Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value

Draft Evidence Report

January 20, 2017

Prepared for

ICER Staff/Consultants	University of Colorado School of Pharmacy (Anschutz Medical Campus) Modeling Group*
Daniel A. Ollendorf, PhD Chief Scientific Officer Institute for Clinical and Economic Review **Rick Chapman, PhD, MS** Director of Health Economics Institute for Clinical and Economic Review **Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review **Varun Kumar, MBBS, MPH, MSc** Health Economist Institute for Clinical and Economic Review **Foluso Agboola, MBBS, MPH** Research Scientist Institute for Clinical and Economic Review **Patricia Synnott, MALD, MS** Senior Research Associate Institute for Clinical and Economic Review **Shanshan Liu, MS, MPH** Research Associate Institute for Clinical and Economic Review **Celia Segel, MPP** Program Manager, New England CEPAC Institute for Clinical and Economic Review **Sonya Khan, MPH** Program Director, Midwest CEPAC Institute for Clinical and Economic Review	**Jonathan Campbell, PhD** Associate Professor Department of Clinical Pharmacy Center for Pharmaceutical Outcomes Research **Melanie D. Whittington, PhD** Professional Research Assistant Department of Clinical Pharmacy **R. Brett McQueen, PhD** Assistant Professor Department of Clinical Pharmacy Center for Pharmaceutical Outcomes Research *The role of the University of Colorado Skaggs School of Pharmacy Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the UC.

DATE OF PUBLICATION: JANUARY 20, 2017

We would also like to thank Margaret Webb, Noah Mwandha, and Erin Lawler of ICER for their contributions to this report.

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

About New England CEPAC

The New England Comparative Effectiveness Public Advisory Council (New England CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. New England CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

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.

For a complete list of stakeholders from whom we requested input, please visit:
https://icer-review.org/material/ra-stakeholder-list/

Patient/Advocacy Reviewers

Kayla Amodeo, PhD, Legislative Research Manager
Guy S. Eakin, PhD, Senior Vice President, Scientific Strategy
Sandie Preiss, MPA, National Vice President, Advocacy and Access
Arthritis Foundation

Jan Wyatt, PhD, RN, FAANP
Patient Advocate

Clinical Reviewers

Andrew L. Concoff, MD, Medical Policy Committee
Max Hamburger MD, President
Andrew J Laster MD FACR, Board of Directors and Medical Policy Committee Member
United Rheumatology

Kent Johnson, MD
University of New South Wales—Sydney

Matthew H. Liang, MD, MPH
Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital

Elizabeth Tindall, MD, FACR
Rheumatology Consultants of Oregon, LLC

Table of Contents

List of Acronyms Used in this Report

ABT	Abatacept
ACPA	Anticitrullinated Protein Antibody
ACR	American College of Rheumatology
ADA	Adalimumab
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
SAR	Sarilumab
SC	Subcutaneous
SDAI	Simplified Disease Activity Index
SF-36	Short Form-36
SMD	Standardized Mean Difference
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
WTP	Willingness-to-pay

Executive Summary

To be included in our revised Evidence Review.

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

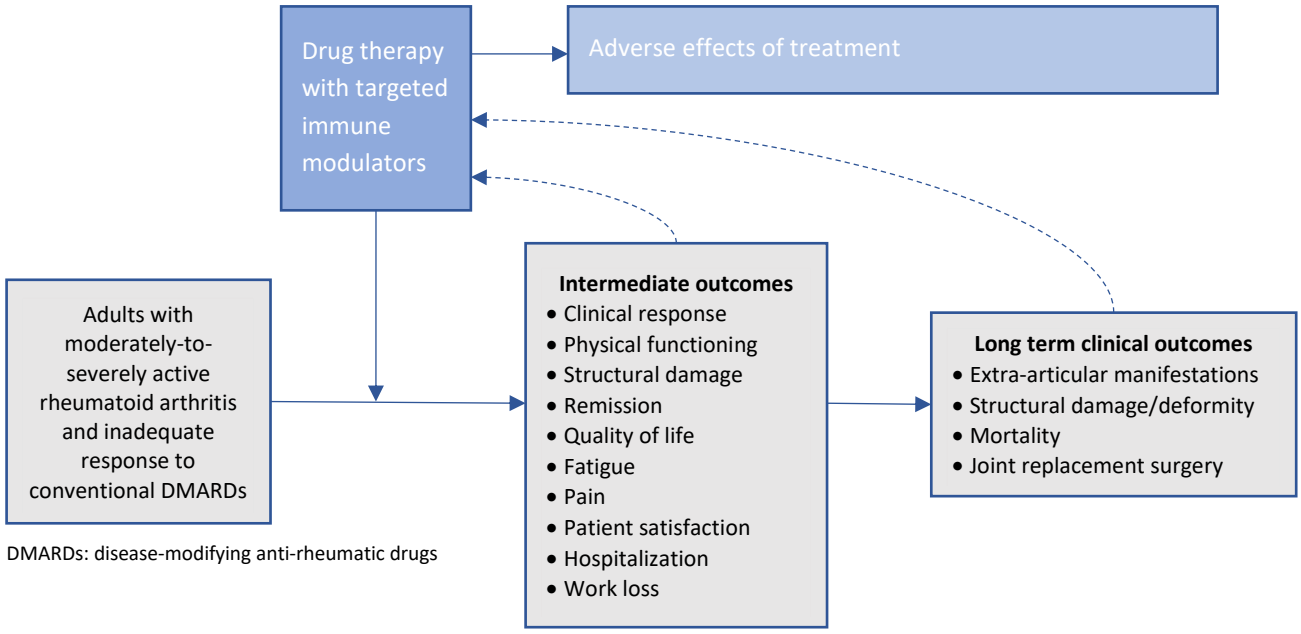
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework.[6] We conducted a systematic literature review using best practices for search strategy development and article retrieval. Data and evidence 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.[7,8]

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.[9]

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 vs. 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

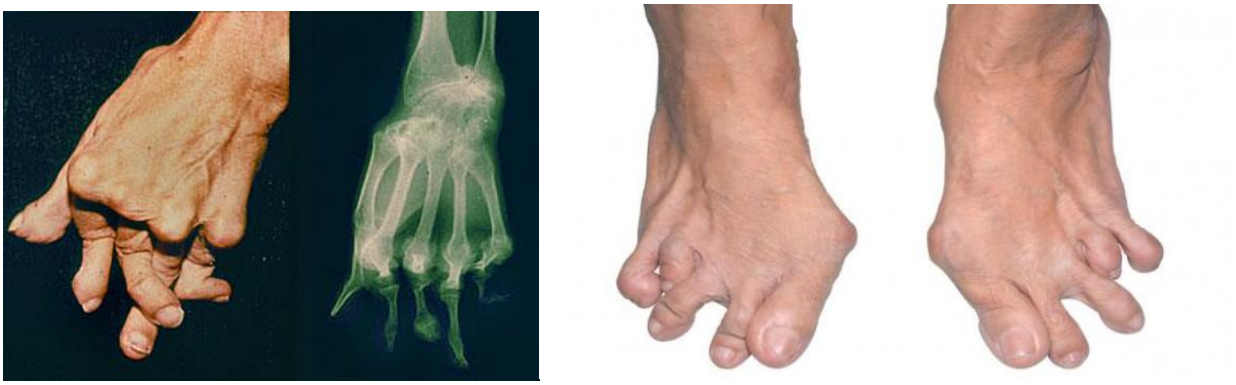
2.1 Overview

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.[10]

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.[11] In addition, the prevalence of specific extra-articular manifestations such as rheumatoid carditis and Felty's syndrome has markedly declined in the biologic era.[12] 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.[13,14]

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.[15] 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.

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.[16] 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.[17] 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.[18] 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.[19] 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.[20] 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.[21] 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.[22] 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.[23]

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).[24] 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 and/or use of sub-therapeutic doses.[25,26]

- ***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.[27]

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 (investigational, 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. Both agents act to reduce IL-6 circulation; tocilizumab binds to the entire IL-6 receptor, while sarilumab targets the alpha subunit of the receptor. 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.[28]

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.

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.[29,30] 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.[31]

Table 1. Targeted immune modulators: dosage forms and administration schedules

TIM	Recommended Dose (mg)	Route of Administration	FDA approval	WAC in January 2017*
Adalimumab (Humira®, AbbVie) ***TNFα inhibitor***	40mg 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	$2,049 per 40mg 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 a 200mg syringe or 200mg 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	$1,024 per 0.98 mL of a 50mg/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	4/24/2009 (SC); 07/19/2013 (IV)	$3,811 per 50mg syringe (SC) or $1,518 per 50mg (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	$1,113 per 100mg
Abatacept (Orencia®, Bristol Myers-Squibb) ***T-cell inhibitor***	Use as monotherapy or with DMARDs other than TNFα inhibitors; IV infusion dosed by weight [<60kg 500mg, 60-100kg 750mg, >100kg 1000mg], at weeks 0, 2, and 4, then every 4 weeks or 125mg SC injection once weekly	Subcutaneous or Intravenous	12/27/2005 (IV); 07/31/2011 (SC)	$957 per 125mg (SC) or $987 per 250mg (IV)
Rituximab (Rituxan®, Genentech/Biogen) ***CD20-directed cytolytic B-cell antibody***	In combination with MTX, two-1000mg 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 10mg/1mL vial ($8350 per 1000 mg dose)

TIM	Recommended Dose (mg)	Route of Administration	FDA approval	WAC in January 2017*
Sarilumab (investigational, Sanofi/Regeneron) ***IL-6 inhibitor***	150mg-200mg 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; 162mg subcutaneous injection every other week, increased to every week based on clinical response (or if patient weighs ≥100kg)	Subcutaneous or Intravenous	1/8/2010 (IV) 10/22/2013 (SC)	$898 per syringe (SC) or $95 per 20mg (IV)
Baricitinib (Olumiant™, Eli Lilly) ***JAK inhibitor***	4 mg once daily	Oral	Expected 4/19/2017	
Tofacitinib (Xeljanz®, Pfizer) ***JAK inhibitor***	5mg twice daily with or without conventional DMARDs or 11mg 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 January 2017)

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.[32] 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.[33] 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.[34]

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[35] 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. In addition, 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.[36] 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.[37] 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.[38]

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.[39] Many payers have created coverage policies that force a particular sequence of treatment, but this is felt to have more to do with medications carrying the largest negotiated discounts and/or rebates 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.[40] 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

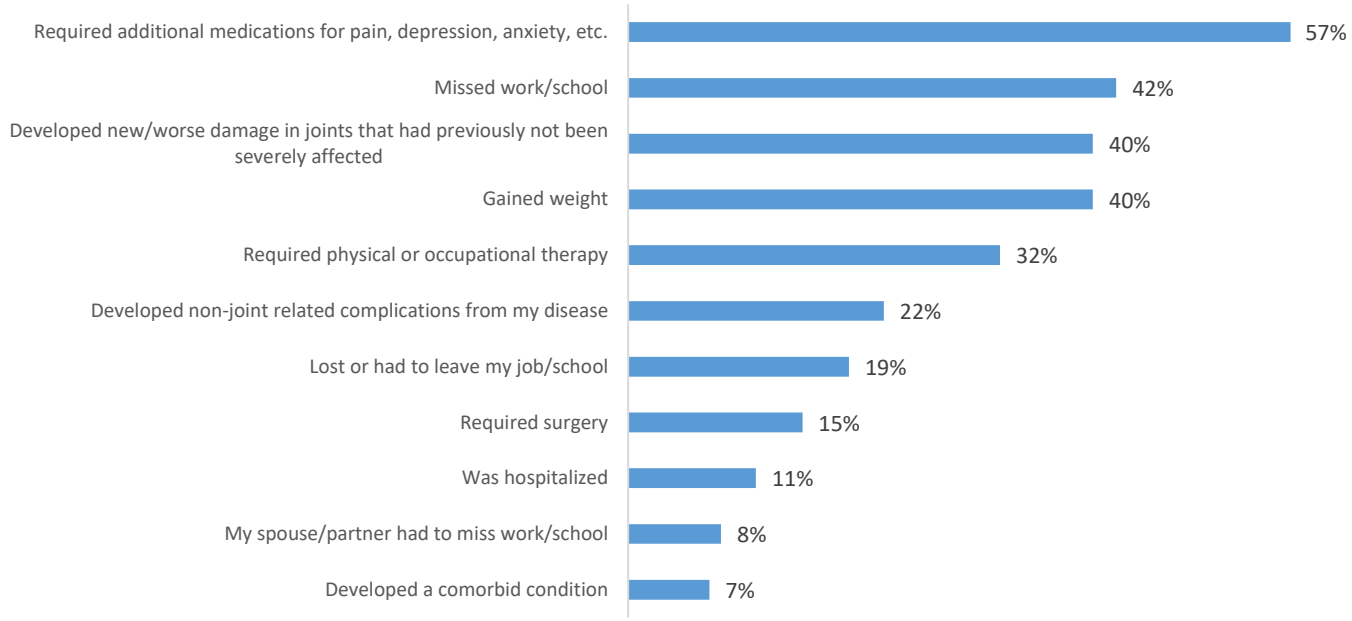
Patient Experiences

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.[41] 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.

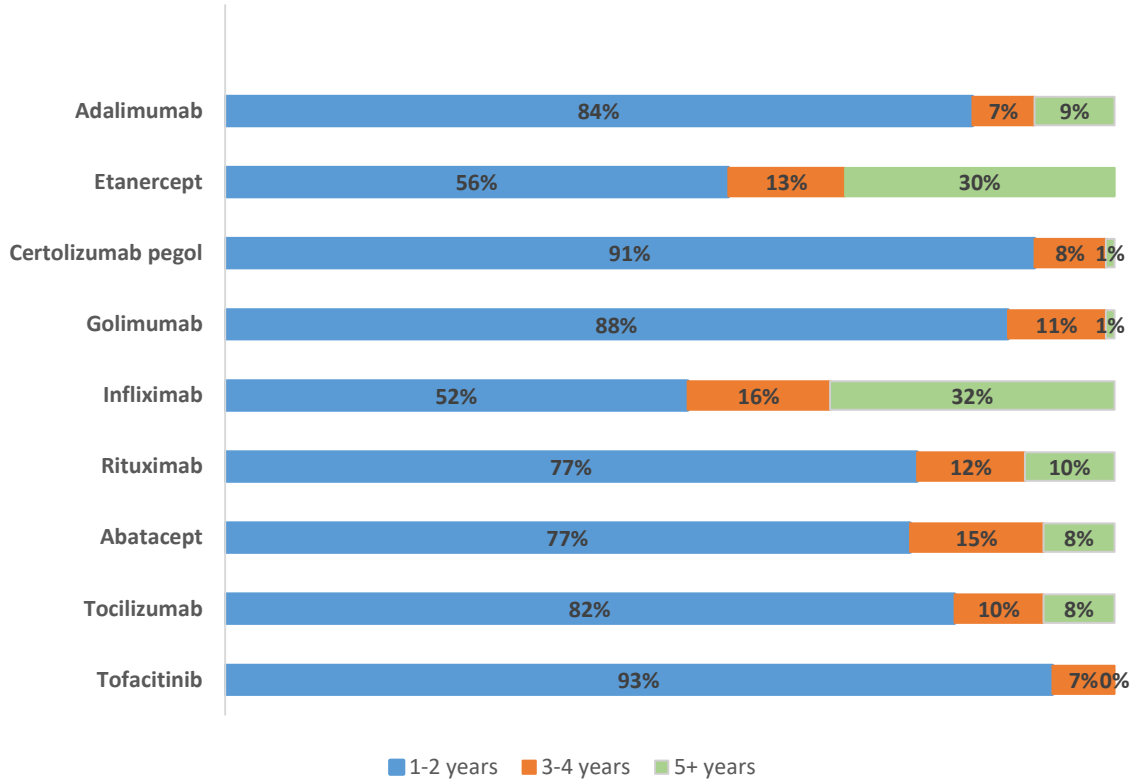
Figure 3. Reported impacts of rheumatoid arthritis during periods when disease was not well-controlled.



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 vs. 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).[42] 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.[43] 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. Twenty-five percent 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%
Tcell 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.[44] 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. Massachusetts, Connecticut and Vermont all require failure of one conventional DMARD and one TNFα inhibitor before providing payment for other agents.

Clinical Guidelines

American College of Rheumatology (ACR)[19]
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 cDMARD 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)[45]
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*[17,46]**
http://ard.bmj.com/content/early/2013/10/23/annrheumdis-2013-204573.short?rss=1&%3bssource=mfr

The European League Against Rheumatism (EULAR) Recommendations were most recently updated in October 2013. A focused recommendation on treating early arthritis was released in December 2016.

If there is no disease response to initial methotrexate monotherapy at three months, EULAR recommends risk stratification. If factors indicating unfavorable prognosis are absent, EULAR encourages considering conventional DMARD combination therapy. If these factors are present, EULAR recommends combination therapy of methotrexate with a TNFα inhibitor, abatacept, or tocilizumab. For patients with certain comorbidities, the panel suggests treatment with rituximab. They did not recommend monotherapy with TNFα inhibitors, rituximab, or abatacept—since combination with methotrexate is more effective—and only recognized tocilizumab as effective as monotherapy in achieving primary clinical endpoints.

EULAR recommends considering tofacitinib only after failure of two rounds of treatments with TNFα inhibitors, abatacept or tocilizumab. In regards to tofacitinib, the panel cautions of higher serious infection rates and lack of long term safety data. In contrast to the ACR, EULAR recommends tapering treatment whenever possible in patients who have achieved stable disease remission.

Patient-Based Recommendations

***Patient Panel (Coordinated by the American College of Rheumatology)*[47]**
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 and/or dose-finding only (i.e., Phase I/II). 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 for 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. Finally, we excluded studies that only compared two different methods of administration (e.g., intravenous vs. subcutaneous) of the same agent.

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.[48] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[6] 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.[49-51] 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).[50] 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 Appendix A.

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,[52] 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. In order 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 in order to support the comparative value analysis.

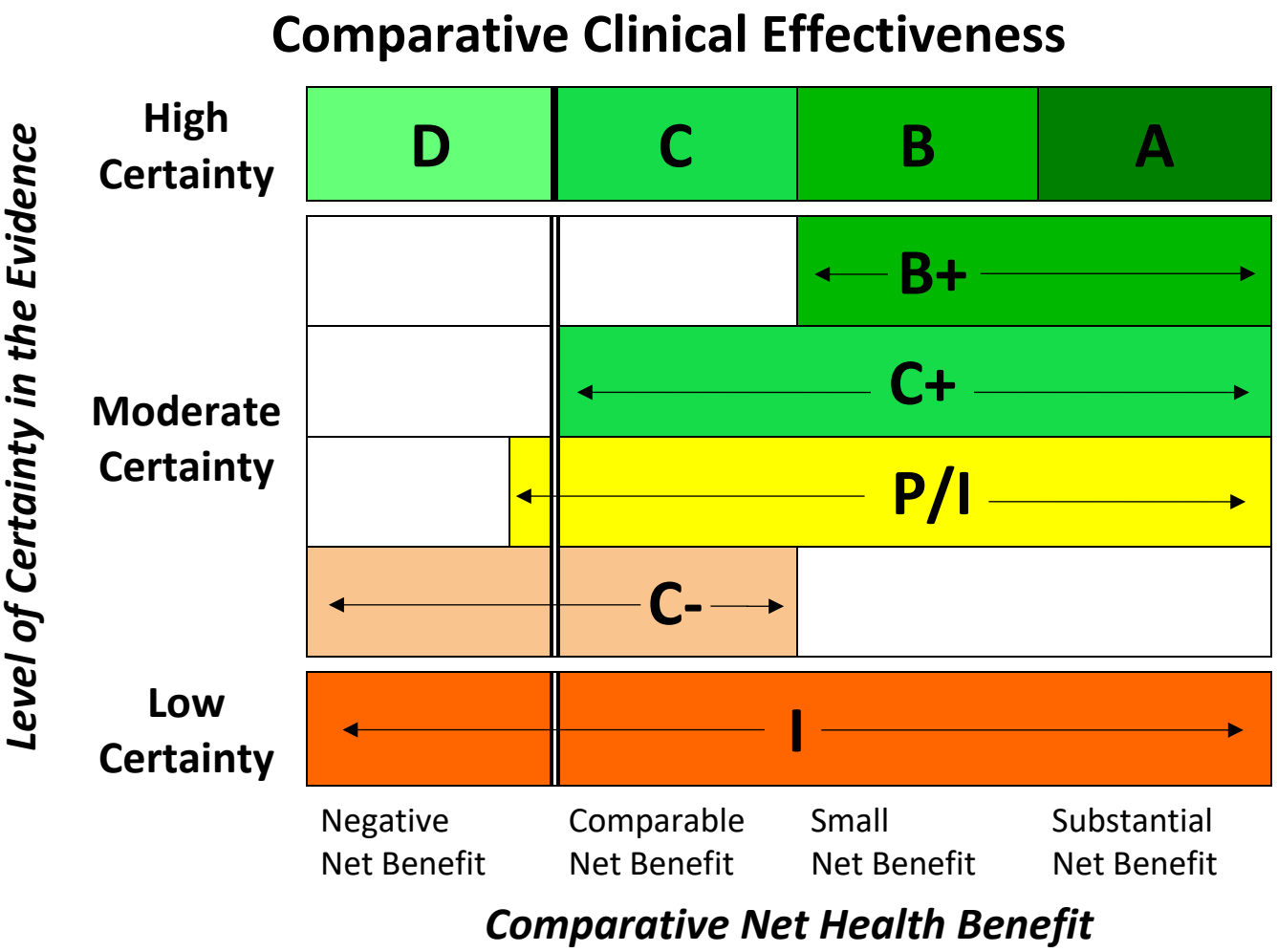
All statistical analyses were run within a Bayesian framework with WinBUGS 1.4.3. Criteria for trial selection, statistical methods and WinBUGS code are detailed in Appendix C.

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.[53]

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 3,588 potentially relevant references (see Appendix A, Figure A1), of which 98 met our inclusion criteria. These citations were comprised of 80 publications and 18 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.[49-51] In total, we included 113 reports of 68 RCTs and 16 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 68 RCTs provided data on a total of 28,130 patient enrollments. Of these RCTs, 59 focused on TIM combination therapy with methotrexate or other conventional DMARDs, six focused exclusively on TIM monotherapy, and three included both combination and monotherapy. The majority (n=63) of the RCTs focused on populations that were primarily (80% or more) TIM-naïve, or exclusively so. We identified five 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, nine involved comparisons of one TIM to another, and ten 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 68 trials to be of good (83%) or fair (18%) quality using criteria from the U.S. Preventive Services Task Force (USPSTF).[54] 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 16 observational studies, two were judged to be good, eleven fair, and three 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.[55] 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[56,57] and Genant[58] 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 380 to 448).[59,60] Consequently, there is substantial uncertainty in the degree of comparability of results between studies. Furthermore, because radiographic progression occurs gradually over

[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

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.

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,[61] or a more stringent 0.3,[62] 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 C. 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 and mixed 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 RCTs compared TIM monotherapy with conventional DMARDs alone on remission measures. Findings were mixed, with results suggesting statistically-significantly higher rates of remission for etanercept and tocilizumab but not for golimumab.

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;[63-66] both trials of tocilizumab and two of the three etanercept trials[63,67] 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.[68] 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. [59]

And 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 16 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 vs. 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, [67] [65,66] while significant differences were not observed in a comparison of golimumab monotherapy to conventional DMARDs. [69]

With regard to 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, [70] 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.[71] 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.[72-75] 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.[72,75] [73,74]

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 51.

Rituximab

We did not identify any head-to-head studies of rituximab.

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.[76,77] We did not identify any head-to-head studies of abatacept monotherapy.

Disease Activity and Remission

In the two RCTs, combination therapy of intravenous abatacept+methotrexate did not produce a statistically significant difference in the proportion of patients achieving DAS28-ESR clinical remission when compared with infliximab+methotrexate at week 24, and subcutaneous abatacept+methotrexate was also similar to adalimumab+methotrexate in proportion of patients achieving DAS28-ESR clinical remission at week 52; differences in other measures of remission as well as mean changes from baseline were also non-significant (see Table 4).[76,77]

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.[77] 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.[76]

Radiographic Progression

Radiographic progression was only reported in the AMPLE trial of subcutaneous abatacept+methotrexate versus adalimumab+methotrexate.[78] 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 versus 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.[76,77] There was also no statistically significant difference between the mean HAQ-DI change from baseline between abatacept+methotrexate and adalimumab+methorexate (see Table 7).[77]

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).[76]

Relative to adalimumab combination therapy, abatacept plus methotrexate-treated patients experienced similar improvements in both pain and fatigue.[77]

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 other patient reported outcomes.

We identified one head-to-head trial that compared tocilizumab monotherapy to TNFα inhibitor adalimumab monotherapy in TIM-naïve patients.[79] 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 clinical remission at week 24 using DAS28-ESR (39.9% vs. 10.5%, p<.0001) and other measures of remission (17% vs. 9% using CDAI, 18% vs. 8% using SDAI, p≤0.04)***;*** differences in mean changes from baseline were also significant (-3.3 vs. -1.8, p<0.0001)***.***[79]

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.[79]

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***.***[79]

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.[79]

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.[80] 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 clinical remission using DAS28-ESR (26.6% vs. 7%, p<.0001) and other measures of remission (7% vs. 3% using CDAI, p≤0.05); differences in mean changes from baseline were also significantly higher in the sarilumab group (-3.28 vs. -2.2, p<0.0001).[80]

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.[80]

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).[80]

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 mental component score; improvements in fatigue were comparable.[80]

JAK Inhibitors: Tofacitinib

In one head-to-head trial, tofacitinib monotherapy produced better results in rates of clinical remission achieved, ACR response across all levels, and improvement in HAQ-DI and other patient

reported outcomes compared with placebo, while differences between adalimumab monotherapy and placebo were not significant. Tofacitinib combination therapy was not statistically different from adalimumab combination therapy in rates of remission achieved, ACR response, and improvement in HAQ-DI in a second head-to head trial.

We identified two head-to-head studies of tofacitinib conducted in mostly TIM-naïve population. One study included both tofacitinib and adalimumab monotherapy arms, although the study was powered to detect differences between placebo and the two active arms and primary results were reported at 12 weeks.[81] Tofacitinib plus methotrexate was directly compared to adalimumab combination therapy in a second study.[82]

Disease Activity and Remission

In the trial of tofacitinib monotherapy, the percentage of patients achieving clinical remission using DAS28-ESR was significantly higher in the tofacitinib group at 12 weeks versus placebo (12.5% vs 3.6%, $p<.05$), but this rate did not differ for adalimumab (3.9%) versus placebo.[81]

In the second head-to-head trial, there was no statistically significant difference observed in the proportion of patients achieving DAS28-ESR remission between combination therapy with tofacitinib plus methotrexate versus adalimumab plus methotrexate.[82]

ACR20/50/70

Monotherapy with tofacitinib was superior to placebo for ACR response at week 12 at all levels of ACR response, but this was not the case for adalimumab. As an example, 59% achieved at least an ACR20 response with tofacitinib versus 36% with adalimumab and 22% for placebo (see Table 5 for details).[81]

At 24 weeks of follow-up in the ORAL Standard trial, combination therapy with tofacitinib+methotrexate versus adalimumab+methotrexate showed statistical differences only at the ACR70 level (20% achieved ACR70 with tofacitinib versus 10% with adalimumab; $p\leq0.01$).[82]

Radiographic Progression

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

HAQ-DI

The mean HAQ-DI change from baseline was greater at 12 weeks in the tofacitinib monotherapy group compared with placebo, but differences were not significant in the adalimumab-placebo comparison.[81]

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 at from baseline at 24 weeks in the two groups.[82]

Other Patient-Reported Outcomes

After twelve weeks of follow-up, patients treated with tofacitinib and adalimumab monotherapy both experienced clinically important improvements in pain.[81] Similarly, patients experienced comparable improvement in quality of life, pain, and fatigue with combination tofacitinib or adalimumab therapy.[83]

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.[84] We did not identify any monotherapy studies.

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 clinical remission using DAS28-ESR and other measures of remission.[84]

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.[84]

Radiographic Progression

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

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%, $p<0.05$).[84]

Other Patient-Reported Outcomes

We did not identify any studies of baricitinib in comparison to another TIM that reported on health-related quality of life or pain; relative to adalimumab+methotrexate, patients treated with baricitinib+methotrexate experienced greater improvement in fatigue (p≤0.05).[84]

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 also produced lower rates of clinical improvement than tofacitinib in an additional trial, but statistical comparisons were performed vs. placebo and not between active arms.

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, tofacitinib, and certolizumab 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.

We identified eight adalimumab head-to-head trials; three 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 eight trials were conducted in TIM-naïve or mostly TIM-naïve populations.[79-81] ***46,77,82,84,85***

Disease Activity and Remission

Seven of the eight 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 methotrexate), while the remaining three trials compared adalimumab monotherapy to sarilumab, tocilizumab and tofacitinib monotherapy. In the three 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≤0.0001) ; tocilizumab (10.5% vs. 39.9% at 24 weeks, p<0.0001); rates were lower versus tofacitinib as well (12.5% vs 3.9% at 12 weeks), but statistical testing was only done versus placebo.[79-81] 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).

Among the combination therapy trials, adalimumab did not differ from abatacept, tofacitinib, baricitinib and certolizumab pegol.[46,77,82,84] 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 eighth trial comparing adalimumab with etanercept,[85] only the mean changes from baseline was reported; adalimumab had a similar level of change from baseline compared with etanercept (see Table 4).

ACR20/50/70

Seven head-to-head RCTs of TIMs reported ACR response using adalimumab as a comparator (see Table 5). In the three trials that evaluated TIM monotherapy, adalimumab was inferior to sarilumab and intravenous tocilizumab across all levels of ACR response, and not different from placebo in the tofacitinib comparison.[79-81] 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); a substantial difference was also noted relative to tofacitinib monotherapy (35.9% vs. 59.2%), and the p-value was significant for tofacitinib versus placebo (22%) but not for adalimumab. 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.[84]

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 or 50, although a significantly smaller proportion of patients achieved ACR70 with adalimumab in the tofacitinib study (10% vs. 20%; $p\leq0.01$).[77,82]

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.[46] Our review identified two observational studies that reported on ACR response.[86,87] 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.[86] 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).[87]

Radiographic Progression

A single head-to-head study reported on radiographic progression.[78] 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 versus 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).

HAQ-DI

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

In the monotherapy trials, adalimumab was observed to be similar to tocilizumab in HAQ-DI improvement,[79] 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, $p=0.0037$).[80] Adalimumab also resulted in lower mean change in HAQ-DI from baseline when compared with tofacitinib (-0.35 vs. -0.51), and this change was significant versus placebo only for tofacitinib.

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%, $p<0.05$),[84] while adalimumab was found to be similar to abatacept, tofacitinib and certolizumab in HAQ-DI improvement.[46,77,82]

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.[80]

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.[79]

Relative to tofacitinib (monotherapy or in combination with methotrexate), adalimumab-treated patients treated experienced similar improvements in quality of life, pain, and fatigue at month 3.[81,83]

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).[85]

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.[46] 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 clinical remission using the DAS28-ESR measure.[46] 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.[46]

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 (with or without 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 (with or without concomitant conventional DMARD therapy) in TIM-naïve patients[85] In addition, we identified three observational studies that compared the three TNFα inhibitors adalimumab, infliximab and etanercept.[86-88]

Disease Activity and Remission

In the one trial that directly compared TNFα inhibitor etanercept with another TNFα inhibitor adalimumab TIM-naive patients, the rates of clinical remission 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.[85]

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).[86] 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).[88] The third study, based on the DANBIO registry in Denmark, did not find a significant difference between etanercept and adalimumab.[87]

ACR20/50/70

We identified head-to-head evidence of ACR response for etanercept in two observational studies.[86,87] In one study from the CORRONA registry, significant differences were not demonstrated between adalimumab, etanercept, or infliximab for any level of response.[86] 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).[87]

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).[85]

TNFα inhibitors: Golimumab

We did not identify any head-to-head studies of golimumab.

