherapy in TIM-naïve patients.[18] We did not identify any combination therapy studies.

Disease Activity and Remission

Sarilumab monotherapy was found to be superior to TNFα inhibitor adalimumab monotherapy in achieving low disease activity (42.9% vs. 14.1%, p<0.0001) and clinical remission (26.6% vs. 7%, p<.0001) using the DAS28-ESR; differences in mean changes from baseline were also significantly higher in the sarilumab group (-3.28 vs. -2.2, p<0.0001) Similar findings were observed in achieving clinical remission using the CDAI disease activity measure.[18]

ACR20/50/70

Relative to adalimumab monotherapy, a significantly greater proportion of TIM-naïve patients achieved ACR20, 50, and 70 with single agent sarilumab in the MONARCH trial. The proportion of patients achieving ACR20 was 72% for sarilumab (vs. 58% for adalimumab; p=0.0074); a similar relative difference was observed at the 50% and 70% response levels.[18]

Radiographic Progression

We did not identify any studies of sarilumab in comparison to another TIM that reported on radiographic progression.

HAQ-DI

Compared to TNFα inhibitor adalimumab**,** the percentage of patients achieving an improvement greater or equal to the minimum clinically important difference threshold of 0.22 and the more stringent 0.3 in HAQ-DI, was statistically-significantly higher in the sarilumab group (0.22 threshold: 67.4% vs. 54.1%; 0.3 threshold: 62% vs. 47.6%, all p<0.01). Difference in mean change in HAQ-DI from baseline was also significantly higher in the sarilumab group (-0.61 vs. -0.43, p=0.0037).[18]

Other Patient-Reported Outcomes

In the MONARCH trial, sarilumab-treated patients experienced a statistically greater improvement in PCS at week 24 (8.7 vs. 6.1; p=0.0006) but a similar change in MCS score; improvements in fatigue were also comparable.[18]

JAK Inhibitors: Tofacitinib

In one head-to-head trial, tofacitinib combination therapy was not statistically different from adalimumab combination therapy in rates of remission achieved, ACR response, and improvement in HAQ-DI after 6 months of follow-up.

We identified one head-to-head study that compared tofacitinib plus methotrexate with adalimumab plus methotrexate conducted in a mostly TIM-naïve population.[95]

Disease Activity and Remission

There was no statistically significant difference observed in the proportion of patients achieving DAS28-ESR clinical remission between combination therapy with tofacitinib plus methotrexate versus adalimumab plus methotrexate.[95]

ACR20/50/70

Relative to adalimumab combination therapy, tofacitinib plus methotrexate showed statistical differences only at the ACR70 level (20% achieved ACR70 with tofacitinib vs. 10% with adalimumab; $p \leq 0.01$) at 24 weeks of follow-up.[95]

Radiographic Progression

We did not identify any studies of tofacitinib in comparison to another TIM that reported on radiographic progression.

HAQ-DI

In the trial comparing tofacitinib combination therapy with TNFα inhibitor adalimumab combination therapy, there was no statistically significant difference observed between the mean HAQ-DI change from baseline at 24 weeks in the two groups.[95]

Other Patient-Reported Outcomes

After twelve weeks of follow-up, patients experienced comparable improvement in quality of life, pain, and fatigue with combination tofacitinib or adalimumab therapy.[96]

JAK Inhibitors: Baricitinib

Baricitinib combination therapy was superior to combination therapy with adalimumab in ACR response across all levels, as well as improvement in HAQ-DI and other patient reported outcomes; there was no difference between baricitinib combination therapy and adalimumab combination therapy in rates of clinical remission achieved.

We identified one head-to-head trial that compared baricitinib plus methotrexate to adalimumab plus methotrexate in mostly TIM-naïve patients.[21] We did not identify any studies comparing baricitinib monotherapy to another TIM that met our inclusion criteria.

Disease Activity and Remission

In the one trial that compared combination therapy of baricitinib+methotrexate with adalimumab+methotrexate, disease activity improved in both groups, but there was no statistical difference observed in the proportion of patients achieving low disease activity and clinical remission using DAS28-ESR and other measures of remission at week 24.[21] At week 52, baricitinib was statistically but modestly better than adalimumab in achieving low disease activity using DAS28-CRP (56% vs. 48%, p<0.01), CDAI (57% vs. 49%, p<0.01) and SDAI (57% vs. 49%, p<0.01) but not DAS28-ESR; differences in clinical remission, however, did not reach statistical significance for all measures of disease activity.

ACR20/50/70

Relative to adalimumab combination therapy, a statistically significantly greater proportion of TIM-naïve patients treated with baricitinib+methotrexate achieved ACR20/50/70 at Week 12 (p<0.05), and ACR20 and 70 at Week 24; 74% achieved at least 20% improvement at Week 24 in the baricitinib group versus 66% in the adalimumab group.[21]

Radiographic Progression

After 52 weeks of follow-up, radiographic progression did not statistically differ between baricitinib+methotrexate and adalimumab+methotrexate (0.71 change in Sharp score with baricitinib vs. 0.60 with adalimumab); approximately 90% of patients in both arms had no evidence of progression (see Table 6).[97]

HAQ-DI

Compared with adalimumab combination therapy, the percentage of patients achieving an improvement greater or equal to the minimum clinically important difference threshold of 0.22 in HAQ-DI, was statistically-significantly higher in the baricitinib group (73% vs. 64%, p<0.05).[21] Difference in mean change in HAQ-DI from baseline was also significantly higher in the baricitinib group (-0.76 vs. -0.6, p<0.001).[98]

Other Patient-Reported Outcomes

Compared with adalimumab+methotrexate, baricitinib combination therapy had a statistically greater improvement in pain (p≤0.01) , fatigue (p≤0.05) and PCS score of the SF-36 (p≤0.01) at 24 weeks, but had a similar level of improvement on the MCS.[21,98]

TNFα inhibitors: Adalimumab

Adalimumab monotherapy was inferior to monotherapy with tocilizumab and sarilumab in rates of clinical remission achieved and ACR responses across all levels; adalimumab also resulted in significantly less improvement in HAQ-DI compared with sarilumab.

Adalimumab combination therapy was inferior to baricitinib combination therapy in ACR response across all levels, as well as on improvement in HAQ-DI, but the two were similar in rates of clinical remission achieved.

In all other head-to-head trials of combination therapy, adalimumab was similar to abatacept, etanercept, tofacitinib, and certolizumab in rates of remission achieved, ACR response across all levels, and/or improvement in HAQ-DI; there was also no statistical difference between abatacept and adalimumab in slowing radiographic progression.

We identified seven adalimumab head-to-head trials: two of the seven trials compared adalimumab monotherapy to other TIMs monotherapy, and adalimumab combination therapy was compared to combination therapy with other TIMs in five trials. All seven trials were conducted in TIM-naïve or mostly TIM-naïve populations.[18-21,66,94,95]

Disease Activity and Remission

Six of the seven adalimumab head-to-head RCTs reported on clinical remission. Of the seven, four compared adalimumab plus methotrexate to abatacept, tofacitinib, baricitinib, and certolizumab combination therapy (i.e., plus conventional DMARD), while the remaining two trials compared adalimumab monotherapy to sarilumab and tocilizumab monotherapy. In the two monotherapy trials, adalimumab was found to be inferior to sarilumab and tocilizumab in achieving clinical remission using DAS28-ESR: sarilumab (7% vs. 27% at 24 weeks, $p \leq 0.0001$); tocilizumab (10.5% vs. 39.9% at 24 weeks, $p < 0.0001$).[18,19] Results of other measures of remission, low disease activity and mean changes in disease activity from baseline were consistent with the result of the DAS28-ESR clinical remission (see Table 4).

Among the combination therapy trials, adalimumab did not differ from abatacept, tofacitinib, baricitinib and certolizumab pegol in achieving clinical remission.[21,66,94,95] Results of other measures of remission, and mean changes in disease activity from baseline were consistent with the result of the DAS28-ESR clinical remission (see Table 4).

In the seventh trial comparing adalimumab with etanercept,[20] only the mean changes from baseline were reported; adalimumab had a similar level of change from baseline compared with etanercept (see Table 4).

ACR20/50/70

Five head-to-head RCTs of TIMs reported ACR response using adalimumab as a comparator (see Table 5). In the two trials that evaluated TIM monotherapy, adalimumab was inferior to sarilumab and intravenous tocilizumab across all levels of ACR response.[18,19] The proportion of patients achieving ACR20, for example, was 58% for adalimumab in the MONARCH trial (vs. 72% for sarilumab; p=0.0074), and 49% in the ADACTA trial (vs. 65% with tocilizumab; p=0.0038). Similarly, the RA-BEAM trial of adalimumab plus methotrexate versus baricitinib plus methotrexate reported a statistically significantly lower proportion of patients who achieved ACR20/50/70 at Week 12 with adalimumab ($p<0.05$), and ACR20 and 70 at Week 24: 66% of patients achieved at least 20% improvement at Week 24 in the adalimumab group versus 74% in the baricitinib group.[21]

Two additional trials compared adalimumab+methotrexate to either abatacept or tofacitinib combination therapy; neither trial detected discernible differences between TIMs in the proportion of patients achieving ACR20 and ACR50 at month 6, although a significantly smaller proportion of patients achieved ACR70 with adalimumab in the tofacitinib study (10% vs. 20%; $p\leq0.01$).[94,95]

Relative to other TNFα inhibitors, adalimumab showed comparable efficacy. In the head-to-head EXXELERATE trial of adalimumab+methotrexate versus certolizumab pegol+methotrexate, patients in both groups achieved comparable levels of response during 104 weeks of follow-up.[66] Our review identified two observational studies that reported on ACR response.[99,100] In one study from the CORRONA registry, significant differences were not demonstrated between the three TIMs that were evaluated (adalimumab, etanercept, or infliximab) for any level of response.[99] Another observational study of the same TIMs used data from the Danish DANBIO registry and found no differences between adalimumab and etanercept in ACR70 response but found adalimumab to be superior to infliximab (adjusted OR for adalimumab 2.05; 95% 1.52 to 2.76).[100]

Radiographic Progression

Two head-to-head studies reported on radiographic progression.[22] The AMPLE trial was a two-year, phase IIIb RCT in TIM-naïve patients who were randomized to receive either adalimumab+methotrexate or subcutaneous abatacept+methotrexate. At Years 1 and 2, similar Sharp scores were reported in both treatment arms (e.g., at year 2, the mean change in Sharp score was 0.9 in the adalimumab group vs. 1.1 in the abatacept group). Patients exhibited little radiographic progression from the start of the study, with 88.6% and 84.8% showing no progression at Year 1 in the adalimumab and abatacept groups, respectively (statistical significance not reported) (see Table 6).

In the RA-BEAM trial of adalimumab and baricitinib combination therapy, radiographic progression did not statistically differ between adalimumab+methotrexate and baricitinib+methotrexate after 52 weeks of follow-up (0.60 change in Sharp score with adalimumab versus 0.71 with baricitinib); approximately 90% of patients in both arms had no progression.[97]

HAQ-DI

Six of the identified adalimumab head-to-head RCTs reported on HAQ-DI. Of the six, two compared adalimumab monotherapy to sarilumab and tocilizumab monotherapy, while the remaining four compared adalimumab+methotrexate to abatacept, baricitinib, tofacitinib and certolizumab combination therapy (i.e. plus conventional DMARD).

In the monotherapy trials, adalimumab was observed to be similar to tocilizumab in HAQ-DI improvement,[19] but inferior to sarilumab in HAQ-DI improvement (47.6% vs. 62% for MCID of 0.3, $p<0.01$; mean change from baseline: -0.43 vs. -0.61, $p=0.0037$).[18]

Among the four trials that compared adalimumab plus methotrexate with combination TIM therapies, adalimumab was found to be inferior to baricitinib in HAQ-DI improvement (percentage of patient achieving an improvement greater or equal to MCID threshold of 0.22 in HAQ-DI was 64% vs. 73%, $p<0.05$),[21] while adalimumab was found to be similar to abatacept, tofacitinib and certolizumab in HAQ-DI improvement.[66,94,95]

Other Patient-Reported Outcomes

In the MONARCH trial, adalimumab-treated patients experienced less improvement in PCS at week 24 than patients treated with sarilumab monotherapy (6.1 vs. 8.7; $p=0.0006$) but a similar change in MCS and fatigue.[18]

In comparison to tocilizumab monotherapy, treatment with single-agent adalimumab led to less improvement in MCS at 24 weeks (5.0 vs. 7.9; $p=0.0497$) but similar improvements in PCS and fatigue.[19]

Relative to tofacitinib plus methotrexate, adalimumab-treated patients experienced similar improvements in quality of life, pain, and fatigue at month 3.[96]

In the RA-BEAM trial, patients treated with adalimumab+methotrexate had less improvement in pain, fatigue and PCS at 24 weeks ($p\leq0.05$) versus baricitinib+methotrexate, but a similar change in MCS.[21,98]

Comparable improvements in quality of life were observed among patients in the adalimumab and etanercept arms of the RED-SEA trial using the EuroQol-5 domain health state profile (EQ-5D).[20]

TNFα inhibitors: Certolizumab Pegol

Evidence from one head-to-head trial of certolizumab pegol plus methotrexate versus adalimumab plus methotrexate found no differences between agents in disease activity, ACR response, or HAQ-DI.

We identified one trial that directly compared combination therapy of TNFα inhibitor certolizumab pegol plus methotrexate with another TNFα inhibitor adalimumab plus methotrexate in TIM-naive patients.[66] We did not identify any monotherapy studies.

Disease Activity and Remission

In the single head-to-head trial comparing certolizumab combination therapy with adalimumab combination therapy, there was no statistical differences observed in the proportion of patients achieving low disease activity and clinical remission using the DAS28-ESR measure and other measures of disease activity.[66] There was no report of mean change from baseline.

ACR20/50/70

Evidence from the EXXELERATE trial showed no discernible differences between certolizumab pegol and adalimumab (both in combination with methotrexate) across all levels of response during 104 weeks of follow-up.[66]

Radiographic Progression

We did not identify any studies of certolizumab pegol in comparison to another TIM that reported on radiographic progression.

HAQ-DI

Compared with adalimumab combination therapy**,** certolizumab did not show statistically significant differences in the mean HAQ-DI change from baseline to week 104 in the two groups (see Table 7).

Other Patient-Reported Outcomes

We did not identify any studies of certolizumab pegol in comparison to another TIM that reported on health-related quality of life, pain, or fatigue.

TNFα inhibitors: Etanercept

One head-to-head trial of etanercept and adalimumab (primarily in combination with concomitant conventional DMARDs) reported similar changes in disease activity and quality of life; observational data suggest no difference in remission or ACR response between etanercept and adalimumab.

We identified one head-to-head trial that compared etanercept with adalimumab added to existing conventional DMARD therapy in TIM-naïve patients.[20] In addition, we identified three observational studies that compared the three TNFα inhibitors adalimumab, infliximab and etanercept.[99-101]

Disease Activity and Remission

In the one trial that directly compared etanercept with adalimumab primarily in combination with existing conventional DMARDs in TIM-naive patients, the rates of clinical remission and low disease activity were not reported. The mean change from baseline in disease activity (based on DAS28-CRP) showed a similar level of change between adalimumab and etanercept at week 24.[20]

In addition to the RCT, we reviewed three observational studies for disease activity. In the first observational study based on data from the CORRONA registry in the US, no statistically significant difference was found in rates of clinical remission among the three TNFα inhibitors evaluated (infliximab, adalimumab and etanercept).[99] The second study, based on the Hellenic Registry of Biologic Therapies in Greece, found no statistically-significant difference in remission between the three agents using the DAS28-ESR definition, but found adalimumab to be superior to both infliximab and etanercept based on CDAI and SDAI defined remission (15% vs. 8% vs. 7%, p=0.022 using CDAI; and 17% vs. 8% vs. 8% using SDAI, p=0.009).[101] The third study, based on the DANBIO registry in Denmark, did not find a significant difference between etanercept and adalimumab.[100]

ACR20/50/70

We identified head-to-head evidence of ACR response for etanercept in two observational studies.[99,100] In one study from the CORRONA registry, significant differences were not demonstrated between adalimumab, etanercept, or infliximab for any level of response.[99] Another observational study of the same TIMs used data from the Danish DANBIO registry and found no differences between adalimumab and etanercept in ACR70 response but found etanercept to be superior to infliximab (adjusted OR 1.78; 95% CI 1.28-2.50).[100]

Radiographic Progression

We did not identify any studies of etanercept in comparison to another TIM that reported on radiographic progression.

HAQ-DI

We did not identify any head-to-head studies of etanercept that reported on HAQ-DI.

Other Patient-Reported Outcomes

Comparable improvements in quality of life were observed among patients in the adalimumab and etanercept arms of the RED-SEA trial using the EuroQol-5 domain health state profile (EQ-5D).[20]

TNFα inhibitors: Golimumab

We did not identify any head-to-head studies comparing golimumab to another TIM of interest.

TNFα inhibitors: Infliximab

Similar improvements in disease activity, ACR response, and HAQ-DI were observed with both infliximab and abatacept combination therapy.

We identified one head-to-head trial in TIM-naïve populations comparing infliximab plus methotrexate with abatacept plus methotrexate.[23] We did not identify any monotherapy studies. In addition, we identified three observational studies that compared three TNFα inhibitors: adalimumab, infliximab and etanercept.[99-101]

Disease Activity and Remission

In the one head-to-head trial that compared combination therapy with infliximab plus methotrexate with abatacept plus methotrexate,[23] disease activity improved in both groups, but there was no statistical difference observed in the proportion of patients achieving DAS28-ESR low disease activity and clinical remission at week 24.[23] At week 52, the proportion of patient achieving low disease activity was lower with infliximab combination therapy compared with abatacept combination therapy (22.4% vs. 35.3%, estimate of difference (95% CI) =12.9 (2.1, 23.7)) while there was no statistical significant difference in patients achieving clinical remission.

In addition to the RCT, we evaluated three observational studies for disease activity. In the first observational study based on data from the CORRONA registry in the US, no statistically significant difference was found in the rates of clinical remission among the three TNFα inhibitors evaluated (infliximab, adalimumab and etanercept).[99] The second study, based on the Hellenic Registry of Biologic Therapies in Greece, found no statistically-significant difference between the rates of remission of the three agents using the DAS28-ESR definition, but found adalimumab to be superior to both infliximab and etanercept based on CDAI and SDAI defined remission(15% vs. 8% vs. 7%, p=0.022 using CDAI; and 17% vs. 8% vs. 8% using SDAI, p=0.009).[101] The third study, based on the DANBIO registry in Denmark, also found adalimumab to be superior to infliximab based on DAS28-CRP clinical remission (39% vs. 27%; OR=1.78 (95%CI=1.32-2.55).[100]

ACR20/50/70

A smaller proportion of patients achieved ACR20 at year 1 of the ATTEST trial with infliximab combination therapy versus abatacept (56% vs 72%; p≤0.05); statistical differences were not detected at the ACR50 and 70 levels, however.[23]

Our review also identified two observational studies that reported on ACR response.[99,100] In one study from the CORRONA registry, significant differences were not demonstrated between the three TIMs that were evaluated (adalimumab, etanercept, or infliximab) for any level of response.[99] Another observational study of the same TIMs used data from the Danish DANBIO registry and

found both adalimumab and etanercept to be superior to infliximab in ACR70 response (adjusted OR for adalimumab 2.05; 95% 1.52 to 2.76; adjusted OR for etanercept 1.78; 95% CI 1.28-2.50).[100]

Radiographic Progression

We did not identify any studies of infliximab in comparison to another TIM that reported on radiographic progression.

HAQ-DI

In the one trial that compared combination therapy of infliximab plus methotrexate with abatacept plus methotrexate**,** there was no statistically significant difference observed between treatment arms in the mean HAQ-DI change from baseline to 24 weeks (see Table 7).

Other Patient-Reported Outcomes

In comparison to intravenous abatacept+methotrexate, patients treated with infliximab therapy had slightly less improvement in the PCS (difference of 1.93; 95% CI 0.02 to 3.84) after one year of follow-up but similar changes in the MCS.[23]

Table 4. Disease Activity Outcomes Across Head-To-Head Trials

Treatment	N	DAS28-ESR or CRP	DAS28 change from baseline (mean)	DAS28 low disease activity (%)	DAS28 remission (%)	CDAI remission (%)	SDAI remission (%)
ATTEST trial at 24 weeks[23]							
Abatacept (iv) + MTX	156	DAS28-ESR	-2.53†	20.7	11.3	NR	NR
Infliximab + MTX	165	DAS28-ESR	-2.25†	25.6	12.8	NR	NR
AMPLE trial at 52 weeks[94]							
Abatacept (sc) + MTX	318	DAS28-CRP	-2.3	59.3	43.3	23.5	23.3
Adalimumab + MTX	328	DAS28-CRP	-2.27	61.4	41.9	24	24.8
ADACTA trial at 24 weeks[19]							
Tocilizumab monotherapy	162	DAS28-ESR	-3.3***	51.5***	39.9***	17.2*	18.4**
Adalimumab monotherapy	163	DAS28-ESR	-1.8	19.8	10.5	9.3	8
MONARCH trial at 24 weeks[18]							
Sarilumab monotherapy	184	DAS28-ESR	-3.28***	42.9***	26.6***	7.1*	NR
Adalimumab monotherapy	185	DAS28-ESR	-2.2	14.1	7	2.7	NR
ORAL Standard trial at 24 weeks[95]							
Tofacitinib + MTX	204	DAS28-ESR	NR	NR	6.2	NR	NR
Adalimumab + MTX	204	DAS28-ESR	NR	NR	6.7	NR	NR
RA-BEAM at 24 weeks[21]							
Baricitinib + MTX	487	DAS28-ESR & CRP	NR	32-ESR; 52-CRP	18-ESR; 35-CRP	16	16
Adalimumab + MTX	330	DAS28-ESR & CRP	NR	34-ESR;48-CRP	18-ESR; 32-CRP	12	14
EXXELERATE at 24 weeks[66]							
Certolizumab + MTX	353	DAS28-ESR	NR	51.8	32.9	24.9	NR
Adalimumab + MTX	361	DAS28-ESR	NR	46	29.4	22.2	NR
RED SEA‡ at 24 weeks[20]							
Etanercept +cDMARD	60	DAS28-CRP	-1.76	NR	NR	NR	NR
Adalimumab +cDMARD	60	DAS28-CRP	-1.44	NR	NR	NR	NR

†statistical significance not reported; ***p <0.001; **p<0.01; *p<0.05

Table 5. ACR20/50/70 Outcomes Across Head-To-Head Trials

Study arm	N	ACR20, %	ACR50, %	ACR70, %
MONARCH[18] at 24 weeks				
Adalimumab monotherapy	185	58.4	29.7	11.9
Sarilumab monotherapy	184	71.7*	45.7*	23.4*
ADACTA[19] at 24 weeks				
Adalimumab monotherapy	163	49.4	27.8	17.9
Tocilizumab (iv) monotherapy	162	65*	47.2*	32.5*
RA-BEAM[21] at 12/24 weeks				
Adalimumab + methotrexate	330	61/66	35/46	13/22
Baricitinib + methotrexate	487	70**/74**	45*/50	19**/30**
ORAL Standard[95] at 24 weeks				
Adalimumab + methotrexate	204	47.2	29.1	10.1
Tofacitinib + methotrexate	204	51.5	36.2	19.9*
AMPLE[94] at 1 year				
Adalimumab + methotrexate	328	63.4	46.0	26.2
Abatacept (sc) + methotrexate	318	64.8	46.2	29.2
EXXELERATE[66] at 104 weeks				
Adalimumab + methotrexate	454	67%	57%	41%
Certolizumab pegol + methotrexate	454	65%	53%	40%
ATTEST[23] at 1 year				
Abatacept (iv) + methotrexate	156	72.4	45.5	26.3
Infliximab + methotrexate	156	55.8**	36.4	20.6

†statistical significance not reported; ***p<0.001; **p<0.01; *p<0.05

Table 6. Radiographic Progression Outcomes Across Head-To-Head Trials

Study arm	Mean change in mTSS from baseline (SD)	Time of evaluation (weeks)	Significance	% Non-progression at Year 1[α]
AMPLE[22,94]				
ADA+cDMARD (n=289)	0.4 (5.0) 0.9 (4.1)	52 104	p=NR	88.6
ABTsc+cDMARD (n=290)	0.6 (3.2) 1.1 (8.7)			84.8
RA-BEAM[97]				
ADA+cDMARD (n=330)	0.33 (NR) 0.60 (NR)	24 52	p≤0.05 at week 24 p=NS at week 52	90.1
BAR+cDMARD (n=487)	0.41 (NR) 0.71 (NR)			89.4

α change from baseline in total score ≤ smallest detectable change using cut-off of 2.8 for AMPLE and 1.47 for RA-BEAM; van der Heijde modified Sharp score; NR=not reported; NS=not significant

Table 7. HAQ-DI Outcomes Across Head to Head Trial

Treatment	N	HAQ-DI mean change from baseline:	% change ≥ predefined threshold	Predefined MCID threshold
ATTEST trial at 24 weeks[23]				
Abatacept + MTX	156	NR	61.5	0.3
Infliximab + MTX	165	NR	58.8	0.3
ADACTA trial at 24 weeks[19]				
Tocilizumab monotherapy	162	-0.7	NR	--
Adalimumab monotherapy	163	-0.5	NR	--
MONARCH trial at 24 weeks[18]				
Sarilumab monotherapy	184	-0.61***	62**	0.3
Adalimumab monotherapy	185	-0.43	47.6	0.3
ORAL Standard trial at 24 weeks[95]				
Tofacitinib + MTX	204	-0.55	NR	--
Adalimumab + MTX	204	-0.49	NR	--
RA-BEAM at 24 weeks[21,98]				
Baricitinib + MTX	487	-0.76***	73*	0.22
Adalimumab + MTX	330	-0.6	64	0.22
EXXELERATE at 104 weeks[66]				
Certolizumab + MTX	353	-0.62	NR	NR
Adalimumab + MTX	361	-0.72	NR	NR

†statistical significance not reported; ***p <0.001; **p<0.01; *p<0.05

Network Meta-Analysis Findings

We employed a random-effects approach to evaluating ACR responses. We assessed information separately for TIM naïve/mixed populations and TIM-experienced populations. Further details on our methods, including data input tables, network diagrams, and league tables of results, can be found in Appendix C. Our approach included both direct and indirect evidence in our calculations. Also, as described further in Appendix C, the model adjusted for control arm response produced similar model-fit statistics to the unadjusted model, suggesting limited or no effect modification. Results presented below are therefore from the unadjusted model.

TIM-Naïve/Mixed Populations

A forest plot of the results for ACR20 response for combination therapy and monotherapy regimens in TIM-naïve/mixed populations can be found in Figures 6 and 7 respectively. The pattern of findings was similar to that observed in the individual studies. All TIMs were between two and three times more likely to achieve ACR20 or better response when used in combination with conventional DMARDs in comparison to conventional DMARDs alone (Figure 6). However, there were wide and overlapping estimates of the credible intervals around the estimates for each TIM combination; as a result, none of the comparisons between TIMs differed statistically.

For example, TIMs that had shown superiority to adalimumab on a head-to-head basis generally generated a greater likelihood of achieving ACR response, while these measures were similar for drugs that had comparable results in head-to-head comparisons with adalimumab. It should be noted, however, that there were wide and overlapping 95% credible intervals (the Bayesian equivalent of confidence intervals) around all estimates. As a result, comparisons between nearly all of the TIM combination therapy regimens yielded showed no statistical differences, as the likelihood of ACR20 response included 1.0 (no difference) in the credible interval (see Appendix C, Figures C2-C4). The only exceptions were certolizumab pegol in comparison to adalimumab and tofacitinib, and etanercept in comparison to combination conventional DMARDs. However, the lower end of the credible interval was also very close to 1.0 in these comparisons.

In monotherapy comparisons between TIMs, tocilizumab, etanercept, and sarilumab all produced significantly greater likelihoods of achieving ACR response in comparison to conventional DMARDs alone. However, tocilizumab and sarilumab also produced significantly greater likelihoods of achieving ACR20 or better response than adalimumab, echoing the findings of head-to-head trials (Appendix C, Figures C6-C8).

Figure 6. Relative Risk (Likelihood) of Patients Achieving ACR20 or Better with Combination Therapy Versus Conventional DMARDs Alone, TIM-Naïve/Mixed Population

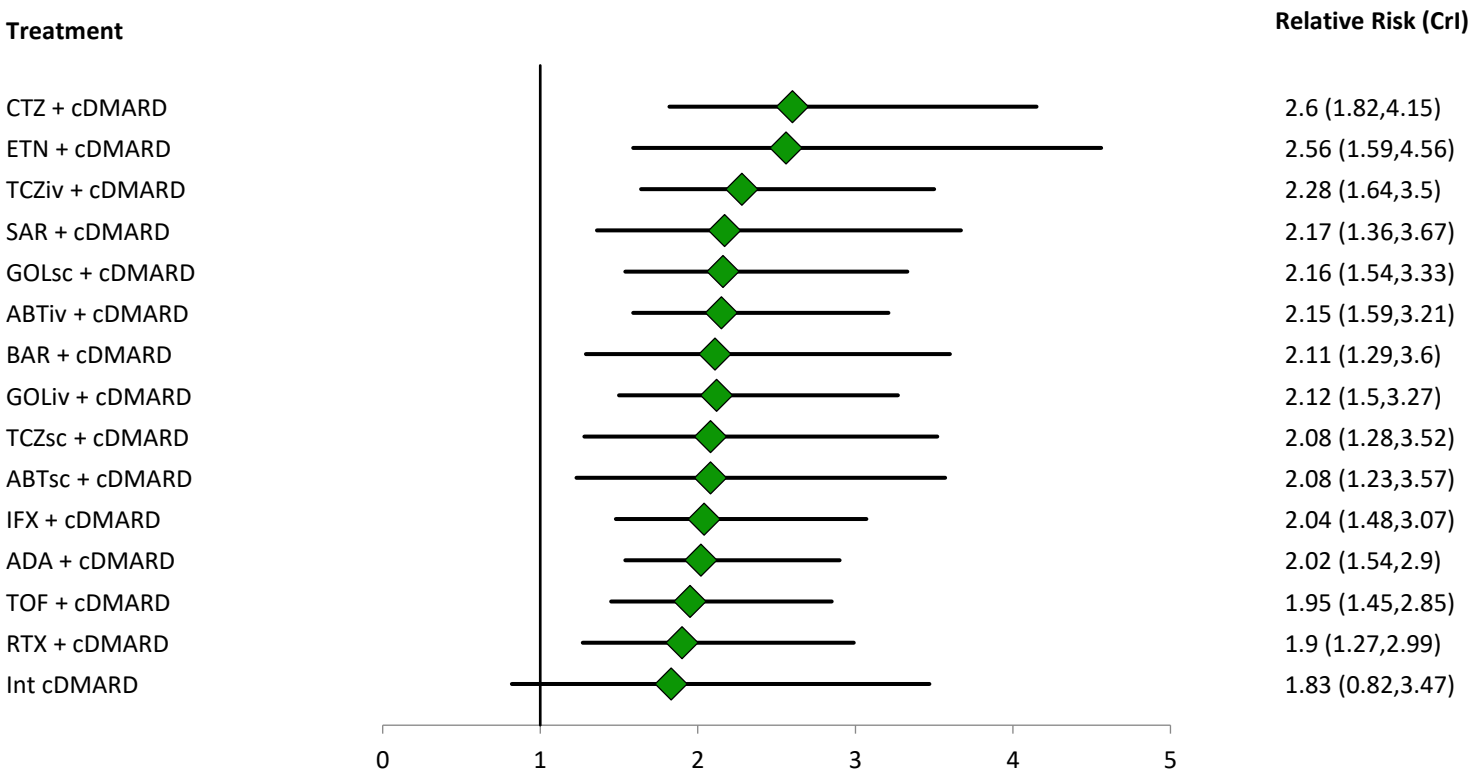
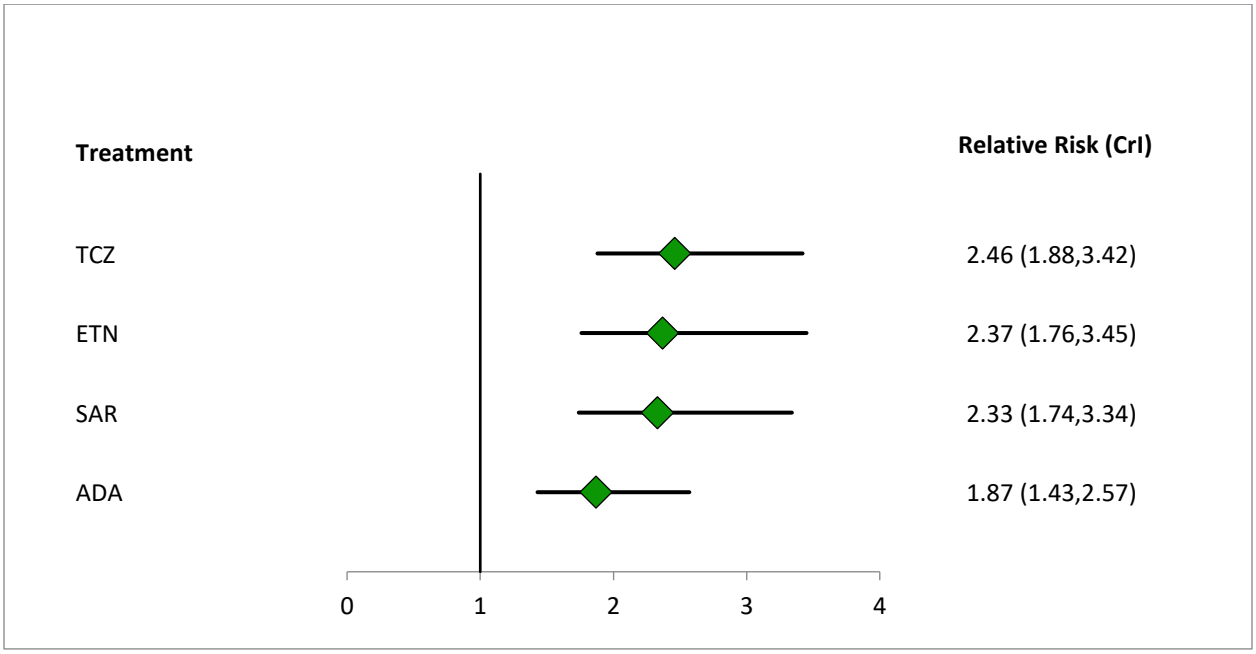


Figure 7. Relative Risk (Likelihood) of Patients Achieving ACR20 or Better with Monotherapy Versus Conventional DMARDs Alone, TIM-Naïve/Mixed Population



The NMA model was also used to generate mutually-exclusive proportions of individuals with different levels of ACR response, primarily as an input to the cost-effectiveness model. As shown in Tables 8 and 9, which are ordered from lowest rate of non-response (ACR <20) to highest, rankings were similar regardless of level of ACR response. However, as noted above, any differences between TIMs should be interpreted with caution.

Table 8. Network Meta-Analysis Derived Proportions of Patients in Each ACR Response Category, by Targeted Immune Modulator Combination Regimen: Mixed Population

Treatment	ACR <20	ACR 20-50	ACR 50-70	ACR 70-100
Etanercept + cDMARD	29%	23%	21%	27%
Certolizumab pegol + cDMARD	29%	23%	21%	26%
Tocilizumab (iv) + cDMARD	38%	23%	19%	19%
Sarilumab + cDMARD	40%	23%	19%	18%
Golimumab (sc) + cDMARD	41%	23%	18%	17%
Abatacept (iv) + cDMARD	42%	23%	18%	17%
Golimumab (iv) + cDMARD	42%	23%	18%	17%
Baricitinib + cDMARD	42%	23%	18%	16%
Tocilizumab (sc) + cDMARD	43%	23%	18%	16%
Abatacept (sc) + cDMARD	43%	23%	18%	16%
Infliximab + cDMARD	45%	23%	17%	15%
Adalimumab + cDMARD	45%	23%	17%	15%
Tofacitinib + cDMARD	47%	23%	17%	14%
Rituximab + cDMARD	48%	23%	16%	13%
Intensive cDMARD*	50%	23%	16%	12%
Conventional DMARD	73%	16%	8%	4%

Table 9. Network Meta-Analysis Derived Proportions of Patients in Each ACR Response Category, by Targeted Immune Modulator Monotherapy Regimen: Mixed Population

Treatment	ACR <20	ACR 20-50	ACR 50-70	ACR 70-100
Tocilizumab (iv)	25%	24%	21%	30%
Etanercept	27%	24%	20%	28%
Sarilumab	28%	25%	20%	27%
Adalimumab	43%	25%	16%	16%
Conventional DMARD	70%	18%	8%	4%

TIM-Experienced Populations

Data were available for only five regimens for TIM-experienced patients, all involving combination therapy with conventional DMARDs. While point estimates differed, findings were similar – all were statistically superior to conventional DMARDs alone, and most comparisons between TIMs suggested no statistical differences (see Appendix C, Figure C14-C16).

Table 10. Network Meta-Analysis Derived Proportions of Patients in each ACR Response Category, by Targeted Immune Modulator Regimen: TIM-Experienced Population

Treatment	ACR <20	ACR 20-50	ACR 50-70	ACR 70-100
Tocilizumab (iv) + cDMARD	38%	24%	19%	19%
Rituximab + cDMARD	42%	24%	18%	17%
Abatacept (iv) + cDMARD	46%	23%	17%	14%
Sarilumab + cDMARD	52%	22%	15%	11%
Baricitinib + cDMARD	56%	21%	13%	9%
Conventional DMARD	77%	14%	6%	3%

Radiographic Progression

Standardized mean differences (SMD) were used in analyses of Sharp score to control for variation in scoring methods used; findings for the TIM-naïve/mixed population are presented in league table format in Appendix C, Figure C18. Both monotherapy regimens with data available (tocilizumab and etanercept) produced significant improvements in Sharp score relative to conventional DMARDs, as denoted by credible intervals that did not cross zero. These two TIMS did not differ when indirectly compared, however. Among combination regimens, all produced significant relative improvements versus conventional DMARDs except for tofacitinib, subcutaneous golimumab, and certolizumab pegol, which had credible intervals that included zero.

Data were insufficient to analyze Sharp score changes based on studies conducted in TIM-experienced populations.

Harms

Rates of short term serious adverse events (within six months) were generally comparable across all treatments, including TIMs and conventional DMARD therapy. Infections (e.g. upper respiratory tract infection, bronchitis, nasopharyngitis), injection site reactions, and infusion related reactions were the most common adverse events during treatment. Based on long term (one year or more) trial data, etanercept, golimumab, infliximab, tocilizumab and abatacept showed comparable overall safety profiles, although the serious infection rate appears to be higher with infliximab.

Data on adverse events, discontinuations due to adverse events, as well as specific adverse events of interest observed in clinical trials with conventional DMARD controls are presented as weighted averages (i.e., according to total sample size across trials) in Table 11. Of note, these represent events as recorded before treatment-arm crossover was permitted. Most adverse events were of mild to moderate severity. The most frequently reported adverse events were mild infections

(upper respiratory tract infection, bronchitis, nasopharyngitis), injection site reactions and infusion related reactions. The overall incidence of serious infections, deaths, and all serious adverse events were comparable between treatments, including conventional DMARD therapy. As noted in the table, however, adverse-event rates for tofacitinib were calculated over a 12-week pre-crossover period, versus 24-28 weeks for the other TIMs.

The rates of serious infection, serious adverse events and discontinuation due to adverse events were generally comparable in the head-to-head trials comparing sarilumab, tocilizumab, etanercept, and baricitinib with adalimumab[18-21] (see Appendix C, Table C18). In the AMPLE trial, however, abatacept had a lower rate of discontinuation due to adverse events at year 2 compared with adalimumab (9.5% vs. 3.8%, estimate of difference: −5.7 [95% CI −9.5 to −1.9).[22] In a separate trial comparing infliximab with abatacept, the incidence of serious adverse events and discontinuation due to AEs were numerically lower with abatacept compared with infliximab (SAEs: 9.6 vs 18.2%; discontinuations due to AEs: 3.2 vs 7.3%, respectively), although statistical significance was not tested.[23] There was no evidence of material differences in the rates of malignancies or death between treatment groups across trials.

Results of adverse events reported from longer term trials (i.e., 1 year or more) are presented in Table 11. Results are presented as rates per 100 patient-years exposure to intervention of interest. Etanercept, golimumab, tocilizumab, abatacept and infliximab had comparable safety profiles in these trials, although the rate of infection and serious infection in infliximab appears to be generally higher than the other TIMs.

Observational study

In a prospective cohort study analyzing data from the Dutch rheumatoid arthritis monitoring (DREAM) registry, patients with RA who have had prior treatment with at least two conventional DMARDs including methotrexate, starting their first TNF inhibitor (adalimumab, infliximab or etanercept), were followed for up to 5 years.[102]

The unadjusted incidence rate of a first serious infection per 100 patient-years was 2.61 (95% CI 2.21 to 3.00) for adalimumab, 3.86 (95% CI 3.33 to 4.40) for infliximab and 1.66 (95% CI 1.09 to 2.23) for etanercept. Age, year of starting anti-TNF therapy, comorbidities at baseline, and DAS28 score over time were included as confounders. No difference in risk for serious infections was found between adalimumab and infliximab (adjusted HR: 0.90 (95% CI 0.55 to 1.48)), but the risk of serious infections was significantly lower for etanercept than both infliximab (adjusted HR=0.49 (95% CI 0.29 to 0.83)) and adalimumab (adjusted HR=0.55 (95% CI 0.44 to 0.67).[102]

Table 11. Adverse Events During the Conventional DMARD Controlled Period

Estimate (%)	Targeted immune modulators plus conventional DMARD											Conventional DMARD + Placebo
	RTX	ABT	TCZ	SAR	TOF†	BAR	ADA	CTZ	ETN	GOL	IFX	
Total (N)[1]	170	217	1,819	184	454	943	780	299	446	704	594	4,683
Any AE	76	79.7	70.7	65.2	50.2	72.1	77.3	74	68.7	54	73.5	64.5
Serious AEs	9	6	6.8	5.4	3.1	5.8	4.2	7.9	3.6	4.2	8.9	5.5
D/C due to AEs	2	0.9	5	9.2	4.3	2.5	2.9	4.8	3.1	3.6	4.8	2.7
Any infection	36	32.8	37.4	30.4	NR	38.2	41.9	30	43.7	44.1	14	29.5
Serious infection	1	1.3	2.9	1.6	NR	1.8	0.9	1.8	1.8	1	2.5	1.5
TB	0	0	0	0	NR	0	0.5	0	0	NR	0	0
Injection site reaction		NR	10.1	8.2	N/A	N/A	16.4	2.5	20.8	3.7	N/A	5
Infusion related reaction	25	5.1	NR	N/A	N/A	N/A	N/A	N/A	N/A	3.3	6.2	4.9
Malignancy	0.5	0.6	0.9	NR	NR	0.5	0.3	0	0	0.3	0.8	0.4
Death	NR	0	0.4	0	0.6	0.3	0.2	0	0.5	0	0	0.2

Note: Serious AEs include specific listed events (e.g., serious infection, malignancy) as well as other events deemed life-threatening or requiring hospitalization by study investigators

* Values are weighted averages of the percentage of patients with event across key trials; color scheme identifies drugs of the same class.

1-Maximum contributing to the weighted average.; not every study contributes to all adverse events therefore, N contributing may be less in some AEs. †Assessment period was between week 24 and 28 for all studies except for TOF that was at week 12

Table 12. Long Term Adverse Events

	Abatacept[23]	Abatacept[103]	Tocilizumab[104]	Etanercept[105]	Golimumab[106]	Infliximab[23]
Length of follow up (Yrs)	1	2	5	2	2	1
Total AEs	326	257	248	170	57	449
Serious AEs	11.8	15.2	11.7	7	10.5	21.1
D/C due to AEs	NR	NR	NR	NR	4.48	NR
Total infection	99.8	86.2	NR	59	41.9	134
Serious infection	2	1.6	3.4	2	2.24	9.2
TB	NR	NR	NR	0	NR	NR
Malignancy	0.7	0.4	1	1	1.9	1.3
Death	0.7	0.7	0.5	NR	0	1.3

Dose Modifications

While not a focus of our systematic review *per se*, we also examined the available evidence for studies documenting modifications to initial dosing and/or assessments of specific dosing strategies. As described in the Topic in Context section, dose intensification may have major cost consequences, particularly to the patient, and dose-tapering strategies have been employed partly to help mitigate these concerns. The impact of these changes on clinical effectiveness is a subject of much debate, however. Findings from recent studies suggest that dose escalation is common for some TIMs, but no clear association between dose escalation and improved clinical outcomes has been demonstrated. Dose-tapering strategies have been employed in variable settings, and their study is complicated in part by the degree of heterogeneity of the disease course following clinical remission. In general, studies have found that dose reductions provide superior results to discontinuation of treatment among patients in remission.

A summary of the recent literature on dose modifications can be found in Appendix C.

Controversies and Uncertainties

Across the 67 RCTs identified for this review, only eight were based on head-to-head comparisons of the TIMs of interest (excluding biosimilar studies). As such, our network meta-analyses of ACR response and Sharp score are largely driven by indirect evidence; however, our findings are relatively consonant with the results of head-to-head studies as well as with our assessment of relative differences in ACR response in comparison to conventional DMARD therapy, and our NMA findings are also comparable to other recent assessments of the evidence.[24-26] Given the longstanding availability of certain types of TIM therapy, there are a large number of observational studies that compare clinical effectiveness, safety, and other measures across drugs. Drawing comparisons across these studies is challenging, however, given differences in datasets as well as attendant selection, information, and other biases in quasi-experimental research.

Even data coming from RCTs poses challenges, however. For one, patients were eligible for rescue therapy and/or treatment-arm crossover 12-24 weeks after randomization, which may not reflect the timing of treatment-switch decisions in typical practice and will limit conclusions regarding the long-term effects of initial treatment. Extending trial-based analyses to longer timepoints requires imputation in many instances, which affects the level of confidence in the results no matter how responsibly it is done. In addition, key outcome measures such as disease activity scores, remission criteria, and modified Sharp score have undergone substantial revision and modification over the years, are employed variably in clinical trials, and not measured in others, making cross-trial comparisons problematic. We attempted to control for variation in our NMA of Sharp score by presenting results as standardized mean differences, but note that this has been infrequently attempted to date. Finally, while comparisons of TIM combination therapy or monotherapy to

conventional DMARDs alone provides important information on the incremental benefits of TIMs, such a comparison does not inform considerations of treatment sequencing. This compounds the already significant challenges with extrapolating RCT-based evidence to real-world settings that are common to all chronic therapies. The best approaches to address these concerns include head-to-head trials and pragmatic trials of treatment sequencing, both of which are currently in short supply.

Because TNFα inhibitors have the longest-standing evidence base of the TIMs of interest for this review, much of the early research in treatment sequencing involved assessments of switches between agents in this class for efficacy or safety reasons (commonly referred to as "cycling"). Now that other classes of agents are available, there is interest in evaluating the effectiveness of switches between versus within classes. The pragmatic Rotation or Change (ROC) trial recently addressed this question[27] by randomizing 300 patients with inadequate response to an initial TNFα inhibitor to receive a different TNFα inhibitor or to switch to a non-TNF biologic agent (tocilizumab, abatacept, or rituximab) at investigator discretion. The proportion of patients with low disease activity on the DAS28-ESR was statistically-significantly greater in the non-TNF group versus the second TNFα-inhibitor group at both weeks 24 (45% vs. 28%, p=.004) and 52 (41% vs. 23%, p=.003). Results from earlier observational studies and systematic reviews of trials in TNF-experienced patients echoed these findings.[28-30]

In the US setting, the potential for even observational study of different treatment sequences is complicated by payer formulary and benefit design. As described earlier in this report and highlighted further in Section 3, most private payers require initial TIM therapy and sometimes second TIM therapy to be within the TNFα-inhibitor class. Many payers also stipulate that etanercept and adalimumab hold preferred status as the first TIM of choice.

The course of RA may feature multiple periods of remission and flares of symptoms due to the complex and heterogeneous nature of the disease. TIM therapies are chronic, and the long-term effects of prolonged immunomodulation – both clinical benefits and potential harms -- are not well-understood for all therapies, particularly for newer classes of TIMs. Evidence is beginning to emerge on the question of whether TIM doses can be modulated or therapy suspended in patients with evidence of durable remission, but early results are limited and mixed. In addition, as noted in the Topic in Context section, the decision to initiate TIM treatment may in part be due to a missed opportunity to optimize conventional DMARD therapy; such challenges are common to other chronic diseases such as diabetes and heart failure as well.

Finally, while the introduction of TIMs has transformed clinical practice in RA and improved the quality of life and functional capacity of many patients, there are still unanswered questions, including the relationship between levels of disease activity and radiographic evidence of joint damage, whether there are patient or clinical factors that predict response to specific therapies,

and the totality of the disease's impact on patients, families, and caregivers. As noted in the Topic in Context section, patient groups do not feel that the current tools for patient-reported outcomes sufficiently capture their experience, but to date no new instruments have been accepted into common use in clinical trials.

Summary

Using the ICER evidence rating matrix, our evidence ratings for selected comparisons of interest are provided in Table 12 for patients with moderately-to-severely active RA who have had an inadequate response to prior conventional DMARD therapy. As described previously, findings of studies using conventional DMARDs as the control indicate clinically- and statistically-significant improvements in most important disease measures for all TIMs whether delivered as monotherapy or combination therapy, so all FDA-approved TIMs would all receive a letter grade of "A" (high certainty of substantial net health benefit) relative to conventional DMARD therapy alone. However, the evidence on long-term effectiveness and safety of the two investigational TIMs (baricitinib and sarilumab) is still emerging, so we judge the comparative clinical effectiveness of these two agents to have moderate certainty of an incremental or better net health benefit ("B+").

Table 13. Evidence Ratings for Comparative Clinical Effectiveness: Selected Comparisons

Regimen Type/Comparison	Intervention	Comparator	Rating
Vs. Conventional DMARDs			
Mono- or Combination Therapy	Sarilumab	Conventional DMARDs	B+
	Baricitinib	Conventional DMARDs	B+
	All other TIMs	Conventional DMARDs	A
Head-to-Head Comparisons			
Monotherapy	Sarilumab	Adalimumab	B+
	Tocilizumab	Adalimumab	B+
Combination Therapy	Baricitinib	Adalimumab	C+
	Tofacitinib	Adalimumab	C
	Abatacept (sc)	Adalimumab	C
	Certolizumab pegol	Adalimumab	C
	Abatacept (iv)	Infliximab	B+
	Etanercept	Adalimumab	C
All Other Head-to-Head Comparisons	---	---	I

TIM Monotherapy

The presence of direct comparative data allowed us to be reasonably confident about the relative net health benefit for some between-agent comparisons. Among monotherapy regimens, sarilumab and tocilizumab (iv form) have been compared to adalimumab for impact on both disease activity and ACR response. Both agents produced statistically-significantly higher rates of response, improvement in disease activity, and remission, as well as improvements in pain, fatigue, and quality of life, leading to moderate certainty of an incremental or better net health benefit for these agents relative to adalimumab ("B+"). Certainty was moderate because only a single trial was available for each comparison.

TIM Combination Therapy with Conventional DMARDs

Single RCTs have also evaluated combination therapy regimens with methotrexate plus baricitinib, tofacitinib, abatacept (subcutaneous form), and certolizumab pegol in comparison to adalimumab + methotrexate. In the RA-BEAM study, baricitinib + methotrexate was associated with a statistically-significantly but modestly higher rate of ACR20 response (74% vs. 66% for adalimumab + methotrexate), and no differences were observed in remission rates. Rates of serious harm or discontinuation due to adverse events were also similar, so we judge the evidence for combination therapy with baricitinib versus adalimumab to represent a comparable or better net health benefit ("C+"). There were no significant differences in clinical outcomes between combination regimes using tofacitinib, abatacept sc, or certolizumab pegol versus adalimumab; the addition of indirect evidence through the NMA also yielded no statistical differences between these TIMs. We therefore assign a net health benefit rating of "C" for all three comparisons.

An additional study (RED SEA) compared adalimumab and etanercept in addition to existing conventional DMARD therapy, but was a noninferiority study focused primarily on continuation of therapy after one year and did not measure ACR response; in addition, disease activity measures did not statistically differ between arms. Given these findings, and bolstered by NMA results that showed no statistical differences between treatment arms, we consider the two agents to provide comparable net health benefits ("C").

Finally, the iv form of abatacept was compared to infliximab, both in combination with methotrexate, in a single trial (ATTEST). The proportion of patients achieving an ACR20 or better response was statistically-significantly greater with abatacept (72% vs. 56%), but neither changes in disease activity nor rates of remission differed between groups. However, rates of serious adverse events, discontinuation due to adverse events, and infusion reactions were lower with abatacept versus infliximab, leading to a judgment of incremental or better net health benefit ("B+").

There is much greater uncertainty in assessing the relative comparative clinical effectiveness of TIMs that have never been compared head to head in a randomized setting. Observational studies might fill in these gaps, but findings have been inconsistent and design and population biases preclude any definitive conclusions. Finally, as presented earlier, our network meta-analysis produced variable estimates of ACR response and radiographic progression; for example, non-response rates ranged from 29-48% across the TIM combination therapy regimens. However, credible intervals were wide and included 0 for nearly all comparisons between TIMs. As a result, we judge there to be insufficient evidence ("I") to differentiate the remaining TIM comparisons, including intra-class comparisons of the remaining TNFα inhibitors, IL-6 inhibitors, and JAK inhibitors.

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples include but are not limited to:

1. Methods of administration that improve or diminish patient acceptability and adherence
2. A public health benefit, e.g., reducing new infections
3. Treatment outcomes that reduce disparities across various patient groups
4. More rapid return to work or other positive effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)
5. New mechanisms of action for treatments of clinical conditions for which the response to currently available treatments varies significantly among patients for unknown reasons (substantial heterogeneity of treatment effect)

Among the TIMs of focus in our analysis, two (baricitinib and tofacitinib) are oral agents, which may provide a benefit to individuals without ready access to infusion centers and those who prefer oral treatment to self-injection (assuming the treatments are clinically comparable for a given patient). In addition, self-injected and infused products are administered at different frequencies that may be more or less convenient for patients given their specific circumstances. Also, because of RA's heterogeneous nature and likelihood that multiple TIMs will be required for many patients, as well as emerging evidence suggesting that switching to an alternative class of agent rather than "cycling" within class may provide clinical benefit, the availability of five distinct classes of TIMs for the treatment of moderately-to-severely active RA with inadequate response to conventional DMARDs is an important consideration. Finally, the ability of each TIM to address key patient-centric concerns such as rapid improvement in function and work capacity, other downstream clinical benefits such as reduced need for joint replacement and reduced caregiver burden are critically important issues, although we note that the current evidence to distinguish the TIMs on these measures is sparse.

6. Long-Term Cost-Effectiveness

6.1 Overview

The aim of this analysis was to estimate the lifetime cost-effectiveness of TIMs for patients with moderately-to-severely active RA who have had an inadequate response to conventional DMARDs alone. We developed a sequential treatment cohort model that assessed the cost-effectiveness of each of the TIMs detailed above relative to conventional DMARDs, as well as against the TIM market leader, adalimumab. Model parameters were estimated from the network meta-analysis described earlier in this report, as well as from the published literature. The primary outcomes of the model included discounted lifetime total payer costs, life years, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios, using a payer/health-system perspective. Uncertainty in the data inputs and assumptions were evaluated using sensitivity and scenario analyses.

6.2 Cost-Effectiveness Model: Methods

Model Structure

The sequential treatment cohort model simulated a hypothetical homogeneous cohort of patients from the initiation of a TIM until death; a lifetime time horizon was used to reflect the chronic nature of RA. The model was developed in Microsoft Excel®. The model framework is depicted in Figure 8. Key risk and benefit evidence from the clinical review (see Section 4) that flowed directly into the cost-effectiveness model included: the American College of Rheumatology (ACR) categories (<20, 20-50, 50-70, >70), the modified Total Sharp Score (mTSS), adverse events associated with treatment discontinuation, and severe adverse events. Note that the primary focus in the model was on TIM-naïve/mixed populations, although TIM-experienced data were used in a separate scenario analysis.

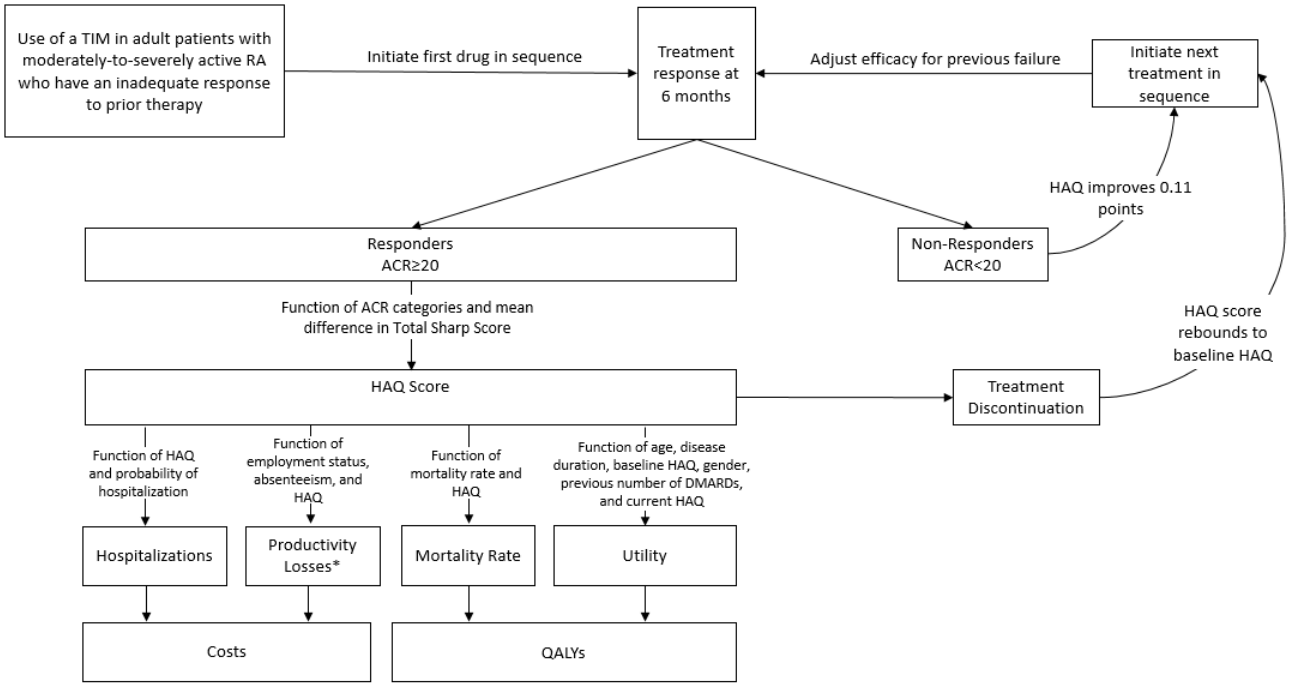
Patients could discontinue a TIM due to lack of effectiveness and/or adverse events. Patients discontinued treatment due to lack of effectiveness if they received an ACR score less than 20 (defined as non-responders) in the first six-month's cycle. Thus, ACR scores >20 were considered treatment responders. A cycle length of six months was used to reflect the time needed to evaluate a treatment's effectiveness.[31] Patients discontinued treatment beyond the first six months only due to the occurrence of adverse events. Upon therapy withdrawal, the model simulated the patient switching therapy up to three different times.

Consistent with prior US and European peer-reviewed RA models,[31,107-110] the Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index (HAQ-DI) was the primary metric that was correlated with the two domains within the QALY (i.e., mortality and morbidity), as well as correlations with hospitalization-related and productivity-related costs (the latter were used only in a modified societal perspective scenario). A lower HAQ suggests lower RA disease activity and better overall functioning. Qualitative and independent directional relationships in the model were as follows: higher general treatment response (defined as ACR>20) lowered HAQ and higher levels of ACR response (e.g., ACR>70) further lowered HAQ; drops in mTSS lowered HAQ; and fewer adverse events associated with treatment discontinuation lowered the HAQ score. A lower HAQ was associated with lower likelihood of death, improved health-related quality-of-life measures (i.e., utilities), fewer RA-related hospitalizations, and better productivity (for the modified societal perspective). Quantitative directional relationships in the model are described below and defined in Appendix D Table D5.

After starting a TIM, the ACR categories were correlated to HAQ improvements.[110,111] In addition to relating ACR response to HAQ, this model framework also related the HAQ score to joint damage and radiographic progression, as measured through the mTSS.[109] HAQ scores were not used directly from the trial evidence, given that the majority of trials did not sub-categorize this measure with respect to treatment responders and non-responders. HAQ scores were simulated through separate contributions of ACR and mTSS,[109] given baseline characteristics of the cohort. The HAQ score was linked to utility, mortality, and hospitalization rates. The simulated utility score and mortality were used to calculate the QALYs gained, and the simulated hospitalization rate factored into total costs from the payer perspective. A link from HAQ to productivity was explored in a scenario analysis that extended the perspective to a modified societal one. The model continued to estimate the long-term HAQ score every six months until last-line treatment or death.

Two additional model structural assumptions were built into this analysis: 1) Time on conventional DMARD therapy alone was assumed to be associated with disease progression and consequent degradation in HAQ, consistent with the US evidence analyzed in the National Institute for Health and Care Excellence Decision Support Unit report,[112] and; 2) the mean difference in mTSS score comparing a TIM to conventional DMARD alone was assumed to be a linear function with time on unique TIM.[109,113] Thus, the longer patients were simulated to be on a TIM, the larger mTSS benefit they were given and the shorter amount of time they were assumed to be on the 4th line conventional DMARD palliative care treatment.

Figure 8. Model Framework



*Productivity losses were investigated in a scenario analysis.
ACR=American College of Rheumatology improvement criteria; *cDMARD*=conventional disease-modifying antirheumatic drug; *DMARD*=disease-modifying antirheumatic drug; *HAQ*=Health Assessment Questionnaire; *IR*= inadequate responder; *QALYs*=quality-adjusted life years

Model Parameters

The economic evaluation was primarily from a health-system perspective, and thus focused on direct medical and pharmacy costs. A separate scenario analysis was conducted to extend the perspective to a modified societal one that included indirect costs due to potential productivity gains or losses.[114] All future costs and outcomes were discounted 3% per year.

The model was informed by several assumptions, which are detailed below.

- Patients can discontinue treatment for two reasons: (1) lack of effectiveness, and (2) occurrence of an adverse event. Consistent with prior models, as compared to real-world observation, the discontinuation assumptions likely overestimate discontinuation in the short-run (lack-of-effectiveness discontinuation), but underestimate discontinuation in the long-run (adverse-event discontinuation).
- A treatment was administered for at least six months before a decision to discontinue was allowed in the model. This is consistent with prior models and consistent with the follow-up duration of many clinical trials.

- Those that discontinue TIM treatment move to the next treatment in the sequence.
- After three different TIM failures, a patient reverts to conventional DMARD palliative care and stays with that therapy for the rest of his/her life. Scenario analyses varied the treatment sequential pathway, including: 1) having the fourth and final treatment be a market basket of all TIMs (instead of palliative care) without an option for discontinuation, and 2) having treatment 2 be the final treatment (removing treatments 3 and 4), consisting of a market basket of all TIMs without an option for discontinuation.
- Each TIM is used in combination with methotrexate for the base-case combination therapy results. For subsequent lines of treatment, all relevant TIM therapies in the market basket were averaged and weighted equally (see Figure 8). For TIMs with available monotherapy evidence, an additional analysis was undertaken that explored these TIMs' cost-effectiveness when used as monotherapy.
- Those patients who had an ACR score less than 20 were assumed to be non-responders to TIM therapy.[110] These patients discontinue due to lack of effectiveness after the first TIM treatment cycle (six months).
- Cost of treatment for those that do not respond was assumed for the full length of the cycle (six months).
- Responders experienced a constant probability of discontinuation due to adverse events for each TIM treatment for cycles two and above.[110]
- A patient's HAQ score was a function of their baseline characteristics, ACR score and mTSS.
- HAQ improved (decreased) with higher ACR scores. An ACR score less than 20 was associated with a HAQ improvement of 0.11 units, ACR between 20 and 49 with a HAQ improvement of 0.44 units, between 50 and 69 with a HAQ improvement of 0.76 units, and an ACR score of 70 or higher was associated with a HAQ improvement of 1.07 units.[110,111]
- HAQ improved (decreased) with lower mTSS scores. The coefficient relating mTSS to HAQ is a weighted average of the remission-like response, as proxied by ACR >70 (coefficient=0.02; 29.6% of weighted average) and the remaining 70.4% with lower levels of response (i.e., ACR 20-69) and corresponding coefficient = 0.0031.[109] This resulted in the weighted coefficient of 0.0081. Further, mean change in mTSS was assumed to be a linear function of time on the same TIM, such that mean change in mTSS at time T = mean change in mTSS from the clinical review * T, where T = years on the same TIM. This continued change in mTSS is consistent with evidence from the PREMIER [109,113]
- The resulting changes in progression for response to TIM treatment over time as measured by mTSS changes generate small improvements in HAQ over time (approximately a 0.05 lower HAQ over time on continued TIM treatment beyond initial improvement). The generated HAQ improvements over time from TIM treatment are consistent with observational studies.[115]
- The cost calculations for intravenously administered therapies accounted for vial wastage (i.e., no vial sharing was allowed).
- The conventional DMARD comparator assumes the continued treatment costs of methotrexate and the clinical outcomes consistent with the clinical review over the

remaining lifetime of the cohort. This comparator represents the long-term costs and outcomes in an environment without TIM treatment. Using the findings from the National Databank for Rheumatic Diseases, for each year on conventional DMARD alone, we applied an increase in HAQ of 0.0269 per year up to 15 years. After 15 years on conventional DMARD, the HAQ increase was fixed at the 15-year value of 15*0.0269 = 0.4035.[112]

Target Population

The primary population for this review included adults with moderately-to-severely active RA and inadequate response to or intolerance to conventional DMARDs. The model simulated a hypothetical homogeneous cohort of patients, with baseline characteristics similar to United States RA registries as summarized by Curtis and colleagues.[116] Table 14 depicts the model characteristics for the population naïve to TIMs or mixed (with a minority [<20%] of those who were TIM experienced). Curtis and colleagues reported baseline mean HAQ values of approximately 1.5. Due to the model's assumption from the clinical review of ACR treatment benefits in the conventional DMARD arm, a baseline HAQ of 1.7 was used so that after the first conventional DMARD treatment cycle the cohort's HAQ was approximately 1.5.

Table 14. Base-Case Model Cohort Characteristics

	Value	Primary Source
Mean age	55 years (range 50 to 60 years old)	Curtis et al., 2010[116]
Female	79% (range 73%,86%)	Curtis et al., 2010[116]
Caucasian	84%	Curtis et al., 2010[116]
Mean weight	170 pounds	National Health and Nutrition Examination Survey data[117]
Baseline HAQ prior to cDMARD treatment benefit	1.7 (range: 1.37 to 2.03)	Curtis et al., 2010[116]
Baseline mTSS	54 (SD: 64)	Lillegraven et al., 2011[118]

HAQ=Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index;
mTSS= modified Total Sharp Score

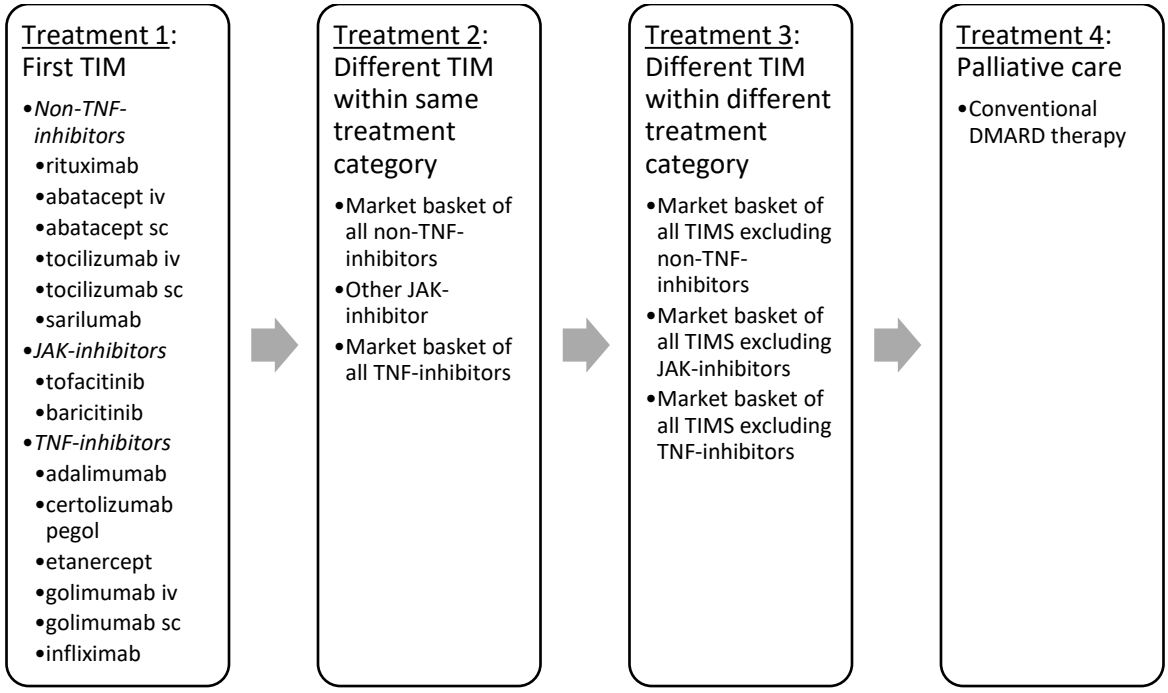
Of these model cohort characteristics, age and gender were used in calculating the risk of mortality. The mean weight was used to calculate average dosing for TIMs administered intravenously, and the baseline HAQ and mTSS score served as the starting point for the model-simulated HAQ score.

Treatment Strategies

The TIMs included for review are those assessed in the evidence review and NMA; their administration schedules are listed in Appendix D. All but two TIMs (baricitinib and sarilumab) are FDA approved. Regimens are based on labeled dosing recommendations (see Table 1 in Section 2).[119-128] For investigational agents, assumed dosing was based on clinical expert input as described in Section 4.

In the clinical setting, it is not uncommon for patients to cycle through multiple therapies before finding a treatment option to which they best respond and tolerate. To partially account for treatment cycles while balancing the number of scenarios and lack of long-term sequential treatment evidence, the model allowed patients who discontinue a TIM (due to lack of effectiveness and/or adverse events) to switch therapy up to three times. The first switch was to an agent within the same treatment category; the second was to an agent within a different treatment category; and the third and final switch was to a palliative care state that involved conventional DMARD therapy. A separate scenario analysis was conducted where treatment 4 consisted of a market basket of all TIMs instead of conventional DMARD therapy. Another scenario analysis was conducted that only allowed patients to switch once (from treatment 1 to treatment 2), where treatment 2 consisted of a market basket of all TIMs. Figure 2 outlines the sequential treatment pattern used in the model's base-case. Note that, based on published clinical data, we assumed that the effectiveness of subsequent treatment was reduced relative to initial treatment using a universal hazard ratio of 0.84.[110,129]

Figure 9. Model Sequential Treatment Pattern*



*Each TIM is used in combination with methotrexate for the base-case results. All therapies in the market basket were averaged and were thus weighted equally. The market-basket average drug cost did not include baricitinib or sarilumab as these two investigational drugs do not have published prices.

As an example, if a patient was modeled on adalimumab for Treatment 1 and that treatment failed, he/she would switch to a market basket of all TNF-inhibitors excluding adalimumab (certolizumab pegol, etanercept, golimumab subcutaneous, golimumab intravenous, and infliximab). If he/she failed the second-line TNF-inhibitor treatment, the patient would switch to a third treatment of a market basket of all TIMs excluding TNF-inhibitors. If the patient failed the third treatment, they would switch to conventional DMARD therapy in the base-case analysis.

Model Inputs

Model inputs were estimated from the network meta-analysis described earlier in this report, as well as from the published literature. The inputs that informed the model are described below, separated into cost and clinical inputs.

Costs

Drug Acquisition Costs

Each intervention was associated with an annual cost based on the acquisition cost, dosing, administration, and monitoring. For drug costs, we obtained data from SSR Health[130] that combined information on net US dollar sales with information on unit sales to derive net pricing at the unit level across all payer types. Data on the approved agents of interest were current through the fourth quarter of 2016. We estimated net prices for these agents by comparing the four-quarter rolling averages (i.e., first quarter 2016 through fourth quarter 2016) of both net prices and wholesale acquisition cost (WAC) per unit to arrive at an average discount from WAC for each drug class. Finally, we applied this average discount (rounded to the nearest 5%) to the most current WAC[131] for each drug to arrive at an estimated net price. The drug discount by class is as follows:

- TNF inhibitors – 30%
- CD-20 directed cytolytic antibody – 15%
- T-cell inhibitors – 30%
- IL-6 inhibitors – 20%
- JAK inhibitors – 5%

Table 15 details the drug unit, current WAC per unit, derived net price per unit, and annual drug cost calculated using the discounted WAC per unit (WAC unit prices updated in February 2017). SSR Health does not track net unit sales and associated price for generic drugs. As there are multiple manufacturers of generic methotrexate, we used the median WAC per unit for conventional DMARD drug costs in the model. The annual drug costs reported in this table were an average over three years of treatment assuming 100% compliance to reduce the variation in the loading dosing schedule for some TIMs. Note that a cost was not assumed for investigational drugs; generated results were limited to clinical outcomes as well as unit prices that would achieve certain cost-effectiveness thresholds. Additional drug inputs, including dose and frequency of administration, can be found in Table D1-D3 of Appendix D.

Table 15. Drug Cost Inputs

Intervention	Administration	Unit	Unit WAC*	Net price per unit	Annual Drug Cost‡
rituximab	iv	100mg	$835	$710	$30,764
abatacept	iv	250mg	$987	$691	$27,637
abatacept	sc	125mg	$957	$814	$42,306
tocilizumab	iv	20mg	$95	$76	$27,627
tocilizumab	sc	162mg	$898	$719	$21,861
sarilumab**	sc	----------	----------	----------	----------
tofacitinib	ORAL	5mg	$63	$60	$43,873
baricitinib**	ORAL	----------	----------	----------	----------
adalimumab	sc	40mg	$2,221	$1,554	$40,415
certolizumab pegol	sc	200mg	$1840	$1,288	$34,775
etanercept	sc	50mg	$1,111	$777	$40,422
golimumab	sc	50mg	$4,150	$2,905	$34,863
golimumab	iv	50mg	$1,592	$1,114	$29,719
infliximab	iv	100mg	$1,168	$817	$28,906
cDMARD (methotrexate)	ORAL	2.5mg	$2.78	-	$1,155

*WAC as of February 2017

**For investigational drugs, no annual cost was assumed except the cost needed to achieve thresholds.

‡The annual drug cost only includes the cost of drug therapy, and does not include any costs associated with administration or monitoring. The annual drug costs reported in this table were an average over three years of treatment assuming 100% compliance to reduce the variation of some TIMs loading dosing schedule.

Administration and Monitoring Costs

Oral treatments were assumed to have no administration costs. Subcutaneous treatments included costs for an annual office visit for training on self-administration and for one subcutaneous administration. The administration cost for treatments administered intravenously included the cost for an intravenous infusion administered in a physician's office, calculated by multiplying the hourly infusion cost by the number of hours required for the infusion. Administration cost inputs for each drug are detailed in Table 2 of Appendix D.

Drug monitoring included office visits, tuberculosis tests, liver tests, and complete blood count tests, as appropriate for each medication. Table 3 of Appendix D details monitoring cost inputs.

Health Care Utilization Costs

The cost per hospital day and cost per office visit were used as health care utilization cost inputs. The cost per hospital day was $2,040[132] and the cost per office visit was $73.40 (HCPCS code 99213).[133] The relationship between hospital days and HAQ is provided in Table D5 of Appendix D.

Severe Adverse Event Costs

Two severe adverse event categories, serious infections and tuberculosis infections, were assumed to impact costs. The cost of a serious infection was assumed to be $13,747 based on weighted average costs of pneumonia and cellulitis (two common serious infections in RA patients) and the cost of a tuberculosis infection was $12,220.[134] Adverse event inputs are detailed in Table D4 of Appendix D.

Productivity Costs

Productivity costs were included in a scenario analysis that extended the perspective to a modified societal one. The average hourly wage used to value time in the model was $23.23.[135] The number of hours missed from work is detailed in Table D5 of Appendix D.

Clinical Events

Response to Treatment

Response to treatment was measured by ACR score. The proportion of patients in each ACR response category (not achieving ACR20, ACR20 but not ACR50, ACR50 but not ACR70, and ACR70) was used in the model to measure response and improvement due to therapy. These categories are mutually exclusive and exhaustive, and were related to the HAQ score using a previously published relationship.[110,111] In addition to relating ACR response to HAQ, the model also accommodated the association of joint damage with HAQ, as measured through mTSS.[109] The model assumed the mTSS TIM benefit based on averages from clinical studies without respect to treatment response. Categorical results for ACR response and mTSS change can be found in Section 4 and Appendix D (Table D6) of this report.

The adverse event discontinuation rates are summarized in Section 4 and specific rates for serious infections and tuberculosis infections (severe adverse events) are summarized in Appendix D.

Model-wide clinical inputs and functions are detailed in Table D5 of Appendix D.

Mortality

Prior evidence suggests that improved (lower) HAQ scores are associated with lower likelihood of death.[136] A US observational study found that HAQ was the most significant predictor of mortality in RA patients.[136] The quantitative relationship between HAQ and mortality was assumed to be the same as that used in a recent US RA cost-effectiveness study.[110] This relationship is detailed in Table D5 of Appendix D.

Utilities

The relationship between HAQ and utility score was based on the Wailoo and colleagues' publication, as shown in Table D5 of Appendix D.[107] The utility scores from Wailoo and colleagues were based on health state time-tradeoff evaluations made by a US general population sample using the EuroQol (EQ-5D) Index, one of the most widely used instruments in health state valuation.[137] We compared the Wailoo et al. utility change from HAQ score moving from 1.0 to 1.5 to the utility change from a more advanced mathematical model.[138] Although the Wailoo et al. relationship produces a higher utility within the HAQ range of 1.0 to 1.5, the change in utility for this HAQ range was approximately 0.1 and this change was deemed consistent with the other model. Further the more complex model[138] included a pain dimension (based on visual analogue scale) that we were not able to estimate across all TIMs. Uncertainty in the Wailoo et al. mapping was evaluated in parameter sensitivity analyses.

Additionally, a disutility (-0.156) was assigned to individuals who experienced a severe adverse event.[139] The disutility lasted for one month[139] for those who experienced a serious infection and for two months[140] for those who contracted tuberculosis. Additional details on adverse event disutilities can be found in Table D4 of Appendix D.

Sensitivity Analyses

The model programming allowed for flexible and comprehensive sensitivity analyses. One-way sensitivity analyses used the low and high bounds from 95% confidence intervals for key model inputs where available. For inputs for which 95% confidence intervals were not available, uncertainty ranges were based on plausible values from the published literature. Tornado diagrams are used to display the results of the one-way sensitivity analyses, focusing on the pairwise comparisons of TIM + conventional DMARDs versus conventional DMARDs alone. Additionally, a probabilistic sensitivity analysis was conducted to vary parameter estimates across their plausible ranges simultaneously.

Scenario Analyses

Multiple scenario analyses were conducted based on feedback from stakeholders: 1) having a market basket of all TIMs as the fourth treatment in the sequential treatment pattern rather than palliative care, 2) having a market basket of all TIMs as treatment two and not modeling any additional switches, 3) extending the perspective to a modified societal one including indirect costs due to potential reduced absenteeism and unemployment, 4) estimating the cost-effectiveness for those TIMs studied in TIM-experienced populations, and 5) evaluating the deterministic results over short-term time horizons (one year and three years) to determine cost-effectiveness and cost per additional first TIM responder.

6.3 Cost-Effectiveness Model: Results

Base Case Results

Table 16 presents the drug cost, total payer cost, average HAQ, life years gained, and QALYs gained over the lifetime horizon for each treatment pathway for TIMs added on to conventional DMARD. Total payer costs included the drug costs (drug costs, administration costs if any, and monitoring costs) as well as other payer-related costs that may differ by treatment including: hospitalization costs and serious adverse event-related costs. The results indicate that a lower HAQ score corresponded to a higher QALY gain, as expected. As discussed in the methods section, HAQ was derived from separate contributions of ACR score and mTSS. Table D6 in Appendix D details the relative contributions of ACR score and mTSS to HAQ. The base-case results indicate that treatment with TIMs over a lifetime horizon leads to substantial QALY improvements, ranging from 1.88 (tofacitinib) to 2.43 (etanercept) as compared to conventional DMARD therapy.

Table 16. Results for the Base-Case for TIMs Added on to Conventional DMARD

Treatment 1	Drug Cost	Total Cost	Average HAQ	Life Years	QALYs
rituximab	$366,768	$464,864	1.25	16.79	12.70
abatacept (iv)	$367,724	$466,733	1.22	16.82	12.78
abatacept (sc)	$452,292	$566,053	1.18	16.87	12.90
tocilizumab (iv)	$369,876	$470,205	1.19	16.85	12.88
tocilizumab (sc)	$329,324	$424,674	1.21	16.83	12.81
sarilumab	-	-	1.21	16.83	12.81
tofacitinib	$467,784	$579,140	1.28	16.75	12.57
baricitinib	-	-	1.25	16.78	12.67
adalimumab	$425,929	$530,720	1.25	16.78	12.68
certolizumab pegol	$417,742	$522,473	1.20	16.84	12.86
etanercept	$470,007	$583,449	1.12	16.94	13.12
golimumab (sc)	$408,413	$512,875	1.25	16.79	12.69
golimumab (iv)	$386,971	$488,380	1.23	16.81	12.75
infliximab	$381,243	$480,448	1.24	16.79	12.73
cDMARD	$18,209	$67,819	1.78	16.16	10.69

Three FDA-approved TIMs (adalimumab, etanercept, tocilizumab iv) had data for monotherapy administration, and thus, treatment with these TIMs as monotherapy (i.e., not in conjunction with conventional DMARDs) was modeled. Table 17 presents the drug cost, total payer cost, average HAQ, life years gained, and QALYs gained over the lifetime horizon for each treatment pathway for TIMs as monotherapy. The TIM monotherapy results indicate that treatment with TIMs over a lifetime horizon leads to QALY improvements ranging from 2.20 (adalimumab) to 2.60 (tocilizumab iv) as compared to conventional DMARD therapy (conventional DMARD resulted in a lifetime discounted QALY of 10.75 for the monotherapy simulation).

Table 17. Results for TIMs as Monotherapy

Treatment 1	Drug Cost	Total Cost	Average HAQ	Life Years	QALYs
tocilizumab (iv)	$384,441	$489,541	1.05	17.03	13.35
sarilumab	-	-	1.07	17.00	13.28
adalimumab	$449,224	$562,748	1.17	16.89	12.95
etanercept	$469,981	$584,952	1.11	16.95	13.16
cDMARD*	$18,235	$67,525	1.76	16.18	10.75

*cDMARD costs and outcomes were slightly different as compared to the combination findings in Table 16 given the different ACR clinical findings for cDMARD in the monotherapy network meta-analysis as compared to the combination therapy network meta-analysis.

Table 18 presents the discounted lifetime incremental cost-effectiveness ratios for each of the TIMs as compared to conventional DMARDs and to the TIM market leader, adalimumab. When comparing the TIMs to conventional DMARD therapy, the incremental comparisons showed that tocilizumab (sc) produced the lowest ratios. Tofacitinib produced the highest cost-effectiveness ratios compared to conventional DMARD therapy. Importantly, however, the cost-effectiveness of all TIMs in combination with conventional DMARDs relative to conventional DMARDs alone exceeded commonly-cited thresholds for cost-effectiveness of $50,000 - $150,000 per QALY gained.

When comparing the TIMs to the market leader adalimumab, eight TIMs were dominant, meaning they were less costly and more effective than adalimumab. Two other TIMs (abatacept sc and etanercept) were more costly but also more effective than adalimumab, with estimated cost-effectiveness ratios of $163,000 and $119,000 per QALY respectively. The final TIM (tofacitinib) was dominated by adalimumab, indicating that it was more costly and less effective. Importantly, however, we note that deterministic point estimates, particularly for QALY gains, are both subject to uncertainty and differ modestly between most of the TIM regimens evaluated. Indeed, findings from probabilistic sensitivity analyses suggest a high degree of overlap in QALY estimates in pairwise TIM comparisons (Appendix D), consistent with our findings in the evidence review.

Table 18. Incremental Cost-Effectiveness Ratios for the Base Case, for TIMs Added on to Conventional DMARD

Treatment 1	ICER (cost per QALY gained) Comparator: cDMARD	ICER (cost per QALY gained) Comparator: adalimumab
rituximab	$198,056	Less costly, More effective
abatacept (iv)	$191,317	Less costly, More effective
abatacept (sc)	$225,853	$163,376
tocilizumab (iv)	$183,949	Less costly, More effective
tocilizumab (sc)	$168,660	Less costly, More effective
tofacitinib	$271,749	More costly, Less effective
adalimumab	$232,644	Reference
certolizumab pegol	$209,736	Less costly, More effective
etanercept	$212,021	$119,233
golimumab (sc)	$222,380	Less costly, More effective
golimumab (iv)	$204,212	Less costly, More effective
infliximab	$202,824	Less costly, More effective

Table 19 presents the discounted lifetime incremental cost-effectiveness ratios for each of the TIMs as monotherapy as compared to conventional DMARDs and to the TIM market leader, adalimumab. Cost-effectiveness was comparable as monotherapy (slightly lower for tocilizumab (iv) and adalimumab vs. conventional DMARD alone) but still exceeded commonly-cited cost-effectiveness thresholds. As was the case with combination therapy, monotherapy results were driven primarily by ACR response and mTSS changes.

Table 19. Incremental Cost-Effectiveness Ratios for TIMs as Monotherapy

Treatment 1	ICER (cost per QALY gained) Comparator: cDMARD	ICER (cost per QALY gained) Comparator: adalimumab
tocilizumab (iv)	$162,038	Less costly, More effective
adalimumab	$225,423	Reference case
etanercept	$214,427	$102,697

Sensitivity Analysis Results

One-way and probabilistic sensitivity analyses were conducted to assess variation and uncertainty in model inputs. The one-way sensitivity analyses identified model inputs with the most influence over the incremental cost-effectiveness ratio. The one-way sensitivity analysis results are presented in a series of tornado diagrams for each TIM in combination with conventional DMARD versus conventional DMARD alone (see Appendix D for all tornado diagrams). Influential inputs often included the HAQ degradation (annual) for conventional DMARD, TIM adverse event discontinuation rate, baseline HAQ score, mTSS score, HAQ improvement over time due to mTSS changes over time, hospital days per HAQ level, and the level of HAQ improvement associated with certain ACR scores.

Figure 9 presents the tornado diagram for the TIM with the most favorable cost-effectiveness ratio from the base-case results (tocilizumab sc at approximately $168,700 per QALY). The resulting incremental cost-effectiveness results from the one-way sensitivity analysis ranged from approximately $132,000 to $230,000 per QALY. Only one input, the annual HAQ degradation for conventional DMARD, resulted in an incremental cost-effectiveness ratio lower than $150,000 per QALY gained from the base-case payer perspective. Table 20, beneath Figure 9, details the range of inputs used in the sensitivity analysis and the resulting cost effectiveness ratios.

Figure 10. Tornado Diagram for Tocilizumab Subcutaneous versus Conventional DMARD

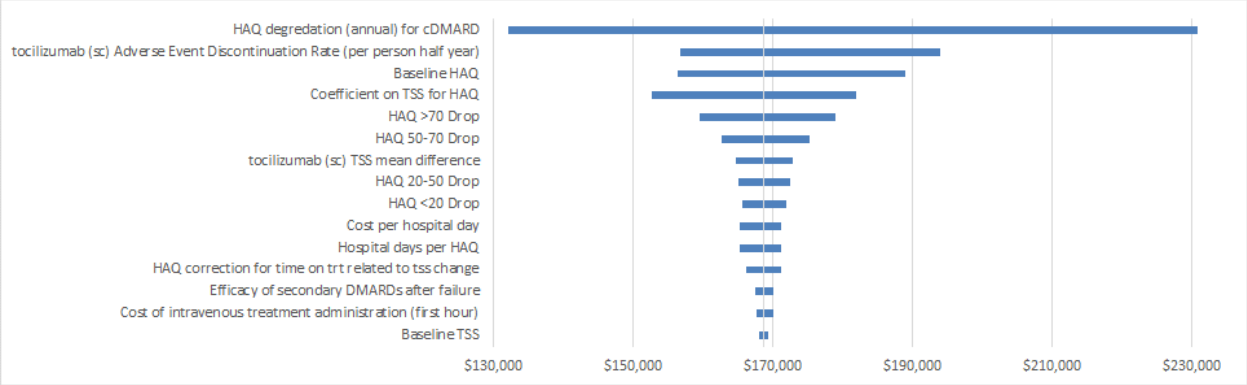


Table 20. Tornado Diagram Inputs and Results for Tocilizumab sc versus Convention DMARD

Input Name	Lower ICER	Upper ICER	Lower Input*	Upper Input*
HAQ degradation (annual) for cDMARD	$132,125	$230,732	0.01	0.05
tocilizumab (sc) Adverse Event Discontinuation Rate (per person half year)	$156,829	$193,928	0.01	0.06
Baseline HAQ	$156,332	$189,031	1.37	2.03
Coefficient on mTSS for HAQ	$152,772	$181,819	0.00	0.02
HAQ >70 Drop	$159,598	$178,971	-1.28	-0.86
HAQ 50-70 Drop	$162,611	$175,272	-0.91	-0.61
tocilizumab (sc) mTSS mean difference	$164,748	$172,866	-1.34	-3.32
HAQ 20-50 Drop	$165,118	$172,410	-0.53	-0.35
HAQ <20 Drop	$165,558	$171,870	-0.13	-0.09
Cost per hospital day	$165,353	$171,253	1,166	3,154
Hospital days per HAQ	$165,353	$171,253	0.22	0.59
HAQ correction for time on trt related to mTSS change	$166,254	$171,141	0.40	0.60
Efficacy of secondary DMARDs after failure	$167,422	$170,118	0.75	0.92
Cost of intravenous treatment administration (first hour)	$167,577	$170,041	77.97	210.93
Baseline mTSS	$168,052	$169,274	43.42	64.58

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Figure 10 presents the tornado diagram for the TIM with the least favorable cost-effectiveness ratio from the base-case results (tofacitinib, at approximately $272,000 per QALY). The resulting ratios from the one-way sensitivity analysis ranged from $210,000 to $380,000 per QALY. No incremental cost-effectiveness ratio fell below $200,000 per QALY gained. Table 21, beneath the figure, details the lower and upper inputs used in the sensitivity analysis and the resulting ratios for each input.

