Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value

Final Evidence Report and Meeting Summary

October 16, 2020

Prepared for

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Daniel A. Ollendorf served as the lead author for the report, led the systematic review and authorship of the comparative clinical effectiveness section, and wrote the background, other benefits, and contextual considerations sections of the report. Lisa Bloudek and Josh J. Carlson developed the cost-effectiveness model and authored the corresponding section of the report. Rick Chapman developed the potential budget impact analysis and authored Section 8. Laura Cianciolo authored the section on coverage policies and clinical guidelines, managed the timeline and public process, and performed quality controls. Pamela Bradt and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Serina Herron-Smith, Avery McKenna, David M. Rind, Monica Frederick, Foluso Agboola, and Tom Chen 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. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical expert provided input that helped guide the ICER team as we shaped our scope and report. Dr. Siddharth Singh is not 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/wp-content/uploads/2019/09/ICER_UC_Key_Stakeholder_List_052620.pdf

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List of Acronyms and Abbreviations Used in this Report

ACG	American College of Gastroenterology
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
BCBS	Blue Cross Blue Shield
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
EIM	Extraintestinal manifestation
evLYG	Equal value of life-years gained
FDA	United States Food and Drug Administration
GDP	Gross domestic product
HBPB	Health-benefit price benchmark
HCSC	Health Care Service Corporation
HCUP	Healthcare Cost and Utilization Project
HR	Hazard ratio
IBD	Inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICER	Institute for Clinical and Economic Review
IV	Intravenous
LCD	Local Coverage Determination
LY	Life year
NCD	National Coverage Determination
NICE	National Institute for Health and Care Excellence
NIS	National Inpatient Sample
NMA	Network meta-analysis
OPUS	Observational Post-Marketing Ulcerative Colitis Study
PCE	Personal consumption expenditure
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Setting
PHC	Personal health care
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PUCAI	Pediatric Ulcerative Colitis Activity Index
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
SF-36	Short Form Health Survey
SPEC	Specialty Drug Evidence and Coverage
TIM	Targeted immune modulator
TNF	Tumor necrosis factor
UC	Ulcerative colitis
UHC	UnitedHealthcare
US	United States
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost
WPAI	Work Productivity and Activity Impairment Questionnaire
WTP	Willingness to pay

Executive Summary

Background

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that affects the mucosa, the innermost lining of the intestinal wall in the large bowel (i.e., the colon and rectum).[1] The disease causes long-lasting inflammation and ulcers in the digestive tract and is typically marked by periods of remission and recurrence of symptoms. Symptoms may include frequent diarrhea, sometimes with blood or pus, abdominal and/or rectal pain, weight loss, and fatigue.[2] When the disease affects children, it can have a detrimental impact on growth, nutritional status, and psychosocial development.[3] It is estimated that approximately 900,000 individuals in the United States (US) have UC.[4] The economic burden of UC is significant, ranging between an estimated $15-32 billion per year.[5]

The management of UC in adults is dependent on the severity of symptoms. The goal of treatment is to induce a clinical response to treatment (as evidenced by a reduction of the disease's key symptoms) or effect a complete remission of the symptoms during a short-term (six to 14 weeks) "induction" phase of treatment, and maintain response or remission via long-term "maintenance" therapy, often at a lower dose. Colectomy (surgical removal of the colon) may be considered in patients whose disease does not respond to maximal medical management. In patients with mild disease, local or topical use of aminosalicylates may induce and maintain remission. Once symptoms become moderate-to-severe, however, the use of oral or ileal/colonic preparations of budesonide as well as systemic corticosteroids is typically warranted.[6]

Those whose disease does not respond to or recurs despite systemic therapy are candidates for a number of targeted immune modulators (TIMs) to induce and/or maintain remission. These agents affect a number of different targets on the inflammatory cascade associated with UC and are summarized in Table ES1 on the following page.

Table ES1. TIMs for the Treatment of UC

Treatment	Brand Name	Route	Dose	Estimated Annual Cost*
TNF Inhibitors				
Adalimumab	Humira®	Injection	160 mg on day 1, then 80 mg 2 weeks later, then 40 mg EOW	$46,933
Golimumab	Simponi®	Injection	200 mg at week 0, 100 mg at week 2, then 100 mg EOW	$41,332
Infliximab	Remicade®	Infusion	5 mg/kg at 0, 2, and 6 weeks, then q8w	$14,614
Infliximab-abda	Renflexis®	Infusion	5 mg/kg at 0, 2, and 6 weeks, then q8w	$13,883
Infliximab-dyyb	Inflectra®	Infusion	5 mg/kg at 0, 2, and 6 weeks, then q8w	$13,451
JAK Inhibitor				
Tofacitinib	Xeljanz®	Oral	10 mg BID for 8 weeks, then 5 mg BID	$35,506
IL-12/23 Inhibitor				
Ustekinumab	Stelara®	Infusion and injection	Weight-based IV dose (≤55 kg: 260 mg, >55 kg to 85 kg: 390 mg; >85 kg: 520 mg) before administering 90 mg SC at week 8, then q8w	$91,609
α4β7 Integrin Inhibitor				
Vedolizumab	Entyvio®	Infusion	300 mg at 0, 2, and 6 weeks, then q8w	$44,224

BID: twice daily, EOW: every other week, IL: interleukin, IV: intravenous, JAK: Janus kinase, kg: kilogram, mg: milligram, q8w: every 8 weeks, TNF: tumor necrosis factor

*Estimated based on average net price to payers per maintenance year (obtained from SSR Health, LLC) for oral and subcutaneously administered products and Medicare ASP pricing for IV-administered products.

Potential Cost-Saving Measures in Ulcerative Colitis

Stakeholder feedback on potential cost-saving measures in UC was limited. The Crohn's and Colitis Foundation described repeated use of steroid therapy to be of low value given its potential for serious adverse effects, and also mentioned insurance-mandated step therapy, in which patients are required to try agents other than the one they or their clinician prefer, even if the use of that medication is contraindicated. Clinical expert input indicated that continued use of aminosalicylates in patients who have been failed by such therapy, and escalated to use of TIMs, is a pervasive and low-value intervention.

Patient Perspectives

From the beginning of this assessment, we sought input from patients, caregivers, and representatives from patient advocacy organizations on the research design of this review (i.e., the PICOTS framework; Population, Intervention, Comparators, Outcomes, Timing, and Setting). We also sought insight on the patient experience of UC and its treatment, including benefits of treatment that may not be described in the clinical literature, any broader potential other benefits or disadvantages associated with treatments, and contextual considerations related to UC, which

are summarized here and reported in detail in Sections 2 and 6. Information was provided primarily by the Crohn's and Colitis Foundation, which described impacts and challenges associated with living with UC in four distinct categories: heterogeneity of disease presentation, benefits and risks of UC treatment, access to care challenges, and gaps in the current management of UC.

As with many chronic diseases, the presentation of symptoms and disease course can vary substantially among patients. In some, the disease course may reflect periods of active disease and remission, while in others, the symptoms are persistent despite escalating medical therapy. A minority of patients may present with a rapidly progressive form of the disease known as fulminant colitis. As noted previously, children as young as five years of age or less may develop UC, with additional complications such as growth failure and delayed puberty. In addition, there are noted but currently poorly understood differences in how racial and ethnic minorities experience UC. Clinical differences in disease presentation by severity as well as patient characteristics have profound impacts on those suffering with UC. Patients with long enough periods of remission may be able to resume normal work, school, or leisure activity, while others with more progressive disease require increasing levels of caregiver support.

Response to treatment is also heterogeneous. Treatments that are successful in some patients may not work for others, and patients frequently report loss of response, development of intolerable side effects, and the need to cycle off a medication. For example, patients may respond differently to the tumor necrosis factor (TNF) inhibitors based on drug composition (e.g., mouse- vs. human-derived, possibly as a result of greater potential immunogenicity with the former) as well as clinical considerations (body mass index, disease severity). Some patients do not clinically respond to TNF inhibitor therapy while others develop immunogenicity to a specific agent; a switch outside of class may be indicated for the former, while a switch in-class may be the best course of action for the latter. The overall lack of information and evidence in this area is frustrating to patients as it potentially delays effective treatment, which may negatively impact various aspects of a patient's quality of life. In addition, caution was urged with regard to surgical intervention. Though colectomy may be curative in some patients, there are long-term complications to consider, which may have substantial and distressing implications for a patient's quality of life and activities of daily living.

Several challenges with accessing appropriate care were noted. For one, requirements for complex treatment regimens may pose a challenge for physicians and, consequently, patients. Primary care providers and gastroenterologists without specific UC experience may not, for example, appreciate the broader benefits of psychosocial and dietary support for long-term care management. Estimates of average annual patient out-of-pocket costs for UC services may total $2,000 to $4,000 annually, which may pose a substantial burden for some.[7] Costs are especially onerous for patients without insurance or those who are unable to work due to their disease. The Crohn's and Colitis Foundation reiterated patient concerns regarding step therapy and its various negative

consequences. Patients are often undertreated if they are failed by multiple biologics, and by the time they gain access to a treatment subject to numerous step therapy protocols, their disease may have progressed considerably, limiting the efficacy of the drug. Other insurance mechanisms may produce additional barriers and sources of stress for UC patients. For example, some UC treatments are covered as a medical benefit and others as a pharmacy benefit, with different criteria for treatment authorization and different expectations for patient financial contribution. Step therapy algorithms typically found in UC are not concordant with authoritative clinical guidelines (see Section 3) and are also not portable; individuals who switch health plans (or whose employer does) often must repeat earlier steps in the treatment algorithm even if those treatments were previously unsuccessful.

Finally, stakeholders noted major gaps in the current management of the disease, manifested primarily in a lack of high-quality evidence. There is a lack of head-to-head clinical trials of TIMs, for example, which limits the ability of patients and their families to make fully informed decisions about their treatment goals and desires. It is a source of frustration for many that the one large head-to-head trial that is available—one that demonstrated vedolizumab's superiority to adalimumab—has not resulted in any appreciable change in insurer coverage policy. Moreover, there is a general need for more comparative effectiveness research given the plethora of drug classes, mechanisms of action, routes of administration, and safety profiles now available.

It was also noted that patient participants in Crohn's and Colitis Foundation-sponsored focus groups voiced concern with UC symptoms not routinely collected in clinical trials, which tend to focus on stool frequency and rectal bleeding. Beyond these, patients also reported concerns with pain and fatigue, ability to concentrate, and fecal urgency. Further, patients also experience challenges with interpersonal relationships and educational and career goals due to the impact of the disease on activities of daily living. Relatedly, patients often face difficulty when sharing the experience of UC symptoms with friends, family, and colleagues, which may lead to feelings of isolation.

Comparative Clinical Effectiveness

We systematically reviewed and synthesized existing evidence from clinical studies to assess the comparative clinical effectiveness of TIMs for moderate-to-severe UC. Full PICOTS criteria are described in Section 1.2. We compared the efficacy, safety, and effectiveness of TIMs (adalimumab, golimumab, infliximab, tofacitinib, ustekinumab, and vedolizumab [intravenous]) to ongoing background conventional therapy (i.e., placebo arms of clinical trials) and to each other. Effectiveness was defined primarily in terms of clinical response and remission (summarized here), and secondarily in terms of endoscopic improvement, health-related quality of life, rates of UC hospitalization, and other outcomes (described in detail in Section 4).

Based in part on stakeholder feedback, we assessed benefits and harms separately for patients without evidence of prior TIM use (i.e., "biologic-naïve") and those with such evidence ("biologic-

experienced"). Within each of these populations, we also examined findings separately for the induction and maintenance phases of available studies. We identified a total of 19 randomized controlled trials (RCTs) of the TIMs of interest, including one head-to-head trial (VARSITY) of vedolizumab and adalimumab.[8] Where feasible, we conducted network meta-analysis (NMA) to combine available direct evidence comparing the TIMs with indirect evidence. Importantly, maintenance phases came from two major categories of study design: so-called "treat-through" trials (in which patients remained on the therapy they were randomized to at the beginning of induction) and "re-randomized" trials (where responders to induction therapy were re-randomized for maintenance therapy). We adjusted data from treat-through trials to more closely resemble re-randomized designs, the more common design employed in our analytic set. Further details on the adjustments made and the conduct of these analyses may be found in Section 4 and Appendix F.

Clinical Benefits

Biologic-Naïve: Induction

A total of 15 RCTs informed the induction phase in the biologic-naïve population. In the VARSITY head-to-head trial comparing the efficacy of vedolizumab and adalimumab, the rate of response was higher with vedolizumab 300 mg compared to adalimumab 160/80 mg at the end of induction (70.1% vs. 49.5%, difference: 20.6; 95% CI for difference: 12.9 to 28.2); however, the rates of achieving remission did not statistically differ.[8] In placebo-controlled trials, TIMs generally demonstrated superior rates of response, remission, or both at the end of induction periods ranging from six to 10 weeks in duration.

We note that, while tofacitinib has been studied in biologic-naïve patients, it is indicated for use only after TNF inhibitor therapy and was not, therefore, included in our biologic-naïve NMA. Results from the NMA showed all TIMs were more likely to achieve response and remission compared to placebo. Specifically, TIMs were 1.4 to 1.9 times more likely to achieve clinical response (Table ES2) and 1.8 to 3.2 times more likely to achieve remission (Table ES3). Additionally, infliximab and vedolizumab were statistically more likely to achieve response and remission compared to adalimumab. No other statistical differences among TIMs were observed.

Table ES2. Risk Ratios for Response at the End of the Induction Phase in Biologic-Naïve Patients

IFX Pooled*					
1.07 (0.93, 1.24)	VEDO				
1.10 (0.93, 1.34)	1.02 (0.84, 1.27)	UST			
1.15 (1.00, 1.35)	1.08 (0.92, 1.27)	1.05 (0.85, 1.28)	GOL Pooled*		
1.37 (1.18, 1.62)	**1.28 (1.14, 1.45)**	1.25 (1.00, 1.53)	1.18 (1.00, 1.42)	ADA	
1.88 (1.67, 2.12)	**1.76 (1.54, 2.02)**	**1.71 (1.41, 2.06)**	**1.63 (1.43, 1.86)**	**1.38 (1.21, 1.56)**	PBO

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

*Infliximab 5 mg/kg and 10 mg/kg pooled; golimumab 200/100 mg and 400/200 mg pooled.

Table ES3. Risk Ratios for Remission at the End of the Induction Phase in Biologic-Naïve Patients

IFX Pooled*					
1.15 (0.87, 1.54)	VEDO				
1.21 (0.85, 1.79)	1.05 (0.71, 1.59)	UST			
1.34 (1.00, 1.80)	1.16 (0.84, 1.62)	1.10 (0.73, 1.63)	GOL Pooled*		
1.84 (1.39, 2.50)	**1.60 (1.29, 1.98)**	1.52 (1.00, 2.26)	1.38 (1.00, 1.92)	ADA	
3.22 (2.60, 3.96)	**2.79 (2.18, 3.58)**	**2.66 (1.86, 3.73)**	**2.41 (1.89, 3.08)**	**1.76 (1.38, 2.19)**	PBO

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

*Infliximab 5 mg/kg and 10 mg/kg pooled; golimumab 200/100 mg and 400/200 mg pooled.

Biologic-Naïve: Maintenance

Data from 11 RCTs were available with data on maintenance therapy through follow-up timepoints ranging from 52 to 60 weeks. In the VARSITY head-to-head trial, vedolizumab 300 mg every eight weeks had higher rates of remission compared to adalimumab 40 mg at the end of maintenance (34.2% vs. 24.3%, p=0.006).[8] Findings from placebo-controlled trials indicated that all TIMs were superior to placebo in achieving clinical response and remission.

The biologic-naïve NMA was adjusted for placebo response rates given observed variability across RCTs. All TIMs were more likely to achieve clinical response (Table ES4) and remission (Table ES5) at the end of maintenance compared to placebo, although no statistical differences from placebo were observed for adalimumab or golimumab. Vedolizumab was shown to be more likely to achieve clinical response and remission compared to adalimumab and golimumab. No other statistical differences between TIMs were observed.

Table ES4. Risk Ratios for Response at the End of the Maintenance Phase in Biologic-Naïve Patients

UST					
1.12 (0.62, 1.77)	VEDO Pooled*				
1.16 (0.77, 1.54)	1.04 (0.69, 1.58)	IFX Pooled*			
1.38 (0.72, 2.18)	**1.21 (1.05, 1.43)**	1.18 (0.74, 1.79)	ADA		
1.46 (0.75, 2.54)	**1.30 (1.01, 1.77)**	1.26 (0.77, 2.03)	1.07 (0.81, 1.50)	GOL	
1.80 (1.13, 2.50)	**1.64 (1.16, 2.02)**	**1.56 (1.10, 2.14)**	1.34 (0.94, 1.78)	1.25 (0.79, 1.70)	PBO

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

*Infliximab 5 mg and 10 mg pooled; vedolizumab 300 mg every 8 weeks and every 4 weeks pooled.

Table ES5. Risk Ratios for Remission at the End of the Maintenance Phase in Biologic-Naïve Patients

UST					
1.18 (0.52, 2.26)	VEDO Pooled*				
1.24 (0.71, 1.83)	1.05 (0.60, 1.86)	IFX Pooled*			
1.56 (0.64, 3.00)	**1.30 (1.06, 1.62)**	1.25 (0.67, 2.22)	ADA		
1.70 (0.68, 3.55)	**1.43 (1.01, 2.15)**	1.37 (0.71, 2.61)	1.10 (0.75, 1.71)	GOL	
2.22 (1.17, 3.57)	**1.93 (1.22, 2.58)**	**1.80 (1.13, 2.86)**	1.47 (0.92, 2.14)	1.35 (0.74, 2.04)	PBO

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

*Infliximab 5 mg and 10 mg pooled; vedolizumab 300 mg every 8 weeks and every 4 weeks pooled.

Biologic-Experienced: Induction

We found no clinical trial evidence for golimumab or infliximab in the biologic-experienced population. Seven of the included RCTs measured the efficacy of TIMs in achieving clinical response and remission at the end of the induction phase (six to 14 weeks). In the VARSITY head-to-head trial comparing the efficacy of vedolizumab and adalimumab,[8] the rate of response was higher with vedolizumab compared to adalimumab at the end of induction (55.7% vs. 32.1%, difference: 23.6; 95% CI for difference: 8.5 to 38.7); however, the rates of achieving remission did not statistically differ. Placebo-controlled data were somewhat more mixed in the biologic-experienced population. In one available RCT of adalimumab, no statistical differences were observed for either response or remission. Two RCTs of vedolizumab showed contrasting results, with findings favorable for response (but not remission) for one and no statistical differences observed in the other. Treatment group imbalances were reported in this latter trial, however, as a possible explanation

for findings.[9] Trials of tofacitinib and ustekinumab reported statistically significantly better rates of response and remission versus placebo.

All seven RCTs were included in the NMA. Tofacitinib, ustekinumab, and vedolizumab were more likely to achieve clinical response and remission compared to placebo; there were no statistical differences between adalimumab and placebo (Table ES6 and ES7). Additionally, tofacitinib, ustekinumab, and vedolizumab were more likely to achieve clinical response and remission compared to adalimumab.

Table ES6. Risk Ratios for Response at the End of the Induction Phase in Biologic-Experienced Patients

UST				
1.01 (0.77, 1.33)	TOF			
1.32 (0.97, 1.87)	1.31 (0.96, 1.84)	VEDO		
2.01 (1.39, 3.13)	**2.00 (1.36, 3.08)**	**1.53 (1.11, 2.15)**	ADA	
2.11 (1.71, 2.62)	**2.11 (1.68, 2.60)**	**1.61 (1.20, 2.05)**	1.05 (0.71, 1.46)	PBO

ADA: adalimumab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab
Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table ES7. Risk Ratios for Remission at the End of the Induction Phase in Biologic-Experienced Patients

UST				
1.02 (0.58, 1.82)	TOF			
1.75 (0.94, 3.45)	1.74 (0.92, 3.38)	VEDO		
3.82 (1.88, 8.49)	**3.75 (1.80, 8.08)**	**2.18 (1.22, 3.95)**	ADA	
4.13 (2.71, 6.26)	**4.10 (2.62, 6.18)**	**2.38 (1.38, 3.80)**	1.09 (0.57, 1.97)	PBO

ADA: adalimumab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab
Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Biologic-Experienced: Maintenance

Seven RCTs were available with maintenance data in the biologic-experienced population. No statistical differences were noted between vedolizumab and adalimumab in the VARSITY head-to-head trial.[8] Statistically significant differences in favor of TIMs were noted in available placebo-controlled RCTs of adalimumab, tofacitinib, ustekinumab, and vedolizumab.

All seven RCTs were included in the NMA; however, placebo adjustment was not performed because the statistical model proved unstable regardless of the number of iterations attempted. All TIMs were more likely to achieve clinical response and remission compared to placebo. Specifically, TIMs were 1.9 to 2.4 times more likely to achieve clinical response (Table ES8), and 2.5 to 3.5 times

more likely to achieve remission (Table ES9). No other statistical differences among TIMs were observed.

Table ES8. Risk Ratios for Clinical Response at the End of the Maintenance Phase in Biologic-Experienced Patients

VEDO Pooled*				
1.12 (0.87, 1.55)	ADA			
1.25 (0.88, 1.86)	1.11 (0.72, 1.72)	UST		
1.26 (0.88, 1.90)	1.12 (0.70, 1.75)	1.00 (0.63, 1.61)	TOF Pooled*	
2.40 (1.87, 3.00)	**2.14 (1.48, 2.89)**	**1.92 (1.34, 2.55)**	**1.92 (1.32, 2.55)**	PBO

ADA: adalimumab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab
Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.
*Tofacitinib 5 and 10 mg pooled; vedolizumab 300 mg every 8 weeks and every 4 weeks pooled.

Table ES9. Risk Ratios for Clinical Remission at the End of the Maintenance Phase in Biologic-Experienced Patients

VEDO Pooled*				
1.19 (0.80, 1.94)	ADA			
1.41 (0.83, 2.5)	1.17 (0.62, 2.27)	UST		
1.41 (0.82, 2.59)	1.18 (0.60, 2.31)	1.01 (0.51, 1.98)	TOF Pooled*	
3.48 (2.43, 5.03)	**2.91 (1.72, 4.65)**	**2.49 (1.49, 3.82)**	**2.49 (1.46, 3.79)**	PBO

ADA: adalimumab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab
Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.
*Tofacitinib 5 and 10 mg pooled; vedolizumab 300 mg every 8 weeks and every 4 weeks pooled.

Harms

Severe and serious adverse events were rare during the induction and maintenance phases of available RCTs. Upper respiratory tract infections and headaches were the most reported adverse events across the TIMs. There was no indication of increased rates of serious infections, tuberculosis, and mortality for any of the agents in available RCTs. Data on serious adverse events in available long-term RCT extensions generally showed similar rates to those observed during randomized periods.

Section 4 also includes a summary of large comparative observational studies. While some showed an increased risk of serious infection in selected comparisons between TIMs and to conventional therapy, differences in study design, data source, and study quality make it difficult to draw firm conclusions regarding long-term safety.

Of note, however, the label for tofacitinib was modified in July 2019 given the results from a long-term clinical trial for safety in rheumatoid arthritis patients.[10] Modifications included warnings

related to thrombotic events (deep vein thrombosis, arterial thrombosis, and pulmonary embolism) as well as cardiovascular mortality in patients receiving the 10 mg twice daily dose. We also note that the three TNF inhibitors (adalimumab, golimumab, and infliximab) as well as tofacitinib carry a black box warning in their FDA labels for an increased risk of lymphomas and other malignancies observed in children, adolescents, and/or young adults based on clinical trials and real-world evidence for these TIMs when studied for other indications (e.g., rheumatoid arthritis).[11-14] In our evidence base for UC, overall rates of new malignancy were very low (<3%) and no study in our sample indicated an increased risk for any TIM.

Controversies and Uncertainties

While the evidence for each TIM of focus in this review suggests a potential net health benefit in comparison to conventional therapy among patients with moderate-to-severe UC, there are several concerns with trial design and results as well as gaps in evidence that bear mention.

First and foremost, a single trial of the 19 RCTs identified included direct evidence comparing the TIMs. Our comparisons were therefore driven almost exclusively by the conduct of NMAs. Our NMAs were limited by several factors, including differences in the definitions of biologic-naïve and biologic-experienced populations. Likewise, the network of evidence was sparse for some of our populations of interest (e.g., maintenance data in the biologic-experienced population), adding uncertainty to our relative estimates of response and remission.

There is currently very limited information with which to ascertain the optimal sequence of treatment, as the definition of "experienced" varied across trials. In some cases, the focus was on failure to achieve response alone, while in others, those achieving and losing response were also included. Some agents have no evidence in the populations of interest, posing challenges in the interpretation and application of data. We note other differences in population characteristics and measurement in available trials. While populations were broadly similar with respect to age and baseline disease severity, variation was noted in disease duration as well as use of conventional therapy at baseline. In addition, substantial variation has been noted in definitions of endoscopic factors, histologic features, and serum or fecal biomarkers across UC trials.[15]

As is often the case with therapies for chronic inflammatory diseases, evidence of long-term safety comes from the conduct of observational studies using large datasets. While such data exist for the more established therapies in our set, there are limited to no long-term data on newer UC therapies, such as tofacitinib, ustekinumab, and vedolizumab. There are uncertainties around not only what has been measured in available UC studies but what has not. Concerns were raised around the extraintestinal manifestations (EIMs) of the disease, but we found very little empiric data on the frequency of these manifestations and, more importantly, the impact of treatment on them. Other concerns raised by patients, such as chronic pain and fatigue as well as fecal urgency, have gone largely unaddressed by available studies. Finally, even though a substantial proportion

of cases of UC are diagnosed in childhood and adolescence, there is essentially a complete absence of robust comparative evidence to inform treatment strategies in this population.

Summary and Comment

Our evidence ratings were based on a combined evaluation of the clinical benefits and potential harms of TIMs across all four of our populations of interest (i.e., induction and maintenance within the biologic-naïve and biologic-experienced populations). We have opted to rate infliximab-dyyb and infliximab-abda, the two biosimilars to infliximab, as comparable ("**C**") to the originator product, and so the evidence ratings in Table ES10 involve comparisons to infliximab as a single entity. This rating is based on the Food and Drug Administration's (FDA) determination that the biosimilars are therapeutically equivalent in UC. We also note some context around ratings of the TIMs versus placebo. These were generally "**A**" (superior) ratings, although they apply only to the biologic-naïve population for golimumab and infliximab. We opted to rate tofacitinib at "**B+**" (small or superior net benefit) given the recent safety warnings; this also applied only to the biologic-experienced population for which its use is indicated.

Table ES10. Summary of ICER Evidence Ratings

TIM	Comparator	Rating
Infliximab	Infliximab biosimilars	C
Infliximab	Placebo	A*
Golimumab	Placebo	A*
Tofacitinib	Placebo	B+†
All other TIMs	Placebo	A
Vedolizumab	Adalimumab	B+
Ustekinumab	Adalimumab	C+
Infliximab	Adalimumab	C+*
Tofacitinib	Adalimumab	P/I†
Vedolizumab	Golimumab	C+*
All other TIM Comparisons	--	I

ICER: Institute for Clinical and Economic Review, TIM: targeted immune modulator
*Biologic-naïve only.
†Biologic-experienced only.

The head-to-head VARSITY study showed substantial and statistically significant differences in remission, response, and other measures of health benefit in favor of vedolizumab versus adalimumab. These findings were generally bolstered by the addition of indirect evidence in our NMAs. However, with just one head-to-head trial available, we concluded that there was only moderate certainty of a small or substantial net health benefit for vedolizumab ("**B+**").

Other comparisons to adalimumab are based on indirect evidence only. We found the evidence directionally consistent across the four populations for both infliximab (in biologic-naïve patients only) and ustekinumab to indicate a net health benefit that is at least comparable, and likely incremental, relative to adalimumab ("**C+**"). While we generally concluded the same for tofacitinib (in biologic-experienced patients only), the safety concerns associated with this agent resulted in a promising but inconclusive ("**P/I**") rating versus adalimumab.

In the comparison of vedolizumab and golimumab (among biologic-naïve patients only), NMA findings were directionally in favor of vedolizumab for both induction and maintenance, with results reasonably robust for maintenance. We judged this evidence to suggest a net health benefit for vedolizumab that was a least comparable, and likely incremental, relative to golimumab ("**C+**").

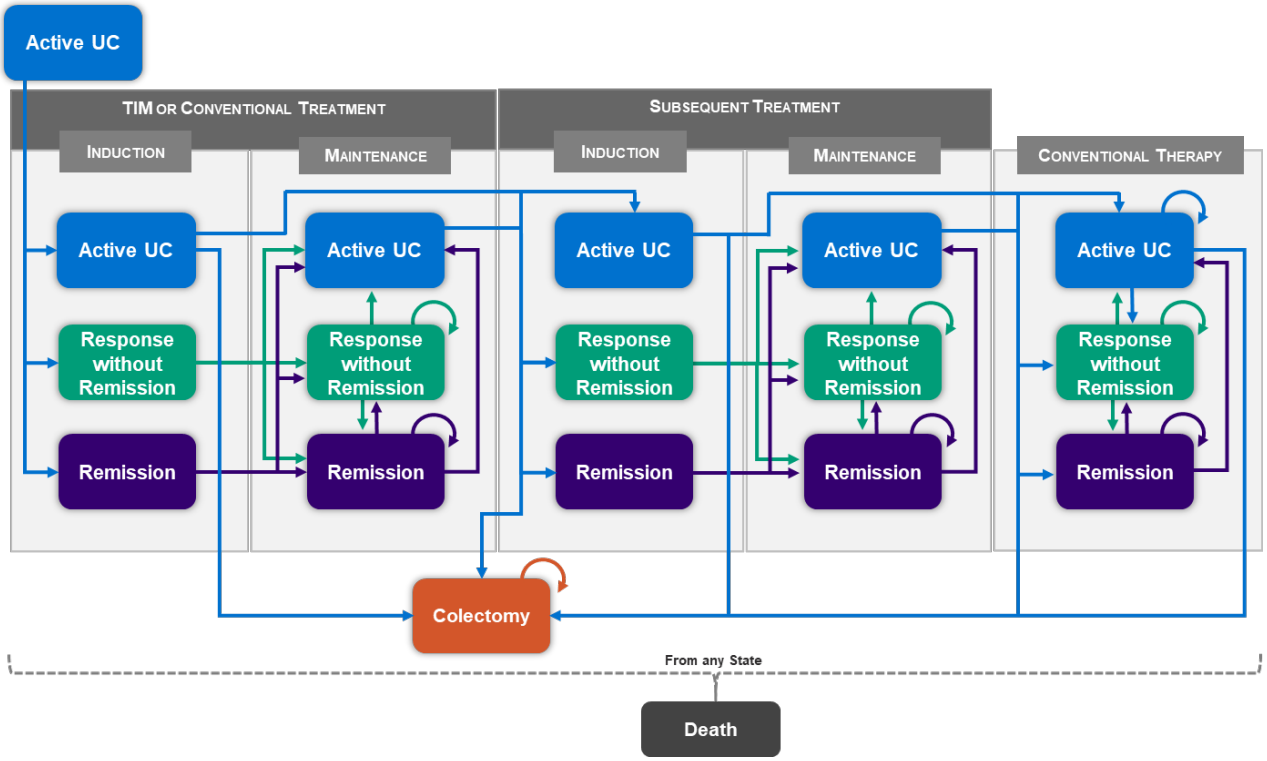
All other comparisons between TIMs reflected insufficient ("**I**") evidence of a net health benefit.

Long-Term Cost Effectiveness

A decision analytic model was developed to estimate the cost effectiveness of TIMs for moderate-to-severe UC in two populations: a biologic-naïve population and a biologic-experienced population. The model compared adalimumab, golimumab, infliximab, infliximab-dyyb, infliximab-abda, tofacitinib, ustekinumab, and vedolizumab to conventional treatment and to each other. The model was structured as a Markov model with eight-week cycles consisting of the health states of active UC, clinical response without remission, clinical remission, post-colectomy (with and without complications), and death. The base-case analysis took a health care sector perspective (i.e., focused on direct medical care costs only), over a lifetime time horizon. Costs and outcomes were discounted at 3% per year.

All patients enter the model in an active moderate-to-severe state. At the end of induction, patients with response (both with and without remission) continue to receive the TIM or conventional treatment. Those without response or those who discontinue after initial response begin induction with a subsequent treatment, represented by a market basket of all TIMs with data in a biologic-experienced population. At the end of induction with subsequent treatment, responders continue to receive the subsequent treatment. Patients who do not respond during the induction phase of subsequent treatment discontinue treatment with TIMs and follow the transition probabilities of the conventional treatment arm for the remainder of the model time horizon. A proportion of patients in the active UC state are assumed to opt for colectomy during each cycle.

Figure ES1. Model Framework



UC: ulcerative colitis

Efficacy data were derived from the results of the ICER NMAs of RCTs of TIMs in moderate-to-severe UC (one each for biologic-naïve and biologic-experienced), with data from the placebo arms used as a proxy for conventional treatment. We used consistent health state utility values across treatments evaluated in the model and across induction and maintenance. Health state utility values are taken from a published multi-center cross-sectional study of moderate-to-severe UC patients in Australia with mean EQ-5D utility values for patients in remission, active mild UC, and active moderate-to-severe UC.[16] Utility for the post-colectomy health state is based on EQ-5D scores from a cross-sectional survey of UC patients in Canada, Australia, and the United Kingdom with a history of colectomy within the prior 10 years.[17] The model also includes an increased risk of mortality associated with UC, which is not impacted by treatment, discontinuation for reasons other than lack of efficacy, disutility associated with serious infections, early complications of colectomy, and late complications (chronic pouchitis).

The model considered cost of drugs, administration, colectomy procedures, direct costs attributable to health states, and adverse events. In a modified societal perspective scenario, we also considered the cost of lost productivity due to intravenous (IV) administration, colectomy procedure, and indirect costs attributable to health states. For TIMs with oral or subcutaneous modes of administration, we obtained net pricing estimates from SSR Health, LLC.[18] For IV-

administered TIMs, we used Centers for Medicare and Medicaid Services Average Sales Prices (ASP) plus 9.5%.[19]

Model outcomes included total costs, life years (LYs), quality-adjusted life years (QALYs), and equal value of life years (evLYG).

Base-Case Results

Biologic-Naïve Population

Total discounted costs ranged from $434,000 to $545,000 over the lifetime time horizon compared to a total cost of $421,000 for conventional treatment. Discounted life expectancy was 22.08 LYs across all treatments. Projected discounted QALYs for TIMs ranged from 15.60 to 15.68 compared with 15.57 QALYs for conventional treatment.

The incremental cost per QALY for TIMs compared to conventional treatment in the biologic-naïve population ranged from $186,000 (infliximab-dyyb) to $1,870,000 (adalimumab). All TIMs had lower or equal LYs and QALYs compared to infliximab at a higher cost with the exception of ustekinumab, which had slightly higher QALYs at a higher cost with a resulting cost per QALY exceeding $2.9 million.

Table ES11. Base-Case Results for TIMs and Conventional Treatment: Biologic-Naïve

Parameter	Total Cost	QALYs	LYs*
Adalimumab	$461,000	15.596	22.077
Golimumab	$458,000	15.600	22.078
Infliximab	$435,000	15.644	22.080
Infliximab-dyyb	$434,000	15.644	22.080
Infliximab-abda	$434,000	15.644	22.080
Ustekinumab	$545,000	15.681	22.081
Vedolizumab	$480,000	15.641	22.080
Conventional Treatment	$421,000	15.574	22.075

LY: life year, QALY: quality-adjusted life year, TIM: targeted immune modulator
Costs rounded to nearest $1,000.
*Small differences in LYs across comparators are not displayed due to rounding.

Table ES12. Pairwise Results for TIMs Compared to Conventional Treatment: Biologic-Naïve

Treatment	Incremental Cost	Incremental QALYs	Incremental LYs	ICER vs. Conventional Treatment
Adalimumab	$40,710	0.02	<0.01	$1,870,000
Golimumab	$37,734	0.03	<0.01	$1,455,000
Infliximab	$14,741	0.07	<0.01	$212,000
Infliximab-dyyb	$12,936	0.07	<0.01	$186,000
Infliximab-abda	$13,606	0.07	<0.01	$195,000
Ustekinumab	$123,883	0.11	<0.01	$1,163,000
Vedolizumab	$59,597	0.07	<0.01	$887,000
Conventional Treatment	Reference	Reference	Reference	Reference

ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year, TIM: targeted immune modulator

Cost per QALY gained rounded to nearest $1,000.

Biologic-Experienced Population

Total discounted costs ranged from $460,000 to $504,000 over the lifetime time horizon compared to a total cost of $434,000 for conventional treatment. Discounted life expectancy was 22.07 LYs across all treatments. Projected discounted QALYs for TIMs ranged from 15.41 to 15.45 for TIMs compared with 15.39 QALYs for conventional treatment.

The incremental cost per QALY for TIMs compared to conventional treatment in the biologic-experienced population ranged from $495,000 (tofacitinib) to $1,885,000 (adalimumab). Treatment with tofacitinib resulted in greater QALYs at a lower cost compared with adalimumab. The cost per additional QALY for ustekinumab and vedolizumab compared with adalimumab was $996,000 and $464,000, respectively.

Table ES13. Base-Case Results for TIMs and Conventional Treatment: Biologic-Experienced

Parameter	Total Cost	QALYs	LYs*
Adalimumab	$465,000	15.410	22.070
Tofacitinib	$460,000	15.445	22.074
Ustekinumab	$504,000	15.449	22.074
Vedolizumab	$482,000	15.446	22.073
Conventional Treatment	$434,000	15.393	22.070

LY: life year, QALY: quality-adjusted life year, TIM: targeted immune modulator

Costs rounded to nearest $1,000.

*Small differences in LYs across comparators are not displayed due to rounding.

Table ES14. Pairwise Results for TIMs Compared to Conventional Treatment: Biologic-Experienced

Treatment	Incremental Cost	Incremental QALYs	Incremental LYs	ICER vs. Conventional Treatment
Adalimumab	$30,462	0.02	<0.01	$1,885,000
Tofacitinib	$25,672	0.05	<0.01	$495,000
Ustekinumab	$70,216	0.06	<0.01	$1,252,000
Vedolizumab	$47,333	0.05	<0.01	$902,000
Conventional Treatment	Reference	Reference	Reference	Reference

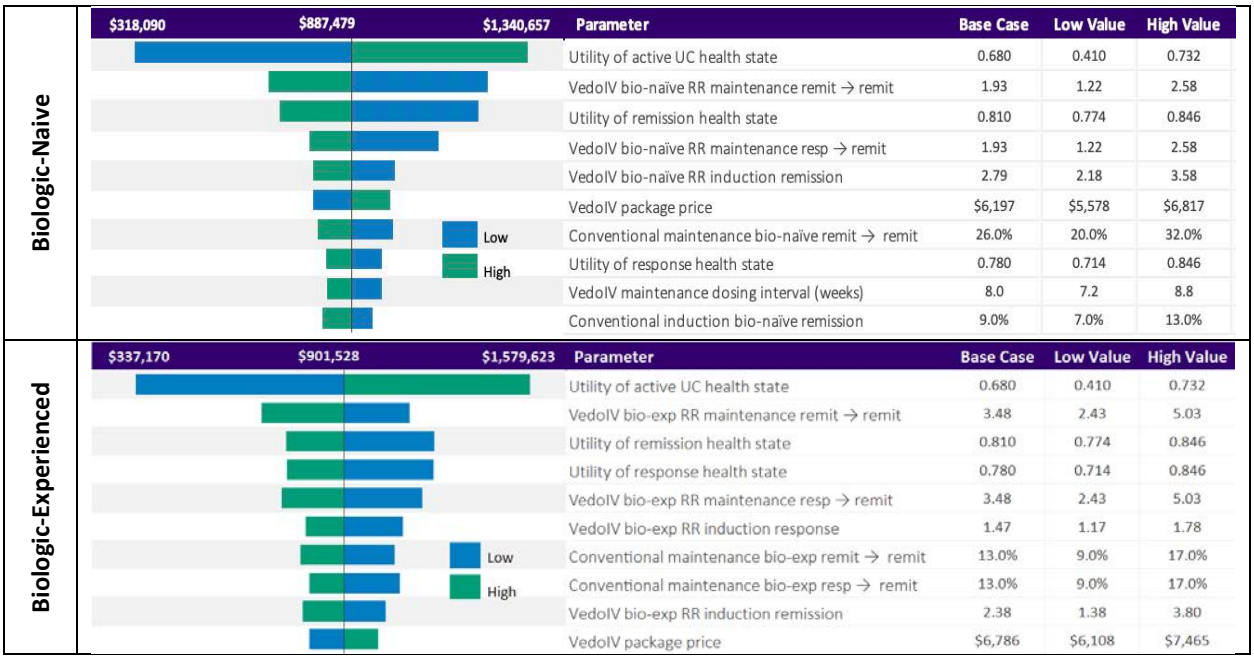
ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year, TIM: targeted immune modulator

Cost per QALY gained rounded to nearest $1,000.

Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., 95% confidence interval [CI]) or reasonable ranges (±10%) to evaluate changes in cost per additional QALY for each TIM compared to conventional treatment. The tornado charts for vedolizumab in a biologic-naïve population and biologic-experienced population are presented in Figure ES2 on the following page as an example. Across all TIMs, utility values and risk ratios for induction and maintenance were the most influential drivers of model results. The results for other comparators were similar and are presented in the Appendix.

Figure ES2. One-way Sensitivity Analysis of Vedolizumab versus Conventional Treatment (Cost per QALY)



Biologic-Naive				
Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
VedoIV bio-naïve RR maintenance remit → remit	1.93	1.22	2.58
Utility of remission health state	0.810	0.774	0.846
VedoIV bio-naïve RR maintenance resp → remit	1.93	1.22	2.58
VedoIV bio-naïve RR induction remission	2.79	2.18	3.58
VedoIV package price	$6,197	$5,578	$6,817
Conventional maintenance bio-naïve remit → remit	26.0%	20.0%	32.0%
Utility of response health state	0.780	0.714	0.846
VedoIV maintenance dosing interval (weeks)	8.0	7.2	8.8
Conventional induction bio-naïve remission	9.0%	7.0%	13.0%

Biologic-Experienced			
Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
VedoIV bio-exp RR maintenance remit → remit	3.48	2.43	5.03
Utility of remission health state	0.810	0.774	0.846
Utility of response health state	0.780	0.714	0.846
VedoIV bio-exp RR maintenance resp → remit	3.48	2.43	5.03
VedoIV bio-exp RR induction response	1.47	1.17	1.78
Conventional maintenance bio-exp remit → remit	13.0%	9.0%	17.0%
Conventional maintenance bio-exp resp → remit	13.0%	9.0%	17.0%
VedoIV bio-exp RR induction remission	2.38	1.38	3.80
VedoIV package price	$6,786	$6,108	$7,465

bio: biologic, exp: experienced, IV: intravenous, resp: response without remission, RR: risk ratio, UC: ulcerative colitis, vedo: vedolizumab

The proportion of probabilistic sensitivity analysis iterations with an incremental cost-effectiveness ratio below $250,000 per QALY gained were <1% for adalimumab, golimumab, vedolizumab, and ustekinumab for the biologic naïve population and <1% for all TIMs in the biologic-experienced population. The cost-effectiveness acceptability curve for infliximab and infliximab biosimilars compared to conventional treatment is presented in Figure ES3; acceptability estimates for the four TIMs with evidence in the biologic-experienced population are presented in Figure ES4.

Figure ES3. Cost-Effectiveness Acceptability Curve for TIMs Compared to Conventional Treatment: Biologic-Naïve Population

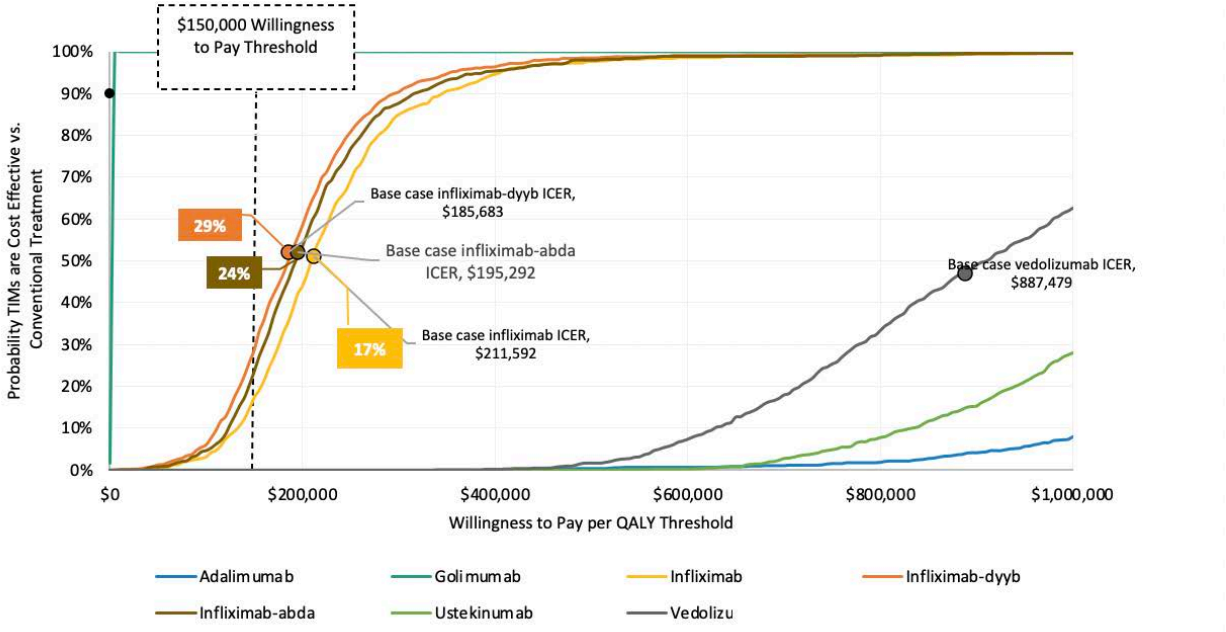
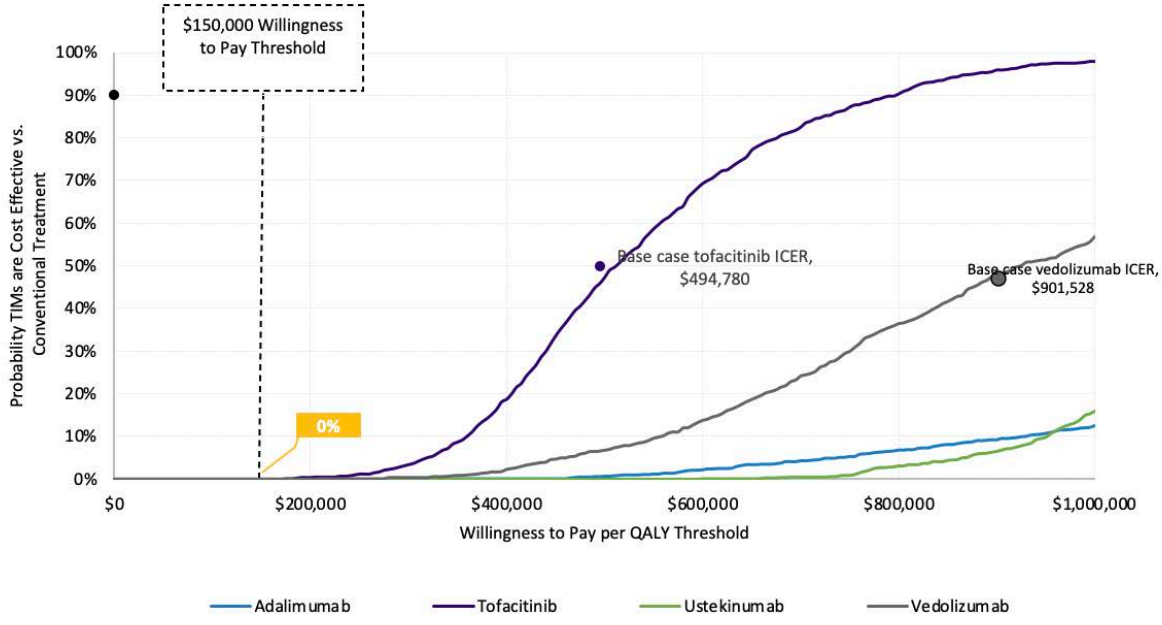


Figure ES4. Cost-Effectiveness Acceptability Curve for TIMs Compared to Conventional Treatment: Biologic-Experienced Population



Threshold Analyses

The dosing, mode of administration, and frequency of administration of some TIMs differs in the induction period compared with the maintenance period. In order to generate a single annual threshold price across TIMs, threshold pricing was conducted for price per maintenance year. The annual drug cost per maintenance year for each TIM to reach an incremental cost per QALY gained compared to conventional treatment at thresholds of $50,000 per QALY, $100,000 per QALY, and $150,000 per QALY are presented in Tables ES15 and ES16. Annual TIM prices at the $150,000 per QALY threshold ranged from $6,824 (adalimumab, biologic-experienced population) to $16,624 (ustekinumab, biologic-naïve population). We note, however, that these results are highly sensitive to what amount to very minor differences in estimated QALYs. For example, the somewhat higher threshold prices for ustekinumab in the biologic-naïve population are driven by a QALY difference of 0.037 in comparison to the next most-effective TIM, which is the equivalent of less than two additional weeks of life. This difference is itself based on parameter inputs, which are based on point estimate differences from our NMA that were not statistically different across ustekinumab and other TIMs. It is also important to note that the threshold prices for ustekinumab are for the subcutaneous injection used in the maintenance period and are independent of the IV product price used in the induction period. This is why, for example, we see the threshold price in the biologic-experienced population rising faster with increasing cost per QALY thresholds versus other TIMs (e.g., vedolizumab).

With these details in mind, the overall results demonstrate that for all TIMs, except infliximab and the infliximab biosimilars, annual net price estimates were far higher than threshold prices all the way up to prices at $150,000 per QALY.

Table ES15. Resulting Prices per Maintenance Year for TIMs to Reach Cost per QALY Thresholds for the Biologic-Naïve Population

Drug	Base-Case Cost	$50,000/QALY	$100,000/QALY	$150,000/QALY
Adalimumab	$46,933	$4,616	$5,778	$6,941
Golimumab	$42,332	$4,991	$6,320	$7,649
Infliximab	$14,614	$6,754	$8,813	$10,872
Infliximab-dyyb	$13,451	$6,754	$8,813	$10,872
Infliximab-abda	$13,883	$6,754	$8,813	$10,872
Ustekinumab	$91,609	$9,220	$12,922	$16,624
Vedolizumab	$44,224	$7,247	$9,454	$11,662

QALY: quality-adjusted life year, WAC: wholesale acquisition cost
Prices rounded to nearest $1,000.

Table ES16. Resulting Prices per Maintenance Year for TIMs to Reach Cost per QALY Thresholds for the Biologic-Experienced Population

Drug	Base-Case Cost	$50,000/QALY	$100,000/QALY	$150,000/QALY
Adalimumab	$46,933	$4,512	$5,668	$6,824
Tofacitinib	$35,506	$9,429	$12,360	$15,292
Ustekinumab	$91,609	$4,523	$8,144	$11,766
Vedolizumab	$44,224	$6,738	$8,939	$11,140

QALY: quality-adjusted life year, WAC: wholesale acquisition cost
Prices rounded to nearest $1,000.

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure that they were consistent with the report. We also conducted sensitivity analyses with extreme input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Summary and Comment

We estimated the cost effectiveness of TIMs in biologic-naïve and biologic-experienced adult patients with moderate-to-severe UC. Patient time spent in health states of active UC, response without remission, and response with remission was summed to provide estimates of life expectancy, quality-adjusted life expectancy, and evLY gained. Annual net health care costs, including net price drug acquisition, administration, adverse events, and colectomy were summed to estimate lifetime costs for TIMs and conventional treatment. Based on these calculations, the cost effectiveness of TIMs was estimated to range from $186,000 to $1,870,000 per QALY in the biologic-naïve population and $495,000 to $1,885,000 per QALY in the biologic-experienced population. In general, the incremental cost of TIMs versus conventional treatment was modest given the annual price of TIMs, the use of subsequent treatments, and a lifetime time horizon. In our model, initial non-responders and those who lose response to a TIM are assumed to discontinue treatment and receive additional treatments. With this assumption, few patients remain on the initial TIM longer than a year. Resulting QALYs were quite similar between TIMs, so even small differences in cost drove the variability in cost per QALY ratios.

Adalimumab, golimumab, ustekinumab, and vedolizumab were unlikely to be cost effective in the biologic-naïve population, with incremental cost-effectiveness ratios exceeding $800,000 in the base case. Infliximab and infliximab biosimilars had the lowest cost-effectiveness ratios in the biologic-naïve population but remained above the $150,000 cost per QALY threshold in the base case.

No TIMs were found to be cost effective compared with conventional treatment in the biologic-experienced population. However, tofacitinib resulted in greater QALYs at a lower cost compared with adalimumab.

Results for both populations were tested under a variety of assumptions and alternative sources of model inputs, none of which drove the incremental cost per QALY below the threshold of $150,000 per QALY gained for TIMs other than infliximab and infliximab biosimilars in the biologic-naïve population.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits 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. These elements are listed in the table below and on the following page.

Potential Other Benefits

Table ES17. Potential Other Benefits

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	N/A
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	N/A
This intervention will significantly reduce caregiver or broader family burden.	The benefits of TIMs relative to conventional therapy may translate into significant and durable periods of clinical remission, allowing patients to resume normal activities and reducing caregiver impact.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	Novel mechanisms of action provide additional options for patients with UC whose disease has stopped responding to other TIM classes. In addition, available UC therapies include oral, self-injectable, and infused products; patients tend to have clear preferences for method of delivery.
This intervention will have a significant impact on improving return to work and/or overall productivity.	The benefits of TIMs relative to conventional therapy may translate into significant and durable periods of clinical remission, allowing patients to resume normal activities and reducing caregiver impact.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	N/A

Contextual Considerations

Table ES18. Potential Contextual Considerations

Considerations	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	UC poses a significant lifetime burden on quality of life, and many patients fear the prospect of surgical intervention and its attendant complications.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	UC poses a significant lifetime burden on quality of life, and many patients fear the prospect of surgical intervention and its attendant complications.
This intervention is the first to offer any improvement for patients with this condition.	N/A
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.	While the safety profile of the TNF inhibitors has been relatively well established in UC and other chronic inflammatory conditions, these data are sparse for newer TIMs, such as tofacitinib, ustekinumab, and vedolizumab.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	While RCTs are comparatively long in duration in UC generally, infliximab remains the only agent with an FDA indication in children and adolescents, and as such, there is substantial uncertainty about the long-term benefits and risks of other TIMs in these patients.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	N/A

Health-Benefit Price Benchmarks

The health benefit price benchmark (HBPB) is a price range suggesting the highest price that a manufacturer should charge for a treatment based on the amount of improvement in overall health that patients receive from that treatment when a higher price would cause disproportionately greater losses in health among other patients due to rising overall costs of health care and health insurance.

Annual prices of each TIM that would achieve incremental cost-effectiveness ratios of $100,000 and $150,000 per QALY for the biologic-naïve and biologic-experienced populations are presented in Tables ES19 and ES20, respectively. The cost per evLYG price ranges are almost identical to the cost per QALY ranges due to the very similar evLYG and QALYs gained in the base-case analysis, and as such, are not presented separately here.

Table ES19. Annual Cost-Effectiveness Threshold Prices per Maintenance Year for TIMs for the Treatment of UC in the Biologic-Naïve Population

	Annual WAC	Annual Estimated Net Price	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Adalimumab	$72,400	$46,900	$5,800	$6,900	90%-92%
Golimumab	$75,300	$42,300	$6,300	$7,600	90%-92%
Infliximab	$27,900	$14,600	$8,800	$10,900	61%-68%
Infliximab-dyyb	$22,600	$13,500	$8,800	$10,900	52%-61%
Infliximab-abda	$18,000	$13,900	$8,800	$10,900	40%-51%
Ustekinumab	$150,400	$91,600	$12,900	$16,600	89%-91%
Vedolizumab	$43,800	$44,200	$9,500	$11,700	73%-78%

WAC: wholesale acquisition cost
Prices rounded to nearest $100.

Table ES20. Annual Cost-Effectiveness Threshold Prices per Maintenance Year for TIMs for the Treatment of UC in the Biologic-Experienced Population

	Annual WAC	Annual Estimated Net Price	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Adalimumab	$72,400	$46,900	$5,700	$6,800	91%-92%
Tofacitinib	$57,200	$35,500	$12,600	$15,300	73%-78%
Ustekinumab	$150,400	$91,600	$8,100	$11,800	92%-95%
Vedolizumab	$43,800	$44,200	$8,900	$11,100	75%-80%

WAC: wholesale acquisition cost
Prices rounded to nearest $100.

Across both populations, the HBPB ranges for adalimumab (approximately $6,000 to $7,000 per year) would require discounts of approximately 90% to 92% from the wholesale acquisition cost (WAC). Golimumab would require discounts of approximately 90% from WAC, for a HBPB range from $6,300 to $7,600 per year. The HBPB range for infliximab ($8,800 to $10,900) would require discounts of 61% to 68% from WAC, with smaller discounts required for infliximab-dyyb (52% to 61%) and infliximab-abda (40% to 51%). The HBPB range for ustekinumab across both populations ranged from $8,100 to $16,600, representing discounts of 89% to 95%. As noted previously, however, the higher threshold prices for ustekinumab must be viewed in the context of the minor differences among TIMs in summary measures of effectiveness, the use of point estimates from NMAs that are not statistically significant, and the sensitivity of the model to variability in costs. For vedolizumab, the HBPB range across both populations is $8,900 to $11,700, requiring 73% to 80% discounts from WAC.

Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of the recently expanded indication of ustekinumab for prevalent individuals in the US with moderate-to-severe UC. In our estimates of potential budget impact, we used the WAC, estimated net price, and $50,000, $100,000, and $150,000 cost-effectiveness threshold prices that were weighted averages of the threshold prices for the biologic-naïve and biologic-experienced populations eligible for ustekinumab. We did not include the other therapies modeled above in this potential budget impact analysis given their established presence on the market for UC.

This potential budget impact analysis includes the estimated number of individuals with UC in the US who would be eligible for treatment with ustekinumab. To estimate the size of the potential candidate populations for treatment, we used an estimate by Turner et al. of the prevalence of individuals with UC in the US of approximately 900,000 patients.[4] The Crohn's and Colitis Foundation has reported that approximately 22% of UC patients have moderate-to-severe disease activity in a given year, which would equate to approximately 198,000 patients with moderate-to-severe UC in the US.[20] To estimate the proportions of these patients who would be biologic-naïve versus biologic-experienced, we used the weighted average of the baseline distribution of patients in the relevant trials that enrolled a "mixed" population (i.e., both biologic-naïve and biologic-experienced), resulting in an estimate of approximately 55% of patients who were not using biologics and 45% who had previously used biologics. For the purposes of this analysis, we assumed that 20% of these patients would initiate ustekinumab in each of the five years, or 21,780 biologic-naïve patients per year and 17,820 biologic-experienced patients per year. Among patients eligible for ustekinumab, we assumed that patients could be drawn from all other available treatment options for biologic-naïve and biologic-experienced patients, respectively.

The average annualized potential budgetary impact when using the list price of ustekinumab was an additional per-patient cost of approximately $36,100 and approximately $15,600 using the net price (Table ES21 on the following page). The weighted-average threshold prices for $50,000 to $150,000 per QALY were estimated to produce cost savings relative to the treatment market basket because of the relatively higher cost offset from the comparator mix ($37,500 per patient), which includes several biologics at their net prices.

Table ES21. Annualized Per-Patient Potential Budget Impact over a Five-Year Time Horizon for Ustekinumab in a UC Population Assuming 55% Biologic-Naïve and 45% Biologic-Experienced

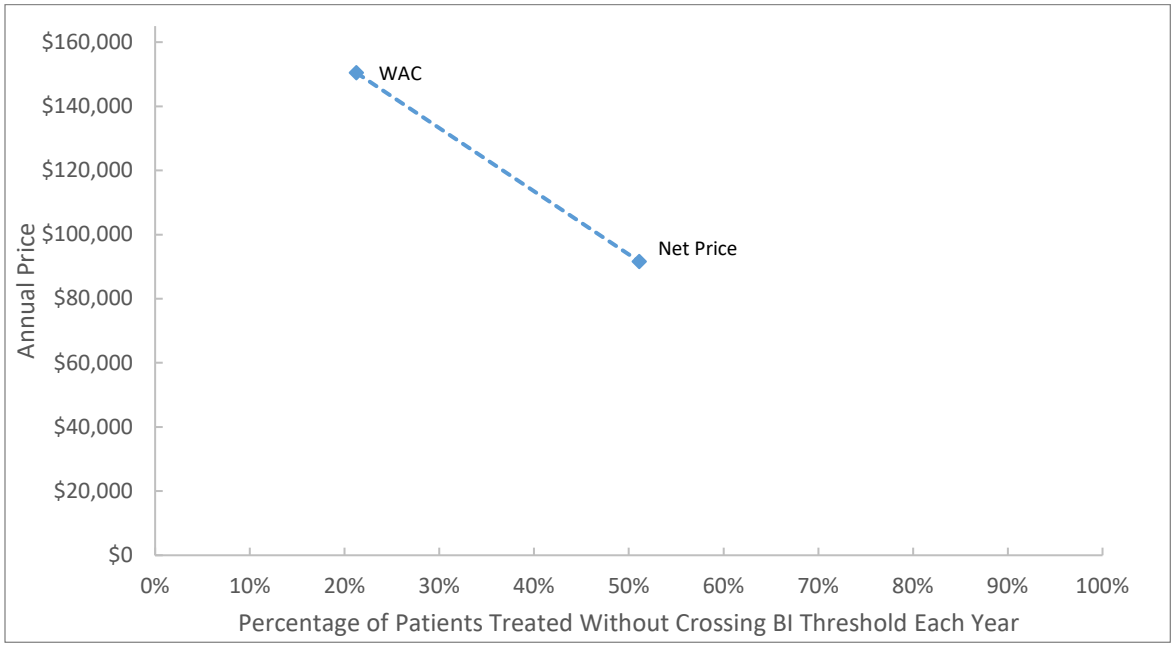
	Average Annual Per Patient Budget Impact				
	At List Price	At Net Price	At $150,000/ QALY Price	At $100,000/ QALY Price	At $50,000/ QALY Price
Ustekinumab	$73,600	$53,100	$28,800	$27,600	$26,400
55% Naïve/45% Experienced Market Basket	$37,500				
Net Impact	$36,100	$15,600	-$8,700	-$9,900	-$11,100

QALY: quality-adjusted life year

All annualized costs include drug and non-drug health care costs. Numbers may not sum due to rounding.