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.[76] We did not identify any monotherapy studies. In addition, we identified three observational studies that compared three TNFα inhibitors: adalimumab, infliximab and etanercept.[86-88]

Disease Activity and Remission

In the one head-to-head trial that compared combination therapy with infliximab plus methotrexate with abatacept plus methotrexate,[76] disease activity improved in both groups, but there was no statistical difference observed in the proportion of patients achieving DAS28-ESR clinical remission.[76]

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) .[86] 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).[88] 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).[87]

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.[76]

Our review also identified two observational studies that reported on ACR response.[86,87] 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.[86] 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).[87]

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.[76]

Table 4: Disease activity outcomes across head-to-head trials

Treatment	N	DAS28-ESR or CRP	DAS28 mean change from baseline	% achieving DAS28 remission	% achieving CDAI remission	% achieving SDAI remission
ATTEST trial at 24 weeks[76]						
Abatacept (IV) + MTX	156	DAS28-ESR	-2.53†	11.8	NR	NR
Infliximab + MTX	165	DAS28-ESR	-2.25†	12.8	NR	NR
AMPLE trial at 52 weeks[77]						
Abatacept (SC) + MTX	318	DAS28-CRP	-2.3	43.3	23.5	23.3
Adalimumab + MTX	328	DAS28-CRP	-2.27	41.9	24	24.8
ADACTA trial at 24 weeks[79]						
Tocilizumab monotherapy	162	DAS28-ESR	-3.3***	39.9***	17.2*	18.4**
Adalimumab monotherapy	163	DAS28-ESR	-1.8	10.5	9.3	8
MONARCH trial at 24 weeks[80]						
Sarilumab monotherapy	184	DAS28-ESR	-3.28***	26.6***	7.1*	NR
Adalimumab monotherapy	185	DAS28-ESR	-2.2	7	2.7	NR
Fleischmann 2012 at 12 weeks						
Tofacitinib monotherapy	*49*	DAS28-ESR	-2.19**	12.5†	NR	NR
Adalimumab monotherapy	*53*	DAS28-ESR	-1.43	3.9	NR	NR
ORAL Standard trial at 24 weeks[82]						
Tofacitinib + MTX	204	DAS28-ESR	NR	6.2	NR	NR
Adalimumab + MTX	204	DAS28-ESR	NR	6.7	NR	NR
RA-BEAM at 24 weeks[84]						
Baricitinib + MTX	487	DAS28-ESR & CRP	NR	18-ESR; 35-CRP	16	16
Adalimumab + MTX	330	DAS28-ESR & CRP	NR	18-ESR; 32-CRP	12	14
EXXELERATE at 24 weeks[46]						
Certolizumab + MTX	353	DAS28-ESR	NR	32.4	NR	NR
Adalimumab + MTX	361	DAS28-ESR	NR	29.4	NR	NR
RED SEA‡ at 24 weeks[85]						
Etanercept	60	DAS28-CRP	-1.76	NR	NR	NR
Adalimumab	60	DAS28-CRP	-1.44	NR	NR	NR

†statistical significance not reported; ***p <0.001; **p<0.01; *p<0.05; ǂ Patients in both treatment arms were on TIM ± baseline conventional DMARD

Table 5. ACR20/50/70 outcomes across head-to-head trials

Study arm	N	ACR20, %	ACR50, %	ACR70, %
Fleischmann 2012[81] at 12 weeks[α]				
Adalimumab monotherapy (n=53)	53	35.9	18.9	3.8
Tofacitinib monotherapy	49	59.2	36.7	12.2
MONARCH[80] at 24 weeks				
Adalimumab monotherapy	185	58.4	29.7	11.9
Sarilumab monotherapy	184	71.7*	45.7*	23.4*
ADACTA[79] at 24 weeks				
Adalimumab monotherapy	163	49.4	27.8	17.9
Tocilizumab (IV) monotherapy	162	65*	47.2*	32.5*
RA-BEAM[84] at 12/24 weeks				
Adalimumab + methotrexate	330	61/66	35/46	13/22
Baricitinib + methotrexate	487	70**/74**	45*/50	19**/30**
ORAL Standard[82] at 24 weeks				
Adalimumab + methotrexate	204	47.2	29.1	10.1
Tofacitinib + methotrexate	204	51.5	36.2	19.9*
AMPLE[77] at 1 year				
Adalimumab + methotrexate	328	63.4	46.0	26.2
Abatacept (SC) + methotrexate	318	64.8	46.2	29.2
EXXELERATE[46] at 104 weeks				
Adalimumab + methotrexate	454	67%	57%	41%
Certolizumab pegol + methotrexate	454	65%	53%	40%
ATTEST[76] 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[77,78]				
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

α change from baseline in total score ≤ smallest detectable change using cut-off of 2.8; van der Heijde modified Sharp score

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[76]				
Abatacept + MTX	156	NR	61.5	0.3
Infliximab + MTX	165	NR	58.8	0.3
ADACTA trial at 24 weeks[79]				
Tocilizumab monotherapy	162	-0.7	NR	--
Adalimumab monotherapy	163	-0.5	NR	--
MONARCH trial at 24 weeks[80]				
Sarilumab monotherapy	184	-0.61***	62**	0.3
Adalimumab monotherapy	185	-0.43	47.6	0.3
Fleischmann 2012 at 12 weeks				
Tofacitinib monotherapy	*49*	-0.51†	NR	NR
Adalimumab monotherapy	*53*	-0.35	NR	NR
ORAL Standard trial at 24 weeks[82]				
Tofacitinib + MTX	204	-0.55	NR	--
Adalimumab + MTX	204	-0.49	NR	--
RA-BEAM at 24 weeks[84]				
Baricitinib + MTX	487	NR	73*	0.22
Adalimumab + MTX	330	NR	64	0.22
EXXELERATE at 104 weeks[46]				
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

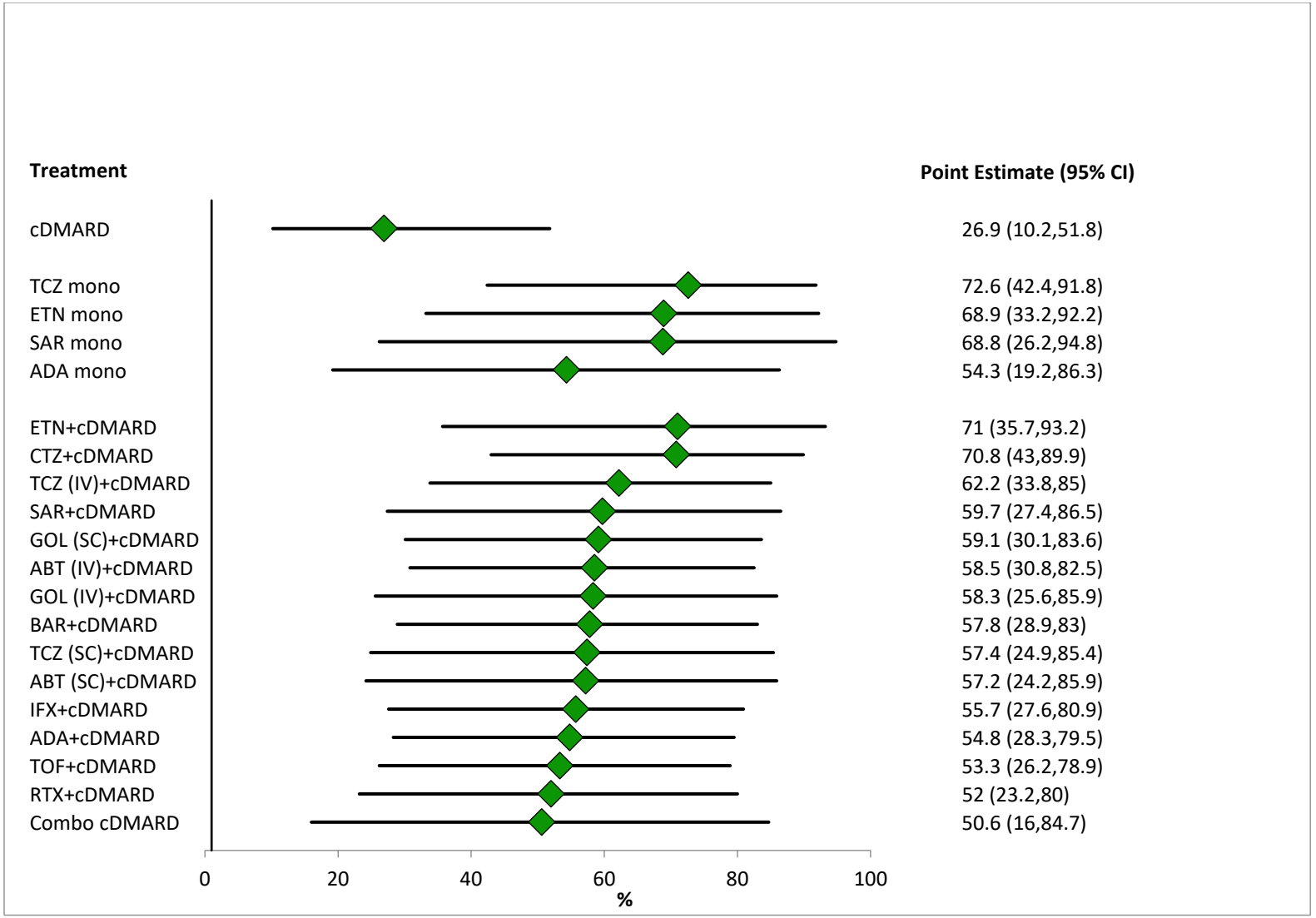
We employed a random-effects approach to evaluating ACR responses. We assessed information separately for TIM naïve/mixed populations and TIM-experienced populations. Further details on our methods, including data input tables, network diagrams, and league tables of results, can be found in Appendix C. Our approach included both direct and indirect evidence in our calculations.

TIM-Naïve/Mixed Populations

A forest plot of the results for ACR20 response among both monotherapy and combination therapy regimens in TIM-naïve/mixed populations can be found in Figure 6. The pattern of findings was similar to that observed in the individual studies. All TIMs were superior to conventional DMARDs, whether as combination therapy or monotherapy, but their relative effects differed. In addition, rankings of the TIMs generally followed findings from head-to-head studies.

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 all of the TIMs yielded showed no statistical differences, as the likelihood of ACR20 response included 1.0 (no difference) in the credible interval for all comparisons (see Appendix C, Figure C2-C4).

Figure 6. Percentage of patients achieving ACR20 or better, 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 Table 8, which is 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, as none were found to be statistically-significant.

Table 8. Network meta-analysis derived proportions of patients in each ACR response category, by targeted immune modulator regimen: Mixed population

Treatment	ACR <20	ACR 20-50	ACR 50-70	ACR 70-100
Tocilizumab (IV) monotherapy	27%	23%	22%	28%
Etanercept + cDMARD	29%	23%	21%	27%
Certolizumab pegol + cDMARD	29%	23%	21%	27%
Etanercept monotherapy	31%	23%	21%	25%
Sarilumab monotherapy	31%	23%	21%	25%
Tocilizumab (IV) + cDMARD	38%	24%	19%	19%
Sarilumab + cDMARD	40%	24%	18%	18%
Golimumab (SC) + cDMARD	41%	24%	18%	17%
Abatacept (IV) + cDMARD	42%	24%	18%	17%
Golimumab (IV) + cDMARD	42%	24%	18%	17%
Baricitinib + cDMARD	42%	24%	18%	16%
Tocilizumab (SC) + cDMARD	43%	24%	18%	16%
Abatacept (SC) + cDMARD	43%	23%	18%	16%
Infliximab + cDMARD	44%	23%	17%	15%
Adalimumab + cDMARD	45%	23%	17%	15%
Adalimumab monotherapy	46%	23%	17%	14%
Tofacitinib + cDMARD	47%	23%	16%	14%
Rituximab + cDMARD	48%	23%	16%	13%
Intensive cDMARD*	49%	23%	16%	12%
Conventional DMARD	73%	16%	8%	4%

*combination therapy with 2-3 conventional DMARDs

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 C6-C8).

Table 9. 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%
cDMARD	77%	14%	6%	3%

Radiographic Progression

Standardized mean difference (SMD) findings for the TIM-naïve/mixed population are presented for Sharp score 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 were directionally in favor of these agents but 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. Etanercept, golimumab, infliximab, tocilizumab and abatacept with long term trial data (i.e. 1 year or more) showed comparable overall safety profile, 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 10. 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 adverse events, serious infections, and deaths 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.

Table 10: Adverse events during the conventional DMARD controlled period

	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	1,214	184	454	943	780	299	446	704	594	4,683
Any AE	76	79.7	72.2	65.2	50.2	72.1	77.3	74	68.7	54	73.5	64.5
Serious AEs	9	6	6.9	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	4.8	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	2.8	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	NR	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

* 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 11: Long term adverse events

	Abatacept[76]	Abatacept[89]	Tocilizumab[90]	Etanercept[91]	Golimumab[92]	Infliximab[76]
Length of follow up (Years)	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

All numbers are events per 100 patient-years, except where indicated

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[79,80,84,85] (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).[78] 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.[76] There was no evidence of increased malignancies, or death between treatment groups in all the 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.[93]

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).[93]

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 68 RCTs identified for this review, only nine 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. 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, 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 is artificial given that patients

have already had inadequate responses to conventional DMARD therapy. 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[39] 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.[94-96]

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. 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.

Finally, while it is clear that 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 as well as 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. 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. There is sufficient uncertainty, however, regarding the long-term effectiveness and safety of the two investigational TIMs (baricitinib and sarilumab), 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 12. 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+
	Tofacitinib	Adalimumab	P/I
	Etanercept	Adalimumab	C
Combination Therapy	Baricitinib	Adalimumab	C+
	Tofacitinib	Adalimumab	C
	Abatacept (SC)	Adalimumab	C
	Certolizumab pegol	Adalimumab	C
	Abatacept (IV)	Infliximab	B+
All Other Head-to-Head Comparisons	---	---	I

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 all 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 in pain, fatigue, and quality of life in single RCTs, 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.

Rates of DAS28 remission and ACR response with tofacitinib were numerically higher than adalimumab, but these differences were not statistically tested (significance testing was only done vs. placebo), and primary measures were assessed at 12 weeks (vs. 24 weeks in most other studies). In addition, our NMA findings showed no material differences in ACR response between the two regimens. As a result, we conclude that tofacitinib's net health benefit is promising but inconclusive ("P/I") relative to adalimumab. An additional monotherapy study (RED SEA) compared adalimumab and etanercept, 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").

Among combination regimens involving methotrexate, baricitinib, tofacitinib, abatacept (subcutaneous form), and certolizumab pegol have also been compared to adalimumab+methotrexate in single trials. In the RA-BEAM study, baricitinib was associated with a statistically-significantly but modestly higher rate of ACR20 response (74% vs. 66% for adalimumab), 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 baricitinib vs. adalimumab to represent a comparable or better net health benefit ("C+"). The three other comparisons yielded no significant or material differences in clinical outcomes between tofacitinib, abatacept SC, or certolizumab pegol vs. 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.

In addition, 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 across the TIMs; for example, non-response rates of 26-49% across the TIMs. However, credible intervals were wide and included 0 for 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 as well as 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 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. 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 7. 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.

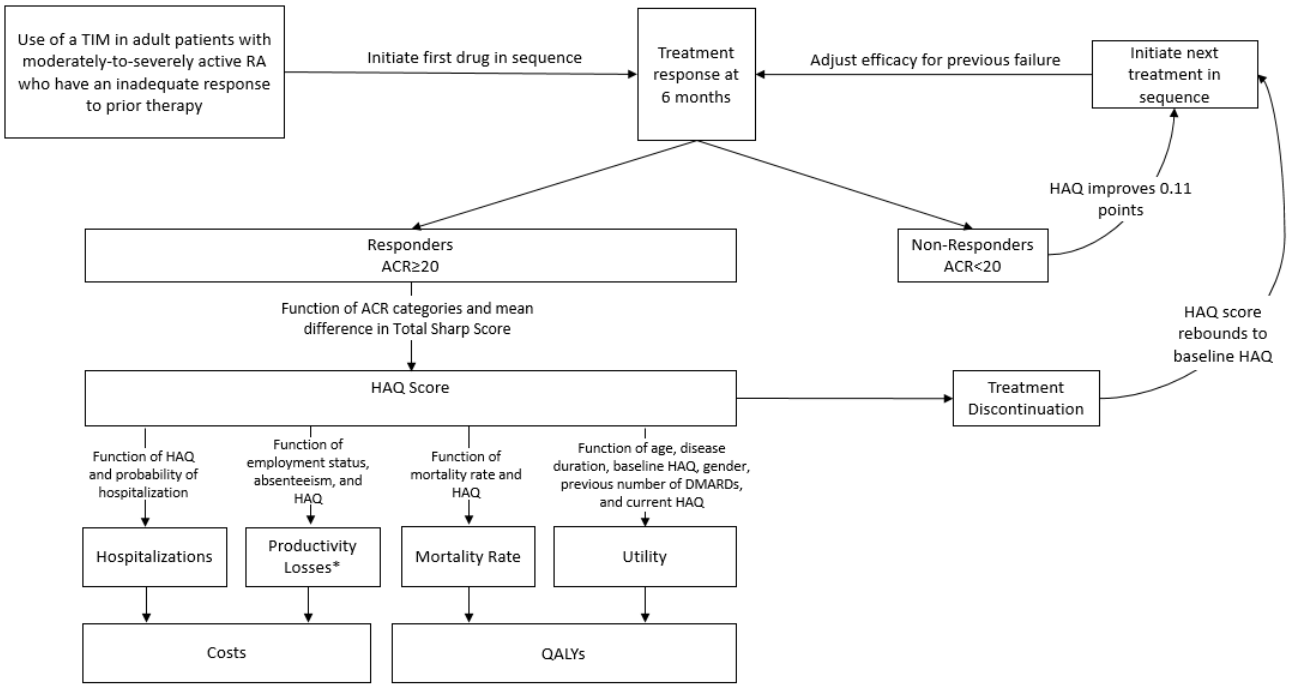
Patients could discontinue a TIM due to lack of effectiveness and/or adverse events. Patients discontinued treatment due to lack of effectiveness if they received an ACR score less than 20 (defined as non-responders) in the first six-months cycle. Thus, ACR scores >20 were considered treatment responders. A cycle length of six months was used to reflect the time needed to evaluate a treatment's effectiveness.[97] 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,[97-101] 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 6.

After starting a TIM, the American College of Rheumatology (ACR) categories were correlated to HAQ improvements.[101,102] In addition to relating ACR response to HAQ, this model framework also related the HAQ score to joint damage and disease progression, as measured through modified Total Sharp Score (mTSS).[100] 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,[100] 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.

Figure 7. Model Framework



*Productivity losses will be 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, including indirect costs due to potential productivity gains or losses.[103] 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 (cDMARD) 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 results. All TIM therapies in the market basket were averaged and weighted equally. A scenario analysis explored the cost-effectiveness of TIMs used as monotherapy, for TIMs with available monotherapy evidence.
- Those patients who had an ACR score less than 20 were assumed to be non-responders to that TIM therapy.[101] 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.[101]
- 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.[101,102]
- HAQ improved (decreased) with lower mTSS scores. A 20-point decrease in mTSS was associated with an approximate 0.2-point improvement (decrease) in HAQ.[100] 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 Study over a two-year observation period.[104]
- The resulting changes in progression for responding to TIM treatment over time as measured by mTSS changes generate small improvements in HAQ over time (approximately 0.03 per year on continued TIM treatment beyond initial improvement). The generated HAQ improvements over time from TIM treatment are consistent with observational studies.[105]
- The cost calculations for intravenously administered therapies accounted for vial wastage (i.e., no vial sharing was allowed).
- The cDMARD 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. The HAQ for the cDMARD comparator does not change over time.

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.[106] Table 13 depicts the model characteristics for the population naïve to TIMs or mixed (with a majority 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 cDMARD arm, a baseline HAQ of 1.7 was used so that after the first cDMARD treatment cycle the cohort's HAQ was approximately 1.5.

Table 13. Base-Case Model Cohort Characteristics

	Value	Primary Source
Mean age	55 years (range 50 to 60 years old)	Curtis et al., 2010[106]
Female	79% (range 73%,86%)	Curtis et al., 2010[106]
Caucasian	84%	Curtis et al., 2010[106]
Mean weight	170 pounds	National Health and Nutrition Examination Survey data[107]
Baseline HAQ prior to cDMARD treatment benefit	1.7 (range: 1.37 to 2.03)	Curtis et al., 2010[106]
Baseline TSS	54 (SD: 64)	Lillegraven et al., 2011[108]

HAQ=Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index; TSS=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.

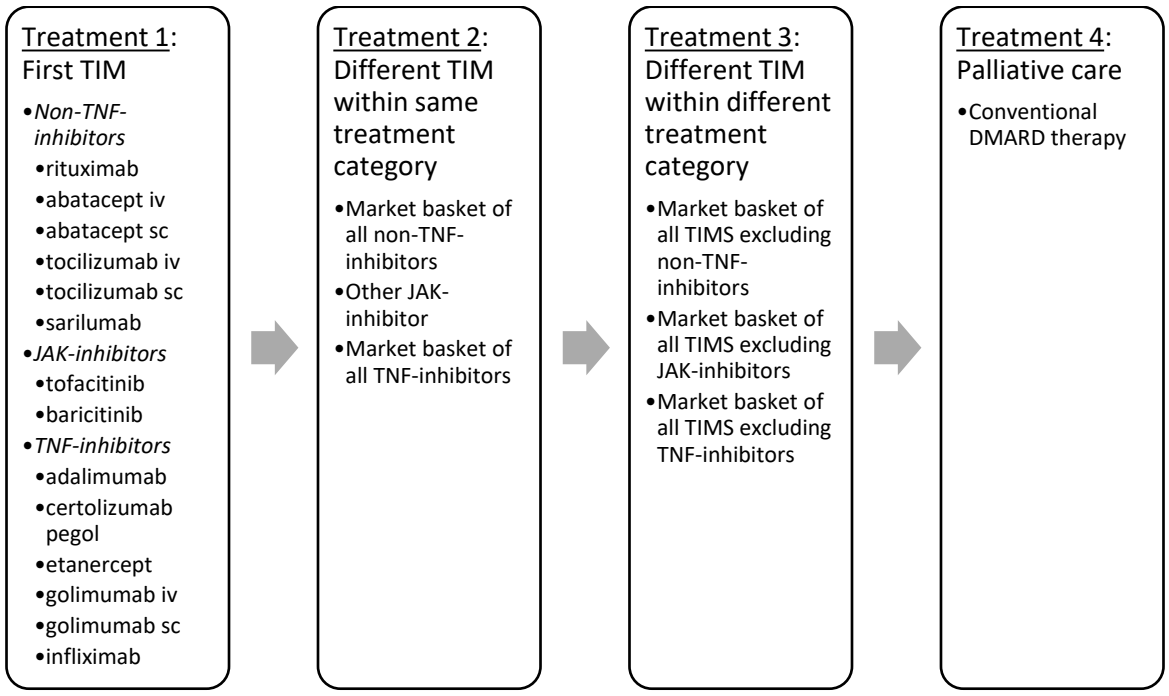
Treatment Strategies

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).[109-118]

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.[101,119]

Figure 8. 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.

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[120] 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 third quarter of 2016. We estimated net prices for these agents by comparing the four-quarter rolling averages (i.e., fourth quarter 2015 through third 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 from WAC (rounded to the nearest 5%) to the most current WAC[121] for each medication 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 14 details the drug unit, WAC unit price, SSR unit price, and annual drug cost calculated using the SSR discounted unit price (WAC unit prices updated in January 2017). Note that for the investigational drugs, the annual drug cost was assumed to equal that of the drug with the same mechanism of action and route of administration (tocilizumab subcutaneous for sarilumab, and tofacitinib for baricitinib). Additional drug inputs, including dose and frequency of administration, can be found in Table 1 of Appendix D.

Table 14. Drug Cost Inputs

Intervention	Administration	Unit	Unit WAC*	SSR Unit Price	Annual Drug Cost‡
rituximab	IV	100mg	$835	$710	$30,764
abatacept	IV	250mg	$987	$691	$27,637
abatacept	SC	125mg	$957	$670	$34,840
tocilizumab	IV	20mg	$95	$76	$27,626
tocilizumab	SC	162mg	$898	$719	$21,861
sarilumab**	SC	----------	----------	----------	$21,861
tofacitinib	ORAL	5mg	$63	$60	$43,873
baricitinib**	ORAL	----------	----------	----------	$43,873
adalimumab	SC	40mg	$2,049	$1,434	$37,283
certolizumab pegol	SC	200mg	$1840	$1,288	$34,775
etanercept	SC	50mg	$1,024	$717	$37,290
golimumab	SC	50mg	$3,811	$2,668	$32,014
golimumab	IV	50mg	$1,518	$1,063	$28,331
infliximab	IV	100mg	$1,113	$779	$27,556
cDMARD (methotrexate)	ORAL	2.5mg	$2.78	Generic	$1,155

*WAC as of January 2017

**For investigational drugs, the annual drug cost was assumed to equal that of the drug with the same mechanism of action and route of administration.

‡The annual drug cost only includes the cost of drug therapy, and does not include any costs associated with administration or monitoring.

Administration and Monitoring Costs

Oral treatments were assumed to have no administration costs. Subcutaneous treatments included costs for an 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[122] and the cost per office visit was $73.40 (HCPCS code 99213).[123] The relationship between hospital days and HAQ is provided in Table 5 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.[124] Adverse event inputs are detailed in Table 4 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.[125] The number of hours missed from work is detailed in Table 5 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.[101,102] In addition to relating ACR response to HAQ, the model also accommodated the association of joint damage with HAQ, as measured through mTSS.[100] 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 5 of Appendix D.

Mortality

Prior evidence suggests that improved (lower) HAQ scores are associated with lower likelihood of death.[126] A US observational study found that HAQ was the most significant predictor of mortality.[126] The quantitative relationship between HAQ and mortality was assumed to be the same as that used in a recent US RA cost-effectiveness study.[101] This relationship is detailed in Table 5 of Appendix D.

Utilities

The relationship between HAQ and utility score was based on the Wailoo and colleagues' publication, as shown in Table 5 of Appendix D.[98] 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.[127] 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.[10] 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.

Additionally, a disutility (-0.156) was assigned to individuals who experienced a severe adverse event.[128] The disutility lasted for one month[128] for those who experienced a serious infection and for two months[129] for those who contracted tuberculosis. Additional details on adverse event disutilities can be found in Table 4 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+cDMARD versus cDMARD 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 that can be administered as monotherapy, 5) estimating the cost-effectiveness for those TIMs studied in TIM-experienced populations, and 6) evaluating the deterministic results over short-term time horizons (one year and three years) to determine cost-effectiveness and cost per additional first TIM (treatment 1) responder.

6.3 Cost-Effectiveness Model: Results

Base Case Results

Table 15 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 cDMARD. 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 6 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 1.37 (tofacitinib) to 2.15 (etanercept) as compared to conventional DMARD therapy.

Table 15. Results for the Base-Case for TIMs Added on to cDMARD

Treatment 1	Drug Cost	Payer Cost	Average HAQ	Life Years	QALYs
rituximab	$362,572	$455,084	1.05	17.04	13.31
abatacept (iv)	$365,123	$458,529	1.02	17.08	13.43
abatacept (sc)	$405,367	$506,394	0.97	17.14	13.56
tocilizumab (iv)	$367,499	$462,269	0.99	17.11	13.52
tocilizumab (sc)	$325,876	$415,768	1.01	17.08	13.44
sarilumab	$324,677	$413,891	1.02	17.07	13.41
tofacitinib	$468,909	$576,419	1.12	16.95	13.08
baricitinib	$472,209	$577,305	1.02	17.08	13.42
adalimumab	$406,580	$504,058	1.06	17.02	13.29
certolizumab pegol	$412,941	$512,859	1.05	17.04	13.34
etanercept	$447,630	$551,497	0.88	17.24	13.86
golimumab (sc)	$387,586	$486,273	1.12	16.96	13.10
golimumab (iv)	$372,707	$469,658	1.12	16.95	13.09
infliximab	$370,148	$461,763	1.02	17.07	13.45
cDMARD	$18,679	$62,894	1.49	16.52	11.71

Four TIMs (adalimumab, etanercept, tocilizumab intravenous, and sarilumab) had data for monotherapy administration, and thus, treatment with these TIMs as monotherapy (i.e., not in conjunction with conventional DMARDs) was modeled. 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 as monotherapy. The TIM monotherapy results indicate that treatment with TIMs over a lifetime horizon leads to QALY improvements ranging from 1.78 (adalimumab) to 2.26 (tocilizumab IV) as compared to conventional DMARD therapy.

Table 16. Results for TIMs as monotherapy

Treatment 1	Drug Cost	Payer Cost	Average HAQ	Life Years	QALYs
tocilizumab (iv)	$381,073	$479,950	0.84	17.29	13.97
sarilumab	$311,962	$399,162	0.87	17.26	13.88
adalimumab	$420,362	$524,380	0.99	17.11	13.49
etanercept	$437,620	$542,527	0.93	17.18	13.70

Table 17 presents the discounted lifetime incremental cost-effectiveness ratios for each of the TIMs as compared to cDMARDs 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 ICER compared to conventional DMARD therapy. Importantly, however, the cost-effectiveness of all TIMs in combination with cDMARDs relative to cDMARDs 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, six TIMs were dominant, meaning they were less costly and more effective than adalimumab. Golimumab (both intravenous and subcutaneous) was less effective and less costly than adalimumab. Four other TIMs (abatacept sc, baricitinib, certolizumab pegol, and etanercept) were more costly but also more effective than adalimumab, with estimated ICERs that ranged from ~$9,000-$500,000 per QALY. 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).

Table 17. Incremental Cost-Effectiveness Ratios for the Base Case, for TIMs Added on to cDMARD

Treatment 1	ICER (cost per QALY gained) Comparator: cDMARD	ICER (cost per QALY gained) Comparator: adalimumab
rituximab	$245,082	Less costly, More effective
abatacept (iv)	$230,131	Less costly, More effective
abatacept (sc)	$239,901	$8,672
tocilizumab (iv)	$220,853	Less costly, More effective
tocilizumab (sc)	$204,629	Less costly, More effective
sarilumab	$206,257	Less costly, More effective
tofacitinib	$375,813	More costly, Less effective
baricitinib	$300,268	$547,160
adalimumab	$279,341	Reference
certolizumab pegol	$275,589	$164,709
etanercept	$227,774	$83,842
golimumab (sc)	$305,121	Less costly, Less effective
golimumab (iv)	$294,995	Less costly, Less effective
infliximab	$229,284	Less costly, More effective

Table 18 presents the discounted lifetime incremental cost-effectiveness ratios for each of the treatment 1 TIMs as monotherapy as compared to conventional DMARDs and to the TIM market leader, adalimumab. For three drugs (tocilizumab, sarilumab, adalimumab), cost-effectiveness was improved as monotherapy but still exceeded commonly-cited cost-effectiveness thresholds. Etanercept was slightly less cost-effective as monotherapy, results that were driven primarily by ACR response and mTSS changes.

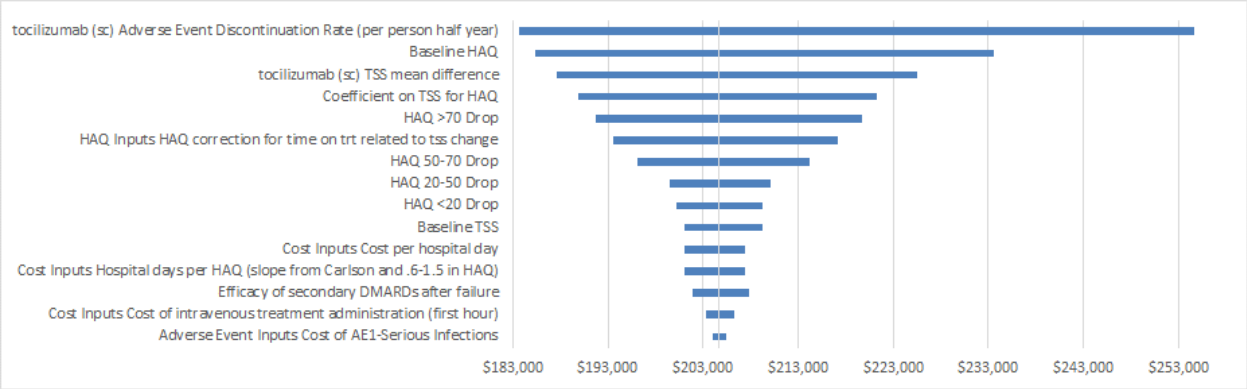
Table 18. Incremental Cost-Effectiveness Ratios for TIMs as monotherapy

Treatment 1	ICER (cost per QALY gained) Comparator: cDMARD	ICER (cost per QALY gained) Comparator: adalimumab
tocilizumab (iv)	$184,436	Less costly, More effective
sarilumab	$154,857	Less costly, More effective
adalimumab	$259,523	Reference case
etanercept	$241,515	$87,362

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 cDMARD versus cDMARD alone (**See Appendix D for all tornado diagrams**). Influential inputs often included the 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 3 presents the tornado diagram for the TIM with the smallest cost-effectiveness ratio from the base-case results (tocilizumab subcutaneous at approximately $205,000 per QALY). The resulting ICERs from the one-way sensitivity analysis ranged from $184,000 to $255,000 per QALY. No ICER fell beneath $150,000 per QALY gained from the base-case payer perspective. The table beneath the figure details the range of inputs used in the sensitivity analysis and the resulting cost effectiveness ratios.

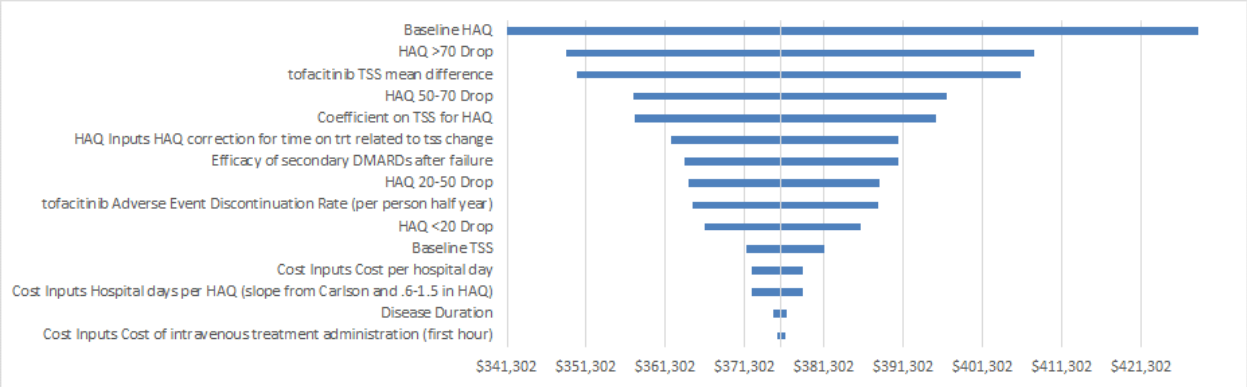
Figure 9. Tornado diagram for tocilizumab subcutaneous versus cDMARD



Input Name	Lower ICER	Upper ICER	Lower Input	Upper Input
tocilizumab (sc) AE Discontinuation Rate (per person half year)	$183,718	$254,619	0.01	0.06
Baseline HAQ	$185,311	$233,529	1.37	2.03
tocilizumab (sc) TSS mean difference	$187,571	$225,507	-1.37	-3.32
Coefficient on TSS for HAQ	$189,820	$221,327	0.02	0.02
HAQ drop for ACR >70 Drop	$191,652	$219,746	-1.28	-0.86
HAQ correction for time on treatment related to TSS change	$193,517	$217,197	0.40	0.60
HAQ drop for ACR 50-70	$196,057	$214,134	-0.91	-0.61
HAQ drop for ACR 20-50	$199,543	$210,064	-0.53	-0.35
HAQ drop for <20	$200,154	$209,288	-0.13	-0.09
Baseline TSS	$201,070	$209,284	43.42	64.58
Cost per hospital day	$201,032	$207,450	1,166.04	3,154.38
Hospital days per HAQ	$201,032	$207,450	0.22	0.59
Efficacy of secondary DMARDs after failure	$201,953	$207,805	0.75	0.92
Cost of IV administration (first hour)	$203,283	$206,346	77.97	210.93
Cost of serious infections adverse event	$203,978	$205,460	7,857.60	21,256.49

Figure 10 presents the tornado diagram for the TIM with the largest cost-effectiveness ratio from the base-case results (tofacitinib, at approximately $376,000 per QALY). The resulting ratios from the one-way sensitivity analysis ranged from $341,000 to $428,000 per QALY. No ICER fell beneath $300,000 per QALY gained. The table beneath the figure details the lower and upper inputs used in the sensitivity analysis and the resulting ratios for each input.

Figure 10. Tornado diagram for tofacitinib versus cDMARD



Input Name	Lower ICER	Upper ICER	Lower Input	Upper Input
Baseline HAQ	$341,303	$428,469	1.37	2.03
HAQ drop for ACR >70	$348,800	$407,883	-1.28	-0.86
tofacitinib TSS mean difference	$350,143	$406,134	0.04	-2.00
HAQ drop for ACR 50-70	$357,167	$396,833	-0.91	-0.61
Coefficient on TSS for HAQ	$357,359	$395,480	0.02	0.02
HAQ correction for time on treatment related to TSS change	$362,050	$390,725	0.40	0.60
Efficacy of secondary DMARDs after failure	$363,776	$390,657	0.75	0.92
HAQ 20-50 Drop	$364,238	$388,330	-0.53	-0.35
tofacitinib AE Discontinuation Rate (per person half year)	$364,784	$388,183	0.02	0.06
HAQ drop for ACR<20	$366,218	$385,881	-0.13	-0.09
Baseline TSS	$371,490	$381,393	43.42	64.58
Cost per hospital day	$372,255	$378,603	1,166.04	3,154.38
Hospital days per HAQ	$372,255	$378,603	0.22	0.59
Disease Duration (years)	$374,968	$376,664	14.99	22.31
Cost of IV administration (first hour)	$375,369	$376,377	77.97	210.93

A probabilistic sensitivity analysis was also conducted to assess variation in all parameters for each TIM compared to cDMARD. None of the Monte Carlo iterations were beneath $100,000 per QALY gained for any of the TIMs. Tocilizumab (SC and IV) and sarilumab (using the assumed WAC with

derived discounts) had very few (0-2%) iterations for these TIMs were beneath a threshold of $150,000 per QALY gained. Table 7.1 in Appendix D details the percent of iterations under certain willingness-to-pay thresholds for each TIM when compared to cDMARD. Table 7.2 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 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. 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 8 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 9 in Appendix D). Results were relatively consistent with the first scenario analysis and seemed to move all ICER findings closer to that of the average TIM versus cDMARD.

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, although no ratio approached $150,000 per QALY gained.

Table 11 in Appendix D focuses on five 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 five TIMs with evidence in the TIM experienced population included: rituximab, abatacept (iv), tocilizumab (iv), sarilumab, and baricitinib. Across all five TIMs, the cost-effectiveness ratios lowered when comparing to cDMARD alone, but remained in the approximate range of $175,000 to $225,000 per QALY range.

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-$900,000 per QALY for a one-year horizon, for example (see Appendix D, Tables 13-14). 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.

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. 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 or treatment 1 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. 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.

6.4 Prior Published Evidence on Costs and Cost-Effectiveness

We searched the literature to identify models that were similar to our analysis, with comparable population, settings, perspective, and treatments.

One manufacturer-funded study[101] modeling tocilizumab monotherapy (8mg/kg monthly) versus adalimumab monotherapy (40mg every other week) in biologic-naïve patients previously treated with cDMARDs 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 (13.97 vs. 13.49); however, tocilizumab is less expensive than adalimumab in the ICER model ($479,950 vs. $524,380). 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. First, 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. Second, 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. Finally, the ICER model uses a market-basket of treatments averaged in cost and efficacy for the subsequent treatment pathway, whereas Carlson et al. modeled subsequent treatment with etanercept, certolizumab, and finally palliative care.

An older study, supported by the Agency for Healthcare Research and Quality (AHRQ)[98], 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 cDMARDs alone immediately following loss of efficacy or AEs resulting from TIM therapy in the AHRQ model, while in the ICER model cDMARDs are used as a fourth-line option.

A UK-focused microsimulation model, by Stephens et al,[100] comparing adalimumab+cDMARD with cDMARD 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 results, in that adalimumab combination therapy yielded more QALYs than cDMARDs alone. 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)[98] 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.

We reviewed other models[51,100,130] as well, but have not included them here owing to factors such as differences in population setting, perspective, and health care systems.