Figure 11. Tornado Diagram for Tofacitinib versus Conventional DMARD

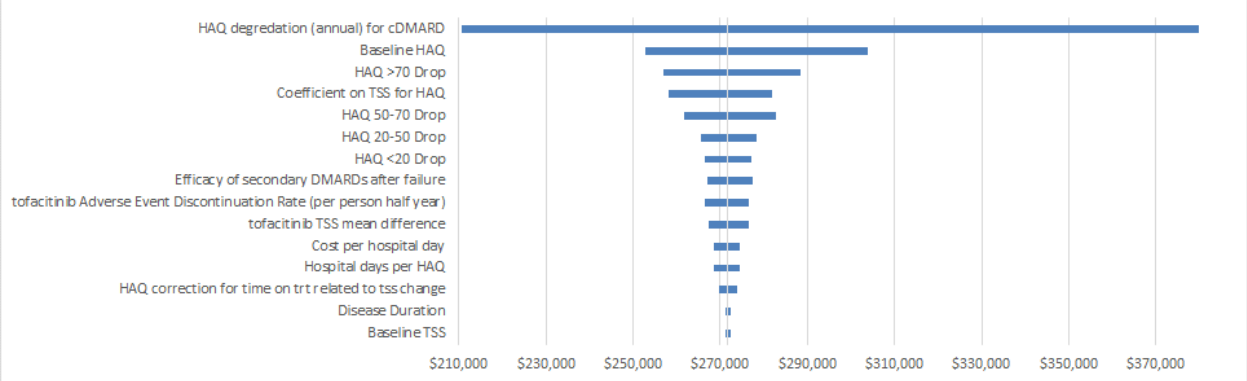


Table 21. Tornado Diagram Inputs and Results for Tofacitinib versus Conventional DMARD

Input Name	Lower ICER	Upper ICER	Lower Input*	Upper Input*
HAQ degradation (annual) for cDMARD	$210,460	$379,770	0.01	0.05
Baseline HAQ	$252,628	$303,968	1.37	2.03
HAQ >70 Drop	$257,072	$288,452	-1.28	-0.86
Coefficient on mTSS for HAQ	$258,162	$282,002	0.00	0.02
HAQ 50-70 Drop	$261,599	$282,879	-0.91	-0.61
HAQ 20-50 Drop	$265,581	$278,302	-0.53	-0.35
HAQ <20 Drop	$266,505	$277,188	-0.13	-0.09
Efficacy of secondary DMARDs after failure	$267,006	$277,414	0.75	0.92
tofacitinib Adverse Event Discontinuation Rate (per person half year)	$266,427	$276,455	0.02	0.06
tofacitinib mTSS mean difference	$267,302	$276,392	0.04	-2.00
Cost per hospital day	$268,462	$274,327	1,166.04	3,154.38
Hospital days per HAQ	$268,462	$274,327	0.22	0.59
HAQ correction for time on treatment related to mTSS change	$269,783	$273,747	0.40	0.60
Disease Duration	$271,241	$272,263	14.99	22.31
Baseline mTSS	$271,256	$272,245	43.42	64.58

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

A probabilistic sensitivity analysis was also conducted to assess variation in all parameters for each TIM compared to conventional DMARD. None of the Monte Carlo iterations were below $100,000 per QALY gained for any of the TIMs. Table D8 in Appendix D details the percent of iterations under certain willingness-to-pay thresholds for each TIM when compared to conventional DMARD. Tocilizumab (sc and iv) had the greatest number (10-27%) of iterations beneath a threshold of $150,000 per QALY gained. Table D9 in Appendix D details the percent of iterations under certain willingness-to-pay thresholds for each TIM when compared to the TIM market leader, adalimumab. Results suggest that the TIMs with favorable deterministic incremental cost-effectiveness ratios as compared to adalimumab (either < $150,000/QALY or less costly and more effective), were also highly likely (>90% likely) to be cost-effective compared to adalimumab at a cost-effectiveness threshold of $150,000/QALY. Figure 4 in Appendix D presents a panel of cost-effectiveness clouds that compare tocilizumab sc, tofacitinib, and adalimumab. The cost-effectiveness cloud depicts all the uncertainty in the outputs that was built into the probabilistic sensitivity analysis. Although there was significant overlap between TIMs in the QALY domain, there is very little overlap between these featured TIMs when comparing together the two domains of QALYs and costs.

Scenario Analyses Results

Because there is not one standard treatment pathway in RA, the sequential treatment pathway was varied in scenario analyses. The first scenario analysis changed the fourth treatment strategy from palliative care in the base-case to a market basket of all TIMs (Table D10 in Appendix D). Findings were similar to those of the base case.

A second scenario analysis explored a sequential treatment pathway that modeled only one switch (Table D11 in Appendix D). Results were relatively consistent with the first scenario analysis and seemed to move all cost-effectiveness findings closer to that of the average TIM versus conventional DMARD.

Additionally, to account for indirect costs due to absenteeism and unemployment (and the potential for reductions in each), the perspective was extended to a modified societal one (Table D12 in Appendix D). Compared to the health care system perspective, the cost-effectiveness ratios for a modified societal perspective were lower, and tocilizumab (iv and sc) ratios were below the cost-effectiveness threshold of $150,000 per QALY gained.

Table D13 in Appendix D focuses on three TIMs with evidence in the TIM-experienced population as combination therapy, using a different set of patient characteristics to better reflect this population (see Appendix D). The three TIMs with evidence in the TIM-experienced population included: rituximab, abatacept (iv), and tocilizumab (iv). Across all three TIMs, the cost-effectiveness ratios remained in the approximate range of $190,000 to $200,000 per QALY.

The final scenario analysis evaluated the base-case results over shorter time horizons (one year and three years). Results are also presented on a cost per additional responder basis (based on ACR results) to inform interim clinical findings. Cost-effectiveness of all TIMs worsened as the time horizon became shorter, approaching $400,000-$820,000 per QALY for a one-year horizon, for example (see Appendix D, Tables D14-15). While the cost-per-responder analysis is more difficult to interpret given the absence of a natural benchmark, results tended to follow the same rank order as the cost-per-QALY scenarios.

Threshold Analyses Results

Table 22 presents the results of the threshold analysis of the base-case using a lifetime horizon and health care system perspective. Each TIM in combination with conventional DMARD therapy was compared to conventional DMARD alone. The table presents the WAC per unit, net price per unit and discount needed to obtain the commonly cited cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY gained. The estimated net price was higher than the $150,000

threshold price for all TIMs, indicating that larger discounts from current WAC would be required to achieve even the higher end of the cost-effectiveness threshold range.

Table 22. Threshold Analysis Results

	WAC per unit	Net price per unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Discount from WAC to reach thresholds
Rituximab (100mg)	$835.22	$709.94	$198.78	$369.17	$539.55	35% to 76%
Abatacept iv (250mg)	$987.03	$690.92	$193.46	$366.19	$538.92	45% to 80%
Abatacept sc (125mg)	$957.14	$813.57	$203.39	$374.24	$545.09	43% to 79%
Tocilizumab iv 20mg	$94.87	$75.89	$21.25	$41.74	$61.48	35% to 78%
Tocilizumab sc (162mg)	$898.31	$718.65	$237.15	$438.38	$639.60	29% to 74%
Sarilumab*	----------		$237.15	$445.56	$646.78	-
Tofacitinib (5mg)	$63.26	$60.10	$13.22	$23.44	$34.26	46% to 79%
Baricitinib*	----------		$13.82	$24.64	$36.06	-
Adalimumab (40mg)	$2,220.62	$1,554.43	$373.06	$699.49	$1,010.38	55% to 83%
Certolizumab pegol (200mg)	$1,839.94	$1,287.95	$347.75	$643.98	$927.33	50% to 81%
Etanercept (50mg)	$1,110.5	$777.35	$209.88	$380.90	$559.69	50% to 81%
Golimumab sc (50mg)	$4,150.38	$2,905.27	$726.32	$1,365.48	$1,975.58	52% to 82%
Golimumab iv (50mg)	$1,592.09	$1,114.46	$300.91	$557.23	$824.70	48% to 81%
Infliximab (100mg)	$1,167.82	$817.47	$220.72	$416.91	$604.93	48% to 81%

*WAC prices for the two investigational drugs were not available as of the date of this report.

6.4 Model Validation and Prior Published Evidence on Costs and Cost-Effectiveness

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, three independent modelers tested the mathematical functions in the model as well as the TIM-specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other rheumatoid arthritis model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

One manufacturer-funded study[110] modeling tocilizumab monotherapy (8mg/kg monthly) versus adalimumab monotherapy (40mg every other week) in biologic-naïve patients previously treated with conventional DMARDs over a lifetime horizon estimated tocilizumab to be more effective (6.66 vs. 6.43 QALYs) and more expensive ($178,643 vs. $170,111) compared to adalimumab. The ICER model also suggests that tocilizumab is more effective than adalimumab at the same approximate QALY gain (13.35 vs. 12.95); however, tocilizumab is less expensive than adalimumab in the ICER model ($489,541 vs. $562,748). While both models are structurally similar, with similar baseline population characteristics with respect to age and gender, and similar treatment efficacy for subsequent treatment lines, there exist key differences between the two models that contribute to the differing results. First, the published model uses a higher, constant discontinuation rate while the ICER model uses a lower and drug-specific discontinuation rate. Second, the ACR response rates for the two drugs in our model are comparatively higher than the same two drugs in the published model. In addition, HAQ score in the ICER model is a function of ACR improvement criteria and mTSS, from which the utilities were derived, while in the published model, utilities were derived from HAQ score alone, mapped to EQ-5D to derive utilities. Response rates in the ICER model are derived from our NMA, while in the published model, rates were derived from the ADACTA head-to-head trial, with responses for subsequent therapy derived from a mixed-treatment comparison. Drug costs in the ICER model are higher than in the published model. Finally, the ICER model uses a market-basket of treatments averaged in cost and efficacy for the subsequent treatment pathway, whereas the ADACTA-based study modeled subsequent treatment with etanercept, certolizumab, and finally palliative care.

An older study, supported by the Agency for Healthcare Research and Quality (AHRQ)[107], modeled RA treatment from a Medicare perspective and found that etanercept achieved the highest QALYs, followed by adalimumab and infliximab, both of which accrued the same QALYs gained. Adalimumab was least expensive, while infliximab was most expensive. The key differences

between this model and ours are: 1) the AHRQ model used a Medicare perspective with substantially discounted costs while the ICER model uses a broader payer perspective, and 2) patients move to conventional DMARDs alone immediately following loss of efficacy or AEs resulting from TIM therapy in the AHRQ model, while in the ICER model conventional DMARDs are used as a fourth-line option.

A UK-focused microsimulation model, by Stephens et al,[109] comparing adalimumab + conventional DMARD with conventional DMARD alone, yielded 6.83 and 3.79 QALYs for each therapy respectively, over a 30-year time period. The ICER base-case analysis reflect similar clinical results. The Stephens model informs the ICER model, relating the mTSS score to HAQ, along with the contribution of ACR response to HAQ. While both models simulate subsequent therapies after failure of first therapy, there are certain key differences between both models: 1) Non-responders in the ICER model are those with ACR<20 while in the Stephens model, are defined as those with ACR<50; 2) all subsequent therapies after failure of first-line therapy are non-biologics in the Stephens model, while in the ICER model, a market-basket of biologics is assumed to be second- and third-line therapy in the base case; 3) the relationship between HAQ and utilities are different in both models, with the Stephens model using the Health Utility Index Mark 3 and the ICER model using the EQ-5D (based on the publication by Wailoo et al)[107] to derive utilities from HAQ changes; and 4) lastly, the Stephens model uses a 30-year time horizon while the ICER model uses a lifetime horizon.

Figure 5 from Appendix D features additional model validation as compared to Stephens et al. [109] for selected TIMs plus conventional DMARD versus conventional DMARD alone on HAQ scores and undiscounted QALYs over the modeled time horizon. As shown in both Figure 5 in Appendix D and Figure 3 from Stephens et al., the HAQ score features a distinctive "swoosh-like" shape (i.e., an initial decline followed by an approximately linear increase over time) with the trend for conventional DMARD being higher in HAQ across time compared to TIMs plus conventional DMARD. The HAQ score does not go above 2 in our model for conventional DMARD, whereas the HAQ increases above 2 after a time horizon of 10 to 15 years in Stephens et al. This difference is likely due to differences assumed in the HAQ degradation, projected over a long time horizon (and different data sources due to differences in jurisdiction/perspective). QALY curves also look to have consistent shapes across models, with the TIM QALY curves being higher than conventional DMARD alone. The starting QALYs in our model are higher than in Stephen et al., owing to differences in HAQ-to-utility mappings as well as different HAQ degradation assumptions.

A US-based study by Claxton et al.[141] modeled the treatment of tofacitinib monotherapy and combination therapy versus other TIMs, namely, adalimumab, etanercept, certolizumab pegol and tocilizumab, in moderate-to-severe RA patients who had failed methotrexate. Unlike in the ICER model, subsequent lines of therapies were limited to abatacept and rituximab in patients who failed

the first TIM. This decision tree model, with a hypothetical health plan cohort, used a one- and two-year time horizon and a 6-month cycle length. Treatment efficacy estimates for study drugs, defined as ACR20 response at six months, were obtained from individual trials directly, unlike in our model, which derived these estimates from an NMA. The model did not report QALYs, but instead a cost per-member per-year, total costs, and costs per ACR20 responder. WAC was used for drug pricing, unlike in the ICER model which used net price per unit. While the one-year tofacitinib costs in both models were similar (Claxton: $47,788; ICER: $46,793), costs for other TIMs were substantially higher in the Claxton model. When comparing the cost per additional ACR20 responder, the ICER model showed results almost twice as high for tofacitinib and adalimumab, and similar costs for etanercept, certolizumab pegol and tocilizumab, compared to the Claxton model. The higher cost per additional responder for tofacitinib and adalimumab in the ICER model is due to the significantly lower percentage of initial TIM responders in the ICER model compared to the Claxton model for these two drugs.

We reviewed other models[25,142,143,144,145] as well, but have not included them here owing to factors such as differences in population setting, perspective, and health care systems. While there may be distinct differences in model structure and/or key assumptions between these models and ours, it is clear that a major difference with the older studies in this set relates to estimates of TIM prices, given the high rate of year-over-year prices increases in this therapeutic area.

7. Value-based Benchmark Prices

Our value-based benchmark prices for each RA treatment are provided in Table 23. As noted in the initial ICER methods document (http://icer-review.org/wp-content/uploads/2016/02/Value-Assessment-Framework-slides-for-July-29-webinar-FINAL-corrected-8-22-1.pdf), the value-based benchmark price for a drug is defined as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained.

For all TIMs, the discounts required to achieve both threshold prices are greater than the current discounts from WAC, which are lowest (at 5%) for tofacitinib and highest (at 30%) for the TNF inhibitors as well as abatacept iv. Tocilizumab sc could achieve a $150,000 cost per QALY with a 29% discount, but the best available estimate of current discount levels for tocilizumab is approximately 20%.

Table 23. Value-based Benchmark Prices for RA Targeted Immune Modulators

	WAC per unit*	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Discount from WAC to reach thresholds*	Average Net Price Within Benchmark Range?
Rituximab (100mg)	$835.22	$369.17	$539.55	35% to 56%	No
Abatacept iv (250mg)	$987.03	$366.19	$538.92	45% to 63%	No
Abatacept sc (125mg)	$957.14	$374.24	$545.09	43% to 61%	No
Tocilizumab iv 20mg	$94.87	$41.74	$61.48	35% to 56%	No
Tocilizumab sc (162mg)	$898.31	$438.38	$639.60	29% to 51%	No
Sarilumab*	----------	$445.56	$646.78	-	N/A
Tofacitinib (5mg)	$63.26	$23.44	$34.26	46% to 63%	No
Baricitinib*	----------	$24.64	$36.06	-	N/A
Adalimumab (40mg)	$2,220.62	$699.49	$1,010.38	55% to 69%	No
Certolizumab pegol (200mg)	$1,839.94	$643.98	$927.33	50% to 65%	No
Etanercept (50mg)	$1,110.5	$380.90	$559.69	50% to 66%	No
Golimumab sc (50mg)	$4,150.38	$1,365.48	$1,975.58	52% to 67%	No
Golimumab iv (50mg)	$1,592.09	$557.23	$824.70	48% to 65%	No
Infliximab (100mg)	$1,167.82	$416.91	$604.93	48% to 64%	No

*WAC as of February 24th, 2017

8. Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of two new treatments for moderate-to-severe RA patients: sarilumab (including monotherapy) and baricitinib (for both of which FDA approval is pending). As the price of these two drugs is currently not known, we used the prices required to achieve cost-effectiveness thresholds of $50,000, $100,000 and $150,000 per QALY in our estimates of budget impact. We did not include other therapies modeled above in this potential budget impact analysis, given their established presence in the market.

Potential Budget Impact Model: Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to see a more realistic impact on the number of patients treated with the new therapies.

The potential budget impact analysis included the entire candidate population for treatment, which consisted of adults with moderate-to-severe RA who have previously failed treatment with conventional DMARDs. To estimate the size of the potential candidate population for treatment with sarilumab or baricitinib, we first determined the estimated prevalence of RA in the US, which has been reported as 0.6%.[32] Based on our review of the literature, we assumed that 50% of these patients were moderate-to-severe cases, and 50% of this subset had failed initial treatment with conventional DMARDs. Applying these proportions to the projected 2016 US population resulted in an estimate of approximately 486,000 patients in the US over a five-year period.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated. The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug or device that would take market share from one or more drugs, and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. Based on input from clinical experts and payers, we assumed that sarilumab and would take market share from tocilizumab (the other drug in its class) and adalimumab (a head-to-head comparator in clinical trials); similarly, baricitinib would take market share from tofacitinib

and adalimumab. In both cases, we assumed that 70% of new users on the drug would come from patients using the other drug in its class, and 30% would come from adalimumab. We tested the potential budget impact of the two new drugs by assuming different unit price points for each (including monotherapy for sarilumab) - namely price to reach cost-effectiveness thresholds of $50,000 per QALY, $100,000 per QALY and $150,000 per QALY, against the calculated discounted WAC for existing drugs.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 24.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $915 million per year for new drugs.

Table 24. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	33.5	FDA, 2016
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

Potential Budget Impact Model: Results

Table 25 below illustrates the per-patient budget impact calculations in more detail, based on the prices to reach $150,000 per QALY for sarilumab ($647 per syringe) and baricitinib ($36 per tablet), and the discounted WAC price of the TIMs they would be displacing. Note that no data matching our study entry criteria are available for baricitinib monotherapy, so budget impact was not calculated.

Table 25. Illustration of Per-Patient Budget Impact Calculation over Five-year Time Horizon

Drugs	Combination therapy	Monotherapy
	Avg. Annual Per-Patient Budget Impact	Avg. Annual Per-Patient Budget Impact
Sarilumab	$24,812	$25,324
Adalimumab + Tocilizumab*	$31,185	$33,445
Net	-$6,373**	-$8,121**
Baricitinib	$27,077	N/A
Adalimumab + Tofacitinib*	$42,450	N/A
sNet	-$15,373**	N/A

*Weighted in the ratio 30:70 for adalimumab:tocilizumab and adalimumab:tofacitinib

†For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

**Indicates cost-saving

When treating the eligible cohort with sarilumab combination therapy, the average potential budgetary impact (adjusted for differing periods of drug utilization and associated cost-offsets over the five-year period) results in cost savings at all three cost-effectiveness threshold prices for the drug, ranging from approximately -$18,400 per patient using the price ($647) to achieve $150,000 per QALY to -$60,800 using the price ($237) to achieve a $50,000 per QALY cost-effectiveness threshold.

Treating the eligible cohort with sarilumab monotherapy also resulted in cost savings across the three cost-effectiveness thresholds ranging from approximately -$23,400 per patient using the price ($647) to achieve $150,000 per QALY to approximately -$64,600 using the price ($237) to achieve the $50,000 per QALY threshold over a five-year time-horizon.

Finally, when treating eligible patients with baricitinib combination therapy, the potential budgetary impact over five years resulted in cost savings ranging from approximately -$45,200 using the price ($36) to achieve a cost-effectiveness threshold of $150,000 per QALY to approximately -$90,300 using the price ($14) to achieve $50,000 per QALY.

9. Summary and Comment: Long-Term Cost Effectiveness and Potential Budget Impact

The base-case findings from our analysis suggest that all TIMs provide substantial clinical benefit in comparison to conventional DMARDs alone; however, their additional costs translate into cost-effectiveness estimates that exceed commonly-cited thresholds, ranging from approximately $170,000 to $270,000 per QALY gained. The deterministic findings suggest that all add-on TIMs were in a relatively small cluster with respect to QALYs gained. Compared to the market leader adalimumab, most TIMs in combination with conventional DMARD were more favorable (i.e., had deterministic findings with lower costs and higher QALYs), except for abatacept sc, tofacitinib, and etanercept. Assuming a willingness-to-pay threshold of $150,000/QALY, etanercept plus conventional DMARDs was found to be cost-effective as a first-line TIM, while abatacept sc in combination with conventional DMARDs was estimated to exceed $150,000/QALY, and tofacitinib was estimated to have higher costs and fewer QALYs gained.

The base-case results were generally robust to the sensitivity analyses. In one-way sensitivity analyses of deterministic results, annual HAQ degradation was the most influential parameter, with estimated cost-effectiveness going below $150,000/QALY for abatacept iv, tocilizumab iv, and tocilizumab sc. In probabilistic sensitivity analysis, tocilizumab iv and tocilizumab sc versus conventional DMARD therapy (the TIMs with the lowest cost-effectiveness ratio) fell below a threshold of $150,000 per QALY gained in 10% and 27% of iterations, respectively; for all other TIMs, that fraction was 4% or less. The probabilistic sensitivity analysis suggested TIMs with favorable deterministic ICERs as compared to adalimumab (either ICER < $150,000/QALY or less costly and more effective), were also highly likely (>90% likely) to be cost-effective compared to adalimumab at a cost-effectiveness threshold of $150,000/QALY. The probabilistic separation across TIMs appeared to be more in the cost domain rather than in the QALY domain.

Additionally, multiple scenario analyses were conducted to assess the impact of certain model assumptions and parameters on the results and conclusions. When adding in productivity effects, tocilizumab iv and sc fell below the cost-effectiveness threshold of $150,000/QALY gained, but results for other TIMs remained above this threshold. Results for TIMs with evidence in the TIM-experienced population (rituximab, abatacept iv, and tocilizumab iv) resulted in better cost-effectiveness ratios, but these remained above $150,000 per QALY gained in all instances.

Finally, results from our budget impact analyses suggest that baricitinib and sarilumab would decrease costs over the TIMs they would displace (i.e., the other agent in class and adalimumab) if

priced to cost $150,000 per QALY or less. We note, however, that because these two agents are investigational their prices (and consequent cost-effectiveness ratios) are currently unknown.

Limitations

Limitations to the present study include using one universal hazard ratio for the reduced efficacy of subsequent treatments, due to the limited drug class-specific data available. This reduced efficacy was tested in a one-way sensitivity analysis and suggested limited impact on the findings. Additionally, modeling a homogeneous RA patient cohort limits the ability to account for the diverse nature of RA treatment. In clinical practice, treatment choice is often based on patients' individual characteristics and risk factors, which may not be consistent with the model's sequential treatment pattern. With a lifetime horizon and a modelling approach that attempts to approximate reality, treatment discontinuation and switching should be included in the modeling framework. By averaging over TIM-specific clinical, discontinuation, and cost inputs in the subsequent TIM treatment patterns modeled, the differential impact of TIMs beyond that of the first-line TIM is minimized. However, the sequential patterns that were modeled tended to move the cost-effectiveness findings closer to the average TIM with less possible separation across TIMs.

Note that TIM adherence was not included in this evaluation over and above that of TIM discontinuation and TIM switching; however, simulated discontinuation rates were similar to those seen in observational studies. Finally, given the desire to understand comparative value with measures other than the QALY, we included treatment 1 response estimates (i.e. those remaining on the first TIM at the one-year and three-year time points) over the one-to-three-year time range, as well as the average HAQ over time. These disease-specific metrics may be more relevant to specific decision-makers and stakeholders, but overall tended to follow the same rank order as the lifetime incremental cost-per-QALY findings.

Conclusions

In summary, our analyses indicate that all the TIMs of interest in this evaluation substantially improved health outcomes compared to conventional DMARDs alone. However, their additional cost led to cost-effectiveness estimates that were well above commonly cited thresholds for cost-effectiveness, and the discounts required to achieve these thresholds are greater than estimated current discounts from WAC. Compared to the market leader adalimumab, most TIMs in combination with conventional DMARDs were more favorable (i.e., had deterministic findings with lower costs and higher QALYs).

10. Summary of the Votes and Considerations for Policy

10.1 About the New England CEPAC Process

During New England CEPAC public meetings, the New England CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to New England CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the New England CEPAC Panel during their deliberation, and help to shape recommendations on ways the evidence can apply to policy and practice.

At each meeting, after the New England CEPAC Panel votes, a Policy Roundtable discussion is held with the New England CEPAC Panel, clinical experts, and representatives from payers, manufacturers and patient groups. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on Policy Roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the March 24, 2017 meeting, the New England CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of targeted immune modulators for the treatment of rheumatoid arthritis. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at 2:20:29), the New England CEPAC Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of treatment options for rheumatoid arthritis. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with comments reflecting considerations mentioned by New England CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the New England CEPAC Panel made use of a value assessment framework with four different components of “long term value for money,” a concept that represents the long-term perspective, at the individual patient level, on patient benefits with a

given intervention and the incremental costs to achieve those benefits. The four components of long term value for money are comparative clinical effectiveness, estimated incremental cost-effectiveness, other benefits or disadvantages, and contextual considerations regarding the illness or therapy. These four components are defined below.

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The New England CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

2. Estimated incremental cost-effectiveness is the average per-patient incremental cost of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, ICER follows common academic and World Health Organization (WHO) standards by using cost per quality-adjusted life years (QALYs) and adopting thresholds at $100,000 per QALY and $150,000 per QALY as guides to reasonable ratios for cost-effectiveness.

3. Other benefits or disadvantages refers to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether other benefits or disadvantages such as these are important enough to factor into the overall judgment of care value. There is no quantitative measure for other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether the condition affects priority populations. There is no quantitative measure for contextual considerations.

10.2 Clinical Effectiveness Voting Results

Comparative Effectiveness of Targeted Immune Modulators as Monotherapy:

7. Is the evidence adequate to demonstrate that the net health benefit of tocilizumab monotherapy is superior to that provided by adalimumab monotherapy?

Yes: 11	No: 0

Comments: The CEPAC recognized that there was a good quality head to head trial that demonstrated superiority of tocilizumab iv monotherapy over adalimumab monotherapy, and the indirect comparison through the NMA was consistent with statistically significant superiority for tocilizumab in achieving key measures of patient benefit. There are no distinct differences between the two drugs in harms. Clinical experts on the panel added for context that in the trial, patients had, on average, a very high disease activity in comparison with an average patient with rheumatoid arthritis.

8. Is the evidence adequate to demonstrate that the net health benefit of sarilumab monotherapy is superior to that provided by adalimumab monotherapy?

Yes: 11	No: 0

Comments: Similarly, there was a good quality head-to-head study that demonstrated superiority of sarilumab monotherapy over adalimumab monotherapy in disease activity, ACR response, mean change in HAQ, and remission. Clinical experts had high confidence in this trial based on more accurate dosing of adalimumab. The vote was unanimous.

9. Is the evidence adequate to distinguish the net health benefit between tocilizumab monotherapy and sarilumab monotherapy?

Yes: 0	***No: 11***

Comments: There were no head to head studies that compared these two therapies, and the findings through the network meta-analysis did not find significant differences between the two. The vote was unanimous.

10. Is the evidence adequate to demonstrate that the net health benefit of tofacitinib monotherapy is superior to that provided by adalimumab monotherapy?

Yes: 0	***No: 11***

Comments: There were no head to head trials that compared these two therapies, and the findings through the network meta-analysis were not statistically significant. The vote was unanimous.

11. Is the evidence adequate to demonstrate that the net health benefit of baricitinib monotherapy is superior to that provided by adalimumab monotherapy?

Yes: 0	***No: 11***

Comments: There were no head to head trials that compared these two therapies, and the findings through the network meta-analysis were not statistically significant. The vote was unanimous.

12. Is the evidence adequate to distinguish the net health benefit between tofacitinib monotherapy and baricitinib monotherapy?

Yes: 0	***No: 11***

Comments: There were no head to head trials that compared these two therapies, and the findings through the network meta-analysis were not statistically significant. The vote was unanimous.

Comparative Effectiveness of Targeted Immune Modulators in Combination With cDMARDs:

14. Is the evidence adequate to demonstrate that the net health benefit of tocilizumab + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes: 1	***No: 10***

Comments: There were no head to head trials that compared these two therapies, and the findings through the network meta-analysis were not statistically significant. However, there was a discussion about whether the evidence demonstrating superiority of tocilizumab monotherapy versus adalimumab monotherapy was sufficient to conclude that tocilizumab would be superior when used in combination therapy as well. The vote of one CEPAC panel member was swayed by this consideration.

15. Is the evidence adequate to demonstrate that the net health benefit of sarilumab + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes: 0	***No: 11***

Comments: There were no head to head trials that compared these two therapies, and the findings through the network meta-analysis were not statistically significant. The vote was unanimous.

16. Is the evidence adequate to distinguish the net health benefit between tocilizumab + cDMARD therapy and sarilumab + cDMARD therapy?

Yes: 0	***No: 11***

Comments: There were no head to head trials that compared these two therapies, and the findings through the network meta-analysis were not statistically significant. The vote was unanimous.

17. Is the evidence adequate to demonstrate that the net health benefit of tofacitinib +cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes: 0	***No: 11***

Comments: There was one good quality head to head trial that compared tofacitinib combination therapy with adalimumab combination therapy. The comparison yielded no statistical differences between the two therapies. The vote was unanimous.

18. Is the evidence adequate to demonstrate that the net health benefit of baricitinib + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes: 6	No: 5

Comments: There was one head to head trial that compared these two therapies when used in combination therapy. The findings suggested statistically significant, modest improvements in disease activity, ACR response, and HAQ. There was a discussion about other findings in the study that were not statistically different, such as remission. One panel member also acknowledged the improvement in pain and fatigue for those patients in the baricitinib arm. The vote on this question was split. Those who voted yes said that the statistical improvement in many of the primary measurements was sufficient to demonstrate superiority of baricitinib. Several panel members who voted no noted the inconsistent outcomes, and that there was no difference in clinical remission, which is important to patients and clinicians. They also emphasized the unknown safety effects of baricitinib as new drug that has not yet entered the market.

19. Is the evidence adequate to distinguish the net health benefit between tofacitinib + cDMARD therapy and baricitinib + cDMARD therapy?

Yes: 0	***No: 11***

Comments: There were no head to head trials that compared these two therapies, and the findings through the network meta-analysis were not statistically significant. The vote was unanimous.

Comparative Value of Targeted Immune Modulators (TIM):

10.3 Care Value Voting Results

20. **Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money for tocilizumab monotherapy in comparison to adalimumab monotherapy?**

Low: 0	Intermediate: 4	***High: 7***

Comments: In the ICER model results, tocilizumab iv monotherapy was less costly and more effective than adalimumab monotherapy. Clinical experts brought up how dose escalation of adalimumab to maintain efficacy (which is not reflected in the model) could widen the gap, and make tocilizumab even more cost-effective. One panel member who voted intermediate value justified his vote by noting the relatively small QALY gain—whereas another panel member who voted intermediate value doubted that the drug costs applied in the model captured the full cost of hospital administration of an infused drug.

21. **Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money for tocilizumab + cDMARD therapy in comparison to adalimumab + cDMARD therapy?**

    No vote taken based on clinical effectiveness vote

22. **Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money for tofacitinib monotherapy in comparison to adalimumab monotherapy?**

    No vote taken based on clinical effectiveness vote

23. **Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money for tofacitinib + cDMARD therapy in comparison to adalimumab + cDMARD therapy?**

    No vote taken based on clinical effectiveness vote

10.4 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC Panel engaged in a moderated discussion about use of targeted immune modulators for the treatment of rheumatoid arthritis with a Policy Roundtable that included two patient representatives, two clinical experts, two payer representatives, and representatives from two manufacturers. The Policy Roundtable discussion with the New England CEPAC Panel reflected multiple perspectives and opinions, and therefore, none of the recommendations below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below.

Table 26. Policy Roundtable Participants

Policy Roundtable	
Thomas Amoroso, MD, MPH Medical Director for Medical Policy Tufts Health Plan	**Himanshu R. Patel, D.O.** Sr. Medical Advisor, Musculoskeletal Medicine Eli Lilly and Company
Andreas Kuznik, PhD Senior Director of HEOR Regeneron Pharmaceuticals	**Sandie Preiss, MPA** National Vice President Arthritis Foundation
Andrew J. Laster, MD, FACR, CCD Board of Directors United Rheumatology Arthritis & Osteoporosis Consultants of the Carolinas	**Janet Stearns Wyatt, PhD, RN, FAANP** Patient, Volunteer for the Arthritis Foundation and Retired Nurse Practitioner
Matthew H. Liang, MD, MPH Professor of Medicine, Harvard Medical School Division of Rheumatology, Immunology, and Allergy Brigham and Women's Hospital	**Robert Zavoski, MD, MPH** Medical Director Connecticut Department of Social Services

The Roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Many of the Roundtable themes revolved around the existing system of price negotiation, which is based on manufacturer rebates and concessions across multiple indications that drive coverage policies for both commercial and public payers. This dynamic often results in high launch prices and substantial year-on-year price increases despite what appears to be vigorous competition among multiple drugs with relatively equivalent clinical outcomes.

Payers and Pharmacy Benefit Managers

1. **Consider including in prior authorization processes the requirement that conventional DMARD therapy dosing be optimized before initiating TIM therapy.**
   Clinicians on the Roundtable commented that patients often receive sub-optimal doses of conventional DMARDs such as methotrexate, and may therefore switch to TIM therapy before clinically necessary. Optimization strategies can include periodic testing for methotrexate polyglutamate levels to ensure therapeutic dosing, and should be employed in prior authorization processes as feasible.

2. **If step therapy protocols require patients to fail one or two TNFα inhibitors before switching to another TIM, develop a quick and transparent exception process for specific situations.**
   Patient testimony and clinicians on the Roundtable and CEPAC panel described onerous processes for getting exceptions to standard step-therapy protocols in RA, which typically involve a trial of adalimumab and/or etanercept before another TIM can be used. These processes, which may involve multiple phone calls at different points during the protocol, should be streamlined to allow for rapid exceptions in specific situations, such as clear contraindications, specific comorbidities, and issues of both geographic (e.g., infusion clinic) and financial (e.g., patient costs for infusion vs. self-administration) barriers in patient access.

3. **Payers should reach out to providers to learn from their experience with prior authorization in order to streamline and improve the process.**
   Payers on the Roundtable felt that their prior authorization processes are already reasonably streamlined, but providers disagreed. The ensuing discussion made it clear that there is no current vehicle for a collaborative effort to improve the process. Payers should therefore engage provider groups with a goal of developing an approach to prior authorization that both sides are comfortable with.

4. **Allow patients who are stable on effective treatment to remain on therapy when they change insurers.**
   New health plan enrollees with RA are sometimes required to start at the beginning of a step-therapy protocol even if they are on a stable later-line treatment that is working for them. This practice should be stopped, so that new patients can continue treatment without interruption.

5. **Reconsider step therapy if pricing becomes better aligned with clinical value.**

At current prices, our analysis indicates that all of the TIMs under review exceed common cost-effectiveness thresholds but have comparable levels of effectiveness. Step therapy is not an unreasonable approach in this case, as the focus can be on the less expensive (or most heavily discounted) TIMs. However, if pricing were to become better aligned with clinical value for these therapies, payers should reconsider whether step therapy remains a viable option.

6. **Negotiate better rebates and share savings with patients.**

The number of TIMs indicated for RA (nine, with two more nearing FDA approval) suggests that payers and PBMs with significant market leverage should be able to negotiate even more favorable discounts and rebates than they already receive. Additional leverage might be gained as an increasing number of biosimilars to the TNFα inhibitors enter the market, since these will also carry multiple indications and evidence accumulated to date suggests that they are clinically equivalent to the originator products. Savings from more aggressive negotiations should be shared with patients, who are struggling to keep up with year-over-year price increases.

7. **Increase transparency around the role of discounting and rebate practice in formulary design.**

Patients and providers expressed concerns around a lack of transparency regarding the connection between discounting/rebate practice and formulary design, as the terms are typically confidential and current designs do not always lead to cost-effective choices. For example, many of the TIMs in our review were more effective than adalimumab in head-to-head study and also less expensive, but are disadvantaged in most formulary designs. Transparency is an important first step in educating the general public on the role of rebates in formulary design as well as how the savings are shared between patients, PBMs, and health plans.

8. **Design innovative risk-sharing payment agreements, including pay-for-performance contracts with manufacturers, value-based contracting with accountable care organizations, and indication-specific pricing.**

The Roundtable discussion mentioned other efforts that might yield cost savings beyond price reductions and rebate negotiations. Pay-for-performance agreements have increased in popularity; as a relevant example, payers might receive an additional rebate for patients who do not achieve clinical remission during TIM therapy. Payers could also develop contracts with ACOs that share both financial risk and savings for optimized use and sequencing of TIM therapies. Finally, if TIMs with multiple indications beyond RA (e.g., Crohn's disease, psoriasis) show markedly different clinical performance and costs, indication-specific formularies should be developed to recognize these differences.

Providers, Clinical Societies, and Payers

9. **Develop clinical guidelines and coverage policies that closely align with the evidence on outcomes of patients stratified by prognostic factors, allowing for earlier use of TIM therapy in patients with poor prognostic factors.**

Patients with RA need to be brought under control quickly. Better risk stratification can help to identify those patients who are unlikely to achieve rapid control. Major guideline statements already recognize the need for aggressive treatment in patients with poor prognostic factors such as high levels of inflammatory markers or early joint erosions; coverage policies and provider practice should follow suit.

Clinical Societies and Manufacturers

10. **Establish standardized assessments to allow for rigorous direct and indirect comparisons of evidence across studies and therapeutic alternatives.**

The field of rheumatology should be applauded for its work in developing core sets of clinical and patient-reported outcome measures with strong internal and external validity in RA clinical studies. However, these measures have proliferated, with variations on the same theme (e.g., multiple disease activity and radiographic progression measures) making cross-study comparisons problematic. Clinical societies and manufacturers should collaborate to develop a standardized *and* limited "must have" list of clinical outcome measures for clinical trials and post marketing studies.

Public Policy Decision Makers

11. **In a dysfunctional market system, in order to protect patients today and improve their future access to innovative therapies, policy makers may need to consider some form of regulatory intervention to ensure that drug prices and price increases do not continue their current upward trajectory, taking them further from reasonable alignment with the added benefits to patients.**

Discussion highlighted that the current "marketplace" for RA drugs is not working to align prices with value in a way that would reward new innovative drugs while also reaping the benefits of competition to keep drugs affordable. One result is that patients and clinicians face heavy access restrictions from insurers who lack other effective methods to control unsustainable cost increases. In addition, innovative companies cannot compete on price for RA-specific products in the face of rebate-driven agreements that cover multiple indications beyond RA. If some or all of the measures described above cannot be

implemented or are not effective, policymakers should consider some form of regulatory intervention to address rebate structures and price increases in order to increase true competition and better protect patients.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).

Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
#		**Checklist item**
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. Search Strategies of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled trials on September 2, 2016; updated February 13, 2017

1	**exp Arthritis, Rheumatoid/**
2	((rheumatoid or rheumatic or rheumat$) adj3 (arthrit$ or diseas$ or condition$)).ti,ab.
3	1 or 2
4	exp abatacept/
5	(abatacept or orencia).ti,ab.
6	exp rituximab/
7	(rituximab or rituxan or mabthera).ti,ab.
8	(tocilizumab or atlizumab or actemra or roactemra).ti,ab.
9	exp infliximab/
10	(infliximab or remicade).ti,ab.
11	exp etanercept/
12	(etanercept or enbrel).ti,ab.
13	exp adalimumab/
14	(adalimumab or humira).ti,ab.
15	exp certolizumab pegol/
16	(certolizumab pegol or cimzia).ti,ab.
17	(golimumab or simponi).ti,ab.
18	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19	3 and 18
20	limit 19 to yr="2010 -Current"
21	(tofacitinib or tasocitinib or tofacitinib citrate or Xeljanz).ti,ab.
22	(sarilumab or REGN88).ti,ab.
23	(baricitinib or LY3009104 or INCB028050).ti,ab.
24	21 or 22 or 23

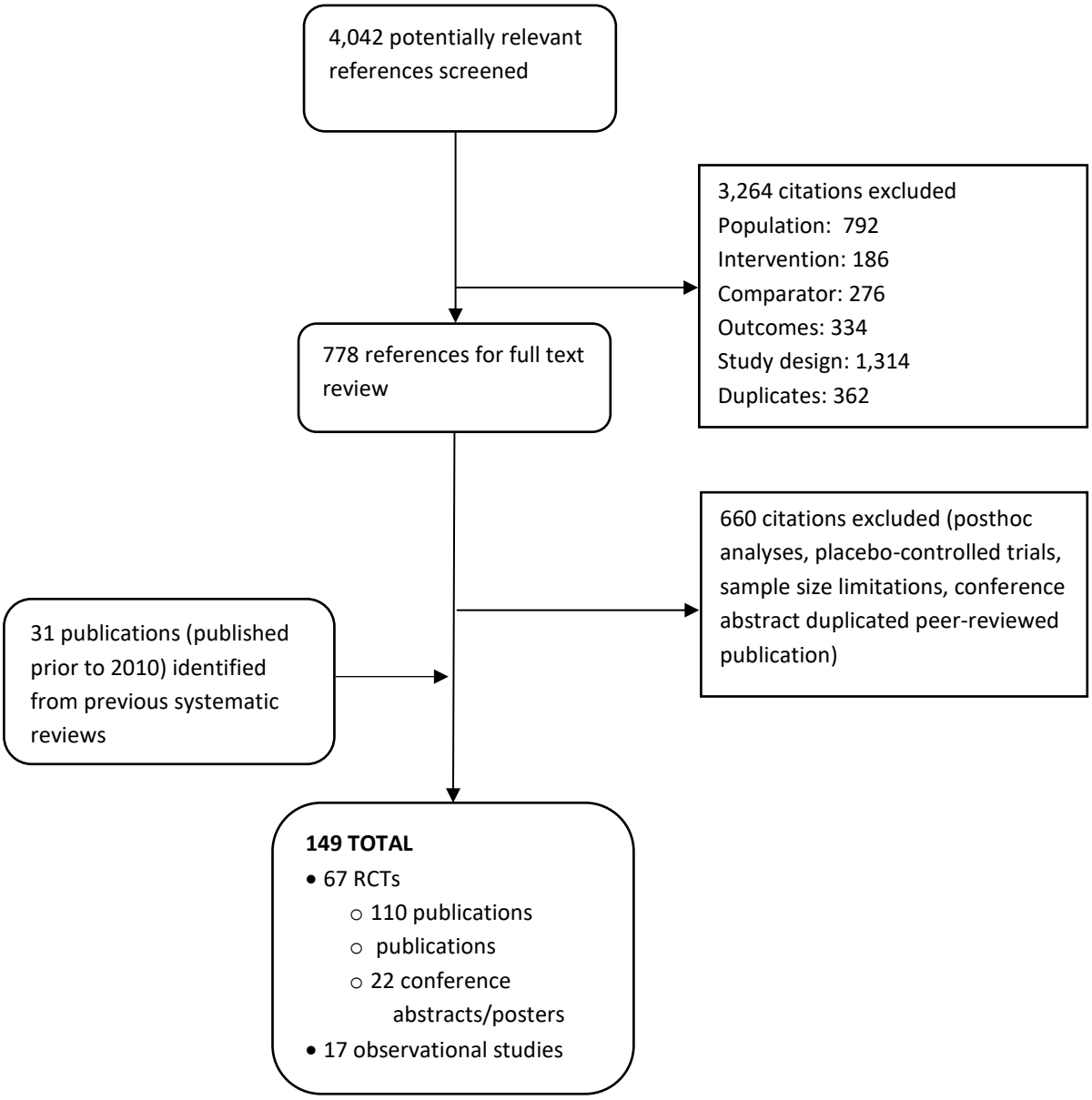
25	24 and 3
26	25 or 20
27	(animals not (humans and animals)).sh.
28	26 not 27
29	limit 28 to english language
30	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.
31	cohort studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or comparative study.pt
32	control Groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or (randomi?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.
33	31 or 32
34	29 not 30
35	34 and 33
36	Remove duplicates from 35

Table A3. Search Strategies of EMBASE on September 2, 2016; updated February 13, 2017

#1	**'rheumatoid arthritis'/exp**
#2	((rheumatoid OR rheumatic OR rheumat*) NEAR/3 (arthrit* OR diseas* OR condition*)):ab,ti
#3	#1 OR #2
#4	'abatacept'/exp OR abatacept:ab,ti OR orencia:ab,ti
#5	'rituximab'/exp OR rituximab:ab,ti OR rituxan:ab,ti OR mabthera:ab,ti
#6	'tocilizumab'/exp OR tocilizumab:ab,ti OR atlizumab:ab,ti OR actemra:ab,ti OR roactemra:ab,ti
#7	'infliximab'/exp OR infliximab:ab,ti OR remicade:ab,ti
#8	'etanercept'/exp OR etanercept:ab,ti OR enbrel:ab,ti

#9	'adalimumab'/exp OR adalimumab:ab,ti OR humira:ab,ti
#10	'certolizumab pegol'/exp OR 'certolizumab pegol':ab,ti OR cimzia:ab,ti
#11	'golimumab'/exp OR golimumab:ab,ti OR simponi:ab,ti
#12	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
#13	#3 AND #12
#14	#13 AND [2010-2016]/py
#15	#14 AND ('chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#16	#14 NOT #15
#17	'tofacitinib'/exp OR tofacitinib:ab,ti OR tasocitinib:ab,ti OR 'tofacitinib citrate':ab,ti OR xeljanz:ab,ti
#18	'baricitinib'/exp OR baricitinib:ab,ti
#19	'sarilumab'/exp OR sarilumab:ab,ti
#20	#17 OR #18 OR #19
#21	#3 AND #20
#22	#21 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#23	#21 NOT #22
#24	#16 OR #23
#25	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#26	'human'/exp
#27	#25 AND #26
#28	#25 NOT #27
#29	#24 NOT #28
#30	#29 AND [english]/lim
#31	#30 AND [medline]/lim
#32	#30 NOT #31

Figure A1. PRISMA flow chart showing results of literature search for rheumatoid arthritis



Appendix B. Public and Representative Private Insurer Coverage Policies

Table B1: Coverage Policies for New England Commercial Payers

	Connecticut		Maine		Massachusetts			New Hampshire		Rhode Island		Vermont
	Anthem (Wellpoint Inc Group)	Connecticare	Anthem (Wellpoint Inc Group)	HPHC Maine	BCBS of MA	Neighborhood Health Plan	Tufts Health Plan	Anthem (Wellpoint Inc Group)	HPHC New Hampshire	BCBS of RI	Neighborhood Health Plan of RI	BCBS of VT
TNFα inhibitors												
etanercept (Tradename: Enbrel; Manufacturer: Amgen)												
How many cDMARDs	1	1	1	1	1	1	1	1	1	1	1	2
How many TNFs	0	0	0	0	0	0	0	0	0	0	0	0
etanercept AND adalimumab?	No	No	No	No	No	No	No	No	No	No	No	No
Preferred Agent	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
infliximab (Tradename: Remicade; Manufacturer: Janssen)												
How many cDMARDs	1	1	1	NL	1	1	1	1	1	1	1	2
How many TNFs	0	2	2	NL	2	0	0	0	2	0	0	2
etanercept AND adalimumab?	No	No	No	NL	No	No	No	No	Yes	No	No	Yes
Preferred Agent	Yes	No	Yes	NL	No	Yes	Yes	Yes	No	Yes	Yes	No
adalimumab (Tradename: Humira; Manufacturer: AbbVie)												
How many cDMARDs	1	1	1	1	1	1	1	1	1	1	1	2
How many TNFs	0	0	0	0	0	0	0	0	1	0	0	0

	Connecticut		Maine		Massachusetts			New Hampshire		Rhode Island		Vermont
	Anthem (Wellpoint Inc Group)	Connecticare	Anthem (Wellpoint Inc Group)	HPHC Maine	BCBS of MA	Neighborhood Health Plan	Tufts Health Plan	Anthem (Wellpoint Inc Group)	HPHC New Hampshire	BCBS of RI	Neighborhood Health Plan of RI	BCBS of VT
etanercept AND adalimumab?	No	No	No	No	No	No	No	No	No	No	No	No
Preferred Agent	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
certolizumab pegol (Tradename: Cimzia; Manufacturer: UCB)												
How many cDMARDs	1	1	1	1	1	1	1	1	1	1	1	2
How many TNFs	2	2	2	1	2	0	0	2	1	2	0	2
etanercept AND adalimumab?	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes
Preferred Agent	No	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes	No
golimumab (Tradename: Simponi; Manufacturer: Janssen)												
How many cDMARDs	1	1	1	1	1	1	1	1	1	1	1	2
How many TNFs	0	2	2	1	2	0	0	0	1	2	0	2
etanercept AND adalimumab?	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes
Preferred Agent	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	No
CD20- directed cytolytic antibodies												
rituximab (Tradename: Rituxan; Manufacturer: Genentech)												
How many cDMARDs	1	1	0	NL	1	NL	1	1	1	1	NL	2
How many TNFs	1	2	1	NL	2	NL	1	1	2	2	NL	2
etanercept AND adalimumab?	No	No	No	NL	Yes	NL	No	No	No	No	NL	Yes
Preferred Agent	No	Yes	No	NL	No	NL	No	No	No	No	NL	No
Tcell inhibitors												
abatacept (Tradename: Orencia; Manufacturer: Bristol Myers Squibb)												

	Connecticut		Maine		Massachusetts			New Hampshire		Rhode Island		Vermont
	Anthem (Wellpoint Inc Group)	Connecticare	Anthem (Wellpoint Inc Group)	HPHC Maine	BCBS of MA	Neighborhood Health Plan	Tufts Health Plan	Anthem (Wellpoint Inc Group)	HPHC New Hampshire	BCBS of RI	Neighborhood Health Plan of RI	BCBS of VT
How many cDMARDs	1	1	1	1	1	1	1	1	1	1	1	2
How many TNFs	2	2	2	1	2	1	1	2	2	2	1	2
etanercept AND adalimumab?	No	No	No	No	Yes	0	0	No	No	No	0	Yes
Preferred Agent	No	No	No	No	No	No	No	No	No	No	No	No
IL-6 inhibitors												
tocilizumab (Tradename: Actemra; Manufacturer: Genentech)												
How many cDMARDs	NF	1	1	1	1	1	1	1	1	1	1	2
How many TNFs	NF	2	2	1	2	0	2	2	1	2	0	2
etanercept AND adalimumab?	NF	No	No	No	Yes	No	Yes	No	No	No	No	Yes
Preferred Agent	NF	No	No	No	No	Yes	No	No	No	No	Yes	No
JAK inhibitors												
tofacitinib (Tradename: Xeljanz; Manufacturer: Pfizer)												
How many cDMARDs	1	1	1	1	1	1	1	NL	NL	1	1	2
How many TNFs	2	2	2	0	2	0	0	NL	NL	2	0	2
etanercept AND adalimumab?	No	No	No	No	Yes	No	No	NL	NL	No	No	Yes
Preferred Agent	No	No	No	Yes	No	Yes	Yes	NL	NL	No	No	No

Table B2. Coverage Policies for New England Medicaid Programs

New England Medicaid Programs						
	Connecticut	Maine	Massachusetts	New Hampshire	Rhode Island	Vermont
TNFα inhibitors						
adalimumab (Tradename: Humira; Manufacturer: AbbVie)						
Step Therapy	Yes	Yes	NL	Yes	NL	NL
PA	Yes	No	Yes	Yes	No	Yes
Preferred Agent	Yes	Yes	No	Yes	Yes	Yes
certolizumab pegol (Tradename: Cimzia; Manufacturer: UCB)						
Step Therapy	Yes	Yes	NL	Yes	NL	NL
PA	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	No	No	No	No	No	No
etanercept (Tradename: Enbrel; Manufacturer: Amgen)						
Step Therapy	Yes	Yes	NL	Yes	NL	NL
PA	Yes	No	Yes	Yes	No	Yes
Preferred Agent	Yes	Yes	No	Yes	Yes	Yes
golimumab (Tradename: Simponi; Manufacturer: Janssen)						
Step Therapy	Yes	Yes	NL	Yes	NL	NL
PA	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	No	No	No	No	No	No
infliximab (Tradename: Remicade; Manufacturer: Janssen)						
Step Therapy	Yes	Yes	NL	Yes	NL	NL
PA	Yes	No	Yes	Yes	Yes	Yes
Preferred Agent	No	No	No	No	No	No
CD20- directed cytolytic antibodies						
rituximab (Tradename: Rituxan; Manufacturer: Genentech)						
Step Therapy	NL	NL	Yes	NL	NL	NL
PA	Yes	NL	Yes	NL	NL	NL
Preferred Agent	NL	NL	No	NL	NL	NL
Tcell inhibitors						
abatacept (Tradename: Orencia; Manufacturer: Bristol Myers Squibb)						
Step Therapy	Yes	Yes	NL	Yes	NL	NL
PA	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	No	No	No	No	No	No
IL-6 inhibitors						
tocilizumab (Tradename: Actemra; Manufacturer: Genentech)						
Step Therapy	Yes	Yes	NL	Yes	NL	NL
PA	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	No	No	No	No	No	No

New England Medicaid Programs						
	Connecticut	Maine	Massachusetts	New Hampshire	Rhode Island	Vermont
JAK inhibitors						
tofacitinib (Tradename: Xeljanz; Manufacturer: Pfizer)						
Step Therapy	Yes	Yes	NL	Yes	NL	NL
PA	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	No	No	No	No	No	No

Appendix C. Comparative Clinical Effectiveness Supplemental Information

Methods: Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F)[72] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Methods of Network Meta-Analysis

Network meta-analyses were conducted to determine comparative effectiveness using measures of treatment response (ACR 20/50/70) and radiographic progression of joint damage (modified total Sharp score).

Selection of trials

Trials included in the NMA were selected from the evidence base according to additional inclusion criteria listed below.

1) RCTs reporting ACR20, ACR50, or ACR70 at approximately 24 weeks and RCTs reporting Sharp score at approximately 52 weeks. The selection of these timepoints is in line with previous health technology assessments and is considered appropriate by clinical experts to assess the treatment effects on these clinical measures.[25]
2) RCTs were limited to those involving patients who have failed conventional DMARDs including methotrexate.
3) RCTs were not excluded on the basis of geographical location.
4) ACR estimates were obtained from pre-crossover follow-up timepoints in all trials. Crossover did occur in several trials prior to Sharp score calculation, but data were typically imputed in trials to account for this.

A number of assumptions were made:

1) All conventional DMARDs (e.g., methotrexate, sulfasalazine) have equivalent efficacy so a single estimate of conventional DMARD performance could be estimated.
2) Different types of administration of the same agents (i.e., iv vs. sc) may have differential performance, and so were evaluated separately in the NMA.
3) Incremental treatment effect is the same regardless of the ACR cut-off (i.e., 20 vs. 50 vs. 70), allowing us to use the data more efficiently and reduce variation.
4) Despite different scaling properties, modified Sharp scores measured the same underlying construct of radiographic damage so that they can be converted to a common metric using standardized mean difference (SMD).

Our primary analysis included RCTs based on populations who were TIM-naïve as well as mixed populations with a minority (approximately 20% or less) of TIM-experienced patients. Sensitivity analyses were undertaken to evaluate trials that focused exclusively on TIM-naïve patients.

Statistical models

ACR outcomes are ordered categorical data with four distinct groups: i.e. ACR<20/No response, ACR20, ACR50, and ACR70, representing an improvement in symptoms of less than 20%, at least

20%, at least 50%, and at least 70%, respectively. These categories can be treated as mutually exclusive, meaning patients cannot be in more than one category. Therefore, a multinomial likelihood model with a probit link was used. Model functions have been previously published.[26] While the primary analysis did not adjust for any covariables, an additional model was explored to adjust for ACR response rate in the conventional DMARD arm of each trial.

The modified total Sharp score is a continuous measure that is calculated on different scales depending on its modification (e.g., Van der Heijde, Genant, or other modified score). In order to aggregate and synthesize the data into a common metric representing the difference between treatment and control, a standardized mean difference (SMD) method was used, as suggested by Lassere et al.[146] SMD was calculated as the difference in mean change from baseline divided by the pooled standard deviation (SD). When data on the pooled SD were missing, it was imputed based on available p-values or 95% confidence intervals, assuming SDs of treatment arms were the same. In order to support comparative value analyses, SMD data were also retransformed to estimates of absolute Sharp score change relative to conventional DMARDs using the equation: (SMD from the NMA) × (pooled SD on the Van der Heijde scale from trials).

All statistical analyses were run within a Bayesian framework with WinBUGS 1.4.3. Review of the deviance information criterion (DIC) statistics as well as comparison of the residual deviance (resdev) to the number of unconstrained data points was used to assess the best model fit under multiple alternative assumptions.[147] Given the expectation of at least some degree of heterogeneity in patient populations and/or study design, there is a general preference for a random-effects approach. But fixed-effect approaches are generally taken when an inadequate evidence base results in large numbers of single connections in the network. A total of 50,000 iterations each were employed for both "burn-in" (for model convergence) and model (for model results) simulations. Relative risks and probabilities of patients having a given ACR response state and SMD compared to cDMARDs on Sharp score were generated. We modified WinBUGS code from a technology assessment published by the National Institute for Health and Care Excellence [26] for ACR outcomes; for the Sharp score analysis, we adapted code from a published NMA of antidepressants for major depressive disorder.[148] All codes are provided in Appendix C.

Additional Comparative Clinical Effectiveness Results

Table C1: DAS28-ESR measure and Number Needed Treated (NNT) in trials of TIMs versus conventional DMARDs

Intervention	DAS28-ESR remission rate		P value	NNT	Number of trials (Total N)
	TIM	Conventional DMARD			
TIMs plus conventional DMARD vs. conventional DMARD TIM Naïve and Mixed Population					
Rituximab[149]	9	2	<0.01	14	1
Abatacept iv[23]	11	3	NR	NC	1
Tocilizumab iv[150-152]	30-38	2-3	<0.001	3-4	3
Tocilizumab sc[153]	32	4	<0.001	4	1
Tofacitinib[95,154]	6-9	1-3	<0.05	17-20	2
Baricitinib[21,155]	16-25	1-5	<0.05	4-8	2
Adalimumab[21,95]	7-18	1-5	<0.05	8-18	2
Certolizumab Pegol[156,157]	17-26	0-6	<0.0001	5-6	2
Etanercept[77,158]	22-25	4-14	<0.03	5-11	2
Golimumab iv[159]	18	5	<0.001	8	1
Golimumab sc [160,161]	20-35	6-7	<0.001	4-7	2
Infliximab[23]	13	3	NR	NC	1
TIMs plus conventional DMARD vs. conventional TIM Experienced					
Sarilumab†[162,163]	29-34	7-14	<0.0001	4-5	2
Baricitinib[90]	9	3	<0.05	17	1
TIMs monotherapy vs. conventional					
Tocilizumab[84,85]	43-59	1.6-3	<0.001	2	2
Etanercept[81]	34	19	<0.01	7	1

* Time point was approximately 6 months for all drugs, except for etanercept monotherapy which was reported only at 52 weeks; †DAS28-CRP was reported for sarilumab because DAS28-ESR was not used in any of studies reviewed

Table C2: Disease activity outcomes in biosimilar studies after 24-30 weeks of follow-up

Treatment	N	DAS28-ESR or CRP	DAS28 mean change from baseline	% achieving DAS28 remission	% achieving CDAI remission	% achieving SDAI remission
Yoo 2015 trial at 24 weeks[164,165]						
Rituximab-bio + MTX	103	DAS28-ESR & CRP	ESR-2.1; CRP-2.0	12.5†	NR	NR
Rituximab-ref + MTX	51	DAS28-ESR & CRP	ESR-2.2; CRP-2.1	3.9	NR	NR
Williams 2016 trial at 24 weeks[166]						
Rituximab-bio + MTX	71	DAS28-CRP	-1.9	NR	NR	NR
Rituximab-ref (EU) + MTX	72	DAS28-CRP	-2	NR	NR	NR
Rituximab-ref (US) + MTX	71	DAS28-CRP	-2.2	NR	NR	NR
HERA trial at 24 weeks[167]						
Etanercept-bio + MTX	115	DAS28	-2.56	34	NR	NR
Etanercept-ref + MTX	118	DAS28	-2.54	31	NR	NR
Choe 2017 trial at 30 weeks[168]						
Infliximab-bio + MTX	290	DAS28-ESR	-2.3	14.6	8.7	9.5
Infliximab-ref + MTX	293	DAS28-ESR	-2.3	15.9	11.7	10.9
Takeuchi 2015 trial at 30 weeks[169]						
Infliximab-bio	50	DAS28-ESR & CRP	ESR-2.2; CRP-2.1	NR	NR	NR
Infliximab-ref	51	DAS28-ESR & CRP	ESR-2; CRP-2	NR	NR	NR
PLANETRA trial at 30 weeks[170]						
Infliximab-bio + MTX	302	DAS28-ESR & CRP	NR	ESR 36; CRP 61	NR	NR
Infliximab-ref + MTX	304	DAS28-ESR & CRP	NR	ESR 27; CRP 56	NR	NR

†statistical significance not reported; ***p <0.001; **p<0.01; *p<0.05

Table C3. Ranges of ACR20/50/70 at approximately 6 months' follow-up

	ACR20		ACR50		ACR70		No.
	TIM	cDMARD	TIM	cDMARD	TIM	cDMARD	RCTs
TIM-Naïve and Mixed Population							
Rituximab[149,171]	50.6 - 51.7	23.3 - 28.6	25.9 - 26.7	9.3 - 11.3	8.3 - 10.0	1.6 - 5.2	2
Abatacept (iv)[172-174]	60.0 - 77.0	21.2 - 39.7	36.5 - 45.9	6.1 - 16.8	16.5 - 21.3	0 - 6.5	3
Abatacept (sc)	*No studies identified*						
Tocilizumab (iv)[152]	60.8	24.5	37.6	9.0	20.5	2.9	1
Tocilizumab (iv) monotherapy[85]	80.3	25.0	49.2	10.9	29.5	6.3	1
Tocilizumab (sc)[153]	61.0	32.0	40.0	12.0	20.0	5.0	1
Sarilumab[89]	67.0	34.0	47.0	18.0	27.0	9.0	1
Tofacitinib[78,154]	51.5 - 52.1	25.3 - 30.8	32.4 - 33.3	8.3 - 12.6	13.0 - 14.6	1.3 - 3.1	2
Baricitinib[21,175]	65.0 – 74.0	37.0 -42.0	44.0 – 50.0	19.0 - 21.0	24.0 – 30.0	8.0	2
Adalimumab[97,176-179]	52.8 - 67.2	14.5 - 36.5	28.9 - 55.2	8.1 – 19.0	14.8 - 26.9	2.5 - 7.9	5
Certolizumab Pegol[156,180-182]	45.9 - 73.2	8.7 - 24.7	18.0 - 54.9	3.1 - 16.9	0 - 29.3	0.8 - 1.3	4
Etanercept[77,82,158,183]	56.0 – 74.0	23.2- 58	36.0 – 83.2	14.0 - 50.0	17.0 - 34.8	2.0 – 11.3	3
Etanercept monotherapy[183]	73.8	28.0	46.6	14.0	21.4	2.0	1
Golimumab (iv)[184]	64.0	32.0	34.9	13.2	17.7	4.1	1
Golimumab (sc)[160,161,185]	42.4 - 70.9	15.9 - 33.0	18.9 - 41.9	6.8 - 14.8	6.1 - 26.7	1.5 - 5.7	3
Infliximab[186-188]	50.0 - 58.0	20.0 - 30.6	27.0 - 33.8	5.0 - 9.7	8.0 - 14.0	0 - 4.7	3
TIM-experienced populations							
Rituximab[93]	51.0	18.0	27.0	5.0	12.0	1.0	1
Abatacept (iv)[91]	50.4	19.5	20.3	3.8	10.2	1.5	1
Tocilizumab (iv)[189]	50.0	10.1	28.8	3.8	12.4	1.3	1
Sarilumab[88,89,162]	61.0 – 66.4	33.0 - 34.0	41.0	12.0 - 18.0	14.8 - 19.0	3.0 - 7.0	2
Baricitinib[190]	46.0	27.0	29.0	13.0	17.0	3.0	1

Table C4. Ranges of ACR20/50/70 in biosimilar studies at 24-30 weeks of follow-up

Biosimilar studies	Study arm	ACR20, %	ACR50, %	ACR70, %
Yoo 2013[165,191] Week 24	RTX-bio+MTX (n=103)	63.0	37.0	16.0
	RTX-ref+MTX (n=51)	66.7	31.3	14.6
Williams 2016[166]	RTX-bio + MTX (n=71)	58	23	19
	RTX-ref (EU) + MTX (n=72)	60	38	18
	RTX-ref (US) + MTX (n=71)	78	33	20
Jani 2015[192] Week 12	ADA-bio+MTX (n=60)	78.3	43.3	13.3
	ADA-ref+MTX (n=60)	79.7	44.1	15.3
Cohen 2015[193] Week 24	ADA-bio+MTX (n=264)	74.6	49.2	26.0
	ADA-ref+MTX (n=262)	72.4	52.0	22.9
Weinblatt 2015[194] Week 24	ADA-bio (n=271)	75.2	38.3	19.2
	ADA-ref (n=273)	72.0	39.8	20.3
HERA[167] Week 24	ETN-bio+MTX (n=115)	79.1	59.0	28.4
	ETN-ref+MTX (n=118)	75.6	46.7	28.2
Emery 2015[195] Week 24	ETN-bio+MTX (n=299)	73.8	43.0	23.2
	ETN-ref+MTX (n=297)	71.7	39.1	19.9
Kay 2014[196] Week 16	IFX-bio (n=127)	85.0	NR	NR
	IFX-ref (n=62)	85.5	NR	NR
Choe 2017[168] Week 30	IFX-bio+MTX (n=290)	55.5	30.7	15.5
	IFX-ref+MTX (n=293)	59.0	33.8	17.1
PLANETRA[170] Week 30	IFX-bio+MTX (n=302)	60.9	35.1	16.6
	IFX-ref+MTX (n=304)	58.6	34.2	15.5
Takeuchi 2015[169] Week 30	IFX-bio (n=50)	78.0	54.0	32.0
	IFX-ref (n=51)	64.7	47.1	27.5

Table C5. Radiographic progression in trials of TIMs versus conventional DMARDs with approximately one year of follow-up

	Study arm	Mean change in mTSS from baseline (SD)[Ω]	Time of evaluation (weeks)	Significance
Biologic-naïve and mixed populations				
RA-SCORE[171β]	MTX (n=63)	1.4 (SD NR)	52	p=0.002
	RTX+MTX (n=60)	0.3 (SD NR)		
AIM[173β]	MTX (n=195)	2.32 (NR)	52	p<0.01
	ABTiv+MTX (n=391)	1.21 (NR)		
SAMURAI[84]*	cDMARD (n=143)	6.1 (4.2, 8.0)	52	p<0.01
	TCZ (n=157)	2.3 (1.5, 3.2)		
LITHE[197β]	MTX (n=294)	1.2 (3.1)	52	Adjusted mean difference (95% CI) 4mg: -0.8 (-1.1, -0.5) 8mg: -0.9 (-1.2, -0.6)
	4mg TCZ+MTX (n=343)	0.3 (1.3)		
	8mg TCZ+MTX (n=353)	0.3 (1.0)		
MOBILITY[162]	MTX (n=398)	2.8 (7.7)	52	p<0.0001
	SAR+MTX (n=398)	0.3 (4.6)		
ORAL-Scan[78]	MTX (n=160)	0.9 (NR)	52	p=0.0558
	TOF+MTX (n=321)	0.3 (NR)		
RA-BEAM[97]	MTX (n=452)	1.80 (NR)	52	BAR+MTX vs. MTX: p≤0.001 ADA+MTX vs. MTX: p≤0.001
	BAR+MTX (n=473)	0.71 (NR)		
	ADA+MTX (n=312)	0.60 (NR)		
DE019[179α]	MTX (n=172)	2.7 (6.8)	52	p≤0.001
	ADA+MTX (n=183)	0.1 (4.8)		
RAPID1[181]	MTX (n=199)	2.8 (NR)	52	p<0.001
	CTZ+MTX (n=393)	0.4 (NR)		
TEMPO[86]*	MTX (n=206/206)	1.5 (0.42, 2.58)/ 3.3 (1.18, 5.50)	52/104	Weeks 52 and 104 ETN mono vs. MTX: p<0.05 ETN+MTX vs. MTX: p<0.05
	ETN mono (n=202/203)	0.3 (-0.18, 0.84)/ 1.1 (0.13, 2.07)		
	ETN+MTX (n=212/213)	-0.8 (-1.16, 0.44)/ -0.6 (-1.05, -0.06)		
Takeuchi 2013[81]	MTX (n=171)	9.8 (15.2)	52	p<0.0001
	ETN (n=181)	3.3 (9.8)		
O'Dell 2013[77]	Triple cDMARD (n=151)	0.5 (1.9)	48	p=NS
	ETN+MTX (n=153)	0.3 (3.3)		
GO-FORWARD[106,198]	MTX (n=122)	1.1 (4.7)/1.2 (4.4)	52/104	p=NS/p=NR
	GOLsc+MTX (n=86)	0.9 (4.9)/0.5 (3.3)		
Swefot[199]	Triple cDMARD (n=104/109)	5.0 (10.6)/7.2 (12.7)	52/104	Mean difference (95% CI) Wk 52: 2.1 (-0.30, 4.48) Wk 104: 3.2 (0.14, 6.3); p=0.009)
	IFX+MTX (n=102/106)	3.0 (6.1)/4.0 (10.1)		
ATTRACT[200]	MTX (n=64)	7 (10.3)	54	vs. MTX

	Study arm	Mean change in mTSS from baseline (SD)[Ω]	Time of evaluation (weeks)	Significance
	3mg/kg IFX+MTX (n=71)	1.3 (6.0)		3 mg/kg: p<0.001 10 mg/kg: p<0.001
	10mg/kg IFX+MTX (n=77)	0.2 (3.6)		
Biologic-experienced populations				
REFLEX[β201,202]	MTX (n=184/187)	2.3/2.8 (SD NR)	56/104	p=0.005/p<0.0001
	RTX+MTX (n=273/281)	1.0/1.1 (SD NR)		
MOBILITY[203∞]	MTX (n=82)	2.2	52	p<0.05
	SAR+MTX (n=78)	0.2		

Ω Van der Heijde modified Sharp score unless otherwise noted; α modified total sharp score (scale 0-398); *95% confidence interval; β Genant modified total sharp score; ∞subpopulation of MOBILITY trial (patients included in entry for mixed population)

Table C6. Radiographic progression in biosimilar trials

	Study arm	Mean change in mTSS from baseline (SD)*	Time of evaluation (weeks)	Significance	% Non-progression at Year 1[α]
Vencovsky 2015[204]	ETN-bio+MTX (n=299)	0.45 (NR)	52	NR	NR
	ETN-ref+MTX (n=297)	0.74 (NR)			
Choe 2017[205]	IFX-bio+MTX (n=291)	0.38 (NR)	54	NR	NR
	IFX-ref+MTX (n=293)	0.37 (NR)	54		
PLANETRA[206]	IFX-bio+MTX (n=302)	1.3 (9.3)	54	NS	51.7
	IFX-ref+MTX (n=304)	0.7 (7.0)			51.4

*Van der Heijde method reported in PLANETRA, other studies did not specify Sharp method; α ≤0 units of change from baseline; NR=not reported; NS=not significant

Table C7. Ranges HAQ-DI outcome in trials of TIMs versus conventional DMARDs at approximately 6 months

TIMs	HAQ-DI mean change from baseline		% of patients with change ≥ predefined MCID threshold‡	
	Absolute difference	Number of trials	Absolute difference	Number of trials
TIMs plus conventional DMARD vs. conventional DMARD				
Rituximab[149,171,207,208]	-0.25 to -0.37***	3	11***	1
Abatacept iv[23,91,172,174]	-0.34 to -0.4***	2	21-37	4
Abatacept sc	*No studies identified*		*No studies identified*	
Tocilizumab iv[152,189]	-0.21 to -0.34***	3	10 to 26***	2
Tocilizumab sc	*No studies identified*		*No studies identified*	
Sarilumab[209]	-0.2***	1	18***	1
Tofacitinib[78,154]	-0.28 to -0.31***	2	NR	--
Baricitinib[90,98,175,190,210,211]	-0.24 to -0.4***	4	18 to 28***	4
Adalimumab[21,176,179]	-0.25***	2	19***	1
Certolizumab Pegol[156,180,182]	-0.23 to -0.37	3	NR	--
Etanercept[83,158]	-0.3 to -0.8***	2	NR	--
Golimumab iv [184]	-0.50	1	22***	1
Golimumab sc [160,161,185]	-0.11 to -0.38***	3	24 to 29***	2
Infliximab[23,187]	0.4**	1	18*	1
TIMs monotherapy vs. conventional DMARD				
Tocilizumab mono[84,85]	NR	--	28 to 33***	2
Etanercept mono[81]	-0.3†	1	29***	1

†statistical significance not reported; ***p <0.001; **p<0.01; *p<0.05; ‡ Most studies used MCID threshold of 0.22 or 0.3; ¥ N was estimated from trial arms of interest i.e. approved (

Table C8. HAQ-DI in biosimilar trials after 24-30 weeks of follow-up

Treatment	N	HAQ-DI mean change from baseline:	% change ≥ predefined threshold
HERA trial at 24 weeks[167]			
Etanercept-bio + MTX	115	-0.49	NR
Etanercept-ref + MTX	118	-0.55	NR
Choe 2017 trial at 30 weeks[168]			
Infliximab-bio + MTX	290	-0.5	NR
Infliximab-ref + MTX	293	-0.5	NR
Takeuchi 2015 trial at 30 weeks[169]			
Infliximab-bio	50	-0.6	NR
Infliximab-ref	51	-0.5	NR
PLANETRA trial at 30 weeks[170]			
Infliximab-bio + MTX	302	-0.55	NR
Infliximab-ref + MTX	304	-0.49	NR

Network Meta-Analysis Results

For the ACR response network meta-analysis, a comparison of residual deviance (resdev) and deviance information criterion (DIC) between the unadjusted model and the model adjusted for conventional DMARD response rate showed no material differences (resdev: 497.1 vs. 497.2 for unadjusted vs. adjusted; DIC: 1765.4 vs. 1766.2 respectively), indicating no effect modification. Further, the response-adjusted model produced universally lower estimates of treatment effect than might be expected from examination of individual trial results. We therefore opted to retain the unadjusted model as our primary analysis.

Figure C1. Network Diagram for Analysis of ACR (Mixed Population, combination therapy)

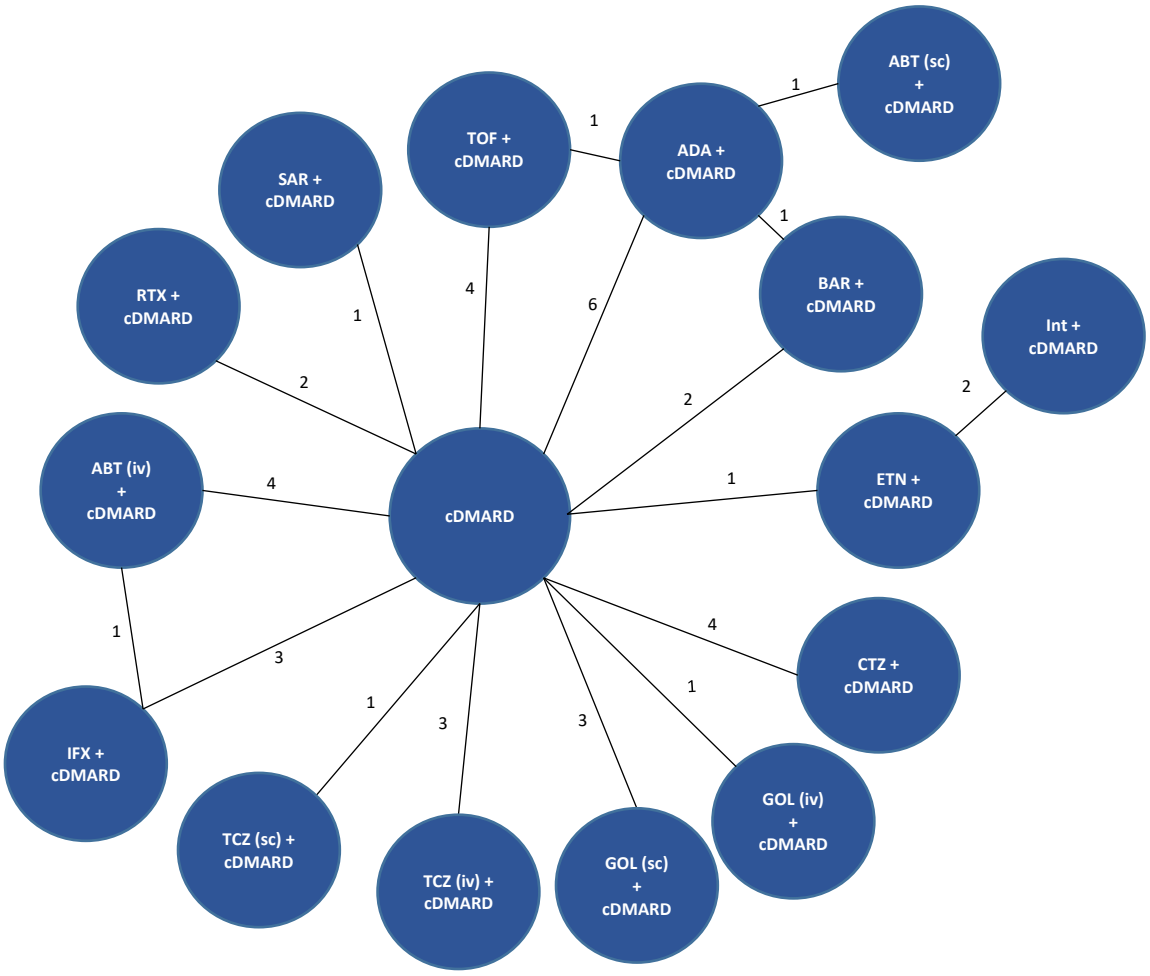


Table C9. ACR Data used in NMA (Mixed population, combination therapy)

Interventions				Mean disease duration	Intervention 1					Intervention 2				
Trial Name	1	2	3	Weeks	No response	ACR20	ACR50	ACR70	n	No response	ACR20	ACR50	ACR70	n
AIM[173]	cDMARD	ABTiv + cDMARD		449	132	50	23	14	219	139	121	87	86	433
AMPLE[94]	ADA + cDMARD	ABTsc + cDMARD		94	117	72	65	74	328	108	65	68	77	318
ARMADA[176]	cDMARD	ADA + cDMARD		607	53	4	2	3	62	22	8	19	18	67
ATTEST[23]	cDMARD	ABTiv + cDMARD	IFX + cDMARD	405	64	24	12	10	110	52	41	31	32	156
ATTRACT[187]	cDMARD	IFX + cDMARD			67	13	4	0	84	82	38	26	22	168
DE019[179]	cDMARD	ADA + cDMARD		569	141	40	14	5	200	76	50	38	43	207
ETN309[183]	cDMARD	ETN + cDMARD	ETN	341	36	7	6	1	50	27	22	27	25	101
GO-FORTH[160]	cDMARD	GOLsc + cDMARD		455	59	16	8	5	88	25	25	13	23	86
GO-FORWARD[87]	cDMARD	GOLsc + cDMARD		421	96	19	11	7	133	36	20	15	18	89
Kim2007[177]	cDMARD	ADA + cDMARD		356	40	14	4	5	63	25	12	14	14	65
LARA[158]	Int cDMARD	ETN + cDMARD		430	71	38	17	16	142	47	59	76	97	279

	Interventions			Mean disease duration	Intervention 1					Intervention 2				
O'Dell[77]	Int cDMARD	ETN + cDMARD		271	70	48	33	8	159	73	32	32	26	163
STAR[178]	cDMARD	ADA + cDMARD		541	207	75	25	11	318	150	76	45	47	318
START[188]	cDMARD	IFX + cDMARD		390	276	54	17	16	363	317	175	127	102	721
TOWARD[152]	cDMARD	TCZ + cDMARD		510	312	64	25	12	413	315	186	137	165	803
RA-BUILD[175]	cDMARD	BAR + cDMARD		390	132	47	31	18	228	79	48	45	55	227
MOBILITY[162]	cDMARD	SAR + cDMARD		460	265	67	37	29	398	134	83	83	99	399
ORAL Scan[78]	cDMARD	TOF + cDMARD		463	120	27	11	2	160	156	61	57	47	321
Kremer 2012[212]	cDMARD	TOF + cDMARD		473	45	7	11	6	69	37	10	10	14	71
LITHE[125]	cDMARD	TCZ + cDMARD		476	287	67	31	8	393	371	199	131	96	797
OPTION[213]	cDMARD	TCZ + cDMARD		398	151	31	18	4	204	195	66	86	71	418
RAPID1[181]	cDMARD	CTZ + cDMARD		319	171	12	9	6	199	162	85	62	84	393
RAPID2[180]	cDMARD	CTZ + cDMARD		308	116	7	3	1	127	105	61	41	39	246
Choy 2012[182]	cDMARD	CTZ + cDMARD		502	92	20	5	2	119	67	35	22	0	124
SERENE[149]	cDMARD	RTX + cDMARD		366	132	24	7	9	172	84	42	27	17	170

	Interventions			Mean disease duration	Intervention 1					Intervention 2				
BREVACTA[153]	cDMARD	TCZsc + cDMARD		577	149	44	15	11	219	170	92	88	87	437
Kremer 2003 [174]	cDMARD	ABTiv + cDMARD			77	28	12	2	119	46	27	23	19	115
ORAL Standard[95]	cDMARD	TOF + cDMARD	ADA + cDMARD	408	41	2	5	8	56	95	30	32	39	196
GO-FURTHER[184]	cDMARD	GOLiv + cDMARD		359	136	35	18	8	197	134	123	68	70	395
ORAL Sync[154]	cDMARD	TOF + cDMARD		462	110	29	15	5	159	151	59	64	41	315
Li 2015[185]	cDMARD	GOLsc + cDMARD		406	111	12	7	2	132	76	31	17	8	132
RA-SCORE[171]	cDMARD	RTX + cDMARD		242	45	11	6	1	63	29	15	11	5	60
Takeuchi 2013[172]	cDMARD	ABTiv + cDMARD		382	52	10	4	0	66	14	19	15	13	61
J-RAPID[156]	cDMARD	CTZ + cDMARD		296	58	6	12	1	77	22	15	21	24	82
RA-BEAM	cDMARD	ADA + cDMARD	BAR + cDMARD	na	307	88	54	39	488	112	66	79	73	330

	Interventions			Mean disease duration	Intervention 3				
ATTEST[23]	cDMARD	ABTiv + cDMARD	IFX + cDMARD	405	67	37	21	40	165

Interventions				Mean disease duration	Intervention 1			Intervention 2	
ORAL Standard[95]	cDMARD	TOF + cDMARD	ADA + cDMARD	408	105	36	38	20	199
RA-BEAM[21]	cDMARD	ADA + cDMARD	BAR + cDMARD	na	127	117	97	146	487

DIC=1455.0; resdev=369.1

Figure C2. League table, base case combination therapy NMA results, ACR20

ETN+cDMARD																
1.00 (0.62-1.40)	CTZ+cDMARD															
1.13 (0.70-1.69)	1.13 (0.89-1.55)	TCZiv+cDMARD														
1.17 (0.69-2.12)	1.18 (0.84-2.02)	1.04 (0.71-1.76)	SAR+cDMARD													
1.19 (0.73-1.87)	1.19 (0.91-1.73)	1.05 (0.76-1.52)	1.01 (0.60-1.57)	GOLsc+cDMARD												
1.20 (0.74-1.82)	1.20 (0.94-1.66)	1.06 (0.78-1.45)	1.02 (0.61-1.52)	1.01 (0.71-1.39)	ABTiv+cDMARD											
1.20 (0.71-2.25)	1.21 (0.85-2.15)	1.06 (0.71-1.87)	1.03 (0.58-1.87)	1.01 (0.65-1.78)	1.00 (0.67-1.75)	GOLiv+cDMARD										
1.21 (0.74-1.94)	1.21 (0.92-1.80)	1.07 (0.77-1.57)	1.03 (0.61-1.62)	1.02 (0.70-1.50)	1.01 (0.73-1.47)	1.01 (0.57-1.59)	BAR+cDMARD									
1.22 (0.71-2.30)	1.22 (0.86-2.19)	1.08 (0.73-1.89)	1.04 (0.59-1.92)	1.03 (0.66-1.81)	1.02 (0.68-1.79)	1.01 (0.55-1.88)	1.01 (0.64-1.78)	TCZsc+cDMARD								
1.22 (0.71-2.39)	1.23 (0.85-2.28)	1.08 (0.71-1.98)	1.04 (0.58-1.98)	1.03 (0.65-1.87)	1.02 (0.67-1.85)	1.02 (0.54-1.95)	1.01 (0.64-1.81)	1.00 (0.54-1.92)	ABTsc+cDMARD							
1.26 (0.78-2.00)	1.26 (0.97-1.85)	1.11 (0.81-1.60)	1.07 (0.64-1.66)	1.06 (0.74-1.54)	1.05 (0.79-1.45)	1.05 (0.60-1.63)	1.04 (0.71-1.51)	1.03 (0.59-1.60)	1.03 (0.57-1.63)	IFX+cDMARD						
1.27 (0.80-1.92)	**1.28 (1.01-1.75)**	1.13 (0.85-1.52)	1.09 (0.66-1.60)	1.07 (0.77-1.46)	1.06 (0.81-1.42)	1.06 (0.62-1.57)	1.05 (0.76-1.40)	1.04 (0.61-1.56)	1.04 (0.63-1.47)	1.01 (0.73-1.37)	ADA+cDMARD					
1.31 (0.82-2.08)	**1.32 (1.02-1.91)**	1.16 (0.86-1.66)	1.12 (0.67-1.72)	1.10 (0.78-1.59)	1.10 (0.81-1.55)	1.09 (0.63-1.70)	1.08 (0.76-1.56)	1.07 (0.62-1.67)	1.07 (0.61-1.67)	1.04 (0.74-1.48)	1.03 (0.80-1.39)	TOF+cDMARD				
1.34 (0.81-2.39)	1.35 (0.97-2.27)	1.19 (0.83-1.95)	1.14 (0.66-1.99)	1.13 (0.75-1.87)	1.12 (0.78-1.84)	1.11 (0.62-1.96)	1.11 (0.73-1.84)	1.10 (0.61-1.93)	1.10 (0.59-1.95)	1.07 (0.71-1.74)	1.05 (0.74-1.69)	1.02 (0.69-1.64)	RTX+cDMARD			
1.39 (1.05-2.51)	1.39 (0.86-3.52)	1.22 (0.73-3.04)	1.17 (0.61-3.02)	1.16 (0.67-2.88)	1.15 (0.68-2.85)	1.15 (0.58-2.94)	1.14 (0.65-2.85)	1.13 (0.56-2.93)	1.13 (0.54-2.92)	1.10 (0.63-2.70)	1.08 (0.65-2.65)	1.05 (0.60-2.56)	1.03 (0.54-2.55)	Int cDMARD		
2.56 (1.59-4.56)	**2.60 (1.82-4.15)**	**2.28 (1.64-3.50)**	**2.17 (1.36-3.67)**	**2.16 (1.54-3.33)**	**2.15 (1.59-3.21)**	**2.11 (1.29-3.60)**	**2.12 (1.50-3.27)**	**2.08 (1.28-3.52)**	**2.08 (1.23-3.57)**	**2.04 (1.48-3.07)**	**2.02 (1.54-2.90)**	**1.95 (1.45-2.85)**	**1.90 (1.27-2.99)**	1.83 (0.82-3.47)	cDMARD	

*To zoom in on numbers, hold the Ctrl key and scroll with mouse or trackpad

Figure C3. League table, base case combination therapy NMA results, ACR50

ETN+cDMARD																
1.01 (0.47-1.77)	CTZ+cDMARD															
1.24 (0.57-2.35)	1.23 (0.82-1.99)	TCZiv+cDMARD														
1.31 (0.56-3.22)	1.31 (0.75-2.90)	1.06 (0.57-2.35)	SAR+cDMARD													
1.34 (0.62-2.69)	1.34 (0.86-2.33)	1.09 (0.65-1.89)	1.02 (0.46-2.02)	GOLsc+cDMARD												
1.36 (0.63-2.61)	1.35 (0.91-2.19)	1.10 (0.69-1.77)	1.03 (0.47-1.93)	1.01 (0.59-1.67)	ABTiv+cDMARD											
1.37 (0.58-3.49)	1.37 (0.76-3.18)	1.11 (0.58-2.53)	1.04 (0.43-2.58)	1.02 (0.51-2.37)	1.01 (0.53-2.30)	GOLiv+cDMARD										
1.38 (0.63-2.84)	1.38 (0.88-2.47)	1.12 (0.67-1.99)	1.05 (0.47-2.12)	1.03 (0.58-1.86)	1.02 (0.61-1.79)	1.01 (0.43-2.07)	BAR+cDMARD									
1.40 (0.59-3.60)	1.40 (0.78-3.25)	1.13 (0.60-2.60)	1.06 (0.44-2.68)	1.04 (0.52-2.42)	1.03 (0.55-2.36)	1.02 (0.41-2.60)	1.01 (0.49-2.36)	TCZsc+cDMARD								
1.40 (0.58-3.79)	1.40 (0.76-3.44)	1.13 (0.58-2.76)	1.07 (0.43-2.80)	1.05 (0.51-2.54)	1.03 (0.53-2.48)	1.02 (0.40-2.75)	1.02 (0.50-2.43)	1.00 (0.39-2.67)	ABTsc+cDMARD							
1.47 (0.68-2.97)	1.47 (0.95-2.54)	1.19 (0.72-2.05)	1.12 (0.51-2.19)	1.09 (0.63-1.92)	1.08 (0.70-1.75)	1.07 (0.46-2.14)	1.06 (0.59-1.89)	1.05 (0.46-2.08)	1.04 (0.43-2.14)	IFX+cDMARD						
1.50 (0.72-2.81)	**1.49 (1.02-2.35**	1.21 (0.78-1.91)	1.14 (0.53-2.08)	1.12 (0.67-1.80)	1.10 (0.72-1.71)	1.10 (0.49-2.04)	1.09 (0.67-1.68)	1.07 (0.48-2.00)	1.07 (0.51-1.83)	1.02 (0.62-1.62)	ADA+cDMARD					
1.57 (0.74-3.14)	**1.57 (1.04-2.68**	1.27 (0.79-2.15)	1.20 (0.55-2.32)	1.17 (0.69-2.02)	1.15 (0.73-1.93)	1.15 (0.51-2.27)	1.14 (0.65-1.97)	1.12 (0.50-2.21)	1.12 (0.48-2.22)	1.07 (0.63-1.82)	1.05 (0.71-1.63)	TOF+cDMARD				
1.62 (0.72-3.81)	1.62 (0.95-3.41)	1.31 (0.74-2.70)	1.23 (0.54-2.84)	1.21 (0.65-2.53)	1.20 (0.67-2.45)	1.18 (0.49-2.78)	1.18 (0.61-2.47)	1.16 (0.48-2.69)	1.16 (0.46-2.75)	1.11 (0.59-2.28)	1.09 (0.63-2.16)	1.04 (0.56-2.08)	RTX+cDMARD			
1.70 (1.09-3.69	1.70 (0.77-6.22)	1.38 (0.59-4.96)	1.29 (0.46-4.97)	1.27 (0.53-4.56)	1.25 (0.54-4.50)	1.24 (0.43-4.73)	1.23 (0.50-4.49)	1.21 (0.41-4.71)	1.21 (0.40-4.76)	1.16 (0.48-4.14)	1.13 (0.50-4.00)	1.08 (0.46-3.80)	1.05 (0.39-3.83)	Int cDMARD		
4.13 (2.01-8.96	**4.20 (2.64-7.46**	**3.38 (2.16-5.81)**	**3.15 (1.56-6.39**	**3.10 (1.93-5.43**	**3.08 (2.04-5.10**	**3.02 (1.44-6.22**	**3.01 (1.84-5.31**	**2.95 (1.42-6.06**	**2.94 (1.34-6.20**	**2.84 (1.81-4.80**	**2.79 (1.94-4.38**	**2.65 (1.76-4.29**	**2.55 (1.40-4.72)**	2.42 (0.76-6.06)	cDMARD	