As shown in Figure ES5, approximately 21% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at the WAC of ustekinumab. Approximately 51% of eligible patients could be treated without crossing the budget impact threshold at its estimated net price. All eligible patients could be treated at the $150,000, $100,000, and $50,000 threshold prices, with potential budget impact estimated to be cost saving across the $150,000 to $50,000 threshold prices.

Figure ES5. Potential Budget Impact Scenarios of Ustekinumab versus Market Basket Treatment Mix at Different Acquisition Prices



BI: budget impact, WAC: wholesale acquisition cost

CTAF Votes

The CTAF Panel deliberated on key questions raised by ICER's report at a virtual public meeting on September 24, 2020. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

1) Is the evidence adequate to demonstrate that the net health benefit of vedolizumab is superior to that provided by adalimumab?[1]

Yes: 12 votes	No: 2 votes

2) Is the evidence adequate to demonstrate that the net health benefit of ustekinumab is superior to that provided by adalimumab?

Yes: 0 votes	***No: 15 votes***

3) Is the evidence adequate to distinguish the net health benefit among tofacitinib, ustekinumab, and vedolizumab?

Yes: 1 vote	***No: 14 votes***

4) When compared to conventional therapy, does treating patients with TIMs offer one or more of the following potential "other benefits"?

These interventions offer reduced complexity that will significantly improve patient outcomes.	2/15
These interventions will significantly reduce caregiver or broader family burden.	9/15
These interventions offer a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	13/15
These interventions will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	12/15
There are other important benefits or disadvantages that should have an important role in judgments of the value of these interventions.	2/15

[1] Due to technological issues, one CTAF Panelist was unable to cast a vote for the first question.

5) Are any of the following contextual considerations important in assessing the long-term value for money of TIMs?

These interventions are intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	12/15
These interventions are intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	13/15
These interventions are the first to offer any improvement for patients with this condition.	0/15
Compared to conventional therapy, there is significant uncertainty about the long-term risk of serious side effects of these interventions.	13/15
Compared to conventional therapy, there is significant uncertainty about the magnitude or durability of the long-term benefits of these interventions.	12/15
There are additional contextual considerations that should have an important role in judgments of the value of these interventions.	0/15

6) Given the available evidence on comparative effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment at current pricing with infliximab, infliximab-abda, and infliximab-dyyb versus conventional treatment?

Low: 3 votes	**Intermediate: 10 votes**	High: 2 votes

Key Policy Implications

Following its deliberation on the evidence, the CTAF Panel engaged in a moderated discussion with a Policy Roundtable about how best to apply the evidence on TIMs for UC to policy and practice. The Policy Roundtable members included two patients/patient advocates, two clinical experts, two payers, and two representatives from manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented on the following pages, and additional information can be found in the full report.

Clinicians, Payers, Manufacturers, and Patient Organizations

- The significantly lower prices seen for infliximab and its biosimilars speaks to the important potential for improved value with broader availability and uptake of biosimilar treatment options. All stakeholders should collaborate to ensure that TIM biosimilars have an increasing and comprehensive role in the UC treatment landscape.

Manufacturers and Payers

- The "bundled rebate" approach, in which rebates are provided at the drug level across all of its possible indications, should be abolished and replaced with an indication- and value-based pricing approach.

Payers

- Insurance coverage should be structured to prevent situations in which patients are forced to choose a treatment approach on the basis of cost.
- Specialty society guidelines and drug labels should be monitored for changes, with coverage policy adjusted accordingly.
- Because there are no clear biomarkers or predictors of the success for any given treatment in UC, it is not unreasonable to consider prior authorization criteria in order to manage the costs of expensive medications and negotiate prices for TIMs priced beyond a fair range. However, prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers.

Patient Organizations

- Patient advocacy organizations should be an active voice in noting the potentially negative effects of TIM pricing on patient access.

Specialty Societies

- Consensus guidelines should be developed across the major gastroenterology societies, in collaboration with patient groups, to ensure a common voice for UC treatment guidance.

Regulators

- Given the maturity and longstanding use of several of the TIMs of focus in this review, the FDA should require the inclusion of active control arms in Phase III clinical trials of UC treatments.

Researchers

- The research community should make a strong commitment to generate real-world evidence that can fill in the gaps from available RCTs and allow for comprehensive comparisons of TIMs.
- Further clinical study should be conducted to ascertain the optimal sequencing of TIM therapy in UC.

1. Introduction

1.1 Background

Background

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that affects the mucosa, the innermost lining of the intestinal wall in the large bowel (i.e., the colon and rectum).[1] The disease causes long-lasting inflammation and ulcers in the digestive tract and is typically marked by periods of remission and recurrence of symptoms. Symptoms may include frequent diarrhea, sometimes with blood or pus, abdominal and/or rectal pain, weight loss, and fatigue.[2] A number of extraintestinal manifestations (EIMs) have also been associated with UC, including musculoskeletal, ocular, dermatologic, hepatobiliary, and psychological effects.[21] When the disease affects children, it can have a detrimental impact on growth, nutritional status, and psychosocial development.[3] It is estimated that approximately 900,000 individuals in the United States (US) have UC.[4] Most individuals are diagnosed between the ages of 15 and 35.[5] The economic burden of UC is significant, ranging between an estimated $15-32 billion per year.[5]

UC is diagnosed based on the presence of symptoms with confirmation of disease via colonoscopy and biopsy. Other disease processes that may cause similar symptoms, such as infection and cancer, should be excluded.[6] UC is typically distinguished from Crohn's disease, another form of IBD, based on diffuse inflammation rather than the focal or patchy patterns typical of Crohn's, and confining of the disease to the colon (i.e., the large intestine), while Crohn's can also affect the small intestine, and particularly the terminal ileum, and often spares the rectum.[22] In a number of cases, differential diagnosis is difficult, and 5% to 15% of patients may be diagnosed as "IBD unclassified."[22]

Management

The management of UC in adults is dependent on the severity of symptoms. The goal of treatment is to induce a clinical response to treatment (as evidenced by reduction of the disease's key symptoms) or effect a complete remission of the symptoms during a short-term (six to 14 weeks) "induction" phase of treatment, and maintain response or remission via long-term "maintenance" therapy, often at a lower dose. Colectomy (surgical removal of the colon) may be considered in patients whose disease does not respond to maximal medical management. Symptoms of interest and overall disease status are typically defined using the Mayo Score, a combined clinical and endoscopic tool, and include stool frequency, rectal bleeding, mucosal status, and the physician's global impression. The tool documents clinical response to treatment (significant improvement from baseline), remission (low total score and individual sub-scores), and endoscopic improvement

(low mucosa sub-score).[23] In patients with mild disease, local or topical use of aminosalicylates may induce and maintain remission. Once symptoms become moderate-to-severe, however, the use of oral or ileal/colonic preparations of budesonide as well as systemic corticosteroids is typically warranted.[6]

Those whose disease does not respond to or recurs despite systemic therapy are candidates for a number of targeted immune modulators (TIMs) to induce and/or maintain remission. These agents affect a number of different targets on the inflammatory cascade associated with UC and are summarized in Table 1.1 below. TIMs may be used alone or in combination with other systemic immunomodulators, such as azathioprine, to prevent relapse.[6]

Table 1.1. TIMs for the Treatment of UC

Treatment	Brand Name	Route	Dose	Estimated Annual Cost†
TNF Inhibitors				
Adalimumab	Humira®	Injection	160 mg on day 1, then 80 mg 2 weeks later, then 40 mg EOW	$46,933
Golimumab	Simponi®	Injection	200 mg at week 0, 100 mg at week 2, then 100 mg EOW	$41,332
Infliximab	Remicade®	Infusion	5 mg/kg at 0, 2, and 6 weeks, then q8w	$14,614
Infliximab-abda	Renflexis®	Infusion	5 mg/kg at 0, 2, and 6 weeks, then q8w	$13,883
Infliximab-dyyb	Inflectra®	Infusion	5 mg/kg at 0, 2, and 6 weeks, then q8w	$13,451
JAK Inhibitor				
Tofacitinib	Xeljanz®	Oral	10 mg BID for 8 weeks, then 5 mg BID	$35,506
IL-12/23 Inhibitor				
Ustekinumab	Stelara®	Infusion and injection	Weight-based IV dose (≤55 kg: 260 mg, >55 kg to 85 kg: 390 mg; >85 kg: 520 mg) before administering 90 mg at week 8, then q8w	$91,609
α4β7 Integrin Inhibitor				
Vedolizumab	Entyvio®	Infusion	300 mg at 0, 2, and 6 weeks, then q8w	$44,224

BID: twice daily, EOW: every other week, IL: interleukin, IV: intravenous, JAK: Janus kinase, kg: kilogram, mg: milligram, q8w: every 8 weeks, TNF: tumor necrosis factor

*Average including biosimilars infliximab-dyyb (Inflectra®, Pfizer) and infliximab-abda (Renflexis®, Merck).

†Estimated based on average net price to payers per maintenance year (obtained from SSR Health, LLC) for oral and subcutaneously administered products and Medicare ASP pricing for IV-administered products.

As shown in the above table, available TIMs differ substantially in terms of how treatment is delivered, dosing levels and their frequency, and their estimated annual cost. A subcutaneous injectable form of vedolizumab was under review by the US Food and Drug Administration (FDA) when this review began; however, on December 20, 2019, the manufacturer announced receipt of a complete response letter from the FDA denying the application, with no details given on whether and how the FDA's concerns will be addressed.[24]

1.2 Scope of the Assessment

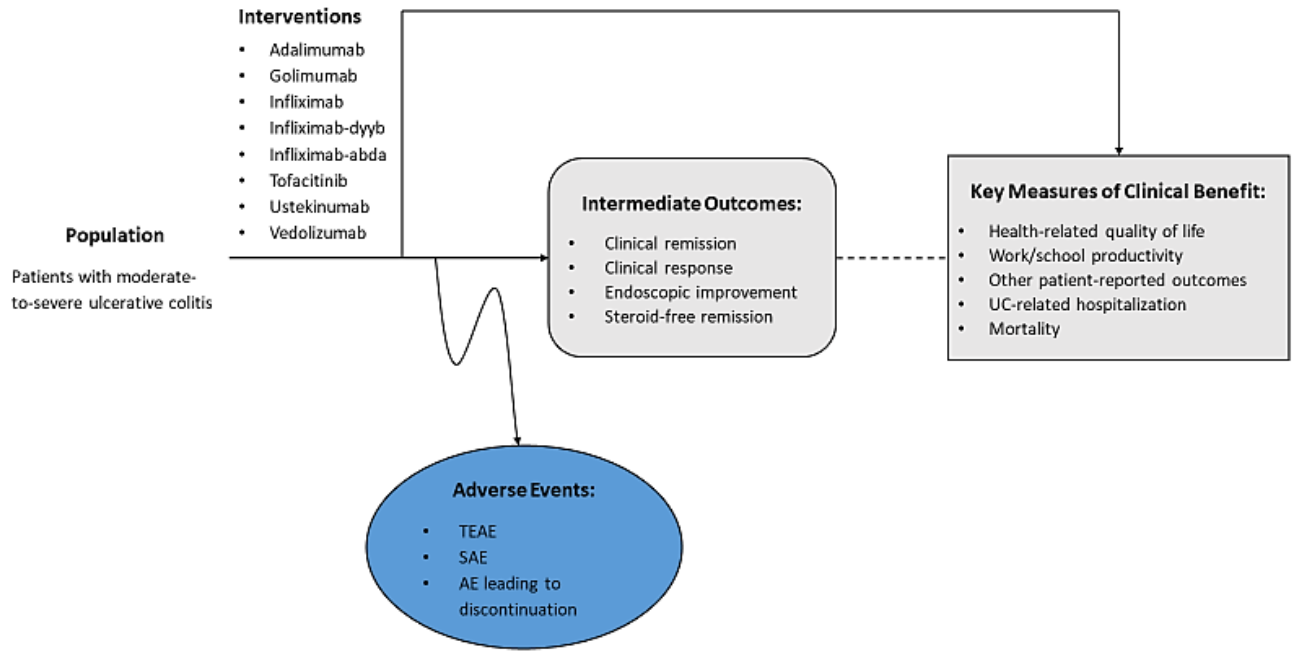
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was abstracted from randomized controlled trials (RCTs) (see "Data Extraction and Quality Assessment" in Section 4); high-quality comparative cohort studies were also included, particularly for long-term outcomes and uncommon adverse events. Our evidence review included input from 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-2/grey-literature-policy/).

All relevant evidence was synthesized qualitatively or quantitatively. Wherever possible, we sought head-to-head studies of the interventions and comparators of interest. We also combined direct and indirect evidence in network meta-analyses (NMAs) of selected outcomes where data permitted. Based on counsel from patient advocacy groups, clinical experts, and manufacturers, most comparisons are stratified by experience with biologic therapy (i.e., naïve vs. experienced) as well as phase of treatment (i.e., induction of response or remission vs. maintenance following response/remission). Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis are provided in a research protocol published on the Open Science Framework website (https://osf.io/cwyn5/).

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.1 on the following page.

Figure 1.1. Analytic Framework



AE: adverse event, SAE: serious adverse event, TEAE: treatment-emergent adverse event, UC: ulcerative colitis

The diagram above begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows, which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., clinical remission), and those within the squared-off boxes are key measures of clinical benefit (e.g., health-related quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of an action (typically treatment), which are listed within the blue ellipse.

Populations

The population of focus for the review was adults with moderate-to-severe UC, whose disease has either inadequate response or intolerance to conventional therapy, such as systemic corticosteroids, azathioprine, or mercaptopurine. While controlled comparative data were extremely limited in children (ages six to 17), we nevertheless summarized the available information. Additionally, as noted above, given that outcomes may differ according to prior use of biologic therapy as well as whether TIM use is intended for induction or maintenance, we stratified our comparisons according to these factors in both the synthesis of available evidence as well as the economic evaluation.

Other subgroups of interest included age (e.g., ≥65), presence of EIMs (e.g., arthritic symptoms, psychological effects), and other key comorbidities.

Interventions

The interventions of interest developed with input from clinicians and patient organizations included:

- Adalimumab (Humira, AbbVie)
- Golimumab (Simponi, Janssen)
- Infliximab (Remicade, Janssen)
- Infliximab-dyyb (Inflectra, Pfizer)
- Infliximab-abda (Renflexis, Merck)
- Tofacitinib (Xeljanz, Pfizer)
- Ustekinumab (Stelara, Janssen)
- Vedolizumab (Entyvio, Takeda), intravenous (IV) formulation

We included all FDA-approved biosimilars of originator products that are currently available on the US market. Importantly, our focus was on patient-centric data for UC only in comparisons of biosimilars to originator products; information limited to pharmacodynamics, pharmacokinetics, or other laboratory parameters was not considered. We did not include other FDA-approved biosimilars (e.g., biosimilars for adalimumab) as their entry to the US marketplace has been substantially delayed due to patent litigation.

Comparators

Based on data availability, we compared the interventions of interest to ongoing background conventional therapy (i.e., placebo arms of clinical trials) and to each other.

Outcomes

The following outcomes of interest were evaluated:

Efficacy

- Clinical remission
- Clinical response
- Endoscopic improvement (often referred to as “mucosal healing”)
- Steroid-free remission
- Health-related quality of life
- Work/school productivity

- Other patient-reported outcomes
- Use of rescue medication
- UC-related hospitalization
- Surgery
- Mortality

Safety

- Serious adverse events
- Adverse events leading to discontinuation
- Treatment-emergent adverse events
    - Infections
    - Headache
    - Nausea
    - Fatigue
    - Pain
    - Pharyngitis
    - Respiratory
    - Autoimmune
    - Demyelinating disease
    - Malignancy
    - Injection reactions
    - Development of neutralizing antibodies

Timing

Evidence on intervention efficacy, safety, and effectiveness was collected from studies testing treatments with at least six weeks' exposure duration.

Settings

Evidence from all relevant settings was considered, with a focus on outpatient settings as well as ambulatory and hospital-based settings.

1.3 Definitions

Clinical Outcome Measures

Outcomes of clinical trials of UC commonly include clinical response, clinical remission, and endoscopic improvement.

Clinical response is defined as a reduction of greater than or equal to 3 points and greater than or equal to 30% from the baseline in total Mayo Score (see definition below) along with a decrease in the rectal bleeding sub-score of greater than or equal to 1 point or an absolute rectal bleeding sub-score of less than or equal to 1 point.

Clinical remission is defined as a Mayo Score of less than or equal to 2 with no individual sub-score greater than 1.

Endoscopic improvement is defined as a Mayo endoscopic sub-score of 0 or 1.

Corticosteroid-free remission is defined as clinical remission in patients using oral corticosteroids at baseline who have discontinued corticosteroids and are in clinical remission at the end of the study.

Delayed response in clinical trials has been defined as clinical response and remission (via partial Mayo Score) achieved by the non-responders to induction therapy.

Mayo Score

The Mayo Score is a disease activity index developed for assessing the severity of UC. It comprises four sub-scores of 3 points each (stool frequency, rectal bleeding score, mucosal appearance at endoscopy, and physical global assessment). The higher the score (maximum 12 points), the more severe the UC. A Mayo Score between 6 and 12 classifies the disease as moderate-to-severe.

Pediatric Ulcerative Colitis Activity Index

The Pediatric Ulcerative Colitis Activity Index (PUCAI) is a disease activity index to assess the severity of UC in children. It is comprised of six sub-scores: abdominal pain, rectal bleeding, stool consistency of most stools, number of stools per 24 hours, nocturnal stools, and activity level. A PUCAI score of 35 to 64 is classified as moderate and 65 and above is classified as severe.

Inflammatory Bowel Disease Questionnaire

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a 32-item questionnaire the measures the overall health-related quality of life in patients with IBD. Scores range from 32 to 224, with higher scores indicating better health-related quality of life.[25] Although there is no minimal clinically

important difference (MCID) established for patients with UC, the MCID for patients living with Crohn's disease is an improvement of at least 16 points. In addition, data have shown that patients with Crohn's in remission generally have an IBDQ score of at least 170 points.[26] Trials in patients with UC have used the thresholds established in patients with Crohn's disease to measure the rates of meaningful improvements in IBDQ score.

Short Form Health Survey

The 36-item short form survey (also known as SF-36)[27] is a generic self-reporting tool to assess functional health and wellbeing. SF-36 consists of 36 questions aggregated across eight domains, namely, physical problems and physical functioning, social functioning, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health perceptions. It captures health-related quality of life with two components, a physical component summary (PCS) and mental component summary (MCS), providing global metrics for physical and mental health, respectively. SF-36 is scored from 0 to 100 and then using the mean scores (mean ± standard deviation [SD]) for the general US population (50±10), the norm-based summary component scores are constructed. Higher summary scores indicate better quality of life. The SF-36 MCID thresholds for clinically meaningful improvement for UC have not been established. However, based on the sample of the general population and Crohn's disease, the range of MCID estimates for the PCS and MCS are between 1.6 and 8.7.[28]

Work Productivity and Activity Impairment Questionnaire

The Work Productivity and Activity Impairment Questionnaire (WPAI) is a six-item questionnaire that collects information on both paid and unpaid work. It measures the impact of health problems on absenteeism, presenteeism, and unpaid activity over the past seven days.[29,30] The WPAI has been validated in several conditions, including IBD.[29,31] The scoring on the WPAI ranges from 0% (no impairment) to 100% (total loss of productivity), with a decrease in scores indicating improvement, and lower scores signifying little impact of disease on work and activity.

EuroQol-5 Dimensions

EuroQol-5 Dimensions (EQ-5D) is a generic three- or five-level tool to assess health-related quality of life.[32] EQ-5D is used to generate a health utility score that varies from 0 (death) to 1 (perfect health). The tool also includes a visual analogue scale (EQ-5D VAS) that varies from 0 to 100 (worst to best). The MCID for UC has not been established; however, EQ-5D VAS MCID estimates ranging from 4.2 to 14.8 have been reported for Crohn's disease.[28]

Biosimilar

The FDA defines a biosimilar as "a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product."[33]

1.4 Potential Cost-Saving Measures in Ulcerative Colitis

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by therapies for UC (e.g., reduced need for surgical colectomy), as these services will be captured in the economic model. Rather, we seek services used in the current management of UC beyond the potential offsets that arise from a new intervention.

During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with UC that could be reduced, eliminated, or made more efficient. The Crohn's and Colitis Foundation described repeated use of steroid therapy to be of low value given its potential for serious adverse effects. The Crohn's and Colitis Foundation also mentioned insurance-mandated step therapy, in which patients are required to try agents other than the one they or their clinician prefer, even if the use of that medication is contraindicated. Clinical expert input indicated that continued use of aminosalicylates in patients who have been failed by such therapy and escalated to use of TIMs is a pervasive and low-value intervention. Finally, patients may prefer a particular route of administration for therapy, and not taking this into account may reduce adherence to therapy. We also note that a Canadian version of the Choosing Wisely campaign for IBD has published a list of potential low-value services, including the use of steroids for maintenance of remission, prolonged use of IV steroids in the absence of clinical response, and the use of abdominal CT in the acute setting without suspicion of an IBD complication or non-IBD etiology.[34]

2. Patient Perspectives

2.1 Methods

From the beginning of this assessment, we sought input from patients, caregivers, and representatives from patient advocacy organizations on the research design of this review (i.e., the PICOTS framework; Population, Intervention, Comparators, Outcomes, Timing, and Setting). We also sought insight on the patient experience of UC and its treatment, including benefits of treatment that may not be described in the clinical literature, any broader potential other benefits or disadvantages associated with treatments, and contextual considerations related to UC, the details of which are reported in this section as well as in Section 6.

We received input on the patient and caregiver perspective from the national Crohn's and Colitis Foundation, which is both a patient advocacy organization and a major sponsor of IBD research. The Crohn's and Colitis Foundation is not responsible for the final content of ICER's report, and it should not be assumed that they support any part of the report, which is solely the work of the ICER team and affiliated researchers.

The Crohn's and Colitis Foundation provided input during the following contacts with ICER:

- Submission of a letter with both research considerations and patient/caregiver concerns during the open input period
- Conference call discussion with ICER research team during the scoping period
- Submission of a letter reacting to the posted draft scoping document
- Participation in ICER's preliminary model presentation, with both written and verbal feedback provided
- Submission of a letter reacting to the posted draft evidence report.

Initial input received informed the selection of the PICOTS elements of the review. For example, our focus on stratified results (e.g., biologic-naïve vs. experienced) rather than on overall intent-to-treat findings was informed in large part by a discussion of the heterogeneity of the patient experience and outcomes in the Crohn's and Colitis Foundation's open input letter. The Crohn's and Colitis Foundation was also instrumental in highlighting specific impacts of UC and its treatment on children and adolescents. During a conference call conducted prior to the posting of the draft scope, participants noted that there is much interest in understanding the most appropriate sequence of therapy for the moderate-to-severe patient, as unnecessary delays in effective treatment could have catastrophic effects in terms of hospitalization and requirement for surgical intervention. Many of these delays are felt to be caused by insurance-mandated step therapy, in which patients are required to step through one or two biologic treatments before a therapy of choice, even if they have previously been failed by treatments in the same class or have

contraindications to them. At the moment, however, there is little to no empiric data on appropriate sequencing to counteract these policies. The Crohn's and Colitis Foundation also highlighted the importance of EIMs in UC, which could include joint/arthritic symptoms, uveitis (painful inflammation of the middle layer of eye tissue), and lung complications.

The Crohn's and Colitis Foundation also responded to our draft scope with comments, and we revised the scope in response to this feedback. Specifically, we added subgroups of particular interest, including by age (in addition to pediatric patients, those ages 65 and older were felt to be of interest), presence of EIMs, and other comorbidities. We also added steroid-free remission as an outcome of interest and were advised to remove pain relief, given its inconsistent and variable collection. Finally, we added demyelinating disease as an adverse event of interest.

We received feedback after the preliminary model presentation suggesting three modifications to our planned approach:

- More than two switches between TIMs to better reflect clinical practice
- A scenario analysis in which infliximab is used in the second line after vedolizumab
- Allow the per-cycle rate of discontinuation to vary over time.

We considered these modifications, but we did not find empiric data with which to estimate them for the base-case analysis. However, we did conduct scenario analyses to address them, including a) evaluating the effect of shorter time horizons on model results, where two TIM switches would represent a more realistic expectation; b) allowing a lower discontinuation rate after one year for those remaining on therapy; and c) use of infliximab in the second line, assuming comparable efficacy for infliximab to that observed in biologic-naïve trials. We also reviewed a publication on the direct health care costs of IBD that was sponsored by the Crohn's and Colitis Foundation[7] for possible inclusion in the model, but opted to use an alternative source that stratified costs the presence of response and remission.

2.2 Impact on Patients

Several themes emerged from conversations and documents received. We have organized them into multiple sections, including heterogeneity in disease presentation; the benefits and risks of UC treatment; challenges of access to care; and gaps in current UC management.

Heterogeneity in Disease Presentation

As with many chronic diseases, the presentation of symptoms and disease course can vary substantially among patients. In some, the disease course may reflect periods of active disease and remission, while in others, the symptoms are persistent despite escalating medical therapy. A

minority of patients may present with a rapidly progressive form of the disease known as fulminant colitis.

UC may also manifest in different locations. In some patients, inflammation may be limited to the rectum ("ulcerative proctitis"), while in others, it may extend from the rectum to the splenic fixture ("left-sided colitis"), and still others may experience inflammation throughout the colon ("pancolitis"). As noted previously, children as young as five years of age or less may develop UC, with additional complications, such as growth failure and delayed puberty. In addition, there are noted but currently poorly understood differences in how racial and ethnic minorities experience UC. Those of Hispanic and Asian descent appear to present more commonly with the pancolonic form of disease. However, despite an estimate of approximately 700,000 minority individuals suffering from UC in the US, very little is known about the epidemiology and progression of disease in these groups. The Crohn's and Colitis Foundation is currently working with the US Centers for Disease Control on a longitudinal study to address these populations.

The clinical differences in disease presentation by severity as well as patient characteristics have profound impacts on those suffering with UC. Patients with long enough periods of remission may be able to resume normal work, school, or leisure activity, while others with more progressive disease require increasing levels of caregiver support. The presence of more severe disease among certain racial and ethnic minorities can exacerbate disparities in access to appropriate care that they may already experience generally.

Benefits and Risks of Ulcerative Colitis Treatment

Input from the Crohn's and Colitis Foundation reiterated that, regardless of presentation or symptoms, the goal of treatment for any UC patient should be sustained and durable steroid-free remission, along with appropriate psychosocial support, normal health-related quality of life, and prevention of morbidity, including hospitalization, surgery, and colorectal cancer. The Crohn's and Colitis Foundation recommends that patient-clinician conversations include preferences for certain medications and/or routes of administration, ability to adhere to a medication regimen, the impact of treatment on daily life, and the patient's expected out-of-pocket costs associated with medical and surgical treatment.

As with the disease itself, the Crohn's and Colitis Foundation mentioned that response to treatment is also heterogeneous. Treatments that are successful in some patients may not work for others, and patients frequently report loss of response, development of intolerable side effects, and the need to cycle off a medication. Patients may respond differently to the TNF inhibitors based on drug composition (e.g., mouse- vs. human-derived, possibly as a result of greater potential immunogenicity with the former) as well as clinical considerations (body mass index, disease severity). Some patients do not clinically respond to TNF inhibitor therapy while others develop immunogenicity to a specific agent; a switch outside of class may be indicated for the former, while

a switch in-class may be the best course of action for the latter. It is also possible that some patients may do well on combination biologic therapy, although this has not been extensively studied. The overall lack of information and evidence in this area is frustrating to patients as it potentially delays effective treatment, which may negatively impact various aspects of a patient's quality of life.

While all TIMs have side effects that patients must weigh when selecting treatment, the Crohn's and Colitis Foundation urged particular caution with regard to surgical intervention. We heard from multiple stakeholders that patients view surgery as a last-resort option. Though colectomy may be curative in some patients, there are long-term complications to consider, which may have substantial and distressing implications for a patient's quality of life and activities of daily living. Further, because UC is an immune-mediated condition, even after surgery, patients may still contend with devastating EIMs.

Up to 80% of patients report symptoms of pouchitis (inflammation of the lining of the pouch created during a colectomy), and up to 20% of these individuals will develop refractory or rapidly relapsing disease. Some patients receiving "J-pouch" surgery (creation of an internal pouch that eliminates the need for an external ostomy) have been later diagnosed with Crohn's disease in other parts of their intestines. The invasiveness of the procedure in conjunction with the potential for long-term complications is a significant source of fear and anxiety among patients living with UC. At the same time, there is also apprehension toward biologic use and its potential effects, which may further complicate how patients weigh these treatment options.

Access to Care Challenges

Several challenges with accessing appropriate care were noted by the Crohn's and Colitis Foundation. For one, requirements for complex treatment regimens may pose a challenge for physicians and, consequently, patients. Primary care providers and gastroenterologists without specific UC experience may not, for example, pursue inpatient treatment with cyclosporine for the patient with acute severe UC, or may not appreciate the broader benefits of psychosocial and dietary support for long-term care management.

The direct medical costs associated with managing UC are substantial. A recent analysis of the Optum Research Database commissioned by the Crohn's and Colitis Foundation found that annual management costs associated with IBD were nearly $23,000, or threefold higher than among a matched set of non-IBD controls.[7] Importantly, estimates of average annual patient out-of-pocket costs for these services and lost wages associated with UC were approximately $2,000 and $3,000, which may pose a substantial burden for some.[7] Costs are especially onerous for patients without insurance or those who are unable to work due to their disease. Reports suggest that out-of-pocket costs for UC diagnostic work-up alone exceed $4,000 in uninsured patients; even after receiving insurance, medication costs may exceed $350 per month.[35 36]

Finally, the Crohn's and Colitis Foundation reiterated patient concerns regarding step therapy and its various negative consequences. Patients are often undertreated if they are failed by multiple biologics, and by the time they gain access to a treatment subject to numerous step therapy protocols, their disease may have progressed considerably, limiting the efficacy of the drug. The Crohn's and Colitis Foundation referenced vedolizumab to further illustrate this issue. Vedolizumab is a gut-selective biologic agent that is recommended as a potential first-line treatment for both induction and maintenance in UC but is often not covered by insurance until failure by other treatment options. In some cases, patients must be failed by treatment with at least two TNF inhibitors before vedolizumab is considered, despite clinical evidence that they do not respond to this biologic class. Other insurance mechanisms may produce additional barriers and sources of stress for UC patients. For example, some UC treatments are covered as a medical benefit and others as a pharmacy benefit, with different criteria for treatment authorization and different expectations for patient financial contribution. Step therapy algorithms typically found in UC are not concordant with authoritative clinical guidelines (see Section 3) and are also not portable; individuals who switch health plans (or whose employer does) often must repeat earlier steps in the treatment algorithm even if those treatments were previously unsuccessful.

Step therapy requirements are exacerbated in the pediatric population, where many TIMs do not carry an FDA-approved indication for use in young patients. There is some evidence that pediatric patients present more frequently with aggressive forms of UC, so time is of the essence in providing effective treatment. Yet, many pediatric patients do not have access to the full range of UC treatments due to such requirements. These delays may cause irreversible impairments in growth and early requirements for surgical intervention, with its own set of consequences.

Gaps in Current Ulcerative Colitis Management

Finally, the Crohn's and Colitis Foundation noted major gaps in the current management of the disease, manifested primarily in a lack of high-quality evidence. There is a lack of head-to-head clinical trials of TIMs, for example, which limits the ability of patients and their families to make fully informed decisions about their treatment goals and desires. It is a source of frustration for the Crohn's and Colitis Foundation, patients, and clinicians that the one large head-to-head trial that is available—one that demonstrated vedolizumab's superiority to adalimumab—has not resulted in any appreciable change in insurer coverage policy. Moreover, there is a general need for more comparative effectiveness research given the plethora of drug classes, mechanisms of action, routes of administration, and safety profiles now available.

As mentioned previously, UC management is increasingly involving shared decision-making between the patient and clinician. Evidence generated from Crohn's and Colitis Foundation-sponsored focus groups suggested room for improvement, as many patients reported that initial therapy was prescribed without discussion or consultation.[37] These same patients, however,

reported that they were able to bring their own research and preferences into discussions at subsequent visits, suggesting that treatment should be highly individualized and integrated into a shared decision-making process. That said, there are some clear factors that influence patient-provider decisions, such as the presence of heart failure or a history of melanoma (contraindications to TNF inhibitors)[37] as well as expected time to clinical response.

It was also noted that patient participants in Crohn's and Colitis Foundation-sponsored focus groups voiced concern with UC symptoms not routinely collected in clinical trials, which tend to focus on stool frequency and rectal bleeding. Beyond these, patients also reported concerns with pain and fatigue, ability to concentrate, and fecal urgency. Further, patients also experience challenges with interpersonal relationships and educational and career goals due to the impact of the disease on activities of daily living. Relatedly, patients often face difficulty when sharing the experience of UC symptoms with friends, family, and colleagues, which may lead to feelings of isolation.

Finally, both the Crohn's and Colitis Foundation and others have noted that management of pain and its sequelae is a major challenge for patients with UC and Crohn's disease. A recent cross-sectional study of nearly 300 patients with IBD (~40% of whom had UC) found that 40% of respondents met criteria for chronic pain and nearly 20% reported opioid use.[38] A number of psychosocial factors were associated with greater pain severity, including depression, anxiety, and reduced self-efficacy.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

We reviewed the Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) Database for US commercial health plan coverage policies for adalimumab, golimumab, infliximab, infliximab-dyyb, infliximab-abda, tofacitinib, ustekinumab, and vedolizumab. Developed by the Center for Evaluation of Value and Risk in Health, the SPEC database features data from more than 290 specialty drugs, more than 175 disease areas, and more than 25,000 decisions from 17 of the largest US national and regional commercial payers: Aetna, Anthem, Blue Cross Blue Shield (BCBS) of Florida (FL), Massachusetts (MA), Michigan (MI), North Carolina (NC), New Jersey (NJ), and Tennessee (TN), CareFirst, Centene, Cigna, Emblem, Health Care Service Corporation (HCSC), Highmark, Humana, Independence Blue Cross (IndepBC), and UnitedHealthcare (UHC).

We also searched for National or Local Coverage Determinations (NCDs or LCDs) from the Centers for Medicare and Medicaid Services (CMS) and from the California Department of Health Care Services. We located two NCDs that describe indications and limitations of coverage for fecal occult blood tests (Record 190.34) and colorectal cancer screening (Record 210.3). In addition, we located five LCDs pertaining to diagnostic and therapeutic colonoscopy (Record L34213), diagnostic colonoscopy and sigmoidoscopy (Record L34614), and Prometheus IBD sgi Diagnostic® test (L37299/L37539).[39-44]

Table 3.1 on the following page summarizes the benefit designs for representative commercial payers. We were unable to locate publicly available coverage policies for adalimumab from BCBSNJ, BCBSTN, Emblem, or HCSB; for golimumab from BCBSNJ, BCBSTN, and Emblem; for tofacitinib from BCBSNJ, BCBSTN, CareFirst, Emblem, HCSC, and Highmark; and for ustekinumab from Aetna, BCBSFL, BCBSTN, CareFirst, Cigna, HCSC, IndepBC, and UHC due to its recent approval. As a note, all therapies except ustekinumab and vedolizumab are approved by the FDA as second-line treatments. The TNF inhibitors are indicated as per the FDA label after inadequate response to conventional therapy and tofacitinib is indicated as per the FDA label following an inadequate response to a TNF inhibitor. Lastly, we do not report several percentages for tofacitinib and vedolizumab because the FDA recently changed the labeled indications of these drugs, and most coverage policies have not yet been updated.

Table 3.1. Benefit Design for Treating Moderate-to-Severe UC across Representative Commercial Payers

			Step Edits After First-Line Therapy				
	% of Plans Excluding Drug from Coverage	% of Plans with Coverage Criteria More Restrictive than FDA Label	0	1	2	3+	% of Plans with Prescriber Restrictions
Adalimumab	0%	25%	83%	8%	8%	0%	25%
Golimumab	0%	43%	43%	43%	14%	0%	21%
Infliximab	0%	24%	71%	18%	12%	0%	18%
Infliximab-dyyb	0%	59%	29%	47%	24%	0%	18%
Infliximab-abda	0%	65%	24%	53%	18%	6%	18%
Tofacitinib	0%	--	--	--	--	--	27%
			Step Edits Imposed by Payer				
			1	2		3	
Ustekinumab	0%	100%	75%	13%		13%	38%
Vedolizumab	0%	--	--	--		--	--

FDA: Food and Drug Administration, IL: interleukin, JAK: Janus kinase, TNF: tumor necrosis factor

Adalimumab

Twelve out of the 17 payers surveyed have publicly available coverage policies for adalimumab. Only a quarter of payers list policies more restrictive than the FDA label. All plans surveyed require a documented diagnosis of moderate-to-severe UC, and all payers list an age restriction consistent with the FDA label (18 years of age or older). Out of all the drugs surveyed, plans overall have the least number of step edits required for access to adalimumab after failure by conventional therapy (83%). The most common step therapy requirement is a trial of multiple conventional therapies, such as corticosteroids, aminosalicylates, and thiopurines.[45]

Golimumab

Of the 17 commercial payers surveyed, 14 companies have publicly available coverage policies for golimumab. All plans surveyed require a documented diagnosis of moderate-to-severe UC, and all payers list an age restriction consistent with the FDA label (18 years of age or older). Compared to the other TNF inhibitors (adalimumab and infliximab), more plans have coverage criteria that is narrower than the FDA label (24-25% vs. 43%, respectively), and a larger number of plans necessitate additional step edits following failure by conventional therapy. Several plans require a trial with adalimumab or tofacitinib before accessing golimumab, while others require trials with multiple conventional therapies.[45]

Infliximab

All 17 payers surveyed have issued coverage policies for infliximab. As noted in the table above, less than a quarter of payers have coverage policies that are more restrictive than the FDA label. All plans surveyed require a documented diagnosis of moderate-to-severe UC. Because infliximab is the only TIM approved in pediatric patients in addition to adults, most plans specify that the patient must be six years of age or older to receive treatment. Similar to adalimumab, most patients are able to access infliximab following failure by conventional treatment with no additional step edits, but some payers require that patients try at least two conventional agents, such as corticosteroids, aminosalicylates, and thiopurines.[45]

Infliximab-dyyb and Infliximab-abda

Most commercial payers surveyed maintain differing coverage criteria for accessing infliximab versus its biosimilars. Compared to infliximab, plans generally have much *more* restrictive coverage conditions for the biosimilars. A larger set of plans require additional step edits (in contrast to the FDA label) in order to access either infliximab-dyyb or infliximab-abda. Most commonly, plans necessitate that patients undergo a trial with infliximab first. Only five of the 17 payers surveyed have coverage policies equivalent to the labeled indication of infliximab-dyyb, and even fewer for infliximab-abda. The most restrictive plan requires that patients seeking infliximab-abda are 1) refractory to or require continuous immunosuppression with high-dose corticosteroids, 2) inadequate responders to aminosalicylates, 3) inadequate responders to thiopurines, 4) inadequate responders to infliximab and infliximab-dyyb, and 5) inadequate responders to additional preferred alternatives, including vedolizumab, golimumab, or tofacitinib.[45,46]

Tofacitinib

Eleven out of the 17 plans surveyed have issued coverage policies for tofacitinib, the only small-molecule drug under review. As noted above, we do not report several percentages because the labeled indication recently changed, and most plans have not yet updated their policies. Currently, according to the FDA label, in order to access tofacitinib, patients must demonstrate an inadequate response or intolerance to a TNF inhibitor. Previously, as indicated in the 2018 FDA label, patients did not have to step through a TNF inhibitor to access tofacitinib.[45,47]

Ustekinumab

Ustekinumab was approved for the treatment of patients with moderate-to-severe UC in October 2019. Currently, ustekinumab has an FDA indication for first-line treatment (i.e., prior to conventional therapy). However, all plans surveyed list coverage criteria narrower than the FDA label; 75% of plans surveyed, require that patients try and be failed by one treatment (either a conventional agent or a TNF inhibitor) before utilizing ustekinumab. A small percentage of plans

(13%) require three step edits; the most restrictive plan requires that patients demonstrate an inadequate response or intolerance to at least two conventional agents and one preferred drug (adalimumab) before accessing ustekinumab.[45]

Vedolizumab

The labeled indication of vedolizumab was changed on March 31, 2020. Previously, in order to access vedolizumab, patients had to first step through a TNF inhibitor. As of the publication of this report, vedolizumab is indicated as a first-line treatment. We surveyed the five largest commercial payers and currently only Aetna and UHC have updated their polices since March 31, 2020; Cigna, Anthem, and Humana have not.

Although Aetna and UHC have issued new policies since the label change, neither explicitly allow for first-line use. Aetna considers vedolizumab medically necessary for patients who have either 1) previously received the treatment or any other biologic or tofacitinib or, 2) were failed by at least one conventional therapy option.[48] UHC requires a history of failure, contraindication, or intolerance to TNF inhibitors, azathioprine or mercaptopurine, or corticosteroids.[49]

3.2 Clinical Guidelines

Below, we review clinical guidelines pertaining to UC from the American Gastrological Association (AGA), the American College of Gastroenterology (ACG), the Toronto Consensus, and National Institute for Health and Care Excellence (NICE). Though all four guidelines contain recommendations for patients with mildly active and acute UC, the summaries below include recommendations targeted only toward non-hospitalized, chronic patients with moderate-to-severe UC.

American Gastrological Association Clinical Practice Guidelines on the Management of Moderate-to-Severe Ulcerative Colitis (2020)[50]

The AGA released its clinical practice guidelines for the treatment of moderate-to-severe UC in January 2020. According to the AGA, "moderate-to-severe disease" refers to patients who are dependent on or refractory to systemic corticosteroids, have severe endoscopic disease activity (including the presence of ulcers), or at high risk of colectomy. For such patients, the AGA recommends the use of adalimumab, golimumab, infliximab, tofacitinib, ustekinumab, or vedolizumab over no treatment due to clinical trial results that demonstrate the superiority of TIMs over placebo. Due to the increased risk of pulmonary embolism and all-cause mortality, the AGA notes that the recommended induction dose of tofacitinib is 10 mg twice daily for eight weeks, and for maintenance, 5 mg twice daily.

The AGA's guidance is further stratified by a patient's previous experience with biologics. In patients who are naïve to biologics, infliximab or vedolizumab is recommended over adalimumab for induction of remission. However, adalimumab may be preferred in patients with less severe disease or those who favor self-administration. For patients with previous experience with infliximab, the AGA recommends ustekinumab or tofacitinib (rather than vedolizumab or adalimumab) for induction, especially for patients with primary nonresponse to infliximab. The AGA recommends that all patients with moderate-to-severe UC combine TNF inhibitors, vedolizumab, or ustekinumab with thiopurines or methotrexate, as opposed to biologic monotherapy or thiopurine monotherapy. Lastly, the AGA recommends the early use of biologics rather than step therapy with aminosalicylates, which may delay effective treatment in patients at high risk of complications, hospitalization, and colectomy.

American College of Gastroenterology Clinical Guideline: Ulcerative Colitis in Adults (2019)[51]

The ACG published its clinical guidelines for the treatment of UC in adults in 2019. After a diagnosis of UC is determined, the ACG recommends treating patients with a treat-to-target approach to achieve endoscopic improvement, which is most likely to produce steroid-free remission and prevent hospitalizations and colectomy. Treatment begins with induction, and the ACG outlines several recommendations for treatment split by induction and maintenance.

Induction of Remission

The ACG offers numerous recommendations for the management of moderately-to-severely active UC. Major recommendations are summarized below:

- For induction of remission in moderately-to-severely active UC, the ACG recommends oral systemic corticosteroids, TNF inhibitors (adalimumab, golimumab, or infliximab), vedolizumab, or tofacitinib
- For patients who achieved induction of remission using infliximab, the ACG recommends the addition of a thiopurine for added clinical efficacy
- The ACG recommends the use of vedolizumab or tofacitinib for induction of remission
- For patients who have been previously failed by a TNF inhibitor, vedolizumab is recommended for induction of remission.

The ACG does not offer specific recommendations concerning sequencing of treatment as head-to-head data is limited. However, it is noted that higher rates of remission and lower rates of corticosteroid usage have been observed with infliximab compared to adalimumab. In addition, adalimumab has been associated with higher rates of all-cause and UC-related hospitalizations compared to other TNF inhibitors.

In addition, the ACG acknowledges that the use of treatments with fewer systemic effects (i.e., vedolizumab) in UC is an emerging clinical practice. Vedolizumab may be preferable for some patient populations, such as older patients who may have a higher risk of infection. In contrast, for patients with several EIMs, systemic therapies may be preferred. Overall, decisions regarding which therapy to use to achieve initial remission should be made by the patient and clinician and should be based on prognostic factors, disease extent and severity, and EIMs among other factors important to the patient.

Maintenance of Remission

Once induction of remission is achieved, patients and providers must work to maintain it. The ACG offers guidance based on how initial remission was achieved. Please see below for major recommendations:

- Systemic corticosteroids are not recommended for maintenance of remission
- Patients who achieved induction with a TNF inhibitor (adalimumab, golimumab, infliximab) should continue to use a TNF inhibitor as maintenance therapy
- Patients who achieved induction of remission with vedolizumab should continue to use vedolizumab as maintenance therapy
- Patients who achieved induction of remission with tofacitinib should continue to use tofacitinib as maintenance therapy.

Clinical Practice Guidelines for the Medical Management of Non-Hospitalized Ulcerative Colitis: The Toronto Consensus (2015)[52]

The Toronto Consensus was released in 2015 and provides guidance for the medical management of patients with moderate-to-severe UC. Of note, the Toronto Consensus was published before Health Canada's approval of tofacitinib for UC,[53] and as such, the guidelines focus primarily on the TNF inhibitors and vedolizumab.

Following a diagnosis of moderate or severe UC, the Toronto Consensus recommends oral corticosteroids as first-line therapy to induce remission. The guidelines advise against thiopurines or methotrexate for induction. Once a patient has achieved remission, the guidelines recommend against the continued use of oral corticosteroids to maintain remission.

If a patient presents with a contraindication to corticosteroids, TNF inhibitors or vedolizumab may be considered as first-line to induce remission and should be combined with thiopurines or methotrexate. Because there are no head-to-head trials among the TNF inhibitors, the guidelines do not offer guidance on which TNF inhibitor to choose. After TNF inhibitor induction therapy, patients should be evaluated at eight to 12 weeks to determine response. If a patient is responding to a TNF inhibitor, the patient should begin maintenance therapy using the same TNF inhibitor used

for induction. In patients with a suboptimal response to TNF inhibitors, the guidelines recommend dose escalation, and if a patient loses response to TNF inhibitor maintenance, the guidelines recommend dose optimization informed by drug monitoring. If patients are ultimately failed by a TNF inhibitor, the guidelines recommend a switch to vedolizumab over a switch to a different TNF inhibitor. Patients on vedolizumab should be assessed between eight and 14 weeks and should continue vedolizumab for maintenance therapy if they demonstrate response.

National Institute for Health and Care Excellence – Ulcerative Colitis: Management[54]

NICE recommends the use of adalimumab, golimumab (only if the manufacturer provides the 100 mg dose at the same cost as the 50 mg dose), and infliximab in patients with moderate-to-severe UC whose disease has not responded adequately to conventional therapy (i.e., corticosteroids, mercaptopurine, azathioprine) or who present with contraindications to conventional therapy. Because there are no head-to-head trials among the TNF inhibitors, NICE recommends that the choice of treatment be made on an individual basis following discussions between the clinician and patient. The choice of treatment should account for therapeutic need and issues of adherence, and if more than one treatment is appropriate, the least costly option should be selected. All three TNF inhibitors should be given as a planned course of therapy until treatment fails or until 12 months after beginning treatment. Clinical symptoms, biological markers, and results from an endoscopy are key to assessment at 12 months to determine whether a patient should continue treatment. If a patient is in remission, the clinician may discuss halting treatment, but should be easily able to resume if the patient relapses.[55]

NICE recommends vedolizumab in patients with moderate-to-severe UC only if the manufacturer provides the treatment with the agreed discount. If the discount is honored, NICE recommends that vedolizumab be used until it stops working or surgery becomes indicated. Similar to the TNF inhibitors, NICE recommends assessment at 12 months following the start of treatment to determine whether treatment should continue. If patients are in complete remission, the clinician may consider stopping treatment, but should resume if the patient relapses.[56]

Lastly, NICE recommends tofacitinib in patients with moderate-to-severe UC if conventional therapy or a biologic agent cannot be tolerated or if the disease has not responded adequately to prior treatment. Similar to vedolizumab, tofacitinib is only recommended if the manufacturer honors the agreed discount.[57]

4. Comparative Clinical Effectiveness

4.1 Overview

To inform the analysis of the comparative clinical effectiveness of TIMs for moderate-to-severe UC, we systematically reviewed and synthesized existing evidence from available clinical studies. Full PICOTS criteria are described in Section 1.2. The drugs and regimens of interest for this review are included in Table 1.1 in Section 1.

In this review, we compared the efficacy, safety, and effectiveness of TIMs (adalimumab, golimumab, infliximab, tofacitinib, ustekinumab, and vedolizumab [IV]) to ongoing background conventional therapy (i.e., placebo arms of clinical trials) and to each other. Our review focused on the clinical benefits important to patients living with UC as well as potential harms. We sought evidence on all outcomes listed in Section 1. The methods and findings of our review of the clinical evidence are described in the sections that follow.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on TIMs for moderate-to-severe UC followed established best research methods.[59,60] The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[61] These guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE and EMBASE for relevant studies through July 2020. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described previously. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE) as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, 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-2/grey-literature-

policy/). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer-review.org/use-of-in-confidence-data/).

Study Selection

After removal of duplicate citations, references went through two levels of screening at both the abstract and full-text levels. Three reviewers independently screened the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada) and disagreements were resolved through consensus. Studies that did not meet PICOTS criteria were excluded.

We included evidence from RCTs and high-quality comparative observational studies, where available (see below for details on quality assessment). Single-arm studies and early clinical phase development studies (i.e., Phase I), were excluded. Further, abstracts that report duplicate data available in the published articles or results from observational studies presented in conference abstracts with insufficient information to evaluate methodological quality were excluded. Only studies that evaluated an FDA-approved dose were included; however, we also included treatment arms with higher dosing levels given the potential for dose escalation in UC. Finally, while concomitant use of conventional systemic agents (e.g., aminosalicylates, thiopurines) was permitted in available trials, we excluded any trial that randomized patients to treatment with TIMs in combination with other agents, given our focus on the incremental benefits of TIM therapy.[62]

Data Extraction and Quality Assessment

Two reviewers extracted data into evidence tables. Extracted data were verified by another researcher. Elements include study name, study year, study design, phase of the trial, study inclusion and exclusion criteria, description of patient populations, sample size, duration of follow-up, funding source, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and quality assessment for each study. The report utilized the criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[63] For more information on data extraction and quality assessment, refer to Appendix D.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[64]

Assessment of Bias

As a part of quality assessment, we examined the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, ClinicalTrials.gov was scanned to identify studies completed more than two years ago. Studies that met the inclusion criteria, and for which no findings have been published or presented publicly, were selected. We found no evidence of publication bias. However, we identified a Phase III RCT (NCT01551290) for infliximab in Chinese patients sponsored by Xian-Janssen that was completed in November 2014; results are only available from a clinical trial report linked to the ClinicalTrials.gov page and have not been published in a peer-reviewed journal.

Data Synthesis and Statistical Analyses

Data for the available comparisons of TIMs for the FDA-approved dose or higher were abstracted in evidence tables (see Appendix D) and synthesized in the text on the following pages. In addition, comparative efficacy of TIMs for patients living with moderate-to-severe UC was assessed by means of NMA, where feasible. Trials that were deemed sufficiently similar in terms of population, intervention type, duration, and outcome definitions were included in the NMAs. Below, we briefly summarize the characteristics of our NMAs. Appendix F contains a more detailed description of the NMA methods.

NMAs focused on clinical efficacy outcomes, including clinical response, clinical remission, and endoscopic improvement, were conducted. Given the expected differences in the clinical efficacy of treatment in patients with and without prior biologic exposure, separate networks were developed for biologic-naïve and biologic-experienced populations. In addition, outcomes were analyzed separately for the induction phase (six to 14 weeks) and maintenance phase (52-60 weeks). Clinical response and remission were analyzed in both induction and maintenance phases. Endoscopic improvement was analyzed only during the induction phase due to limited data availability and trial design differences.

The evidence base of the included trials in the maintenance phase is a combination of "treat-through" designs, where patients were randomized at baseline and followed through until the end of maintenance, and "re-randomized" designs, where responders to treatment from one or two induction trials were re-randomized in the maintenance phase. The re-randomized trials report clinical response and remission at the end of maintenance among induction responders. In order to analyze all trials in a comparable fashion in a single network, results from treat-through trials were adjusted to more closely resemble results from re-randomized trials.

Data were available for all TIMs (adalimumab, golimumab, infliximab, tofacitinib, ustekinumab, and vedolizumab) in the biologic-naïve population. However, it was noted that the use of tofacitinib is no longer feasible in a biologic-naïve population based on an FDA-enforced label change (July 2019) that now requires that tofacitinib use be reserved for "…patients who have failed or do not tolerate tumor necrosis factor (TNF) blockers."[65] Based on this information, tofacitinib was not included in the NMAs for induction or maintenance outcomes within the biologic-naïve population. Data were available for adalimumab, tofacitinib, ustekinumab, and vedolizumab in the biologic-experienced population; data were not available for golimumab or infliximab, so we were unable to generate comparative efficacy estimates for these drugs.

The population of focus for this review included patients with moderate-to-severe UC who had inadequate response to conventional treatment. Despite this relatively narrow definition, trial populations may differ in terms of prior conventional therapies used, other demographic or clinical risk factors, timing of trial assessments, and other concerns. Adjusting for placebo response in an NMA design is frequently performed as means of controlling for differences in population characteristics and baseline risk; we considered placebo adjustment in situations where a) model fit and convergence was not compromised; and b) inclusion of such an adjustment materially changed model findings.

While different doses of some of TIMs were studied in available trials, we found no statistically significant differences in rates of key response or remission outcomes between doses in any relevant trial, so these data were pooled at the drug level for our primary NMAs. Additionally, we included trials conducted exclusively in Asian populations in our primary NMAs. To explore the impact of these characteristics on our results, we conducted two sensitivity analyses: 1) using unpooled doses for relevant TIMs; and 2) restricting included trials to those that enrolled subjects from multiple countries. Results from these analyses were generally consistent with the primary results (see Appendix F for more details).

All NMAs were conducted in a Bayesian framework using either the gemtc or R2jags package in R.[66,67]

4.3 Results

Study Selection

Our literature review search identified a total of 6,836 potentially relevant references. We included 53 references, of which 42 related to 19 unique RCTs in adults,[8,9,68-106] two references related to one RCT and one observational study in children,[107,108] and nine references related to nine high-quality comparative observational studies in adults.[109-117] The primary reasons for study exclusion were that the intervention or comparators used were outside the scope of this review, another study population was of focus (e.g., patients with mild-to-moderate UC), the study design was non-

comparative, or conference abstracts reported duplicative data to the full publications. In the results that follow, we focus on the comparative efficacy and safety of TIMs in the adult population; the RCT conducted in children is described later under Special Populations.

Of the 19 included trials in the adult population, one trial was a head-to-head trial comparing vedolizumab and adalimumab (VARSITY), and the other trials were placebo controlled. The trials enrolled patients with moderate-to-severe UC (Mayo Score ≥6 with an endoscopic sub-score ≥2) whose disease had not responded to conventional systemic agents. The trials assessed disease severity using the Mayo Score at the end of induction (week six to 14) or at the end of maintenance (week 52-60), or both. Although we preferred the use of the total Mayo Score to measure disease severity, we use data based on the partial Mayo Score (i.e., all components except the endoscopic sub-score) if data based on the total Mayo Score were not available. Use of conventional systemic agents (e.g., azathioprine, aminosalicylates) was permitted alongside active and placebo therapy in all trials, although we note substantial variation in levels of utilization of conventional treatments across trials. For example, baseline corticosteroid use ranged from 40-65% across trials, and immunomodulator use from 12-44%; in certain trials, detailed use of conventional treatments at baseline was not reported. Across the trials, the demographic and clinical characteristics of trial populations were broadly similar. Overall, the included trials were comparable with respect to age (range: 34-43 years) and disease severity as measured by the Mayo Score (range: 8.0-9.1). However, there was some variation in the disease duration across trials, ranging from 3.7 to 8.3 years (see Table 4.1). Trials excluded patients who had been diagnosed with Crohn's disease, severe or extensive colitis requiring colectomy, and with a history of malignancy. Additional details of included references and their study characteristics have been summarized in Appendix D, and the trials included in the review are summarized in Table 4.1 on the following page.

Table 4.1. Study Design and Baseline Characteristics of Included RCTs[8,9,68,77,79-81,86,90,93-96,99,101]

Trial (IND/MAINT Timepoints) TT or RR*	Naïve (%) Exp (%)	Randomized Treatment Arms† (n)		Mean Baseline Characteristics			Primary Endpoint**	Inclusion in Response/ Remission NMA§
		Induction	Maintenance	Age	Disease Duration	Mayo Score		
Head-to-Head								
VARSITY (14/52 Weeks), TT	Naïve (79%) Exp (21%)	1) VEDO 300 mg (n=383) 2) ADA 160/80 mg (n=386)	1) VEDO 300 mg q8w (n=383) 2) ADA 40 mg (n=386)	40.6	6.8	8.7	Remission at week 52	IND MAINT
Adalimumab								
ULTRA 1 (8 Weeks)	Naïve (100%)	1) ADA 160/80 mg (n=130) 2) Placebo (n=130)	--	37.8‡	6.1‡	8.8	Remission at week 8	IND
ULTRA 2 (8/52 Weeks), TT	Naïve (60%) Exp (40%)	1) ADA 160/80 mg (n=248) 2) Placebo (n=246)	1) ADA 40 mg (n=248) 2) Placebo (n=246)	40.4	8.3	8.9	Remission at week 8 and at week 52	IND MAINT
Suzuki 2014 (8/52 Weeks), TT	Naïve (100%)	1) ADA 160/80 mg (n=87) 2) Placebo (n=96)	1) ADA 40 mg (n=177) 2) Placebo (n=96)	42.7	7.9	8.5	Not specified	IND§
Golimumab								
PURSUIT-SC (6 Weeks)	Naïve (100%)	1) GOL 200/100 mg (n=294) 2) GOL 400/200 mg (n=298) 3) Placebo (n=292)	--	40.0	6.3	8.5	Response at week 6	IND
PURSUIT-M (54 Weeks), RR	Naïve (100%)	--	1) GOL 100 mg (n=154) 2) Placebo (n=156)	40.2	7.0	8.3	Response through week 54	MAINT
PURSUIT-J (54 Weeks), RR	Naïve (100%)	--	1) GOL 100 mg (n=32) 2) Placebo (n=31)	41.1	5.5‡	8.0‡	Response through week 54	--§
Infliximab								
ACT 1 (8/54 Weeks), TT	Naïve (100%)	1) IFX 5 mg/kg (n=121) 2) IFX 10 mg/kg (n=122) 3) Placebo (n=121)	1) IFX 5 mg/kg (n=121) 2) IFX 10 mg/kg (n=122) 3) Placebo (n=121)	41.8	6.8	8.4	Response at week 8	IND MAINT

Trial (IND/MAINT Timepoints) TT or RR*	Naïve (%) Exp (%)	Randomized Treatment Arms† (n)		Mean Baseline Characteristics			Primary Endpoint**	Inclusion in Response/ Remission NMA§
		Induction	Maintenance	Age	Disease Duration	Mayo Score		
ACT 2 (8/30 Weeks), TT	Naïve (100%)	1) IFX 5 mg/kg (n=121) 2) IFX 10 mg/kg (n=120) 3) Placebo (n=123)	1) IFX 5 mg/kg (n=121) 2) IFX 10 mg/kg (n=120) 3) Placebo (n=123)	40.0	6.6	8.4	Response at week 8	IND§
Kobayashi 2016 (8/30 Weeks), TT	Naïve (100%)	1) IFX 5 mg/kg (n=104) 2) Placebo (n=104)	1) IFX 5 mg/kg (n=73) 2) Placebo (n=72)	38.9	7.6	8.6	Response at week 8	IND§
Jiang 2015 (8/30 Weeks), TT	Naïve (100%)	1) IFX 5 mg/kg (n=41) 2) Placebo (n=41)	1) IFX 5 mg/kg (n=41) 2) Placebo (n=41)	34.4	4.4	NR	Response at week 8	IND§
NCT01551290 (8/26 Weeks), TT	Naïve (100%)	1) IFX 5 mg/kg (n=49) 2) Placebo (n=50)	1) IFX 5 mg/kg (n=50) 2) Placebo (n=49)	37‡	3.7‡	8‡	Response at week 8	--§
Tofacitinib								
OCTAVE 1 (8 Weeks)	Naïve (47%) Exp (53%)	1) TOF 10 mg (n=476) 2) Placebo (n=122)	--	41.6	6.3‡	9.1	Remission at week 8	IND
OCTAVE 2 (8 Weeks)	Naïve (45%) Exp (55%)	1) TOF 10 mg (n=476) 2) Placebo (n=112)	--	40.8	6.1‡	9.0	Remission at week 8	IND
OCTAVE SUSTAIN (52 Weeks), RR	Naïve (52%) Exp (48%)	--	1) TOF 5 mg (n=198) 2) TOF 10 mg (n=197) 3) Placebo (n=198)	42.7	6.8‡	NR¤	Remission at week 52	MAINT
Ustekinumab								
UNIFI (8/52 Weeks), RR	Naïve (49%) Exp (51%)	1) UST 6 mg/kg (n=322) 2) Placebo (n=319)	1) UST 90 mg q8w (n=176) 2) Placebo (n=175)	41.7	8.1	8.9	Remission at week 8 and at week 52	IND MAINT
Vedolizumab								
GEMINI 1 (6/52 Weeks), RR	Naïve (52%) Exp (48%)	1) VEDO 300 mg (n=225) 2) Placebo (n=149)	1) VEDO 300 mg q8w (n=122) 2) VEDO 300 mg q4w (n=125) 3) Placebo (n=126)	40.3	6.9	8.6	Response at week 6 and at week 52	IND MAINT

Trial (IND/MAINT Timepoints) TT or RR*	Naïve (%) Exp (%)	Randomized Treatment Arms† (n)		Mean Baseline Characteristics			Primary Endpoint**	Inclusion in Response/ Remission NMA§
		Induction	Maintenance	Age	Disease Duration	Mayo Score		
Motoya 2019 (10/60 Weeks), RR	Naïve (49%) Exp (51%)	1) VEDO 300 mg (n=164) 2) Placebo (n=82)	1) VEDO 300 mg q8w (n=41) 2) Placebo (n=42)	42.9	8.3	8.2	Response at week 10 and remission at week 60	IND MAINT
VISIBLE 1†† (6/52 Weeks), RR	Naïve (61%) Exp (39%)	--	1) VEDO 300 mg q8w (n=54) 2) Placebo (n=56)	39.3	7.9	9.0‡	Remission at week 52	MAINT

ADA: adalimumab, GOL: golimumab, Exp: experienced, IFX: infliximab, IND: induction, kg: kilogram, MAINT: maintenance, M week: maintenance week, mg: milligram, N: total number, n: number, q4w: every 4 weeks, q8w: every 8 weeks, PBO: placebo, RR: re-randomized, TOF: tofacitinib, TT: treat-through, UST: ustekinumab, VEDO: vedolizumab

*Treat-through or re-randomized design for trials with maintenance phases.