6.5 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 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 cDMARDs. 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%.[131] 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 cDMARDs. 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. In this analysis, 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 assumed WAC, discounted WAC as calculated from the SSR database, and price to reach WTP thresholds of $50,000/QALY, $100,000/QALY and $150,000/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/Value-Assessment-Framework-slides-for-July-29-webinar-FINAL-corrected-8-22-1.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. The original annual threshold was $904 million, which has now been updated to $915 million for 2017-18. Calculations are performed as shown in Table 19.

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

Table 19. 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 20 below illustrates the per-patient budget impact calculation in more detail, based on discounted WAC prices for both the new agents and the TIMs they would be displacing. Note that no data matching our study entry criteria are available as of yet for baricitinib monotherapy.

Table 20. Illustration of Per-Patient Budget Impact Calculation, Using Discounted WAC Pricing

Drugs	Combination therapy		Monotherapy	
	Avg. Annual Per-Patient BI (over 5-year horizon)	Weighted Avg. Per-Patient BI (over 5-year horizon)	Avg. Annual Per-Patient BI (over 5-year horizon)	Weighted Avg. Per-Patient BI (over 5-year horizon)
Sarilumab	$26,819	$80,232	$24,487	$73,396
Weighted Adalimumab + Tocilizumab*	$30,084	$89,463	$32,355	$96,022
Net	-$3,265**	-$9,231**	-$7,868**	-$22,626**
Baricitinib	$43,529	$127,806	N/A	N/A
Weighted Adalimumab + Tofacitinib*	$41,601	$122,259	N/A	N/A
Net	$1,928	$5,547	N/A	N/A

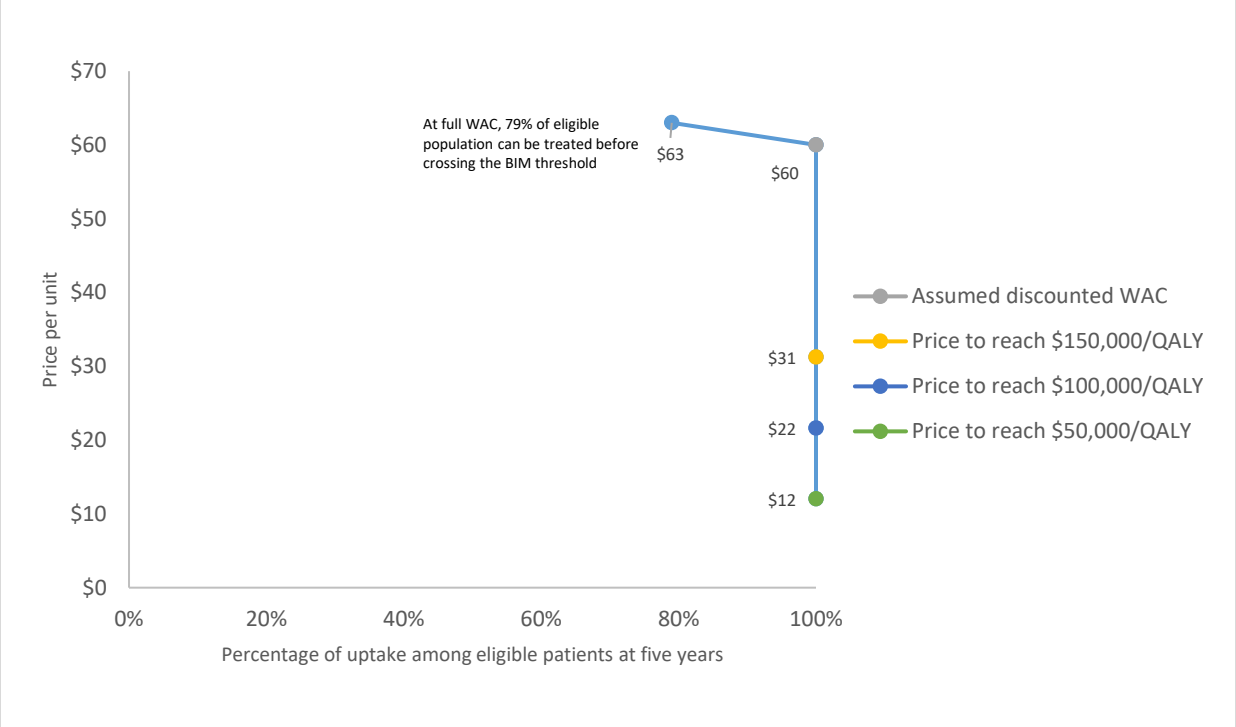
*weighted in the ratio 30:70 for adalimumab:tocalizumab/adalimumab:tofacitinib
**indicates cost-saving

When treating the eligible cohort with sarilumab combination therapy, the weighted potential budgetary impact (adjusted for differing periods of drug utilization and associated cost-offsets over the five-year period) per patient results in cost-savings in all but one scenario, ranging from approximately -$9,200 using discounted assumed WAC to approximately -$62,000 using the price to achieve a $50,000/QALY cost-effectiveness threshold. When the undiscounted WAC (i.e., list price) was used, weighted per-patient costs increased by approximately $9,000; even at this budget impact, however, 100% of the candidate population of 486,000 could be treated without crossing the $915 million budget impact threshold in any given year.

Treating the eligible cohort with sarilumab monotherapy resulted in weighted cost-savings at all assumed prices, ranging from approximately -$6,000 using full WAC to approximately -$65,000 using the price to achieve the $50,000/QALY threshold over a five-year time horizon.

Finally, when treating eligible patients with baricitinib, prices (per tablet) that would achieve each of the three commonly used cost-effectiveness thresholds resulted in cost-savings. However, when using full WAC and discounted WAC prices, the per patient weighted potential budgetary impacts over the five-year time horizon were approximately $12,000 and $5,500 respectively. As shown in the Figure 11 below, 100% of patients could be treated in a given year without crossing the ICER budget impact threshold at the three threshold prices as well as discounted WAC, while 79% of the population could be treated without crossing the threshold at the full WAC.

Figure 11. Budgetary impact of baricitinib combination therapy



6.6 Value-based Benchmark Prices

Value-based benchmark prices are not provided in the draft report.

6.7 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 $200,000 to $375,000 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, TIMs in combination with cDMARD that were more favorable (i.e., had deterministic findings with lower costs and higher QALYs) included: tocilizumab IV, tocilizumab SC, sarilumab (assuming tocilizumab SC annual price), infliximab, abatacept IV, and rituximab. Assuming a willingness-to-pay threshold of $150,000/QALY, etanercept plus cDMARD, and abatacept sc plus cDMARD were also found to be cost-effective as a first-line TIM, with both higher QALYs and higher costs than adalimumab.

The base-case results were robust to the sensitivity analyses. When accounting for parameter variation, no cost-effectiveness ratio that resulted from the one-way sensitivity analyses of deterministic results was less than $150,000/QALY. Further, only 2% of the probabilistic sensitivity analysis iterations of tocilizumab SC versus cDMARD therapy (the TIM with the lowest cost-effectiveness ratio) fell below a threshold of $150,000 per QALY gained. 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 WTP 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 SC and sarilumab were closest to the WTP threshold of $150,000/QALY gained, but results remained above this threshold. Results for TIM monotherapy as well as combination therapy in the TIM-experienced population 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 not increase costs over the TIMs they would displace (i.e., the other agent in class and adalimumab) to an extent that would compromise patient access to these medications. For both new agents, only one scenario (baricitinib at the full WAC equivalent to tofacitinib) would cross the annual ICER budget impact threshold of $915 million. We note, however, that because these two agents are investigational their true price is currently unknown.

****

References

1. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum.* 2008;58(1):15-25.
2. Crane MM, Juneja M, Allen J, et al. Epidemiology and Treatment of New-Onset and Established Rheumatoid Arthritis in an Insured US Population. *Arthritis Care Res (Hoboken).* 2015;67(12):1646-1655.
3. Huizinga TW, Pincus T. In the clinic. Rheumatoid arthritis. *Ann Intern Med.* 2010;153(1):ITC1-1-ITC1-15; quiz ITC11-16.
4. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis.* 2010;69(9):1580-1588.
5. van Nies JA, de Jong Z, van der Helm-van Mil AH, Knevel R, Le Cessie S, Huizinga TW. Improved treatment strategies reduce the increased mortality risk in early RA patients. *Rheumatology (Oxford).* 2010;49(11):2210-2216.
6. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery (London, England).* 2010;8(5):336-341.
7. National Institute for Health and Care Excellence. NICE DSU Technical Support Document 3. Heterogeneity: Subgroups, Meta-Regression, Bias and Bias-Adjustment. 2011; http://www.nicedsu.org.uk/TSD3%20Heterogeneity.final%20report.08.05.12.pdf. Accessed August 23, 2016.
8. Warn DE, Thompson SG, Spiegelhalter DJ. Bayesian random effects meta-analysis of trials with binary outcomes: methods for the absolute risk difference and relative risk scales. *Statistics in medicine.* 2002;21(11):1601-1623.
9. Weiss JE, Ilowite NT. Juvenile idiopathic arthritis. *Rheumatic diseases clinics of North America.* 2007;33(3):441-470, vi.
10. Mian AN, Ibrahim F, Scott IC, et al. Changing clinical patterns in rheumatoid arthritis management over two decades: sequential observational studies. *BMC musculoskeletal disorders.* 2016;17:44.
11. David G. Rheumatoid Arthritis and Joint Replacement: Impact of Biologics. *American journal of pharmacy benefits.* 2014;6(6):9.
12. Bartels CM, Bell CL, Shinki K, Rosenthal A, Bridges AJ. Changing trends in serious extra-articular manifestations of rheumatoid arthritis among United State veterans over 20 years. *Rheumatology (Oxford).* 2010;49(9):1670-1675.
13. Widdifield J, Bernatsky S, Paterson JM, et al. Trends in Excess Mortality Among Patients With Rheumatoid Arthritis in Ontario, Canada. *Arthritis Care Res (Hoboken).* 2015;67(8):1047-1053.
14. Zhang Y, Lu N, Peloquin C, et al. Improved survival in rheumatoid arthritis: a general population-based cohort study. *Ann Rheum Dis.* 2016.
15. Dennis G, Jr., Holweg CT, Kummerfeld SK, et al. Synovial phenotypes in rheumatoid arthritis correlate with response to biologic therapeutics. *Arthritis research & therapy.* 2014;16(2):R90.
16. Ortiz EC, Shinada S. Evolution of classification criteria for rheumatoid arthritis: how do the 2010 criteria perform? *Rheumatic diseases clinics of North America.* 2012;38(2):345-353.

17. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis.* 2014;73(3):492-509.
18. Anderson J, Caplan L, Yazdany J, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. *Arthritis Care Res (Hoboken).* 2012;64(5):640-647.
19. Singh JA, Saag KG, Bridges SL, Jr., et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol.* 2016;68(1):1-26.
20. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis.* 2010;69(4):631-637.
21. American College of Rheumatology, Academy for Academic Leadership. Workforce Study of Rheumatology Specialists in the United States. 2015; http://www.rheumatology.org/portals/0/files/ACR-Workforce-Study-2015.pdf. Accessed December 22, 2016.
22. International Foundation for Autoimmune Arthritis. Early Symptoms of Autoimmune Arthritis. Investigation into patient-reported symptoms of early disease and onset experiences. 2015; http://nebula.wsimg.com/f6d485aef25c35f9cb2abc87fdcc03e6?AccessKeyId=9BD8916C246CAC51B04E&disposition=0&alloworigin=1. Accessed December 21, 2016.
23. Nair SC, Bijlsma JW, van der Werf JH, et al. Do radiographic joint damage and disease activity influence functional disability through different mechanisms? Direct and indirect effects of disease activity in established rheumatoid arthritis. *J Rheumatol.* 2013;40(9):1505-1512.
24. Seo JH. Overview of immunosuppressive and conventional (non-biologic) disease-modifying drugs in the rheumatic diseases. Furst DE, ed. 2016; UpToDate. Waltham, MA. Accessed January 5, 2017.
25. Rohr MK, Mikuls TR, Cohen SB, Thorne CJ, O'Dell JR. The Underuse of Methotrexate in the treatment of RA: A National Analysis of Prescribing Practices in the U.S. *Arthritis Care Res (Hoboken).* 2016.
26. Manara M, Bianchi G, Bruschi E, et al. Adherence to current recommendations on the use of methotrexate in rheumatoid arthritis in Italy: results from the MARI study. *Clin Exp Rheumatol.* 2016;34(3):473-479.
27. Furst DE. Overview of biologic agents and kinase inhibitors in the rheumatic diseases. Schur PH, ed. 2016; UpToDate. Waltham, MA. Accessed January 5, 2017.
28. Sanofi Genzyme. Sanofi and Regeneron Receive Complete Response Letter from FDA for Sarilumab, an Investigational Treatment for Rheumatoid Arthritis. Press Release. October 28, 2016; http://news.genzyme.com/press-release/sanofi-and-regeneron-receive-complete-response-letter-fda-sarilumab-investigational-tr. Accessed December 20, 2016.
29. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum.* 2006;54(3):692-701.
30. Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. *Arthritis Rheum.* 2007;56(5):1433-1439.
31. van Herwaarden N, den Broeder AA, Jacobs W, et al. Down-titration and discontinuation strategies of tumor necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. *Cochrane database of systematic reviews.* 2014(9).

32. Rubenfire A. Rheumatoid arthritis drug prices on the rise. Modern Healthcare. April 1, 2016; http://www.modernhealthcare.com/article/20160401/NEWS/160409993. Accessed December 22, 2016.
33. Langreth R, Keller M, Cannon CP. Decoding Big Pharma's Secret Drug Pricing Practices. Bloomberg. June 29, 2016; https://www.bloomberg.com/graphics/2016-drug-prices/. Accessed December 22, 2016.
34. PharmaCompass. Top drugs by sales revenue in 2015: Who sold the biggest blockbuster drugs? March 10, 2016; http://www.pharmacompass.com/radio-compass-blog/top-drugs-by-sales-revenue-in-2015-who-sold-the-biggest-blockbuster-drugs. Accessed December 22, 2016.
35. U.S. Centers for Medicare and Medicaid Services. 2015 Medicare Drug Spending Dashboard. 2016; https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/2015Medicare.html. Accessed December 22, 2016.
36. Arthritis Foundation. Medication Cost Survey Results. Unpublished raw data, Atlanta, GA. Cited with permission. August 2016.
37. Red Book Online. Greenwood Village, CO: Truven Health Analytics. Inflectra. 2016; http://www.micromedexsolutions.com/. Accessed January 18, 2017.
38. Chingcuanco F, Segal JB, Kim SC, Alexander GC. Bioequivalence of Biosimilar Tumor Necrosis Factor-alpha Inhibitors Compared With Their Reference Biologics: A Systematic Review. *Ann Intern Med.* 2016;165(8):565-574.
39. Gottenberg JE, Brocq O, Perdriger A, et al. Non-TNF-Targeted Biologic vs a Second Anti-TNF Drug to Treat Rheumatoid Arthritis in Patients With Insufficient Response to a First Anti-TNF Drug: A Randomized Clinical Trial. *Jama.* 2016;316(11):1172-1180.
40. Stettin G. Inflammatory Conditions Care Value Program Makes America's Costliest Medication Class More Affordable. Express Scripts. September 8, 2016; https://lab.express-scripts.com/lab/insights/drug-options/inflammatory-conditions-care-value-program-makes-americas-costliest-medication-class-more-affordable. Accessed December 22, 2016.
41. Arthritis Foundation. Step Therapy Utilization Survey. Unpublished raw data. Atlanta, GA. Cited with permission. November 2016.
42. Arthritis Foundation. Impact of innovative therapyies on rheumatoid arthritis patients. Unpublished raw data, Atlanta, GA. Cited with permission. December 2016.
43. Bartlett SJ, Orbai AM, Duncan T, et al. Reliability and Validity of Selected PROMIS Measures in People with Rheumatoid Arthritis. *PloS one.* 2015;10(9):e0138543.
44. Chambers JD, Wilkinson CL, Anderson JE, Chenoweth MD. Variation in Private Payer Coverage of Rheumatoid Arthritis Drugs. *Journal of Managed Care & Specialty Pharmacy.* 2016;22(10):1176-1181.
45. Excellence NIfHaC. Rheumatoid arthritis in adults: management. 2015.
46. Smolen JS, Burmester GR, Combe B, et al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. *Lancet.* 2016;388(10061):2763-2774.
47. Fraenkel L, Miller AS, Clayton K, et al. When Patients Write the Guidelines: Patient Panel Recommendations for the Treatment of Rheumatoid Arthritis. *Arthritis care & research.* 2016;68(1):26-35.
48. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
49. Singh J, Hossain A, Tanjong Ghogomu E, et al. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic

drugs: a systematic review and network meta-analysis. *Cochrane Database of systematic reviews.* 2016(5).
50. Donahue K, Jonas D, Hansen R, et al. Drug Therapy for Rheumatoid Arthritis in Adults: An Update. Comparative Effectiveness Review No. 55. (Prepared by RTI-UNC Evidence-based Practice Center under Contract No. 290-02-0016-I.) Rockville, MD: Agency for Healthcare Research and Quality. April 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
51. Stevenson M, Archer R, Tosh J, et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. *Health technology assessment (Winchester, England).* 2016;20(35):1-610.
52. Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment. 2011; last updated April 2012; available from http://www.nicedsu.org.uk.
53. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
54. U.S. Preventive Services Task Force. Procedure Manual. Agency for Healthcare Research and Quality. 2008.
55. van Tuyl LH, Vlad SC, Felson DT, Wells G, Boers M. Defining remission in rheumatoid arthritis: results of an initial American College of Rheumatology/European League Against Rheumatism consensus conference. *Arthritis Rheum.* 2009;61(5):704-710.
56. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol.* 2000;27(1):261-263.
57. van der Heijde D, Simon L, Smolen J, et al. How to report radiographic data in randomized clinical trials in rheumatoid arthritis: guidelines from a roundtable discussion. *Arthritis Rheum.* 2002;47(2):215-218.
58. Genant HK, Jiang Y, Peterfy C, Lu Y, Redei J, Countryman PJ. Assessment of rheumatoid arthritis using a modified scoring method on digitized and original radiographs. *Arthritis Rheum.* 1998;41(9):1583-1590.
59. O'Dell JR, Mikuls TR, Taylor TH, et al. Therapies for active rheumatoid arthritis after methotrexate failure. *The New England journal of medicine.* 2013;369(4):307-318.
60. van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis and rheumatism.* 2013;65(3):559-570.
61. Kosinski M, Zhao SZ, Dedhiya S, Osterhaus JT, Ware JE, Jr. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arthritis Rheum.* 2000;43(7):1478-1487.
62. Ward MM, Guthrie LC, Alba MI. Clinically important changes in individual and composite measures of rheumatoid arthritis activity: thresholds applicable in clinical trials. *Ann Rheum Dis.* 2015;74(9):1691-1696.
63. Combe B, Codreanu C, Fiocco U, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. *Ann Rheum Dis.* 2006;65(10):1357-1362.
64. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet.* 2004;363(9410):675-681.

65. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. *Ann Rheum Dis.* 2007;66(9):1162-1167.
66. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Mod Rheumatol.* 2009;19(1):12-19.
67. Takeuchi T, Miyasaka N, Zang C, et al. A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. *Modern rheumatology / the Japan Rheumatism Association.* 2013;23(4):623-633.
68. van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum.* 2006;54(4):1063-1074.
69. Keystone E, Genovese MC, Klareskog L, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. *Annals of the rheumatic diseases.* 2010;69(6):1129-1135.
70. Fleischmann R, Castelar-Pinheiro G, Brzezicki J, et al. Efficacy and safety of sarilumab in combination with csdmards in patients with active rheumatoid arthritis who were inadequate responders or intolerant of anti-TNF-+/- therapy: Results from a phase 3 study. *Arthritis and Rheumatology.* 2015;67(no pagination).
71. Fleischmann R, Decktor DL, Fan C, Van Hoogstraten H, Genovese MC. Comparable efficacy with sarilumab plus methotrexate in biologic-experienced and biologic-naïve patients with moderate-to-severe rheumatoid arthritis from a phase 3, randomized, double-blind, placebo-controlled, international study. *Arthritis and Rheumatology.* 2014;66:S1232-S1233.
72. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in Patients with Refractory Rheumatoid Arthritis. *The New England journal of medicine.* 2016;374(13):1243-1252.
73. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med.* 2005;353(11):1114-1123.
74. Strand V, Burmester GR, Ogale S, Devenport J, John A, Emery P. Improvements in health-related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. *Rheumatology (Oxford).* 2012;51(10):1860-1869.
75. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum.* 2006;54(9):2793-2806.
76. Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis.* 2008;67(8):1096-1103.
77. Weinblatt ME, Schiff M, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. *Arthritis and rheumatism.* 2013;65(1):28-38.

78. Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. *Annals of the rheumatic diseases.* 2014;73(1):86-94.
79. Gabay C, Emery P, van Vollenhoven R, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet (London, England).* 2013;381(9877):1541-1550.
80. Burmester GR, Lin Y, Patel R, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. *Ann Rheum Dis.* 2016.
81. Fleischmann R, Cutolo M, Genovese MC, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis and rheumatism.* 2012;64(3):617-629.
82. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *The New England journal of medicine.* 2012;367(6):508-519.
83. Strand V, van Vollenhoven RF, Lee EB, et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a phase 3 study of active rheumatoid arthritis. *Rheumatology (Oxford).* 2016;55(6):1031-1041.
84. Taylor P, Keystone E, Van Der Heijde D, et al. Baricitinib versus placebo or adalimumab in patients with active rheumatoid arthritis (RA) and an inadequate response to background methotrexate therapy: Results of a phase 3 study. *Arthritis and Rheumatology.* 2015;67(no pagination).
85. Jobanputra P, Maggs F, Deeming A, et al. A randomised efficacy and discontinuation study of etanercept versus adalimumab (RED SEA) for rheumatoid arthritis: A pragmatic, unblinded, non-inferiority study of first TNF inhibitor use: Outcomes over 2 years. *BMJ Open.* 2012;2(6).
86. Greenberg JD, Reed G, Decktor D, et al. A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. *Annals of the rheumatic diseases.* 2012;71(7):1134-1142.
87. Hetland ML, Christensen IJ, Tarp U, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis and rheumatism.* 2010;62(1):22-32.
88. Flouri I, Markatseli TE, Voulgari PV, et al. Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the Hellenic Registry of Biologics: Low rates of remission and 5-year drug survival. *Seminars in arthritis and rheumatism.* 2014;43(4):447-457.
89. Schiff M, Keiserman M, Codding C, et al. Clinical response and tolerability to abatacept in patients with rheumatoid arthritis previously treated with infliximab or abatacept: open-label extension of the ATTEST Study. *Annals of the rheumatic diseases.* 2011;70(11):2003-2007.
90. Kremer JM, Blanco R, Halland A-M, et al. Clinical efficacy and safety maintained up to 5 years in patients with rheumatoid arthritis treated with tocilizumab in a randomised trial. *Clinical and experimental rheumatology.* 2016;34(4):625-633.
91. Machado DA, Guzman R, Xavier RM, et al. Two-Year Safety and Efficacy Experience in Patients with Methotrexate-Resistant Active Rheumatoid Arthritis Treated with Etanercept and Conventional Disease-Modifying Anti-rheumatic Drugs in the Latin American Region. *The open rheumatology journal.* 2016;10:13-25.

92. Keystone EC, Genovese MC, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: results through 2 years of the GO-FORWARD study extension. *The Journal of rheumatology.* 2013;40(7):1097-1103.
93. van Dartel SA, Fransen J, Kievit W, et al. Difference in the risk of serious infections in patients with rheumatoid arthritis treated with adalimumab, infliximab and etanercept: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. *Ann Rheum Dis.* 2013;72(6):895-900.
94. Favalli EG, Biggioggero M, Marchesoni A, Meroni PL. Survival on treatment with second-line biologic therapy: a cohort study comparing cycling and swap strategies. *Rheumatology (Oxford).* 2014;53(9):1664-1668.
95. Kim HL, Lee MY, Park SY, et al. Comparative effectiveness of cycling of tumor necrosis factor-alpha (TNF-alpha) inhibitors versus switching to non-TNF biologics in rheumatoid arthritis patients with inadequate response to TNF-alpha inhibitor using a Bayesian approach. *Archives of pharmacal research.* 2014;37(5):662-670.
96. Lloyd S, Bujkiewicz S, Wailoo AJ, Sutton AJ, Scott D. The effectiveness of anti-TNF-alpha therapies when used sequentially in rheumatoid arthritis patients: a systematic review and meta-analysis. *Rheumatology (Oxford).* 2010;49(12):2313-2321.
97. Athanasakis K, Tarantilis F, Tsalapati K, Konstantopoulou T, Vritzali E, Kyriopoulos J. Cost-utility analysis of tocilizumab monotherapy in first line versus standard of care for the treatment of rheumatoid arthritis in Greece. *Rheumatol Int.* 2015;35(9):1489-1495.
98. Wailoo AJ, Bansback N, Brennan A, Michaud K, Nixon RM, Wolfe F. Biologic drugs for rheumatoid arthritis in the Medicare program: a cost-effectiveness analysis. *Arthritis Rheum.* 2008;58(4):939-946.
99. National Institute for Health and Care Excellence. Tocilizumab for the treatment of rheumatoid arthritis. 2012; nice.org.uk/guidance/ta247.
100. Stephens S, Botteman MF, Cifaldi MA, van Hout BA. Modelling the cost-effectiveness of combination therapy for early, rapidly progressing rheumatoid arthritis by simulating the reversible and irreversible effects of the disease. *BMJ Open.* 2015;5(6):e006560.
101. Carlson JJ, Ogale S, Dejonckheere F, Sullivan SD. Economic evaluation of tocilizumab monotherapy compared to adalimumab monotherapy in the treatment of severe active rheumatoid arthritis. *Value Health.* 2015;18(2):173-179.
102. Gabay C, Emery P, van Vollenhoven R, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *The Lancet.*381(9877):1541-1550.
103. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.
104. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* 2006;54(1):26-37.
105. Gibson L, Alava MH, Wailoo A. Progression of disease in people with rheumatoid arthritis treated with non biologic therapies. 2015.
106. Curtis JR, Jain A, Askling J, et al. A comparison of patient characteristics and outcomes in selected European and U.S. rheumatoid arthritis registries. *Semin Arthritis Rheum.* 2010;40(1):2-14.e11.

107. Frayer CD, Gu Q, Ogden CL. Anthropometric reference data for children and adults: United States, 2007-2010. National Center for Health Statistics. *Vital Health Stat.* 2012;11(252).
108. Lillegraven S, Prince FH, Shadick NA, et al. Remission and radiographic outcome in rheumatoid arthritis: application of the 2011 ACR/EULAR remission criteria in an observational cohort. *Ann Rheum Dis.* 2012;71(5):681-686.
109. U.S. Food and drug Administration. Orencia (abatacept) Prescribing Information. 2014; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125118s179lbl.pdf. Accessed October 17, 2016.
110. U.S. Food and drug Administration. Rituxan (rituximab) Prescribing Information. 2014; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103705s5432lbl.pdf. Accessed October 17, 2016.
111. U.S. Food and drug Administration. Xeljanz (tofacitinib) Prescribing Information. 2015; http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203214s010lbl.pdf. Accessed October 27, 2016.
112. Administration USFad. Cimzia (R) [package insert]. *UCB.* 2015(Smyrna, Georgia).
113. Administration USFad. Simponi(R) [package insert]. *Janssen Biotech Inc.* 2016(Horsham, PA).
114. Administration USFaD. Simponi Aria (R) [package insert]. *Janssen Biotech Inc.* 2016(Horsham, PA).
115. U.S. Food and Drug Administration. Actemra(R) [package insert]. *Genentech, Inc* 2014(San Francisco, CA).
116. Administration USFad. Enbrel (R) [package insert]. *Amgen.* 2015(Thousand Oaks, CA).
117. Administration USFad. Remicade (R) [package insert]. *Janssen Biotech Inc.* 2015(Horsham, PA).
118. Administration USFad. Humira (R) [package insert]. *AbbVie Inc.* 2016(North Chicago, IL).
119. Karlsson JA, Kristensen LE, Kapetanovic MC, Gulfe A, Saxne T, Geborek P. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. *Rheumatology (Oxford).* 2008;47(4):507-513.
120. SSRHealth. US Brand Rx Net Price. *Access-restricted document.*2016.
121. RED BOOK - Truven Health Analytics.
122. Kaiser Family Foundation. Kaiser State Health Facts. 2016; http://kff.org/other/state-indicator/expenses-per-inpatient-day-by-ownership/#notes. Accessed June 21, 2016.
123. Physicians' Fee & Coding Guide 2016. Atlanta, GA: InGauge Health Solutions.
124. Medicare Provider Utilization and Payment Data. Baltimore, MD: Centers for Medicare and Medicaid Services; 2014.
125. Bureau of Labor Statistics. Labor Force Statistics from the Current Population Survey. 2016; http://www.bls.gov/cps/cpsaat03.htm.
126. Wolfe F, Michaud K, Gefeller O, Choi HK. Predicting mortality in patients with rheumatoid arthritis. *Arthritis Rheum.* 2003;48(6):1530-1542.
127. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care.* 2005;43(3):203-220.
128. National Institute for Health and Care Excellence. Adalimumab, etanercept, inflfliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. 2016.
129. Centers for Disease Control and Prevention. Treatment for TB Disease. http://www.cdc.gov/tb/topic/treatment/tbdisease.htm. Accessed November 22, 2016.

130. Vera-Llonch M, Massarotti E, Wolfe F, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate. *Rheumatology (Oxford).* 2008;47(4):535-541.
131. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. *Arthritis & Rheumatism.* 2008;58(1):26-35.
132. Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). *Annals of the rheumatic diseases.* 2010;69(9):1629-1635.
133. Yazici Y, Curtis JR, Ince A, et al. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. *Annals of the rheumatic diseases.* 2012;71(2):198-205.
134. Halland AM. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate at one year - The LITHE study. *European Musculoskeletal Review.* 2012;7(2):108-111.
135. Kivitz A, Olech E, Borofsky M, et al. Subcutaneous tocilizumab versus placebo in combination with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. *Arthritis care & research.* 2014;66(11):1653-1661.
136. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum.* 2008;58(10):2968-2980.
137. Kremer J, Li Z-G, Hall S, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Annals of internal medicine.* 2013;159(4):253-261.
138. Dougados M, Van Der Heijde D, Chen YC, et al. Baricitinib, an oral janus kinase (jak)1/jak2 inhibitor, in patients with active rheumatoid arthritis (RA) and an inadequate response to cDMARD therapy: Results of the phase 3 Ra-build study. *Annals of the Rheumatic Diseases.* 2015;74:79-80.
139. Yamamoto K, Takeuchi T, Yamanaka H, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. *Modern rheumatology / the Japan Rheumatism Association.* 2014;24(5):715-724.
140. Smolen JS, Emery P, Ferraccioli GF, et al. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial. *Annals of the rheumatic diseases.* 2015;74(5):843-850.
141. Machado DA, Guzman RM, Xavier RM, et al. Open-label observation of addition of etanercept versus a conventional disease-modifying antirheumatic drug in subjects with active rheumatoid arthritis despite methotrexate therapy in the Latin American region. *Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases.* 2014;20(1):25-33.
142. Tanaka Y, Harigai M, Takeuchi T, et al. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. *Annals of the rheumatic diseases.* 2012;71(6):817-824.

143. Genovese MC, Fleischmann R, Kivitz AJ, et al. Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate: Results of a Phase III Study. *Arthritis & rheumatology (Hoboken, NJ).* 2015;67(6):1424-1437.
144. Fleischmann R, van Adelsberg J, Lin Y, et al. Sarilumab and Non-Biologic Disease-Modifying Antirheumatic Drugs in Patients With Active RA and Inadequate Response or Intolerance to TNF Inhibitors. *Arthritis Rheumatol.* 2016.
145. Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis.* 2009;68(6):789-796.
146. Yoo D-H, Park W, Suh CH, et al. Efficacy and safety of rituximab biosimilar candidate (CT-P10) and innovator rituximab in patients with rheumatoid arthritis: Results from phase I randomized controlled trial over 72 weeks. *Arthritis and Rheumatology.* 2015;67(no pagination).
147. Bae SC, Kim J, Choe JY, et al. A phase III, multicentre, randomised, double-blind, active-controlled, parallel-group trial comparing safety and efficacy of HD203, with innovator etanercept, in combination with methotrexate, in patients with rheumatoid arthritis: The HERA study. *Annals of the Rheumatic Diseases.* 2016.
148. Choe J-Y, Prodanovic N, Niebrzydowski J, et al. A randomized, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product (Remicade) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy: 54-week results. *Arthritis and Rheumatology.* 2015;67(no pagination).
149. Takeuchi T, Yamanaka H, Tanaka Y, et al. Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and innovator infliximab in Japanese patients with rheumatoid arthritis. *Modern Rheumatology.* 2015;25(6):817-824.
150. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Annals of the rheumatic diseases.* 2013;72(10):1613-1620.
151. Peterfy C, Emery P, Tak PP, et al. MRI assessment of suppression of structural damage in patients with rheumatoid arthritis receiving rituximab: Results from the randomised, placebo-controlled, double-blind RA-SCORE study. *Annals of the Rheumatic Diseases.* 2016;75(1):170-177.
152. Takeuchi T, Matsubara T, Nitobe T, et al. Phase II dose-response study of abatacept in Japanese patients with active rheumatoid arthritis with an inadequate response to methotrexate. *Modern rheumatology / the Japan Rheumatism Association.* 2013;23(2):226-235.
153. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med.* 2006;144(12):865-876.
154. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med.* 2003;349(20):1907-1915.
155. Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis.* 2016.
156. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* 2003;48(1):35-45.

157. Kim H-Y, Lee S-K, Song. Y ea. A randomized, double-blind, placebo-controlled, phase III study of the human anti-necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. *APLAR Journal of Rheumatology.* 2007;10(1):9-16.
158. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol.* 2003;30(12):2563-2571.
159. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum.* 2004;50(5):1400-1411.
160. Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis.* 2009;68(6):797-804.
161. Keystone E, van der Heijde D, Mason D, Jr., et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum.* 2008;58(11):3319-3329.
162. Choy E, McKenna F, Vencovsky J, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. *Rheumatology (Oxford, England).* 2012;51(7):1226-1234.
163. Combe B, Codreanu C, Fiocco U, et al. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. *Ann Rheum Dis.* 2009;68(7):1146-1152.
164. Weinblatt ME, Bingham CO, 3rd, Mendelsohn AM, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. *Annals of the rheumatic diseases.* 2013;72(3):381-389.
165. Kremer J, Ritchlin C, Mendelsohn A, et al. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. *Arthritis and rheumatism.* 2010;62(4):917-928.
166. Li Z, Zhang F, Kay J, et al. Efficacy and safety results from a Phase 3, randomized, placebo-controlled trial of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite methotrexate therapy. *International Journal of Rheumatic Diseases.* 2015.
167. Kim J, Ryu H, Yoo D-H, et al. A clinical trial and extension study of infliximab in Korean patients with active rheumatoid arthritis despite methotrexate treatment. *Journal of Korean medical science.* 2013;28(12):1716-1722.
168. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet.* 1999;354(9194):1932-1939.
169. Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. *Arthritis Rheum.* 2006;54(4):1075-1086.

170. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis.* 2008;67(11):1516-1523.
171. Genovese MC, Kremer J, Zamani O, et al. Baricitinib, an oral janus kinase (jak)1/jak2 inhibitor, in patients with active rheumatoid arthritis (RA) and an inadequate response to TNF inhibitors: Results of the phase 3 Ra-beacon study. *Annals of the Rheumatic Diseases.* 2015;74:75-76.
172. Yoo D-H, Park W, Jeka S, et al. A randomized, controlled, multicenter, 2-arm, parallel-group, double-blind study to demonstrate the equivalence of CT-P10 to innovator rituximab with respect to pharmacokinetic profile in patients with rheumatoid arthritis. *Arthritis and rheumatism.* 2013;65:S736.
173. Jani RH, Gupta R, Bhatia G, et al. A prospective, randomized, double-blind, multicentre, parallel-group, active controlled study to compare efficacy and safety of biosimilar adalimumab (Exemptia; ZRC-3197) and adalimumab (Humira) in patients with rheumatoid arthritis. *Int J Rheum Dis.* 2015.
174. Cohen SB, Genovese MC, Choy EH, et al. Randomized, double-blind, phase 3 study of efficacy and safety of ABP 501 compared with adalimumab in subjects with moderate to severe rheumatoid arthritis. *Arthritis and Rheumatology.* 2015;67(no pagination).
175. Weinblatt M, Baranauskaite A, Niebrzydowski J, et al. A phase III, randomized, double-blind clinical study comparing SB5, an adalimumab biosimilar, with adalimumab reference product (humira) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy (24-week results). *Arthritis and Rheumatology.* 2015;67(no pagination).
176. Emery P, Vencovskỳ J, Sylwestrzak A, et al. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Annals of the Rheumatic Diseases.* 2015.
177. Kay J, Chopra A, Chandrashekara S, et al. A phase 3, randomized, double-blind, active comparator study of the efficacy and safety of BOW015, a biosimilar infliximab, in patients with active rheumatoid arthritis on stable methotrexate doses. *Annals of the rheumatic diseases.* 2014;73.
178. Choe J-Y, Prodanovic N, Niebrzydowski J, et al. A randomised, double-blind, phase III study comparing sb2, an infliximab biosimilar, to the infliximab reference product (remicade) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Annals of the rheumatic diseases.* 2015;74:706.
179. U.S. Food and drug Administration. Actemra (tocilizumab) Prescribing Information. 2016; http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125276s107_125472s018lbl.pdf. Accessed October 17, 2016.
180. Emery P, Fleischmann R, van der Heijde D, et al. The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. *Arthritis and rheumatism.* 2011;63(5):1200-1210.
181. van Vollenhoven RF, Geborek P, Forslind K, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. *The Lancet.* 2012;379(9827):1712-1720.

182. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med.* 2000;343(22):1594-1602.
183. Cohen SB, Keystone E, Genovese MC, et al. Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate. *Annals of the rheumatic diseases.* 2010;69(6):1158-1161.
184. Keystone E, Emery P, Peterfy CG, et al. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. *Ann Rheum Dis.* 2009;68(2):216-221.
185. Van Der Heijde D, Genovese MC, Fan C, Fiore S, Decktor DL, Fleischmann R. Clinical and radiographic efficacy of sarilumab plus methotrexate in biologic-experienced and biologic-naïve patients with rheumatoid arthritis in a phase 3, randomized, double-blind, placebo-controlled international study. *Annals of the Rheumatic Diseases.* 2015;74:722.
186. Vencovsky J, Sylwestrzak A, Leszczynski P, et al. A phase III, randomized, double-blind clinical study comparing SB4, an etanercept biosimilar, with etanercept reference product (Enbrel) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy (52-week results). *Arthritis and Rheumatology.* 2015;67(no pagination).
187. Yoo DH, Racewicz A, Brzezicki J, et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. *Arthritis research & therapy.* 2016;18(82):1-12.
188. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum.* 2006;54(5):1390-1400.
189. Keystone E, Burmester GR, Furie R, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. *Arthritis Rheum.* 2008;59(6):785-793.
190. Genovese MC, Decktor DL, Parrino J, Boddy A, Graham N. Effect of increased sarilumab dose on efficacy and safety outcomes in poorly responding rheumatoid arthritis (RA) patients: The mobility study. *Annals of the Rheumatic Diseases.* 2015;74:727.
191. Keystone E, Taylor P, Genovese M, et al. Safety and efficacy of baricitinib through 128 weeks in an open-label, long-term extension study in patients with rheumatoid arthritis. *Journal of Rheumatology.* 2015;42(7):1292.
192. Genovese MC, Han C, Keystone EC, et al. Effect of golimumab on patient-reported outcomes in rheumatoid arthritis: results from the GO-FORWARD study. *J Rheumatol.* 2012;39(6):1185-1191.
193. Strand V, Burmester GR, Zerbini CA, et al. Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial. *Arthritis Care Res (Hoboken).* 2015;67(4):475-483.
194. Bingham CO, 3rd, Weinblatt M, Han C, et al. The effect of intravenous golimumab on health-related quality of life in rheumatoid arthritis: 24-week results of the phase III GO-FURTHER trial. *J Rheumatol.* 2014;41(6):1067-1076.
195. Emery P, Gaich C, DeLozier A, et al. Patient-Reported Outcomes from a Phase 3 Study of Baricitinib in Patients with Rheumatoid Arthritis with Inadequate Response to Conventional Synthetic Disease-Modifying Antirheumatic Drugs [Abstract}. *Arthritis Rheumatol.* 2015;67(suppl 10).

196. Smolen JS, Kremer JM, Gaich CL, et al. Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). *Ann Rheum Dis.* 2016.
197. Kremer JM, Cohen S, Wilkinson BE, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis and rheumatism.* 2012;64(4):970-981.
198. Emery P, Decktor DL, Nguyen D, Fan C, Kavanaugh A. Clinical and radiographic efficacy of sarilumab in rheumatoid arthritis patients with varied disease duration. *Annals of the Rheumatic Diseases.* 2015;74:730.
199. Bingham CO, 3rd, Mendelsohn AM, Kim L, et al. Maintenance of Clinical and Radiographic Benefit With Intravenous Golimumab Therapy in Patients With Active Rheumatoid Arthritis Despite Methotrexate Therapy: Week-112 Efficacy and Safety Results of the Open-Label Long-Term Extension of a Phase III, Double-Blind, Randomized, Placebo-Controlled Trial. *Arthritis care & research.* 2015;67(12):1627-1636.
200. Russell AS, Wallenstein GV, Li T, et al. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. *Ann Rheum Dis.* 2007;66(2):189-194.
201. Westhovens R, Cole JC, Li T, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. *Rheumatology (Oxford).* 2006;45(10):1238-1246.
202. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics.* 1993;4(5):353-365.
203. Fleischmann R, Weinblatt ME, Schiff M, et al. Patient-Reported Outcomes From a Two-Year Head-to-Head Comparison of Subcutaneous Abatacept and Adalimumab for Rheumatoid Arthritis. *Arthritis Care Res (Hoboken).* 2016;68(7):907-913.
204. Eriksson JK, Neovius M, Bratt J, et al. Biological vs. conventional combination treatment and work loss in early rheumatoid arthritis: a randomized trial. *JAMA internal medicine.* 2013;173(15):1407-1414.
205. Li T, Wells G, Westhovens R, Tugwell P. Validation of a simple activity participation measure for rheumatoid arthritis clinical trials. *Rheumatology (Oxford).* 2009;48(2):170-175.
206. Li T, Wells G, Westhovens R, Emery P, Becker JC, Tugwell P. Improvements in participation in usual daily activities in patients with rheumatoid arthritis treated with abatacept. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2011;14(2):361-370.
207. Asai S, Kojima T, Oguchi T, et al. Effects of Concomitant Methotrexate on Large Joint Replacement in Patients With Rheumatoid Arthritis Treated With Tumor Necrosis Factor Inhibitors: A Multicenter Retrospective Cohort Study in Japan. *Arthritis Care Res (Hoboken).* 2015;67(10):1363-1370.
208. Ferriols-Lisart R, Ferriols-Lisart F. Dose modifications of anti-TNF drugs in rheumatoid arthritis patients under real-world settings: a systematic review. *Rheumatology international.* 2015;35(7):1193-1210.
209. Pappas DA, John A, Curtis JR, et al. Dosing of Intravenous Tocilizumab in a Real-World Setting of Rheumatoid Arthritis: Analyses from the Corrona Registry. *Rheumatology and therapy.* 2016;3(1):103-115.

210. Darkow T, Chastek B, Rosenblatt L, et al. Dose Escalation Among Rheumatoid Arthritis Patients Treated with Infliximab or Abatacept: Comparison in Claims Data [Abstract]. *Arthritis Rheum.* 2011;63(Suppl 10).
211. Fowler R, McMorrow D, Smith D, Nadkarni A. FRI0364 Real-World Incidence of Biologic Dose Escalation and Impact on Biologic Costs Among Patients with Rheumatoid Arthritis Treated with Intravenous Agents Abatacept, Infliximab or Tocilizumab [Abstract]. *Ann Rheum Dis.* 2015;74:558.
212. Canadian Agency for Drugs and Technologies in Health (CADTH). Biologics Dose Escalation for the Treatment of Rheumatoid Arthritis: A Review of the Clinical and Cost-Effectiveness. Rapid Response Report. 2015; https://www.cadth.ca/sites/default/files/pdf/htis/sep-2015/RC0710%20Biologics%20Dose%20Escalation%20for%20the%20Treatment%20of%20Rheumatoid%20Arthritis%20Clinical%20and%20Cost-Effectiveness%20Final.pdf. Accessed December 23, 2017.
213. Emery P, Hammoudeh M, FitzGerald O, et al. Sustained remission with etanercept tapering in early rheumatoid arthritis. *N Engl J Med.* 2014;371(19):1781-1792.
214. Smolen JS, Nash P, Durez P, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet.* 2013;381(9870):918-929.
215. Huizinga TW, Conaghan PG, Martin-Mola E, et al. Clinical and radiographic outcomes at 2 years and the effect of tocilizumab discontinuation following sustained remission in the second and third year of the ACT-RAY study. *Ann Rheum Dis.* 2015;74(1):35-43.
216. Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: Comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. *Annals of the Rheumatic Diseases.* 2016.
217. Furst DE, Shaikh SA, Greenwald M, et al. Two dosing regimens of certolizumab pegol in patients with active rheumatoid arthritis. *Arthritis Care and Research.* 2015;67(2):151-160.
218. Physician and Other Supplier Data CY 2014. Baltimore, MD: Centers for Medicare and Medicaid Services; 2014.
219. Symmons DP, Silman AJ. The Norfolk Arthritis Register (NOAR). *Clin Exp Rheumatol.* 2003;21(5 Suppl 31):S94-99.
220. Kavanaugh A, Smolen JS, Emery P, et al. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. *Arthritis Rheum.* 2009;61(11):1592-1600.
221. Osterhaus JT, Purcaru O. Discriminant validity, responsiveness and reliability of the arthritis-specific Work Productivity Survey assessing workplace and household productivity within and outside the home in patients with axial spondyloarthritis, including nonradiographic axial spondyloarthritis and ankylosing spondylitis. *Arthritis Res Ther.* 2014;16(4):R164.
222. Han C, Li N, Peterson S. Minimal important difference in HAQ: A validation from health economic perspectives in patient with rheumatoid arthritis using real-world data. . Paper presented at: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 20152015; San Francisco, CA.
223. Barnabe C, Hazlewood G, Barr S, Martin L. Comparison of radiographic scoring methods in a cohort of RA patients treated with anti-TNF therapy. *Rheumatology.* 2012:ker418.

224. Strand V, Ahadieh S, French J, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. *Arthritis research & therapy.* 2015;17:362.
225. Lahiri M, Dixon WG. Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis. *Best practice & research Clinical rheumatology.* 2015;29(2):290-305.
226. Ai JW, Zhang S, Ruan QL, et al. The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor-alpha Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies. *J Rheumatol.* 2015;42(12):2229-2237.
227. Singh JA, Hossain A, Tanjong Ghogomu E, Mudano AS, Tugwell P, Wells GA. Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and networkmeta-analysis (NMA) (Review). *Cochrane Database of Systematic Reviews.* 2016(issue 11).
228. Blumenauer B, Judd M, Wells G, et al. Infliximab for the treatment of rheumatoid arthritis (Review). *Cochrane Database of systematic reviews.* 2002(Issue 3).
229. Lethaby A, Lopez-Olivo MA, Maxwell L, Burls A, Tugwell P, Wells G. Etanercept for the treatment of rheumatoid arthritis (Review). *Cochrane Database of systematic reviews.* 2013(Issue 5).
230. Lopez-Olivo MA, Amezaga U, McGahan L, Pollono EN, Suarez-Almazor ME. Rituximab for rheumatoid arthritis (Review). *Cochrane Database of systematic reviews.* 2015(Issue 1).
231. Lopez-Olivo MA, Bavineni M, Suarez-Almazor ME. Tofacitinib for rheumatoid arthritis (Protocol). *Cochrane Database of systematic reviews.* 2013(Issue 4).
232. Maxwell L, Singh A. Abatacept for rheumatoid arthritis (Review). *Cochrane Database of systematic reviews.* 2010(issue 1).
233. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis (Review). *Cochrane Database of systematic reviews.* 2005(Issue 3).
234. Ruiz Garcia G, Jobanputra P, Burls A, et al. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults (Review). *Cochrane Database of systematic reviews.* 2014(Issue 9).
235. Singh A, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis (Review). *Cochrane Database of systematic reviews.* 2010(Issue 7).
236. Singh JA, Beg S, Lopez-Olivo MA. Tocilizumab for rheumatoid arthritis (Review). *Cochrane Database of systematic reviews.* 2010(Issue 7).
237. Singh JA, Christensen R, Wells GA, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews (Review). *Cochrane Database of systematic reviews.* 2009(issue 4).
238. (CADTH) CAfDaTiH. *Biological Response Modifier Agents for Adults with Rheumatoid Arthritis.* 2010.
239. Baddley JW, Winthrop KL, Chen L, et al. Non-viral opportunistic infections in new users of tumour necrosis factor inhibitor therapy: results of the SAfety Assessment of Biologic ThERapy (SABER) study. *Ann Rheum Dis.* 2014;73(11):1942-1948.
240. Chen JS, Makovey J, Lassere M, Buchbinder R, March LM. Comparative effectiveness of anti-tumor necrosis factor drugs on health-related quality of life among patients with inflammatory arthritis. *Arthritis Care Res (Hoboken).* 2014;66(3):464-472.
241. Chiu YM, Lang HC, Lin HY, et al. Risk of tuberculosis, serious infection and lymphoma with disease-modifying biologic drugs in rheumatoid arthritis patients in Taiwan. *Int J Rheum Dis.* 2014;17 Suppl 3:9-19.
242. Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. *Ann Rheum Dis.* 2016;75(10):1843-1847.

243. Curtis JR, Yang S, Patkar NM, et al. Risk of hospitalized bacterial infections associated with biologic treatment among US veterans with rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2014;66(7):990-997.
244. Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor alpha agents, a retrospective cohort study. *Arthritis research & therapy.* 2015;17:319.
245. Galloway JB, Hyrich KL, Mercer LK, et al. Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis.* 2011;70(10):1810-1814.
246. Gomez-Reino JJ, Maneiro JR, Ruiz J, et al. Comparative effectiveness of switching to alternative tumour necrosis factor (TNF) antagonists versus switching to rituximab in patients with rheumatoid arthritis who failed previous TNF antagonists: the MIRAR Study. *Annals of the rheumatic diseases.* 2012;71(11):1861-1864.
247. Grijalva CG, Chen L, Delzell E, et al. Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. *Jama.* 2011;306(21):2331-2339.
248. Johnston SS, Turpcu A, Shi N, Fowler R, Chu BC, Alexander K. Risk of infections in rheumatoid arthritis patients switching from anti-TNF agents to rituximab, abatacept, or another anti-TNF agent, a retrospective administrative claims analysis. *Semin Arthritis Rheum.* 2013;43(1):39-47.
249. Fleischmann R, Connolly SE, Maldonado MA, Schiff M. Brief Report: Estimating Disease Activity Using Multi-Biomarker Disease Activity Scores in Rheumatoid Arthritis Patients Treated With Abatacept or Adalimumab. *Arthritis Rheumatol.* 2016;68(9):2083-2089.
250. Yun H, Xie F, Delzell E, et al. Comparative Risk of Hospitalized Infection Associated With Biologic Agents in Rheumatoid Arthritis Patients Enrolled in Medicare. *Arthritis Rheumatol.* 2016;68(1):56-66.
251. Matsumoto A, Pavelka K, Rizzo W, et al. Secondary efficacy endpoints: Results from a phase 3 study comparing ABP 501 with adalimumab in subjects with moderate to severe rheumatoid arthritises. *Arthritis and Rheumatology.* 2015;67(no pagination).
252. Kay J, Chopra A, Chandrashekara S, et al. Secondary efficacy outcomes from a phase 3 study support clinical equivalence between BOW015 and infliximab in patients with active rheumatoid arthritis on stable methotrexate doses. *Annals of the rheumatic diseases.* 2015;74:1034.
253. Yoo D, Miranda P, Piotrowski M, et al. A randomized, double-blind, phase 3 study demonstrates clinical equivalence of CT-P13 to infliximab when co-administered with methotrexate in patients with active rheumatoid arthritis. *Annals of the Rheumatic Disease.* 2013;71.
254. Kremer JM, Dougados M, Emery P, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum.* 2005;52(8):2263-2271.
255. Emery P, Kosinski M, Li T, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. *J Rheumatol.* 2006;33(4):681-689.
256. Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis and rheumatism.* 2011;63(3):609-621.

257. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet.* 2008;371(9617):987-997.
258. Strand V, Kosinski M, Chen CI, et al. Sarilumab plus methotrexate improves patient-reported outcomes in patients with active rheumatoid arthritis and inadequate responses to methotrexate: results of a phase III trial. *Arthritis research & therapy.* 2016;18:198.
259. Kavanaugh A, Decktor DL, Fan C, Van Adelsberg J, Martincova R, Genovese MC. A profile of the efficacy of sarilumab plus methotrexate in rheumatoid arthritis patients: Results of a 52-week, phase 3, randomized, double-blind, placebo-controlled, international study. *Arthritis and Rheumatology.* 2014;66:S1233-S1234.
260. Burmester GR, Blanco R, Charles-Schoeman C, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet (London, England).* 2013;381(9865):451-460.
261. Keystone EC, Taylor PC, Drescher E, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. *Annals of the Rheumatic Diseases.* 2015;74(2):333-340.
262. Strand V, Smolen JS, van Vollenhoven RF, et al. Certolizumab pegol plus methotrexate provides broad relief from the burden of rheumatoid arthritis: analysis of patient-reported outcomes from the RAPID 2 trial. *Ann Rheum Dis.* 2011;70(6):996-1002.
263. van der Heijde D, Klareskog L, Landewe R, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum.* 2007;56(12):3928-3939.
264. Morgan CL, Emery P, Porter D, et al. Treatment of rheumatoid arthritis with etanercept with reference to disease-modifying anti-rheumatic drugs: long-term safety and survival using prospective, observational data. *Rheumatology (Oxford).* 2014;53(1):186-194.
265. Tanaka Y, Harigai M, Takeuchi T, et al. Clinical efficacy, radiographic progression, and safety through 156 weeks of therapy with subcutaneous golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis despite prior methotrexate therapy: final results of the randomized GO-FORTH trial. *Modern Rheumatology.* 2016;26(4):481-490.
266. Weinblatt ME, Westhovens R, Mendelsohn AM, et al. Radiographic benefit and maintenance of clinical benefit with intravenous golimumab therapy in patients with active rheumatoid arthritis despite methotrexate therapy: results up to 1 year of the phase 3, randomised, multicentre, double blind, placebo controlled GO-FURTHER trial. *Annals of the rheumatic diseases.* 2014;73(12):2152-2159.
267. Karlsson JA, Neovius M, Nilsson JA, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in early rheumatoid arthritis: 2-year quality-of-life results of the randomised, controlled, SWEFOT trial. *Ann Rheum Dis.* 2013;72(12):1927-1933.

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

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

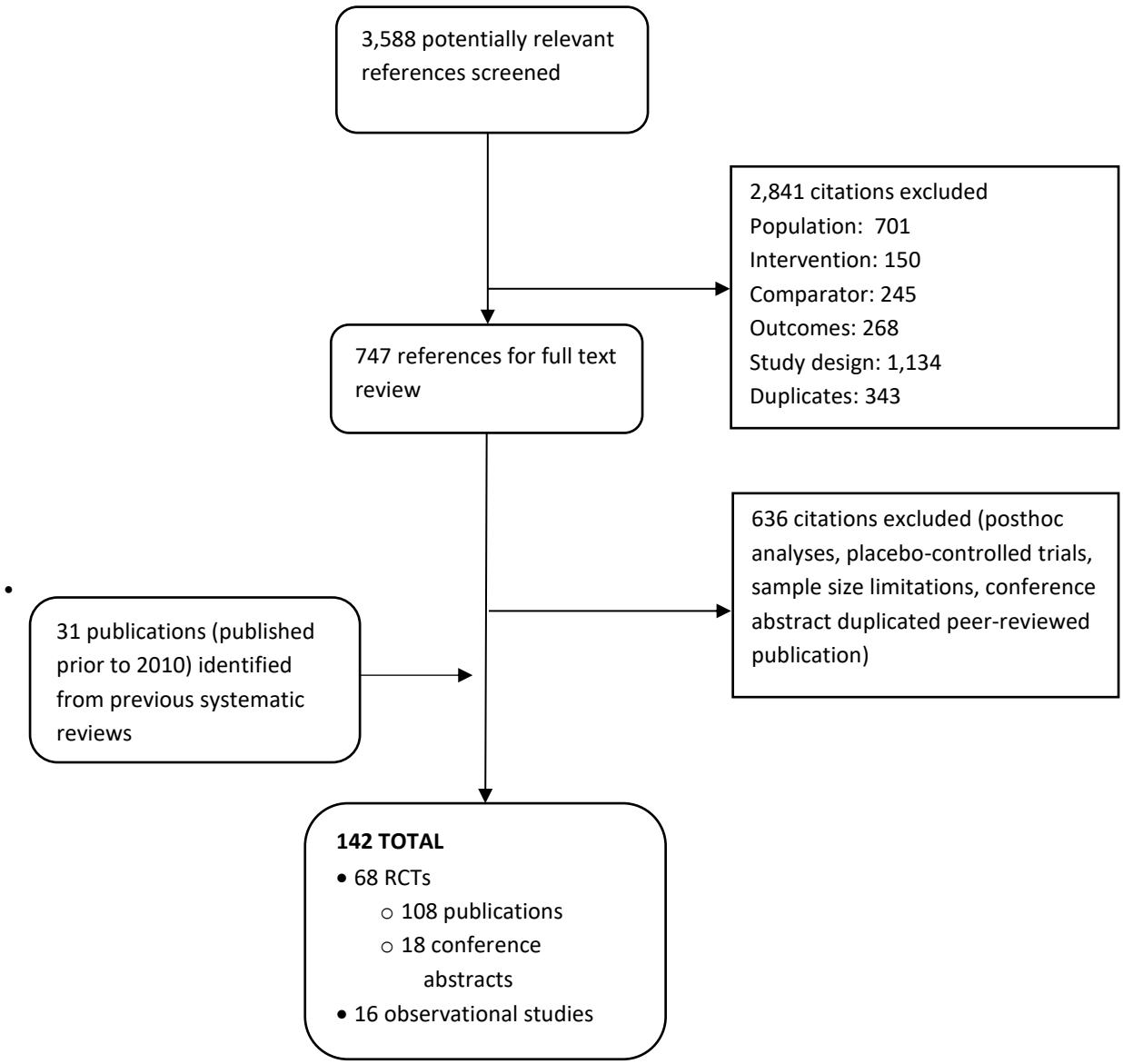
25	24 and 3
26	25 or 20
27	(animals not (humans and animals)).sh.
28	26 not 27
29	limit 28 to english language
30	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or case report or comment or congresses or consensus development conference or duplicate publication 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

#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)[54] 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.*

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)
	Biologic	Conventional DMARD			
TIMs plus conventional DMARD vs. conventional DMARD Biologic Naïve and Mixed Population					
Rituximab[132]	9	2	<0.01	14	1
Abatacept[76]	11	3	NR	NC	1
Tocilizumab[133-136]	30-38	2-4	<0.001	3-4	3
Tofacitinib[82,137]	6-9	1-3	<0.05	17-20	2
Baricitinib[84,138]	16-25	1-5	<0.05	4-8	2
Adalimumab[82,84]	7-18	1-5	<0.05	8-18	2
Certolizumab[139,140]	17-26	0-6	<0.0001	5-6	2
Etanercept[59,141]	22-25	4-14	<0.03	5-11	2
Golimumab[69,142]	20-35	6-7	<0.001	4-7	2
Infliximab[76]	13	3	NR	NC	1
TIMs plus conventional DMARD vs. conventional Biologic Experienced					
Sarilumab†[143,144]	29-34	7-14	<0.0001	4-5	2
Baricitinib[72]	9	3	<0.05	17	1
TIMs monotherapy vs. conventional					
Tocilizumab[65,66]	43-59	1.6-3	<0.001	2	2
Etanercept[67]	34	19	<0.01	7	1
Golimumab[145]	12	6	NS	NC	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

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[146]						
Rituximab-bio + MTX	103	DAS28-ESR & CRP	ESR-2.5; CRP-2.4	12.5†	NR	NR
Rituximab-ref + MTX	51	DAS28-ESR & CRP	ESR-2; CRP-2	3.9	NR	NR
HERA trial at 24 weeks[147]						
Etanercept-bio + MTX	115	DAS28	-2.56	34	NR	NR
Etanercept-ref + MTX	118	DAS28	-2.54	31	NR	NR
Choe 2015 trial at 30 weeks[148]						
Infliximab-bio + MTX	318	DAS28-ESR	-2.3	14.6	NR	9.5
Infliximab-ref + MTX	328	DAS28-ESR	-2.3	15.9	NR	10.9
Takeuchi 2015 trial at 30 weeks[149]						
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[150]						
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		Number of RCTs
	TIM	cDMARD	TIM	cDMARD	TIM	cDMARD	
Biologic Naïve and Mixed Population							
Rituximab[132,151]	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)[152-154]	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)[136]	60.8	24.5	37.6	9.0	20.5	2.9	1
Tocilizumab (IV) monotherapy[66]	80.3	25.0	49.2	10.9	29.5	6.3	1
Tocilizumab (SC)[135]	61.0	32.0	40.0	12.0	20.0	5.0	1
Sarilumab[71]	67.0	34.0	47.0	18.0	27.0	9.0	1
Tofacitinib[60,137]	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[155]	65.0	42.0	44.0	21.0	24.0	8.0	1
Adalimumab[156-159]	52.8 - 67.2	14.5 - 36.5	28.9 - 55.2	8.1 - 14.3	14.8 - 26.9	2.5 - 7.9	5
Certolizumab Pegol[139,160-162]	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[59,63,141,163]	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[163]	73.8	28.0	46.6	14.0	21.4	2.0	1
Golimumab (IV)[164,165]	43.6 - 65.0	24.8 - 32.0	21.8 - 34.9	9.3 - 13.2	7.0 - 17.7	3.1 - 4.1	2
Golimumab (SC)[142,145,166]	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[167-169]	50.0 - 58.0	20.0 - 30.6	27.0 - 33.8	5.0 - 9.7	8.0 - 14.0	0 - 4.7	3
Biologic-experienced populations							
Rituximab[75]	51.0	18.0	27.0	5.0	12.0	1.0	1
Abatacept (IV)[73]	50.4	19.5	20.3	3.8	10.2	1.5	1
Tocilizumab (IV)[170]	50.0	10.1	28.8	3.8	12.4	1.3	1
Sarilumab[70,71,143]	61.0 – 66.4	33.0 - 34.0	41.0	12.0 - 18.0	14.8 - 19.0	3.0 - 7.0	2
Baricitinib[171]	46.0	27.0	29.0	13.0	17.0	3.0	1

TIMs taken in combination with cDMARD unless noted as 'mono'; a few studies cited in the biologic-naïve section included a minority of patients (<20% of study population) with prior exposure to a TNFi or non-TNFi biologic.

Table C4. Ranges of ACR20/50/70 in biosimilar studies

Biosimilar studies	Study arm	ACR20, %	ACR50, %	ACR70, %
Yoo 2013[172] Week 24	RTX-bio+MTX (n=103)	63.0	37.0	16.0
	RTX-ref+MTX (n=51)	66.7	31.3	14.6
Jani 2015[173] 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[174] 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[175] Week 24	ADA-bio (n=271)	75.2	38.3	19.2
	ADA-ref (n=273)	72.0	39.8	20.3
HERA[147] 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[176] 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[177] Week 16	IFX-bio (n=127)	85.0	NR	NR
	IFX-ref (n=62)	85.5	NR	NR
Choe 2015[178] Week 30	IFX-bio+MTX (n=291)	55.5	30.7	15.5
	IFX-ref+MTX (n=293)	59.0	33.8	17.1
PLANETRA[150] 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[149] 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

	Study arm	Mean change in mTSS from baseline (SD)[Ω]	Time of evaluation (weeks)	Significance
Biologic-naïve and mixed populations				
RA-SCORE[151β]	MTX (n=63)	1.4 (SD NR)	52	p=0.002
	RTX+MTX (n=60)	0.3 (SD NR)		
AIM[109β]	MTX (n=195)	2.43 (NR)	52	p<0.01
	ABTiv+MTX (n=391)	1.07 (NR)		
SAMURAI[65]*	cDMARD (n=143)	6.1 (4.2, 8.0)	52	p<0.01
	TCZ (n=157)	2.3 (1.5, 3.2)		
LITHE[179β]	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)		

	Study arm	Mean change in mTSS from baseline (SD)Ω	Time of evaluation (weeks)	Significance
MOBILITY[143]	MTX (n=398)	2.8 (7.7)	52	p<0.0001
	SAR+MTX (n=398)	0.3 (4.6)		
ORAL-Scan[60]	MTX (n=160)	0.9 (NR)	52	p=0.0558
	TOF+MTX (n=321)	0.3 (NR)		
DE019[159α]	MTX (n=172)	2.7 (6.8)	52	p≤0.001
	ADA+MTX (n=183)	0.1 (4.8)		
RAPID1[161]	MTX (n=199)	2.8 (NR)	52	p<0.001
	CTZ+MTX (n=393)	0.4 (NR)		
TEMPO[68]*	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[67]	MTX (n=171)	9.8 (15.2)	52	p<0.0001
	ETN (n=181)	3.3 (9.8)		
O'Dell 2013[59]	Triple cDMARD (n=151)	0.5 (1.9)	48	p=NS
	ETN+MTX (n=153)	0.3 (3.3)		
GO-FORWARD[92,180]	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[181]	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[182]	MTX (n=64)	7 (10.3)	54	vs. MTX 3 mg/kg: p<0.001 10 mg/kg: p<0.001
	3mg/kg IFX+MTX (n=71)	1.3 (6.0)		
	10mg/kg IFX+MTX (n=77)	0.2 (3.6)		
Biologic-experienced populations				
REFLEX[β183,184]	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[185∞]	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)

Appendix Table 6. 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[186]	ETN-bio+MTX (n=299)	0.45 (NR)	52	NR	NR
	ETN-ref+MTX (n=297)	0.74 (NR)			
Choe 2015[148]	IFX-bio+MTX (n=291)	0.38 (NR)	54	NR	NR
	IFX-ref+MTX (n=293)	0.37 (NR)	54		
PLANETRA[187]	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[132,151,188,189]	-0.25 to -0.37***	3	11***	1
Abatacept[73,76,152,154]	-0.34 to -0.4***	2	21-37	4
Tocilizumab[136,170]	-0.21 to -0.34***	3	10 to 26***	2
Sarilumab[190]	-0.2***	1	18***	1
Tofacitinib[60,137]	-0.28 to -0.31***	2	NR	--
Baricitinib[155,171,191]	-0.24 to -0.26***	3	18 to 28***	4
Adalimumab[84,156,159]	-0.25***	2	19***	1
Certolizumab[139,160,162]	-0.23 to -0.37	3	NR	--
Etanercept[64,141]	-0.3 to -0.8***	2	NR	--
Golimumab[164,166,192]	-0.25 to -0.34***	3	20 to 22***	2
Infliximab[76]	NR	--	18*	1
TIMs monotherapy vs. conventional DMARD				
Tocilizumab mono[65,66]	NR	--	28 to 33***	2
Etanercept mono[67]	-0.3†	1	29***	1
Golimumab[145]	0	1	NR	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 outcome in biosimilar trials

Treatment	N	HAQ-DI mean change from baseline:	% change ≥ predefined threshold
HERA trial at 24 weeks[147]			
Etanercept-bio + MTX	115	-0.49	NR
Etanercept-ref + MTX	118	-0.55	NR
Choe 2015 trial at 30 weeks[148]			
Infliximab-bio + MTX	318	-0.5	NR
Infliximab-ref + MTX	328	-0.5	NR
Takeuchi 2015 trial at 30 weeks[149]			
Infliximab-bio	50	-0.6	NR
Infliximab-ref	51	-0.5	NR
PLANETRA trial at 30 weeks[150]			
Infliximab-bio + MTX	302	-0.55	NR
Infliximab-ref + MTX	304	-0.49	NR

Network Meta-Analysis Results

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

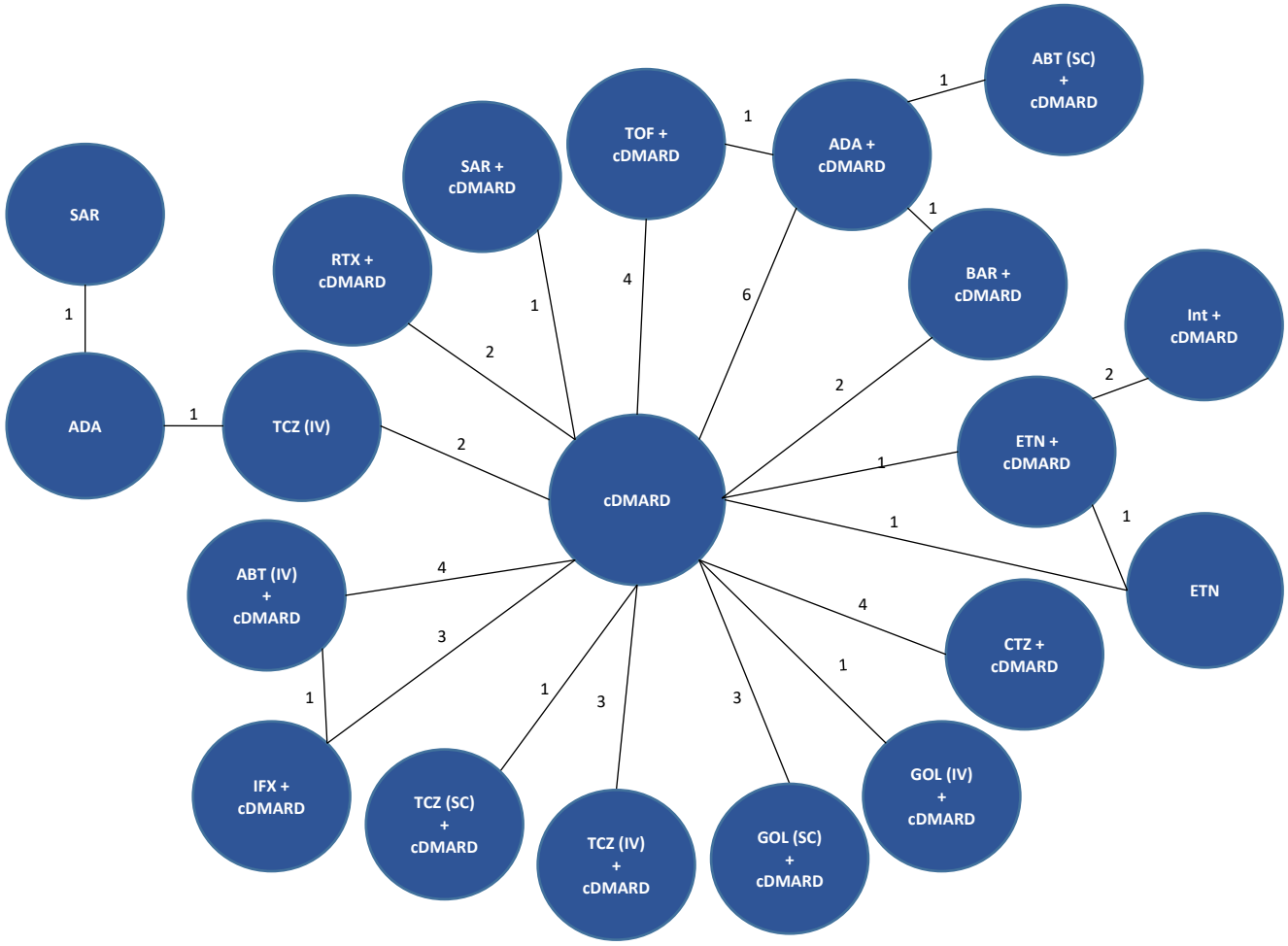


Table C9: ACR Data used in NMA (Mixed population)