*To zoom in on numbers, hold the Ctrl key and scroll with mouse or trackpad

Figure C4. League table, base case combination therapy NMA results, ACR70

ETN+cDMARD																
1.01 (0.34-2.35)	CTZ+cDMARD															
1.37 (0.46-3.44)	1.36 (0.75-2.65)	TCZiv+cDMARD														
1.49 (0.44-5.21)	1.49 (0.66-4.34)	1.09 (0.45-3.23)	SAR+cDMARD													
1.54 (0.51-4.11)	1.53 (0.81-3.26)	1.13 (0.55-2.43)	1.03 (0.35-2.70)	GOLsc+cDMARD												
1.57 (0.53-3.96)	1.56 (0.87-3.00)	1.15 (0.59-2.23)	1.05 (0.36-2.54)	1.02 (0.48-2.05)	ABTiv+cDMARD											
1.58 (0.46-5.77)	1.58 (0.67-4.90)	1.16 (0.46-3.55)	1.06 (0.31-3.71)	1.03 (0.38-3.24)	1.01 (0.41-3.10)	GOLiv+cDMARD										
1.60 (0.53-4.42)	1.59 (0.82-3.51)	1.17 (0.56-2.59)	1.07 (0.36-2.87)	1.04 (0.46-2.37)	1.02 (0.50-2.23)	1.02 (0.32-2.78)	BAR+cDMARD									
1.63 (0.47-6.00)	1.63 (0.69-5.05)	1.19 (0.48-3.68)	1.09 (0.32-3.91)	1.06 (0.40-3.33)	1.04 (0.42-3.21)	1.03 (0.29-3.75)	1.02 (0.37-3.22)	TCZsc+cDMARD								
1.64 (0.46-6.39)	1.64 (0.66-5.43)	1.20 (0.46-3.96)	1.10 (0.31-4.13)	1.07 (0.38-3.55)	1.05 (0.41-3.43)	1.04 (0.28-3.98)	1.02 (0.37-3.33)	1.00 (0.27-3.82)	ABTsc+cDMARD							
1.75 (0.59-4.70)	1.74 (0.92-3.64)	1.28 (0.64-2.69)	1.17 (0.40-3.01)	1.13 (0.52-2.47)	1.11 (0.60-2.16)	1.10 (0.35-2.92)	1.09 (0.49-2.40)	1.07 (0.35-2.80)	1.06 (0.32-2.92)	IFX+cDMARD						
1.80 (0.63-4.37)	1.79 (1.04-3.30)	1.32 (0.70-2.45)	1.20 (0.43-2.80)	1.17 (0.57-2.26)	1.15 (0.63-2.09)	1.14 (0.38-2.73)	1.13 (0.57-2.06)	1.10 (0.37-2.67)	1.10 (0.40-2.36)	1.03 (0.52-1.95)	ADA+cDMARD					
1.92 (0.66-5.05)	1.91 (1.05-3.89)	1.41 (0.72-2.88)	1.29 (0.45-3.23)	1.25 (0.60-2.64)	1.23 (0.64-2.46)	1.21 (0.40-3.15)	1.20 (0.56-2.54)	1.18 (0.39-3.04)	1.17 (0.37-3.06)	1.10 (0.53-2.28)	1.07 (0.62-1.95)	TOF+cDMARD				
2.01 (0.63-6.44)	2.01 (0.93-5.33)	1.47 (0.65-3.87)	1.35 (0.43-4.21)	1.31 (0.54-3.54)	1.29 (0.58-3.37)	1.27 (0.38-4.05)	1.26 (0.51-3.44)	1.23 (0.37-3.92)	1.23 (0.35-4.04)	1.15 (0.48-3.04)	1.12 (0.52-2.81)	1.05 (0.45-2.68)	RTX+cDMARD			
2.15 (1.15-5.62)	2.14 (0.67-11.53)	1.57 (0.47-8.38)	1.43 (0.33-8.57)	1.39 (0.40-7.46)	1.37 (0.41-7.31)	1.35 (0.31-8.00)	1.34 (0.38-7.35)	1.31 (0.29-7.90)	1.31 (0.28-8.06)	1.23 (0.35-6.55)	1.19 (0.37-6.18)	1.12 (0.33-5.76)	1.07 (0.27-5.93)	Int cDMARD		
7.02 (2.58-19.07)	**7.11 (4.00-14.05)**	**5.19 (2.91-9.99)**	**4.71 (1.81-11.73)**	**4.59 (2.44-9.18)**	**4.52 (2.66-8.42)**	**4.45 (1.62-11.38)**	**4.41 (2.27-8.97)**	**4.30 (1.59-10.97)**	**4.28 (1.46-11.35)**	**4.05 (2.23-7.80)**	**3.94 (2.49-6.80)**	**3.68 (2.14-6.67)**	**3.50 (1.56-7.71)**	3.26 (0.70-11.2)	cDMARD	

*To zoom in on numbers, hold the Ctrl key and scroll with mouse or trackpad

Figure C5. Network Diagram for Analysis of ACR (Mixed Population, monotherapy)

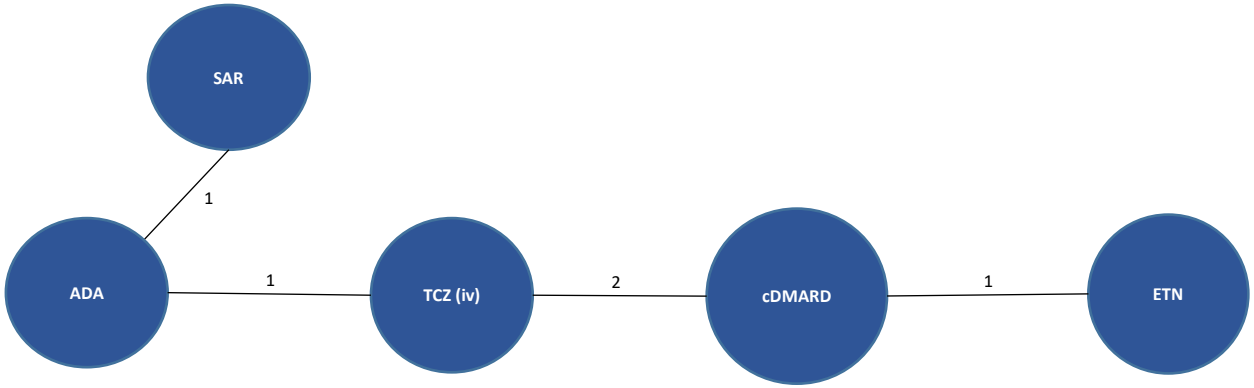


Table C10: ACR Data used in NMA (Mixed population, monotherapy)

			Mean disease duration	Intervention 1					Intervention 2				
Trial Name	1	2	Weeks	No response	ACR20	ACR50	ACR70	n	No response	ACR20	ACR50	ACR70	n
ADACTA[19]	ADA	TCZ	354	82	35	16	29	162	57	29	24	53	163
ETN309[183]	cDMARD	ETN	341	36	7	6	1	50	27	28	26	22	103
SAMURAI[84]	cDMARD	TCZ	119	89	30	16	10	145	28	39	37	53	157
SATORI[85]	cDMARD	TCZ	447	48	9	3	4	64	12	18	12	19	61
MONARCH[18]	ADA	SAR		77	53	33	22	185	52	48	41	43	184

DIC=188.5; resdev=41.8

Figure C6. League table, base case monotherapy NMA results, ACR20

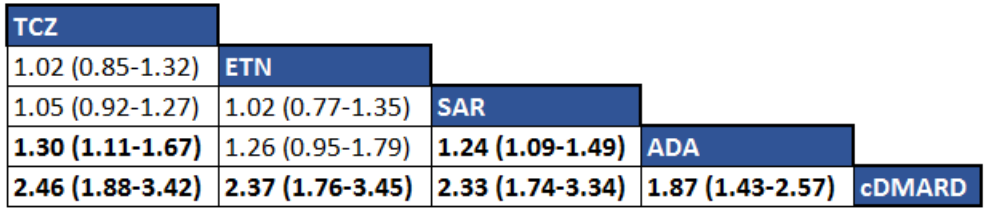


Figure C7. League table, base case monotherapy NMA results, ACR50

TCZ				
1.05 (0.74-1.62)	ETN			
1.09 (0.85-1.50)	1.04 (0.64-1.69)	SAR		
1.58 (1.21-2.25)	1.50 (0.91-2.58)	**1.45 (1.17-1.89)**	ADA	
4.13 (2.88-6.31)	**3.90 (2.50-6.53)**	**3.75 (2.45-6.21)**	**2.59 (1.74-4.05)**	cDMARD

Figure C8. League table, base case monotherapy NMA results, ACR70

TCZ				
1.07 (0.64-1.97)	ETN			
1.13 (0.79-1.76)	1.06 (0.52-2.12)	SAR		
1.91 (1.33-3.02)	1.78 (0.88-3.73)	**1.68 (1.26-2.39)**	ADA	
6.78 (4.39-11.23)	**6.28 (3.46-12.04)**	**5.95 (3.38-11.21)**	**3.52 (2.07-6.23)**	cDMARD

Figure C9. Network Diagram for Analysis of ACR (combined analysis of monotherapy and combination therapy)

Table C11: ACR Data used in NMA (combined analysis of monotherapy and combination therapy)

	Interventions			Mean disease duration	Intervention 1					Intervention 2				
Trial Name	1	2	3	Weeks	No response	ACR20	ACR50	ACR70	n	No response	ACR20	ACR50	ACR70	n
ADACTA[19]	ADA	TCZ		354	82	35	16	29	162	57	29	24	53	163
AIM[173]	cDMARD	ABTiv + cDMARD		449	132	50	23	14	219	139	121	87	86	433
AMPLE[94]	ADA + cDMARD	ABTsc + cDMARD		94	117	72	65	74	328	108	65	68	77	318
ARMADA[176]	cDMARD	ADA + cDMARD		607	53	4	2	3	62	22	8	19	18	67
ATTEST[23]	cDMARD	ABTiv + cDMARD	IFX + cDMARD	405	64	24	12	10	110	52	41	31	32	156
ATTRACT[187]	cDMARD	IFX + cDMARD			67	13	4	0	84	82	38	26	22	168
DE019[179]	cDMARD	ADA + cDMARD		569	141	40	14	5	200	76	50	38	43	207
ETN309[183]	cDMARD	ETN + cDMARD	ETN	341	36	7	6	1	50	27	22	27	25	101
GO-FORTH[160]	cDMARD	GOLsc + cDMARD		455	59	16	8	5	88	25	25	13	23	86
GO-FORWARD[87]	cDMARD	GOLsc + cDMARD		421	96	19	11	7	133	36	20	15	18	89
Kim2007[177]	cDMARD	ADA + cDMARD		356	40	14	4	5	63	25	12	14	14	65
LARA[158]	Int cDMARD	ETN + cDMARD		430	71	38	17	16	142	47	59	76	97	279

	Interventions			Mean disease duration	Intervention 1					Intervention 2				
O'Dell[77]	Int cDMARD	ETN + cDMARD		271	70	48	33	8	159	73	32	32	26	163
SAMURAI[84]	cDMARD	TCZ		119	89	30	16	10	145	28	39	37	53	157
SATORI[85]	cDMARD	TCZ		447	48	9	3	4	64	12	18	12	19	61
STAR[178]	cDMARD	ADA + cDMARD		541	207	75	25	11	318	150	76	45	47	318
START[188]	cDMARD	IFX + cDMARD		390	276	54	17	16	363	317	175	127	102	721
TOWARD[152]	cDMARD	TCZ + cDMARD		510	312	64	25	12	413	315	186	137	165	803
RA-BUILD[175]	cDMARD	BAR + cDMARD		390	132	47	31	18	228	79	48	45	55	227
MOBILITY[162]	cDMARD	SAR + cDMARD		460	265	67	37	29	398	134	83	83	99	399
ORAL Scan[78]	cDMARD	TOF + cDMARD		463	120	27	11	2	160	156	61	57	47	321
Kremer 2012[212]	cDMARD	TOF + cDMARD		473	45	7	11	6	69	37	10	10	14	71
LITHE[125]	cDMARD	TCZ + cDMARD		476	287	67	31	8	393	371	199	131	96	797
OPTION[213]	cDMARD	TCZ + cDMARD		398	151	31	18	4	204	195	66	86	71	418
RAPID1[181]	cDMARD	CTZ + cDMARD		319	171	12	9	6	199	162	85	62	84	393
RAPID2[180]	cDMARD	CTZ + cDMARD		308	116	7	3	1	127	105	61	41	39	246

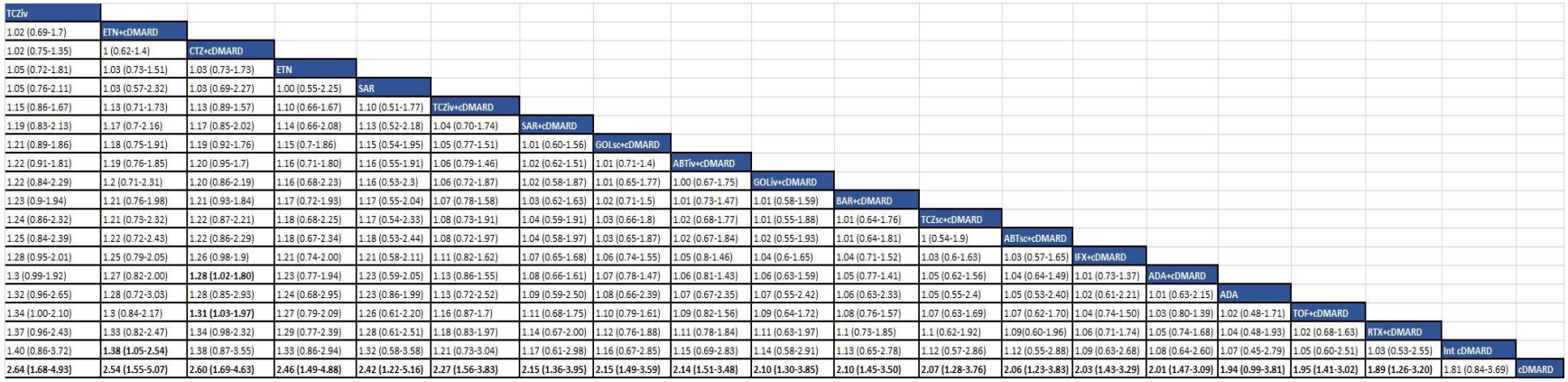
	Interventions			Mean disease duration	Intervention 1					Intervention 2				
Choy 2012[182]	cDMARD	CTZ + cDMARD		502	92	20	5	2	119	67	35	22	0	124
SERENE[149]	cDMARD	RTX + cDMARD		366	132	24	7	9	172	84	42	27	17	170
BREVACTA[153]	cDMARD	TCZsc + cDMARD		577	149	44	15	11	219	170	92	88	87	437
Kremer 2003[174]	cDMARD	ABTiv + cDMARD			77	28	12	2	119	46	27	23	19	115
ORAL Standard[95]	cDMARD	TOF + cDMARD	ADA + cDMARD	408	41	2	5	8	56	95	30	32	39	196
GO-FURTHER[184]	cDMARD	GOLiv + cDMARD		359	136	35	18	8	197	134	123	68	70	395
ORAL Sync[154]	cDMARD	TOF + cDMARD		462	110	29	15	5	159	151	59	64	41	315
Li 2015[185]	cDMARD	GOLsc + cDMARD		406	111	12	7	2	132	76	31	17	8	132
RA-SCORE[171]	cDMARD	RTX + cDMARD		242	45	11	6	1	63	29	15	11	5	60
Takeuchi 2013[172]	cDMARD	ABTiv + cDMARD		382	52	10	4	0	66	14	19	15	13	61
J-RAPID[156]	cDMARD	CTZ + cDMARD		296	58	6	12	1	77	22	15	21	24	82
RA-BEAM[21]	cDMARD	ADA + cDMARD	BAR + cDMARD	na	307	88	54	39	488	112	66	79	73	330
MONARCH[18]	ADA	SAR			77	53	33	22	185	52	48	41	43	184

Table C11 (continued): ACR Data used in NMA (combined analysis of monotherapy and combination therapy)

	Interventions			Mean disease duration	Intervention 3				
Trial Name	1	2	3	Weeks	No response	ACR20	ACR50	ACR70	n
ATTEST[23]	cDMARD	ABTiv + cDMARD	IFX + cDMARD	405	67	37	21	40	165
ETN309[183]	cDMARD	ETN + cDMARD	ETN	341	27	28	26	22	103
ORAL Standard[95]	cDMARD	TOF + cDMARD	ADA + cDMARD	408	105	36	38	20	199
RA-BEAM[21]	cDMARD	ADA + cDMARD	BAR + cDMARD	na	127	117	97	146	487

DIC=1765.4; resdev=497.1

Figure C10. League table, NMA results of combined analysis (monotherapy and combination therapy), ACR20



TCZiv																					
1.02 (0.69-1.7)	ETN+cDMARD																				
1.02 (0.75-1.35)	1 (0.62-1.4)	CTZ+cDMARD																			
1.05 (0.72-1.81)	1.03 (0.73-1.51)	1.03 (0.73-1.73)	ETN																		
1.05 (0.76-2.11)	1.03 (0.57-2.32)	1.03 (0.69-2.27)	1.00 (0.55-2.25)	SAR																	
1.15 (0.86-1.67)	1.13 (0.71-1.73)	1.13 (0.89-1.57)	1.10 (0.66-1.67)	1.10 (0.51-1.77)	TCZiv+cDMARD																
1.19 (0.83-2.13)	1.17 (0.7-2.16)	1.17 (0.85-2.02)	1.14 (0.66-2.08)	1.13 (0.52-2.18)	1.04 (0.70-1.74)	SAR+cDMARD															
1.21 (0.89-1.86)	1.18 (0.75-1.91)	1.19 (0.92-1.76)	1.15 (0.7-1.86)	1.15 (0.54-1.95)	1.05 (0.77-1.51)	1.01 (0.60-1.56)	GOLsc+cDMARD														
1.22 (0.91-1.81)	1.19 (0.76-1.85)	1.20 (0.95-1.7)	1.16 (0.71-1.80)	1.16 (0.55-1.91)	1.06 (0.79-1.46)	1.02 (0.62-1.51)	1.01 (0.71-1.4)	ABTiv+cDMARD													
1.22 (0.84-2.29)	1.2 (0.71-2.31)	1.20 (0.86-2.19)	1.16 (0.68-2.23)	1.16 (0.53-2.3)	1.06 (0.72-1.87)	1.02 (0.58-1.87)	1.01 (0.65-1.77)	1.00 (0.67-1.75)	GOLiv+cDMARD												
1.23 (0.9-1.94)	1.21 (0.76-1.98)	1.21 (0.93-1.84)	1.17 (0.72-1.93)	1.17 (0.55-2.04)	1.07 (0.78-1.58)	1.03 (0.62-1.63)	1.02 (0.71-1.5)	1.01 (0.73-1.47)	1.01 (0.58-1.59)	BAR+cDMARD											
1.24 (0.86-2.32)	1.21 (0.73-2.32)	1.22 (0.87-2.21)	1.18 (0.68-2.25)	1.17 (0.54-2.33)	1.08 (0.73-1.91)	1.04 (0.59-1.91)	1.03 (0.66-1.8)	1.02 (0.68-1.77)	1.01 (0.55-1.88)	1.01 (0.64-1.76)	TCZsc+cDMARD										
1.25 (0.84-2.39)	1.22 (0.72-2.43)	1.22 (0.86-2.29)	1.18 (0.67-2.34)	1.18 (0.53-2.44)	1.08 (0.72-1.97)	1.04 (0.58-1.97)	1.03 (0.65-1.87)	1.02 (0.67-1.84)	1.02 (0.55-1.93)	1.01 (0.64-1.81)	1 (0.54-1.9)	ABTsc+cDMARD									
1.28 (0.95-2.01)	1.25 (0.79-2.05)	1.26 (0.98-1.9)	1.21 (0.74-2.00)	1.21 (0.58-2.11)	1.11 (0.82-1.62)	1.07 (0.65-1.68)	1.06 (0.74-1.55)	1.05 (0.8-1.46)	1.04 (0.6-1.65)	1.04 (0.71-1.52)	1.03 (0.6-1.63)	1.03 (0.57-1.65)	IFX+cDMARD								
1.3 (0.99-1.92)	1.27 (0.82-2.00)	**1.28 (1.02-1.80)**	1.23 (0.77-1.94)	1.23 (0.59-2.05)	1.13 (0.86-1.55)	1.08 (0.66-1.61)	1.07 (0.78-1.47)	1.06 (0.81-1.43)	1.06 (0.63-1.59)	1.05 (0.77-1.41)	1.05 (0.62-1.56)	1.04 (0.64-1.49)	1.01 (0.73-1.37)	ADA+cDMARD							
1.32 (0.96-2.65)	1.28 (0.72-3.03)	1.28 (0.85-2.93)	1.24 (0.68-2.95)	1.23 (0.86-1.99)	1.13 (0.72-2.52)	1.09 (0.59-2.50)	1.08 (0.66-2.39)	1.07 (0.67-2.35)	1.07 (0.55-2.42)	1.06 (0.63-2.33)	1.05 (0.55-2.4)	1.05 (0.53-2.40)	1.02 (0.61-2.21)	1.01 (0.63-2.15)	ADA						
1.34 (1.00-2.10)	1.3 (0.84-2.17)	**1.31 (1.03-1.97)**	1.27 (0.79-2.09)	1.26 (0.61-2.20)	1.16 (0.87-1.7)	1.11 (0.68-1.75)	1.10 (0.79-1.61)	1.09 (0.82-1.56)	1.09 (0.64-1.72)	1.08 (0.76-1.57)	1.07 (0.63-1.69)	1.07 (0.62-1.70)	1.04 (0.74-1.50)	1.03 (0.80-1.39)	1.02 (0.48-1.71)	TOF+cDMARD					
1.37 (0.96-2.43)	1.33 (0.82-2.47)	1.34 (0.98-2.32)	1.29 (0.77-2.39)	1.28 (0.61-2.51)	1.18 (0.83-1.97)	1.14 (0.67-2.00)	1.12 (0.76-1.88)	1.11 (0.78-1.84)	1.11 (0.63-1.97)	1.1 (0.73-1.85)	1.1 (0.62-1.92)	1.09(0.60-1.96)	1.06 (0.71-1.74)	1.05 (0.74-1.68)	1.04 (0.48-1.93)	1.02 (0.68-1.63)	RTX+cDMARD				
1.40 (0.86-3.72)	**1.38 (1.05-2.54)**	1.38 (0.87-3.55)	1.33 (0.86-2.94)	1.32 (0.58-3.58)	1.21 (0.73-3.04)	1.17 (0.61-2.98)	1.16 (0.67-2.85)	1.15 (0.69-2.83)	1.14 (0.58-2.91)	1.13 (0.65-2.78)	1.12 (0.57-2.86)	1.12 (0.55-2.88)	1.09 (0.63-2.68)	1.08 (0.64-2.60)	1.07 (0.45-2.79)	1.05 (0.60-2.51)	1.03 (0.53-2.55)	Int cDMARD		
2.64 (1.68-4.93)	**2.54 (1.55-5.07)**	**2.60 (1.69-4.63)**	**2.46 (1.49-4.88)**	**2.42 (1.22-5.16)**	**2.27 (1.56-3.83)**	**2.15 (1.36-3.95)**	**2.15 (1.49-3.59)**	**2.14 (1.51-3.48)**	**2.10 (1.30-3.85)**	**2.10 (1.45-3.50)**	**2.07 (1.28-3.76)**	**2.06 (1.23-3.83)**	**2.03 (1.43-3.29)**	**2.01 (1.47-3.09)**	**1.94 (0.99-3.81)**	**1.95 (1.41-3.02)**	**1.89 (1.26-3.20)**	1.81 (0.84-3.69)	cDMARD	

Figure C11. League table, NMA results of combined analysis (monotherapy and combination therapy), ACR50

TCZiv																			
1.03 (0.55-2.30)	ETN+cDMARD																		
1.04 (0.64-1.63)	1.00 (0.47-1.76)	CTZ+cDMARD																	
1.09 (0.58-2.51)	1.05 (0.60-1.90)	1.05 (0.59-2.31)	ETN																
1.09 (0.62-3.04)	1.05 (0.41-3.62)	1.05 (0.53-3.41)	1.00 (0.38-3.43)	SAR															
1.28 (0.79-2.22)	1.23 (0.59-2.39)	1.23 (0.83-2.01)	1.17 (0.53-2.26)	1.17 (0.37-2.51)	TCZiv+cDMARD														
1.35 (0.74-3.14)	1.31 (0.57-3.27)	1.31 (0.76-2.89)	1.24 (0.52-3.08)	1.24 (0.37-3.36)	1.06 (0.58-2.29)	SAR+cDMARD													
1.38 (0.83-2.59)	1.33 (0.64-2.74)	1.33 (0.87-2.36)	1.27 (0.57-2.62)	1.26 (0.40-2.90)	1.08 (0.66-1.87)	1.02 (0.46-1.99)	GOLsc+cDMARD												
1.40 (0.86-2.48)	1.35 (0.65-2.64)	1.35 (0.92-2.23)	1.29 (0.59-2.51)	1.28 (0.41-2.81)	1.10 (0.69-1.79)	1.04 (0.48-1.91)	1.01 (0.59-1.68)	ABTiv+cDMARD											
1.41 (0.75-3.49)	1.36 (0.59-3.56)	1.36 (0.77-3.22)	1.29 (0.54-3.38)	1.29 (0.39-3.64)	1.10 (0.59-2.52)	1.04 (0.44-2.57)	1.02 (0.51-2.34)	1.00 (0.53-2.28)	GOLiv+cDMARD										
1.43 (0.85-2.77)	1.37 (0.66-2.91)	1.37 (0.89-2.51)	1.31 (0.60-2.77)	1.3 (0.41-3.06)	1.12 (0.67-2.00)	1.05 (0.48-2.12)	1.03 (0.59-1.85)	1.02 (0.61-1.78)	1.01 (0.44-2.05)	BAR+cDMARD									
1.45 (0.77-3.55)	1.39 (0.60-3.60)	1.39 (0.80-3.26)	1.32 (0.55-3.43)	1.32 (0.39-3.70)	1.13 (0.61-2.59)	1.06 (0.45-2.65)	1.04 (0.53-2.38)	1.03 (0.55-2.34)	1.02 (0.41-2.59)	1.01 (0.50-2.32)	TCZsc+cDMARD								
1.45 (0.75-3.71)	1.39 (0.59-3.84)	1.4 (0.77-3.44)	1.33 (0.54-3.63)	1.32 (0.39-3.93)	1.13 (0.59-2.73)	1.07 (0.43-2.76)	1.05 (0.51-2.51)	1.03 (0.53-2.45)	1.03 (0.40-2.68)	1.02 (0.50-2.41)	1.01 (0.39-2.61)	ABTsc+cDMARD							
1.51 (0.92-2.88)	1.46 (0.70-3.05)	1.46 (0.96-2.61)	1.39 (0.64-2.90)	1.38 (0.44-3.23)	1.19 (0.73-2.07)	1.11 (0.52-2.21)	1.09 (0.64-1.92)	1.08 (0.71-1.75)	1.07 (0.48-2.15)	1.06 (0.60-1.88)	1.05 (0.47-2.11)	1.04 (0.44-2.15)	IFX+cDMARD						
1.55 (0.98-2.69)	1.49 (0.73-2.94)	1.49 (1.04-2.43)	1.42 (0.67-2.79)	1.41 (0.46-3.11)	1.21 (0.79-1.93)	1.14 (0.55-2.09)	1.12 (0.69-1.80)	1.10 (0.72-1.71)	1.10 (0.50-2.05)	1.08 (0.67-1.69)	1.07 (0.49-1.99)	1.07 (0.52-1.85)	1.02 (0.62-1.62)	ADA+cDMARD					
1.58 (0.94-4.09)	1.51 (0.59-5.19)	1.51 (0.76-4.84)	1.43 (0.55-4.95)	1.42 (0.80-2.76)	1.23 (0.59-3.81)	1.15 (0.45-3.80)	1.13 (0.51-3.52)	1.12 (0.53-3.41)	1.11 (0.41-3.65)	1.10 (0.48-3.41)	1.08 (0.40-3.60)	1.08 (0.38-3.57)	1.04 (0.46-3.13)	1.01 (0.48-3.00)	ADA				
1.62 (1.00-3.06)	1.55 (0.76-3.28)	1.56 (1.05-2.76)	1.48 (0.70-3.09)	1.47 (0.48-3.44)	1.26 (0.80-2.21)	1.19 (0.56-2.35)	1.17 (0.70-2.04)	1.15 (0.74-1.95)	1.14 (0.52-2.29)	1.13 (0.67-1.96)	1.12 (0.51-2.23)	1.11 (0.49-2.25)	1.07 (0.64-1.83)	1.04 (0.71-1.63)	1.03 (0.35-2.29)	TOF+cDMARD			
1.67 (0.93-3.78)	1.60 (0.73-3.93)	1.61 (0.96-3.46)	1.53 (0.67-3.72)	1.52 (0.48-4.09)	1.3 (0.74-2.73)	1.23 (0.55-2.82)	1.21 (0.65-2.53)	1.19 (0.68-2.45)	1.18 (0.50-2.77)	1.17 (0.62-2.47)	1.16 (0.49-2.67)	1.15 (0.47-2.73)	1.10 (0.59-2.26)	1.08 (0.62-2.13)	1.06 (0.34-2.71)	1.03 (0.56-2.05)	RTX+cDMARD		
1.75 (0.77-6.72)	**1.69 (1.1-3.75)**	1.69 (0.78-6.18)	1.59 (0.78-4.75)	1.58 (0.44-6.67)	1.37 (0.60-4.90)	1.28 (0.46-4.81)	1.26 (0.53-4.45)	1.24 (0.55-4.41)	1.23 (0.43-4.67)	1.22 (0.51-4.32)	1.20 (0.42-4.57)	1.20 (0.40-4.61)	1.15 (0.48-4.06)	1.13 (0.50-3.88)	1.11 (0.31-4.43)	1.08 (0.45-3.70)	1.05 (0.39-3.80)	Int cDMARD	
4.33 (2.37-9.39)	**4.1 (1.99-10.04)**	**4.20 (2.42-8.41)**	**3.89 (1.85-9.48)**	**3.83 (1.33-10.6)**	**3.37 (2.05-6.40)**	**3.12 (1.58-6.91)**	**3.09 (1.87-5.88)**	**3.06 (1.93-5.57)**	**2.99 (1.47-6.70)**	**2.99 (1.80-5.69)**	**2.93 (1.44-6.47)**	**2.91 (1.36-6.67)**	**2.82 (1.76-5.16)**	**2.78 (1.86-4.67)**	**2.68 (0.99-6.70)**	**2.64 (1.71-4.57)**	**2.54 (1.41-5.05)**	2.40 (0.79-6.40)	cDMARD

*To zoom in on numbers, hold the Ctrl key and scroll with mouse or trackpad

Figure C12. League table, NMA results of combined analysis (monotherapy and combination therapy), ACR70

TCZiv																			
1.05 (0.41-3.24)	ETN+cDMARD																		
1.06 (0.52-2.04)	1.01 (0.35-2.31)	CTZ+cDMARD																	
1.13 (0.45-3.62)	1.08 (0.49-2.47)	1.07 (0.46-3.20)	ETN																
1.14 (0.49-4.52)	1.08 (0.27-5.87)	1.07 (0.39-5.34)	1.00 (0.25-5.44)	SAR															
1.44 (0.71-3.08)	1.36 (0.48-3.46)	1.36 (0.77-2.65)	1.27 (0.42-3.22)	1.26 (0.26-3.79)	TCZiv+cDMARD														
1.57 (0.64-4.84)	1.49 (0.46-5.22)	1.48 (0.67-4.27)	1.38 (0.40-4.80)	1.37 (0.26-5.54)	1.09 (0.46-3.1)	SAR+cDMARD													
1.61 (0.76-3.76)	1.53 (0.53-4.17)	1.52 (0.82-3.27)	1.42 (0.46-3.88)	1.42 (0.29-4.58)	1.12 (0.56-2.37)	1.03 (0.35-2.62)	GOLsc+cDMARD												
1.65 (0.81-3.55)	1.56 (0.55-3.94)	1.55 (0.88-3.03)	1.45 (0.49-3.67)	1.45 (0.30-4.44)	1.14 (0.6-2.24)	1.05 (0.37-2.49)	1.02 (0.49-2.05)	ABTiv+cDMARD											
1.66 (0.66-5.52)	1.57 (0.47-5.80)	1.56 (0.68-4.91)	1.45 (0.43-5.37)	1.45 (0.27-6.13)	1.15 (0.47-3.5)	1.06 (0.32-3.65)	1.03 (0.39-3.16)	1.01 (0.41-3.04)	GOLiv+cDMARD										
1.69 (0.79-4.10)	1.59 (0.56-4.46)	1.59 (0.84-3.55)	1.48 (0.49-4.16)	1.47 (0.30-4.91)	1.17 (0.57-2.59)	1.08 (0.37-2.85)	1.05 (0.48-2.33)	1.02 (0.50-2.21)	1.02 (0.33-2.72)	BAR+cDMARD									
1.72 (0.68-5.64)	1.62 (0.49-5.88)	1.61 (0.71-4.99)	1.50 (0.44-5.52)	1.50 (0.28-6.22)	1.19 (0.49-3.62)	1.09 (0.33-3.78)	1.06 (0.41-3.22)	1.04 (0.43-3.12)	1.03 (0.29-3.67)	1.02 (0.38-3.13)	TCZsc+cDMARD								
1.72 (0.66-5.99)	1.63 (0.48-6.44)	1.63 (0.68-5.34)	1.52 (0.42-5.90)	1.50 (0.27-6.78)	1.2 (0.47-3.86)	1.10 (0.31-3.98)	1.07 (0.39-3.45)	1.05 (0.41-3.35)	1.04 (0.28-3.84)	1.02 (0.38-3.27)	1.01 (0.28-3.69)	ABTsc+cDMARD							
1.84 (0.88-4.32)	1.74 (0.61-4.76)	1.73 (0.94-3.72)	1.61 (0.54-4.44)	1.60 (0.34-5.28)	1.28 (0.65-2.7)	1.17 (0.41-3.01)	1.14 (0.54-2.45)	1.11 (0.62-2.15)	1.11 (0.37-2.90)	1.09 (0.50-2.38)	1.07 (0.36-2.83)	1.06 (0.33-2.90)	IFX+cDMARD						
1.90 (0.97-3.94)	1.79 (0.65-4.54)	**1.79 (1.05-3.38)**	1.66 (0.58-4.21)	1.65 (0.35-5.00)	1.32 (0.72-2.46)	1.21 (0.44-2.80)	1.17 (0.60-2.24)	1.15 (0.63-2.09)	1.14 (0.39-2.72)	1.12 (0.58-2.05)	1.11 (0.39-2.62)	1.10 (0.42-2.38)	1.03 (0.52-1.94)	ADA+cDMARD					
1.94 (0.90-6.53)	1.82 (0.48-9.32)	1.82 (0.66-8.23)	1.70 (0.43-8.72)	1.67 (0.74-3.97)	1.34 (0.47-5.91)	1.23 (0.33-5.99)	1.19 (0.39-5.33)	1.17 (0.40-5.08)	1.16 (0.29-5.70)	1.15 (0.36-5.10)	1.12 (0.29-5.55)	1.12 (0.27-5.53)	1.05 (0.34-4.55)	1.02 (0.36-4.26)	ADA				
2.01 (1.00-4.65)	1.90 (0.69-5.19)	1.90 (1.07-3.98)	1.77 (0.61-4.80)	1.76 (0.37-5.75)	1.4 (0.74-2.92)	1.28 (0.46-3.26)	1.24 (0.62-2.64)	1.22 (0.65-2.46)	1.21 (0.41-3.14)	1.19 (0.57-2.51)	1.17 (0.40-3.01)	1.17 (0.39-3.07)	1.09 (0.54-2.27)	1.06 (0.62-1.93)	1.04 (0.25-3.18)	TOF+cDMARD			
2.10 (0.90-6.14)	1.99 (0.64-6.64)	1.99 (0.95-5.37)	1.84 (0.57-6.10)	1.84 (0.37-7.09)	1.46 (0.66-3.86)	1.34 (0.44-4.12)	1.30 (0.55-3.50)	1.27 (0.58-3.33)	1.26 (0.39-4.01)	1.24 (0.51-3.38)	1.23 (0.38-3.82)	1.22 (0.36-3.97)	1.15 (0.49-2.98)	1.11 (0.52-2.76)	1.09 (0.24-3.92)	1.05 (0.46-2.62)	RTX+cDMARD		
2.24 (0.68-12.73)	**2.12 (1.16-5.65)**	2.12 (0.69-11.25)	1.95 (0.70-7.98)	1.94 (0.32-13.20)	1.56 (0.48-8.13)	1.42 (0.34-8.08)	1.39 (0.41-7.19)	1.36 (0.43-7.00)	1.34 (0.31-7.75)	1.33 (0.38-6.89)	1.30 (0.3-07.51)	1.30 (0.29-7.60)	1.22 (0.36-6.34)	1.18 (0.37-5.89)	1.15 (0.20-7.35)	1.11 (0.33-5.55)	1.06 (0.27-5.78)	Int cDMARD	
7.43 (3.47-18.64)	**6.92 (2.59-21.12)**	**7.07 (3.65-15.76)**	**6.40 (2.32-19.43)**	**6.33 (1.45-23.48)**	**5.14 (2.78-10.98)**	**4.65 (1.85-12.54)**	**4.55 (2.39-9.85)**	**4.48 (2.53-9.12)**	**4.39 (1.67-12.04)**	**4.35 (2.26-9.46)**	**4.25 (1.62-11.43)**	**4.22 (1.51-12.05**	**4.01 (2.18-8.26)**	**3.9 (2.39-7.19)**	**3.76 (0.99-12.34)**	**3.66 (2.09-7.03)**	**3.47 (1.57-8.18)**	3.25 (0.73-11.63)	cDMARD

*To zoom in on numbers, hold the Ctrl key and scroll with mouse or trackpad

Figure C13. Network Diagram for Analysis of ACR (TIM-Experienced Population)

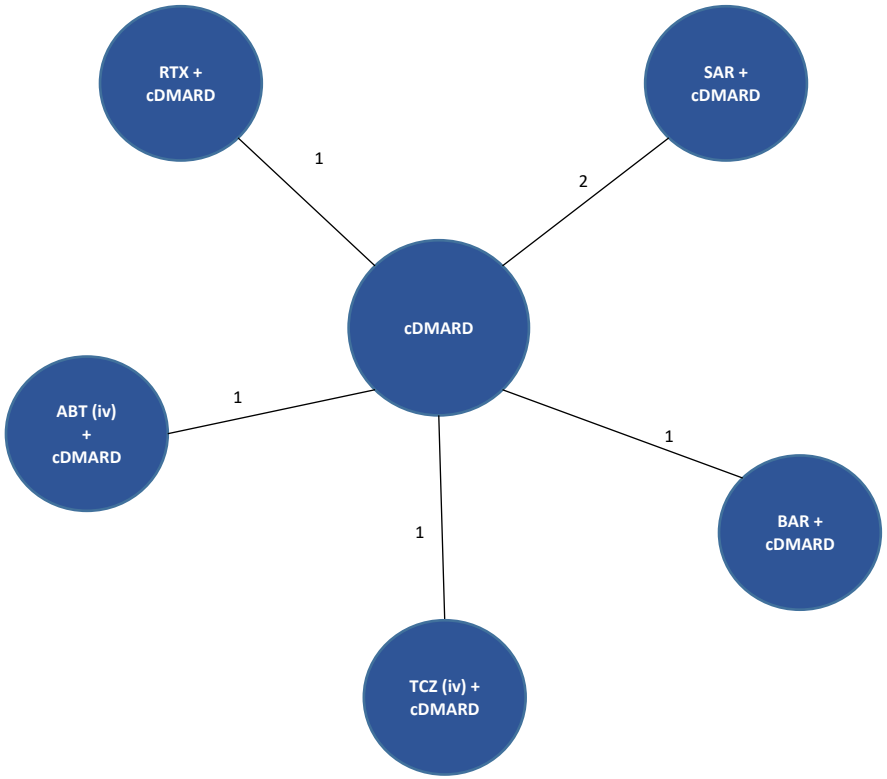


Table C12. ACR Data used in NMA (TIM-experienced population)

	Interventions		Mean disease duration	Intervention 1					Intervention 2				
Trial Name	1	2	Weeks	No response	ACR20	ACR50	ACR70	n	No response	ACR20	ACR50	ACR70	n
RA-BEACON[90]	cDMARD	BAR + cDMARD	728	128	25	17	6	176	95	30	22	30	177
REFLEX[93]	cDMARD	RTX + cDMARD	621	165	26	8	2	201	146	72	44	36	298
RADIATE[189]	cDMARD	TCZ + cDMARD	625	142	10	4	2	158	197	58	47	29	331
ATTAIN[91]	cDMARD	ABTiv + cDMARD	620	107	21	3	2	133	127	77	26	26	256
TARGET[88]	cDMARD	SAR + cDMARD		119	29	20	13	181	72	37	46	29	184
MOBILITY[89]	cDMARD	SAR + cDMARD	460	73	23	9	4	109	40	25	24	21	110

DIC=226.7; resdev=49.9

Figure C14. League table, NMA results TIM-experienced population, ACR20

TCZiv+cDMARD					
1.06 (0.83-1.40)	RTX+cDMARD				
1.14 (0.88-1.61)	1.08 (0.84-1.47)	ABTiv+ cDMARD			
1.26 (1.00-1.77)	1.19 (0.96-1.60)	1.10 (0.85-1.49)	SAR+cDMARD		
1.38 (1.05-2.11)	**1.30 (1.01-1.93)**	1.21 (0.90-1.76)	1.09 (0.84-1.51)	BAR+cDMARD	
2.70 (1.76-4.76)	**2.55 (1.72-4.28)**	**2.34 (1.62-3.88)**	**2.12 (1.55-3.21)**	**1.92 (1.42-2.94)**	cDMARD

Figure C15. League table, NMA results TIM-experienced population, ACR50

TCZiv+cDMARD					
1.09 (0.74-1.67)	RTX+cDMARD				
1.24 (0.82-2.03)	1.13 (0.76-1.77)	ABTiv+ cDMARD			
1.45 (1.00-2.31)	1.32 (0.95-2.00)	1.17 (0.78-1.80)	SAR+cDMARD		
1.65 (1.07-2.94)	**1.51 (1.01-2.57)**	1.33 (0.85-2.26)	1.14 (0.77-1.81)	BAR+cDMARD	
4.25 (2.50-8.42)	**3.89 (2.39-7.19)**	**3.41 (2.13-6.30)**	**2.93 (1.98-4.79)**	**2.54 (1.68-4.29)**	cDMARD

Figure C16. League table, NMA results TIM-experienced population, ACR70

TCZiv+cDMARD					
1.14 (0.66-2.03)	RTX+cDMARD				
1.35 (0.75-2.64)	1.19 (0.68-2.17)	ABTiv+ cDMARD			
1.68 (1.00-3.10)	1.48 (0.92-2.53)	1.24 (0.71-2.20)	SAR+cDMARD		
2.02 (1.11-4.22)	**1.77 (1.01-3.51)**	1.49 (0.80-2.96)	1.20 (0.70-2.20)	BAR+cDMARD	
6.92 (3.66-15.29)	**6.09 (3.41-12.30)**	**5.07 (2.85-10.41)**	**4.10 (2.58-7.23)**	**3.39 (2.02-6.36)**	cDMARD

Table C13. Relative Risk (Likelihood) of Patients Achieving ACR20 or Better, TIM-Experienced Population

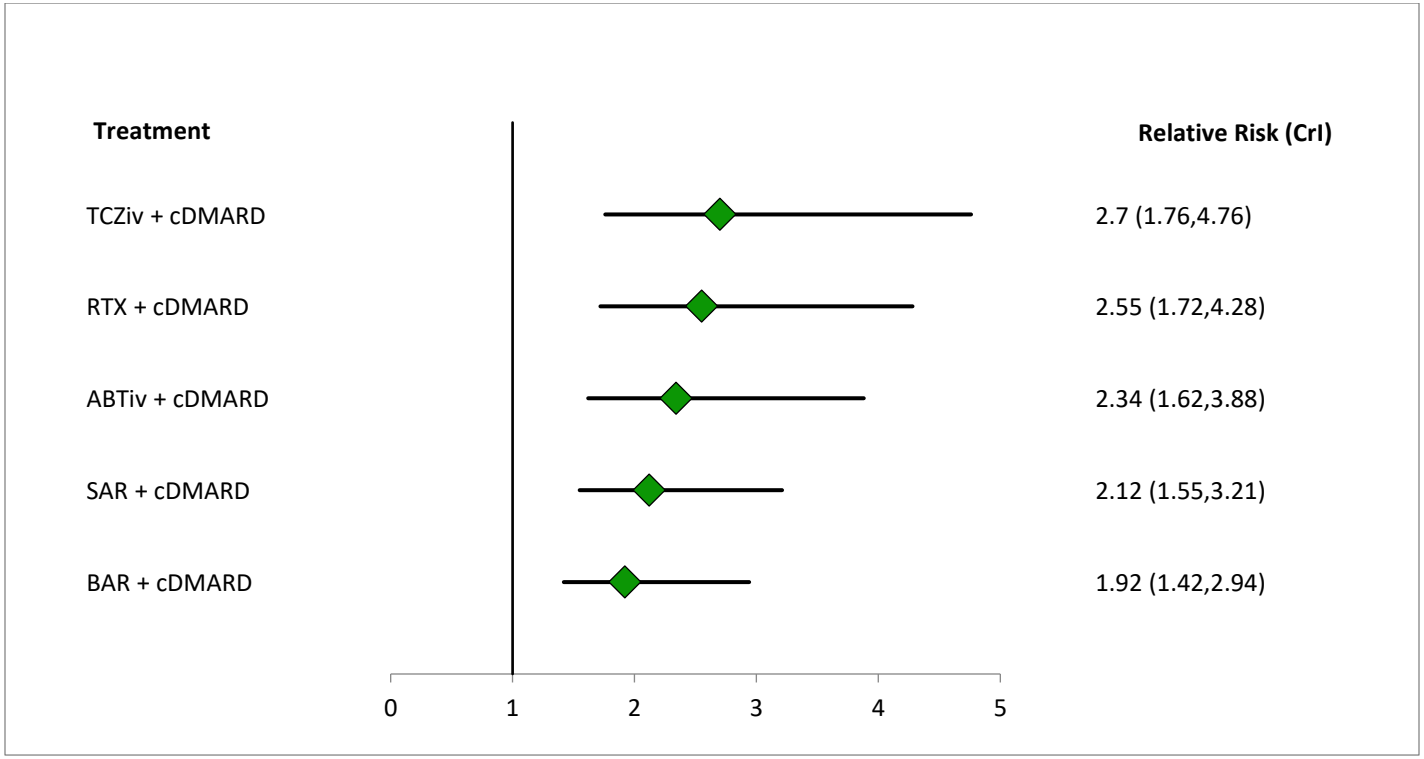


Figure C17. Network Diagram for Analysis of Radiographic Progression (Mixed Population)

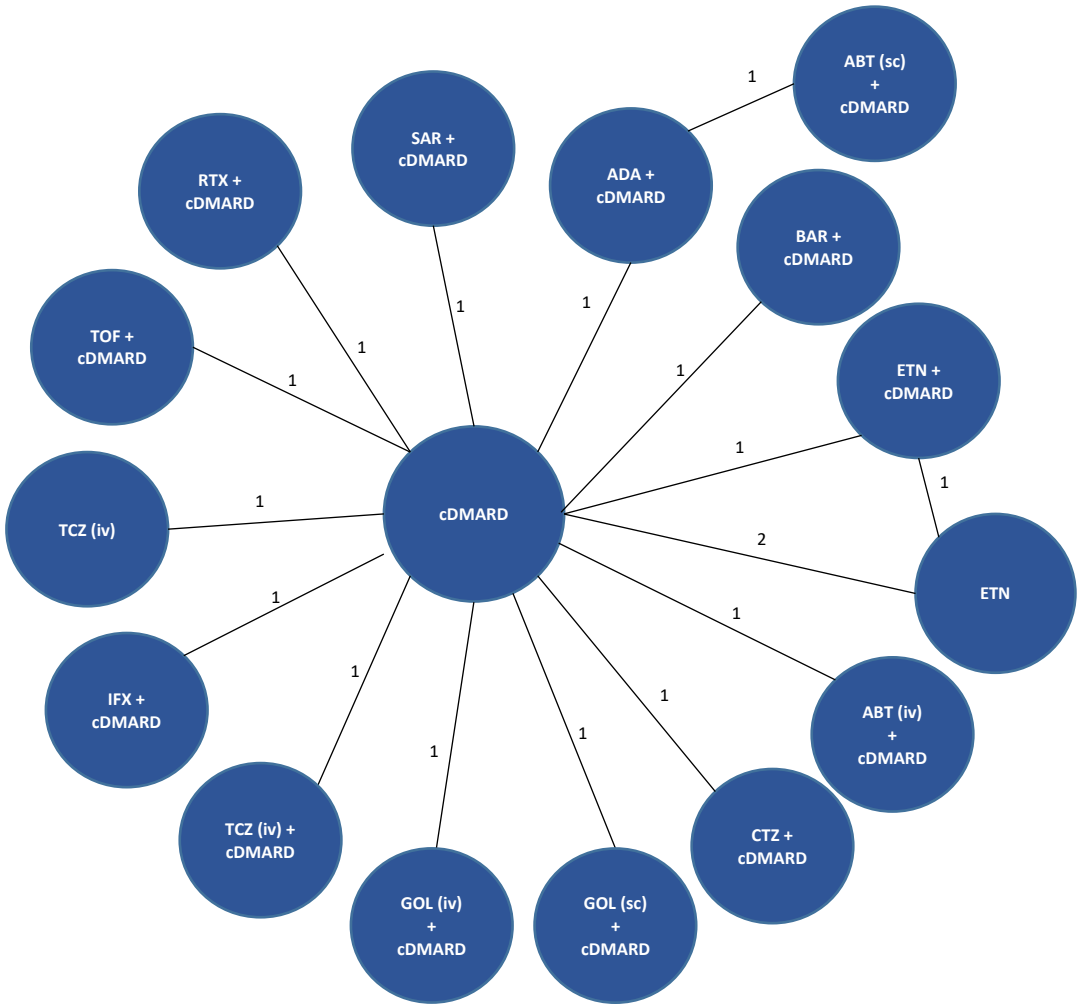


Table C14. Radiographic Progression Data used in NMA (Mixed population Sharp Score)

Trial	Intervention 1	Intervention2	Intervention 3	N (1)	N (2)	N (3)	Mean (1)	SD (1)	Mean (2)	SD (2)	Mean (3)	SD (3)
ATTRACT[200]	cDMARD	IFX + cDMARD		64	173		7.00	10.30	0.73	4.93		
TEMPO[83]	cDMARD	ETN	ETN + cDMARD	212	212	218	2.80	12.70	0.52	4.64	-0.54	3.50
RA-SCORE[171]	cDMARD	RTX + cDMARD		63	60		1.37	NR	0.29	NR		
MOBILITY[162]	cDMARD	SAR + cDMARD		398	399		2.78	7.70	0.25	4.61		
Takeuchi 2013[81]	cDMARD	ETN		171	181		9.82	15.20	3.33	9.82		
LITHE[125]	cDMARD	TCZiv + cDMARD		294	696		1.17	3.14	0.29	1.15		
SAMURAI[84]	cDMARD	TCZiv		143	157		6.10	11.60	2.30	5.43		
ORAL-Scan[78]	cDMARD	TOF + cDMARD		160	321		0.92	NR	0.29	NR		
AMPLE[94]	ADA + cDMARD	ABTsc + cDMARD		289	290		0.38	5.00	0.58	3.22		
AIM[173]	cDMARD	ABTiv + cDMARD		195	391		2.32	NR	1.21	NR		
DE019[179]	cDMARD	ADA + cDMARD		200	207		2.70	6.80	0.10	4.80		
GO-FORWARD[198]	cDMARD	GOLsc + cDMARD		122	86		1.10	4.70	0.93	4.86		
GO-FURTHER[214]	cDMARD	GOLiv + cDMARD		193	391		1.22	3.98	0.13	3.11		
RAPID1[181]	cDMARD	CTZ + cDMARD		199	393		2.80	NR	0.4	NR		
RA-BEAM[97]	cDMARD	BAR + cDMARD	ADA+cDMARD	452	473	312	1.8	3.83	0.71	4.02	0.6	10.6

DIC=53.3; resdev=32.3

Figure C18: League table, NMA results Mixed population, Sharp Score

IFX+cDMARD																
0.39 (-0.03, 0.79)	ETN+cDMARD															
0.40 (-0.10, 0.90)	0.01 (-0.35, 0.38)	RTX+cDMARD														
0.45 (0.03, 0.87)	0.07 (-0.18, 0.31)	0.05 (-0.33, 0.43)	TCZiv+cDMARD													
0.48 (0.04, 0.92)	0.09 (-0.19, 0.37)	0.08 (-0.32, 0.48)	0.03 (-0.27, 0.32)	TCZiv												
0.50 (0.10, 0.90)	0.11 (-0.10, 0.33)	0.10 (-0.26, 0.46)	0.05 (-0.18, 0.28)	0.02 (-0.25, 0.29)	SAR+cDMARD											
0.51 (0.10, 0.91)	**0.12 (0.02, 0.21)**	0.10 (-0.26, 0.47)	-0.07 (-0.31, 0.18)	0.02 (-0.25, 0.30)	0.00 (-0.20, 0.21)	ETN										
0.54 (0.15, 0.94)	0.16 (-0.04, 0.35)	0.14 (-0.20, 0.49)	0.09 (-0.13, 0.31)	0.06 (-0.19, 0.32)	0.04 (-0.14, 0.22)	0.04 (-0.15, 0.23)	ADA+cDMARD									
0.58 (0.16, 0.10)	0.19 (-0.05, 0.44)	0.18 (-0.20, 0.56)	0.13 (-0.14, 0.39)	0.10 (-0.19, 0.40)	0.08 (-0.15, 0.31)	0.19 (-0.05, 0.44)	0.04 (-0.18, 0.25)	GOLiv+cDMARD								
0.59 (0.17, 1.01)	0.21 (-0.05, 0.46)	0.19 (-0.19, 0.57)	0.14 (-0.13, 0.41)	0.11 (-0.19, 0.41)	0.09 (-0.15, 0.33)	0.09 (-0.16, 0.33)	0.05 (-0.11, 0.21)	0.01 (-0.26, 0.28)	ABTsc+cDMARD							
0.60 (0.20, 0.99)	**0.21 (0.01, 0.42)**	0.20 (-0.15, 0.55)	0.15 (-0.08, 0.37)	0.12 (-0.14, 0.38)	0.10 (-0.09, 0.28)	0.10 (-0.10, 0.29)	0.06 (-0.08, 0.19)	0.02 (-0.20, 0.24)	0.01 (-0.20, 0.22)	BAR+cDMARD						
0.69 (0.27, 1.11)	**0.30 (0.06, 0.55)**	0.29 (-0.09, 0.66)	0.24 (-0.03, 0.50)	0.21 (-0.09, 0.50)	0.19 (-0.04, 0.42)	0.19 (-0.05, 0.43)	0.14 (-0.07, 0.36)	0.11 (-0.15, 0.37)	0.10 (-0.17, 0.37)	0.09 (-0.13, 0.3)	ABTiv+cDMARD					
0.71 (0.29, 1.13)	**0.32 (0.07, 0.57)**	0.31 (-0.07, 0.69)	0.26 (-0.01, 0.52)	0.23 (-0.07, 0.5)	0.21 (-0.03, 0.45)	0.21 (-0.04, 0.45)	0.17 (-0.06, 0.39)	0.13 (-0.14, 0.40)	0.12 (-0.16, 0.396)	0.11 (-0.12, 0.34)	0.02 (-0.25, 0.29)	TOF+cDMARD				
0.72 (0.30, 1.13)	**0.33 (0.09, 0.57)**	0.32 (-0.06, 0.69)	**0.27 (0.00, 0.53)**	0.24 (-0.05, 0.53)	0.22 (-0.01, 0.45)	0.21 (-0.02, 0.45)	0.17 (-0.04, 0.39)	0.14 (-0.12, 0.40)	0.13 (-0.143, 0.39)	0.12 (-0.10, 0.34)	0.03 (-0.23, 0.23)	0.01 (-0.26, 0.27)	CTZ+cDMARD			
0.86 (0.40, 1.32)	**0.47 (0.16, 0.79)**	**0.46 (0.03, 0.88)**	**0.41 (0.08, 0.73)**	**0.38 (0.03, 0.73)**	**0.36 (0.06, 0.66)**	**0.36 (0.05, 0.66)**	**0.32 (0.03, 0.61)**	0.28 (-0.05, 0.60)	0.27 (-0.06, 0.60)	0.26 (-0.03, 0.55)	0.17 (-0.15, 0.50)	0.15 (-0.18, 0.48)	0.14 (-0.18, 0.47)	GOLsc+cDMARD	
0.89 (0.52, 1.27)	**0.51 (0.34, 0.67)**	**0.49 (0.16, 0.82)**	**0.44 (0.25, 0.63)**	**0.41 (0.19, 0.64)**	**0.40 (0.26, 0.53)**	**0.39 (0.24, 0.54)**	**0.35 (0.24, 0.46)**	**0.31 (0.13, 0.50)**	**0.30 (0.11, 0.50)**	**0.29 (0.17, 0.42)**	**0.21 (0.02, 0.39)**	0.18 (-0.01, 0.38)	0.18 (-0.00, 0.36)	0.03 (-0.23, 0.30)	cDMARD

*To zoom in on numbers, hold the Ctrl key and scroll with mouse or trackpad

Figure C19. Network Diagram for Sensitivity Analysis of ACR (TIM-Naïve Population)

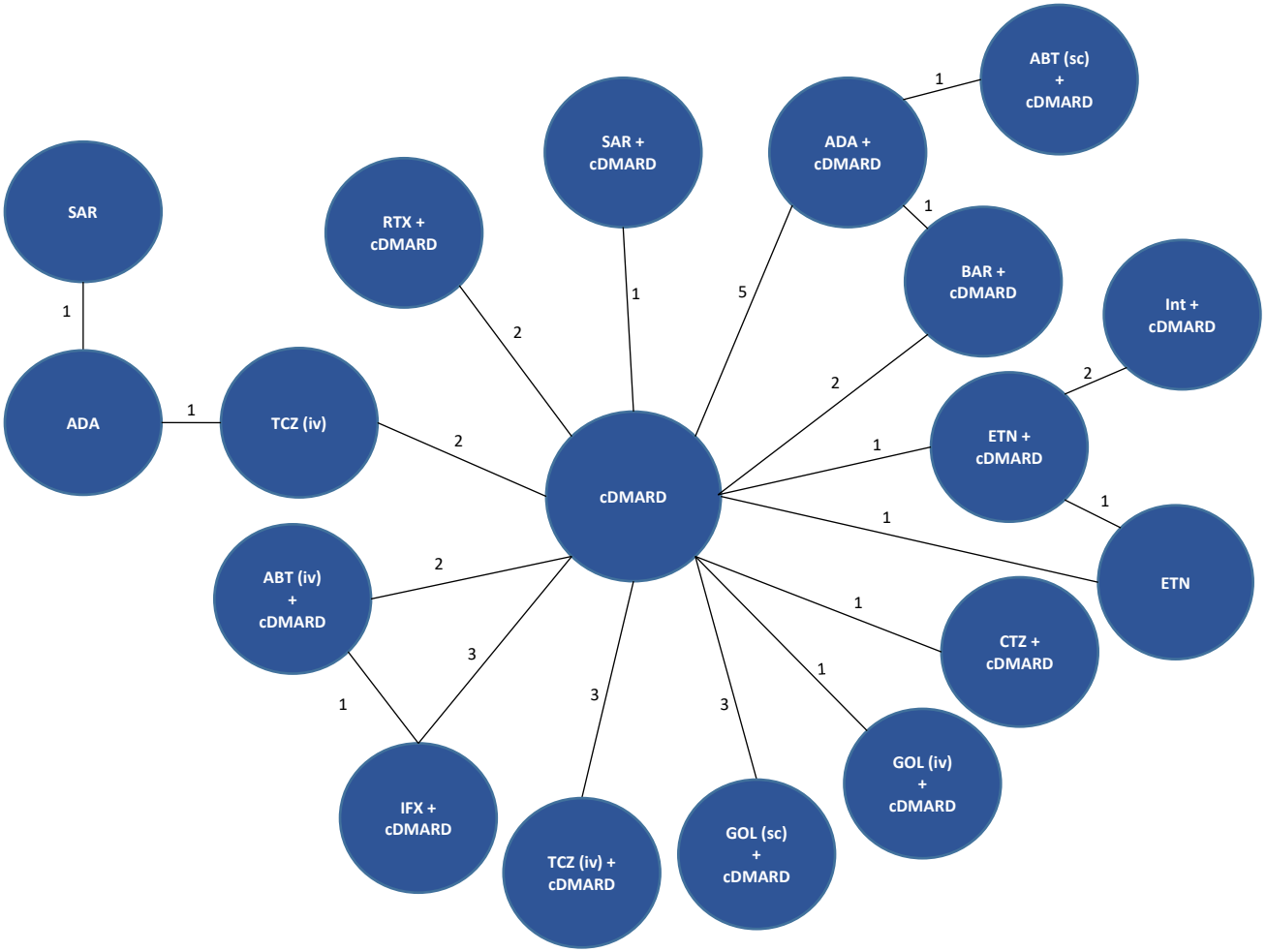


Table C15: ACR Data used in NMA (Sensitivity Analysis TIM-naïve population)

	Interventions			Mean disease duration	Intervention 1					Intervention 2				
Trial Name	1	2	3	Weeks	No response	ACR20	ACR50	ACR70	n	No response	ACR20	ACR50	ACR70	n
ADACTA[19]	ADA	TCZ		354	82	35	16	29	162	57	29	24	53	163
AIM[173]	cDMARD	ABTiv + cDMARD		449	132	50	23	14	219	139	121	87	86	433
AMPLE[94]	ADA + cDMARD	ABTsc + cDMARD		94	117	72	65	74	328	108	65	68	77	318
ARMADA[176]	cDMARD	ADA + cDMARD		607	53	4	2	3	62	22	8	19	18	67
ATTEST[23]	cDMARD	ABTiv + cDMARD	IFX + cDMARD	405	64	24	12	10	110	52	41	31	32	156
ATTRACT[187]	cDMARD	IFX + cDMARD			67	13	4	0	84	82	38	26	22	168
DE019[179]	cDMARD	ADA + cDMARD		569	141	40	14	5	200	76	50	38	43	207
ETN309[183]	cDMARD	ETN + cDMARD	ETN	341	36	7	6	1	50	27	22	27	25	101
GO-FORTH[160]	cDMARD	GOLsc + cDMARD		455	59	16	8	5	88	25	25	13	23	86
GO-FORWARD[87]	cDMARD	GOLsc + cDMARD		421	96	19	11	7	133	36	20	15	18	89
Kim2007[177]	cDMARD	ADA + cDMARD		356	40	14	4	5	63	25	12	14	14	65

	Interventions			Mean disease duration	Intervention 1						Intervention 2			
LARA[158]	Int cDMARD	ETN + cDMARD		430	71	38	17	16	142	47	59	76	97	279
O'Dell[77]	Int cDMARD	ETN + cDMARD		271	70	48	33	8	159	73	32	32	26	163
SAMURAI[84]	cDMARD	TCZ		119	89	30	16	10	145	28	39	37	53	157
SATORI[85]	cDMARD	TCZ		447	48	9	3	4	64	12	18	12	19	61
STAR[178]	cDMARD	ADA + cDMARD		541	207	75	25	11	318	150	76	45	47	318
START[188]	cDMARD	IFX + cDMARD		390	276	54	17	16	363	317	175	127	102	721
TOWARD[152]	cDMARD	TCZ + cDMARD		510	312	64	25	12	413	315	186	137	165	803
RA-BUILD[175]	cDMARD	BAR + cDMARD		390	132	47	31	18	228	79	48	45	55	227
MOBILITY[162]	cDMARD	SAR + cDMARD		460	191	46	26	26	289	95	58	58	78	289
Choy 2012[182]	cDMARD	CTZ + cDMARD		502	92	20	5	2	119	67	35	22	0	124
SERENE[149]	cDMARD	RTX + cDMARD		366	132	24	7	9	172	84	42	27	17	170
GO-FURTHER[184]	cDMARD	GOLiv + cDMARD		359	136	35	18	8	197	134	123	68	70	395
Li 2015[185]	cDMARD	GOLsc + cDMARD		406	111	12	7	2	132	76	31	17	8	132
RA-SCORE[171]	cDMARD	RTX + cDMARD		242	45	11	6	1	63	29	15	11	5	60

	Interventions			Mean disease duration	Intervention 1					Intervention 2				
MONARCH[18]	ADA	SAR			77	53	33	22	185	52	48	41	43	184
RA-BEAM[97]	cDMARD	ADA + cDMARD	BAR + cDMARD	na	307	88	54	39	488	112	66	79	73	330

	Interventions			Mean disease duration	Intervention 3				
Trial Name	1	2	3	Weeks	No response	ACR20	ACR50	ACR70	n
ATTEST[23]	cDMARD	ABTiv + cDMARD	IFX + cDMARD	405	67	37	21	40	165
ETN309[183]	cDMARD	ETN + cDMARD	ETN	341	27	28	26	22	103
RA-BEAM[97]	cDMARD	ADA + cDMARD	BAR + cDMARD	na	127	117	97	146	487

DIC=1096.7; resdev=236.5

Figure C20. League table, NMA results TIM-naïve population, ACR20

TCZiv																	
1.02 (0.74-1.61)	ETN+cDMARD																
1.04 (0.79-1.91)	1.02 (0.62-2.05)	SAR															
1.04 (0.76-1.69)	1.02 (0.76-1.43)	1.00 (0.50-1.71)	ETN														
1.08 (0.81-1.69)	1.06 (0.68-1.70)	1.04 (0.52-1.73)	1.04 (0.64-1.66)	TCZiv+cDMARD													
1.15 (0.84-2.01)	1.12 (0.71-2.01)	1.10 (0.55-2.02)	1.10 (0.67-1.94)	1.06 (0.68-1.83)	ABTsc+cDMARD												
1.15 (0.85-1.96)	1.13 (0.72-1.96)	1.10 (0.56-1.97)	1.10 (0.68-1.91)	1.06 (0.68-1.79)	1.00 (0.59-1.69)	SAR+cDMARD											
1.17 (0.91-1.74)	1.14 (0.76-1.76)	1.12 (0.59-1.80)	1.12 (0.72-1.71)	1.08 (0.73-1.59)	1.02 (0.63-1.50)	1.01 (0.63-1.49)	BAR+cDMARD										
1.17 (0.91-1.72)	1.14 (0.76-1.75)	1.12 (0.59-1.78)	1.12 (0.72-1.70)	1.08 (0.73-1.57)	1.02 (0.62-1.50)	1.01 (0.63-1.48)	1.00 (0.72-1.38)	GOLsc+cDMARD									
1.18 (0.87-2.06)	1.15 (0.73-2.05)	1.13 (0.58-2.08)	1.13 (0.70-2.00)	1.09 (0.70-1.88)	1.03 (0.60-1.78)	1.02 (0.61-1.75)	1.01 (0.68-1.66)	1.01 (0.69-1.65)	GOLiv+cDMARD								
1.18 (0.94-1.66)	1.16 (0.78-1.69)	1.13 (0.59-1.74)	1.13 (0.74-1.65)	1.09 (0.75-1.53)	1.03 (0.68-1.36)	1.02 (0.65-1.43)	1.01 (0.76-1.28)	1.01 (0.75-1.31)	1.00 (0.62-1.40)	ADA+cDMARD							
1.24 (0.97-1.90)	1.21 (0.81-1.93)	1.18 (0.63-1.96)	1.19 (0.77-1.87)	1.14 (0.78-1.74)	1.08 (0.67-1.66)	1.07 (0.68-1.62)	1.06 (0.78-1.51)	1.06 (0.78-1.51)	1.05 (0.65-1.59)	1.05 (0.82-1.46)	IFX+cDMARD						
1.25 (0.97-2.34)	1.21 (0.75-2.63)	1.18 (0.88-1.83)	1.19 (0.71-2.55)	1.15 (0.71-2.40)	1.08 (0.61-2.28)	1.07 (0.62-2.24)	1.06 (0.68-2.14)	1.06 (0.69-2.14)	1.05 (0.59-2.18)	1.05 (0.71-2.10)	1.00 (0.63-1.98)	ADA					
1.27 (0.97-2.04)	1.24 (0.82-2.07)	1.21 (0.64-2.08)	1.21 (0.78-2.00)	1.16 (0.79-1.87)	1.10 (0.68-1.78)	1.09 (0.69-1.73)	1.08 (0.78-1.63)	1.08 (0.79-1.62)	1.07 (0.66-1.71)	1.07 (0.82-1.58)	1.02 (0.76-1.43)	1.02 (0.52-1.68)	ABTiv+cDMARD				
1.29 (0.97-2.20)	1.26 (0.83-2.22)	1.23 (0.64-2.25)	1.23 (0.78-2.15)	1.19 (0.79-1.99)	1.12 (0.67-1.89)	1.11 (0.69-1.86)	1.10 (0.78-1.76)	1.10 (0.78-1.74)	1.09 (0.66-1.82)	1.09 (0.81-1.70)	1.04 (0.72-1.61)	1.03 (0.52-1.80)	1.02 (0.67-1.60)	RTX+cDMARD			
1.33 (0.88-3.30)	1.31 (1.03-2.34)	1.26 (0.63-3.22)	1.27 (0.89-2.66)	1.22 (0.73-2.97)	1.15 (0.64-2.78)	1.14 (0.64-2.74)	1.13 (0.71-2.63)	1.13 (0.71-2.64)	1.12 (0.62-2.67)	1.12 (0.73-2.60)	1.06 (0.65-2.46)	1.06 (0.50-2.59)	1.04 (0.61-2.40)	1.03 (0.57-2.38)	int cDMARD		
1.40 (0.97-3.01)	1.37 (0.86-2.95)	1.33 (0.67-2.97)	1.33 (0.81-2.86)	1.29 (0.80-2.69)	1.21 (0.70-2.53)	1.20 (0.72-2.47)	1.19 (0.78-2.38)	1.19 (0.79-2.37)	1.18 (0.68-2.45)	1.18 (0.81-2.32)	1.12 (0.73-2.18)	1.12 (0.54-2.37)	1.10 (0.69-2.15)	1.08 (0.64-2.13)	1.05 (0.45-2.24)	CTZ+cDMARD	
2.30 (1.50-4.23)	**2.21 (1.41-4.30)**	**2.13 (1.17-4.35)**	**2.15 (1.37-4.13)**	**2.08 (1.37-3.79)**	**1.94 (1.26-3.53)**	**1.94 (1.27-3.46)**	**1.94 (1.36-3.21)**	**1.94 (1.38-3.19)**	**1.89 (1.24-3.36)**	**1.93 (1.40-3.05)**	**1.82 (1.32-2.88)**	**1.78 (1.00-3.33)**	**1.77 (1.27-2.85)**	**1.73 (1.21-2.86)**	1.66 (0.82-3.19)	1.58 (0.92-2.82)	cDMARD

*To zoom in on numbers, hold the Ctrl key and scroll with mouse or trackpad

Figure C21. League table, NMA results TIM-naïve population, ACR50

ACR50																	
TCZiv																	
1.03 (0.59-2.18)	ETN+cDMARD																
1.07 (0.65-2.76)	1.04 (0.44-3.16)	SAR															
1.08 (0.61-2.37)	1.04 (0.63-1.79)	1.01 (0.33-2.46)	ETN														
1.16 (0.69-2.36)	1.12 (0.53-2.42)	1.08 (0.36-2.52)	1.07 (0.49-2.31)	TCZiv+cDMARD													
1.29 (0.73-3.03)	1.24 (0.57-3.06)	1.19 (0.39-3.16)	1.19 (0.52-2.91)	1.11 (0.52-2.62)	ABTsc+cDMARD												
1.30 (0.75-2.91)	1.25 (0.59-2.98)	1.20 (0.40-3.05)	1.20 (0.54-2.84)	1.12 (0.54-2.53)	1.01 (0.43-2.33)	SAR+cDMARD											
1.33 (0.84-2.44)	1.28 (0.64-2.54)	1.23 (0.44-2.65)	1.23 (0.59-2.41)	1.14 (0.60-2.14)	1.03 (0.49-1.95)	1.02 (0.48-1.93)	BAR+cDMARD										
1.33 (0.85-2.41)	1.28 (0.65-2.51)	1.23 (0.43-2.63)	1.23 (0.59-2.40)	1.14 (0.60-2.09)	1.03 (0.48-1.96)	1.02 (0.49-1.89)	1.00 (0.59-1.69)	GOLsc+cDMARD									
1.35 (0.78-3.13)	1.30 (0.60-3.15)	1.25 (0.42-3.29)	1.24 (0.56-3.02)	1.16 (0.56-2.71)	1.05 (0.45-2.50)	1.04 (0.46-2.41)	1.02 (0.54-2.19)	1.02 (0.55-2.18)	GOLiv+cDMARD								
1.36 (0.90-2.26)	1.31 (0.66-2.39)	1.26 (0.45-2.54)	1.25 (0.61-2.28)	1.17 (0.63-2.00)	1.05 (0.55-1.68)	1.04 (0.51-1.81)	1.02 (0.65-1.50)	1.02 (0.63-1.56)	1.00 (0.48-1.75)	ADA+cDMARD							
1.48 (0.95-2.75)	1.42 (0.71-2.88)	1.36 (0.49-3.02)	1.36 (0.66-2.76)	1.27 (0.67-2.42)	1.14 (0.53-2.26)	1.13 (0.55-2.16)	1.11 (0.66-1.92)	1.11 (0.68-1.90)	1.09 (0.52-2.10)	1.08 (0.72-1.80)	IFX+cDMARD						
1.49 (0.94-3.63)	1.42 (0.61-4.50)	1.36 (0.81-2.53)	1.36 (0.57-4.26)	1.27 (0.56-3.82)	1.14 (0.45-3.55)	1.13 (0.46-3.42)	1.11 (0.53-3.14)	1.11 (0.54-3.17)	1.09 (0.43-3.28)	1.09 (0.56-3.05)	1.00 (0.47-2.78)	ADA					
1.53 (0.94-3.09)	1.47 (0.73-3.18)	1.41 (0.50-3.29)	1.40 (0.67-3.03)	1.31 (0.68-2.70)	1.18 (0.55-2.50)	1.17 (0.56-2.38)	1.14 (0.67-2.14)	1.14 (0.68-2.12)	1.13 (0.53-2.32)	1.12 (0.72-2.03)	1.03 (0.64-1.74)	1.03 (0.37-2.31)	ABTiv+cDMARD				
1.57 (0.94-3.41)	1.50 (0.73-3.53)	1.44 (0.50-3.66)	1.44 (0.67-3.35)	1.34 (0.68-2.95)	1.21 (0.54-2.72)	1.20 (0.56-2.64)	1.17 (0.67-2.37)	1.18 (0.67-2.35)	1.16 (0.53-2.54)	1.15 (0.71-2.25)	1.06 (0.59-2.08)	1.05 (0.37-2.54)	1.03 (0.53-2.05)	RTX+cDMARD			
1.65 (0.80-6.05)	**1.59 (1.07-3.48)**	1.51 (0.47-6.02)	1.51 (0.81-4.31)	1.41 (0.59-5.12)	1.26 (0.48-4.67)	1.26 (0.49-4.53)	1.23 (0.56-4.20)	1.23 (0.57-4.24)	1.21 (0.47-4.36)	1.21 (0.58-4.11)	1.11 (0.49-3.77)	1.11 (0.34-4.19)	1.08 (0.45-3.62)	1.05 (0.41-3.60)	int cDMARD		
1.80 (0.94-5.29)	1.72 (0.76-5.23)	1.64 (0.54-5.36)	1.65 (0.70-4.94)	1.54 (0.69-4.45)	1.38 (0.57-4.08)	1.37 (0.59-3.93)	1.34 (0.67-3.64)	1.34 (0.67-3.62)	1.31 (0.54-3.89)	1.32 (0.70-3.49)	1.21 (0.60-3.19)	1.20 (0.40-3.71)	1.17 (0.55-3.12)	1.14 (0.50-3.10)	1.09 (0.30-3.43)	CTZ+cDMARD	
3.76 (2.10-8.16)	**3.54 (1.79-8.52)**	**3.35 (1.28-8.98)**	**3.38 (1.70-8.04)**	**3.17 (1.7-6.94)**	**2.83 (1.43-6.34)**	**2.81 (1.47-6.07)**	**2.78 (1.7-5.29)**	**2.78 (1.73-5.23)**	**2.7 (1.4-5.83)**	**2.75 (1.79-4.84)**	**2.50 (1.60-4.49)**	**2.45 (1.00-5.90)**	**2.4 (1.47-4.47)**	**2.33 (1.35-4.53)**	2.20 (0.76-5.59)	2.03 (0.89-4.51)	cDMARD

Figure C22. League table, NMA results TIM-naïve population, ACR70

TCZiv																		
1.06 (0.45-3.05)	ETN+cDMARD																	
1.12 (0.52-4.03)	1.06 (0.30-5.02)	SAR																
1.13 (0.48-3.39)	1.07 (0.51-2.30)	1.01 (0.21-3.75)	ETN															
1.26 (0.58-3.39)	1.19 (0.40-3.56)	1.13 (0.24-3.85)	1.11 (0.36-3.34)	TCZiv+cDMARD														
1.47 (0.62-4.67)	1.39 (0.44-4.82)	1.31 (0.27-5.17)	1.30 (0.40-4.49)	1.17 (0.40-3.80)	ABTsc+cDMARD													
1.49 (0.65-4.45)	1.41 (0.47-4.65)	1.33 (0.29-4.93)	1.32 (0.41-4.36)	1.18 (0.41-3.67)	1.01 (0.31-3.28)	SAR+cDMARD												
1.54 (0.78-3.53)	1.45 (0.53-3.79)	1.37 (0.32-4.13)	1.36 (0.48-3.55)	1.22 (0.48-2.95)	1.05 (0.37-2.60)	1.04 (0.37-2.55)	BAR+cDMARD											
1.54 (0.79-3.44)	1.45 (0.54-3.72)	1.37 (0.32-4.07)	1.36 (0.48-3.50)	1.22 (0.49-2.86)	1.05 (0.36-2.63)	1.03 (0.37-2.47)	1.00 (0.48-2.08)	GOLsc+cDMARD										
1.58 (0.68-4.91)	1.49 (0.48-5.02)	1.40 (0.30-5.46)	1.39 (0.44-4.72)	1.25 (0.44-4.01)	1.07 (0.33-3.58)	1.06 (0.34-3.42)	1.02 (0.41-2.95)	1.02 (0.42-2.92)	GOLiv+cDMARD									
1.59 (0.85-3.18)	1.50 (0.56-3.51)	1.42 (0.33-3.91)	1.40 (0.51-3.29)	1.26 (0.52-2.68)	1.08 (0.44-2.11)	1.07 (0.39-2.33)	1.03 (0.55-1.77)	1.03 (0.53-1.87)	1.01 (0.36-2.23)	ADA+cDMARD								
1.79 (0.92-4.11)	1.69 (0.62-4.47)	1.59 (0.38-4.90)	1.58 (0.57-4.19)	1.41 (0.57-3.44)	1.21 (0.42-3.17)	1.20 (0.44-2.95)	1.16 (0.56-2.47)	1.16 (0.58-2.43)	1.13 (0.40-2.82)	1.13 (0.63-2.24)	IFX+cDMARD							
1.80 (0.90-5.71)	1.69 (0.49-7.91)	1.58 (0.74-3.56)	1.58 (0.44-7.33)	1.43 (0.43-6.23)	1.22 (0.33-5.65)	1.20 (0.34-5.35)	1.16 (0.40-4.67)	1.16 (0.41-4.72)	1.14 (0.31-5.02)	1.13 (0.43-4.46)	1.00 (0.35-3.92)	ADA						
1.88 (0.92-4.77)	1.77 (0.64-5.11)	1.67 (0.39-5.52)	1.65 (0.58-4.76)	1.48 (0.59-3.99)	1.27 (0.44-3.63)	1.26 (0.45-3.34)	1.21 (0.57-2.86)	1.22 (0.58-2.81)	1.19 (0.41-3.23)	1.18 (0.63-2.64)	1.05 (0.54-2.13)	1.05 (0.26-3.25)	ABTiv+cDMARD					
1.96 (0.91-5.44)	1.83 (0.65-5.81)	1.73 (0.39-6.28)	1.72 (0.57-5.42)	1.54 (0.58-4.44)	1.32 (0.43-4.02)	1.31 (0.45-3.82)	1.26 (0.56-3.24)	1.27 (0.58-3.21)	1.23 (0.41-3.63)	1.23 (0.61-3.00)	1.09 (0.48-2.73)	1.08 (0.26-3.66)	1.04 (0.42-2.67)	RTX+cDMARD				
2.09 (0.71-11.36)	**1.98 (1.13-5.18)**	1.84 (0.35-11.68)	1.83 (0.73-7.10)	1.65 (0.46-9.00)	1.41 (0.36-7.96)	1.39 (0.36-7.56)	1.35 (0.43-6.82)	1.35 (0.44-6.85)	1.31 (0.34-7.19)	1.32 (0.46-6.53)	1.16 (0.36-5.79)	1.16 (0.23-6.97)	1.11 (0.33-5.52)	1.07 (0.29-5.48)	Int cDMARD			
2.36 (0.91-9.45)	2.21 (0.67-9.59)	2.07 (0.42-10.19)	2.07 (0.60-8.85)	1.86 (0.59-7.56)	1.58 (0.46-6.74)	1.57 (0.47-6.34)	1.52 (0.56-5.62)	1.53 (0.57-5.60)	1.48 (0.43-6.23)	1.48 (0.60-5.30)	1.32 (0.49-4.68)	1.30 (0.28-5.98)	1.25 (0.43-4.58)	1.21 (0.38-4.55)	1.13 (0.20-5.35)	CTZ+cDMARD		
6.29 (3.03-15.85)	**5.82 (2.29-17.46)**	**5.41 (1.39-19.31)**	**5.44 (2.10-16.03)**	**4.91 (2.12-12.87)**	**4.17 (1.62-11.58)**	**4.13 (1.69-10.88)**	**4.03 (2.13-8.77)**	**4.03 (2.20-8.63)**	**3.89 (1.57-10.31)**	**3.95 (2.35-7.71)**	**3.47 (1.94-7.03)**	**3.40 (1.00-10.65)**	**3.29 (1.70-7.07)**	**3.15 (1.49-7.22)**	2.93 (0.70-9.94)	2.60 (0.86-7.33)	cDMARD

*To zoom in on numbers, hold the Ctrl key and scroll with mouse or trackpad

Figure C23. Network Diagram for Sensitivity Analysis of ACR (by Class, Mixed Population)

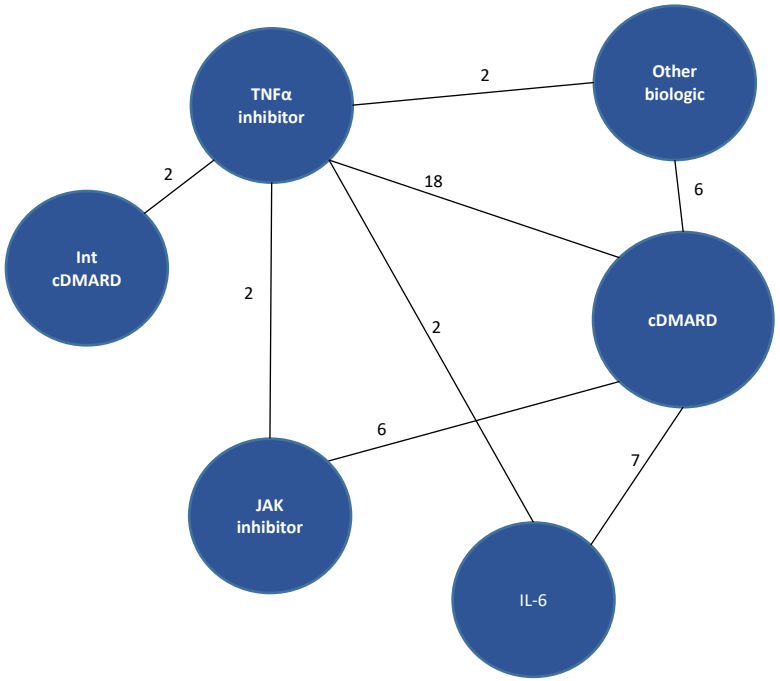


Table C16: ACR Data used in (Sensitivity analysis by class, Mixed population)

Trial Name	Interventions			Mean disease duration	Intervention 1					Intervention 2				
	1	2	3	Weeks	No response	ACR20	ACR50	ACR70	n	No response	ACR20	ACR50	ACR70	n
ADACTA[19]	TNFi	IL-6		354	82	35	16	29	162	57	29	24	53	163
AIM[173]	cDMARD	Other biologic		449	132	50	23	14	219	139	121	87	86	433
AMPLE[94]	TNFi	Other biologic		94	117	72	65	74	328	108	65	68	77	318
ARMADA[176]	cDMARD	TNFi		607	53	4	2	3	62	22	8	19	18	67
ATTEST[23]	cDMARD	Other biologic	TNFi	405	64	24	12	10	110	52	41	31	32	156
ATTRACT[187]	cDMARD	TNFi			67	13	4	0	84	82	38	26	22	168
DE019[179]	cDMARD	TNFi		569	141	40	14	5	200	76	50	38	43	207
ETN309[183]	cDMARD	TNFi	TNFi	341	36	7	6	1	50	27	22	27	25	101
GO-FORTH[160]	cDMARD	TNFi		455	59	16	8	5	88	25	25	13	23	86
GO-FORWARD[87]	cDMARD	TNFi		421	96	19	11	7	133	36	20	15	18	89
Kim2007[177]	cDMARD	TNFi		356	40	14	4	5	63	25	12	14	14	65
LARA[158]	Int cDMARD	TNFi		430	71	38	17	16	142	47	59	76	97	279
O'Dell[77]	Int cDMARD	TNFi		271	70	48	33	8	159	73	32	32	26	163
SAMURAI[84]	cDMARD	IL-6		119	89	30	16	10	145	28	39	37	53	157
SATORI[85]	cDMARD	IL-6		447	48	9	3	4	64	12	18	12	19	61
STAR[178]	cDMARD	TNFi		541	207	75	25	11	318	150	76	45	47	318

Trial Name	Interventions			Mean disease duration	Intervention 1					Intervention 2				
	1	2	3	Weeks	No response	ACR20	ACR50	ACR70	n	No response	ACR20	ACR50	ACR70	n
START[188]	cDMARD	TNFi		390	276	54	17	16	363	317	175	127	102	721
TOWARD[152]	cDMARD	IL-6		510	312	64	25	12	413	315	186	137	165	803
RA-BUILD[175]	cDMARD	JAKi		390	132	47	31	18	228	79	48	45	55	227
MOBILITY[162]	cDMARD	IL-6		460	265	67	37	29	398	134	83	83	99	399
ORAL Scan[78]	cDMARD	JAKi		463	120	27	11	2	160	156	61	57	47	321
Kremer 2012[212]	cDMARD	JAKi		473	45	7	11	6	69	37	10	10	14	71
LITHE[125]	cDMARD	IL-6		476	287	67	31	8	393	371	199	131	96	797
OPTION[213]	cDMARD	IL-6		398	151	31	18	4	204	195	66	86	71	418
RAPID1[181]	cDMARD	TNFi		319	171	12	9	6	199	162	85	62	84	393
RAPID2[180]	cDMARD	TNFi		308	116	7	3	1	127	105	61	41	39	246
Choy 2012[182]	cDMARD	TNFi		502	92	20	5	2	119	67	35	22	0	124
SERENE[149]	cDMARD	Other biologic		366	132	24	7	9	172	84	42	27	17	170
BREVACTA[153]	cDMARD	IL-6		577	149	44	15	11	219	170	92	88	87	437
Kremer 2003[174]	cDMARD	Other biologic			77	28	12	2	119	46	27	23	19	115
ORAL Standard[95]	cDMARD	JAKi	TNFi	408	41	2	5	8	56	95	30	32	39	196
GO-FURTHER[184]	cDMARD	TNFi		359	136	35	18	8	197	134	123	68	70	395
ORAL Sync[154]	cDMARD	JAKi		462	110	29	15	5	159	151	59	64	41	315
Li 2015[185]	cDMARD	TNFi		406	111	12	7	2	132	76	31	17	8	132
RA-SCORE[171]	cDMARD	Other biologic		242	45	11	6	1	63	29	15	11	5	60

Trial Name	Interventions			Mean disease duration	Intervention 1					Intervention 2				
	1	2	3	Weeks	No response	ACR20	ACR50	ACR70	n	No response	ACR20	ACR50	ACR70	n
Takeuchi 2013[172]	cDMARD	Other biologic		382	52	10	4	0	66	14	19	15	13	61
J-RAPID[156]	cDMARD	TNFi		296	58	6	12	1	77	22	15	21	24	82
RA-BEAM[97]	cDMARD	TNFi	JAKi	na	307	88	54	39	488	112	66	79	73	330
MONARCH[18]	TNFi	IL-6			77	53	33	22	185	52	48	41	43	184

Trial Name	Interventions			Mean disease duration	Intervention 3				
	1	2	3	Weeks	No response	ACR20	ACR50	ACR70	n
ATTEST[23]	cDMARD	Other biologic	TNFi	405	67	37	21	40	165
ETN309[183]	cDMARD	TNFi	TNFi	341	27	28	26	22	103
ORAL Standard[95]	cDMARD	JAKi	TNFi	408	105	36	38	20	199
RA-BEAM[97]	cDMARD	TNFi	JAKi	nr	127	117	97	146	487

DIC=1626.3; resdev=410.6

Figure C24. League table, NMA results by Class, ACR20

IL-6					
1.12 (1.00-1.34)	**TNFi**				
1.14 (0.97-1.46)	1.02 (0.87-1.22)	**Other Biologic**			
1.17 (1.00-1.54)	1.05 (0.90-1.28)	1.03 (0.83-1.31)	**JAKi**		
1.75 (1.19-3.36)	**1.55 (1.10-2.77)**	**1.52 (1.05-2.80)**	**1.48 (1.02-2.68)**	**Int cDMARD**	
2.44 (1.65-4.06)	**2.16 (1.55-3.28)**	**2.11 (1.52-3.29)**	**2.05 (1.49-3.14)**	1.36 (0.87-2.16)	**cDMARD**

Figure C25. League table, NMA results by Class, ACR50

IL-6					
1.21 (1.00-1.56)	**TNFi**				
1.24 (0.95-1.76)	**1.03 (0.81-1.35)**	**Other Biologic**			
1.30 (1.00-1.90)	**1.07 (0.84-1.45)**	**1.05 (0.75-1.49)**	**JAKi**		
2.37 (1.34-5.49)	**1.95 (1.18-4.14)**	**1.89 (1.09-4.22)**	**1.81 (1.02-3.97)**	**Int cDMARD**	
3.77 (2.33-6.81)	**3.11 (2.08-5.01)**	**3.00 (1.98-5.09)**	**2.86 (1.91-4.75)**	**1.56 (0.83-2.92)**	**cDMARD**

Figure C26. League table, NMA results by Class, ACR70

IL-6					
1.32 (1.00-1.84)	**TNFi**				
1.36 (0.94-2.16)	1.04 (0.74-1.50)	**Other Biologic**			
1.46 (0.99-2.39)	1.11 (0.79-1.66)	1.07 (0.68-1.74)	**JAKi**		
3.30 (1.53-9.27)	**2.5 (1.26-6.29)**	**2.40 (1.12-6.51)**	**2.25 (1.03-6.01)**	**Int cDMARD**	
6.01 (3.45-11.66)	**4.55 (2.89-7.75)**	**4.34 (2.66-7.98)**	**4.06 (2.5-7.34)**	1.79 (0.79-3.98)	**cDMARD**