†Only including randomized treatment arms of FDA-approved dosing or higher.

‡Median reported.

§Refer to Appendix F for more details on reasons for exclusion from induction or maintenance NMAs.

¤The mean Mayo Score at the start of treatment was not reported; however, the mean Mayo Score at beginning of the maintenance phase was reported (3.3).

**Response and remission based on the Mayo Score.

††In our review, we only include evidence from the IV vedolizumab arm and not the subcutaneous vedolizumab arm.

Quality of Individual Studies

We used the USPSTF criteria to rate the quality of the included RCTs (see Appendix D). The RCTs were rated "good" or "fair." Of note, we did not rate the one trial of infliximab that was only available in grey literature (NCT01551290) and this trial was not included in our NMA. Generally, good, and fair quality trials had comparable groups at baseline, clear definitions of outcomes and interventions, and valid outcome measurements. For efficacy endpoints, most RCTs performed intent-to-treat analysis while some performed modified intent-to-treat analysis; additionally, most RCTs employed appropriate methods to handle missing data (e.g., non-responder imputation for response and remission). Randomized patients who received at least one dose of the study drug were evaluated for safety endpoints.

Furthermore, we noted that some trials had imbalances across arms in certain baseline characteristics, which may have affected findings. Specifically, Motoya and colleagues noted imbalances in key disease characteristics that could have led to unusually high placebo response rates, specifically in the biologic-experienced group.[9] Additionally, we noted that across the trials, the rates of trial and treatment discontinuation were generally high; in some trials, the rates were uneven, which may have affected results. Also, in the re-randomized trials, patients randomized to placebo in the maintenance phase had already received active treatment. This could have potentially resulted in unblinding to maintenance treatment among patients, although we note that the primary measures of effectiveness in this review were objective in nature and unlikely to be materially affected by patient unblinding.

Quality of the Network Meta-Analysis Evidence Base

Generally, the trials were comparable in terms of populations studied and outcomes measured. However, we did note some differences across trials. First, the trials conducted in a "mixed" population used different criteria regarding prior exposure to biologics to define their strata when reporting subgroup results. Some trials defined subgroups by prior use of a biologic (e.g., "biologic-naïve" and "biologic-experienced"), while the other trials defined subgroups by prior failure by a biologic (e.g., "biologic-failure" and "biologic non-failure"). Throughout our review, we refer to the populations across the trials as "biologic-naïve" and "biologic-experienced"; however, it should be noted that differences in how the populations were defined could potentially affect findings.

Further, the clinical efficacy outcomes of response and remission were generally defined comparably across trials (see Section 1) with a few exceptions. Importantly, for the head-to-head VARSITY trial, the rate of response at the end of maintenance used in our NMA was based on the partial Mayo Score (including all components except the endoscopic sub-score) and not the total Mayo Score. This may lead to higher effect sizes relative to total Mayo results and possibly biased estimates of treatment effect. Secondly, the OCTAVE trials used a stricter definition of clinical remission compared to other trials by requiring the rectal bleeding score to be 0 (rather than 0 or 1)

in addition to the other criteria. Moreover, while most trials used a local endoscopy reading, the OCTAVE trials used a centralized system.[96] Lastly, the adalimumab trials used the worst rank method to measure Mayo Scores (i.e., taking the highest score in a three-day period) as opposed to using an average of the scores for their primary and key secondary endpoints, which may have underestimated effect sizes relative to average scores.[101]

We attempted placebo adjustment for all four populations of interest in our NMAs. Material changes in findings were observed in both maintenance populations (i.e., biologic-naïve and biologic-experienced populations). However, results were highly unstable in the biologic-experienced maintenance NMA, regardless of the number of iterations attempted, in all likelihood due to the sparsity of the available network. We therefore included a placebo adjustment only in the maintenance NMA for the biologic-naïve population.

We conducted inconsistency tests for each of the NMA populations using the node-splitting approach. We found no statistical differences between direct and indirect estimates in any of our populations of interest. Further details are available in Appendix F.

Clinical Benefits

Adults

Biologic-Naïve

Induction Outcomes from Randomized Controlled Trials

- ***In the head-to-head VARSITY trial, vedolizumab had a higher rate of clinical response compared to adalimumab, although rates of remission were similar.***
- ***In placebo-controlled trials, TIMs generally had higher rates of clinical response and remission compared to placebo, a finding that was also reflected in NMAs.***
- ***The NMA showed infliximab and vedolizumab had higher rates of response and remission compared to adalimumab.***
- ***The NMA showed all TIMs had higher rates of endoscopic improvement compared to placebo; additionally, infliximab had higher rates of endoscopic improvement compared to adalimumab.***

Response and Remission

Fifteen of the included RCTs[8,9,68,77,80,81,86,90,93,95,96,99,101] measured the efficacy of TIMs in achieving clinical response and remission at the end of the induction phase (six to 14 weeks) in the biologic-naïve population. One trial was head-to-head (vedolizumab vs. adalimumab) and 14 were placebo

controlled. Data were available for all TIMs included in our review. The rates in each of the individual 15 RCTs are described below and reported in Table 4.2.

Head-to-Head Trial

Vedolizumab versus Adalimumab

In the VARSITY head-to-head trial comparing the efficacy of vedolizumab and adalimumab, the rate of response was higher with vedolizumab 300 mg compared to adalimumab 160/80 mg at the end of induction (70.1% vs. 49.5%, difference: 20.6; 95% CI for difference: 12.9 to 28.2); however, the rates of achieving remission did not statistically differ (Table 4.2).[8]

Placebo-Controlled Trials

Adalimumab

Three RCTs measured the efficacy of adalimumab compared to placebo (ULTRA 1, ULTRA 2, and Suzuki 2014).[86,93,101] In one RCT (ULTRA 2), adalimumab 160/80 mg had higher rates compared to placebo of clinical response (59.3% vs. 36.8%, p<0.0001) and remission (21.3% vs. 11.0%, p=0.017) at the end of induction.[93] Evidence was mixed in the other RCTs; in one RCT (ULTRA 1), adalimumab 160/80 mg had higher rates compared to placebo of remission (18.5% vs. 9.2%, p=0.031) but not clinical response,[86] and in the other RCT (Suzuki 2014), adalimumab 160/80 mg had higher rates compared to placebo of clinical response (50.0% vs. 35.4%, p=0.044) but not remission (Table 4.2).[101] As mentioned earlier, all adalimumab trials used the worst rank method to assign Mayo Scores, which likely led to lower effect sizes.

Golimumab

In the one RCT of golimumab versus placebo (PURSUIT-SC),[95] both golimumab 200/100 mg and golimumab 400/200 mg had higher rates compared to placebo of clinical response (51.0% and 54.9% vs. 30.3%, respectively, p<0.0001 for both) and remission (17.8% and 17.9% vs. 6.4%, respectively, p<0.0001 for both) in the Phase III population at the end of induction (Table 4.2). In our NMA, we used rates from the pooled Phase II and III population, which were similar to the rates observed in the Phase III population. Both golimumab 200/100 mg and golimumab 400/200 mg had numerically higher rates compared to placebo of clinical response (50.0% and 54.7% vs. 30.5%, respectively) and remission (17.7% and 18.8% vs. 6.8%, respectively); the significance of the difference was not reported for the pooled analysis.

Infliximab

Five RCTs measured the efficacy of infliximab compared to placebo (ACT 1, ACT 2, Jiang 2015, Kobayashi 2016, and NCT01551290);[68,80,81,90] all five of the trials assessed infliximab 5 mg/kg and two trials also assessed infliximab 10 mg/kg.[90] In all five RCTs, infliximab had higher rates of clinical response at the end of induction compared to placebo. In three RCTs, infliximab had higher rates of clinical remission at the end of induction compared to placebo,[80,90] while one RCT found marginal significance (p=0.05) and another RCT found no difference (Kobayashi 2016 and NCT01551290) (Table 4.2).[68,81] As noted earlier, NCT01551290 was not included in the NMA as it was only available in grey literature.

Tofacitinib

Two RCTs measured the efficacy of tofacitinib compared to placebo (OCTAVE 1 and OCTAVE 2).[96] In a pooled analysis of the two trials, tofacitinib 10 mg had higher rates compared to placebo of clinical response (64.5% vs. 39.1%, p<0.0001) and remission (24.1% vs. 11.8%, p<0.01) at the end of induction (Table 4.2).[72] As noted previously, we have not included these data in our NMA due to the FDA label change.

Ustekinumab

In the one RCT of ustekinumab versus placebo (UNIFI), ustekinumab 6 mg/kg had higher rates compared to placebo of clinical response (66.7% vs. 35.4%, p<0.001) and remission (18.6% vs. 9.5%, p=0.022) at the end of induction (Table 4.2).[98]

Vedolizumab

Two RCTs measured the efficacy of vedolizumab (IV) compared to placebo (GEMINI 1 and Motoya 2019).[9,77] In one RCT, vedolizumab 300 mg had higher rates compared to placebo of clinical response (53.1% vs. 26.3%, difference: 26.4, 95% CI for difference: 12.4 to 40.4) and remission (23.1% vs. 6.6%, difference: 15.5, 95% CI for difference: 5.1 to 25.9) at the end of induction (GEMINI 1),[77] but these measures did not differ between vedolizumab and placebo in the other RCT (Motoya 2019) (Table 4.2).[9] As previously noted, Motoya and colleagues describe several treatment group imbalances that may have contributed to unusually high placebo response and remission rates.

Table 4.2. Response and Remission Rates at the End of Induction in the Biologic-Naïve Population[8,9,68,77,80,81,86,90,93,95,96,99,101]

Trial	Week	N	Arm	Response		Remission	
				%	Significance	%	Significance
Head-to-Head							
VARSITY	14	304	VEDO 300 mg	70.1	Diff. (95% CI): 20.6 (12.9, 28.2)	27.6	Diff. (95% CI): 4.0 (-2.9, 10.9)
		305	ADA 160/80 mg	49.5		23.6	
Adalimumab							
ULTRA 1	8	130	ADA 160/80 mg	54.6	NS	18.5	p=0.031
		130	PBO	44.6	--	9.2	--
ULTRA 2	8	150	ADA 160/80 mg	59.3	p<0.001	21.3	p=0.017
		145	PBO	38.6	--	11.0	--
Suzuki 2014	8	90	ADA 160/80 mg	50.0	p=0.044	10.0	NS
		96	PBO	35.4	--	11.5	--
Golimumab							
PURSUIT-SC (Phase III)*	6	294	GOL 200/100 mg	51.0	p<0.0001	17.8	p<0.0001
		298	GOL 400/200 mg	54.9	p<0.0001	17.9	p<0.0001
		292	PBO	30.3	--	6.4	--
Infliximab							
ACT 1	8	121	IFX 5 mg/kg	69.4	p<0.001	38.8	p<0.001
		122	IFX 10 mg/kg	61.5	p<0.001	32.0	p=0.002
		121	PBO	37.2	--	14.9	--
ACT 2	8	121	IFX 5 mg/kg	64.5	p<0.001	33.9	p<0.001
		120	IFX 10 mg/kg	69.2	p<0.001	27.5	p<0.001
		123	PBO	29.3	--	5.7	--
Jiang 2015	8	41	IFX 5 mg/kg	78.1	p=0.00	53.7	p=0.003
		41	PBO	36.6	--	21.9	--
Kobayashi 2016	8	104	IFX 5 mg/kg	54.8	p=0.005	20.2	NS
		104	PBO	35.6	--	10.6	--
NCT0155129†	8	50	IFX 5 mg/kg	64.0	p=0.0021	22.0	NS
		49	PBO	32.7	--	10.2	--
Tofacitinib							
OCTAVE 1 & 2 (Pooled)‡	8	440	TOF 10 mg	64.5	p<0.0001	24.1	p<0.01
		110	PBO	39.1	--	11.8	--
Ustekinumab							
UNIFI	8	156	UST 6 mg/kg	66.7	p<0.001	18.6	p=0.022
		158	PBO	35.4	--	9.5	--
Vedolizumab							
GEMINI 1	6	130	VEDO 300 mg	53.1	Diff. (95% CI): 26.4 (12.4 to 40.4)	23.1	Diff. (95% CI): 15.5 (5.1 to 25.9)
		76	PBO	26.3		6.6	
Motoya 2019	10	79	VEDO 300 mg	53.2	Diff. (95% CI): 16.6 (-1.8 to 35.0)	27.8	Diff. (95% CI): 13.2 (-1.4 to 27.9)
		41	PBO	36.6		14.6	

ADA: adalimumab, CI: confidence interval, GOL: golimumab, IFX: infliximab, kg: kilogram, mg: milligram, NR: not reported, NS: not significant, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab

*Pooled Phase II and III results were used in NMA.

†Data for trial only available in grey literature and not included in NMA.

‡Data not included in NMA given tofacitinib's label change.

Network Meta-Analyses

Twelve of the 15 available RCTs were included in the induction NMA for the biologic-naïve population (all but the tofacitinib trials and the infliximab trial available in grey literature [NCT01551290]); refer to Appendix F for more details on reasons for exclusion from the NMA. Results from the NMA showed all TIMs were more likely to achieve response and remission compared to placebo. Specifically, TIMs were 1.4 to 1.9 times more likely to achieve clinical response (Table 4.3) and 1.8 to 3.2 times more likely to achieve remission (Table 4.4) compared to placebo. Additionally, infliximab and vedolizumab were more likely to achieve response and remission compared to adalimumab (Table 4.3 and 4.4). No other statistical differences among TIMs were observed.

Table 4.3. Risk Ratios for Response at the End of the Induction Phase in Biologic-Naïve Patients

IFX Pooled*					
1.07 (0.93, 1.24)	**VEDO**				
1.10 (0.93, 1.34)	1.02 (0.84, 1.27)	**UST**			
1.15 (1.00, 1.35)	1.08 (0.92, 1.27)	1.05 (0.85, 1.28)	**GOL Pooled***		
1.37 (1.18, 1.62)	**1.28 (1.14, 1.45)**	1.25 (1.00, 1.53)	1.18 (1.00, 1.42)	**ADA**	
1.88 (1.67, 2.12)	**1.76 (1.54, 2.02)**	**1.71 (1.41, 2.06)**	**1.63 (1.43, 1.86)**	**1.38 (1.21, 1.56)**	**PBO**

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

*Infliximab 5 mg/kg and 10 mg/kg pooled; golimumab 200/100 mg and 400/200 mg pooled.

Table 4.4. Risk Ratios for Remission at the End of the Induction Phase in Biologic-Naïve Patients

IFX Pooled*					
1.15 (0.87, 1.54)	**VEDO**				
1.21 (0.85, 1.79)	1.05 (0.71, 1.59)	**UST**			
1.34 (1.00, 1.80)	1.16 (0.84, 1.62)	1.10 (0.73, 1.63)	**GOL Pooled***		
1.84 (1.39, 2.50)	**1.60 (1.29, 1.98)**	1.52 (1.00, 2.26)	1.38 (1.00, 1.92)	**ADA**	
3.22 (2.60, 3.96)	**2.79 (2.18, 3.58)**	**2.66 (1.86, 3.73)**	**2.41 (1.89, 3.08)**	**1.76 (1.38, 2.19)**	**PBO**

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

*Infliximab 5 mg/kg and 10 mg/kg pooled; golimumab 200/100 mg and 400/200 mg pooled.

Endoscopic Improvement

Fourteen of the included placebo-controlled RCTs[9,68,77,80,81,90,93,95,96,99,101] measured the efficacy of TIMs in achieving endoscopic improvement at the end of the induction phase (six to 14 weeks) in the biologic-naïve population. Results for endoscopic improvement stratified by prior biologic exposure at week 14 were not available for the VARSITY head-to-head trial. Data were available for all TIMs included in our review. The rates in each of the individual 14 RCTs are reported in Appendix Table D5. Generally, all TIMs showed higher rates of endoscopic improvement compared to placebo at the end of induction.

Network Meta-Analysis

Eleven trials were included in our NMA (all but the tofacitinib trials and the infliximab trial available in grey literature [NCT01551290]); refer to Appendix F for more details on reasons for exclusion from the NMA. Results from our NMA showed all TIMs were significantly more likely to achieve endoscopic improvement compared to placebo (Table 4.5). Specifically, TIMs were 1.3 to 1.8 times more likely to achieve endoscopic improvement compared to placebo. Infliximab was more likely to induce endoscopic improvement than adalimumab. No other statistical differences were observed among TIMs.

Table 4.5. Risk Ratios for Endoscopic Improvement at the End of the Induction Phase in Biologic-Naïve Patients

IFX Pooled*					
1.07 (0.74, 1.51)	VEDO				
1.17 (0.77, 1.75)	1.1 (0.67, 1.80)	UST			
1.19 (0.92, 1.55)	1.12 (0.77, 1.65)	1.02 (0.67, 1.57)	GOL Pooled*		
1.43 (1.13, 1.81)	1.34 (0.94, 1.95)	1.22 (0.81, 1.85)	1.2 (0.92, 1.57)	ADA	
1.83 (1.56, 2.17)	**1.71 (1.27, 2.4)**	**1.56 (1.08, 2.3)**	**1.53 (1.26, 1.9)**	**1.28 (1.08, 1.53)**	PBO

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab
Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.
*Infliximab 5 mg/kg and 10 mg/kg pooled; golimumab 200/100 mg and 400/200 mg pooled.

Maintenance Outcomes from Randomized Controlled Trials

- ***The head-to-head VARSITY trial showed the rate of clinical remission was higher with vedolizumab compared to adalimumab.***
- ***In placebo-controlled trials, TIMs generally had higher rates of clinical response and remission compared to placebo, a finding that was also reflected in the NMAs.***
- ***The NMA also showed that vedolizumab had higher rates of clinical response and remission compared to adalimumab and golimumab.***

Response and Remission

Eleven RCTs measured the efficacy of TIMs in achieving clinical response and remission at the end of the maintenance phase (52-60 weeks) in the biologic-naïve population. One RCT was head-to-head (vedolizumab vs. adalimumab), and 10 trials were placebo controlled. Data were available for all TIMs included in our review. Four of the trials had a treat-through design[8,90,93,101] and seven utilized a re-randomized approach.[9,77,79,92,94,96,99]

In the following section, we describe results for the key outcome measures in the biologic-naïve population as reported in the published trials (i.e., measures designated as primary and key secondary outcomes for the overall population). As discussed earlier, we adjusted the rates from the treat-through trials to more closely resemble results from re-randomized trials to enable comparisons in our NMA. Additionally, for some re-randomized trials, we preferred manufacturer-submitted inputs or other published secondary outcomes over the results described below, as they provided us with more comparable outcomes for our NMA (e.g., response *at* end of maintenance vs. response *through* the end of maintenance). For more details on the inputs used in the NMAs, refer to Appendix F.

Published Results from Treat-Through Trials

Head-to-Head Trial

Vedolizumab versus Adalimumab

In the VARSITY head-to-head trial, vedolizumab 300 mg every eight weeks had higher rates of remission compared to adalimumab 40 mg at the end of maintenance (Table 4.6).[8]

Placebo-Controlled Trials

Both adalimumab 40 mg and infliximab (5 mg/kg and 10 mg/kg doses) had higher rates of response and remission compared to placebo at the end of maintenance in available trials (Table 4.6).[90,93,101]

Table 4.6. Response and Remission Rates Among all Patients in Treat-Through Trials in Biologic-Naïve Patients[8,90,93,101]

Trial	Week	N	Arm	Response		Remission	
				%	Significance	%	Significance
VARSITY	52	304	VEDO 300 mg q8w	NR		34.2	Diff. (95% CI): 9.9 (2.8 to 17.1)
		305	ADA 40 mg			24.3	
ULTRA 2	52	150	ADA 40 mg	36.7	p=0.019	22.0	p=0.029
		145	PBO	24.1	--	12.4	--
Suzuki 2014	52	177	ADA 40 mg	31.0	p=0.021	23.3	p=0.011
		96	PBO	17.7	--	7.3	--
ACT 1	54	121	IFX 5 mg/kg	45.5	p<0.001	34.7	p=0.001
		122	IFX 10 mg/kg	44.3	p<0.001	34.4	p=0.001
		121	PBO	19.8	--	16.5	--

ADA: adalimumab, CI: confidence interval, IFX: infliximab, kg: kilogram, mg: milligram, NR: not reported, PBO: placebo, q8w: every 8 weeks, VEDO: vedolizumab

Published Results from Re-Randomized Trials

Placebo-Controlled Trials

Golimumab

Golimumab 100 mg had higher rates of maintaining response through week 54 and of achieving remission at both week 30 *and* 54 compared to placebo in PURSUIT-J and PURSUIT-M (Table 4.7).[79,94]

Tofacitinib

Tofacitinib 5 mg and 10 mg had higher rates of achieving response and remission at week 52 compared to placebo in OCTAVE SUSTAIN (Table 4.7).[72] As noted previously, we have not included tofacitinib in our biologic-naïve NMA due to the FDA label change.

Ustekinumab

Ustekinumab 90 mg had higher rates of maintaining response through week 52 and remission at maintenance week 52 compared to placebo in UNIFI (Table 4.7).[98]

Vedolizumab

Vedolizumab 300 mg every eight weeks had higher rates of response compared to placebo in GEMINI 1 and Motoya 2019, and higher rates of remission compared to placebo in GEMINI 1 but not in Motoya 2019 at week 52.[9,77] Additionally, vedolizumab 300 mg every four weeks showed higher rates of response and remission compared to placebo in GEMINI 1. In VISIBLE 1, rates of

remission were numerically higher with vedolizumab 300 mg every eight weeks compared to placebo, although the significance of the difference was not reported (Table 4.7).[92]

Table 4.7. Response and Remission Rates Among Induction Responders in Re-Randomized Trials in Biologic-Naïve Patients[8,9,77,79,90,92-94,99]

Trial	Week	N	Arm	Response		Remission	
				%	Significance	%	Significance
PURSUIT-M	54	151	GOL 100 mg	49.7	p<0.001	27.8	p=0.004
		154	PBO	31.2	--	15.6	--
PURSUIT-J	54	32	GOL 100 mg	56.3	Diff. (95% CI): 36.9 (14.8, 59.0)	50.0	Diff. (95% CI): 43.6 (24.2, 62.9)
		31	PBO	19.4		6.5	
OCTAVE SUSTAIN	52	115	TOF 5 mg	56.6	p<0.0001	41.7	p<0.0001
		104	TOF 10 mg	64.4	p<0.0001	44.2	p<0.0001
		109	PBO	24.8	--	11.0	--
UNIFI	52	85	UST 90 mg q8w	77.6	p<0.001	48.2	p=0.024
		87	PBO	50.6		31.0	
GEMINI 1	52	73	VEDO 300 mg q4w	56.2	Diff. (95% CI): 9.2 (13.7, 44.7)	47.9	Diff. (95% CI): 28.4 (13.7, 43.1)
		72	VEDO 300 mg q8w	65.3	Diff. (95% CI): 38.2 (22.6, 53.8)	45.8	Diff. (95% CI): 26.6 (11.8, 41.4)
		79	PBO	26.6	--	19.0	--
Motoya 2019	60	24	VEDO 300 mg q8w	66.7	Diff. (95% CI): 31.0 (5.1, 56.9)	54.2	Diff. (95% CI): 18.5 (-8.2, 45.1)
		28	PBO	35.7		35.7	
VISIBLE 1	52	32	VEDO 300 mg q8w	NR	NR	53.1	NR
		37	PBO	NR		18.9	

CI: confidence interval, GOL: golimumab, IFX: infliximab, mg: milligram, NR: not reported, PBO: placebo, q4w: every 4 weeks, q8w: every 8 weeks, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Network Meta-Analysis

Eight RCTs were included in our NMA (all trials except for Suzuki 2014, PURSUIT-J, and OCTAVE SUSTAIN); please refer to Appendix F for more details on reasons for exclusion from the NMA. As mentioned previously, placebo adjustment was performed for the maintenance NMA in this population. Our NMA showed all TIMs were more likely to achieve clinical response and remission at the end of maintenance compared to placebo, although no statistical differences from placebo were observed for adalimumab or golimumab. Vedolizumab was shown to be more likely to achieve clinical response and remission compared to adalimumab and golimumab. No other statistical differences between TIMs were observed.

Table 4.8. Risk Ratios for Response at the End of the Maintenance Phase in Biologic-Naïve Patients

UST					
1.12 (0.62, 1.77)	VEDO Pooled*				
1.16 (0.77, 1.54)	1.04 (0.69, 1.58)	IFX Pooled*			
1.38 (0.72, 2.18)	**1.21 (1.05, 1.43)**	1.18 (0.74, 1.79)	ADA		
1.46 (0.75, 2.54)	**1.30 (1.01, 1.77)**	1.26 (0.77, 2.03)	1.07 (0.81, 1.50)	GOL	
1.80 (1.13, 2.50)	**1.64 (1.16, 2.02)**	**1.56 (1.10, 2.14)**	1.34 (0.94, 1.78)	1.25 (0.79, 1.70)	PBO

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

*Infliximab 5 mg and 10 mg pooled; vedolizumab 300 mg every 8 weeks and every 4 weeks pooled.

Table 4.9. Risk Ratios for Remission at the End of the Maintenance Phase in Biologic-Naïve Patients

UST					
1.18 (0.52, 2.26)	VEDO Pooled*				
1.24 (0.71, 1.83)	1.05 (0.60, 1.86)	IFX Pooled*			
1.56 (0.64, 3.00)	**1.30 (1.06, 1.62)**	1.25 (0.67, 2.22)	ADA		
1.70 (0.68, 3.55)	**1.43 (1.01, 2.15)**	1.37 (0.71, 2.61)	1.10 (0.75, 1.71)	GOL	
2.22 (1.17, 3.57)	**1.93 (1.22, 2.58)**	**1.80 (1.13, 2.86)**	1.47 (0.92, 2.14)	1.35 (0.74, 2.04)	PBO

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

*Infliximab 5 mg and 10 mg pooled; vedolizumab 300 mg every 8 weeks and every 4 weeks pooled.

Endoscopic Improvement

One head-to-head and eight placebo-controlled RCTs measured the efficacy of TIMs in achieving endoscopic improvement at the end of the maintenance phase in the biologic-naive population. Compared to placebo, patients treated with adalimumab, golimumab, infliximab, tofacitinib, and ustekinumab reported achieving higher rates of endoscopic improvement.[8,9,77,79,90,93,94,96,99,101] All TIMs reported the rates of achieving endoscopic improvement at the end of maintenance, while the PURSUIT-M and PURSUIT-J trials for golimumab used a stricter reporting criterion for maintaining endoscopic improvement at both week 30 and week 54. As mentioned previously, an NMA was not conducted for endoscopic improvement at the end of the maintenance phase.

Biologic-Experienced

Induction Outcomes from Randomized Controlled Trials

- ***In the head-to-head VARSITY trial, vedolizumab had a higher rate of response compared to adalimumab, although rates of remission were similar.***
- ***In placebo-controlled trials, rates of response and remission were higher with tofacitinib and ustekinumab compared to placebo but similar with adalimumab compared to placebo. Evidence was mixed for vedolizumab, with one trial reporting higher rates of response compared to placebo.***
- ***The NMA showed tofacitinib, ustekinumab, and vedolizumab had higher rates of clinical response and remission compared to placebo and adalimumab; adalimumab did not statistically differ from placebo.***
- ***The NMA showed tofacitinib and ustekinumab had higher rates of endoscopic improvement; vedolizumab or adalimumab did not statistically differ from placebo.***

Response and Remission

Seven of the included RCTs measured the efficacy of TIMs in achieving clinical response and remission at the end of the induction phase (six to 14 weeks) in the biologic-experienced population. One RCT was a head-to-head trial (vedolizumab vs. adalimumab) and six were placebo controlled. Data were available for adalimumab, tofacitinib, ustekinumab, and vedolizumab, but not for golimumab or infliximab.

Head-to-Head Trial

Vedolizumab versus Adalimumab

In the VARSITY head-to-head trial comparing the efficacy of vedolizumab and adalimumab,[8] the rate of response was higher with vedolizumab compared to adalimumab at the end of induction (55.7% vs. 32.1%, difference: 23.6; 95% CI for difference: 8.5 to 38.7); however, the rates of achieving remission did not statistically differ (Table 4.10).

Placebo-Controlled Trials

Adalimumab

In a single trial of adalimumab 160/80 mg versus placebo (ULTRA 2),[93] there were no significant differences in achieving clinical response or remission at the end of induction (Table 4.10).

Tofacitinib

Two RCTs measured the efficacy of tofacitinib compared to placebo (OCTAVE 1 and OCTAVE 2).[96] In a pooled analysis of the two trials,[72] tofacitinib 5 mg and 10 mg had higher rates compared to placebo of clinical response (51% vs. 23.4%, p <0.0001) and remission (11.4% vs. 0.8%, p<0.01) at the end of induction (Table 4.10).

Ustekinumab

In the one RCT of ustekinumab versus placebo, ustekinumab 6 mg/kg had higher rates compared to placebo of clinical response (57.2% vs. 27.3%, p<0.001) and remission (12.7% vs. 1.2%, p<0.001) at the end of induction (Table 4.10).[99]

Vedolizumab

Two RCTs measured the efficacy of vedolizumab compared to placebo.[9,77] In one RCT, vedolizumab 300 mg had higher rates compared to placebo of clinical response (39.0% vs. 20.6%, difference: 18.1, 95% CI for difference: 2.8 to 33.5) but not remission at the end of induction,[77] and the other RCT found no difference in clinical response and remission rates (Motoya 2019) (Table 4.10).[9] As previously noted, Motoya and colleagues describe several treatment group imbalances that may have contributed to unusually high placebo response and remission rates.

Table 4.10. Response and Remission Rates at the End of Induction in the Biologic-Experienced Population[8,9,77,93,96,99]

Trial	Week	N	Arm	Response		Remission	
				%	Significance	%	Significance
VARSITY	14	79	VEDO 300 mg	55.7	Diff. (95% CI):	22.8	Diff. (95% CI):
		81	ADA 160/80 mg	32.1	23.6 (8.5, 38.7)	12.3	10.3 (-1.5, 22.2)
ULTRA 2	8	98	ADA 160/80 mg	36.7	NS	9.2	NS
		101	PBO	28.7	--	6.9	--
OCTAVE 1 & 2 (Pooled)	8	465	TOF 10 mg	51.0	p<0.0001	11.4	p<0.01
		124	PBO	23.4	--	0.8	--
UNIFI	8	166	UST 6 mg/kg	57.2	p<0.001	12.7	p<0.001
		161	PBO	27.3	--	1.2	--
GEMINI 1	6	82	VEDO 300 mg	39.0	Diff. (95% CI):	9.8	Diff. (95% CI):
		63	PBO	20.6	18.1 (2.8, 33.5)	3.2	7.0 (-1.3, 15.2)
Motoya 2019	10	85	VEDO 300 mg	27.1	Diff. (95% CI):	9.4	Diff. (95% CI):
		41	PBO	29.3	-2.2 (-19.0, 41.6)	9.8	-0.3 (-11.3, 10.7)

ADA: adalimumab, CI: confidence interval, GOL: golimumab, IFX: infliximab, kg: kilogram, mg: milligram, NS: not specified, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Network Meta-Analysis

All seven RCTs were included in the NMA. Results from our NMA showed tofacitinib, ustekinumab, and vedolizumab were more likely to achieve clinical response and remission compared to placebo; there were no statistical differences between adalimumab and placebo (Table 4.11 and Table 4.12). Additionally, tofacitinib, ustekinumab, and vedolizumab were more likely to achieve clinical response and remission compared to adalimumab.

Table 4.11. Risk Ratios for Response at the End of the Induction Phase in Biologic-Experienced Patients

UST				
1.01 (0.77, 1.33)	TOF			
1.32 (0.97, 1.87)	1.31 (0.96, 1.84)	VEDO		
2.01 (1.39, 3.13)	**2.00 (1.36, 3.08)**	**1.53 (1.11, 2.15)**	ADA	
2.11 (1.71, 2.62)	**2.11 (1.68, 2.60)**	**1.61 (1.20, 2.05)**	1.05 (0.71, 1.46)	PBO

ADA: adalimumab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab
Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table 4.12. Risk Ratios for Remission at the End of the Induction Phase in Biologic-Experienced Patients

UST				
1.02 (0.58, 1.82)	TOF			
1.75 (0.94, 3.45)	1.74 (0.92, 3.38)	VEDO		
3.82 (1.88, 8.49)	**3.75 (1.80, 8.08)**	**2.18 (1.22, 3.95)**	ADA	
4.13 (2.71, 6.26)	**4.10 (2.62, 6.18)**	**2.38 (1.38, 3.80)**	1.09 (0.57, 1.97)	PBO

ADA: adalimumab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab
Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Endoscopic Improvement

Six of the included placebo-controlled RCTs measured the efficacy of TIMs in achieving endoscopic improvement at the end of the induction phase in the biologic-experienced population.[8,9,77,93,96] Data were available for adalimumab, tofacitinib, ustekinumab, and vedolizumab. Higher rates of endoscopic improvement compared to placebo were achieved with tofacitinib (22.0% vs. 6.1%, $p<0.001$) and ustekinumab (21.1% vs. 6.8%, $p<0.01$).

Network Meta-Analysis

All six RCTs were included in the NMA. Results from our NMA showed that patients treated with tofacitinib and ustekinumab were more likely to achieve endoscopic improvement compared to placebo. Similarly, tofacitinib and ustekinumab were also more likely to achieve endoscopic

improvement than vedolizumab and adalimumab. We note, however, that credible intervals are particularly wide for this analysis, in large part due to the sparseness of the network and relatively smaller sample size of the biologic-experienced population included in these trials.

Table 4.13. Risk Ratios for Endoscopic Improvement at the End of the Induction Phase in Biologic-Experienced Patients

TOF				
1.22 (0.48, 3.30)	**UST**			
3.24 (1.50, 7.84)	**2.65 (1.25, 5.93)**	**VEDO**		
3.60 (1.64, 8.85)	**2.94 (1.37, 6.70)**	1.11 (0.60, 2.07)	**ADA**	
3.92 (2.09, 8.65)	**3.21 (1.75, 6.46)**	1.21 (0.81, 1.89)	1.1 (0.70, 1.73)	**PBO**

ADA: adalimumab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab
Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Maintenance Outcomes in Randomized Controlled Trials

- ***In the head-to-head VARSITY trial, the rate of clinical remission was similar with vedolizumab and adalimumab.***
- ***In placebo-controlled trials, rates of response and remission were higher with adalimumab, tofacitinib, and ustekinumab. Evidence was mixed for vedolizumab, with two trials reporting higher rates of remission compared to placebo.***
- ***The NMA showed all TIMs had higher rates of response and remission compared to placebo. No differences among TIMs were observed.***

Response and Remission

Seven RCTs measured the efficacy of TIMs in maintaining clinical response and remission in the biologic-experienced population. Six of the RCTs were placebo-controlled, and one RCT was head-to-head (VARSITY).[8] Data was available for adalimumab, tofacitinib, ustekinumab, and vedolizumab, but not for golimumab or infliximab.

Two of the trials had a treat-through design (ULTRA 2 and VARSITY)[8,93] and five had re-randomized designs (GEMINI 1, Motoya 2019, VISIBLE 1, OCTAVE SUSTAIN, and UNIFI).[9,77,92,96,99]

In the section that follows, we describe results for the key outcomes in the biologic-experienced population as reported in the published trials. As discussed earlier, we adjusted the rates from the treat-through trials to resemble results more closely from re-randomized trials to enable comparisons in our NMA. Additionally, for some re-randomized trials, we preferred manufacturer-submitted inputs or other published secondary outcomes over the results described below, as they provided us with more comparable outcomes for our NMA (e.g., response *at* end of maintenance

vs. response *through* the end of maintenance). For more details on the inputs used in the NMAs, refer to Appendix F.

Published Results from Treat-Through Trials

Head-to-Head Trial

Vedolizumab versus Adalimumab

In the VARSITY head-to-head trial, the rates of remission were similar with vedolizumab 300 mg every eight weeks and adalimumab 40 mg at week 52 (Table 4.14).[8]

Placebo-Controlled Trials

Adalimumab

Adalimumab 40 mg had higher rates of response and remission at the end of maintenance compared to placebo at week 52 in ULTRA-2 (Table 4.14).[93]

Table 4.14. Response and Remission Rates Among all Patients in the Treat-Through Trials in Biologic-Experienced Patients[8,93]

Trial		N	Arm	Response		Remission	
				%	Significance	%	Significance
VARSITY	52	79	VEDO 300 mg q8w	NR		20.3	Diff. (95% CI): 4.2 (-7.8, 16.5)
		81	ADA 40 mg			16.0	
ULTRA 2	52	98	ADA 40 mg	20.4	0.038	10.2	p=0.039
		101	PBO	9.9	--	3.0	--

ADA: adalimumab, CI: confidence interval, mg: milligram, NR: not reported, PBO: placebo, q8w: every 8 weeks, VEDO: vedolizumab

Published Results from Re-Randomized Trials

Placebo-Controlled Trials

Tofacitinib

Tofacitinib 5 mg and 10 mg had higher rates of response and remission at week 52 compared to placebo in OCTAVE SUSTAIN (Table 4.15).[72]

Ustekinumab

Ustekinumab 90 mg had higher rates of response through week 52 and remission at week 52 compared to placebo in UNIFI (Table 4.15).[98]

Vedolizumab

Vedolizumab 300 mg every eight weeks had higher rates of remission compared to placebo in GEMINI 1 and Motoya 2019 and had higher rates of response compared to placebo in GEMINI 1 but not in Motoya 2019.[9,77] Additionally, vedolizumab 300 mg every four weeks had significantly higher rates of response and remission compared to placebo in GEMINI 1. In VISIBLE 1, rates of remission were numerically higher with vedolizumab compared to placebo, although the significance of the difference was not reported (Table 4.15).[92]

Table 4.15. Response and Remission Rates in Re-Randomized Trials in Biologic-Experienced Patients[9,72,77,92,98]

Trial	Week	Arm	N	Response		Remission	
				%	Significance	%	Significance
OCTAVE SUSTAIN	52	TOF 5 mg	83	44.6	p<0.0001	24.1	p<0.05
		TOF 10 mg	93	59.1	p<0.0001	36.6	p<0.0001
		PBO	89	14.6	--	11.2	--
UNIFI	52	UST 90 mg q8w	91	64.8	p<0.001	39.6	p<0.001
		PBO	88	38.6		17.0	
GEMINI 1	52	VEDO 300 mg q4w	43	42.5	Diff. (95% CI): 25.9 (5.8, 45.9)	35.0	Diff. (95% CI): 31.3 (13.2, 49.3)
		VEDO 300 mg q8w	40	46.5	Diff. (95% CI): 26.8 (7.4, 46.2)	37.2	Diff. (95% CI): 27.8 (10.6, 45.0)
		PBO	38	15.8	--	5.3	--
Motoya 2019	60	VEDO 300 mg q8w	17	64.7	Diff. (95% CI): 29.0 (-4.9, 62.8)	58.8	Diff. (95% CI): 37.4 (5.6, 69.2)
		PBO	14	35.7		21.4	
VISIBLE 1	52	VEDO 300 mg q8w	22	NR		27.3	NR
		PBO	19			5.3	

CI: confidence interval, mg: milligram, N: number, NR: not reported, PBO: placebo, q4w: every 4 weeks, q8w: every 8 weeks, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Network Meta-Analysis

All seven RCTs were included in the NMA. All TIMs were more likely to achieve clinical response and remission compared to placebo. Specifically, TIMs were 1.9 to 2.4 times more likely to achieve clinical response compared to placebo (Table 4.16), and 2.5 to 3.5 times more likely to achieve remission compared to placebo (Table 4.17). No other statistical differences among TIMs were observed.

Table 4.16. Risk Ratios for Clinical Response at the End of the Maintenance Phase in Biologic-Experienced Patients

VEDO Pooled*				
1.12 (0.87, 1.55)	ADA			
1.25 (0.88, 1.86)	1.11 (0.72, 1.72)	UST		
1.26 (0.88, 1.90)	1.12 (0.70, 1.75)	1.00 (0.63, 1.61)	TOF Pooled*	
2.40 (1.87, 3.00)	**2.14 (1.48, 2.89)**	**1.92 (1.34, 2.55)**	**1.92 (1.32, 2.55)**	PBO

ADA: adalimumab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab
Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.
*Tofacitinib 5 and 10 mg pooled; vedolizumab 300 mg every 8 weeks and every 4 weeks pooled.

Table 4.17. Risk Ratios for Clinical Remission at the End of the Maintenance Phase in Biologic-Experienced Patients

VEDO Pooled*				
1.19 (0.80, 1.94)	ADA			
1.41 (0.83, 2.5)	1.17 (0.62, 2.27)	UST		
1.41 (0.82, 2.59)	1.18 (0.60, 2.31)	1.01 (0.51, 1.98)	TOF Pooled*	
3.48 (2.43, 5.03)	**2.91 (1.72, 4.65)**	**2.49 (1.49, 3.82)**	**2.49 (1.46, 3.79)**	PBO

ADA: adalimumab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab
Each box represents the estimated risk ratios and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.
*Tofacitinib 5 and 10 mg pooled; vedolizumab 300 mg every 8 weeks and every 4 weeks pooled.

Endoscopic Improvement

Five of the included placebo-controlled RCTs and one head-to-head trial measured the efficacy of TIMs in achieving endoscopic improvement at the end of the maintenance phase in the biologic-experienced population. Data stratified by prior biologic exposure were available for adalimumab, tofacitinib, ustekinumab, and vedolizumab. Higher rates of endoscopic improvement were reported with tofacitinib 5 mg and 10 mg (30.1% and 39.8% vs. 12.4% for placebo, $p<0.01$ and <0.001, for both comparisons), ustekinumab (45.1% vs. 22.7%, $p<0.001$) and vedolizumab (44.6% vs. 7.9%, difference: 34.9; 95% CI for difference: 17.1 to 52.8). Differences were not statistically significant in the ULTRA 2 trial of adalimumab.

Other Outcomes

Delayed Responders

As noted previously, some patients may respond to induction therapy after FDA-mandated timepoints for clinical trials. We sought evidence on delayed response from all available RCTs and observational studies, and identified data for adalimumab, tofacitinib, and vedolizumab on an overall basis (i.e., not stratified by prior biologic use). Delayed response stratified by prior biologic use was available for golimumab, tofacitinib, and ustekinumab. Data are summarized in Appendix Table D7. Overall, with vedolizumab, 39% of induction non-responders achieved delayed response by week 14, based on data from GEMINI 1.[56] With tofacitinib, 50.1% of induction non-responders achieved delayed response, of which 13.9% achieved remission by week 16, based on the combined data for OCTAVE 1 and 2.[118] Among adalimumab recipients in ULTRA 2, 4.1% achieved delayed remission (data were not available for delayed response).[93]

When stratified by prior biologic exposure, among biologic-experienced ustekinumab induction non-responders in the UNIFI trial, 43.1% and 1.7% achieved delayed response and remission respectively by week 16. Additionally, in biologic-naïve populations, delayed response (79.1%) and remission (18.6%) was achieved with ustekinumab at week 16.[71] Further, among biologic-experienced tofacitinib induction non-responders, 42.6% and 39.7% achieved delayed response and remission. Among biologic-naïve induction non-responders with tofacitinib, 56.2% and 18.8% achieved response and remission.[118] A total of 28.1% of golimumab induction non-responders (all biologic-naïve) achieved response at the end of week 16 in PURSUIT-SC.[70]

Corticosteroid-Free Remission

Concomitant corticosteroid use at baseline was permitted across the trials and the dose remained unaltered through the induction phase. The use of corticosteroids was then tapered, and corticosteroid-free remission was assessed at the end of the maintenance phase. Overall, one head-to-head and nine placebo-controlled trials reported corticosteroid-free remission, with six trials reporting corticosteroid-free remission stratified by prior biologic exposure (see Appendix Table D10 for details). In the VARSITY trial, a numerically higher proportion of patients treated with adalimumab achieved corticosteroid-free remission relative to vedolizumab, but the results were not statistically significant.[8] Further, corticosteroid-free remission was higher with tofacitinib (both 5 mg and 10 mg) in the overall population as compared to placebo (27.6% vs. 10.9, p=0.003).[96] Findings were similar when stratified by prior biologic use. In the placebo-controlled trials, a higher proportion of biologic-naïve patients achieved corticosteroid-free remission at the end of maintenance when treated with infliximab 5 mg (25.7% vs. 8.9%; p=0.006), vedolizumab (44.6% vs. 18.6%; difference: 26.3; 95% CI: 8.7 to 43.9), and ustekinumab (37.4 vs. 15.9, p<0.001). A higher proportion of biologic-experienced patients achieved corticosteroid-free remission at the end of

maintenance when treated with tofacitinib (27.6% vs. 10.9%, p=0.002), vedolizumab (26.7% vs. 4.3%; difference: 21.3; 95% CI: 1.7-40.8), and ustekinumab (49.4 vs. 32.1, p=0.03).[77,90,99]

Ulcerative Colitis-Related Hospitalization and Surgeries

The rates of UC-related hospitalizations and surgeries were not commonly reported in trials included in this review. Where available, results were reported in the overall population and not stratified by biologic-naïve and biologic-experienced. Data were available from the head-to-head VARSITY trial and placebo-controlled trials of adalimumab, infliximab, and ustekinumab. In the VARSITY trial, the rates of UC-related hospitalizations and procedures were slightly numerically higher for adalimumab compared to vedolizumab at week 52 (5.2% vs. 3.9% for hospitalizations and 2.1% vs. 1.8% for procedures); these rates were not compared statistically.[8] The rates of UC-related hospitalizations were lower with adalimumab compared to placebo (incidence ratio [IR]: 0.12 vs. 0.22, p=0.002)[73] and with infliximab compared to placebo (20 vs. 40 events per 100 patient years [PY], p=0.003).[91] In UNIFI, the rates of UC-related hospitalizations were numerically lower for ustekinumab 90 mg every eight weeks compared to placebo (1.7% vs. 5.7%); these rates were not statistically compared.[99] The rates of UC-related procedures were lower with infliximab compared to placebo (21 vs. 34 events per 100 PY, p=0.03, respectively).[91] However, there was no difference in colectomy rates between adalimumab and placebo (IR: 0.04 vs. 0.05, p-value: NR).[73] In UNIFI, the rates of surgeries were numerically higher with placebo compared to ustekinumab 90 mg every eight weeks at week 52 (1.7% vs. 0.6%); these rates were not statistically compared.[99]

Quality of Life

Trials measured health-related quality of life (HRQoL) using various measures including the IBDQ, the SF-36, and the EQ-5D. In general, results were presented on an overall basis alone; stratified findings for the biologic-naïve and biologic-experienced populations are reported where available.

Inflammatory Bowel Disease Questionnaire

As described previously, an MCID on the IBDQ has not been established in UC. However, a 16-point or better improvement from baseline is used in Crohn's disease, and a 170-point or better score is also indicative of Crohn's remission. These thresholds have been used in available UC trials. Rates of achieving a change ≥16 points ("IBDQ response") or a score ≥170 points ("IBDQ remission") at the end of maintenance were reported for VARSITY and placebo-controlled trials of adalimumab, golimumab, tofacitinib, ustekinumab, and vedolizumab.[8,74,79,93,97,101,119]

In the VARSITY head-to-head trial, the rates of achieving "IBDQ response" and "IBDQ remission" were higher with vedolizumab 300 mg compared to adalimumab 40 mg at the end of maintenance. In the placebo-controlled trials, adalimumab, golimumab, tofacitinib, and ustekinumab had higher rates of IBDQ response compared to placebo. Additionally, patients treated with tofacitinib,

ustekinumab, and vedolizumab achieved higher rates of IBDQ remission compared to placebo at the end of the maintenance. Finally, stratification by prior biologic exposure was available for adalimumab and higher rates of IBDQ response were reported among biologic-naïve patients but not biologic-experienced patients. A summary of relevant results can be found in Appendix Tables D8 and D11.

36-Item Short Form Survey

SF-36 was assessed in the placebo-controlled trials of infliximab, tofacitinib, and vedolizumab stratified by prior biologic exposure. The trials reported improvement in the quality of life by MCID thresholds and mean component summary scores. As described previously, MCID for the SF-36 PCS and MCS summary scores ranged from 1.6 to 7.0 and 2.3 to 8.7, respectively, depending on the approach.[28] However, the MCID threshold on the SF-36 has not been established in UC; the MCID thresholds ranged from 3 to 5 points in the included trials. A higher proportion of patients achieved ≥3-point MCID for both physical and mental component scores with infliximab compared to placebo (PCS: 59.1% vs. 40.6%; MCS: 50% vs. 34%; p<0.05 for both comparisons) and ≥5-point (PCS: 49% vs. 32.4%; MCS: 43% vs. 29.9%; p<0.05 for both comparisons) improvement.[75] Similarly, higher proportions of patients were reported to have achieved ≥5-point improvements on the physical component score with vedolizumab every eight weeks compared to placebo (65% vs. 48%).[74]

Further, among the biologic-naïve population, significant improvements in mean PCS and MCS patients were reported with infliximab, tofacitinib, and vedolizumab, compared to placebo at the end of induction and maintenance phases.[75,74,83] Additionally, in the biologic-experienced population, statistically significant improvement in PCS and MCS scores was reported with tofacitinib compared to placebo.[83] A summary of relevant results can be found in Appendix Tables D9 and D12.

EuroQol-5D

EQ-5D results were reported in vedolizumab trials (GEMINI 1 and VISIBLE 1).[77,92] The EQ-5D results were reported as the differences in mean scores between vedolizumab and placebo for the utility index and MCID for the VAS. While an MCID threshold has not been established in UC, a change of ≥10 in the MCID score was used as the threshold in the GEMINI 1 trial as per the MCID estimates ranging from 4.2-14.8 established for Crohn's disease.[28] In biologic-naïve patients, significant differences in the EQ-5D VAS (10.6, 95% CI: 4.9-16.3) and utility scores (0.062, 95% CI: 0.003-0.120) were reported in the vedolizumab treated group compared to placebo at the end of the maintenance phase.[74] Similar results were reported for EQ-5D VAS in the vedolizumab IV group in the VISIBLE 1 trial (LS mean difference: 13.1, 95% CI: 5.5-20.8), compared to placebo.[92]

Work Productivity and Activity Impairment

Three trials assessed work productivity among patients living with UC using the WPAI-UC questionnaire at the end of induction.[96,99,106] Work productivity in the trials was reported as the mean percent change from baseline, at the end of induction and maintenance, for the overall population. MCID thresholds for UC were not reported. At the end of induction, patients treated with tofacitinib and ustekinumab were associated with statistically significant reductions in work-related impairments.

At the end of the maintenance phase, statistically significant improvements with tofacitinib 5 mg and 10 mg, ustekinumab, and vedolizumab were reported for some or all components of the WPAI relative to placebo (see Appendix, Tables D13 and D14 for details). Improvements achieved at the end of induction were consistent through the end of maintenance. However, the WPAI-UC score of patients in the placebo group for all four domains worsened (increased) at the end of the maintenance phase.

Special Populations

Pediatric Population

The efficacy and safety of TIMs for UC have not been studied widely in children and adolescents. Among the TIMs of interest for our review, only infliximab has been approved by the FDA for use among patients ages <18 years. Only one Phase III, open-label RCT evaluating the efficacy and safety of infliximab in both induction (open-label) and maintenance phases was identified; this was, in fact, a comparison of multiple doses of infliximab with no placebo or active comparator.[107] No other RCTs or comparative observational studies were identified based on the inclusion criteria for our review, including the intervention of interest, outcomes of interest, and minimum sample size (n≥20) requirement for the UC cohort.

The patient population was six to 17 years old living with moderate-to-severe UC, with a median PUCAI of 55 and a median Mayo Score of 8.0. The patients received infliximab open-label dosing of 5 mg/kg, before being randomized equally based on the response at week eight to one of the two infliximab regimens (i.e., infliximab 5 mg/kg every eight weeks or every 12 weeks). Across treatment groups, the mean age was 15 years, was primarily female, and had a mean disease duration of one to two years. Patients were also required to have prior experience with at least one conventional agent (including aminosalicylates, azathioprine, mercaptopurine, or oral or IV corticosteroids).

All the enrolled patients received an open-label induction regimen of infliximab 5 mg/kg. At week eight, the clinical response defined by Mayo Score was achieved by 73.3% (44 of 60 patients). Clinical remission at week eight was achieved by 40% (24 of 60) and 33.3% (17 of 51) of patients

based on Mayo Score and PUCAI, respectively. Remission was maintained at comparable levels at weeks 30 and 54 among patients in the every-eight-week group at rates that were numerically higher than those in the every-12-week group.

Of all the treated patients in this RCT, 95% experienced more than one adverse event. The number of patients experiencing at least one serious adverse event was similar in both infliximab every-eight-week and every-12-week arms: 18.2% (4/22) and 21.7% (5/23), respectively. More than half of patients treated with infliximab reported the occurrence at least one infection (51.7%).

In addition, we identified one observational study conducted in Australia that compared colectomy rates among 204 children diagnosed with UC in two time periods: 2005 to 2010 (group 1, n=71) and 2011 to 2016 (group 2, n=133). The 2011 cutoff was chosen based on the timing of approval of infliximab for children in Australia. The two-year cumulative probability of colectomy significantly decreased between these two time periods from 14% to 3% (p=0.02). The use of infliximab was independently associated with the decreased rates of colectomy (OR: 3.7; 95% CI: 1.1 to 11.7, p=0.02).[108]

Geriatric Population

Geriatric patients with IBD (UC and Crohn's disease) can be divided into two groups: patients with long-standing disease (i.e., first diagnosis at a younger age) and patients with a late onset of disease.[120,121] The symptoms of disease activity including abdominal pain, fecal urgency, and rectal bleeding are largely similar to those of younger patients.[20,122] While the prevalence of UC in elderly populations has been increasing steadily, the availability of evidence is very limited in elderly patients as compared to younger patient populations. Most published trials do not report outcomes stratified by age (>65 years). Only two trials included in this review reported subgroup analyses stratified by age group, one head-to-head trial[8] and one placebo-controlled trial (GEMINI 1).[123]

In GEMINI 1, of the total randomized population (n=895), only 15 patients ages 65 years or older were included. At the end of maintenance, one patient in each of the vedolizumab every-eight-week and placebo arms and two patients in vedolizumab every-four-week arm achieved clinical remission. Further, in VARSITY,[8] of the total randomized patients (n=769), a total of 19 patients over the age of 65 years were randomized to the vedolizumab group only. At the end of maintenance, 26.3% of these patients achieved clinical remission, with 42.1% achieving endoscopic improvement. Among the five elderly patients receiving corticosteroids at baseline, only one patient achieved corticosteroid-free remission.

Extraintestinal Manifestations

Systemic EIMs can affect other organ systems (including dermatological, hepatopancreatobiliary, ocular, oral, and musculoskeletal) and occur independently of colon-related disease activity. Despite the increased interest in assessing the role of TIMs in the effective management of EIMs, the evidence base for the effects of treatment on these outcomes is very limited.

In the updated search, we identified a subgroup analysis of the three double-blind RCTs (OCTAVE 1, 2, and SUSTAIN) for tofacitinib. In OCTAVE Induction 1&2 and OCTAVE SUSTAIN, 27.0% and 9.0% of patients had experienced EIMs at baseline, respectively. The most common active EIM was peripheral arthritis, for which the majority of patients in the induction and maintenance periods reported either no change or improvement from baseline.[124]

Comparative Observational Studies

Nine comparative observational studies met our inclusion criteria (sample size ≥500 in adults) and were deemed to be of high quality. All studies included at least 500 UC patients (before propensity-score matching), presented results from analyses adjusted for disease characteristics, and generally had similar follow-up across groups. The key study characteristics are listed in Table 4.18. Eight of the studies had a retrospective study design,[109-111,113,116,117] and one was prospective.[112] Seven studies compared originator TIMs to each other,[109,110,113,116,117] one study compared the infliximab originator to an infliximab biosimilar (infliximab-dyyb; CT-P13),[111] and one study compared infliximab to conventional therapy.[112]

Table 4.18. Key Characteristics and Design of Included Comparative Observational Studies[109-117]

Study	Design	Location	Population	Comparison	Outcomes
Sandborn 2016	Retrospective chart review	US	• N=804 • ≥18 years with moderate-to-severe UC • TNF-naïve	ADA vs. IFX	• Partial Mayo Score • Remission
Singh 2017	A propensity-matched retrospective registry study	Denmark	• N=1,719 (before matching); 275 (after matching) • ≥15 years with UC • Biologic-naïve	ADA vs. IFX	• Hospitalizations • Colectomy • Steroid use • Serious infections
Singh 2016	A propensity-matched database study (Optum)	US	• N=1,400 (before matching); 816 after matching • ≥18 years with UC • Had not received biologic therapy in prior 12 months	ADA vs. IFX	• Hospitalizations • Colectomy • Steroid use • Serious infections
Han 2020*	Retrospective database study (administrative claims)	South Korea	• N=862 • UC: age not specified • Biologic-naïve	ADA vs. IFX	• Colectomy • ER visits • Hospitalization • Steroid use
Long 2019	Retrospective database study (IBM)	US	• N=3,562 • ≥18 years with UC • Had not received biologic therapy in prior 12 months	ADA vs. IFX vs. GOL vs. VEDO vs. IMM therapy	• Remaining steroid free • Hospitalizations
Panes 2019	Prospective registry study (OPUS)	Multi-national	• N=2,239 • ≥18 years with moderate-to-severe UC • IFX-naïve or IFX-free for ≥90 days	IFX vs. conventional therapy	• AEs including serious infection
Yarur 2019*	Retrospective chart review	Multi-national	• N= 527 (VEDO pts= 325; anti-TNF-202) • ≥18 years with UC • Biologic-naïve	VEDO vs. TNFs	• Effectiveness and AEs including serious AEs and serious infections
Dubinsky 2018	Retrospective database study (Truven)	US	• N=26,505 • ≥18 years with IBD (CD, n=18,055; UC, n=8,450) • TNF-naïve	VEDO vs. TNFs	• Rate of newly diagnosed EIMs
Meyer 2019	Retrospective database study (administrative claims)	France	• N=3,112 • ≥15 years with UC • IFX naïve	IFX vs. IFX-dyyb	• Composite endpoint (death, UC-related surgery, all-cause hospitalization, or reimbursement of another TIM) • Serious infections

ADA: adalimumab, AE: adverse event, EIM: extraintestinal manifestation, ER: emergency room, GOL: golimumab, IBD: inflammatory bowel disease, IFX: infliximab, IMM: immunomodulator, N: number, OPUS: Observational Post-Marketing Ulcerative Colitis Study, TIM: targeted immune modulator, TNF: tumor necrosis factor, UC: ulcerative colitis, US: United States, VEDO: vedolizumab

*Identified in updated search.