Intervention 1	Intervention 2	Intervention 3	Mean Disease Duration	Intervention 1					Intervention 2					Intervention 3				
			Weeks	No response	ACR 20	ACR 50	ACR 70	Total N	No response	ACR 20	ACR 50	ACR 70	total N	No response	ACR 20	ACR 50	ACR 70	Total N
ADA	TCZ		354	82	35	16	29	162	57	29	24	53	163					
cDMARD	ABTiv +cDMARD		449	132	50	23	14	219	139	121	87	86	433					
ADA+cDMARD	ABTsc +cDMARD		94	117	72	65	74	328	108	65	68	77	318					
cDMARD	ADA +cDMARD		607	53	4	2	3	62	22	8	19	18	67					
cDMARD	ABTiv +cDMARD	IFX+cDMARD	405	64	24	12	10	110	52	41	31	32	156	67	37	21	40	165
cDMARD	IFX +cDMARD			67	13	4	0	84	82	38	26	22	168					
cDMARD	ADA +cDMARD		569	141	40	14	5	200	76	50	38	43	207					
cDMARD	ETN +cDMARD	ETN	341	36	7	6	1	50	27	22	27	25	101	27	28	26	22	103
cDMARD	GOLsc +cDMARD		455	59	16	8	5	88	25	25	13	23	86					
cDMARD	GOLsc +cDMARD		421	96	19	11	7	133	36	20	15	18	89					
cDMARD	ADA +cDMARD		356	40	14	4	5	63	25	12	14	14	65					
Int cDMARD	ETN +cDMARD		430	71	38	17	16	142	47	59	76	97	279					
Int cDMARD	ETN +cDMARD		271	70	48	33	8	159	73	32	32	26	163					
cDMARD	TCZ		119	89	30	16	10	145	28	39	37	53	157					
cDMARD	TCZ		447	48	9	3	4	64	12	18	12	19	61					
cDMARD	ADA +cDMARD		541	207	75	25	11	318	150	76	45	47	318					
cDMARD	IFX +cDMARD		390	276	54	17	16	363	317	175	127	102	721					
cDMARD	TCZ		510	312	64	25	12	413	315	186	137	165	803					

	+cDMARD																	
cDMARD	BAR +cDMARD		390	132	47	31	18	228	79	48	45	55	227					
cDMARD	SAR +cDMARD		460	265	67	37	29	398	134	83	83	99	399					
cDMARD	TOF +cDMARD		463	120	27	11	2	160	156	61	57	47	321					
cDMARD	TOF +cDMARD		473	45	7	11	6	69	37	10	10	14	71					
cDMARD	TCZ +cDMARD		476	287	67	31	8	393	371	199	131	96	797					
cDMARD	TCZ +cDMARD		398	151	31	18	4	204	195	66	86	71	418					
cDMARD	CTZ +cDMARD		319	171	12	9	6	199	162	85	62	84	393					
cDMARD	CTZ +cDMARD		308	116	7	3	1	127	105	61	41	39	246					
cDMARD	CTZ +cDMARD		502	92	20	5	2	119	67	35	22	0	124					
cDMARD	RTX+cDMARD		366	132	24	7	9	172	84	42	27	17	170					
cDMARD	TCZsc +cDMARD		577	149	44	15	11	219	170	92	88	87	437					
cDMARD	ABTiv +cDMARD			77	28	12	2	119	46	27	23	19	115					
cDMARD	TOF +cDMARD	ADA+cDMARD	408	41	2	5	8	56	95	30	32	39	196	105	36	38	20	199
cDMARD	GOLiv +cDMARD		359	136	35	18	8	197	134	123	68	70	395					
cDMARD	TOF +cDMARD		462	110	29	15	5	159	151	59	64	41	315					
cDMARD	GOLsc +cDMARD		406	111	12	7	2	132	76	31	17	8	132					
cDMARD	RTX +cDMARD		242	45	11	6	1	63	29	15	11	5	60					
cDMARD	ABTiv +cDMARD		382	52	10	4	0	66	14	19	15	13	61					
cDMARD	CTZ +cDMARD		296	58	6	12	1	77	22	15	21	24	82					
cDMARD	ADA +cDMARD	BAR+cDMARD	na	307	88	54	39	488	112	66	79	73	330	127	117	97	146	487
ADA	SAR			77	53	33	22	185	52	48	41	43	184					

	Interventions			Mean disease duration	Intervention 1					Intervention 2				
Trial Name	1	2	3	Weeks	No response	ACR20	ACR50	ACR70	n total population	No response	ACR20	ACR50	ACR70	n total population
ADACTA	ADA	TCZ		354	82	35	16	29	162	57	29	24	53	163
AIM	cDMARD	ABTiv + cDMARD		449	132	50	23	14	219	139	121	87	86	433
AMPLE	ADA + cDMARD	ABTsc + cDMARD		94	117	72	65	74	328	108	65	68	77	318
ARMADA	cDMARD	ADA + cDMARD		607	53	4	2	3	62	22	8	19	18	67
ATTEST	cDMARD	ABTiv + cDMARD	IFX + cDMARD	405	64	24	12	10	110	52	41	31	32	156
ATTRACT	cDMARD	IFX + cDMARD			67	13	4	0	84	82	38	26	22	168
DE019	cDMARD	ADA + cDMARD		569	141	40	14	5	200	76	50	38	43	207
ETN309	cDMARD	ETN + cDMARD	ETN	341	36	7	6	1	50	27	22	27	25	101
GO-FORTH	cDMARD	GOLsc + cDMARD		455	59	16	8	5	88	25	25	13	23	86
GO-FORWARD	cDMARD	GOLsc + cDMARD		421	96	19	11	7	133	36	20	15	18	89
Kim2007	cDMARD	ADA + cDMARD		356	40	14	4	5	63	25	12	14	14	65
LARA	Int cDMARD	ETN + cDMARD		430	71	38	17	16	142	47	59	76	97	279
O'Dell	Int cDMARD	ETN + cDMARD		271	70	48	33	8	159	73	32	32	26	163

SAMURAI	cDMARD	TCZ		119	89	30	16	10	145	28	39	37	53	157
SATORI	cDMARD	TCZ		447	48	9	3	4	64	12	18	12	19	61
STAR	cDMARD	ADA + cDMARD		541	207	75	25	11	318	150	76	45	47	318
START	cDMARD	IFX + cDMARD		390	276	54	17	16	363	317	175	127	102	721
TOWARD	cDMARD	TCZ + cDMARD		510	312	64	25	12	413	315	186	137	165	803
RA-BUILD	cDMARD	BAR + cDMARD		390	132	47	31	18	228	79	48	45	55	227
MOBILITY	cDMARD	SAR + cDMARD		460	265	67	37	29	398	134	83	83	99	399
ORAL Scan	cDMARD	TOF + cDMARD		463	120	27	11	2	160	156	61	57	47	321
Kremer 2012	cDMARD	TOF + cDMARD		473	45	7	11	6	69	37	10	10	14	71
LITHE	cDMARD	TCZ + cDMARD		476	287	67	31	8	393	371	199	131	96	797
OPTION	cDMARD	TCZ + cDMARD		398	151	31	18	4	204	195	66	86	71	418
RAPID1	cDMARD	CTZ + cDMARD		319	171	12	9	6	199	162	85	62	84	393
RAPID2	cDMARD	CTZ + cDMARD		308	116	7	3	1	127	105	61	41	39	246
Choy 2012	cDMARD	CTZ + cDMARD		502	92	20	5	2	119	67	35	22	0	124
SERENE	cDMARD	RTX + cDMARD		366	132	24	7	9	172	84	42	27	17	170
BREVACTA	cDMARD	TCZsc + cDMARD		577	149	44	15	11	219	170	92	88	87	437
Kremer 2003	cDMARD	ABTiv + cDMARD			77	28	12	2	119	46	27	23	19	115
ORAL Standard	cDMARD	TOF + cDMARD	ADA + cDMARD	408	41	2	5	8	56	95	30	32	39	196

GO-FURTHER	cDMARD	GOLiv + cDMARD		359	136	35	18	8	197	134	123	68	70	395
ORAL Sync	cDMARD	TOF + cDMARD		462	110	29	15	5	159	151	59	64	41	315
Li 2015	cDMARD	GOLsc + cDMARD		406	111	12	7	2	132	76	31	17	8	132
RA-SCORE	cDMARD	RTX + cDMARD		242	45	11	6	1	63	29	15	11	5	60
Takeuchi 2013	cDMARD	ABTiv + cDMARD		382	52	10	4	0	66	14	19	15	13	61
J-RAPID	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
MONARCH	ADA	SAR			77	53	33	22	185	52	48	41	43	184

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

Figure C2. League table, Base Case NMA results, 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 C3. League table, Base Case NMA results, 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 C4. League table, Base Case NMA results, 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 C5. Network Diagram for Analysis of ACR (TIM-Experienced Population)

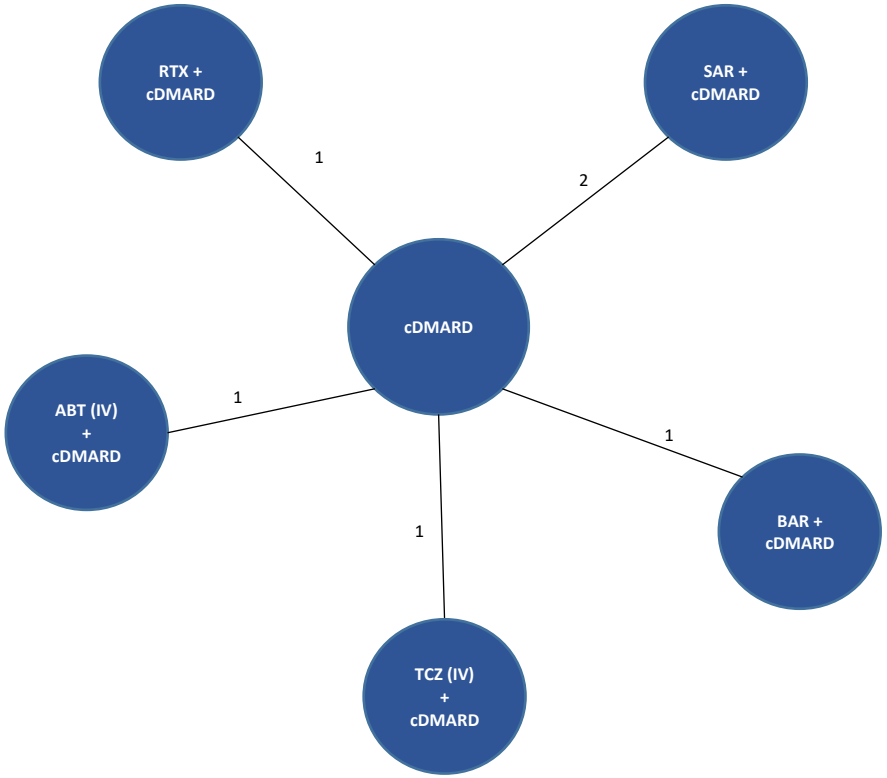


Table C11. ACR Data used in NMA (TIM-experienced population)

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

Figure C6. 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 C7. 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 C8. 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 C12. Percentage of patients achieving ACR20 or better, TIM-experienced population

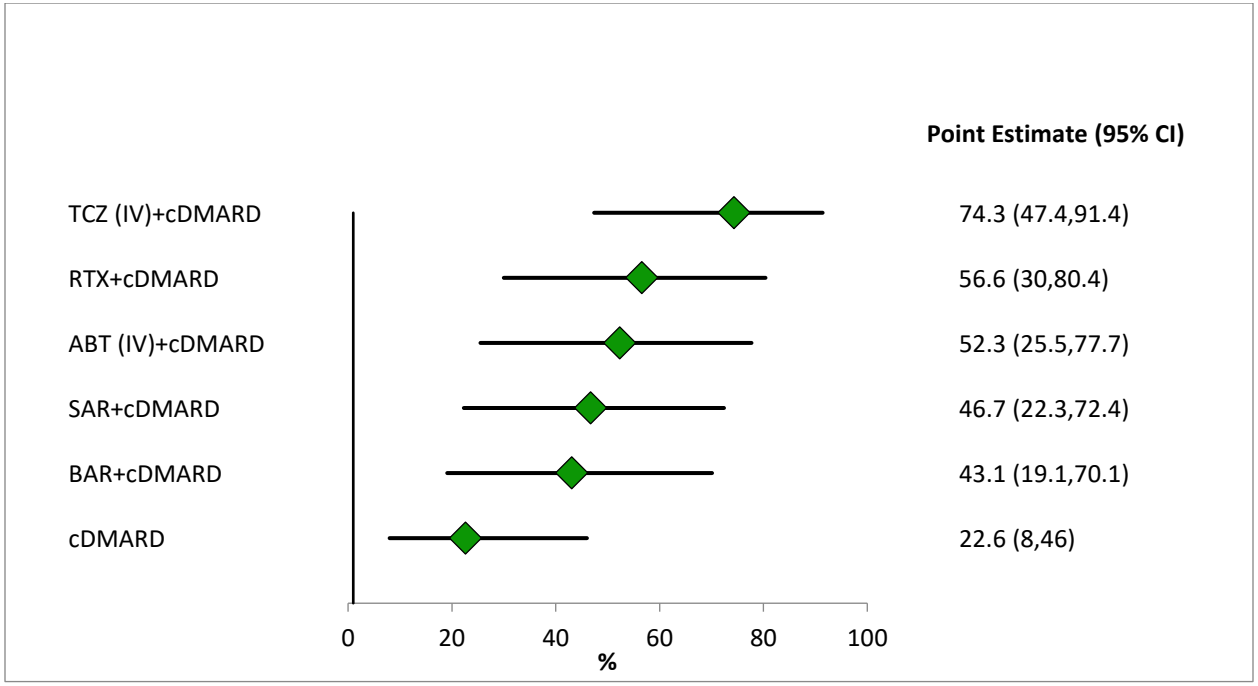


Figure C9. Network Diagram for Analysis of Radiographic Progression (Mixed Population)

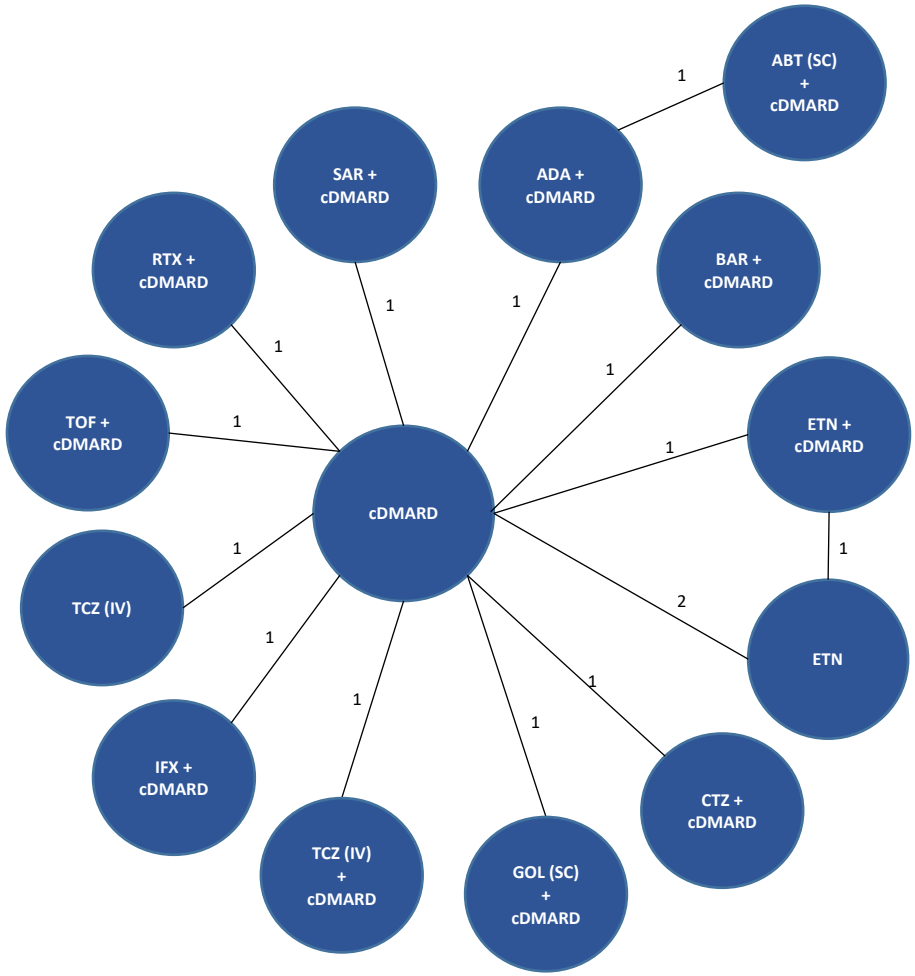


Table C13. Sharp Score Data used in NMA (Mixed population)

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	cDMARD	IFX + cDMARD		64	173		7.00	10.30	0.73	4.93		
TEMPO	cDMARD	ETN	ETN + cDMARD	212	212	218	2.80	12.70	0.52	4.64	-0.54	3.50
RA-SCORE	cDMARD	RTX + cDMARD		63	60		1.37	NR	0.29	NR		
MOBILITY	cDMARD	SAR + cDMARD		398	399		2.78	7.70	0.25	4.61		
Takeuchi 2013	cDMARD	ETN		171	181		9.82	15.20	3.33	9.82		
LITHE	cDMARD	TCZ + cDMARD		294	696		1.17	3.14	0.29	1.15		
SAMURAI	cDMARD	TCZ		143	157		6.10	11.60	2.30	5.43		
ORAL-Scan	cDMARD	TOF + cDMARD		160	321		0.92	NR	0.29	NR		
AMPLE	ADA + cDMARD	ABTsc + cDMARD		289	290		0.38	5.00	0.58	3.22		
DE019	cDMARD	ADA + cDMARD		200	207		2.70	6.80	0.10	4.80		
GO-FORWARD	cDMARD	GOLsc + cDMARD		122	86		1.10	4.70	0.93	4.86		
RAPID1	cDMARD	CTZ + cDMARD		199	393		2.80	NR	0.4	NR		
RA-BUILD	cDMARD	BAR + cDMARD		228	227		1.37	NR	0.28	NR		

Figure C10: League table, NMA results Mixed population, Sharp Score

IFX+ cDMARD													
-0.38 (-0.8, 0.03)	**ETN+ cDMARD**												
-0.38 (-0.81, 0.04)	0 (-0.25, 0.24)	**BAR+ cDMARD**											
-0.39 (-0.9, 0.11)	-0.01 (-0.38, 0.36)	-0.01 (-0.39, 0.37)	**RTX+ cDMARD**										
-0.44 (-0.87,-0.03)	-0.07 (-0.31, 0.18)	-0.06 (-0.32, 0.2)	-0.05 (-0.43, 0.33)	**TCZ+ cDMARD**									
-0.45 (-0.88, -0.03)	-0.07 (-0.32, 0.18)	-0.07 (-0.34, 0.19)	-0.06 (-0.45, 0.32)	-0.01 (-0.27, 0.26)	**ADA+ cDMARD**								
-0.47 (-0.92, -0.03)	-0.09 (-0.37, 0.19)	-0.09 (-0.38, 0.2)	-0.08 (-0.49, 0.32)	-0.03 (-0.32, 0.27)	-0.02 (-0.32, 0.28)	**TCZiv**							
-0.49 (-0.9, -0.09)	-0.11 (-0.33, 0.1)	-0.11 (-0.34, 0.11)	-0.1 (-0.47, 0.26)	-0.05 (-0.28, 0.18)	-0.04 (-0.28, 0.2)	-0.02 (-0.29, 0.24)	**SAR+ cDMARD**						
-0.5 (-0.91, -0.09)	**-0.12 (-0.21, -0.02)**	-0.12 (-0.35, 0.12)	-0.11 (-0.47, 0.26)	-0.05 (-0.29, 0.19)	-0.04 (-0.29, 0.2)	-0.03 (-0.3, 0.25)	0 (-0.21, 0.2)	**ETN**					
-0.5 (-0.96, -0.05)	-0.12 (-0.42, 0.18)	-0.12 (-0.43, 0.19)	-0.11 (-0.53, 0.31)	-0.05 (-0.37, 0.25)	-0.05 (-0.21, 0.11)	-0.03 (-0.37, 0.31)	0 (-0.29, 0.28)	0 (-0.29, 0.29)	**ABTsc+ cDMARD**				
-0.7 (-1.13, -0.28)	**-0.32 (-0.58, -0.07)**	**-0.32 (-0.58, -0.06)**	-0.31 (-0.7, 0.07)	-0.26 (-0.52, 0.01)	-0.25 (-0.52, 0.02)	-0.23 (-0.53, 0.07)	-0.21 (-0.44, 0.03)	-0.21 (-0.45, 0.04)	-0.2 (-0.52, 0.11)	**TOF+ cDMARD**			
-0.71 (-1.14, -0.29)	**-0.33 (-0.58, -0.09)**	**-0.33 (-0.59, -0.07)**	-0.32 (-0.7, 0.06)	**-0.27 (-0.52, -0.01)**	-0.26 (-0.52, 0.01)	-0.24 (-0.53, 0.05)	-0.22 (-0.44, 0.01)	-0.22 (-0.45, 0.02)	-0.21 (-0.52, 0.1)	-0.01 (-0.27, 0.26)	**CTZ+ cDMARD**		
-0.85 (-1.32, -0.39)	**-0.47 (-0.79, -0.16)**	**-0.47 (-0.8, -0.15)**	**-0.46 (-0.89, -0.04)**	**-0.41 (-0.74, -0.08)**	**-0.4 (-0.73, -0.07)**	**-0.38 (-0.74, -0.03)**	**-0.36 (-0.66, -0.06)**	**-0.36 (-0.67, -0.05)**	-0.35 (-0.72, 0.01)	-0.15 (-0.48, 0.18)	-0.14 (-0.47, 0.18)	**GOLsc+cDMARD**	
-0.89 (-1.27, -0.51)	**-0.51 (-0.67, -0.35)**	**-0.51 (-0.69, -0.33)**	**-0.5 (-0.83, -0.16)**	**-0.44 (-0.63, -0.26)**	**-0.44 (-0.63, -0.24)**	**-0.42 (-0.65, -0.19)**	**-0.39 (-0.53, -0.26)**	**-0.39 (-0.55, -0.24)**	**-0.39 (-0.64, -0.14)**	-0.19 (-0.38, 0.01)	-0.18 (-0.36, 0.005)	-0.03 (-0.3, 0.24)	**cDMARD**

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

Figure C11. Network Diagram for Sensitivity Analysis of ACR (TIM-Naïve Population)

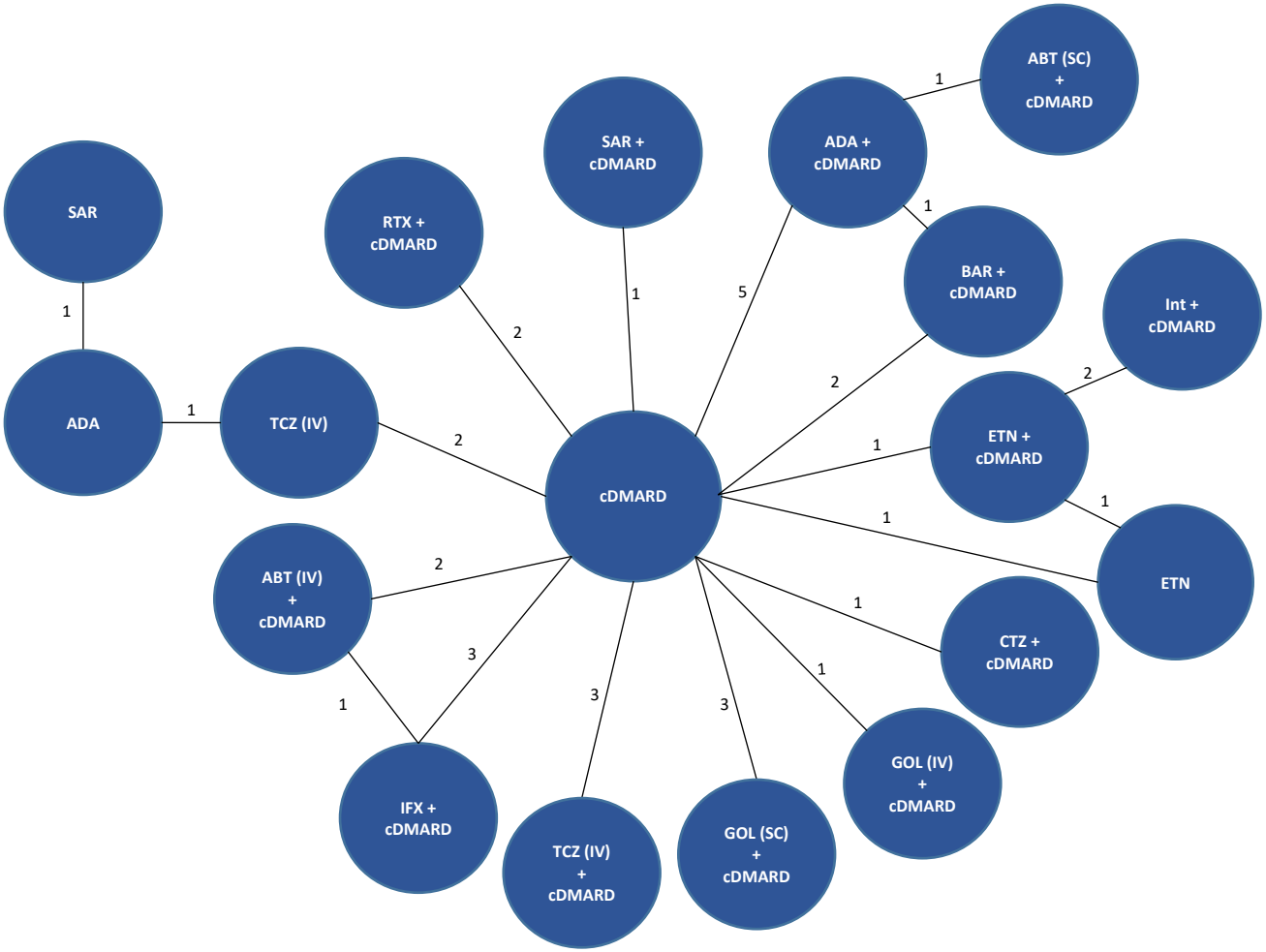


Table C14: ACR Data used in NMA (Sensitivity Analysis TIM-naïve population)

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

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

	Interventions			Mean disease duration	Intervention 1					Intervention 2				
MONARCH	ADA	SAR			77	53	33	22	185	52	48	41	43	184
RA-BEAM	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 total population
ATTEST	cDMARD	ABTiv + cDMARD	IFX + cDMARD	405	67	37	21	40	165
ETN309	cDMARD	ETN + cDMARD	ETN	341	27	28	26	22	103
RA-BEAM	cDMARD	ADA + cDMARD	BAR + cDMARD	na	127	117	97	146	487

Figure C12. 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 C13. 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 C14. 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 C15. Network Diagram for Sensitivity Analysis of ACR (by Class, Mixed Population)

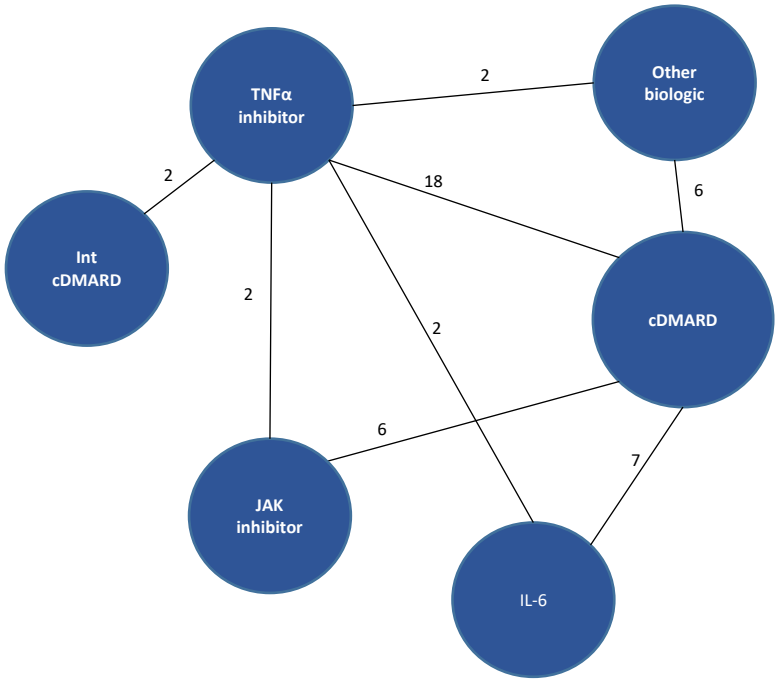


Table C17: ACR Data used in (Sensitivity analysis by class, Mixed population)

Trial Name	Interventions			Mean disease duration	Intervention 1					Intervention 2				
	1	2	3	Weeks	No response	ACR20	ACR50	ACR70	n total population	No response	ACR20	ACR50	ACR70	n total population
ADACTA	TNFi	IL-6		354	82	35	16	29	162	57	29	24	53	163
AIM	cDMARD	Other biologic		449	132	50	23	14	219	139	121	87	86	433
AMPLE	TNFi	Other biologic		94	117	72	65	74	328	108	65	68	77	318
ARMADA	cDMARD	TNFi		607	53	4	2	3	62	22	8	19	18	67
ATTEST	cDMARD	Other biologic	TNFi	405	64	24	12	10	110	52	41	31	32	156
ATTRACT	cDMARD	TNFi			67	13	4	0	84	82	38	26	22	168
DE019	cDMARD	TNFi		569	141	40	14	5	200	76	50	38	43	207
ETN309	cDMARD	TNFi	TNFi	341	36	7	6	1	50	27	22	27	25	101
GO-FORTH	cDMARD	TNFi		455	59	16	8	5	88	25	25	13	23	86
GO-FORWARD	cDMARD	TNFi		421	96	19	11	7	133	36	20	15	18	89
Kim2007	cDMARD	TNFi		356	40	14	4	5	63	25	12	14	14	65
LARA	Int cDMARD	TNFi		430	71	38	17	16	142	47	59	76	97	279
O'Dell	Int cDMARD	TNFi		271	70	48	33	8	159	73	32	32	26	163
SAMURAI	cDMARD	IL-6		119	89	30	16	10	145	28	39	37	53	157
SATORI	cDMARD	IL-6		447	48	9	3	4	64	12	18	12	19	61
STAR	cDMARD	TNFi		541	207	75	25	11	318	150	76	45	47	318
START	cDMARD	TNFi		390	276	54	17	16	363	317	175	127	102	721
TOWARD	cDMARD	IL-6		510	312	64	25	12	413	315	186	137	165	803
RA-BUILD	cDMARD	JAKi		390	132	47	31	18	228	79	48	45	55	227

Trial Name	Interventions			Mean disease duration	Intervention 1					Intervention 2				
	1	2	3	Weeks	No response	ACR20	ACR50	ACR70	n total population	No response	ACR20	ACR50	ACR70	n total population
MOBILITY	cDMARD	IL-6		460	265	67	37	29	398	134	83	83	99	399
ORAL Scan	cDMARD	JAKi		463	120	27	11	2	160	156	61	57	47	321
Kremer 2012	cDMARD	JAKi		473	45	7	11	6	69	37	10	10	14	71
LITHE	cDMARD	IL-6		476	287	67	31	8	393	371	199	131	96	797
OPTION	cDMARD	IL-6		398	151	31	18	4	204	195	66	86	71	418
RAPID1	cDMARD	TNFi		319	171	12	9	6	199	162	85	62	84	393
RAPID2	cDMARD	TNFi		308	116	7	3	1	127	105	61	41	39	246
Choy 2012	cDMARD	TNFi		502	92	20	5	2	119	67	35	22	0	124
SERENE	cDMARD	Other biologic		366	132	24	7	9	172	84	42	27	17	170
BREVACTA	cDMARD	IL-6		577	149	44	15	11	219	170	92	88	87	437
Kremer 2003	cDMARD	Other biologic			77	28	12	2	119	46	27	23	19	115
ORAL Standard	cDMARD	JAKi	TNFi	408	41	2	5	8	56	95	30	32	39	196
GO-FURTHER	cDMARD	TNFi		359	136	35	18	8	197	134	123	68	70	395
ORAL Sync	cDMARD	JAKi		462	110	29	15	5	159	151	59	64	41	315
Li 2015	cDMARD	TNFi		406	111	12	7	2	132	76	31	17	8	132
RA-SCORE	cDMARD	Other biologic		242	45	11	6	1	63	29	15	11	5	60
Takeuchi 2013	cDMARD	Other biologic		382	52	10	4	0	66	14	19	15	13	61
J-RAPID	cDMARD	TNFi		296	58	6	12	1	77	22	15	21	24	82
RA-BEAM	cDMARD	TNFi	JAKi	na	307	88	54	39	488	112	66	79	73	330
MONARCH	TNFi	IL-6			77	53	33	22	185	52	48	41	43	184

Table C17: ACR Data used in (Sensitivity analysis by class, Mixed population *continued*)

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

Figure C16. 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 C17. 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 C18. 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.[163,193-196]

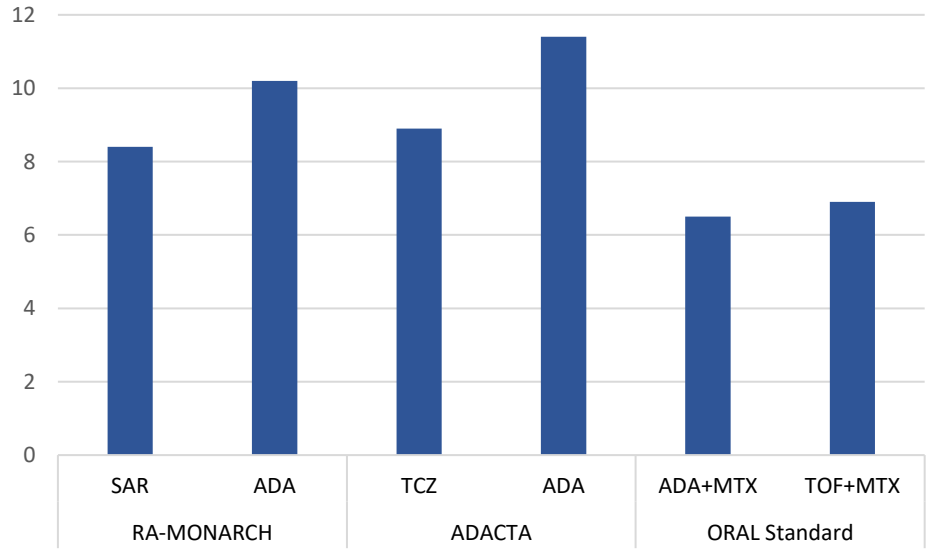
Pain

We identified 13 conventional DMARD-controlled trials that reported outcomes related to pain. Of these, nine trials reported pain using the 0-100 VAS scale, while the remaining four 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.[60,139,141,156,157,162,191,197,198] 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.[168,199]

Fatigue

Twenty-one conventional DMARD-controlled studies reported outcomes related to fatigue; details are provided in Appendix Table X. Statistically significant differences favoring treatment with a TIM over conventional DMARD were observed in all 15 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, six of the seven trials in which clinically-important differences in the FACIT-F were measured reported a significantly greater proportion of patients who met or exceeded the MCID with a TIM versus conventional DMARD.[74,189,192-196] When evaluated with a VAS, fatigue scores declined from baseline (indicating improvement) significantly more with a TIM than with conventional DMARD therapy.[91,200,201]

Figure C19. 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.[202] 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.[203] 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).[203]

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 trial 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 (adjusted mean change -26.3 vs. -15.2; p≤0.001), but reductions in impaired work time and work productivity loss were not statistically different.[196] 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.[91,141] 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; differences increased somewhat at 21 months in favor of triple therapy (-6.2 vs. -4.9 for infliximab; adjusted difference 1.6; 95% CI -1.2 to 4.4;p=NR).[204]

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.[205] 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).[206]

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%).[91,141] 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.[91]

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.[207] 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).[207]

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. [208] 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. [209]

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.[210,211] 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.[212] 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. [213] 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, $p \leq .009$). 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.[214] 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.[215] 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.[31] 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 C18: Adverse events in comparative trials

Trial	Intervention	Length of follow up	Any AE	Serious AEs	D/C due to AEs	Any infection	Serious infection	TB	Malignancy	Death
MONARCH[80]	ADA	24 weeks	63.6	6.5	7.1	27.7	1.1	NR	3.3	0
	SAR	24 weeks	64.1	4.9	6	28.8	1.1	NR	7.6	0.5
ADACTA[79]	ADA	24 weeks	83	10	NR	42	3	NR	1	0
	TCZ	24 weeks	82	12	NR	48	3	NR	1	2
RED SEA[85]	ADA	52 weeks	NR	10	NR	NR	NR	NR	1.7	2.2
	ETN	52 weeks	NR	11.6	NR	NR	NR	NR	1.7	0
AMPLE[77]	ADA	2 years	91.5	16.5	9.5	61.3	2.7	NR	2.1	0
	ABT	2 years	92.8	13.8	3.8	63.2	2.2	NR	2.2	0.3