WinBUGS Code for Network Meta-Analyses

ACR BASE CASE (UNADJUSTED), Random Effects

```
# Binomial likelihood, probit link (different categories)
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
p[i,k,1] <- 1 # Pr(PASI >0)
for (j in 1:nc[i]-1) { # LOOP THROUGH CATEGORIES
r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j]) # binomial likelihood
q[i,k,j] <- 1-(p[i,k,C[i,j+1]]/p[i,k,C[i,j]]) # conditional probabilities
theta[i,k,j] <- mu[i] + delta[i,k] + z[j] # linear predictor
rhat[i,k,j] <- q[i,k,j] * n[i,k,j] # predicted number events
dv[i,k,j] <- 2 * (r[i,k,j]*(log(r[i,k,j])-log(rhat[i,k,j])) #Deviance contribution of each category
+(n[i,k,j]-r[i,k,j])*(log(n[i,k,j]-r[i,k,j]) - log(n[i,k,j]-rhat[i,k,j])))
}
dev[i,k] <- sum(dv[i,k,1:nc[i]-1]) # deviance contribution of each arm
for (j in 2:nc[i]) { # LOOP THROUGH CATEGORIES
p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j] # link function
# adjust link function phi(x) for extreme values that can give numerical errors
# when x< -5, phi(x)=0, when x> 5, phi(x)=1
phi.adj[i,k,j] <- step(5+theta[i,k,j-1])
* (step(theta[i,k,j-1]-5)
+ step(5-theta[i,k,j-1])*phi(theta[i,k,j-1]) )
}
}
for (k in 2:na[i]) { # LOOP THROUGH ARMS
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LHR distributions, with multi-arm trial correction
taud[i,k] <- tau *2*(k-1)/k # precision of LHR distributions (with multi-arm trial correction)
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment, multi-arm RCTs
sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
}
resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
}
z[1] <- 0 # set z50=0
for (j in 2:Cmax-1) { # Set priors for z, for any number of categories
```

```
z.aux[j] ~ dunif(0,5) # priors
z[j] <- z[j-1] + z.aux[j] # ensures z[j]~Uniform(z[j-1], z[j-1]+5)
}



totresdev <- sum(resdev[]) #Total Residual Deviance
d[1] <- 0 # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
A~dnorm(meanA, precA)

# calculate prob of achieving ACR 20/50/70 on treat k
for (k in 1:nt) {
for (j in 1: Cmax-1) {
pacr[k,j] <- 1 - phi(A+d[k] + z[j])}
}

for (k in 1:nt-1) {
for (kk in k+1:nt){
RR20[k,kk] <- ppasi[k,1]/ppasi[kk,1]
RR20[kk,k]<- 1/RR20[k,kk]
 }
}

for (k in 1:nt-1) {
for (kk in k+1:nt){
RR50[k,kk] <- ppasi[k,2]/ppasi[kk,2]
RR50[kk,k]<- 1/RR50[k,kk]
}
}

for (k in 1:nt-1) {
for (kk in k+1:nt){
RR70[k,kk] <- ppasi[k,3]/ppasi[kk,3]
RR70[kk,k]<-1/RR70[k,kk]
 }
}
} # *** PROGRAM ENDS
```

ACR UNADJUSTED, Fixed Effects

```
# Binomial likelihood, probit link (different categories)
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS

for(i in 1:ns){ # LOOP THROUGH STUDIES
mu[i] ~ dnorm(0,.001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
p[i,k,1] <- 1 # Pr(PASI >0)
for (j in 1:nc[i]-1) { # LOOP THROUGH CATEGORIES
r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j]) # binomial likelihood
q[i,k,j] <- 1-(p[i,k,C[i,j+1]]/p[i,k,C[i,j]]) # conditional probabilities
theta[i,k,j] <- mu[i] + d[t[i,k]]-d[t[i,1]] + z[j]
rhat[i,k,j] <- q[i,k,j] * n[i,k,j] # predicted number events
dv[i,k,j] <- 2 * (r[i,k,j]*(log(r[i,k,j])-log(rhat[i,k,j])) #Deviance contribution of each category
+(n[i,k,j]-r[i,k,j])*(log(n[i,k,j]-r[i,k,j]) - log(n[i,k,j]-rhat[i,k,j])))
}
dev[i,k] <- sum(dv[i,k,1:nc[i]-1]) # deviance contribution of each arm
for (j in 2:nc[i]) { # LOOP THROUGH CATEGORIES
p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j] # link function
# adjust link function phi(x) for extreme values that can give numerical errors
# when x< -5, phi(x)=0, when x> 5, phi(x)=1
phi.adj[i,k,j] <- step(5+theta[i,k,j-1])
* (step(theta[i,k,j-1]-5)
+ step(5-theta[i,k,j-1])*phi(theta[i,k,j-1]) )
}
}

resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
}
z[1] <- 0 # set z50=0
for (j in 2:Cmax-1) { # Set priors for z, for any number of categories
z.aux[j] ~ dunif(0,5) # priors
z[j] <- z[j-1] + z.aux[j] # ensures z[j]~Uniform(z[j-1], z[j-1]+5)
}

totresdev <- sum(resdev[]) #Total Residual Deviance
d[1] <- 0 # treatment effect is zero for reference treatment


for (k in 2:nt){
d[k] ~ dnorm(0,.0001)
```

```
} # vague priors for treatment effects

A ~ dnorm(meanA,precA)

# calculate prob of achieving ACR 20/50/70 on treat k

for (k in 1:nt) {
for (j in 1: Cmax-1) {
pacr[k,j] <- 1 - phi(A+d[k] + z[j])}
}

for (k in 1:nt-1) {
for (kk in k+1:nt){
RR20[k,kk] <- ppasi[k,1]/ppasi[kk,1]
RR20[kk,k] <- ppasi[kk,1]/ppasi[k,1]
 }
}


for (k in 1:nt-1) {
for (kk in k+1:nt){
RR50[k,kk] <- ppasi[k,2]/ppasi[kk,2]
RR50[kk,k] <- ppasi[kk,2]/ppasi[k,2] }
}


for (k in 1:nt-1) {
for (kk in k+1:nt){
RR70[k,kk] <- ppasi[k,3]/ppasi[kk,3]
RR70[kk,k] <- ppasi[kk,3]/ppasi[k,3] }
}

} # *** PROGRAM ENDS
```

ACR ADJUSTED, Random Effects

```
# Binomial likelihood, probit link (different categories)
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.001) # vague priors for all trial baselines
```

```
for (k in 1:na[i]) { # LOOP THROUGH ARMS
p[i,k,1] <- 1 # Pr(PASI >0)
for (j in 1:nc[i]-1) { # LOOP THROUGH CATEGORIES
r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j]) # binomial likelihood
q[i,k,j] <- 1-(p[i,k,C[i,j+1]]/p[i,k,C[i,j]]) # conditional probabilities
theta[i,k,j] <- mu[i] + delta[i,k] + z[j]+(beta[t[i,k]]-beta[t[i,1]])*(mu[i]-mx) # linear predictor
rhat[i,k,j] <- q[i,k,j] * n[i,k,j] # predicted number events
dv[i,k,j] <- 2 * (r[i,k,j]*(log(r[i,k,j])-log(rhat[i,k,j])) #Deviance contribution of each category
+(n[i,k,j]-r[i,k,j])*(log(n[i,k,j]-r[i,k,j]) - log(n[i,k,j]-rhat[i,k,j])))
}
dev[i,k] <- sum(dv[i,k,1:nc[i]-1]) # deviance contribution of each arm
for (j in 2:nc[i]) { # LOOP THROUGH CATEGORIES
p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j] # link function
# adjust link function phi(x) for extreme values that can give numerical errors
# when x< -5, phi(x)=0, when x> 5, phi(x)=1
phi.adj[i,k,j] <- step(5+theta[i,k,j-1])
* (step(theta[i,k,j-1]-5)
+ step(5-theta[i,k,j-1])*phi(theta[i,k,j-1]) )
}
}
for (k in 2:na[i]) { # LOOP THROUGH ARMS
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LHR distributions, with multi-arm trial correction
taud[i,k] <- tau *2*(k-1)/k # precision of LHR distributions (with multi-arm trial correction)
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment, multi-arm RCTs
sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
}
resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
}
z[1] <- 0 # set z50=0
for (j in 2:Cmax-1) { # Set priors for z, for any number of categories
z.aux[j] ~ dunif(0,5) # priors
z[j] <- z[j-1] + z.aux[j] # ensures z[j]~Uniform(z[j-1], z[j-1]+5)
}



totresdev <- sum(resdev[]) #Total Residual Deviance
d[1] <- 0 # treatment effect is zero for reference treatment
beta[1]<-0

for (k in 2:nt){
```

```
d[k] ~ dnorm(0,.0001)
beta[k]<-B #common covariate effect
} # vague priors for treatment effects

sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
A ~ dnorm(meanA,precA)
B ~ dnorm(0,.0001) #vague prior for covariate effect

# calculate prob of achieving ACR 20/50/70 on treat k
for (k in 1:nt) {
for (j in 1: Cmax-1) {
pACR[k,j] <- 1 - phi(A+d[k] + z[j])}
}

for (k in 1:nt-1) {
for (kk in k+1:nt){
RR20[k,kk] <- ppasi[k,1]/ppasi[kk,1]
RR20[kk,k]<- 1/RR20[k,kk]
 }
}

for (k in 1:nt-1) {
for (kk in k+1:nt){
RR50[k,kk] <- ppasi[k,2]/ppasi[kk,2]
RR50[kk,k]<- 1/RR50[k,kk]
}
}

for (k in 1:nt-1) {
for (kk in k+1:nt){
RR70[k,kk] <- ppasi[k,3]/ppasi[kk,3]
RR70[kk,k]<-1/RR70[k,kk]
 }
}

} # *** PROGRAM ENDS
```

SHARP BASECASE, Fixed Effects

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
```

```
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
se[i,k]<-sdd[i,k]/sqrt(n[i,k])
var[i,k] <- pow(se[i,k],2) # calculate variances
prec[i,k] <- 1/var[i,k] # set precisions
y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # normal likelihood
theta[i,k] <- (mu[i] + delta[i,k])*psd[i] # model for linear predictor
dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k] #Deviance contribution

#calculate the pooled
nom1[i,k]<-n[i,k]*sdd[i,k]*sdd[i,k]  #nominator for the pooled sd
}
resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
ss[i]<-sum(n[i,1:na[i]])-nt+na[i]  #total sample size in a study
nom[i]<-sum(nom1[i,1:na[i]])  #nominator for the pooled sd
psd[i]<-sqrt(nom[i]/(ss[i]-na[i]))  #pooled sd

for (k in 2:na[i]) { # LOOP THROUGH ARMS
delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of treat effects distributions (with multi-arm trial
correction)
taud[i,k] <- tau *2*(k-1)/k # precision of treat effects distributions (with multi-arm trial
correction)
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs
sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
}
}

totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects
sd ~ dunif(0,5) # vague prior for between-trial SD.
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)


# Collection of results#
# pairwise SMDs
# for all comparisons
for (c in 1:(nt-1)) { for (k in (c+1):nt) {
```

```
SMD[c,k] <-d[k] -d[c]
SMD[k,c] <-d[c]-d[k]
}  #to have negative values
}

#Fit of the Model#
for(i in 1:ns) {
for(k in 1:na[i]) {
Darm[i,k]<-(y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])/var[i,k]
}
D[i]<-sum(Darm[i,1:na[i]])
}
D.bar<-sum(D[])