Four retrospective studies compared infliximab and adalimumab (Singh 2016, Singh 2017, Sandborn 2016, and Han 2020). Singh 2017 and Singh 2016 were similarly designed retrospective, propensity score-matched studies comparing adalimumab and infliximab on outcomes including hospitalizations, colectomy, steroid use, and serious infections.[114,115] Singh 2017 included 1,719 biologic-naïve patients with UC in Denmark. After propensity score matching based on variables including demographic characteristics and disease severity, 275 patients were included in the analysis, 171 in the infliximab group and 104 in the adalimumab group. Adalimumab was shown to have a higher risk of all-cause hospitalizations compared to infliximab (HR: 1.84; 95% CI: 1.18 to 2.85) and a trend towards a higher risk of UC-related hospitalizations (HR: 1.71; 95% CI: 0.95 to 3.07).[114] Rates of colectomy did not differ between the groups. Adalimumab had a higher risk of serious infections requiring hospitalization compared to infliximab (HR: 5.11 95% CI: 1.20 to 21.80).[114] Singh 2016 included 1,400 patients with UC that had not been treated with a biologic in the previous 12 months. After propensity score matching, 816 patients were analyzed, 544 in the infliximab group, and 272 in the adalimumab group. In contrast to the evaluation above, there were no differences in the risk of all-cause hospitalizations, UC-related hospitalizations, steroid use, or serious infections.[115]

One study compared the safety of infliximab and conventional therapy (Panes 2019).[112] This study was a prospective study, called the Observational Post-Marketing Ulcerative Colitis Study (OPUS), in 2,239 patients treated with infliximab (n=1,059) or conventional therapy (n=1,180). Patients were followed for up to five years. In the time-to-event analysis adjusted for multiple patient characteristics, such as disease severity, infliximab was shown to have a significantly higher risk of serious infections compared to conventional therapy (hazard ratio [HR]: 1.98; 95% CI: 1.34 to 2.91).

Sandborn 2016[113] was a chart review of 804 TNF-naïve adults with UC that compared the effectiveness of adalimumab (n=380) and infliximab (n=424) in achieving remission, as measured by partial Mayo Score. At six months, the rates of remission with adalimumab and infliximab were similar (76.8% vs. 71.0%, respectively, no statistical differences). Additionally, in a time-to-event analysis adjusted for multiple patient characteristics, such as disease severity, the likelihood of remission was similar for adalimumab and infliximab (HR: 1.07; 95% CI: 0.87 to 1.31). Of note, the rates of clinical remission observed in this real-world study are higher than those observed in RCTs. The authors suggest that higher rates of remission observed in this study could be attributed to a number of factors; these factors include using the partial Mayo Score as opposed to full the Mayo Score to measure remission, the inclusion of only biologic-naïve patients, and shorter disease duration at baseline (mean disease duration in this study was 4.4 to 4.8 years). Han 2020 was a database study of 862 biologic-naïve patients with UC treated with infliximab (n=630) or adalimumab (n=232) in South Korea. After a median follow-up of 1.8 years, there were no significant differences between infliximab and adalimumab in the risk of colectomy (HR: 1.87; 95% CI: 0.30 to 11.63), emergency room visits (HR: 1.58; 95% CI: 0.79 to 3.16), hospitalizations (HR: 0.83;

95% CI: 0.59 to 1.17), or corticosteroid use (HR: 1.16; 95% CI: 0.76 to 1.78) in analyses adjusted for multiple patient characteristics.

Three retrospective studies compared vedolizumab and the TNF inhibitors; one study compared all agents to each other (Long 2019) and two compared vedolizumab to the TNF inhibitors as a class (Dubinksy 2018 and Yarur 2019). Long 2019[110] was a database study in 3,562 adults with UC that compared the effectiveness of adalimumab (n=1,291), golimumab (n=127), infliximab (n=810), and vedolizumab (n=103); additionally, the TIMs were also compared to immunosuppressant therapy alone (N=1,231) in unadjusted analyses. The proportions of patients remaining steroid-free and the proportion of patients experiencing a UC-related hospitalization at 12 months are reported in Table 4.19. Results are shown for unadjusted analyses as well as analyses adjusted for multiple patient characteristics, such as disease severity. The significance of the differences of the rates is only reported in adjusted analyses; adalimumab was chosen as the reference cohort given its larger sample size. Additionally, the rates with immunosuppressant therapy are only reported in the unadjusted analysis for remaining steroid-free. In the adjusted analysis, the proportion of patients remaining steroid-free at 12 months was moderately higher for infliximab compared to adalimumab (43.9% vs. 39.4%, p<0.05). In contrast, the adjusted proportion of patients with a UC-related hospitalization was higher with infliximab compared to adalimumab (20.4% vs. 16.3%, p<0.05).

Table 4.19. Effectiveness Outcomes from Long 2019 at 12 Months[110]

Treatment	N	Remaining Steroid-Free			UC-Related Hospitalizations		
		Unadjusted Analysis	Adjusted Analysis*		Unadjusted Analysis	Adjusted Analysis*	
		%	%	p-Value	%	%	p-Value
ADA	1,291	43.6	39.4	Reference	12.9	16.3	Reference
GOL	127	41.7	38.2	NS	8.7	10.5	NS
IFX	810	48.3	43.9	<0.05	18.3	20.4	<0.05
VEDO	103	46.6	41.4	NS	9.7	15.6	NS
IMM	1,231	52.7	NR		NR	NR	NR

ADA: adalimumab, GOL: golimumab, IFX: infliximab, IMM: immunomodulator, N: number, NR: not reported, NS: not specified, UC: ulcerative colitis, VEDO: vedolizumab

*Adjusted for patient characteristics, such as disease severity.

Dubinsky 2018[109] was a retrospective database study of 26,505 TNF-naïve adults with IBD (Crohn's disease, n=18,055; UC, n=8,450) conducted in the US. The study compared vedolizumab and TNF inhibitors for incidence of EIMs. In patients with UC, there were no significant differences in the rate of newly diagnosed EIMs between the vedolizumab group (n=554) and the TNF inhibitor group (n=7,896) in an analysis adjusted for disease characteristics (incidence rate ratio [IRR]: 1.20, 95% CI: 0.91 to 1.59). However, UC patients were reported to be 3.67 times more likely to develop aphthous stomatitis with vedolizumab compared to TNF inhibitors (IRR, 3.67; 95% CI, 1.30-10.34).

Yarur 2019[117] was a comparative chart review (the EVOLVE study) of 527 biologic-naïve UC patients treated with vedolizumab (n=325) or TNF inhibitors (n=202 [adalimumab: 58, infliximab: 120, and golimumab: 24]). At 24 months, the cumulative rates of clinical response (91% vs. 86%), remission (79% vs. 66%), and mucosal healing (92% vs. 84%) did not differ significantly between the vedolizumab and TNF inhibitor groups. However, the risk of experiencing UC exacerbation (HR: 0.7, 95% CI: 0.5 to 0.9, p=0.02) and serious adverse events (HR: 0.5, 95% CI: 0.3 to 0.8, p<0.01) was statistically significantly lower for vedolizumab in comparison to the TNF inhibitors.

Lastly, Meyer 2019[111] compared the infliximab originator product to an infliximab biosimilar (infliximab-dyyb/CT-P13). This study was a retrospective database study in 3,112 infliximab-naïve patients treated with infliximab (n=1,434) or infliximab-dyyb (n=1,678) in France. The main outcome was a composite endpoint (death, UC-related surgery, all-cause hospitalization, or reimbursement of another TIM). The cumulative incidence (95% CI) of the composite endpoint was 43.0% (40.5-45.6) and 57.5% (54.9-60.0) for infliximab at 12 and 24 months, respectively, compared to 45.1% (42.7-47.5) and 59.8% (57.5-62.1) for infliximab-dyyb; these rates did not statistically differ between groups. Regarding safety, however, fewer serious infections were observed with infliximab-dyyb compared to infliximab (HR: 0.65; 95% CI: 0.48 to 0.88).

Harms

- ***Severe and serious adverse events were rare during the induction and maintenance phases. Upper-respiratory tract infections and headaches were the most reported adverse events across the TIMs. There was no indication of increased rates of serious infections, tuberculosis, and mortality for any of the agents in available RCTs.***

Randomized Controlled Trials

Data on adverse events and discontinuations due to adverse events as well as administration reactions and infections observed in induction (see Appendix Table D15) and maintenance (see Table 4.20) phases of the clinical trials have been summarized. Since safety data were not consistently reported according to stratification by prior biologic exposure, we summarized these data on the overall population for the relevant doses used in each trial phase.

Mortality rates across trials were low during both induction as well as maintenance phases. Overall, one event was reported in PURSUIT-SC (0.3%), GEMINI (2.2%), OCTAVE 1 (0.2%), and UNIFI (0.3%) during the induction phase. In the maintenance phase, the PURSUIT-M trial reported three (1.9%) deaths. Of note, the label for tofacitinib was modified in July 2019 given the results from a long-term clinical trial for safety in rheumatoid arthritis patients.[10] Modifications included warnings related to thrombotic events (deep vein thrombosis, arterial thrombosis, and pulmonary embolism) as well as cardiovascular mortality in patients receiving the 10 mg twice daily dose. We note that the three TNF inhibitors (adalimumab, golimumab, and infliximab) as well as tofacitinib carry a black

box warning in their FDA labels for an increased risk of lymphomas and other malignancies observed in children, adolescents, and/or young adults based on clinical trials and real-world evidence for these TIMs when studied for other indications (e.g., rheumatoid arthritis).[11-14] In our evidence base for UC, overall rates of new malignancy were very low (<3%) and no study in our sample indicated an increased risk for any TIM.

The most frequently reported adverse events across the placebo-controlled trials were mild infections (e.g., upper respiratory tract infections), administration reactions, including injection site reaction, headache, and nausea. In the induction trials, the rates of adverse events were low across the trials. Analyses of the maintenance phase of ACT 1 indicated a higher proportion of patients experiencing upper respiratory tract infections in the infliximab 10 mg/kg arm (23.8%) than in the infliximab 5 mg /kg arm (16.5%), but rates were comparable to the placebo arm (23.1%). In the VISIBLE 1 trial for vedolizumab, a higher proportion of patients experienced adverse events in the placebo arm than the vedolizumab IV arm (32.1% vs. 11.1%).

The rates of serious infection, serious adverse events, and discontinuations due to adverse events were generally low and comparable in the head-to-head trial comparing vedolizumab with adalimumab. In placebo-controlled trials, the risk of severe or serious adverse events and serious infections was low and generally comparable between the treatment and placebo groups. There was one report of tuberculosis in Suzuki 2014 (1.1%). There was no evidence on the increased risk of serious infections in the placebo-controlled trials. In the infliximab trials, no serious infections were reported for the placebo arms of the Asian trials (Jiang 2015, Kobayashi 2016, and NCT01551290).[68,80,81] In the PURSUIT-M trial, the rate of serious infections was marginally higher in the golimumab treatment arms than the placebo arm (3.2% vs. 1.9%), but this was not statistically tested.[94] Further, the rates of new-onset autoimmune disease and demyelinating disease were low across the trials.

Immunogenicity to TIM therapy (i.e., development of neutralizing antibodies) is a relatively commonly identified effect that may negatively impact rates of response and/or remission.[125,126] The development of neutralizing antibodies was reported in nine trials. Rates ranged tightly from 3-6% at some point after the first infusion, with no one TIM showing significantly higher rates.[80,90]

Long-Term Extensions of Randomized Controlled Trials

Most adverse events in the open-label extension studies were mild-to-moderate in severity. The long-term safety data from the RCTs and open-label extension studies report low rates of serious infections (see Appendix Table D16). Higher rates for discontinuations (249 per 110 PY), serious adverse events (414 per 100 PY), and serious infections (79 per 100 PY) were reported in the ULTRA-2 adalimumab long-term trial, however. Furthermore, the FDA label for tofacitinib was modified in July 2019 given the results from the long-term clinical trial for safety in rheumatoid arthritis patients.[10] In the OCTAVE open-label extension study, rates of serious infection (3.4%) and

serious adverse events (11.8%) were slightly higher than those reported for tofacitinib 10 mg during the RCT. The incidence rate of malignancy for excluding nonmelanoma skin cancer was reported to be 0.69 and 0.75 per 100 patient years for tofacitinib 5 mg and 10 mg, respectively.[103] The risk of thromboembolic events during tofacitinib exposure of up to 6.1 years was estimated for deep vein thrombosis (IR: 0.04, 95% CI: 0.00-0.23) and pulmonary embolism (IR:0.16; 95% CI: 0.04-0.41).[104]

In the PURSUIT maintenance extension study, seven of nine (overall IR: 0.44, 95% CI: 0.18, 0.90) deaths occurred in patients treated with golimumab 100 mg through week 212.[84] The safety profile for ustekinumab was largely similar to that observed in the RCT. No malignancy was reported, and the rates of serious infections remained low (1.4%) in the long-term extension (through week 96) among responders to ustekinumab IV induction.[105]

Table 4.20. Adverse Events During the Maintenance Phase

Trial	Arm	N	Any AE	SAE	AE Leading to D/C	Overall Infections	Serious Infections	Infusion or Injection Site Reaction	URTI	Headache	Antibodies n/N (%)
Head-to-Head											
VARSITY	VEDO 300 mg	383	240 (62.7)	42 (11.0)	10 (2.6)	103 (23.4)	7 (1.6)	NR	55 (12.5)	NR	NR
	ADA 40 mg	386	267 (69.2)	53 (13.7)	13 (3.4)	124 (34.6)	8 (2.2)	NR	65 (18.1)	NR	NR
Infliximab											
ACT 1	IFX 5 mg/kg	121	106 (87.6)	26 (21.5)	10 (8.3)	53 (43.8)	3 (2.5)	12 (9.9)	20 (16.5)	22 (18.2)	14/243 (5.8)
	IFX 10 mg/kg	122	111 (91.0)	29 (23.8)	11 (9.0)	60 (59.2)	8 (6.6)	15 (12.3)	29 (23.8)	18 (14.8)	
	PBO	121	103 (85.1)	31 (25.6)	11 (9.1)	47 (38.8)	5 (4.1)	13 (10.7)	28 (23.1)	27 (22.3)	--
ACT 2	IFX 5 mg/kg	121	99 (81.8)	13 (10.7)	2 (1.7)	33 (27.3)	2 (2.5)	14 (11.6)	16 (13.2)	19 (21.7)	12/241 (5.0)
	IFX 10 mg/kg	120	96 (80.0)	11 (9.2)	5 (4.2)	34 (28.3)	3 (1.7)	14 (11.7)	14 (11.7)	26 (15.7)	
	PBO	123	90 (73.2)	24 (19.5)	12 (9.8)	29 (23.6)	1 (0.8)	10 (8.1)	14 (11.4)	18 (14.6)	--
Jiang 2015	IFX 5 mg/kg	41	17 (41.5)	3 (7.3)	1 (2.4)	6 (14.6)	1 (2.4)	3 (7.3)	NR	NR	2/40 (5.0)
	PBO	41	16 (39.0)	4 (9.8)	2 (4.9)	5 (12.2)	0 (0)	2 (4.9)	NR	NR	--
Kobayashi 2016	IFX 5 mg/kg	73	100 (96.2)	18 (17.3)	7 (6.7)	62 (59.6)	1 (1)	16 (15.4)	NR	NR	NR
	PBO	72	94 (90.4)	19 (18.3)	8 (7.7)	51 (49.0)	2 (1.9)	11 (10.6)	NR	NR	--
NCT01551290	IFX 5 mg/kg	50	33 (66.0)	7 (14.0)	4 (8.0)	13 (26.0)	0 (0)	NR	NR	NR	
	PBO	49	31 (63.3)	4 (8.2)	2 (4.1)	7 (14.3)	0 (0)	NR	NR	NR	--
Adalimumab											
ULTRA 2	ADA 40 mg	248	213 (82.8)	31 (12.1)	23 (8.9)	116 (45.1)	4 (1.6)	31 (12.1)	NR	NR	7/245 (2.9)
	PBO	246	218 (83.8)	32 (12.3)	34 (13.1)	103 (39.6)	5 (1.9)	10 (3.8)	NR	NR	--
Suzuki 2014 ***(Per 100 PY)***	ADA 40 mg	177	538 (547.9)	33 (33.6)	22 (13.4)	134 (136.5)	8 (8.1)	20 (20.4)	NR	NR	5/177 (2.8)
	PBO	96	273 (609.4)	14 (31.3)	6 (22.4)	70 (156.3)	2 (4.5)	4 (8.9)	NR	NR	--
Golimumab											
PURSUIT-M	GOL 100 mg	154	113 (73.4)	22 (14.3)	14 (9.1)	60 (39.0)	5 (3.2)	11 (7.1)	9 (5.8)	12 (7.8)	32/1103 (2.9)
	PBO	156	103 (66.0)	12 (7.7)	10 (6.4)	44 (28.2)	3 (1.9)	3 (1.9)	4 (2.6)	14 (9.0)	--
PURSUIT-J	GOL 100 mg	32	31 (96.9)	1 (3.1)	0 (0)	21 (65.6)	NR	6 (18.8)	NR	NR	4/63 (2.5)
	PBO	31	22 (71.0)	4 (12.9)	1 (3.2)	11 (35.5)	NR	0 (0)	NR	NR	--

Trial	Arm	N	Any AE	SAE	AE Leading to D/C	Overall Infections	Serious Infections	Infusion or Injection Site Reaction	URTI	Headache	Antibodies n/N (%)
Vedolizumab											
GEMINI 1	VEDO 300 mg q4w	125	101 (81)	11 (9)	NR	90 (72)	2 (2)	10 (11)	12 (10)	NR	NR
	VEDO 300 mg q8w	122	100 (82.0)	10 (8.0)	NR	87 (71.0)	3 (2.0)	7 (5.7)	12 (9.8)	NR	NR
	PBO	126	106 (84.0)	20 (16.0)	NR	89 (71.0)	4 (3.0)	2 (1.6)	13 (10.3)	NR	--
Motoya 2019	VEDO 300 mg	41	36 (87.8)	4 (9.8)	2 (4.9)	NR	9 (2.4)	NR	3 (7.3)	2 (4.9)	NR
	PBO	42	33 (78.6)	3 (7.1)	6 (14.3)	NR	10 (2.4)	NR	1 (2.4)	1 (2.4)	--
VISIBLE 1	VEDO 300mg q8w	54	41 (75.6)	7 (13.0)	2 (3.7)	15 (27.8)	NR	1 (1.8)	2 (3.7)	0	3/54 (6.0)
	PBO	56	43 (76.8)	6 (10.7)	5 (8.9)	14 (25.0)	NR	0	1 (1.8)	6 (10.7)	--
Tofacitinib											
OCTAVE SUSTAIN	TOF 5 mg	198	143 (72.2)	10 (5.1)	18 (9.1)	71 (35.9)	2 (1.0)	NR	NR	17 (8.6)	NR
	TOF 10 mg	196	156 (79.6)	11 (5.6)	19 (9.7)	78 (39.8)	1 (0.5)	NR	NR	6 (3.1)	NR
	PBO	198	149 (75.3)	13 (6.6)	37 (18.7)	48 (24.2)	2 (1.0)	NR	NR	12 (6.1)	--
Ustekinumab											
UNIFI	UST 90mg q8w	176	136 (77.3)	15 (8.5)	5 (2.8)	86 (48.9)	3 (1.7)	5 (2.8)	16 (9.1)	18 (10.2)	23/505 (4.6)
	PBO	175	138 (78.9)	17 (9.7)	20 (11.4)	81 (46.3)	4 (2.3)	4 (2.3)	8 (4.6)	7 (4.0)	--

ADA: adalimumab, AE: adverse event, D/C: discontinuation, GOL: golimumab, I: induction, IFX: infliximab, kg: kilogram, M: maintenance, mg: milligram, NA: not applicable, NR: not reported, PBO: placebo, PY: patient year, q4w: every 4 weeks, q8w: every 8 weeks, SAE: serious adverse event, TOF: tofacitinib, URTI: upper respiratory tract infection, UST: ustekinumab, VEDO: vedolizumab

Controversies and Uncertainties

While the evidence for each TIM of focus in this review suggests a potential net health benefit in comparison to conventional therapy among patients with moderate-to-severe UC, there are several concerns with trial design and results as well as gaps in evidence that bear mention.

First and foremost, a single trial of the 19 RCTs identified included direct evidence comparing the TIMs. Our comparisons were therefore driven almost exclusively by the conduct of NMAs. Our NMAs were limited by several factors, including differences in the definitions of biologic-naïve and biologic-experienced populations. Likewise, the network of evidence was sparse for some of our populations of interest (e.g., maintenance data in the biologic-experienced population), adding uncertainty to our relative estimates of response and remission.

As noted by the Crohn's and Colitis Foundation, there is currently very limited information with which to ascertain the optimal sequence of treatment. Some insight can be gleaned from assessing results for the biologic-naïve and biologic-experienced populations, but the definition of "experienced" varied across trials. In some cases, the focus was on failure to achieve response alone, while in others, those achieving and losing response were also included. Still, other trials focused on experience only with certain drug classes (e.g., TNF inhibitors). Finally, some agents have no evidence in the populations of interest, posing challenges in the interpretation and application of data. For example, clinicians mentioned great interest in the use of infliximab following failure by vedolizumab, but there are no randomized data for this treatment sequence, likely due to infliximab's status as the first biologic agent approved for UC.

We note other differences in population characteristics and measurement in available trials. While populations were broadly similar with respect to age and baseline disease severity, variation was noted in disease duration as well as use of conventional therapy at baseline. Regarding measurement, some studies used central endoscopy reading to inform Mayo Scores, while others allowed these readings to occur at study sites. While variability in local readings is unlikely to have biased within-trial comparisons, the impact on indirect comparisons in our NMA is less clear. We also had only partial Mayo Scores to inform maintenance rates used in our NMA in the one head-to-head trial available. In addition, substantial variation has been noted in definitions of endoscopic factors, histologic features, and serum or fecal biomarkers across UC trials.[15]

As is often the case with therapies for chronic inflammatory diseases, evidence of long-term safety comes from the conduct of observational studies using large datasets. While such data exist for the more established therapies in our set, there are limited to no long-term data on newer UC therapies, such as tofacitinib, ustekinumab, and vedolizumab. We note, for example, that the FDA recently changed the label for tofacitinib to allow use in UC only after initial TNF inhibitor therapy and added boxed warnings for elevated risks of pulmonary embolism and all-cause mortality. But these changes were based on observations in populations with rheumatoid arthritis, not UC.

There are uncertainties around not only what has been measured in available UC studies but what has not. Concerns were raised around the EIMs of the disease, but we found very little empiric data on the frequency of these manifestations and, more importantly, the impact of treatment on them. Other concerns raised by patients, such as chronic pain and fatigue as well as fecal urgency, have gone largely unaddressed by available studies. Finally, even though a substantial proportion of cases of UC are diagnosed in childhood and adolescence, there is essentially a complete absence of robust comparative evidence to inform treatment strategies in this population. Only one of the TIMs, infliximab, carries an FDA indication for treatment in patients age <18 years, and this comes only on the strength of a dose-finding study without comparison to alternative TIMs or even to conventional therapy. While there is no obvious reason to believe that TIMs would operate differently in children and adolescents, the absence of comparative data among those most likely to benefit from early intervention is nevertheless troubling.

4.4 Summary and Comment

As mentioned previously, we organized our review and synthesis of the evidence by a) prior biologic use and b) use of therapy during the induction versus maintenance phases of treatment. However, while clinical guideline statements also employ these strata in their reviews of the evidence, recommendations are not specific to patient population or phase of treatment. For example, if a therapy is recommended to induce remission, continued maintenance treatment with that therapy is also recommended. In addition, FDA labeling and payer coverage policies (see Section 3) do not make these distinctions.

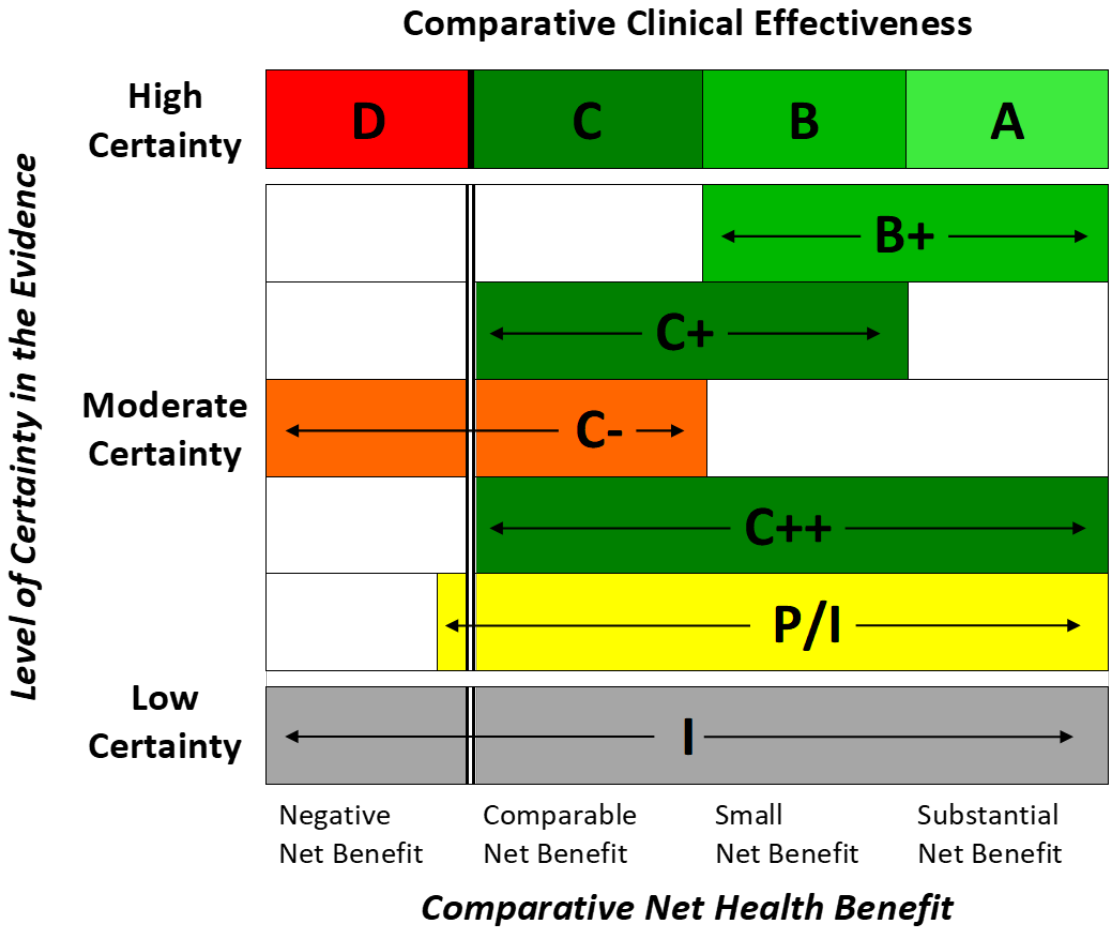
Therefore, we produced a single set of evidence ratings for all therapy comparisons using the ICER Evidence Rating Matrix, considering therapy performance across all strata. We note the few instances in which our evidence ratings apply to a specific population due to FDA labeling or evidentiary limitations. As mentioned earlier, there was only one head-to-head trial available in the evidence base, so all remaining comparisons between TIMs were based on our assessment of their benefits in placebo-controlled trials and observational studies as well as our NMAs. Further, safety data were not consistently reported across studies and populations and were therefore not quantitatively synthesized. Nevertheless, safety concerns identified in RCTs, open-label extension studies, and observational or real-world evidence played a role in determining the evidence ratings for each agent.

Note that we have opted to rate infliximab-dyyb and infliximab-abda, the two biosimilars to infliximab, as comparable ("**C**") to the originator product, and so the evidence ratings that follow involve comparisons to infliximab as a single entity. This rating is based on the FDA's determination that the biosimilars are therapeutically equivalent in UC.

Finally, while there is no obvious reason to suggest that TIM performance would markedly differ in children and adolescents versus adults, we note the complete lack of robust comparative evidence

in pediatric populations for both between-TIM and placebo-controlled comparisons. The ratings summarized below should therefore be considered relevant to adult populations only.

Figure 4.1. 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 Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable 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 small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Table 4.21. Summary of ICER Evidence Ratings

TIM	Comparator	Rating
Infliximab	Infliximab biosimilars	C
Infliximab	Placebo	A*
Golimumab	Placebo	A*
Tofacitinib	Placebo	B+†
All other TIMs	Placebo	A
Vedolizumab	Adalimumab	B+
Ustekinumab	Adalimumab	C+
Infliximab	Adalimumab	C+*
Tofacitinib	Adalimumab	P/I†
Vedolizumab	Golimumab	C+*
All other TIM Comparisons	--	I

TIM: targeted immune modulator

*Biologic-naïve only.

†Biologic-experienced only.

Targeted Immune Modulators versus Placebo

Across populations stratified by prior biologic use and phase of treatment, the addition of TIMs to conventional therapy consistently performed better than conventional therapy alone in RCTs. For all placebo comparisons other than tofacitinib, we felt there was high certainty of a substantial net benefit (an "**A**" rating), as no serious safety signals were evident from RCTs (note that this rating applies to the biologic-naïve population for golimumab and infliximab, given a lack of evidence in biologic-experienced patients).

Given the recent black-box warnings regarding thrombosis and cardiovascular death for tofacitinib, however, our certainty was only moderate. We judged the evidence to indicate a small or substantial benefit ("**B+**"), given the uncertainty in how the benefits seen with tofacitinib would trade-off against its risks. We further note that this rating is applicable to the biologic-experienced population only given the recent FDA labeling changes.

Between Targeted Immune Modulator Comparisons

The only comparison between TIMs that involved direct head-to-head evidence is that of vedolizumab versus adalimumab. The VARSITY study showed substantial and statistically significant differences in remission, response, and other measures of health benefit in favor of vedolizumab. These findings were generally bolstered by the addition of indirect evidence in our NMAs. However, with only one head-to-head trial available, and variation in apparent effect size across the four NMAs, we concluded that there was only moderate certainty of a small or substantial net health benefit for vedolizumab in relation to adalimumab ("**B+**").

Other comparisons to adalimumab are based on indirect evidence only. We found the evidence directionally consistent across the four populations for both infliximab (in biologic-naïve patients only) and ustekinumab to indicate a net health benefit that is at least comparable, and likely incremental, relative to adalimumab ("**C+**"). While we generally concluded the same for tofacitinib (in biologic-experienced patients only), the safety concerns associated with this agent resulted in a promising but inconclusive ("**P/I**") rating versus adalimumab.

In comparison of vedolizumab and golimumab (among biologic-naïve patients only), NMA findings were directionally in favor of vedolizumab for both induction and maintenance, with results reasonably robust for maintenance. We judged this evidence to suggest a net health benefit for vedolizumab that was a least comparable, and likely incremental, relative to golimumab ("**C+**").

For all other comparisons between TIMs, there was variability in the rankings between them across our populations of interest, wide confidence intervals around the estimates of effect, or both. Because of this variability, we judged all these comparisons to reflect insufficient ("**I**") evidence of a net health benefit.

5. Long-Term Cost Effectiveness

5.1 Overview

A decision analytic model was developed for this evaluation, informed by key clinical trials and prior relevant economic models, to estimate the cost effectiveness of TIMs for moderate-to-severe UC in biologic-naïve and biologic-experienced populations. The model compared all eight treatments to each other and to conventional treatment. The base-case analysis took a health care sector perspective (i.e., focused on direct medical care costs only), over a lifetime time horizon. Due to uncertainty of treatment patterns over a lifetime time horizon, shorter time horizons of two, five, and 10 years were explored as additional scenario analyses. The model was structured as a Markov model with eight-week cycles, based on a common point of assessment in clinical trials to mark the end of induction and beginning of maintenance treatment. Costs and outcomes were discounted at 3% per year.

The TIMs evaluated include:

- Adalimumab
- Golimumab
- Infliximab
- Infliximab-dyyb
- Infliximab-abda
- Tofacitinib
- Ustekinumab
- Vedolizumab (IV)

Model outcomes included total costs, life years (LYs), quality-adjusted life years (QALYs), and equal value of life years gained (evLYG). Methods used to calculate evLYG can be found in Appendix E.[127]

5.2 Methods

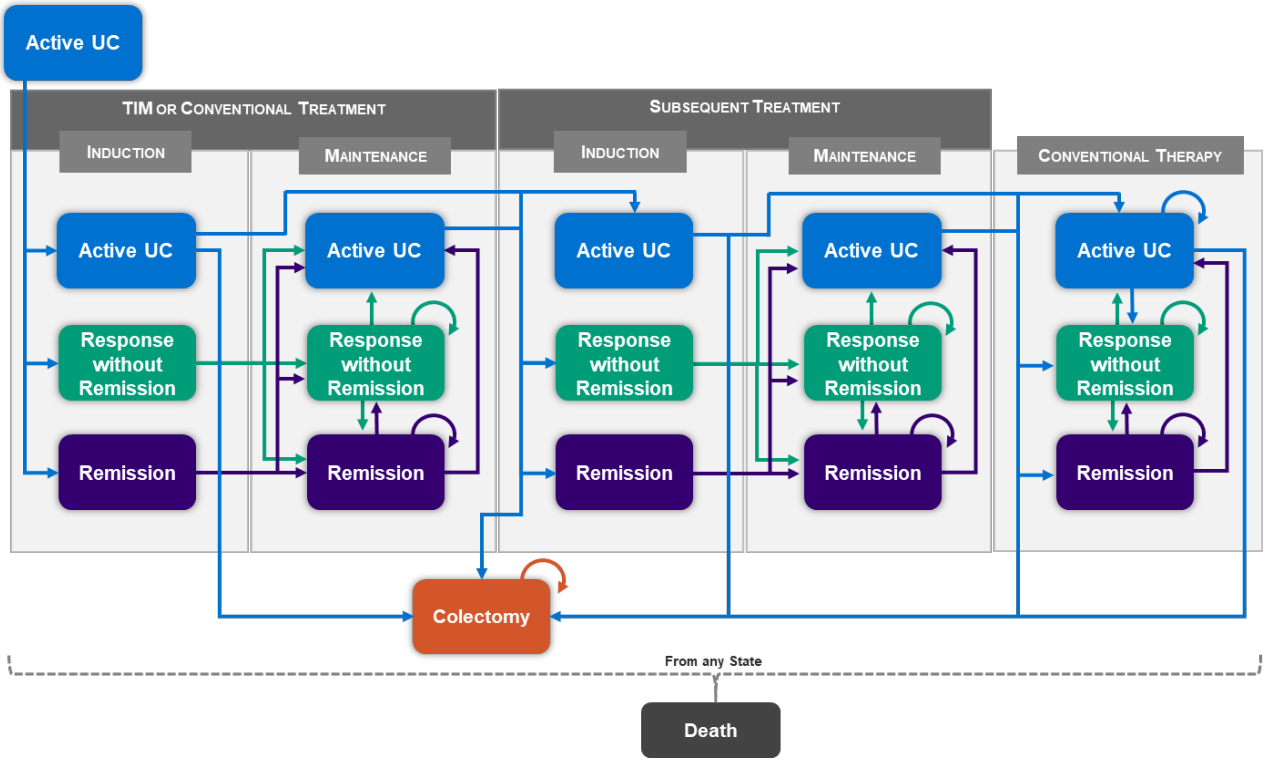
Model Structure

A Markov model was developed in Microsoft Excel 365 consisting of the health states of active UC, clinical response without remission, clinical remission, post-colectomy (with and without complications), and death (Figure 5.1). The model structure and health states were chosen based on the disease course, the impact of treatment, and prior economic models in UC. Moderate-to-severe UC patients enter the model at the beginning of induction of a TIM or conventional treatment. At the end of induction, patients with response (both with and without remission)

continue to receive the TIM or conventional treatment. Those without response or those who discontinue after initial response begin induction with a subsequent treatment, represented by a market basket of all TIMs with data in a biologic-experienced population. At the end of induction with subsequent treatment, responders continue to receive the subsequent treatment. Patients who do not respond during the induction phase of subsequent treatment discontinue treatment with TIMs and follow the transition probabilities of the conventional treatment arm (e.g., corticosteroids, other systemic immunomodulators). A proportion of patients in the active UC state are assumed to opt for colectomy during each cycle.[128]

Patients remain in the model until death. All patients can transition to death from all causes from any of the alive health states. In addition, patients can die from surgical complications of colectomy.

Figure 5.1. Model Framework



UC: ulcerative colitis

Target Population

The economic evaluation includes two target populations: 1) biologic-naïve and 2) biologic-experienced. These two groups are generally similar in age, gender, and weight but have been shown to differ in clinical response to TIMs. The cost-effectiveness and threshold prices were evaluated for both patient populations, with an eventual health benefit price benchmark (HBPB)

weighted by the estimated proportions of patients with and without prior biologic use. When TIM efficacy data were not available for one of the populations or if a TIM was not labeled for use in a specific population, the TIM was not assessed in that population.

Table 5.1. Baseline Population Characteristics

	Mean Age	Percent Male	Weight	Source
Biologic-Naïve	40 years	59%	74.3 kg	GEMINI 1[77]
Biologic-Experienced	40 years	59%	74.3 kg	GEMINI 1[77]

kg: kilogram

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. The full list of interventions is as follows:

- Adalimumab
- Golimumab
- Infliximab
- Infliximab-dyyb
- Infliximab-abda
- Tofacitinib
- Ustekinumab
- Vedolizumab (IV)
- Conventional treatment (corticosteroids for induction followed by azathioprine or mercaptopurine)

Key Model Characteristics and Assumptions

Below is a list of key model choices in the base-case analysis.

- Cycle length of eight weeks
- Lifetime time horizon
- Three percent annual discount rate for costs and outcomes
- Probability of achieving response without remission or response with remission at the end of induction informed by the results of the ICER NMA
- Given response at the end of induction, probability of being in clinical response without remission or clinical remission at the end of maintenance is informed by the results of the ICER NMA
- Patients remaining in active UC at the end of induction will discontinue the treatment and initiate the next line of therapy

- Constant per-cycle rate of discontinuation unrelated to clinical response (e.g., adverse events, other reasons) based on discontinuation rates for reasons other than lack of efficacy from RCTs
- The model considers initial treatment and subsequent treatment with a TIM; after failure of subsequent treatment, patients are assumed to discontinue to conventional treatment
- Constant per-cycle probability of elective colectomy only from the active UC health state
- Direct health state costs, including hospitalization, emergency department visits, and outpatient visits, based on published claims analysis
- Mortality based on US Life Tables, adjusted for elevated risk of mortality due to UC
- Model includes one-time risk of mortality associated with colectomy
- Costs and disutility of serious infection with TIMs and conventional treatment and complications of colectomy are included

Our model includes several key assumptions stated in Table 5.2 below.

Table 5.2. Key Model Assumptions

Assumption	Rationale
Conventional treatment is represented by the control arm of RCTs.	In the real world and in controlled trials, background conventional treatment is taken in addition to TIMs.
All patients will cycle through initial treatment and subsequent treatment before discontinuing to conventional treatment.	Multiple TIMs may be tried over a lifetime time horizon; however, the focus of this evaluation is to estimate the cost effectiveness of the initial choice of TIM in a biologic-naïve or biologic-experienced population rather than entire treatment pathways.
Choice of the subsequent treatment is represented by a market basket of equal distribution of all TIMs with data in a biologic-experienced population. Efficacy, safety, and cost are informed by an average of treatments in the biologic-experienced population. Probabilities for any given patient to receive any given therapy in the market basket are assumed to be equal in the absence of contemporary real-world data on utilization patterns in the US.	Incomplete data exists on the efficacy of specific treatment sequences; thus, the market basket approach is taken to focus the analysis on the intervention of interest.
The transition probabilities for clinical response without remission and clinical remission to subsequent health states in the maintenance phase are equal.	Data is only available for transitions from the end of induction to the end of maintenance for response (with and without remission) combined.

RCT: randomized controlled trial, TIM: targeted immune modulator, US: United States

Model Inputs

Clinical Inputs

Efficacy data were derived from the results of the ICER NMAs of RCTs of TIMs in moderate-to-severe UC (one each for biologic-naïve and biologic-experienced), with data from the placebo arms used as a proxy for conventional treatment.

Clinical Probabilities/Response to Treatment

For each of the biologic-naïve and biologic-experienced populations, a set of transition probabilities was created based on the placebo group of the NMA for the induction phase (Cycle 1) and maintenance phases (Cycles 2+). In the induction phase, we calculated the probability of achieving response without remission and clinical remission at the end of induction. Conditional upon achieving response entering the maintenance phase, we calculated the probability of achieving clinical response without remission, clinical remission, or losing response at the end of maintenance.

Table 5.3. Conventional Treatment Induction Outcomes

Population	Active UC	Response	Remission	Source
Biologic-Naive	65%	26%	9%	ICER NMA
Biologic-Experienced	74%	22%	4%	ICER NMA

ICER: Institute for Clinical and Economic Review, NMA: network meta-analysis, UC: ulcerative colitis

Table 5.4. Conventional Treatment Maintenance Outcomes

Biologic-Naïve	Active UC	Response	Remission	Source
Clinical Remission	60%	14%	26%	ICER NMA
Clinical Response without Remission	60%	14%	26%	ICER NMA
No Response (Active UC)	88%	9%	3%	ULTRA 2*[93]
Biologic-Experienced	**Active UC**	**Response**	**Remission**	**Source**
Clinical Remission	73%	14%	13%	ICER NMA
Clinical Response without Remission	73%	14%	13%	ICER NMA
No Response (Active UC)	95%	4%	1%	ULTRA 2*[93]

ICER: Institute for Clinical and Economic Review, NMA: network meta-analysis, UC: ulcerative colitis

*Calculated based on the probability of clinical remission and clinical response without remission among placebo non-responders at the end of maintenance.

Based on the results of the NMAs for the biologic-naïve population and biologic-experienced population, risk ratios for each TIM relative to placebo were calculated and applied to the probability of achieving clinical response (with and without remission) with conventional treatment (Table 5.5 through Table 5.8). The risk ratio for clinical response (with and without remission) at the end of the maintenance for each TIM relative to placebo was applied to the probability of achieving

clinical response (with and without remission) with conventional treatment. The probability of maintaining response (with and without remission) at the end of the maintenance phase was then converted to eight-week cycles. Due to data limitations, we were unable to calculate the risk ratio for maintenance of response without remission specifically among those with response without remission at the start of induction for all treatments. Therefore, the same risk ratio for clinical remission and clinical response without remission at the end of maintenance was applied to patients entering the maintenance phase, regardless of entering maintenance in the clinical response without remission or clinical remission health states.

We also note that, consistent with findings from Section 4, we assumed that clinical performance for infliximab biosimilars was identical to that of the originator product.

Table 5.5. Induction Risk Ratios for the Biologic-Naïve Population

	Clinical Response without Remission	Clinical Remission
Placebo	Reference	Reference
Adalimumab	1.24 (1.13, 1.36)	1.76 (1.38, 2.19)
Golimumab	1.34 (1.22, 1.50)	2.41 (1.89, 3.08)
Infliximab	1.39 (1.22, 1.58)	3.22 (2.60, 3.96)
Infliximab-dyyb	1.39 (1.22, 1.58)	3.22 (2.60, 3.96)
Infliximab-abda	1.39 (1.22, 1.58)	3.22 (2.60, 3.96)
Ustekinumab	1.36 (1.21, 1.54)	2.66 (1.86, 3.73)
Vedolizumab	1.37 (1.23, 1.55)	2.79 (2.18, 3.58)

Table 5.6. Maintenance Risk Ratios for the Biologic-Naïve Population

	Response without Remission	Response with Remission
Placebo	Reference	Reference
Adalimumab	1.09 (0.93, 1.20)	1.47 (0.92, 2.14)
Golimumab	1.08 (0.85, 1.19)	1.35 (0.74, 2.04)
Infliximab	1.09 (0.86, 1.20)	1.80 (1.13, 2.86)
Infliximab-dyyb	1.09 (0.86, 1.20)	1.80 (1.13, 2.86)
Infliximab-abda	1.09 (0.86, 1.20)	1.80 (1.13, 2.86)
Ustekinumab	1.01 (0.49, 1.17)	2.22 (1.17, 3.57)
Vedolizumab	1.08 (0.88, 1.20)	1.93 (1.22, 2.58)

Table 5.7. Induction Risk Ratios for the Biologic-Experienced Population

	Response without Remission	Response with Remission
Placebo	Reference	Reference
Adalimumab	1.04 (0.74, 1.37)	1.09 (0.57, 1.97)
Tofacitinib	1.75 (1.49, 2.07)	4.10 (2.62, 6.18)
Ustekinumab	1.76 (1.50, 2.09)	4.13 (2.71, 6.26)
Vedolizumab	1.47 (1.17, 1.78)	2.38 (1.38, 3.80)

Table 5.8. Maintenance Risk Ratios for the Biologic-Experienced Population

	Response without Remission	Response with Remission
Placebo	Reference	Reference
Adalimumab	1.42 (1.20, 1.69)	2.91 (1.72, 4.65)
Tofacitinib	1.40 (1.18, 1.64)	2.49 (1.46, 3.79)
Ustekinumab	1.40 (1.19, 1.65)	2.49 (1.49, 3.82)
Vedolizumab	1.47 (1.17, 1.78)	3.48 (2.43, 5.03)

Patients have a constant per-cycle risk of elective colectomy from the active UC health state. The per-cycle probability of colectomy is based on a cumulative rate of 25.4% at 20 years (95% CI, 19.8% to 30.8%) from UC diagnosis observed from a cohort of UC patients in Olmstead County, Minnesota from 1997 to 2004, converted to an annual probability of 1.45% (or 0.23% per eight-week cycle).[128]

Delayed Response/Extended Induction

Evidence exists for a few TIMs that some additional patients achieve response if the induction period is extended beyond eight weeks. Furthermore, clinicians engaged during the scoping period of this review also commented that it is not uncommon in clinical practice to wait longer than eight weeks to determine response and non-response to TIMs. Therefore, delayed response was explored in a scenario analysis for TIMs where there is evidence of benefit with extended induction. In this scenario, a 16-week induction period was allowed for a proportion of patients to mirror real-world practice patterns. In the extended induction scenario, patients discontinue at week eight only for reasons other than lack of efficacy. The gain in response with the extended induction scenario is presented in Table 5.9. Detailed calculations to derive these estimates may be found in the Appendix.

Table 5.9. Gain in Response or Remission at 16 Weeks for the Extended Induction Efficacy Scenario

	Clinical Response without Remission	Clinical Remission	Source
Adalimumab	No data	5.7%	Sandborn 2012[93]
Golimumab	No data	28.1%	Colombel 2016[70]
Infliximab	No evidence of additional benefit with extended induction		
Infliximab-dyyb*	No evidence of additional benefit with extended induction		
Infliximab-abda*	No evidence of additional benefit with extended induction		
Tofacitinib	36.3%	13.9%	Rubin 2019[89]
Ustekinumab	Biologic-naïve: 56.6% Biologic-experienced: 41.4%	Biologic-naïve: 18.9% Biologic-experienced: 1.7%	Danese 2019[71]
Vedolizumab	39.0%	No data	NICE FAD[56]

*Assumed to be equivalent to infliximab.

Discontinuation

At the end of induction, patients who remain in active UC discontinue treatment with the TIM or conventional treatment and initiate the next line of therapy. In the maintenance phase, patients who revert to active UC will discontinue treatment with the TIM or conventional treatment and initiate the next line of therapy. The model also considers discontinuation for reasons other than loss of efficacy. For the health states of clinical response without remission and clinical remission, a per-cycle probability of discontinuation was applied based on rates observed in RCTs (Table 5.10). Discontinuation is based on rates of discontinuation for reasons other than loss of efficacy and converted to a per-cycle probability. Based on clinical expert opinion, discontinuation rates are lower among patients who remain on TIMs for a year or more. Elimination of certain discontinuation rates after one year for the initial TIM is explored as a scenario analysis. Note that in this scenario, patients still can discontinue the initial TIM due to loss of efficacy.

Table 5.10. Discontinuation

Parameter	Discontinuation	Per-Cycle Discontinuation	Source
Adalimumab	31/254 (12.2%) had discontinued at 52 weeks	1.98%	ULTRA 2[93]
Golimumab	23/154 (14.9%) had discontinued at 54 weeks	2.37%	PURSUIT[94]
Infliximab	59/229 (25.7%) had discontinued at 152 weeks	1.56%	ACT-1 and ACT-2[88]
Infliximab-dyyb	Assume same as infliximab	--	--
Infliximab-abda	Assume same as infliximab	--	--
Tofacitinib	34/394 (8.6%) had discontinued at 52 weeks	1.38%	OCTAVE Sustain[96]
Ustekinumab	[redacted]	[redacted]	Manufacturer
Vedolizumab	14/122 (11.5%) had discontinued at 52 weeks	1.86%	GEMINI 1[77]

Mortality

Gender- and age-specific mortality are sourced from the Human Mortality Database's US-specific tables.[129] In addition, an elevated risk of mortality is assumed among patients with UC based on a published meta-analysis, which showed a slightly elevated risk of mortality among patients with UC.[130]

UC has been associated with an increased risk of colorectal cancer and colorectal cancer death in large epidemiologic studies.[130,131] The exact pathology of excess colorectal cancer risk is unknown but may be linked to mucosal inflammation.[132,133] The impact of TIMs on the risk of colorectal cancer incidence and mortality is unknown and early research does not suggest a clear beneficial effect.[134] However, TIMs have a hypothetical potential to reduce incidence of colorectal cancer in UC patients through reduced mucosal inflammation. Colorectal cancer incidence and deaths among UC patients have declined over time, which may be attributed partly to improved treatments for UC, among other factors.[135]

A mortality multiplier for colorectal cancer-related mortality was applied for all patients with a colon (i.e., without colectomy) to SEER colorectal cancer-related death rates by age to generate the proportion of elevated mortality risk in UC that is attributable to colorectal cancer.[136] We removed this elevated risk of mortality due to colorectal cancer in the remission health state to capture a potential long-term beneficial effect of endoscopic improvement. No impact of TIMs on non-colorectal cancer-related mortality will be assumed, as data to date does not provide conclusive evidence of impact.[137]

Table 5.11. Mortality Inputs

Parameter	Value	Source
All-Cause Mortality	Gender- and age-specific	US Life Tables[138]
Standardized Mortality Ratio for UC	1.19 (95% CI 1.06-1.35)	Bewtra 2013[130]
Standardized Mortality Ratio for Colorectal Cancer-Related Death in UC	2.82 (95% CI 1.30-1.63)	Bewtra 2013[130]
One-Time Probability of Mortality Among Patients Undergoing Laparoscopic Colectomy	0.2%	Causey 2013[139]
One-Time Probability of Mortality Among Patients Undergoing Open Colectomy Procedure	1.7%	Causey 2013[139]

CI: confidence interval, UC: ulcerative colitis, US: United States

Health State Utilities

We used consistent health state utility values across treatments evaluated in the model and across induction and maintenance. Health state utility values are taken from a published multi-center cross-sectional study of moderate-to-severe UC patients in Australia with mean EQ-5D utility values for patients in remission, active mild UC, and active moderate-to-severe UC.[16](Table 5.12). The impact of alternative sources of utility estimates was evaluated by extending the parameter range of a one-way sensitivity analysis to include lower estimates for active UC and post-colectomy health states from an alternative source of utility values, which have been used in previous cost-effectiveness evaluations in UC.[140,141] An alternative scenario was explored whereby health state utility for active moderate-to-severe UC was informed by an average of EQ-5D scores at baseline across the InspireADA, GEMINI 1, and GO-COLITIS trials, 0.6, 0.675, and 0.7, respectively (average of 0.658).[74,142,143]

Considerable uncertainty exists regarding utility for the post-colectomy health state. In the base case, utility is based on EQ-5D scores from a cross-sectional survey of UC patients in Canada, Australia, and the United Kingdom with a history of colectomy within the prior 10 years.[17] Disutility associated with short-term complications of colectomy and chronic pouchitis is also captured (see Table 5.12). Other long-term complications and the long-term impact of colectomy are assumed to be captured within the utility score applied to the post-colectomy health state. We assume in the model that colectomy induces remission of UC, but at a lower utility compared to drug-induced

remission because of the health consequences of removing the colon and the potential for long-term complications and adverse events not otherwise captured in the disutility of perioperative complications and chronic pouchitis (e.g., fertility, fatigue). The utility value used in the base case (0.79) is similar to the average EQ-5D utility index score reported for another overall post-colectomy UC cohort in the United Kingdom (0.74). This same study also reported a lower utility score for the subset of patients who experienced long-term complications (0.71), which was explored as the lower bound of the point estimate in one-way sensitivity analysis.[144]

Table 5.12. Utility Values for Health States

Parameter	Value (95% CI)	Source	Range for OWSA	Source
Active UC	0.68 (0.63, 0.73)	[16]	0.41 to 0.73	[140]
Clinical Response without Remission*	0.78 (0.71, 0.85)	[16]	0.71 to 0.85	95% CI (calculated)
Clinical Remission	0.81 (0.77, 0.85)	[16]	0.77 to 0.85	95% CI (calculated)
Post-Colectomy	0.79 (0.77, 0.81)	[17]	0.71 to 0.81	[140,144,17]

CI: confidence interval, OWSA: one-way sensitivity analysis, UC: ulcerative colitis
*Response without remission utility value represented by mild UC cohort in Malinowski et al. 2016.

Adverse Events

Disutility associated with serious infections with TIMs and conventional treatment (e.g., respiratory infections, gastrointestinal infections, sepsis), early complications of colectomy, and late complications (chronic pouchitis) are included in the model (Table 5.13). The rate of serious infection is informed by the rates for the maintenance phase of clinical trials and adjusted to an eight-week cycle length. A reduction in utility of 52% is applied to the patients' health state and is assumed for the duration of the cycle with a serious infection event.

A small but statistically significant increased risk of malignancy with the use of TIMs has been documented in the literature, with potential for long-term impacts on quality of life and cost.[145] However, long-term studies have not consistently demonstrated an elevated risk, and the comparative risk across agents is unknown.[107,112,146] Due to data limitations, risk of malignancy is not included in the model.

Multiple different surgical techniques are used to perform colectomy procedures, with differing safety outcomes and rates of complications. While subtle differences may exist among various procedures, the most notable division exists between open procedures and laparoscopic (closed) procedures. Table 5.13 presents the incidence of early complications in open and laparoscopic colectomy procedures as well as the probability of the long-term complication of chronic pouchitis that is applicable to both procedures.

Table 5.13. Adverse Events

Parameter	Value	Source	Utility	Source
Serious Infection (Per Year)				
Adalimumab	1.6%	ULTRA 2[93]	-52% disutility	NICE STA342[56]
Golimumab	3.2%	PURSUIT[147]		
Infliximab, Infliximab-dyyb, and Infliximab-abda 5 mg/kg	2.1%	ACT 1 and 2[90]		
Tofacitinib 5 mg	1.0%	OCTAVE SUSTAIN[96]		
Ustekinumab 90 mg q8w	1.7%	UNIFI[99]		
Vedolizumab	1.9%	GEMINI 1[77]		
Conventional Treatment	2%	*		
Colectomy Complications				
Early Complications of Colectomy (Open Procedure)	25.3% incidence	Zogg 2016[148]	0.49	Arseneau 2006[149]
Early Complications of Colectomy (Laparoscopic)	17.3% incidence	Zogg 2016[148]	0.49	Arseneau 2006[149]
Chronic Pouchitis	15.5% prevalence	Zogg 2016[148]	0.40	Arseneau 2006[149]

kg: kilogram, mg: milligram, q8w: every 8 weeks

*Based on pooled placebo arms of treat through trials.

Economic Inputs

Drug Utilization

Table 5.14 on the following page outlines inputs for dose and frequency of administration of TIMs in UC. Conventional treatment is modeled as an induction period of prednisone 40 mg orally once daily, followed by mercaptopurine 1-1.5 mg/kg per day or azathioprine 2-3 mg/kg per day (assuming a 50:50 split between mercaptopurine and azathioprine).

Table 5.14. Treatment Regimen Recommended Dosage

Generic Name	ADA	GOL	IFX	IFX-dyyb	IFX-abda	TOF	UST	VEDO
Brand Name	Humira	Simponi	Remicade	Inflectra	Renflexis	Xeljanz	Stelara	Entyvio
Manufacturer	AbbVie	Janssen	Janssen	Pfizer	Merck	Pfizer	Janssen	Takeda
Route of Admin.	SC	SC	IV	IV	IV	Oral	SC	IV
Dosing	160 mg on day 1, then 80 mg 2 weeks later, then 40 mg EOW	200 mg at week 0, 100 mg at week 2, then 100 mg q4w	5 mg/kg at 0, 2, 6 weeks, then q8w	5 mg/kg at 0, 2, 6 weeks, then q8w	5 mg/kg at 0, 2, 6 weeks, then q8w	10 mg twice daily for 8 weeks, then 5 mg twice daily	One 390 mg IV dose, followed by 90 mg SC q8w	300 mg at 0, 2, 6 weeks, then q8w

ADA: adalimumab, admin.: administration, EOW: every other week, GOL: golimumab, IFX: infliximab, IV: intravenous, kg: kilogram, mg: milligram, q4w: every 4 weeks, q8w: every 8 weeks, SC: subcutaneous, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Dose Escalation

Dose escalation is considered in a scenario as an additional cost through a higher dose and/or frequency of administration for a proportion of patients in the maintenance phase. The frequency of dose escalation for each TIM was taken from a recent claims analysis of greater than expected dosing of TIMs in patients with IBD.[150] As no data were available for tofacitinib, the prevalence of dose escalation was assumed as the average of all other TIMs.

Table 5.15. Assumptions for Dose Escalation

Parameter	Escalated Maintenance Regimen in the Model	Proportion of Patients	Source
Adalimumab	40 mg every week	27.5%	MacDougall 2019[150]
Golimumab	200 mg q4w	14.3%	MacDougall 2019[150]
Infliximab, Infliximab-dyyb, Infliximab-dyyb	5 mg/kg q4w	39.4%	MacDougall 2019[150]
Tofacitinib	10 mg twice daily	25%	Assumption
Ustekinumab	90 mg q4w	21.6%	MacDougall 2019[150]
Vedolizumab	300 mg q4w	22.7%	MacDougall 2019[150]

kg: kilogram, mg: milligram, q4w: every 4 weeks

Drug Acquisition Costs

For TIMs with oral or subcutaneous modes of administration we obtained net pricing estimates from SSR Health, LLC, which combines data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, to derive a net price.[18] We estimated net prices by comparing the four-quarter averages of both net prices and wholesale acquisition cost (WAC) per unit to arrive at a

mean discount from WAC for the drug. Finally, we applied this average discount to the most recent available WAC (May 6, 2020) to arrive at an estimated net price per dose. For IV-administered TIMs, we used Centers for Medicare and Medicaid Services Average Sales Prices (ASP) plus 9.5%.[19] Infliximab and infliximab biosimilar doses, which are weight based, were rounded up to the nearest vial.

Table 5.16. Drug Unit Costs

Drug	Price per Unit	Source of Cost Data*	Units	Discount from WAC[18]
Adalimumab (40 mg)	$5,556.97	WAC	Two 40 mg doses	35.2%
Golimumab (100 mg)	$5,779.26	WAC	One 100 mg dose	43.8%
Infliximab (5 mg/kg)	$51.20	ASP	10 mg	N/A
Infliximab-dyyb (5 mg/kg)	$47.13	ASP	10 mg	N/A
Infliximab-abda (5 mg/kg)	$48.64	ASP	10 mg	N/A
Tofacitinib (10 mg)	$4,700.18	WAC	Sixty 10 mg tabs	37.9%
Ustekinumab IV (130 mg)	$12.17	ASP	1 mg	N/A
Ustekinumab SC (90 mg)	$23,082.84	WAC	One 90 mg dose	39.1%
Vedolizumab (300 mg)	$ 20.66	ASP	1 mg	18.3%
Prednisone (20 mg)	$20.72	WAC	One hundred 20 mg tabs	--
Mercaptopurine	$79.25	WAC	25 tabs	N/A
Azathioprine	$45.00	WAC	100 tabs	N/A

ASP: average sale price, IV: intravenous, kg: kilogram, mg: milligram, N/A: not applicable, SC: subcutaneous, WAC: wholesale acquisition cost

*WAC as of May 6, 2020[151]; ASP pricing effective July 1, 2020 through September 30, 2020.[19]

Please refer to the ICER Reference Case for more details on drug pricing.

Table 5.17. Cost of Induction and Maintenance

Drug	Units Per Eight Week Induction	Net Price per Eight Week Induction	Units per Maintenance Year	Net Price per Maintenance Year
Adalimumab (40 mg)	8	$14,403.67	26.1	$46,933
Golimumab (100 mg)	4	$12,991.78	13.0	$42,332
Infliximab (5 mg/kg)	3 weight-based doses	$6,727.68	6.5 weight-based doses	$14,614
Infliximab-dyyb (5 mg/kg)	3 weight-based doses	$6,192.36	6.5 weight-based doses	$13,451
Infliximab-abda (5 mg/kg)	3 weight-based doses	$6,390.90	6.5 weight-based doses	$13,883
Tofacitinib (5 or 10 mg)	112	$5,448.45	729.9	$35,506
Ustekinumab IV (130 mg)	3	$5,197.20	N/A	N/A
Ustekinumab SC (90 mg)	N/A	N/A	6.5	$91,609
Vedolizumab (300 mg)	3	$20,358.46	6.5	$44,224
Prednisone (20 mg)	3	$23.21	N/A	N/A
Mercaptopurine	N/A	N/A	729.9	$2,314
Azathioprine	N/A	N/A	1094.8	$493

IV: intravenous, kg: kilogram, mg: milligram, N/A: not applicable, SC: subcutaneous

Direct Cost of Administration and Monitoring

Administration costs are included for IV formulations at a cost of $72.80 per infusion based on the Centers for Medicare and Medicaid Use Physician Fee Schedule average non-facility price for CPT 96365 (IV infusion, for therapy, prophylaxis, or diagnosis [specify substance or drug]; initial, up to one hour).[152] The average non-facility price for CPT 96366 ($21.98) was added for infliximab, infliximab-dyyb, and infliximab-abda to account for a second hour of infusion time per product labeling.[153]

Direct Cost of Colectomy Procedure

A cost of $33,871 per admission for colectomy is assumed, calculated by the weighted average cost of emergent and non-emergent cost per admission from the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) database, after inflation to 2019 US dollars using the personal health care (PHC) expenditure deflator up to 2017 then the personal consumption expenditure (PCE) price index to update from 2017 to 2019.[154-156]

Other Costs of UC Management

Non-drug costs of UC management include the average cost of hospitalization, emergency department visits, and outpatient visits by health state (Table 5.18). Direct health care utilization costs were calculated based on previously published estimates of mean unadjusted annual costs

among privately-insured employed people with UC and a matched cohort without UC.[157] The active UC health state is informed by the moderate-to-severe cohort of the study, defined by investigators as having a hospitalization with a primary diagnosis of UC or treatment with biologics, immunosuppressants, or systemic corticosteroids. The clinical response without remission health state is informed by the overall UC study population, which includes all patients with at least two diagnoses of UC. Finally, the clinical remission health state is informed by the non-UC control cohort.