Trial	Intervention	Length of follow up	Any AE	Serious AEs	D/C due to AEs	Any infection	Serious infection	TB	Malignancy	Death
ATTEST[76]	IFX	52 weeks	93.3	18.2	7.3	NR	8.5	NR	1.2	NR
	ABT	52 weeks	89.1	9.6	3.2	NR	1.9	NR	0.6	NR
RA-BEAM[84]	ADA	24 weeks	67	1.8	NR	33.3	0.6	0.3	0	0
	BAR	24 weeks	70.8	4.5	NR	35.7	1	0	0.4	0.4
ORAL Standard[82]	ADA	12 weeks	51.5	2.5	4.9	NR	0	NR	NR	NR
	TOF	12 weeks	52	5.9	6.9	NR	1.5	NR	NR	NR
BIOSIMILARS										
Yoo 2015[146]	RTX-bio	24 weeks	71.6	13.7	5.9	38.2	NR	NR	0	NR
	RTX-ref	24 weeks	84.3	13.7	7.8	41.2	NR	NR	2	NR
HERA [147]	ETN-bio	48 weeks	NR	12.9	6.8	37.4	NR	NR	NR	0
	ETN-ref	48 weeks	NR	12.3	7.5	41.1	NR	NR	NR	1.4
Choe 2015[148]	IFX-bio	54 weeks	57.6	9	7.2	29.3	3.1	0.3	0.7	0
	IFX-ref	54 weeks	58	8.9	3.4	37.5	2	0.3	0	0.3
Vencovsky 2015[186]	ETN-bio	52 weeks	NR	6	5	NR	0.3	0	NR	0.7
	ETN-ref	52 weeks	NR	5.1	6.4	NR	1.7	0	NR	0
Takeuchi 2015[149]	IFX-bio	54 weeks	88.2	15.7	17.6	NR	NR	NR	NR	NR
	IFX-ref	54 weeks	86.8	15.1	11.3	NR	NR	NR	NR	NR
PLANETRA[216]	IFX-bio	54 weeks	70.5	13.9	10.9	NR	NR	1	NR	0
	IFX-ref	54 weeks	70.3	10.3	15.7	NR	NR	0	NR	1
Cohen 2015[174]	ADA-bio	26 weeks	50	3.8	1.9	NR	0.8	NR	NR	NR
	ADA-ref	26 weeks	54.6	5	0.8	NR	1.1	NR	NR	NR

* Data presented are percentages of patients with each event

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

Intervention	Route	Dose	Frequency of Administration	Annual Monitoring Utilization	Administration Utilization
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
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

Intervention	Route	Dose	Frequency of Administration	Annual Monitoring Utilization	Administration Utilization
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
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

Intervention	Route	Dose	Frequency of Administration	Annual Monitoring Utilization	Administration Utilization
cDMARD	ORAL	2.5mg	8 per week (20mg weekly)	1 office visit 1 TB test 4 Liver labs 4 Blood labs	none

Table D2. Administration Cost Inputs

Input	Value	Source
Cost of iv treatment administration (first hour)	$136.41	Physicians' Fee and Coding Guide, 2016[217] (HCPCS code 96413)
Cost of iv treatment administration (each additional hour)	$28.64/hour	Physicians' Fee and Coding Guide, 2016[217] (HCPCS code 96415)
Cost of subcutaneous treatment administration	$25.42	Physicians' Fee and Coding Guide, 2016[217] (HCPCS code 96372)
Cost per office visit	$73.40	Physicians' Fee and Coding Guide, 2016[217] (HCPCS code 99213)

Table D3. Drug Monitoring Unit Cost Inputs

Input	Value	Source
Cost per office visit	$73.40	Physicians' Fee and Coding Guide, 2016[217] (HCPCS code 99213)
Drug monitoring cost: TB Test	$84.96	Physician and Other Supplier Data[218] (HCPCS code 86480)
Drug monitoring cost: Liver Test	$7.63	Physician and Other Supplier Data[218] (HCPCS code 80076)
Drug monitoring cost: Complete Blood Count	$10.67	Physician and Other Supplier Data[218] (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[124]	Weighted by 2/3rd for pneumonia and 1/3rd by cellulitis
Cost of Tuberculosis Infection	$12,220	Medicare Provider Utilization and Payment Data[124]	
Serious Infection Disutility	-0.156	National Institute for Health and Care Excellence[128]	Disutility applied for one-month[128]
Tuberculosis Infection Disutility	-0.156	National Institute for Health and Care Excellence[128]	Disutility applied for two-months[129]

Table D5. 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[101] Gabay et al., 2013[102]
HAQ Score relationship with Total Sharp Score	E(HAQ) on treatment= exp(-1.73+0.02*(baseline TSS+TSS mean difference(T))) / 1 + exp(-1.73+0.02*(baseline TSS+TSS mean difference(T)))*3 E(HAQ) at baseline= exp(-1.73+0.02*baseline TSS) / 1+exp(-1.73+0.02*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[100] Breedveld et al., 2006[104]
Mortality rate relationship with HAQ score	US RA-severity specific mortality rate = Mortality from life table*1.33^{HAQ}	Carlson et al., 2015[101] Wolfe et al., 2003[126]
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[98]
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[101] Symmons et al. 2003[219]
Baseline missed worked days per month due to RA	4 days	Kavanaugh et al., 2009[220]
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[221]

Input	Value	Source
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[222] US Bureau of Labor and Statistics[125]
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[101] Karlsson et al., 2008[119]

Table D6. Contributions of ACR and mTSS to HAQ, for TIMs Added on to cDMARD

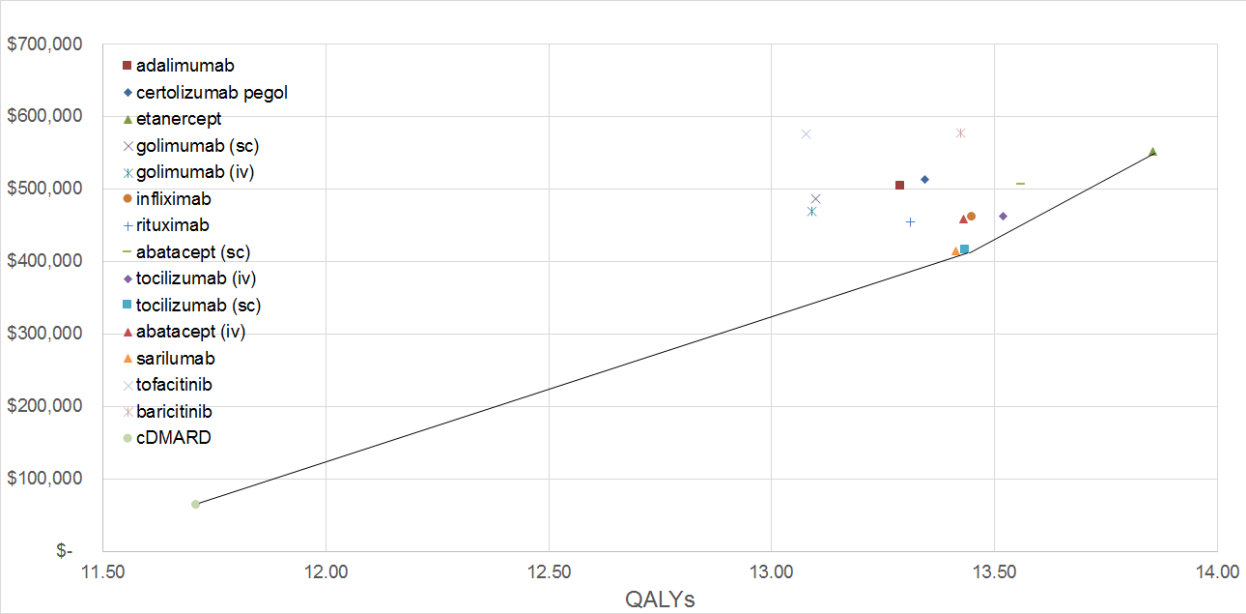
Treatment 1	Average Proportion of HAQ Contribution from ACR	Average Proportion of HAQ Contribution from mTSS
rituximab	77.9%	22.1%
abatacept (iv)	77.7%	22.3%
abatacept (sc)	75.6%	24.4%
tocilizumab (iv)	75.8%	24.2%
tocilizumab (sc)	76.6%	23.4%
sarilumab	78.0%	22.0%
tofacitinib	85.4%	14.6%
baricitinib	74.7%	25.3%
adalimumab	79.2%	20.8%
certolizumab pegol	84.2%	15.8%
etanercept	71.6%	28.4%
golimumab (sc)	89.8%	10.2%
golimumab (iv)	89.9%	10.1%
infliximab	73.1%	26.9%

Table D7. 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[223]

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. The line visually appears to also include sarilumab, but is slightly lower than this point. It is important to note that all TIMs look relatively tightly clustered in Figure 1, 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

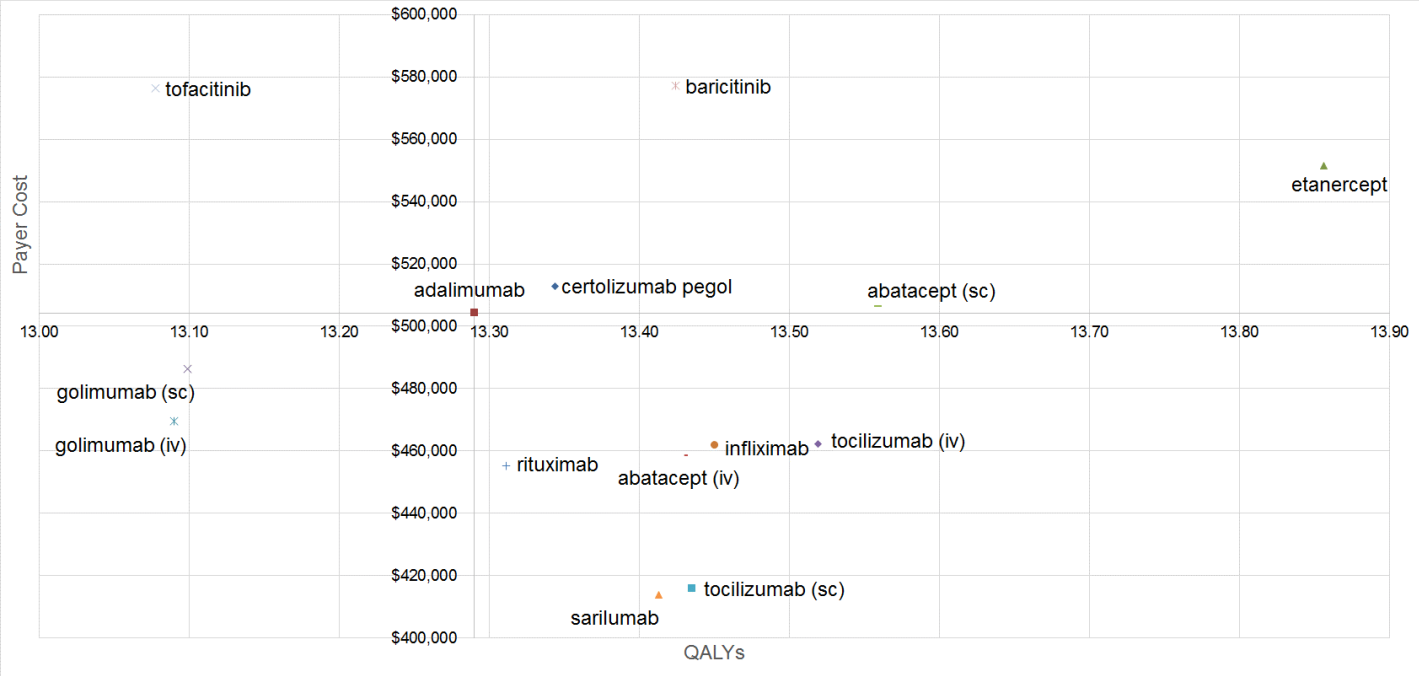
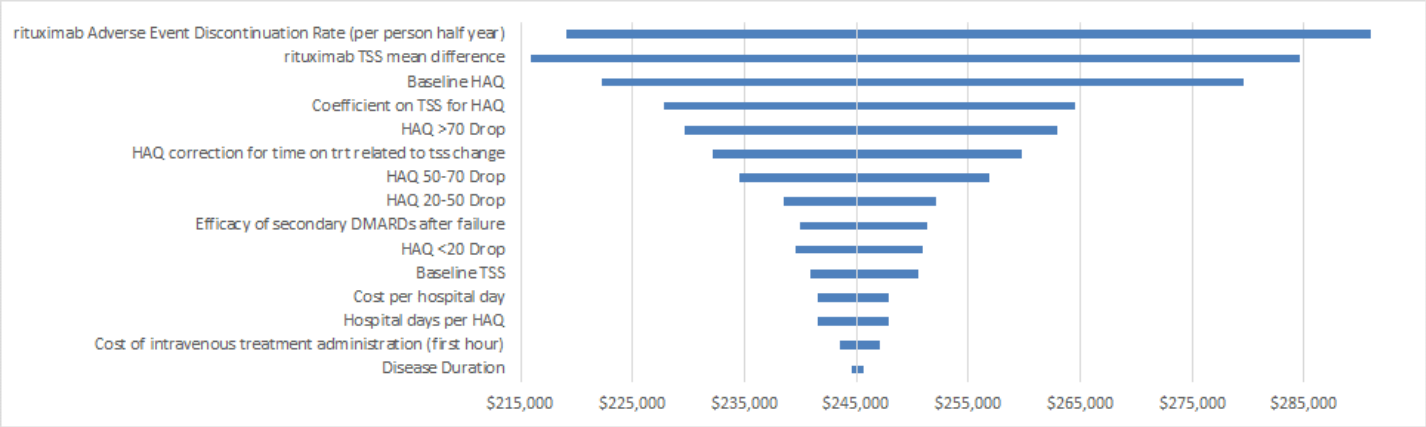


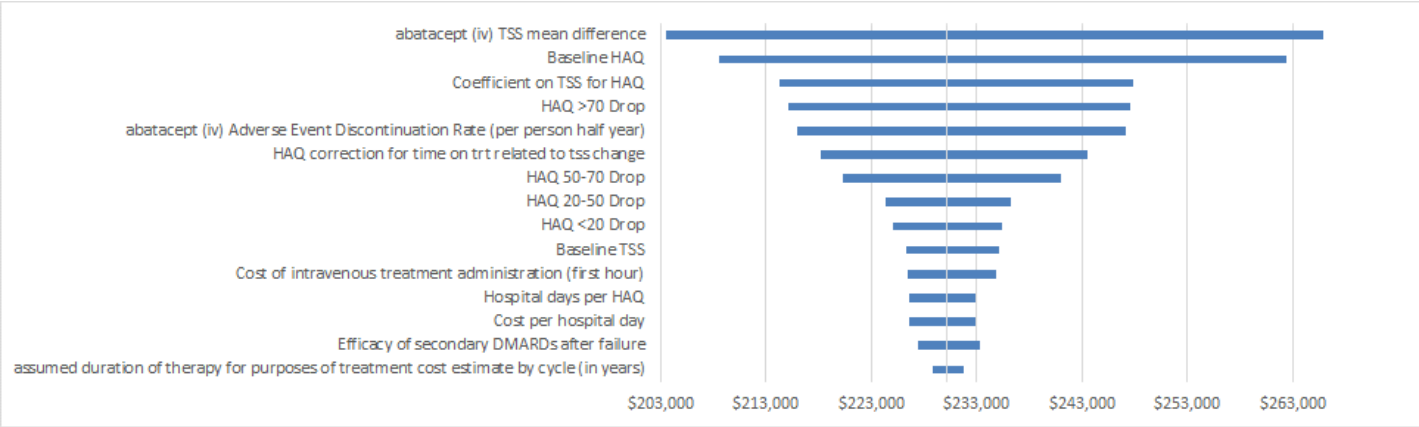
Figure 2 graphs the TIM market leader, adalimumab, as the reference case and plots all other TIMs on the cost-effectiveness plane relative to adalimumab's estimated cost and QALYs gained. Therapies in the upper right quadrant are more costly, but also more effective. Therapies in the upper left quadrant 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)

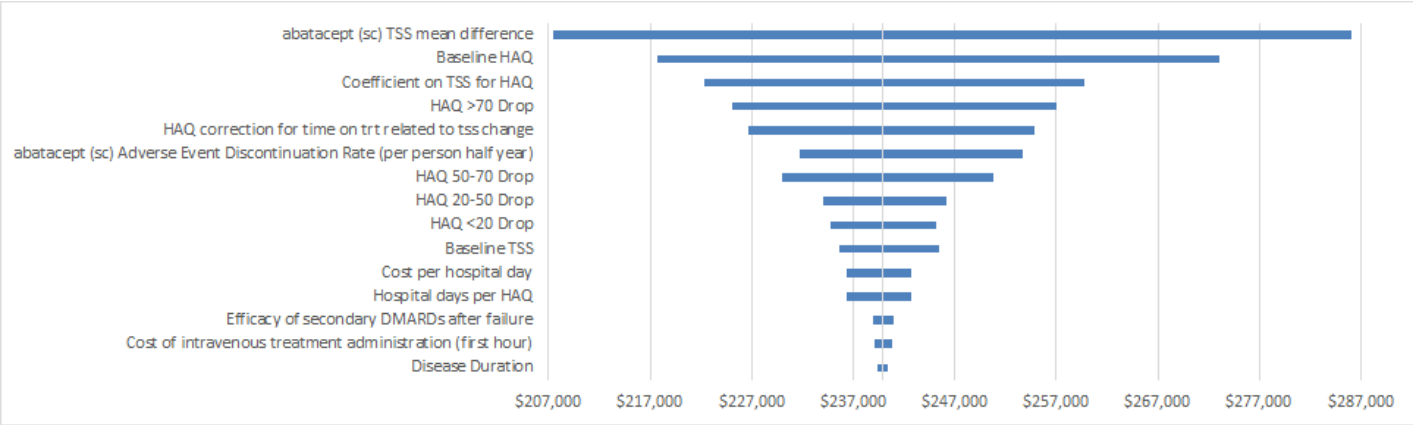
rituximab vs. cDMARD



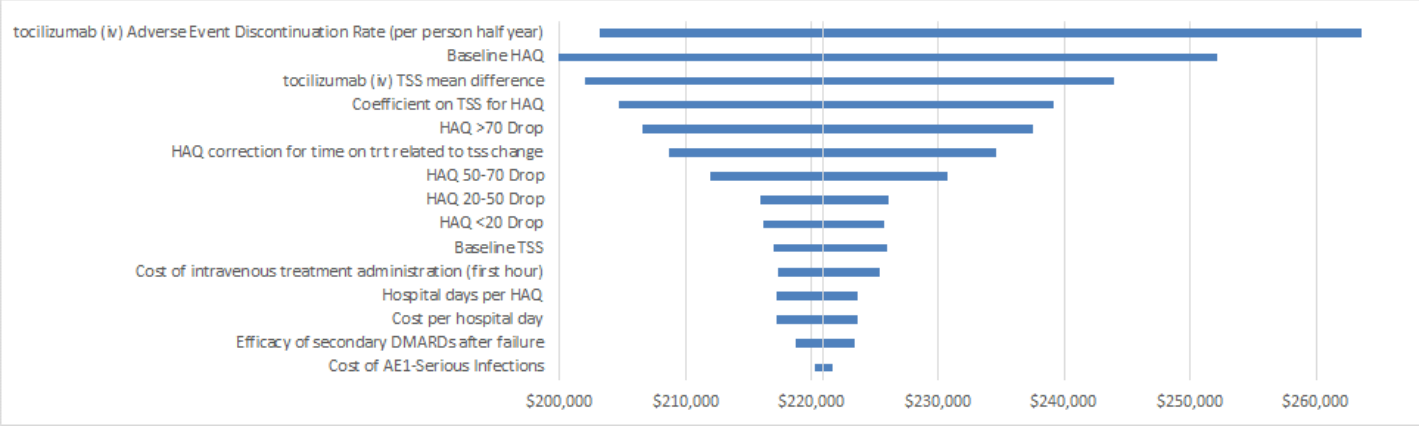
abatacept iv vs. cDMARD



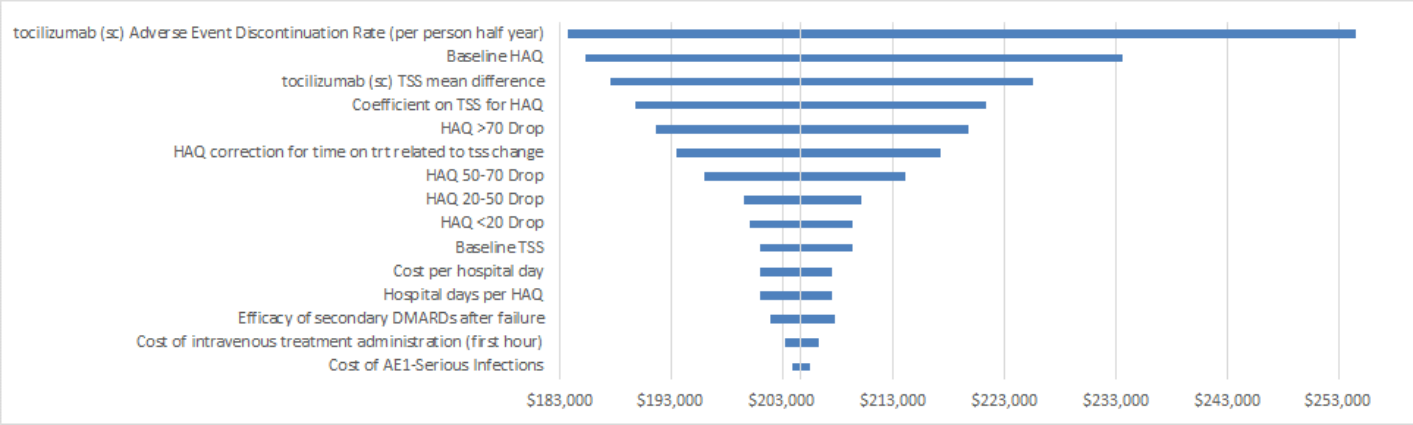
abatacept subcutaneous vs. cDMARD



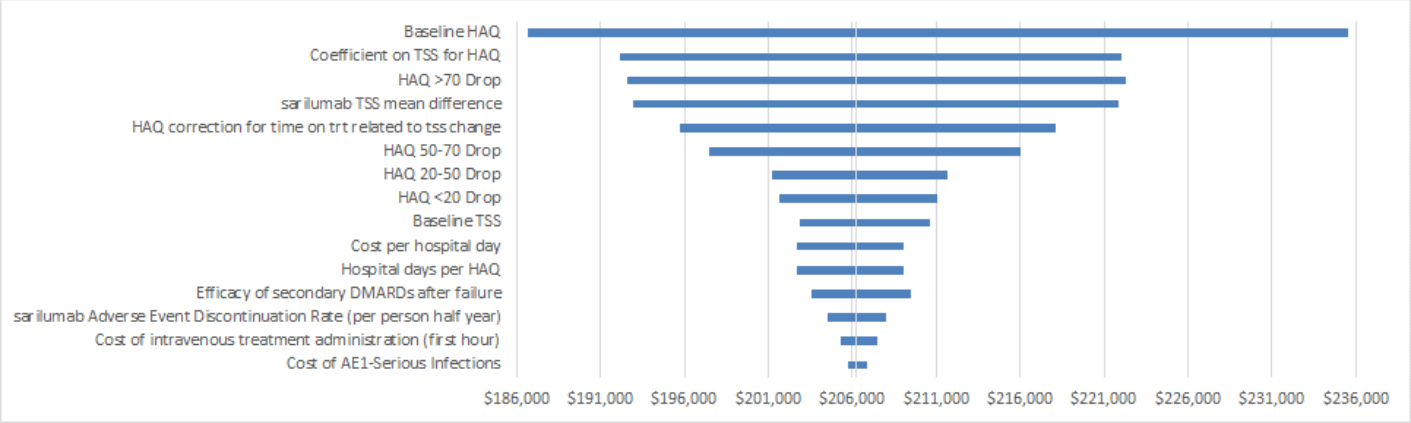
tocilizumab iv vs. cDMARD



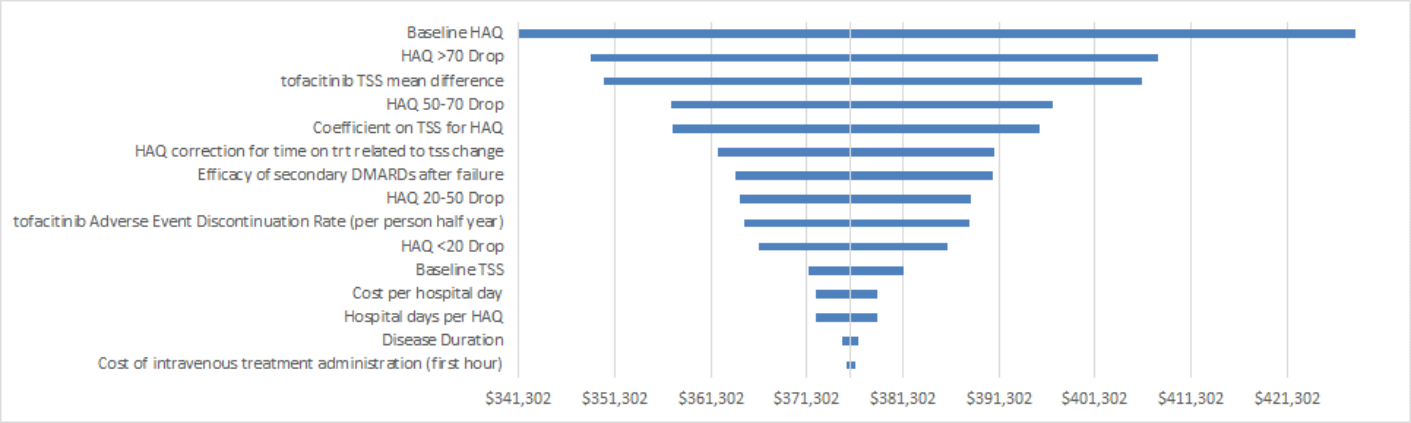
tocilizumab subcutaneous vs. cDMARD



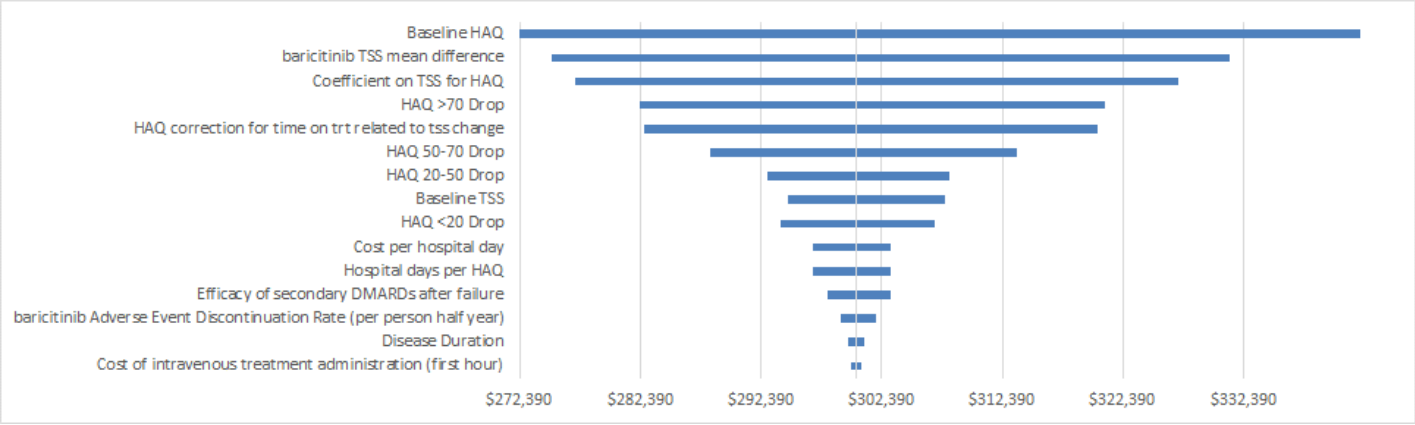
sarilumab vs. cDMARD



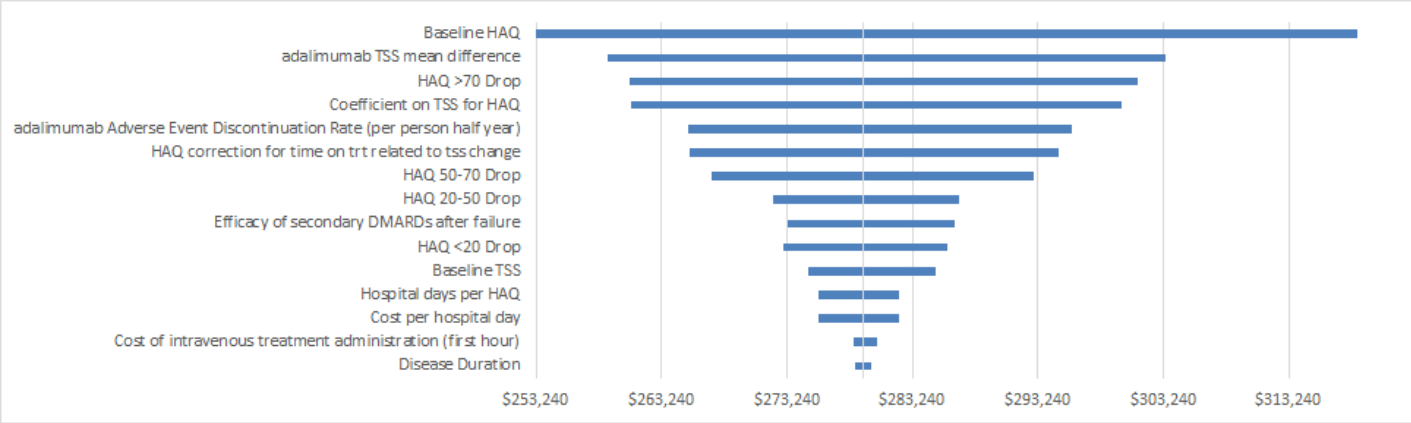
tofacitinib vs. cDMARD



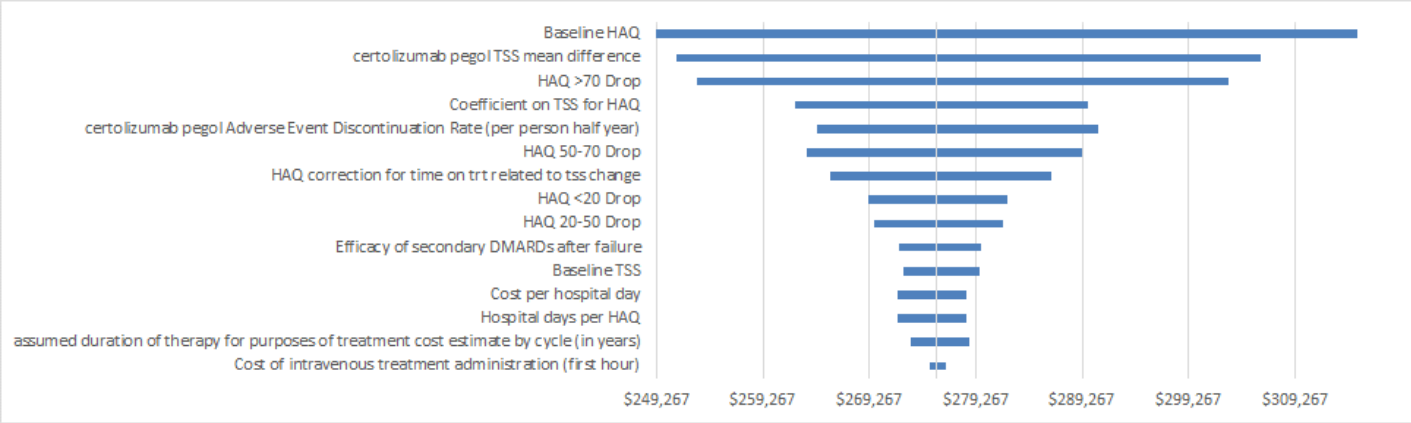
baricitinib vs. cDMARD



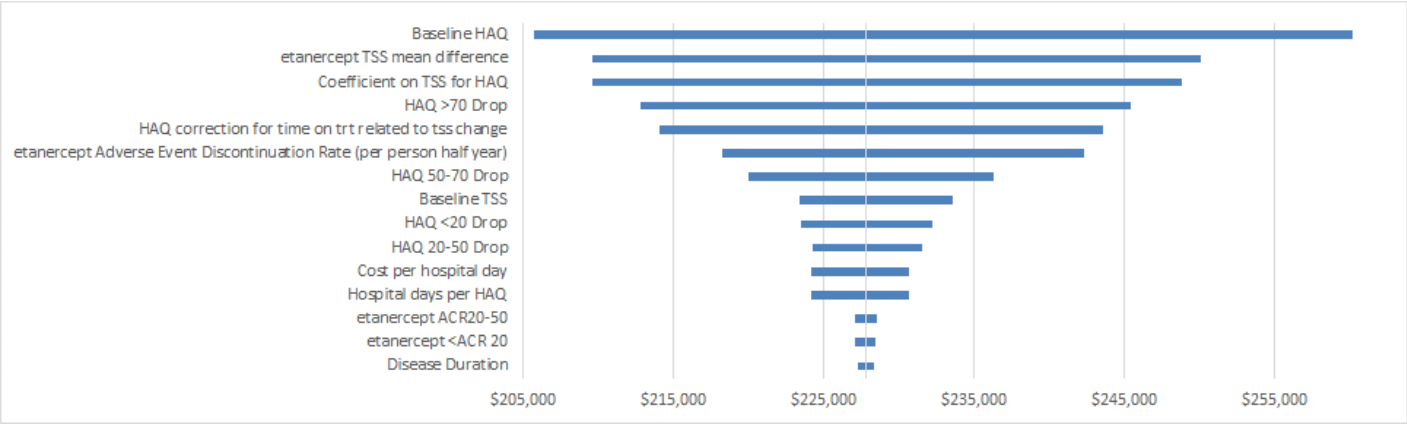
adalimumab vs. cDMARD



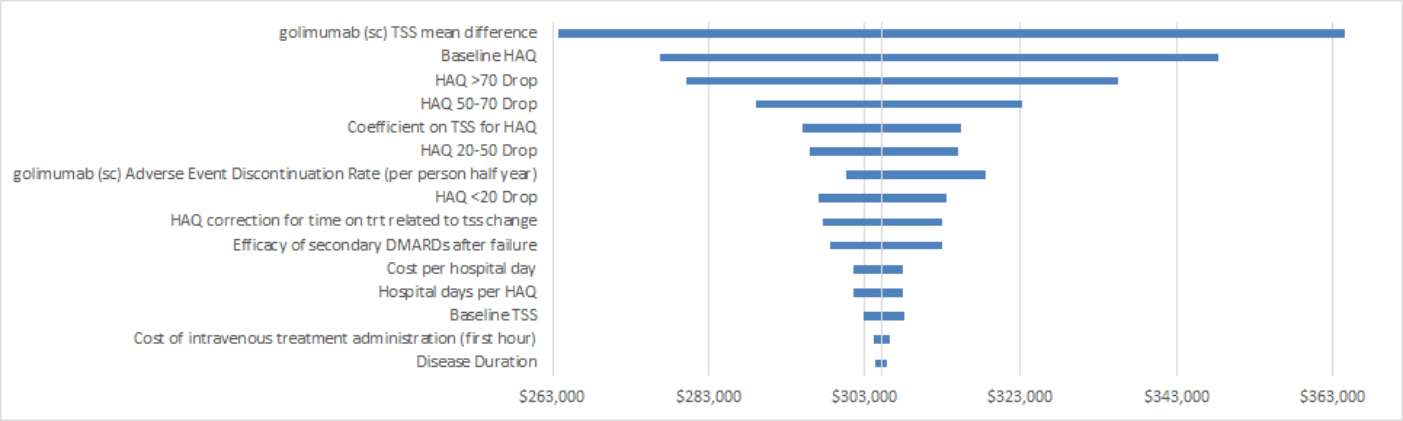
certolizumab pegol vs. cDMARD



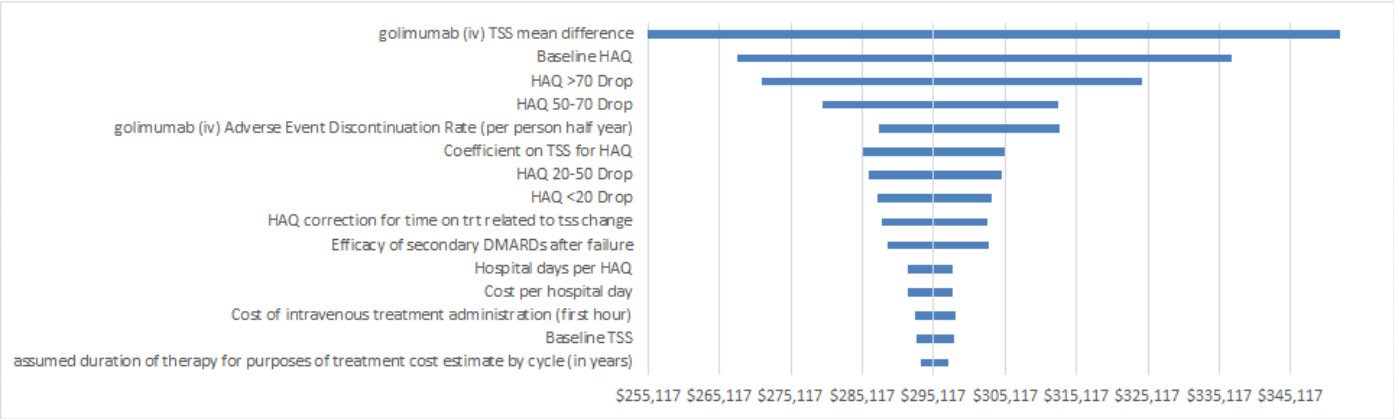
etanercept vs. cDMARD



golimumab subcutaneous vs. cDMARD



golimumab iv vs. cDMARD



infliximab vs. cDMARD

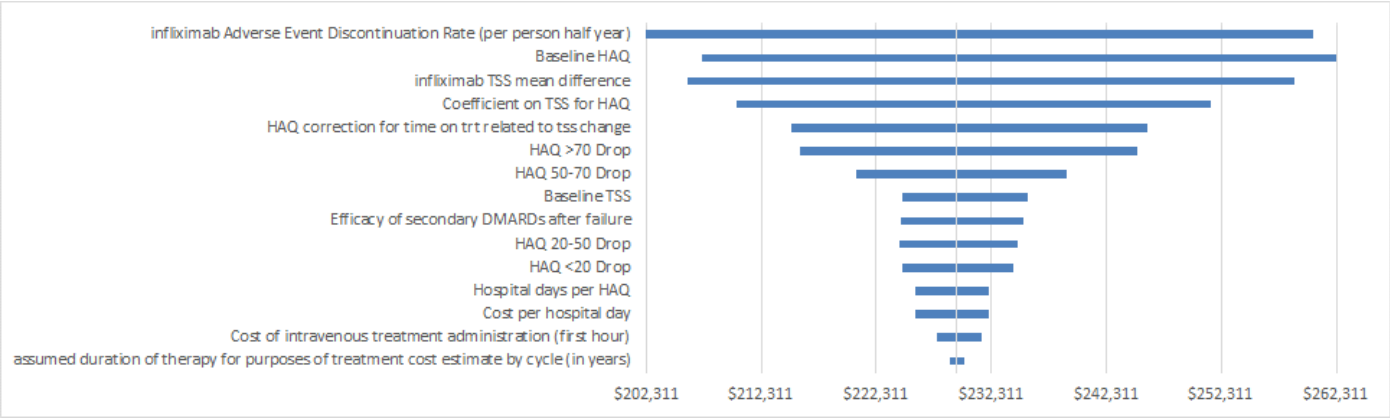


Table D8.1. Probabilistic Sensitivity Analysis Results: TIMs vs. conventional DMARD therapy