} # *** PROGRAM ENDS
```

Patient-Reported Outcomes

Health-related Quality of Life

The majority of conventional DMARD-controlled studies that reported change data on health-related quality of life used the SF-36. Statistically significant differences in PCS scores favoring TIM treatment over comparator were consistently reported, with 45-76% of patients meeting or exceeding an MCID of 5 across studies. Changes in MCS scores were more moderate, and did not consistently report significant improvements with a TIM over conventional therapy. Statistically significant differences in EQ-5D index scores favoring TIMs were reported in five trials.[183,215-218]

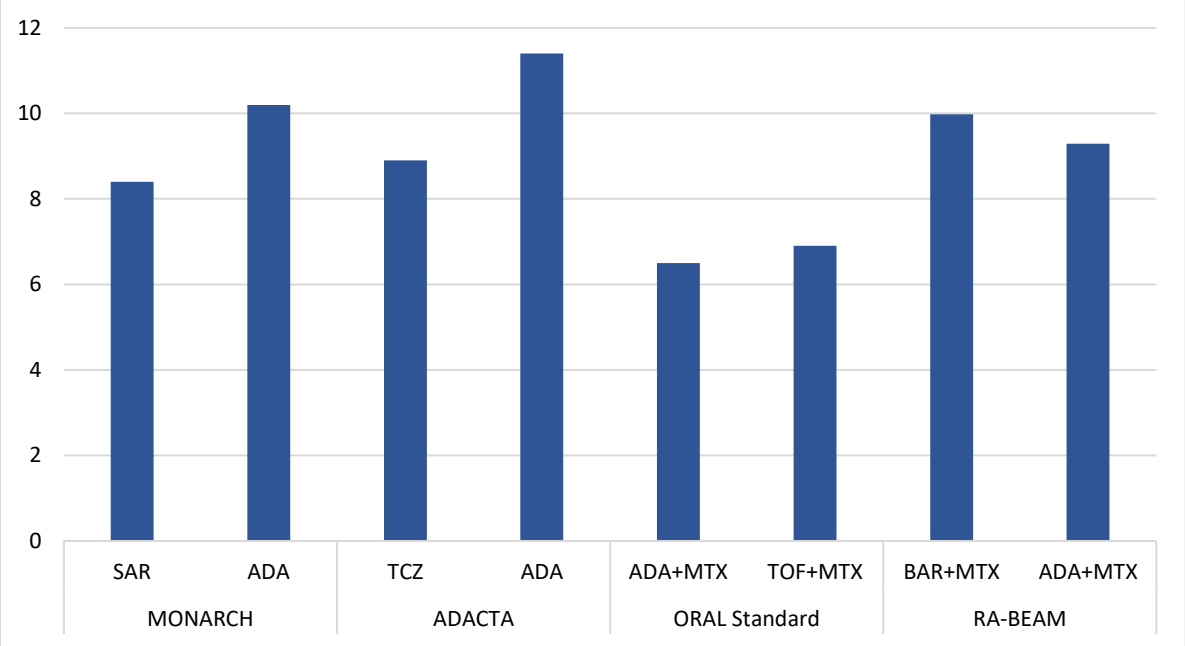
Pain

About 70% of conventional DMARD-controlled trials that reported outcomes related to pain used the 0-100 VAS scale, while the remaining trials used a scale of 0-10. Among the trials that used the 0-100 scale, all TIMs had a statically-significantly greater improvement in pain compared with the conventional DMARD, with the improvement values ranging from 21.8 to 40.9 points for the TIMs versus 7.3 to 15.7 points in the conventional DMARD group.[78,98,156,158,176,177,182,212,217,219,220] In the trials that used VAS 0-10, improvement from baseline ranged from 2.8 to 3.2 points for the TIMs while conventional DMARD improvements ranged from 0.8- to 1 point.[187,221]

Fatigue

Statistically significant differences favoring treatment with a TIM over conventional DMARD were observed in all trials that reported on the FACIT-F. Across studies, scores improved 6.5-10.1 points with a TIM, while conventional DMARD-treated patients showed much more variation: scores ranged from a 2.2-point worsening to a 7.9-point improvement. In addition, the majority of trials that reported on clinically-important differences in the FACIT-F showed a significantly greater proportion of patients who met or exceeded the MCID with a TIM versus conventional DMARD.[92,208,215-218,222] When evaluated with a VAS, fatigue scores declined from baseline (indicating improvement) significantly more with a TIM than with conventional DMARD therapy.[105,223,224]

Figure C27. Improvement in FACIT-F between baseline and Month 6 in head-to-head trials



Work Productivity

Few studies reported on work productivity. In one head-to-head trial of subcutaneous abatacept plus methotrexate versus adalimumab plus methotrexate, both treatment arms experienced similar improvements in absenteeism, reduced on-the-job effectiveness, work productivity loss, and activity impairment over two years of follow-up. Evidence from trials that compared TIMs to conventional DMARDs was inconsistent.

Several available studies used the Work Productivity and Activity Impairment Questionnaire-Rheumatoid Arthritis (WPAI-RA) scale to measure overall work productivity and impairment of regular activities on a weekly basis. WPAI-RA scores are calculated as impairment percentages, with higher percentages indicating greater impairment and less productivity.[225] An MCID for WPAI-RA has been defined as a 7% absolute change score, although the proportion meeting or exceeding the MCID was only reported in one of our included studies.[226] In the head-to-head AMPLE trial of subcutaneous abatacept plus MTX versus adalimumab plus MTX, both treatment arms experienced similar improvements in absenteeism, reduced on-the-job effectiveness, work productivity loss, and activity impairment over two years of follow-up; improvements in on-the-job effectiveness, work productivity loss, activity gained, and ability to perform daily activities reached an MCID at all assessment timepoints (month 6, year 1, and year 2).[226] Similarly, in the RA-BEAM trial of adalimumab and baricitinib combination therapy, 52-week improvements in daily activity and work productivity were similar for both regimens.[227]

Conventional DMARD-controlled trials showed overall improvement in productivity and ability to perform daily activities, although TIMs were not consistently superior to conventional DMARDs. In the RA-BEACON and RA-BUILD trials of baricitinib versus placebo (with or without concomitant therapy with conventional DMARDs), for example, patients treated with baricitinib reported a significant reduction in daily activity impairment compared with the placebo arm (RA-BEACON: adjusted mean change -26.3 vs. -15.2; $p \leq 0.001$), but differences in other elements of the WPAI were not consistently maintained.[218,227] Similarly, Machado and colleagues report that patients treated with etanercept plus methotrexate experienced a greater improvement in the percentage of overall impairment caused by RA in the past seven days relative to conventional DMARD therapy (adjusted mean change -33.4 vs. -21.5; $p=0.0188$); however, the proportion of patients who experienced overall work impairment was comparable between groups after 128 weeks of follow-up.[105,158] Analyses from the Swefot trial of triple therapy with conventional DMARDs versus infliximab plus methotrexate did not demonstrate greater improvement in work loss outcomes with TIM therapy: patients in both groups experienced similar reductions in the number of days per month on sick leave and disability pension at 12 months and at 7 years.[228,229]

Activity participation was also evaluated in two conventional DMARD-controlled studies that used the Activity Participation Questionnaire (APaQ). The APaQ measures the degree to which patients are limited in participating in self-defined daily activities, such as employment, household chores, and child rearing over the past 30 days.[230] In both the AIM (abatacept versus methotrexate in TIM naïve patients) and ATTAIN (abatacept versus conventional DMARD in TIM-experienced patients) trials of combination therapy, activity completion scores showed significantly greater improvements with abatacept relative to methotrexate or conventional DMARDs during months 3 through 12 of follow-up. Abatacept-treated patients gained 8.4 and 7.3 days in activity participation, in the AIM

and ATTAIN trials, respectively, compared with 4.5 and 1.4 days in the conventional DMARD groups (p<0.005 in both trials).[231]

Use of Healthcare Resources

Healthcare resource use was not commonly reported in clinical trials. One study of etanercept plus MTX versus conventional DMARD therapy showed comparable proportions of patients visiting the emergency department or a rheumatologist over 128 weeks of follow-up; requirements for caregiver assistance declined more with etanercept combination therapy.

Healthcare resource use was measured in only a single RCT that met our inclusion criteria. In this RCT, patients treated with etanercept plus methotrexate reported a statistically greater but small reduction in the mean number of emergency department visits over six months than with conventional DMARD therapy (-0.5 vs. -0.4; p=0.0039); however, after 128 weeks of follow-up, a similar percentage of patients in both treatment arms reported visiting the emergency department (0.9% vs. 0.9%).[105,158] The percentage of patients who had visited a rheumatologist in the past six months fluctuated over the course of the study, falling from 11.5% at baseline to 7.7% at week 24 in the etanercept group and from 13.5% to 9.5% in the conventional DMARD group; by week 128, the proportion of patients who reported visiting a rheumatologist increased again in both groups and approached baseline levels.

The same study was the only trial in our set that reported on caregiver burden. Meaningful reductions in the proportion of patients requiring caregiver assistance in the past month were observed in both groups between baseline and week 128, although the reduction was slightly greater among etanercept-treated patients (from 58% to 11.9% with etanercept and 55.6% to 18.2% with conventional DMARDs); statistical significance was not reported.[105]

We did not identify any RCTs or observational studies that met our inclusion criteria and reported on requirements for joint replacement or other major surgery. Although it did not meet our inclusion criteria, a multicenter retrospective cohort study (n=803; median age 59; 83% female; median DAS28-ESR 5.3; 22% biologic experienced) from Asai and colleagues used propensity score matching to evaluate the incidence of large joint replacement in RA patients treated with either adalimumab or etanercept.[232] The overall cumulative incidence of large joint replacement was approximately 10% five years after initiation of treatment, with a lower incidence in patients who received concomitant MTX (p=0.032). Treatment with adalimumab versus etanercept was not a significant predictor of joint replacement (HR 0.90; 95% CI 0.46 to 1.72).[232]

Dose Escalation

Among FDA-approved products in our scope, increases in dose during the maintenance phase of TIM therapy have been most frequently studied among the TNF-α inhibitors, in a variety of observational settings (e.g., health care claims data, registries, medical record review). A recent systematic review of observational data on the five TNF-α inhibitors of interest for this review comprised information on over 50,000 patients from 34 studies worldwide. [233] The pooled mean percentages of patients experiencing at least one dose escalation were 4.5% for etanercept, 10.5% for adalimumab, and 46.3% for infliximab (p=.01 for adalimumab and infliximab vs. etanercept). Note that adalimumab and infliximab allow for dose escalation via reductions in dosing intervals and/or increase in amount of drug administered as part of their product labels. No observational evidence was obtained for certolizumab pegol and golimumab, but we note that labeled total dosing is fixed for these products.

The IL-6 inhibitor tocilizumab also has a flexible dosing schedule in its label; patients initiating on the 4 mg/kg dose can escalate to 8 mg/kg if response is inadequate. A recent report of data from the CORRONA registry indicates that such increases are relatively frequent, as 52% of patients were found to have escalated their dose within three months of treatment initiation. [234]

Observational data on rituximab dosing is limited; information available indicates that, rather than increases in dose from the labeled two 1,000 mg infusions every six months, a lower-dose regimen of two 500 mg infusions every six months has been studied. We found no published studies of dose escalation with abatacept; however, data from conference proceedings suggests that this is a relatively infrequent event.[235,236] Finally, we found no published or presented observational evidence of dose escalation with tofacitinib.

While observational studies have focused attention primarily on the frequency of dose escalation as an event, clinical interest lies in whether dose escalation provides a benefit in patients without a response to standard dosing. A recent review conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) identified four such studies, one RCT and three observational studies.[237] The RCT compared rituximab treatment strategies involving a lower dose, the standard labeled dose, and escalation from lower to higher dose in 314 patients who had inadequate response to methotrexate and were followed for 48 weeks; no statistical differences were observed between arms in disease activity, remission, or ACR20/EULAR response. Two additional prospective cohort studies, one an open label extension of certolizumab in 508 patients that evaluated escalation from 200 mg every other week to 400 mg every other week, and the other of infliximab in 198 patients receiving initial dosing of 3 mg/kg or escalated doses of 5 or 7 mg/kg, showed no effect of dose escalation on measures of disease activity or treatment response. The final study was a retrospective assessment of dose-escalation strategies for golimumab in 74 patients;

treatment groups were unbalanced and statistical significance of group differences was not reported. In addition, no discernible pattern between dose escalation and treatment benefit was observed.

Dose Tapering Strategies

Evidence is beginning to emerge on the clinical effects of reducing the dose or withdrawing treatment in RA patients with a stable remission. Early findings appear to support dose reductions over complete cessation of TIM therapy, although results vary; this is at least in part a reflection on the heterogeneity of disease course following remission.

The PRIZE study was an RCT of 306 patients who received one year of treatment with etanercept and methotrexate at standard dosing; 193 of these met criteria for remission at that time and were randomized to reduced-dose etanercept with methotrexate, methotrexate alone, or placebo. [238] At the end of a 39-week double blind phase, patients in the combination therapy group were statistically-significantly more likely to achieve remission (63% vs. 40% for MTX alone and 23% for placebo, p≤.009). All treatment was withdrawn for another 26 weeks. Rates of remission dropped in all groups; remission levels remained numerically higher for combination therapy (44% vs. 29% for MTX alone and 23% for placebo), but statistically significant only in the placebo comparison.

In addition, the PRESERVE study of standard-dose (50 mg weekly) or reduced-dose (25 mg weekly) etanercept as well as placebo in combination with methotrexate assessed the effectiveness of both dose reduction and drug cessation strategies in 604 patients over one year of follow-up after a 9-month induction period of standard-dose etanercept-methotrexate treatment.[239] Similar percentages of patients in the standard- and reduced-dose groups (83% and 79% respectively) achieved low disease activity or remission during follow-up, both of which were statistically-significantly higher than placebo patients discontinuing etanercept (43%, p=.0001 for both comparisons).

In contrast, discontinuation of tocilizumab in 556 patients initially randomized to combination therapy with methotrexate or monotherapy was assessed over three years of follow-up in the ACT-RAY trial.[240] Approximately 50% of patients discontinued tocilizumab after 12 weeks of sustained remission, although only 6% were able to discontinue all RA drug therapy. Over the next year of follow-up, the majority of patients (84%) experienced a flare in symptoms after a median of 113 tocilizumab-free days and required reintroduction of therapy, although improvement in disease activity measures was rapid following reintroduction.

These findings are supported by a 2014 Cochrane review of dose-tapering strategies involving etanercept or adalimumab.[55] A total of seven clinical trials were summarized (N=1,428). Dose reductions (etanercept only) resulted in clinical outcomes that were similar to those for dose-

continuation strategies, while drug discontinuation during remission was associated with higher levels of disease activity, a reduced likelihood of maintaining low disease activity or remission, and worsening of radiographic and functional outcomes.

Adverse events

Table C17: Adverse events in comparative trials

* Data presented are percentages of patients with each event

Trial	Intervention	Follow up (weeks)	Any AE	Serious AEs	D/C due to AEs	Any infection	Serious infection	TB	Malignancy	Death
MONARCH[18]	ADA	24	63.6	6.5	7.1	27.7	1.1	NR	3.3	0
	SAR	24	64.1	4.9	6	28.8	1.1	NR	7.6	0.5
ADACTA[19]	ADA	24	83	10	NR	42	3	NR	1	0
	TCZ	24	82	12	NR	48	3	NR	1	2
RED SEA[20]	ADA	52	NR	10	NR	NR	NR	NR	1.7	2.2
	ETN	52	NR	11.6	NR	NR	NR	NR	1.7	0
AMPLE[94]	ADA	104	91.5	16.5	9.5	61.3	2.7	NR	2.1	0
	ABT	104	92.8	13.8	3.8	63.2	2.2	NR	2.2	0.3
ATTEST[23]	IFX	52	93.3	18.2	7.3	NR	8.5	NR	1.2	NR
	ABT	52	89.1	9.6	3.2	NR	1.9	NR	0.6	NR
RA-BEAM[21]	ADA	24	67	1.8	NR	33.3	0.6	0.3	0	0
	BAR	24	70.8	4.5	NR	35.7	1	0	0.4	0.4
ORAL Standard[95]	ADA	12	51.5	2.5	4.9	NR	0	NR	NR	NR
	TOF	12	52	5.9	6.9	NR	1.5	NR	NR	NR
BIOSIMILAR trials										
Yoo 2015[164]	RTX-bio	24	71.6	13.7	5.9	38.2	NR	NR	0	NR
	RTX-ref	24	84.3	13.7	7.8	41.2	NR	NR	2	NR
HERA [167]	ETN-bio	48	NR	12.9	6.8	37.4	NR	NR	NR	0
	ETN-ref	48	NR	12.3	7.5	41.1	NR	NR	NR	1.4
Choe 2017[205]	IFX-bio	30	57.6	9	7.2	29.3	3.1	0.3	0.7	0
	IFX-ref	30	58	8.9	3.4	37.5	2	0.3	0	0.3
Vencovsky 2015[204]	ETN-bio	52	NR	6	5	NR	0.3	0	NR	0.7
	ETN-ref	52	NR	5.1	6.4	NR	1.7	0	NR	0
Takeuchi 2015[169]	IFX-bio	54	88.2	15.7	17.6	NR	NR	NR	NR	NR
	IFX-ref	54	86.8	15.1	11.3	NR	NR	NR	NR	NR
PLANETRA[241]	IFX-bio	54	70.5	13.9	10.9	NR	NR	1	NR	0
	IFX-ref	54	70.3	10.3	15.7	NR	NR	0	NR	1
Cohen 2015[193]	ADA-bio	26	50	3.8	1.9	NR	0.8	NR	NR	NR
	ADA-ref	26	54.6	5	0.8	NR	1.1	NR	NR	NR

Appendix D. Comparative Value Supplemental Information

Table D1. Dose, Frequency of Administration, and Annual Monitoring and Administration Utilization

Intervention	Route	Dose	Frequency of Administration	Annual Monitoring Utilization	Administration Utilization
rituximab	iv	Two 1000mg bags	Every 24 weeks	4 Blood labs	2.5-hour infusion per administration
abatacept	iv	750mg (for weight between 60-100kg)	Weeks: 0, 2, then every 4 weeks	1 office visit 1 TB test 4 Liver labs 4 Blood labs	30-minute infusion per administration
abatacept	sc	125mg	Weekly	1 office visit 1 TB test 4 Liver labs 4 Blood labs	1 annual office visit, 1 subcutaneous injection
tocilizumab*	iv	25% received 4 mg/kg; 75% received 8 mg/kg	Every 4 weeks	1 office visit 1 TB test 4 Liver labs 4 Blood labs	1-hour infusion per administration
tocilizumab	sc	162mg	83% every other week; 17% every week	1 office visit 1 TB test 4 Liver labs 4 Blood labs	1 annual office visit, 1 subcutaneous injection
sarilumab	sc	150-200mg	Every 2 weeks	1 office visit 1 TB test 4 Liver labs 4 Blood labs	1 annual office visit, 1 subcutaneous injection

Intervention	Route	Dose	Frequency of Administration	Annual Monitoring Utilization	Administration Utilization
tofacitinib	ORAL	5mg	2x per day	4 Liver labs 4 Blood labs	none
baricitinib	ORAL	4mg	1x per day	4 Liver labs 4 Blood labs	none
adalimumab	sc	40mg	Every 2 weeks	1 office visit 1 TB test 4 Liver labs 4 Blood labs	1 annual office visit, 1 subcutaneous injection
certolizumab pegol	sc	200mg (after first 3 doses=400mg)	Every 2 weeks	1 office visit 1 TB test 4 Liver labs 4 Blood labs	1 annual office visit, 1 subcutaneous injection
etanercept	sc	50mg	weekly	1 office visit 1 TB test 4 Liver labs 4 Blood labs	1 annual office visit, 1 subcutaneous injection
golimumab	sc	50mg	monthly	1 office visit 1 TB test 4 Liver labs 4 Blood labs	1 annual office visit, 1 subcutaneous injection
golimumab	iv	2mg/kg	Weeks: 0, 4, every 8 weeks	1 office visit 1 TB test 4 Liver labs 4 Blood labs	30-minute infusion per administration

Intervention	Route	Dose	Frequency of Administration	Annual Monitoring Utilization	Administration Utilization
infliximab	iv	58% received 3 mg/kg; 42% received 10 mg/kg	every 7.5 weeks	1 office visit 1 TB test 4 Liver labs 4 Blood labs	2-hour infusion per administration
cDMARD	ORAL	2.5mg	8 per week (20mg weekly)	1 office visit 1 TB test 4 Liver labs 4 Blood labs	none

* tocilizumab iv was assumed to 8mg/kg for the monotherapy evaluation.

Table D2. Administration Cost Inputs

Input	Value	Source
Cost of iv treatment administration (first hour)	$136.41	Physicians' Fee and Coding Guide, 2016[242 133]
Cost of iv treatment administration (each additional hour)	$28.64/hour	Physicians' Fee and Coding Guide, 2016[242 133]
Cost of subcutaneous treatment administration	$25.42	Physicians' Fee and Coding Guide, 2016[242 133]
Cost per office visit	$73.40	Physicians' Fee and Coding Guide, 2016[242 133]

Table D3. Drug Monitoring Unit Cost Inputs

Input	Value	Source
Drug monitoring cost: TB Test	$84.96	Physician and Other Supplier Data[243] (HCPCS code 86480)
Drug monitoring cost: Liver Test	$7.63	Physician and Other Supplier Data[243] (HCPCS code 80076)
Drug monitoring cost: Complete Blood Count	$10.67	Physician and Other Supplier Data[243] (HCPCS code 85025)

Table D4. Adverse Event Cost and Utility Inputs

Input	Value	Source	
Cost of Serious Infection	$13,747	Medicare Provider Utilization and Payment Data[134]	Weighted by 2/3rd for pneumonia and 1/3rd by cellulitis
Cost of Tuberculosis Infection	$12,220	Medicare Provider Utilization and Payment Data[134]	
Serious Infection Disutility	-0.156	National Institute for Health and Care Excellence[139]	Disutility applied for one-month[139]
Tuberculosis Infection Disutility	-0.156	National Institute for Health and Care Excellence[139]	Disutility applied for two-months[140]

Table D5. Discontinuation due to Adverse Events Inputs

TIM	Risk ratio	95% CI	
		LL	UL
Etanercept	0.85	0.57	1.31
Adalimumab	1.43	0.91	2.22
Infliximab	1.80	1.13	2.78
Abatacept (IV)	0.97	0.53	1.59
Rituximab	1.32	0.52	3.70
Certolizumab Pegol	1.36	0.76	2.34
Golimumab (SC)	1.21	0.48	3.11
Tofacitinib	1.81	1.02	2.90
Abatacept (SC)	0.54	0.27	1.05
Tocilizumab	1.04	0.37	2.77
Baricitinib	1.01	0.98	1.05
Sarilumab	1.11	1.06	1.16
Reference: Methotrexate	4.11%		

All regimens are in combination with methotrexate; all agents except baricitinib and sarilumab were taken from Singh JA, Christensen R, Wells GA, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews (Review). *Cochrane Database Syst Rev.* 2009(issue 4). Pooled trial data were used for baricitinib and sarilumab

Table D6. Model-Wide Clinical Inputs and Functions

Input	Value	Source
HAQ Score relationship with ACR score/categories	ACR70→HAQ score drop of 1.07 ACR50→HAQ score drop of 0.76 ACR20→HAQ score drop of 0.44 Sub-ACR20→HAQ score drop of 0.11	Carlson et al., 2015[110] Gabay et al., 2013[111]
HAQ Score relationship with Total Sharp Score	E(HAQ) on treatment= exp(-1.73+0.0081*(baseline TSS+TSS mean difference(T))) / 1 + exp(-1.73+0.0081*(baseline TSS+TSS mean difference(T)))*3 E(HAQ) at baseline= exp(-1.73+0.0081*baseline TSS) / 1+exp(-1.73+0.0081*baseline TSS)*3 Change in HAQ=E(HAQ) on treatment – E(HAQ) at baseline The TSS mean difference is assumed to be a function of time on TIM where TSS mean difference at T = TSS mean difference * T, where T = time in years on TIM	Stephens et al., 2015[109] Breedveld et al., 2006[113] Note: the 0.0081 coefficient is a weighted average assumed to be 29.6% in remission (coefficient=0.02) and the remaining with coefficient = 0.0031. The average TIM had 29.6% achieve ACR70 for those ACR20 or greater.
Mortality rate relationship with HAQ score	US RA-severity specific mortality rate = Mortality from life table*1.33^{HAQ}	Carlson et al., 2015[110] Wolfe et al., 2003[136]
Utility score relationship with HAQ score	EQ-5D score = 1 – 1/(1+ exp(2.0734 + 0.0058*age + 0.0023*disease duration – 0.2004*baseline HAQ – 0.2914*male + 0.0249*previous DMARDs – 0.8647*current HAQ))	Wailoo et al., 2008[107]
Hospital days relationship with HAQ score (per model cycle = 6 months)	Expected value of hospital days = 0.38 days * HAQ Estimated as linear relationship between HAQ values of 0.6 and 1.6.	Carlson et al. 2015[110] Symmons et al. 2003[244]
Baseline missed worked days per month due to RA	4 days	Kavanaugh et al., 2009[245]
Days missed from work relationship with HAQ score	ACR Responders: 1.93 fewer missed work days per month ACR non-responders: 0.71 more missed work days per month	Osterhaus et al., 2009[246]
Unemployment relationship with HAQ score	A 0.25 increase in HAQ is associated with a 30% increased likelihood for unemployed status (OR=1.30, 95% CI=1.22, 1.39). Baseline unemployment = 3.8% for all ages ≥ 55 years old.	Han et al., 2015[247] US Bureau of Labor and Statistics[135]

Input	Value	Source
Efficacy of non-primary TIMs and cDMARD after insufficient response to previous treatment	HR: 0.84 (applied to HAQ decrements estimated from ACR and from mTSS).	Carlson et al., 2015[110] Karlsson et al., 2008[129]
HAQ degradation for time on cDMARD	For each year on cDMARD, we applied an increase in HAQ of 0.0269 up to 15 years. After 15 years on cDMARD, the HAQ increase was fixed at the 15 year value of 15*0.0269 = 0.4035.	National Institute for Health and Care Excellence Decision Support Unit[112]

Table D7. Contributions of ACR and mTSS to HAQ, for TIMs Added on to cDMARD

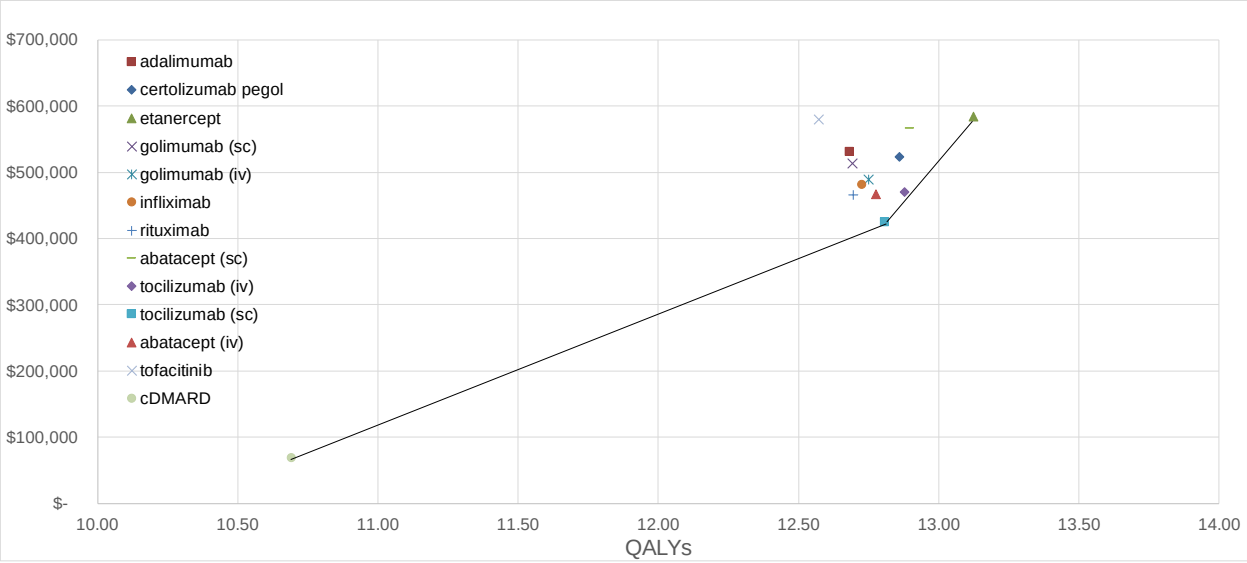
Treatment 1	Average Proportion of HAQ Contribution from ACR	Average Proportion of HAQ Contribution from mTSS
rituximab	92.1%	7.9%
abatacept (iv)	94.5%	5.5%
abatacept (sc)	92.4%	7.6%
tocilizumab (iv)	91.1%	8.9%
tocilizumab (sc)	91.4%	8.6%
sarilumab	92.1%	7.9%
tofacitinib	95.7%	4.3%
baricitinib	93.4%	6.6%
adalimumab	93.4%	6.6%
certolizumab pegol	94.6%	5.4%
etanercept	88.9%	11.1%
golimumab (sc)	96.7%	3.3%
golimumab (iv)	93.2%	6.8%
infliximab	89.8%	10.2%

Table D8. Model Cohort Characteristics for TIM Experienced Population

	Value	Primary Source
Mean age	57 years	Pappas et al, 2014
Female	79.90%	Pappas et al, 2014
Caucasian	83.90%	Pappas et al, 2014
Mean weight	170 lbs	National Health and Nutrition Examination Survey
Baseline HAQ prior to cDMARD treatment benefit	1.79	Calculation (weighted average from biologic-experienced trials)
Baseline TSS	93	Barnabe et al, 2012[248]

HAQ=Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index; TSS=Total Sharp Score

Figure D1. Cost-Effectiveness Frontier for TIMs Added on to cDMARD



Drugs that are farther to the right provide the greatest clinical benefit and drugs higher on the y-axis are more expensive. Etanercept as the initial treatment is the most expensive therapy, but is also associated with the highest QALY gains. Conversely, cDMARD therapy is the least expensive therapy, but is associated with the lowest QALY gains. The line on the graph depicts the cost-effectiveness efficiency frontier. Those therapies that lie to the left of the frontier are dominated by therapies that lie on the frontier. Thus, therapies to the left of the frontier, using only the deterministic findings, are considered to not be as cost-effective as those therapies on the frontier. The line starts (left to right) from cDMARD therapy to tocilizumab sc because tocilizumab sc has the smallest ICER. The frontier then extends to etanercept because etanercept is the only therapy that produces more QALYs gained, but also at a higher cost. It is important to note that all TIMs look relatively tightly clustered in Figure D1, as well as that this figure does not include estimates of uncertainty.

Figure D2. Comparisons to the TIM Market Leader; all TIMs added on to cDMARD

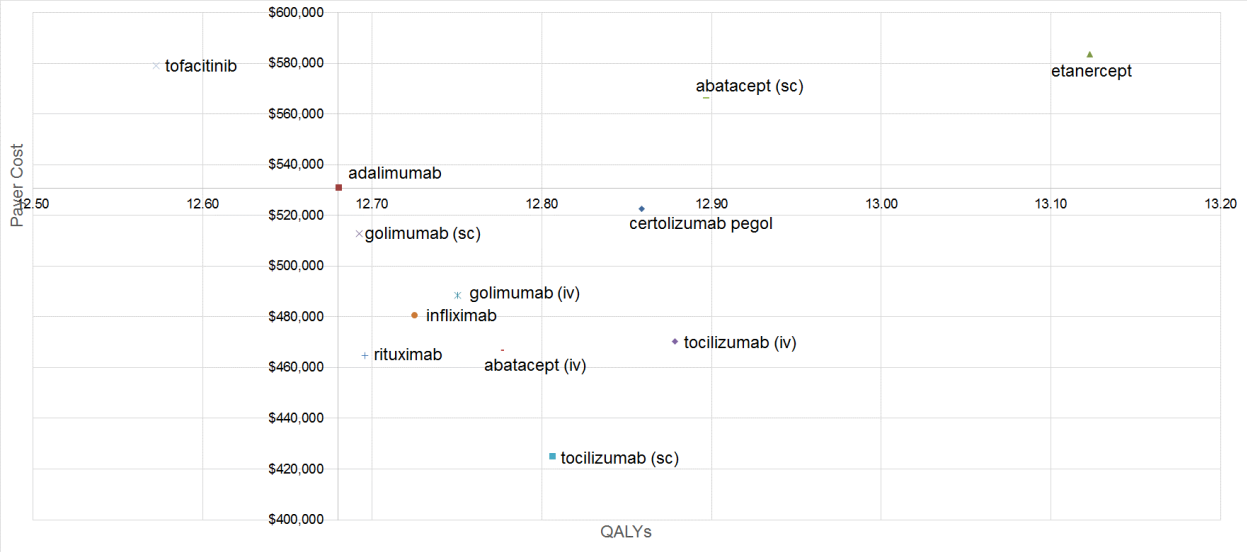
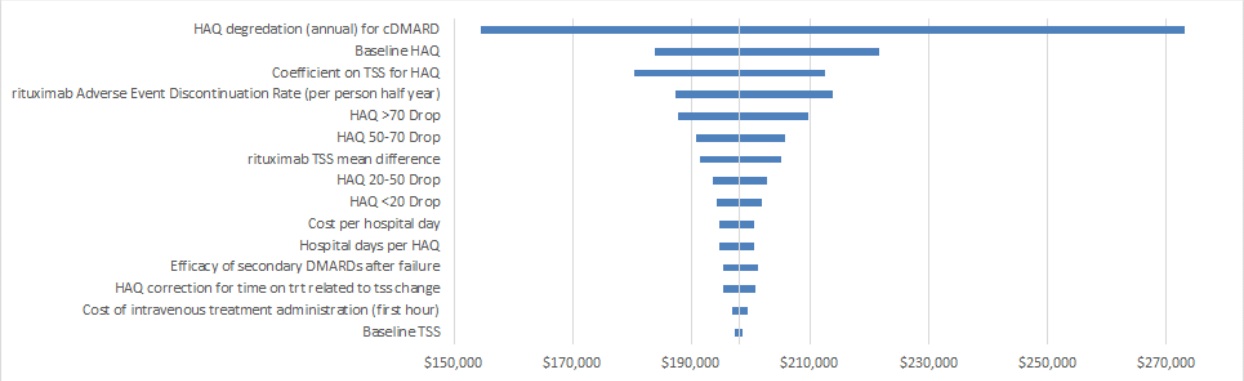


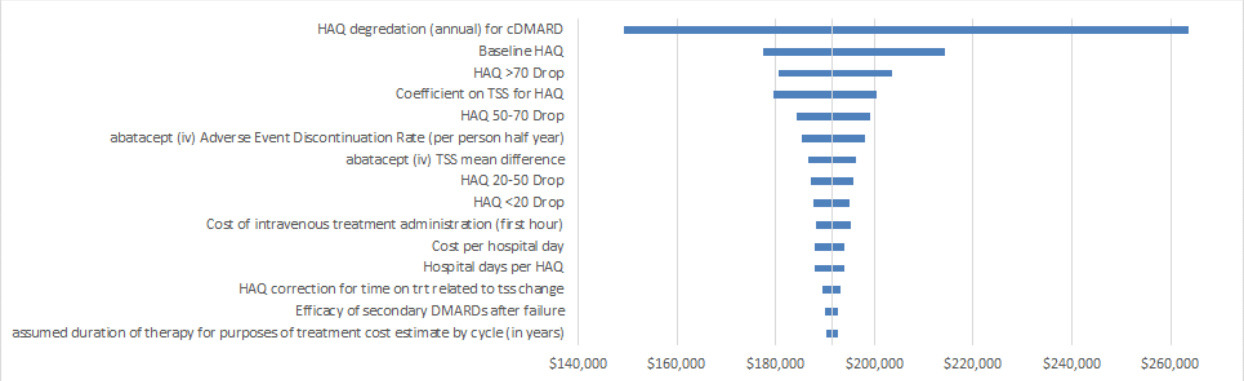
Figure D2 graphs the TIM market leader, adalimumab, as the reference case and plots all other TIMs on the cost-effectiveness plane relative to adalimumab's estimated cost and QALYs gained. Therapies in the upper right quadrant are more costly, but also more effective. Therapies in the upper left quadrant are more costly and less effective (and therefore dominated). Therapies in the lower left quadrant are less costly, but also less effective. Finally, therapies in the lower right quadrant are considered dominant, meaning they are less costly and more effective than adalimumab.

Figure D3. Tornado Diagrams (TIM+cDMARD vs. cDMARD)

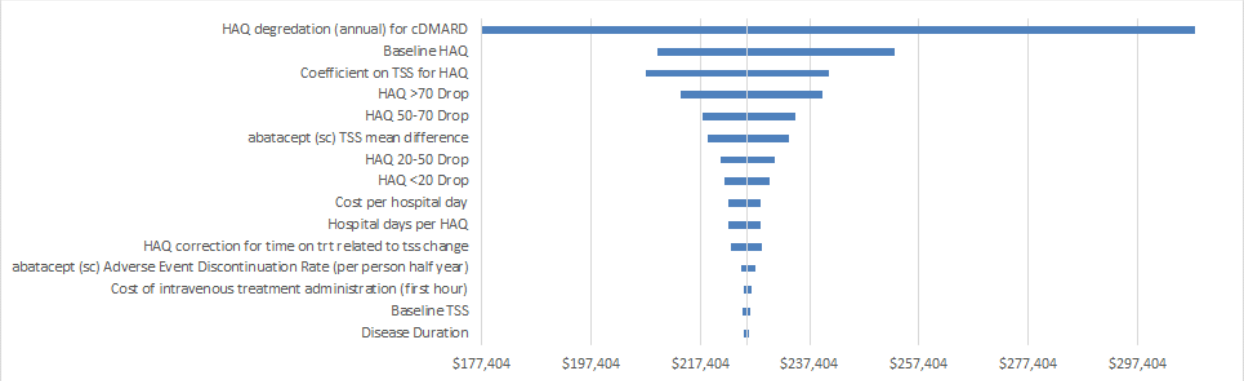
Rituximab vs. cDMARD



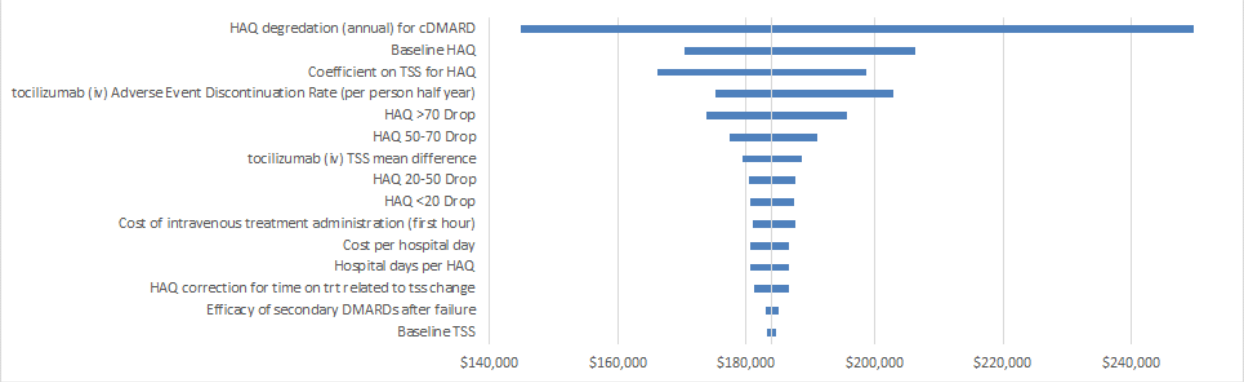
Abatacept (iv) vs. cDMARD



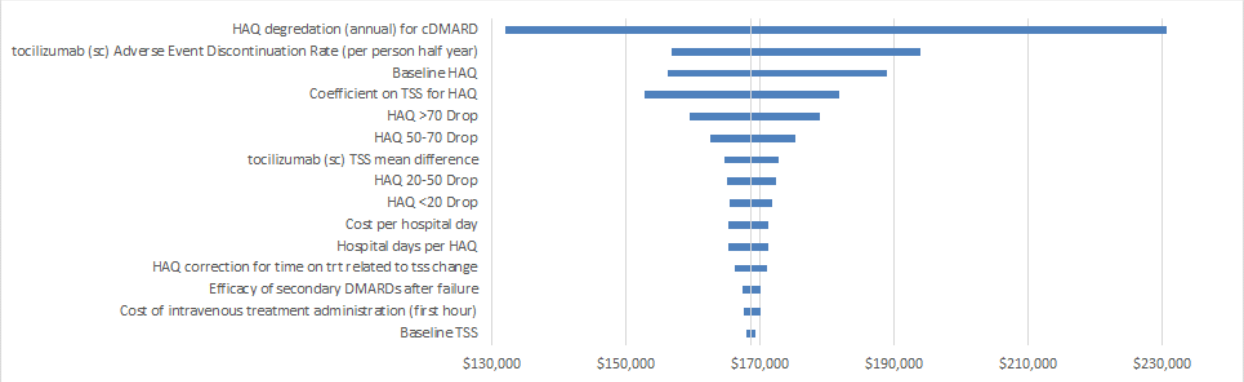
Abatacept (subcutaneous) vs. cDMARD



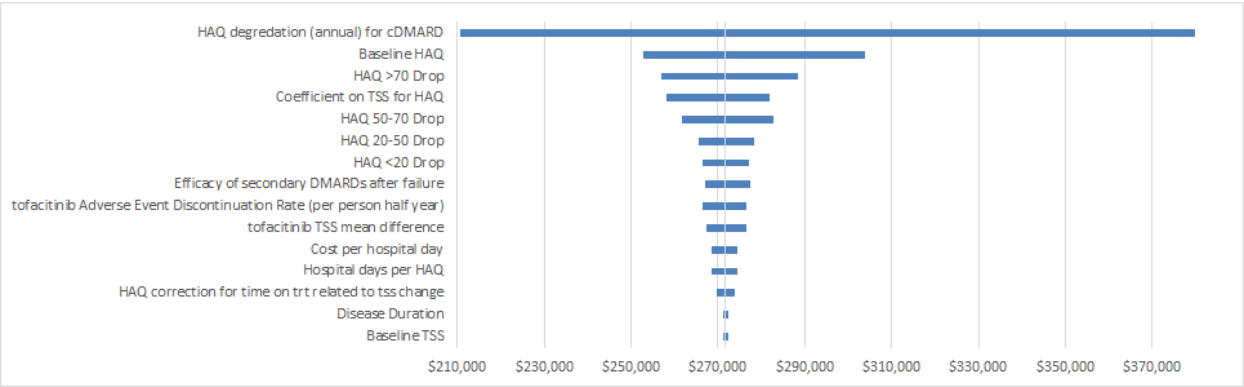
Tocilizumab (iv) vs. cDMARD



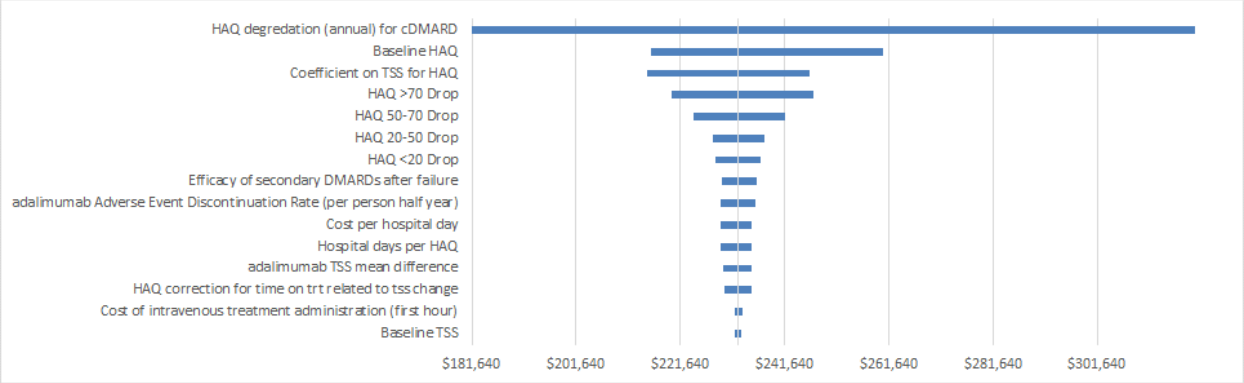
Tocilizumab (subcutaneous) vs. cDMARD



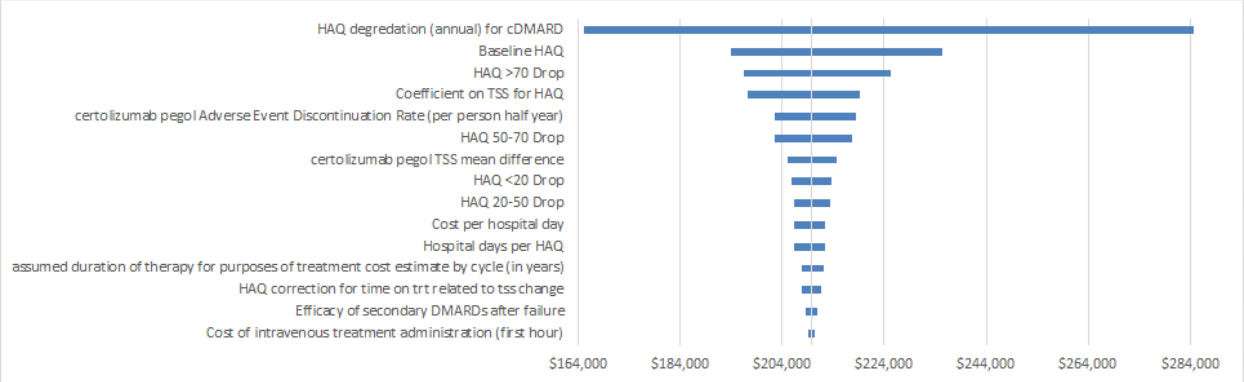
Tofacitinib vs. cDMARD



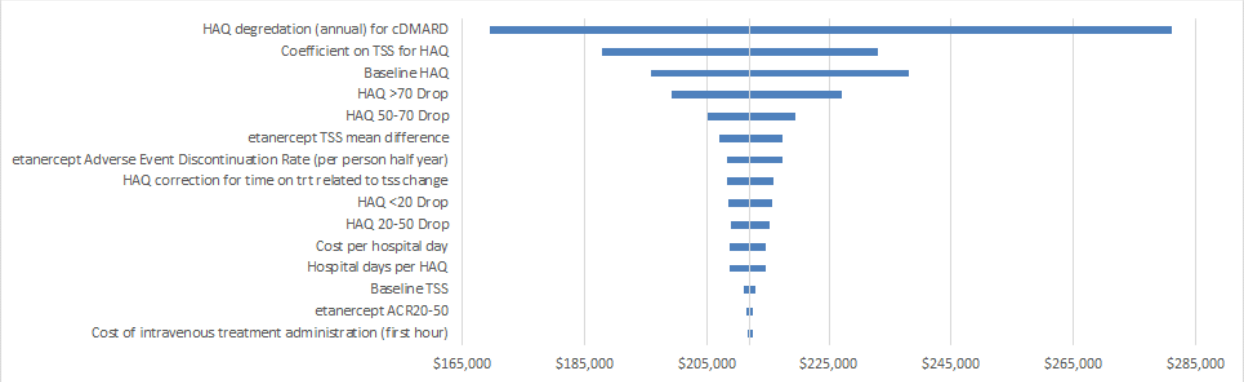
Adalimumab vs. cDMARD



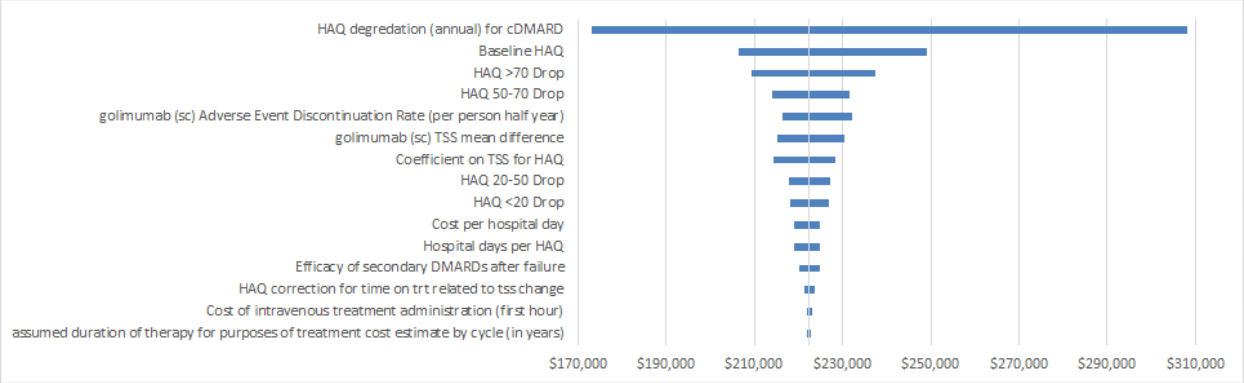
Certolizumab pegol vs. cDMARD



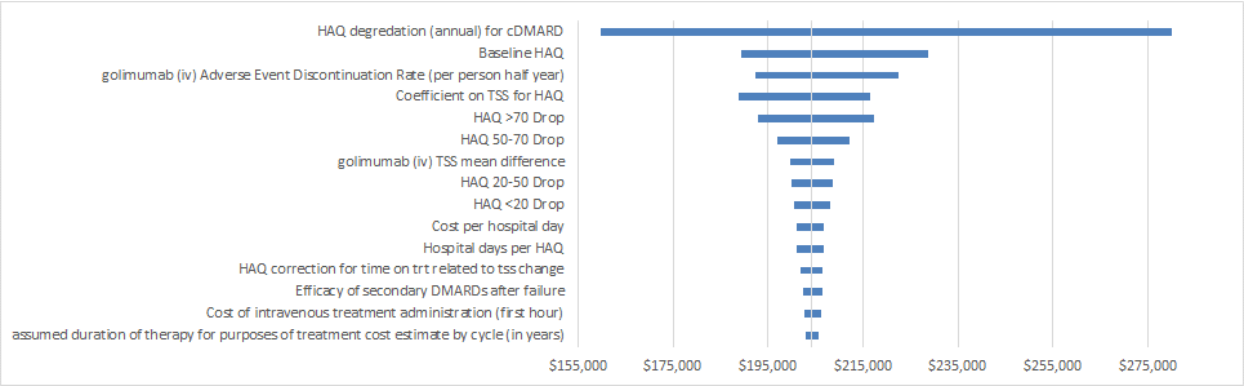
Etanercept vs. cDMARD



Golimumab (subcutaneous) vs. cDMARD



Golimumab (iv) vs. cDMARD



Infliximab vs. cDMARD

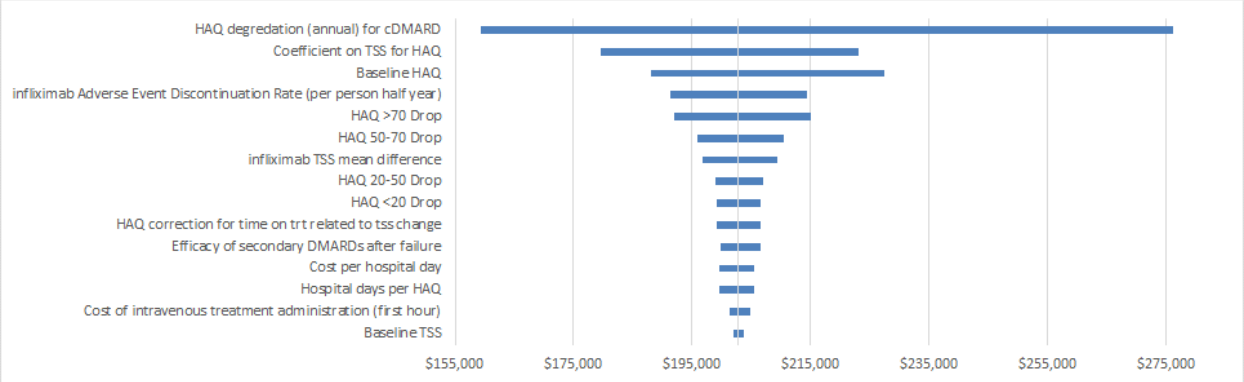

HAQ degredation (annual) for cDMARD
Coefficient on TSS for HAQ
Baseline HAQ
infliximab Adverse Event Discontinuation Rate (per person half year)
HAQ >70 Drop
HAQ 50-70 Drop
infliximab TSS mean difference
HAQ 20-50 Drop
HAQ <20 Drop
HAQ correction for time on trt related to tss change
Efficacy of secondary DMARDs after failure
Cost per hospital day
Hospital days per HAQ
Cost of intravenous treatment administration (first hour)
Baseline TSS
$155,000
$175,000
$195,000
$215,000
$235,000
$255,000
$275,000

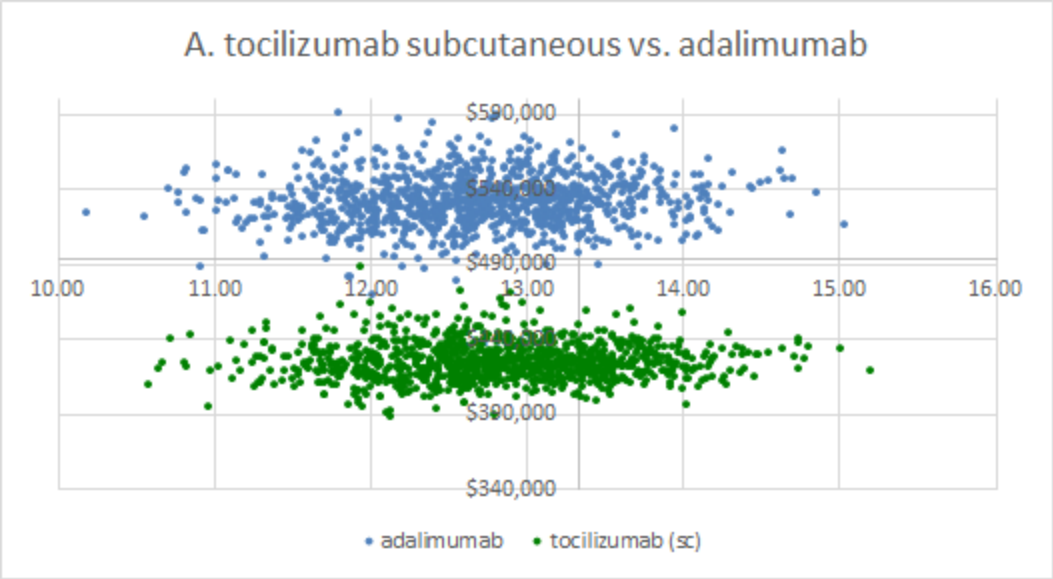
Table D9. Probabilistic Sensitivity Analysis Results: TIMs vs. conventional DMARD therapy

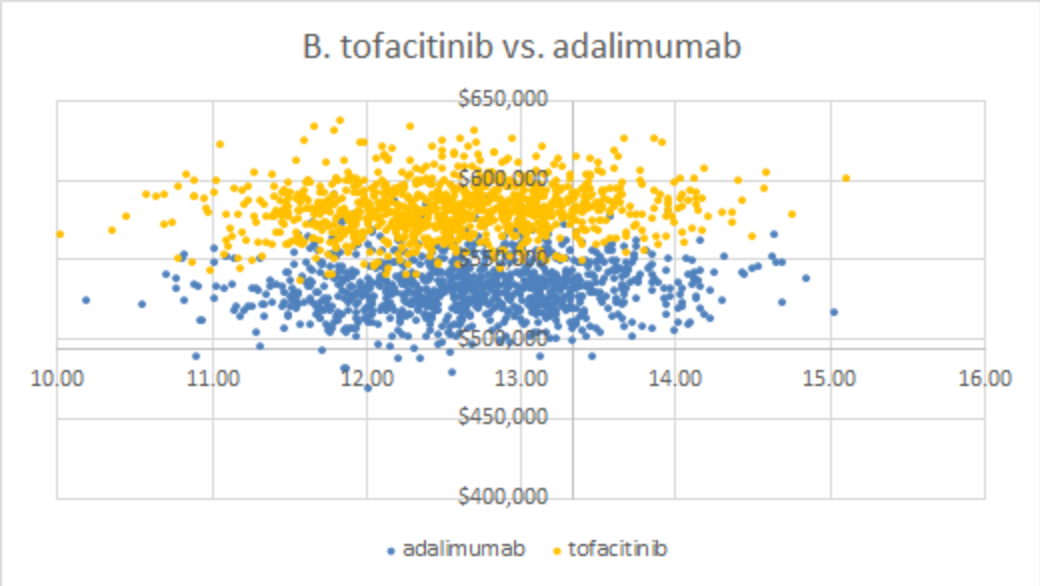
	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY	Cost-Effective at $200,000 per QALY	Cost-Effective at $250,000 per QALY
rituximab	0%	0%	4%	53%	90%
abatacept (iv)	0%	0%	4%	58%	93%
abatacept (sc)	0%	0%	0%	21%	71%
tocilizumab (iv)	0%	0%	10%	69%	96%
tocilizumab (sc)	0%	0%	27%	83%	98%
tofacitinib	0%	0%	0%	1%	30%
adalimumab	0%	0%	0%	17%	64%
certolizumab pegol	0%	0%	1%	37%	84%
etanercept	0%	0%	1%	34%	84%
golimumab (sc)	0%	0%	0%	25%	73%
golimumab (iv)	0%	0%	1%	46%	88%
infliximab	0%	0%	2%	46%	87%

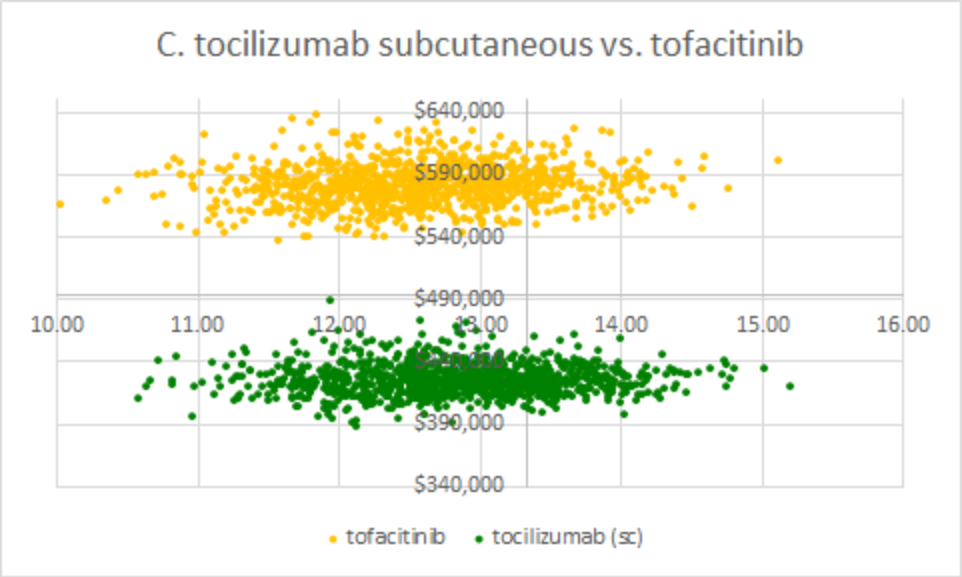
Table D10. Probabilistic Sensitivity Analysis Results: TIMs vs. adalimumab

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY	Cost-Effective at $200,000 per QALY	Cost-Effective at $250,000 per QALY
rituximab	100%	100%	100%	100%	100%
abatacept (iv)	100%	100%	100%	100%	100%
abatacept (sc)	2%	6%	34%	75%	91%
tocilizumab (iv)	100%	100%	100%	100%	100%
tocilizumab (sc)	100%	100%	100%	100%	100%
tofacitinib	0%	0%	0%	0%	0%
certolizumab pegol	98%	100%	100%	100%	100%
etanercept	0%	20%	86%	99%	100%
golimumab (sc)	94%	98%	96%	94%	88%
golimumab (iv)	100%	100%	100%	100%	100%
infliximab	100%	100%	100%	100%	100%

Figure D4. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds







This panel presents three cost-effectiveness clouds from the probabilistic sensitivity analysis. Panel A plots the cost-effectiveness clouds for the TIM with the smallest ICER (tocilizumab sc) and the TIM market leader, adalimumab. There is very little overlap between the two clouds. Panel B presents the cost-effectiveness clouds for the TIM with the highest ICER (tofacitinib) and the TIM market leader, adalimumab. There is more overlap between the two clouds as compared to Panel A. Panel C plots the TIM with the smallest ICER (tocilizumab sc) and the TIM with the highest ICER (tofacitinib). There is clear separation in the cost domain between these two TIMs that had the highest and lowest ICER when accounting for uncertainty. There remains sufficient overlap in lifetime discounted QALYs.

Table D11. Scenario Analysis Results: Treatment 4 as a Market Basket of all TIMs

Treatment 1	ICER (cost per QALY gained) Comparator: cDMARD	ICER (cost per QALY gained) Comparator: adalimumab
rituximab	$209,345	Less costly, More effective
abatacept (iv)	$202,701	Less costly, More effective
abatacept (sc)	$230,026	Less costly, More effective
tocilizumab (iv)	$196,568	Less costly, More effective
tocilizumab (sc)	$185,677	Less costly, More effective
tofacitinib	$264,109	More costly, Less effective
adalimumab	$234,764	Reference
certolizumab pegol	$216,163	Less costly, More effective
etanercept	$217,940	$74,709
golimumab (sc)	$226,611	Less costly, Less effective
golimumab (iv)	$213,272	Less costly, More effective
infliximab	$213,782	Less costly, More effective

Table D12. Scenario Analysis Results: Treatment 2 as a Market Basket of all TIMs

Treatment 1	ICER (cost per QALY gained) Comparator: cDMARD	ICER (cost per QALY gained) Comparator: adalimumab
rituximab	$231,965	Less costly, More effective
abatacept (iv)	$220,523	Less costly, More effective
abatacept (sc)	$247,869	$185,946
tocilizumab (iv)	$213,221	Less costly, More effective
tocilizumab (sc)	$201,552	Less costly, More effective
tofacitinib	$262,703	More costly, Less effective
adalimumab	$252,082	Reference
certolizumab pegol	$228,159	Less costly, More effective
etanercept	$227,889	$66,005
golimumab (sc)	$240,901	Less costly, More effective
golimumab (iv)	$226,136	Less costly, More effective
infliximab	$229,134	Less costly, More effective

Table D13. Scenario Analysis Results: Societal Perspective

Treatment 1	ICER (cost per QALY gained) Comparator: cDMARD	ICER (cost per QALY gained) Comparator: adalimumab
rituximab	$159,880	Less Costly, More Effective
abatacept (iv)	$152,784	Less Costly, More Effective
abatacept (sc)	$188,200	$137,017
tocilizumab (iv)	$145,555	Less Costly, More Effective
tocilizumab (sc)	$130,522	Less Costly, More Effective
tofacitinib	$232,738	More Costly, Less Effective
adalimumab	$193,763	Reference
certolizumab pegol	$169,724	Less Costly, More effective
etanercept	$173,345	$81,481
golimumab (sc)	$183,025	Less Costly, More Effective
golimumab (iv)	$165,380	Less Costly, More Effective
infliximab	$164,194	Less Costly, More Effective

Table D14. Scenario Analysis Results: TIM Experienced Population versus Mixed Population*

	ICER (biologic experienced population)	ICER (mixed population)
rituximab	$196,634	$231,965
abatacept (iv)	$193,664	$220,523
tocilizumab (iv)	$189,370	$213,221

*Mixed population assumed to be the same as the "Treatment 2 as a Market Basket of all TIMs" scenario since in the TIM Experienced scenario, we assumed that the second treatment was a market basket of all remaining TIMs.

Table D15. Cost per QALY Gained and Cost per Additional Responder for TIM vs. cDMARD, with a One-Year Time Horizon

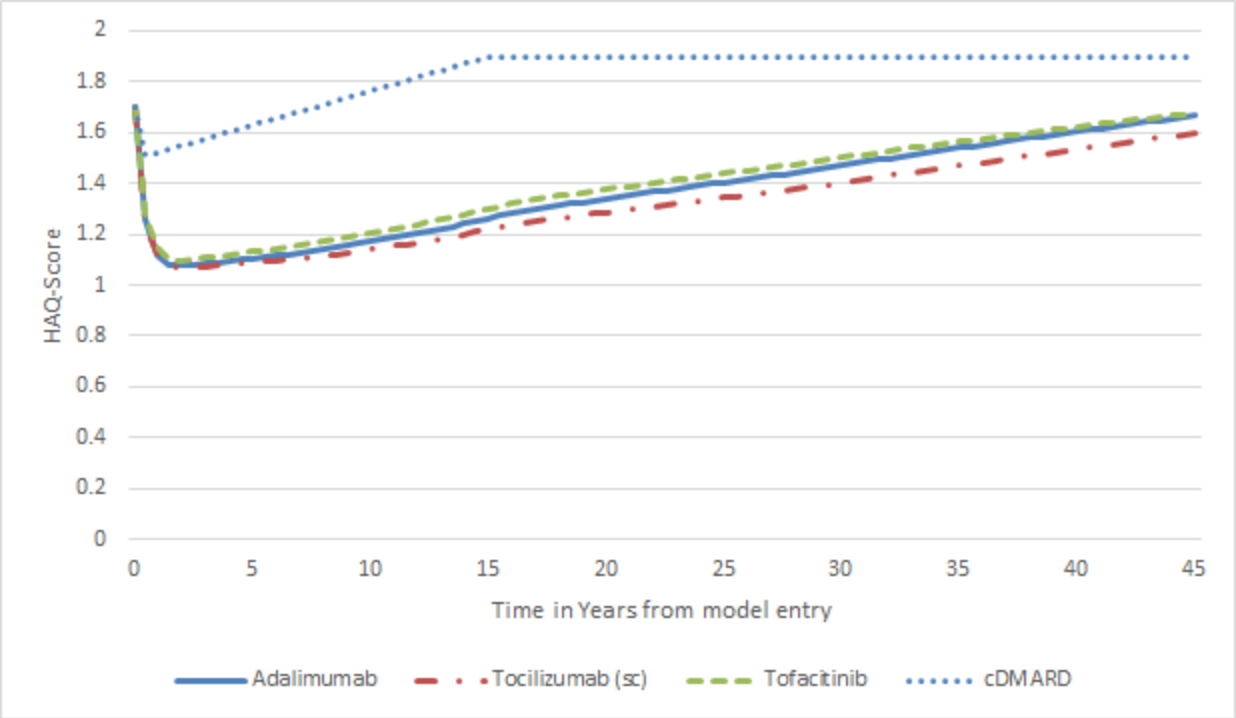
Intervention	Payer Cost	Percent on initial TIM (responder)	QALYs	ICER (cost per additional QALY)	ICER (cost per additional responder)
rituximab	$33,766	51.18%	0.7348	$570,715	$119,161
abatacept (iv)	$32,564	57.74%	0.7413	$487,761	$90,713
abatacept (sc)	$42,121	56.45%	0.7403	$660,794	$125,978
tocilizumab (iv)	$32,703	61.34%	0.7455	$457,453	$81,857
tocilizumab (sc)	$27,323	56.52%	0.7402	$406,376	$77,134
sarilumab	-	58.93%	0.7427	-	-
tofacitinib	$46,793	52.42%	0.7350	$816,193	$162,974
baricitinib	-	57.01%	0.7394	-	-
adalimumab	$42,287	54.07%	0.7385	$684,816	$137,276
certolizumab pegol	$38,008	69.91%	0.7560	$463,939	$77,957
etanercept	$42,623	70.15%	0.7574	$517,109	$87,996
golimumab (sc)	$38,232	58.09%	0.7422	$575,149	$107,415
golimumab (iv)	$35,017	57.35%	0.7419	$523,746	$99,674
infliximab	$34,684	54.81%	0.7400	$534,962	$107,320
cDMARD	$3,813	26.04%	0.6823		

Table D16. Cost per QALY Gained and Cost per Additional Responder for TIM vs. cDMARD, with a Three-Year Time Horizon

Intervention	Payer Cost	Percent on initial TIM (responder)	QALYs	ICER (cost per additional QALY)	ICER (cost per additional responder)
rituximab	$95,461	45.11%	2.1762	$409,189	$390,628
abatacept (iv)	$93,061	52.40%	2.1884	$375,268	$283,597
abatacept (sc)	$114,914	53.10%	2.1884	$475,424	$350,840
tocilizumab (iv)	$93,475	55.35%	2.1982	$360,993	$258,632
tocilizumab (sc)	$81,287	51.00%	2.1873	$322,931	$255,210
sarilumab	-	52.87%	2.1920	-	-
tofacitinib	$126,798	44.32%	2.1729	$570,359	$556,102
baricitinib	-	51.57%	2.1831	-	-
adalimumab	$115,074	47.22%	2.1824	$489,537	$438,610

certolizumab pegol	$107,040	61.43%	2.2175	$387,627	$252,952
etanercept	$118,508	64.33%	2.2250	$421,268	$263,077
golimumab (sc)	$106,604	51.67%	2.1885	$437,177	$339,076
golimumab (iv)	$99,319	51.02%	2.1896	$401,791	$320,652
infliximab	$98,662	46.39%	2.1873	$403,031	$382,674
cDMARD	$11,180	23.53%	1.9702		

Figure D5. Consequences of treatment throughout model time horizon



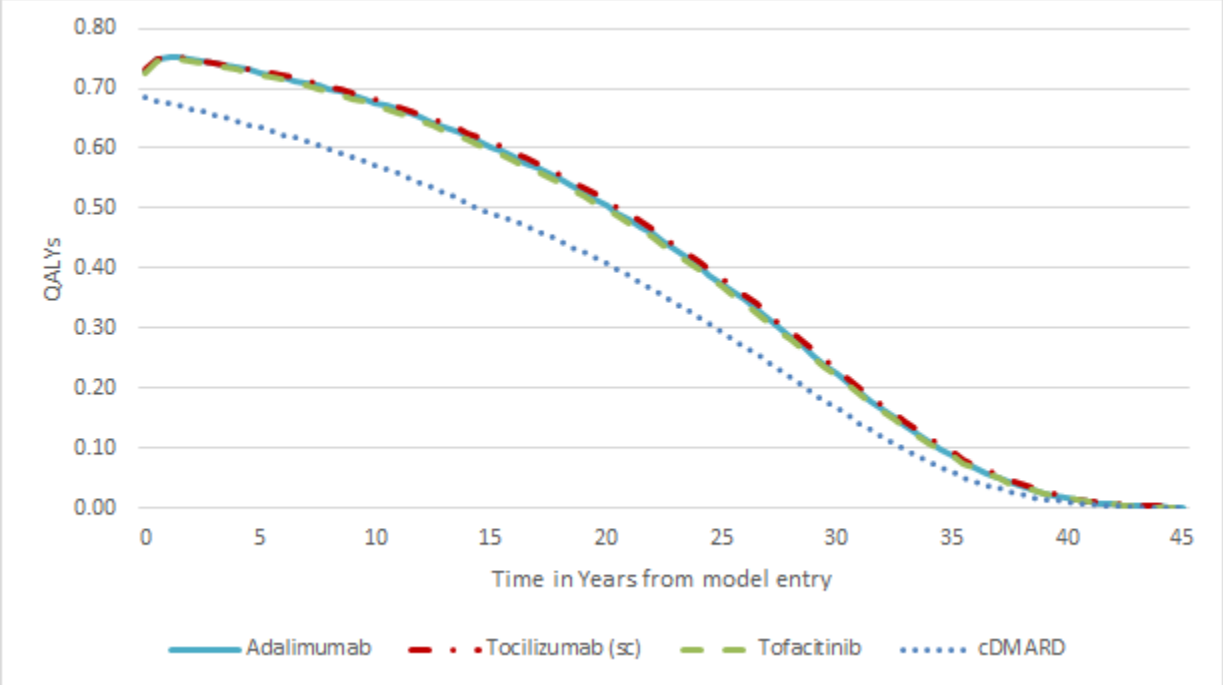


Table D17. Rates of Serious Infection

Intervention	Events	Patient-years follow up	Event per 1,000 PY
Rituximab[249]	17	664	25.6
Abatacept[249]	19	1422	13.4
Tocilizumab[249]	83	1468	56.5
Sarilumab[162]	28	734	38.2
Tofacitinib[249]	19	2845	6.7
Baricitinib[250]	16	421	38
TNFα inhibitors[249]	106	3279	32.3
MTX[249]	95	6332	15

Table D18. Rates of Tuberculosis Infection

Intervention	Events	Patient-years follow up	Event per 1,000 PY
Rituximab[251]	2	11962	0.17
Abatacept[252]	4	4215	0.95
Tocilizumab[253]	--	1842	0
Sarilumab[162]	--	734	0
Tofacitinib[154]	2	647	3.09
Baricitinib[21,175,190,220]	1	884	1.13
TNFα inhibitors[254]	36	10495	3.43
MTX[254]	57	241119	0.24

Appendix E. Previous Systematic Reviews and Technology Assessments

We examined five systematic reviews comparing the effectiveness of targeted immune modulators in patients 18 years or older with moderately-to-severely active rheumatoid arthritis and inadequate response to or intolerance of conventional DMARDs.

NICE Technology Assessment Report[25]

https://www.nice.org.uk/guidance/TA375/chapter/1-Recommendations

https://www.nice.org.uk/guidance/indevelopment/gid-tag438

The National Institute for Health and Care Excellence (NICE) recommends adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, and abatacept, all in combination with methotrexate, for treating rheumatoid arthritis if the disease is severe, has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs), and the manufacturers provide certolizumab pegol, golimumab, abatacept and tocilizumab as agreed in their patient access schemes. Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for individuals who have contraindications or intolerance to methotrexate when the criteria above is met. NICE further recommends that patients continue treatment only if there is a moderate response, measured using European League Against Rheumatism (EULAR) criteria, six months after starting therapy; if a moderate EULAR response is not maintained, treatment should be withdrawn. Patients should start treatment with the least expensive drug, which may necessarily vary by individual due to different modes of administration and treatment schedules. NICE's recommendations also apply to biosimilar products of the technologies that have a marketing authorization allowing the use of the biosimilar for the same indication.

NICE is currently developing guidance on tofacitinib for the treatment of RA after failure of conventional DMARDs, with expected publication in January 2018; an appraisal of rituximab was suspended in 2011 after the manufacturer decided to terminate its license application in this indication.

AHRQ comparative effectiveness review[69]

https://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf

In this systematic review and network meta-analysis, benefits and harms of biologic DMARDs and oral (conventional) DMARDS in adults with rheumatoid arthritis were evaluated. Findings from the network meta-analysis using Bayesian methods for ACR suggested a higher odd of reaching ACR 50 response for etanercept compared with abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab (ACR 50 OR range for etanercept 2.39-5.20). The differences showed statistically significant improvements in disease activity with etanercept than with abatacept, adalimumab, anakinra, infliximab, rituximab, or tocilizumab, but no statistically significant differences between etanercept and golimumab. Similarly, indirect analyses from randomized trials indicate that patients taking certolizumab or etanercept are less likely to withdraw treatment than patients taking other biologic DMARDs. The authors concluded that there was limited head-to-head comparative evidence to support one therapy over another in adults with rheumatoid arthritis, and that the strength of evidence from the NMA results which suggested some differences was low.

Cochrane review[24]

This systematic review and meta-analysis examined the use of biologics and conventional DMARDs (or placebo) in people with RA in whom treatment with conventional DMARDs including methotrexate had failed. Efficacy outcomes, including ACR, function, remission, radiographic progression, and safety outcomes were analyzed using standard meta-analysis for calculating direct estimates and Bayesian mixed treatment comparison for NMA estimates. Findings suggest that the use of biologics + MTX was associated with a clinically important improvement in function, higher ACR50 and remission rates, and increased risk of serious adverse events than the comparator (MTX and other conventional DMARD). On radiographic progression, biologic + MTX was also associated with significantly less progression versus conventional DMARD, with a mean difference of -2.61 (95% CI -4.08 to -1.14) sharp score units; however, the clinical significance of this result was less clear since the absolute reduction was small. In addition, results were inconclusive for whether biologics + MTX are associated with an increased risk of cancer or withdrawals due to adverse events.

Cochrane[255]

This systematic review and meta-analysis evaluated the benefits and harms of biologic monotherapy in people with RA in whom treatment with conventional DMARDs including methotrexate had failed. Based on direct evidence, the use of biologic monotherapy was associated with a clinically meaningful and statistically significant improvement in ACR50 and HAQ scores compared with MTX or other conventional DMARDs with a RR of 1.54 (95% CI, 1.14 to 2.08)

and mean difference in HAQ of -0.27 (95% CI, -0.40 to -0.14), but there was no statistically significant or clinically meaningful difference for direct estimates of biologic monotherapy versus conventional DMARDs for clinical remission. NMA findings were consistent with these results except in the case of clinical remission, where NMA results showed a statistically significant and clinically meaningful difference versus conventional DMARD for TNF monotherapy (absolute improvement 7% (95% CI, 2% to 14%)) and non-TNF biologic monotherapy (absolute improvement 19% (95% CrI, 7% to 36%). On radiographic progression, biologic monotherapy was also associated with significantly less progression versus conventional DMARD, though the clinical significance of this result was less clear since the absolute reduction was small (-0.97% (95% CI -1.69% to -0.25%).

There were 10 other Cochrane reviews that examined the use of specific targeted immune modulators in rheumatoid arthritis.[256-264]

CADTH[265]

https://www.cadth.ca/drugs-management-rheumatoid-arthritis

https://www.cadth.ca/drugs-management-rheumatoid-arthritis

This review from the Canadian Agency for Drugs and Technologies in Health (CADTH) focused on assessing the comparative efficacy and harms of biological agents (especially TNF-alpha inhibitors) in the treatment of adults with rheumatoid arthritis. NMA results showed that there were no statistically significant differences between adalimumab, etanercept, golimumab, infliximab, abatacept, anakinra, and rituximab on estimates of ACR50 response. Similar trends were observed for ACR70, except that the absolute proportion of patients achieving a response was lower for ACR70 compared with ACR50. The proportion of patients reporting serious adverse events was similar for all biologic agents based on a meta-analysis of placebo-controlled trials. An economic evaluation was also conducted to examine the relative cost-effectiveness of biologic agents (abatacept, adalimumab, etanercept, infliximab, and golimumab) in patients who had failed prior treatment with conventional DMARDs. Based on the model, the most effective first-line biologic agent, in terms of time with an ACR50 response, was adalimumab. Abatacept, infliximab, and golimumab were all less expensive than adalimumab, but they were also less effective.

CADTH is currently updating its 2010 review to include newer agents approved since 2010 (e.g., tofacitinib), drugs in development (e.g., baricitinib), and biosimilars. The report will evaluate conventional DMARDs, biologic DMARDs, and small molecule DMARDs in adults with moderate to severe RA who have previously been treated; it is scheduled for publication on March 10, 2016.

Appendix F. Evidence Tables

Table F1. Head-to-Head Trials: Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Baddley J *Annals of the rheumatic diseases* 2014[266] SABER Fair	FDA, US DHHS and AHRQ grant	Retrospective cohort of four large US data system. The median (IQR) follow-up time in the TNFi and cDMARD was 170 (299) and 104 (166) days, respectively	USA	1) TNFi (n=24, 384) 1a) ADA (n=5,888) 1b) ETN (n=10,283) 1c) IFX (n=8,212) 2) cDMARD (leflunomide, sulfasalazine or hydroxychloroquine) (n=11,828) Both TNFi and cDMARD regimens allowed the concurrent use (continuation or addition) of MTX	≥16 with RA with availability of a baseline period of 365 days with continuous enrollment in the respective data system preceding the first qualifying new drug prescription fill or infusion. Patients initiating TNFi, leflunomide, sulfasalazine, hydroxychloroquine after MTX failures	Mean age (SD) 1) 57.73 (14.53) 2) 58.47 (14.27) Female, n (%) 1) 20, 955 (85.9) 2) 10, 205 (86.3)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Burmester G *Ann Rheum Dis* 2016[18] MONARCH Good	Sanofi	RCT, active controlled, double-blind, double-dummy, phase III 24 weeks	86 centers in Europe, Israel, Russia, South Africa, South Korea, and the USA	1) ADA (n=185) 2) SAR (n=184) Patients were randomized to q2w 200mg SAR + PBO or q2W 40mg ADA + PBO for sc administration. After week 16, dose escalation to weekly ADA or matching PBO in the SAR group was permitted for patients who did not achieve ≥20% improvement in TJC & SJC	≥18 years with active RA (i.e. ≥6 SJC & ≥8 TJC; CRP≥8mg/L or ESR≥28mm/hr; DAS28-ESR>5.1); RA duration ≥ 3month; intolerant or inadequately responded to adequate MTX dose for ≥12 weeks. Exclusion: Patients with prior bDMARD were excluded.	Mean age (SD) 1) 53.6 (11.9) 2) 50.9 (12.6) Female, n (%) 1) 150 (81.1) 2) 157 (85.3) Mean duration of RA, yrs (SD) 1) 6.6 (7.8) 2) 8.1 (8.1) Mean HAQ-DI (SD) 1) 1.6 (0.6) 2) 1.6 (0.6) Mean DAS28-ESR (SD) 1) 6.8 (0.8) 2) 6.8 (0.8) Mean DAS28-CRP (SD) 1) 6 (0.9) 2) 6 (0.9)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Chen J *Arthritis care & research* 2014[267] Poor	Supported by an Australian National Health and Medical Research Council Enabling Grant	Retrospective database study	Australia	1) ETN (n=1,243) 2) ADA (n=863) 3) IFX (n=159)	Patients with diagnosed RA, AS, and PsA in the Australian Rheumatology Association Database between 2001–2011 and taking an anti-TNF	*Grouped by disease* Mean age (SD) 55.6 Female, n (%) 74 Mean duration of RA, yrs (SD) 14.8 Mean DAS28-CRP (SD) NR Mean HAQ-DI (SD) NR Mean mTSS [0-448] (SD) NR

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Chiu YM *International journal of rheumatic diseases* 2014[268] Poor	Pfizer Inc	Retrospective longitudinal database study Participants were matched using propensity scoring Total follow-up time for ETN ranged from 3, 028-3,132 patient years for ETN and for ADA ranged from 685-697 patient years	Taiwan	1) ETN (n=1,492) 2) ADA (n=746) *cDMARD was not compared with individual drug	≥18 years with RA diagnosis; must have been prescribed a cDMARD or bDMARD at least once during the study period. [BHNI treatment provisions allow a patient to receive bDMARD treatment for RA only after having failed at least two cDMARDs with a 6-month interval for each therapy]	Mean age 1) 56.5 2) 56 Female, n (%) 1) 1, 225 (82.1) 2) 605 (81.1) Mean duration of RA, yrs 1) 7 2) 6.9

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Curtis J *Annals of the Rheumatic Diseases* 2016[269] Fair	Investigator initiated	Retrospective cohort Total follow-up for ABT, RTX, TNFi, TOC, and TOF are 8,960, 4,115, 27,122, 4,632, and 982 respectively.	USA	1) ABT (n=12,305) 2) RTX (n=5,078) 3) TNFi (n=42,850) 3a) ADA 3b) CTZ 3c) ETN 3d) GOL 3e) IFX 4) TCZ (n=6,967) 5) TOF (n=2,526)	≥18 years and to have two or more physician billing diagnoses for RA, with at least one from a rheumatologist. ≥12 months of medical and pharmacy coverage prior to follow-up which began at first use of TOF or RA biologics	Mean age (SD) 1) 61.2 (13.4) 2) 61.2 (13) 3) 57.7 (13.5) 4) 60.1 (13.5) 5) 55.4 (11.8) Female, % 1) 83.2 2) 80.8 3) 79.6 4) 82.2 5) 83.2
Curtis J *Arthritis care & research* 2014[270] Fair	AHRQ grant	Retrospective cohort of US veterans The median duration of follow-up time was slightly more than one year in all groups.	USA	1) ABT (n=451) 2) RTX (n=596) 3) ADA (n=1,885) 4) ETN (n=844) 5) IFX (n=382)	RA diagnosis ≥2 rheumatologists on separate days or a single RA diagnosis plus pharmacy dispensing bDMARD or cDMARD. TNFi exposure was limited to patients who had prior exposure to a different anti-TNF	Mean age (SD) 1) 60.3 (10.6) 2) 60.8 (10.6) 3) 60.1 (10.8) 4) 59.9 (10.7) 5) 57.9 (10.5) Male, % 1) 83.6 2) 87.6 3) 88 4) 88.5 5) 84.8

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Curtis J *Arthritis research & therapy* 2015[271] Fair	NR	Retrospective cohort Mean follow up: 0.7 years	USA	1) TNFi (n=7,951) 1a) ETN 1b) ADA 1c) IFX 1d) CTZ 1e) GOL 2) TCZ (n=1,528) 3) RTX (n=1,134) 4) ABT (n=2,683)	≥18 years with RA diagnosis; prescription or administration of new bDMARD between Jan 1, 2010 and June 30, 2012; past discontinuation of a different biologic.	Mean age (SD) 1) 51.7 (12.5) 2) 53.8 (12) 3) 53.8 (12.1) 4) 53.9 (12.6) Female, % 1) 81.3 2) 82.9 3) 82.1 4) 83 Mean no of prior bDMARD use 1) 1.4 2) 2.1 3) 1.9 4) 1.6

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Dartel SAA *Annals of Rheumatic Diseases* 2013[102] DREAM registry Fair	Pfizer, Abbott, Schering-Plough, Roche, UCB Pharma, Bristol-Meyers Squibb	Prospective cohort observational study Follow-up time: 5 years	Netherlands	1) ETN (n=959) 2) ADA (n=776) 3) IFX (n=621)	Dutch Rheumatoid Arthritis Monitoring (DREAM) registry since 2003 and preceding biological registry from Radboud University Nijmegen Medical Centre (RUNMC) before 2003 (same inclusion criteria: diagnosis of RA per the 1987 ACR criteria, who have DAS28 >3.2; prior treatment with at least 2 DMARDs including MTX, weekly dose up to 25 mg; no contraindication for TNF-inhibiting therapy	Mean age, yrs (SD) 1) 55 (13) 2) 53 (13) 3) 55 (13) Female, % 1) 66 2) 70 3) 71

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Flouri I *Seminars in arthritis and rheumatism* 2014[101] Good	Hellenic Rheumatology Society	Prospective cohort Median follow up: 2.9 years	Greece	1) IFX (n=560) 2) ADA (n=435) 3) ETN (n=302)	Inclusion: RA patients with active disease (i.e. DAS28>5.1 or >3.2 plus 2 of the following: RF or anti-CCP positivity; bone erosion in hand and feet radiography; HAQ score>1; large joint involvement; extra-articular manifestation); and have failed DMARD. No specific exclusion criteria	Age, median (IQR) 1) 58 (17) 2) 59 (18) 3) 57 (19) Female, % 1) 74 2) 81 3) 80 Median duration of RA, yrs (IQR) 1) 8.5 (12.7) 2) 7.8 (12.8) 3) 7.4 (10.6) Median HAQ (0-3) (IQR) 1) 1 (0.9) 2) 1 (0.9) 3) 1 (0.9) Mean DAS28(0-9.35) 1) 5.4 (1.5) 2) 5.6 (1.6) 3) 5.7 (1.6)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Gabay C *Lancet* 2013[19] ADACTA Good	Hoffmann-La Roche	RCT double-blind, active comparator, parallel-group phase iv 24 weeks	76 centers in 15 countries in North and South America, Australia, and Europe	1) ADA (n=163) 2) TCZ (n=162) All patients were randomized 1:1 to 8mg/kg iv TCZ every 4 weeks + PBO sc every 2 weeks or ADA 40mg sc every 2 weeks + PBO iv every 4 weeks.	≥18 years with RA for >6 months; currently on MTX or cannot tolerate MTX. All DMARD are stopped before start of study Exclusion: Patients previously treated with biologics	Mean age (SD) 1) 53.3 (12.4) 2) 54.4 (13) Female, n (%) 1) 133 (82) 2) 129 (79) Mean duration of RA, yrs (SD) 1) 6.3 (6.9) 2) 7.3 (8.1) Mean DAS (SD) 1) 6.8 (0.9) 2) 6.7 (0.9) Mean HAQ score (SD) 1) 1.7 (0.6) 2) 1.6 (0.6)
Galloway J *Annals of the rheumatic diseases* 2011[272] Fair	Investigator initiated	Prospective observational study 3 years	UK	1) cDMARD (n=3,673) 2) ETN (n=3,475) 3) IFX (n=3,475) 4) ADA (n=4,267)	RA patients using TNFi and a comparison cohort of patients with active RA receiving cDMARD and are biologically naïve.	Mean age (SD) 1) 60 (12) 2) 56 (12) 3) 56 (12) 4) 57 (12)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Gomez-Reino JJ *Annals of the rheumatic diseases* 2012[273] MIRAR Fair	Roche	Prospective multicenter observational 12 months	100 centers in Spain	1) RTX (n=575) 2) TNFis (n=513) 2a) ETN 2b) ADA/IFX 2c) Other TNTis	Patients with RA who received either RTX or an alternative TNF antagonist after failing treatment with ≥1 TNFi in routine clinical practice	Mean age (SD) 1) 55.3 (12.8) 2) 54.5 (13.5) Female, n (%) 1) 472 (82) 2) 413 (80.5) RA duration >5yrs, n (%) 1) 430 (79.3) 2) 327 (67.4) Prior TNFs>1, n (%) 1) 208 (37) 2) 58 (11.4) Mean DAS28 (SD) 1) 5.5 (1.2) 2) 5 (1.3)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Greenberg JD *Annals of the rheumatic diseases* 2012[99] CORRONA registry Fair	Centocor	Prospective multicenter observational cohort 12 months	83 centers in USA	Intervention (n= biological naïve (BN)/ first time switchers (FTS)) 1) ADA (n=460/311) 2) ETN (n=480/139) 3) IFX (n=535/166)	Inclusion: Patients in CORRONA registry with newly prescribed anti-TNF With ≥ 1 follow-up visit between Feb 2002 and Mar 2008 Exclusion: RA patients in remission at baseline (i.e. CDAI ≤ 2.8 DAS28-ESR< 2.6); previous use of non-TNF agent	Mean age (BN/FTS) (SD) 1) 55 (12) / 56 (13) 2) 54 (13) / 56 (13) 3) 61 (13) / 56 (12) Female (BN/ FTS), % 1) 78 / 82 2) 76/ 79 3) 72 / 82 Mean duration of RA (BN/FTS), yrs (SD) 1) 8.9 (9.5) / 12.7 (9.7) 2) 8.8 (9.2) / 10.6 (10) 3) 9.6 (9.9) / 11.8 (9.4) Mean mHAQ score (BN/ FTS) (SD) 1) 0.5 (0.5) / 0.6 (0.5) 2) 0.5 (0.5) / 0.6 (0.5) 3) 0.4 (0.5) / 0.4 (0.4) Mean DAS28 (BN/FTS) 1) 4.49 / 4.55 2) 4.48 / 4.39 3) 4.53 / 4.46

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Grijalva CG *JAMA* 2011 [274] Fair	FDA, US DHHS, and AHRQ grant	Retrospective database cohort study 365 days	USA	1) TNFi (n=10,242) 1a) ETN (42.9%) 1b) IFX (37.3%) 1c) ADA (19.8%) 2) cDMARD (leflunomide, sulfasalazine or hydroxychloroquine) (n=10,082)	Patient with study defined autoimmune disease (RA and other disease exclusive categories) who subsequently filled a prescription or received an infusion for a TNF-antagonist or comparator medication (after MTX failure) with a baseline period of 365 days with continuous enrollment preceding the first infusion or prescription fill in the respective databases Exclusion: Patients with diagnoses for more than 1 autoimmune disease	Mean age, (SD) 1) 58.1 (14.1) 2) 58.4 (14.4) Female, n (%) 1) 9,069 (86.5) 2) 9,077 (86.6) 70% of TNFi patients used MTX at baseline

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Harigai, M *Mod Rheumatol* 2016[275] Poor	Japan College of Rheumatology; database administered by Department of Pharmacovigilance of Tokyo Medical and Dental University	Retrospective database cohort study Patients retrieved from SECURE database March 31, 2013; mean observation period 41.1 months	Japan	N=14,440 1. ETN (n=7,698) 2. IFX (n=6,620) 3. TCZ (n=2,952) 4. ADA (n=2,277) 5. ABA (n=928) 6. GOL (n=200)	Inclusion: Patients in SECURE cohort: nation-wide cohort of Japanese RA patients ever treated with biologics. Patients must have clinical diagnosis RA; treatment with biologics approved in Japan for RA; ≥20 y.o.	Mean age, yrs: 57.0 Female, %: 81.0 Number of biologics used, 1/2/3/4/5 biologics, %: 67.6/23.7/6.9/1.4/0.3

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Hetland ML *Arthritis and rheumatism* 2010[100] DANBIO registry Fair	Abbott, Wyeth, and Schering-Plough, Bristol-Myers Squibb, Roche, and UCB-Nordic	Prospective observational cohort 12 months	Denmark	1) ADA (n=544) 2) ETN (n=425) 3) IFX (n=908) The treatment regimens reflected routine care: standard doses plus concomitant MTX (or other DMARD) and prednisolone were administered per the decision of the treating rheumatologist	Patients with RA treated with ≥1 cDMARD and failed treatment; ETN, ADA or IFX initiated as first bDMARD	Mean age (range) 1) 56 (15-85) 2) 58 (19-89) 3) 57 (17-85) Male, % 1) 25 2) 28 3) 27 Mean duration of RA, yrs (range) 1) 9 (0-51) 2) 8 (0-47) 3) 9 (0-68) Mean DAS28 (range) 1) 5.3 (3.3-8.3) 2) 5.4 (3.3-8.4) 3) 5.4 (3.3-8.3)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Jobanputra P *BMJ Open* 2012[20] RED SEA Fair	University Hospital Birmingham NHS Foundation Trust	RCT, parallel group, non-blinded, non-inferiority 52 weeks	4 centers in England	1) ADA + cDMARD (n=60) 2) ETN + cDMARD (n=60) Patients were randomized to subcutaneous ADA 40 mg every other week or ETN 50 mg weekly. Clinician could modify drug doses	Patients with active RA despite prior or current use of 2 DMARDs including MTX Exclusion: prior use of biological TNFi	Mean age (SD) 1) 55 (12.5) 2) 53.2 (13.4) Female, n (%) 1) 45 2) 42 Mean duration of RA, yrs (range) 1) 7 (3.3 -13) 2) 5.5 (2-14.5) Mean DAS28-CRP (SD) 1) 5.6 (0.9) 2) 5.8 (0.9)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Johnston S *Semin Arthritis Rheum* 2013[276] Fair	Truven Health Analytics was paid by Genentech, Inc. to conduct study; Genentech, Inc. had no role in the decision to submit the manuscript for publication.	Retrospective analysis of large U.S. claims database Median follow-up time in days and total person-years of follow-up (regardless of the occurrence of infection and severe infection) for each group: 1) ABT 330 days and 1004 yrs 2) ADA 365 days and 1772 yrs 3) ETN 379 days and 1392 yrs 4) IFX 348 days and 789 yrs 5) RTX 335 days and 463 yrs	USA	1) ABT (n=870) 2) ADA (n=1378) 3) ETN (n=1026) 4) IFX (n=649) 5) RTX (n=409) Dosing not controlled for; results are "reflective of the spectrum of doses that are typically administered in 'real world' clinical practice"	Diagnosis of RA (ICD-9-CM 714.0x) on a non-diagnostic claim during 1/1/2003–3/31/2010; age ≥18 yrs as of the first-line anti-TNF index; ≥12 prior mos of continuous enrollment in health insurance at start of each treatment episode, during which baseline characteristics were measured Excluded if ≥1 inpatient or outpatient non-diagnostic claim for alternative indication for biologic treatment or a condition that may have complicated analysis of infection during baseline	Mean age (SD) 1) 57.0 (12.6) 2) 54.3 (12.0) 3) 54.6 (12.7) 4) 54.3 (12.8) 5) 56.4 (12.0) Female, % 1) 83.1 2) 80.3 3) 77.2 4) 77.8 5) 77.5 Second-line episode trial, % 1) 64.9 2) 86.9 3) 80.6 4) 69.8 5) 57.2

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Weinblatt ME *Arthritis and rheumatism* 2013[94] AMPLE Good See also Schiff M *Annals of the rheumatic diseases* 2014[22], Fleischmann R *Arthritis and Rheumatology* 2016[277]	Bristol-Myers Squibb	RCT multicenter single-blind Phase IIIB 12 months	120 sites in United States, Argentina, Canada, Chile, Peru	1) ABTsc+MTX (n=318) 2) ADAsc+MTX (n=328) 125 mg ABT sc once per wk (without intravenous loading dose), or 40 mg ADA sc every other wk, both given in combination with MTX (≥15 and ≤25 mg/wk); patients could receive either sulfasalazine or hydroxychloroquine	ACR 1987 criteria for RA; age ≥18; diagnosis for ≤5 years; inadequate response to MTX; no previous bDMARD therapy; active disease (DAS28-CRP≥3.2defined); seropositivity for anti–cyclic citrullinated peptide antibodies or rheumatoid factor, and/or ESR or CRP level	Mean age (SD) 1) 51.4 (12.6) 2) 51.0 (12.8) Female (%) 1) 81.4 2) 82.3 Mean duration of RA, yrs (SD) 1) 1.9 (1.4) 2) 1.7 (1.4) Mean HAQ-DI (SD) 1) 1.5 (0.7) 2) 1.5 (0.7) DAS28-CRP (SD) 1) 5.5 (1.1) 2) 5.5 (1.1) Mean mTSS [0-448] (SD) 1) 24.8 (37.1) 2) 24.2 (32.9)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Schiff M *Annals of the rheumatic diseases* 2008[23] ATTEST Good See also Schiff M *Annals of the rheumatic diseases* 2011[103]	Bristol-Myers Squibb	RCT multicenter double-blind Phase III 12 months	86 sites in the US (20 sites), Europe (18 sites (5 in Poland, 4 in Spain, 4 in Sweden, 2 in Russia, 2 in Denmark and 1 in Switzerland)), Canada (11 sites), Australia (6 sites), Mexico (10 sites), Argentina (5 sites), Brazil (8 sites), Peru (5 sites) and South Africa (3 sites)	1) ABTiv+MTX (n=156) 2) PBO+MTX (n=110) 3) IFX+MTX (n=156) ABT dosed according to weight: <60 kg, 60-100 kg, >100 kg received 500 mg, 750 mg, or 1000 mg of ABT, respectively. ABT administered by iv infusion on days 1, 15 and 29, and every 28 days thereafter, up to and including day 337 IFX dosed at 3 mg/kg for all patients. IFX administered on days 1, 15, 43 and 85, and every 56 days thereafter PBO patients reallocated to ABT on day 198 (with blinding maintained	Met ACR criteria for RA; age ≥18 yrs; RA diagnosis for ≥1 yr; inadequate response to MTX (at randomization >10 swollen joints, >12 tender joints, and CRP >1 mg/dL); received MTX >15 mg/wk for >3 months prior to randomization and washed out all DMARDs (>28 days prior) except MTX; no prior ABT or anti-TNFs	Mean age (SD) 1) 49.0 (12.5) 2) 49.4 (11.5) 3) 49.1 (12.0) Female (%) 1) 83.3 2) 87.3 3) 82.4 Mean duration of RA, yrs (SD) 1) 7.9 (8.5) 2) 8.4 (8.6) 3) 7.3 (6.2) Mean HAQ-DI (SD) 1) 1.8 (0.6) 2) 1.8 (0.7) 3) 1.7 (0.7) Mean DAS28-ESR (SD) 1) 6.9 (1.0) 2) 6.8 (1.0) 3) 6.8 (0.9)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Smolen JS *The Lancet* 2016[66] EXXELERATE Fair	UCB Pharma	RCT, single-blind (double-blind until wk12 and investigator blind after), parallel-group Phase iv 104 wk (2 yr)	151 centers in North America, Europe, Australia	1) CTZ + MTX (n=454) 2) ADA + MTX (n=454) CTZ administered 400 mg at wks 0, 2, and 4 (loading dose), then 200 mg once every 2 wks plus MTX ADA administered 40 mg once every 2 wks plus MTX At wk 12, patients achieving DAS28-ESR ≤3.2 or a reduction from baseline of ≥1.2 randomized to CTZ switched to receive ADA regimen while those randomized to ADA switched to receive CTZ (start at loading dose).	Age ≥18yrs; RA diagnosis by 2010 ACR/EULAR criteria; positive rheumatoid factor or ACPA result or both; DAS28-ESR > 3.2; ≥4 swollen joints; hsCRP ≥10 mg/L or ESR ≥28mm/h or both; bDMARD-naïve; ≥ 12-week course of MTX therapy, ≥28 days of stable dose MTX (15–25mg/wk) pre-baseline. Exclusion: serious infections within 12 months prior to baseline; TB; history of congestive heart failure, demyelinating disorders; active malignancy or a history of cancer.	Mean age, yrs (SD) 1) 53.5 (12.3) 2) 52.9 (12.8) Female, n (%) 1) 360 (79%) 2) 362 (79%) Mean duration of RA, yrs (SD) 1) 6.0 (6.9) 2) 5.8 (6.9) Mean CRP mg/L (SD) 1) 15.8 (21.8) 2) 15.4 (21.0) Mean DAS28-ESR (SD) 6.5 (0.9) both groups Mean HAQ-DI (SD) 1.5 (0.6) both groups

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Taylor PC *N Engl J Med* 2017[97] RA-BEAM Good See also Taylor P *Arthritis and Rheumatology* 2015[21], Smolen JS *Ann Rheum Dis* 2016 POSTER[227], Keystone E *Ann Rheum Dis* 2016 POSTER[98]	Eli Lilly and Company	Phase III RCT double-blind placebo- and active-controlled parallel-group 52 weeks Non-responders were rescued from Wk 16. At Wk 24, pts on PBO switched to BAR	281 centers in 26 countries	1) PBO + cDMARD (n=488) 2) BAR + cDMARD (n=487) 3) ADA + cDMARD (n=330) 4 mg of BAR once daily, or 40 mg of sc ADA every other week, in addition to existing background therapy (including methotrexate). Concomitant stable doses of cDMARDs, nonsteroidal anti-inflammatory drugs, analgesics, or glucocorticoids (≤10 mg of prednisone or the equivalent per day) were permitted.	Age ≥18; active RA; ≥6 tender joints and ≥6 swollen joints; CRP ≥6mg/L; inadequate response to MTX; ≥12 wks of MTX before trial entry at stable doses for ≥8 wks; ≥3 joint erosions or ≥1 joint erosions plus seropositivity for rheumatoid factor or anti-citrullinated peptide antibodies. Exclusion: previous biologic; laboratory abnormalities; recent clinically serious infection	Mean age (SD) 1) 53 (2) 2) 54 (2) 3) 53 (12) Female (%) 1) 78 2) 77 3) 76 Mean duration of RA, yrs (SD) 1) 10 (9) 2) 10 (9) 3) 10 (9) Mean HAQ-DI (SD 1) 1.55 (0.67) 2) 1.57 (0.68) 3) 1.59 (0.70) Mean DAS28-CRP/ESR 1) 5.7 (1.0) / 6.4 (1.0) 2) 5.8 (0.9) / 6.5 (0.9) 3) 5.8 0.9) / 6.4 (1.0)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
van Vollenhoven RF *The New England journal of medicine* 2012[95] ORAL Standard Good See also Strand V *Rheumatology* 2016[96]	Pfizer	RCT multicenter double-blind Phase III 12 months	115 centers worldwide United States, Australia, Bosnia and Herzegovina, Bulgaria, Canada, Chile, Costa Rica, Croatia, Czech Republic, Denmark, Dominican Republic, Finland, Germany, Korea, Mexico, Philippines, Poland, Slovakia, Spain, Thailand, United Kingdom	1) PBO+MTX → TOF 5mg (n=56) or 10mg (n=52) 2) TOF 5mg +MTX (n=204) 3) ADA+MTX (n=204) 4) TOF 10mg +MTX (n=201) 5-10 mg TOF twice daily, 40 mg sc ADA once every 2 wks; all patients took background MTX. PBO patients without 20% reduction in no. swollen and tender joints after 3 months randomly assigned to 5 or 10mg TOF; after 6 months, all PBO patients blindly switched to 5 mg or 10 mg TOF **TOF 10 mg & PBO → TOF 10mg excluded from table*	Age ≥18; active RA; ≥6 tender or painful joints and ≥6 swollen joints; either ESR>28 mm/hr or CRP>7 mg/L; receiving 7.5- 25 mg MTX weekly and had an incomplete response Key exclusion criteria were current treatment with other antirheumatic agents, including biologic agents; prior ADA; lack of response to prior anti-TNF; and current infection or evidence of active or inadequately treated infection with *Mycobacterium tuberculosis*.	Mean age (SD) 1) 55.5 (13.7) 2) 53.0 (11.9) 3) 52.5 (11.7) Female (%) 1) 76.8 2) 85.3 3) 79.4 Mean duration of RA, yrs 1) 6.9 2) 7.6 3) 8.1 Mean HAQ-DI 1) 1.5 2) 1.5 3) 1.5 Mean DAS28-CRP/ESR 1) 5.6/6.6 2) 5.4/6.6 3) 5.3/6.4 Prior anti-TNF: 5.9-9.6%

<table>
<tr><th>Author & Year of Publication (Trial Name) Quality rating</th><th>Study sponsor</th><th>Study Design and Duration of Follow-up</th><th>Geographic location of study</th><th>Interventions (n) & Dosing Schedule</th><th>Inclusion and Exclusion Criteria</th><th>Baseline patient Characteristics</th></tr>
<tr>
<td>Yun H Arthritis & Rheumatology 2016 [278]

Good</td>
<td>Agency for Healthcare Research and Quality</td>
<td>Observational
Retrospective cohort study
5 year follow-up</td>
<td>United States</td>
<td>1) ADA (n=4,845)
2) CTZ (n=1,866)
3) ETN (n=3,814)
4) GOL (n=1,394)
5) IFX (n=3,944)
6) RTX (n=4,718)
7) TCZ (n=2,016)
8) ABT (n=9,204)</td>
<td>Data found using 2006-2011 Medicare claims data for all RA patient beneficiaries from Centers for Medicare and Medicaid Services (CMS) Chronic Condition Data Warehouse.
Patients had prior treatment with different biologic agent; patients had to have continuous “full coverage” (traditional Medicare fee-for-service coverage with Part D Medicare coverage).
Exclusions: Medicare claim with diagnosis of PsA, psoriasis, AS, IBD</td>
<td>
<table>
<tr><th>Group</th><th>Mean age</th><th>% women</th></tr>
<tr><td>1</td><td>61.8 (13.5)</td><td>83.9</td></tr>
<tr><td>2</td><td>64.1 (13.3)</td><td>86.3</td></tr>
<tr><td>3</td><td>61.8 (13.3)</td><td>85.6</td></tr>
<tr><td>4</td><td>60.4 (13.5)</td><td>88.7</td></tr>
<tr><td>5</td><td>65.3 (12.5)</td><td>84.9</td></tr>
<tr><td>6</td><td>65.0 (12.2)</td><td>85.0</td></tr>
<tr><td>7</td><td>66.4 (11.9)</td><td>85.3</td></tr>
<tr><td>8</td><td>66.8 (12.1)</td><td>85.5</td></tr>
</table>

No. biologic agents used prior to index date, %
<table>
<tr><th></th><th colspan="3">Number of agents</th></tr>
<tr><th>Group</th><th>1</th><th>2</th><th>≥3</th></tr>
<tr><td>1</td><td>83.9</td><td>13.0</td><td>3.1</td></tr>
<tr><td>2</td><td>49.7</td><td>30.7</td><td>19.6</td></tr>
<tr><td>3</td><td>79.4</td><td>16.6</td><td>4.0</td></tr>
<tr><td>4</td><td>47.1</td><td>35.2</td><td>17.5</td></tr>
<tr><td>5</td><td>75.8</td><td>20.2</td><td>4.0</td></tr>
<tr><td>6</td><td>60.3</td><td>31.4</td><td>8.3</td></tr>
<tr><td>7</td><td>32.7</td><td>40.0</td><td>27.3</td></tr>
<tr><td>8</td><td>76.5</td><td>20.1</td><td>3.4</td></tr>
</table>
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Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Biosimilar studies						
Bae S-C *Ann Rheum Dis* 2016[167] HERA Good	Hanwha Chemical	Multicenter Double-blind Active-controlled Parallel-group RCT Phase III 48 weeks	37 study sties in the Republic of Korea	1) ETN-bio+MTX (n=115) 2) ETN-ref+MTX (n=118) 25 mg administered subcutaneously twice weekly with stable dose of oral/intramuscular or sc MTX (7.5-25 mg/wk) for 48 weeks	Age ≥20 yrs; RA diagnosis according to the 1987 ACR criteria; active disease defined as ≥6 swollen joints, ≥6 tender joints, CRP ≥1.0 mg/dL or ESR ≥28 mm/h; ACR functional class I to III; positive for RF or anti-CCP antibody or bone erosions in the hands and/or feet on X-ray; insufficient clinical response to MTX during ≥6 mos of treatment prior to screening.	Mean age (SD) 1) 51.0 (12.0) 2) 51.3 (12.4) Female n, (%) 1) 101 (87.8) 2) 101 (85.6) Mean duration of RA, yrs (SD) 1) 7.19 (7.39) 2) 8.05 (7.43) Mean DAS28 (SD) 1) 6.15 (0.85) 2) 6.16 (0.86) Mean HAQ-DI (SD) 1) 1.1 (0.7) 2) 1.1 (0.7)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Choe J-Y *Ann Rheum Dis* 2015[168] Good See also Choe J-Y *Arthritis Rheumatology* 2015[205], Smolen J *Arthritis Rheumatol* 2016[279]	Samsung Bioepis Co., Ltd.	Multicenter Double-blind Parallel group RCT Phase III 54-week main study + 24-week switching study; this publication reports results up to week 30	73 centers in 11 countries from Europe and Asia	1) IFX-bio+MTX (n=291) 2) IFX-ref+MTX (n=293) Infusion of 3 mg/kg intravenous IFX over 2 hrs at week 0, 2, 6, 14, 22, 30, 38, and 46. Dose increases could occur from week 30 by 1.5 mg/kg per visit, up to a total of 7.5 mg/kg. corticosteroids, antihistamines or paracetamol allowed at investigator discretion. Oral or parenteral MTX 10-25 mg/wk with 5-10 mg/wk folic acid	Age 18-75 yrs; RA classified by 1987 ACR criteria; RA diagnosis ≥6 mos; ≥6 tender and ≥6 swollen joints; ESR ≥28 mm/h or CRP ≥1.0 mg/dL; MTX for ≥6 mos and under stable dose for ≥4 wks prior to randomization	Mean age (SD) 1) 51.6 (11.9) 2) 52.6 (11.7) Female (%) 1) 79.7 2) 80.5 Mean duration of RA, yrs (SD) 1) 6.3 (5.9) 2) 6.6 (6.0) Mean HAQ-DI (SD) 1) 1.5 (0.6) 2) 1.5 (0.6) Mean DAS28-ESR (SD) 1) 6.5 (0.8) 2) 6.5 (0.8)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Cohen SB *Arthritis Rheumatology* 2015[193] Abstract See also Matsumoto AK *Arthritis Rheumatology* 2015[280]	Amgen	Double-blind Active-controlled Equivalence study RCT Phase III 26 weeks	NR	1) ADA-bio+MTX (n=264) 2) ADA-ref+MTX (n=262) 40 mg ADA administered subcutaneously every 2 weeks until week 22; 7.5-25 mg/wk MTX	Age ≥18 and ≤80 yrs; diagnosed with RA ≥3 mos before baseline; active RA defined as ≥6 swollen joints and ≥6 tender joints at screening and baseline; taking MTX for ≥12 consecutive weeks and on stable dose of 7.5-25 mg/wk for >8 wks prior to receiving study drug; no known history of active TB Exclusion criteria: class iv RA, Felty's syndrome or history of prosthetic or native joint infection; major chronic inflammatory disease other than RA; prior use of ≥2 biologics for RA; prior ADA	Baseline characteristics well balanced between groups; further detail NR

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Emery P *Ann Rheum Dis* 2015[195] Good See also Vencovsky J *Arthritis Rheumatology* 2015[204]	Samsung Bioepis Co., Ltd.	Multicenter Double-bind Parallel-group RCT Phase III 52-week study; publication reports results from 24 weeks	73 centers across 10 countries in Europe, Latin America, and Asia	1) ETN-bio+MTX (n=299) 2) ETN-ref (n=297) Self-administered 50 mg ETN once weekly for up to 52 wks via subcutaneous injection; 10-25 mg/wk MTX; 5-10 mg/wk folic acid	Age 18-75 yrs; RA diagnosis according to 1987 ACR criteria for ≥6 months and ≤15 yrs prior to screening; active disease defined as ≥6 swollen and ≥6 tender joints and either ESR ≥28 mm/h or CRP ≥1.0 mg/dL despite MTX for ≥6 mos (stable dose of 10-25 mg/wk for ≥4 wks prior to screening) Exclusion criteria: prior treatment with biologics; history of lymphoproliferative disease; CHF; demyelinating disorders; TB; pregnancy/ breastfeeding	Mean age (SD) 1) 52.1 (11.72) 2) 51.6 (11.63) Female, n (%) 1) 249 (83.3) 2) 253 (85.2) Mean RA duration, yrs (SD) 1) 6.0 (4.20) 2) 6.2 (4.41) Mean DAS28-ESR (SD) 1) 6.5 (0.91) 2) 6.5 (0.88) Mean HAQ-DI (SD) 1) 1.49 (0.553) 2) 1.50 (0.560)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Jani RH *Int J Rheum Dis* 2015[192] Good	Cadila Healthcare Limited, the Zydus Group Company, India	Multicenter Double-blind Active controlled, parallel arm RCT 12 weeks	11 investigational sites across India	1) ADA-bio+MTX (n=60) 2) ADA-ref+MTX (n=60) 40 mg scADA administered every other week for 12 wks	Age ≥18 and ≤65yrs; history of RA for ≥6 mos; moderate to severe active seropositive disease; history of treatment with MTX 10-25 mg/week for ≥12 wks with stable dose in last 4 wks before screening; negative pregnancy test Exclusion criteria: significant systemic manifestations of RA; breastfeeding female; rheumatic autoimmune disease other than RA; ACR functional class iv; history of DMARD use other than MTX; prior anti-TNF; vaccine within 4 wks of enrollment; uncontrolled concomitant disease	Mean age (SD) 1) 45 (11.06) 2) 45 (10.92) Female, n (%) 1) 51 (85.0) 2) 48 (80.0) Mean RA duration, yrs (SD) 1) 3.3 (4.19) 2) 4.0 (4.98) Mean DAS28-CRP (SD) 1) 5.9 (0.94) 2) 6.0 (0.78) Mean DAS28-ESR (SD) 1) 6.9 (0.74) 2) 6.9 (0.72) Mean HAQ-DI (SD) 1) 1.7 (0.61) 2) 1.6 (0.58)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Kay J *Ann Rheum Dis* 2014[196] Abstract See also Kay J *Ann Rheum Dis* 2015[281]	NR	Double-blind Active comparator RCT Phase III 16 weeks Responders to IFX-bio were continued on treatment and responders to IFX-ref were crossed over to biosimilar during an open-label phase in which all subjects treated every 8 wks through Wk 46	NR	1) IFX-bio (n=127) 2) IFX-ref (n=62) 3 mg/kg iv IFX on wks 0, 2, 6, and 14	Active RA according to 2010 ACR/EULAR criteria; on stable doses of oral MTX (0-20 mg/wk); CRP ≥10 mg/L at screening	87.8% female Mean age 44.8 Baseline values were similar for subjects in both treatment arms; further detail NR

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Smolen J *Arthritis Rheumatol* 2016[279] See also Choe J-Y *Ann Rheum Dis* 2015[168]	*See Choe J-Y Ann Rheum Dis 2015[168] above*	*See Choe J-Y Ann Rheum Dis 2015[168] above*	*See Choe J-Y Ann Rheum Dis 2015[168] above*	At re-randomization, weeks 54-78: 1) IFX/SB2 [IFX-bio] (n=94) 2) IFX/IFX (n=101) 3) SB2/SB2 (n=201)	*See Choe J-Y Ann Rheum Dis 2015[168] above*	Disease activity at re-randomization, week 54 HAQ-DI, mean (SD) 1) 0.99 (0.624) 2) 0.95 (0.648) 3) 0.98 (0.668) DAS28-ESR, mean (SD) 1) 3.88 (1.274) 2) 4.08 (1.452) 3) 3.97 (1.434)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Takeuchi T *Modern Rheumatology* 2015[169]	Nippon Kayaku Co., Ltd., Celltrion, Group	RCT multicenter double-blind Phase III 54 weeks	20 sites in Japan	1) IFX-bio (n=50) 2) IFX-ref (n=51) Patient received a 2-hour iv infusion of 3 mg/kg IFX-bio or IFX-ref at weeks 0, 2, and 6, and each 8 weeks afterward up to week 54. MTX and folic acid were co-administered.	≥20yrs and ≤75yrs with active RA for ≥1yr with inadequate response to MTX; within 6 weeks prior to study, patients should have ≥6 TJC &SJC and at least 2 0f the following: morning stiffness ≥45mins, ESR≥28mm/h, and CRP≥2mg/dl.	Mean age (SD) 1) 54.5 (13) 2) 53.8 (13.4) Female, n (%) 1) 40 (80) 2) 41 (80.4) Mean duration of RA, yrs (SD) 1) 7.1 (7.3) 2) 8 (7.3) Mean HAQ-DI (SD) 1) 1.03 (0.67) 2) 1.12 (0.65) Mean DAS28-ESR (SD) 1) 5.929 (1.005) 2) 6.104 (0.841) Mean DAS28-CRP (SD) 1) 5.19 (1.012) 2) 5.301 (0.9)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Weinblatt ME *Arthritis Rheumatology* 2015[194] Abstract	Samsung Bioepis Co., Ltd.	Double-blind Parallel-assignment RCT Phase III 52-week study; conference abstract reports 24-wk results	NR	1) ADA-bio (n=271) 2) ADA-ref (n=273) Patients randomly assigned to receive 40 mg of either ADA-bio or ADA-ref administered subcutaneously every other wk for 24 wks. At wk 24, patients in ADA-ref group were randomized again to receive 40 mg of either ADA-bio or ADA-ref for additional 28 wks. Patients in ADA-bio group continued to receive ADA-bio.	Age 18-75 yrs; diagnosis of RA according to 1987 ACR criteria for ≥6 mos and ≤15 yrs; moderate to severe active disease, defined as ≥6 swollen and ≥6 tender joints, either ESR ≥28 mm/h or CRP ≥1.0 mg/dL; treated with MTX for ≥6 mos prior to randomization; stable rte. of administration and dose (10-25 mg/wk) for ≥4 wks prior to screening Exclusion criteria: treated previously with biologic	Baseline demographic and disease characteristic were comparable between two treatment groups; further detail NR

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Williams J *Br J Clin Pharmacol* 2016[166] Good	Pfizer	RCT Double-blind Multi-center Phase I/II	United States, Australia, Canada, Colombia, Germany, Israel, Mexico, Russian Federation, South Africa, United Kingdom	1. PF-05280586 [RTX-bio] (n=71) 2. RTX-EU (n=72) 3. RTX-US (n=71)	Inclusion: Age ≥18 yrs; Confirmed diagnosis of RA; Class I, II, or III or ACR 1991 Revised Criteria; RA seropositivity, stable dose MTX; inadequate response to TNF inhibitors; ≥6 swollen joints; DAS28-CR >3.2 at screening Exclusion: Any prior treatment with lymphocyte depleting therapies; history of active TB infection; known or screen test positive for specific viruses or indicators of viral infection	Mean age, yrs 1. 54.8 2. 55.7 3. 53.8 Male, % 1. 18.3 2. 22.2 3. 26.8 Mean DAS28-CRP 1. 5.64 2. 5.80 3. 6.2 HAQ-DI 1. 1.67 2. 1.61 3. 1.74 CRP, mg/dL 1. 12.4 2. 14.7 3. 18.2

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Yoo DH *Ann Rheum Dis* 2013[170] PLANETRA Good See also Yoo D-H *Arthritis Res Ther* 2016,[206]Yoo D-H *Ann Rheum Dis* 2016,[241], Yoo D-H *Ann Rheum Dis* 2013[282]	CELLTRION Inc, Incheon, Republic of Korea	RCT multicenter double-blind Phase III 30 weeks	100 centers across 19 countries in Europe, Asia, Latin America and Middle East	1) IFX-bio+MTX (n=302) 2) IFX-ref+MTX (n=304) intravenous infusion of either 3 mg/kg of CT-P13 or IFX at weeks 0, 2, 6, and then q8 weeks up to week 30. Premedication with antihistamine (chlorpheniramine 2–4 mg or dose of equivalent antihistamine) 30–60 min prior to the start of infusion at investigator's discretion. Weekly MTX (12.5–25 mg/week, oral or parenteral dose) and folic acid (≥5 mg/week, oral dose)	Active RA according to 1987 ACR criteria for ≥1 year prior to screening; ≥6 swollen and ≥6 tender joints; at least two of the following: morning stiffness lasting ≥45 min; serum CRP concentration >2.0 mg/dl and ESR >28 mm/h despite MTX therapy for ≥3 months (stable dose of 12.5–25 mg/week for ≥4 weeks prior to screening).	Median age (range) 1) 50 (18–75) 2) 50 (21–74) Female, n (%) 1) 245 (81.1) 2) 256 (84.2) Mean DAS28-CRP (SD) 1) 5.9 (0.8) 2) 5.8 (0.9) Mean HAQ (SD) 1) 1.6 (0.6) 2) 1.6 (0.6)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Yoo D-H *Annals of the Rheumatic Diseases* 2016[241] PLANETRA Good See also Yoo DH *Ann Rheum Dis* 2013,[170] Yoo D-H *Arthritis Res Ther* 2016,[206], Yoo D-H *Ann Rheum Dis* 2013[282]	CELLTRION Inc, Incheon, Republic of Korea	Open-label single-arm extension study following a 52 RCT 1 year	69 centers in 16 countries in Europe, Asia, Latin America and the Middle East	1) IFX-bio-maintenance group (n=158) 2) IFX-bio-switch group (n=144) During the whole study period, IFX-bio was administered via 2 hr iv infusion at a fixed dose of 3 mg/kg	18-75 years old with active RA for ≥1year; inadequate response to ≥3months use of MTX and received stable dose of MTX for ≥4 weeks before study.	Mean age (range) 1) 50 (18-73) 2) 49 (23-74) Female, n (%) 1) 125 (79.1) 2) 122 (84.7) Other baseline characteristics: *See Yoo DH Ann Rheum Dis 2013[170]* Week 54 mean DAS28-CRP (range) 1) 3.3 (1.1-7) 2) 3.3 (1.5-7.4) Week 54 mean DAS28-ESR (range) 1) 4 (1.1-8) 2) 4 (1.5-7.4)

<table>
<tr><th>Author & Year of Publication (Trial Name) Quality rating</th><th>Study sponsor</th><th>Study Design and Duration of Follow-up</th><th>Geographic location of study</th><th>Interventions (n) & Dosing Schedule</th><th>Inclusion and Exclusion Criteria</th><th>Baseline patient Characteristics</th></tr>
<tr>
<td>Yoo D-H Arthritis Rheum 2013[191]

Abstract & Publication

Good

See also Yoo D-H Arthritis Rheum 2015 [164] and Yoo D-H Ann Rheum Dis 2016[165]</td>
<td>Celltrion</td>
<td>Multicenter
Parallel-group
Double-blind
RCT
Phase I

24 weeks

The second course of treatment was initiated between weeks 24 ~ 48 based on disease activity and predefined safety criteria</td>
<td>Republic of Korea</td>
<td>1) RTX-bio+MTX (n=102)
2) RTX-ref+MTX (n=51)

2 infusions (1000 mg, iv each) of RTX (n=51) with a 2-week interval between infusions, both co-administered with weekly MTX and folic acid.</td>
<td>Diagnosis of RA according to 1987 ACR criteria for ≥6 mons prior to randomization; active disease as defined by the presence of ≥6 swollen joints and ≥6 tender joints and either CRP ≥1.5 mg/dL or ESR≥28 mm/hr