Table 5.18. Annual Direct Health Care Costs by Health State*

Parameter	Hospitalization Value (95% CI)	Emergency Department Value (95% CI)	Outpatient/Other Value (95% CI)	Source
Active UC	$8,048 ($33,476)	$581 ($1,722)	$10,114 ($16,787)	Cohen 2015[157]
Clinical Response without Remission†	$4,461 ($23,436)	$410 ($1,436)	$7,506 ($14,561)	Cohen 2015[157]
Clinical Remission‡	$969 ($8,137)	$223 ($992)	$2,722 ($8,266)	Cohen 2015[157]

CI: confidence interval, UC: ulcerative colitis
Health states apply to both induction and maintenance phases.
*Inflated 2019 US dollars using the PHC expenditure deflator up to 2017 then the PCE price index to update from 2017 to 2019.
†Informed by overall UC population.
‡Informed by non-UC control group.

Adverse Event Costs

Costs associated with serious infections with TIMs, early complications of colectomy, and late complications (chronic pouchitis) are included (Table 5.19). Serious infection events are assigned a cost of $10,238 based on HCUP net mean hospital costs for an inpatient stay with ICD-10 diagnosis of pneumonia (J12-J18), as pneumonia is a commonly reported serious infection, an approach that has been taken in another recent model of UC.[158] Table 5.19 also presents the cost per short-term complication in open and laparoscopic colectomy procedures as well as chronic pouchitis.

Table 5.19. Cost of Adverse Events

Parameter	Cost	Source
Serious Infection	$10,238	AHRQ[159]
Early Complications of Colectomy (Open Procedure)	$11,435*	Zogg 2016[148]
Early Complications of Colectomy (Laparoscopic)	$8,293*	Zogg 2016[148]
Chronic Pouchitis	$1,581 per month*	Park 2012[160]

AHRQ: Agency for Healthcare Research and Quality
*Inflated 2019 US dollars using the PHC expenditure deflator up to 2017 then the PCE price index to update from 2017 to 2019.

Productivity Costs

A modified societal perspective including indirect costs of disability, medical-related absenteeism, and presenteeism by time spent in clinical response without remission, remission, or active UC health states is included as a scenario analysis. Days of disability and medical-related absenteeism are sourced from the claims analysis as described for direct health state costs, assuming eight hours per day lost due to disability or absenteeism and average hourly wage in the US ($28.18).[157,161] For presenteeism, WPAI presenteeism estimates from a US patient survey are combined with US Bureau of Labor Statistics average working hours per week (38.6) and average hourly wage ($28.18).[161-163]

Table 5.20. Annual Indirect Health Care Costs by Health State

Parameter	Disability	Medical-Related Absenteeism	Presenteeism	Total Indirect Costs per Year	Source
Active UC	$2,773	$2,593	$13,694	$19,059	Cohen 2015,[157] Ding 2019,[163] US Bureau of Labor Statistics[145-147]
Clinical Response without Remission	$1,781†	$1,916†	$7,843†	$11,540*	
Clinical Remission	$1,014‡	$1,195‡	$3,056	$5,266	

UC: ulcerative colitis, US: United States
Health states apply to both induction and maintenance phases.
*Response without remission utility value represented by mild UC cohort.
†Informed by overall UC population.
‡Informed by non-UC control group.

The modified societal perspective also includes lost productivity related to UC treatments, including patient time spent to and from a medical visit to receive an IV infusion (vs. self-administration of subcutaneous or oral TIMs) (121 minutes per infusion)[164] and absenteeism due to colectomy procedure (conservative approach of 100 days of absenteeism related to open procedures).[165] For both inputs, a human capital approach was taken whereby the average time spent was multiplied by average hourly wage ($28.18), assuming eight hours of absenteeism per day, to estimate indirect cost.

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We used normal distributions for costs, rates, multipliers, and ages; gamma distributions for disutilities; and beta distributions for probabilities and utilities. For the TIM risk ratios, we sampled from the NMA codas directly.

Additionally, we performed a threshold analysis by systematically altering the price of each TIM to estimate the maximum prices that would correspond to given willingness-to-pay (WTP) thresholds in the biologic-naïve and biologic-experienced populations.

Scenario Analyses

We conducted the following scenario analyses:

- Time horizons of two, five, and 10 years
- Dose escalation
- Extended induction/delayed response
- Modified societal perspective that includes productivity losses
- Elimination of reduced risk of colorectal cancer death for patients in remission state
- Alternative sources of health state utility estimates
- Lower rates of discontinuation after one year, with discontinuation due to loss of response only
- Use of infliximab following initial vedolizumab therapy, assuming comparable efficacy to that in a biologic-naïve population.

Model Validation

We used several approaches to validate the model and followed standard practices in the field. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. We also shared the draft model with participating manufacturers during the public commenting period. We tested all mathematical functions in the model to ensure that they were consistent with the report. We also conducted sensitivity analyses with extreme input values to ensure the model was producing findings consistent with expectations. Finally, we compared results to other cost-effectiveness models in this therapy area.

5.3 Results

Base-Case Results

Biologic-Naïve Population

Total discounted initial TIM drug costs, total costs, LYs, and QALYs for the biologic-naïve population over the lifetime time horizon are shown in Table 5.21. Undiscounted results are presented in Appendix Tables E2-E4. Discounted drug costs for initial TIMs ranged from $22,000 to $138,000 and total costs ranged from $434,000 to $545,000 over the lifetime time horizon compared to a total cost of $421,000 for conventional treatment. Discounted life expectancy from age of initiation (age

40 years) was 22.08 LY across all treatments, although small differences exist across TIMs that are not presented in Table 5.21 due to rounding. Projected discounted QALYs for TIMs ranged from 15.60 to 15.68 for TIMs compared with 15.57 QALYs for conventional treatment. As the TIMs resulted in minimal gains in LY, QALYs closely approximated evLY.

The incremental cost per QALY for TIMs compared to conventional treatment in the biologic-naïve population ranged from $186,000 (infliximab-dyyb) to $1,870,000 (adalimumab) (Table 5.21). The incremental cost per QALY for TIMs compared to infliximab, a market share leader in the biologic-naïve population, is presented in Table 5.22. All TIMs had lower or equal LYs and QALYs compared to infliximab at a higher cost with the exception of ustekinumab, which had slightly higher QALYs at higher cost with a resulting cost per QALY exceeding $2.9 million. Full pairwise comparisons are presented in Appendix Table E8. Infliximab and its biosimilars had lower costs and greater QALYs than adalimumab, golimumab and vedolizumab. Ustekinumab resulted in the greatest number of QALYs but was not cost effective compared with infliximab-dyyb.

Table 5.21. Results for the Base Case for TIMs and Conventional Treatment: Biologic-Naïve

Parameter	Initial Drug Cost	Total Cost	LYs*	QALYs	evLY
Adalimumab	$44,000	$461,000	22.077	15.596	15.598
Golimumab	$41,000	$458,000	22.078	15.600	15.602
Infliximab	$24,000	$435,000	22.080	15.644	15.646
Infliximab-dyyb	$22,000	$434,000	22.080	15.644	15.646
Infliximab-abda	$23,000	$434,000	22.080	15.644	15.646
Ustekinumab	$138,000	$545,000	22.081	15.681	15.683
Vedolizumab	$68,000	$480,000	22.080	15.641	15.644
Conventional Treatment	$600	$421,000	22.075	15.574	15.576

evLY: equal value of life year, LY: life year, N/A: not applicable, QALY: quality-adjusted life year, TIM: targeted immune modulator

Costs rounded to nearest $1,000.

*Small differences in LYs across comparators are not displayed due to rounding.

Table 5.22. Incremental Cost-Effectiveness Ratios for the Base Case Compared to Conventional Treatment: Biologic-Naïve

Treatment	Cost per LY Gained	Cost per QALY Gained	Cost per evLY Gained
Adalimumab	$21,624,000	$1,870,000	$1,847,000
Golimumab	$12,981,000	$1,455,000	$1,432,000
Infliximab	$3,021,000	$212,000	$209,000
Infliximab-dyyb	$2,651,000	$186,000	$184,000
Infliximab-abda	$2,788,000	$195,000	$193,000
Ustekinumab	$23,615,000	$1,163,000	$1,155,000
Vedolizumab	$13,767,000	$887,000	$880,000
Conventional Treatment	Reference	Reference	Reference

evLY: equal value of life year, LY: life year, QALY: quality-adjusted life year

Cost per LY gained rounded to the nearest $10,000; cost per QALY gained rounded to nearest $1,000.

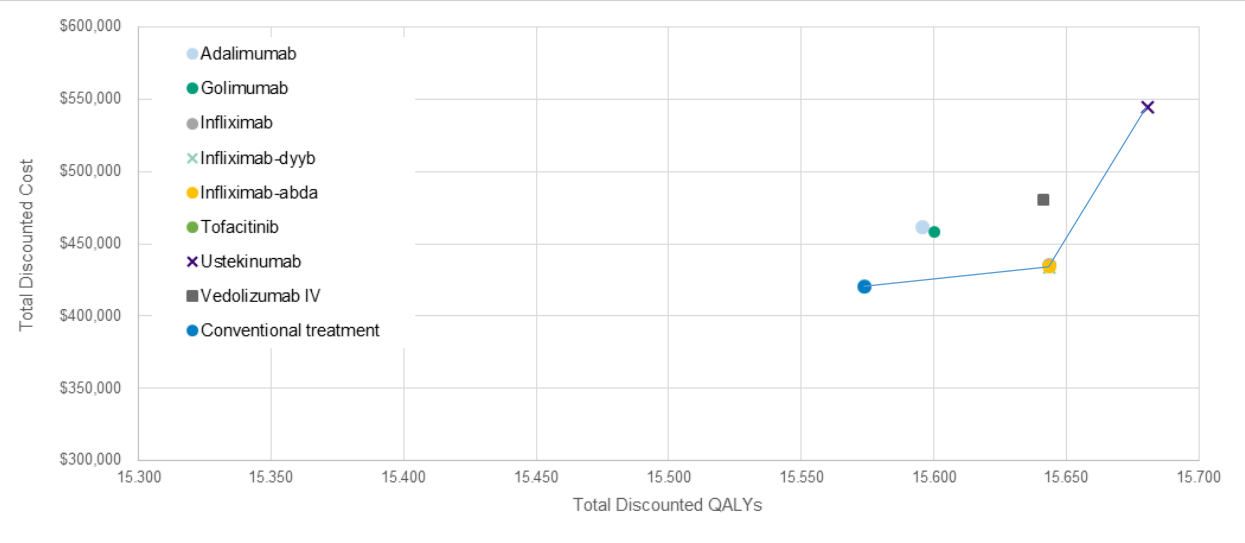
Table 5.23. Incremental Cost-Effectiveness Ratios for the Base Case Compared to Infliximab: Biologic-Naïve

Treatment	Cost per LY Gained	Cost per QALY Gained	Cost per evLY Gained
Adalimumab	Higher cost, fewer LYs	Higher cost, fewer QALYs	Higher cost, fewer evLYs
Golimumab	Higher cost, fewer LYs	Higher cost, fewer QALYs	Higher cost, fewer evLYs
Infliximab	Reference	Reference	Reference
Infliximab-dyyb	Lower cost, equal LYs	Lower cost, equal QALYs	Lower cost, equal evLYs
Infliximab-abda	Lower cost, equal LYs	Lower cost, equal QALYs	Lower cost, equal evLYs
Ustekinumab	$297,831,000	$2,960,000	$2,956,000
Vedolizumab	Higher cost, fewer LYs	Higher cost, fewer QALYs	Higher cost, fewer evLYs

evLY: equal value of life year, LY: life year, QALY: quality-adjusted life year

Cost per LY gained rounded to the nearest $10,000; cost per QALY gained rounded to nearest $1,000.

Figure 5.2. Cost-Effectiveness Frontier for TIMs in the Base Case: Biologic-Naïve



IV: intravenous, QALY: quality-adjusted life year

Drugs that are farther to the right in Figure 5.2 above provide greater clinical benefit and drugs higher on the y-axis are more expensive. 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.

Biologic-Experienced Population

Total discounted initial TIM drug costs, total costs, LYs, and QALYs for the biologic-experienced population over the lifetime time horizon are shown in Table 5.24. Undiscounted results are presented in Appendix Tables E5-E7. Discounted drug costs for initial TIMs ranged from $32,000 to $76,000 and total costs ranged from $460,000 to $504,000 over the lifetime time horizon compared to a total cost of $434,000 for conventional treatment. Discounted life expectancy from age of initiation (age 40 years) was 22.07 LYs across all treatments, although small differences exist across TIMs that are not presented due to rounding. Projected discounted QALYs for TIMs ranged from 15.41 to 15.45 for TIMs compared with 15.39 QALYs for conventional treatment. As the TIMs resulted in minimal gains in LYs, QALYs closely approximated evLY.

The incremental cost per QALY for TIMs compared to conventional treatment in the biologic-experienced population ranged from $495,000 (tofacitinib) to $1,885,000 (adalimumab). The incremental cost per QALY for TIMs compared to each other is located in Appendix E9 and Table 5.25 for TIMs compared to adalimumab, a market share leader in the biologic-experienced population. Treatment with tofacitinib resulted in greater QALYs at a lower cost compared with adalimumab. Ustekinumab had an incremental cost-effectiveness ratio of $996,000 per QALY

gained compared to adalimumab. The additional cost per QALY was $464,000 for vedolizumab compared with adalimumab. Although QALYs were very similar between ustekinumab and vedolizumab, ustekinumab had an incremental cost-effectiveness ratio of $6,422,000 per QALY gained compared to vedolizumab. Please note that due to the incremental cost-effectiveness calculation being a ratio, it increases rapidly with small differences in QALYs as is the case here.

Table 5.24. Results for the Base Case for TIMs and Conventional Treatment: Biologic-Experienced

Parameter	Initial Drug Cost	Total Cost	LYs*	QALYs	evLY
Adalimumab	$33,000	$465,000	22.070	15.410	15.412
Tofacitinib	$32,000	$460,000	22.074	15.445	15.448
Ustekinumab	$76,000	$504,000	22.074	15.449	15.452
Vedolizumab	$54,000	$482,000	22.073	15.446	15.448
Conventional Treatment	$323	$434,000	22.070	15.393	15.395

evLY: equal value of life year, LY: life year, N/A: not applicable, QALY: quality-adjusted life year, TIM: targeted immune modulator

Costs rounded to nearest $1,000.

*Small differences in LYs across comparators are not displayed due to rounding.

Table 5.25. Incremental Cost-Effectiveness Ratios for the Base Case Compared to Conventional Treatment: Biologic-Experienced

Treatment	Cost per LY Gained	Cost per QALY Gained	Cost per evLY Gained
Adalimumab	$79,822,000	$1,885,000	$1,878,000
Tofacitinib	$6,281,000	$495,000	$489,000
Ustekinumab	$16,640,000	$1,252,000	$1,239,000
Vedolizumab	$17,707,000	$902,000	$895,000
Conventional Treatment	Reference	Reference	Reference

evLY: equal value of life year, LY: life year, QALY: quality-adjusted life year

Cost per LY gained rounded to the nearest $10,000; cost per QALY gained rounded to nearest $1,000.

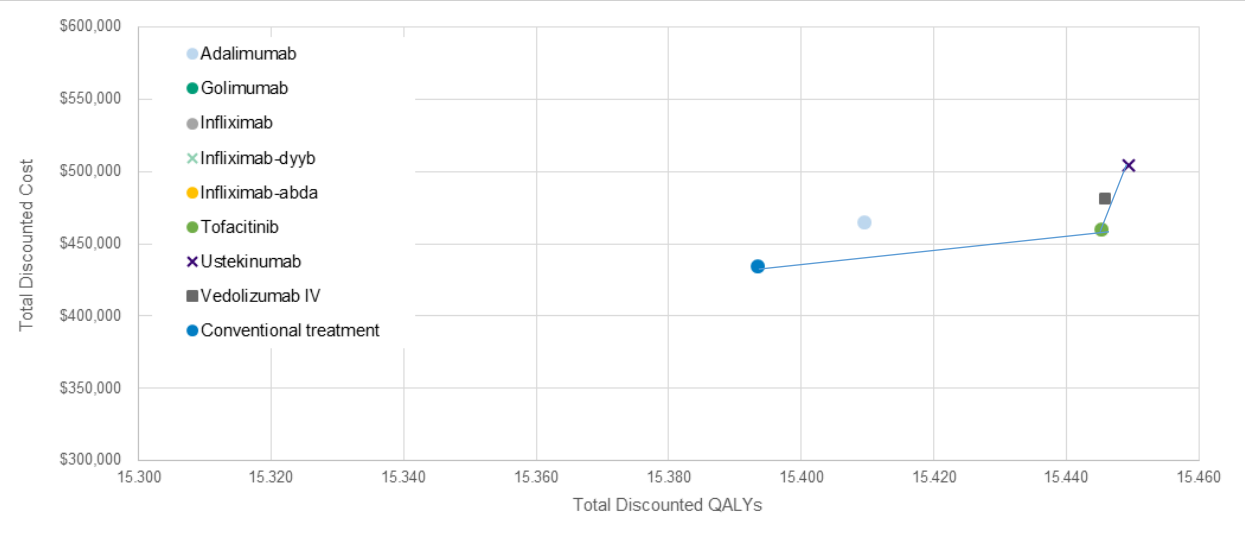
Table 5.26. Incremental Cost-Effectiveness Ratios for the Base Case Compared to Adalimumab: Biologic-Experienced

Treatment	Cost per LY Gained	Cost per QALY Gained	Cost per evLY Gained
Adalimumab	Reference	Reference	Reference
Tofacitinib	Lower cost, greater LYs	Lower cost, greater QALYs	Lower cost, greater evLYs
Ustekinumab	$10,358,000	$996,000	$982,000
Vedolizumab	$7,362,000	$464,000	$460,000

evLY: equal value of life year, LY: life year, QALY: quality-adjusted life year

Cost per LY gained rounded to the nearest $10,000; cost per QALY gained rounded to nearest $1,000.

Figure 5.3. Cost-Effectiveness Frontier for TIMs in the Base Case: Biologic-Experienced



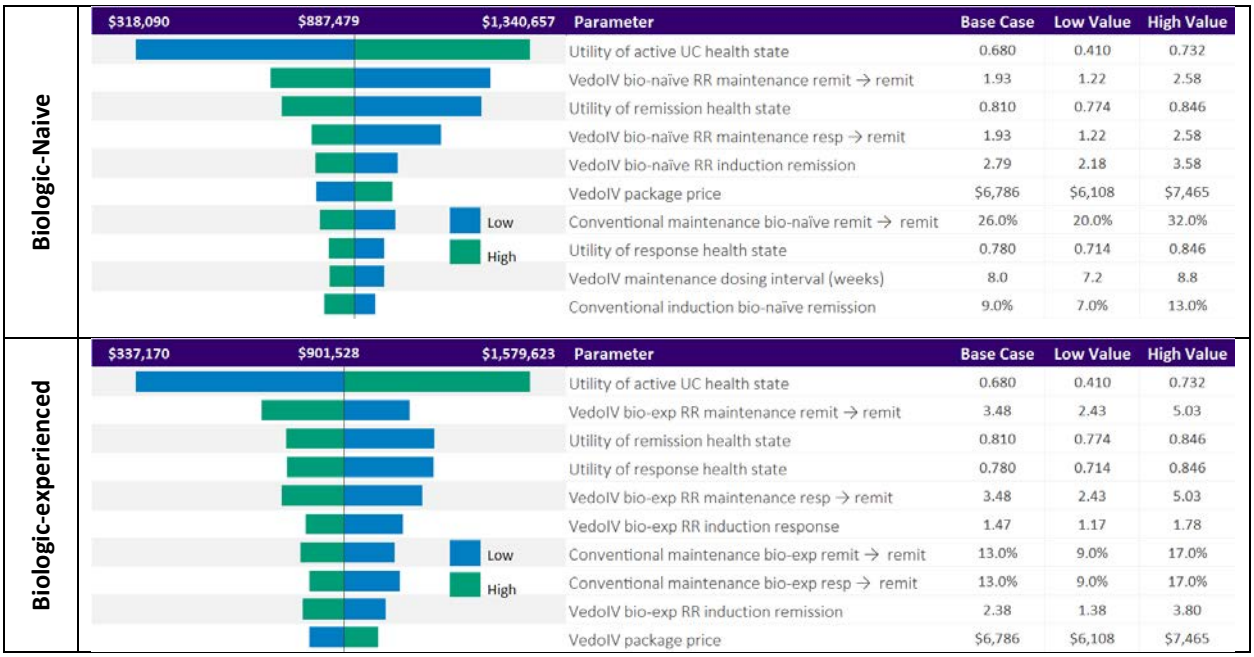
IV: intravenous, QALY: quality-adjusted life year

Drugs that are farther to the right in Figure 5.3 provide greater clinical benefit and drugs higher on the y-axis are more expensive. 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.

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., 95% CI) or reasonable ranges (±10%) to evaluate changes in cost per additional QALY for each TIM compared to conventional treatment. The tornado charts for vedolizumab in a biologic-naïve population and biologic-experienced population are presented in Figure 5.4 as an example. The results for other comparators were similar and are presented in the Appendix. For all comparisons, the health state utility of active UC was the most important driver of model results, with the cost per QALY for infliximab falling below the $150,000 per QALY threshold when the low estimate for utility was applied. Other key drivers across most comparisons were utility of the response and remission health states, efficacy of TIMs, and cost of TIMs.

Figure 5.4. Tornado Diagram for One-Way Sensitivity Analyses of Vedolizumab versus Conventional Treatment (Cost per QALY)



Biologic-Naive			
Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
VedoIV bio-naïve RR maintenance remit → remit	1.93	1.22	2.58
Utility of remission health state	0.810	0.774	0.846
VedoIV bio-naïve RR maintenance resp → remit	1.93	1.22	2.58
VedoIV bio-naïve RR induction remission	2.79	2.18	3.58
VedoIV package price	$6,786	$6,108	$7,465
Conventional maintenance bio-naïve remit → remit	26.0%	20.0%	32.0%
Utility of response health state	0.780	0.714	0.846
VedoIV maintenance dosing interval (weeks)	8.0	7.2	8.8
Conventional induction bio-naïve remission	9.0%	7.0%	13.0%

Biologic-experienced			
Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
VedoIV bio-exp RR maintenance remit → remit	3.48	2.43	5.03
Utility of remission health state	0.810	0.774	0.846
Utility of response health state	0.780	0.714	0.846
VedoIV bio-exp RR maintenance resp → remit	3.48	2.43	5.03
VedoIV bio-exp RR induction response	1.47	1.17	1.78
Conventional maintenance bio-exp remit → remit	13.0%	9.0%	17.0%
Conventional maintenance bio-exp resp → remit	13.0%	9.0%	17.0%
VedoIV bio-exp RR induction remission	2.38	1.38	3.80
VedoIV package price	$6,786	$6,108	$7,465

bio: biologic, exp: experienced, IV: intravenous, resp: response without remission, QALY: quality-adjusted life year, RR: risk ratio, UC: ulcerative colitis, vedo: vedolizumab

The proportion of probabilistic sensitivity analysis iterations with an incremental cost-effectiveness ratio below thresholds ranging from $50,000 to $250,000 per QALY gained are presented in Table 5.27 for the biologic-naïve population and Table 5.28 for the biologic-experienced population. Full results of probabilistic sensitivity analysis are presented in Appendix Tables E10 and E11. The mean probabilistic estimate of cost per QALY was above $150,000 for all TIMs in both populations. For the biologic-naïve population, infliximab-dyyb had the highest probability of being cost effective at $150,000 per QALY at 29%. The lower bound of the 95% credible interval for adalimumab, golimumab, ustekinumab, and vedolizumab did not fall below $150,000 in the biologic-naïve population. For the biologic-experienced population, no TIMs were likely (>50%) to be cost effective at any of the thresholds and the lower bound of the 95% credible interval for the incremental cost-effectiveness ratios did not fall below $150,000 for any TIMs.

Table 5.27. Probabilistic Sensitivity Analysis Results: TIMs versus Conventional Treatment: Biologic-Naïve

	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
Adalimumab	0%	0%	0%	0%	0%
Golimumab	0%	0%	0%	0%	0%
Infliximab	0%	3%	17%	44%	69%
Infliximab-dyyb	1%	6%	29%	59%	81%
Infliximab-abda	1%	5%	24%	54%	77%
Ustekinumab	0%	0%	0%	0%	0%
Vedolizumab	0%	0%	0%	0%	0%

QALY: quality-adjusted life year

Table 5.28. Probabilistic Sensitivity Analysis Results: TIMs versus Conventional Treatment: Biologic-Experienced

	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
Adalimumab	0%	0%	0%	0%	0%
Tofacitinib	0%	0%	0%	0%	1%
Ustekinumab	0%	0%	0%	0%	0%
Vedolizumab	0%	0%	0%	0%	0%

QALY: quality-adjusted life year

Scenario Analyses Results

Shorter Time Horizons

The model assumes that patients try a second TIM after lack of response, loss of response, or discontinuation of the first TIM. In clinical practice, patients may try many interventions for UC over a lifetime time horizon. Our model is a simplification of a complex and highly individualized treatment pathway in order to focus on the cost effectiveness of the TIM of interest. In order to increase focus on the TIM of interest, analyses with time horizons of two, five, and 10 years were conducted. Shorter time horizons had a variable impact on cost per QALY estimates, but not alter base-case conclusions.

Table 5.29. Incremental Cost-Effectiveness Ratios for the Shorter Time Horizon Scenario: Biologic-Naïve

Treatment	Base-Case Cost per QALY Gained	10 Year Time Horizon Cost per QALY Gained	Five Year Time Horizon Cost per QALY Gained	Two Year Time Horizon Cost per QALY Gained
Adalimumab	$1,870,000	$1,743,564	$1,870,602	$2,781,164
Golimumab	$1,455,000	$1,390,522	$1,443,954	$1,921,569
Infliximab	$212,000	$187,276	$176,265	$198,221
Infliximab-dyyb	$186,000	$161,834	$147,553	$154,055
Infliximab-abda	$195,000	$171,270	$158,202	$170,436
Ustekinumab	$1,163,000	$1,125,847	$1,269,998	$1,784,835
Vedolizumab	$887,000	$848,232	$934,151	$1,418,486
Conventional Treatment	Reference	Reference	Reference	Reference

QALY: quality-adjusted life year

Incremental cost-effectiveness ratios rounded to nearest $1,000.

Table 5.30. Incremental Cost-Effectiveness Ratios for the Shorter Time Horizon Scenario: Biologic-Experienced

Treatment	Cost per QALY Gained	10 Year Time Horizon Cost per QALY Gained	Five Year Time Horizon Cost per QALY Gained	Two Year Time Horizon Cost per QALY Gained
Adalimumab	$1,885,000	$1,623,246	$1,798,937	$3,516,694
Tofacitinib	$495,000	$453,742	$454,364	$553,737
Ustekinumab	$1,252,000	$1,180,697	$1,235,494	$1,629,824
Vedolizumab	$902,000	$831,989	$910,179	$1,509,651
Conventional Treatment	Reference	Reference	Reference	Reference

QALY: quality-adjusted life year

Incremental cost-effectiveness ratios rounded to nearest $1,000.

Dose Escalation

A higher dose and/or frequency of administration may be required for a proportion of patients in the maintenance phase to maintain response. Higher cost of TIMs led to an increase in cost per QALY across all TIMs compared to conventional treatment.

Table 5.31. Incremental Cost-Effectiveness Ratios for the Dose Escalation Scenario: Biologic-Naïve

Treatment	Base-Case Cost per QALY Gained	Cost per QALY Gained Considering Dose Escalation
Adalimumab	$1,870,000	$2,248,519
Golimumab	$1,455,000	$1,605,081
Infliximab	$212,000	$302,295
Infliximab-dyyb	$186,000	$269,279
Infliximab-abda	$195,000	$281,524
Ustekinumab	$1,163,000	$1,433,705
Vedolizumab	$887,000	$1,048,395
Conventional Treatment	Reference	Reference

QALY: quality-adjusted life year

Incremental cost-effectiveness ratios rounded to nearest $1,000.

Table 5.32. Incremental Cost-Effectiveness Ratios for the Dose Escalation Scenario: Biologic-Experienced

Treatment	Base-Case Cost per QALY Gained	Cost per QALY Gained Considering Dose Escalation
Adalimumab	$1,885,000	$2,202,210
Tofacitinib	$495,000	$492,377
Ustekinumab	$1,252,000	$1,529,360
Vedolizumab	$902,000	$1,043,476
Conventional Treatment	Reference	Reference

QALY: quality-adjusted life year

Incremental cost-effectiveness ratios rounded to nearest $1,000.

Extended Induction

An additional efficacy benefit from extended induction was calculated for adalimumab, golimumab, tofacitinib, ustekinumab, and vedolizumab. Allowing for an additional eight weeks of induction did not substantially alter conclusions based on incremental cost-effectiveness ratios and all remained above the $150,000 per QALY threshold. It is important to note that our cost-effectiveness analysis was not constructed with the intent of evaluating the most appropriate duration of induction for TIMs in UC. The results of this scenario analysis are limited by assumptions surrounding the efficacy of the second TIM and the market basket and are not intended to inform quantity limits or treatment decisions.

Table 5.33. Incremental Cost-Effectiveness Ratios for the Extended Induction Scenario: Biologic-Naïve

Treatment	Base-Case Cost per QALY Gained	Cost per QALY Gained Considering Extended Induction
Adalimumab	$1,870,000	Higher cost, fewer QALYs
Golimumab	$1,455,000	Higher cost, fewer QALYs
Ustekinumab	$1,163,000	$1,519,412
Vedolizumab	$887,000	$1,714,386
Conventional Treatment	Reference	Reference

QALY: quality-adjusted life year

Incremental cost-effectiveness ratios rounded to nearest $1,000.

Table 5.34. Incremental Cost-Effectiveness Ratios for the Extended Induction Scenario: Biologic-Experienced

Treatment	Base-Case Cost per QALY Gained	Cost per QALY Gained Considering Extended Induction
Adalimumab	$1,885,000	Higher cost, fewer QALYs
Tofacitinib	$495,000	$1,244,000
Ustekinumab	$1,252,000	$3,926,000
Vedolizumab	$902,000	$1,687,000
Conventional Treatment	Reference	Reference

QALY: quality-adjusted life year

Incremental cost-effectiveness ratios rounded to nearest $1,000.

Modified Societal Perspective

A modified societal perspective scenario was undertaken, which considered absenteeism, presenteeism, and disability due to UC. In this scenario, the cost per QALY was reduced substantially for all TIMs, with infliximab and infliximab biosimilars falling to or below the $100,000 per QALY threshold for the biologic-naïve population.

Table 5.35. Incremental Cost-Effectiveness Ratios for the Modified Societal Perspective Scenario: Biologic-Naïve

Treatment	Base-Case Cost per QALY Gained	Including Indirect Costs per QALY Gained
Adalimumab	$1,870,000	$1,745,283
Golimumab	$1,455,000	$1,334,762
Infliximab	$212,000	$100,932
Infliximab-dyyb	$186,000	$75,023
Infliximab-abda	$195,000	$84,633
Ustekinumab	$1,163,000	$1,041,891
Vedolizumab	$887,000	$775,740
Conventional Treatment	Reference	Reference

QALY: quality-adjusted life year
Incremental cost-effectiveness ratios rounded to nearest $1,000.

Table 5.36. Incremental Cost-Effectiveness Ratios for the Modified Societal Perspective Scenario: Biologic-Experienced

Treatment	Base-Case Cost per QALY Gained	Including Indirect Costs per QALY Gained
Adalimumab	$1,885,000	$1,753,157
Tofacitinib	$495,000	$384,312
Ustekinumab	$1,252,000	$1,142,920
Vedolizumab	$902,000	$793,415
Conventional Treatment	Reference	Reference

QALY: quality-adjusted life year
Incremental cost-effectiveness ratios rounded to nearest $1,000.

Exclusion of Reduced Risk of Colorectal Cancer Death for Patients in Remission

A risk of mortality in UC, which excludes colorectal cancer-related mortality, was applied to patients in the remission health state to capture a potential long-term benefit effect of endoscopic improvement. Excluding this impact had a negligible impact on the incremental cost-effectiveness ratios due to the relatively low incidence of colorectal cancer.

Alternative Health State Utility Estimates

Health state utility estimates for active UC, response without remission, and response with remission are a major driver of model results. As a scenario analysis, we applied an alternative estimate for active UC based on an average of baseline EQ-5D scores across the InspireADA, GEMINI 1, and GO-COLITIS trials (0.658).[74,142,143] The lower estimate of utility for active UC led to an increase in QALYs gained with TIMs compared to conventional treatment, corresponding to lower incremental cost-effectiveness ratios for all TIMs. No TIMs fell below the $150,000 per QALY threshold.

Table 5.37. Incremental Cost-Effectiveness Ratios for the Alternative Utility for Active UC Scenario: Biologic-Naïve

Treatment	Base-Case Cost per QALY Gained	Using Alternative Utility Cost per QALY Gained
Adalimumab	$1,870,000	$1,612,000
Golimumab	$1,455,000	$1,259,000
Infliximab	$212,000	$185,000
Infliximab-dyyb	$186,000	$162,000
Infliximab-abda	$195,000	$170,000
Ustekinumab	$1,163,000	$1,017,000
Vedolizumab	$887,000	$775,000
Conventional Treatment	Reference	Reference

QALY: quality-adjusted life year
Incremental cost-effectiveness ratios rounded to nearest $1,000.

Table 5.38. Incremental Cost-Effectiveness Ratios for the Alternative Utility for Active UC Scenario: Biologic-Experienced

Treatment	Base-Case Cost per QALY Gained	Alternative Utility Cost per QALY Gained
Adalimumab	$1,885,000	$1,600,000
Tofacitinib	$495,000	$428,000
Ustekinumab	$1,252,000	$1,082,000
Vedolizumab	$902,000	$780,000
Conventional Treatment	Reference	Reference

QALY: quality-adjusted life year
Incremental cost-effectiveness ratios rounded to nearest $1,000.

Lower Discontinuation Rates after One Year

The scenario of assuming lower discontinuation rates after one year for the initial TIM had reduced the cost per QALY for all TIMs. No TIMs fell below the $150,000 per QALY threshold.

Table 5.39. Incremental Cost-Effectiveness Ratios for Lower Discontinuation Rates Scenario: Biologic-Naïve

Treatment	Base-Case Cost per QALY Gained	Excluding Discontinuation for Reasons Other Than Lack of Efficacy After One Year
Adalimumab	$1,870,000	$1,535,000
Golimumab	$1,455,000	$1,224,000
Infliximab	$212,000	$183,000
Infliximab-dyyb	$186,000	$160,000
Infliximab-abda	$195,000	$168,000
Ustekinumab	$1,163,000	$1,112,000
Vedolizumab	$887,000	$771,000
Conventional Treatment	Reference	Reference

QALY: quality-adjusted life year

Incremental cost-effectiveness ratios rounded to nearest $1,000.

Table 5.40. Incremental Cost-Effectiveness Ratios for Lower Discontinuation Rates Scenario: Biologic-Experienced

Treatment	Base-Case Cost per QALY Gained	Excluding Discontinuation for Reasons Other Than Lack of Efficacy After One Year
Adalimumab	$1,885,000	$1,526,000
Tofacitinib	$495,000	$472,000
Ustekinumab	$1,252,000	$1,227,000
Vedolizumab	$902,000	$788,000
Conventional Treatment	Reference	Reference

QALY: quality-adjusted life year

Incremental cost-effectiveness ratios rounded to nearest $1,000.

Use of Infliximab Following Initial Vedolizumab Therapy or Conventional Treatment

No RCT data was identified for infliximab or infliximab biosimilars in a biologic-experienced population, so these therapies were excluded from the market basket of second TIMs, which by definition would be a biologic-experienced population. However, clinicians consulted during the course of this review indicated that using infliximab after failure by vedolizumab was a common treatment sequence used in real-world clinical practice. Therefore, we conducted a scenario whereby all patients who are initiated on vedolizumab or conventional treatment and switch to subsequent treatment are switched to infliximab as the subsequent treatment. As no data are available in a biologic-experienced population for infliximab, we assumed comparable efficacy to that in a biologic-naïve population. Although absolute QALYs are higher for both vedolizumab and conventional treatment in this scenario, the incremental cost per QALY gained for vedolizumab compared with conventional treatment is equal to the base case in both the biologic-naïve and biologic-experienced populations.

Table 5.41. Incremental Cost-Effectiveness Ratios for Infliximab Following Initial Vedolizumab Scenario: Biologic-Naïve

Treatment	Base-Case Cost per QALY Gained	Infliximab as Subsequent Treatment Instead of Market Basket
Vedolizumab	$887,000	$886,000
Conventional Treatment	Reference	Reference

QALY: quality-adjusted life year

Incremental cost-effectiveness ratios rounded to nearest $1,000.

Table 5.42. Incremental Cost-Effectiveness Ratios for Infliximab Following Initial Vedolizumab Scenario: Biologic-Experienced

Treatment	Cost per QALY Gained	Infliximab as Subsequent Treatment Instead of Market Basket
Vedolizumab	$902,000	$899,000
Conventional Treatment	Reference	Reference

QALY: quality-adjusted life year

Incremental cost-effectiveness ratios rounded to nearest $1,000.

Threshold Analyses Results

The dosing, mode of administration, and frequency of administration of some TIMs differs in the induction period compared with the maintenance period. In order to generate a single annual threshold price across TIMs, threshold pricing was conducted for price per maintenance year. The annual drug cost per maintenance year for each TIM to reach an incremental cost per QALY gained compared to conventional treatment at thresholds of $50,000 per QALY, $100,000 per QALY, and $150,000 per QALY are presented in Tables ES15 and ES16. Annual TIM prices at the $150,000 per QALY threshold ranged from $6,824 (adalimumab, biologic-experienced population) to $16,624 (ustekinumab, biologic-naïve population). We note, however, that these results are highly sensitive to what amount to very minor differences in estimated QALYs. For example, the somewhat higher threshold prices for ustekinumab in the biologic-naïve population are driven by a QALY difference of 0.037 in comparison to the next most-effective TIM, which is the equivalent of less than two additional weeks of life. This difference is itself based on parameter inputs based on point estimate differences from our NMA that were not statistically different across ustekinumab and other TIMs. It is also important to note that the threshold prices for ustekinumab are for the subcutaneous injection used in the maintenance period and are independent of the IV product price used in the induction period. This is why, for example, we see the threshold price in the biologic-experienced population rising faster with increasing cost per QALY thresholds versus other TIMs (e.g., vedolizumab).

With these details in mind, the overall results demonstrate that for all TIMs, except infliximab and the infliximab biosimilars, annual net price estimates were far higher than threshold prices all the way up to prices at $150,000 per QALY.

Table 5.43. Threshold Analysis Results – Per Maintenance Year for the Biologic-Naïve Population

	WAC	Net Price	Price to Achieve $50,000/QALY	Price to Achieve $100,000/QALY	Price to Achieve $150,000/QALY
Adalimumab	$72,427	$46,933	$4,616	$5,778	$6,941
Golimumab	$75,324	$42,332	$4,991	$6,320	$7,649
Infliximab	$27,930	$14,614*	$6,754	$8,813	$10,872
Infliximab-dyyb	$22,632	$13,451*	$6,754	$8,813	$10,872
Infliximab-abda	$18,018	$13,883*	$6,754	$8,813	$10,872
Ustekinumab	$150,425	$91,609	$9,220	$12,922	$16,624
Vedolizumab	$43,842	$44,224*	$7,247	$9,454	$11,662

ASP: average sales price, QALY: quality-adjusted life year, WAC: wholesale acquisition cost
Prices rounded to nearest $1,000.
*Net prices represented by ASP plus 9.5%.

Table 5.44. Threshold Analysis Results – Per Maintenance Year for the Biologic-Experienced Population

	WAC	Net Price	Price to Achieve $50,000/QALY	Price to Achieve $100,000/QALY	Price to Achieve $150,000/QALY
Adalimumab	$72,427	$46,933	$4,512	$5,668	$6,824
Tofacitinib	$57,176	$35,506	$9,429	$12,360	$15,292
Ustekinumab	$150,425	$91,609	$4,523	$8,144	$11,766
Vedolizumab	$43,842	$44,224*	$6,738	$8,939	$11,140

QALY: quality-adjusted life year, WAC: wholesale acquisition cost
Prices rounded to nearest $1,000.
*Net prices represented by ASP plus 9.5%.

Prior Economic Models

We reviewed the literature for recent cost-effectiveness analyses of treatments for UC, for comparison to the results from our model. A 2018 analysis by Scott et al.[166] used a model to simulate outcomes for vedolizumab compared to colectomy. While this analysis included QALY estimates, it did not include costs and used a time horizon of only one to seven years, and so was not directly comparable to our analysis. A cost-effectiveness analysis in the same year by Beilman et al.[167] examined the cost effectiveness of vedolizumab compared to infliximab in Canada. They found that vedolizumab and infliximab had similar effectiveness, but vedolizumab was considered

more cost effective due to its lower cost over a five-year time horizon. Our model found similar or slightly higher efficacy for vedolizumab compared with infliximab. However, our conclusions would be the opposite, with infliximab considered more cost effective, as vedolizumab has the higher price in the US. This analysis did not include a lifetime horizon scenario. Milev et al.[158] have conducted a cost analysis of tofacitinib treatment from the perspective of a US payer over a two-year time horizon, but their analysis did not include QALY estimates.

Tappenden et al.[168] evaluated adalimumab, golimumab, and infliximab in moderate-to-severe UC patients for whom conventional therapy had failed, using a United Kingdom National Health Services perspective and a lifetime horizon. Their analysis estimated that colectomy would be more effective and less costly than these medical treatments. In patients for whom colectomy was not an option, the cost effectiveness of adalimumab compared to conventional therapy was estimated at just over £50,000 per QALY, with infliximab and golimumab dominated by adalimumab. Their analysis used a similar cohort as ours in terms of starting age, proportion male, and mean body mass index, but did not stratify by prior biologic experience. Their model produced fewer QALYs in general, perhaps because they used a lower utility value for active UC. Their model estimated approximately 0.35 incremental QALYs for adalimumab compared to conventional therapy, which was much higher than our estimates of 0.02, primary due to the availability of subsequent treatment in our conventional therapy arm. Costs were not comparable across the different health care systems of the US and United Kingdom.

Wu et al.[169] used a Markov model to examine the cost effectiveness of 14 possible treatment sequences (consisting of up to two lines of therapy followed by conventional treatment) for patients with moderate-to-severe UC, using Chinese and United Kingdom perspectives and costs. They reported that treatment sequences including tofacitinib and vedolizumab were most cost effective in the United Kingdom, while treatment with tofacitinib was most cost effective in China. Their cost estimates from China and the United Kingdom were not comparable to those in our US-based analysis, but this analysis also reported lower QALYs than our present analysis, again likely due to the use of lower utility values for active UC (0.42) compared to the value used in the current analysis (0.680) as well as higher discount rates (3.5% for the United Kingdom and 5% for China). This, along with the use of generally higher response rate estimates, led to greater incremental QALY gains (and consequently lower estimated cost-effectiveness ratios) than were found in our analysis.

More recently, Lohan et al.[170] conducted an NMA and Markov model of tofacitinib compared to biologics and conventional therapy for the treatment of moderate-to-severe UC using a United Kingdom National Health Service perspective and lifetime horizon. Non-responders in their model were assumed to move directly to conventional therapy rather than to another biologic. As with the analyses above, this model used a lower utility value for active UC (0.41) and a higher discount

rate (3.5%) than in our analysis. This resulted in lower estimated lifetime QALYs and larger incremental QALY gains from treatment in general.

Limitations

We have attempted to model TIMs for the treatment of UC to both reflect clinical practice and accommodate the limits of available data. The latter has placed some restrictions on how accurately we can model UC treatment with TIMs. Outcomes for conventional treatment are based on the placebo arm of clinical trials and may not fully reflect the clinical course of disease in the real world. In addition, patients may try several treatment options over a lifetime time horizon whereas our model was limited to only a trial of two TIMs before moving to conventional treatment. For this reason, our model does not reflect a comprehensive disease model of UC but is instead constructed with the intent to evaluate the cost effectiveness of the initial TIM of interest while keeping other factors, such as later line treatment options, relatively constant.

The available options for a second TIM are limited to those with efficacy data in a biologic-experienced population. Market shares for the second TIM meeting all inclusion criteria are assumed to be equally distributed. These assumptions may not be reflective of real-world treatment patterns. Some TIMs without RCT data in a biologic-experienced population may be prescribed by some clinicians as a second TIM (e.g., infliximab as a second TIM after non-response or loss of response to vedolizumab as the initial TIM). Without efficacy data in a pre-treated population, we are unable to generate reliable estimates for how well these would perform in a biologic-experienced population and have excluded them from the market basket.

This analysis is based on efficacy inputs from the NMA. All limitations of the NMA (e.g., differences in clinical trial design) are also limitations of the model, which heavily relies on these inputs to derive treatment benefit.

Finally, we assumed that patients who enter the maintenance phase have the same risk ratio for response without remission and response with remission regardless of whether the patient achieved response with remission or response without remission during induction. We acknowledge that these may differ in reality (e.g., a patient entering in remission may have a higher likelihood of maintaining remission). However, due to data limitations, we are unable to create more granular sets of risk ratios for all comparators.

Conclusions

In summary, our analyses indicate that TIMs improved health outcomes compared to conventional treatment in both the biologic-naïve and biologic-experienced populations. Using net prices, incremental cost-effectiveness ratio results were above commonly cited thresholds for cost effectiveness for all TIMs in the base-case analysis.

In the biologic-naive population, cost-effectiveness ratios for all TIMs were above $150,000 per QALY compared to conventional treatment for nearly all scenarios, with the exception of infliximab and its biosimilars in the modified societal perspective and infliximab-dyyb using a five-year time horizon. None of the TIMs were cost effective compared to infliximab.

In the biologic-experienced population, no TIMs had a cost per QALY gained compared to conventional treatment below the $150,000 per QALY threshold. Compared to adalimumab, tofacitinib resulted in lower cost and greater QALYs. Ustekinumab and vedolizumab resulted in greater QALYs but were not cost effective.

5.4 Summary and Comment

We estimated the cost effectiveness of TIMs, considering a lifetime time horizon for adult patients with moderate-to-severe UC in biologic-naïve and biologic-experienced populations. Patient time spent in health states of active UC, response without remission, and response with remission was summed to provide estimates of life expectancy, quality-adjusted life expectancy, and evLY gained. Annual net health care costs, including net price drug acquisition, administration, adverse events, and colectomy were summed to estimate lifetime costs for TIMs and conventional treatment. We used a transition matrix for conventional treatment based on the placebo arm of RCTs and applied a risk ratio for TIMs for response without remission and response with remission to derive TIM-specific transition probabilities between health states for induction and maintenance. Based on these assumptions, the cost effectiveness of TIMs was estimated to range from $186,000 to $1,870,000 per QALY in the biologic-naïve population and $495,000 to $1,885,000 per QALY in the biologic-experienced population. It is important to note that the magnitude of difference in the total QALY estimates across interventions was not large (largest difference was 0.11), suggesting an increased importance for the cost differences when interpreting the results. Results for cost per evLY gained were similar but slightly lower than cost per QALY, as a result of a small decrease in mortality with the use of TIMs due to avoidance of colectomy. In general, the incremental cost of TIMs versus conventional treatment was modest given the annual price of TIMs, the use of subsequent treatments, and a lifetime time horizon. In our model, initial non-responders and those who lose response to a TIM are assumed to discontinue treatment. With this assumption, few patients remain on the initial TIM longer than a year. Appendix Table E12 shows the distribution of patients across health states at the end of one, five, and 10 years. Approximately 20% of biologic-naïve patients and 10% of biologic-experienced patients remain in clinical remission or response without remission health states at five years.

Scenarios in which TIMs resulted in cost per QALY estimates below the $150,000 per QALY threshold were infliximab and infliximab biosimilars compared with conventional treatment in the biologic-naïve population in the modified societal perspective, infliximab-dyyb using a five-year

time horizon, and for tofacitinib compared with adalimumab in the biologic-experienced population.

Considerable uncertainty exists in our model, primarily driven by estimates of health utility values, wide confidence intervals of risk ratio estimates produced in the NMA, and subsequent treatment pathways. However, results of the probabilistic sensitivity analysis showed that TIMs are unlikely to be cost effective at the $150,000 per QALY threshold.

Based on our analysis, the cost per additional QALY for TIMs is expected to exceed usual thresholds for cost effectiveness. These results were tested under a variety of assumptions and alternative sources of model inputs, few of which drove the incremental cost per QALY below the threshold of $150,000 per QALY gained.

6. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits 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. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in Table 6.1, and the subsequent text provides detail about the elements that are applicable to the comparison of TIMs to conventional therapy in UC. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting panel of clinicians, patients, and health services researchers. As part of their deliberations, Panel members will judge whether a treatment may substantially impact the considerations listed in Table 6.1. The presence of substantial other benefits or contextual considerations may shift a Panel member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a Panel member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Panel member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Panel member to vote for a lower value category. A Panel member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's Value Assessment Framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report and Meeting Summary, which is released after the public meeting.

This section, as well as the Panel's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 6.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to conventional therapy, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to conventional therapy, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

6.1 Potential Other Benefits

As noted in Sections 1 and 2, UC confers a significant burden to patients and their caregivers. As a disease that is diagnosed primarily before age 30, UC has an important impact on return to work and/or school as well as overall productivity (i.e., both absenteeism and presenteeism). The benefits of TIMs relative to conventional therapy may translate into significant and durable periods of clinical remission, allowing patients to resume normal activities and reducing caregiver impact.

We also heard from both patient advocacy organizations and clinicians that, similar to other chronic inflammatory conditions, UC is a disease with treatment patterns that involve relatively frequent switching due to lack of or loss of response, both within and across classes of TIMs. Novel mechanisms of action, such as that offered by ustekinumab, the newest addition to the armamentarium, provide additional options for patients with UC whose disease has stopped responding to other TIM classes. In addition, available UC therapies include oral, self-injectable, and infused products; patients tend to have clear preferences for method of delivery. For example, some may value the freedom and independence provided by oral or self-injectable treatments,

while others may place more weight on the regular clinician interactions that come with scheduled infusions.

Finally, we heard from the Crohn's and Colitis Foundation that there are important aspects of the condition (e.g., pain, fatigue, fecal urgency) not adequately captured by trial-based clinical endpoints and therefore not fully reflected in the economic model. If TIM therapy addresses these concerns wholly or in part, there may be benefits to patients and caregivers that have not been captured by this review.

6.2 Contextual Considerations

As noted above, UC poses a significant lifetime burden on quality of life, and many patients fear the prospect of surgical intervention and its attendant complications.

In comparison to other chronic inflammatory diseases, RCT evidence for UC is actually relatively lengthy, with comparative information available out to one year or more in most circumstances. However, comparative long-term observational data, particularly on safety concerns that may have been raised during clinical development, vary in availability. For example, while the safety profile of the TNF inhibitors has been relatively well established in UC and other chronic inflammatory conditions, these data are sparse for newer TIMs, such as tofacitinib, ustekinumab, and vedolizumab.

It should be noted that uncertainty surrounding both clinical effectiveness and safety is most pronounced in pediatric populations where we identified only a single RCT that was not actually a comparison of alternative TIM therapies (i.e., a comparison of two dose regimens of infliximab). Infliximab remains the only agent with an FDA indication in children and adolescents, and as such, there is substantial uncertainty about the long-term benefits and risks of other TIMs in these patients—uncertainty that will hopefully be addressed by future clinical trials and/or high-quality observational studies.

7. Health-Benefit Price Benchmarks

The health benefit price benchmark (HBPB) is a price range suggesting the highest price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good.

Annual prices of each TIM that would achieve incremental cost-effectiveness ratios of $100,000 and $150,000 per QALY for the biologic-naïve and biologic-experienced populations are presented in Tables 7.1 and 7.2, respectively. The cost per evLYG price ranges are almost identical to the cost per QALY ranges due to the very similar evLYG and QALYs gained in the base-case analysis, and as such, are not presented separately here.

Table 7.1. Annual Cost-Effectiveness Threshold Prices per Maintenance Year for TIMs for the Treatment of UC in the Biologic-Naïve Population

	Annual WAC	Annual Estimated Net Price	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Adalimumab	$72,400	$46,900	$5,800	$6,900	90%-92%
Golimumab	$75,300	$42,300	$6,300	$7,600	90%-92%
Infliximab	$27,900	$14,600	$8,800	$10,900	61%-68%
Infliximab-dyyb	$22,600	$13,500	$8,800	$10,900	52%-61%
Infliximab-abda	$18,000	$13,900	$8,800	$10,900	40%-51%
Ustekinumab	$150,400	$91,600	$12,900	$16,600	89%-91%
Vedolizumab	$43,800	$44,200	$9,500	$11,700	73%-78%

WAC: wholesale acquisition cost
Prices rounded to nearest $100.

Table 7.2. Annual Cost-Effectiveness Threshold Prices per Maintenance Year for TIMs for the Treatment of UC in the Biologic-Experienced Population

	Annual WAC	Annual Estimated Net Price	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Adalimumab	$72,400	$46,900	$5,700	$6,800	91%-92%
Tofacitinib	$57,200	$35,500	$12,600	$15,300	73%-78%
Ustekinumab	$150,400	$91,600	$8,100	$11,800	92%-95%
Vedolizumab	$43,800	$44,200	$8,900	$11,100	75%-80%

WAC: wholesale acquisition cost
Prices rounded to nearest $100.

Across both populations, the HBPB ranges for adalimumab (approximately $6,000 to $7,000 per year) would require discounts of approximately 90% to 92% from WAC. Golimumab would require discounts of approximately 90% from WAC, for a HBPB range from $6,300 to $7,600 per year. The HBPB range for infliximab ($8,800-$10,900) would require discounts of 61% to 68% from WAC, with smaller discounts required for infliximab-dyyb (52% to 61%) and infliximab-abda (40% to 51%). The HBPB range for ustekinumab across both populations ranged from $8,100 to $16,600, representing discounts of 89% to 95%. For vedolizumab, the HBPB range across both populations is $8,900 to $11,700, requiring 73% to 80% discounts from WAC.

8. Potential Budget Impact

8.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of the recently expanded indication of ustekinumab for prevalent individuals in the US with moderate-to-severe UC. In our estimates of potential budget impact, we used the WAC, estimated net price, and $50,000, $100,000, and $150,000 cost-effectiveness threshold prices that were weighted averages of the threshold prices for the biologic-naïve and biologic-experienced populations eligible for ustekinumab. We did not include the other therapies modeled above in this potential budget impact analysis given their established presence on the market for UC.

8.2 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 this new therapy rather than relevant existing therapies 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 a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

This potential budget impact analysis includes the estimated number of individuals with UC in the US who would be eligible for treatment with ustekinumab. To estimate the size of the potential candidate populations for treatment, we used an estimate by Turner et al. of the prevalence of individuals with UC in the US of approximately 900,000 patients.[4] The Crohn's and Colitis Foundation has reported that approximately 22% of UC patients have moderate-to-severe disease activity in a given year, which would equate to approximately 198,000 patients with moderate-to-severe UC in the US.[20] To estimate the proportions of these patients who would be biologic-naïve versus biologic-experienced, we used the weighted average of the baseline distribution of patients in the relevant trials that enrolled a "mixed" population (i.e., both biologic-naïve and biologic-experienced), resulting in an estimate of approximately 55% of patients who were not using biologics and 45% who had previously used biologics. Applying these proportions resulted in estimates of 108,900 eligible patients who were biologic-naïve and 89,100 who were biologic-experienced. For the purposes of this analysis, we assumed that 20% of these patients would initiate ustekinumab in each of the five years, or 21,780 biologic-naïve patients per year and 17,820 biologic-experienced patients per year.

For patients eligible for ustekinumab, we assumed that patients could be drawn from all other available treatment options for biologic-naïve patients (i.e., adalimumab, golimumab, infliximab, infliximab-dyyb, infliximab-abda, vedolizumab, and conventional treatment), and from all other available treatment options for biologic-experienced patients (i.e., adalimumab, tofacitinib, vedolizumab, and conventional treatment). As in the base-case cost-effectiveness analysis, proportions of treatments in each population were assumed to be equal in the absence of contemporary real-world data on utilization patterns in the US.

ICER's methods for estimating potential budget impact are described in detail elsewhere[171] and have been recently updated. The intent of our revised approach to potential budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

8.3 Results

Table 8.1 illustrates the five-year annualized per-patient potential budget impact of ustekinumab compared to the blended market basket of treatments in the biologic-naive and biologic-experienced populations, assuming a fixed ratio of 55% biologic-naïve and 45% biologic-experienced patients (based on the baseline distribution of patients in the trials). The results are based on the list price ($150,425 per year), the net price ($91,609 per year), and the annual weighted-average threshold prices (i.e., in a mixed population of biologic-naïve and biologic-experienced patients) for cost-effectiveness thresholds of $150,000, $100,000, and $50,000 per QALY versus conventional treatment (approximately $14,400, $10,800, and $7,100, respectively). Note that this analysis uses results from the cost-effectiveness model, which accounts for treatment discontinuation and impact of treatments on total net costs.

The average annualized potential budgetary impact when using the list price of ustekinumab was an additional per-patient cost of approximately $36,100 and approximately $15,600 using the net price. The weighted-average threshold prices for $50,000 to $150,000 per QALY were estimated to produce cost savings relative to the treatment market basket, because of the relatively higher cost offset from the comparator mix ($37,500 per patient), which includes several biologics at their net prices.

Table 8.1. Annualized Per-Patient Potential Budget Impact Over a Five-Year Time Horizon for Ustekinumab in a UC Population Assuming 55% Biologic-Naïve and 45% Biologic-Experienced

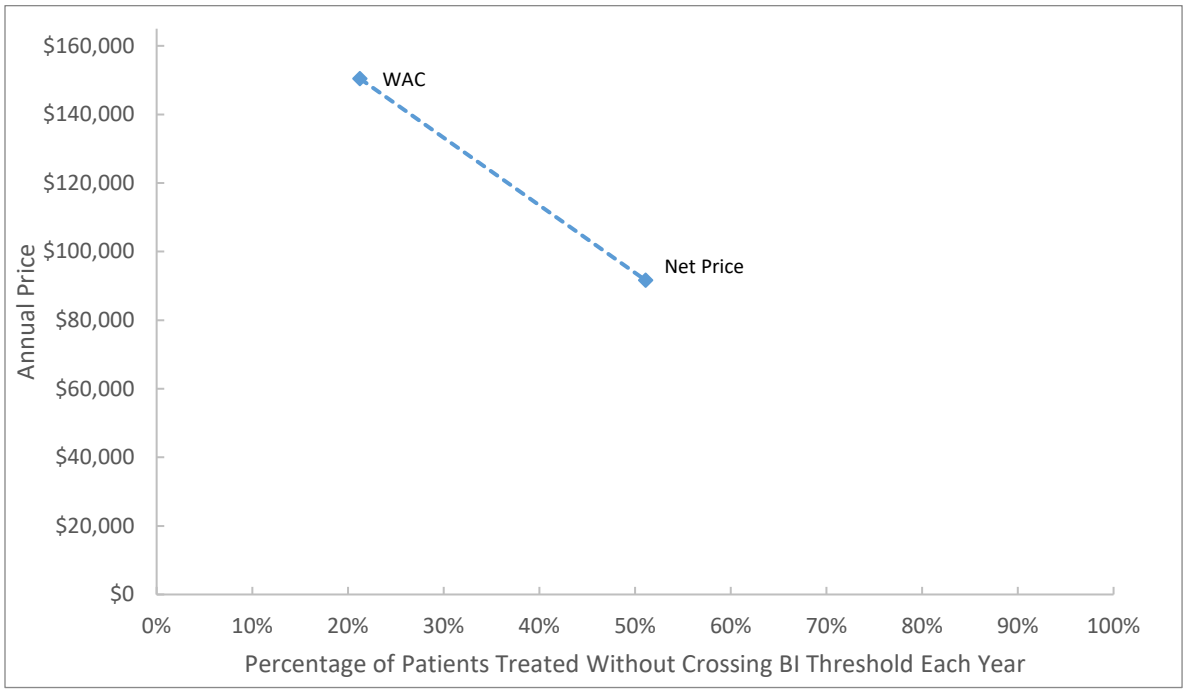
	Average Annual Per Patient Budget Impact				
	At List Price	At Net Price	At $150,000/ QALY Price	At $100,000/ QALY Price	At $50,000/ QALY Price
Ustekinumab	$73,600	$53,100	$28,800	$27,600	$26,400
55% Naïve/45% Experienced Market Basket	$37,500				
Net Impact	$36,100	$15,600	-$8,700	-$9,900	-$11,100

QALY: quality-adjusted life year

All annualized costs include drug and non-drug health care costs. Numbers may not sum due to rounding.