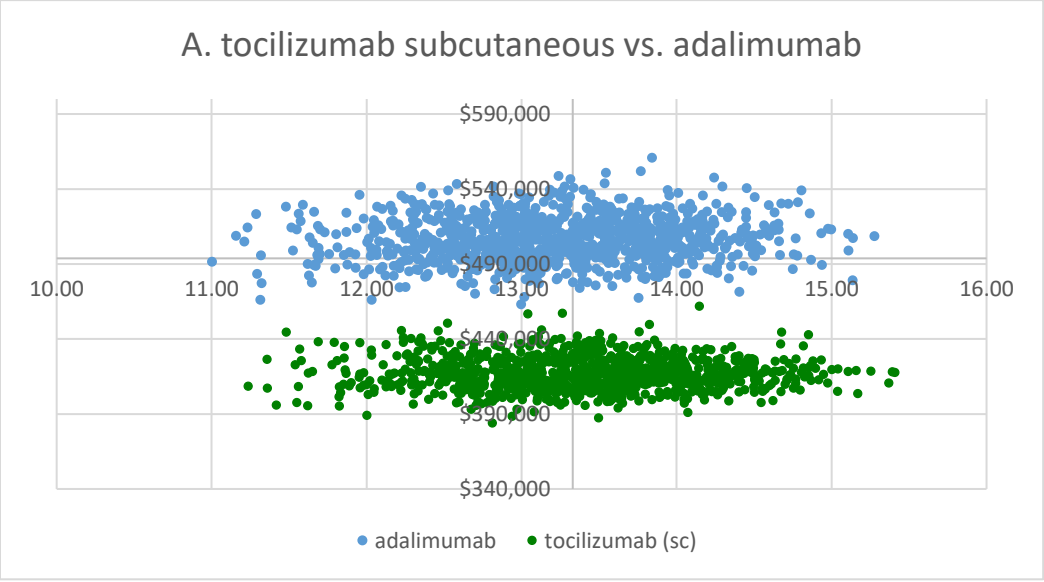
	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY	Cost-Effective at $200,000 per QALY	Cost-Effective at $250,000 per QALY
rituximab	0%	0%	0%	9%	55%
abatacept (iv)	0%	0%	0%	11%	73%
abatacept (sc)	0%	0%	0%	5%	61%
tocilizumab (iv)	0%	0%	0%	22%	83%
tocilizumab (sc)	0%	0%	2%	46%	92%
sarilumab	0%	0%	0%	35%	96%
tofacitinib	0%	0%	0%	0%	0%
baricitinib	0%	0%	0%	0%	3%
adalimumab	0%	0%	0%	0%	12%
certolizumab pegol	0%	0%	0%	0%	17%
etanercept	0%	0%	0%	10%	78%
golimumab (sc)	0%	0%	0%	0%	4%
golimumab (iv)	0%	0%	0%	0%	9%
infliximab	0%	0%	0%	14%	73%

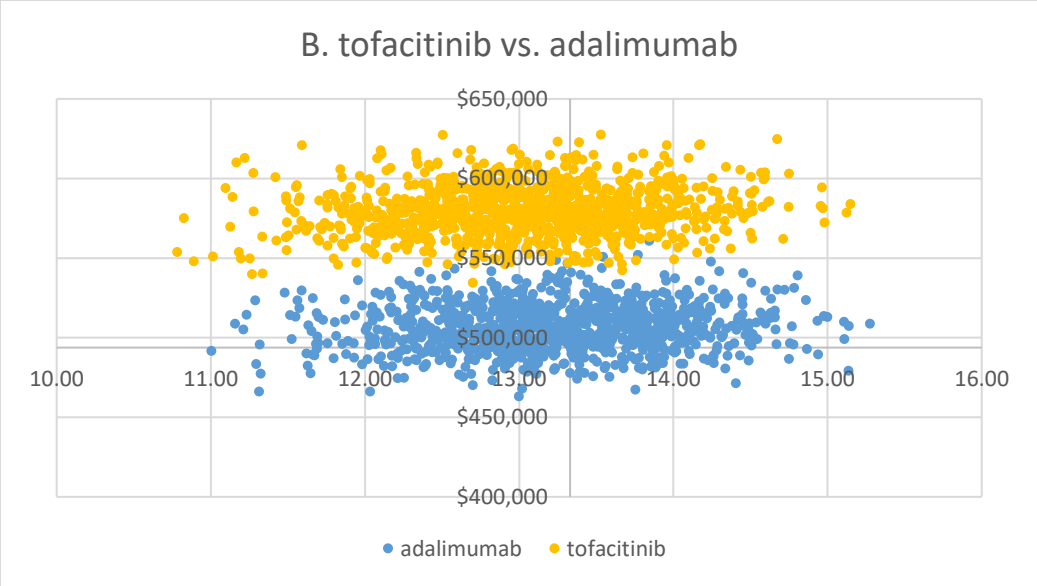
Table D8.2. Probabilistic Sensitivity Analysis Results: TIMs vs. adalimumab

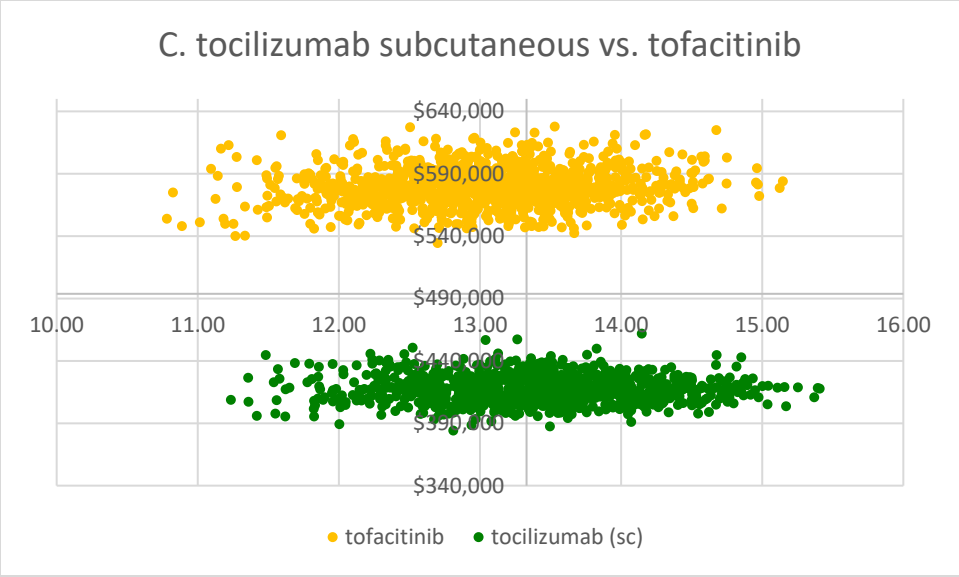
	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY	Cost-Effective at $200,000 per QALY	Cost-Effective at $250,000 per QALY
rituximab	100%	100%	100%	95%	91%
abatacept (iv)	100%	100%	100%	100%	99%
abatacept (sc)	85%	93%	93%	92%	93%
tocilizumab (iv)	100%	100%	100%	100%	99%
tocilizumab (sc)	100%	100%	100%	100%	100%
sarilumab	100%	100%	100%	100%	100%

	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
tofacitinib	0%	0%	0%	0%	0%
baricitinib	0%	0%	0%	2%	7%
certolizumab pegol	26%	40%	50%	55%	57%
etanercept	2%	74%	97%	99%	100%
golimumab (sc)	78%	47%	29%	20%	18%
golimumab (iv)	99%	86%	59%	41%	33%
infliximab	100%	100%	100%	100%	99%

Figure D4. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds




B. tofacitinib vs. adalimumab
$650,000
$600,000
$550,000
$500,000
$450,000
$400,000
10.00
11.00
12.00
13.00
14.00
15.00
16.00
adalimumab
tofacitinib



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. Similarly, there is little overlap between the two clouds. 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.

Table D9. 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	$253,016	Less costly, More effective
abatacept (iv)	$240,134	Less costly, More effective
abatacept (sc)	$247,611	Less costly, More effective
tocilizumab (iv)	$232,571	Less costly, More effective

Treatment 1	ICER (cost per QALY gained) Comparator: cDMARD	ICER (cost per QALY gained) Comparator: adalimumab
tocilizumab (sc)	$221,286	Less costly, More effective
sarilumab	$222,102	Less costly, More effective
tofacitinib	$342,427	More costly, Less effective
baricitinib	$295,070	$557,164
adalimumab	$277,270	Reference
certolizumab pegol	$272,375	Less costly, More effective
etanercept	$236,370	$41,822
golimumab (sc)	$292,070	Less costly, Less effective
golimumab (iv)	$284,922	Less costly, Less effective
infliximab	$243,659	Less costly, More effective

Table D10. 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	$257,170	Less costly, More effective
abatacept (iv)	$242,921	Less costly, More effective
abatacept (sc)	$250,254	Less costly, More effective
tocilizumab (iv)	$235,653	Less costly, More effective
tocilizumab (sc)	$223,005	Less costly, More effective
sarilumab	$224,227	Less costly, More effective
tofacitinib	$305,874	More costly, Less effective
baricitinib	$274,231	$274,952
adalimumab	$274,175	Reference
certolizumab pegol	$268,444	Less costly, More effective
etanercept	$235,115	$42,845
golimumab (sc)	$285,362	Less costly, Less effective
golimumab (iv)	$277,775	Less costly, Less effective
infliximab	$241,720	Less costly, More effective

Table D11. Scenario Analysis Results: Societal Perspective

Treatment 1	ICER (cost per QALY gained) Comparator: cDMARD	ICER (cost per QALY gained) Comparator: adalimumab
rituximab	$209,868	Less Costly, More Effective
abatacept (iv)	$194,860	Less Costly, More Effective
abatacept (sc)	$205,877	Less Costly, More Effective
tocilizumab (iv)	$185,615	Less Costly, More Effective
tocilizumab (sc)	$169,612	Less Costly, More Effective
sarilumab	$170,615	Less Costly, More Effective
tofacitinib	$338,263	More Costly, Less Effective
baricitinib	$265,832	$533,611
adalimumab	$243,134	Reference
certolizumab pegol	$236,609	Less Costly, More effective
etanercept	$192,923	$52,777
golimumab (sc)	$265,997	Less costly, Less effective
golimumab (iv)	$255,934	Less costly, Less effective
infliximab	$194,367	Less Costly, More Effective

Table D12. Scenario Analysis Results: TIM Experienced Population versus Mixed Population*

	ICER (biologic experienced population)	ICER (mixed population)
rituximab	$205,530	$257,170
abatacept (iv)	$204,895	$242,921
tocilizumab (iv)	$188,744	$235,653
sarilumab	$200,184	$224,227
baricitinib	$227,673	$274,231

*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 D13. 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	$33,388	51.37%	0.7373	$577,690	$117,345
abatacept (iv)	$32,233	57.80%	0.7436	$494,423	$89,872
abatacept (sc)	$36,282	56.57%	0.7425	$575,832	$106,796
tocilizumab (iv)	$32,399	61.49%	0.7478	$463,668	$80,964
tocilizumab (sc)	$26,974	56.73%	0.7426	$410,750	$75,814
sarilumab	$26,710	59.05%	0.7448	$390,427	$69,684
tofacitinib	$46,770	52.63%	0.7364	$854,666	$162,316
baricitinib	$46,808	57.10%	0.7422	$766,603	$138,971
adalimumab	$39,454	54.13%	0.7408	$652,203	$127,446
certolizumab pegol	$37,637	70.10%	0.7572	$475,843	$77,021
etanercept	$39,675	70.32%	0.7601	$485,315	$81,250
golimumab (sc)	$35,593	58.40%	0.7429	$559,872	$98,626
golimumab (iv)	$33,468	57.62%	0.7421	$530,235	$94,310
infliximab	$33,119	55.00%	0.7440	$506,234	$101,656
cDMARD	$3,782	26.14%	0.6861		

Table D14. 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	$93,752	45.28%	2.1886	$428,551	$382,255
abatacept (iv)	$91,565	52.47%	2.2009	$392,224	$279,440
abatacept (sc)	$100,820	53.22%	2.2000	$439,170	$303,606
tocilizumab (iv)	$92,088	55.49%	2.2105	$377,100	$254,534
tocilizumab (sc)	$79,721	51.20%	2.1993	$337,139	$249,335
sarilumab	$78,966	52.97%	2.2030	$327,605	$231,667
tofacitinib	$126,303	44.50%	2.1798	$625,488	$552,426
baricitinib	$126,311	51.66%	2.1979	$569,590	$411,436
adalimumab	$107,940	47.28%	2.1942	$487,765	$409,976
certolizumab pegol	$105,558	61.60%	2.2240	$413,797	$249,084
etanercept	$110,668	64.50%	2.2398	$407,977	$243,935
golimumab (sc)	$99,854	51.95%	2.1919	$452,458	$313,796
golimumab (iv)	$95,032	51.26%	2.1902	$431,543	$304,208
infliximab	$94,223	46.56%	2.2071	$393,226	$362,926
cDMARD	$10,973	23.63%	1.9954		

Table D15 Rates of Serious Infection

Intervention	Events per 1, 000 patient-years	Source
Rituximab	25.6	Strand et al., 2015[224]

Abatacept	13.4	Strand et al., 2015[224]
Tocilizumab	56.5	Strand et al., 2015[224]
Sarilumab	38.2	Genovese et al., 2015[143]
Tofacitinib	6.7	Strand et al., 2015[224]
Baricitinib	30.9	Dougados et al., 2016[155]
TNFα inhibitors	32.3	Strand et al., 2015[224]
MTX	15	Strand et al., 2015[224]

Table D16 Rates of Tuberculosis Infection

Intervention	Events per 1, 000 patient-years	Source
Rituximab	0.17	Lahiri et al., 2015[225]
Abatacept	0.95	Lahiri et al., 2015[225]
Tocilizumab	0	Lahiri et al., 2015[225]
Sarilumab	0	Assumed identical rates with Tocilizumab
Tofacitinib	3.09	Lahiri et al., 2015[225]
Baricitinib	3.09	Assumed identical rates with Tofacitinib
TNFα inhibitors	0.97	Ai et al., 2015[226]
MTX	0.24	Ai et al., 2015[226]

Appendix E. Previous Systematic Reviews and Technology Assessments

We examined five systematic reviews comparing the effectiveness of targeted immunomodulators 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[51]

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[50]

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[49]

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[227]

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 immunomodulators in rheumatoid arthritis.[228-237]

CADTH[238]

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 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[239] 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[80] 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[240] 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[241] 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
Curtis J *Annals of the Rheumatic Diseases* 2016[242] 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

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 care & research* 2014[243] 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[244] Fair	Not clear	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[93] 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

<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>Fleischmann R
Arthritis and rheumatism 2012[81]

Fleischmann 2012

Good</td>
<td>Pfizer</td>
<td>RCT
double-blind, placebo controlled, active comparator, parallel-group phase IIb

24 weeks</td>
<td>63 centers in the United States, Europe, Latin America, and the Republic of Korea</td>
<td>1) PBO (n=59)
2) TOF 1mg (n=54)
3) TOF 3mg (n=51)
4) TOF 5mg (n=49)
5) TOF 10mg (n=61)
6) TOF 15mg (n=57)
7) ADA 40mg (n=53)

TOF and PBO were administered orally twice a day and ADA was injected SC at 40mg every 2 weeks followed by reassignment to receive TOF at wk 12, administered at 5mg irrespective of patients' response. TOF 1mg, 3mg and PBO were also reassigned to 5mg TOF at 12weeks if response is inadequate.</td>
<td>Inclusion:
18 years with RA for ≥6 months which was active i.e. ≥6 SJC and TJC, and either CRP≥7mg/l or ESR≥ULN; No previous biologic treatment for RA; Failure of at ≥1 DMARD and washout of all DMARDs except anti-malarial

Exclusion:
Discontinuation of previous TNFi for either lack of benefit or safety; previous ADA therapy for any reason; evidence of blood disorders, chronic infections or untreated TB</td>
<td>Mean age (SD)
<table><tr><td>1</td><td>4</td><td>5</td><td>6</td><td>7</td></tr><tr><td>53 (14)</td><td>54 (14)</td><td>52 (11)</td><td>53 (13)</td><td>54 (12)</td></tr></table>
Female, %
<table><tr><td>1</td><td>4</td><td>5</td><td>6</td><td>7</td></tr><tr><td>88</td><td>87.8</td><td>87</td><td>87.7</td><td>84.9</td></tr></table>
Mean RA duration, yrs
<table><tr><td>1</td><td>4</td><td>5</td><td>6</td><td>7</td></tr><tr><td>10.8</td><td>8.1</td><td>8.6</td><td>8.7</td><td>7.7</td></tr></table>
HAQ DI, mean (scale 0-3)
<table><tr><td>1</td><td>4</td><td>5</td><td>6</td><td>7</td></tr><tr><td>1.54</td><td>1.4</td><td>1.49</td><td>1.62</td><td>1.44</td></tr></table>
4-variable DAS28-ESR, mean
<table><tr><td>1</td><td>4</td><td>5</td><td>6</td><td>7</td></tr><tr><td>6.6</td><td>6.6</td><td>6.5</td><td>6.5</td><td>6.3</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
Flouri I *Seminars in arthritis and rheumatism* 2014[88] 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[79] 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[245] 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[246] 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[86] 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 [247] 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
Hetland ML *Arthritis and rheumatism* 2010[87] 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[85] RED SEA Fair	University Hospital Birmingham NHS Foundation Trust	RCT, parallel group, non-blinded, non-inferiority 52 weeks	4 centers in England	1) ADA (n=60) 2) ETN (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[248] 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[77] AMPLE Good	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* 2014[78] AMPLE Good	See Weinblatt ME *Arthritis and rheumatism* 2013[77]	See Weinblatt ME *Arthritis and rheumatism* 2013[77] 2-yr results	See Weinblatt ME *Arthritis and rheumatism* 2013[77]	See Weinblatt ME *Arthritis and rheumatism* 2013[77]	See Weinblatt ME *Arthritis and rheumatism* 2013[77]	See Weinblatt ME *Arthritis and rheumatism* 2013[77]
Fleischmann R *Arthritis and Rheumatology* 2016[249] AMPLE Good	See Weinblatt ME *Arthritis and rheumatism* 2013[77]	See Weinblatt ME *Arthritis and rheumatism* 2013[77] 2-yr results	See Weinblatt ME *Arthritis and rheumatism* 2013[77]	See Weinblatt ME *Arthritis and rheumatism* 2013[77]	See Weinblatt ME *Arthritis and rheumatism* 2013[77]	See Weinblatt ME *Arthritis and rheumatism* 2013[77]

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[76] ATTEST Good See also Schiff M *Annals of the rheumatic diseases* 2011[89]	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
Schiff M *Annals of the rheumatic diseases* 2011[89] ATTEST Good	See Schiff M *Annals of the rheumatic diseases* 2008[76]	Schiff M *Annals of the rheumatic diseases* 2008[76]	Schiff M *Annals of the rheumatic diseases* 2008[76]	Schiff M *Annals of the rheumatic diseases* 2008[76]	Schiff M *Annals of the rheumatic diseases* 2008[76]	Schiff M *Annals of the rheumatic diseases* 2008[76]

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[46] 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 P *Arthritis and Rheumatology* 2015[84] RA-BEAM *Abstract*	Eli Lilly and Company	Phase III RCT double-blind 52 weeks Non-responders were rescued from Wk 16. At Wk 24, pts on PBO switched to BAR	Unclear	1) PBO + MTX (n=488) 2) BAR 4 mg once daily (n=487) 3) ADA 40 mg biweekly (n=330)	Patients with active RA and an inadequate response to conventional synthetic DMARDs or biologic DMARDs	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
van Vollenhoven RF *The New England journal of medicine* 2012[82] ORAL Standard Good See also Strand V *Rheumatology* 2016[83]	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 [250]

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>
</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
Biosimilar studies						
Bae S-C *Ann Rheum Dis* 2016[147] 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[178] Good See also Choe J-Y *Arthritis Rheumatology* 2015[148]	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[174] Abstract See also Matsumoto AK *Arthritis Rheumatology* 2015[251]	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[176] Good See also Vencovsky J *Arthritis Rheumatology* 2015[186]	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[173] 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[177] Abstract See also Kay J *Ann Rheum Dis* 2015[252]	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
Takeuchi T *Modern Rheumatology* 2015[149]	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[175] 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
Yoo DH *Ann Rheum Dis* 2013[150] PLANETRA Good See also Yoo D-H *Arthritis Res Ther* 2016,[187]Yoo D-H *Ann Rheum Dis* 2016,[216], Yoo D-H *Ann Rheum Dis* 2013[253]	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[216] PLANETRA Good See also Yoo DH *Ann Rheum Dis* 2013,[150] Yoo D-H *Arthritis Res Ther* 2016,[187], Yoo D-H *Ann Rheum Dis* 2013[253]	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 52 weeks RCT phase, patient received IFX-ref or IFX-bio. During extension phase, all patients receive six infusions of IFX-bio from week 62 to week 102. 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*[150] 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)

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 *Arthritis Rheum* 2013[172] Abstract See also Yoo D-H *Arthritis Rheum* 2015 [146]	Celltrion	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	Republic of Korea	1) RTX-bio+MTX (n=103) 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.	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	Mean DAS28-CRP (SD) 1) 6.0 (0.9) 2) 6.0 (0.8) Mean DAS28-ESR (SD) 1) 6.8 (0.8) 2) 6.7 (0.8) Further detail NR

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[80] 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

<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>Fleischmann R
Arthritis and rheumatism 2012[81]</td>
<td>1) PBO (n=59)
2) TOF 1mg (n=54)
3) TOF 3mg (n=51)
4) TOF 5mg (n=49)
5) TOF 10mg (n=61)
6) TOF 15mg (n=57)
7) ADA 40mg (n=53)

2), 3), 5), and 6) excluded from table</td>
<td>ACR20, %
<table><tr><th></th><th>Wk 12</th><th>Wk 24</th></tr><tr><td>1</td><td>22</td><td>25.4</td></tr><tr><td>4</td><td>59.2*</td><td>51*</td></tr><tr><td>7</td><td>35.9</td><td>------</td></tr></table>ACR50, %
<table><tr><th></th><th>Wk 12</th><th>Wk 24</th></tr><tr><td>1</td><td>10.2</td><td>10.2</td></tr><tr><td>4</td><td>36.7*</td><td>34.7*</td></tr><tr><td>7</td><td>18.9</td><td>------</td></tr></table>ACR70, %
<table><tr><th></th><th>Wk 12</th><th>Wk 24</th></tr><tr><td>1</td><td>3.4</td><td>6.8</td></tr><tr><td>4</td><td>12.2</td><td>20.4*</td></tr><tr><td>7</td><td>3.8</td><td>------</td></tr></table>*significant p value vs. PBO</td>
<td>Week 12
DAS28-ESR<2.6, %
1) 3.6
4) 12.5
7) 3.9

DAS 28-ESR
Mean change from baseline
@ Wk 12
1) -1.21
4) -2.19 (p<0.001)
7) -1.43

@Wk 24
1) -1.43
4) -2.35 (p<0.01)
7) -2.03</td>
<td>NR</td>
<td>Week 12 mean HAQ-DI change from baseline (SEM)
1) -0.25 (0.08)
4) -0.51 (0.08)
7) -0.35 (0.08)</td>
<td>Week 12 mean CRP (mg/L) change from baseline (SEM)
1) 14.06 (2.56)
2) -3.88 (2.61)
3) -10.41 (2.58)
4) -14.56 (2.61)
5) -16.54 (2.37)
6) -18.06 (2.42)
7) -7.43 (2.59)</td>
</tr>
</table>

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Flouri I *Seminars in arthritis and rheumatism* 2014[88]	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[79] 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[246] 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[86] 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[87] 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[85] RED SEA	1) ADA (n=60) 2) ETN (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[77] 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[78] 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[249] 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[76] 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[89] 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[46] 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 P *Arthritis and Rheumatology* 2015[84] RA-BEAM	1) PBO + MTX (n=488) 2) BAR 4 mg once daily + MTX (n=487) 3) ADA 40 mg biweekly + MTX (n=330)	Week 24 ACR20, % 1) 37 2) 74*ǂ 3) 66* ACR50, % 1) 19 2) 50* 3) 46* ACR70, % 1) 8 2) 30*ǂ 3) 22* *p≤0.001 vs. PBO ǂp≤0.05 vs. ADA	Week 24 remission DAS28-CRP <2.6 1) 8 2) 35* 3) 32* DAS28-ESR <2.6 1) 5 2) 18* 3) 18* CDAI ≤2.8 1) 4 2) 16* 3) 12* SDAI ≤3.3 1) 3 2) 16* 3) 14* *p≤0.001 vs. PBO ǂp≤0.05 vs. ADA	NR	@ 24 weeks HAQ-DI MCID ≥0.22 1) 45 2) 73*ǂ 3) 64* *p≤0.001 vs. PBO ǂp≤0.05 vs. ADA	NR

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[82] 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

<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[147]

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[178]	1) IFX-bio+MTX (n=291) 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[148] 54-week results of Choe J-Y *Ann Rheum Dis* 2015[178]	1) IFX-bio+MTX (n=291) 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[174]	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
Matsumoto AK *Arthritis Rheumatology* 2015[251] Secondary endpoints from Cohen SB *Arthritis Rheumatology* 2015[174]	1) ADA-bio+MTX (n=264) 2) ADA-ref+MTX (n=262)	See Matsumoto AK *Arthritis Rheumatol* 2015[251] 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
Emery P *Ann Rheum Dis* 2015[176]	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

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Vencovsky J *Arthritis Rheumatol* 2015[186] 52-week results of Emery P *Ann Rheum Dis* 2015[176]	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[173]	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[177]	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[252]	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[149]	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[175]	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
Yoo DH *Ann Rheum Dis* 2013[150] 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[216] 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[253] 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[216]	Week 54 DAS28-CRP Remission, % 1) 26.4 2) 27.8	See Yoo D-H *Arthritis Res Ther* 2016[216]	See Yoo D-H *Arthritis Res Ther* 2016[216]	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[216] 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[172]	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[146]	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	

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[239] 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[80] 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[241]	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[242]	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[243]	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[244]	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[93] 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
Fleischmann R *Arthritis and rheumatism* 2012[81]	1) PBO (n=59) 2) TOF 1mg (n=54) 3) TOF 3mg (n=51) 4) TOF 5mg (n=49) 5) TOF 10mg (n=61) 6) TOF 15mg (n=57) 7) ADA 40mg (n=53) TOF and PBO were administered orally twice a day and ADA was injected SC at 40mg every 2 weeks followed by reassignment to receive TOF at wk 12, administered at 5mg irrespective of patients' response. TOF 1mg, 3mg and PBO were also reassigned to 5mg TOF at 12weeks if response is inadequate.		Serious infections, n (%) 1) 1 (2.9) 2) 2 (5.9) 3) 0 4) 0 5) 0 6) 1 (1.8) 7) 0		Serious AEs, n (%) 1) 2 (5.9) 2) 2 (5.4) 3) 1 (2.9) 4) 0 5) 1 (1.6) 6) 4 (7) 7) 1 (1.9) 4 serious AEs occurred in ADA patients reassigned to TOF 5mg at 12 weeks. Discontinuation due to AE, n (%) 1) 1 (2.9) 2) 4 (10.8) 3) 3 (8.8) 4) 1 (2) 5) 1 (1.6) 6) 3 (5.3) 7) 4 (7.5) 1 death was reported in patient taking TOF 15mg.