Exclusion criteria: Unresponsive or intolerable to ≥2 biologic agents; allergies or hypersensitivity to murine, chimeric, human, or humanized proteins; chronic infection with hepatitis B, hepatitis C, or HIV</td>
<td>Age, yrs
1) 49.8
2) 51.3

Female, %
1) 86.3
2) 90.2

White, %
1) 67.6
2) 68.6

Mean DAS28-CRP/ESR (SD)
1) 6.0 (0.9)/ 6.8 (0.8)
2) 6.0 (0.8)/ 6.7 (0.8)

Prior TNF-antagonists used, %
<table>
<tr><th></th><th>Group 1</th><th>Group 2</th></tr>
<tr><td>ADA</td><td>36.3</td><td>35.3</td></tr>
<tr><td>CTZ</td><td>2.9</td><td>3.9</td></tr>
<tr><td>ETN</td><td>29.4</td><td>37.3</td></tr>
<tr><td>GOL</td><td>11.8</td><td>5.9</td></tr>
<tr><td>IFX</td><td>31.4</td><td>37.3</td></tr>
<tr><td>Other*</td><td>2.9</td><td>2.0</td></tr>
</table>
*Investigational drug</td>
</tr>
</table>

Table F2. Head-to-Head Trials Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Burmester G *Ann Rheum Dis* 2016[18] MONARCH	1) ADA (n=185) 2) SAR (n=184)	Week 24 ACR20, n (%) 1) 108 (58.4) 2) 132 (71.7) p=0.0074 Week 24 ACR50, n (%) 1) 55 (29.7) 2) 84 (45.7) p=0.0017 Week 24 ACR70, n (%) 1) 22 (11.9) 2) 43 (23.4) p=0.0036	Week 24 Mean change from baseline (SD) 1) -2.2 (0.106) 2) -3.28 (0.105) p<0.0001 Week 24 DAS28-ESR <2.6 remission, n (%) 1) 13 (7) 2) 49 (26.6) p<0.0001 Week 24 CDAI ≤2.8 remission, n (%) 1) 5 (2.7) 2) 13 (7.1) p<0.05	NR	Week 24 mean change in HAQ-DI (SD) 1) -0.43 (0.05) 2) -0.61 (0.05) P=0.0037	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Flouri I *Seminars in arthritis and rheumatism* 2014[101]	1) IFX (n=560) 2) ADA (n=435) 3) ETN (n=302)	Month 6 good EULAR response, % 1) 20 2) 24 3) 19 Year 1 good EULAR response, % 1) 26 2) 30 3) 24	Week 24/ Year 1 remission DAS28, % 1) 13/15 2) 16/23 3) 16/19 P=0.587/0.098 CDAI, % 1) 5.7/7.8 2) 11/15 3) 9.8/6.6 P=0.061/0.022 SDAI, % 1) 5.6/7.6 2) 12/17 3) 11/8.3 P=0.024/0.009	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Gabay C *Lancet* 2013[19] ADACTA	1) ADA (n=162) 2) TCZ (n=163)	Week 24 ACR 20 response, n (%) 1) 80 (49.4) 2) 106 (65) p=0.0038 Week 24 ACR 50 response, n (%) 1) 45 (27.8) 2) 77 (47.2) p=0.0002 Week 24 ACR 70 response, n (%) 1) 29 (17.9) 2) 53 (32.5) p=0.0023 Week 24 EULAR good, n (%) 1) 32 (19.8) 2) 84 (51.5) p<0.0001	Week 24 mean change from baseline DAS28 1) -1.8 2) -3.3 p<0.0001 Week 24 remission DAS28<2.6, n (%) 1) 17 (10.5) 2) 65 (39.9) p<0.0001 CDAI, n (%) 1) 15 (9.3) 2) 28 (17.2) P=0.0389 SDAI, n (%) 1) 13 (8) 2) 30 (18.4) P<0.0067	NR	Week 24 mean change from baseline HAQ score 1) -0.5 2) -0.7 P=0.0653 HAQ score≥0.22, n (%) 1) 83 (51.2) 2) 92 (56.4)	

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Gomez-Reino JJ *Annals of the rheumatic diseases* 2012[273] MIRAR	1) RTX (n=575) 2) TNFis (n=513) 2a) ETN 2b) ADA/IFX 2c) Other TNFis	Month 6 good EULAR response, n 1) 59 2) 45 P=0.025 Month 9 good EULAR response, n 1) 51 2) 56 Month 12 good EULAR response, n 1) 64 2) 60	Month 6 mean change from baseline DAS28 1) -1.61 2a) -1.32 (p=0.19) 2b) -1.04 (p=0.001) Month 9 mean change from baseline DAS28 1) -1.35 2a) -1.66 (p=0.79) 2b) -1.39 (p=0.36) Month 12 mean change from baseline DAS28 1) -1.81 2a) -1.66 (p=0.36) 2b) -1.55 (p=0.05) *p value vs. RTX	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Greenberg JD *Annals of the rheumatic diseases* 2012[99] CORRONA registry	Intervention (n= biological naïve (BN)/ first time switchers (FTS)) 1) ADA (n=460/ 311) 2) ETN (n=480/139) 3) IFX (n=535/166)	Month 12 ACR20 responders (BN/FTS), % 1) 26.8/11.4 2) 31.5/22.6 3) 26.9/18.2 Month 12 ACR50 responders (BN/FTS), % 1) 17.4/ 8.3 2) 20.8/13.2 3) 20.3/10.6 Month 12 ACR70 responders (BN/FTS), % 1) 12.1/0.8 2) 11.8/5.7 3) 12.1/7.6 *All difference not significant between drugs	Month 12 DAS28-ESR remission (BN/FTS), % 1) 33.3/10.5 2) 37.5/26.3 3) 33.8/25 *Difference was not significant between drugs Month 12 CDAI remission (BN/FTS), % 1) 12.9/4.4 2) 18.5/9.1 3) 17.1/15.3 *Differences not significant between drugs	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Hetland ML *Arthritis and rheumatism* 2010[100] DANBIO registry	1) ADA (n=544) 2) ETN (n=425) 3) IFX (n=908)	ACR 50, % Month 6 1) 45 2) 40 3) 31 Month 12 1) 53 2) 45 3) 38 P<0.0001 ACR 70, % Month 6 1) 24 2) 21 3) 14 Month 12 1) 30 2) 27 3) 17 P<0.0001 Good EULAR response, % Month 6/ month 12 1) 52/57 2) 42/49 3) 34/40 P<0.0001	DAS28 remission, % Month 6 1) 32 2) 26 3)21 P<0.0001 Month 12 1) 39 2) 33 3) 27 P<0.0001 CDAI remission Month 6 1) 18 2)13 3) 10 P=0.0001 Month 12 1) 25 2) 18 3) 16 P=0.0003	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Jobanputra P *BMJ Open* 2012[20] RED SEA	1) ADA + cDMARD (n=60) 2) ETN + cDMARD (n=60)	NR	Month 12 DAS28, median (IQR) 1) 3.5 (2.7-4.2) 2) 3.6 (3-4.4)	NR	NR	Month 12 CRP, median (IQR) 1) 5 (3-12) 2) 7 (3-13)
Weinblatt ME *Arthritis and rheumatism* 2013[94] AMPLE	1) ABTsc+MTX (n=318) 2) ADAsc+MTX (n=328)	1 yr, % (95% CI) ACR20 1) 64.8 (59.5 to 70.0) 2) 63.4 (58.2 to 68.6) ACR50 1) 46.2 (40.7 to 51.7) 2) 46.0 (40.6 to 51.4) ACR70 1) 29.2 (24.2 to 34.2) 2) 26.2 (21.5 to 31.0)	1 yr Mean DAS28-CRP (SEM) 1) -2.30 (0.08) 2) -2.27 (0.08) % (95% CI) DAS28-CRP≤3.2 1) 59.3 (53.5 to 65.1) 2) 61.4 (55.6 to 67.3) Remission DAS28-CRP<2.6 1) 43.3 (37.4 to 49.1) 2) 41.9 (36.0 to 47.9) CDAI, % (95% CI) 1) 23.5 (18.5 to28.5) 2) 24.0 (18.8 to 29.1) SDAI, % (95% CI) 1) 23.3 (18.3 to 28.3) 2) 24.8 (19.6 to 30)	1 yr mean change from baseline mTSS (Van der Heijde) (SD) 1) 0.58 (3.22) 2) 0.38 (5)	1 yr mean change from baseline HAQ-DI (SEM) 1) -0.60 (0.04) 2) -0.59 (0.03)	Mean change from baseline (SD) CRP 1) 0.80 (1.13) 2) 0.65 (1.21)

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Schiff M *Annals of the rheumatic diseases* 2014[22] AMPLE	1) ABTsc+MTX (n=318) 2) ADAsc+MTX (n=328)	Year 2, % (95% CI) ACR20 1) 59.7 (54.4 to 65.1) 2) 60.1 (54.8 to 65.4) ACR50 1) 44.7 (39.2 to 50.1) 2) 46.6 (41.2 to 52.0) ACR70 1) 31.1 (26.0 to 36.2) 2) 29.3 (24.3 to 34.2) 30.2% patients in both treatment groups maintained ACR70 score for ≥6 mos	Year 2 Mean DAS28-CRP (SD) 1) 3.1 (1.5) 2) 3.2 (1.5) Adjusted mean change from baseline DAS28-CRP (SE) 1) -2.4 (0.1) 2) -2.3 (0.1) Remission DAS28-CRP<2.6, % (95% CI) 1) 50.6 (44.4 to 56.8) 2) 53.3 (47.0 to 59.5) CDAI, % (95% CI) 1) 32 (26.2 to 37.8) 2) 30.3 (24.6 to 36.1) SDAI, % (95% CI) 1) 31.2 (25.5 to 36.9) 2) 32.5 (26.6 to 38.4)	Year 2 Change from baseline mTSS (SD) 1) 0.9 (4.1) 2) 1.1 (8.7) p=NR Change from baseline ≤0.5, % 1) 70.8 2) 73.1 p=NR	Year 2 Adjusted mean change in HAQ-DI (SEM) 1) -0.60 (0.04) 2) -0.58 (0.04) p=NR	Year 2 Mean CRP, mg/dL (%) 1) 0.80 (1.6) 2) 0.7 (1.3) p=NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Fleischmann R *Arthritis Rheumatology* 2016[277] AMPLE	1) ABTsc+MTX (n=318) 2) ADAsc+MTX (n=328)	NR	Year 2 remission DAS28-CRP <2.6, n (%) 1) 70 (53) 2) 66 (52) CDAI remission, n (%), 1) 48 (36.4) 2) 43 (34.1) SDAI remission, n (%); 1) 47 (35.6) 2) 45 (35.7) RAPID-3 remission, n (%) 1) 46 (35.1) 2) 30 (24.6)	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Schiff M *Annals of the rheumatic diseases* 2008[23] ATTEST	1) ABTiv+MTX (n=156) 2) PBO+MTX (n=110) 3) IFX+MTX (n=165)* **Group 3 switched to ABT at Day 365*	Day 197 ACR20, % 1) 66.7 (vs. 2: p<0.001) 2) 41.8 3) 59.4 (vs. 2: p=0.006) ACR50, % 1) 40.4 (vs. 2: p<0.001) 2) 20.0 3) 37.0 (vs. 2: p=0.004) ACR70, % 1) 20.5 (vs. 2 p=0.019) 2) 9.1 3) 24.2 (vs. 2: p=0.002) Day 365 ACR20/50/70 1) 72.4/45.5/26.3 3) 55.8/36.4 /20.6 Diff. ACR20 16.7 95% CI (5.5 to 27.8) Diff. ACR50 9.1 95% CI (-2.2 to 20.5) Diff ACR70 5.7 95% CI (-4.2 to 15.6)	Adjusted mean change from baseline DAS28-ESR Day 197 1) -2.53 (vs. 2: p<0.001) 2) -1.48 3) -2.25 (vs. 2: p<0.001) Day 365 1) -2.88 3) -2.25 Est. of difference -0.62 95% CI (-0.96 to -0.29) Remission DAS28-ESR<2.6, % Day 197 1) 11.3 2) 2.9 3) 12.8 Day 365 1) 18.7 3) 21.2	NR	% with clinically meaningful improvement in HAQ-DI Month 6 1) 61.5 (vs. 2: p=0.001) 2) 40.9 3) 58.8 (vs. 2: p=0.005) Day 365 1) 57.7 3) 52.7 Diff. 5.0 95% CI (-6.5 to 16.5)	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Schiff M *Annals of the rheumatic diseases* 2011[103] ATTEST	1) ABTiv+MTX (n=156) 2) PBO+MTX (n=110) 3) IFX+MTX (n=165)* **Group 3 switched to ABT at Day 365*	Year 2 responders ACR20, % 1) 86.6 3) 84.3 ACR50, % 1) 60.7 3) 70.9 ACR70, % 1) 40.8 3) 44.9	Year 2 Mean DAS28-ESR 1) 3.5 3) 3.5 Remission DAS28-ESR<2.6, % (95% CI) 1) 26.1 (18.1 to 34.1) 3) 28.6 (20.7 to 36.5) SDAI, % (95% CI) 1) 21.7 (14.2 to 29.3) 3) 24.6 (17.1 to 32.1)	NR	Year 2 mean change from baseline HAQ-DI 1) -0.83 3) -0.84	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Smolen JS *The Lancet* 2016[66] EXXELERATE	1) CTZ + MTX (n=454) 2) ADA + MTX (n=454)	Week 12 ACR20, n (%) 1) 314 (69) 2) 324 (71) Week 104, primary responder population ACR20, % 1) 64.9 2) 66.8 ACR50, % 1) 53.3 2) 56.8 ACR70, % 1) 39.7 2) 41.3	DAS28-ESR ≤3.2, n (%) Week 24 1) 184 (41) 2) 166 (37) Week 52 1) 189 (42) 2) 174 (38) Week 104 1) 161 (35) 2) 152 (33) P=0.532	NR	Week 104 HAQ-DI mean change from baseline 1) -0.62 2) -0.72	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Taylor PC *N Engl J Med* 2017[97] See also Taylor P *Arthritis and Rheumatology* 2015[21] RA-BEAM	1) PBO + cDMARD (n=488) 2) BAR + cDMARD (n=487) 3) ADA + cDMARD (n=330)	Week 24/52 ACR20, % 1) 37/NA 2) 74*ǂ/71^{+} 3) 66*/62 ACR50, % 1) 19/NA 2) 50*/56ǂ 3) 46*/47 ACR70, % 1) 8/NA 2) 30*ǂ/37 3) 22*/31 *p≤0.001 vs. PBO +p≤0.01 vs. ADA ǂp≤0.05 vs. ADA	Week 24/52 remission DAS28-CRP <2.6 1) 8/NA 2) 34*/40 3) 32*/39 DAS28-ESR <2.6 1) 5/NA 2) 18*/23 3) 18*/22 CDAI ≤2.8 1) 4/NA 2) 16*/22 3) 12*18 SDAI ≤3.3 1) 3/NA 2) 16*/23 3) 14*18 *p≤0.001 vs. PBO ǂp≤0.05 vs. ADA	Week 24 Change from baseline mTSS 1) 0.83 2) 0.38* 4) 0.31* Week 52 Change from baseline mTSS 1) 1.80 2) 0.71* 3) 0.60* p≤0.001 vs. PBO	24 weeks HAQ-DI MCID ≥0.22 1) 45 2) 73*ǂ 3) 64* *p≤0.001 vs. PBO ǂp≤0.05 vs. ADA 52 weeks HAQ-DI MCID ≥0.22 1) NA 2) 68 3) 58 p≤0.01	Week 24/52 Change from baseline CRP, mg/L 1) -2.94/NA 2) -15.13/-13.93 3) -11.69/-10.68 ESR, mm/h 1) -6.6/NA 2) -20.0/-19.6 3) -18.2/-17.3

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
van Vollenhoven RF *The New England journal of medicine* 2012[95] ORAL Standard	1) PBO+MTX (n=108) 2) 5mg TOF+MTX (n=204) 3) 40 ADA+MTX (n=204)	Month 6 ACR20, n (%) 1) 30 (28.3) 2) 101 (51.5) 3) 94 (47.2)	Month 6 Remission DAS28-ESR<2.6, n (%) 1) 1 (1.1) 2) 11 (6.2) 3) 12 (6.7)	NR	Month 3 mean change from baseline HAQ-DI 1) -0.24 2) -0.55 3) -0.49	NR
Biosimilar studies						

<table>
<tr><th>Author & Year of Publication (Trial Name)</th><th>Interventions</th><th>Treatment Response</th><th>Disease Activity</th><th>Structural Damage</th><th>Function</th><th>Laboratory indices</th></tr>
<tr>
<td>Bae S-C Ann Rheum Dis 2016[167]

HERA</td>
<td>1) ETN-bio+MTX (n=115)
2) ETN-ref+MTX (n=118)</td>
<td>Full analysis set
ACR20, n (%)
<table><tr><th></th><th>Wk24</th><th>Wk48</th></tr><tr><td>1)</td><td>106 (79.10)</td><td>110 (82.09)</td></tr><tr><td>2)</td><td>102 (75.56)</td><td>108 (80.00)</td></tr></table>
ACR50, n (%)
<table><tr><th></th><th>Wk24</th><th>Wk48</th></tr><tr><td>1)</td><td>79 (58.96)</td><td>82 (61.19)</td></tr><tr><td>2)</td><td>63 (46.67)</td><td>67 (49.63)</td></tr></table>
ACR70, n (%)
<table><tr><th></th><th>Wk24</th><th>Wk48</th></tr><tr><td>1)</td><td>38 (28.36)</td><td>45 (33.58)</td></tr><tr><td>2)</td><td>38 (28.15)</td><td>43 (31.85)</td></tr></table>
</td>
<td>Full analysis set
Least squares mean change from baseline (SE)
CDAI
<table><tr><th></th><th>Wk24</th><th>Wk48</th></tr><tr><td>1)</td><td>-21.25 (0.67)</td><td>-22.82 (0.69</td></tr><tr><td>2)</td><td>-21.34 (0.68)</td><td>-21.60 (0.69)</td></tr></table>
SDAI
<table><tr><th></th><th>Wk24</th><th>Wk48</th></tr><tr><td>1)</td><td>-22.64 (0.70)</td><td>-24.28 (0.72)</td></tr><tr><td>2)</td><td>-22.55 (0.70)</td><td>-22.75 (0.72)</td></tr></table>
DAS28 mean change from baseline (SD)
<table><tr><th></th><th>Wk24</th><th>Wk48</th></tr><tr><td>1)</td><td>2.56 (1.29)</td><td>2.70 (1.29)</td></tr><tr><td>2)</td><td>2.54 (1.10)</td><td>2.53 (1.18)</td></tr></table>
DAS28 remission, n (%)
<table><tr><th></th><th>Wk24</th><th>Wk48</th></tr><tr><td>1)</td><td>34 (25.56)</td><td>37 (27.82)</td></tr><tr><td>2)</td><td>31 (23.48)</td><td>35 (26.52)</td></tr></table>
</td>
<td>NR</td>
<td>Per-protocol population
HAQ-DI mean change from baseline (SD)
Week 24
1) -0.49 (0.63)
2) -0.53 (0.59)

Week 48
1) -0.49 (0.60)
2) -0.53 (0.56)</td>
<td>NR</td>
</tr>
</table>

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Choe J-Y *Ann Rheum Dis* 2015[168]	1) IFX-bio+MTX (n=290) 2) IFX-ref+MTX (n=293)	Week 30, full analysis set ACR20, n (%) 1) 161 (55.5) 2) 173 (59.0) Treatment difference= -2.95% (95% CI -10.88 to 4.97%) ACR50, n (%) 1) 89 (30.7) 2) 99 (33.8) Treatment difference= -2.53% (95% CI -10.07% to 5.00%) ACR70, n (%) 1) 45 (15.5) 2) 50 (17.1) Treatment difference = -1.08% (95% CI -7.06% to 4.91%)	Week 30 Mean change from baseline (SD) DAS28-ESR 1) -2.3 (1.4) 2) -2.3 (1.5) SDAI 1) -23.5 (14.1) 2) -23.6 (14.5) CDAI 1) -23.3 (13.7) 2) -23.1 (14.2) Remission DAS28-ESR, % 1) 14.6 2) 15.9 Remission SDAI, % 1) 9.5 2) 10.9	NR	Week 30 Mean change from baseline (SD) HAQ-DI 1) -0.5 (0.6) 2) -0.5 (0.6)	Week 30 Mean change from baseline (SD) CRP 1) -3.7 (21.6) 2) -5.2 (19.9) ESR 1) -15.4 (19.8) 2) -15.5 (22.7)

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Choe J-Y *Arthritis Rheumatology* 2015[205] 54-week results of Choe J-Y *Ann Rheum Dis* 2015[168]	1) IFX-bio+MTX (n=290) 2) IFX-ref+MTX (n=293)	Week 54 Full analysis set ACR20, % 1) 50.7 2) 52.6 ACR50, % 1) 32.1 2) 29.7 ACR70, % 1) 18.3 2) 17.7	NR	54 week mean change mTSS 1) 0.38 2) 0.37	NR	NR
Cohen SB *Arthritis Rheumatology* 2015[193]	1) ADA-bio+MTX (n=264) 2) ADA-ref+MTX (n=262)	Week 24 ACR20, n (%) 1) 194 (74.6) 2) 189 (72.4) RR 1.039 90% CI (0.954-1.133) ACR50, n (%) 1) 120 (49.2) 2) 131 (52.0) ACR70, n (%) 1) 64 (26.0) 2) 58 (22.9)	NR	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Emery P *Ann Rheum Dis* 2015[195]	1) ETN-bio+MTX (n=299) 2) ETN-ref (n=297)	Full analysis set Week 24 ACR20, n (%) 1) 220 (73.8) 2) 213 (71.7) ACR50, n (%) 1) 128 (43.0) 2) 116 (39.1) ACR70, n (%) 1) 69 (23.2) 2) 59 (19.9)	Full analysis set Week 24 Mean change from baseline DAS28-ESR 1) 2.6 2) 2.5 Remission DAS28-ESR ≤2.6, n (%) 1) 16.7 2) 16.2	NR	NR	NR
Matsumoto AK *Arthritis Rheumatology* 2015[280] Secondary endpoints from Cohen SB *Arthritis Rheumatology* 2015[193]	1) ADA-bio+MTX (n=264) 2) ADA-ref+MTX (n=262)	See Matsumoto AK *Arthritis Rheumatol* 2015[280] Week 24 ACR50 RR: 0.95 90% CI (0.819 to 1.097) ACR70 RR: 1.13 90% CI (0.872 to 1.464)	Week 24 Difference in mean change from baseline in DAS28-CRP: -0.01 90% CI (-0.18 to 0.17)	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Smolen J *Arthritis Rheumatol* 2016[279]	At re-randomization, weeks 54-78: 1) IFX/SB2 [IFX-bio] (n=94) 2) IFX/IFX (n=101) 3) SB2/SB2 (n=201)	Week 78 ACR20, n/N (%) 1) 54/85 (63.5) 2) 64/93 (68.8) 3) 123/180 (68.3) ACR50, n/N (%) 1) 32/85 (37.6) 2) 44/93 (47.3) 3) 73/180 (40.6) ACR70, n/N (%) 1) 19/85 (22.4) 2) 29/93 (31.2) 3) 46/180 (25.6) EULAR Good response, % 1) 32.9 2) 34.4 3) 35.6 EULAR Moderate response, % 1) 51.8 2) 50.5 3) 51.7	Week 78 DAS28-ESR change from 54 week re-randomization, mean (SD) 1) -0.12 (1.36) 2) 0.12 (0.92) 3) 0.13 (0.96) DAS28-ESR change from Week 0 baseline, mean (SD) 1) 2.52 (1.52) 2) 2.58 (1.56) 3) 2.62 (1.42)	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Vencovsky J *Arthritis Rheumatol* 2015[204] 52-week results of Emery P *Ann Rheum Dis* 2015[195]	1) ETN-bio+MTX (n=299) 2) ETN-ref (n=297)	Full analysis set Week 52 ACR20, n (%) 1) 210 (70.2) 2) 195 (65.7) ACR50, n (%) 1) 143 (47.8) 2) 125 (42.1) ACR70, n (%) 1) 91 (30.4) 2) 73 (24.6)	NR	52 weeks mean change from baseline mTSS 1) 0.45 2) 0.74	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Jani RH *Int J Rheum Dis* 2015[192]	1) ADA-bio+MTX (n=60) 2) ADA-ref+MTX (n=60)	Week 12 ACR20, n (%) 1) 47 (78.33) 2) 47 (79.66) p=NS ACR50, n (%) 1) 26 (43.33) 2) 26 (44.07) p=NS ACR70, n (%) 1) 8 (13.33) 2) 9 (15.25) p=NS	Change from baseline at week 12 (SD) DAS28-CRP 1) -2.1 (1.05) 2) -2.1 (1.17) DAS28-ESR 1) -2.0 (1.04) 2) -2.1 (1.11)	NR	Change from baseline at week 12 (SD) HAQ-DI 1) -0.8 (0.61) 2) -0.8 (0.59)	Change from baseline at week 12 (SD) CRP 1) -5.8 (12.45) 2) 0.4 (26.38) ESR 1) -9.0 (19.88) 2) 6.1 (16.98)
Kay J *Ann Rheum Dis* 2014[196]	1) IFX-bio (n=127) 2) IFX-ref (n=62)	Week 16, ITT ACR20 (%) 1) 85.0 2) 85.5 95% CI for difference (-11.2% to 10.3%)	NR	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Kay J *Ann Rheum Dis* 2015[281]	1) IFX-bio (n=127) 2) IFX-ref (n=62)	No significant difference in the proportion of subjects achieving ACR20, 50, or 70 responses between treatment groups; these remained stable throughout the open label phase	NR	NR	NR	Wk 16 mean change from baseline CRP, mg/L 1) -13.4 2) -16.48 ESR, mm/h 1) -26.5 2) -23.7 Open label phase, mean change from baseline to wk 54 CRP: -13.9 mg/L ESR: -24.1

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Takeuchi T *Modern Rheumatology* 2015[169]	1) IFX-bio(n=50) 2) IFX-ref (n=51)	Week 30/week 54 ACR20, % 1) 78/64 2) 64.7/49 p=NS Week 30/week 54 ACR50, % 1) 54/50 2)47.1/31.4 p=NS Week 30/week 54 ACR70, % 1) 32/42 2) 27.5/13.7 Week 30 p=NS Week 54 p=0.002	Week 30/week 54 Mean change from baseline, DAS28-ESR 1) -2.142/-2.097 2) -1.961/-1.537 P=NS Week 30/week 54 Mean change from baseline, DAS28-CRP 1) -2.080/-2.077 2) -1.955/-1.431 Week 30 p =NS Week 54 p=0.033 Week 30/week 54 Mean change from baseline, CDAI 1) -17.55/-17.39 2) -17.08/-13.66 p =NS	NR	Week 30 Mean change from baseline, HAQ-DI 1) -0.47 2) -0.36 P=NS Week 54 Mean change from baseline, HAQ-DI 1) -0.54 2) -0.25 P=0.007	

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Weinblatt ME *Arthritis Rheumatol* 2015[194]	1) ADA-bio (n=271) 2) ADA-ref (n=273)	Per-protocol population Week 24 ACR20, n (%) 1) 174 (75.2) 2) 170 (72.0) ACR50, % 1) 38.3 2) 39.8 ACR70, % 1) 19.2 2) 20.3	NR	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Williams J *Br J Clin Pharmacol* 2016[166]	1. PF-05280586 [RTX-bio] (n=71) 2. RTX-EU (n=72) 3. RTX-US (n=71)	24 weeks ACR20, % (estimated from graph): 1. 58 2. 60 3. 78 ACR50, % (estimate): 1. 23 2. 38 3. 33 ACR70, % (estimate): 1. 19 2. 18 3. 20	24 weeks DAS-28 change from baseline (estimated from graph): 1. -1.9 2. -2 3. -2.2			

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Yoo DH *Ann Rheum Dis* 2013[170] PLANETRA	1) IFX-bio+MTX (n=302) 2) IFX-ref+MTX (n=304)	Week 30 ACR20, n (%) 1) 184 (60.9) 2) 178 (58.6) Treatment difference= 2% (95% CI: -6%-10%) ACR50, n (%) 1) 106 (35.1) 2) 104 (34.2) ACR70, n (%) 1) 50 (16.6) 2) 47 (15.5)	Week 30 Mean change from baseline (SD) CDAI 1) -25.2 (13.3) 2) -23.6 (13.0) p=NS SDAI 1) -25.8 (14.0) 2) -24.4 (13.6) p=NS DAS28-ESR Remission, n (%) 1) 36 (15) 2) 27 (11) DAS28-CRP Remission, n (%) 1) 61 (25) 2) 56 (22)	NR	Week 30 Mean change from baseline (SD) HAQ 1) -0.6 (0.6) 2) -0.5 (0.6) p=NS	Week 30 Mean change from baseline (SD) CRP 1) -0.6 (2.0) 2) -0.8 (1.9) p=NS

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Yoo D-H *Arthritis Res Ther* 2016[241] PLANETRA 54-week results	1) IFX-bio+MTX (n=302) 2) IFX-ref+MTX (n=304)	Week 54 ITT population ACR20, % 1) 57.0 2) 52.0 ACR50, % 1) 33.1 2) 31.6 ACR70, % 1) 16.2 2) 15.2	Week 54 ITT population Mean DAS28-ESR (SD) 1) 4.2 2) 4.2 DAS28-CRP (SD) 1) 3.6 2) 3.6 Mean SDAI (SD) 1) 15.7 2) 16.5 Mean CDAI (SD) 1) 14.8 2) 15.2	Week 54 Mean change from baseline mTSS (SD) 1) 1.3 (9.3) 2) 0.7 (7.0) p=NS No radiographic progression in mTSS, n (%) 1) 153 (51.7) 2) 151 (51.4) p=NS	Week 54 Mean change from baseline (SD) HAQ estimate of physical ability 1) -0.60 (0.61) 2) -0.52 (0.59)	NR
Yoo D-H *Ann Rheum Dis* 2013[282] PLANETRA Additional 54-week results	1) IFX-bio+MTX (n=302) 2) IFX-ref+MTX (n=304)	See Yoo D-H *Arthritis Res Ther* 2016[241]	Week 54 DAS28-CRP Remission, % 1) 26.4 2) 27.8	See Yoo D-H *Arthritis Res Ther* 2016[241]	See Yoo D-H *Arthritis Res Ther* 2016[241]	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Yoo D *Annals of the Rheumatic Diseases* 2016[241] PLANETRA	1) IFX-bio-maintenance group (n=158) 2) IFX-bio-switch group (n=144)	Week 102 ACR20, % 1) 71.7 2) 71.8 CI of differences (-10,10) Week 102 ACR50, % 1) 48 2) 51.4 CI of differences (-15, 8) Week 102 ACR70, % 1) 24.3 2) 26.1 CI of differences (-12, 8)	Week 102 mean change from 52wks DAS28-ESR 1) -2.60 2) -2.69 p=NS Week 102 mean change from 52wks DAS28-CRP 1) -2.40 2) -2.48 p=NS Week 102 DAS28 remission, % ESR/CRP 1) 13.8/27 2) 12.7/31.7 p=NS CDAI remission 1) 11.8 2) 16.9 P=NS	NR	Week 102 mean change from baseline HAQ-DI 1) -0.64 2) -0.63 p=NS	

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Yoo D-H *Arthritis Rheum* 2013[191]	1) RTX-bio+MTX (n=103) 2) RTX-ref+MTX (n=51)	Week 24 ACR20 (%) 1) 63.0 2) 66.7 ACR50 (%) 1) 37.0 2) 31.3 ACR70 (%) 1) 16.0 2) 14.6	NR	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Yoo D-H *Arthritis Rheum* 2015[164]	1) RTX-bio+MTX (n=103) 2) RTX-ref+MTX (n=51)	NR	Changes at Week 24 after 1st course DAS28-CRP (SD) 1) -1.9 (1.2) 2) -2.0 (1.5) DAS28-ESR (SD) 1) -2.1 (1.2) 2) -2.1 (1.5) Changes at Week 24 after 2nd course DAS28-CRP (SD) 1) -2.4 (1.3) 2) -2.0 (1.2) DAS28-ESR (SD) 1) -2.5 (1.3) 2) -2.0 (1.2)	NR	NR	

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Yoo D-H *Ann Rheum Dis* 2016[165] ADDITIONAL 24 WEEK RESULTS	1) RTX-bio+MTX (n=102) 2) RTX-ref+MTX (n=51)	Week 24 Good or moderate EULAR-ESR, % 1) 73.0 2) 70.9 Good or moderate EULAR-CRP, % 1) 78.0 2) 75.0	Week 24 DAS28-ESR change from baseline 1) -2.09 2) -2.21 DAS28-CRP change from baseline 1) -1.98 2) -2.09 CDAI change from baseline 1) -23.45 2) -23.23 SDAI change from baseline 1) -24.29 2) -24.46	NR	NR	Week 24 Change in CRP (mg/dL) 1) -0.8 2) -1.1

Table F3. Head-to-Head Trials: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Baddley J *Annals of the rheumatic diseases* 2014[266] SABER	1) TNFi (n=24, 384) 1a) ADA (n=5,888) 1b) ETN (n=10,283) 1c) IFX (n=8,212) 2) cDMARD (leflunomide, sulfasalazine or hydroxychloroquine) (n=11,828) Both TNFi and cDMARD regimens allowed the concurrent use (continuation or addition) of MTX	NR	Adjusted hazard of non-viral opportunistic infection, (95% CI) *vs. ETN* 1a) 2.5 (0.9-7.3) 1b) ref 1c) 1.6 (0.8-3.1) Adjusted hazard of non-viral opportunistic infection, (95% CI) *vs. cDMARD* 1a) 2.8 (0.8-9.9) 1b) 1.7 (0.7-4.1) 1c) 1.7 (0.9-3.4) *HR corrected for baseline glucocorticoid use.	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Burmester G *Ann Rheum Dis* 2016[18] MONARCH	1) ADA (n=185) 2) SAR (n=184)		Serious infection, n (%) 1) 2 (1.1) 2) 2 (1.1)		Serious AEs, n (%) 1) 12 (6.5) 2) 9 (4.9) Discontinuation due to AEs, n (%) 1) 13 (7.1) 2) 11 (6) Death, n (%) 1) 0 2) 1 (0.5)
Chiu YM *International journal of rheumatic diseases* 2014[268]	1) ETN (n=1,492) 2) ADA (n=746)	Incident rate ratio of Lymphoma *vs. ETN* 1) ref 2) 1.49 (0.03-18.66)	Incident rate ratio of TB cases *vs. ETN* 1) ref 2) 2.35 (1.29 -4.15) Incident rate ratio of serious bacterial infection *vs. ETN* 1) ref 2) 1.83 (1.19-2.77)	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Curtis J *Annals of the Rheumatic Diseases* 2016[269]	1) ABT (n=12,305) 2) RTX (n=5,078) 3) TNFi (n=42,850) 3a) ADA 3b) CTZ 3c) ETN 3d) GOL 3e) IFX 4) TOC (n=6,967) 5) TOF (n=2,526)	NR	Adjusted hazard ratio of Herpes zoster and herpes simplex, (95% CI) *vs. ABT* 1) ref 2) 0.98 (0.83-1.15) 3a) 0.89 (0.77-1.03) 3b) 1 (0.83-1.19) 3c) 0.86 (0.74-1) 3d) 1.01 (0.8-1.27) 3e) 1.06 (0.93-1.21) 4) 1.15 (0.99-1.34) 5) 1.4 (1.09-1.81)	NR	NR
Curtis J *Arthritis care & research* 2014[270]	1) ABT (n=451) 2) RTX (n=596) 3) ADA (n=1,885) 4) ETN (n=844) 5) IFX (n=382)	NR	Adjusted hazard ratio of hospitalized bacterial infection, (95% CI) *vs. ETN* 1) 1.1 (0.6-2.1) 2) 1.4 (0.8-2.6) 3) 1.4 (0.9-2.2) 4) ref 5) 2.3 (1.3-4)	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Curtis J *Arthritis research & therapy* 2015[271]	1) TNFi (n=7,951) 1a) ETN 1b) ADA 1c) IFX 1d) CTZ 1e) GOL 2) TCZ (n=1,528) 3) RTX (n=1,134) 4) ABT (n=2,683)	NR	Interstitial lung disease rate (specific definition) per 1000 PY (95% CI) 1a) 0 (0-3) 1b) 1.8 (0.4-5.2) 1c) 4.1 (0.8-12) 1d) 3.2 (0.7-9.3) 1e) 0 (0-2.7) 2) 1 (0-5.5) 3) 4.7 (1.3-12.1) 4) 1.1 (0.1-4.1)	NR	NR
Dartel SAA *Annals of Rheumatic Diseases* 2013[102] DREAM registry	1) ETN + MTX (n=959) 2) ADA + MTX (n=776) 3) IFX + MTX (n=621)		Incidence rate serious infections per 100 patient-years 1) 1.66 2) 2.61 3) 3.86 Serious infections, n (%) 1) 31 (3.2) 2) 43 (5.5) 3) 51 (8.2) Lower respiratory tract, n (%) 1) 9 (1.0) 2) 15 (2.0) 3) 21 (3.4)		Drop out <5 years follow-up: 1) 82 2) 69 3) 43

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Gabay C *Lancet* 2013[19] ADACTA	1) ADA (n=163) 2) TCZ (n=162)	Malignancies, n (%) 1) 1 (1) 2) 0	Serious infection, n (%) 1) 5 (3) 2) 5 (3)	Stroke, n (%) 1) 1 (1) 2) 1 (1) Myocardial infarction, n (%) 1) 2 (1) 2) 2 (1)	Serious AE, n (%) 1) 16 (10) 2) 19 (12) Death, n (%) 1) 0 2) 2 (1)
Galloway J *Annals of the rheumatic diseases* 2011[272]	1) cDMARD (n=3,673) 2) ETN (n=3,475) 3) IFX (n=3,475) 4) ADA (n=4,267)	NR	Adjusted hazard ratio of septic arthritis, (95%CI) *vs. cDMARD* 1) ref 2) 2.5 (1.3-4.9) 3) 2.4 (1-5.8) 4) 1.9 (0.9-4)	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Grijalva CG *JAMA* 2011 [274]	1) TNFi (n=10,242) 1a) ETN (42.9%) 1b) IFX (37.3%) 1c) ADA (19.8%) 2) cDMARD (leflunomide, sulfasalazine or hydroxychloroquine) (n=10,082)	NR	Adjusted hazard ratio of serious infection, (95%CI) *Vs Non-biologic DMARD* 1a) 0.91 (0.76-1.08) 1b) 1.25 (1.07-1.48) 1c) 1.05 (0.85-1.3) Adjusted hazard ratio of serious infection, (95%CI) *vs. ETN* 1b) 1.26 (1.07-1.47) 1c) 1.05 (0.87-1.25) *IFX vs. ADA* 1b) 1.23 (1.02-1.48)	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Harigai M *Mod Rheumatol* 2016[275]	1) ETN (n=7,698) 2) IFX (n=6,620) 3) TCZ (n=2,952) 4) ADA (n=2,277) 5) ABA (n=928) 6) GOL (n=200)	Non-hematopoietic malignancies (NHM), n=245 Malignant lymphoma (ML), n=72 NHM/ML while taking drug, n 1) 116/14 2) 64/37 3) 25/4 4) 18/3 NHM/ML if ever exposed to drug, n 1) 152/26 2) 123/54 3) 32/9 4) 29/3 Prior use of biologics at malignancy diagnosis, ML/NHM, % 1) 19.4/46.5 2) 51.4/25.3 3) 5.6/9.4 4) 4.2/6.9 5) 4.2/0 6) 0/0.4 None: 15.3/11.4	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Jobanputra P *BMJ Open* 2012[20] RED SEA	1) ADA + cDMARD (n=60) 2) ETN + cDMARD (n=60)	Malignancy 1) 1 2) 1		Injection site reactions 1) 9 2) 19	Serious AEs, n 1) 6 2) 7 Death, n 1) 2 2) 0
Johnston S *Semin Arthritis Rheum* 2013[276]	1) ABT (n=870) 2) ADA (n=1378) 3) ETN (n=1026) 4) IFX (n=649) 5) RTX (n=409)	NR	Adjusted hazard of infection, (95% CI) *vs. RTX* 1) 1.18 (0.98-1.41) p=NS 2) 1.31 (1.10-1.56) p<0.001 3) 1.44 (1.20-1.72) p<0.05 4) 1.30 (1.07-1.57) p<0.001 Adjusted hazard of severe infection, (95% CI) *vs. RTX* 1) 1.21 (0.78-NR) 2) 1.10 (0.72-1.68) 3) 1.27 (0.83-1.95) 4) 1.62 (1.03-2.55) IFX vs. RTX p<0.05 p=NS for other comparisons	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Schiff M *Annals of the rheumatic diseases* 2014[22] AMPLE	1) ABTsc+MTX (n=318) 2) ADAsc+MTX (n=328)	Year 2 Malignancies, n (%) 1) 7 (2.2) 2) 7 (2.1) 1) (2 squamous cell carcinomas of the skin, 1 diffuse large B cell lymphoma, 1 acute myeloid leukemia, 1 squamous cell carcinoma of lung, 1 prostate cancer and 1 uterine cancer 2) 2 basal cell carcinomas, 2 transitional cell carcinomas, 1 breast cancer, 1 malignant melanoma and 1 small cell lung cancer	Year 2 Infections and infestations, n (%) 1) 12 (3.8) 2) 19 (5.8) Serious infections, n (%) 1) 12 (3.8) 2) 19 (5.8) Pneumonia, n (%) 1) 3 (0.9) 2) 4 (1.2)	Year 2 Local injection site reactions, n (%) 1) 13 (4.1) 2) 34 (10.4)	Year 2 Discontinuation due to AEs, n (%) 1) 12 (3.8) 2) 31 (9.5) Serious AEs, n (%) 1) 44 (13.8) 2) 54 (16.5) Deaths, n (%) 1) 1 (0.3) 2) 1 (0.3)

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Schiff M *Annals of the rheumatic diseases* 2008[23] ATTEST	1) ABTiv+MTX (n=156) 2) PBO+MTX (n=110) 3) IFX+MTX (n=165)* **Group 3 switched to ABT at Day 365* *PBO results from days 1-197 only*	Days 1-365 Malignant neoplasms, n (%) 1) 1 (0.6) 3) 2 (1.2)	Days 1-365 Serious infections, n (%) 1) 3 (1.9) 3) 14 (8.5)	Days 1-365 Hypotension, n (%) 1) 0 3) 8 (4.8)	Days 1-365 Discontinuation due to AEs, n (%) 1) 5 (3.2) 2) 0 3) 12 (7.3) Serious Adverse events, n (%) 1) 15 (9.6) 2) 13 (11.8) 3) 30 (18.2) Deaths, n (%) 1) 1 (0.6) 2) 0 3) 2 (1.2)

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Schiff M *Annals of the rheumatic diseases* 2011[103] ATTEST	1) ABTiv+MTX (n=156) 2) PBO+MTX (n=110) 3) IFX+MTX (n=156)* **Group 3 switched to ABT at Day 365* Cumulative 2-yr study period (ABT, n=399)	Two malignancies (including basal cell carcinoma in a patient originally randomly assigned to ABT, which was possibly related to treatment) Incidence rate (95% CI) Neoplasms: 2.7 (1.5 to 4.5) Malignant neoplasms: 0.4 (0.0 to 1.3)	The most common infections (≥10% of patients) were nasopharyngitis, urinary tract infection, upper respiratory tract infection, influenza and pharyngitis; and for serious infections were pneumonia and urinary tract infection (three patients each)		Cumulative 2-yr study period (ABT, n=399) Discontinuation due to AEs during Yr 2, n: 7 Incidence rate (95% CI) Serious AEs: 15.2 (12.0 to 19.0) Deaths: 0.7 (0.2 to 1.8)

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Smolen JS *The Lancet* 2016[66] EXXELERATE	1) CTZ + MTX (n=454) 2) ADA + MTX (n=454)	Week 104 All malignancies, n 1) 8 2) 7	Week 104 Infections and infestations, incidence rate: 1) 59.9 2) 59.1 Serious infections and infestations, n (%) 1) 17 (3) 2) 16 (3) Opportunistic infections (excluding TB): 3 for each treatment group 1 case of TB in ADA group		Week 104 Serious treatment-emergent AEs, n (%) 1) 67 (13) 2) 58 (11) P=0.391 Discontinuation due to treatment-emergent adverse events, n (%) 1) 65 (13) 2) 63 (12) Deaths: 3 in each treatment group

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Taylor PC *N Engl J Med* 2017[97] See also Taylor P *Arthritis and Rheumatology* 2015[21] RA-BEAM	1) PBO + cDMARD (n=488) 2) BAR + cDMARD (n=487) 3) ADA + cDMARD (n=330)	Week 52, n (%) 1) 3 (<1) 2) 3 (<1) (Breast cancer, squamous-cell cancer, clear-cell renal carcinoma) 3) 0	Week 52, n (%) Any infection 1) 134 (27)* 2) 233 (48) 3) 145 (44) Serious infection 1) 7 (1)* 2) 10 (2) 3) 5 (2) Herpes zoster 1) 2 (<1)* 2) 11 (2) 3) 5 (2) Tuberculosis 1) 0* 2) 0 3) 1 (<1) *PBO arm reports 24 week data	Week 24 TEAEs (%) 1) 60 2) 70.8 3) 67.0	Week 0-24/0-52, n (%) SAEs 1) 22 (5)/NA 2) 23 (5)/38 (8) 3) 6 (2)/13 (4) Discontinuation due to AEs 1) 117 (3)/NA 2) 24 (5)/36 (7) 3) 7 (2)/13 (4) Deaths, n 1) 1 2) 2 3) 1 1 additional death in a PBO patient who received rescue treatment with BAR

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
van Vollenhoven RF *The New England journal of medicine* 2012[95] ORAL Standard	1) PBO+MTX (n=106) 2) TOF 5mg +MTX (n=204) 3) ADA 40 +MTX (n=204)	Neoplasm benign, malignant, and unspecified, including cysts and polyps 1) 0 2) Salivary-gland neoplasm, hair follicle tumor benign, metastatic renal-cell carcinoma, non–small-cell lung cancer 3) Non–small-cell lung cancer	Serious infections, n (%) Months 0-3, 3-6 1) 1 (0.9), 0 2) 3 (1.5), 2 (1.0) 3) 0, 2 (1.) Months 6-12 1) 0 [PBO→TOF 5] 2) 2 (1.0) 3) 1 (0.5) 0 cases of pulmonary or extrapulmonary tuberculosis or other major opportunistic infections		Discontinuation due to AEs, n (%) 1) 3 (2.8) 2) 25 (12.3) 3) 23 (11.3) 1 (3.6) discontinuation PBO→ TOF 5 mg Serious AEs, n (%) Months 0-3, 3-6 1) 2 (1.9), 2 (3.4) 2) 12 (5.9), 10 (4.9) 3) 5 (2.5), 6 (2.9) Months 6-12 1) 1 (1.8) [PBO→TOF 5] 2) 10 (4.9) 3) 7 (3.4) Deaths, n 1) 0 2) 1 3) 1

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Weinblatt ME *Arthritis and rheumatism* 2013[94] AMPLE	1) ABTsc+MTX (n=318) 2) ADAsc+MTX (n=328)	Year 1 Malignancies, n (%) 1) 5 (1.6) 2) 4 (1.2)	Year 1 Infection, % 1) 63.2 2) 61.3 Serious infections, n (%) 1) 7 (2.2) 2) 9 (2.7	Year 1 Local injection site reactions, n (%) 1) 12 (3.8) 2) 30 (9.1)	Year 1 Discontinuation due to AEs, n (%) 1) 11 (3.5) 2) 20 (6.1) Serious AEs, n (%) 1) 32 (10.1) 2) 30 (9.1) Deaths, n 1) 1 2) 0

<table>
<tr><th>Author & Year of Publication

(Trial Name)</th><th>Interventions</th><th>Malignancies</th><th>Infections</th><th>Other Adverse Events</th><th>Discontinuation, Serious AE rate, Deaths</th></tr>
<tr><td>Yun H Arthritis & Rheumatology 2016[278]</td><td>1) ADA (n=4,845)
2) CTZ (n=1,866)
3) ETN (n=3,814)
4) GOL (n=1,394)
5) IFX (n=3,944)
6) RTX (n=4,718)
7) TCZ (n=2,016)
8) ABT (n=9,204)</td><td></td><td>Overall incidence rate hospitalized infections: 15.3/100 person-years

Total infections, n (%)
1) 397 (8.2)
2) 116 (6.2)
3) 336 (8.8)
4) 99 (7.1)
5) 472 (12.0)
6) 643 (13.6)
7) 134 (6.6)
8) 926 (10.1)

Upper respiratory tract infection (URTI), genitourinary tract infection (GTI), %
<table><tr><td>Grp</td><td>URTI</td><td>GTI</td></tr><tr><td>1</td><td>31.7</td><td>26.5</td></tr><tr><td>2</td><td>30.2</td><td>29.3</td></tr><tr><td>3</td><td>31.3</td><td>26.2</td></tr><tr><td>4</td><td>32.3</td><td>35.4</td></tr><tr><td>5</td><td>35.2</td><td>24.4</td></tr><tr><td>6</td><td>35.9</td><td>21.8</td></tr><tr><td>7</td><td>32.1</td><td>22.4</td></tr><tr><td>8</td><td>29.9</td><td>28.8</td></tr></table></td><td></td><td>Mortality during or within 30 days after hospitalization, %
1) 5.3
2) 7.8
3) 4.5
4) 4.0
5) 5.1
6) 4.5
7) 5.9
8) 5.7</td></tr>
<tr><td colspan="6">Biosimilar studies</td></tr>
</table>

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Bae S-C *Ann Rheum Dis* 2016[167] HERA	1) ETN-bio+MTX (n=115) 2) ETN-ref+MTX (n=118)	NR	Week 48 Infection, % 1) 37.4 2) 41.1 Latent tuberculosis, n (%) 1) 14 (9.5) 2) 8 (5.5)	Week 48 Injection-site reaction, n (%) 1) 3 (2.0) 2) 8 (5.5) Upper abdominal pain, n (%) 1) 9 (6.1) 2) 5 (3.4) Nasopharyngitis, n (%) 1) 22 (15.0) 2) 34 (23.3)	Week 48 Discontinuation due to AEs, n (%) 1) 10 (6.8) 2) 11 (7.5) Serious AEs, n (%) 1) 19 (12.9) 2) 18 (12.3) Deaths, n (%) 1) 0 2) 2 (1.4) (cerebral hemorrhage and acute renal failure/sepsis)
Choe J-Y *Ann Rheum Dis* 2015[168]	1) IFX-bio+MTX (n=290) 2) IFX-ref+MTX (n=293)	Week 30 Malignancy 1) 2 (prostate cancer and breast cancer) 2) 0	Week 30 Serious infection or TB, n (%) 1) 9 (3.1) 2) 6 (2.0) 4.1 cases/100 PY vs. 2.7 cases/100 PY Active TB, n 1) 1 2) 1 Opportunistic infections: 0	Week 30 TEAEs related to study drug, % 1) 21.4 2) 20.1 Infusion related reactions, n (%) 1) 15 (5.2) 2) 13 (4.4)	Week 30 Discontinuation due to AEs, n (%) 1) 21 (7.2) 2) 10 (3.4) Serious TEAEs, n (%) 1) 26 (9.0) 2) 26 (8.9) Deaths, n 1) 0 2) 1 (heart failure)

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Choe J-Y *Arthritis Rheumatol* 2015[205] 54-week results of Choe J-Y *Ann Rheum Dis* 2015[168]	1) IFX-bio+MTX (n=290) 2) IFX-ref+MTX (n=293)	Week 54 Malignancy, n (%) 1) 2 (0.7) 2) 0	Week 54 Total infections, n (%) 1) 85 (29.3) 2) 110 (37.5) Serious infections, n (%) 1) 9 (3.1) 2) 6 (2.0) Tuberculosis, n (%) 1) 1 (0.3) 2) 1 (0.3)	Week 54 Infusion-related reaction, n (%) 1) 17 (5.9) 2) 15 (5.1)	Week 54 Serious AEs, n (%) 1) 29 (10.0) 2) 31 (10.6) Death, n (%) 1) 0 2) 1 (0.3)
Cohen SB *Arthritis Rheumatol* 2015[193]	1) ADA-bio+MTX (n=264) 2) ADA-ref+MTX (n=262)	NR	Week 26 Serious infections, % 1) 0.8 2) 1.1 Upper respiratory tract infection, % 1) 1.5 2) 3.8	Week 26 Nasopharyngitis, % 1) 6.4 2) 7.3 Headache, % 1) 4.5 2) 4.2 Arthralgia, % 1) 3.0 2) 3.4	Week 26 Discontinuation due to AEs, % 1) 1.9 2) 0.8 Serious TEAEs, % 1) 3.8 2) 5.0

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Emery P *Ann Rheum Dis* 2015[195]	1) ETN-bio+MTX (n=299) 2) ETN-ref (n=297)	Week 24 Malignancies, n (%) 1) 3 (1.0) (basal cell carcinoma, breast cancer, lung cancer metastatic) 2) 1 (0.3) (invasive ductal breast carcinoma)	Week 24 Serious infections, n (%) 1) 1 (0.3) 2) 4 (1.3) Upper respiratory tract infection, n (%) 1) 21 (7.0) 2) 15 (5.1) Viral infection, n (%) 1) 7 (2.3) 2) 5 (1.7)	Week 24 TEAEs related to study drug, n (%) 1) 83 (27.8) 2) 106 (35.7) Injection site erythema, n (%) 1) 6 (2.0) 2) 33 (11.1) Injection site rash, n (%) 1) 2 (0.7) 2) 6 (2.0) Injection site reaction, n (%) 1) 1 (0.3) 2) 7 (2.4)	Week 24 Discontinuation due to TEAEs, n (%) 1) 15 (5.0) 2) 19 (6.4) Serious TEAEs, n (%) 1) 13 2) 13 Deaths, n 1) 1 (cardiorespiratory failure) 2) 0
Vencovsky J *Arthritis Rheumatol* 2015[204] 52-week results of Emery P *Ann Rheum Dis* 2015[195]	1) ETN-bio+MTX (n=299) 2) ETN-ref (n=297)	Malignancy, n (%) 1) 4 (1.3) 2) 1 (0.3)	Serious infections, n (%) 1) 1 (0.3) 2) 5 (1.7) Tuberculosis: 0	Injection site reactions, n (%) 1) 11 (3.7) 2) 52 (17.5)	Serious AEs, n (%) 1) 18 (6.0) 2) 15 (5.1) Death, n (%) 1) 2 (0.7) 2) 0

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Jani RH *Int J Rheum Dis* 2015[192]	1) ADA-bio+MTX (n=60) 2) ADA-ref+MTX (n=60)	NR	NR	Week 12 Pyrexia, headache and cough were commonly reported in both treatment groups	Week 12 Discontinuation due to AEs, n 1) 2 2) 0 Serious AEs, n 1) 2 2) 1
Kay J *Ann Rheum Dis* 2014[196]	1) IFX-bio (n=127) 2) IFX-ref (n=62)	NR	Week 16 Infectious AEs, % 1) 15.8 2) 9.7 p=NS	Week 16 TEAEs, % 1) 43.3 2) 50.0	
Takeuchi T *Modern Rheumatology* 2015[169]	1) IFX-bio (n=50) 2) IFX-ref (n=51)		Week 54 Serious infection, n 1) 5 2) 3	Week 54 Infusion reaction 1) 2 2) 2	Week 54 Serious AEs, n (%) 1) 8 (15.7) 2) 8 (15.1) Discontinuation due to AEs, n (%) 1) 9 (17.6) 2) 6 (11.3)

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Weinblatt ME *Arthritis Rheumatol* 2015[194]	1) ADA-bio (n=271) 2) ADA-ref (n=273)	Week 24 Malignancy, n (%) 1) 0 2) 2 (0.7)	Week 24 Serious infection, n (%) 1) 1 (0.3) 2) 2 (0.7) Tuberculosis: 0	Week 24 Injection site reactions, n (%) 1) 8 (3.0) 2) 8 (2.9)	Week 24 Serious TEAEs, n (%) 1) 3 (1.1) 2) 7 (2.6) Death, n (%) 1) 0 2) 2 (0.7)
Yoo D-H *Ann Rheum Dis* 2013[170] PLANETRA	1) IFX-bio+MTX (n=302) 2) IFX-ref+MTX (n=304)	Week 30 2 patients in IFX-ref group withdrawn due to malignancy (breast cancer, cervix carcinoma)	Week 30 Latent TB related to study treatment, n 1) 13 2) 14 Urinary tract infection 1) 4 91.3) 2) 7 (2.3)	Week 30 Increased ALT, n 1) 12 2) 11 Increased AST, n 1) 8 2) 8 Infusion-related reactions, n (%) 1) 20 (6.6) 2) 25 (8.3)	Week 30 Discontinuation due to AEs, n (%) 1) 28 (9) 2) 26 (9) Serious TEAEs, n (%) 1) 30 (10) 2) 21 (7) Deaths: 0

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Yoo D-H *Arthritis Res Ther* 2016[241] PLANETRA 54-week results	1) IFX-bio+MTX (n=302) 2) IFX-ref+MTX (n=304)	Malignancies 1) 2 (Breast cancer, ovarian cancer) 2) 1 (renal neoplasm)	Upper respiratory tract infection, n (%) 1) 23 (7.6) 2) 14 (4.7) Urinary tract infection, n (%) 1) 9 (3.0) 2) 11 (3.7) Latent TB, n (%) 1) 22 (7.3) 2) 20 (6.7) Active TB, n (%) 1) 3 (1) 2) 0	TEAEs related to study drug, n (%) 1) 132 (43.7) 2) 135 (45.0) Infusion-related reaction, n (%) 1) 30 (9.9) 2) 43 (14.3) Abnormal liver function test, n (%) 1) 22 (7.3) 2) 14 (4.7)	Discontinuation due to AEs, n (%) 1) 33 (10.9) 2) 47 (15.7) Serious TEAEs, n (%) 1) 42 (13.9) 2) 31 (10.3) Deaths, n 1) 0 2) 1
Yoo D-H *Annals of the Rheumatic Diseases* 2016[241] PLANETRA	1) IFX-bio-maintenance group (n=158) 2) IFX-bio-switch group (n=144)		No TB cases during extension study. Latent TB, n (%) 1) 9 (5.7) 2) 4 (2.8)	Infusion-related reaction, n (%) 1) 11 (6.9) 2) 4 (2.8)	Serious AEs, n (%) 1) 12 (7.5) 2) 13 (9.1) Discontinuation due to AEs, n (%) 1) 16 (10.1) 2) 8 (5.6)

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Yoo D-H *Arthritis Rheum* 2013[191]	1) RTX-bio+MTX (n=103) 2) RTX-ref+MTX (n=51)	NR	Week 24 Infections, % 1) 23.5 2) 25.5	Week 24 TEAEs, n 1) 166 2) 88 Infusion reactions, % 1) 16.7 2) 19.6	Week 24 Serious AEs, % 1) 16.7 2) 17.6
Yoo D-H *Arthritis Rheum* 2015[164]	1) RTX-bio+MTX (n=103) 2) RTX-ref+MTX (n=51)	Week 72 Malignancy, n (%) 1) 0 2) 1 (2.0) (cervix carcinoma stage 0)	Week 72 Infection, n (%) 1) 39 (38.2) 2) 21 (41.2)	Week 72 Infusion-related reaction, n (%) 1) 20 (19.6) 2) 10 (19.6)	Week 72 Discontinuation due to AEs, n (%) 1) 6 (5.9) 2) 4 (7.8) Serious AEs, n (%) 1) 14 (13.7) 2) 7 (13.7) Deaths: 0
Yoo D-H *Ann Rheum Dis* 2016[165] (Updated safety data)	1) RTX-bio+MTX (n=102) 2) RTX-ref+MTX (n=51)			Infusion reaction, n (%) 1) 17 (16.7) 2) 10 (19.6)	Serious AEs, n (%) 1) 5 (4.9) 2) 3 (5.9)

Table F4. Head-to-Head Trials: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Burmester G *Ann Rheum Dis* 2016[18] MONARCH	1) ADA (n=185) 2) SAR (n=184)	Week 24 mean change from baseline SF-36 (SD) PCS 1) 6.1 (0.6) 2) 8.7 (0.6) P=0.0006 Week 24 mean change from baseline SF-36 (SD) MCS 1) 6.8 (0.8) 2) 7.9 (0.8) P=NS	NR	Week 24 mean change from baseline FACIT-Fatigue 1) 8.4 (0.7) 2) 10.2 (0.7) p=NS

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Chen J *Arthritis care & research* 2014[267]	1) ETN (n=1,243) 2) ADA (n=863) 3) IFX (n=159) *Linear regression modeling used to evaluate outcomes*	After adjusting for some baseline characteristics and using etanercept as reference group SF-36 PCS 2) 0.15, p=NS 3) 0.69 SF-36 MCS 2) -1.17, p=0.001 3) -0.78, p=NS AQoL 2) -0.012, p=NS 3) -0.012, p=NS HAQ-DI 2) 0.028, p=NS 3) 0.069, p=NS	NR	*Subsequent vs. first time use, coefficient* SF-36 PCS 1) -1.84, p=0.007 2) -1.47, p=0.02 3) -2.51, p=NS SF-36 MCS 1) 0.34, p=NS 2) -0.05, p=NS 3) 0.81, p=NS AQoL 1) -0.026, p=NS 2) -0.035, p=0.02 3)-0.036, p=0.32 HAQ-DI 1) 0.013, p=NS 2) 0.121, p=0.006 3) 0.241, p=0.03

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Schiff M *Annals of the rheumatic diseases* 2008[23] ATTEST	1) ABTiv+MTX (n=156) 2) PBO+MTX (n=110) 3) IFX+MTX (n=165)* **Group 3 switched to ABT at Day 365* *PBO results from days 1-197 only*	Day 365 Change from baseline SF-36 PCS 1) ~9 3) ~7 *Imputed from chart* Diff. 1.93 95% CI (0.02 to 3.84) MCS 1) ~6 2) ~4 Diff. 1.92 95% CI (-0.30 to 4.15) all eight subscales numerically higher with ABT vs IFX	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Jobanputra P *BMJ Open* 2012[20] RED SEA	1) ADA + cDMARD (n=60) 2) ETN + cDMARD (n=60)	EQ5D utility score 1) 0.69 (0.59-0.76) 2) 0.64 (0.52-0.8)	NR	Month 12 patient global assessment (0-100) 1) 25 (15-50) 2) 34 (20-50) Treatment satisfaction score a) Global 1) 92 2) 92 b) Effectiveness 1) 83 2) 83 c) Side effects 1) 100 2) 100 d) Convenience 1) 83 2) 89
Weinblatt ME *Arthritis and rheumatism* 2013[94] AMPLE	1) ABTsc+MTX (n=318) 2) ADAsc+MTX (n=328)	1-yr mean change from baseline RAPID-3, (95% CI) 1) -2.87 (-3.10 to -2.63) 2) -2.74 (-2.98 to -2.51)		1-yr mean change from baseline 100-mm VAS patient assessment of fatigue severity 1) -23.2 2) -21.4

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Schiff M *Annals of the rheumatic diseases* 2014[22] AMPLE	1) ABTsc+MTX (n=318) 2) ADAsc+MTX (n=328		Year 2 Adjusted mean improvement in patient pain (SEM) 1) 53.5 (6.2) 2) 38.5 (6.1) Adjusted difference 15.2 (-1.2, 31.6)	
Strand V *Rheumatology* 2016 [96] ORAL standard	1) PBO+MTX → TOF 5mg (n=56) or 10mg (n=52) 2) TOF 5mg +MTX (n=204) 3) ADA+MTX (n=204) 4) TOF 10mg +MTX (n=201)	Month 3 LSM (SE) change from baseline PCS change (SE) 1) 3.17 (0.70) 2) 6.98 (0.52) 3) 7.81 (0.52) p<0.0001 for 2-3 4) 6.26 (0.52) p<0.001 for 4 MCS change (SE) 1) 1.77 (0.88) 2) 3.16 (0.66) 3) 6.09 (0.66) p<0.0001 for 3 4) 3.38 (0.65)	Month 3 LSM (SE) pain change from baseline 1) -9.50 (2.19) 2) -26.74 (1.63) 3) -27.82 (1.64) 4) -22.49 (1.62) p<0.0001 for 2-4	Month 3 LSM (SE) FACIT-F change from baseline 1) 1.57 (0.79) 2) 5.85 (0.59) 3) 6.88 (0.59) p<0.0001 for 2-3 4) 5.04 (0.58) p<0.001 for 4

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Fleischmann R *Arthritis care & research* 2016[226] AMPLE See Schiff M *Annals of the rheumatic diseases* 2014	1) ABTsc+MTX (n=318) 2) ADAsc+MTX (n=328)			@ year 2 VAS, 0-100mm 1) -23.4 2) -21.6 p=NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Keystone E *Ann Rheum Dis* 2016 POSTER[98] RA-BEAM	1) PBO + cDMARD (n=488) 2) BAR + cDMARD (n=487) 3) ADA + cDMARD (n=330)	Week 24/Week 52 SF-36 PCS, change from baseline (estimated from graph): 1) 4.9/NR 2) 9.8*±/10.2±± 3) 8*/8.3 *p≤0.001 vs. PBO ±p<0.001 vs. ADA ±±p≤0.01 vs. ADA SF-36 MCS, change from baseline (estimated from graph): 1) 2.2/NR 2) 3.8**/4.4 3) 3.2/3.1 **p≤0.01 vs. PBO Week 24/52 EQ-5D VAS mean change from baseline (estimated from graph): 1) 3.8/NR 2) 15.8*±/19± 3) 10*/11.5 *p≤0.001 vs. PBO ±p≤0.001 vs. ADA	Week 24/week 52 Pain, 0-100 mm VAS 1) -17.4*/NR 2) -33.6*/-36.3 Ω 3) -28.6*/-30.2 *p≤0.001 vs. PBO Ω p≤0.001 vs. ADA	Week 24/week52 LSM FACIT-F change from baseline 1) 6.5/NR 2) 9.9*/10.7Ω 3) 9.2*/9.2 *p≤0.001 vs. PBO Ω p≤0.05 vs. ADA

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Taylor PC *N Engl J Med* 2017[97] See also Taylor P *Arthritis and Rheumatology* 2015[21], Keystone E *Ann Rheum Dis* 2016 POSTER[98] RA-BEAM	1) PBO + cDMARD (n=488) 2) BAR + cDMARD (n=487) 3) ADA + cDMARD (n=330)	NR	Week 24/52 Pain, 0-100 mm 1) -17.5/NA 2) -33.6/-36.1 3) -28.8 Week 12 Worst joint pain, least means squared from baseline 1) 4.6 2) 3.4*ǂ 3) 4.0* *p≤.001 vs. PBO ǂp≤0.001 vs. ADA	Week 12 Worst tiredness, least means squared from baseline 1) 4.3 2) 3.6*ǂ 3) 3.9* *p≤.001 vs. PBO ǂp≤0.05 vs. ADA Week 24/52 Patient's global assessment, 0-100 mm VAS 1) -17.0/NA 2) -33.1/-36.3 3) -29.1/-30.3

<table>
<tr><th>Author & Year of Publication (Trial Name)</th><th>Interventions</th><th>Health-related quality of life</th><th>Pain</th><th>Fatigue & other PROs</th></tr>
<tr><td>Bae S-C Ann Rheum Dis 2016[167]

HERA</td><td>1) ETN-bio+MTX (n=115)
2) ETN-ref+MTX (n=118)</td><td>Mean change from baseline SF-36 (SD)
Week 24
PCS
1) 8.04 (8.14)
2) 7.15 (9.11)

MCS
1) 5.42 (11.54)
2) 5.18 (10.28)

Week 48
PCS
1) 8.50 (8.66)
2) 8.54 (8.82)

MCS
1) 5.02 (11.84)
2) 4.48 (11.28)</td><td>Pain/discomfort (from EQ-5D), n (%)

Week 24
Moderate pain
1) 84 (73.04)
2) 93 (78.81)

Extreme pain
1) 7 (6.09)
2) 5 (4.2)

Week 48
Moderate pain
1) 81 (79.41)
2) 80 (76.19)

Extreme pain
1) 1 (0.98)
2) 2 (1.90)</td><td>Mean change from baseline FACIT-F (SD)<table><tr><td></td><td>Wk24</td><td>Wk48</td></tr><tr><td>1)</td><td>16.43 (21.01)</td><td>16.88 (22.97)</td></tr><tr><td>2)</td><td>15.61 (20.09)</td><td>15.00 (22.49)</td></tr></table>“Some problems”, n (%)
Mobility<table><tr><td></td><td>Wk24</td><td>Wk48</td></tr><tr><td>1)</td><td>52 (45.22)</td><td>46 (45.10)</td></tr><tr><td>2)</td><td>61 (51.69)</td><td>43 (40.95)</td></tr></table>Self-care<table><tr><td></td><td>Wk24</td><td>Wk48</td></tr><tr><td>1)</td><td>36 (31.30)</td><td>27 (26.47)</td></tr><tr><td>2)</td><td>36 (30.51)</td><td>31 (29.52)</td></tr></table>Usual activities<table><tr><td></td><td>Wk24</td><td>Wk48</td></tr><tr><td>1)</td><td>62 (53.91)</td><td>51 (51.96)</td></tr><tr><td>2)</td><td>66 (55.93)</td><td>57 (54.29)</td></tr></table>Anxiety/depression<table><tr><td></td><td>Wk24</td><td>Wk48</td></tr><tr><td>1)</td><td>45 (39.13)</td><td>44 (43.14)</td></tr><tr><td>2)</td><td>50 (42.37)</td><td>45 (42.86)</td></tr></table></td></tr>
<tr><td>Choe J-Y Ann Rheum Dis 2015[168]</td><td>1) IFX-bio+MTX (n=290)
2) IFX-ref+MTX (n=293)</td><td>NR</td><td>Week 30
Mean change in pain VAS, mm (SD)
1) -21.9 (24.0)
2) -25.9 (27.2)</td><td>NR</td></tr>
</table>

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Jani RH *Int J Rheum Dis* 2015[192]	1) ADA-bio+MTX (n=60) 2) ADA-ref+MTX (n=60)	NR	Mean change from baseline, week 12 Patient assessment of pain 1) -30.1 (17.52) 2) -29.1 (17.10)	NR
Kay J *Ann Rheum Dis* 2015[196]	1) IFX-bio (n=127) 2) IFX-ref (n=62)	NR	Mean change from baseline, wk 16 Subject Pain assessment (VAS), cm 1) -3.4 2) -3.2 Open-label phase: mean change from baseline to wk 54 in subject pain: -4 cm	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Yoo D-H *Ann Rheum Dis* 2013[170] PLANETRA	1) IFX-bio+MTX (n=302) 2) IFX-ref+MTX (n=304)	Week 30 Mean change from baseline (SD) SF-36 PCS 1) 7.1 (7.9) 2) 6.5 (7.6) p=NS MCS 1) 7.1 (10.0) 2) 6.6 (10.4) p=NS	Week 30 Mean change from Patient's assessment of pain, VAS (SD) 1) -29.5 (25.5) 2) -27.8 (24.9) p=NS	NR
Yoo D-H *Arthritis Res Ther* 2016[241] PLANETRA 54-week results	1) IFX-bio+MTX (n=302) 2) IFX-ref+MTX (n=304)	Week 54 Mean change from baseline (SD) SF-36 PCS 1) 7.6 (8.1) 2) 6.6 (8.4) MCS 1) 7.1 (10.1) 2) 6.9 (11.2)	Week 54 Mean change from baseline Patient's assessment of pain, VAS (SD) 1) -30.2 (23.8) 2) -28.4 (26.9)	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Yoo D *Annals of the Rheumatic Diseases* 2016[241] PLANETRA	1) IFX-bio-maintenance group (n=158) 2) IFX-bio-switch group (n=144)	NR	Week 102 mean change from 52week Patient's assessment of pain, 100 mm VAS 1) -31.8 2) -34 p=NS	NR

Table F5. Head-to-Head Trials: Non-healthcare Outcomes

Author & Year of Publication (Trial Name)	Interventions	Requirements for surgical intervention	Hospitalization, Rehabilitation, Assisted living	Productivity Loss	Caregiver Burden	Other outcomes
Fleischmann R *Arthritis care & research* 2016[226] AMPLE See Schiff M *Annals of the rheumatic diseases* 2014[22]	1) ABTsc+MTX (n=318) 2) ADAsc+MTX (n=328)	NR	NR	@ year 2 WPAI:RA, % mean improvement Work time gained 1) 7.4 2) 5.9 Reduced impairment while working 1) 23.6 2) 19.0 Overall reduced work impairment 1) 25.4	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Requirements for surgical intervention	Hospitalization, Rehabilitation, Assisted living	Productivity Loss	Caregiver Burden	Other outcomes
				2) 20.5 Activity gained 1) 29.3 2) 23.0 *Statistical measures NR*		

Table F6. Rituximab versus conventional DMARD: Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Cohen SB Arthritis Rheum. 2006 [93] REFLEX Good See also Cohen SB *Annals of the rheumatic diseases* 2010[201], Keystone E *Arthritis Rheum* 2008 [208], Keystone E *Ann Rheum Dis* 2009 [202]	Hoffman-La Roche, Biogen Idec, Inc; Genentech, Inc. and partly supported by NIH grant from the National Center for Research Resources	RCT, Multicenter, Double-Blind, Placebo-Controlled, Phase III trial Two periods of 24 weeks followed by a check every 2 months for 18 months resulting in a 24-month study duration	114 rheumatology centers in the US, Europe, Canada, and Israel	1) PBO+MTX (n=209) 2) RTX+MTX (n=308) iv RTX administered on days 1 and 15. All patients received iv methylprednisolone 100 mg before each infusion & oral prednisone during the 2-week treatment period. From weeks 16-24, patients who failed to respond to treatment could receive rescue therapy i.e. PBO pts →RTX & RTX pts → standard care	RA for≥6 months per ACR 1987 revised criteria; taking MTX (10-25 mg/week for ≥12 weeks with last 4 weeks at stable dosage Excluded if: 1) history of a RAD other than RA 2) significant systemic involvement secondary to RA 3) ACR functional class iv disease	Mean age, yrs (SD) 1) 52.8 (12.6) 2) 52.2 (12.2) Female, n (%) 1) 169 (81) 2) 251 (81) Mean RA duration, yrs (SD) 1) 11.7 (7.7) 2) 12.1 (8.3) Mean HAQ-DI (SD) 1) 1.9 (0.5) 2) 1.9 (0.6) Mean DAS-28 (SD) 1) 6.8 (1.0) 2) 6.9 (1.0) Mean mTSS (SD) 1) 47.9 (36.0) 2) 48.3 (34.9)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Emery P Arthritis Rheum. 2006 [207] DANCER Good	Genentech, Inc; Biogen Idec, Inc; Hoffmann-La Roche	RCT, international, multifactorial, double-blind, placebo-controlled, dose-ranging, phase IIb trial 24 weeks	US and international	1) PBO (n=149) 2) RTX, 2×500mg (n=124) 3) RTX, 2×1000mg (n=192) RTX given to RF+ patients: PBO (days 1 and 15) at 500mg or 1000mg; glucocorticoids given as PBO methylprednisolone before infusions on days 1 and 15 plus oral prednisone (60 mg on days 2-7, 30 mg on days 8-14); RF- patients given PBO/RTX (2×1000 mg) with or without glucocorticoids All patients received MTX (10-25 mg) on weekly regimen with folate (≥5 mg/wk)	Inclusion: 18-80 years who have moderate to severe RA per ACR revised criteria for≥6 months prior to randomization despite MTX (10-25 mg/wk) treatment for ≥12 wks before randomization with stable dose for ≥4 wks; failed prior treatment with ≥1 but ≤5 DMARDs; no DMARDs except MTX for ≥4 wks and no IFX, ADA, and leflunomide for ≥8 wks Exclusion: Significant systemic involvement secondary to RA; past treatment with ART or lymphocyte-depleting therapies; history of recurrent significant infection	Mean age, yrs 1) 51.1 2) 51.4 3) 51.1 Female, % 1) 80 2) 83 3) 80 Mean RA duration, yrs 1) 9.3 2) 11.1 3) 10.8 Mean HAQ-DI at baseline, score 1) 1.7 2) 1.8 3) 1.7 Mean DAS28 1) 6.8 2) 6.8 3) 6.7

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Emery P *Annals of the rheumatic diseases* 2010[149] SERENE Good	Genentech, Inc.	RCT, double-blind, placebo controlled, phase III study 48 weeks	102 centers in 11 countries	1) PBO+MTX (n=172) 2) (2×500mg) RTX+MTX (n=168) 3) (2 ×1000mg) RTX+MTX (n=172) Randomized to RTX 2×500 mg, RTX 2×1000 mg, or PBO administered by iv infusion on days 1 and 15. All infusions (including PBO) were pre-medicated with 100mg iv methylprednisolone. Between week 16 and week 23, patients with <20% improvement in TJC and SJC versus baseline were allowed rescue treatment with one non-biological DMARD.	Inclusion: 18–80 years with RA for ≥6 months which was active despite 10-12mg/ week MTX for at least 12 weeks. Active RA defined as ≥8 SJC and TJC, and either CRP≥0.6mg/dl or ESR≥28mm/h; No previous biologic treatment for RA	Mean age, yrs (SD) 1) 52.2 (12.4) 2) 51.9 (12.9) 3) 51.3 (12.6) Female, n (%) 1) 147 (85.5) 2) 133 (79.6) 3) 138 (81.2) Mean RA duration, yrs (SD) 1) 7.5 (7.6) 2) 7.1 (7) 3) 6.6 (7.3) Mean DAS28-ESR (SD) 1) 6.54 (1.02) 2) 6.4 (0.95) 2) 6.49 (1.06) Mean DAS28-CRP (SD) 1) 5.95 (0.97) 2) 5.81 (0.91) 3) 5.86 (0.97)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Peterfy C *Annals of the Rheumatic Diseases* 2016[171] RA-SCORE Good	Hoffmann-La Roche	RCT multicenter double-blind Phase IIIb 52 weeks	Argentina, Brazil, Canada, Czech Republic, Denmark, Estonia, France, Germany, Greece, Latvia, Lithuania, Netherlands, Norway, Romania, Russian Federation, Serbia, Spain, Switzerland, Turkey *RTX 500mg+MTX excluded from table*	1) PBO+MTX (n=63) 2) 1000mg RTX+MTX (n=60) 3) 500mg RTX+MTX (n=62) Two infusions of PBO or RTX 1000 mg intravenously on days 1 and 15. Analgesics, antihistamines and methylprednisolone 100 mg before RTX infusions; stable MTX and folic acid/folate (≥5 mg/week). Oral glucocorticoids (≤10 mg/day) allowed. Rescue therapy at wk 16 if <20% improvement in tender & swollen joints. RTX retreatment after wk 24 if DAS28-CRP ≥2.6 and no contraindications	Met ACR criteria for RA; disease duration of ≥3 months and ≤10 years; active RA (DAS28-CRP ≥3.2); incomplete response to 12.5–25 mg/wk MTX for ≥12 weeks; biologic naïve; positive for anticyclic citrullinated protein (≥20 U) or RF (≥20 IU/mL); erosion and/or synovitis in a single joint Key exclusion criteria: history of rheumatic autoimmune disease other than RA or significant systemic involvement secondary to RA	Mean age, yrs (SD) 1) 50.3 (11.9) 2) 50.7 (11.7) Female, n (%) 1) 48 (76.2) 2) 50 (83.3) Mean RA duration, yrs (SD) 1) 4.4 (3.1) 2) 4.9 (2.9) Mean HAQ-DI (SD) 1) 1.5 (0.8) 2) 1.3 (0.7) Mean DAS28-CRP (SD) 1) 5.6 (1.1) 2) 5.3 (1.0) Mean DAS28-ESR (SD) 1) 6.3 (1.1) 2) 6.0 (1.1) Mean mTSS (SD) 1) 20.2 (18.9) 2) 19.8 (18.8)

Table F7. Rituximab versus conventional DMARD: Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Cohen SB Arthritis Rheum. 2006 [93] REFLEX	1) PBO+MTX (n=209) 2) RTX+MTX (n=308)	Week 24 ACR20, % 1) 18 2) 51 (p<0.0001) ACR50, % 1) 5 2) 27 (p<0.0001) ACR70, % 1) 1 2) 12 (p<0.0001)	Week 24 Achieved remission, % (DAS28<2.8) 1) 0 2) 9	Week 24 Mean (SD) total Genant-modified SHARP radiographic score 1) 1.2 (3.3) 2) 0.6 (1.9) p= 0.169 for 1-2	Week 24 (amongst ITT population) HAQ-DI level of 0, n (%) 1) 0.5 (0) 2) 18 (6)	Week 24 (amongst ITT population) From elevated to normal range CRP levels, n (%) 1) 18 (10) 2) 80 (281) Mean ESR reduction levels 1) 4.1 mm/hour 2) 18.5 mm/hour

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Cohen SB *Annals of the rheumatic diseases* 2010[201] REFLEX	1) PBO+MTX (n=187) 2) RTX+MTX (n=281)	NR	NR	Week 104 mean change from baseline mTSS 1) 2.81 2) 1.14 p<0.0001 Year 2 mean change from baseline mTSS 1) 1.78 2) 0.66 p<0.005 Year 2 % with no change in mTSS from baseline 1)39 2) 57 p<0.0001	NR	NR
Keystone E Arthritis Rheum 2008 [208] REFLEX	1) PBO+MTX (n=201) 2) RTX+MTX (n=298), (1000mg ×2)	NR	NR	NR	Week 24 mean changed from baseline HAQ-DI (SD) 1) -0.07 (0.45) 2) -0.44 (0.60) p< 0.0001 for 1-2	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Keystone E Ann Rheum Dis. 2009 [202] REFLEX	1) PBO+MTX (n=186) 2) RTX+MTX (n=277)	NR	First quartile (lowest) DAS28, quartile range From 3-6 Change in TSG 1) 2.02 2) 0.41 Second quartile (highest) DAS28, quartile range From 8-9 Change in TSG 1) 4.17 2) 2.4	Week 56 Mean TSG change 1) 2.31 2) 1.00 p=0.005 for 1-2	First quartile (lowest) HAQ-DI, quartile range From 0-2 Change in TSG 1) 1.35 2) 1.08 Second quartile (highest) HAQ-DI, quartile range From 2-3 Change in TSG 1) 1.66 2) 1.02	First quartile (lowest) CRP, quartile range From 0-1 Change in TSG 1) 0.91 2) 0.46 Second quartile (highest) CRP, quartile range From 5-24 Change in TSG 1) 4.86 2) 2.23

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Emery P Arthritis Rheum. 2006 [207] DANCER	1) PBO (n=149) 2) RTX, 2×500mg (n=124) 3) RTX, 2×1000mg (n=192)	Week 24 ACR20, % 1) 28 2) 55 3) 54 p≤0.001 for 2-3 ACR50, % 1) 13 2) 33 3) 34 p≤0.001 for 2-3 ACR70, % 1) 5 1) 13 (p=0.029) 2) 20 (p≤0.001)	Week 24 Mean DAS change from baseline 1) -0.67 (p<0.0001) 2) -1.79 3) -2.05	NR	Week 24 Mean HAQ-DI change from baseline 1) -0.16 2) -0.43 3) -0.49	Week 24 Mean CRP change from baseline 1) -0.1 2) -1.7 3) -1.7

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Emery P *Annals of the rheumatic diseases* 2010[149] SERENE	1) PBO+MTX (n=172) 2) (2×500mg) RTX+MTX (n=167) 3) (2 ×1000mg) RTX+MTX (n=170)	Week 24 % ACR20 1) 23.3 2) 54.5 (p<0.0001) 3) 50.6 (p<0.0001) Week 24 % ACR50 1) 9.3 2) 26.3 (p<0.0001) 3) 25.9 (p<0.0001) Week 24 % ACR70 1) 5.2 2) 9 3) 10 Good EULAR response, n (%) 1) 8 (4.7) 2) 29 (17.5) 3) 20 (11.8) (p<0.0001)	Week 24 mean change from baseline DAS28-ESR 1) -0.75 2) -1.76 (p<0.0001) 3) -1.69 (p<0.0001) Week 24 remission DAS28-ESR <2.6, % (p value *vs PBO*) 1) 2.3 2) 9.6 (p<0.01) 3) 9.4 (p<0.01)	NR	Week 24 mean change from baseline HAQ-DI 1) 82 (47.7) 2) 109 (66.1) p<0.001 3) 99 (58.2) p<0.001 Week 24 mean change from baseline SF-36 mental component 1) 1.66 2) 3.31 3) 4.58 (p<0.001) SF-36 physical component 1) 2.49 2) 5.91 (p<0.0001) 3) 5.7 (p<0.0001)	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Peterfy C *Annals of the Rheumatic Diseases* 2016[171] RA-SCORE	1) PBO+MTX (n=63) 2) 1000mg RTX+MTX (n=60)	Week 24 ACR20, % 1) 28.6 2) 51.7 (p=0.006) ACR50, % 1) 11.1 2) 26.7 (p=0.013) ACR70, % 1) 1.6 2) 8.3 (p=0.085) Week 52 ACR20, % 1) 28.6 2) 68.3 (p<0.001) ACR50, % 1) 14.3 2) 35.0 (p=0.005) ACR70, % 1) 6.3 2) 16.7 (p=0.049)	Mean change from baseline DAS28-ESR Week 24 1) -0.85 2) -1.64 (p=NS) Week 52 1) -0.81 2) -1.90 (p=NS)	Mean change from baseline Genant mTSS Week 24 1) 0.76 2) 0.30 (p=NS) Week 52 1) 1.37 2) 0.29 (p=0.002)	Mean change from baseline HAQ-DI Week 24 1) -0.19 2) -0.44 (p=NS) Week 52 1) -0.18 2) -0.42 (p=NS)	NR

Table F8. Rituximab versus conventional DMARD: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Cohen SB Arthritis Rheum. 2006 [93] REFLEX	1) PBO+MTX (n=209) 2) RTX+MTX (n=308)	NR	Rate of serious infections per 100 patient-years, rate (n) 1) 3.7 (3) 2) 5.2 (7)	Acute infusion reactions, n (%) First infusion 1) 38 (18) 2) 72 (23) Second infusion 1) 24 (11) 2) 26 (8)	NR

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Emery P Arthritis Rheum. 2006 [207] DANCER	1) PBO (n=149) 2) RTX, 2×500mg (n=124) 3) RTX, 2×1000mg (n=192)	NR	Serious infections, n (%) 1) 2 (1) 2) 0 3) 4 (2)	Adverse events classified as infections and infestations, % 1) 28 2) 35 3) 35 1st Infusion-associated events, % 1) 18 2) 31 3) 38 1st Acute-infusion reactions, % 1) 17 2) 23 3) 32 Serious noninfection AE events, n (%) 1) 2(1) 2) 9 (7) 3) 4 (2)	Week 24 Serious AE events, n (%) 1) 4 (3) 2) 9 (7) 3) 13 (7) Discontinuation due to AEs, n (%) 1) 0 2) 3 (2) 3) 6 (3) AE events, n (%) 1) 105 (70) 2) 100 (81) 3) 164 (85)

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Emery P *Annals of the rheumatic diseases* 2010[149] SERENE	1) PBO+MTX (n=172) 2) (2×500mg) RTX+MTX (n=167) 3) (2 ×1000mg) RTX+MTX (n=170)	Malignancy, n (%) 1) 1 (<1) 2) 1 (<1) 3) 2 (1)	Serious infection, n (%) 1) 4 (2) 2) 3 (2) 3) 3 (2)	NR	Serious AEs, n (%) 1) 15 (9) 2) 13 (8) 3) 17 (10) Discontinuation due to AE, n (%) 1) 2 (1) 2) 3 (2) 3) 7 (4) Deaths, n (%) 1) 0 2) 2 (10 3) 0

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Peterfy C *Annals of the Rheumatic Diseases* 2016[171] RA-SCORE	1) PBO+MTX (n=63) 2) 1000mg RTX+MTX (n=60)	Neoplasms benign, malignant, and unspecified (including cysts and polyps), n (%) 1) 0 2) 1 (1.7) (Papillary serous endometrial carcinoma)	Any infection, n (%) 1) 16 (25.4) 2) 27 (45.0) Serious infections (events/100 PY) 1) 0.0 2) 3.4 Bronchitis, n (%) 1) 2 (3.2) 2) 6 (10.0) Viral infection, n (%) 1) 2 (3.2) 2) 3 (5.0) 2 serious infections in 1000mg RTX+MTX: bronchitis and omphalitis due to Escherichia coli	Treatment-related TEAEs, n (%) 1) 14 (22.2) 2) 9 (15.0) Infusion-related reactions, % first/second course 1) 0/0 2) 15.0/5.0	Discontinuation due to AEs, n (%) 1) 2 (3.2) 2) 0 Serious TEAEs, n (%) 1) 0 2) 3 (5.0) Serious TEAEs (Events/100 PY) 1) 0.0 2) 3.4 Deaths: 0

Table F9. Rituximab versus conventional DMARD: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Cohen SB Arthritis Rheum. 2006 [93] REFLEX	1) PBO+MTX (n=209) 2) RTX+MTX (n=308)	Week 24 PCS score increase, n 1) 0.9 2) 5.8 p= 0.0002 for 1-2 MCS score increase, n 1) 1.3 2) 4.7 p= 0.0002 for 1-2	Week 24 VAS scale, n (SD) 1) -2.5 (23.3) 2) -23.4 (29.4) p= 0.0045 for 1-2	Week 24 Mean point reduction in FACIT-F scale, n 1) 0.5 2) 9.1
Keystone E Arthritis Rheum 2008 [208] REFLEX	1) PBO+MTX (n=201) 2) RTX+MTX (n=298), (1000mg ×2)	Week 24 Mean PCS (SD) 1) 1.48 (7.32) 2) 6.64 (8.74) p< 0.0001 for 1-2 Mean MCS (SD) 1) 2.25 (12.33) 2) 5.32 (12.41) p<0.0001 for 1-2	Week 24 Mean change from baseline VAS-pain (SD) 1) -2.50 (23.30) 2) -23.37 (29.35)	Week 24 Mean change from baseline FACIT-F (SD) 1) -0.54 (9.84) 2) -9.14 (11.31)

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Emery P Arthritis Rheum. 2006 [207] DANCER	1) PBO (n=149) 2) RTX, 2×500mg (n=124) 3) RTX, 2×1000mg (n=192)	NR	NR	Week 24 FACIT-F percentage improvement, % 1) 4 2) 20 3) 28
Emery P *Annals of the rheumatic diseases* 2010[149] SERENE	1) PBO+MTX (n=172) 2) (2×500mg) RTX+MTX (n=167) 3) (2 ×1000mg) RTX+MTX (n=170)	NR	NR	Week 24 mean change from baseline 1) 2.12 2) 5.51 (p<0.001) 3) 6.53 (p<0.0001)

Table F10. Abatacept versus conventional DMARD: Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Takeuchi T *Modern rheumatology* 2013[172] Takeuchi 2013 Good	Bristol-Myers Squibb	RCT multicenter double-blind Phase II dose-response 24 weeks	42 sites in Japan	1) 10mg ABTiv+MTX (n=61) 2) PBO+MTX (n=66) 3) 2mg ABTiv+MTX (n=67) Continued MTX (6–8 mg/wk); Intravenous ABT was infused in a fixed volume of 100 mL saline or 5 % glucose over 30 min on weeks 0, 2, 4, 8, 12, 16 and 20 of the study at a dose of 10mg/kg *ABTiv 2mg+MTX excluded from table*	Japanese; age ≥20 yrs; diagnosis of RA; functional status of Class I, II, or III; previous treatment with MTX at 6-8mg weekly ≥12 wks, with a stable dose for at ≥4 wks before registration; ≥10/66 swollen joints or ≥12/68 tender joints or CRP ≥1.0 mg/dL Exclusion criteria: Vasculitis of major organ system; hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic or cerebral disease; HIV, hepatitis B or C; opportunistic or serious infections; active TB; severe asthma, cancer	Mean age, yrs (SD) 1) 53.4 (11.3) 2) 53.4 (12.0) Female, n (%) 1) 49 (80.3) 2) 52 (78.8) Mean RA duration, yrs (SD) 1) 7.4 (5.7) 2) 7.3 (6.2) Mean HAQ-DI (SD) 1) 1.33 (0.59) 2) 1.50 (0.73) DAS28-CRP (SD) 1) 6.0 (0.7) 2) 6.0 (0.7)

<table>
<tr><th>Author & Year of Publication (Trial Name) Quality rating</th><th>Study sponsor</th><th>Study Design and Duration of Follow-up</th><th>Geographic location of study</th><th>Interventions (n) & Dosing Schedule</th><th>Inclusion and Exclusion Criteria</th><th>Baseline patient Characteristics</th></tr>
<tr>
<td>Genovese MC New England Journal of Medicine 2005[91]

ATTAIN

Good

See also Li T Value in Health 2011[231]</td>
<td>Bristol-Meyers Squibb</td>
<td>RCT
multicenter, double-blind, Phase III

24 weeks</td>
<td>89 sites in North America and Europe</td>
<td>1) weight-based dosing [<60kg 500mg, 60-100kg 750mg, >100kg 1000mg] ABTiv + oral DMARD (n=258)
2) PBO + oral DMARD (n=133)

Treatment was administered in a 30-min iv infusion on days 1, 15, and 29 and every 28 days thereafter, up to and including day 141.</td>
<td>Age ≥ 18 yrs; diagnosis of RA for at least 1 yr; inadequate response to anti-TNF-α therapy with ETN, IFX, or both at the approved dose ≥3 months treatment; ≥10 swollen joints; ≥12 tender joints; C-reactive protein levels ≥1mg/dL; oral DMARD or anakinra ≥3 months; stable dose oral DMARD ≥28 days.</td>
<td>
<table>
<tr><td>Mean age, yrs (SD)</td><td>Female, n (%)</td></tr>
<tr><td>1) 53.4 (12.4)</td><td>1) 199 (77.1)</td></tr>
<tr><td>2) 52.7 (11.3)</td><td>2) 106 (79.7)</td></tr>
</table>
Mean RA duration, yr (SD)
1) 12.2 (8.5)
2) 11.4 (8.9)

Mean DAS28 (SD)
1) 6.5 (0.9)
2) 6.5 (0.8)

Mean HAQ-DI baseline score (SD)
1.8 (0.6) for both groups

Anti-TNF-α history, n (%)
<table>
<tr><td></td><td>1)</td><td>2)</td></tr>
<tr><td>ETN</td><td>83 (32.2)</td><td>53 (39.8)</td></tr>
<tr><td>IFX</td><td>175 (67.8)</td><td>80 (60.2)</td></tr>
<tr><td>ADA</td><td>6 (2.3)</td><td>2 (1.5)</td></tr>
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Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Kremer JM *New England Journal of Medicine* 2003[174] Kremer 2003 Good See also Kremer JM *Arthritis and Rheumatism* 2005 [283], Emery P *Journal of Rheumatology* 2006 [284]	Bristol-Meyers Squibb	RCT Multicenter, double-blind, 1 year		1) 10mg/kg ABTiv + MTX (n=115) 2) 2mg/kg ABTiv + MTX (n=105) 3) PBO + MTX (n=119) ABT (2 mg/kg or 10 mg/kg) or PBO was infused intravenously over a 30-minute period on days 1, 15, and 30 and every 30 days thereafter.	American Rheumatism Association criteria for RA at ACR functional class I, II, or III; >10 swollen, >12 tender joints, C-reactive protein level >1mg/dl signifying active disease; treated with MTX ≥6months and stable dose 28 days prior to enrollment; washed-out of all DMARD other than MTX for at least 28 days prior to treatment Exclusions: pregnant/breastfeeding	Mean age, yrs (range) 1) 55.8 (17-83) 2) 54.4 (23-80) 3) 54.7 (23-80) Female, % 1) 74.8 2) 62.9 3) 66.4 Mean RA duration, yrs (SD) 1) 9.7 (9.8) 2) 9.7 (8.1) 3) 8.9 (8.3)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Kremer JM *Annals of Internal Medicine* 2006[173] AIM Good See also Russell AS *Annals of Rheumatic Diseases* 2007[223], Li T *Value in Health* 2011[231]	Bristol-Meyers Squibb	RCT Multicenter, double-blind 1 year	116 centers worldwide (21% N. America, 41% S. America, 32% Europe, 6% other)	1) 10mg/kg ABTiv + MTX (n=433) 2) PBO + MTX (n=219) Study treatment was administered by 30-minute intravenous infusion on days 1, 15, and 29 and then every 28 days up to and including day 337. All patients were to receive methotrexate, 15 mg or more per week, although methotrexate at 10 mg per week was acceptable if the patient had a history of toxicity.	Age ≥ 18 years; rheumatoid arthritis ≥1 year diagnosis; American Rheumatism Association criteria for RA; MTX treatment of ≥15 mg/wk for 3 months or longer, with stable dose for 28 days before enrollment; wash-out of disease modifying anti-rheum drugs at least 28 days pre-randomization; ≥10 swollen joints, ≥12 tender joints; C-reactive protein levels ≥10.0mg/L; tuberculin skin testing pre-randomization Exclusion: TB positive test results	Mean age, yrs (SD) 1) 51.5 (12.9) 2) 50.4 (12.4) Female, % 1) 77.8 2) 81.7 Mean disease duration, yrs (SD) 1) 8.5 (7.3) 2) 8.9 (7.1) Mean HAQ-DI baseline score (SD) 1) 1.7 (0.7) 2) 1.7 (0.6) Mean DAS28 baseline score (SD) 1) 6.4 (0.08) 2) 6.4 (0.11) Mean APaQ, Days of limited activity baseline (SD) 1) 14.2 (11) 2) 14.4 (12)

Table F11. Abatacept versus conventional DMARD: Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Takeuchi T *Modern rheumatology* 2013[172] Takeuchi 2013	1) 10mg ABTiv+MTX (n=61) 2) PBO+MTX (n=66)	Week 24, % ACR20 1) 77.0 2) 21.2 p<0.001 ACR50 1) 45.9 2) 6.1 p<0.001 ACR70 1) 21.3 2) 0 p<0.001	Week 24 DAS28-CRP score (SD) 1) 3.5 (1.3) 2) 5.3 (1.2) p=NR DAS28-CRP<2.6 (%) 1) 24.6 2) 1.5 p=NR	NR	Week 24 HAQ, score (SD) 1) 0.8 (0.6) 2) 1.4 (0.7) reduction in HAQ score ≥0.3, % 1) 60.7 2) 24.2	Week 24 CRP, mg/dL (SD) 1) 0.9 (1.5) 2) 3.4 (2.7)

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Genovese MC *New England Journal of Medicine* 2005 [91] ATTAIN	1) 10mg/kg ABTiv + oral DMARD (n=258) 2) PBO + oral DMARD (n=133)	Week 24, % ACR20 1) 50.4 2) 19.5 P<0.001 ACR50 1) 20.3 2) 3.8 P<0.001 ACR70 1) 10.2 2) 1.5 P=0.003	Week 24, % DAS28≤ 3.2 1) 17.1 2) 3.1 P<0.001 DAS28< 2.6 1) 10.0 2) 0.8 P<0.001	NR	Week 24 Reduction in HAQ≥0.3, % 1) 47.3 2) 23.3 P<0.001 HAQ, mean score reduction 1) 0.45 2) 0.11 P<0.001	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Kremer JM *Arthritis and Rheumatism* 2005 [283] Kremer 2005 See also Kremer JM *New England Journal of Medicine* 2003[174] And Emery P *Journal of Rheumatology* 2006 [284]	1) 10mg/kg ABTiv + MTX (n=115) 2) 2mg/kg ABTiv + MTX (n=105) 3) PBO + MTX (n=119)	1 year, % ACR20 1) 62.6 3) 36.1 P<0.001 ACR50 1) 41.7 3) 20.2 P<0.001 ACR70 1) 20.9 3) 7.6 P=0.003	24 weeks, % DAS28 <2.6 1) 26.1 3) 9.2 P<0.001 DAS28 <3.2 1) 40.0 3) 19.3 P<0.05 1 year, % DAS28 <2.6 1) 34.8 3) 10.1 P<0.001 DAS28 <3.2 1) 49.6 3) 21.9 P<0.001	NR	1 year HAQ mean improvement, % 1) 42.3 3) 10.3 P<0.001 Clinically important HAQ improvements, % 1) 49.6 3) 27.7 P<0.001 HAQ score of 0, % 1) 15.7 3) 7.6 P=0.05 24 weeks Clinically important HAQ improvements, % 1) 58.3 3) 33.6 P<0.001 HAQ score of 0, % 1) 20.0 3) 7.6 P<0.01	1 year CRP level, mg/dl Mean improvement, % 1) 27.6 3) -31.3 P<0.001

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Kremer JM *New England Journal of Medicine* 2003[174] Kremer 2003 See also Kremer JM *Arthritis and Rheumatism* 2005 [283] And Emery P *Journal of Rheumatology* 2006 [284]	1) 10mg/kg ABTiv + MTX (n=115) 2) 2mg/kg ABTiv + MTX (n=105) 3) PBO + MTX (n=119)	24 weeks, % ACR20 1) 60.0 3) 35.3 P<0.001 ACR50 1) 36.5 3) 11.8 P<0.001 ACR70 1) 16.5 3) 1.7 P<0.001	NR	NR	HAQ 24 weeks, mean change from baseline 1) 41.5 3) 14.1 P<0.05	24 weeks, mean change from baseline CRP level 1) 31.5 3) -23.6 P<0.05

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Kremer JM *Annals of Internal Medicine* 2006[173] AIM	1) 10mg/kg ABTiv + MTX (n=433) 2) PBO + MTX (n=219)	24 weeks, % ACR20 1) 67.9 2) 39.7 ACR50 1) 39.9 2) 16.8 ACR70 1) 19.8 2) 6.5 All P values <0.001 1 year, % ACR20 1) 73.1 2) 39.7 ACR50 1) 48.3 2) 18.2 ACR70 1) 28.8 2) 6.1 All P values <0.001	24 weeks DAS28≤3.2, % 1) 30.1 2) 10.0 P<0.001 DAS28<2.6, % 1) 14.8 2) 2.8 P<0.001 1 year DAS28≤3.2, % 1) 42.5 2) 9.9 DAS28<2.6, % 1) 23.8 2) 1.9 P<0.001	1 year Sharp total score, change from baseline 1) 1.21 2) 2.32	1 year, % HAQ-DI improvement from baseline 1) 63.7 2) 39.3 P<0.001	NR

Table F12. Abatacept versus conventional DMARD: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Takeuchi T *Modern rheumatology* 2013[172] Takeuchi 2013	1) 10mg ABTiv+MTX (n=61) 2) PBO+MTX (n=66)	NR	Infections and infestations, n (%) 1) 20 (32.8) 2) 16 (24.2) Nasopharyngitis, n (%) 1) 13 (21.3) 2) 8 (12.1)	Gastrointestinal disorders, n (%) 1) 15 (24.6) 2) 13 (19.7) Upper respiratory tract inflammation, n (%) 1) 5 (8.2) 2) 3 (4.5) Constipation, n (%) 1) 1 (1.6) 2) 4 (6.1)	Discontinuation due to AEs, n (%) 1) 0 2) 2 (3.0) Serious AEs, n (%) 1) 5 (8.2) 2) 6 (9.1) Treatment-emergent SAEs, n (%) 1) 2 (3.3) 2) 1 (1.5) Deaths: 0
Genovese MC *New England Journal of Medicine* 2005[91] ATTAIN	1) 10mg/kg ABTiv + oral DMARD (n=258) 2) PBO + oral DMARD (n=133)	NR	Serious infections, n (%) 1) 6 (2.3) 2) 3 (2.3) P=0.97 Nasopharyngitis, n (%) 1) 20 (7.8) 2) 8 (6.0)	Headache, n (%) 1) 32 (12.4) 2) 7 (5.3)	Discontinuation due to AEs, n (%) 1) 9 (3.5) 2) 5 (3.8) P=0.89 Serious AEs, n (%) 1) 7 (2.7) 2) 2 (1.5) Deaths: 0

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Kremer JM *Arthritis and Rheumatism* 2005 [283] Kremer 2005 See also Kremer JM *New England Journal of Medicine* 2003[174] And Emery P *Journal of Rheumatology* 2006 [284]	1) 10mg/kg ABTiv + MTX (n=115) 2) 2mg/kg ABTiv + MTX (n=105) 3) PBO + MTX (n=119)	Malignancies*, n 1) 4 3) 3 *Considered by investigator to be unrelated to study treatment	Upper respiratory tract infections, n (%) 1) 13 (11.3) 3) 9 (7.6) Nasopharyngitis, n (%) 1) 17 (14.8) 3) 11 (9.2) AEs related to study treatment: Upper respiratory tract infections, n (%) 1) 5 (4.3) 3) 1 (0.8) Nasopharyngitis, n (%) 1) 7 (6.1) 3) 4 (3.4)	NR	Discontinuation due to AEs, n (%) 1) 6 (5.2) 3) 11 (9.2) Serious AEs, n (%) 1) 14 (12.2) 3) 19 (16.0) Serious AEs related to study treatment, n (%) 1) 2 (1.7) 3) 2 (1.7) Deaths, n 1) 0 2) 1* 3) 0 *Investigator reported death as unrelated to the investigational drug

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Kremer JM *New England Journal of Medicine* 2003[174] Kremer 2003 See also Kremer JM *Arthritis and Rheumatism* 2005 [283] And Emery P *Journal of Rheumatology* 2006 [284]	1) 10mg/kg ABTiv + MTX (n=115) 2) 2mg/kg ABTiv + MTX (n=105) 3) PBO + MTX (n=119)	0 at 24 weeks	24 weeks Upper respiratory tract infection, n (%) 1) 15 (13.0) 3) 12 (10.1) Pharyngitis, n (%) 1) 12 (10.4) 3) 7 (5.9)	24 weeks Fatigue, n (%) 1) 6 (5.2) 3) 13 (10.9) Musculoskeletal pain, n (%) 1) 8 (7.0) 3) 15 (12.6)	24 weeks Discontinuation due to AEs, n (%) 1) 2 (1.7) 3) 7 (5.8) Serious AEs, n (%) 1) 3 (2.6) 3) 12 (10.1) P=0.03 Serious AEs related to study treatment, n (%) 1) 0 3) 1 (0.8) Deaths: 0

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Kremer JM *Annals of Internal Medicine* 2006[173] Kremer 2006 AIM	1) 10mg/kg ABTiv + MTX (n=433) 2) PBO + MTX (n=219)	Malignancies: 1) 1 large B-cell lymphoma, thyroid 2) 1 endometrial carcinoma	Infections, n (%) 1) 17 (3.9) 2) 5 (2.3) Serious infections, n (%) 1) 11 (2.5) 2) 2 (0.9) Tuberculosis: 1 case each group, neither confirmed bacteriologically	Headache, n (%) 1) 76 (17.6) 2) 26 (11.9)	Discontinuations due to adverse events, n (%) 1) 18 (4.2) 2) 4 (1.8) Serious adverse AEs, n (%) 1) 65 (15.0) 2) 26 (11.9) Death, n (%) 1) 1 (0.2) 2) 1 (0.5)

Table F13. Abatacept versus conventional DMARD: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Genovese MC *New England Journal of Medicine* 2005 [91] ATTAIN	1) 10mg/kg ABTiv + oral DMARD (n=258) 2) PBO + oral DMARD (n=133)	Week 24 SF-36, PCS: P<0.001 SF-36, MCS: P<0.01	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Emery P *Journal of Rheumatology* 2006 [284] Emery 2006 See also Kremer JM *New England Journal of Medicine* 2003[174] And Kremer JM *Arthritis and Rheumatism* 2005[283]	1) 10mg/kg ABTiv + MTX (n=115) 2) 2mg/kg ABTiv + MTX (n=105) 3) PBO + MTX (n=119)	Week 24 SF-36 PCS, mean change from baseline (SE) 1) 8.0 (0.8) 3) 2.6 (0.7) SF-36 MCS, mean change from baseline (SE) 1) 5.7 (0.9) 3) 2.8 (0.9)	NR	NR
Kremer JM *Arthritis and Rheumatism* 2005 [283] Kremer 2005 See also Kremer JM *New England Journal of Medicine* 2003[174] And Emery P *Journal of Rheumatology* 2006 [284]	1) 10mg/kg ABTiv + MTX (n=115) 2) 2mg/kg ABTiv + MTX (n=105) 3) PBO + MTX (n=119)		1 year, % Pain VAS 0-100mm, Mean improvement from baseline 1) 44.9 2) 12.6 P<0.001	

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Kremer JM *New England Journal of Medicine* 2003 [174] Kremer 2003 See also Kremer JM *Arthritis and Rheumatism* 2005 [283] And Emery P *Journal of Rheumatology* 2006 [284]	1) 10mg/kg ABTiv + MTX (n=115) 2) 2mg/kg ABTiv + MTX (n=105) 3) PBO + MTX (n=119)		24 weeks Mean improvement from baseline 1) 46.4 3) 8.4 P<0.05	
Kremer JM *Annals of Internal Medicine* 2006 [173] AIM	1) 10mg/kg ABTiv + MTX (n=433) 2) PBO + MTX (n=219)	24 weeks SF-36 PCS P<0.001 SF-36 MCS P=0.009 1 year SF-36 PCS P<0.001 SF-36 MCS P=0.038	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Russell AS *Annals of Rheumatic Diseases* 2007[223] Russell 2007 AIM	1) 10mg/kg ABTiv + MTX (n=433) 2) PBO + MTX (n=219)			1 year Fatigue VAS P<0.001

Table F14. Abatacept versus conventional DMARD: Non-healthcare Outcomes

Author & Year of Publication (Trial Name)	Interventions	Requirements for surgical intervention	Hospitalization, Rehabilitation, Assisted living	Productivity Loss	Caregiver Burden	Other outcomes
Li T *Value in Health* 2011[231] ATTAIN & AIM	AIM 1a) 10mg/kg ABTiv + MTX (n=433) 2a) PBO + MTX (n=219) ATTAIN 1b) 10mg/kg ABTiv + oral DMARD (n=258) 2b) PBO + oral DMARD (n=133)	NR	NR	Differences in gains in days of activity participation Month 6/12 gains (days per month) AIM 1a) 7.7/8.4 2a) 3.9/4.5 p<0.0001 ATTAIN Month 6 gains 2a) 7.3 (57.5) 2b) 1.4 (9.9) P=0.0002	NR	Over the 12-month AIM study, ABT-treated patients gained a cumulative 100.1 days of activity participation vs. 58.2 days in the MTX group in the 6-month ATTAIN study patients treated with ABT gained a cumulative 38.1 days vs. 12.8 days for patients treated with MTX

Table F15. Tocilizumab versus conventional DMARD: Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Yazici Y *Annals of the rheumatic diseases* 2012[150] ROSE Fair	Roche; third-party writing assistance provided by Embryon & F Hoffmann-La Roche	RCT multicenter double-blind Phase IIIb 24 weeks	United States	1) TCZ+cDMARD (n=412) 2) PBO+cDMARD (n=207) 1) 8 mg/kg intravenously every 4 weeks + stable antirheumatic therapy including DMARD 2) intravenous placebo every 4 weeks + CDMARD at stable dose	Adults with active RA for ≥6 months who had inadequate response to DMARD; ≥6 swollen joints and ≥6 tender joints at screening and baseline; CRP ≥95.24 nmol/l or ESR ≥28 mm/h at screening	Mean age, yrs (SD) 1) 55.2 (12.06) 2) 55.8 (12.42) Female, n (%) 1) 325 (79.5) 2) 172 (83.9) Mean RA duration, yrs (SD) 1) 8.62 y (8.93) 2) 8.52 y (9.05) Mean DAS28 (SD) 1) 6.53 (1.03) 2) 6.55 (1.01) Prior anti-TNF, n (%) 1) 155 (37.9) 2) 78 (38)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Kremer JM *Arthritis and rheumatism* 2011[285] LITHE Good See also Halland AM *European Musculoskeletal Review* 2012[151]	Hoffmann-La Roche	RCT placebo-controlled, parallel-group Phase III 1 year Additional 1 year of open-label therapy.	152 study locations in 16 countries: USA, Australia, Brazil, china, Denmark, Finland, France, Greece, Italy, Mexico, Norway, Poland, Puerto Rico, South Africa, Spain, Switzerland	1) PBO+MTX (n=393) 2) 4mg/kg TCZ+MTX (n=399) 3) 8mg/kg TCZ+MTX (n=398) Patients were randomized 1:1:1 to PBO or either 4mg/kg or 8mg/kg of TCZ every 4 weeks + 10 to 25mg MTX every week. Patients with <20% improvement from baseline in SJC and TJC were eligible for rescue therapy.	≥18 years with severe to moderate RA who are inadequate responders to ≥ 12 weeks MTX (all other DMARDS withdrawn before study); previous TNFi discontinuation for reasons other than inefficacy; SJC ≥ 6 and TJC≥8: elevated acute phase reactants: ≥1 joint RA erosion on radiology.	Mean age, yrs (SD) 1) 51.3 (12.4) 2) 51.4 (12.6) 3) 53.4 (11.7) Female, % 1) 83 2) 84 3) 82 Mean RA duration, yrs 1) 9 2) 9.4 3) 9.3 Mean HAQ-DI (SD) 1) 1.5 (0.6) 2) & 3) 1.5 (0.6) Mean DAS28 (SD) 1) 6.6 (1) 2) 6.5 (0.9) 3) 6.5 (1) Mean mTSS 1) 28.8 2) 28.7 3) 28.5