To estimate potential budget impact in the overall population eligible for ustekinumab, we assumed a fixed ratio of 55% biologic-naïve and 45% biologic-experienced patients, as above. In the overall population eligible for ustekinumab, as shown in Figure 8.1, approximately 21% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at the WAC of ustekinumab. Approximately 51% of eligible patients could be treated without crossing the budget impact threshold at its estimated net price. All eligible patients could be treated at the $150,000, $100,000, and $50,000 threshold prices, with potential budget impact estimated to be cost saving across the $150,000 to $50,000 threshold prices.

Figure 8.1. Potential Budget Impact Scenarios of Ustekinumab versus Market Basket Treatment Mix at Different Acquisition Prices



BI: budget impact, WAC: wholesale acquisition cost

8.4 Summary

Potential budget impact in the overall population eligible for ustekinumab could be relatively high, with treatment of approximately 51% of eligible patients surpassing the budget impact threshold at its estimated net price. In contrast, all eligible patients could be treated at the $150,000, $100,000, and $50,000 threshold prices, with the potential for cost savings at these prices.

9. Summary of the Votes and Considerations for Policy

9.1 About the CTAF Process

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

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

After the CTAF Panel votes, a policy roundtable discussion is held with the CTAF Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the September 24 meeting, the CTAF Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of TIMs for UC. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, the CTAF Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to TIMs. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by CTAF Panel members during the voting process.

In its deliberations and votes related to value, the CTAF Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 9.1 below):

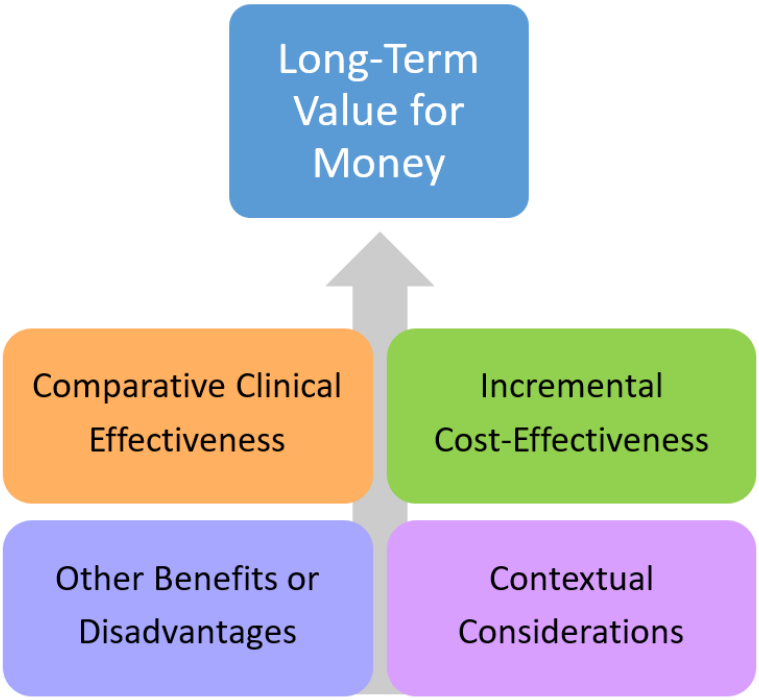
1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. CTAF uses the ICER Evidence Rating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

2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the CTAF Panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

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

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 9.1. Conceptual Structure of Long-Term Value for Money



9.2 Voting Results

1) Is the evidence adequate to demonstrate that the net health benefit of vedolizumab is superior to that provided by adalimumab?[2]

Yes: 12 votes	No: 2 votes

A majority of the Panel determined that the evidence was adequate to demonstrate a superior net health benefit of vedolizumab versus adalimumab. The Panel was persuaded by the results of the head-to-head VARSITY trial, in which vedolizumab demonstrated higher rates of clinical response compared to adalimumab.

2) Is the evidence adequate to demonstrate that the net health benefit of ustekinumab is superior to that provided by adalimumab?

Yes: 0 votes	***No: 15 votes***

The Panel unanimously judged that the evidence was inadequate to demonstrate a superior net health benefit of ustekinumab versus adalimumab. The Panel cited the results of the ICER NMA and

[2] Due to technological issues, one CTAF Panelist was unable to cast a vote for the first question.

indirect evidence that concluded that ustekinumab demonstrates a health benefit that is at least comparable, *but not superior*, relative to adalimumab

3) Is the evidence adequate to distinguish the net health benefit among tofacitinib, ustekinumab, and vedolizumab?

Yes: 1 vote	***No: 14 votes***

A majority of the Panel concluded that the evidence was inadequate to distinguish the net health benefit among tofacitinib, ustekinumab, and vedolizumab. The Panel vote was driven by the results of the NMA and the lack of head-to-head trials comparing the TIMs.

4) When compared to conventional therapy, does treating patients with TIMs offer one or more of the following potential "other benefits"? (Select all that apply.)

These interventions offer reduced complexity that will significantly improve patient outcomes.	2/15
These interventions will significantly reduce caregiver or broader family burden.	9/15
These interventions offer a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	13/15
These interventions will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	12/15
There are other important benefits or disadvantages that should have an important role in judgments of the value of these interventions.	2/15

A majority of the Panel recognized the impact that TIMs may offer on caregiver or broader family burden. Numerous Panel members also stressed that TIMs may have a significant impact on a patient's ability to return to work or school. Panelists cited patient testimony: patient experts on the Policy Roundtable emphasized the potential benefits offered by TIMs, such as long-lasting remission, which supports increased independence, ability to commute to work and/or school and remain focused throughout the day, and attend and graduate high school and college.

Panelists also noted that the existence of multiple classes of TIMs each with different mechanisms of action helps ensure that patients are more likely to find an optimal treatment. Though patients may cycle through multiple drugs before they find the best treatment, the ability to switch to a different medication within a different class is essential to achieving and maintaining remission.

5) Are any of the following contextual considerations important in assessing the long-term value for money of TIMs? (Select all that apply.)

These interventions are intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	12/15
These interventions are intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	13/15
These interventions are the first to offer any improvement for patients with this condition.	0/15
Compared to conventional therapy, there is significant uncertainty about the long-term risk of serious side effects of these interventions.	13/15
Compared to conventional therapy, there is significant uncertainty about the magnitude or durability of the long-term benefits of these interventions.	12/15
There are additional contextual considerations that should have an important role in judgments of the value of these interventions.	0/15

A majority of the Panel recognized that UC is a condition of high severity with substantial impacts on quality of life. The Panel also noted that significant uncertainty remains regarding the magnitude or durability of long-term benefits, as well as the long-term risks associated with TIMs. Though some TIMs, such as the TNF inhibitors, have been on the market for a long period of time, there is more limited evidence regarding the long-term durability and safety around newer treatments like tofacitinib, ustekinumab, and vedolizumab.

6) Given the available evidence on comparative effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment at current pricing with infliximab, infliximab-abda, and infliximab-dyyb versus conventional treatment?

Low: 3 votes	**Intermediate: 10 votes**	High: 2 votes

A majority of the Panel judged the long-term value for money of treatment with infliximab, infliximab-abda, and infliximab-dyyb as "intermediate." The intermediate vote was driven by the clinical and economic evidence and the various potential other benefits and contextual considerations offered by infliximab and its biosimilars.

In a majority of RCTs, infliximab had higher rates of both clinical response and clinical remission compared to placebo. In addition, rates of endoscopic improvement were higher for infliximab compared to placebo as well. In conjunction, Panelists emphasized that the safety and side effect profile is relatively well established as infliximab has been on the market for a while. Though infliximab and its biosimilars carry black box warnings for increased risk of lymphomas and malignancies, the Panel noted that in the evidence base, overall rates of new malignancy were very low (<3%) for TNF inhibitors.

The "intermediate" vote was also driven by the results of the base-case economic analysis as well as other scenario analyses in which infliximab and its biosimilars fell near, at, or below commonly cited

cost-effectiveness thresholds. Although Panelists acknowledged that the cost of infliximab and its biosimilars is still too high, taking the clinical and economic evidence and potential other benefits and contextual considerations into account, the Panel determined an overall intermediate long-term value for money.

9.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the CTAF Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on TIMs for UC to policy and practice. The policy roundtable members included two patients/patient experts, two clinical experts, two payers, and two representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in the Appendix.

Table 9.1 Policy Roundtable Participants

Name	Title and Affiliation
Thomas Brownlie, PhD, MS	Senior Director, US Payer Policy, Pfizer
Deborah Gan, MBA	Leader, US Payer Marketing, Primary Care, Merck
Patrick Gleason, PharmD	Assistant Vice President, Health Outcomes, Prime Therapeutics
Bruce Sands, MD, MS	Professor of Medicine and Chief, Division of Gastroenterology, Mount Sinai
Siddharth Singh, MD	Assistant Professor of Medicine, UC San Diego School of Medicine; Gastroenterologist, UC San Diego Health
Megan Starshak	Patient Advocate
Fernando Velayos, MD	Director, Inflammatory Bowel Disease Program, Kaiser Permanente Northern California
Laura Wingate	Senior Vice President, Education, Support, and Advocacy, Crohn's & Colitis Foundation

Clinicians, Payers, Manufacturers, and Patient Groups

The significantly lower prices seen for infliximab and its biosimilars speaks to the important potential for improved value with broader availability and uptake of biosimilar treatment options. All stakeholders should collaborate to ensure that TIM biosimilars have an increasing and comprehensive role in the UC treatment landscape.

The biosimilar market is a $2.8 billion annualized business with health care savings now estimated at $5.6 billion per year. A recent analysis by Bernstein analyst Ronny Gal estimated that biosimilar versions of infliximab accounted for 42% of the savings as the price for the brand-name biologic dropped about 48%.[172] Although the resulting net price for infliximab and its biosimilars did not reach traditional cost-effectiveness thresholds in the ICER analysis, their cost effectiveness was far superior to that of other treatment options. Roundtable participants emphasized the benefit of

having biosimilars to infliximab available in the UC treatment armamentarium and expressed frustration that other biosimilars are FDA-approved (e.g., adalimumab) but not yet available on the US market. In addition, it was noted that the Affordable Care Act (ACA), which provided the regulatory pathway for biosimilar agents, is under threat. Clinicians, payers, manufacturers, and patient groups should collaborate to develop an approach for broader biosimilar access, including a contingency plan in the event the ACA is overturned.

Manufacturers and Payers

The "bundled rebate" approach, in which rebates are provided at the drug level across all of its possible indications, should be abolished and replaced with an indication- and value-based pricing approach.

Several TIMs in this review carry indications for multiple inflammatory conditions. Manufacturers have historically been able to negotiate on a "bundled" basis, offering a single price and rebate across all indications. Our cost-effectiveness analyses indicated that the pricing of all TIMs (with the possible exception of infliximab biosimilars) was far out of alignment with the benefits delivered. Abolishing the bundled rebate approach and replacing it with pricing that is tied to the value brought by a given TIM for each indication, would allow payers to relax certain step therapy requirements and increase patient access to all TIMs.

Payers

Insurance coverage should be structured to prevent situations in which patients are forced to choose a treatment approach on the basis of cost.

Patient input on the Roundtable indicated a variety of views on and experiences with surgical colectomy. Some also suggested that, due to copayment and coinsurance structures, some reluctant patients might nevertheless opt for colectomy as a "cheaper" option if they are having difficulty paying for their medications. Payers should take particular pains to ensure that benefit structures are sufficiently flexible so that patients wishing to avoid a colectomy have other options at their disposal.

Specialty society guidelines and drug labels should be monitored for changes, with coverage policy adjusted accordingly.

Findings from our review and discussion at the Roundtable noted several instances in which payer coverage policy has not matched changes in clinical guidelines or in the drug label. For example, vedolizumab's label changed in 2019 to remove the requirement for an initial trial of TNF inhibitors. Despite this change, payer coverage policies have generally continued to require use of a TNF

inhibitor before vedolizumab can be given. Payers should routinely monitor guidelines and label changes just as they would for new clinical evidence and modify coverage policy accordingly.

Because there are no clear biomarkers or predictors of the success for any given treatment in UC, it is not unreasonable to consider prior authorization criteria in order to manage the costs of expensive medications and negotiate prices for TIMs priced beyond a fair range. However, prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers.

Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Patient Eligibility Criteria

- **Diagnosis**: Because a diagnosis of UC is made based on clinical symptoms and endoscopic investigation, physician attestation is sufficient for diagnosis.
- **Patient population:** Patients eligible for TIMs include those with moderate-to-severe UC whose disease has had an inadequate response to conventional systemic therapy. Patient eligibility criteria should be flexible given that clinical trials used tools (e.g., Mayo Score for disease severity) that are not routinely used in clinical practice. Relying on physician attestation of the level of disease severity is the most common approach taken by insurers. Inadequate response to conventional systemic therapy is the facet of clinical criteria that insurers may choose to define by specifying particular types of systemic therapies, number of attempts, or duration. This approach is reasonable as long as there is a valid citation or reference for the specifications given. Measurement of therapy "failure" in clinical trials is based on the Mayo Score, but as noted, this should not be used as a criterion within insurance coverage.
- **Exclusions**: UC patients with mild disease and those without a prior trial of conventional systemic agents are not eligible for TIM therapy.

Step Therapy

Given the lack of biomarkers and other predictors of TIM treatment success in UC, it is not unreasonable to use step therapy in this case to manage the costs of treatment. Step therapy among agents for UC appears to meet criteria for reasonable step therapy:

- Use of the first-step therapy reduces overall health care spending, not just drug spending.
- The first-step therapy is clinically appropriate for all or nearly all patients and does not pose a greater risk of any significant side effect or harm.
- Patients will have a reasonable chance to meet their clinical goals with first-step therapy.

- Failure of the first-step drug and the resulting delay in beginning the second-step agent will not lead to long-term harm for patients.

For step therapy to be reasonable, it must ensure that patients are not required to retry a first-line drug with which they have previously had adverse side effects or an inadequate response at a reasonable dose and duration. In addition, the exception process must be rapid, transparent, and *administratively competent*; electronic systems for exceptions should be employed whenever possible to minimize time and paperwork burdens for patients and providers. Similarly, any cost savings realized from step therapy protocols (e.g., originator to biosimilar switch) should be returned to the patient as efficiently as possible, using electronic systems as feasible.

Required Switching

- **Required switching of TIM therapy for patients who are stable on current treatment should be limited to switches to another medication with the same mechanism of action or from an originator to a biosimilar agent.** Given the availability of multiple classes of TIMs for UC and the benefits that sustained remission provide to patients, requiring a switch to another class for a patient who is currently responding to treatment raises a risk that the patient could have new significant side effects or insufficient response, either of which renders this kind of switch unreasonable. Required switches should be within-class only (e.g., between TNF inhibitors) or from an originator to a biosimilar product (e.g., infliximab). Even for required switches within the same class, if the switch requires the patient to adopt a different route of administration, e.g., IV infusion instead of subcutaneous injection, there should be provisions to allow for exceptions if a patient's living or caregiver situation makes the switch infeasible. In addition, as with step therapy, any switching policy must ensure that patients are not required to switch to a drug that they have used before at a reasonable dose and duration with inadequate response and/or significant side effects, including earlier use under a different payer. We note that switching policies can be deeply resented by patients and clinicians and should only be contemplated if coordinated efforts are also made to educate providers and patients; the success of Kaiser Permanente's initiative to switch patients from the originator infliximab to a biosimilar is an example of such a comprehensive approach.

Provider Qualification Restrictions

- **TIM therapy should be prescribed and managed by gastroenterologists with specific training and expertise in UC.** Several stakeholders have noted gaps in clinical practice when the care of UC patients is managed by those without specific training and expertise, including overuse of steroids to manage recurrence of symptoms.

Patient Advocacy Organizations

Patient advocacy organizations should be an active voice in noting the potentially negative effects of TIM pricing on patient access.

Patient Roundtable participants recognized the challenges posed by TIM pricing (and payer response to this) on patients' ability to access the drug they need at the time they need it. Patient groups can represent a strong voice for pricing moderation to align more closely with clinical value, increased use of and access to biosimilars, and other efforts to modulate the pricing-access tension.

Specialty Societies

Consensus guidelines should be developed across the major gastroenterology societies, in collaboration with patient groups, to ensure a common voice for UC treatment guidance.

Several Roundtable participants noted that, unlike other specialties such as cardiology, the major gastroenterology societies (the AGA and the ACG) maintain separate guidelines. Development of common consensus guidelines, with direct input from patient groups, would allow payers to more closely align coverage policy. Such guidelines should involve clinical experts who are free from significant financial or other conflicts of interest to ensure their patient-centricity.

Regulators

Given the maturity and longstanding use of several of the TIMs of focus in this review, the FDA should require the inclusion of active control arms in Phase III clinical trials of UC treatments.

As noted in this review, only one of the 19 RCTs in the available evidence base featured a head-to-head comparison between TIMs. This is despite the longstanding availability of several of these TIMs on the US market. Clinical trials of new agents for other chronic inflammatory conditions such as rheumatoid arthritis and psoriasis now routinely feature an active comparator, including some of the same TIMs featured in this review (e.g., adalimumab). There is no obvious reason why the same approach cannot be taken in UC.

Researchers

The research community should make a strong commitment to generate real-world evidence that can fill in the gaps from available RCTs and allow for comprehensive comparisons of TIMs.

Our review noted several gaps in evidence that RWE may be positioned to fill, such as ongoing monitoring of the safety of newer TIMs as well as information on clinical benefits observed in populations without RCT evidence but with clear real-world experience (e.g., infliximab in biologic-experienced patients). In addition, there is limited understanding of the trajectory of disease and relative effectiveness of TIMs in African American, Asian, and LatinX population. The Crohn's and Colitis Foundation's IBD Plexus initiative is a nationwide registry of over 16,000 patients with UC and Crohn's disease, and research is already underway to gain a better understanding of how IBD affects minority populations, the quality of IBD care, and better understanding of disease severity in pediatric populations. This should be supplemented with other efforts to fill in data gaps both in IBD Plexus and other large data networks such as PCORNet and the Sentinel Research Network.

Further clinical study should be conducted to ascertain the optimal sequencing of TIM therapy in UC.

Clinical experts on the roundtable noted that there are currently no available tools with which to predict response to specific UC treatments, and there is no current evidence that involves robust comparisons of different sequences of TIM therapy. Future clinical study could compare clinical benefit and safety for sequences involving within-class switching versus switching outside of class, for example, or long-term outcomes when the same agent is used for both induction and maintenance in comparison to a switch after induction.

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This is the first CTAF review of TIMs for UC.

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Appendix

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., I2) for each meta-analysis.

	#	Checklist Item
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.
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., health care 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 for Medline (via Ovid)

No.	Query
1	colitis, ulcerative
2	((ulcera* adj3 colitis) or inflammatory bowel disease* or IBD or UC).mp
3	(Infliximab or Infliximab-abda or Renflexis or Infliximab-dyyb or Inflectra or Remicade or CT P13).mp.
4	infliximab.af.
5	(Humira or Adalimumab ABTD2E7 or ABT D2E7).mp.
6	adalimumab.af.
7	(Entyvio or MLN0002 or Vedolizumab).mp.
8	vedolizumab.af.
9	(golimumab or simponi or CNTO 148).mp.
10	golimumab.af.
11	ustekinumab.af.
12	(ustekinumab or stelara or CNTO1275 or CNTO 1275).mp.
13	(tofacitinib or tofacitinib citrate or Xeljanz or CP 690?550).mp.
14	tofacitinib.af.
15	(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 videoaudio media).pt.
16	(animals not (humans and animals)).sh.
17	exp cohort studies/ or comparative study.pt. or observational study.pt. or exp case-control studies/ or cohort.tw. or (observational adj2 stud*).tw or prospective.tw or retrospective.tw or longitudinal.tw. or compa*.tw OR groups.tw OR case control.tw OR multivariate.tw
18	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.
19	1 or 2
20	or/3-14
21	19 and 20
22	21 not 15
23	22 not 16
24	17 or 18
25	23 and 24
26	limit 25 to english language
27	remove duplicates from 26

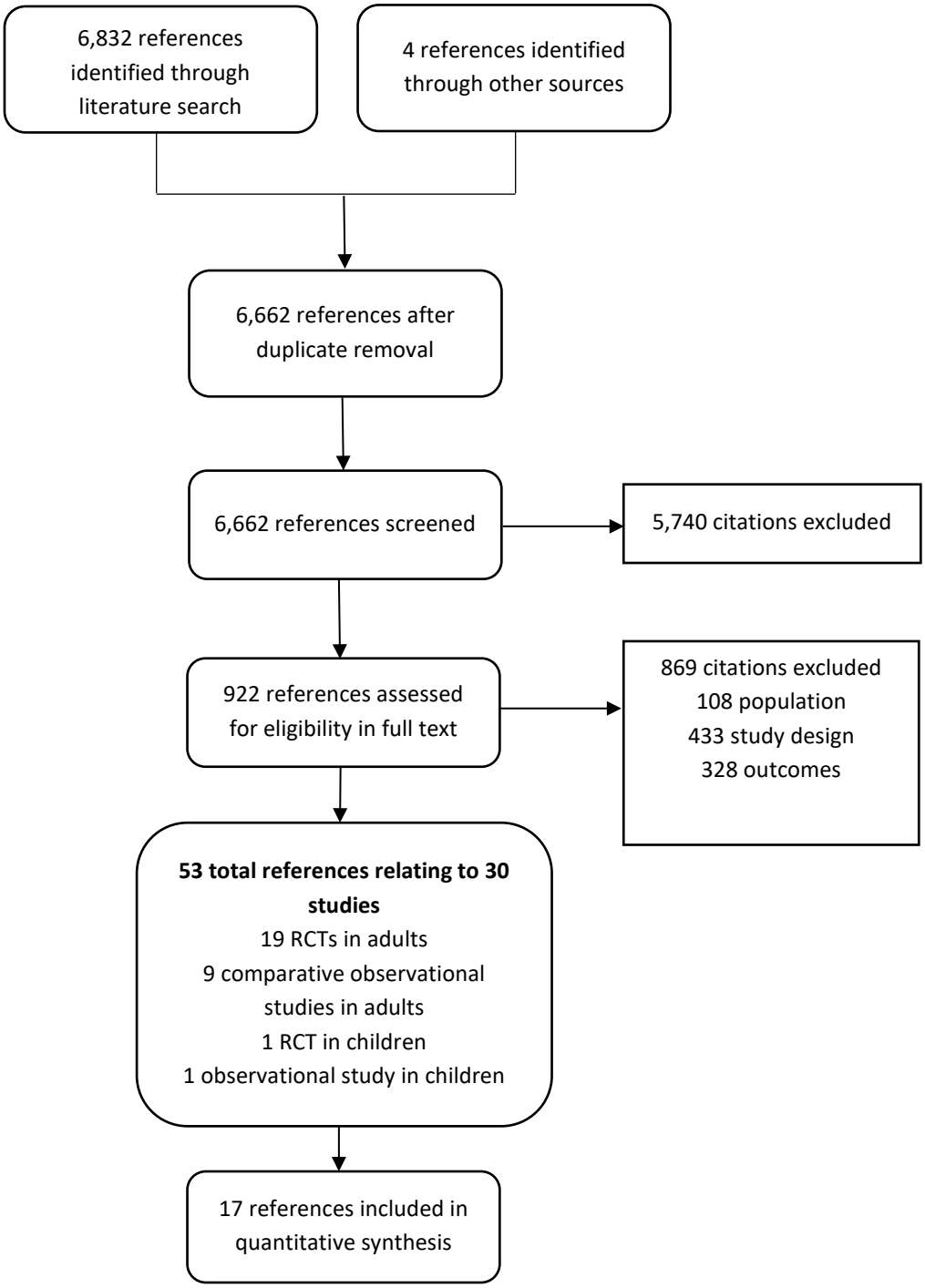
Date of Search: November 20, 2019; updated July 17, 2020.

Table A3. Search Strategies for Embase

No.	Query
#1	'ulcerative colitis'/exp
#2	((ulcera* NEAR/3 colitis):ab,ti) OR 'inflammatory bowel disease*':ab,ti OR uc:ti,ab OR ibd:ti,ab
#3	#1 OR #2
#4	'infliximab'/exp OR infliximab:ab,ti OR 'remicade':ab,ti OR 'renflexis':ab,ti OR 'inflectra':ab,ti OR 'infliximab-adba' OR 'infliximab-dyyb':ab,ti OR 'ct p13':ab,ti
#5	'tofacitinib'/exp OR tofacitinib:ab,ti OR tasocitinib:ab,ti OR 'tofacitinib citrate':ab,ti OR xeljanz:ab,ti OR 'cp 690 550':ab,ti OR 'cp 690550':ab,ti
#6	'adalimumab'/exp OR adalimumab:ab,ti OR humira:ab,ti OR abtd2e7:ab,ti OR 'abt d2e7':ab,ti
#7	'golimumab'/exp OR 'golimumab':ab,ti OR 'simponi':ab,ti OR 'cnto 148':ab,ti
#8	'ustekinumab'/exp OR ustekinumab:ab,ti OR stelara:ab,ti OR cnto1275:ab,ti OR 'cnto 1275':ab,ti
#9	'vedolizumab'/exp OR vedolizumab:ab,ti OR entyvio:ab,ti OR mln0002:ab,ti
#10	#4 OR #5 OR #6 OR #7 OR #8 OAR #9
#11	#3 AND #10
#12	#11 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#13	#12 NOT [medline]/lim
#14	#13 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)
#15	#14 AND [english]/lim
#16	clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'observational study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'longitudinal study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compa*':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab OR retrospective:ti,ab OR prospective:ti,ab OR longitudinal:ti,ab OR ((observational NEAR/2 stud*):ti,ab)
#17	('clinical':ti,ab AND 'trial':ti,ab) OR 'clinical trial'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab or control*:ti,ab OR 'control group'/exp OR 'drug therapy':lnk
#18	#16 OR #17
#19	#15 AND #18

Date of Search: November 20, 2019; updated July 17, 2020.

Figure A1. PRISMA Flow Chart Showing the Results of the Literature Search for TIMs for UC



Appendix B. Previous Systematic Reviews and Technology Assessments

Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review: Adalimumab (Humira), 2016

Health Canada has approved adalimumab for the treatment of adult patients with moderately-to-severely active UC who have had an inadequate response to conventional therapy including corticosteroids, azathioprine and/or mercaptopurine or who are intolerant to such therapies. CADTH agrees with the labeled indication given by Health Canada but also highlights the mechanism of action as a novel way to improve patient access. Only ULTRA 2 allowed the inclusion of patients with prior TNF inhibitor use, so there is uncertainty about its use in those populations. There is also a lack of head-to-head data between adalimumab and other biologics, so a recommendation has not been given on its place in therapy. CADTH suggests that, according to patient preference, patients who achieve remission may discontinue treatment. CADTH's reimbursement recommendation was informed by a review of the manufacturer's pharmacoeconomic submission. CADTH concluded that the incremental cost-utility ratio for adalimumab plus standard of care (SOC) compared to SOC alone is between $67,000 per QALY and $130,000 per QALY. CADTH notes that the surgery costs may be overestimated, the rates of dose escalation and SOC costs may be underestimated and treatment discontinuation between weeks eight and 104 was not considered.

Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review: Golimumab (Simponi), 2013

Health Canada has approved of golimumab 50 mg and 100 mg doses for the use of maintenance in UC, however CADTH states that the clinical benefit of golimumab 50 mg remains unclear as the PURSUIT studies have not reported any significant findings for the lower dose. CADTH's reimbursement recommendation was informed by the review of a manufacturer-provided cost-utility analysis. Based on this analysis, it was concluded that golimumab could lie in the range of $52,000 to $104,000 per QALY for patients with moderate-to-severely active UC.

Canadian Agency for Drugs and Technologies in Health (CADTH): Infliximab versus Adalimumab for Patients with Moderate-to-Severe Ulcerative Colitis: Clinical and Cost-Effectiveness, 2008

CADTH collected three systematic reviews on infliximab (Lawson, Gisbert, and Rahimi) as well as five RCTs for infliximab versus placebo and two RCTs versus corticosteroids and an observational study (Peyrin-Biroulet) on adalimumab. Because of the limited evidence available on adalimumab

at the time and that no available head-to-head trials comparing infliximab to adalimumab, CADTH was unable to draw conclusions on the efficacy of the two treatments versus each other.

Canadian Agency for Drugs and Technologies in Health (CADTH): Common Drug Review Tofacitinib (Xeljanz), 2019

CADTH's review of tofacitinib aligns with Health Canada's approval of tofacitinib for treatment of moderately-to-severely active UC in adult patients with an inadequate response or intolerance to conventional UC therapy or a TNF inhibitor. Because of the high rate of infection, CADTH recommends that patients should be advised to undergo vaccination against herpes zoster infection prior to the start of treatment. No conclusions could be made about tofacitinib's effects on patients' health-related quality of life due to limited data. CADTH's reimbursement recommendation was informed using a manufacturers' cost-utility analysis. The manufacturers' analysis concluded that tofacitinib is associated with incremental cost-utility ratios is $8,897 compared to adalimumab, $145,184 compared to infliximab biosimilar, and $118,387 compared to continued conventional UC treatment for mixed populations. CADTH conducted its own economic analysis for two populations: biologic-naïve and biologic-experienced patients. Price reductions of 44% for biologic-experienced populations and 74% for biologic-naïve populations would be needed for the optimal willingness-to-pay threshold of $50,000 per QALY.

Canadian Agency for Drugs and Technologies in Health (CADTH): Common Drug Review: Ustekinumab (Stelara). Expected Publication Date TBD.

CADTH will be assessing ustekinumab (Stelara) for the treatment of adult patients with moderately-to-severely active UC. Ustekinumab's subcutaneous formulation was recently approved by Health Canada and is indicated for patients with moderately-to-severely active UC.

Canadian Agency for Drugs and Technologies in Health (CADTH): Common Drug Review: Vedolizumab (Entyvio). Expected Publication Date TBD.

CADTH will be assessing the subcutaneous formulation of vedolizumab for the treatment of UC in adult patients with moderately-to-severely active UC who have an inadequate response, loss of response to, or were intolerant to conventional therapy or infliximab. The IV formulation has already been approved by Health Canada in the same population. CADTH has also previously assessed vedolizumab's IV formulation and researchers noted a significant discontinuation rate amongst patients but said the safety profile did not reveal any significant safety concerns. CADTH also conducted an economic assessment using data provided by the manufacturer and found that the incremental cost-effectiveness ratio for vedolizumab IV compared to conventional therapy is between $60,000 to $150,000 per QALY range.

NICE: Tofacitinib for Moderately-to-Severely Active Ulcerative Colitis (TA547), 2018

NICE recommends tofacitinib, within the marketing authorization, for treating moderately-to-severely active UC in adults with an intolerance, inadequate response, or loss of response to either conventional therapy or a biological agent only if the company provides the discount for tofacitinib as agreed upon in the commercial arrangement. Evidence from the clinical trial demonstrates tofacitinib is more effective than placebo. Indirect comparisons show tofacitinib is more effective than adalimumab and golimumab as a maintenance therapy in those who are biologic-naïve. For biologic-experienced patients, tofacitinib is more effective than adalimumab in the induction phase. A cost-effectiveness analysis was conducted by the manufacturer and reflected tofacitinib as a cost-effective treatment for the indicated population. For biologic-naïve patients, the incremental cost-effectiveness ratio as compared to conventional therapy was £8,564 per QALY gained and for biologic-experienced patients, the incremental cost-effectiveness ratio was £10,311 per QALY gained. For both groups, tofacitinib produced fewer QALYs than vedolizumab but at a lower cost.

NICE: Infliximab, Adalimumab, and Golimumab for Treating Moderately-to-Severely Active Ulcerative Colitis after the Failure of Conventional Therapy (TA329), 2015

NICE recommends adalimumab, golimumab, and infliximab, within their marketing authorizations, for adults with moderately-to-severely active UC whose disease has medical contraindications, intolerance, or inadequate response to conventional therapy (e.g., corticosteroids, mercaptopurine, or azathioprine). NICE recommends golimumab only if the manufacturer provides the 100 mg dose at the same cost as the 50 mg dose (as agreed in the patient access scheme). Deciding among the three treatments is recommended to be done at an individual level between the patient and clinician where advantages and disadvantages can be discussed. If more than one treatment can be of use, the least expensive option should be chosen. Further, NICE recommends infliximab as an option of treating severely active UC in children between six and 17 years of age who respond inadequately, are intolerant, or have medical contraindications to conventional therapy. The three biologics should be given as a planned course of treatment until failure or until 12 months after starting treatment. Patients should be reassessed every 12 months.

An NMA using the placebo-controlled RCTs was conducted to compare the three biologics to each other. Within the RCTs, the TNF inhibitors were clinically effective as compared with placebo. However, due to high uncertainty within the results of the NMA, no conclusion was drawn in relation to the relative effectiveness of the TNF inhibitors. Three sensitivity analyses were conducted and reported infliximab as having the greatest effect on inducing clinical response or remission. The systematic review of cost effectiveness identified three economic evaluations of TNF inhibitors for UC, but none were considered by the assessment group as the assessment group concluded they did not accurately represent the natural history of the disease. The assessment group extrapolated the results of the NMA to inform modeling.

NICE: Ustekinumab for Treating Moderately-to-Severely Active Ulcerative Colitis [ID1511]. Expected Publication Date: 13 May 2020

NICE is currently evaluating the clinical and cost effectiveness of ustekinumab for the treatment of moderately-to-severely active UC. Proposed comparators include TNF inhibitors (adalimumab, golimumab, and infliximab), tofacitinib, vedolizumab, and conventional therapies (without biological treatments). Outcomes of interest include mortality, measures of disease activity, rates of and duration of response, relapse, and remission, rates of hospitalization and of surgical intervention, endoscopic healing, mucosal healing, corticosteroid-free remission, adverse effects of treatment, and health-related quality of life. If evidence allows, the following subgroups will be explored: people who have been previously treated with one or more biologics and people who have not received prior biologics.

NICE: Vedolizumab for Treating Moderately-to-Severely Active Ulcerative Colitis (TA342), 2015

NICE recommends vedolizumab as an option to treat adults with moderately-to-severely active UC, within its marketing authorization, if the company provides the discount agreed upon in the patient access scheme. NICE recommends vedolizumab to be given until there is a loss of response/remission or surgery is needed and patients should be reassessed after 12 months on treatment. NICE did not conduct their own NMA. NMA data presented by the company was considered but the committee notes that the evidence was not powered to test for treatment effects of vedolizumab between populations (biologic-naïve and biologic-experienced patients) and the data available for effectiveness after TNF-inhibitor failure was limited to one comparison: adalimumab. The company provided deterministic base-case results for its modeled populations. For the overall population, the incremental cost-effectiveness ratio for vedolizumab as compared to conventional therapy was £33,297 per QALY gained. In the biologic-naïve population, the incremental cost-effectiveness ratio for vedolizumab was £6,634 per QALY gained when compared to adalimumab and £4,862 per QALY gained as compared to conventional therapy. In the biologic-experienced population, vedolizumab had an incremental cost-effectiveness ratio of £64,999 per QALY gained as compared with conventional therapy. The ERG carried out its own exploratory base case (combining three scenario analyses) and concluded that in the overall population, the incremental cost-effectiveness ratio for vedolizumab as compared to conventional therapy is £53,084 per QALY gained. It also concluded that in the biologic-naïve population, adalimumab dominates vedolizumab and in the biologic-experienced population, the incremental cost-effectiveness ratio for vedolizumab as compared to conventional therapy is £48,205 per QALY gained.

Welty, M. et al. Efficacy of Ustekinumab versus Advanced Therapies for the Treatment of Moderately-to-Severely Active Ulcerative Colitis: a Systematic Review and Network Meta-Analysis[173]

Researchers conducted a systematic review and NMA to compare the efficacy of ustekinumab to other advanced therapies for the treatment of moderately-to-severely active UC. Using data taken from trials of ustekinumab, infliximab, adalimumab, golimumab, vedolizumab, and tofacitinib, they conducted two fixed-effects Bayesian NMAs: one for the induction phase of the trials alone (six to eight weeks) and another for the maintenance period (one year). They also conducted separate analyses for patients who had not been failed by a prior biologic (NBF) and patients who had (BF).

The induction phases of the included trials had consistent designs and could be evaluated using a standard approach; however, the maintenance phases were either structured as treat-through or re-randomized. To conduct the analysis, trials with a re-randomized response design were re-calculated to correspond to a treat-through design to maintain the randomization used at the start of induction. Researchers cite that this approach factors in both initial and delayed responders. In trials where maintenance data for the placebo was missing for induction responders or non-responders, the data was imputed.

In the maintenance phase one-year NMA in NBF patients, doses were pooled as there is no conclusive evidence of a relationship between dose and efficacy. In clinical response data analyzed from six studies for NBF patients, ustekinumab had higher odds of response versus adalimumab (OR 4.76, 95% CI: 2.25 to 10.16), golimumab (OR: 3.76, 95% CI: 1.90 to 7.57), infliximab (OR: 2.62, 95% CI: 1.2 to 5.60), and tofacitinib (OR: 2.27; 95% CI: 1.06 to 4.86). Based on the results analyzed from seven studies for clinical remission, pooled ustekinumab had higher odds of clinical remission than adalimumab (OR: 2.43, 95% CI 1.10 to 5.42) and golimumab (OR: 2.40, 95% CI: 1.40 to 5.22). Results for patients who were failed a prior biologic (BF) are not presented with pooled doses because there is a potential dose-response relationship. There were not statistical differences between ustekinumab and any TIM in the BF population. In the induction phase NMA at six to eight weeks in NBF patients, ustekinumab 6 mg/kg had higher odds of response versus adalimumab (OR: 1.94, 95% CI 1.10 to 3.45). In BF patients, ustekinumab 6 mg/kg had higher had higher odds of response versus adalimumab (OR: 2.48, 95% CI 1.17 to 5.31).

Overall, in patients with moderately-to-severely active UC who have not been failed by prior biologic therapy, patients on ustekinumab have a higher probability of clinical remission and response versus other advanced therapies. Patients who have previously been failed by a biologic have a similar probability versus other therapies, but they were associated with greater uncertainty because of smaller patient counts and power placebo efficacy rates.

Lohan, C. et al. Tofacitinib for the Treatment of Moderately-to-Severely Active Ulcerative Colitis: A Systematic Review, Network Meta-Analysis and Economic Evaluation[170]

Researchers conducted a systematic review, NMA, and economic evaluation to evaluate the efficacy and safety of available treatments for patients with moderately-to-severely active UC. The treatments included in the review include TNF inhibitors (adalimumab, golimumab, and infliximab) as well as tofacitinib and vedolizumab. Varying doses and dosing regimens were seen as comparators within the review. The outcomes of interest were efficacy outcomes (clinical response and remission) and serious infection. Twenty-two RCTs were included in the review and 17 of those RCTs were included in the NMA. To be included in the NMA, RCTs needed to have data for either an induction period and/or a maintenance period, reporting on the previously mentioned outcomes. The data from three treat-through trials were recalculated to match the data from five studies that re-randomized participants after the induction phase, and the differences in placebo response rates were not adjusted for. Separate analyses for the populations of biologic-naïve and biologic-experiences were conducted. For both biologic-naïve and biologic-experienced, the results of the NMA showed no significant differences among the treatments. For the biologic-naïve population, all the treatments were more effective than placebo in the induction phase, however, no results were statistically different in the maintenance phase due to large credible intervals. For the biologic-experienced population during induction, tofacitinib was the only treatment to have statistically greater efficacy than placebo for clinical response (OR: 4.28, 95% CI to 1.27-18.59) and for clinical remission (OR: 5.61, 95% CI, 1.36 to 4.53). During maintenance, tofacitinib and vedolizumab were the only treatments to appear more efficacious than placebo. For tofacitinib, significant results were seen for clinical response and clinical remission for both the 5 mg (OR: 4.53, 95% CI: 2.1 to 22.23; OR: 4.7 95% CI: 2.12 to 26.64) dose and the 10 mg dose (OR: 8.66, 95% CI: 3.87 to 65.79; OR: 8.98, 95% CI: 3.91 to 80.19), respectively. Similarly, significant results were seen for both clinical response and clinical remission for vedolizumab 300 mg every eight weeks (OR: 6.51, 95% CI: 2.45 to 46.58; OR: 6.78, 95% CI: 2.49 to 56.15) and 300 mg every four weeks (OR: 5.74, 95% CI: 1.91 to 41.39; OR: 5.97, 95% CI: 1.94 to 49.09), respectively. No significant differences were seen among the treatments for serious infections.

A cost-effectiveness analysis was conducted. For the biologic-naïve population, the incremental cost-effectiveness ratio for tofacitinib as compared with conventional treatment was £21,338 per QALY. Patients treated with tofacitinib are predicted to gain more QALYs that patients treated with infliximab. Additionally, it was suggested that a mixed strategy of conventional therapy and tofacitinib would provide more QALYs overall. For the biologic-experienced population, the incremental cost-effectiveness ratio for tofacitinib as compared with conventional treatment was £22,816 per QALY. Similarly, tofacitinib is predicted to result in more QALYs than infliximab. The QALYs between vedolizumab and tofacitinib reflected near equivalence in both populations with vedolizumab having a higher total cost over the lifetime than tofacitinib, £8,730 and £4,981, respectively.

Appendix C. Ongoing Studies

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
Infliximab					
Infliximab Accelerated Induction in Moderate to Severe Pediatric UC (INDUCE) NCT03209232 **Schneider Children's Medical Center, Israel**	Randomized, Parallel Assignment, OL Study Estimated Enrollment: 84	Intervention Accelerated induction of IFX at 0, 1, 3 wks (5 mg/kg) and then at wk 7, 11, 15 Active Comparator Per protocol induction of IFX at 0, 2, 6 wks (5 mg/kg) and then at wk 14	Inclusion Ages 6-17 years with UC diagnosis Naïve to biologics Planned to initiate IFX PUCAI ≥35 Exclusion Acute severe colitis Renal failure or toxic megacolon Prior treatment with IFX or ADA	Clinical remission on IFX at week 20	April 2022
Adalimumab					
Efficacy and Safety of Adalimumab in Pediatric Subjects with Moderate to Severe Ulcerative Colitis NCT02065557 **AbbVie**	Phase III, MC, DB, RCT Estimated Enrollment: 100	Intervention ADA 0.6 mg/kg every wk Intervention ADA 0.6 mg/kg EOW	Inclusion Active UC with diagnosis for at least 12 weeks prior to screening Ages 4-17 Exclusion Subject with CD or indeterminate colitis Current diagnosis of fulminant colitis and/or toxic megacolon	Percentage of participants who: Respond at wk 8 per PMS and achieve clinical remission at wk 52 Achieve clinical remission at wk 8	September 2020
Long-term Safety and Efficacy of Adalimumab in Pediatric Subjects with Ulcerative Colitis NCT02632175 **AbbVie**	Phase III, MC, OL extension Estimated Enrollment: 93	Intervention ADA	Inclusion Successfully enrolled and completed M11-290 study Exclusion Considered unsuitable candidate by investigator	Proportion of subjects who achieve: Clinical remission (PMS) Clinical response (PMS) PUCAI response PUCAI remission	March 2026

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
A Long-Term Registry of Humira®(Adalimumab) in Patients with Moderately to Severely Active Ulcerative Colitis (UC) NCT01848561 **AbbVie**	Long-term Observational Prospective Cohort Estimated Enrollment: 8,250	Intervention ADA Intervention IMM therapy	Inclusion ADA group Patients with mod-to-sev UC currently taking ADA for at least 8 wks or entering after participation in AbbVie or Abbott sponsored UC study IMM group Patients with mod-to-severe UC prescribed with or currently taking IMM therapy for at least 12 wks Exclusion Patients on IMM therapy without a concurrent biologic if they cannot continue being treated with IMM therapy Patients treated with other investigational agents	Evaluation of long-term safety of ADA in patients with mod-to-severe active UC	April 2027
Golimumab					
A Study to Assess the Efficacy and Safety of Golimumab in Pediatric Participants with Moderately to Severely Active Ulcerative Colitis (PURSUIT 2) NCT03596645 **Janssen Research & Development, LLC**	Phase III, OL RCT Estimated Enrollment: 125	Intervention 1 GOL SC through wk 50 Intervention 2 IFX IV through wk 46	Inclusion Mod-to-sev UC Must either be currently receiving treatment with, or have a history of having failed to respond to, or have a medical contraindication to at least 1 of the following therapies: oral or IV corticosteroids, MP, and azathioprine OR must either have or have has history of corticosteroid dependency Exclusion Contraindications to the use of GOL or IFX or TNFs per local prescribing information	Clinical remission at wk 6	September 2024

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
			History of malignancy or macrophage activation syndrome Have UC limited to rectum only or to <20% of the colon		
An Observational Prospective Long-term Exposure Registry of Adult Patients with Moderate-to-Severe Ulcerative Colitis (OPAL) **NCT02808780** **Janssen Biotech, Inc.**	Prospective, Cohort Study Estimated Enrollment: 6000	Intervention GOL Comparator Participants receiving thiopurines	Inclusion Mod-to-sev UC *Cohort 1* Currently receiving GOL or is continuing to receive after participation in a UC study, or schedule to receive GOL within 30 days after enrollment *Cohort 2* Currently receiving thiopurine Must not be receiving approved biologics agents Exclusion Patients who cannot be treated with GOL or thiopurines Currently receiving investigational or biologic agent other than GOL	Incidence of lymphoma	July 2031
Vedolizumab					
Entyvio (Vedolizumab) Long Term Safety Study (Entyvio PASS) **NCT02674308** **Takeda**	Prospective Observational Cohort Estimated Enrollment: 5,302	Intervention VEDO or other biologic agents (ADA, certolizumab pegol, GOL, IFX)	Inclusion 18+ years of age Initiating VEDO or another biologic agent for UC or CD Exclusion Prior treatment with VEDO Enrollment in a clinical trial in which treatment for CD or UC is managed through a protocol	Percentage of participants with AE of special interest	July 2021
Vedolizumab IV in Pediatric Participants With	Phase II, Randomized, DB, Dose-ranging Study	Intervention High dose VEDO	Inclusion ≥10 kg at time of randomization Mod-to-sev active UC	Serum concentration at wk 14	December 2020

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
Ulcerative Colitis (UC) or Crohn's Disease (CD) **NCT03138655** **Takeda**	Estimated Enrollment: 80	Comparator Low dose VEDO	Evidence of UC extending proximal to rectum Inadequate response to, loss of response to, or intolerance to at least one of: corticosteroids, IMM, TNF Exclusion Previous exposure to approved or investigations anti-integrins Prior exposure to VEDO Use of topical treatment with ASA or corticosteroids within 2 wks of first administration of drug dose		
Long-term Safety With Vedolizumab Intravenous (IV) in Pediatric Participants With Ulcerative Colitis (UC) or Crohn's Disease **NCT03196427** **Takeda**	Phase IIb, randomized extension study Estimated Enrollment: 80	Intervention High dose VEDO Comparator Low dose VEDO	Inclusion 2-17 years old Completed Study MLN0002-2003 and at wk 22, achieved clinical response Exclusion Hypersensitivity or allergies to VEDO Withdrew from study MLN0002-2003	Percentage of participants with treatment-emergent AEs	July 2025
Vedolizumab Subcutaneous Long-Term Open-Label Extension Study **NCT02620046** **Takeda**	Phase IIIb non-randomized, OL Estimated Enrollment: 692	Intervention Group A: VEDO SC 108 mg Q2W Group B: VEDO SC 108 mg QW	Inclusion Prior participation in study MLN0002SC-3027 or MLN0002SC-3031 Exclusion Surgical intervention for IBD during or after previously mentioned studies Withdrawal from previous studies due to study-drug related AE	Percentage of participants with study drug related treatment-emergent AEs and SAEs	February 2022

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
Tofacitinib					
Long-Term Study of CP-690, 550 in Subjects with Ulcerative Colitis NCT01470612 **Pfizer**	OL, long-term extension study Estimated enrollment: 944	Intervention: CP-690 5 mg for 12 months Intervention: CP-690 10 mg for 12 months	Inclusion Subjects who completed A3921094 or A3921095 and were classified as not meeting clinical response criteria Subjects who completed maintenance study A3921096 or who discontinued treatment early in study A3921096 due to treatment failure Exclusion Subjects who had a major protocol violation in A3921094, A3921095 or A3921096 Presence of indeterminate colitis, or findings suggestive of CD Subjects who had surgery for UC or are likely to require surgery	Safety measured by the number of reported AEs	July 2020

ADA: adalimumab, AE: adverse event, ASA: aminosalicylates, CD: Crohn's disease, DB: double blind, GOL: golimumab, IBD: inflammatory bowel disease, IFX: infliximab, IMM: immunomodulator, IV: intravenous, kg: kilogram, MC: multicenter, mg: milligram, mod-to-sev: moderate-to-severe, MP: mercaptopurine, OL: open label, PUCAI: Pediatric Ulcerative Colitis Activity Index, Q2W: every two weeks, RCT: randomized controlled trial, SAE: serious adverse event, SC: subcutaneous, TNF: tumor necrosis factor, UC: ulcerative colitis, VEDO: vedolizumab, wk: week

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies).

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We used criteria published by the USPSTF to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor." 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.*

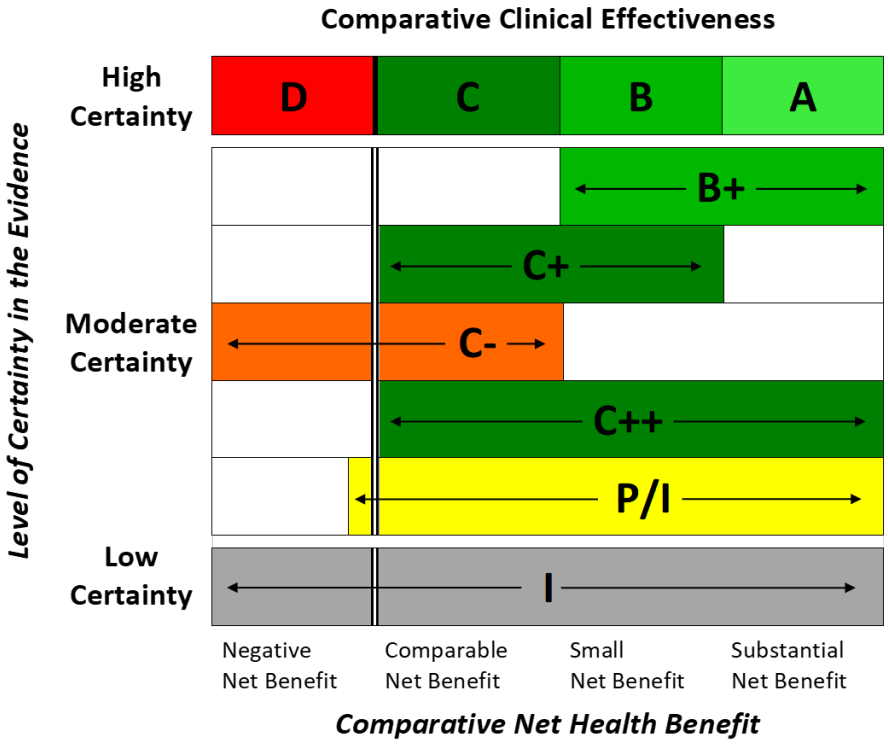
Note that case series are not considered under this rating system; because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

- 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
- The level of certainty in the best point estimate of net health benefit.[64,174]

Figure D1. 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 Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable 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 small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Table D1. Study Design of Included RCTs

Trial/ Timepoint TT or RR*	N	Naïve (%) Exp (%)†	Treatment Arms (n)			Trial Inclusion Criteria	Trial Exclusion Criteria
			Induction	→	Maintenance		
Infliximab							
ACT 1/ Rutgeerts 2005 IND + MAINT (8/54 Wks) TT	364	Naïve (100%)	1) IFX 5 mg/kg (n=121) 2) IFX 10 mg/kg (n=122) 3) PBO (n=121) at wk 0, 2, and 6	All patients moved to MAINT	1) IFX 5 mg/kg (n=121) 2) IFX 10 mg/kg (n=122) 3) PBO (n=121) q8w through wk 46	Mayo Score 6-12 & endoscopic subscore ≥2 Inadequate response to, or had failed to tolerate, ≥1 of the following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; or were CS dependent	Indeterminate colitis or CD; received rectally administered CSs or medications containing ASAs within 2 wks of screening; previously exposed to IFX or other TNF
ACT 2/ Rutgeerts 2005 IND + MAINT (8/30 Wks) TT	364	Naïve (100%)	1) IFX 5 mg/kg (n=121) 2) IFX 10 mg/kg (n=120) 3) PBO (n=123) at wk 0, 2, and 6	All patients moved to MAINT	1) IFX 5 mg/kg (n=121) 2) IFX 10 mg/kg (n=120) 3) PBO (n=123) q8w through wk 22		
Kobayashi 2016 IND + MAINT (8/30 Wks) TT	208	Naïve (100%)	1) IFX 5 mg/kg (n=104) 2) PBO (n=104) at wk 0, 2, and 6	Only responders moved to MAINT	1) IFX 5 mg/kg (n=73) 2) PBO (n=72) q8w through wk 22	Mayo Score 6-12 & endoscopic subscore ≥2 Inadequate response to, or had failed to tolerate, ≥1 of the following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; or were CS dependent	Recent bowel surgery or complications; bowel complications: stricture, fistula, or dysplasia; treatment with other biologics, MTX, calcineurin inhibitors, or cytapheresis within previous 18 mo
Jiang 2015 IND + MAINT (8/30 Wks) TT	82	Naïve (100%)	1) IFX 3.5 mg/kg (n=41) 2) IFX 5 mg/kg (n=41) 3) PBO (n=41) at wk 0, 2, and 6	All patients moved to MAINT	1) IFX 3.5 mg/kg (n=41) 2) IFX 5 mg/kg (n=41) 3) PBO (n=41) q8w through wk 22	Mayo Score 6-12 & endoscopic subscore ≥2 Inadequate response to, or had failed to tolerate, ≥1 of the following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP	Indeterminate colitis or CD; recent infection, positive TB tests; received rectally administered CSs or drugs containing ASAs within 2 wks of screening; previously exposed to IFX or other TNF
NCT01551290 IND + MAINT (8/26 Wks) TT	99	Naïve (100%)	1) IFX 5 mg/kg (n=49) 2) PBO (n=50) at wk 0, 2, and 6	All patients moved to MAINT	1) IFX 5 mg/kg (n=50) 2) PBO (n=49) q8w through wk 22	Mayo Score 6-12 & endoscopic subscore ≥2 Active UC despite treatment with CSs, AZA, MP, or ASA	Extensive colitis or UC limited to only rectum or less than 20 cm of colon; treatment with cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 8 wks

Trial/ Timepoint TT or RR*	N	Naïve (%) Exp (%)†	Treatment Arms (n)			Trial Inclusion Criteria	Trial Exclusion Criteria
			Induction	→	Maintenance		
Adalimumab							
ULTRA 1/ Reinisch 2011 IND only (8 Wks)	390	Naïve (100%)	1) ADA 160/80 mg (n=130) 160 mg at wk 0, 80 mg at wk 2, 40 mg at wks 4 and 6 2) ADA 80/40 mg (n=130) 80 mg at wk 0, 40 mg at wks 2, 4, and 6 3) PBO (n=130)	--	--	Mayo Score 6-12 & endoscopic subscore ≥2 Inadequate response to, loss of response to, or intolerance to at least 1, either oral CS, and/or IMM	Ulcerative proctitis, previous receipt of TNF or biologic including ADA, IV CS, cyclosporine, tacrolimus, mycophenolate mofetil or MTX 30-60 days prior to baseline
ULTRA 2/ Sandborn 2012 IND + MAINT (8/52 Wks) TT	494	Naïve (60%) Exp (40%)	1) ADA 160/80 mg (n=248) 160 mg at wk 0, 80 mg at wk 2, then 40 mg EOW 2) PBO (n=246)	Starting at wk 12, inadequate responders could receive OL ADA	1) ADA 40 mg EOW (n=248) 2) PBO (n=246) through wk 52	Mayo Score 6-12 & endoscopic subscore ≥2 Inadequate response to, or had failed to tolerate, ≥1 of the following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; TNF-experienced other than ADA	History of subtotal colectomy, Kock pouch, or planned bowel surgery; previous treatment with ADA; receipt of IV CSs within 2 wks of screening; receipt of therapeutic enema or suppository, other than required for endoscopy, within 2 wks of the screening
Suzuki 2014 IND + MAINT (8/52 Wks) TT	273	Naïve (100%)	1) ADA 160/80 mg (n=87) 160 mg at wk 0, 80 mg at wk 2, then 40 mg EOW 2) ADA 80/40 mg (n=90) 80 mg at wk 0 then 40 mg EOW 3) PBO (n=96)	Starting at wk 8, inadequate responders entered into "rescue arm"	1) ADA 40 mg EOW (n=177) 2) PBO (n=96) through wk 52	Mayo Score 6-12 & endoscopic subscore ≥2 Inadequate response to, or had failed to tolerate, ≥1 of following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; TNF-naïve	Indeterminate colitis or CD; planned bowel surgery; received CS injection, cyclosporine, tacrolimus, or mycophenolate mofetil within 4 wks; prior treatment with TNFs or biologic
Golimumab							
PURSUIT SC/ Sandborn 2014/ IND Only (6 Wks)	773	Naïve (100%)	1) GOL 200/100 mg (n=257) 200 mg at wk 0 and 100 mg at wk 2 2) GOL 400/200 mg (n=258) 400 mg at wk 0 and 200 mg at wk 2 3) PBO (n=258)	--	--	Mayo Score 6-12 & endoscopic subscore ≥2 Inadequate response to, or had failed to tolerate, ≥1 of following conventional therapies: oral ASAs, oral CSs, AZA,	TNF(s), natalizumab or other agents targeting a-4 integrin, B-cell depleting agents, or T-cell depleting agents within 12 mo of first study-agent injection; cyclosporine within 8

Trial/ Timepoint TT or RR*	N	Naïve (%) Exp (%)†	Treatment Arms (n)			Trial Inclusion Criteria	Trial Exclusion Criteria
			Induction	→	Maintenance		
						and/or MP; or CS dependent	wks before first study agent injection
PURSUIT M/ Sandborn 2014 MAINT (54 Wks) RR	464	Naïve (100%)	PURSUIT-SC and PURSUIT-IV	Responders at wk 6 were randomized in MAINT	1) GOL 50 mg (n=154) 2) GOL 100 mg (n=154) 3) PBO (n=156) q4w through wk 52	Mayo Score 6-12 & endoscopic subscore ≥2 Inadequate response to, or had failed to tolerate, ≥1 of following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; CS dependent	Patients with isolated proctitis, patients with TB
PURSUIT J/ Hibi 2017 MAINT (54 Wks) RR	144	Naïve (100%)	1) OL GOL 200/100 mg (n=144) 200 mg at wk 0, 100 mg at wk 2	Responders at wk 6 were randomized in MAINT	1) GOL 100 mg (n=32) 2) PBO (n=31) q4w through wk 52	Mayo Score 6-12 & endoscopic subscore ≥2 Inadequate response to, or had failed to tolerate, ≥1 of following conventional therapies: oral ASAs, oral CSs, AZA, and/or MP; CS dependent	Severe and extensive colitis requiring colectomy; colitis limited to 20 cm of colon; any prior abdominal surgery
Vedolizumab							
GEMINI 1/ Feagan 2013 IND + MAINT (6/52 Wks) RR	895	Naïve (52%) Experienced (48%)	Cohort 1 1) VEDO 300 mg (n=225) 2) PBO (n=149) Cohort 2 1) OL VEDO 300 mg (n=521) at wk 0 and 2	Responders at wk 6 were randomized in MAINT	1) VEDO q8w (n=122) 2) VEDO q4w (n=125) 3) PBO (n=126) through wk 52	Mayo Score 6-12 & endoscopic subscore of ≥2 Inadequate response to, or had failed to tolerate, ≥1 of following conventional therapies: glucocorticoids, AZA, MP, or TNFs	Received TNF within 60 days prior to enrollment; cyclosporine, thalidomide, or investigational drugs within 30 days of enrollment; previous VEDO, natalizumab, efalizumab, or rituximab
VISIBLE 1‡/ Sandborn 2019 IND + MAINT (6/52 Wks) RR	383	Naïve (61%) Exp (39%)	1) OL VEDO 300 mg (n=383) at wk 0 and 2	Responders at wk 6 were randomized in MAINT	1) VEDO 108 mg (SC) q2w (n=106) 2) VEDO 300 mg (IV) q8w (n=154) 3) PBO (n=56) through wk 52	Mayo Score 6-12 & endoscopic subscore ≥2 Inadequate response to, loss of response to, or intolerance to at least 1, either a CS, IMM, or TNF	Exposure to any biologics within 60 days or 5 half-lives of screening; exposure to any nonbiologic therapies such as cyclosporine,

Trial/ Timepoint TT or RR*	N	Naïve (%) Exp (%)†	Treatment Arms (n)			Trial Inclusion Criteria	Trial Exclusion Criteria
			Induction	→	Maintenance		
							tacrolimus, thalidomide, MTX, or TOF within 30 days or 5 half-lives of screening was also not permitted
Motoya 2019 IND + MAINT (10/60 Wks) RR	292	Naïve (49%) Exp (51%)	Cohort 1 1) VEDO 300 mg (n=164) 2) Placebo (n=82) Cohort 2 1) OL VEDO 300 mg (n=46) at wk 0, 2, and 6	Responders at wk 6 were randomized in MAINT	1) VEDO 300 mg q8w (n=41) 2) PBO (n=42) through wk 52	Mayo Score 6-12 & endoscopic subscore ≥2 Total or left-side diagnosis with treatment failure with CSs, IMMs, or TNF	Suspected abdominal abscess or toxic megacolon; history of colectomy or recent enterectomy or previously treatment with VEDO, natalizumab, efalizumab, or rituximab
Head-to-Head							
VARSITY/ Sands 2019 IND + MAINT (14/52 Wks) TT	769	Naïve (79%) Exp (21%)	1) VEDO 300 mg (n=383) at wk 0, 2, and 6 2) ADA 160/80mg (n=386) 160 mg at wk 0, 80 mg at wk 2, and 40 mg at wk 4 and 6	All patients moved to MAINT	1) VEDO 300 mg q8w (n=383) 2) ADA 40 mg EOW (n=386) through wk 50	Mayo Score 6-12 & endoscopic subscore ≥2 No response or loss of response to conventional treatments or discontinued treatment with a TNF (except ADA) or TNF-naïve	Crohn's colitis, or indeterminate colitis; subtotal or total colectomy; active infection, cyclosporine, tacrolimus, thalidomide within 30 days; history of malignancy
Tofacitinib							
OCTAVE 1/ Sandborn 2017 IND only (8 Wks)	598	Naïve (47%) Exp (53%)	1) TOF 10 mg (n=476) 2) PBO (n=122) twice daily for 8 wks	--	--	Mayo Score 6-12 & rectal bleeding subscore of 1 to 3 & endoscopic subscore of ≥2 Inadequate response to, or had failed to tolerate, ≥1 of following conventional therapies: oral or IV glucocorticoids, AZA, and/or MP, IFX, or ADA	Presence of CD, UC limited to distal 15 cm of colon, signs of fulminant colitis, toxic megacolon, or indeterminate, microscopic, ischemic, or infectious colitis
OCTAVE 2/ Sandborn 2017 IND only (8 Weeks)	588	Naïve (45%) Exp (55%)	1) TOF 10 mg (n=476) 2) PBO (n=112) twice daily for 8 wks	--	--		

Trial/ Timepoint TT or RR*	N	Naïve (%) Exp (%)†	Treatment Arms (n)			Trial Inclusion Criteria	Trial Exclusion Criteria
			Induction	→	Maintenance		
OCTAVE SUSTAIN/ Sandborn 2017 MAINT (52 Wks), RR	593	Naïve (52%) Exp (48%)	OCTAVE 1 and 2	Responders at wk 8 were randomized in MAINT	1) TOF 5 mg (n=198) 2) TOF 10 mg (n=197) 3) PBO (n=198) twice daily for 52 wks	Adults who completed OCTAVE induction 1 or 2 and had clinical response during induction trial	Patients who met criteria for treatment failure and received rescue therapy during IND trial
Ustekinumab							
UNIFI/ Sands 2019 IND + MAINT (8/52 Wks), RR	961	Naïve (49%) Exp (51%)	1) UST 130 mg (n=320) 2) UST 6 mg/kg (n=322) 3) PBO (n=319) single dose	Responders at wk 8 were randomized in MAINT	1) UST 90 mg SC q12w (N=172) 2) UST 90 mg SC q8w (N=176) through wk 52	Mayo Score 6-12 & endoscopic subscore ≥2 Inadequate response to or unacceptable side effects from TNFs, VEDO, or conventional (i.e., nonbiologic) therapy	Severe extensive colitis and at imminent risk of colectomy, have UC limited to rectum, presence of a stoma or history of a fistula, history of extensive colonic resection, or history of mucosal dysplasia

ADA: adalimumab, ASA: acetylsalicylic acid, AZA: azathioprine, CD: Crohn's disease, cm: centimeter, CS: corticosteroid, EOW: every other week, Exp: Experienced, GOL: golimumab, IFX: infliximab, IMM: immunomodulator, IND: induction, IV: intravenous, MAINT: maintenance, mg: milligram, mg/kg: milligram per kilogram, MP: mercaptopurine, mo.: month, MTX: methotrexate, n: number, N: total number, OL: open label, PBO: placebo, q12w: every 12 weeks, q8w: every 8 weeks, q4w: every 4 weeks, RR: re-randomized, SC: subcutaneous, TB: tuberculosis, TNF: tumor necrosis factor, TOF: tofacitinib, TT: treat through, UC: ulcerative colitis, UST: ustekinumab, VEDO: vedolizumab, Wk: week

*Treat-through or re-randomized trial for trials with maintenance phase.