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Gabay C *Lancet* 2013[79] 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[245]	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 [247]	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)		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)		
Jobanputra P *BMJ Open* 2012[85] RED SEA	1) ADA (n=60) 2) ETN (n=60)				Serious AEs, n 1) 6 2) 7 Death, n 1) 2 2) 0

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Johnston S *Semin Arthritis Rheum* 2013[248]	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[78] 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[76] 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[89] 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[46] EXXELERATE	1) CTZ + MTX (n=454) 2) ADA + MTX (n=454)	All malignancies, n 1) 8 2) 7	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		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
Taylor P *Arthritis and Rheumatology* 2015 [84] RA-BEAM	1) PBO+MTX (n=488) 2) BAR 4 mg once daily + MTX (n=487) 3) ADA 40 mg biweekly + MTX (n=330)	Week 24 (%) 1) 0.6 2) 0.4 3) 0.0	Week 24 (%) 1) 27.0 2) 35.7 3) 33.3	Week 24 TEAEs (%) 1) 60 2) 70.8 3) 67.0	Week 24 SAEs (%) 1) 4.3 2) 4.5 3) 1.8 Serious infections (%) 1) 1.4 2) 1.0 3) 0.6

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[82] 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[77] 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[250]</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><th>Grp</th><th>URTI</th><th>GTI</th></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>
</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[147] HERA	1) ETN-bio+MTX (n=115) 2) ETN-ref+MTX (n=118)	NR	Infection, % 1) 37.4 2) 41.1 Latent tuberculosis, n (%) 1) 14 (9.5) 2) 8 (5.5)	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)	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[178]	1) IFX-bio+MTX (n=291) 2) IFX-ref+MTX (n=293)	Malignancy 1) 2 (prostate cancer and breast cancer) 2) 0	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	TEAEs related to study drug, % 1) 21.4 2) 20.1 Infusion related reactions, n (%) 1) 15 (5.2) 2) 13 (4.4)	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[148] 54-week results of Choe J-Y *Ann Rheum Dis* 2015[178]	1) IFX-bio+MTX (n=291) 2) IFX-ref+MTX (n=293)	Malignancy, n (%) 1) 2 (0.7) 2) 0	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)	Infusion-related reaction, n (%) 1) 17 (5.9) 2) 15 (5.1)	Serious AEs, n (%) 1) 29 (10.0) 2) 31 (10.6) Death, n (%) 1) 0 2) 1 (0.3)
Cohen SB *Arthritis Rheumatol* 2015[174]	1) ADA-bio+MTX (n=264) 2) ADA-ref+MTX (n=262)	NR	Serious infections, % 1) 0.8 2) 1.1 Upper respiratory tract infection, % 1) 1.5 2) 3.8	Nasopharyngitis, % 1) 6.4 2) 7.3 Headache, % 1) 4.5 2) 4.2 Arthralgia, % 1) 3.0 2) 3.4	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[176]	1) ETN-bio+MTX (n=299) 2) ETN-ref (n=297)	Malignancies, n (%) 1) 3 (1.0) (basal cell carcinoma, breast cancer, lung cancer metastatic) 2) 1 (0.3) (invasive ductal breast carcinoma)	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)	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)	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[186] 52-week results of Emery P *Ann Rheum Dis* 2015[176]	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[173]	1) ADA-bio+MTX (n=60) 2) ADA-ref+MTX (n=60)	NR	NR	Pyrexia, headache and cough were commonly reported in both treatment groups	Discontinuation due to AEs, n 1) 2 2) 0 Serious AEs, n 1) 2 2) 1
Kay J *Ann Rheum Dis* 2014[177]	1) IFX-bio (n=127) 2) IFX-ref (n=62)	NR	Infectious AEs, % 1) 15.8 2) 9.7 p=NS	TEAEs, % 1) 43.3 2) 50.0	
Takeuchi T *Modern Rheumatology* 2015[149]	1) IFX-bio (n=50) 2) IFX-ref (n=51)		Serious infection, n 1) 5 2) 3	Infusion reaction 1) 2 2) 2	Serious AEs, n (%) 1) 8 (15.7) 2) 8 (15.1) Discontinuation due to AEs, n (%) 1) 9 (17.6) 2) 6 (11.3)
Weinblatt ME *Arthritis Rheumatol* 2015[175]	1) ADA-bio (n=271) 2) ADA-ref (n=273)	Malignancy, n (%) 1) 0 2) 2 (0.7)	Serious infection, n (%) 1) 1 (0.3) 2) 2 (0.7) Tuberculosis: 0	Injection site reactions, n (%) 1) 8 (3.0) 2) 8 (2.9)	Serious TEAEs, n (%) 1) 3 (1.1) 2) 7 (2.6) Death, n (%) 1) 0 2) 2 (0.7)

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Yoo D-H *Ann Rheum Dis* 2013 [150] PLANETRA	1) IFX-bio+MTX (n=302) 2) IFX-ref+MTX (n=304)	2 patients in IFX-ref group withdrawn due to malignancy (breast cancer, cervix carcinoma)	Latent TB related to study treatment, n 1) 13 2) 14 Urinary tract infection 1) 4 91.3) 2) 7 (2.3)	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)	Discontinuation due to AEs, n (%) 1) 28 (9) 2) 26 (9) Serious TEAEs, n (%) 1) 30 (10) 2) 21 (7) Deaths: 0
Yoo D-H *Arthritis Res Ther* 2016[216] 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

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Yoo D-H *Annals of the Rheumatic Diseases* 2016[216] 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)
Yoo D-H *Arthritis Rheum* 2013[172]	1) RTX-bio+MTX (n=103) 2) RTX-ref+MTX (n=51)		Infections, % 1) 23.5 2) 25.5	TEAEs, n 1) 166 2) 88 Infusion reactions, % 1) 16.7 2) 19.6	Serious AEs, % 1) 16.7 2) 17.6
Yoo D-H *Arthritis Rheum* 2015[146]	1) RTX-bio+MTX (n=103) 2) RTX-ref+MTX (n=51)	Malignancy, n (%) 1) 0 2) 1 (2.0) (cervix carcinoma stage 0)	Infection, n (%) 1) 39 (38.2) 2) 21 (41.2)	Infusion-related reaction, n (%) 1) 20 (19.6) 2) 10 (19.6)	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

Table F4. Head-to-Head Trials: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Burmester G *Ann Rheum Dis* 2016[80] 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	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	Patient Satisfaction	Fatigue	Other outcomes
Chen J *Arthritis care & research* 2014[240]	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	NR	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	Patient Satisfaction	Fatigue	Other outcomes
Fleischmann R *Arthritis and rheumatism* 2012[81]	1) PBO (n=59) 2) TOF 1mg (n=54) 3) TOF 3mg (n=51) 4) TOF 5mg (n=49) 5) TOF 10mg (n=61) 6) TOF 15mg (n=57) 7) ADA 40mg (n=53)	Week 12 mean change from baseline (SE) SF-36 1) 2.8 4) 7 (p<0.05) 5) 10.1 (p<0.0001) 6) 10.9 (p<0.0001) *P values vs. PBO	Week 12 mean change from baseline (SE) Patient's assessment of pain, 100 mm VAS 1) -16.56 (3.19) 2) -13.92 (3.25) 3) -17.91 (3.25) 4) -30.76 (3.29) 5) -34.28 (2.95) 6) -35.79 (3.05) 7)-20.85 (3.24)			Week 12 mean change from baseline (SE) Patient's global assessment of disease activity, 100 mm VAS 1) -16.45 (3.21) 2) -15.51 (3.28) 3) -18.96 (3.28) 4) -31.15 (3.32) 5) -33.17 (2.97) 6) -35.77 (3.06) 7) -18.66 (3.26)

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Schiff M *Annals of the rheumatic diseases* 2008[76] 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	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Jobanputra P *BMJ Open* 2012[85] RED SEA	1) ADA (n=60) 2) ETN (n=60)	EQ5D utility score 1) 0.69 (0.59-0.76) 2) 0.64 (0.52-0.8)	NR	Month 12 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	NR	Month 12 patient global assessment (0-100) 1) 25 (15-50) 2) 34 (20-50)
Weinblatt ME *Arthritis and rheumatism* 2013[77] 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	Patient Satisfaction	Fatigue	Other outcomes
Schiff M *Annals of the rheumatic diseases* 2014[78] 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 [83] 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	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Fleischmann R *Arthritis care & research* 2016[203] 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	
Taylor P *Arthritis and Rheumatology* 2015[84] RA-BEAM	1) PBO + MTX (n=488) 2) BAR 4 mg once daily + MTX (n=487) 3) ADA 40 mg biweekly + MTX (n=330)	NR	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	NR	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	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Bae S-C *Ann Rheum Dis* 2016[147] HERA	1) ETN-bio+MTX (n=115) 2) ETN-ref+MTX (n=118)	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)	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)	NR	Mean change from baseline FACIT-F (SD) Week 24 1) 16.43 (21.01) 2) 15.61 (20.09) Week 48 1) 16.88 (22.97) 2) 15.00 (22.49)	"Some problems" with other elements of EQ-5D, n (%) Mobility Wk24: 1) 52 (45.22); 2) 61 (51.69) Wk48: 1) 46 (45.10); 2) 43 (40.95) Self-care Wk24: 1) 36 (31.30); 2) 36 (30.51) Wk48: 1) 27 (26.47); 2) 31 (29.52) Usual activities Wk24: 1) 62 (53.91); 2) 66 (55.93) Wk48: 1) 51 (51.96); 2) 57 (54.29) Anxiety/depression Wk24: 1) 45 (39.13); 2) 50 (42.37) Wk48: 1) 44 (43.14); 2) 45 (42.86)

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Choe J-Y *Ann Rheum Dis* 2015[178]	1) IFX-bio+MTX (n=291) 2) IFX-ref+MTX (n=293)	NR	Week 30 Mean change in pain VAS, mm (SD) 1) -21.9 (24.0) 2) -25.9 (27.2)	NR	NR	NR
Jani RH *Int J Rheum Dis* 2015[173]	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	NR	NR
Kay J *Ann Rheum Dis* 2015[177]	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	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Yoo D-H *Ann Rheum Dis* 2013[150] 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	NR	NR
Yoo D-H *Arthritis Res Ther* 2016[216] 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	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Yoo D *Annals of the Rheumatic Diseases* 2016[216] 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	NR	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[203] AMPLE See Schiff M *Annals of the rheumatic diseases* 2014[78]	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	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Requirements for surgical intervention	Hospitalization, Rehabilitation, Assisted living	Productivity Loss	Caregiver Burden	Other outcomes
				1) 25.4 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 [75] REFLEX Good See also Cohen SB *Annals of the rheumatic diseases* 2010[183]; Keystone E Arthritis Rheum 2008 [189]; Keystone E Ann Rheum Dis. 2009 [184]	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) Randomized at a 3:2 ratio to receive RTX or PBO on days 1 and 15	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
Cohen SB *Annals of the rheumatic diseases* 2010[183] REFLEX Good	F Hoffmann-La Roche Ltd, Genentech, Inc; Biogen Idec, Inc; and partly supported by grant by NIH National Center for Research Resources	RCT, double-blind, placebo controlled, phase III study 104 weeks	USA, UK	1) PBO+MTX (n=187) 2) RTX+MTX (n=281) IV RTX was 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 to 24, patients who failed to respond to treatment could receive rescue therapy i.e. PBO pts →RTX & RTX pts → standard care	Inclusion: Active RA despite treatment with ≥10 mg/week MTX; inadequate response to at least one TNF inhibitor	Mean Age, yrs (SD) 1) 52.9 (12.1) 2) 52.5 (12.2 Female, n (%) 1) 150 (80) 2) 228 (81) Mean RA duration, yrs (SD) 1) 11.7 (7.7) 2) 11.9 (8.2) Mean HAQ-DI (SD) 1) 1.9 (0.54) 2) 1.8 (0.57) Mean TSS (SD) 1) 32.5 (31.5) 2) 30.6 (26.7

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 Rheum 2008 [189] REFLEX Good	Hoffmann-La Roche	RCT, multicenter, placebo-controlled, double-blind, phase III trial 24 weeks	114 rheumatology centers in the US, Europe, Canada, and Israel	1) PBO+MTX (n=201) 2) RTX+MTX (n=298), (1000mg ×2) Randomized at ratio of 3:2 to receive RTX or PBO on days 1 and 15; both groups continuously received MTX (10-25 mg/wk), folate (≥5 mg/wk), intravenous steroid (100 mg before each infusion), and oral prednisone (60 mg on days 2-7, 30 mg on days 8-14)	Patients have active RA per 1987 ACR criteria for ≥6 months with failed treatment with ≥1 anti-TNF therapies	Mean age, yrs (SD) 1) 52.89 (12.31) 2) 52.24 (12.20) Female, n (%) 1) 164 (82) 2) 242 (81) Mean RA duration, yrs (SD) 1) 11.74 (7.68) 2) 12.15 (8.4) Mean HAQ-DI (SD) 1) 1.91 (0.54) 2) 1.86 (0.58) Mean DAS (SD) 1) 6.81 (0.93) 2) 6.88 (1.00)

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 Ann Rheum Dis. 2009 [184] REFLEX Good	F Hoffmann-La Roche Ltd. And Biogen Idec, Inc.	RCT, double-blind, placebo-controlled, phase III study Tested at 24 weeks and then again at week 54	114 rheumatology centers in the USA, Europe, Canada, and Israel	1) PBO+MTX (n=186) 2) RTX+MTX (n=277) RTX /PBO was given in 1000 mg on days 1 and 15; 100 mg of methylprednisolone 30 min before infusion Weeks 16-24 <20% improvement in SJC could receive rescue therapy; Patients originally given PBO could receive RTX and patients given RTX at first could receive standard of care; at week 24, those who had ≥20% reduction in swollen joints could receive more RTX	≥18 years old with active RA, per ACR 1987 criteria, for ≥6 months despite ≥10 mg/wk of MTX; experienced inadequate response to previous or current treatment with ≥1 TNF inhibitor; had at least one joint erosion due to RA Concurrent treatment with any DMARD other than MTX or TNF inhibitor therapy was prohibited during study	Mean age, yrs 1) 53.0 2) 52.5 Female, n (%) 1) 149 (80) 2) 225 (81) Mean RA duration, yrs 1) 11.6 2) 12.0 Mean HAQ-DI score 1) 1.9 2) 1.8 Mean DAS28 1) 6.8 2) 6.8 Mean TSG 1) 46.2 2) 46.2 Mean CRP 1) 3.6 2) 3.7

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 Arthritis Rheum. 2006 [188] DANCER Good	Genetech, 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[132] 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[151] 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 [75] 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[183] 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 [189] 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 [184] 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 [188] 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[132] 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[151] 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 [75] 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 [188] 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[132] 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[151] 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	Patient Satisfaction	Fatigue	Other outcomes
Cohen SB Arthritis Rheum. 2006 [75] 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	NR	Week 24 Mean point reduction in FACIT-F scale, n 1) 0.5 2) 9.1	NR
Keystone E Arthritis Rheum 2008 [189] 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)	NR	Week 24 Mean change from baseline FACIT-F (SD) 1) -0.54 (9.84) 2) -9.14 (11.31)	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Emery P Arthritis Rheum. 2006 [188] DANCER	1) PBO (n=149) 2) RTX, 2×500mg (n=124) 3) RTX, 2×1000mg (n=192)	NR	NR	NR	Week 24 FACIT-F percentage improvement, % 1) 4 2) 20 3) 28	NR
Emery P *Annals of the rheumatic diseases* 2010[132] SERENE	1) PBO+MTX (n=172) 2) (2×500mg) RTX+MTX (n=167) 3) (2 ×1000mg) RTX+MTX (n=170)	NR	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[152] 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[73]

ATTAIN

Good

See also Li T Value in Health 2011[206]</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>
</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
Kremer JM *New England Journal of Medicine* 2003[154] Kremer 2003 Good See also Kremer JM *Arthritis and Rheumatism* 2005 [254] And Emery P *Journal of Rheumatology* 2006 [255]	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[153] AIM Good See also Russell AS *Annals of Rheumatic Diseases* 2007[200] See also Li T *Value in Health* 2011[206]	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[152] 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 [73] 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

Kremer JM *Arthritis and Rheumatism* 2005 [254] Kremer 2005 See also Kremer JM *New England Journal of Medicine* 2003[154] And Emery P *Journal of Rheumatology* 2006 [255]	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 Pts achieving 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 Pts achieving 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[154] Kremer 2003 See also Kremer JM *Arthritis and Rheumatism* 2005 [254] And Emery P *Journal of Rheumatology* 2006 [255]	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[153] 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[152] 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[73] 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 [254] Kremer 2005 See also Kremer JM *New England Journal of Medicine* 2003[154] And Emery P *Journal of Rheumatology* 2006 [255]	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[154] Kremer 2003 See also Kremer JM *Arthritis and Rheumatism* 2005 [254] And Emery P *Journal of Rheumatology* 2006 [255]	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[153] 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	Patient Satisfaction	Fatigue	Other outcomes
Genovese MC *New England Journal of Medicine* 2005 [73] 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	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Emery P *Journal of Rheumatology* 2006 [255] Emery 2006 See also Kremer JM *New England Journal of Medicine* 2003[154] And Kremer JM *Arthritis and Rheumatism* 2005[254]	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	NR	NR
Kremer JM *Arthritis and Rheumatism* 2005 [254] Kremer 2005 See also Kremer JM *New England Journal of Medicine* 2003[154] And Emery P *Journal of Rheumatology* 2006 [255]	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	Patient Satisfaction	Fatigue	Other outcomes
Kremer JM *New England Journal of Medicine* 2003 [154] Kremer 2003 See also Kremer JM *Arthritis and Rheumatism* 2005 [254] And Emery P *Journal of Rheumatology* 2006 [255]	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 [153] 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	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Russell AS *Annals of Rheumatic Diseases* 2007[200] 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[206] 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[133] 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
[84]Halland AM *European Musculoskeletal Review* 2012[134] LITHE Good	Roche	2 years RCT double-blind, placebo-controlled phase III & 3 years open-label extension	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=219) 2) 4 mg/kg TCZ+MTX (n=241) 3) 8 mg/kg TCZ+MTX (n=244) *n is the radiographic population 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 radioiology.	See Kremer JM *Arthritis and rheumatism* 2011[256]

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[256] LITHE Good	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[135] 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[170] RADIATE Good See also Strand V *Rheumatology* 2012[74]	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[136] 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, Czach 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[65] 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[66] 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[257] 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[133] 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[134] 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[256] 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[135] 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[170] 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[136] 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[65] 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[66] 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[257] 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[133] 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[256] 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*[135] 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[170] 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[136] 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[65] 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[66] 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[257] 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	Patient Satisfaction	Fatigue	Other outcomes
Yazici Y *Annals of the rheumatic diseases* 2012[133] 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	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	NR
Genovese M *Arthritis and rheumatism* 2008[136] 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	NR	Week 24 mean change from baseline FACIT-F 1) 3.6 2) 8 P<0.0001	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Smolen J *Lancet* 2008[257] 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	NR	Week 24 mean change from baseline FACIT-F 1) 4 3) 8.6 P<0.0001	NR
Strand V *Rheumatology* 2012[74] 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	NR	Week 24 mean change from baseline FACIT-F 1) 4.22 3) 8.83 P=0.015	NR

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* 2015[70] TARGET *Abstract*	Sanofi	RCT double-blind, placebo controlled phase III 24 weeks	NR	1) PBO+cDMARD (n=181) 2) 150mg SAR+cDMARD (n=181) 3) 200mg SAR+cDMARD (n=184) SC SAR was taken every 2 weeks. At week 12, patients who did not respond adequately to treatment were rescued with SAR 200 mg.	Adults with active, moderate-to-severe RA with inadequate response or intolerance to ≥1 TNF inhibitor(s)	Baseline demographic and disease characteristics were balanced among treatment 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
Fleischmann R Arthritis and Rheumatology 2016 [144] TARGET Fair	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[143] MOBILITY Good See also Strand V Arthritis Rheumatol. 2015 [258]	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)

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
Kavanaugh A *Arthritis and Rheumatology* 2014[259] MOBILITY Good	See Genovese MC. *Arthritis & rheumatology* 2015[143]	See Genovese MC. *Arthritis & rheumatology* 2015[143]	See Genovese MC. *Arthritis & rheumatology* 2015[143]	See Genovese MC. *Arthritis & rheumatology* 2015[143] 1) PBO+MTX (n=398) 2) 150mg SAR+MTX (n=400) 3) 200mg SAR+MTX (n=399)	See Genovese MC. *Arthritis & rheumatology* 2015[143]	See Genovese MC. *Arthritis & rheumatology* 2015[143]
Fleischmann R *Arthritis and Rheumatology* 2014[71] MOBILITY *Abstract*	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143]	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143] Sub analysis of MOBILITY study involving patients with prior biologic use and biologic naïve patients.	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143]	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) SAR 150mg +MTX (n=292) 3) SAR 200mg +MTX (n=289)	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143]	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143]

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 *Annals of the Rheumatic Diseases.* 2015[185] MOBILITY *Abstract*	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143]	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143] Post hoc study which categorized patients according to prior biologic exposure, including a subset of patients with prior anti-TNF therapy.	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143]	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)	See Genovese MC. Arthritis & rheumatology (Hoboken, N.J.). 2015[143]	See Genovese MC. Arthritis & rheumatology (Hoboken, N.J.). 2015[143] *No additional breakdown by subgroup*

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* 2015[198] MOBILITY *Abstract*	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143]	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143] Stratified by duration of RA	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143]	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143] Stratified by RA duration into: 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)	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143]	See Genovese MC. *Arthritis & rheumatology (Hoboken, N.J.).* 2015[143]

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[70] 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 [144] 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[143] 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*[259] 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[143]	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[71] 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[185] 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[198] 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[70] 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 [144] 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[143] 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	Patient Satisfaction	Fatigue	Other outcomes
Fleischmann R Arthritis and Rheumatology 2016 [144] 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	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Strand V Arthritis Rheumatol. 2015 [258] 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	NR	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	NR

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[260] ORAL Step Good See also Strand V Arthritis Care Res (Hoboken). 2015 [193]	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 [137] 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[197] 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[60] 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[260] 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 [137]	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[197]	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[60] 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[260] 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 [137]	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[197]	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[60] 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	Patient Satisfaction	Fatigue	Other outcomes
Burmester GR *Lancet* 2013[260] 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)	NR	Improvement in FACIT-F at month 3 1) 1.1 2) 6.3 (p<0.0001) 3) 4.6 (p=0.0043)	NR
Kremer JM *Arthritis and rheumatism* 2012[197]	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	NR	NR	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	Patient Satisfaction	Fatigue	Other outcomes
Strand V Arthritis Care Res (Hoboken) 2015[193] 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	NR	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	NR
van der Heijde D *Arthritis and rheumatism* 2013[60] 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	NR	Month 6 LS mean change from baseline FACIT-F 1) 2.1 2) 5.6 p<0.001	NR

Table F27. Baracitinib 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[155] RA-BUILD Good	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)

Genovese MC *The New England journal of medicine* 2016 [72] RA-BEACON Good See also Smolen JS Ann Rheum Dis. 2016 [196]	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)
Genovese MC *Annals of the Rheumatic Diseases* 2015[171] RA-BEACON *Abstract*	See Genovese MC *The New England journal of medicine* 2016 [72]	See Genovese MC *The New England journal of medicine* 2016 [72]	See Genovese MC *The New England journal of medicine* 2016 [72]	See Genovese MC *The New England journal of medicine* 2016 [72]	See Genovese MC *The New England journal of medicine* 2016 [72]	See Genovese MC *The New England journal of medicine* 2016 [72]

Table F27. Baracitinib 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
Keystone EC *Annals of the Rheumatic Diseases* 2015[261] 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. Baracitinib 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*[155] 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)[195] 1) -21.9 3) -40.3 (p<0.001)	NR

<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[171]

RA-BEACON</td>
<td>1) PBO + cDMARD (n=176)
2) 2mg BAR + cDMARD (n=174)
3) 4mg BAR + cDMARD (n=177)</td>
<td>%ACR20
<table>
<tr><th></th><th>Wk 12</th><th>Wk 24</th></tr>
<tr><td>1</td><td>27</td><td>27</td></tr>
<tr><td>3</td><td>55*</td><td>46*</td></tr>
</table>
%ACR 50
<table>
<tr><th></th><th>Wk 12</th><th>Wk 24</th></tr>
<tr><td>1</td><td>8</td><td>13</td></tr>
<tr><td>3</td><td>28*</td><td>29*</td></tr>
</table>
%ACR 70
<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>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
<table>
<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* [72] 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[261]

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
<table><tr><th></th><th>Wk 12</th><th>Wk 24</th></tr><tr><td>1</td><td>41</td><td>--</td></tr><tr><td>4</td><td>75*</td><td>78</td></tr></table>% ACR 50
<table><tr><th></th><th>Wk 12</th><th>Wk 24</th></tr><tr><td>1</td><td>10</td><td>--</td></tr><tr><td>4</td><td>35*</td><td>48</td></tr></table>%ACR 70
<table><tr><th></th><th>Wk 12</th><th>Wk 24</th></tr><tr><td>1</td><td>2</td><td>--</td></tr><tr><td>3</td><td>8</td><td>10</td></tr><tr><td>4</td><td>23*</td><td>28</td></tr></table>*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. Baracitinib 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[155] 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[171] 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 [72] 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[261] 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. Baracitinib versus conventional DMARD: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Emery P *Arthritis and Rheumatology* 2015[195] RA-BUILD See Dougados M *Ann Rheum Dis* 2016[155]	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	NR	@ 24 weeks FACIT-F 1) 42.5 3) 59.9* *p≤0.001 vs. placebo	@ 24 weeks 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	Patient Satisfaction	Fatigue	Other outcomes
Keystone EC *Annals of the Rheumatic Diseases.* 2015[261] 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

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Smolen JS Ann Rheum Dis. 2016 [196] 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	NR	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. 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 [158] 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[159] 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 [157] 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[156] 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 F32. 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 [158] 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[159] DE019	1) 40mg + MTX every 2 wk (n=207) 2) 20mg + 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 [157] 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[156] 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 F33. 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 [158] 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[159] DE019	1) 40mg + MTX every 2 wk (n=207) 2) 20mg + 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 [157] 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 F34. Adalimumab versus conventional DMARD: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Keystone EC *Arthritis & Rheumatism* 2004[159] DE019	1) 40mg + MTX every 2 wk (n=207) 2) 20mg + 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 [157] 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	NR	
Weinblatt ME *Arthritis & Rheumatism* 2003[156] 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 F35. 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[162] 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[217] 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[139] 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[161] 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[160]

RAPID2

See also Strand V Annals of Rheumatic Diseases 2011 [262]</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>
</table>
<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>
</table>
<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>
</table>
</td>
</tr>
</table>

Table F36. Certolizumab Pegol versus conventional DMARDs: Key Clinical Outcomes

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Certolizumab pegol						
Choy E *Rheumatology* 2012[162]	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[217] 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[139] 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[161] 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[160] 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 F37. Certolizumab Pegol versus conventional DMARDs: Harms

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Certolizumab pegol					
Choy E *Rheumatology* 2012[162]	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[217] 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[139] 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 [217] 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[161] 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[160] 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 F38. Certolizumab Pegol versus conventional DMARDs: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Choy E *Rheumatology* 2012[162]	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	NR	NR	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[139] 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	Patient Satisfaction	Fatigue	Other outcomes
Keystone E *Arthritis & Rheumatism* 2008[161] 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[160] 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 [262] 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 F39. 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[63] ETN309 Fair See also Combe B *Ann Rheum Dis* 2009[163]	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[64] TEMPO Good See also Van der Heijde D *Arthritis Rheum* 2006[68] and Van der Heijde D *Arthritis Rheum* 2007[263]	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[141] LARA Good See also Machado DA *The open rheumatology journal* 2016[91]	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 (i.e. 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
Machado DA *The open rheumatology journal* 2016[91] LARA Good	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	104-week extension study of open-label RCT **No statistical comparison of findings	5 countries in Latin America (i.e. Argentina, Chile, Colombia, Mexico, and Panama)	N=386 (91% of original study population) 1) ETN+MTX (n=260) 2) cDMARD (hydroxychloroquine, or sulfasalazine) + MTX (n=126) Doses of MTX, hydroxychloroquine, or sulfasalazine selected at week 24 could be titrated at the discretion of the investigator, but no new treatment could be initiated after treatment selection for patients entering the extension	See Machado DA *Journal of clinical rheumatology: practical reports on rheumatic & musculoskeletal diseases* 2014[141]	Mean age, yrs (SD) 1) 48.4 (11.8) 2) 48.4 (11.2) Female, n (%) 1) 227, 87.3 2) 115, 91.3 Mean RA duration, yrs (SD) 1) 7.8 (6.9) 2) 9.0 (7.7) Mean HAQ-DI (SD) 1) 1.6 (0.7) 2) 1.6 (0.7) Mean DAS28 (SD) 1) 6.6 (0.8) 2) 6.7 (0.8) 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 [264] 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[59] Good RACAT	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[67] 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 F40. 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[63] 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[163] 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[64] 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[68] 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[263] 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[141] 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[91] 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[59] 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[67] 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 F41. 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[63] 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[64] 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 [264] 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[68] 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[263] 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[141] 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[91] 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[59] 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[67] 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 F42. Etanercept versus conventional DMARDs: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Combe B *Ann Rheum Dis* 2006 [63] 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	NR	NR
Van der Heijde D *Arthritis Rheum* 2006[68] 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	NR	NR	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	Patient Satisfaction	Fatigue	Other outcomes
Machado DA *Journal of clinical rheumatology* 2014[141] 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	Improvements in subject satisfaction, physician satisfaction, and subject's willingness to retake medications were in favor of ETN + MTX (p<0.0001 for all) *No additional data reported*	week 24 (adjusted mean changes) VAS, fatigue 1) -29.6 2) -17.3 p<0.0001	week 24 (adjusted mean changes) HADS-A 1) -2.2 2) -1.7 P=NS HADS-D 1) -2.8 2) -1.9 P=0.007 VAS, general health 1) -33.7 2) -19.3 P<0.0001

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Machado DA *The open rheumatology journal.* 2016[91] 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	*Only physician satisfaction reported*	@ week 128 VAS, fatigue 1) -30.5 2) -30.4	@ week 128 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	Patient Satisfaction	Fatigue	Other outcomes
O'Dell JR *The New England journal of medicine* 2013[59] 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)*	NR	NR	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	Patient Satisfaction	Fatigue	Other outcomes
Takeuchi T *Modern rheumatology* 2013[67] 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 F43. 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[141] 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[91] 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 F44. 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[142] GO-FORTH Good	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 double-blind 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)

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 *Modern Rheumatology* 2016[265] GO-FORTH Good	See Tanaka Y *Annals of the rheumatic diseases* 2012[142]	Tanaka Y *Annals of the rheumatic diseases* 2012[142] Final results of GO-FORTH trial collected at 156 weeks	See Tanaka Y *Annals of the rheumatic diseases* 2012[142]	See Tanaka Y *Annals of the rheumatic diseases* 2012[142] After week 52, patients who were receiving GOL 100mg could have their dose reduced to 50mg at the investigator's discretion. The final GOL administration was at week 152	See Tanaka Y *Annals of the rheumatic diseases* 2012[142]	See Tanaka Y *Annals of the rheumatic diseases* 2012[142]

<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[145]

GO-FORWARD

Good</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 week 16, patients with <20% improvement in both the tender joint count and the swollen joint count 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 24 weeks, patients still on PBO initiated blinded 50mg GOL inj.</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
Keystone E *Annals of the rheumatic diseases* 2010[69] GO-FORWARD Good	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145] At 24 weeks, patients still on PBO initiated blinded 50mg GoI inj.	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]

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 *The Journal of rheumatology* 2013[92] GO-FORWARD Good	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145] LTE following a RCT, double-blind, placebo-controlled 268 weeks	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145] At 24 weeks, patients still on PBO initiated blinded 50mg Gol inj. After 52 weeks, LTE is started and blind is broken. At the investigator's discretion, the GOL dose could be increased from 50 mg to 100 mg and MTX doses could be adjusted or added.	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]

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 and rheumatism* 2011[180] GO-FORWARD & GO-BEFORE **GO-BEFORE patients were MTX naïve therefore not abstracted** Good	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]	Mean mTSS (SD) 1) 36.7 (52.1) 2) 37.4 (52.5) 3) 29.7 (39.3) 4) 39.6 (56.1) See Keystone E *Annals of the rheumatic diseases* 2009[145] for additional baseline characteristics
Genovese MC *The Journal of Rheumatology*. 2012[192] Go-FORWARD Good	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]	See Keystone E *Annals of the rheumatic diseases* 2009[145]

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[164] GO-FURTHER Good See also Bingham CO J Rheumatol. 2014 [194]	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
Weinblatt ME *Annals of the rheumatic diseases* 2014[266] GO-FURTHER Good	See Weinblatt ME *Annals of the rheumatic diseases* 2013[164]	See Weinblatt ME *Annals of the rheumatic diseases* 2013[164]	See Weinblatt ME *Annals of the rheumatic diseases* 2013[164]	See Weinblatt ME *Annals of the rheumatic diseases* 2013[164]	See Weinblatt ME *Annals of the rheumatic diseases* 2013[164]	See Weinblatt ME *Annals of the rheumatic diseases* 2013[164]
Bingham CO 3rd *Arthritis care & research* 2015[199] GO-FURTHER Good	Centocor, Inc. and Schering-Plough	See Weinblatt ME *Annals of the rheumatic diseases* 2013[164]	See Weinblatt ME *Annals of the rheumatic diseases* 2013[164]	See Weinblatt ME *Annals of the rheumatic diseases* 2013[164]	See Weinblatt ME *Annals of the rheumatic diseases* 2013[164]	See Weinblatt ME *Annals of the rheumatic diseases* 2013[164]

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 *Arthritis and rheumatism* 2010[165] Good	Centocor, Inc.	RCT double-blind, placebo-controlled phase III 48 weeks	72 centers in 15 countries: USA, Argentina, Australia, Colombia, Germany, Hungary, Latvia, Lithuania, Malaysia, Malta, Mexico, New Zealand, Peru, Poland, Ukraine	1) PBO+MTX (n=129) 2) GOL (n=257) 3) GOL+MTX (n=257) IV PBO plus MTX or IV GOL at a dose of 2 mg/kg or 4 mg/kg, with or without MTX.	Adult patients with active RA despite treatment with MTX at a dosage of 15–25 mg/week	Mean age, yrs (SD) 1) 50.2 (51) 2) 49.2 (50) 3) 49.6 (51) Female, % 1) 79.8 2) 82.5 3) 78.6 Mean RA duration, yrs (SD) 1) 7.4 (5.6) 2) 7.9 (6.1) 3) 8.8 (6.6) Mean HAQ-DI (SD) 1) 1.5 (1.5) 2) 1.5 (1.5) 3) 1.5 (1.5)

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
Li Z *International Journal of Rheumatic Diseases* 2015[166] 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 F45. 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[142] 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>
<td>Tanaka Y Modern Rheumatology 2016[265]

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><th>wk</th><th>1)</th><th>2)</th></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>
</table>
ACR50, n (%)
<table>
<tr><th>wk</th><th>1)</th><th>2)</th></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><th>wk</th><th>1)</th><th>2)</th></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><th>wk</th><th>1)</th><th>2)</th></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><th>wk</th><th>1)</th><th>2)</th></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><th>wk</th><th>1)</th><th>2)</th></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><th>wk</th><th>1)</th><th>2)</th></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><th>wk</th><th>1)</th><th>2)</th></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[145] 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[180]	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[69] 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[180]	See Genovese, MC. *The Journal of rheumatology*. 2012[192]	NR

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Keystone EC *The Journal of rheumatology* 2013[92] 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[180] 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[192] GO-FORWARD Good	1) PBO[166]+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[69]	See Keystone E. *Annals of the rheumatic diseases.* 2010[69]	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[164] 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[266]	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[266] 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[199] 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)	

Author & Year of Publication (Trial Name)	Interventions	Treatment Response	Disease Activity	Structural Damage	Function	Laboratory indices
Kremer J *Arthritis and rheumatism* 2010[165]	1) PBO+MTX (n=129) 2) GOL (n=257) 3) GOL+MTX (n=257)	Week 24 ACR20, % 1) 24.8 2) 26.1 (NS) 3) 43.6 (p<0.001) Week 24 ACR50, % 1) 9.3 2) 10.1 (NS) 3) 21.8 (p=0.002) Week 24 ACR70, % 1) 3.1 2) 4.7 (NS) 3) 7 (NS)	Week 24 DAS-28 CRP moderate/good, % 1) 40.3 2) 43.2 (NS) 3) 60.7 (p<0.001) Week 24 DAS-28 CRP remission, % 1) 7 2) 8.6 (NS) 3) 18.7 (p=0.002)	NR	Week 14 Mean change from baseline HAQ-DI 1) -9.7 2) -14.4 (p=0.004) 3) -34.3 (p<0.001)	Week 14 Median change from baseline CRP 1) 9.2 2) 40 3) 50 Week 14 Mean change from baseline ESR 1) 7.2 2) 4.6 (NS) 3) 22.2 (p<0.001)
Li Z *International Journal of Rheumatic Diseases* 2015[166]	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 F46. 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[142] 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[265] 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[145] 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[69] 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[92] 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[164] 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[266] 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[199] 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)
Kremer J *Arthritis and rheumatism* 2010[165]	1) PBO+MTX(n=129) 2) GOL (n=257) 3) GOL+MTX (n=257)		Serious infection, n (%) 1) 2 (1.6) 2) 8 (3.1) 3)15 (3.2) 2 cases of TB in GOL group	NR	Serious AEs, n (%) 1) 7 (5.4) 2) 18 (7.1) 3) 45 (9.6) 3 cases of death in GOL group through week 48

Author & Year of Publication (Trial Name)	Interventions	Malignancies	Infections	Other Adverse Events	Discontinuation, Serious AE rate, Deaths
Li Z *International Journal of Rheumatic Diseases* 2015[166]	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 F47. Golimumab versus conventional DMARDs: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Genovese MC *The Journal of rheumatology* 2012[192] 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	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	NR

<table>
<tr><th>Author & Year of Publication (Trial Name)</th><th>Interventions</th><th>Health-related quality of life</th><th>Pain</th><th>Patient Satisfaction</th><th>Fatigue</th><th>Other outcomes</th></tr>
<tr>
<td>Bingham CO J Rheumatol. 2014 [194]

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>NR</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>
<td>NR</td>
</tr>
</table>

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Bingham CO 3rd *Arthritis care & research* 2015[199] 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)	NR	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)	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Kremer J *Arthritis and rheumatism* 2010[165]	1) PBO+MTX(n=129) 2) GOL (n=257) 3) GOL+MTX (n=257)	Week 14 Mean change from baseline SF-36 PCS 1) 4.3 2) 4.0 (NS) 3) 6.9 (p=0.014)	Week 14 Patient's assessment of pain (% improvement from baseline) 1) 18.1 2) 15.7 (p=0.031) 3) 31.2 (p<0.001)	NR	NR	Week 14 Mean change from baseline patient's assessment of disease activity 1) 7.9 2) 21.9 (p=0.016) 3) 31.8 (p<0.001)
Li Z *International Journal of Rheumatic Diseases* 2015[166]	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)	NR	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 F48. 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[167] 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[168] ATTRACT Good See also Lipsky PE N Engl J Med 2000[182]	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
Lipsky PE N Engl J Med 2000[182] ATTRACT Good	Centocor Inc.	Multicenter, placebo controlled Every 4 or 8 weeks for 54 weeks	United States of America	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) Patients were randomly assigned the same dose of MTX as before the study plus infusions of PBO or IFX at 3 or 10 mg per kg of body weight for 54 weeks	Patients were eligible if they had active RA despite treatment with ≥12.5 mg of MTX per week No other disease-modifying drug were allowed	Mean age, yrs (SD) 1) 51 (12) 2) 54 (11) 3) 52 (13) 4) 54 (12) 5) 52 (11) Female (%) 1) 80 2) 81 3) 77 4) 77 5) 73 Median RA duration, yrs (SD) 1) 11 (8) 2) 10 (8) 3) 9 (8) 4) 11 (9) 5) 12 (9) 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)

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[181] SWEFOT Good See also Eriksson JK *JAMA Internal Medicine* 2013[204] See also Karlsson JA Ann Rheum Dis. 2013 [267]	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 [169] 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 F49. 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[167]	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[168] 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[182] 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[181] 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 [169] 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 F50. 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[167]	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[168] 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[182] 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 [169] 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[181] 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 F51. Infliximab versus conventional DMARDs: Patient-reported Outcomes

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Karlsson JA Ann Rheum Dis. 2013 [267] 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	NR	NR
Kim J *Journal of Korean medical science* 2013[167]	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	NR	NR
Maini R *Lancet* 1999[168] 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	NR	NR

Author & Year of Publication (Trial Name)	Interventions	Health-related quality of life	Pain	Patient Satisfaction	Fatigue	Other outcomes
Lipsky PE N Engl J Med 2000[182] 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	NR	NR

Table F52. 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[204] 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 1) -4.1 (1.2) 2) -4.0 (1.1) @21 months 1) -4.9 (1.2) 2) -6.2 (1.0) Work loss, mean d/mo (SD) @12 months 1) 13 (13) 2) 13 (13) @21 months 1) 12 (13) 2) 10 (12)	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)