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Kivitz A *Arthritis care & research* 2014[153] BREVACTA Good	Roche	RCT double-blind, placebo-controlled, parallel group, 2-arm phase III (24 weeks) followed open label (72 weeks)	141 centers in 22 countries in Europe, North America, South America, Australia, Africa and, Asia	1) PBO+MTX (n=219) 2) TCZsc+MTX (n=437) Patients were randomized 2:1 to receive sc TCZ 162 mg every other week or sc PBO every other week for 24 weeks. From week 12, patients initially randomized to receive TCZ or PBO every other week could receive escape therapy with TCZ 162 mg weekly at the investigators' discretion if there was <20% improvement in SJC and TJC from baseline.	≥18 years of age with RA for ≥6 months with ≥SJS and ≥8 TJC, radiographical evidence of ≥1 erosion and CRP≥10mg/L and/or ESR≥28 mm/h and inadequate response to ≥cDMARDs	Mean age, yrs (SD) 1) 52 (11.71) 2) 52.1 (11.45) Female, n (%) 1) 181 (82.6) 2) 375 (85.8) Mean RA duration, yrs (SD) 1) 11.1 (8.24) 2) 11.1 (8.39) Mean HAQ-DI (SD) 1) 1.6 (0.62) 2) 1.6 (0.62) Mean DAS28 (SD) 1) 6.7 (0.92) 2) 6.6 (0.94) Mean mTSS (SD) 1) 59.01 (65.9) 2) 60.38 (66.47)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Emery P *Annals of the rheumatic diseases* 2008[189] RADIATE Good See also Strand V *Rheumatology* 2012[92]	Hoffmann-La Roche	RCT double-blind, placebo-controlled, parallel-group Phase III 24 weeks	North America and western Europe	1) PBO+MTX (n=158) 2) 4mg/kg TCZ+MTX (n=161) 3) 8mg/kg TCZ+MTX (n=170) Patients were randomly assigned to 8 mg/kg or 4 mg/kg of iv TCZ every 4 weeks or iv PBO every 4 weeks. All patients received stable MTX (10-25mg weekly). Rescue therapy (8mg/kg TCZ) was offered at week 16 in all cases of treatment failure (<20% improvement in both SJC and TJC).	≥18 years of age with moderate to severe RA and failure to respond or intolerance to ≥1 TNFi in the past year. Patients had active RA for ≥6months with ≥6 SJC, ≥8 TJC, CRP > 1mg/dl or ESR >28mm/h	Mean age, yrs (SD) 1) 53.4 (13.3) 3) 53.9 (12.7) Female, % 1) 79 3) 84 Mean RA duration, yrs (SD) 1) 11.4 (9.2) 3) 12.6 (9.3) Mean HAQ-DI (SD) 1) 1.7 (0.6) 3) 1.7 (0.6) Mean DAS28 score (SD) 1) 6.80 (1.06) 3) 6.79 (0.93)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Genovese M *Arthritis and rheumatism* 2008[152] TOWARD Good	Hoffmann-La Roche	RCT double-blind, placebo-controlled, parallel-group Phase III 24 weeks	146 locations in 18 countries: United States, Argentina, Australia, Brazil, Canada, China, Costa Rica, Czech Republic, Finland, France, Germany, Mexico, Panama, Russia, South Africa, Spain, Sweden, Thailand	1) PBO+MTX (n=413) 2) 8mg/kg TCZ+MTX (n=803) Patients were randomly assigned to 8 mg/kg of iv TCZ or iv PBO every 4 weeks	≥18 years of age diagnosed with moderate to severe RA of ≥6months duration with ≥6 SJC, ≥8 TJC, CRP ≥ 1mg/dl or ESR ≥28mm/h. Patients must have received stable dose of conventional DMARD for ≥8 weeks prior to study Exclusion: Patients who were unsuccessfully treated with TNFi or were previously treated with any cell-depleting therapy were excluded	Mean age, yrs (SD) 1) 54 (13) 2) 53 (13) Female, % 1) 84 2) 81 Mean RA duration, yrs (SD) 1) 9.8 (9.1) 2) 9.8 (8.8) Mean HAQ-DI (SD) 1) 1.5 (0.6) 2) 1.5 (0.6) Mean DAS28 (SD) 1) 6.6 (1) 2) 6.7 (1)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Nishimoto N *Annals of the rheumatic diseases* 2007[84] SAMARAI Good	Chugai Pharmaceutical	RCT, parallel-group, open-label 52 weeks	28 locations in Japan	1) cDMARD (n=145) 2) 8mg/kg TCZ (n=157) Patients were randomly assigned to 8 mg/kg of iv TCZ or conventional DMARD therapy 85% of cDMARD patients were on MTX (29% on MTX monotherapy and 56% on MTX plus other cDMARD) and 15% received other cDMARD an/ or immunosuppressant other than corticosteroids	>20 years with RA for ≥6months and < 5years, with ≥6 TJC, ≥6 SJC, ESR ≥30mm/h and CRP ≥20mg/l and inadequate response to ≥1 DMARD. Use of TNFi and leflunomide were not allowed within 3 months prior to first dose	Mean age, yrs (SD) 1) 53.1 (12.5) 2) 52.9 (11.6) Female, n 1) 119 2) 125 Mean RA duration, yrs (SD) 1) 2.4 (1.3) 2) 2.2 (1.4) Mean DAS28 (SD) 1) 6.4 (0.9) 2) 6.5 (0.8) Mean mTSS (SD) 1) 30.6 (42) 2) 28.3 (43.9)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Nishimoto N *Modern Rheumatology* 2009[85] SATORI Good	Chugai Pharmaceutical	RCT double-blind, parallel-group Phase III 24 weeks	25 locations in Japan	1) MTX (n=64) 2) 8mg/kg TCZ (n=61) Patients were randomly assigned to TCZ 8 mg/kg every 4 weeks plus MTX placebo (TCZ group) or TCZ placebo plus MTX 8 mg/week (MTX group) for 24 weeks	Patients between 20 and 75 years old, with RA duration >6months, with ≥6 TJC, ≥6 SJC, ESR ≥30mm/h or CRP ≥10mg/l and inadequate response to MTX. Patients were not allowed to have received prior TNFi or leflunomide (within 12 weeks prior to the first dose	Mean age, yrs (SD) 1) 50.8 (12.2) 2) 52.6 (10.6) Female, n 1) 48 2) 55 Mean RA duration, yrs (SD) 1) 8.7 (7.1) 2) 8.5 (8.4) Mean DAS28 (SD) 1) 6.2 (0.9) 2) 6.1 (0.9)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Smolen J *Lancet* 2008[213] OPTION Good	Hoffmann-La Roche	RCT double-blind, placebo-controlled, parallel-group Phase III 24 weeks	73 centers in 17 countries: Argentina, Australia, Austria, Brazil, Bulgaria, Canada, China, France, Germany, Hungary, Israel, Italy, Mexico, Singapore, Slovakia, Switzerland & Thailand	1) PBO+MTX (n=204) 2) 4mg/kg TCZ+MTX (n=213) 3) 8mg/kg TCZ+MTX (n=205) Patients were randomly assigned to receive PBO TCZ 4 mg/kg, or TCZ 8 mg/kg intravenously every 4 weeks for 24 weeks with weekly stable dose of MTX (10–25 mg) Patients who had not achieved ≥20% improvement in both SJC & TJC by week 16 were eligible for rescue therapy with TCZ 8 mg/kg and, if necessary, intra-articular steroids	Adult patients with moderate to severe active rheumatoid Arthritis for >6months with inadequate response to MTX. Active RA was defined as ≥6 SJC, ≥8 TJC, CRP > 10mg/dl or ESR ≥28mm/h. Patients were to receive MTX for 12 weeks or more before start of study	Mean age, yrs (SD) 1) 50.6 (12.1) 2) 51.4 (12.8) 3) 50.8 (11.8) Female, % 1) 78 2) 82 3) 85 Mean RA duration, yrs (SD) 1) 7.8 (7.2) 2) 7.4 (7.4) 3) 7.5 (7.3) Mean HAQ-DI (SD) 1) 1.5 (0.6) 2) 1.6 (0.6) 3) 1.6 (0.6) Mean DAS28 (SD) 1) 6.8 (0.9) 2) 6.8 (0.9) 3) 6.8 (0.9)

Table F16. Tocilizumab versus conventional DMARD: Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Yazici Y *Annals of the rheumatic diseases* 2012[150] ROSE	1) TCZ+cDMARD (n=412) 2) PBO+cDMARD (n=207)	Week 24, % ACR20 1) 46.1 2) 26.7 p<0.0001 ACR50 1) 30.1 2) 11.2 p<0.0001 ACR70 1) 16 2) 2.1 p<0.0001 Good EULAR response 1) 32.5 2) 5.9 p<0.0001	Week 24 Remission (DAS28[ESR]<2.6), % 1) 38.4 2) 2 p<0.0001 DAS28 (ESR) 1) 3.24 2) 5.18 p<0.0001	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Halland AM *European Musculoskeletal Review* 2012[151] LITHE *Poster*	1) PBO+MTX (n=219) 2) 4 mg/kg TCZ+MTX (n=241) 3) 8 mg/kg TCZ+MTX (n=244) *n is the radiographic population	NR	NR	Mean change from baseline mTSS 1) 3.02 2/3) 1.34 Patient with no mTSS change from baseline at week 260, % 1) 34.9 2/3) 52.7	NR	NR
Kremer JM *Arthritis and rheumatism* 2011[285] LITHE	1) PBO+MTX (n=393) 2) 4mg/kg TCZ+MTX (n=399) 3) 8mg/kg TCZ+MTX (n=398)	Week 52 ACR20, % 1) 22 2) 48 3) 55 p<0.0001 Week 52 ACR50, % 1) 9 2) 30 3) 35 p<0.0001 *values approx. from figure.	Week 52 DAS28 remission, % 1) 7.9 2) 30.2 (p<0.0001) 3) 47.2 (p<0.0001)	Week 52 Mean change from baseline mTSS 1) 1.13 2) 0.34 (p<0.0001) 3) 0.29 (p<0.0001)	Week 52 Mean change from baseline HAQ-DI 1) -58.1 2) -128.4 3) -144.1 P<0.0001 Week 52 HAQ- DI≥0.3, % 1) 52.7 2) 59.6 3) 62.7	

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Kivitz A *Arthritis care & research* 2014[153] BREVACTA	1) PBO+MTX (n=219) 2) 162 mg TCZsc+MTX (n=437)	Week 24 ACR20, % 1) 32 2) 61 p<0.0001 Week 24 ACR50, % 1) 12 2) 40 p<0.0001 Week 24 ACR70, % 1) 5 2) 20 p<0.0001	Week 24 DAS28-ESR remission, % 1) 4 2) 32 p<0.0001	Week 24 mean change from baseline mTSS 1) 1.23 2) 0.62 p=0.0149		
Emery P *Annals of the rheumatic diseases* 2008[189] RADIATE	1) PBO+MTX (n=158) 2) 4mg/kg TCZ+MTX (n=161) 3) 8mg/kg TCZ+MTX (n=170)	Week 24 ACR20, % 1) 10.1 3) 50 P<0.001 Week 24 ACR50, % 1) 28.8 3) 3.8 P<0.001 Week 24 ACR70, % 1) 12.4 3) 1.3 P=0.001	Week 24 DAS28 remission, % 1) 1.6 3) 30.1 P=0.001	NR	Week 24 mean change from baseline HAQ-DI 1) -0.05 3) -0.39 P<0.001	Week 24 mean CRP 1) NR 3) <0.3mg/dl

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Genovese M *Arthritis and rheumatism* 2008[152] TOWARD	1) PBO+MTX (n=413) 2) 8mg/kg TCZ+MTX (n=803)	Week 24 ACR20, % 1) 24.5 2) 60.8 p<0.0001 Week 24 ACR50, % 1) 9 2) 37.6 p<0.0001 Week 24 ACR70, % 1) 2.9 2) 20.5 p<0.0001	Week 24 DAS28 improvement from baseline 1) -1.16 2) -3.17 P<0.0001 Week 24 DAS28 remission, % 1) 3.4 2) 30.2 P<0.0001	NR	Week 24 Mean change from baseline HAQ-DI 1) -0.2 2) -0.5 P<0.0001 Week 24 HAQ- DI≥0.3, % 1) 34 2) 60 P<0.0001	Week 24 mean change in CRP from baseline 1) -0.27 2)-2.2 P<0.0001 Week 24 mean change in ESR from baseline 1) -4.7 2) -35.6 p<0.0001
Nishimoto N *Annals of the rheumatic diseases* 2007[84] SUMARAI	1) cDMARD (n=145) 2) 8mg/kg TCZ (n=157)	Week 52 ACR20, % 1) 34 2) 78 p<0.001 Week 52 ACR50, % 1) 13 2) 64 p<0.001 Week 52 ACR70, % 1) 6 2) 44 p<0.001	Week 52 DAS28 remission 1) 3 2) 59 P<0.001	Week 52 mean change in TSS (95% CI) 1) 6.1 (4.2 to 8) 2) 2.3 (1.5 to 3.2) P<0.01	Week 52 MHAQ score>0.22 1) 40 2) 68 P<0.001	

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Nishimoto N *Modern Rheumatology* 2009[85] SATORI	1) MTX (n=64) 2) 8mg/kg TCZ (n=61)	Week 24 ACR20, % 1) 25 2) 80.3 p<0.001 Week 24 ACR50, % 1) 10.9 2) 49.2 p<0.001 Week 24 ACR70, % 1) 6.3 2) 29.5 p<0.001	Week 24 DAS28 remission, % 1) 1.6 2) 43.1 P<0.001	NR	Week 24 MHAQ score>0.22 1) 34 2) 67 P<0.001	NR
Smolen J *Lancet* 2008[213] OPTION	1) PBO+MTX (n=204) 2) 4mg/kg TCZ+MTX (n=213) 3) 8mg/kg TCZ+MTX (n=205)	Week 24 ACR20, % 1) 26 3) 59 p<0.0001 Week 24 ACR50, % 1) 11 3) 44 p<0.0001 Week 24 ACR70, % 1) 2 3) 22 p<0.0001	Week 24 DAS28 remission, % 1) 0.8 3) 27 P<0.0001	NR	Week 24 Mean change from baseline HAQ-DI 1) -0.34 3) -0.55 P=0.0082 Week 24 HAQ-DI score≥0.3 1) 46 3) 59 P<0.001	Week 24 Mean change from baseline CRP 1) -3.5 3) -25.1 P<0.0001 Week 24 Mean change from baseline ESR 1) -7.1 3) -39.5 P<0.0001

Table F17. Tocilizumab versus conventional DMARD: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Yazici Y *Annals of the rheumatic diseases* 2012[150] ROSE	1) TCZ+cDMARD (n=412) 2) PBO+cDMARD (n=207)	Neoplasms, n 1) 4 2) 3	Serious infections, n 1) 12 2) 1 Cellulitis, n 1) 3 2) NR Pneumonia, n 1) 3 2) NR 0 cases of tuberculosis	RA exacerbation, % 1) 2.2 2) 8.3	Discontinuation due to AEs, n (%) 1) 27 (6.6) 2) 8 (3.9) Serious AEs, n (%) 1) 30 (7.3) 2) 11 (5.4) Deaths, n 1) 3 (2 possibly treatment-related) 2) 0
Kremer JM *Arthritis and rheumatism* 2011[285] LITHE	1) PBO+MTX (n=393) 2) 4mg/kg TCZ+MTX (n=399) 3) 8mg/kg TCZ+MTX (n=398)	Solid malignancies, n 1) 1 2) 5 3) 2 There were 7 other cases of non-solid malignancies in TCZ group.	Serious infection, N per 100 PY 1) 2.3 2) 3.7 3) 4	NR	Serious AEs, N per 100 PY 1) 10.2 2) 12.8 3) 11.5

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Kivitz A *Arthritis care & research 2014*[153] BREVACTA	1) PBO+MTX (n=219) 2) 162 mg TCZsc+MTX (n=437)	NR	Serious infection, n (%) 1) 4 (1.8) 2) 9 (2.1)	NR	Discontinuation due to AEs, n (%) 1) 3 (1) 2) 9 (2) Serious AEs, n (%) 1) 8 (3.7) 2) 20 (4.6) Death 1) 0 2) 3 (<1)
Emery P *Annals of the rheumatic diseases* 2008[189] RADIATE	1) PBO+MTX (n=158) 2) 4mg/kg TCZ+MTX (n=161) 3) 8mg/kg TCZ+MTX (n=170)	NR	Serious infection, n (%) 1) 5 (3.1) 3) 8 (4.6)	Infusion reaction, % 1) 6.3 3) 9.1	Discontinuation due to AEs, n (%) 1) 8 (5) 3) 10 (5.7) Serious AEs, n (%) 1) 18 (11.3) 3) 11 (6.3) 0 deaths in all groups

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Genovese M *Arthritis and rheumatism* 2008[152] TOWARD	1) PBO+MTX (n=413) 2) 8mg/kg TCZ+MTX (n=803)	NR	Serious infection, n (%) 1) 8 (1.9) 2) 22 (2.7) Rates of serious infection (per 100 patient-years) 1) 4.7 2) 5.9	NR	Any AE, n (%) 1) 253 (61.1) 2) 584 (72.8) Serious AE, n (%) 1) 18 (4.3) 2) 54 (6.7) Discontinuation due to AE, n (%) 1) 8 (1.9) 2) 31 (3.9) Death, n (%) 1) 2 (<1) 2) 2 (<1)
Nishimoto N *Annals of the rheumatic diseases* 2007[84] SUMARAI	1) cDMARD (n=145) 2) 8mg/kg TCZ (n=157)	Malignancies, n 1) 0 2) 3	Serious infection, n 1) 8 2) 12 There was no TB case	Infusion reaction, n (%) 1) NA 2) 11 (7)	Serious AE, % 1) 13 2) 18
Nishimoto N *Modern Rheumatology* 2009[85] SATORI	1) MTX (n=64) 2) 8mg/kg TCZ (n=61)	NR	There was no TB case	Infusion reaction, n (%) 1) NA 2) 7 (11.5)	Serious AE, % 1) 4.7 2) 6.6

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Smolen J *Lancet* 2008[213] OPTION	1) PBO+MTX (n=204) 2) 4mg/kg TCZ+MTX (n=213) 3) 8mg/kg TCZ+MTX (n=205)	NR	Serious infection: NR Any infection, n (%) 1) 56 (27) 3) 66 (32)	NR	NR

Table F18. Tocilizumab versus conventional DMARD: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Yazici Y *Annals of the rheumatic diseases* 2012[150] ROSE	1) TCZ+cDMARD (n=412) 2) PBO+cDMARD (n=207)	Week 24 mean change from baseline RAPID3 1) -2.33 2) -1.29 p<0.0001	NR	Week 24 mean change from baseline FACIT-F 1) 8.43 2) 5.89 Difference in adjusted mean change from baseline: 2.73 (95% CI 0.45 to 5.00) p=0.0188
Genovese M *Arthritis and rheumatism* 2008[152] TOWARD	1) PBO+MTX (n=413) 2) 8mg/kg TCZ+MTX (n=803)	Week 24 mean change from baseline SF-36 Physical 1) 4.1 2) 8.9 Mental 1) 2.3 3) 5.3 p<0.0001	NR	Week 24 mean change from baseline FACIT-F 1) 3.6 2) 8 p<0.0001

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Smolen J *Lancet* 2008[213] OPTION	1) PBO+MTX (n=204) 2) 4mg/kg TCZ+MTX (n=213) 3) 8mg/kg TCZ+MTX (n=205)	Week 24 mean change from baseline SF-36 Physical 1) 5 3) 9.5 p<0.0001 Mental 1) 2.7 3) 7.3 p=0.0012	NR	Week 24 mean change from baseline FACIT-F 1) 4 3) 8.6 p<0.0001
Strand V *Rheumatology* 2012[92] RADIATE	1) PBO+MTX (n=158) 2) 4mg/kg TCZ+MTX (n=161) 3) 8mg/kg TCZ+MTX (n=170)	Week 24 mean change from baseline SF-36 PCS 1) 2.22 3) 8.02 p=0.0003 SF-36 MCS 1) 4.07 3) 4.06	Pain VAS, Mean change from baseline 1) -8.6 3) -32.5 p<0.0001	Week 24 mean change from baseline FACIT-F 1) 4.22 3) 8.83 p=0.015

Table F19. Sarilumab versus conventional DMARD: Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Fleischmann R Arthritis and Rheumatology 2016 [163] TARGET Fair See also Fleischmann R *Arthritis and Rheumatology* 2015[88]	Sanofi and Regeneron Pharmaceuticals, Inc.	RCT, 3-arm, multicentered, double-blind, placebo-controlled, phase 3 clinical trial Duration was 34 weeks including 4 weeks of screening, 24 weeks of treatment, and 6 weeks of posttreatment follow up	155 study centers across 27 countries	1) PBO+csDMARDs (n=181) 2) 150mg SAR+csDMARDs (n=181) 3) 200mg SAR+csDMARDs (n=184) Interventions were given every 2 weeks for 24 weeks; after 12, patients with <20% improvement from baseline in SJC or TJC for 2 joint assessments ≥4 wks apart were offered rescue therapy with open-label SAR 200mg q2w	Inclusion: ≥18 years old with s had active RA (≥6 SJC, ≥8 TJC, and ≥8 mg/L hs-CRP) RA duration of ≥6 months and inadequate response to or intolerance of ≥1 anti-TNF therapies; required continuous treatment with standard dose of 1 or a combo of background cDMARDs Exclusion: Uncontrolled concomitant diseases, significant extra-articular manifestations of RA, functional class iv RA, current/recurrent infections, other inflammatory diseases, receiving prednisone (>10 mg/day or equivalent)	Mean age, yrs (SD) 1) 51.9 (12.4) 2) 54.0 (11.7) 3) 52.9 (12.9) Female, n (%) 1) 154 (85.1) 2) 142 (78.5) 3) 151 (82.1) Mean RA duration, yrs (SD) 1) 12.0 (10.0) 2) 11.6 (8.6) 3) 12.7 (9.6) Mean DAS28-CRP (SD) 1) 6.2 (0.9) 2) 6.1 (0.9) 3) 6.3 (1.0) Mean HAQ-DI score (SD) 1) 1.8 (0.6) 2) 1.7 (0.6) 3) 1.8 (0.6)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Genovese MC *Arthritis & rheumatology* 2015[162] MOBILITY Good See also Strand V *Arthritis Rheumatol* 2015 [286], Kavanaugh A *Arthritis and Rheumatology* 2014[287], Fleischmann R *Arthritis and Rheumatology* 2014[89], Van Der Heijde D *Annals of the Rheumatic Diseases.* 2015[203], Emery P *Annals of the Rheumatic Diseases* 2015[219]	Sanofi	RCT, double-blind, placebo controlled phase II and III 52 weeks	262 centers in 31 countries in North and South America, Australia, Asia, Africa and Europe	1) PBO+MTX (n=398) 2) 150mg SAR+MTX (n=400) 3) 200mg SAR+MTX (n=399) Patients were randomized to every 2 weeks SAR or placebo plus weekly MTX. From week 16, patients who did not achieve ≥20% improvement from baseline in the SJC or TJC at 2 consecutive assessments were offered rescue therapy with open-label SAR 200 mg every 2 weeks	18-75 year olds with active RA (i.e. ≥6 SJC, ≥8 TJC and hsCRP≥0.6mg/dl); with RA duration ≥3 months despite treatment with MTX for a minimum of 12 weeks; At least documented bone erosion or positive anti-CCP or RF Exclusion: Prior nonresponse to bDMARD; other uncontrolled diseases; significant extraarticular manifestation; current/ recurrent infection; functional class iv RA	Mean age, yrs (SD) 1) 50.9 (11.2) 2) 50.1 (11.9) 3) 50.8 (11.8) Female, % 1) 81 2) 80 3) 85 Mean RA duration, yrs (range) 1) 9.1 (0.3-44) 2) 9.5 (0.3-44.7) 3) 8.6 (0.3-34.2) Mean DAS28-CRP(SD) 1) 5.9 (0.9) 2) & 3) 6 (0.9) Mean mTSS (SD) 1) 48 (65.2) 2) 54.7 (63.4) 3) 46.3 (57.4) Mean HAQ 1) 1.6 (0.7) 2) 1.6 (0.6) 3) 1.7 (0.6)

Table F20. Sarilumab versus conventional DMARD: Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Fleischmann R *Arthritis and Rheumatology* 2015[88] TARGET *Abstract*	1) PBO+cDMARD (n=181) 2) 150mg SAR+cDMARD (n=181) 3) 200mg SAR+cDMARD (n=184)	Week 24 % ACR20 1) 34 2) 56 p<0.0001) 3) 61 (p<0.0001) Week 24 % ACR50 1) 18 2) 37 (p<0.0001) 3) 41 (p<0.0001) Week 24 % ACR70 1) 7 2) 20 (p<0.025) 3) 16 (p<0.025)	NR	NR	Week 12 mean change from baseline HAQ-DI (SD) 1) -0.29 (0.54) 2) -0.5 (0.64) p=0.0007 3) -0.49 (0.56) p=0.0004	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Fleischmann R Arthritis and Rheumatology 2016 [163] TARGET	1) PBO+csDMARDs (n=181) 2) 150mg SAR+csDMARDs (n=181) 3) 200mg SAR+csDMARDs (n=184)	Week 24 ACR20, n (%) 1) 61 (33.7) 2) 101 (55.8) 3) 112 (60.9) p<0.0001 for 2-3 ACR50, n (%) 1) 33 (18.2) 2) 67 (37.0) 3) 75 (40.8) p<0.0001 for 2-3 ACR70, n (%) 1) 13 (7.2) 2) 36 (19.9) p<0.001 3) 30 (16.3) p<0.01	Week 24 Mean DAS28-CRP change from baseline (SE) 1) -1.4 (0.12) 2) -2.4 (0.11) 3) -2.8 (0.11)	NR	Week 12 Mean HAQ-DI change from baseline (SE) 1) -0.26 (0.04) 2) -0.46 (0.04) 3) -0.47 (0.04)	Week 24 CRP, mg/L (SD) 1) -3.6 (1.56) 2) -15.2 (1.46) 3) -23.3 (1.42)

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Genovese MC *Arthritis & rheumatology* 2015[162] MOBILITY	1) PBO+MTX (n=398) 2) 150mg SAR+MTX (n=400) 3) 200mg SAR+MTX (n=399)	Week 24 ACR20, % 1) 33.4 2) 58 (p<0.0001) 3) 66.4 (p<0.0001) Week 52 ACR20 % 1) 31.7 2) 53.5 (p<0.0001) 3) 58.6 (p<0.0001) Week 24 ACR70 % 1) 3 2) 12.8 (p<0.0001) 3) 14.8 (p<0.0001)	Week 24 DAS28 CRP<2.6, % 1) 10.1 2) 27.8 (p<0.0001) 2) 34.1 (p<0.0001) Week 24 CDAI <2.8, % 1) 5 2) 10.3 (p<0.0001) 3) 13.8 (p<0.0001)	Week 52 mean change from baseline mTSS (SD) 1) 2.78 (7.73) 2) 0.9 (4.66) p<0.0001 3) 0.25 (4.61) p<0.0001	Week 16 mean change from baseline, mean (SD) 1) -0.29 (0.03) 2) -0.53 (0.03) p<0.0001 3) -0.55 (0.03) p<0.0001 Week 24 HAQ DI response (MCID≥0.3), n (%) 1) 133 (33.4) 2) 204 (51) p<0.0001 3) 205 (51.4) p<0.0001 Week 52 HAQ DI response (MCID≥0.3) 1) 104 (26.1) 2) 188 (47) p<0.0001 3) 190 (47.6) p<0.0001	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Kavanaugh A *Arthritis and Rheumatology 2014*[287] MOBILITY	1) PBO+MTX (n=398) 2) 150mg SAR+MTX (n=400) 3) 200mg SAR+MTX (n=399)	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[162]	Week 52 mean change from baseline DAS28 1) -1.36 2) -2.78 (p<0.0001) 3) -2.95 (p<0.0001) Week 52 remission DAS28 CRP<2.6, % 1) 8.5 2) 31 (p<0.0001) 3) 34.1 (p<0.0001) Week 52 mean change from baseline CDAI 1) -17.5 2) -26.96 (p<0.0001) 3) -27.26 (p<0.0001) Week 52 remission CDAI <2.8, % 1) 4.8 2) 14.8 (p<0.0001) 3) 18 (p<0.0001)	Week 52 No radiographic progression, n (%) 1) 154 (38.7) 2) 191 (47.8) 3) 222 (55.6)	Week 24 mean change from baseline, mean (SD) 1) -0.4 2) -0.6 (p<0.0001) 3) -0.6 (p<0.0001) Week 52 mean change from baseline, mean (SD) 1) -0.5 2) -0.7 (p<0.0001) 3) -0.8 (p<0.0001)	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Fleischmann R *Arthritis and Rheumatology* 2014[89] MOBILITY *Abstract*	Prior biologic 1) PBO+MTX (n=109) 2) 150mg SAR+MTX (n=108) 3) 200mg SAR+MTX (n=110) Biologic naive 1) PBO+MTX (n=289) 2) 150mg SAR+MTX (n=292) 3) 200mg SAR+MTX (n=289)	Wk 24 ACR20, % Prior biologic 1) 33 2) 59 (p<0.0001) 3) 64 (p<0.0001) Biologic naïve 1) 34 2) 58 (p<0.0001) 3) 67 (p<0.0001) Wk 24 ACR50, % Prior biologic 1) 12 2) 36 (p<0.0001) 3) 41 (p<0.0001) Biologic naïve 1) 18 2) 37 (p<0.0001) 3) 47 (p<0.0001) Wk 24 ACR70, % Prior biologic 1) 4 2) 20 (p<0.0001) 3) 19 (p=0.0003) Biologic naïve 1) 9 2) 20 (p=0.0002) 3) 27 (p<0.0001)	Week 52 mean change from baseline DAS28-CRP Prior biologic 1) -1.85 2) -2.8 3) -3.15 Biologic naïve 1) -1.93 2) -3.24 3) -3.29 Week 52 mean change from baseline CDAI Prior biologic 1) -23.23 2) -28.45 (p<0.01) 3) -28.81 Biologic naïve 1) -24.52 2) -31.35 3) -30.33 All p<0.001	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Van Der Heijde D *Annals of the Rheumatic Diseases.* 2015[203] MOBILITY *Abstract*	Biologic naive 1) PBO+MTX (n=316) 2) 150mg SAR+MTX (n=318) 3) 200mg SAR+MTX (n=321) Prior biologic 1) PBO+MTX (n=82) 2) 150mg SAR+MTX (n=82) 3) 200mg SAR+MTX (n=78) Prior Anti-TNF 1) PBO+MTX (n=51) 2) 150mg SAR+MTX (n=44) 3) 200mg SAR+MTX (n=58) **Statistical significance difficult to read from available table*	@ week 52 ACR20 (%) Biologic naive 1) 33.5 2) 57.9 3) 88.7 Prior biologic 1) 32.9 2) 58.5 3) 65.4 Prior Anti-TNF 1) 31.4 2) 54.5 3) 62.1	Week 52 mean change from baseline DAS28 Biologic naive 1) -1.34 2) -2.82 3) -2.92 Prior biologic 1) -1.33 2) -2.57 3) -2.98 Prior Anti-TNF 1) -0.92 2) -2.32 3) -2.71 CDAI Biologic naive 1) -17.39 2) -27.14 3) -28.83 Prior biologic 1) -16.08 2) -24.02 3) -27.20 Prior Anti-TNF 1) -12.02 2) -24.48 3) -24.44	@ week 52 mTSS, mean change Biologic naive 1) 2.93 2) 1.03 3) 0.27 Prior biologic 1) 2.23 2) 0.41 3) 0.16 Prior Anti-TNF 1) 2.15 2) 0.64 3) 0.81 mTSS, no progression (%) Biologic naive 1) 39.5 2) 45.3 3) 56.1 Prior biologic 1) 36.6 2) 57.3 3) 53.8 Prior Anti-TNF 1) 37.3 2) 59.1 3) 53.4	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Emery P *Annals of the Rheumatic Diseases* 2015[219] MOBILITY *Abstract*	RA duration ≤ 3 years 1) PBO+MTX (n=103) 2) 150mg SAR+MTX (n=107) 3) 200mg SAR+MTX (n=98) RA duration >3 years 1) PBO+MTX (n=295) 2) 150mg SAR+MTX (n=293) 3) 200mg SAR+MTX (n=301)	Week 24 ACR20, % RA≤3yrs/ RA>3yrs 1) 37.9/31.9 2) 56.1/ 58.7 3) 71.4/64.8 Week 24 ACR50, % RA≤3yrs/ RA>3yrs 1) 25.2/13.6 2) 36.4/37.2 3)58.2/41.6 Week 24 ACR70, % RA≤3yrs/ RA>3yrs 1) 16.5/4.1 2) 21.4/19.1 3) 39.8/19.9	NR	Week 52 Mean change from baseline mTSS RA≤3yrs/ RA>3yrs 1) 2.89/2.74 2) 0.84/0.92 3) 0.17/0.28	Week 16 Mean change from baseline HAQ_DI LS RA≤3yrs/ RA>3yrs 1) -0.31/-0.28 2) -0.58/-0.5 3) -0.62/-0.53	NR

Table F21. Sarilumab versus conventional DMARD: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Fleischmann R *Arthritis and Rheumatology* 2015[88] TARGET *Abstract*	1) PBO+cDMARD (n=181) 2) 150mg SAR+cDMARD (n=181) 3) 200mg SAR+cDMARD (n=184)	NR	NR	NR	Serious AEs, % 1) 3.3 2) 5.4 3) 3.3 Death, n 1) 1 2) 0 3) 0
Fleischmann R Arthritis and Rheumatology 2016 [163] TARGET	1) PBO+csDMARDs (n=181) 2) 150mg SAR+csDMARDs (n=181) 3) 200mg SAR+csDMARDs (n=184)	NR	Serious infections, % 1) 1.1 2) 0.6 3) 1.1	NR	Serious AEs, n (%) 1) 6 (3.3) 2) 6 (3.3) 3) 10 (5.4) Discontinuation due to AEs, n (%) 1) 8 (4.4) 2) 14 (7.7) 3) 17 (9.2) Deaths, n 1) 1 2) 0 3) 0

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Genovese MC *Arthritis & rheumatology* 2015[162] MOBILITY	1) PBO+MTX (n=398) 2) 150mg SAR+MTX (n=400) 3) 200mg SAR+MTX (n=399)	Malignancies, n 1) 1 2) 4 3) 3	Serious infections, % 1) 2.3 2) 2.6 3) 4 0 cases of TB	NR	Serious AEs, n (%) 1) 23 (5.4) 2) 38 (8.8) 3) 48 (11.3) Discontinuation due to AEs, n (%) 1) 20 (4.7) 2) 54 (12.5) 3) 59 (13.9) Death due to AEs, n (%) 1) 2 (0.5) 2) 2 (0.5) 3) 1 (0.2)

Table F22. Sarilumab versus conventional DMARD: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Fleischmann R Arthritis and Rheumatology 2016 [163] TARGET	1) PBO+csDMARDs (n=181) 2) 150mg SAR+csDMARDs (n=181) 3) 200mg SAR+csDMARDs (n=184)	NR	Week 24 Mean patient's assessment of pain change from baseline (VAS, 0-100 mm) (SD) 1) -21.3 (2.25) 2) -31.9 (2.09) 3) -33.7 (2.04)	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Strand V Arthritis Rheumatol. 2015 [286] MOBILITY	1) PBO+MTX (n=398) 2) 150mg SAR+MTX (n=400) 3) 200mg SAR+MTX (n=399)	Week 24 LSM (SE) PCS change 1) 5.2 (0.5) 2) 8.0 (0.5) 3) 8.4 (0.5) p<0.0001 for 2-3 LSM (SE) MCS change 1) 3.9 (0.6) 2) 5.7 (0.6) p<0.5 3) 8.2 (0.6) p<0.0001 Week 52 LSM (SE) PCS change 1) 5.6 (0.6) 2) 9.2 (0.5) 3) 9.1 (0.5) p<0.0001 for 2-3 LSM (SE) MCS change 1) 5.5 (0.7) 2) 7.1 (0.6) 3) 8.4 (0.6) p<0.001	Week 24 LSM (SE) pain VAS change 1) -15.4 (1.4) 2) -28.5 (1.4) 3) -31.8 (2.3) p<0.0001 for 2-3 Week 52 LSM (SE) pain VAS change 1) -19.3 (1.6) 2) -32.7 (1.4) 3) -33.1 (1.4) p<0.0001 for 2-3	Week 24 LSM (SE) FACIT-F change 1) 5.8 (0.5) 2) 8.6 (0.5) 3) 9.2 (0.5) p<0.0001 for 2-3 Week 52 LSM (SE) FACIT-F change 1) 6.1 (0.5) 2) 9.1 (0.5) 3) 9.2 (0.5) p<0.0001 for 2-3

Table F23. Tofacitinib versus conventional DMARD: Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Burmester GR *Lancet* 2013[288] ORAL Step Good See also Strand V *Arthritis Care Res (Hoboken)* 2015 [215]	Pfizer	RCT multicenter double-blind Phase III 6 months	82 centers in North America, Europe, and Latin America	1) PBO+MTX (n=132) 2) 5mg TOF+MTX (n=133) 3) 10mg TOF+MTX (n=134) Patients were randomly assigned in a 2:2:1:1 ratio to tofacitinib 5 mg twice a day; tofacitinib 10 mg twice a day; placebo for 3 months then advanced to 5 mg tofacitinib twice a day; or placebo for 3 months then advanced to 10 mg tofacitinib twice a day.	Inclusion: ≥18 years with active moderate-to severe RA i.e. ≥6 swollen joints and ≥6 tender joints with ESR > 28mm/h or CRP >66.67mmol/L; inadequate response or intolerance to ≥ 1 TNFi; and must be on MTX for ≥4 months Exclusion: Hb < 90g/L, Hct <30%, WBC C1.2 $\times 10^9$ /L or PLT < 100 $\times 10^9$ /L; GFR <40mL/min; total bilirubin, AST or ALT > 1.5 times ULN; chronic or recurrent infection; or malignancy	Female, n (%) 1) 106 (80.3) 2) 113 (85) Mean age, yrs (SD) 1) 54.4 (11.3) 2) 55.4 (11.5) Mean RA duration, yrs 1) 11.3 2) 13 Mean HAQ-DI (SD) 1) & 2) 1.6 (0.7) Mean DAS28 (SD) DAS28-ESR / DAS28-CRP 1) 6.4 (1.1) / 5.4 (1) 2) 6.5 (1.1) / 5.4 (1)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Kremer J *Annals of internal medicine* 2013[154] ORAL Sync Good	Pfizer	RCT double-blind, placebo-controlled 1 year	114 centers in North America, Latin America, Europe, China, Australia, Thailand, Malaysia	1) PBO group 1/ PBO group 2 +cDMARD(s) (n=159) 2) 5mg TOF+cDMARD(s) (n=315) 3) 10mg TOF+cDMARD(s) (n=318) Patients were randomly assigned 4:4:1:1 at baseline to 1 of 4 twice-daily treatment sequences: 5 mg TOF; 10 mg TOF; PBO group 1 advanced to 5mg TOF (at month 6) and PBO group 2 advanced to 10 mg TOF (at month 6). AT month 3, PBO who achieved ≤20% reduction from baseline were blindly advanced to 5mg or 10mg TOF	≥18 years with RA diagnosis with active RA (i.e. ≥4 TJC&SJC, ESR>28mm/h or CRP >66.7nmol/L). Patients were required to have inadequate response to ≥1 bDMARD or cDMARD before study and continue 1 cDMARD before study.	Mean age, yrs 1) 50.8/53.3 2) 52.7 3) 51.9 Female, % 1) 79.7/75 2) 83.8 3) 81.1 Mean duration of RA, yrs 1) 9.5/ 10.2 2) 8.1 3) 9.2 Mean HAQ-DI 1) 1.45/ 1.24 2) 1.44 3) 1.43 Mean DAS28-ESR 1) 6.44/6.14 2) 6.27 3) 6.36

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Kremer JM *Arthritis and rheumatism* 2012[212] Good	Pfizer	RCT double-blind, phase IIB 24 weeks	72 centers in US, Europe, and Latin America	1) PBO+MTX (n=69) 2) 5mg TOF+MTX (n=71) TOF doses+MTX: 3) 1mg bid (n=70) 4) 3mg bid (n=68) 5) 10mg bid (n=74) 6) 15mg bid (n=75) 7) 20mg/day (n=80) Patients receiving 1mg bid, 3mg bid, and 20 mg/day TOF & PBO with <20% reduction from baseline in SJC % TJC at week 12 were reassigned 5 mg bid TOF for the remaining 12 weeks of study (blinding maintained). 3), 4), 5), 6), and 7) excluded from table	≥18 years with ≥6 month RA diagnosis; Active RA (i.e. SJC ≥ 6 and TJC≥8: elevated acute phase reactants); MTX for ≥ 4 months and continues stable MTX during study. Discontinue all other bDMARD and cDMARD.	Mean age, yrs 1) 53 2) 52 Female, % 1) 81 2) 80 Mean RA duration, yrs 1) 9.2 2) 9 Mean HAQ-DI 1) 1.2 2) 1.4 4-variable Mean DAS28-ESR 1) 6.1 2) 6.1 3-variable Mean DAS28-CRP 1) 5.3 2) 5.1

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
van der Heijde D *Arthritis and rheumatism* 2013[78] ORAL Scan Good	Pfizer	RCT multicenter double-blind Phase III 12-month data from a 24-month study	111 centers in North America, South America, Europe, Asia, and Australia **TOF 10 mg and PBO→TOF 10mg excluded from table*	1) PBO+MTX→ TOF 5mg (n=81) & PBO→TOF 10mg (n=79) 2) TOF 5mg +MTX (n=321) 3) TOF 10mg +MTX (n=316) TOF 5mg twice daily or PBO twice daily; 15-25 mg MTX weekly PBO patients who did not achieve ≥20% improvement in swollen and tender joint counts after 3 months blindly randomized to TOF 5 or 10mg; all remaining PBO patients advanced in a blinded manner to TOF after 6 months	age ≥18 years; diagnosis of active RA; ≥6 tender/painful joints and ≥6swollen joints; ESR >28 mm/hr or CRP >7 mg/L; ≥3 distinct joint erosions on posteroanterior hand and wrist radiographs or anteroposterior foot radiographs or IgM RF positivity or anti-CCP; stable doses of MTX (15-25 mg weekly for ≥6 wks); prior use of biologic or nonbiologic DMARDs permitted Key exclusion criteria: abnormal lab values; current/past/chronic infection (hepatitis B or C or HIV, *Mycobacterium tuberculosis*), lymphoproliferative disorder, malignancy	Mean age, yrs (SD) 1) 53.2 (11.5) 2) 53.7 (11.6) Female, n (%) 1) 65 (80.2) 2) 269 (83.8) Mean RA duration, yrs 1) 8.8 2) 8.9 Mean HAQ-DI 1) 1.40 2) 1.41 Mean DAS28-CRP/ESR 1) 5.14/6.25 2) 5.22/6.34 Mean mTSS 1) 35.0 2) 31.1 Prior anti-TNF: 8.9-19.3%

Table F24. Tofacitinib versus conventional DMARD: Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Burmester GR *Lancet* 2013[288] ORAL Step	1) PBO+MTX (n=132) 2) 5mg TOF+MTX (n=133) 3) 10mg TOF+MTX (n=134)	Month 3, % (p value vs. PBO) ACR20 1) 24.4 2) 41.7 (p=0.0024) 3) 28.1 (p<0.0001) ACR50 1) 8.4 2) 26.5 (p<0.0001) 3) 27.8 (p<0.0001) ACR70 1) 1.5% 2) 13.6 (p<0.0001) 3) 10.5 (p=0.0017)	Month 3, % (p value vs. PBO) DAS28<2.6 1) 1.7 2) 6.7 (p=0.0496) 3) 8.8 (p=0.0105) DAS28-4(ESR)≤3.2 1) 5 2) 14.3 (p=0.0138) 3) 20.8 (p=0.0001) SDAI≤3.3 1) 0 2) 6.1 (p=0.0035) 3) 8.3 (p=0.0005)	NR	Month 3 HAQ-DI improvement from baseline 1)-0.18 2)-0.43 (p<0.0001) 3)-0.46 (p<0.0001)	Month 3 ESR mean change from baseline (SD) 1) 0.97 (25) 2) -14.04 (22) 3) -15.39 (21.7) Month 3 CPR mean change from baseline (SD) 1) 29.71 (186.58) 2) -124.57 (245.24) 3) -101.81 (187.05)

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Kremer J *Annals of internal medicine* 2013[154]	1) PBO group 1/ PBO group 2+cDMARD(s) (n=159) 2) 5mg TOF+cDMARD(s) (n=315) 3) 10mg TOF+cDMARD(s) (n=318)	Month 6 ACR20, n (%) 1) 49 (30.8) 2) 164 (52.1) (p<0.001) 3) 180 (56.6) (p<0.001) ACR50, n (%) 1) 20 (12.6) 2) 105 (33.3) 3) 113 (35.6) p=NR ACR70, n (%) 1) 5 (3.1) 2) 41 (13.0) 3) 50 (15.7) p=NR	Month 6 DAS28-ESR <2.6, % 1) 2.6 2) 8.5 (p=0.005) 3) 12.5 (p<0.001)	NR	Month 6 Mean change from baseline LSM HAQ-DI 1) -0.16 2) -0.44 (p<0.001) 3) -0.53 (p<0.001)	NR
Kremer JM *Arthritis and rheumatism* 2012[212]	1) PBO+MTX (n=69) 2) 5mg TOF+MTX (n=71)	Week 12 ACR20 % 1) 33.3 2) 50.7 p<0.05 ACR20 response rate and significance sustained at 24 weeks.	Week 12 Mean change from baseline DAS28-CRP 1) -0.84 2) -1.69 p<0.0001 DAS 28 mean change from baseline and significance sustained at 24 weeks.	NR	Week 12 Mean change from baseline HAQ-DI 1) -0.16 2) -0.49 p<0.001	Week 12 Mean change from baseline CRP 1) 3.04 2) -10.11 p<0.0001

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
van der Heijde D *Arthritis and rheumatism* 2013[78] ORAL Scan	1) PBO+MTX→ TOF 5mg (n=81) 2) 5mg TOF+MTX (n=321)	Month 6/month 12 ACR20, % 1) 25.3/NR 2) 51.5/48.5 ACR50, % 1) 8.3/NR 2) 32.4/32.7 ACR70, % 1) 1.3/NR 2) 14.6/18.8 p<0.0001 for all	Month 6/Month 12 DAS28-ESR<2.6, % 1) 1.6/NR 2) 7.2/10.6 p=NR/NR LSM change from baseline DAS28-ESR 1) -1.3/NR 2) -2.1/-2.3 p<0.0001/NR	Month 6 Mean change from baseline mTSS (Van der Heijde 0-448) 1) 0.47 2) 0.12 p=0.0792 Month 12 Mean change from baseline mTSS 1) 0.92 2) 0.29 p=0.0558 No radiographic progression, % 1) 77.7/74.1 2) 88.8/86.0 p<0.01 for mo 6 & 12	Month 6 LSM change in HAQ-DI, (SE) 1) -0.17 (0.05) 2) -0.48 (0.03) p<0.0001	Month 6 LSM change from baseline CRP, mg/L (SE) 1) 0.82 (1.61) 2) -9.52 (0.92) p<0.0001

Table F25. Tofacitinib versus conventional DMARD: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Burmester GR *Lancet* 2013[288] ORAL Step	1) PBO+MTX (n=132) 2) 5mg TOF+MTX (n=133) 3) 10mg TOF+MTX (n=134)	0 cases of malignant disease	Serious infection, n (%) 1) 0 2) 2 (1.5) 3) 2 (1.5) 1 (1.5) serious infection PBO→ TOF 5 mg	NR	Serious AE, n (%) 1) 6 (4.5) 2) 7 (5.3) 3) 8 (5.9) 3 (4.5) serious AE PBO→ TOF 5 mg and 2 (3) PBO→ TOF 10 mg Discontinuation due to AE, n (%) 1) 7 (5.3) 2) 12 (9) 3) 13 (9.7) 1 (1.5) discontinuation PBO→ TOF 5 mg and 2 (3) discontinuations PBO→ TOF 10 mg Death, n (%) 1(1.5) death PBO→ TOF 10 mg. No other case of death

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Kremer J *Annals of internal medicine* 2013 [154]	1) PBO group 1/ PBO group 2 +cDMARD(s) (n=159) 2) 5mg TOF (n=315) 3) 10mg TOF (n=318)	NR	7 cases of serious infection in TOF group 2 cases of TB in the TOF group	NR	Serious AEs, 1) 6 2) 22 3) 23 Discontinuation due to AEs, 1) 3 2) 20 3) 31 Death, n 1) 0 2) 2 3) 2
Kremer JM *Arthritis and rheumatism* 2012[212]	1) PBO+MTX (n=69) 2) 5mg TOF+MTX (n=71)	NR	Serious infectious were reported by 5 patients receiving tofacitinib	NR	Discontinuation due to AEs, % 1) 5.9 2) 6.1 3) 3.6 4) 4.2 5) 6.8 6) 13.3 7) 9 1 patient receiving TOF died

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
van der Heijde D *Arthritis and rheumatism* 2013[78] ORAL Scan	1) PBO+MTX→ TOF 5mg (n=81) 2) 5mg TOF+MTX (n=321)	Carcinoma, n 1) 0 2) 5 (3 basal cell, 1 stomach adenocarcinoma, 1 bone squamous cell carcinoma)	Serious infection Months 0-3 1) 0 2) 2 (0.6) Months 3-6 1) 1 (1.2) [PBO→TOF 5] 2) 8 (2.5) Months 6-12 1) 0 [PBO→TOF 5] 2) 1 (0.3)	NR	Discontinuation due to AEs, n (%) 1) 5 (3.1) [mos 0-3] 2) 40 (12.5) PBO→TOF 2 (4.8) [mos 3-6] 2 (2.5) [mos 6-12] Deaths, n 1) 1 2) 4 Serious AEs, n (%) Months 0-3 1) 5 (3.1) 2) 12 (3.7) Months 3-6 1) 1 (2.4) [PBO→TOF 5] 2) 17 (5.3) Months 6-12 1) 1 (1.2) [PBO→TOF 5] 2) 13 (4.0)

Table F26. Tofacitinib versus conventional DMARD: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Burmester GR *Lancet* 2013[288] ORAL Step	1) PBO+MTX (n=132) 2) 5mg TOF+MTX (n=133) 3) 10mg TOF+MTX (n=134)	NR	Month 3 mean change in pain from baseline 1) -8.3 2) -27.2 (p<0.0001) 3) -25 (p<0.0001)	Improvement in FACIT-F at month 3 1) 1.1 2) 6.3 (p<0.0001) 3) 4.6 (p=0.0043)
Kremer JM *Arthritis and rheumatism* 2012[212]	1) PBO+MTX (n=69) 2) 5mg TOF+MTX (n=71)	NR	Week 12 Mean change of patient's assessment of pain, 0-100 mm VAS 1) -13.03 2) -27.37 p<0.001	Week 12 Mean change of patient's global assessment of disease activity, 0-100 mm VAS 1) -22.75 2) -33.84 p<0.001

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Strand V Arthritis Care Res (Hoboken) 2015[215] ORAL Step	1) PBO+MTX (n=132) 2) 5mg TOF+MTX (n=133) 3) 10mg TOF+MTX (n=134)	Month 3 LSM (SE) PCS change 1) 2.03 (0.69) 2) 5.65 (0.68) 3) 6.57 (0.69) p<0.0001 for 2-3 LSM (SE) MCS change 1) 0.37 (0.94) 2) 3.52 (0.92) 3) 3.96 (0.93) p<0.05 for 2-3	Month 3 LSM (SE) Pain (VAS) change 1) -8.26 (2.41) 2) -27.16 (2.43) 3) -24.95 (2.48) p<0.0001 for 2-3	Month 3 LSM (SE) FACIT-F change 1) 1.11 (1.04) 2) 6.27 (1.01) p<0.0001 3) 4.57 (1.03) p<0.05
van der Heijde D *Arthritis and rheumatism* 2013[78] ORAL Scan	1) PBO+MTX→ TOF 5mg (n=81) 2) 5mg TOF+MTX (n=321)	NR	Month 6 LS mean change from baseline Patient's assessment of pain, 0-100 mm VAS 1) -15.70 (2.44) 2) -26.4 (1.42) p<0.01	Month 6 LS mean change from baseline FACIT-F 1) 2.1 2) 5.6 p<0.001

Table F27. Baricitinib versus conventional DMARD: Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Dougados M *Ann Rheum Dis* 2016[175] RA-BUILD Good See also Smolen JS *Ann Rheum Dis* 2016 POSTER[227], Emery P *Arthritis Rheumatol* 2015 POSTER[217]	Eli Lilly and Company and Incyte Corporation	RCT, double-blind, placebo controlled, parallel-group phase III study 24 weeks	182 centers in 22 countries	1) PBO+/-cDMARD(s) (n=228) 2) 2mg BAR+/-cDMARD(s) (n=229) 3) 4mg BAR+/-cDMARD(s) (n=227) Patients were randomized 1:1:1 to once daily doses of PBO or BAR 2 or 4 mg + any stable background cDMARD therapies. Rescue treatment (BAR 4 mg) was assigned at week 16 for patients whose tender and swollen joint counts improved from baseline by <20% at both week 14 and week 16	Inclusion: ≥18 years old with active RA (≥6/68 TJC and ≥6/66 SJC; (CRP) ≥3.6 mg/L) and an insufficient response (despite prior therapy) or intolerance to ≥1 cDMARDs Exclusion: prior biologic use, selected lab abnormalities; current or recent clinically significant comorbidity	Mean age, yrs (SD) 1) 51 (13) 3) 52 (12) Female, n (%) 1) 189 (83) 3) 187 (82) Mean RA duration, yrs (SD) 1) 7 (8) 3) 8 (8) Mean HAQ-DI(SD) 1) 1.5 (0.6) 3) 1.55 (0.6) Mean DAS28-ESR (SD) 1) 6.2 (1) 3) 6.2 (0.9) Mean mTSS unit (SD) 1) 19 (31) 3) 24 (40)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Genovese MC *The New England journal of medicine* 2016 [90] RA-BEACON Good See also Smolen JS Ann Rheum Dis. 2016[218], Genovese MC *Annals of the Rheumatic Diseases* 2015[190], Smolen JS *Ann Rheum Dis* 2016 POSTER[227]	Eli Lilly and Company	RCT double-blind, placebo-controlled 24 weeks	178 centers in 24 countries	1) PBO + cDMARD (n=176) 2) 2mg BAR + cDMARD (n=174) 3) 4mg BAR + cDMARD (n=177) Patients were randomized 1:1:1 to placebo (PBO) or BAR (2 or 4 mg) QD for 24 wks in addition to the therapies they were receiving at enrollment.	≥ 18 years old with active moderate to severe RA (i.e. TJC & SJC ≥6, hsCRP ≥3mg/L) on conventional DMARDs. Must have received ≥1 TNF and discontinued because of insufficient response. All bDMARDs were discontinued ≥28d prior to treatment	Mean age, yrs (SD) 1) 56 (11) 2) 55 (11) 3) 56 (11) Female, n (%) 1) 145 (82) 2) 137 (79) 3) 149 (84) Mean RA duration, yrs (SD) 1) 14 (10) 2) 14 (8) 3) 14 (9) Mean HAQ-DI (0-3 score) (SD) 1) 1.78 (0.57) 2) 1.71 (0.55) 3) 1.74 (0.59) Mean DAS28-CRP/ ESR (SD) 1) 5.9 (0.9) / 6.6 (0.9) 2) 6 (0.9)/ 6.7 (1) 3) 5.9 (1)/ 6.6 (1.1)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Keystone EC *Annals of the Rheumatic Diseases* 2015[211] I4V-MC-JADA Good	Eli Lilly and Company	RCT, double-blind, placebo-controlled phase IIb 24 weeks	69 centers in 9 countries: USA, Mexico, India, Poland, Ukraine, the Czech Republic, Hungary, Romania and, Croatia	1) PBO + cDMARD (n=98) 2) 1mg BAR + cDMARD (n=49) 3) 2mg BAR + cDMARD (n=52) 4) 4mg BAR + cDMARD (n=52) 5) 8mg BAR +cDMARD (n=50) Patients were randomized 2:1:1:1:1 to receive PBO or 1of 4 once-daily BAR doses (1, 2, 4, or 8 mg) for 12 wks. Pts assigned to 2 mg, 4 mg or 8 mg continued blinded treatment for an additional 12 weeks	18-75 years with adult onset RA for ≥6months and <15 years; moderate to severe RA (i.e. ≥8 SJC & TJC and either CRP>1.2× ULN or ESr >28mm/h. Regular use of MTX is required. Concurrent use with stable doses of other cDMARDS were allowed.	Mean age, yrs (SD) 1) 49 (12) 4) 53 (10) Female, % 1) 87 4) 71 Mean RA duration, yrs(SD) 1) 5.4 (4.3) 4) 5.3 (4.5) Mean HAQ-DI (SD) 1) 1.2 (0.7) 4) 1 (0.6) Mean DAS28-ESR 1) 6.3 (0.8) 4) 6 (0.9)

Table F28. Baricitinib versus conventional DMARD: Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Dougados M *Ann Rheum Dis 2016*[175] RA-BUILD	1) PBO+/-cDMARD(s) (n=228) 2) 2mg BAR+/-cDMARD(s) (n=229) 3) 4mg BAR+/-cDMARD(s) (n=227)	Week 12 % ACR20 1) 39 3) 62 (p<0.001) %ACR50 1) 13 3) 33 %ACR70 1) ~4 3) ~18 Week 24 % ACR20 1) 42 3) 65 %ACR 50 1) 21 3) 44 %ACR70 1) ~8 3) ~24	Week 24 remission, % DAS28-CRP≤2.6 1) 11 3) 33 DAS28-ESR≤2.6 1) 4 3) 16 CDAI 1) 4 3) 15 SDAI 1) 4 3) 15 All p value vs. PBO <0.001	Week 24 mean change from baseline mTSS 1) 0.7 3) 0.15 (p<0.001)	Week 24 mean change from baseline, HAQ-DI 1) -0.38 3) -0.62 (p<0.001) Week 24, HAQ-DI (% achieving MCID)[217] 1) -21.9 3) -40.3 (p<0.001)	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Emery P *Arthritis Rheumatol* 2015 POSTER[217] RA-BUILD	1) PBO+/-cDMARD(s) (n=228) 2) 2mg BAR+/-cDMARD(s) (n=229) 3) 4mg BAR+/-cDMARD(s) (n=227)				Week 24 % patients achieved HAQ-DI MCID ≥0.22 1) 42 2) 64* 3) 60* *p≤0.001 % patients achieved HAQ-DI MCID ≥0.3 1) 37 2) 58* 3) 55*	

<table>
<tr><th>Author & Year of Publication (Trial Name)</th><th>Interventions</th><th>Treatment Response</th><th>Disease Activity</th><th>Structural Damage</th><th>Function</th><th>Laboratory indices</th></tr>
<tr>
<td>Genovese MC Annals of the Rheumatic Diseases 2015[190]

RA-BEACON</td>
<td>1) PBO + cDMARD (n=176)
2) 2mg BAR + cDMARD (n=174)
3) 4mg BAR + cDMARD (n=177)</td>
<td>%ACR20
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<tr><th></th><th>Wk 12</th><th>Wk 24</th></tr>
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<tr><td>3</td><td>55*</td><td>46*</td></tr>
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%ACR 50
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<tr><td>3</td><td>28*</td><td>29*</td></tr>
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%ACR 70
<table>
<tr><th></th><th>Wk 12</th><th>Wk 24</th></tr>
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<tr><td>3</td><td>11*</td><td>17*</td></tr>
</table>
*p≤0.05 vs. PBO.</td>
<td>DAS28-ESR <2.6
<table>
<tr><th></th><th>Wk 12</th><th>Wk 24</th></tr>
<tr><td>1</td><td>1</td><td>3</td></tr>
<tr><td>3</td><td>6*</td><td>9*</td></tr>
</table>
DAS28-hsCRP<2.6
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<tr><th></th><th>Wk 12</th><th>Wk 24</th></tr>
<tr><td>1</td><td>4</td><td>6</td></tr>
<tr><td>3</td><td>16*</td><td>22*</td></tr>
</table>
CDAI ≤2.8
<table>
<tr><th></th><th>Wk 12</th><th>Wk 24</th></tr>
<tr><td>1</td><td>2</td><td>3</td></tr>
<tr><td>3</td><td>6</td><td>9*</td></tr>
</table>
*p≤0.05 vs. PBO.</td>
<td></td>
<td>Week 12 HAQ-DI≥0.22
1) 43
3) 67*

Week 24 HAQ-DI ≥0.22
1) 30
3) 53*
*p≤0.05 vs. PBO.</td>
<td></td>
</tr>
</table>

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Genovese MC *The New England journal of medicine 2016* [90] RA-BEACON	1) PBO + cDMARD (n=176) 2) 2mg BAR + cDMARD (n=174) 3) 4mg BAR + cDMARD (n=177)	Week 20 % ACR20 1) 27 3) 55 (p≤0.001)	Week 24 mean change from baseline DAS28-CRP 1) -0.8 3) -1.8 (p≤0.001) Remission, % (p value *vs. PBO*) DAS28-CRP<2.6 1) 6 3) 22 (p<0.001) DAS28-ESR<2.6 1) 3 3) 9 (p<0.05) CDAI≤2.8 1) 3 3) 9 (p≤0.01) SDAI≤3.3, % 1) 2 3) 9 (p≤0.01)		Week 24 mean change from baseline HAQ-DI (approx. from figure) 1) -0.18 3) -0.42 (p≤0.001)	

<table>
<tr><th>Author & Year of Publication (Trial Name)</th><th>Interventions</th><th>Treatment Response</th><th>Disease Activity</th><th>Structural Damage</th><th>Function</th><th>Laboratory indices</th></tr>
<tr>
<td>Keystone EC Annals of the Rheumatic Diseases 2015[211]

I4V-MC-JADA</td>
<td>1) PBO+cDMARD (n=98)
2) 1mg BAR+cDMARD (n=49)
3) 2mg BAR +cDMARD (n=52)
4) 4mg BAR+cDMARD (n=52)
5) 8mg BAR+cDMARD (n=50)

2) and 5) excluded from table</td>
<td>%ACR 20
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% ACR 50
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%ACR 70
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*p<0.05 vs. PBO</td>
<td>% DAS28CRP<2.6
<table><tr><th></th><th>Wk 12</th><th>Wk 24</th></tr><tr><td>1</td><td>4</td><td>--</td></tr><tr><td>4</td><td>37*</td><td>34</td></tr></table>
% DAS28ESR<2.6
<table><tr><th></th><th>Wk 12</th><th>Wk 24</th></tr><tr><td>1</td><td>1</td><td>--</td></tr><tr><td>4</td><td>25*</td><td>25</td></tr></table>
% CDAI<2.8
<table><tr><th></th><th>Wk 12</th><th>Wk 24</th></tr><tr><td>1</td><td>1</td><td>--</td></tr><tr><td>4</td><td>21*</td><td>23</td></tr></table>
% SDAI<3.3
<table><tr><th></th><th>Wk 12</th><th>Wk 24</th></tr><tr><td>1</td><td>1</td><td>--</td></tr><tr><td>4</td><td>17*</td><td>23</td></tr></table>
*p<0.05 vs. PBO</td>
<td>NR</td>
<td>Week 12 mean change from baseline, HAQ-DI
1) -0.1
4) -0.33 (p<0.001 vs. PBO)

Week 24 mean change from baseline, HAQ-DI
1) -0.18
4) -0.44</td>
<td>Week 12 mean change from baseline, ESR
1) -5.5
4) -9 (p<0.01 vs. PBO)

Week 24 mean change from baseline, ESR
1) -6
3) -11</td>
</tr>
</table>

Table F29. Baricitinib versus conventional DMARD: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Dougados M *Ann Rheum Dis* 2016[175] RA-BUILD	1) PBO+/-cDMARD(s) (n=228) 2) 2mg BAR+/-cDMARD(s) (n=229) 3) 4mg BAR+/-cDMARD(s) (n=227)	Non-melanoma skin cancer, n (%) 1) 0 2) 0 3) 1 (<1)	Serious infection, n (%) 1) 4 (2) 2) 2 (<1) 3) 4 (2)		Discontinuation due to AEs, n (%) 1) 10 (4) 2) 10 (4) 3) 12 (5) Serious AEs, n (%) 1) 11 (5) 2) 6 (3) 3) 12 (5) Death, n (%) 1) 2 (<1) 2) 0 3) 0
Genovese MC *Annals of the Rheumatic Diseases* 2015[190] RA-BEACON	1) PBO+cDMARD (n=176) 2) 2mg BAR+cDMARD (n=174) 3) 4mg BAR+cDMARD (n=177)	Non-melanoma skin cancer, n 1) 0 2) 0 3) 2	Serious infection, % 1) 3 2) 2 3) 3 0 cases of TB	2 cardiovascular events occurred in 4mg BAR group	Serious AEs, % 1) 7 2) 4 3) 10

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Genovese MC *The New England journal of medicine* 2016 [90] RA-BEACON	1) PBO + cDMARD (n=176) 2) 2mg BAR + cDMARD (n=174) 3) 4mg BAR + cDMARD (n=177)	Malignancies, n (%) 1) 0 2) 0 3) 2 (1)	Serious infection, n (%) 1) 5 (3) 2) 4 (2) 3) 6 (3)		Week 24 Serious AEs, n (%) 1) 13 (7) 2) 7 (4) 3) 18 (10) Discontinuation due to AEs, n (%) 1) 7 (4) 2) 7 (4) 3) 11 (6)
Keystone EC *Annals of the Rheumatic Diseases* 2015[211] I4V-MC-JADA	1) PBO + cDMARD (n=98) 2) 1mg BAR + cDMARD (n=49) 3) 2mg BAR + cDMARD (n=52) 4) 4mg BAR + cDMARD (n=52) 5) 8mg BAR +cDMARD (n=50)	NR	Week 12 serious infection, n (%) 1) 0 2) 0 3) 2 (4) 4) 0 5) 0 Week 24 serious infection, n (%) 3) 2 (4) 4) 0 5) 1(2) 0 cases of TB		Week 12 serious AEs, n (%) 1) 3 (3) 2) 0 3) 3 (6) 4) 0 5) 1(2) Week 24 serious AEs, n (%) 1) 3 (6) 2) 0 3) 4(8)

Table F30. Baricitinib versus conventional DMARD: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Emery P *Arthritis and Rheumatology* 2015[217] RA-BUILD See Dougados M *Ann Rheum Dis* 2016[175]	1) PBO+/-cDMARD(s) (n=228) 2) 2mg BAR+/-cDMARD(s) (n=229) 3) 4mg BAR+/-cDMARD(s) (n=227)	@ 24 weeks SF-36 PCS score 1) 5.3 3) 9.1* SF-36 PCS MCID (≥5) (%) 1) 33.8 3) 55.9* SF-36 MCS score 1) 2.6 3) 3.4 SF-36 MCS MCID (≥5) (%) 1) 28.1 3) 32.6 EQ-5D (Health State Index Score, US algorithm) 1) 0.062 3) 0.131* *p≤0.001 vs. PBO	@ 24 weeks VAS 1) 7.9 3) 11.0 Patient Assessment of Pain, VAS % least mean change from baseline 1) -23.2 3) -38.3 *p≤0.001 vs. placebo	@ 24 weeks FACIT-F 1) 42.5 3) 59.9* *p≤0.001 vs. placebo Patients' Global Assessment of Disease Activity 1) -15.6 3) -15.0 p=NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain		Fatigue & other PROs
Emery P *Arthritis Rheumatol* 2015[217] RA-BUILD	1) PBO+/-cDMARD(s) (n=228) 2) 2mg BAR+/-cDMARD(s) (n=229) 3) 4mg BAR+/-cDMARD(s) (n=227)	Week 24 SF-36 PCS MCID ≥5, % 1) 34.0 2) 56* 3) 56* SF-36 MCS MCID ≥5, % 1) 28 2) 31 3) 33 EQ-5D VAS, mean change from baseline 1) 7.9 2) 13.9** 3) 11 *p≤0.001, **p≤0.01	Week 24 Patient's assessment of pain (0-100mm VAS) mean change from baseline (estimated from graph): 1) -22 2) -27.9* 3) -28* *p≤0.001	Week 24 FACIT-F % of patients with MCID 1) 43 2) 59* 3) 60* Patient's Global Assessment of Disease Activity (0-100mm VAS), mean change from baseline (estimated from graph): 1) -19 2) -28* 3) -29.5* *p≤0.001	

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Keystone EC *Annals of the Rheumatic Diseases.* 2015[211] I4V-MC-JADA	1) PBO + cDMARD (n=98) 2) 1mg BAR + cDMARD (n=49) 3) 2mg BAR + cDMARD (n=52) 4) 4mg BAR + cDMARD (n=52) 5) 8mg BAR +cDMARD (n=50)		Week 12 mean change in pain (0-100) from baseline 1) -8.8 4) -25 (p<0.001) 5) -25.3 (p<0.001) Week 24 mean change in pain (0-100) from baseline 3) -14.7 4) -27.3 5) -26.9	Week 12 mean change in baseline patient global assessment of disease activity 1) -10.3 4) -25.4 (p<0.001) 5) 29.8 (p<0.001) Week 24 mean change in baseline patient global assessment of disease activity 3) -16.9 4) -30.2 5) -30
Smolen JS Ann Rheum Dis. 2016 [218] RA-BEACON	1) PBO + cDMARD (n=176) 2) 2mg BAR + cDMARD (n=174) 3) 4mg BAR + cDMARD (n=177)	Week 24 LSM PCS change 1) 1.9 3) 7.1 p≤0.001 for 2-3 LSM MCS change 1) 1.9 3) 2.7	Week 12 LSM pain VAS change 1) -8.8 3) -23.0 p≤0.001 for 2-3 Week 24 LSM pain VAS change 1) -8.8 3) -24.8 p≤0.001 for 2-3	Week 12 LSM FACIT-F change 1) 5.2 3) 8.1 p≤0.01 for 2-3 Week 24 LSM FACIT-F change 1) 5.7 3) 9.2 (p≤0.01)

Table F31. Baricitinib versus conventional DMARD: Non-Healthcare Outcomes

Author & Year of Publication (Trial Name)	Interventions	Productivity Loss
Smolen JS *Ann Rheum Dis* 2016[227] POSTER	1. RA-BEGIN trial MTX (n=210)/BAR 4mg (n=159)/BAR 4mg + MTX (n=215) 2. RA-BEAM trial PBO (n=488)/BAR 4mg (n=487)/ADA (n=330) 3. RA-BUILD trial PBO (n=228)/BAR 2mg (n=229)/BAR 4mg (n=227) 4. RA-BEACON trial PBO (n=176)/BAR 2mg (n=174)/BAR 4mg (n=177)	WPAI-RA Questionnaire results: Week 24 Impairment in Regular Daily Activities, n 1. 184/145***/192*** 2. 333/430$^{\alpha\alpha}$/272$^{\Delta}$ 3. 141/187/187 4. 91/119$^{\alpha}$/125$^{\alpha\alpha}$ Absenteeism, n 1. 76/56*/90* 2. 118/139/102 3. 44/62/56 4. 22/37/38 Presenteeism, n 1. 70/51*/86** 2. 110/134$^{\alpha\alpha}$/99$^{\Delta\Delta}$ 3. 44/61/53 4. 22/37/38 Overall Work Productivity Impairment, n 1. 70/51*/86** 2. 110/134/99$^{\Delta\Delta}$ 3. 44/61/53 4. 91/119/125 ***p≤0.001 for bari 4 vs. MTX; **p≤0.01 for bari 4 vs. MTX; *p≤0.05 for bari 4 vs. MTX; $^{\alpha}$p≤0.05 for bari vs. PBO; $^{\alpha\alpha}$p≤0.001 for bari vs. PBO; $^{\Delta}$p≤0.001 for ADA vs. PBO; $^{\Delta\Delta}$p≤0.01 for ADA vs. PBO

Table F32. Adalimumab versus conventional DMARD: Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Furst DE J Rheumatol. 2003 [178] STAR Good	Abbott Laboratories	RCT, double-blind, placebo-controlled	69 study sites in United States and Canada	1) ADA+cDMARD, 40mg (n=318) 2) PBO+cDMARD (n=318) Patients were given ADA every other week until the 24th week; continued to receive baseline SAT doses which includes DMARD but only if stable doses for ≥28 days Patients that failed to meet or maintain ≥ACR20 response at week 12 allowed a single increase in dosage of DMARD and/or corticosteroid therapy	Inclusion: ≥18 years with active RA (defined by ≥6 swollen joints and ≥9 tender joins and met 1987 ACR criteria) for ≥3 months Exclusion: 1) those in other trials of other biologic DMARD in RA 2) treated with anti-CD4 therapy or biologic DMARD 3) history of an active inflammatory arthritide other than RA 4) history of major infections	Mean age, yrs (SD) 1) 55.0 (12.8) 2) 55.8 (12.4) Female, n (%) 1) 253 (79.6) 2) 252 (79.2) Mean RA duration, yrs (SD) 1) 9.3 (8.8) 2) 11.5 (9.7) Mean HAQ-DI (0-3), n (SD) 1) 1.37 (0.62) 2) 1.43 (0.60)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Keystone EC *Arthritis & Rheumatism* 2004[179] DE019 Good	Abbott Laboratories	RCT Multicenter, double-blind 1 year	89 sites in the US and Canada	1) 40mg ADA + MTX every 2 wk (n=207) 2) 20mg ADA + MTX every 1 wk (n=212) 3) PBO + MTX (n=200)	Age ≥18 years; RA diagnosis per 1987 ACR criteria; ≥9 TJC and ≥6 SJC; CRP concentration >1mg/dl; either RF positivity or at least 1 joint erosion on radiographs of hands and feet; MTX therapy ≥3months at stable dose of 12.5-25mg/wk for ≥4wks. Exclusion: prior use of anti-CD4 antibody therapy or TNF antagonists; history of active listeriosis or mycobacterial infection; history of malignancy besides non-melanoma skin cancer within 5 yrs; major episode of infection	Mean age, yrs (SD) / Female, n (%) 1) 56.1 (13.5) / 1) 158 (76.3) 2) 57.3 (10.5) / 2) 160 (75.5) 3) 56.1 (12.0) / 3) 146 (73.0) Mean disease duration, yrs (SD) 1) 11.0 (9.2) 2) 11.0 (9.4) 3) 10.9 (8.8) Mean HAQ-DI baseline (SD) 1) 1.45 (0.63) 2) 1.44 (0.64) 3) 1.48 (0.59) Mean CRP, mg/dl (SD) 1) 1.8 (2.3) 2) 1.4 (1.4) 3) 1.8 (2.1) Mean mTSS baseline score (SD) 1) 72.1 (60.7) 2) 66.4 (56.3) 3) 66.4 (47.4)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Kim APLAR 2007 [177] Kim 2007 Good	Abbott Laboratories	RCT, double-blind, placebo-controlled, phase III trial Washout period of 6 weeks followed by a placebo-controlled period of up to 24 weeks	6 sites in Korea	1) PBO (n=63) 2) ADA (n=65), 40 mg Received either PBO or ADA eow by sc injection for up to 24 weeks; at week 18, patients with no response (<20% reduction in tender and swollen joint count compared to baseline) could switch to rescue therapy with open-label ADA 40 mg sc eow	Inclusion: ≥18 years with active RA per ACR criteria and had ≥6 swollen joints and ≥9 tender joints; received ≥1 prior DMARD other than MTX and treated with MTX for ≥6 months with ≥4 weeks of stable dosage Exclusion: Acute inflammatory joint diseases other than RA; active Listeria or TB infection; positive serology for HIV antibody, Hep B surface antigen, or Hep C antibody; calcified granuloma and/or pleural scarring on chest radiograph	Mean age, yrs (SD) 1) 49.8 (10.5) 2) 48.5 (10.2) Female, n (%) 1) 54 (85.7) 2) 62 (95.4) Mean RA duration, yrs (SD) 1) 6.9 (4.5) 2) 6.8 (4.2) Patient's assessment of Pain, mm VAS (SD) 1) 59.4 (18.6) 2) 57.6 (18.2) Mean KHAQ-DI (SD) 1) 1.3 (0.6) 2) 1.4 (0.6) Mean CRP, mg/L (SD) 1) 2.7 (2.6) 2) 2.2 (2.2)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Weinblatt ME *Arthritis & Rheumatism* 2003[176] ARMADA Good	Abbott Laboratories and Knoll Pharmaceuticals	RCT Double-blind Multicenter 24 week	35 sites in the US and Canada	1) 20mg ADA + MTX (n=69) 2) 40mg ADA + MTX (n=67) 3) 80mg ADA + MTX (n=73) 4) PBO + MTX (n=62) Study treatment administered subcutaneously every other week as 2 injections of 1.6 ml per injection. Patients were instructed in self-injection techniques.	Age ≥18yrs; RA diagnosis according to 1987 ACR criteria; ≥9 tender joints and ≥6 swollen joints; MTX treatment ≥6months with stable dose 12.5-25mg/week for at least 4 wks prior to study; failure with treatment ≥1 DMARD besides MTX but <4 DMARDs. Exclusion: treatment with anti-CD4 therapy or TNFα antagonists; history of listeriosis or mycobacterial infection; major episode of infection requiring hospitalization or iv antibiotics within 30 days or oral antibiotics within 14 days prior to screening	Mean age, yrs (SD) 2) 57.2 (11.4) 4) 56.0 (10.8) Female, % 2) 74.6 4) 82.3 Mean disease duration, yrs (SD) 2) 12.2 (11.1) 4) 11.1 (8.0) Pain VAS baseline, 0-100mm (SD) 2) 53.0 (22.0) 4) 57.2 (21.0) Mean HAQ-DI baseline (SD) 2) 1.55 (0.61) 4) 1.64 (0.63) Mean CRP baseline, mg/dl (SD) 2) 2.1 (1.8) 4) 3.1 (3.9)

Table F33. Adalimumab versus conventional DMARD: Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Furst DE J Rheumatol. 2003 [178] STAR	1) ADA+cDMARD, 40mg (n=318) 2) PBO+cDMARD (n=318)	Week 24 ACR20, % 1) 52.8 2) 34.9 ACR50, % 1) 28.9 2) 11.3 ACR70, % 1) 14.8 2) 3.5 p≤0.001	NR	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Keystone EC Arthritis & Rheumatism 2004[179] DE019	1) 40mg ADA + MTX every 2 wk (n=207) 2) 20mg ADA + MTX every 1 wk (n=212) 3) PBO + MTX (n=200)	Week 24, n (%) ACR20 1) 131 (63.3)* 3) 59 (29.5) ACR50 1) 81 (39.1)* 3) 19 (9.5) ACR70 1) 43 (20.8)* 3) 5 (2.5) *1 year, n (%) ACR20 1) 122 (58.9)* 3) 48 (24.0) ACR50 1) 86 (41.5)* 3) 19 (9.5) ACR70 1) 48 (23.2)* 3) 9 (4.5) *P≤0.001		1 year mTSS mean change from baseline (SD) 1) 0.1 (4.8) 2) 0.8 (4.9) 3) 2.7 (6.8) P≤0.001	Week 24 HAQ-DI absolute change from baseline, mean (SD) 1) -0.56 (0.52) 2) -0.60 (0.53) 3) -0.24 (0.52) P≤0.001 1 year HAQ-DI absolute change from baseline, mean (SD) 1) -0.59 (0.57) 2) -0.61 (0.55) 3) -0.25 (0.56) P≤0.001	Week 24 CRP absolute change from baseline, mg/dl (SD) 1) -1.0 (2.9) 2) -0.8 (1.3) 3) -0.2 (1.9) P≤0.001 1 year CRP absolute change from baseline, mg/dl (SD) 1) -0.7 (1.4) 2) -0.7 (1.4) 3) -0.1 (1.9) P≤0.001

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Kim APLAR 2007 [177] Kim 2007	1) PBO (n=63) 2) ADA (n=65), 40 mg	Week 24 ACR20, n (%) 1) 23 (36.5) 2) 40 (61.5) p<0.01 for 1-2 ACR50, % 1) 14.3 2) 43.1 p<0.001 for 1-2 ACR70, % 1) 7.9 2) 21.5 p<0.05	NR	NR	Week 24 Mean change in KHAQ-DI (SD) 1) -0.2 (0.5) 2) -0.5 (0.55) p=0.002 for 1-2	Week 24 Mean change in CRP, mg/L (SD) 1) -0.4 (1.94) 2) -1.4 (3.23) p=0.001

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Weinblatt ME *Arthritis & Rheumatism* 2003[176] ARMADA	1) 20mg ADA + MTX (n=69) 2) 40mg ADA + MTX (n=67) 3) 80mg ADA + MTX (n=73) 4) PBO + MTX (n=62)	Week 24, n (%) ACR20 2) 45 (67.2) 4) 9 (14.5) ACR50 2) 37 (55.2) 4) 5 (8.1) ACR70 2) 18 (26.9) 4) 3 (4.8) P<0.001	NR	NR	Week 24 HAQ-DI absolute change from baseline, mean (SD) 2) -0.62 (0.63) 4) -0.27 (0.57) P<0.001	Week 24 CRP absolute change from baseline, mg/dl (SD) 2) -1.6 (1.6) 4) 0.1 (2.4) P<0.001

Table F34. Adalimumab versus conventional DMARD: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Furst DE J Rheumatol. 2003 [178] STAR	1) ADA+cDMARD, 40mg (n=318) 2) PBO+cDMARD (n=318)	1 case of peripheral T cell lymphoma in the ADA group	Infections, n (%) 1) 166 (52.2) 2) 157 (49.4) Serious Infections, n (%) 1) 4 (1.3) 2) 6 (1.9)	Adverse events, n (%) 1) 275 (86.5) 2) 263 (82.7)	Discontinuation due to AEs, n 1) 9 2) 8 Serious AE events, n (%) 1) 17 (5.3) 2) 22 (6.9)

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Keystone EC *Arthritis & Rheumatism* 2004[179] DE019	1) 40mg ADA + MTX every 2 wk (n=207) 2) 20mg ADA + MTX every 1 wk (n=212) 3) PBO + MTX (n=200)	4 patients developed non-skin cancers: non-Hodgkin's lymphoma, adenocarcinoma, testicular seminoma, breast cancer	Serious infections, n (%) 1) 11 (5.3)* 2) 5 (2.4) 3) 1 (0.5) *P≤0.01 Infection, n (%) 1) 15 (7.2) 2) 33 (15.6) 3) 9 (4.5) Upper respiratory tract infection, n (%) 1) 41 (19.8) 2) 41 (19.3) 3) 27 (13.5) 1 ADA-treated patient developed TB	Headache, n (%) 1) 26 (12.6) 2) 29 (13.7) 3) 12 (6.0) Diarrhea, n (%) 1) 19 (9.2) 2) 24 (11.3) 3) 30 (15.0) Arthralgia, n (%) 1) 14 (6.8) 2) 29 (13.7) 3) 24 (12.0) Joint disorder, n (%) 1) 13 (6.3) 2) 14 (6.6) 3) 23 (11.5) Clinical-flare reaction, n (%) 1) 12 (5.8) 2) 8 (3.8) 3) 29 (14.5)	Serious AEs, n (%) Adalimumab-treated: 60 (14.3) AEs, n (%) Adalimumab-treated: 391 (93.3) Placebo-treated: 181 (90.5) Withdrawal due to AEs, n (%) 1) 26 (12.6) 2) 16 (7.5) 3) 13 (6.5) Deaths: 1) 2 (1 multiple fractures and 1 urosepsis) 2) 1 (chemotherapy complications) 3) 0

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Kim APLAR 2007 [177] Kim 2007	1) PBO (n=63) 2) ADA (n=65), 40 mg	NR	Incidence of infectious AEs, % 1) 34.9 2) 36.9 1 case of TB observed in the ADA group	NR	Serious AE rate, % 1) 0 2) 4.6 Discontinuations due to AEs, n (%) 1) 4 (6.3) 2) 4 (6.2) Deaths, n 1) 0 2) 1 (pneumonia)

Table F35. Adalimumab versus conventional DMARD: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Keystone EC *Arthritis & Rheumatism* 2004[179] DE019	1) 40mg ADA + MTX every 2 wk (n=207) 2) 20mg ADA + MTX every 1 wk (n=212) 3) PBO + MTX (n=200)		Pain VAS 0-100mm absolute change from baseline, mean (SD) Week 24 1) -28.2 (25.8) 2) -27.9 (27.0) 3) -12.6 (26.1) 1 Year 1) -29.4 (26.4) 2) -27.4 (28.5) 3) -11.2 (27.7) P≤0.001	
Kim APLAR 2007 [177] Kim 2007	1) PBO (n=63) 2) ADA (n=65), 40 mg	NR	Week 24 Mean patient pain VAS change (SD) 1) -10.7 (24.85) 2) -23.7 (26.54) p=0.004 for 1-2	NR
Weinblatt ME *Arthritis & Rheumatism* 2003[176] ARMADA	1) 20mg ADA + MTX (n=69) 2) 40mg ADA + MTX (n=67) 3) 80mg ADA + MTX (n=73) 4) PBO + MTX (n=62)		Pain VAS 0-100mm absolute change from baseline, mean (SD) 2) 53.0 (22.0) 4) 57.2 (21.0) P<0.001	24 weeks Mean increase over baseline, FACIT fatigue scale 2) 8.5 4) 3.0 P=0.001

Table F36. Certolizumab Pegol versus conventional DMARDs: Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Choy E *Rheumatology* 2012[182] Good	UCB Pharma	RCT double-blind placebo controlled and parallel-group study 24 weeks	43 centers in 7 countries - Austria, Belgium, Czech Republic, Germany, Ireland, USA and the UK	1) PBO + MTX (n=121) 2) CTZ + MTX (n=126) Patients were randomized on a 1:1 to sc CTZ 400mg or PBO every 4 weeks from baseline to week 20 in combination with MTX 15-25 mg/week	Inclusion: 18 - 75 years with adult-onset RA of ≥ 6 months; active RA i.e. ≥ 9 tender joints, ≥ 9 swollen joints; 1 or more of the following criteria: ≥45 min of morning stiffness, ESR ≥28 mm/h or CRP >10 mg/l; and must be on MTX ≥ 6 months Exclusion: Inflammatory arthritis other than RA; history of chronic, serious or life-threatening infection, current infection, history or chest X-ray of TB, or positive PPD skin test	Mean age, yrs (SD) 1) 55.6 (11.7) 2) 53 (12.3) Female, n (%) 1) 80 (66.1) 2) 91 (72.2) Mean RA duration, yrs (SD) 1) 9.9 (7.8) 2) 9.4 (7.5) Mean HAQ-DI (SD) 1) 1.5 (0.7) 2) 1.4 (0.6) Mean DAS28-3 (SD) 1) 6.3 (0.99) 2) 6.2 (0.98)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Furst DE *Arthritis Care and Research* 2015[242] DOSEFLEX Good	UCB Pharma	Phase IIIb with an open-label run-in period, followed by a double-blind, placebo-controlled RCT period 34 weeks	US, France, Canada	1) CTZ 200mg → PBO +MTX (n=69) 2) CTZ 200mg → CTZ200mg +MTX (n=70) 3) CTZ 200mg → CTZ400mg +MTX (n=70) All patients received a CTZ loading dose followed by 200 mg CTZ every 2 weeks up to week 16 during open label run in. At week 18 ACR20 non-responders were withdrawn and responders were randomized 1:1:1 to either 200 mg CTZ every 2 weeks, 400 mg CTZ every 4 weeks, or PBO during the double-blind phase	Inclusion: 18 years with RA for 6 months – 15 yrs with moderate to severe active disease (i.e. ≥6 TJC and ≥4 SJC, and either CRP≥10mg/dl or ESR≥28mm/hr; RF or anti-CCP positivity); Insufficient control by MTX; must have taken DMARD for ≥3 months	Mean age, yrs (SD) 1) 51.5 (13.2) 2) 55.6 (10.7) 30 53.1 (13.8) Female, % 1) 81.2 2) 70 3) 82.9 Mean RA duration, yrs (SD) 1) 6.5 (4.6) 2) 5.9 (4.2) 3) 6.4 (4.7) Mean HAQ DI (SD) 1) 1.42 (0.55) 2) 1.57 (0.65) 3) 1.41 (0.61) Mean DAS28-ESR (SD) 1) 6.4 (1) 2) 6.4 (0.8) 3) 6.2 (1) Prior anti-TNF use overall, n (%): 111 (53.1)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Yamamoto K *Modern rheumatology* 2014[156] J-RAPID Good	Otsuka Pharmaceutical Co., Ltd.	RCT multicenter double-blind Phase II/III 24 weeks	67 centers in Japan	1) PBO+MTX (n=77) 2) CTZ 200 mg +MTX (n=82) 3) CTZ 100 mg +MTX (n=72) * 4) CTZ 400 mg +MTX (n=85)* Subcutaneous CTZ or saline placebo plus MTX every 2 weeks; patients randomized to CTZ +MTX received induction doses of 200 mg (100 mg group) or 400 mg (200 and 400 mg groups) at Weeks 0, 2 and 4; PBO group received an equivalent injection regimen of saline solution to maintain blinding. *Not abstracted	age 20 – 74; RA diagnosis for 0.5 – 15 years; active RA with ≥9 tender and ≥9 swollen joints at screening and baseline; ESR ≥30 mm/hour or CRP ≥1.5 mg/dL; ≥6 months MTX before study drug administration, with the MTX dose fixed ≥ 2 months	Mean age, yrs (SD) 1) 51.9 (11.1) 2) 50.6 (11.4) Female, n (%) 1) 66 (85.7) 2) 69 (84.1) Mean RA duration, yrs (SD) 1) 5.8 y (4.1) 2) 5.6 y (4.2) Mean DAS28-ESR (SD) 1) 6.5 (0.9) 2) 6.2 (0.8) Prior anti-TNF, n (%) 1) 15 (19.5) 2) 11 (13.4) Mean HAQ-DI (SD) 1) 1.2 (0.7) 2) 1.1 (0.7)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Keystone E *Arthritis & Rheumatism* 2008[181] RAPID1	UCB Pharma	RCT multicenter, double-blind, parallel-group Phase III 1 year	147 centers worldwide (47% North America, 9% South America, 27% Europe, 18% other)	1) 200mg CTZ + MTX (n=393) 2) 400mg CTZ + MTX (n=390) 3) PBO + MTX (n=199) CTZ: 400 mg at wks 0, 2, and 4, followed by 200 mg or 400 mg every 2 wks thereafter, administered sc as a reconstituted, preservative-free injection <20% improvement (ACR20) (12) at wks 12 and 14 were withdrawn from the study at wk 16. Patients who withdrew at wk 16 or who completed the trial could enroll in an open-label extension study of CTZ 400 mg every 2 wks	Age ≥18 yrs; active RA ≥6months but for <15 yrs; ≥9 TJC and ≥9 SJC; ESR ≥30mm/hr or CRP>15mg/L; MTX treatment ≥6months, with dosage of ≥10mg/wk for ≥2months prior to baseline. Exclusions: receiving any biologic therapy within 6 months (or etanercept and/or anakinra within 3months) of baseline and/or any previous biologic therapy that resulted in severe hypersensitivity or anaphylactic reaction; previous failure to respond to treatment with an anti-TNF	Mean age, yrs (SD) 1) 51.4 (11.6) 2) 52.4 (11.7) 3) 52.2 (11.2) Female, % 1) 82.4 2) 83.6 3) 83.9 Mean RA duration, yrs (SD) 1) 6.1 (4.2) 2) 6.2 (4.4) 3) 6.2 (4.4) Mean HAQ-DI (SD) 1) 1.7 (0.6) 2) 1.7 (0.6) 3) 1.7 (0.6)

<table>
<tr><th>Author & Year of Publication (Trial Name) Quality rating</th><th>Study sponsor</th><th>Study Design and Duration of Follow-up</th><th>Geographic location of study</th><th>Interventions (n) & Dosing Schedule</th><th>Inclusion and Exclusion Criteria</th><th>Baseline patient Characteristics</th></tr>
<tr>
<td>Smolen J Annals of Rheumatic Diseases 2009[180]

RAPID2

See also Strand V Annals of Rheumatic Diseases 2011 [289]</td>
<td>UCB Pharma</td>
<td>RCT
Multicenter, double-blind
Phase III

24 weeks</td>
<td>76 sites in US, Bulgaria, Chile, Croatia, Czech Republic, Estonia, Israel, Latvia, Lithuania, Mexico, Poland, Russian Federation, Serbia, Slovakia, Ukraine</td>
<td>1) 200mg CTZ + MTX (n=246)
2) 400mg CTZ + MTX (n=246)
3) PBO + MTX (n=127)

Groups 1 and 2 were treated with
400 mg at weeks 0, 2 and 4, followed by 200 or
400 mg every 2 weeks</td>
<td>Age ≥18 yrs; diagnosis of RA defined by ACR 1987 criteria; diagnosis ≥6months but <15 years; active disease at screening and baseline; prior MTX for ≥6months, stable dose ≥10mg/wk for ≥2months before baseline

Exclusion: treatment with RA biologic agent within 6months prior (3month anakira or etanercept); previous treatment with a biologic resulting in a severe hypersensitivity or anaphylactic reaction; no response to previous anti-TNF therapy; history/positive test TB; positive PPD skin test unless BCG vaccine related</td>
<td>
<table>
<tr><th>Mean age, yrs (SD)</th><th>Female, n (%)</th></tr>
<tr><td>1) 52.2 (11.1)</td><td>1) 206 (83.7)</td></tr>
<tr><td>3) 51.5 (11.8)</td><td>3) 107 (84.3)</td></tr>
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<table>
<tr><th>Mean RA duration, yrs (SD)</th><th>Mean HAQ-DI baseline (SD)</th></tr>
<tr><td>1) 6.1 (4.1)</td><td rowspan="2">1.6 (0.6), all groups</td></tr>
<tr><td>3) 5.6 (3.9)</td></tr>
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<table>
<tr><th>Mean mTSS baseline (SD)</th><th>Mean DAS28-ESR baseline (SD)</th></tr>
<tr><td>1) 39.6 (50.1)</td><td>1) 6.85 (0.84)</td></tr>
<tr><td>3) 46.5 (58.6)</td><td>3) 6.83 (0.87)</td></tr>
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Table F37. Certolizumab Pegol versus conventional DMARDs: Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Choy E *Rheumatology* 2012[182]	1) PBO + MTX (n=121) 2) CTZ 400mg + MTX (n=126)	Week 24, % ACR20 1) 22.9 2) 45.9 P<0.001 *Significantly improved ACR20 response from wk 1* ACR50 1) 5.9 2) 18.0 P=0.004 *Significantly improved ACR50 response from wk 12* ACR70 1) 1.7 2) 0	Week 24 Remission (DAS28-ESR-3<2.6), % 1) 3.1 2) 9.3 Mean change from baseline (SE) DAS28-3 1) -0.8 2) -1.8 P<0.001	NR	Week 24 mean change from baseline (SE) HAQ-DI 1)-0.09 2) -0.32 P<0.001	Week 24 mean change from baseline 1) 0.9 2) 0.6

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Furst DE *Arthritis Care and Research* 2015[242] DOSEFLEX	1) CTZ 200mg → PBO +MTX (n=69) 2) CTZ 200mg → CTZ200mg +MTX (n=70) 3) CTZ 200mg → CTZ400mg +MTX (n=70)	Week 34, % ACR20 1) 44.9 2) 67.1 (p<0.01) 3) 65.2 Week 34, % ACR50 1) 30.4 2) 50 (p<0.05) 3) 52.2 (p<0.05) Week 34, % ACR70 1) 15.9 2) 30 3) 37.7 (p<0.01)	Week 34 Remission (DAS 28-ESR < 2.6), % 1) 5.8 2) 24.3 3) 36.2 Week 34 Remission (CDAI ≤2.8) 1) 17.4 2) 27.1 3) 31.9 Week 34 Remission (SDAI ≤3.3) 1) 13 2) 22.9 3) 36.2	NR	Week 34 mean change from baseline (SD) 1) 1.05 (0.68) 2) 0.81 (0.6) 3) 0.79 (0.64)	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Yamamoto K *Modern rheumatology* 2014[156] J-RAPID	1) PBO+MTX (n=77) 2) CTZ 200 mg +MTX (n=82)	Week 24, % ACR20 1) 24.7 2) 73.2 p<0.0001 *Significantly improved ACR20 response from wk 1* ACR50 1) 16.9 2) 54.9 p<0.0001 ACR70 1) 1.3 2) 29.3 p<0.001 Moderate/good EULAR response 1) 29.9 2) 85.4%	Week 24 Remission (DAS28[ESR]<2.6), % 1) 0 2) 17.1 Mean change from baseline (SE) DAS28 (ESR) 1) -0.63 (0.15) 2) -2.46 (0.15) P<0.0001	Week 24 mean change from baseline mTSS 1) 2.8 2) 0.2 p<0.001	Week 24 mean change from baseline (SE) HAQ-DI 1) -0.18 (0.06) 2) -0.55 (0.05) p<0.0001	Week 24 mean ratio to baseline CRP 1) 0.76 2) 0.28 ESR 1) 0.8 2) 0.4

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Keystone E *Arthritis & Rheumatism* 2008[181] RAPID1	1) 200mg CZP + MTX (n=393) 2) 400mg CZP + MTX (n=390) 3) PBO + MTX (n=199)	Week 24, % ACR20 1) 58.8 3) 13.6 P<0.001 ACR50 P<0.001 ACR70 P<0.001	Mean change from baseline (SD) DAS28-ESR 1) -3.3 (1.3) 3) -2.4 (1.3) P<0.001	24 weeks, mTSS P<0.001 1 year, mTSS Mean change from baseline 1) 0.4 3) 2.8 P<0.001	1 year, HAQ-DI change from baseline P<0.001	NR
Smolen J *Annals of Rheumatic Diseases* 2009[180] RAPID2	1) 200mg CTZ + MTX (n=246) 2) 400mg CTZ + MTX (n=246) 3) PBO + MTX (n=127)	Week 24, % ACR20 1) 57.3 3) 8.7 P≤0.001 ACR50 1) 32.5 3) 3.1 P<0.001 ACR70 1) 15.9 3) 0.8 P≤0.01	Week 24 Mean change from baseline (SD) DAS28-ESR 1) -2.27 (1.38) 3) -0.50 (1.05) P<0.001 DAS28-ESR <2.6, % 1) 9.4 3) 0.8 P≤0.05	Week 24 Mean change from baseline, mTSS 1) 0.2 3) 1.2 P≤0.01	Week 24 HAQ-DI, adjusted mean change from baseline (SE) 1) -0.50 (0.03) 3) -0.14 (0.04)	Week 24 CRP, adjusted geometric mean (95% CI) – ratio to baseline 1) 0.42 (0.35 – 0.49) 3) 0.92 (0.74 – 1.14)

Table F38. Certolizumab Pegol versus conventional DMARDs: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Choy E *Rheumatology* 2012[182]	1) PBO + MTX (n=121) 2) CTZ + MTX (n=126)	0 cases of malignant disease	Serious infection, n (%) 1) 2 (1.7) 2) 3 (2.4) 0 cases of tuberculosis		Discontinuation due to AEs, n (%) 1) 6 (5) 2) 7 (5.6) Serious AEs, n (%) 1) 12 (10.1) 2) 16 (12.9) 0 deaths
Furst DE *Arthritis Care and Research* 2015[242] DOSEFLEX	1) CTZ 200mg → PBO +MTX (n=69) 2) CTZ 200mg → PBO +MTX (n=70) 3) CTZ 200mg → PBO +MTX (n=70)	0 cases of malignant disease	Serious infection, n (%) 1) 0 2) 3 (4.3) 3) 0		Discontinuation due to AEs, n (%) 1) 0 2) 4 (5.7) 3) 1 (1.4) Serious AEs, n (%) 1) 0 2) 5 (7.1) 3) 2 (2.9) 0 deaths

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Yamamoto K *Modern rheumatology* 2014[156] J-RAPID	1) PBO+MTX (n=77) 2) CTZ 200 mg +MTX (n=82)	0 cases of malignant disease	0 cases of tuberculosis	RA exacerbation, n (%) 1) 9 (11.7) 2) 4 (4.9)	Discontinuation due to AEs, n (%) 1) 2 (2.6) 2) 3 (3.7) Serious AEs, n (%) 1) 1 (1.3) 2) 4 (4.9) 0 deaths
Furst DE Arthritis Care Res (Hoboken). 2015 [242] DOSEFLEX			Serious infection, n (%) 1) 0 2) 3 (4.3) 3) 0		Serious AEs, n (%) 1) 0 2) 5 (7.1) 3) 2 (2.9) AE leading to withdrawal, n (%) 1) 8 (11.6) 2) 12 (17.1) 3) 6 (8.7) 0 deaths

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Keystone E *Arthritis & Rheumatism* 2008[181] RAPID1	1) 200mg CZP + MTX (n=393) 2) 400mg CZP + MTX (n=390) 3) PBO + MTX (n=199)	Malignant neoplasms, n 1) 7 2) 4 3) 1	Rate per 100 patient-yrs: Serious infections and infestations 1) 5.3 2) 7.3 3) 2.2 Infections and infestations 1) 56.4 2) 58.4 3) 56.9 Urinary tract infections 1) 7.6 2) 10.5 3) 14.2 Nasopharyngitis 1) 6.9 2) 9.5 3) 3.3 Upper respiratory tract infections 1) 7.9 2) 6.7 3) 5.5	Headache, incidence rate per 100 patient-yrs 1) 7.3 2) 5.7 3) 12.0 Hypertension, incidence rate per 100 patient-yrs 1) 8.2 2) 10.2 3) 2.2 Back pain, incidence rate per 100 patient-yrs 1) 5.6 2) 6.4 3) 2.2	Serious adverse events, n (%) 1) 45 (11.5) 2) 48 (12.3) 3) 11 (5.5) AE leading to withdrawal, n (%) 1) 17 (4.3) 2) 22 (5.6) 3) 3 (1.5) Deaths, n 1) 2 2) 4 3) 1

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Smolen J *Annals of Rheumatic Diseases* 2009[180] RAPID2	1) 200mg CTZ + MTX (n=246) 2) 400mg CTZ + MTX (n=246) 3) PBO + MTX (n=127)	1 malignant neoplasm in each treatment group; 3 total	Any infections, n (%) 1) 69 (27.8) 2) 53 (21.5) 3) 26 (20.8) Serious Infections, n (%) 1) 8 (3.2) 2) 6 (2.4) 3) 0 Tuberculosis, n 1) 3 2) 2		SAEs, n (%) 1) 18 (7.3) 2) 18 (7.3) 3) 4 (3.2) AE leading to withdrawal, n (%) 1) 12 (4.8) 2) 7 (2.8) 3) 2 (1.6) AEs leading to death, n (%) 1) 1 (0.4) 2) 1 (0.4) 3) 0

Table F39. Certolizumab Pegol versus conventional DMARDs: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Choy E *Rheumatology* 2012[182]	1) PBO + MTX (n=121) 2) CTZ + MTX (n=126)	Week 24 mean change from baseline (SE) SF-36 1) 3.6 2) 14.47 p<0.001	Week 24 mean change from baseline Patient's assessment of pain, 0-100 VAS 1) -8.5 2) -21.8 p<0.001	Week 24 mean change in patient's global assessment, 1-5 point Likert scale 1) -0.3 2) -0.6 p<0.001
Yamamoto K *Modern rheumatology* 2014[156] J-RAPID	1) PBO+MTX (n=77) 2) CTZ 200 mg +MTX (n=82)	Week 24 mean change from baseline (SE) SF-36 PCS 1) 4.3 (1.1) 2) 10.2 (1.1) p<0.001 SF-36 MCS 1) 1.2 (1.1) 2) 5.6 (1.0) p<0.005	Week 24 mean change from baseline (SE) Patient's assessment of pain, 100 mm VAS 1) -10.6 (2.6) 2) -27.9 (2.5) p<0.0001	Week 24 mean change from baseline (SE) Patient's assessment of global disease activity, 100 mm VAS 1) -7.3 (2.6) 2) -27.2 (2.5)

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Keystone E *Arthritis & Rheumatism* 2008[181] RAPID1	1) 200mg CZP + MTX (n=393) 2) 400mg CZP + MTX (n=390) 3) PBO + MTX (n=199)		Week 12 Patient's assessment of arthritis pain, mean % change from baseline 1) -38.2 3) -4.8 P<0.001	
Smolen J *Annals of Rheumatic Diseases* 2009[180] RAPID2	1) 200mg CTZ + MTX (n=246) 2) 400mg CTZ + MTX (n=246) 3) PBO + MTX (n=127)	Week 24 Adjusted mean change from baseline SF-36, PCS 1) 5.2 3) 0.9 P<0.001 SF-36, MCS p<0.001		
Strand V *Annals of Rheumatic Diseases* 2011 [289] RAPID2	1) 200mg CTZ + MTX (n=246) 2) 400mg CTZ + MTX (n=246) 3) PBO + MTX (n=127)		Week 24 Patient's assessment of pain VAS, mean change from baseline 1) -23.7 3) -4.7 p<0.001	Week 24 Mean change from baseline FAS (range 0-10) 1) -2.0 3) -0.5 p<0.001

Table F40. Etanercept versus conventional DMARDs: Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Combe B *Ann Rheum Dis* 2006[82] ETN309 Fair See also Combe B *Ann Rheum Dis* 2009[183]	Wyeth Research	Multicenter Parallel Double-blind RCT Two years; results from 24-week timepoint	Europe and Australia	1) Sulfasalazine (n=50) 2) ETN mono (n=103) 3) ETN+sulfasalazine (n=101) ETN (25 mg subcutaneous injections twice weekly and oral PBO once daily); sulfasalazine tablets (2, 2.5 or 3 g daily and sc PBO twice weekly); or ETN and sulfasalazine (sc ETN 25 mg twice weekly and sulfasalazine 2, 2.5 or 3 g once daily). Stable doses of oral corticosteroids, 1 NSAID, analgesics with no anti-inflammatory action or daily aspirin allowed	Age ≥18 years; adult-onset RA despite treatment with sulfasalazine (2-3 g daily for ≥4 mos before screening); disease duration ≤20 years; ≥6 swollen and ≥10 painful joints and ESR ≥28 mm/hr or CRP ≥20 mg/L or morning stiffness ≥45 min Exclusion criteria: prior ETN or other TNF antagonists; received a DMARD other than sulfasalazine within 3 months before baseline	Mean age, yrs (SD) 1) 53.3 (12.8) 2) 51.3 (13.5) 3) 50.6 (12.3) Female, n (%) 1) 41.0 (82.0) 2) 81.0 (78.6) 3) 81.0 (80.2) Mean RA duration, yrs (SD) 1) 5.6 (4.4) 2) 7.1 (5.2) 3) 6.5 (5.1) Mean DAS (SD) 1) 5.0 (1.1) 2) 5.1 (1.1) 3) 5.2 (1.2) Median HAQ (SD) 1) 1.6 (0.5) 2) 1.7 (0.6) 3) 1.6 (0.6)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Klareskog L *Lancet* 2004[83] TEMPO Good See also Van der Heijde D *Arthritis Rheum* 2006[86] and Van der Heijde D *Arthritis Rheum* 2007[290]	Wyeth research	Double-blind Parallel group Phase III RCT 3-year study; results from 52 weeks	Australia, Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Israel, Italy, Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, United Kingdom	1) MTX (n=228) 2) ETN mono (n=223) 3) ETN+MTX (n=231) 25 mg ETN administered subcutaneously twice a week; oral MTX (7.5 mg escalated to 20 mg) once a week; 5 mg folic acid supplement twice a week	Age ≥18; disease duration 6 mos to 20 yrs; active, adult-onset RA; ≥10 swollen and ≥12 painful joints and at least one of the following: ESR ≥28 mm/h, plasma CRP ≥20 mg/L, or morning stiffness for ≥45 min; less than satisfactory response at the discretion of the investigator to at least one DMARD other than MTX; Exclusion criteria: previous TNFi; immunosuppressive drugs within 6 mos of screening; biologic within 3 mos of screening presence of relevant comorbidity, including active infection	Mean age, yrs (SD) 1) 53.0 (12.8) 2) 53.2 (13.8) 3) 52.5 (12.4) Female, n (%) 1) 180 (79) 2) 171 (77) 3) 171 (74) Mean RA duration, yrs (SD) 1) 6.8 (5.5) 2) 6.3 (5.1) 3) 6.8 (5.4) Mean DAS (SD) 1) 5.5 (1.2) 2) 5.7 (1.1) 3) 5.5 (1.2) Median mTSS (SD) 1) 26.8 (5.5-70.5) 2) 21.8 (7.5-58.6) 3) 21.8 (5.5-61.6) Mean number of previous DMARDs: 2.3

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Machado DA *Journal of clinical rheumatology: practical reports on rheumatic & musculoskeletal diseases* 2014[158] LARA Good See also Machado DA *The open rheumatology journal* 2016[105]	Funded by Wyeth, which was acquired by Pfizer in October 2009. Medical writing support was provided by Donna McGuire, CMPP, of Engage Scientific Solutions and was funded by Pfizer	24-week open-label RCT **Primary and secondary outcomes based on mITT (LOCF)**	5 countries in Latin America (Argentina, Chile, Colombia, Mexico, and Panama)	N=429 1) ETN+MTX (n=284) 2) cDMARD (hydroxychloroquine, or sulfasalazine) + MTX (n=145)	Age ≥18 years; active disease (≥8 tender/≥6 swollen joints and ESR ≥28 mm/h) despite treatment with MTX (7.5 to 25 mg/week) for at least 3 months	Mean age, yrs (SD) 1) 48.4 (12.0) 2) 48.6 (11.3) Female, n (%) 1) 248, 88.3 2) 128, 90.1 Mean RA duration, yrs (SD) 1) 7.9 (7.0) 2) 9.0 (7.5) Mean HAQ-DI (SD) 1) 1.6 (0.7) 2) 1.6 (0.7) Mean DAS28 (SD) 1) 6.6 (0.7) 2) 6.7 (0.7) Mean mTSS (SD) NR

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Morgan CLI Rheumatology (Oxford). 2014 [291] BSR Biologics Register Fair	Pfizer	Maximum 10.1 year follow up, open-label study	England	1) cDMARDs (n=2864) 2) ETN (n=3529)	Inclusion: Active RA (DAS28>5.1), treated with an anti-TNF agent, physician diagnosis of RA, minimum of one consultant follow-up after baseline registration Exclusion: Patients registered >90 after treatment initiation	Mean age, yrs (SD) 1) 59.8 (12.4) 2) 55.3 (12.1) Female, n (%) 1) 2135 (74.5) 2) 2727 (77.3) Mean RA duration, yrs (SD) 1) 9.6 (10.4) 2) 13.5 (9.4) Mean DAS28 (SD) 1) 5.6 (0.9) 2) 6.6 (1.0) Mean HAQ (SD) 1) 1.6 (0.7) 2) 2.1 (0.6)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
O'Dell JR *The New England journal of medicine* 2013[77] Good	Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development, and others Amgen donated the placebo etanercept but had no role in the design of the study, the collection or analysis of the data, the writing of the manuscript, or the decision to submit the manuscript for publication.	RCT Double-blind 48 weeks Patients who did not have an improvement at 24 weeks per a prespecified threshold were switched to the other treatment group in a blinded fashion	16 Veteran Affairs hospitals, 12 Rheumatoid Arthritis Investigational Network sites, and 8 Canadian medical centers	N=353 1) cDMARD triple combination therapy (methotrexate+ sulfasalazine+ hydroxychloroquine) (n=178) 2) ETN + MTX (n=175) Participants who were assigned to the triple-therapy group received sulfasalazine at a dose of 1 g daily for the first 6 weeks, with the dose increased thereafter to 2g daily, and also received hydroxychloroquine, at a dose of 400 mg daily, and an injection of placebo ETN weekly.	Age ≥18 years; active disease despite treatment with MTX (stable doses of 15 to 25 mg weekly for at least 12 weeks); DAS28 ≥4.4	Mean age, yrs (SD) 1) 57.8 (13.0) 2) 56.0 (13.2) Female, n (%) 1) 77, 43.3 2) 85, 48.6 Mean RA duration, yrs (SD) 1) 5.5 (9.3) 2) 4.9 (8.0) Mean HAQ-DI (SD) 1) 1.4 (0.8) 2) 1.5 (0.8) Mean DAS28 (SD) 1) 5.8 (0.9) 2) 5.9 (0.9) Mean mTSS (SD) 1) 20.4 2) 16.3

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Takeuchi T *Modern rheumatology* 2013[81] Takeuchi Mod Rheum 2013 Good	Pfizer	RCT multicenter double-blind Phase III 52 weeks	40 sites in Japan	1) ETN 25mg (n=182) 2) MTX (n=176) 3) ETN 10mg (n=192) Monotherapy ETN 25mg BIW administered subcutaneously, or oral MTX (up to 8.0 mg) once weekly (QW) *ETN 10mg excluded from table*	Japanese ancestry; age 20-75 yrs; living in Japan; diagnosis of RA with ≥6 swollen joints, ≥6 tender/painful joints, and either ESR ≥28 mm/h or CRP ≥2.0 mg/dL or morning stiffness duration ≥45 mins; diagnosis ≤10 yrs from screening; unsatisfactory response to at least one DMARD; no prior anti-TNF	Mean age, yrs (SD) 1) 51.8 (11.1) 2) 50.4 (11.9) Female, n (%) 1) 145 (79.7) 2) 140 (79.6) Mean RA duration, yrs (SD) 1) 3.0 (2.6) 2) 3.0 (2.7) Mean HAQ-DI (SD) 1) 1.1 (0.7) 2) 1.0 (0.7) DAS28-ESR (SD) 1) 5.8 (1.0) 2) 5.8 (1.1) Mean mTSS (SD) 1) 41.98 (41.51) 2) 43.01 (46.78)