†Reported are the proportions of biologic-naïve and biologic-experienced populations. Note that trials used different criteria regarding prior exposure to biologics to define their strata when reporting subgroup results. ULTRA 2, Motoya 2019, and VARSITY defined subgroups as "TNF-naïve" and "TNF-experienced." GEMINI 1 and VISIBLE 1 defined subgroups as "TNF-naïve" and "TNF-failure." The OCTAVE trials defined subgroups as "no TNF-failure" and "TNF-failure." UNIFI defined subgroups as "biologic failure" and "biologic non-failure." Of note, UNIFI allowed patients who were failed by vedolizumab to enroll.

‡For VISIBLE 1, subcutaneous vedolizumab was not an intervention of interest, but we have presented data in the appendices.

Table D2. Study Quality of Included RCTs

Trial	Comparable Groups	Non-Differential Lost to Follow-Up	Patient/Investigator Blinding (Double-Blind)	Clear Definition of Intervention	Clear Definition of Outcomes	Measurements Valid	Intention to Treat Analysis	Approach to Missing Data†	USPSTF Rating
ACT 1	Yes	Yes	Yes	Yes	Yes	Yes	ITT	NRI	Fair
ACT 2	Yes	No	Yes	Yes	Yes	Yes	ITT	NRI	Fair
Jiang 2015	Yes	No	Yes	Yes	Yes	Yes	ITT	NRI	Fair
Kobayashi 2016	Yes	Yes	Yes	Yes	Yes	Yes	ITT	NRI/LOCF	Fair
NCT01551290	Unclear	Yes	Yes	Yes	Yes	Yes	mITT	NRI	*
ULTRA 1	Yes	Yes	Yes	Yes	Yes	Yes	mITT	NRI	Good
ULTRA 2	Yes	Yes	Yes	Yes	Yes	Yes	ITT	NRI	Good
Suzuki 2014	Yes	Yes	Yes	Yes	Yes	Yes	mITT	NRI	Good
PURSUIT-SC	Yes	Yes	Yes	Yes	Yes	Yes	ITT	NRI	Good
PURSUIT-M	Yes	Yes	Yes	Yes	Yes	Yes	ITT	NRI	Good
PURSUIT-J	Yes	No	Yes	Yes	Yes	Yes	ITT	NRI/LOCF	Fair
OCTAVE 1	Yes	Yes	Yes	Yes	Yes	Yes	ITT	NRI	Good
OCTAVE 2	Yes	Yes	Yes	Yes	Yes	Yes	ITT	NRI	Good
OCTAVE SUSTAIN	Yes	Yes	Yes	Yes	Yes	Yes	ITT	NRI	Good
UNIFI	Yes	Yes	Yes	Yes	Yes	Yes	ITT	NRI	Good
GEMINI 1	Yes	Yes	Yes	Yes	Yes	Yes	ITT	NRI	Good
Motoya 2019	Yes	Yes	Yes	Yes	Yes	Yes	mITT	NRI	Good
VISIBLE 1	Yes	Yes	Yes	Yes	Yes	Yes	mITT	NRI	Good
VARSITY	Yes	Yes	Yes	Yes	Yes	Yes	mITT	NRI	Good

ITT: intention-to-treat, LOCF: last observation carried forward, mITT: modified intention-to-treat, NRI: non-responder imputation, USPSTF: United States Preventive Services Task Force

*Data was only available in grey literature. Due to this, we did not assign an overall quality rating for the trial.

†For response and remission outcomes.

Table D3. Baseline Characteristics in Included RCTs

Study Name/ Trial Identifier	Arms	N	Age (Yrs), Mean (SD)	Female, n (%)	Weight (kg), Mean (SD)	Disease Duration (Yrs), Mean (SD)	Prior TNF Use, n (%)	Disease Severity Classification (Mayo), n (%)		Mayo Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)
								Moderate	Severe			
ACT 1	IFX 5 mg/kg	121	42.4 (14.3)	43 (35.5)	80 (17.8)	5.9 (5.4)	N/A	NR	NR	8.5 (1.7)	Left Side: 63 (52.9) Extensive: 56 (47.1)	1.4 (1.9)
	IFX 10 mg/kg	122	41.8 (14.6)	50 (41.0)	76.9 (17.1)	8.4 (8.1)	N/A	NR	NR	8.4 (1.4)	Left Side: 67 (55.4) Extensive: 54 (44.6)	1.6 (2.3)
	PBO	121	41.4 (13.7)	49 (40.5)	76.8 (16.2)	6.2 (5.9)	N/A	NR	NR	8.4 (1.8)	Left Side: 66 (55) Extensive: 54 (45)	1.7 (2.7)
ACT 2	IFX 5 mg/kg	121	40.5 (13.1)	45 (37.2)	78.4 (17.8)	6.7 (5.3)	N/A	NR	NR	8.3 (1.5)	Left Side: 70 (59.3) Extensive: 48 (40.7)	1.3 (2.3)
	IFX 10 mg/kg	120	40.3 (13.3)	52 (43.3)	40.3 (13.3)	6.5 (5.8)	N/A	NR	NR	8.3 (1.6)	Left Side: 75 (62.5) Extensive: 45 (37.5)	1.4 (2.2)
	PBO	123	39.3 (13.5)	52 (42.3)	39.3 (13.5)	6.5 (6.7)	N/A	NR	NR	8.5 (1.5)	Left Side: 70 (58.3) Extensive: 50 (41.7)	1.6 (2.9)
Kobayashi 2016	IFX 5 mg/kg	104	40 (12.7)	38 (36.5)	57.6 (12.7)	8.1 (7.2)	N/A	NR	NR	8.6 (1.4)	Left Side: 21 (20.3) Extensive: 83 (79.8)	1.0 (1.5)
	PBO	104	37.8 (12.9)	37 (35.6)	60.3 (11.6)	7.1 (6.6)	N/A	NR	NR	8.5 (1.4)	Left Side: 20 (19.2) Extensive: 84 (80.8)	0.7 (1.1)
Jiang 2015	IFX 5 mg/kg	41	34.3 (14.3)	15 (36.6)	62.8 (14.9)	4.4 (2.8)	N/A	15 (36.6)	26 (63.4)	NR	Left Side: 16 (39.1) Pancolitis: 25 (60.9)	3.6 (2.26)
	PBO	41	34.5 (14.9)	16 (39.1)	61.2 (15.7)	4.4 (2.6)	N/A	16 (31.9)	25 (60.9)	NR	Left Side: 17 (41.5) Pancolitis: 24 (58.5)	3.5 (1.8)
NCT01551290	IFX 5 mg/kg	50	37 (Median)	NR	NR	3.7 (Median)	N/A	NR	NR	8.0 (Median)	NR	NR
	PBO	49		NR	NR		N/A	NR	NR		NR	NR
GEMINI 1	VEDO 300 mg (Cohort 1)	225	40.1 (13.1)	93 (41.3)	72.4 (17.1)	6.1 (5.1)	95 (42.2)	N/A	NR	8.5 (1.8)	Rectum and Sigmoid Colon Only: 25 (11.1); Left Side: 92 (40.9); Proximal to the splenic flexure: 25 (11.1); All: 83 (36.9)	NR
	PBO	149	41.2 (12.5)	57 (38.3)	72.4 (17.6)	7.1 (7.2)	73 (49)	NR	NR	8.6 (1.7)	Rectum and Sigmoid Colon Only: 22 (14.8); Left Side: 59 (39.6); Proximal to the splenic flexure: 18 (12.1); All: 50 (33.6)	NR
VISIBLE 1	VEDO 108 mg (SC)	106	38.1 (13.1)	41 (38.7)	71.6 (17.2)	9 (6.2)	40 (37.7)	46 (43.4)	60 (56.6)	9.0 (Median)	Proctosigmoiditis: 15 (14.2) Left Side: 46 (43.4) Extensive: 7 (6.6) Pancolitis: 37 (34.9)	NR

Study Name/ Trial Identifier	Arms	N	Age (Yrs), Mean (SD)	Female, n (%)	Weight (kg), Mean (SD)	Disease Duration (Yrs), Mean (SD)	Prior TNF Use, n (%)	Disease Severity Classification (Mayo), n (%)		Mayo Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)
								Moderate	Severe			
	VEDO 300 mg (IV)	54	41.6 (14.1)	23 (42.6)	77 (16.9)	8.2 (5.9)	24 (44.4)	17 (31.5)	37 (68.5)	9.0 (Median)	Proctosigmoiditis: 7 (13) Left Side: 21 (38.9) Extensive: 7 (13) Pancolitis:19 (35.2)	NR
	PBO	56	39.4 (11.7)	22 (39.3)	74 (20.9)	7.4 (7.1)	20 (35.7)	20 (35.7)	36 (64.3)	9.0 (Median)	Proctosigmoiditis: 7 (12.5) Left Side: 24 (42.9) Extensive: 4 (7.1) Pancolitis: 21 (37.5)	NR
Motoya 2019	VEDO 300 mg (Cohort 1)	164	42.3 (14.4)	65 (39.6)	NR	7.2 (6.2)	85 (51.8)	NR	NR	8.3 (1.5)	Total Colitis: 101 (61.6) Left Side: 63 (38.4)	<3 mg/L: 76 (46.3) ≥3 mg/L: 50 (61.0)
	PBO	82	44.0 (16.0)	27 (32.9)	NR	8.6 (8.0)	41 (50.0)	NR	NR	8.1(1.5)	Total Colitis: 51 (62.2) Left Side: 31 (37.8)	<3 mg/L: 88 (53.7) ≥3 mg/L: 32 (39.0)
VARSITY	ADA 160/80/40 mg	386	40.5 (13.4)	170 (44.0)	73.4 (18.4)	6.4 (6.0)	80 (21.0)	169 (43.8)	210 (54.4)	8.7 (1.5)	NR	NR
	VEDO 300 mg	385	40.8 (13.7)	111 (39.2)	72.7 (17)	7.3 (7.2)	80 (20.8)	154 (40.0)	217 (56.4)	8.7 (1.6)	NR	NR
ULTRA 1	ADA 80/40	130	40 (Median)	52 (40)	76.8 (15)	6.91 (Median)	N/A	NR	NR	9 (1.62)	Left Side: 36.9 Extensive: 53.8 Other: 9.2	0.64 (Median)
	ADA 160/80	130	36.5 (Median)	47 (36.2)	75.5 (14.2)	6.06 (Median)	N/A	NR	NR	8.8 (1.61)	Left Side: 46.9 Extensive: 46.2 Other: 6.9	0.33 (Median)
	PBO	130	37 (Median)	48 (36.9)	78.7 (17.4)	5.4 (Median)	N/A	NR	NR	8.7 (1.56)	Left Side: 32.3 Extensive: 56.2 Other: 11.5	0.32 (Median)
ULTRA 2	ADA 160/80/40	248	39.6 (12.47)	106 (42.7)	75.3 (17.71)	8.1 (7.09)	98 (39.1)	NR	NR	8.9 (1.5)	Pancolitis: 120 (48.4) Descending Colon: 96 (38.7) Other: 32 (12.9)	1.5 (3.2)
	PBO	246	41.3 (13.22)	94 (38.2)	77.1 (17.31)	8.5 (7.37)	101 (41.1)	NR	NR	8.9 (1.8)	Pancolitis: 120 (48.8) Descending Colon: 96 (39) Other: 30 (12.2)	1.3 (3.7)
Suzuki 2014	ADA 160/80	90	42.5 (14.6)	29 (32.2)	60.1 (12.3)	7.8 (7.1)	N/A	NR	NR	8.6 (1.4)	Pancolitis: 63 (70) Descending colon: 27 (30)	0.22 (Median)

Study Name/ Trial Identifier	Arms	N	Age (Yrs), Mean (SD)	Female, n (%)	Weight (kg), Mean (SD)	Disease Duration (Yrs), Mean (SD)	Prior TNF Use, n (%)	Disease Severity Classification (Mayo), n (%)		Mayo Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)
								Moderate	Severe			
	ADA 80/40	87	44.4 (15)	37 (42.5)	58.7 (11.1)	8.3 (7.7)	N/A	NR	NR	8.5 (1.4)	Pancolitis: 54 (62.1) Descending Colon: 32 (36.8)	0.31 (Median)
	PBO	96	41.3 (13.6)	26 (27.1)	60.8 (14.1)	7.8 (6.6)	N/A	NR	NR	8.5 (1.6)	Pancolitis: 59 (61.5) Descending Colon: 35 (36.5)	0.34 (Median)
PURSUIT-SC	GOL 100/50 mg	72	40.9 (12.19)	32 (44.4)	NR	6.6 (7.33)	N/A	49 (68.1)	23 (31.9)	8.2 (1.36)	Left Side: 43 (59.7) Extensive: 29 (40.3)	0.8 (1.0)
	GOL 200/100 mg	331	40.0 (13.54)	151 (45.6)	NR	6.4 (6.17)	N/A	182 (55.2)	148 (44.8)	8.6 (1.53)	Left Side: 193 (58.3) Extensive: 138 (41.7)	1.1 (1.5)
	GOL 400/ 200 mg	331	40.7 (13.75)	130 (39.3)	NR	6.4 (6.27)	N/A	195 (59.5)	133 (40.5)	8.5 (1.47)	Left Side: 191 (57.7) Extensive: 140 (42.3)	1.3 (2.6)
	PBO	331	39 (13.04)	146 (47.1)	NR	6.0 (6.65)	N/A	209 (63.7)	119 (36.3)	8.3 (1.50)	Left Side: 188 (57.0) Extensive: 142 (43.0)	1.1 (1.7)
PURSUIT-M	GOL 50 mg	154	41.4 (13.84)	77 (50.0)	NR	6.8 (6.93)	N/A	145 (94.2)	143 (92.9)	8.1 (1.38)	NR	0.9 (1.3)
	GOL 100 mg	154	39.1 (13.11)	65 (42.2)	NR	7.2 (7.04)	N/A	9 (5.8)	11 (7.1)	8.5 (1.34)	NR	0.9 (1.5)
	PBO	156	40.2 (14.05)	81 (51.9)	NR	6.9 (6.96)	N/A	145 (92.9)	11(7.1)	8.3 (1.37)	NR	1.0 (1.5)
PURSUIT-J	OL-IND: GOL SC 200 mg	144	42.40 (14.74)	46 (32)	61.51 (11.18)	5.08 (Median)	N/A	141 (98)	N/A	8.0 (Median)	Left Side: 89 (62) Extensive: 55 (38)	0.4 (1.1)
	GOL 100 mg	32	39.30 (12.00)	13 (41)	64.59 (14.73)	5.35 (Median)	N/A	31(97)	N/A	8.0 (Median)	Left Side: 20 (63) Extensive: 12 (38)	0.5 (1.5)
	PBO	31	42.90 (14.41)	12 (39)	59.48 (9.73)	5.74 (Median)	N/A	30(97)	N/A	8.0 (Median)	Left Side: 19 (61) Extensive: 12 (39)	0.4 (0.8)
OCTAVE 1	TOF 10 mg	476	41.3 (14.1)	199 (41.8)	72.9 (16.8)	6.5 (Median)	254 (53.4)	NR	NR	9.0 (1.4)	Proctosigmoiditis: 65 (13.7) Left Side: 158 (33.3) Extensive Colitis or Pancolitis: 252 (53.1)	0.4 (Median)
	PBO	122	41.8 (15.3)	45 (36.9)	72.7 (16.7)	6.0 (Median)	65 (53.3)	NR	NR	9.1 (1.4)	Proctosigmoiditis: 19 (15.6) Left Side: 37 (30.3) Extensive Colitis or Pancolitis: 66 (54.1)	0.5 (Median)
OCTAVE 2	TOF 10 mg	429	41.1 (13.5)	170 (39.6)	74.4 (16.8)	6.0 (Median)	234 (54.5)	NR	NR	9.0 (1.5)	Proctosigmoiditis: 67 (15.7) Left Side: 149 (34.8) Extensive Colitis or Pancolitis: 211 (49.3)	0.5 (Median)
	PBO	112	40.4 (13.2)	61 (50.9)	73.2 (16.2)	6.2 (Median)	65 (58.0)	NR	NR	8.9 (1.5)	Proctosigmoiditis: 16 (14.4) Left Side: 39 (35.1)	0.5 (Median)

Study Name/ Trial Identifier	Arms	N	Age (Yrs), Mean (SD)	Female, n (%)	Weight (kg), Mean (SD)	Disease Duration (Yrs), Mean (SD)	Prior TNF Use, n (%)	Disease Severity Classification (Mayo), n (%)		Mayo Score, Mean (SD)	Disease Localization, n (%)	CRP (mg/dL), Mean (SD)
								Moderate	Severe			
											Extensive Colitis or Pancolitis: 56 (50.5)	
OCTAVE SUSTAIN	TOF 10 mg	197	42.9 (14.4)	87 (44.2)	74.6 (15.1)	6.8 (Median)	101 (51.3)	NR	NR	3.4 (1.8)	Proctosigmoiditis: 33 (16.8) Left Side: 60 (30.6) Extensive Colitis or Pancolitis: 103 (52.6)	0.09 (Median)
	TOF 5 mg	198	41.9 (13.7)	95 (48)	73.4 (17.8)	6.5 (Median)	90 (45.5)	NR	NR	3.3 (1.8)	Proctosigmoiditis: 28 (14.3) Left Side: 66 (33.7) Extensive Colitis or Pancolitis: 102 (52.0)	0.07 (Median)
	PBO	198	43.4 (14.0)	82 (41.4)	76.2 (16.7)	7.2 (Median)	92 (46.5)	NR	NR	3.3 (1.8)	Proctosigmoiditis: 21 (10.6) Left Side: 68 (34.3) Extensive Colitis or Pancolitis: 108 (54.5)	0.1 (Median)
UNIFI	UST 6 mg/kg	322	41.7 (13.7)	39.4	73 (19.3)	8.2 (7.8)	NR	276 (86.0)	46 (14.0)	8.9 (1.5)	Left Side: 168 (52.5)	0.5 (0.2-1.3)
	UST 130 mg	320	42.2 (13.9)	40.6	73.7 (16.8)	8.1 (7.2)	NR	271 (84.7)	49 (15.3)	8.9 (1.6)	Left Side: 183 (57.5)	0.5 (0.2-0.9)
	PBO	319	41.2 (13.5)	38.2	72.9 (16.8)	8 (7.2)	NR	263 (82.4)	56 (17.6)	8.9 (1.6)	Left Side: 167 (52.8)	0.5 (0.2-1.0)

ADA: adalimumab, AZA: azathioprine, DB: double blind GOL: golimumab, IFX: infliximab, IV: intravenous, kg: kilogram, mg/L: milligram per liter, mg/dL: milligrams per deciliter, N: total number, N/A: not applicable, NR: not reported, OL: open label, PBO: placebo, SC: subcutaneous, SD: standard deviation, TNF: tumor necrosis factor, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab, Yrs: years

Table D4. Baseline Medication Use in Included RCTs

Study Name/ Trial Identifier	Arms	N	Concomitant Medication, n (%)						
			CS	CS ≥20 mg/Day	ASA	IMM	AZA	MERC	CS + IMM
Infliximab									
ACT 1	IFX 5 mg	121	70 (57.9)	45 (37.2)	82 (67.8)	66 (54.5)	45 (37.2)	15 (12.3)	NR
	IFX 10 mg	122	73 (59.8)	46 (37.7)	86 (70.5)	59 (48.4)	44 (36.1)	21 (17.4)	NR
	PBO	121	79 (65.3)	54 (44.6)	85 (70.2)	53 (43.8)	36 (29.8)	17 (14.0)	NR
ACT 2	IFX 5 mg	121	60 (49.6)	40 (33.1)	92 (76)	52 (43)	41 (33.9)	11 (9.1)	NR
	IFX 10 mg	120	66 (55)	47 (39.2)	47 (39.2)	50 (41.7)	37 (30.8)	13 (10.8)	NR
	PBO	123	60 (48.8)	43 (35)	43 (35)	54 (43.9)	35 (28.5)	19 (15.4)	NR
Kobayashi 2016	IFX 5 mg	104	68 (65.4)	NR	77 (74.0)	50 (48.1)	38 (36.5)	12 (11.5)	NR
	PBO	104	69 (66.3)	NR	70 (67.3)	49 (47.1)	34 (32.7)	15 (14.4)	NR
Jiang 2015	IFX 5 mg	41	22 (53.7)	14 (34.1)	34 (82.9)	NR	12 (29.3)	NR	NR
	PBO	41	21 (51.2)	14 (34.1)	35 (85.4)	NR	13 (31.7)	NR	NR
NCT01551290	IFX 5 mg	50	30 (60)	NR	NR	NR	NR	NR	NR
	Placebo	49	39 (80)	NR	NR	NR	NR	NR	NR
Vedolizumab									
GEMINI 1	VEDO Cohort 1	225	79 (35.1)*	NR	NR	28 (12.4)*	NR	NR	NR
	PBO	149	58 (38.9)*	NR	NR	18 (12.1)*	NR	NR	NR
VISIBLE 1	VEDO SC	106	45 (42.5)	NR	NR	NR	NR	NR	NR
	VEDO IV	54	21 (38.9)	NR	NR	NR	NR	NR	NR
	PBO	56	32 (57.1)	NR	NR	NR	NR	NR	NR
Motoya 2019	VEDO	164	31 (18.9)*	NR	145 (88.4)	59 (36.0)*	NR	NR	21 (12.8)
	PBO	82	11 (13.4)*	NR	75 (91.5)	29 (35.4)*	NR	NR	14 (17.1)
Head-to-Head									
VARSITY	ADA	386	140 (36.3)*	NR	NR	100 (25.9)*	NR	NR	NR
	VEDO	385	139 (36.1)*	NR	NR	101 (26.2)*	NR	NR	NR
Adalimumab									
ULTRA 1	ADA 80/40	130	48 (36.9)*	NR	99 (76.2)	25 (19.2)*	NR	NR	26 (20.0)
	ADA 160/80	130	48 (36.9)*	NR	105 (80.8)	28 (21.5)*	NR	NR	23 (17.7)
	PBO	130	55 (41.5)*	NR	98 (75.4)	18 (13.8)*	NR	NR	34 (26.1)
ULTRA 2	ADA	248	150 (60.5)	NR	146 (58.9)	93 (37.5)	NR	NR	NR
	PBO	246	140 (56.9)	NR	155 (63)	80 (32.5)	NR	NR	NR
Suzuki 2014	ADA 160/80	90	57 (63.3)	NR	83 (92.2)	41 (45.6)	NR	NR	NR
	ADA 80/40	87	63 (72.4)	NR	84 (96.6)	38 (43.7)	NR	NR	NR
	PBO	96	58 (60.4)	NR	89 (92.7)	52 (54.2)	NR	NR	NR

Study Name/ Trial Identifier	Arms	N	Concomitant Medication, n (%)						
			CS	CS ≥20 mg/Day	ASA	IMM	AZA	MERC	CS + IMM
Golimumab									
PURSUIT SC	GOL 100/50 mg	72	35 (48.6)	25 (34.7)	59 (81.9)	27 (37.5)	27 (37.5)		NR
	GOL 200/100 mg	331	142 (42.9)	85 (25.7)	27 (81.6)	105 (31.7)	100 (30.2)		NR
	GOL 400/200 mg	331	145 (43.8)	93 (28.1)	267 (80.7)	107 (32.3)	103 (31.1)		NR
	PBO	331	134 (40.5)	78 (23.6)	276 (83.4)	106 (32.0)	102 (30.8)		NR
PURSUIT-M	GOL 50 mg	154	77 (50.0)	52 (33.8)	128 (83.1)	47 (30.5)	45 (29.2)		NR
	GOL 100 mg	154	79 (51.3)	55 (35.7)	119 (77.3)	48 (31.2)	48 (31.2)		NR
	PBO	156	83 (53.2)	59 (37.8)	125 (80.1)	52 (33.3)	51 (32.7)		NR
PURSUIT-J	Induction: GOL SC 200 mg	144	42 (29)	12 (8)	128 (89)	NR	64 (44)		NR
	DB MAINT: GOL SC 100 mg	32	9 (28)	4 (13)	29 (91)	NR	16 (50)		NR
	DB MAINT: PBO 100 mg	31	9 (29)	5 (16)	27 (87)	NR	13 (42)		NR
Tofacitinib									
OCTAVE 1	TOF 10 mg	476	214 (45.0)	NR	NR	NR	NR	NR	NR
	PBO	122	58 (47.5)	NR	NR	NR	NR	NR	NR
OCTAVE 2	TOF 10 mg	429	198 (46.2)	NR	NR	NR	NR	NR	NR
	PBO	112	55 (49.1)	NR	NR	NR	NR	NR	NR
OCTAVE SUSTAIN	TOF 10 mg	197	87 (44.2)	NR	NR	NR	NR	NR	NR
	TOF 5 mg	198	101 (51.0)	NR	NR	NR	NR	NR	NR
	PBO	198	100 (50.5)	NR	NR	NR	NR	NR	NR
Ustekinumab									
UNIFI	UST 6 mg/kg	322	168 (52.2)	NR	238 (73.9)	89 (27.6)	NR	NR	NR
	UST 130 mg	320	173 (54.1)	NR	215 (67.2)	93 (29.1)	NR	NR	NR
	PBO	319	157 (49.2)	NR	207 (64.9)	89 (27.9)	NR	NR	NR

ADA: adalimumab, ASA: aminosalicylates, AZA: azathioprine, CS: corticosteroids, DB: double blind, GOL: golimumab, IFX: infliximab, IMM: immunomodulator, IV: intravenous, MERC: mercaptopurine, mg: milligram, mg/kg: milligram per kilogram, N: total number, N/A: not applicable, NR: not reported, OL: open label, PBO: placebo, SC: subcutaneous, SD: standard deviation, TNF: tumor necrosis factor, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

*Reported as the proportion of patients taking IMM or CS alone.

Table D5. Response, Remission, and Endoscopic Improvement in the Induction Phase (Week Six to 14)*

Trial	Arm	Induction Phase (Week 6-14)											
		Response				Remission				Endoscopic Improvement			
		n	N	%	Significance	n	N	%	Significance	n	N	%	Significance
ACT 1 IFX	Week 8												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	84	121	69.4	p<0.001	47	121	38.8	p<0.001	75	121	62	p<0.001
	IFX 10 mg/kg	75	122	61.5	p<0.001	39	122	32.0	p=0.002	72	122	59	p<0.001
	PBO	45	121	37.2	--	18	121	14.9	--	41	121	33.9	--
	Biologic-Experienced (Population Not Studied)												
ACT 2 IFX	Week 8												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	78	121	64.5	p<0.001	41	121	33.9	p<0.001	73	121	60.3	p<0.001
	IFX 10 mg/kg	83	120	69.2	p<0.001	33	120	27.5	p<0.001	74	120	61.7	p<0.001
	PBO	36	123	29.3	--	7	123	5.7	--	38	123	30.9	--
	Biologic-Experienced (Population Not Studied)												
Jiang 2015 IFX	Week 8												
	Overall – Biologic-Naïve												
	IFX 3.5 mg/kg	30	41	73.1	p=0.001	21	41	51.2	p=0.006	23	41	56.1	p=0.003
	IFX 5 mg/kg	32	41	78.1	p=0.00	22	41	53.7	p=0.003	24	41	58.5	p=0.002
	PBO	15	41	36.6	--	9	41	21.9	--	10	41	24.4	--
	Biologic-Experienced (Population Not Studied)												
Kobayashi 2016 IFX	Week 8												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	57	104	54.8	p=0.005	21	104	20.2	NS	48	104	46.2	p=0.006
	PBO	37	104	35.6	--	11	104	10.6	--	29	104	27.9	--
	Biologic-Experienced (Population Not Studied)												
NCT01551290 IFX	Week 8												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	32	50	64.0	p=0.0021	11	50	22.0	NS	17	50	34.0	p=0.045
	PBO	16	49	32.7	--	5	49	10.2	--	8	49	16.3	--
	Biologic-Experienced (Population Not Studied)												
ULTRA 1 ADA	Week 8												
	Overall – Biologic-Naïve												
	ADA 80/40 mg	67	130	51.5	NS	13	130	10	NS	49	130	37.7	NR
	ADA 160/80 mg	71	130	54.6	NS	24	130	18.5	P=0.031	61	130	46.9	NR
	PBO	58	130	44.6	--	12	130	9.2	--	54	130	41.5	--
	Biologic-Experienced (Population Not Studied)												
	Week 8												

Trial	Arm	Induction Phase (Week 6-14)											
		Response				Remission				Endoscopic Improvement			
		n	N	%	Significance	n	N	%	Significance	n	N	%	Significance
ULTRA 2 ADA	*Overall*												
	ADA 160/80 mg	125	248	50.4	p<0.005	41	248	16.5	p<0.05	102	248	41.1	p<0.05
	PBO	85	246	34.6	--	23	246	9.3	--	78	246	31.7	--
	Biologic-Naïve												
	ADA 160/80 mg	89	150	59.3	p<0.001	32	150	21.3	p=0.017	74	150	49.3	p=0.014
	PBO	56	145	38.6	--	16	145	11	--	51	145	35.2	--
	Biologic-Experienced												
	ADA 160/80 mg	36	98	36.7	NS	9	98	9.2	NS	28	98	28.5	p=0.77
	PBO	29	101	28.7	--	7	101	6.9	--	27	101	26.7	--
Suzuki 2014 ADA	Week 8												
	Overall – Biologic-Naïve												
	ADA 80/40 mg	37	87	43	NS	12	87	14	NS	34	87	39	NS
	ADA 160/80 mg	45	90	50	p=0.044	9	90	10	NS	40	90	44	p=0.045
	PBO	34	96	35.4	--	11	96	11.5	--	29	96	30	-
	Biologic-Experienced (Population Not Studied)												
PURSUIT-SC GOL	Week 6												
	Overall – Biologic-Naïve												
	GOL 200/100 mg	129	253	51.0	p<0.0001	45	253	17.8	p<0.0001	107	253	42.3	p<0.001
	GOL 400/200 mg	141	257	54.9	p<0.0001	46	257	17.9	p<0.0001	116	257	45.1	p=0.001
	PBO	76	251	30.3	--	16	251	6.4	--	72	251	28.7	--
	Biologic-Experienced (Population Not Studied)												
GEMINI 1 VEDO	Week 6												
	Overall												
	VEDO 300mg	106	225	47.1	p<0.001	38	225	16.9	p=0.001	92	225	40.9	p=0.001
	PBO	38	149	25.5	--	8	149	5.4	--	37	149	24.8	--
	Biologic-Naïve												
	VEDO 300 mg	69	130	53.1	Diff. (95% CI): 26.4 (12.4 to 40.4)	30	130	23.1	Diff. (95% CI): 15.5 (5.1 to 25.9)	64	130	49.2	Diff. (95% CI): 23.9 (10.0, 37.7)
	PBO	20	76	26.3		5	76	6.6		19	76	25.0	
	Biologic-Experienced												
	VEDO 300 mg	32	82	39	Diff. (95% CI): 18.1 (2.8, 33.5)	8	82	9.8	Diff. (95% CI): 7.0 (-1.3, 15.2)	25	82	30.5	Diff. (95% CI): 9.9 (-4.7,24.4)
	PBO	13	63	20.6		2	63	3.2		13	63	20.6	
Motoya 2019 VEDO	Week 10												
	Overall												
	VEDO 300 mg	65	164	39.6	p=0.2722	30	164	18.3	p=0.1980	60	164	36.6	0.3168
	PBO	27	82	32.9	--	10	82	12.2	--	25	82	30.5	--
	Biologic-Naïve												

Trial	Arm	Induction Phase (Week 6-14)											
		Response				Remission				Endoscopic Improvement			
		n	N	%	Significance	n	N	%	Significance	n	N	%	Significance
	VEDO 300 mg	42	79	53.2	Diff. (95% CI): 16.6 (-1.8 to 35.0)	22	79	27.8	Diff. (95% CI): 13.2 (-1.4 to 27.9)	38	79	48.1	Diff. (95% CI): 16.4 (-1.6, 34.4)
	PBO	15	41	36.6		6	41	14.6		13	41	31.7	
	Biologic-Experienced												
	VEDO 300 mg	23	85	27.1	Diff. (95% CI): -2.2 (-19.0, 41.6)	8	85	9.4	Diff. (95% CI): -0.3 (-11.3, 10.7)	22	85	25.9	Diff. (95% CI): -3.4 (-20.14, 13.37)
	PBO	12	41	29.3		4	41	9.8		12	41	29.3	
VARSITY VEDO vs. ADA	Week 14												
	Overall												
	VEDO 300 mg	257	383	67.1	Diff. (95% CI): 21.2 (14.4, 28.0)	102	383	26.6	Diff. (95% CI): 5.4 (-0.7, 11.4)	NR	NR	NR	NR
	ADA 40 mg	177	386	45.9		82	386	21.2		NR	NR	NR	NR
	Biologic-Naïve												
	VEDO 300 mg	213	304	70.1	Diff. (95% CI): 20.6 (12.9, 28.2)	84	304	27.6	Diff. (95% CI): 4.0 (-2.9, 10.9)	NR	NR	NR	NR
	ADA 40 mg	151	305	49.5		72	305	23.6		NR	NR	NR	NR
	Biologic-Experienced												
	VEDO 300 mg	44	79	55.7	Diff. (95% CI): 23.6 (8.5, 38.7)	18	79	22.8	Diff. (95% CI): 10.3 (-1.5, 22.2)	NR	NR	NR	NR
	ADA 40 mg	26	81	32.1		10	81	12.3		NR	NR	NR	NR
OCTAVE 1 TOF	Week 8												
	Overall												
	TOF 10 mg	285	476	59.9	p<0.001	88	476	18.5	p=0.007	149	476	31.3	p<0.001
	PBO	40	122	32.8	--	10	122	8.2	--	19	122	15.6	--
	Biologic-Naïve												
	TOF 10 mg	NR	NR	NR	NR	NR	NR	NR	NR	88	222	39.6	p=0.06
	PBO	NR	NR	NR	NR	NR	NR	NR	NR	15	57	26.3	--
	Biologic-Experienced												
	TOF 10 mg	NR	NR	NR	NR	NR	NR	NR	NR	61	254	24	p=0.001
	PBO	NR	NR	NR	NR	NR	NR	NR	NR	4	65	6.2	--
OCTAVE 2 TOF	Week 8												
	Overall												
	TOF 10 mg	236	429	55	p<0.001	72	429	16.6	p<0.001	122	429	28.4	p<0.001
	PBO	32	112	28.6	--	4	112	3.6	--	13	112	11.6	--
	Biologic-Naïve												
	TOF 10 mg	NR	NR	NR	NR	NR	NR	NR	NR	71	195	36.4	p=0.02
	PBO	NR	NR	NR	NR	NR	NR	NR	NR	9	47	19.1	--
	Biologic-Experienced												
	TOF 10 mg	NR	NR	NR	NR	NR	NR	NR	NR	51	234	21.8	p=0.004

Trial	Arm	Induction Phase (Week 6-14)											
		Response				Remission				Endoscopic Improvement			
		n	N	%	Significance	n	N	%	Significance	n	N	%	Significance
	PBO	NR	NR	NR	NR	NR	NR	NR	NR	4	65	6.2	--
OCTAVE 1 and 2 Pooled	Week 8												
	Overall												
	TOF 10 mg	521	905	57.6	--	159	905	17.6	--	271	905	29.9	p<0.001
	PBO	72	234	30.8	--	14	234	6	--	32	234	13.7	--
	Biologic-Naïve												
	TOF 10 mg	284	440	64.5	p<0.0001	106	440	24.1	p<0.01	168	440	38.2	p<0.01
	PBO	43	110	39.1	--	13	110	11.8		24	110	21.8	--
	Biologic-Experienced												
	TOF 10 mg	237	465	51	p<0.0001	53	465	11.4	p<0.01	103	465	22.0	p<0.001
	PBO	29	124	23.4	--	1	124	0.8	--	8	124	6.1	--
UNIFI UST	Week 8												
	Overall												
	UST 130 mg	164	320	51.3	p<0.001	50	320	15.6	p<0.001	65	320	26.3	p<0.001
	UST 6 mg/kg	199	322	61.8	p<0.001	50	322	15.5	p<0.001	59	322	27.0	p<0.001
	PBO	100	319	31.3	--	17	319	5.3	--	28	319	13.8	-
	Biologic-Naïve												
	UST 130 mg	90	156	57.7	p<0.001	31	156	19.9	p=0.009	54	156	34.6	p=0.006
	UST 6 mg/kg	104	156	66.7	p<0.001	29	156	18.6	p=0.022	52	156	33.3	p=0.01
	PBO	56	158	35.4	--	15	158	9.5	--	33	158	20.9	--
	Biologic-Experienced												
	UST 130 mg	74	164	45.1	p<0.001	19	164	11.6	p<0.001	30	164	18.3	p=0.002
	UST 6 mg/kg	95	166	57.2	p<0.001	21	166	12.7	p<0.001	35	166	21.1	p<0.001
	PBO	44	161	27.3	--	2	161	1.2	--	11	161	6.8	--

ADA: adalimumab, GOL: golimumab, IFX: infliximab, mg: milligram, mg/kg: milligram per kilogram, n: number, N: total number, NR: not reported, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

*Available results reported in published trials; for data used in our NMA refer to Appendix Tables F3-F5.

Table D6. Response and Remission in the Maintenance Phase*

Maintenance Phase (Week 30-60)													
Trial	Arm	Response			Sustained Response†			Remission			Sustained Remission		
		n	N	%	n	N	%	n	N	%	n	N	%
ACT 1 IFX	Week 54												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	55	121	45.5	47	121	38.8	42	121	34.7	24	121	19.8
	IFX 10 mg/kg	54	122	44.3	45	122	36.9	42	122	34.4	25	122	20.5
	PBO	24	121	19.8	17	121	14.0	20	121	16.5	8	121	6.6
	Biologic-Experienced (Population Not Studied)												
ACT 2 IFX	Week 30												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	57	121	47.1	50	121	41.3	31	121	25.6	18	121	14.9
	IFX 10 mg/kg	72	120	60	64	120	53.3	43	120	35.8	27	120	22.5
	PBO	32	123	26	19	123	15.4	13	123	10.6	3	123	2.4
	Biologic-Experienced (Population Not Studied)												
Jiang 2015 IFX	Week 30												
	Overall – Biologic-Naïve												
	IFX 3.5 mg/kg	26	41	63.4	NR			20	41	48.8	NR		
	IFX 5 mg/kg	27	41	65.8	NR			21	41	51.2	NR		
	PBO	11	41	26.8	NR			10	41	24.4	NR		
	Biologic-Experienced (Population Not Studied)												
Kobayashi 2016 IFX	Week 30												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	48	104	46.2	NR			22	104	21.2	NR		
	PBO	33	104	31.7	NR			17	104	16.3	NR		
	Biologic-Experienced (Population Not Studied)												
NCT01551290 IFX	Week 26												
	Overall – Biologic-Naïve												
	IFX 5 mg/kg	29	50	58.0	27	50	54.0	14	50	28.0	7	50	14.0
	PBO	26	49	53.1	12	49	24.5	5	49	10.2	2	49	4.1
	Biologic-Experienced (Population Not Studied)												
ULTRA 2 ADA	Week 52												
	Overall												
	ADA 40 mg	75	248	30.2	59	248	23.8	43	248	17.3	21	248	8.5
	PBO	45	246	18.3	30	246	12.2	21	246	8.5	10	246	4.1
	Biologic-Naïve												
	ADA 40 mg	55	150	36.7	44	150	29.3	33	150	22.0	16	150	10.7

Maintenance Phase (Week 30-60)													
	PBO	35	145	24.1	24	145	16.6	18	145	12.4	9	145	6.2
	Biologic-Experienced												
	ADA 40 mg	20	98	20.4	15	98	15.3	10	98	10.2	5	98	5.1
	PBO	10	101	9.9	6	101	5.9	3	101	3.0	1	101	1.0
Suzuki 2014 ADA	Week 52												
	Overall – Biologic-Naive												
	ADA 40 mg	55	177	31	50	82	61	41	177	23	NR	NR	NR
	PBO	17	96	18	NR	NR	NR	7	96	7	NR	NR	NR
	Biologic-Experienced (Population Not Studied)												
PURSUIT-M GOL	Week 54												
	Overall – Biologic-Naive												
	GOL 50 mg	71	151	47	71	151	47	35	151	23.2	19	151	12.6
	GOL 100 mg	75	151	49.7	75	151	49.7	42	151	27.8	21	151	13.9
	PBO	48	154	31.2	48	154	31.2	24	154	15.6	13	154	8.4
	Biologic-Experienced (Population Not Studied)												
PURSUIT-J GOL	Week 54												
	Overall – Biologic-Naive												
	GOL 100 mg	18	32	56.3	18	32	56.3	16	32	50.0	9	32	28.1
	PBO	6	31	19.4	6	31	19.4	2	31	6.5	2	31	6.5
	Biologic-Experienced (Population Not Studied)												
VISIBLE 1 VEDO	Week 52												
	Overall												
	VEDO 108 mg (SC)	68	106	64.2	68	106	64.2	49	106	46.2	16	106	15.1
	VEDO 300 mg (iv)	39	54	72.2	39	54	72.2	23	54	42.6	10	54	16.7
	PBO	17	56	28.6	17	56	28.6	8	56	14.3	3	56	5.4
	Biologic-Naive												
	VEDO 108 mg (SC)	NR			NR			36	67	53.7	NR		
	VEDO 300 mg (iv)	NR			NR			17	32	53.1	NR		
	PBO	NR			NR			7	37	18.9	NR		
	Biologic-Experienced												
	VEDO 108 mg (SC)	NR			NR			13	39	33.3	NR		
	VEDO 300 mg (iv)	NR			NR			6	22	27.3	NR		
	PBO	NR			NR			1	19	5.3	NR		
GEMINI 1 VEDO	*Week 52*												
	Overall												
	VEDO 300 mg q4w	65	125	52	65	125	52	56	125	44.8	30	125	24
	VEDO 300 mg q8w	69	122	56.6	69	122	56.6	51	122	41.8	25	122	20.5
	PBO	30	126	23.8	30	126	23.8	20	126	15.9	11	126	8.7
	Biologic-Naive												

Maintenance Phase (Week 30-60)													
	VEDO 300 mg q4w	41	73	56.2	41	73	56.2	35	73	47.9	21	73	28.8
	VEDO 300 mg q8w	47	72	65.3	47	72	65.3	33	72	45.8	16	72	22.2
	PBO	21	79	26.6	21	79	26.6	15	79	19.0	10	79	12.7
	Biologic-Experienced												
	VEDO 300 mg q4w	17	40	42.5	17	40	42.5	14	40	35.0	5	40	12.5
	VEDO 300 mg q8w	20	43	46.5	20	43	46.5	16	43	37.2	9	43	20.9
	PBO	6	38	15.8	6	38	15.8	2	38	5.3	1	38	2.6
Motoya 2019 VEDO	Week 60												
	Overall												
	VEDO 300 mg	27	41	65.9	27	41	65.9	23	41	56.1	11	41	26.8
	PBO	15	42	35.7	15	42	35.7	13	42	31	7	42	16.7
	Biologic-Naive												
	VEDO 300 mg	16	24	66.7	16	24	66.7	13	24	54.2	3	17	17.6
	PBO	10	28	35.7	10	28	35.7	10	28	35.7	1	14	7.1
	Biologic-Experienced												
	VEDO 300 mg	11	17	64.7	11	17	64.7	10	17	58.8	3	17	17.6
	PBO	5	14	35.7	5	14	35.7	3	14	21.4	1	14	7.1
VARSITY VEDO vs. ADA	*Week 52*												
	Overall												
	VEDO 300 mg	211	383	55.1	NR	NR	NR	120	383	31.3	70	383	18.3
	ADA 40 mg	166	386	43.0	NR	NR	NR	87	386	22.5	46	386	11.9
	Biologic-Naive												
	VEDO 300 mg	NR			NR			104	304	34.2	NR		
	ADA 40 mg	NR			NR			74	305	24.3	NR		
	Biologic-Experienced												
	VEDO 300 mg	NR			NR			16	79	20.3	NR		
	ADA 40 mg	NR			NR			13	81	16.0	NR		
OCTAVE SUSTAIN TOF	Week 52												
	Overall												
	TOF 5 mg	102	198	51.5	97	198	49	68	198	34.3	44	198	22.2
	TOF 10 mg	122	197	61.9	117	197	59.4	80	197	40.6	50	197	25.4
	PBO	40	198	20.2	38	198	19.2	22	198	11.1	10	198	5.1
	Biologic-Naive												
	TOF 5 mg	65	115	56.5	65	115	56.5	48	115	41.7	NR	NR	NR
	TOF 10 mg	67	104	64.4	67	104	64.4	46	104	44.2	NR	NR	NR
	PBO	27	109	24.8	27	109	24.8	12	109	11.0	NR	NR	NR
	Biologic-Experienced												
	TOF 5 mg	37	83	44.6	37	83	44.6	20	83	24.1	NR	NR	NR
	TOF 10 mg	55	93	59.1	55	93	59.1	34	93	36.6	NR	NR	NR

Maintenance Phase (Week 30-60)													
	PBO	13	89	14.6	13	89	14.6	10	89	11.2	NR	NR	NR
UNIFI UST	Week 52												
	Overall												
	UST 90 mg q12w	117	172	68.0	117	172	68.0	66	172	38.4	26	40	65
	UST 90 mg q8w	125	176	71.0	125	176	71.0	77	176	43.8	22	38	58
	PBO	78	175	44.6	78	175	44.6	42	175	24	17	45	38
	Biologic-Naïve												
	UST 90 mg q12w	78	102	76.5	78	102	76.5	50	102	49.0	21	30	70.0
	UST 90 mg q8w	66	85	77.6	66	85	77.6	41	85	48.2	12	16	75.0
	PBO	44	87	50.6	44	87	50.6	27	87	31.0	9	25	36.0
	Biologic-Experienced												
	UST 90 mg q12w	39	70	55.7	39	70	55.7	16	70	22.9	23	32	71.9
	UST 90 mg q8w	59	91	64.8	59	91	64.8	36	91	39.6	12	18	66.7
	PBO	34	88	38.6	34	88	38.6	15	88	17.0	9	25	36.0

ADA: adalimumab, GOL: golimumab, IFX: infliximab, mg: milligram, mg/kg: milligram per kilogram, n: number, N: total number, NR: not reported, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

*Available results reported in published trials; for data used in our NMA refer to Appendix Table F6.

†Sustained response in treat-through trials is defined as having response at end of induction and end of maintenance. Note that for re-randomized trials, the rates of response are among induction responders, so "response" and "sustained response" rates in this table are equivalent.

Table D7. Delayed Response Among Non-Responders to Induction Therapy

Trial	Prior Biologic Exposure	Treatment Arms	Week	Response %	Remission %
ULTRA 2	Overall	Adalimumab	16	NR	4.1
OCTAVE 1 and 2	Biologic-naïve	Tofacitinib	16	56.2	18.8
	Biologic-experienced			42.6	39.7
	Overall			50.1	13.9
UNIFI	Biologic-naïve	Ustekinumab 6 mg/kg	16	79.1	18.6
	Biologic-experienced			43.1	1.7
GEMINI 1	Overall	Vedolizumab	14	39.0	NR
		Placebo		20.7	NR
PURSUIT-SC	Naïve	Golimumab	16	28.1	NR

kg: kilogram, mg: milligram, NR: not reported

Table D8. IBDQ Outcomes in the Induction Phase

Trial	Arm	Induction Phase (Week 6-14)								
		IBDQ Score					IBDQ Response / Remission*			
		Data Type (Estimate)	Value	Data Type (Error)	Value	p-value	n	N	%	p-value
ACT 1-2 POOLED Infliximab	Week 8									
	Overall									
	IFX 5 mg/kg	Mean Δ	40	SD	34	<0.05	169	242	69.7	<0.05
	IFX 10 mg/kg	Mean Δ	36	SD	34	<0.05	164	242	67.8	<0.05
	PBO	Mean Δ	21	SD	28	--	121	244	49.6	--
	Stratified Biologic-Naïve and Experienced Data Not Reported									
ULTRA 2 Adalimumab	Week 8									
	Overall									
	ADA 160/80 mg	NR					144	248	58.1	0.006
	PBO	NR					112	246	45.5	--
	Biologic-Naïve									
	ADA 160/80 mg	NR					102	150	68	0.004
	PBO	NR					75	145	51.7	--
	Biologic-Experienced									
	ADA 160/80 mg	NR					42	98	42.9	0.370
	PBO	NR					37	101	36.6	--
Suzuki 2014 Adalimumab	Week 8									
	Overall – Biologic-Naive									
	ADA 80/40 mg	NR					42	87	48.3	--
	ADA 160/80 mg	NR					38	90	42.2	--
	PBO	NR					38	96	39.6	--
	Biologic-Experienced (Population Not Studied)									
PURSUIT-SC Golimumab	Week 6									
	Overall – Biologic-Naive									
	GOL 200/100 mg	Mean Δ	27.0	SD	33.72	<0.001	NR			
	GOL 400/200 mg	Mean Δ	26.9	SD	34.28	<0.001	NR			
	PBO	Mean Δ	14.8	SD	31.25	--	NR			
	Biologic-Experienced (Population Not Studied)									
OCTAVE 1 Tofacitinib	Week 8									
	Overall									
							Remission			
	TOF 10 mg	Mean Δ	40.7	SE	1.7	<0.0001	206	476	43.3	<0.001

Trial	Arm	Induction Phase (Week 6-14)								
		IBDQ Score					IBDQ Response / Remission*			
		Data Type (Estimate)	Value	Data Type (Error)	Value	p-value	n	N	%	p-value
	PBO	Mean Δ	21	SE	2.9	--	32	122	26.2	--
							Response			
	TOF 10 mg	--					307	476	64.5	<0.001
	PBO						56	122	45.9	--
	Stratified Biologic-Naïve and Experienced Data Not Reported									
OCTAVE 2 Tofacitinib	Week 8									
	Overall									
							Remission			
	TOF 10 mg	Mean Δ	44.6	SE	1.8	<0.0001	173	429	40.3	<0.001
	PBO	Mean Δ	25	SE	3.3	-	20	112	17.9	--
							Response			
	TOF 10 mg	--					288	429	67.1	<0.001
	PBO						54	112	48.2	--
	Stratified Biologic-Naïve and Experienced Data Not Reported									
UNIFI Ustekinumab	Week 8									
	Overall									
							Response			
	UST 130 mg	Mean Δ	33.4	SD	32.5	<0.001	213	320	66.6	<0.001
	UST 6 mg/kg	Mean Δ	35.0	SD	31.9	<0.001	221	322	68.6	<0.001
	PBO	Mean Δ	16.1	SD	31.4	--	141	319	44.2	-
	UST 130 mg	--					141	320	44.2	<0.001
	UST 6 mg/kg						150	322	46.6	<0.001
	PBO						101	319	31.7	--
	Stratified Biologic-Naïve and Experienced Data Not Reported									

Table D9. 36-Item Short Form Survey Outcomes in the Induction Phase

Trial	Arm	Induction (Week 6-14)									
		SF-36 (Mental)					SF-36 (Physical)				
		Data Type (Estimate)	Value	Data Type (Error)	Value	p-value	Data Type (Estimate)	Value	Data Type (Error)	Value	p-value
ACT 1-2 POOLED QoL Infliximab	Week 8										
	Overall – Biologic-Naive										
	IFX 5 mg/kg	Mean Δ	3.0	SD	9.6	<0.05	Mean Δ	3.7	SD	6.5	<0.05
	IFX 10 mg/kg	Mean Δ	5.9	SD	10.5	<0.05	Mean Δ	6.8	SD	7.6	<0.05
	PBO	Mean Δ	6.1	SD	10.9	---	Mean Δ	6.4	SD	7.7	---
	Biologic-Experienced (Population not Studied)										
OCTAVE 1 Tofacitinib	Week 8										
	Overall										
	TOF 10 mg	Mean Δ	6.8	SE	0.5	<0.0001	Mean Δ	6.8	SE	0.2	<0.0001
	PBO	Mean Δ	3.5	SE	0.9		Mean Δ	2.5	SE	0.5	
	Stratified Biologic-Naïve and Experienced Data Not Reported										
OCTAVE 2 Tofacitinib	Week 8										
	Overall										
	TOF 10 mg	Mean Δ	7.6	SE	0.5	<0.01	Mean Δ	6.8	SE	0.3	<0.01
	PBO	Mean Δ	4.4	SE	0.9		Mean Δ	4.6	SE	0.5	
	Stratified Biologic-Naïve and Experienced Data Not Reported										
OCTAVE 1 and 2 POOLED	*Overall*										
	NR										
	Biologic-Naive										
	TOF 10 mg	Mean Δ	8.3	SE	0.6	<0.001	Mean Δ	7.3	SE	0.4	<0.001
	PBO	Mean Δ	4.1	SE	1	--	Mean Δ	4.7	SE	0.7	--
	Biologic-Experienced										
	TOF 10 mg	Mean Δ	6	SE	0.5	<0.001	Mean Δ	6.2	SE	0.3	<0.001
	PBO	Mean Δ	3.4	SE	0.9	--	Mean Δ	2.3	SE	0.6	--

Table D10. Endoscopic Improvement and Corticosteroid-Free Remission in the Maintenance Phase

Trial	Arm	Maintenance (Week 30-60)							
		Endoscopic Improvement				Corticosteroid-Free Remission			
		n	N	%	Significance	n	N	%	Significance
ACT 1 Infliximab	Week 54								
	Overall – Biologic-Naïve								
	IFX 5 mg/kg	55	121	45.5	<0.001	18	70	25.7	0.006
	IFX 10 mg/kg	57	122	46.7	<0.001	12	73	16.4	0.15
	PBO	22	121	18.2	--	7	79	8.9	--
	Biologic-Experienced (Population Not Studied)								
ACT 2 Infliximab	Week 30								
	Overall – Biologic-Naïve								
	IFX 5 mg/kg	56	121	46.3	0.009	11	60	18.3	0.010
	IFX 10 mg/kg	68	120	56.7	<0.001	18	66	27.3	<0.001
	PBO	37	123	30.1	--	2	60	3.3	--
	Biologic-Experienced (Population Not Studied)								
Jiang 2015 Infliximab	Week 30								
	Overall – Biologic-Naïve								
	IFX 3.5 mg/kg	21	41	51.2	0.006	NR	NR	NR	NR
	IFX 5 mg/kg	22	41	53.7	0.003	NR	NR	NR	NR
	PBO	9	41	21.9	--	NR	NR	NR	NR
	Biologic-Experienced (Population Not Studied)								
Kobayashi 2016 Infliximab	Week 30								
	Overall – Biologic-Naïve								
	IFX 5 mg/kg	43	104	41.3	0.057	NR	NR	NR	NR
	PBO	30	104	28.8	--	NR	NR	NR	NR
	Biologic-Experienced (Population Not Studied)								
NCT01551290 Infliximab	Week 26								
	Overall – Biologic-Naïve								
	IFX 5 mg/kg	20	50	40.0	0.1781	5	30	16.7	0.0428
	PBO	13	49	26.5	--	1	39	2.6	--
	Biologic-Experienced (Population Not Studied)								
ULTRA 2 Adalimumab	Week 52								
	Overall								
	ADA 40 mg	71	248	25	<0.05	20	248	13.3	0.04
	PBO	38	246	15.4	--	8	246	5.7	--
	Overall – Biologic-Naïve								
	ADA 40 mg	47	150	31.3	0.02	15	150	13.6	0.09

Trial	Arm	Maintenance (Week 30-60)							
		Endoscopic Improvement				Corticosteroid-Free Remission			
		n	N	%	Significance	n	N	%	Significance
	PBO	28	145	19.3	--	5	145	6.2	--
	Biologic-Experienced								
	ADA 40 mg	15	98	15.3	0.25	5	98	12.5	0.26
	PBO	10	101	9.9	--	3	101	5.1	--
Suzuki 2014 Adalimumab	Week 52								
	Overall – Biologic-Naïve								
	ADA 40 mg	51	177	29	0.02	17	177	14.2	--
	PBO	15	96	16	--	4	96	6.9	--
	Biologic-Experienced (Population Not Studied)								
PURSUIT-M Golimumab	Week 54								
	Overall – Biologic-Naïve								
	GOL 50 mg	63	151	41.7	0.011	30	78	28.2	0.003
	GOL 100 mg	64	151	42.4	0.002	25	82	23.2	0.14
	PBO	41	154	26.6	--	18	87	18.4	--
	Biologic-Experienced (Population Not Studied)								
PURSUIT-J Golimumab	Week 54*								
	Overall – Biologic-Naïve								
	GOL 100 mg	20	32	62.5	NR	5	9	55.6	NR
	PBO	5	16	31.3	--	1	9	11.1	--
	Biologic-Experienced (Population Not Studied)								
VISIBLE 1 Vedolizumab	Week 52								
	Overall								
	VEDO 108 mg (SC)	60	106	56.6	p<0.001	31	106	28.9	p=0.067
	VEDO 300 mg (IV)	29	54	53.7	NR	6	21	28.6	NR
	PBO	41	56	21.4	--	2	24	8.3	--
	Stratified Biologic-Naïve and Experienced Data Not Reported								
GEMINI 1 Vedolizumab	Week 52								
	Overall								
	VEDO 300 mg q4w	70	125	56	p<0.001	33	73	45.2	p<0.001
	VEDO 300 mg q8w	63	122	51.6	p<0.001	22	70	31.4	p=0.0100
	PBO	25	126	19.8	--	10	72	13.9	--
	Biologic-Naïve								