Table F41. Etanercept versus conventional DMARDs: Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Combe B *Ann Rheum Dis* 2006[82] ETN309	1) Sulfasalazine (n=50) 2) ETN mono (n=103) 3) ETN+sulfasalazine (n=101)	Week 24 ACR20, % 1) 28.0 2) 73.8 3) 74.0 p<0.01 ACR50, % 1) 14.0 2) 46.6 3) 52.0 p<0.01 ACR70, % 1) 2.0 2) 21.4 3) 25.0 p<0.01 Response rates were not significantly different between the 2 grps receiving ETN	Week 24 % improvement in DAS 1) 19.6 2) 48.2 3) 49.7 p<0.01	NR	Improvements in physical function, as measured by mean HAQ scores, started at week 2 and were sustained to week 24 (p<0.01) Week 24 Mean HAQ 1) 1.5 2) 1.1 3) 1.0	The improvement in CRP and ESR, in both the groups receiving ETN, was significantly greater than that in the group receiving sulfasalazine (from week 2 onwards; p<0.01)

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Combe B *Ann Rheum Dis* 2009[183] ETN309	1) Sulfasalazine (n=50) 2) ETN mono (n=103) 3) ETN+sulfasalazine (n=101)	Week 104 (approximated from chart) ACR20, % 1) ~35 2) ~68 3) ~78 ACR50, % 1) ~10 2) ~46 3) ~59 ACR70, % 1) ~3 2) ~25 3) ~28	Significantly lower mean DAS values were observed during wks 68–104 for group (3) vs. (2) ($p<0.05$) Week 104 DAS 1) 4.5 2) 2.8 3) 2.5 DAS<2.4, % 1) 4.0 2) 45.6 3) 57.0	NR	Significantly more patients in groups (2) and (3) attained the threshold of HAQ improvement ≥0.22 by week 104 vs. those receiving sulfasalazine ($p<0.01$ compared with sulfasalazine alone)	

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Klareskog L *Lancet* 2004[83] TEMPO	1) MTX (n=228) 2) ETN mono (n=223) 3) ETN+MTX (n=231)	Week 52 ACR20, % (95% CI) 1) 75 (69-80) 2) 76 (70-81) 3) 85 (80-89) p=0.0091 ETN+MTX vs. MTX p=0.0151 ETN+MTX vs. ETN mono ACR50, % (95% CI) 1) 43 (36-49) 2) 48 (42-55) 3) 69 (63-75) p<0·0001 for ETN+MTX vs. MTX and vs. ETN mono ACR70, % (95% CI) 1) 19 (14-25) 2) 24 (19-30) 3) 43 (36-50) p<0·0001 for ETN+MTX vs. MTX and vs. ETN mono	Week 52 Mean DAS, (95% CI) 1) 3.0 (2.8-3.2) 3) 3.0 (2.8-3.1) 3) 2.3 (2.1-2.5) p<0·0001 for ETN+MTX vs. MTX and vs. ETN mono Remission (DAS<1.6), % (95% CI) 1) 13 (9-18) 2) 16 (11-21) 3) 35 (29-41) p<0·0001 for ETN+MTX vs. MTX and vs. ETN mono p=NS ETN mono vs. MTX	Week 52 Mean change from baseline mTSS (95% CI) 1) 2.80 (1.08 to 4.51) 2) 0.52 (-0.10 to 1.15) 3) -0.54 (-1.0 to -0.07) p=0·0469 ETN mono *vs* MTX p<0·0001 ETN+MTX *vs* MTX p=0·0006 ETN+MTX *vs* ETN mono % with no progression (mTSS ≤0.5), (95% CI) 1) 57 (50-64) 2) 68 61-74) 3) 80 (74-85) p<0·0001 for ETN+MTX vs. MTX; p=0.0043 ETN+MTX vs. ETN mono; p=0.00213 ETN mono vs. MTX	Week 52 mean change from baseline HAQ-DI, (95% CI) 1) 1.1 (1.0-1.1) 2) 1.0 (1.0-1.1) 3) 0.8 (0.7-0.9) p<0·0001 for ETN+MTX vs. MTX and vs. ETN mono p=NS ETN mono vs. MTX	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Van der Heijde D *Arthritis Rheum* 2006[86] TEMPO	1) MTX (n=228) 2) ETN mono (n=223) 3) ETN+MTX (n=231)	Week 100 ACR20, % 1) 71 2) 75 3) 86 p<0.01 ETN+MTX vs. ETN mono or MTX ACR50, % 1) 42 2) 54 3) 71 p<0.01 ETN+MTX vs. ETN mono or MTX ACR70, % 1) 21 2) 27 3) 49 p<0.01 ETN+MTX vs. ETN mono or MTX	Week 100 Mean DAS 1) 3.0 2) 2.9 3) 2.2 p<0.01 ETN+MTX vs. ETN mono or MTX Remission (DAS<1.6), % 1) 15.8 2) 23.3 3) 40.7 p<0.01 ETN+MTX vs. ETN mono or MTX	Year 2 Mean change from baseline mTSS (95% CI) 1) 3.34 (1.18-5.50) 2) 1.10 (0.13-2.07) 3) -0.56 (-1.05 to -0.06) p<0.05 ETN mono vs. MTX p<0.05 ETN+MTX vs. MTX or ETN mono % with no progression (mTSS ≤0.5) 1) 60 2) 68 3) 78 p<0.05	Year 2 Mean HAQ (% improvement from baseline) 1) 1.1 (35.8) 2) 1.0 (38.8) 3) 0.7 (55.8) p<0.01 ETN+MTX vs. MTX; p<0.05 ETN+MTX vs. ETN	Year 2 Mean CRP, mg/L (% improvement from baseline) 1) 14.2 (49.2) 2) 14.6 (54.2) 3) 7.7 (75.3)

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Van der Heijde D *Arthritis Rheum* 2007[290] TEMPO	1) MTX (n=228) 2) ETN mono (n=223) 3) ETN+MTX (n=231)	Year 3 ACR20, % 1) 70.2 2) 70.9 3) 85.3 p<0.01 ETN+MTX vs. ETN mono or MTX ACR50, % 1) 43.9 2) 45.7 3) 67.1 p<0.01 ETN+MTX vs. ETN mono or MTX ACR70, % 1) 21.1 2) 26.0 3) 47.2 p<0.01 ETN+MTX vs. ETN mono or MTX	Year 3 Remission (DAS<1.6), % 1) 17.5 2) 21.5 3) 40.7 Year 1/2/3 Remission (DAS28<2.6), % 1) 17.1/18.9/18.9 2) 17.5/22.4/20.6 3) 38.1/42.4/40.3 ETN+MTX vs. MTX p<0.01 for all measures ETN+MTX vs. ETN mono p<0.01 for all measures	Year 3 Mean change from baseline mTSS (95% CI) 1) 5.95 (2.96, 8.94) 2) 1.61 (0.41, 2.81) 3) -0.14 (-1.07, 0.78) p<0.01	Year 3 % improvement from baseline HAQ 1) 33.3 2) 37.0 3) 55.0 p<0.01 ETN+MTX vs. ETN mono or MTX % with no disability (HAQ=0) 1) 32.9 2) 35.4 3) 48.1 p<0.01 ETN+MTX vs. ETN mono or MTX	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Machado DA *Journal of clinical rheumatology* 2014[158] LARA	1) ETN+MTX (n=284) 2) cDMARD (hydroxychloroquine, or sulfasalazine) + MTX (n=145)	@ week 24 ACR20 (%) 1) 62.0 2) 23.2 ACR50 (%) 1) 83.2 2) 50.0 ACR70 (%) 1) 34.8 2) 11.3 p<0.0001 all outcomes	@ week 24 DAS28 LDA (%) 1) 47.0 2) 12.0 DAS28-ESR remission (%) 1) 25.1 2) 3.5 DAS28 (mean score) 1) -3.2 2) -1.7 p<0.0001 all outcomes	mTSS (mean change) 1) 0.4 2) 1.4 mTSS ≤0 (%) 1) 75.3 2) 68.1 p=NS both outcomes	HAQ-DI score (mean change) 1) -0.9 2) -0.1 p<0.0001	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Machado DA *The open rheumatology journal* 2016[105] LARA	1) ETN+MTX (n=260) 2) cDMARD (hydroxychloroquine, or sulfasalazine) + MTX (n=126)	@ week 128 ACR20 (%) 1) 89.2 2) 89.2 ACR50 (%) 1) 70.5 2) 65.0 ACR70 (%) 1) 49.0 2) 40.0 EULAR moderate or good response (%) 1) 91.8 2) 64.8 P<0.0001 EULAR good response (%) 1) 47.0 2) 12.0 P<0.0001	@ week 128 DAS28<3.2 LDA (%) 1) 57.7 2) 55.0 DAS28<2.6 remission (%) 1) 39.8 2) 33.3 DAS28 (mean score) 1) -4.8 2) -4.8	NR	HAQ-DI score (% normal score) 1) 51.5 2) 40.8 HAQ-DI score (mean change) 1) -0.8 2) -0.9	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
O'Dell JR *The New England journal of medicine* 2013[77] RACAT	1) cDMARD triple combination therapy (MTX+ sulfasalazine+ hydroxychloroquine) (n=178) 2) ETN+MTX (n=175)	@ week 24 ACR20 (%) 1) 58 2) 56 P=NS ACR50 (%) 1) 27 2) 36 P=NS ACR70 (%) 1) 5 2) 17 P=0.001	@ week 24 DAS28≤3.2 (%) 1) 24.8 2) 34.8 P=0.05 DAS28≤2.6 (%) 1) 12.7 2) 21.7 P=0.03 DAS (mean change) 1) -1.79 2) -2.06 P=NS CDAI (mean change) 1) -17.8 2) -18.72 P=NS	mTSS (mean change) 1) 0.42 2) 0.003 P=NS	HAQ II score (mean change) 1) -0.44 2) -0.51 P=NS	Erythrocyte Sedimentation Rate (0-200 mm/h) (mean change) 1) -7.01 2) -10.79 P=NS

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Takeuchi T *Modern rheumatology* 2013[81] Takeuchi Mod Rheum 2013	1) ETN 25mg (n=182) 2) MTX (n=176)	Week 52, n (%) ACR20 1) 143 (78.6) 2) 110 (62.5) p<0.001 ACR50 1) 113 (62.1) 2) 65 (36.9) p<0.0001 ACR70 1) 66 (36.3) 2) 28 (15.9) p<0.0001	Week 52 Mean score DAS28-ESR (% improvement from baseline) 1) 3.3 (42.9) 2) 4.1 (29.1) p<0.0001 Remission DAS28-ESR <2.6, n (%) 1) 62 (34.1) 2) 34 (19.3) p<0.01	Week 52 Change from baseline mTSS-van der Heijde (SE) 1) 3.33 (0.73) 2) 9.82 (1.16) p<0.0001 mTSS change ≤0, n (%) 1) 79 (43.6) 2) 39 (22.8) p<0.001 Week 24 change from baseline mTSS-van der Heijde (SE) 1) 1.74 (0.45) 2) 5.11 (0.58) p<0.0001	Week 52 Mean score HAQ-DI (% improvement from baseline) 1) 0.5 (58.1) 2) 0.7 (29.2) p<0.0001	Week 52 Mean score CRP, mg/L (% improvement from baseline) 1) 7.0 (83.3) 2) 15.9 (50.0) p<0.0001 ESR, mm/h (% improvement from baseline) 1) 24.8 (38.9) 2) 32.3 (11.0) p<0.0001

Table F42. Etanercept versus conventional DMARDs: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Combe B *Ann Rheum Dis* 2006[82] ETN309	1) Sulfasalazine (n=50) 2) ETN mono (n=103) 3) ETN+sulfasalazine (n=101)	2 patients treated with ETN mono were diagnosed with a malignancy: 1 actinic squamous cell carcinoma and 1 myelodysplastic syndrome	Total infections, n (%) 1) 13 (26.0) 2) 47 (45.6) 3) 31 (30.7) 3 serious infections (sinusitis, pharyngitis and septic arthritis) occurred in 2 patients receiving ETN Pharyngitis or laryngitis, n (%) 1) 3 (6.0) 2) 12 (11.7) 3) 5 (5.0) Upper respiratory tract infection, n (%) 1) 5 (10.0) 2) 10 (9.7) 3) 11 (10.9)	Injection site reaction, n (%) 1) 1 (2.0) 2) 33 (32.0) 3) 16 (15.8) Headache, n (%) 1) 4 (8.0) 2) 5 (4.9) 3) 15 (14.9) Nausea, n (%) 1) 3 (6.0) 2) 3 (2.9) 3) 12 (11.9) Asthenia, n (%) 1) 1 (2.0) 2) 3 (2.9) 3) 10 (9.9)	Discontinuation due to AEs, n 1) 1 2) 1 3) 1 Serious, non-infectious AEs, n (%) 1) 1 (2.0) 2) 3 (2.9) 3) 5 (5.0) Deaths: 0

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Klareskog L *Lancet* 2004[83] TEMPO	1) MTX (n=228) 2) ETN mono (n=223) 3) ETN+MTX (n=231)	Malignant diseases, n 1) 1 (basal-cell carcinoma of skin) 2) 4 (1 basal-cell carcinoma of skin, 1 breast cancer, 1 rectal cancer, 1 melanoma) 3) 1 (basal-cell carcinoma of skin) National Cancer Institute grade 3 or 4 abnormalities of hepatic enzymes, n 1) 5 2) 2 3) 2	Any infection, n (%) 1) 147 (64) 2) 131 (59) 3) 154 (67) Serious infections, n (%) 1) 10 (4) 2) 10 (4) 3) 10 (4) No cases of tuberculosis or opportunistic infections	Injection site reaction, n (%) 1) 4 (2) 2) 46 (21) 3) 23 (10) Nausea, n (%) 1) 73 (32) 2) 22 (10) 3) 55 (24) Vomiting n (%) 1) 26 (11) 2) 7 (3) 3) 12 (5)	Discontinuation due to AEs, n 1) 32 2) 25 3) 24 Serious AEs other than infection, n (%) 1) 27 (12) 2) 25 (11) 3) 19 (8) Deaths, n 1) 1 (pulmonary embolism/suspected sepsis) 2) 1 (heart failure/suspected sepsis) 3) 1 (stroke/pneumonia)
Morgan CLI Rheumatology (Oxford). 2014 [291] BSR Biologics Register	1) cDMARDs (n=2864) 2) ETN (n=3529)	Cancer, n (%) 1) 254 (23.9) 2) 241 (14.7)	Serious infections, n (%) 1) 375 (36.2) 2) 538 (35.1) Tuberculosis, n 1) 1 2) 5		Other serious AEs, n (%) 1) 310 (29.6) 2) 327 (20.3) Deaths, n 1) 223 2) 203

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Van der Heijde D *Arthritis Rheum* 2006[86] TEMPO	1) MTX (n=228) 2) ETN mono (n=223) 3) ETN+MTX (n=231)	Year 2 Malignancies 1) 2 2) 5 3) 5 Malignancies that occurred between Year 1 & 2 1) 1 (breast Cancer) 2) 1 (basal cell skin carcinoma) 3) 3 (2 gastrointestinal cancers, 1 lung cancer) risk of malignancies was comparable with that in the general US population	Year 2 Any infection, n (%) 1) 172 (75) 2) 159 (71) 3) 175 (76) Serious infection, n (%) 1) 15 (7) 2) 14 (6) 13 (6) no cases of tuberculosis and 1 case of bronchopulmonary aspergillosis (ETN+MTX group)	Year 2 Nausea, n (%) 1) 90 (39) 2) 28 (13) 3) 66 (29) Injection-site reaction, n (%) 1) 5 (2) 2) 46 (21) 3) 25 (11) Vomiting, n (%) 1) 32 (14) 2) 10 (4) 3) 20 (9) Back pain, n (%) 1) 28 (12) 2) 38 (17) 3) 36 (16) Hypertension, n (%) 1) 12 (5) 2) 29 (13) 3) 21 (9)	Year 2 Discontinuation due to AEs (between yrs 1 & 2), n 1) 15 2) 9 3) 13 No significant differences in incidence of serious AEs No additional deaths reported in Year 2

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Van der Heijde D *Arthritis Rheum* 2007[290] TEMPO	1) MTX (n=228) 2) ETN mono (n=223) 3) ETN+MTX (n=231)	NR	Serious infections, n (%) 1) 19 (8.3) 2) 15 (6.7) 3) 17 (7.4) Pneumonia, n (%) 1) 4 (1.8) 2) 4 (1.8) 3) 6 (2.6) reactivation of tuberculosis developed in no patients with history of TB; TB was diagnosed in 1 patient in grp 3)	NR	Noninfectious serious AEs, % 1) 18.9 2) 22.9 3) 23.4 During year 3, 1 patient receiving ETN mono died from acute pulmonary edema, and 1 patient receiving ETN+MTX died from cardiac arrest

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Machado DA *Journal of clinical rheumatology* 2014[158] LARA	1) ETN+MTX (n=284) 2) cDMARD (hydroxychloroquine, or sulfasalazine) + MTX (n=145)	NR	Treatment-emergent infections ≥1 (% of patients) 1) 38.1 2) 21.8 p=NS	Any TEAEs (% of patients) 1) 68.7 2) 68.3 p=NS Most common AE was bronchitis (% of patients) 1) 5.7 2) 2.1 p=NS	SAEs (1% of patients) 1) 3.6 2) 1.4 Discontinuation rate NR
Machado DA *The open rheumatology journal.* 2016[105] LARA	1) ETN+MTX (n=260) 2) cDMARD (hydroxychloroquine, or sulfasalazine) + MTX (n=126)	*Only reported for patients exposed to etanercept*	*Only reported for patients exposed to etanercept*	*Only reported for patients exposed to etanercept*	*Only reported for patients exposed to etanercept*

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
O'Dell JR *The New England journal of medicine* 2013[77] RACAT	1) cDMARD triple combination therapy (methotrexate+ sulfasalazine+ hydroxychloroquine) (n=178) 2) ETN+MTX (n=175)	NR	AEs in ≥5% of patients Infections and infestations (% of patients) 1) 25.2 2) 37.4 p=0.006	Any AEs (% of patients) 1) 76.6 2) 75.3 Gastrointestinal disorders occurred more frequently with triple therapy (5 vs. 4), whereas infections and skin and subcutaneous disorders occurred more frequently with ETN-MTX therapy (12 vs. 4)	SAEs in ≥1% of patients Serious infections and infestations (% of patients) 1) 1.8 2) 4.1 Discontinuation due to any AE (% of patients) 1) 5.4 2) 2.3

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Takeuchi T *Modern rheumatology* 2013[81] Takeuchi Mod Rheum 2013	1) ETN 25mg (n=182) 2) MTX (n=176)	52 week Malignancy, n (%) 1) 2 (1.1) (2 breast cancer) 2) 2 (1.1) (1 breast cancer, 1 prostate cancer)	52 week Serious infections, n (%) 1) 0 2) 1 (0.6) (appendicitis) most common treatment emergent infections were nasopharyngitis, upper respiratory tract infection, and pharyngitis	52 week Most common TEAEs were increased liver enzymes, rash, eczema, and constipation Increased alanine aminotransferase, n (%) 1) 10 (5.5) 2) 22 (12.5) Increased aspartate aminotransferase, n (%) 1) 10 (5.5) 2) 22 (12.5)	52 week Discontinuation due to AEs, n (%) 1) 19 (10.4) 2) 9 (5.1) Serious AEs, n (%)* 1) 11 (6.0) 2) 10 (5.7) *excludes serious infections Deaths: 0

Table F43. Etanercept versus conventional DMARDs: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Combe B *Ann Rheum Dis* 2006 [82] ETN309	1) Sulfasalazine (n=50) 2) ETN mono (n=103) 3) ETN+sulfasalazine (n=101)	At all visits, the improvements in both the groups receiving etanercept were not different from each other EuroQOL was significantly improved in groups 2) and 3) compared with group 1) (p<0.01)	At all visits, the improvements in both the groups receiving etanercept were not different from each other Pain VAS was significantly improved in groups 2) and 3) compared with group 1) (p<0.01)	NR
Van der Heijde D *Arthritis Rheum* 2006[86] TEMPO	1) MTX (n=228) 2) ETN mono (n=223) 3) ETN+MTX (n=231)	NR	Year 2 Pain, 0–100 VAS (% improvement from baseline) 1) 36.4 (43.0) 2) 33.9 (47.1) 3) 24.8 (61.4) p<0.01 ETN+MTX vs. MTX; p<0.05 ETN+MTX vs. ETN	Year 2 Patient's global assessment, 0-10 scale (% improvement from baseline) 1) 4.0 (40.9) 2) 3.8 (44.5) 3) 2.8 (59.8) p<0.01 ETN+MTX vs. MTX; p<0.05 ETN+MTX vs. ETN

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Machado DA *Journal of clinical rheumatology* 2014[158] LARA	1) ETN + MTX (n=284) 2) cDMARD (hydroxychloroquine, or sulfasalazine) + Methotrexate (n=145)	week 24 (adjusted mean changes) SF-36 MCS 1) 7.3 2) 3.3 p=0.0002 SF-36 PCS 1) 12.4 2) 7.4 p<0.0001 SF-36 Vitality 1) 3.8 2) 2.4 p=0.0003	week 24 (adjusted mean changes) VAS, pain 1) -40.9 2) -24.0 p<0.0001	week 24 (adjusted mean changes) VAS, fatigue 1) -29.6 2) -17.3 p<0.0001 VAS, general health 1) -33.7 2) -19.3 p<0.0001 Improvements in subject satisfaction, physician satisfaction, and subject's willingness to retake medications were in favor of ETN + MTX (p<0.0001 for all)

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Machado DA *The open rheumatology journal.* 2016[105] LARA	1) ETN+MTX (n=260) 2) cDMARD (hydroxychloroquine, or sulfasalazine) + MTX (n=126)	@ week 128 SF-36 MCS 1) +8 2) +8 SF-36 PCS 1) +11 2) +11 SF-36 Vitality 1) +4 2) +4	@ week 128 VAS, pain 1) -42.0 2) -40.6	@ week 128 VAS, fatigue 1) -30.5 2) -30.4 VAS, general health 1) -4.3 2) -3.2 PGA, mean change 1) -5.2 2) -5.2 Subject global assessment, mean change 1) -4.3 2) -3.8

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
O'Dell JR *The New England journal of medicine* 2013[77] RACAT	1) cDMARD triple combination therapy (MTX+sulfasalazine+ hydroxychloroquine) (n=178) 2) ETN+MTX (n=175)	NR	@ week 24 Pain, VAS (mean change) 1) -1.00 2) -2.32 p=NS *(data in supplement)*	Switching (% of patients): 1) 27.0 2) 26.7 Outcomes for those who switched vs. those who continued treatment were not different between groups PGA, mean change 1) -24.44 2) -25.71 Patient Global Assessment, mean change 1) -1.92 2) 2.45

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Takeuchi T *Modern rheumatology* 2013[81] Takeuchi Mod Rheum 2013	1) ETN 25mg (n=182) 2) MTX (n=176)		Week 52 mean score (% improvement from baseline) Pain, VAS (0-100 mm) 1) 24.3 (51.4) 2) 34.9 (28.7) p<0.0001	Week 52 mean score (% improvement from baseline) Patient general health, VAS (0-100 mm) 1) 24.6 (46.5) 2) 35.0 (31.4) p<0.0001

Table F44. Etanercept versus conventional DMARDs: Non-healthcare Outcomes

Author & Year of Publication (Trial Name)	Interventions	Requirements for surgical intervention	Hospitalization, Rehabilitation, Assisted living	Productivity Loss	Caregiver Burden	Other outcomes
Machado DA *Journal of clinical rheumatology* 2014[158] LARA	1) ETN+MTX (n=260) 2) cDMARD (hydroxychloroquine, or sulfasalazine) + MTX (n=126)	NR	@ week 24 ED Visits for RA in the past 6 months (adjusted mean change with ANCOVA) 1) -0.5 2) -0.4 p=0.0039	@ week 24 Overall work impairment due to RA in the past 7 days (adjusted mean change with ANCOVA) 1) -33.4 2) -21.5 p=0.0188	NR	NR
Machado DA *The open rheumatology journal.* 2016[105] LARA	1) ETN+MTX (n=260) 2) cDMARD (hydroxychloroquine, or sulfasalazine) + MTX (n=126)	NR	@ week 128 ED Visits for RA in the past 6 months 1) 0.9 2) 0.9	@ wk 128 WPAI:RA Work time missed due to RA in the past 7 days (%) 1) 8.6 2) 2.3 Overall work impairment due to RA in the past 7 days (%) 1) 26.0; 2) 25.4 Currently Employed (%) 1) 33.6; 2) 25.8	@ week 128 Required caregiver assistance in past 6 months (%) 1) 11.9 2) 18.2	@ week 128 Rheumatologist visits in last 6 months 1) 12.9 2) 13.8

Table F45. Golimumab versus conventional DMARDs: Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Tanaka Y *Annals of the rheumatic diseases* 2012[160] GO-FORTH Good See also Tanaka Y *Modern Rheumatology* 2016[292]	Janssen Pharmaceutical K.K. and Mitsubishi Tanabe Pharma Corporation	RCT multicenter double-blind Phase II/III 24-week data from a 3-yr study	89 investigational sites in Japan	1) PBO+MTX (n=88) 2) 50mg GOLsc+MTX (n=86) 3) 100mg GOLsc+MTX (n=87) PBO injection + oral MTX (Group 1) or sc GOL 50 mg injection + oral MTX (Group 2) at wk 0 and every 4 wks to wk 24 At wk 16, <20% improvement in TJC and SJC entered DB early escape: PBO added GOL 50mg & GOL 50mg increased to GOL 100mg; at wk 24 all PBO patients received GOL 50mg;	Age 20-75 years; RA diagnosis for ≥3 months; received ≥6mg/wk oral MTX for ≥3 mos before study agent initiation; stable MTX dose (6-8 mg/wk) for ≥4 weeks before start of study; active RA (≥4/66 SJC and ≥4/68 TJC at screening/baseline); at least 2 of the following: 1) CRP>1.5 mg/dl or ESR>28 mm/hr; 2) morning stiffness lasting ≥30 min; 3) radiographic evidence of erosion; 4) anti-CCP or RF-positive; no prior anti-TNFs *GOLsc 100mg +MTX excluded from table*	Mean age, yrs (SD) 1) 51.1 (11.6) 2) 50.4 (9.9) Female, n (%) 1) 73 (83.0) 2) 73 (84.9) Mean RA duration, yrs (SD) 1) 8.7 (8.2) 2) 8.8 (8.8) Mean HAQ-DI (SD) 1) 1.0 (0.68) 2) 1.0 (0.61) Mean DAS28-ESR (SD) 1) 5.6 (0.99) 2) 5.5 (1.18) Mean mTSS (SD) 1) 54.2 (62.9) 2) 58.0 (62.4)

<table>
<tr><th>Author & Year of Publication (Trial Name) Quality rating</th><th>Study sponsor</th><th>Study Design and Duration of Follow-up</th><th>Geographic location of study</th><th>Interventions (n) & Dosing Schedule</th><th>Inclusion and Exclusion Criteria</th><th>Baseline patient Characteristics</th></tr>
<tr>
<td>Keystone E Annals of the rheumatic diseases 2009[161]

GO-FORWARD

Good

See also Keystone E Annals of the rheumatic diseases 2010[87], Keystone EC The Journal of rheumatology 2013[106], Emery P Arthritis and rheumatism 2011[198], Genovese MC The Journal of Rheumatology 2012[222]</td>
<td>Centocor, Inc.</td>
<td>RCT, double-blind, placebo-controlled phase III

52 weeks</td>
<td>52 centers in 11 countries: USA, Argentina, Australia, Chile, Germany, Hungary, Korea, Mexico, New Zealand, Poland, Taiwan</td>
<td>1) PBO+MTX (n=133)
2) 100mg GOL+PBO (n=133)
3) 50mg GOL+MTX (n=89)
4) 100mg GOL+MTX (n=89)

At wk 16, patients with <20% improvement in TJC and SJC entered a double-blind early escape phase i.e. group 1 →GOL 50 mg +MTX, group 2 →GOL 100 mg + MTX, group 3 →GOL 100 mg + MTX. At wk 24, PBO patients initiated blinded 50mg GOL inj. After 52 weeks, blind broken. GOL dose could increase to 100 mg and MTX doses adjusted</td>
<td>Inclusion: ≥18 years with active RA (i.e. ≥4 SJC & TJC or at least 2 of the following: 1) CRP≥1.5mg/dl or ESR>28mm/hr; 2) 30 min stiffness 3) bone erosion 4) RF positivity) despite stable MTX dose for ≥4 weeks

Exclusion: hypersensitivity to GOL or human immunoglobulin, previous use of TNFi, RTX, natalizumab, cytotoxic agents, or any DMARD except MTX; or iv/IM/IA corticosteroids within 4 weeks of study</td>
<td>Mean age, yrs
<table>
<tr><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>52</td><td>51</td><td>52</td><td>50</td></tr>
</table>
Female, %
<table>
<tr><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>82</td><td>78.9</td><td>80.9</td><td>80.9</td></tr>
</table>
Mean RA duration, yrs
<table>
<tr><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>6.5</td><td>5.9</td><td>4.5</td><td>6.7</td></tr>
</table>
Mean HAQ-DI
<table>
<tr><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>1.25</td><td>1.375</td><td>1.375</td><td>1.375</td></tr>
</table>
Mean DAS28-ESR
<table>
<tr><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>6.111</td><td>6.013</td><td>6.105</td><td>5.905</td></tr>
</table>
</td>
</tr>
</table>

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Weinblatt ME *Annals of the rheumatic diseases* 2013[184] GO-FURTHER Good See also Bingham CO *J Rheumatol* 2014 [216], Weinblatt ME *Annals of the rheumatic diseases* 2014[214], Bingham CO 3rd *Arthritis care & research* 2015[221]	Centocor, Inc. and Schering-Plough	RCT multicenter double-blind Phase III Average follow-up: 43.5 weeks	92 sites in 3 Latin American (n=119 patients), 5 European (n=355), 1 North American (n=61) and 4 Asia Pacific (n=57) countries	1) PBO+MTX (n=197) 2) GOLiv+MTX (n=395) Intravenous GOL 2 mg/kg or placebo infusions at wk 0, 4, and then q8w up to wk 100; all patients received stable regimen of 15-25 mg/wk MTX PBO patients who did not EE crossed over to GOL at wk24 and wk28 and then q8w. Patients assigned to GOL also received PBO infusions at wk16 and wk24 to maintain blinding	Adults with active RA despite ≥3 months MTX; ≥6 swollen joints and ≥6 tender joints at screening and baseline; CRP ≥1.0 mg/dL; positive for rheumatoid factor and/or anticyclic citrullinated protein at screening; anti-TNF naïve	Mean age, yrs (SD) 1) 51.4 (11.26) 2) 51.9 (12.55) Female, n (%) 1) 157 (79.7) 2) 326 (82.5) Mean RA duration, yrs (SD) 1) 7.0 (7.24) 2) 6.9 (7.00) Mean DAS28-CRP (SD) 1) 5.9 (0.93) 2) 6.0 (0.82) Mean HAQ-DI (SD) 1) 1.6 (0.62) 2) 1.6 (0.67) Mean mTSS [0-448] (SD) 1) 50.3 (59.85) 2) 47.6 (54.63)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Li Z *International Journal of Rheumatic Diseases* 2015[185] Good	Centocor, Inc.	Phase III RCT Double-blind Multicenter 52 weeks	15 sites in China China	1) PBO+MTX (n=132), sc injections w/ crossover to 50mg GOL+MTX at wk 24 2) 50mg GOL+MTX (n=132) every 4 wks Group 1 could enter blinded early escape to 50mg GOL at week 16 if they had <20% improvement from baseline in TJC & SJC. At week 24, all group 1 cross over to 50mg GOL	≥18 years with RA diagnosis for ≥6 months; Received stable MTX for ≥4 weeks before study: ≥4 SJC & TJC despite MTX use: CRP≥15mg/L or ESR ≥28mm/h: and anti CCP or RF positive.	Mean age, yrs (SD) 1) 46.7 (12.2) 2) 47.7 (11.5) Female, n (%) 1) 104 (78.8) 2) 110 (83.3) Mean RA duration, yrs (SD) 1) 8 (7.3) 2) 7.6 (7.1) Mean HAQ-DI (SD) 1) 1.2 (0.7) 2) 1.3 (0.7) Mean DAS28-CRP (0-10 score) (SD) 1) 5.5 (1.1) 2) 5.4 (1.1)

Table F46. Golimumab versus conventional DMARDs: Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Tanaka Y *Annals of the rheumatic diseases* 2012[160] GO-FORTH	1) PBO+MTX (n=88) 2) 50mg GOL+MTX (n=86)	Month 6, n (%) ACR20 1) 29 (33.0) 2) 61 (70.9) p<0.0001 ACR50 1) 13 (14.8) 2) 36 (41.9) p<0.0001 ACR70 1) 5 (5.7) 2) 23 (26.7) p<0.0002	Month 6 Change from baseline DAS28-ESR (SD) 1) -0.60 (1.38) 2) -2.05 (1.2) p<0.0001 DAS28-ESR remission, n (%) 1) 6 (6.8) 2) 30 (34.9) p<0.0001	Month 6 Change from baseline mTSS (Van der Heijde) (SD) 1) 2.51 (5.52) 2) 1.05 (3.71) p=0.0203 Change in mTSS<0, n (%) 1) 44 (50.0) 2) 51 (59.3) p=0.2179	Month 6 Change from baseline HAQ-DI (SD) 1) 0.03 (0.58) 2) 0.33 (0.42) p<0.0001	

<table>
<tr><th>Author & Year of Publication (Trial Name)</th><th>Interventions</th><th>Treatment Response</th><th>Disease Activity</th><th>Structural Damage</th><th>Function</th><th>Laboratory indices</th></tr>
<tr>
<td>Tanaka Y Modern Rheumatology 2016[292]

GO-FORTH</td>
<td>1) PBO+MTX→GOL 50mg+MTX (n=88)
2) 50 mg GOL+MTX (n=86)</td>
<td>ACR20, n (%)
<table>
<tr><td>wk</td><td>1)</td><td>2)</td></tr>
<tr><td>52</td><td>55 (67.9)</td><td>62 (86.10</td></tr>
<tr><td>104</td><td>61 (87.1)</td><td>63 (94.0)</td></tr>
<tr><td>156</td><td>33 (97.1)</td><td>32 (94.1)</td></tr>
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ACR50, n (%)
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<tr><td>wk</td><td>1)</td><td>2)</td></tr>
<tr><td>52</td><td>41 (50.6)</td><td>48 (66.7)</td></tr>
<tr><td>104</td><td>52 (74.3)</td><td>49 (73.1)</td></tr>
<tr><td>156</td><td>27 (79.4)</td><td>30 (88.2)</td></tr>
</table>
ACR70, n (%)
<table>
<tr><td>wk</td><td>1)</td><td>2)</td></tr>
<tr><td>52</td><td>25 (30.9)</td><td>26 (36.1)</td></tr>
<tr><td>104</td><td>31 (44.3)</td><td>33 (49.3)</td></tr>
<tr><td>156</td><td>21 (61.8)</td><td>23 (67.6)</td></tr>
</table>
</td>
<td>Change from baseline in DAS28-ESR (SD)
<table>
<tr><td>wk</td><td>1)</td><td>2)</td></tr>
<tr><td>52</td><td>-2.2 (1.3)</td><td>-2.5 (1.1)</td></tr>
<tr><td>104</td><td>-2.7 (1.2)</td><td>-2.7 (1.1)</td></tr>
<tr><td>156</td><td>-3.1 (1.1)</td><td>-3.0 (1.0)</td></tr>
</table>
DAS28-ESR remission (<2.6), n (%)
<table>
<tr><td>wk</td><td>1)</td><td>2)</td></tr>
<tr><td>52</td><td>28 (34.6)</td><td>32 (44.4)</td></tr>
<tr><td>104</td><td>31 (44.3)</td><td>33 (49.3)</td></tr>
<tr><td>156</td><td>19 (55.9)</td><td>21 (61.8)</td></tr>
</table>
</td>
<td>Comprehensive remission*, n (%)
<table>
<tr><td>wk</td><td>1)</td><td>2)</td></tr>
<tr><td>52</td><td>16 (19.8)</td><td>18 (25.0)</td></tr>
<tr><td>104</td><td>14 (20.0)</td><td>19 (28.4)</td></tr>
<tr><td>156</td><td>8 (23.5)</td><td>12 (35.3)</td></tr>
</table>
*DAS28-ESR<2.6, HAQ-DI<0.5, and change in van der Heijde-mTSS≤0

Change from baseline in mTSS (SD)
<table>
<tr><td>wk</td><td>1)</td><td>2)</td></tr>
<tr><td>52</td><td>2.0 (8.7)</td><td>1.6 (7.4)</td></tr>
<tr><td>104</td><td>1.5 (12.0)</td><td>2.3 (10.0)</td></tr>
<tr><td>156</td><td>-0.2 (8.1)</td><td>4.1 (13.4)</td></tr>
</table>
</td>
<td>Change from baseline in HAQ-DI (SD)
<table>
<tr><td>wk</td><td>1)</td><td>2)</td></tr>
<tr><td>52</td><td>0.37 (0.54)</td><td>0.45 (0.46)</td></tr>
<tr><td>104</td><td>0.46 (0.57)</td><td>0.54 (0.51)</td></tr>
<tr><td>156</td><td>0.54 (0.56)</td><td>0.75 (0.53)</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Keystone E *Annals of the rheumatic diseases* 2009[161] GO-FORWARD	1) PBO+MTX (n=133) 2) 100mg GOL+PBO (n=133) 3) 50mg GOL+MTX (n=89) 4) 100mg GOL+MTX (n=89)	Week 24 ACR20, % (p *vs. 1*) 1) 27.8 2) 35.3 (p=NS) 3) 59.6 (p<0.001) 4) 59.6 (p<0.001) ACR50, % (p *vs. 1*) 1) 13.5 2) 19.5 (p=NS) 3) 37.1 (p<0.001) 4) 32.6 (p<0.001) ACR70, % (p *vs. 1*) 1) 5.3 2) 11.3 (p=NS) 3) 20.2 (p<0.001) 4) 14.6 (p=0.017) ACR90, % (p *vs. 1*) 1) 0.8 2) 2.3 (p=NS) 3) 5.6 (p=0.028) 4) 2.2 (p=NS)	Week 24 remission DAS28-ESR, % 1) 6 2) 12 (p=NS) 3) 20.2 (p=0.001) 4) 22.5 (p<0.001)	NR See Emery P *Arthritis and rheumatism* 2011[198]	Week 24 mean improvement from baseline HAQ-DI 1) -0.13 (-0.38 to 0.13) 2) -0.13 (-0.63 to 0.25) 3) -0.38* (-0.75 to -0.13) 4) -0.5* (-0.75 to -0.13) *p<0.001	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Keystone E *Annals of the rheumatic diseases* 2010[87] GO-FORWARD Good (Note: patients in the PBO+MTX group who discontinued the study before receiving any GOL doses were not included in the Week 52 analysis)	1) PBO+MTX (n=133) 2) 100mg GOL+PBO (n=133) 3) 50mg GOL+MTX (n=89) 4) 100mg GOL+MTX (n=89)	Week 52 ACR20, % 1) 43.6 2) 45.1 3) 64 4) 58.4 Week 52 ACR50, % 1) 27.8 2) 28.6 3) 43.8 4) 44.9 Week 52 ACR70, % 1) 15 2) 17.3 3) 24.7 4) 33.7	Week 52 Sustained DAS28-CRP remission, % 1) 10.1 2) 14.4 3) 21.1 4) 25	NR See Emery P *Arthritis and rheumatism* 2011[198]	See Genovese, MC. *The Journal of rheumatology*. 2012[222]	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Keystone EC *The Journal of rheumatology* 2013[106] GO-FORWARD	1) PBO+MTX (n=133) 2) 100mg GOL+PBO (n=133) 3) 50mg GOL+MTX (n=89) 4) 100mg GOL+MTX (n=89)	Wk 104 ACR20, % 1) 78.1 2) 85.5 3) 82.5 4) 87 Wk 104 ACR50, % 1) 59.6 2) 78 3) 78 4) 77.1 Wk 104 ACR70, % 1) 64 2) 69.6 3) 81 4) 71.4	Week 104 DAS28-CRP <2.6, % 1) 71 2) 68.8 3) 70.6 4) 75.8 Week 104 DAS28-CRP median change from baseline 1) -2.1 2) -2.1 3) -2.5 4) -2.6	Week 104 mean SHS change from baseline 1) 1.15 2) 1.87 3) 0.51 4) 0.54 No radiographic progression at week 104, % 1) 50.9 2) 51.9 3) 67.5 4) 66.7	Week 104 median change from baseline HAQ-DI 1) 0.4 2) 0.5 3) 0.6 4) 0.4	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Emery P *Arthritis and rheumatism* 2011[198] GO-FORWARD & GO-BEFORE **GO-BEFORE patients were MTX naïve therefore not abstracted**	1) PBO+MTX (n=133) 2) 100mg GOL+PBO (n=133) 3) 50mg GOL+MTX (n=89) 4) 100mg GOL+MTX (n=89)	NR	NR	Week 24 mean change from baseline mTSS, (SD) 1) 0.55 (2.35) 2) 0.27 (1.6) 3) 0.6 (2.74) 4) 0.23 (1.34) Week 52 mean change from baseline mTSS, (SD) 1) 1.1 (4.68) 2) 0.89 (3.37) 3) 0.93 (4.86) 4) 0.15 (1.64) Week 24 Change in mTSS<0, n/n evaluated 1) 81/122 2) 85/ 124 3) 57/86 4) 58/84 All p=NS	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Genovese MC *The Journal of rheumatology* 2012[222] GO-FORWARD Good	1) PBO[185]+MTX (n=133) 2) 100mg GOL+PBO (n=133) 3) 50mg GOL+MTX (n=89) 4) 100mg GOL+MTX (n=89)	See Keystone E. *Annals of the rheumatic diseases.* 2010[87]	See Keystone E. *Annals of the rheumatic diseases.* 2010[87]	NR	@ 24 weeks HAQ-DI, improvement from baseline 1) 0.13 2) 0.24 3) 0.47 4) 0.45 3 & 4 vs. 1, p<0.001	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Weinblatt ME *Annals of the rheumatic diseases* 2013[184] GO-FURTHER	1) PBO+MTX (n=197) 2) GOLiv+MTX (n=395)	Week 14 ACR20, n (%) 1) 49 (24.9) 2) 231 (58.5) p<0.001 Week 24, % ACR20 (approx. from fig) 1) 65 2) 32 ACR50 1) 13.2 2) 34.9 p<0.001 ACR70 1) 4.1 2) 17.7 p<0.001 Week 52 ACR50, n (%) 1) 26 (13.2) 2) 138 (34.9) p<0.001	Week 24 mean change from baseline (SD) DAS28-CRP 1) -0.8 (1.43) 2) -2.0 (1.40) CDAI 1) 8.1 (17.63) 2) 19.2 (12.8) SDAI 1) 8.6 (18) 2) 22.1 (15.33) Week 24 remission, % CDAI 1) 2.5 2) 6.3 SDAI 1) 2 2) 7.3 P<0.01 for all	See Weinblatt ME *Annals of the rheumatic diseases* 2014[214]	Week 14 mean change from baseline in HAQ, n (%) 1) 0.19 (0.56) 2) 0.50 (0.58) p<0.001 Improvement in HAQ ≥0.25 units from baseline, n (%) Week 14 1) 85 (43.1) 2) 270 (68.4) p<0.001 Week 24 1) 89 (45.2) 2) 266 (67.3) p<0.001	

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Weinblatt ME *Annals of the rheumatic diseases* 2014[214] GO-FURTHER	1) PBO+MTX (n=197) 2) GOLiv+MTX (n=395)	Week 52, n (%) ACR20 1) 121 (61.4) 2) 260 (65.8) ACR50 1) 62 (31.5) 2) 153 (38.7) ACR70 1) 29 (14.7) 2) 72 (18.2)	Week 52 DAS28–CRP moderate/good response, n (%) 1) 149 (75.6) 2) 321 (81.3) Week 52 remission, % CDAI 1) 7.6 2) 8.4 SDAI 1) 8.1 2) 9.1	Week 24 mean change from baseline mTSS, SD 1) 1.09 (3.19) 2) 0.03 (1.90) p<0.001 Change in mTSS ≤0, % 1) 57.4 2) 70.6 p=0.001 Week 52 mean change from baseline mTSS, SD 1) 1.22 2) 0.13 p=0.001	Week 52 HAQ-DI improvement ≥0.25 units, n (%) 1) 123 (62.4) 2) 253 (64.1)	

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Bingham CO 3rd *Arthritis care & research* 2015[221] GO-FURTHER	1) PBO+MTX (n=197) 2) GOLiv+MTX (n=395)	Week 100, n (%) ACR20 1) 130 (66) 2) 273 (69.1) ACR50 1) 81 (41.1) 2) 178 (45.1) ACR70 1) 47 (23.9) 2) 92 (23.3)	Baseline to week 100 Mean DAS28-CRP (SD) 1) 2.2 (1.5) 2) 2.4 (1.5) Mean CDAI (SD) 1) 23.2 (15.2) 2) 23.6 (14.6) Week 100 DAS28–CRP moderate/good response, n (%) 1) 153 (77.7) 2) 332 (84.1)	Baseline to week 100 mean total SHS change (SD) 1) 2.1 (7.42) 2) 0.74 (6.32) P=0.0005 Baseline to week 100 total SHS <0, n (%) 1) 108 (54.8) 2) 244 (61.8)	Week 100 mean change from baseline in HAQ, n (%) 1) 0.47 (0.62) 2) 0.53 (0.66) Week 100 HAQ-DI improvement ≥0.25 units, n (%) 1) 131 (66.5) 2) 266 (67.3)	
Li Z *International Journal of Rheumatic Diseases* 2015[185]	1) PBO+MTX (n=132), sc injections w/ crossover to 50mg GOL+MTX at wk 24 2) 50mg GOL+MTX (n=132) every 4 wks	Week 24 ACR20, % 1) 15.9 2) 42.4 (p<0.0001) Week 24 ACR50, % 1) 6.8 2) 18.9 (p <0.01) Week 24 ACR70, % 1) 1.5 2) 6.1 (p<0.05)	Week 24 DAS 28-CRP remission, % 1) 7.6 2) 18.9 (p<0.01) Week 24 DAS 28-ESR remission, % 1) 3 2) 7.6 (p<0.01)		Week 24 HAQ-DI≥0.25, % 1) 29.5 2) 49.2 (p<0.001) Week 24 Median % change from baseline HAQ-DI 1) 0 2) 14.3 (p<0.0001)	Week 24 Median % change from baseline CRP 1) -4.5 2) 570.8(p<0.0001)

Table F47. Golimumab versus conventional DMARDs: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Tanaka Y *Annals of the rheumatic diseases* 2012[160] GO-FORTH	1) PBO+MTX (n=88) 2) 50mg GOL+MTX (n=86)	0 events of neoplasia or malignancy at wk 16; 2 events of neoplasia at wk 24 in group 2	0 serious infections at wk 16 and wk 24		Week 24 Discontinuation due to AEs, n (%) 1) 1 (1.1) 2) 4 (4.7) Serious AEs, n (%) 1) 1 (1.1) 2) 2 (2.3) Deaths: 0
Tanaka Y *Modern Rheumatology* 2016[292] GO-FORTH	1) PBO+MTX→GOL 50mg+MTX (n=88) 2) 50 mg GOL+MTX (n=170) PBO+MTX results from wks 0-24; GOL+MTX results from 156 wks	Malignancies, n (%) 1) 0 2) 5 (2.9)	Serious infections, n (%) 1) 0 2) 12 (7.1) 0 events of tuberculosis Pneumonia, 0 (%) 1) 1 (1.1) 2) 3 (1.8)	n (%) Nasopharyngitis 1) 22 (25.0) 2) 82 (48.2) Pharyngitis 1) 3 (3.4) 2) 26 (15.3) Bronchitis 1) 2 (2.3) 2) 16 (9.4)	Discontinuation due to AEs, n (%) 1) 1 (1.1) 2) 25 (14.7) Serious AEs, n (%) 1) 2 (2.3) 2) 36 (21.2) Deaths: 0

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Keystone E *Annals of the rheumatic diseases* 2009[161] GO-FORWARD	1) PBO + MTX (n=133) 2) 100 mg GOL + PBO (n=133) 3) 50mg GOL + MTX (n=89) 4) 100mg Gol + MTX (n=89)	Week 24 Malignancies, n (%) 1) 1 (0.7) 2) 2 (1.5) 3) 0 (0) 4) 1 (1)	Week 24 serious infection, n (%) 1) 1 (0.7) 2) 4 (3) 3) 2 (0.9) 4) 5 (4.8)	Injection site reactions 1) 4 (3) 2) 10 (7.5) 3) 5 (2.4) 4) 5 (4.8)	Serious AEs, n (%) 1) 5 (3.7) 2) 8 (6) 3) 9 (4.2) 4) 13 (12.4)
Keystone E *Annals of the rheumatic diseases* 2010[87] GO-FORWARD	1) PBO + MTX (n=133) 2) 100 mg GOL + PBO (n=133) 3) 50mg GOL + MTX (n=89) 4) 100mg Gol + MTX (n=89)	Malignancies, n 1) 1 2) 1 3) 1 4) 3	Serious infection, n 1) 2 2) 8 3) 2 4) 7	NR	Serious AEs, n 1) 8 2) 23 3) 12 4) 16
Keystone EC *The Journal of rheumatology* 2013[106] GO-FORWARD	1) PBO + MTX (n=133) 2) 100 mg GOL + PBO (n=133) 3) 50mg GOL + MTX (n=89) 4) 100mg Gol + MTX (n=89)	Malignancies, n (%) 1) 2 (1.6) 2) 3 (2.3) 3) 6 (2.8) 4) 5 (2.1)	Serious infection, n (%) 1) 0 2) 8 (6.1) 3) 7 (3.3) 4) 15 (5.9)	NR	Serious AEs, n (%) 1) -- 2) 26 (19.7) 3) 33 (15.6) 4) 73 (18.9) Death, n (%) 1) 0 2) 3 (2.3) 3) 0 4) 1 (0.4)

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Weinblatt ME *Annals of the rheumatic diseases* 2013[184] GO-FURTHER	1) PBO+MTX (n=197) 2) GOLiv+MTX (n=395)	Treatment-emergent malignancy, n 1) 0 2) 1 Non-treatment-emergent malignancy, n 1) 1 2) 0	Infections, n (%) 1) 0 2) 4 (0.9)	NR	Discontinuation due to AEs, n (%) 1) 2 (1.0) 2) 9 (2.3) Serious AEs, n (%) 1) 2.0 2) 4.1 Deaths, n 1) 1 2) 0
Weinblatt ME *Annals of the rheumatic diseases* 2014[214] GO-FURTHER	1) PBO+MTX (n=197) 2) GOLiv+MTX (n=395)	Malignancies among GOL+MTX treated patients: 3 (a previously reported case of breast cancer prior to wk24,6 one case of cervical carcinoma stage 0 and a basal cell carcinoma between wk24 and wk52)	Serious infections occurred in 1.9% of all GOL+MTX treated patients No serious opportunistic infections were documented up to wk52	Serious cardiovascular events between wk24 and wk 52: 1) 1 2) 2	Discontinuation due to AEs through wk 52, n (%) 1) 4 (2.0) 2) 14 (3.5) Serious AEs among all GOL+MTX treated patients increased from wk24 (4.1%) to wk52 (8.6%) Deaths between wk24 and 52 1) 1 2) 1

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Bingham CO 3rd *Arthritis care & research* 2015[221] GO-FURTHER	1) PBO+MTX (n=197) 2) GOLiv+MTX (n=395)	Malignancies, n 1) 1 2) 6	Serious infections occurred in 6.2% of all GOL+MTX treated patients TB occurred in 3 GOL +MTX treated patients	NR	Serious AEs occurred in 18.2% of all GOL + MTX treated patients through wk 112 Death through week 112, n (%) 1) 1 (0.5) 2) 3 (0.8)
Li Z *International Journal of Rheumatic Diseases* 2015[185]	1) PBO+MTX (n=132), sc injections w/ crossover to 50mg GOL+MTX at wk 24 2) 50mg GOL+MTX (n=132) every 4 wks	NR	Week 24 Serious infection, n (%) 1) 0 2) 2 (1.5) 1 TB case at week 48	NR	Week 24 Discontinued due to AEs, n (%) 1) 0 2) 5 (3.8) Serious AEs, n (%) 1) 1 (0.8) 2) 5 (3.8) 1 death in group 2 t week 28

Table F48. Golimumab versus conventional DMARDs: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Genovese MC *The Journal of rheumatology* 2012[222] GO-FORWARD	1) PBO + MTX (n=133) 2) 100 mg GOL + PBO (n=133) 3) 50mg GOL + MTX (n=89) 4) 100mg Gol + MTX (n=89)	Week 24 improvement from baseline SF-36 PCS (p *vs.1*) 1) 2.54 2) 4.74 (p=NS) 3) 8.28 (p<0.001) 4) 7.01 (p<0.001) SF-36 MCS 1) 0.75 2) 3.37 (p=NS) 3) 1.83 (p=NS) 4) 4.33 (p=0.014) % with ≥5-point improvement SF-36 PCS MCID 1) 30.6 2) 36.1 (p=NS) 3) 64.0 (p<0.001) 4) 57.3 (p<0.001) SF-36 MCS MCID 1) 29.0 2) 36.8 3) 37.1 (p=NS) 4) 44.9 (p<0.001)	NR	@week 24, FACIT-Fatigue, improvement from baseline 1) 2.16 2) 5.55 3) 7.30 4) 7.16 3 & 4 vs. 1, p<0.001 FACIT-Fatigue, MCID (% ≥4-point improvement) 1) 44.1 2) 60.0 3) 62.5 4) 63.2 3) & 4) vs. 1), p<0.01

<table>
<tr><th>Author & Year of Publication (Trial Name)</th><th>Interventions</th><th>Health-related quality of life</th><th>Pain</th><th>Fatigue & other PROs</th></tr>
<tr>
<td>Bingham CO J Rheumatol. 2014 [216]

GO-FURTHER</td>
<td>PBO+MTX (n=197)
2) GOLiv+MTX (n=395)</td>
<td>Week 16 (p<0.001 for 1-2)
<table>
<tr><th>Mean PCS score (SD)</th><th>Mean MCS score (SD)</th></tr>
<tr><td>1) 3.77 (7.51)</td><td>1) 1.33 (9.70)</td></tr>
<tr><td>2) 7.42 (8.11)</td><td>2) 7.23 (10.25)</td></tr>
</table>
Week 24 (p<0.001 for 1-2)
<table>
<tr><th>Mean PCS score (SD)</th><th>Mean MCS score (SD)</th></tr>
<tr><td>1) 3.82 (7.30)</td><td>1) 1.21 (10.07)</td></tr>
<tr><td>2) 8.28 (8.32)</td><td>2) 6.94 (10.28)</td></tr>
</table>
</td>
<td>Week 12
Mean EQ-5D VAS score (SD)
1) 2.53 (27.26)
2) 11.43 (28.87)
p<0.001 for 1-2

Week 16
Mean EQ-5D VAS score (SD)
1) 3.53 (25.34)
2) 17.69 (28.08)
p<0.001 for 1-2

Week 24
Mean EQ-5D VAS score (SD)
1) 8.25 (24.62)
19.12 (29.87)
p<0.001 for 1-2</td>
<td>Week 12
Mean FACIT-F score (SD)
1) 2.05 (9.04)
2) 5.38 (10.32)
p<0.001 for 1-2

Week 16
Mean FACIT-F score (SD)
1) 2.16 (9.70)
2) 7.54 (10.55)
p<0.001 for 1-2

Week 24
Mean FACIT-F score (SD)
1) 2.54 (10.22)
2) 7.96 (10.79)
p<0.001 for 1-2</td>
</tr>
</table>

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Bingham CO 3rd *Arthritis care & research* 2015[221] GO-FURTHER	1) PBO+MTX (n=197) 2) GOLiv+MTX (n=395)	Mean change from baseline (SE) SF-36 PCS Week 24: 1) 3.8 (7.3) 2) 8.3 (8.3) p=0.001 Week 52 1) 6.9 (8) 2) 8.1 (8.8) Week 112 1) 7(8.5) 2) 7.6 (9.1) Mean change from baseline (SE) SF-36 MCS Week 24: 1) 1.2 (10.1) 2) 6.9 (10.3) p=0.001 Week 52 1) 3.9 (11.2) 2) 6.9 (11.2) Week 112 1) 3.7 (11.3) 2) 5.7 (11.2)	Mean change from baseline (SE) VAS scale 0-10 Week 24: 1) 1 (3) 2) 2.8 (2.9) Week 52: 1) 1.9 (3.1) 2) 2.6 (3.4) Week 112 1) 1.3 (4) 2) 2.2 (3.2)	Mean change from baseline (SE) FACIT-F Week 24: 1) 2.5 (10.2) 2) 8 (10.8) Week 52: 1) 6.2 (10.3) 2) 8.4 (11.1) Week 112: 1) 6.1 (10.6) 2) 7 (11)

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Li Z *International Journal of Rheumatic Diseases* 2015[185]	1) PBO+MTX (n=132), sc injections w/ crossover to 50mg GOL+MTX at wk 24 2) 50mg GOL+MTX (n=132) every 4 wks	Week 24 Mean change from baseline SF-36 PCS 1) -0.9 2) 4.3 (p<0.001) Week 24 Mean change from baseline SF-36 MCS 1) -2.7 2) 2.2 (p<0.001)	Week 24 Patient's assessment of pain (Percent improvement from baseline) 1) -3.2 2) 18.5 (p<0.0001)	Week 24 Mean change from baseline FACIT-Fatigue 1) -2.2 2) 3.4 (p<0.001) Week 14 Mean change from baseline patient's assessment of disease activity 1) -1.5 2) 20.5 (p<0.001)

Table F49. Infliximab versus conventional DMARDs: Study Characteristics

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Kim J *Journal of Korean medical science* 2013[186] Fair	Merck Sharp & Dohme Corp	RCT double-blind, placebo-controlled followed by extension 30 weeks for RCT	Korea	1) PBO+MTX (n=72) 2) IFX+MTX (n=71) 3 mg/kg IFX or PBO intravenous infusions at weeks 0, 2, and 6 and every 8 weeks thereafter through 22 weeks. Patients continued their baseline dose of methotrexate or corticosteroids during the trial.	Patients with active RA (i.e. ≥4 SJC & TJC or at least 2 of the following: 1) CRP≥2mg/dl or ESR>28mm/h 2) 30 min stiffness 3) bone erosion 4) RF positivity) despite stable MTX for ≥4 weeks.	Mean age, yrs (SD) 1) 49.3 (10.1) 2) 51.4 (11.4) Female, n (%) 1) 64 (90.1) 2) 64 (88.9) Median RA duration, yrs (range) 1) 7.4 (0.6-35.7) 2) 9.8 (0.7-45.7) Mean KHAQ* (SD) 1) 1.4 (0.7) 2) 1.4 (0.7) *Korean Health Assessment Questionnaire

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Maini R *Lancet* 1999[187] ATTRACT Good See also Lipsky PE N Engl J Med 2000[200]	Centocor Inc.	International, double-blind, placebo controlled, phase III Every 4 weeks for 30 weeks	34 sites in North America and Europe	1) PBO (n=88) 2) IFX, 3mg/kg every 8 wk (n=86) 3) IFX, 3mg/kg every 4 wk (n=86) 4) IFX, 10mg/kg every 8 wk (n=87) 5) IFX, 10mg/kg every 4 wk (n=81) Additional infusion of same dose given every 4 or 8 wks with steady dose of methotrexate (median 15 mg/wk for ≥6 months)	Patients with active RA and had received continuous MTX for ≥ 3 months and constant dose for ≥ 4 wks; if patient was using oral corticosteroids or NSAIDs 1) must have been stable dose for ≥4 wks 2) if not using those drugs, could not have received either for ≥4 wks Patients were excluded if: 1) prior DMARD other than MTX, corticosteroids in 4 wks prior to screening 2) prior TNF or alkylating agents 3) serious and/or opportunistic infections	Mean age, yrs (range) 1) 51 (19.0-75.0) 2) 56 (25.0-74.0) 3) 51 (19.0-78.0) 4) 55 (19.0-80.0) 5) 52 (23.0-74.0) Female, n (%) 1) 70 (80) 2) 70 (81) 3) 66 (77) 4) 67 (77) 5) 59 (73) Median RA duration, yrs (range) 1) 8.9 (0.8-35.0) 2) 8.4 (0.7-45.0) 3) 7.2 (0.5-33.8) 4) 9.0 (0.5-49.9) 5) 8.7 (0.6-47.0)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
van Vollenhoven RF *The Lancet* 2012[199] SWEFOT Good See also Eriksson JK *JAMA Internal Medicine* 2013[228], Karlsson JA Ann Rheum Dis. 2013 [293], Eriksson J *Arthritis Care and Research* 2016[229]	Karolinska Institutet	RCT multicenter open label 2-year follow-up	15 rheumatology units in Sweden	1)MTX + sulfasalazine+ hydroxychloroquine (n=130) 2) IFX+MTX (n=128) all patients given one dose of MTX 20 mg every week. Patients whose DAS28 after 3-4 mos was >3.2 randomly allocated to group 1) or 2) sulfasalazine, 1000 mg twice a day; hydroxychloroquine, 400 mg once a day; and IFX 3 mg/kg body weight, rounded up to the nearest 100 mg increment and given intravenously at weeks 0, 2, and 6, and every 8 weeks thereafter; MTX continued	Age ≥18; diagnosis of RA with symptom duration <1 yr; no previous DMARD treatment; no oral glucocorticoid treatment or stable glucocorticoid treatment for at least 4 wks of at most 10mg daily prednisolone (or equivalent); DAS28≥3.2	Mean age, yrs (SD) 1) 52.9 (13.9) 2) 51.1 (13.3) Female, n (%) 1) 101 (78) 2) 79 (76) Mean RA duration, mo (SD) 1) 6.3 (3.6) 2) 6.2 (3.5) Mean HAQ-DI (SD) at baseline 1) 1.32 (0.60) 2) 1.27 (0.60) Mean DAS28-(unspecified) at randomization (SD) 1) 4.79 (1.05) 2) 4.91 (0.98)

Author & Year of Publication (Trial Name) Quality rating	Study sponsor	Study Design and Duration of Follow-up	Geographic location of study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Baseline patient Characteristics
Westhovens R Arthritis Rheum. 2006 [188] START Good	Centocor Research and Development, Inc.	Randomized, double-blind, placebo controlled 54 weeks	International and United States of America	1) PBO + MTX (n=363) 2) IFX + MTX, 3mg/kg (n=360) 3) IFX + MTX, 10mg/kg (n=361) Given at weeks 0, 2, 6, and 14 At week 22, patients in PBO group began receiving 3 mg/kg IFX and patients in group 3 continued their dose. Patients in group 2 who didn't meet predefined response criteria received increasing doses of IFX in 1.5 mg/kg increments	Active RA per ACR criteria despite MTX treatment for ≥3 months and stable dose for ≥4 weeks; could have been treated with other concomitant DMARDs Chest radiography must show no evidence of malignancy, infection, fibrosis, or active TB; excluded if: 1) opportunistic/serious infections during the 2 months prior to screening 2) HIV; active or history of TB 3) congestive heart failure 4) had been treated with an investigational drug within 3 months or 5 half-lives from time of screening	Median age, yrs (range) 1) 52.0 (44-61) 2) 53.0 (45-61) 3) 52.0 (43-60) Female, n (%) 1) 302 (83.2) 2) 288 (80.0) 3) 281 (77.8) Median RA duration, yrs (range) 1) 8.4 (4-15) 2) 7.8 (3-15) 3) 6.3 (3-14) Median HAQ-DI (range) at baseline, scale 0-3 1) 1.5 (1-2 2) 1.5 (1-2) 3) 1.5 (1-2)

Table F50. Infliximab versus conventional DMARDs: Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Kim J *Journal of Korean medical science* 2013[186]	1)PBO+MTX (n=72) 2) IFX+MTX (n=71)	Week 30 ACR20, % 1) 30.6 2) 50.7 p=0.014 ACR50, % 1) NR 2) 33.8	NR	NR	Week 30 mean change from baseline KHAQ 1) -10.8 2) -35.5 p=0.00	Week 30 rate of change of CRP, % 1) 11.5 2) 77.6 Week 30 rate of change of ESR, % 1) 20.5 2) 34

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Maini R *Lancet* 1999[187] ATTRACT	1) PBO (n=88) 2) IFX, 3mg/kg every 8 wk (n=86) 3) IFX, 3mg/kg every 4 wk (n=86) 4) IFX, 10mg/kg every 8 wk (n=87) 5) IFX, 10mg/kg every 4 wk (n=81)	Week 30 ACR20, % (estimated from graphic) 1) 20 2) 50 3) 53 4) 51 5) 56 ACR50, n (%) 1) 4 (5) p=NR 2) 22 (27) 3) 25 (29) 4) 26 (31) 5) 21 (26) p<0.001 for all above ACR70, n (%) 1) 0 (0) p=NR 2) 7 (8) p=0.007 3) 9 (11) p=0.002 4) 15 (18) p<0.001 5) 9 (11) p=0.002	NR	NR	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Lipsky PE N Engl J Med 2000[200] ATTRACT	1) MTX + PBO (n=88) 2) IFX + MTX (3mg every 8 wks, n=86) 3) IFX + MTX (3mg every 4 wks, n=86) 4) IFX + MTX (10mg every 8 wks, n=87) 5) IFX + MTX (10mg every 4 wks, n=81)	54 Weeks ACR20, (%) 1) 17 2) 42 3) 48 4) 59 5) 59 p<0.001 for 2-5 ACR50, (%) 1) 8 2) 21 p=0.027 3) 34 4) 39 5) 38 p<0.001 for 3-5 ACR70, (%) 1) 2 2) 10 p=0.04 3) 17 p=0.001 4) 25 5) 19 p<0.001 for 4-5	NR	Total radiographic score (SD) 1) 82 (77) 2) 79 (73) 3) 71 (73) 4) 67 (61) 5) 76 (72)	Mean HAQ-DI (SD) at baseline 1) 1.7 (0.6) 2) 1.8 (0.6) 3) 1.7 (0.6) 4) 1.7 (0.6) 5) 1.7 (0.6)	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
van Vollenhoven RF *The Lancet* 2012[199] SWEFOT	1) MTX+sulfasalazine +hydroxychloroquine (n=130) 2) IFX+MTX (n=128)	12 months ACR20, n (%) 1) 37 (28) 2) 54 (42) ACR50, n (%) 1) 19 (15) 2) 32 (25) ACR70, n (%) 1) 9 (7) 2) 15 (12) 24 months ACR20, n (%) 1) 43 (33) 2) 51 (40) ACR 50, n, (%) 1) 28 (22) 2) 38 (30) ACR70, n (%) 1) 18 (14) 2) 21 (16)	NR	Month 12 mean change from baseline mTSS (Van der Heijde), (SD) 1) 5.04 (10.64) 2) 2.95 (6.07) Month 24 mean change from baseline mTSS (Van der Heijde), (SD) 1) 7.23 (12.72) 2) 4.00 (10.05)	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Westhovens R Arthritis Rheum. 2006 [188] START	1) PBO + MTX (n=363) 2) IFX + MTX, 3mg/kg (n=360) 3) IFX + MTX, 10mg/kg (n=361)	22 Weeks ACR20, n (%) 1) 87 (25.5) 2) 199 (58.0) 3) 205 (61.0) p<0.001 for 2-3 ACR50, n (%) 1) 33 (9.7) 2) 110 (32.1) 3) 119 (35.4) p<0.001 for 2-3 ACR70, n (%) 1) 16 (4.7) 2) 48 (14.0) 3) 54 (16.1) p<0.001 for 2-3	Mean DAS28 response (SD) 1) 4.4 (1.4 2) 3.5 (1.4) 3) 3.3 (1.3) p<0.001 for 2-2 Remission (DAS28 < 2.6), n (%) 1) 48 (14) 2) 106 (31) 3) 110 (32) p<0.001 for 2-3 High disease activity (DAS28 > 5.1), n (%) 1) 110 (33) 2) 41 (12) 3) 35 (10) p<0.001 for 2-3 Good or moderate response, n (%) 1) 146 (44) 2) 250 (75) 3) 263 (79) p<0.001 for 2-3	NR	NR	CRP, mg/dl at baseline (range) 1) 1.2 (1-3) 2) 1.6 (1-3) 3) 1.6 (1-3)

Table F51. Infliximab versus conventional DMARDs: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Kim J *Journal of Korean medical science* 2013[186]	1)PBO+MTX (n=72) 2) IFX+MTX (n=71)	Malignancies, n 1) 1 2) 0	No TB reported	NR	NR
Maini R *Lancet* 1999[187] ATTRACT	1) PBO (n=88) 2) IFX, 3mg/kg every 8 wk (n=86) 3) IFX, 3mg/kg every 4 wk (n=86) 4) IFX, 10mg/kg every 8 wk (n=87) 5) IFX, 10mg/kg every 4 wk (n=81)	4 cancers in 3 IFX treated patients in 359 patients through years of follow up (2 epithelial cell cancer and 1 lymphoma)	1 instance of TB in patient treated with IFX	1 instance of coccidiomycosis	Discontinuation due to AEs, n (%) PBO – 7 (8) IFX – 6 (7) Serious AEs, n (%) 1) 14 (16) 2) 8 (9) 3) 11 (13) 4) 8 (9) 5) 10 (13) Deaths, n (%) PBO – 3 (3) IFX – 2 (0.6)

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Lipsky PE N Engl J Med 2000[200] ATTRACT	1) MTX + PBO (n=88) 2) IFX + MTX (3mg every 8 wks, n=86) 3) IFX + MTX (3mg every 4 wks, n=86) 4) IFX + MTX (10mg every 8 wks, n=87) 5) IFX + MTX (10mg every 4 wks, n=81)	5 cases of cancer in IFX + MTX treatment (2 were recurrences and 3 were new cases)	Serious infections, n (%) 1) 7 (8) 2) 2 (2) 3) 6 (7) 4) 7 (8) 5) 6 (7)	NR	Serious adverse events, n (%) 1) 18 (21) 2) 10 (11) 3) 14 (16) 4) 17 (20) 5) 16 (20) Discontinuation due to AEs, n 1) 7 2) 5 3) 9 4) 4 5) 8 Deaths, n (%) MTX + PBO – 3 (3) IFX + MTX – 5 (1)

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Westhovens R Arthritis Rheum. 2006 [188] START	1) PBO + MTX (n=363) 2) IFX + MTX, 3mg/kg (n=360) 3) IFX + MTX, 10mg/kg (n=361)	26 patients reported development of 30 tumors during the trial 19 of the 30 malignancies were nonmelanoma skin cancers, benign neoplasms, or carcinoma in situ 1) 0 (5 receiving 3 mg/kg IFX) 2) 9 3) 5	Through 22 weeks Serious infections, n (%) 1) 6 (1.7) 2) 6 (1.7) 3) 18 (5)	Common serious infections in IFX + MTX, n Pneumonia (7) TB (4) Cellulitis (2) UTI (2) In PBO + MTX, n Bronchitis (2) Latent TB (1)	Before Week 22 Discontinuation due to AEs, n (%) 1) 8 (2.2) 2) 18 (5) 3) 20 (5.5) After Week 22 Discontinuation due to AEs, n (%) 1) 18 (5) 2) 14 (3.9) 3) 17 (4.7) Before Week 22 Incidence of AEs, % 1) 7.5 2) 7.8 3)7.8 After Week 22 Incidence of AEs, % 1) 11.8 2) 9.9 3) 10.3

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
van Vollenhoven RF *The Lancet* 2012[199] SWEFOT	1) MTX+sulfasalazine +hydroxychloroquine (n=130) 2) IFX+MTX (n=128)	1 acute myeloid leukemia in a patient treated with IFX+MTX	Infectious AEs, n (%) 1) 1 (1) 2) 8 (6)	Gastrointestinal AEs, n (%) 1) 18 (14) 2) 3 (2)	Discontinuation due to AEs, n (%) 1) 22 (17) 2) 19 (15) Serious AEs, n 1) 1 2) 2 Deaths, n 1) 0 2) 1

Table F52. Infliximab versus conventional DMARDs: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Karlsson JA Ann Rheum Dis. 2013 [293] SWEFOT	1) MTX + sulfasalazine+ hydroxychloroquine (n=130) 2) IFX+MTX (n=128)	Month 21 Mean EQ-5D (SD) score 1) 0.73 (0.24) 2) 0.68 (0.26)	NR	NR
Kim J *Journal of Korean medical science* 2013[186]	1) PBO+MTX (n=72) 2) IFX+MTX (n=71)	Week 30 mean change from baseline SF-36 PCS 1) 1.2 2) 6.1 p<0.001	NR	NR
Maini R *Lancet* 1999[187] ATTRACT	1) PBO (n=88) 2) IFX, 3mg/kg every 8 wk (n=86) 3) IFX, 3mg/kg every 4 wk (n=86) 4) IFX, 10mg/kg every 8 wk (n=87) 5) IFX, 10mg/kg every 4 wk (n=81)	NR	Pain score range (VAS 0 – 10 cm), (30 weeks) 1) 6.7 (5.9) 2) 7.0 (3.8) 3) 6.9 (3.5) 4) 6.7 (3.1) 5) 6.6 (3.7)	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Fatigue & other PROs
Lipsky PE N Engl J Med 2000[200] ATTRACT	1) MTX + PBO (n=88) 2) IFX + MTX (3mg every 8 wks, n=86) 3) IFX + MTX (3mg every 4 wks, n=86) 4) IFX + MTX (10mg every 8 wks, n=87) 5) IFX + MTX (10mg every 4 wks, n=81)	Week 54 mean change from baseline SF-36 MCS, % (~) 1) 9 2) 10 3) 10 4) 12 5) 11 PCS, % (~) 1) 18 2) 23 3) 43 4) 50 5) 39	NR	NR

Table F53. Infliximab versus conventional DMARDs: Non-healthcare Outcomes

Author & Year of Publication (Trial Name)	Interventions	Requirements for surgical intervention	Hospitalization, Rehabilitation, Assisted living	Productivity Loss	Caregiver Burden	Other outcomes
Eriksson JK *JAMA Internal Medicine* 2013[228] SWEFOT The current analysis of the Swefot trial population included only patients with early RA of working age (<63 years) at randomization	1) MTX+sulfasalazine+ hydroxychloroquine (n=105) 2) IFX+MTX (n=99) 3) Controls from general population without RA (n=1020) Controls were identified from the Swedish Register of the Total Population by sampling 5 sex-, age-, education-, and county-matched controls per patient with RA	NR	NR	Change vs. baseline in days on sick leave and disability pension, d/mo (SE) @12 months/21 months 1) -4.1 (1.2)/ -4.9 (1.2) 2) -4.0 (1.1)/ -6.2 (1.0) Work loss, mean d/mo (SD) @12 months/21 months 1) 13 (13)/ 12 (13) 2) 13 (13)/ 10 (12)	NR	NR

Eriksson, J *Arthritis Care and Research* 2016[229] SWEFOT	1) MTX+sulfasalazine+ hydroxychloroquine (n=101) 2) IFX+MTX (n=109) 3) MTX responders (n=91) 4) Controls from general population without RA (n=455) Controls were identified from the Swedish Register of the Total Population by sampling 5 sex-, age-, education-, and county-matched controls per patient with RA	NR	NR	Change vs. baseline in annual days on sick leave and disability pension, days (SD) @ 7 years 1) -26 (12) 2) -25 (13)	NR	NR

Appendix G. Ongoing Studies

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Clinical Trial Evaluating Methotrexate + Biologic Versus Methotrexate, Salazopyrine and Hydroxychloroquine in Patients With Rheumatoid Arthritis and Insufficient Response to Methotrexate **University Hospital, Strasbourg, France** **NCT02714634**	Phase 4 Open label RCT	1) MTX+biologic (chosen by investigator) 2) Triple therapy (MTX, salazopyrine, hydroxychloroquine)	Inclusion criteria • RA • DAS28-CRP>3.2 • Insufficient response to MTX after ≥3 months • Radiographic erosions and/or serum RF associated to anti-CCP • Age ≥18 Exclusion criteria • Prior biologic • Prior triple therapy • Absence of TB screening • Corticosteroids at dose >15 mg/d of equivalent prednisone ≥4 weeks prior to inclusion	Primary • Participant with low disease activity (DAS28-CRP<3.2) and a daily dose ≤ 7.5 mg/day of equivalent prednisone at 12 months Secondary • SAE rate • CDAI • DAS28-CRP • ACR20/50/70, Boolean remission • Vdh-mTSS • Costs • Treatment compliance	February 2020

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Comparative and Pragmatic Study of Golimumab Intravenous (iv) (Simponi Aria) Versus Infliximab (Remicade) in Rheumatoid Arthritis (AWARE) **Janssen Scientific Affairs, LLC** **NCT02728934**	Prospective, observational (patient registry) cohort	1) GOLiv 2) IFX	Inclusion criteria • Age ≥18 • Confirmed diagnosis of RA • May or may not have had prior biologic, including GOLsc Exclusion criteria • Received investigational drug, vaccine, or device within 28 days • Prior GOLiv or IFX	Primary • % with infusion reaction at week 52 l) Secondary • Severe/Serious infusion reaction • Discontinuation due to infusion reaction • CDAI • Discontinuation due to lack of effectiveness • Adherence • AEs and SAEs • Cost effectiveness (medical resource utilization and healthcare economics)	February 2021

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
An Efficacy and Safety Study Evaluating Tofacitinib With and Without Methotrexate Compared to Adalimumab with Methotrexate (ORAL STRATEGY) **Pfizer** **NCT02187055**	Phase 4 Double blind RCT	1) TOF (5mg, twice daily) + MTX 2) TOF (5 mg, twice daily) monotherapy 3) ADA (40 mg every other wk) + MTX	Inclusion criteria • Age ≥18 • Moderate to severe RA • On MTX but inadequately controlled • No active TB or inadequately treated TB infection Exclusion criteria • Previous ADA or TOF • Current or prior malignancy • Lab abnormalities • Infections	Primary • ACR50 at month 6 Secondary • SDAI change • CDAI change • DAS28-CRP change • DAS28-ESR change • ACR20/70 • HAQ-DI change • SF-36 • WPAI • EQ-5D • FACIT-F • Remission • LDA • AEs	December 2016

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of Baricitinib (LY3009104) in Participants with Rheumatoid Arthritis **Eli Lilly and Company** **NCT02265705**	Phase 3 Double blind RCT	1) BAR (4 mg) + MTX 2) PBO + MTX	Inclusion criteria • Adult-onset RA diagnosis • Moderately to severely active RA • CRP ≥6 mg/L • Regular MTX for at least 12 weeks prior to study Exclusion criteria • Corticosteroids at doses >10 mg of prednisone/day • Recent NSAIDs • Receiving concomitant treatment with MTX or other cDMARDs within 8 weeks of study entry • Physiotherapy for RA in 2 weeks prior to study entry • Prior biologic or JAKi	Primary • ACR20 at week 12 Secondary • HAQ-DI change • DAS28-CRP change • SDAI≤3.3 • Duration/severity of morning joint stiffness • Worst tiredness • Worst pain	June 2017

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study Comparing ABT-494 to Placebo and to Adalimumab in Subjects with Rheumatoid Arthritis Who Are on a Stable Dose of Methotrexate and Who Have an Inadequate Response to Methotrexate (SELECT-COMPARE) **AbbVie** **NCT02629159** **See also NCT02675426, NCT02706951, NCT02720523, and NCT02706847**	Phase 3 Double blind RCT	1) ABT-494 2) PBO 3) ADA	Inclusion criteria • Age ≥18 • RA diagnosis ≥3 months • MTX ≥3 months with stable Rx 15-25 mg/wk for ≥4 weeks • ≥6/66 swollen joints, ≥6/68 tender joints • Erosions and/or positive anti-CCP antibodies • Prior exposure to 1 biologic in up to 20% of total population if exposure limited Exclusion criteria • Prior JAK inhibitor • Prior ADA or inadequate response to prior biologic	Primary • ACR20 at week 12 • % remission based on DAS28-CRPN2.6 at week 12 Secondary • DAS28-CRP change • Vdh-mTSS change • HAQ-DI change • ACR50/70 • SF-36 • FACIT-F • Work instability • Morning stiffness • LDA • % no radiographic progression •	September 2020

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies

Appendix H. Conflict of Interest Disclosures for Expert Reviewers

Name	Title	Disclosures
Arthritis Foundation **Kayla Amodeo, PhD** **Guy S. Eakin, PhD** **Sandie Preiss, MPA**	 Legislative Research Manager Senior Vice President, Scientific Strategy National Vice President, Advocacy and Access	Receipt or potential receipt of anything of monetary value in excess of $5,000; Equity interests such as individual stocks, stock options or other ownership interests in excess of $10,000; Manufacturer support of research in the clinical area of this meeting in which you are participating The Foundation receives grants from healthcare companies, funds research and funds Fellowships.
Andrew L. Concoff, MD	Medical Policy Committee United Rheumatology	Equity interests in excess of $10,000; status or position as an owner or employee of a health care company which receives more than 25% of its funding from health care companies; and intellectual property rights related to activities as president and co-founder of mPortent Biodata, Inc.
Max Hamburger, MD	President United Rheumatology	No conflicts to disclose.
Kent Johnson, MD	University of New South Wales—Sydney Kent Johnson Consulting LLC	Receipt of payments in excess of $5,000 from health care companies.
Andrew J Laster, MD, FACR	Board of Directors and Medical Policy Committee Member United Rheumatology	Receipt of payments in excess of $5,000 from a health care company related to advisory board and speakers bureau participation for Amgen, Genentech/Roche, Pfizer, UCB, Bristol-Meyers Squibb, and Crescendo Bioscience.

Name	Title	Disclosures
Matthew H. Liang, MD, MPH	Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital	*Awaiting response*
Elizabeth Tindall, MD, FACR	Rheumatology Consultants of Oregon, LLC	No conflicts to disclose.
Jan Wyatt, PhD, RN, FAANP	Patient Advocate	No conflicts to disclose.

Appendix I. Public Comments

This section includes summaries of the public comments prepared for the New England CEPAC Public Meeting on March 24, 2017 in Boston, MA. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery.

A video recording of these comments can be found on our site here at minute 2:20:29. Conflict of interest disclosures are included at the bottom of each statement.

Margaret Michalska, MD, Medical Director for Immunology; Medical Affairs, Genentech

Genentech is committed to advancing research and innovating therapies in RA. We support well-conducted frameworks that enable meaningful discussions on value and believe that treatment decisions should be made by the physician and patient.

Treatment recommendations are not generalizable to all populations and depend on a variety of factors. Selecting the right medicine for the right patient poses a significant challenge due to market dynamics unique to RA. Access to therapies targeting various mechanisms of action is important to allow for individualized treatment of patients who continue to have active disease despite prior treatment(s).

Actemra and Rituxan offer long-term efficacy and safety experience in diverse patient populations with RA. In patients who respond to Actemra and Rituxan treatment, clinically meaningful improvements in RA signs, symptoms, and patient-reported outcomes have been demonstrated.

We recommend the following to improve ICER's evaluation:

- Consider evidence-based guidelines and real-world clinical practice in the sequential treatment algorithm to support better access to appropriate TIMs for patients who have failed first-line TIM or methotrexate therapy.
- Account for Actemra and Rituxan data derived from clinical trials and post-marketing settings. These data reflect real-world treatment patterns and dosing, and long-term efficacy and safety from over a decade, which are important to audiences that ICER seeks to inform.
- Increase transparency by providing economic models for manufacturer feedback.
- Revise ICER's Evidence Report as new data becomes available (ex. Investigational drug approval).

Brad Stolshek, Pharm.D., Director, Global Health Economics – Inflammation; Amgen

The forgotten memories of joint deterioration, severe chronic pain, walking difficulties and job loss seen with inadequately treated moderate to severe rheumatoid arthritis (RA) before the introduction of TIMs can lead to a complacency enabling the crippling and disabling nature of the disease quickly becoming a reality again. The current ICER RA model is a symptom of that complacency and has fundamental shortcomings:

- ICER's use of cDMARDs as a comparator in patients who already had an inadequate response to cDMARDs is inappropriate and contrary to clinical practice. Maintaining patients on cDMARDs risks accelerated progression to joint destruction and disability and should create a larger decrement in effect for these patients continuing on cDMARD treatments.
- The full impact of disability is not included for the cDMARD patients who experience significant disability and surgeries found in long-term observational data. Amgen modeled the real world TIMs utilization following consensus recommendations, and addressing ICER failures on clinical approach, disability, productivity and individual patient variation. This peer-reviewed publication shows the TIMs are cost effective below $150K/QALY.

We must avoid stepping backwards, shortchanging patients who have failed cDMARDs by forcing them to remain on cDMARDs as ICER does. We must preserve patient choice for RA treatments based on specific disease characteristics, clinical expertise and individual patient need.

If ICER had included the right comparator and long-term disability data, the TIMS would provide substantial value in their model. ICER should update their model to recognize the full value of TIMs in RA.

Tammy Curtice, PharmD, MS; Director, Health Economics & Outcomes Research; Bristol-Myers Squibb

Bristol-Myers Squibb (BMS) asked that ICER consider 2 key areas:

1. Treatment based on clinical presentation and biomarker status

- ICER acknowledged "There are multiple phenotypic and genotypic variations in the pathogenesis of the disease that affect both the course of RA and the outcome of therapy".
- ACR and EULAR guidelines present criteria to consider in the treatment of RA and recommend risk stratification to guide treatment selection based on clinical presentation; biomarker data, such as ACPA and C-reactive protein; and radiographic findings.

- However, no attempt was made to run the cost-effectiveness model for scenarios to show the variance in value across treatment strategies and the potential value of targeting based on prognostic biomarkers.
- We recommend additional analyses with scenarios for particular subgroups (for example, prognostic biomarkers).

2. Real World/Registry Data (RWD)

- While modeling is needed to fill data gaps, it is still important to consider available RWD to inform the model versus assumptions.
- For example, the use of utility data derived from HAQ scores—derived from changes in ACR scores and modified Total Sharp Score—may dilute effects in over-translation across sets of outcomes, which may cause underestimation of treatment effects.
- We recommend using RWD to supplement models when available.

In closing, I would like to emphasize that BMS supports a comprehensive and current approach to value that incorporates key elements: a real-world approach, patient priorities (including consideration of patient access and unmet medical needs), and total societal value over specific timelines or budgets, multi-stakeholder input, along with the most up-to-date clinical science.

BMS recommends that ICER:

- Avoid biopharmaceutical budget caps that unduly delay patient access to innovation and can potentially disadvantage RA patients
- Incorporate clinical benefits & harms in a manner that recognizes the heterogeneity of treatment effect rather that the average response.

Andrew Koenig D.O., F.A.C.R., Inflammation & Immunology Group Lead; Pfizer

On behalf of my colleagues who work in inflammation on ICER's draft evidence report that seeks to examine the clinical and economic value of targeted immune modulators for rheumatoid arthritis we have identified the following areas for improvement:

1. Address or adjust for significant changes in RA treatments over time.
2. Address treatment discontinuation and switching that limits switching from an initial therapy to another treatment in the same class.
3. Address ACR classification - not been validated and does not reflect real-world practice.
4. Address Sharp analysis - critical methodological challenges that significantly limits both the validity of its findings and relevance to clinical practice.

5. Use reported HAQ scores instead of estimating from a post study calculation since there is consistent measurement in clinical trials.
6. Use product, not class-specific price discounts
7. Fully engage and leverage insights from stakeholders- especially patient stakeholders to inform the report's methodology and findings.

We agree that a collaborative effort to objectively examine clinical and economic evidence to help enable the most efficient use of the healthcare resources in the treatment of RA is a positive goal. We hope that ICER will seek to better recognize and acknowledge the limitations in its final report and will use this analysis to begin a broader dialogue about how we can utilize current and evolving treatments to best meet the needs of RA patients and their caregivers.

Andreas Kuznik, Ph.D., Senior Director, Health Economics and Outcomes Research; Regeneron Pharmaceuticals

Sanofi-Genzyme and Regeneron would like to reiterate concerns with the final cost-effectiveness model.

- We recognize that the cost-effectiveness model now accounts for HAQ degradation among palliative care patients using a rate of 0.0269 per year for a period of 15 years. However, we believe that this revision does not fully represent the disease progression in the absence of biologic therapies. In the ICER model, cDMARD patients would merely progress to a HAQ of 2.1 over lifetime, which appears inconsistent with the substantial disease burden in the pre-biologic era described in multiple patient testimonies at the ICER public meeting on 3/24/2017. We reiterate our recommendation to use a previously reported rate in the NDB of 0.032 per year and to extend this HAQ progression over the entire model follow-up. In addition, we recommend that higher rates of HAQ progression, such as 0.045 per year reported in multiple NICE appraisals, are explored in sensitivity analyses.
- We continue to disagree with the use of a modified Wailoo equation for the utility function and performing sensitivity analyses using the confidence interval from the original equation. We strongly encourage exploring the impact of alternative utility equations in sensitivity or scenario analyses (Hurst et al. 1997, Bansback et al. 2005)
- Pricing assumptions for the individual therapies should not be extracted from the treatment sequence in the threshold analysis. Instead, we suggest proportionately reducing the cost of the entire sequence of therapies until the cost effectiveness thresholds are met.

References:

Hurst et al. in Chen, Y.F., Jobanputra, P., Barton, P., Jowett, S., Bryan, S., Clark, W. et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technology Assessment (Winchester, England) 2006; 10(42):iii-iiv

Bansback NJ, Brennan A, Ghatnekar O. Cost effectiveness of adalimumab in the treatment of patients with moderate to severe rheumatoid arthritis in Sweden. Ann Rheum Dis 2005;64:995-1002.

Dr Jeff Stark, Head of Medical Affairs, Rheumatology; UCB

UCB will describe the positive attributes of certolizumab pegol (Cimzia®) that were omitted, as well as comment on the ICER approach.

- Cimzia has the lowest WAC price for all anti-TNFs. This is contrary to ICER's review. ICER failed to convert the WAC per unit prices to reflect dosage variation for agents with weight-based dosing. Additionally, ICER did not take into account the high rates of dose escalation that frequently occur with other products, or the administration cost difference for intravenous products. These omissions lead to inaccurate comparisons of costs across all agents.
- Cimzia has additional clinical benefits unrecognized by ICER:
    - EXXELERATE demonstrates that Cimzia combination therapy is equivalent to adalimumab combination therapy. Again, contrary to the conclusion drawn by ICER, this is significant because it demonstrates that access to a second anti-TNF with a unique molecular structure for primary non-responders has strong therapeutic value.
    - Cimzia has significant efficacy as monotherapy, demonstrated in the FAST4WRD trial and recognized with a formal monotherapy indication.
    - Demonstrated efficacy across many patient subtypes (MTX-naïve, DMARD-IR, TNF-experienced, etc.).
    - Stable, non-weight-based dosing provides lower and more predictable costs for patients.
    - Ability to make a clinical decision based on 12-week response
    - CRIB and CRADLE examine Cimzia safety in women who are pregnant or nursing.

UCB questions ICER's decision to compare products to conventional DMARDs which do not optimally prevent disease progression and are not the current standard of care. Not using adalimumab for the ultimate assessment of cost-effectiveness distorted the final result.

Dr. Christopher Phillips, American College of Rheumatology

The American College of Rheumatology supports comparative effectiveness research (CER) that informs treatment decisions and helps us understand the strengths and weaknesses of one treatment versus another, with respect to safety, effectiveness and cost. However, we are unsure this document accomplishes that goal.

Multiple assumptions in this report build off each other and may not reflect reality. HAQ and sharp scores are translated into QALYs based on various different models. Drug costs are estimated but may vary widely between WACs, ASPs, and discounts negotiated between PBMs and pharma. With each link in this path, the confidence interval regarding comparative cost effectiveness widens. ACR agrees high costs for TIMs is of concern and supports efforts which would allow the healthcare economy to better bear the costs of effective RA therapy. We are not able to comment on factors that go into TIM pricing; however, drug pricing and medical appropriateness are separate issues that should not be conflated. We should not pretend that an analysis based on drug prices in the current healthcare environment says anything about medical appropriateness.

ACR feels that a report such as this should not become proscriptive towards drug coverage. We are concerned this document will raise barriers preventing the appropriate use of biologic drugs by increasing non biological treatments required before allowing biologics, by narrowing the scope of which biologics will be covered through step edits, or claiming that biologics won't be covered.

ACR believes CER should be used to inform, not constrain, decisions made by a provider and patient. The ACR will continue to support quality CER that informs patients and their providers and assists decision making but we will resist attempts couched in CER to inappropriately constrain them.

Conflict of Interest Disclosure. AbbVie - speaker bureau; AbbVie - clinical research

Dr. Liana Fraenkel, Professor of Medicine, Yale

The ACR appreciates the effort that went into the creation of the report. While the cost-effectiveness analysis methods used are sound, there are several issues that merit discussion prior to dissemination.

While several sensitivity analyses were performed, the base model does not reflect clinical practice. Current standards based on strong evidence require that rheumatologists recommend treatment in

order to minimize inflammation– as fast as possible and to the greatest degree possible. This strategy is based on data demonstrating accumulation of irreversible damage as early as after 3 months of untreated disease. A related body of evidence now also supports a treat-to-target strategy which also requires access to TIMs. The comparator strategy is not consistent with evidence based guidelines (both ACR and EULAR) or what patients and doctors would consider standard of care for rheumatoid arthritis in 2017. In addition, best practices generally recommend that cost is considered from the societal (not the payer) perspective.

Beyond the underlying strategies in the model is the question of whether a cost-effectiveness model is an appropriate metric by which to judge the value of TIMs. While we appreciate that cost effectiveness models are a key tool to be able to compare strategies, using this metric to compare treatment options whose costs cannot be measured on the same scale is not informative. It is clear, given the current costs (regardless of whether or not patients are insured and which type of coverage they have), that TIMs cannot be shown to be cost effective when compared to conventional DMARDs from the payer perspective. Comparing an effective class of much more costly medications to baseline treatment that is MUCH cheaper will never meet benchmarks set in an era before the development of biologics and small molecules. This is true for RA as well as other chronic potentially debilitating diseases.

The ACR acknowledges the importance of providing high-value care. The output from this significant body of work should not imply that TIMs are not sufficiently effective, but should highlight their cost and call for efforts to maximize value in caring for RA.

Conflict of Interest Disclosure. None to disclose

Chantelle Marcial, Global Healthy Living Foundation—Member

I would like to thank you for allowing us patient advocates the time to speak before you all. As I mentioned, GHLF has a great level of transparency listing all donors and sponsors. After a bit of a search I found the funding page on the ICER site. To me, it looks like there is a heavy insurance presence and that makes me, as a patient, feel that the study was probably weighted toward cheaper, older DMARD therapies strictly because of the cost savings and not based on actual patient success with biologics.

The ICER arthritis report uses short-term clinical trial data and ignores the nearly two-decades-old benefits of substituting legs for wheelchairs. Calculating the economic benefits to society derived from sustained worker productivity and quality-of-life that results from the use of biologics is imperative.

CreakyJoints, through a multi-year PCORI contract, has built and is populating a patient-reported-outcomes registry of people with arthritis. It is called ArthritisPower. We are using many components of the ICER RA model as instructive of what NOT to do, such as reliance on short-term clinical trials data, lack of observational research, dismissing co-morbidities, not clearly defining the benefits of infusion vs. injected, not accepting my patient data as well as population data, and relying on a small universe of HAQ scores. Instead, we are focused on long-term patient data which can be combined with clinical and payer data. The objective is to reduce healthcare costs by incorporating societal as well as short- and long-term health benefits with the patient, not the payer, driving the conclusions.

Conflict of Interest Disclosure. Global Healthy Living Foundation corporate sponsors include UCB, Takeda, Pfizer, Janssen, Horizon Pharma, Genentech, Endo, Crescendo, Bristol Myers Squibb, AstraZeneca, Amgen, AbbVie

Jen Melanson, Arthritis Foundation Advocate & Arthritis Patient

RA attacked me quite suddenly, literally threatening my life. On March 6, 2012, I woke up feeling as if I might have the flu. But just five days later, I was very seriously ill. Isn fact, I was in heart failure. While it took a year to finally get a definitive diagnosis of RA, my doctor treated me early and aggressively, based on my symptoms. I was started first on DMARDs and methotrexate within weeks of onset, and moved very quickly to biologics when those weren't enough. The first biologic didn't work, so within 6 months my doctor switched me to another. Still, this was almost two full years after my onset. For those two years, I endured horribly painful, swollen joints. I missed countless hours of work, ultimately having to give up my job in favor of a position that was less physically-demanding. I missed hockey games and band concerts and birthday parties and family gatherings. I became very depressed, even seriously considered taking my own life. But I am one of the "lucky" ones, having found a biologic that works for me, allowing me to resume a "normal" life. Still, I worry about my medication regime someday failing, as often happens for RA patients. This is why it is crucial that patients be allowed access to as many treatment options as possible. RA is not a one-size-fits-all disease. And for me, access to effective treatment was not just life-changing, it is life-sustaining.

Renay Houlem, Arthritis Foundation Advocate & Arthritis Patient
[No summary testimony was submitted. A video of public comments can be found **here**, beginning at 2:20:29]

Anna Legassie, Arthritis Foundation Advocate & Arthritis Patient
[No summary testimony was submitted. A video of public comments can be found **here**, beginning at 2:20:29]

Conflict of Interest Disclosure. Arthritis Foundation corporate sponsors include AbbVie, Aleve, Arthro-7, Instaflex, Iroko Pharmaceuticals, Janssen, Move Free: Total Joint Health, Amgen, Advil, Ferring Pharmaceuticals, Eli Lilly, Novartis, Pfizer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Genentech, Gilead, GlaxoSmithKline, Horizon, Mallinckrodt, Merck, Samumed, Sanofi-Regeneron, Takeda, UCB