Trial	Arm	Maintenance (Week 30-60)							
		Endoscopic Improvement				Corticosteroid-Free Remission			
		n	N	%	Significance	n	N	%	Significance
	VEDO 300 mg q4w	44	73	60.3	Diff (95% CI): 35.5 (19.9, 51.0)	23	73	52.3	Diff (95% CI): 33.7 (13.8, 53.6)
	VEDO 300 mg q8w	43	72	59.7	Diff (95% CI): 35.4 (19.8, 51.1)	14	72	35.9	Diff (95% CI): 17.0 (-2.0, 36.0)
	PBO	19	79	21.1	--	8	43	18.6	--
	Biologic-Experienced								
	VEDO 300 mg q4w	19	40	47.5	Diff (95% CI): 39.3 (19.3, 59.3)	23	73	52.3	Diff (95% CI): 33.7 (13.8, 53.6)
	VEDO 300 mg q8w	18	43	41.9	Diff (95% CI): 29.8 (11.6, 48.1)	14	72	35.9	Diff (95% CI): 17.0 (-2.0, 36.0)
	PBO	3	381	7.9	--	8	43	18.6	--
Motoya 2019 Vedolizumab	Week 60								
	Overall								
	VEDO 300 mg	26	41	63.4	0.006	NR	NR	NR	NR
	PBO	14	42	33.3	--	NR	NR	NR	NR
	Biologic-Naïve								
	VEDO 300 mg	15	24	62.5	Diff. (95% CI): 26.8 (0.52, 53.1)	4	9	44.4	Diff (95% CI): 22.2 (-20.1, 64.6)
	PBO	10	28	35.7		2	9	22.2	
	Biologic-Experienced								
	VEDO 300 mg	11	17	64.7	Diff. (95% CI): 36.1 (3.3, 68.9)	2	4	50	Diff (95% CI): 33.3 (-24.0, 90.7)
	PBO	4	14	28.6		1	2	16.7	
VARSITY VEDO vs. ADA	Week 52								
	Overall								
	VEDO 300 mg	152	383	39.7	Diff. (95% CI): 11.9 (5.3, 18.5)	14	383	12.6	Diff. (95% CI): -9.3 (-18.9, 0.4)
	ADA 40 mg	107	386	27.7		26	386	21.8	
	Biologic-Naïve								
	VEDO 300 mg	131	304	43.1	Diff. (95% CI): 13.6 (6.0, 21.2)	13	87	14.9	Diff (95% CI): -6.8 (-18.1, 4.5)
	ADA 40 mg	90	305	29.5		20	92	21.7	
	Biologic-Experienced								
	VEDO 300 mg	21	79	26.6	Diff. (95% CI): 5.5 (-7.7, 18.8)	1	24	4.2	Diff (95% CI): -18.1 (-44.2, 10.0)
	ADA 40 mg	17	81	21		6	27	22.2	
	Week 52								
	Overall								

Trial	Arm	Maintenance (Week 30-60)							
		Endoscopic Improvement				Corticosteroid-Free Remission			
		n	N	%	Significance	n	N	%	Significance
OCTAVE SUSTAIN Tofacitinib	TOF 5 mg	74	198	37.4	<0.001	23	65	35.4	<0.001
	TOF 10 mg	90	196	45.7	<0.001	26	55	47.3	<0.001
	PBO	26	198	13.1	--	3	59	5.1	--
	Biologic-Naïve								
	TOF 5 mg	49	115	42.6	<0.001	19	47	40.4	<0.01
	TOF 10 mg	53	104	51	<0.001	19	37	51.4	<0.001
	PBO	15	109	13.8	--	2	38	5.3	--
	Biologic-Experienced								
	TOF 5 mg	25	83	30.1	<0.01	4	18	22.2	--
	TOF 10 mg	37	93	39.8	<0.001	7	18	38.9	<0.01
	PBO	11	89	12.4	--	1	21	4.8	--
UNIFI Ustekinumab	Week 52								
	Overall								
	UST 90 mg q12w	88	172	51.1	<0.001	65	172	37.8	0.0020
	UST 90 mg q8w	77	176	43.6	<0.001	74	176	42	<0.001
	PBO	50	175	28.6	--	41	175	23.4	--
	Biologic-Naïve								
	UST 90 mg q12w	57	102	55.9	0.007	49	102	48.0	0.028
	UST 90 mg q8w	49	85	57.6	0.002	40	85	47.1	0.034
	PBO	30	87	34.5	--	27	87	31.0	--
	Biologic-Experienced								
	UST 90 mg q12w	18	70	25.7	p=0.163	16	70	22.9	0.026
	UST 90 mg q8w	41	91	45.1	p<0.001	34	91	37.4	<0.001
	PBO	20	88	22.7	--	14	88	15.9	--

Table D11. IBDQ and EQ-5D Outcomes in the Maintenance Phase

Trial	Arm	IBDQ Score					IBDQ Response/Remission*				EQ-5D (Visual Analogue Scale)				
		Data Type	Value	Data Type	Value	p-value	n	N	%	p-value	Data Type	Value	Data Type	Value	p-value
ACT 1 Infliximab	Week 54														
	Overall – Biologic-Naïve														
	IFX 5 mg/kg	Mean Δ	32.8	95% CI	25.8-38.8	<0.05	NR				NR				
	IFX 10 mg/kg	Mean Δ	31.8	95% CI	24.8-38.8	<0.05	NR				NR				
	PBO	Mean Δ	12.8	95% CI	6.8-17.9	--	NR				NR				
	Biologic-Experienced (Population Not Studied)														
ACT 2 Infliximab	Week 30														
	Overall – Biologic-Naïve														
	IFX 5 mg/kg	Mean Δ	31.9	95% CI	24.9-37.8	<0.05	NR				NR				
	IFX 10 mg/kg	Mean Δ	36.1	95% CI	28.8-42.7	<0.05	NR				NR				
	PBO	Mean Δ	17.9	95% CI	11.8-22.8	--	NR				NR				
	Biologic-Experienced (Population Not Studied)														
ULTRA 2 Adalimumab	Week 52														
	Overall														
	ADA 40 mg	NR					65	248	26.2	0.0070	NR				
	PBO	NR					40	246	16.3	--					
	Biologic-Naive														
	ADA 40 mg	NR					48	150	32.0	0.0390	NR				
	PBO	NR					31	145	21.4	--	NR				
	Biologic-Experienced														
	ADA 40 mg	NR					17	98	17.3	0.078	NR				
	PBO	NR					9	101	8.9	--	NR				
Suzuki 2014 Adalimumab	Week 52														
	Overall – Biologic-Naïve														
	ADA 40 mg	NR					45	177	25.4	<0.01	NR				
	PBO	NR					12	96	12.5	--	NR				
	Biologic-Experienced (Population Not Studied)														
PURSUIT J Golimumab	Week 54														
	Overall – Biologic-Naïve														
	GOL 100 mg	NR					11	20	55.0	NR	NR				
	PBO	NR					6	27	22.2	--	NR				
	Biologic-Experienced (Population Not Studied)														
	Week 52														
	Overall														

Trial	Arm	IBDQ Score					IBDQ Response/Remission*				EQ-5D (Visual Analogue Scale)				
		Data Type	Value	Data Type	Value	p-value	n	N	%	p-value	Data Type	Value	Data Type	Value	p-value
VISIBLE 1 Vedolizumab	VEDO 108 mg (SC)	Diff vs. PBO	43.9	95% CI	30.6-57.1	<.001	NR				Diff vs. PBO	17.6	95% CI	11-24.3	< .001
	VEDO 300 mg (iv)	Diff vs. PBO	37.1	95% CI	21.9-52.4	<.001	NR				Diff vs. PBO	13.1	95% CI	5.5-20.8	.001
	PBO	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Stratified Biologic-Naïve and Biologic-Experienced Data Not Reported														
GEMINI 1 Vedolizumab	Week 52														
	Overall														
							Remission								
	VEDO 300 mg q4w	Mean Δ	49	SE	3.3	NR	85	125	68	NR	Mean	19.4	SE	1.7	NR
	VEDO 300 mg q8w	Mean Δ	48.4	SE	3.4	NR	72	122	59	NR	Mean Δ	19	SE	1.7	NR
	PBO	Mean Δ	27.3	SE	3.3	NR	48	126	38	NR	Mean Δ	9.7	SE	1.7	NR
	Biologic-Naive														
	VEDO 300 mg q4w	Diff. vs PBO	25.8	95% CI	14.7-36.9	NR	NR				Diff. vs PBO	11.1	95% CI	5.5-16.7	NR
	VEDO 300 mg q8w	Diff. vs PBO	25.9	95% CI	14.6-37.3	NR	NR				Diff. vs PBO	10.6	95% CI	4.9-16.3	NR
	PBO	–	–	–	–	–	NR				–	–	–	–	–
	Biologic-Experienced														
	VEDO 300 mg q4w	Diff. vs PBO	13.4	95% CI	-3.4-30.2	NR	NR				Diff. vs PBO	6.9	95% CI	-2.0-15.7	NR
	VEDO 300 mg q8w	Diff. vs PBO	14.1	95% CI	-2.5-30.5	NR	NR				Diff. vs PBO	6.8	95% CI	-1.8-15.5	NR
	PBO	–	–	–	–	–					–	–	–	–	–
VARSITY VEDO vs. ADA	Week 52														
	Overall														
							Remission								
	VEDO 300 mg	NR					192	383	50.1	NR	NR				
	ADA 40 mg	NR					156	386	40.4	--	NR				
							Response								
	VEDO 300 mg	–					199	383	52.0	NR	NR				
	ADA 40 mg						164	386	42.2	--	NR				
	Stratified Biologic-Naïve and Biologic-Experienced Data Not Reported														

Trial	Arm	IBDQ Score					IBDQ Response/Remission*				EQ-5D (Visual Analogue Scale)				
		Data Type	Value	Data Type	Value	p-value	n	N	%	p-value	Data Type	Value	Data Type	Value	p-value
OCTAVE SUSTAIN Tofacitinib	Week 52														
	Overall														
							Remission				NR				
	TOF 5 mg	Mean Δ	3.7	SE	3.4	<.0001	76	198	38.4	<.001					
	TOF 10 mg	Mean Δ	4.8	SE	3.2	<.0001	95	197	48.2	<.001					
	PBO	Mean Δ	-26.5	SE	3.8	–	29	198	14.6	–					
							Response								
	TOF 5 mg	–					92	198	46.5	<.001	NR				
	TOF 10 mg						106	197	53.8	<.001	NR				
	PBO						38	198	19.2	–	NR				
	Stratified Biologic-Naive and Experienced Not Reported														
UNIFI Ustekinumab	Week 52														
	Overall														
							Response				NR				
	UST 90 mg q12w	Mean Δ	-3.0	SD	32.9	NR	118	172	68.6	<.001					
	UST 90 mg q8w	Mean Δ	3.9	SD	31.5	NR	129	176	73.3	<.001					
	PBO	Mean Δ	-15.1	SD	35.4	–	83	175	47.4	–					
							Remission								
	UST 90 mg q12w	–					97	172	56.4	.004	NR				
	UST 90 mg q8w						111	176	63.1	<.001	NR				
	PBO						72	175	41.1	–	NR				
	Stratified Biologic-Naïve and Experienced Data Not Reported														

Table D12. 36-Item Short Form Survey Outcomes in the Maintenance Phase

Trial	Arm	SF-36 (Mental)					SF-36 (Physical)				
		Data Type	Value	Data Type	Value	p-value	Data Type	Value	Data Type	Value	p-value
GEMINI 1 Vedolizumab	Week 52										
	Biologic-Naive										
	VEDO 300 mg q4w	Diff. vs PBO	6.2	95% CI	3.2-9.1	NR	Diff. vs PBO	3.6	95% CI	1.4-5.8	NR
	VEDO 300 mg q8w	Diff. vs PBO	6	95% CI	2.9-9.0	NR	Diff. vs PBO	3.9	95% CI	1.7-6.2	NR
	PBO	--	--	--	--	--	--	--	--	--	--
	Biologic- Experienced										
	VEDO 300 mg q4w	Diff. vs PBO	2.2	95% CI	-2.3-6.7	NR	Diff. vs PBO	1.1	95% CI	-2.1-4.4	NR
	VEDO 300 mg q8w	Diff. vs PBO	3.3	95% CI	-1.2-7.8	NR	Diff. vs PBO	2.2	95% CI	-1.0-5.4	NR
	PBO	--	--	--	--	--	--	--	--	--	--
OCTAVE SUSTAIN Tofacitinib	Week 52										
	Overall										
	TOF 5 mg	Mean Δ	-1	SE	0.9	<0.0001	Mean Δ	0	SE	0.8000	<0.0001
	TOF 10 mg	Mean Δ	0.1	SE	1.9	<0.0001	Mean Δ	0.3	SE	0.7000	<0.0001
	PBO	Mean Δ	-6.7	SE	1.2	–	Mean Δ	-5.2	SE	0.9000	–
	Biologic-Naive										
	TOF 5 mg	Mean Δ	-1.7	SE	1.1	<0.001	Mean Δ	-1.2	SE	0.9	<0.001
	TOF 10 mg	Mean Δ	-1	SE	1.1	<0.0001	Mean Δ	-0.2	SE	0.9	<0.001
	PBO	Mean Δ	-8.5	SE	1.5	--	Mean Δ	-5.9	SE	1.1	--
	Biologic-Experienced										
	TOF 5 mg	Mean Δ	-2.2	SE	1.2	<0.01	Mean Δ	-0.9	SE	1	<0.001
	TOF 10 mg	Mean Δ	-0.8	SE	1.1	<0.001	Mean Δ	-1.2	SE	0.9	<0.001
	PBO	Mean Δ	-6.7	SE	1.5	--	Mean Δ	-6.1	SE	1.2	--

Table D13. Induction and Maintenance WPAI Questionnaire I*

Trial	Arm	WPAI (Absenteeism)					WPAI (Presenteeism)				
		Data Type	Value	Data Type	Value	p-value	Data Type	Value	Data Type	Value	p-value
ULTRA 2 Adalimumab	Induction – Week 8 (*Data Not Reported)*										
	Maintenance – Week 52										
	ADA 160/80 mg	Mean	7	NR	NR	NR	Mean	21	NR	NR	NR
	PBO	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
OCTAVE 1 Tofacitinib	Induction only – Week 8										
	TOF 10 mg	Mean Δ	-11.2	95% CI	-9.9, 1.6	0.16	Mean	-22.1	95% CI	-19.8, -6.0	0.003
	PBO	Mean Δ	-7.1	--	--	--	Mean	-9.2	--	--	--
OCTAVE 2 Tofacitinib	Induction only – Week 8										
	TOF 10 mg	Mean Δ	-7.3	95% CI	-4.4, 8.5	0.53	Mean	-18.6	95% CI	-12.0, 2.2	0.18
	PBO	Mean Δ	-9.3	--	--	--	Mean	-13.7	--	--	--
OCTAVE SUSTAIN Tofacitinib	Maintenance only – Week 52										
	TOF 5 mg	Mean Δ	-4.5	95% CI	-12.2, 1.0	0.09	Mean Δ	-3.6	95% CI	-18.9, -2.8	0.008
	TOF 10 mg	Mean Δ	-3.1	95% CI	-10.7, 2.4	0.21	Mean Δ	-4.3	95% CI	-19.5, -3.4	0.005
	PBO	Mean Δ	1.1	--	--	--	Mean Δ	7.2	--	--	--
UNIFI Ustekinumab	Induction – Week 8										
	UST 130 mg	Mean Δ	-5.9	SD	31.39	<0.05	Mean Δ	-15.1	SD	29.17	<0.05
	UST 6 mg/kg	Mean Δ	-9.1	SD	23.84	<0.01	Mean Δ	-20.4	SD	24.11	<0.001
	PBO	Mean Δ	-3.7	SD	30.41	--	Mean Δ	-6.9	SD	21.89	--
	Maintenance – Week 52										
	UST 90 mg q12w	Mean Δ	-2	NR	NR	0.133	Mean Δ	-1.6	NR	NR	0.017
	UST 90 mg q8w	Mean Δ	-2.1	NR	NR	0.172	Mean Δ	-6.4	NR	NR	<0.001
	PBO	Mean Δ	4.7	NR	NR	--	Mean Δ	7.4	NR	NR	--

ADA: adalimumab, diff: difference, IV: intravenous, kg: kilogram, mg: milligram, n: number, N: total number, NA: not applicable, NR: not reported, PBO: placebo, q8w: every 8 weeks, q12w: every 12 weeks, SC: subcutaneous, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab, WPAI: work productivity and activity impairment questionnaire

All other trials did not report WPAI.

*Stratified biologic-naïve and experienced data not reported.

Table D14. Induction and Maintenance WPAI Questionnaire II*

Trial	Arm	WPAI (Work Productivity Loss)					WPAI (Non-Work Productivity Loss)				
		Data Type	Value	Data Type	Value	p-value	Data Type	Value	Data Type	Value	p-value
ULTRA 2 Adalimumab	Induction – Week 8 (*Data Not Reported)*										
	Maintenance – Week 52										
	ADA 160/80 mg	Mean	24	NR	NR	NR	Mean	23	NR	NR	NR
	PBO	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
OCTAVE 1 Tofacitinib	Induction only – Week 8										
	TOF 10 mg	Mean Δ	-19.1	95% CI	-19.1, -2.1	0.0143	Mean Δ	-25.4	95% CI	-19, -8.9	<0.0001
	PBO	Mean Δ	-8.5	-	--	--	Mean Δ	-11.5	--	--	--
OCTAVE 2 Tofacitinib	Induction only – Week 8										
	TOF 10 mg	Mean Δ	-14.7	95% CI	-11.9, 4.9	0.412	Mean	-24.0	95% CI	-17.2, -6.4	<0.0001
	PBO	Mean Δ	-11.2	--	--	--	Mean	-12.2	--	--	--
OCTAVE SUSTAIN Tofacitinib	Maintenance only – Week 52										
	TOF 5 mg	Mean Δ	-3.4	95% CI	-17.8, 9.0	0.519	Mean Δ	-2.8	95% CI	-20.6, -7.5	<0.0001
	TOF 10 mg	Mean Δ	-6.6	95% CI	-20.6, -5.4	0.253	Mean Δ	-3.1	95% CI	-20.8, -5.4	<0.0001
	PBO	Mean Δ	1.0	--	-17.8, 9.0	0.519	Mean Δ	11.3	--	--	--
UNIFI Ustekinumab	Induction – Week 8										
	UST 130 mg	Mean Δ	-17.2	SD	30.36	<0.01	Mean Δ	-17.7	SD	29.45	<0.01
	UST 6 mg/kg	Mean Δ	-21.8	SD	26.26	<0.001	Mean Δ	-20.8	SD	26.27	<0.001
	PBO	Mean Δ	-8	SD	24.83	--	Mean Δ	-10.9	SD	28.66	--
	Maintenance – Week 52										
	UST 90 mg q12w	Mean Δ	-2.2	NR	NR	0.013	Mean Δ	0.8	NR	NR	0.002
	UST 90 mg q8w	Mean Δ	-6.1	NR	NR	<0.001	Mean Δ	-4.2	NR	NR	<0.001
	PBO	Mean Δ	7.7	NR	NR	--	Mean Δ	9.3	NR	NR	--
VISIBLE Vedolizumab	Maintenance only – Week 52										
	VEDO 300 mg (IV)	Mean	27	95% CI	-27.9, -0.6	0.04	Mean	22	95% CI	-33.2, -13.2	<0.001
	PBO	Mean	39	--	--		Mean	45	--	--	--

ADA: adalimumab, diff: difference, IV: intravenous, kg: kilogram, mg: milligram, n: number, N: total number, NA: not applicable, NR: not reported, PBO: placebo, q8w: every 8 weeks, q12w: every 12 weeks, SC: subcutaneous, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab, WPAI: work productivity and activity impairment questionnaire
All other trials did not report WPAI.
*Stratified biologic-naïve and experienced data not reported.

Table D15. Safety in the Induction Phase

Trial	Arm	Any AE	Related AE	D/C due to AE	Death	Serious AE	Severe AE	Anti-bodies	Infusion/ Injection Site Reaction	Infections	Serious Infections	TB
Kobayashi 2016	IFX 5 mg/kg	81.7	NR	4.8	NR	8.7	NR	NR	10.6	31.7	1	NR
	PBO	82.7	NR	7.7	NR	12.5	NR	NR	8.7	33.7	1.9	NR
ULTRA 1	ADA 80/40 mg	53.8	NR	6.2	0	3.8	6.9	NR	5.4	20	1.5	NR
	ADA 160/80 mg	50.2	NR	5.4	0	4	8.5	NR	5.8	14.3	0	NR
	PBO	48.4	NR	5.4	0	7.6	7.6	NR	3.1	15.7	1.3	NR
Suzuki 2014	ADA 80/40 mg	56.3	16.1	0	NR	2.3	NR	--	5.7	12.6	0	0
	ADA 160/80 mg	44.4	13.3	6.7	NR	4.4	NR	--	7.8	18.9	3.3	1.1
	PBO	46.9	10.4	4.2	NR	7.3	NR	--	2.1	15.6	0	0
PURSUIT-SC	GOL 200/100 mg	37.5	NR	0.3	0	2.7	NR	0.3	3.3	11.8	0.3	0
	GOL 400/200 mg	38.9	NR	0.3	0.3	3.3	NR	0.6	3	12.3	0.9	0
	PBO	38.2	NR	0.9	0	3.9	NR	NR	1.5	12.1	1.8	0
GEMINI 1	VEDO 300 mg	45	NR	6.7	2.2	3	NR	NR	<1	14	<1	NR
	PBO	46	NR	0	0	7	NR	NR	<1	15	2	NR
Motoya 2019	VEDO 300 mg	50	10.4	4.9	0	6.1	NR	NR	3	NR	0.6	NR
	PBO	52.4	14.6	2.4	0	2.4	NR	NR	2.4	NR	2.4	NR
OCTAVE 1	TOF 10 mg	56.5	NR	3.8	0.21	3.4	NR	NR	NR	23.3	1.3	0
	PBO	59.8	NR	1.6	0	4.1	NR	NR	NR	15.6	0	0
OCTAVE 2	TOF 10 mg	54.1	NR	4	0	4.2	NR	NR	NR	18.2	0.2	0
	PBO	52.7	NR	7.1	0	8	NR	NR	NR	15.2	0	0
UNIFI	UST 130 mg	41.4	NR	NA	0	3.7	NR	NR	2.2	15.9	0.6	NR
	UST 6 mg/kg	50.6	NR	NA	0.3	3.4	NR	NR	0.9	15.9	0.3	NR
	PBO	48	NR	NA	0	6.9	NR	NR	1.9	15.4	1.6	NR

ADA: adalimumab, AE: adverse event, D/C: discontinuation, GOL: golimumab, IFX: infliximab, kg: kilogram, mg: milligram, NA: not applicable, NR: not reported, PBO: placebo, TB: tuberculosis, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Table D16. Treatment Emergent Adverse Events from Open-Label Extensions

Intervention	Arms	Duration	N	Discontinuations	SAE	Any AE	Serious Infections
Suzuki OLE Per 100-PY	Any ADA	4 years	266	72 (12.4)	129 (22.3)	2900 (431.5)	23 (4.0)
ULTRA OLE Per 100-PY	ADA 160/80/40 mg	4 years	1010	249 (10.7)	414 (17.7)	8,057 (344.6)	79 (3.4)
PURSUIT M Extension Per 100-PY	GOL 50 mg	139 weeks	94	2.89 (1.16, 5.95)	7.84 (4.72, 12.24)	187.68 (170.83, 205.74)	1.24 (0.26, 3.62)
	GOL 100 mg		524	6.18 (4.93, 7.66)	10.23 (8.6, 12.08)	211.45 (203.78, 219.32)	2.65 (1.86, 3.67)
	Combined		599	5.69 (4.58, 6.98)	9.87 (8.39, 11.54)	207.85 (200.84, 215.03)	2.44 (1.73, 3.33)
ACT 1 & 2 Extn Per 100-PY	IFX	152 weeks	230	4.63	21	506	3.4
OCTAVE OLE N (%)	TOFA 5/10 mg	6.1 years	1157	NR	109 (11.5)	764 (80.9)	32 (3.4)
GEMINI LTS N (%)	VEDO 300 mg	152 weeks	894	87 (10)	183 (20)	789 (88)	45 (5)

ADA: adalimumab, AE: adverse event, GOL: golimumab, LTS: long term study, mg: milligram, N: number, OLE: open-label extension, PY: patient year, SAE: serious adverse event, TOFA: tofacitinib, VEDO: vedolizumab

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact	Included in This Analysis from… Perspective?		Notes on Sources
		Health Care	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	☐	☐	Assume no direct impact on mortality outside of potential reduction in colectomy-associated mortality
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	Direct health state costs
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	

NA: not applicable

Adapted from Sanders et al.[175]

Description of evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[127]
2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).
3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.
4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.
5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.
6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

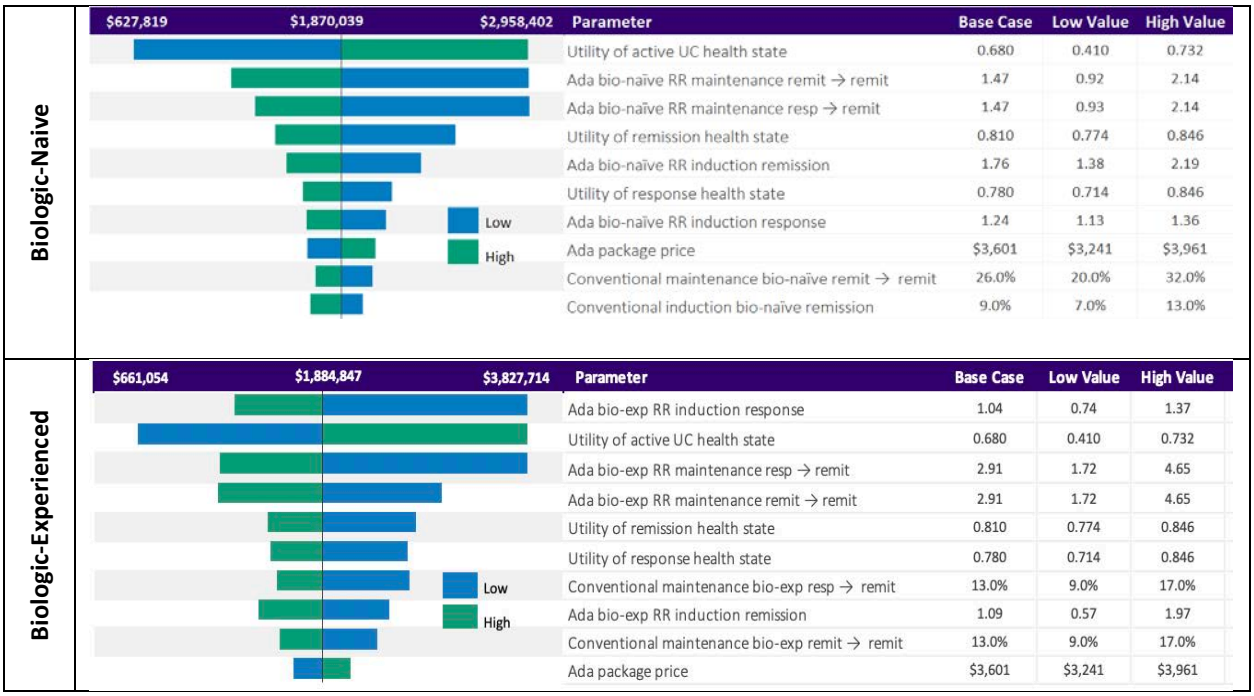
Extended Induction Calculations

Additional efficacy benefit from extended induction was calculated for adalimumab, golimumab, tofacitinib, ustekinumab, and vedolizumab. For adalimumab, 28.6% of patients achieved remission at eight weeks and 32.7% did at 16 weeks, an absolute gain of 4.1%. If the 71.4% who did not achieve remission at eight weeks continued to be treated, 5.7% of these patients (4.1%/71.4%=5.7%) would be expected to achieve remission at 16 weeks to equal a total of 32.7% at 16 weeks.[93] For golimumab, 112 of 398 clinical non-responders at eight weeks in the PURSUIT trial who continued to receive golimumab achieved partial Mayo response at week eight of maintenance (week 16 since treatment initiation), 28.1%.[70] No information was available for clinical response without remission. For tofacitinib, of 295 non-responders at end of induction in OCTAVE, 148 achieved response (with and without remission) at 16 weeks. Of these, 41 achieved remission (13.9%) and 107 (148-41) were in response without remission. Therefore, 36.3% (107/295) of patients with active UC at eight weeks will move to the response without remission health state at week 16.[118] For ustekinumab in the biologic-naïve population, of 43 non-responders at end of induction in OCTAVE, 34 achieved response (with and without remission) at 16 weeks at the 6 mg/kg dosing.[71] Of these, eight achieved remission (18.6%) and 26 (34 minus eight) were in response without remission. Therefore 60.5% (26/43) of patients with active UC at eight weeks will

move to the response without remission health state at week 16. For the biologic-experienced population, one of 58 (1.7%) non-responders at the end of induction achieved remission at week 16 and 25 achieved response (with or without remission).[71] For vedolizumab, 39% of non-responders at the end of six weeks had response (with or without remission) at 14 weeks. The proportion achieving remission at 14 weeks was not reported.[56]

One-Way Sensitivity Analysis Tornado Charts

Figure E1. Tornado Diagram for One-Way Sensitivity Analyses of Adalimumab versus Conventional Treatment (Cost per QALY)

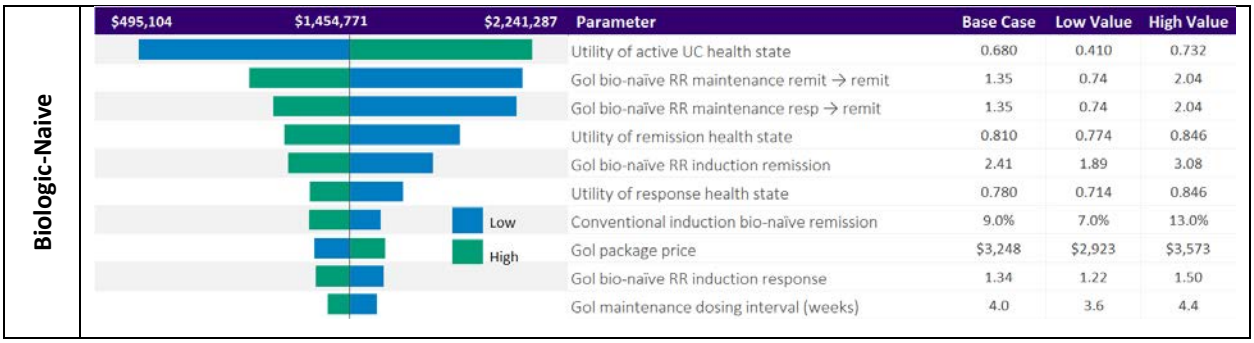


Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
Ada bio-naïve RR maintenance remit → remit	1.47	0.92	2.14
Ada bio-naïve RR maintenance resp → remit	1.47	0.93	2.14
Utility of remission health state	0.810	0.774	0.846
Ada bio-naïve RR induction remission	1.76	1.38	2.19
Utility of response health state	0.780	0.714	0.846
Ada bio-naïve RR induction response	1.24	1.13	1.36
Ada package price	$3,601	$3,241	$3,961
Conventional maintenance bio-naïve remit → remit	26.0%	20.0%	32.0%
Conventional induction bio-naïve remission	9.0%	7.0%	13.0%

Parameter	Base Case	Low Value	High Value
Ada bio-exp RR induction response	1.04	0.74	1.37
Utility of active UC health state	0.680	0.410	0.732
Ada bio-exp RR maintenance resp → remit	2.91	1.72	4.65
Ada bio-exp RR maintenance remit → remit	2.91	1.72	4.65
Utility of remission health state	0.810	0.774	0.846
Utility of response health state	0.780	0.714	0.846
Conventional maintenance bio-exp resp → remit	13.0%	9.0%	17.0%
Ada bio-exp RR induction remission	1.09	0.57	1.97
Conventional maintenance bio-exp remit → remit	13.0%	9.0%	17.0%
Ada package price	$3,601	$3,241	$3,961

ada: adalimumab, bio: biologic, exp: experienced, IV: intravenous, resp: response without remission, RR: risk ratio, tx: treatment, UC: ulcerative colitis

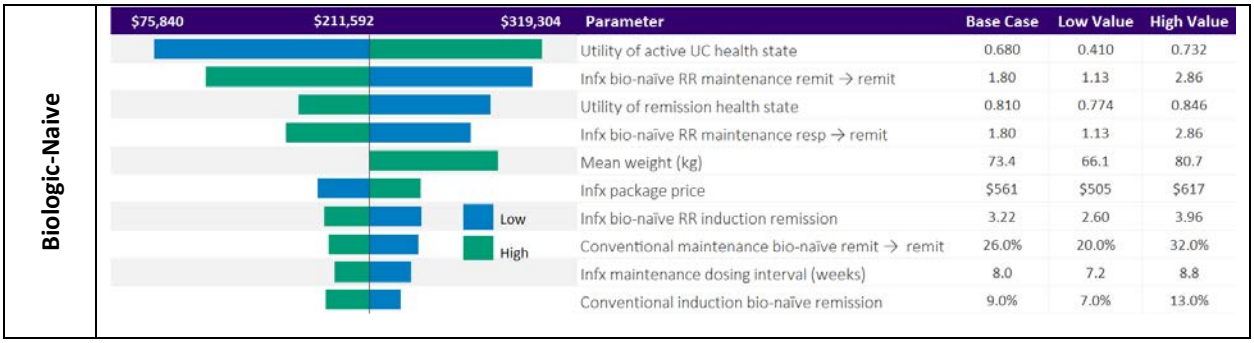
Figure E2. Tornado Diagram for One-Way Sensitivity Analyses of Golimumab versus Conventional Treatment (Cost per QALY)



Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
GoI bio-naïve RR maintenance remit → remit	1.35	0.74	2.04
GoI bio-naïve RR maintenance resp → remit	1.35	0.74	2.04
Utility of remission health state	0.810	0.774	0.846
GoI bio-naïve RR induction remission	2.41	1.89	3.08
Utility of response health state	0.780	0.714	0.846
Conventional induction bio-naïve remission	9.0%	7.0%	13.0%
GoI package price	$3,248	$2,923	$3,573
GoI bio-naïve RR induction response	1.34	1.22	1.50
GoI maintenance dosing interval (weeks)	4.0	3.6	4.4

IV: intravenous, resp: response without remission, RR: risk ratio, UC: ulcerative colitis

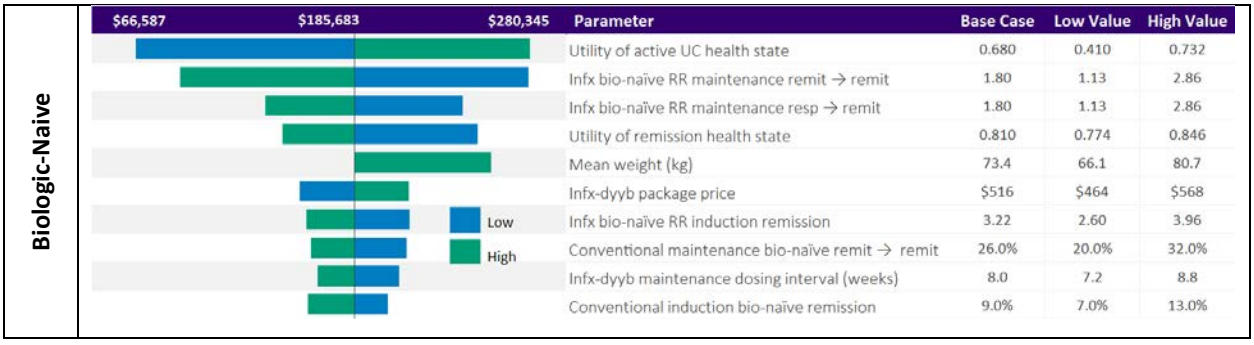
Figure E3. Tornado Diagram for One-Way Sensitivity Analyses of Infliximab versus Conventional Treatment (Cost per QALY)



Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
Infx bio-naïve RR maintenance remit → remit	1.80	1.13	2.86
Utility of remission health state	0.810	0.774	0.846
Infx bio-naïve RR maintenance resp → remit	1.80	1.13	2.86
Mean weight (kg)	73.4	66.1	80.7
Infx package price	$561	$505	$617
Infx bio-naïve RR induction remission	3.22	2.60	3.96
Conventional maintenance bio-naïve remit → remit	26.0%	20.0%	32.0%
Infx maintenance dosing interval (weeks)	8.0	7.2	8.8
Conventional induction bio-naïve remission	9.0%	7.0%	13.0%

bio: biologic, infx: infliximab, resp: response without remission, RR: risk ratio, UC: ulcerative colitis

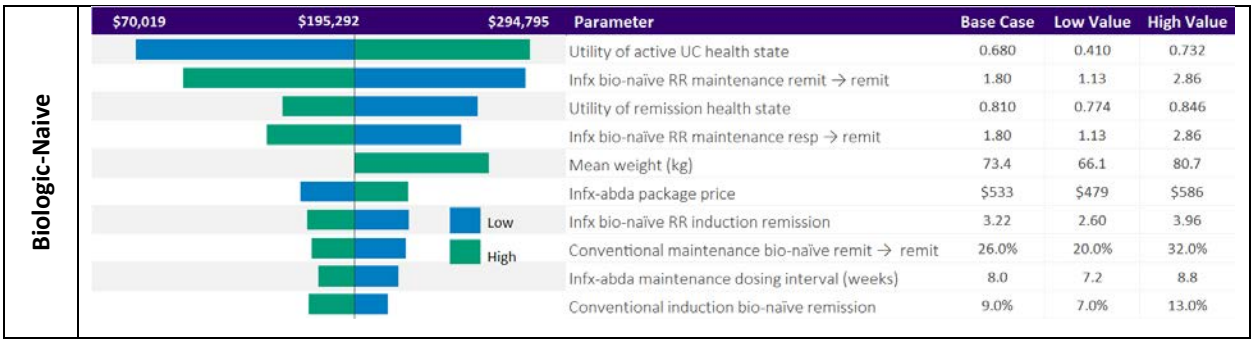
Figure E4. Tornado Diagram for One-Way Sensitivity Analyses of Infliximab-dyyb versus Conventional Treatment (Cost per QALY)



Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
Infx bio-naïve RR maintenance remit → remit	1.80	1.13	2.86
Infx bio-naïve RR maintenance resp → remit	1.80	1.13	2.86
Utility of remission health state	0.810	0.774	0.846
Mean weight (kg)	73.4	66.1	80.7
Infx-dyyb package price	$516	$464	$568
Infx bio-naïve RR induction remission	3.22	2.60	3.96
Conventional maintenance bio-naïve remit → remit	26.0%	20.0%	32.0%
Infx-dyyb maintenance dosing interval (weeks)	8.0	7.2	8.8
Conventional induction bio-naïve remission	9.0%	7.0%	13.0%

bio: biologic, infx: infliximab, resp: response without remission, RR: risk ratio, tx: treatment, UC: ulcerative colitis, ust: ustekinumab

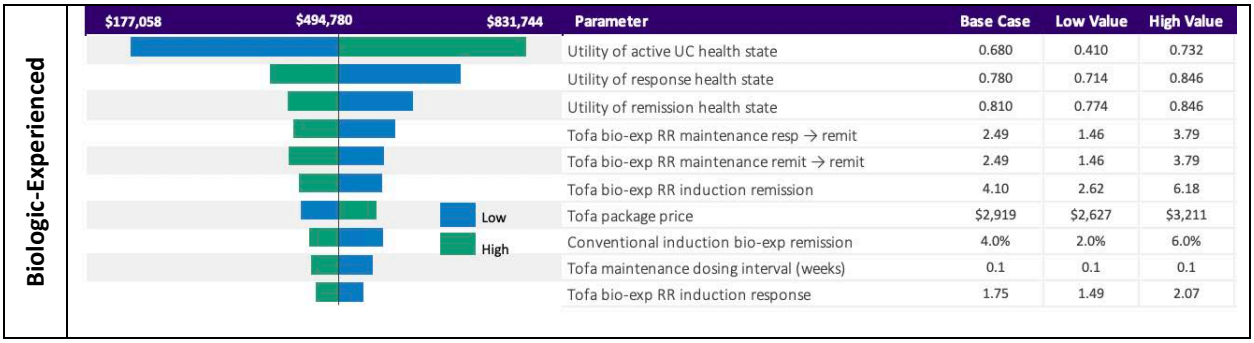
Figure E5. Tornado Diagram for One-Way Sensitivity Analyses of Infliximab-abda versus Conventional Treatment (Cost per QALY)



Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
Infx bio-naïve RR maintenance remit → remit	1.80	1.13	2.86
Utility of remission health state	0.810	0.774	0.846
Infx bio-naïve RR maintenance resp → remit	1.80	1.13	2.86
Mean weight (kg)	73.4	66.1	80.7
Infx-abda package price	$533	$479	$586
Infx bio-naïve RR induction remission	3.22	2.60	3.96
Conventional maintenance bio-naïve remit → remit	26.0%	20.0%	32.0%
Infx-abda maintenance dosing interval (weeks)	8.0	7.2	8.8
Conventional induction bio-naïve remission	9.0%	7.0%	13.0%

bio: biologic, infx: infliximab, resp: response without remission, RR: risk ratio, UC: ulcerative colitis

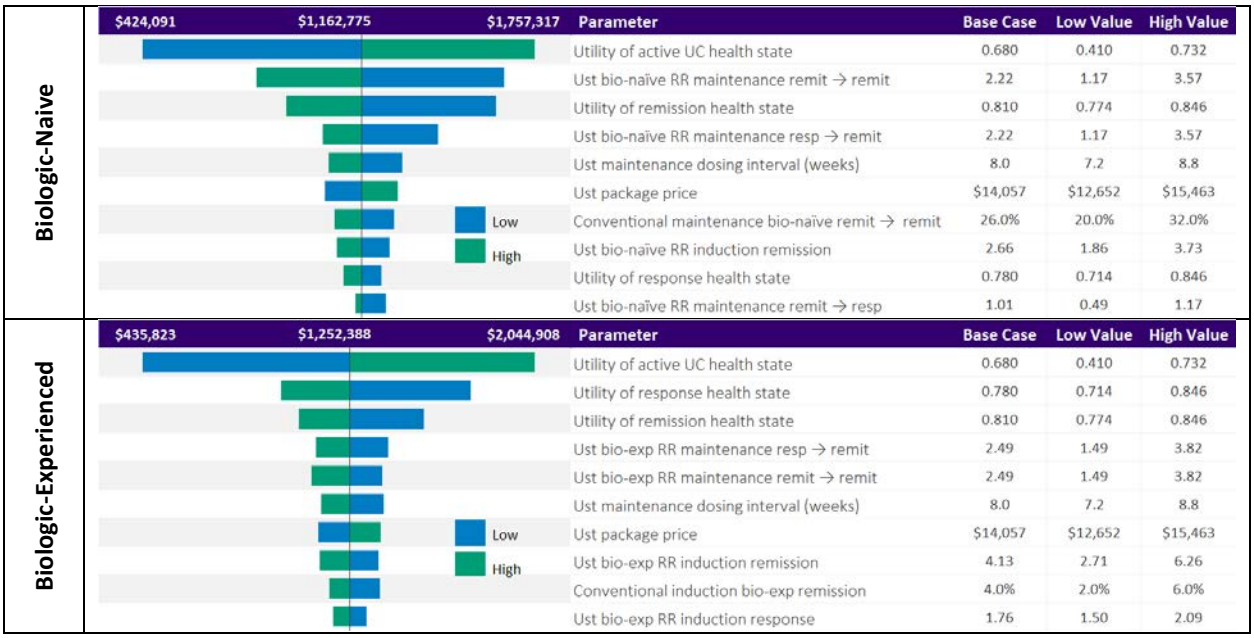
Figure E6. Tornado Diagram for One-Way Sensitivity Analyses of Tofacitinib versus Conventional Treatment (Cost per QALY)



Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
Utility of response health state	0.780	0.714	0.846
Utility of remission health state	0.810	0.774	0.846
Tofa bio-exp RR maintenance resp → remit	2.49	1.46	3.79
Tofa bio-exp RR maintenance remit → remit	2.49	1.46	3.79
Tofa bio-exp RR induction remission	4.10	2.62	6.18
Tofa package price	$2,919	$2,627	$3,211
Conventional induction bio-exp remission	4.0%	2.0%	6.0%
Tofa maintenance dosing interval (weeks)	0.1	0.1	0.1
Tofa bio-exp RR induction response	1.75	1.49	2.07

bio: biologic, exp: experienced, resp: response without remission, tofa: tofacitinib, UC: ulcerative colitis

Figure E7. Tornado Diagram for One-Way Sensitivity Analyses of Ustekinumab versus Conventional Treatment (Cost per QALY)

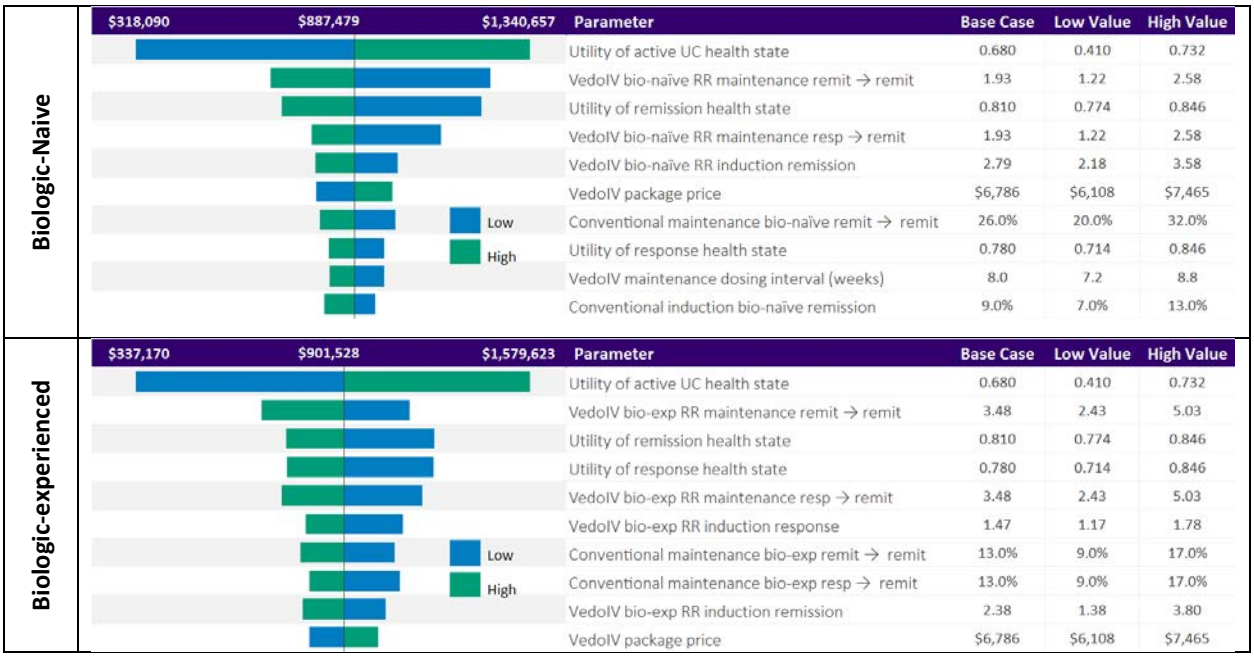


Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
Ust bio-naïve RR maintenance remit → remit	2.22	1.17	3.57
Utility of remission health state	0.810	0.774	0.846
Ust bio-naïve RR maintenance resp → remit	2.22	1.17	3.57
Ust maintenance dosing interval (weeks)	8.0	7.2	8.8
Ust package price	$14,057	$12,652	$15,463
Conventional maintenance bio-naïve remit → remit	26.0%	20.0%	32.0%
Ust bio-naïve RR induction remission	2.66	1.86	3.73
Utility of response health state	0.780	0.714	0.846
Ust bio-naïve RR maintenance remit → resp	1.01	0.49	1.17

Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
Utility of response health state	0.780	0.714	0.846
Utility of remission health state	0.810	0.774	0.846
Ust bio-exp RR maintenance resp → remit	2.49	1.49	3.82
Ust bio-exp RR maintenance remit → remit	2.49	1.49	3.82
Ust maintenance dosing interval (weeks)	8.0	7.2	8.8
Ust package price	$14,057	$12,652	$15,463
Ust bio-exp RR induction remission	4.13	2.71	6.26
Conventional induction bio-exp remission	4.0%	2.0%	6.0%
Ust bio-exp RR induction response	1.76	1.50	2.09

bio: biologic, exp: experienced, resp: response without remission, RR: risk ratio, tx: treatment, UC: ulcerative colitis, ust: ustekinumab

Figure E8. Tornado Diagram for One-Way Sensitivity Analyses of Vedolizumab versus Conventional Treatment (Cost per QALY)



Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
VedoIV bio-naïve RR maintenance remit → remit	1.93	1.22	2.58
Utility of remission health state	0.810	0.774	0.846
VedoIV bio-naïve RR maintenance resp → remit	1.93	1.22	2.58
VedoIV bio-naïve RR induction remission	2.79	2.18	3.58
VedoIV package price	$6,786	$6,108	$7,465
Conventional maintenance bio-naïve remit → remit	26.0%	20.0%	32.0%
Utility of response health state	0.780	0.714	0.846
VedoIV maintenance dosing interval (weeks)	8.0	7.2	8.8
Conventional induction bio-naïve remission	9.0%	7.0%	13.0%

Parameter	Base Case	Low Value	High Value
Utility of active UC health state	0.680	0.410	0.732
VedoIV bio-exp RR maintenance remit → remit	3.48	2.43	5.03
Utility of remission health state	0.810	0.774	0.846
Utility of response health state	0.780	0.714	0.846
VedoIV bio-exp RR maintenance resp → remit	3.48	2.43	5.03
VedoIV bio-exp RR induction response	1.47	1.17	1.78
Conventional maintenance bio-exp remit → remit	13.0%	9.0%	17.0%
Conventional maintenance bio-exp resp → remit	13.0%	9.0%	17.0%
VedoIV bio-exp RR induction remission	2.38	1.38	3.80
VedoIV package price	$6,786	$6,108	$7,465

bio: biologic, exp: experienced, IV: intravenous, resp: response without remission, RR: risk ratio, UC: ulcerative colitis, vedo: vedolizumab

Undiscounted Results, Biologic-Naïve Population

Table E2. Undiscounted Results for the Base-Case for TIMs and Conventional Treatment: Biologic-Naïve

Parameter	Initial TIM Drug Cost	Total Cost	LY	QALYs	evLYs
Adalimumab	$45,000	$734,000	38.879	27.436	27.443
Golimumab	$42,000	$731,000	38.883	27.442	27.450
Infliximab	$25,000	$709,000	38.888	27.490	27.498
Infliximab-dyyb	$23,000	$707,000	38.888	27.490	27.498
Infliximab-abda	$23,000	$708,000	38.888	27.490	27.498
Ustekinumab	$148,000	$828,000	38.886	27.530	27.539
Vedolizumab	$71,000	$756,000	38.886	27.486	27.495
Conventional Treatment	$600	$692,000	38.874	27.412	27.419

evLY: equal value of life years, LY: life year, N/A: not applicable, QALY: quality-adjusted life year, TIM: targeted immune modulator

Costs rounded to nearest $1,000.

Table E3. Undiscounted Incremental Cost-Effectiveness Ratios for the Base Case Compared to Conventional Treatment: Biologic-Naïve

Treatment	Cost per LY Gained	Cost per QALY Gained	Cost per evLY Gained
Adalimumab	$7,417,000	$1,810,000	$1,749,000
Golimumab	$4,209,000	$1,347,000	$1,288,000
Infliximab	$1,222,000	$224,000	$218,000
Infliximab-dyyb	$1,089,000	$199,000	$194,000
Infliximab-abda	$1,138,000	$208,000	$203,000
Ustekinumab	$10,562,000	$1,157,000	$1,139,000
Vedolizumab	$5,249,000	$862,000	$842,000
Conventional Treatment	Reference	Reference	Reference

evLY: equal value of life years, LY: life year, QALY: quality-adjusted life year
Incremental cost-effectiveness ratios rounded to nearest $1,000 or $10,000, if over $1,000,000.

Table E4. Undiscounted Incremental Cost-Effectiveness Ratios for the Base Case Compared to Infliximab: Biologic-Naïve

Treatment	Cost per LY Gained	Cost per QALY Gained	Cost per evLY Gained
Adalimumab	Higher cost and fewer LYs	Higher cost and fewer QALYs	Higher cost and fewer evLYs
Golimumab	Higher cost and fewer LYs	Higher cost and fewer QALYs	Higher cost and fewer evLYs
Infliximab	Reference	Reference	Reference
Infliximab-dyyb	Lower cost and equal LYs	Lower cost and equal QALYs	Lower cost and equal evLYs
Infliximab-abda	Lower cost and equal LYs	Lower cost and equal QALYs	Lower cost and equal evLYs
Ustekinumab	Higher cost and fewer LYs	$2,930,000	$2,950,000
Vedolizumab	Higher cost and fewer LYs	Higher cost and fewer QALYs	Higher cost and fewer evLYs

evLY: equal value of life years, LY: life year, QALY: quality-adjusted life year
Incremental cost-effectiveness ratios rounded to nearest $1,000 or $10,000, if over $1,000,000.

Undiscounted Results, Biologic-Experienced Population

Table E5. Undiscounted Results for the Base-Case for TIMs and Conventional Treatment: Biologic-Experienced

Parameter	Initial TIM Drug Cost	Total Cost	LY	QALYs	evLYs
Adalimumab	$34,000	$742,000	38.863	27.142	27.149
Tofacitinib	$33,000	$739,000	38.876	27.184	27.192
Ustekinumab	$80,000	$786,000	38.876	27.188	27.197
Vedolizumab	$55,000	$761,000	38.870	27.183	27.190
Conventional Treatment	$300	$711,000	38.863	27.127	27.134

evLY: equal value of life years, LY: life year, N/A: not applicable, QALY: quality-adjusted life year, targeted immune modulator

Costs rounded to nearest $1,000.

Table E6. Undiscounted Incremental Cost-Effectiveness Ratios for the Base Case Compared to Conventional Treatment: Biologic-Experienced

Treatment	Cost per LY Gained	Cost per QALY Gained	Cost per evLY Gained
Adalimumab	$76,500,000	$2,104,000	$2,094,000
Tofacitinib	$2,224,000	$498,000	$482,000
Ustekinumab	$5,767,000	$1,225,000	$1,188,000
Vedolizumab	$7,110,000	$910,000	$893,000
Conventional Treatment	Reference	Reference	Reference

evLY: equal value of life years, LY: life year, QALY: quality-adjusted life year

Incremental cost-effectiveness ratios rounded to nearest $1,000.

Table E7. Undiscounted Incremental Cost-Effectiveness Ratios for the Base Case Compared to Adalimumab: Biologic-Experienced

Treatment	Cost per LY Gained	Cost per QALY Gained	Cost per evLY Gained
Adalimumab	Reference	Reference	Reference
Tofacitinib	Lower cost and greater LYs	Lower cost and greater QALYs	Lower cost and greater evLYs
Ustekinumab	$3,434,000	$937,000	$901,000
Vedolizumab	$2,807,000	$464,000	$453,000

evLY: equal value of life years, LY: life year, QALY: quality-adjusted life year

Incremental cost-effectiveness ratios rounded to nearest $1,000.

Table E8. League Table of Incremental Cost-Effectiveness Ratios for TIMs Against Conventional Treatment and Each Other, Biologic-Naïve Population

	Total Costs	Total QALYs	ICER
Conventional with Subsequent tx	$421,000	15.57	Reference
Adalimumab	$461,000	15.60	Dominated
Golimumab	$458,000	15.60	Dominated
Vedolizumab IV	$480,000	15.64	Dominated
Infliximab	$435,000	15.64	Dominated by extension
Infliximab-abda	$434,000	15.64	Dominated by extension
Infliximab-dyyb	$434,000	15.64	$186,000
Ustekinumab	$545,000	15.68	$3,010,000

ICER: incremental cost-effectiveness ratio, IV: intravenous, QALY: quality-adjusted life year, tx: treatment
Incremental cost-effectiveness ratios rounded to nearest $1,000 or $10,000, if over $1,000,000.

Table E9. League Table of Incremental Cost-Effectiveness Ratios for TIMs Against Conventional Treatment and Each Other, Biologic-Experienced Population

	Total Costs	Total QALYs	ICER
Conventional with Subsequent tx	$434,000	15.39	--
Adalimumab	$465,000	15.41	Dominated
Tofacitinib	$460,000	15.45	$495,000
Vedolizumab IV	$482,000	15.45	$35,130,000
Ustekinumab	$504,000	15.45	$10,660,000

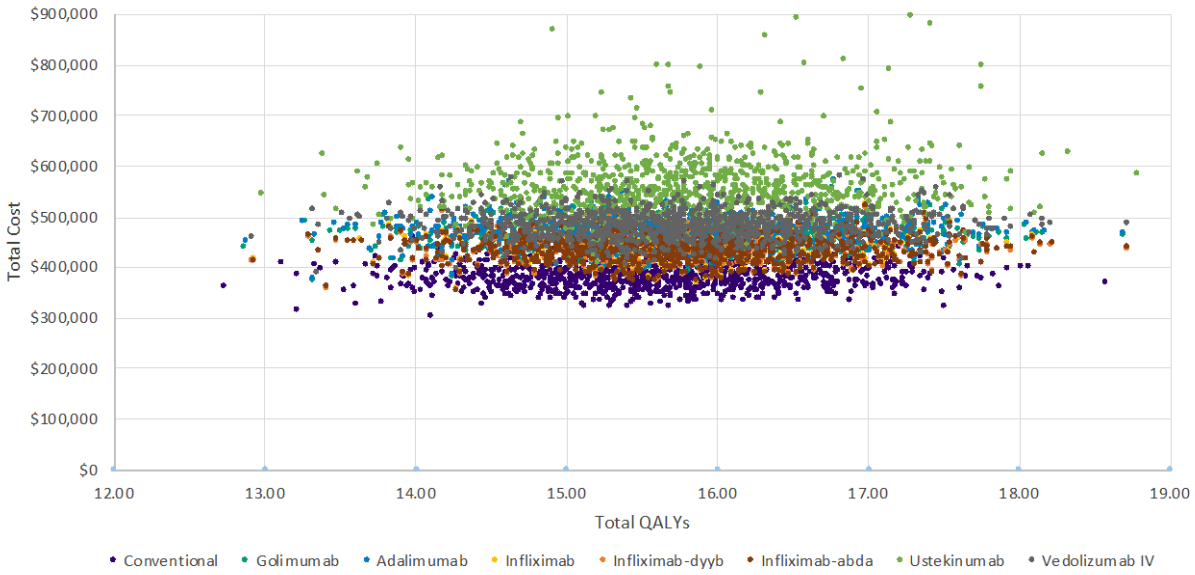
ICER: incremental cost-effectiveness ratio, IV: intravenous, QALY: quality-adjusted life year, tx: treatment

Table E10. Results of Probabilistic Sensitivity Analysis for TIMs versus Conventional Treatment: Biologic-Naïve

	TIM		Conventional Treatment		Incremental	
	Mean	95% Credible Range	Mean	95% Credible Range	Mean	95% Credible Range
Adalimumab						
Total Costs	$467,492	($418,174, $520,639)	$383,551	($338,041, $433,003)	$43,231	($34,129, $56,589)
Total QALYs	15.7	(14.1, 17.4)	15.6	(13.9, 17.3)	0.03	(0.00, 0.06)
ICER	--	--	--	--	$1,536,040	($918,951, $7,192,797)
Golimumab						
Total Costs	$462,452	($412,330, $517,893)	$383,551	($338,041, $433,003)	$38,191	($30,034, $48,979)
Total QALYs	15.7	(14.1, 17.4)	15.6	(13.9, 17.3)	0.03	(0.00, 0.06)
ICER	--	--	--	--	$1,375,614	($761,547, $8,322,842)
Infliximab						
Total Costs	$439,069	($391,499, $489,736)	$383,551	($338,041, $433,003)	$14,808	($11,395, $18,669)
Total QALYs	15.8	(14.1, 17.4)	15.6	(13.9, 17.3)	0.08	(0.03, 0.17)
ICER	--	--	--	--	$192,451	($111,199, $404,398)
Infliximab-dyyb						
Total Costs	$437,113	($389,159, $488,141)	$383,551	($338,041, $433,003)	$12,852	($9,717, $16,244)
Total QALYs	15.8	(14.1, 17.4)	15.6	(13.9, 17.3)	0.08	(0.03, 0.17)
ICER	--	--	--	--	$166,730	($98,353, $345,518)
Infliximab-abda						
Total Costs	$437,913	($390,243, $489,800)	$383,551	($338,041, $433,003)	$13,653	($10,410, $17,233)
Total QALYs	15.8	(14.1, 17.5)	15.6	(13.9, 17.3)	0.08	(0.03, 0.17)
ICER	--	--	--	--	$177,482	($103,715, $371,439)
Ustekinumab						
Total Costs	$562,291	($470,587, $707,054)	$383,551	($338,041, $433,003)	$138,030	($58,199, $281,954)
Total QALYs	15.8	(14.2, 17.5)	15.6	(13.9, 17.3)	0.13	(0.02, 0.35)
ICER	--	--	--	--	$1,093,362	($811,762, $2,414,141)
Vedolizumab						
Total Costs	$484,525	($431,282, $541,474)	$383,551	($338,041, $433,003)	$60,265	($45,732, $78,911)
Total QALYs	15.8	(14.1, 17.4)	15.6	(13.9, 17.3)	0.07	(0.02, 0.14)
ICER	--	--	--	--	$863,528	($579,730, $1,893,411)

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year, TIM: targeted immune modulator

Figure E9. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds: Biologic-Naïve



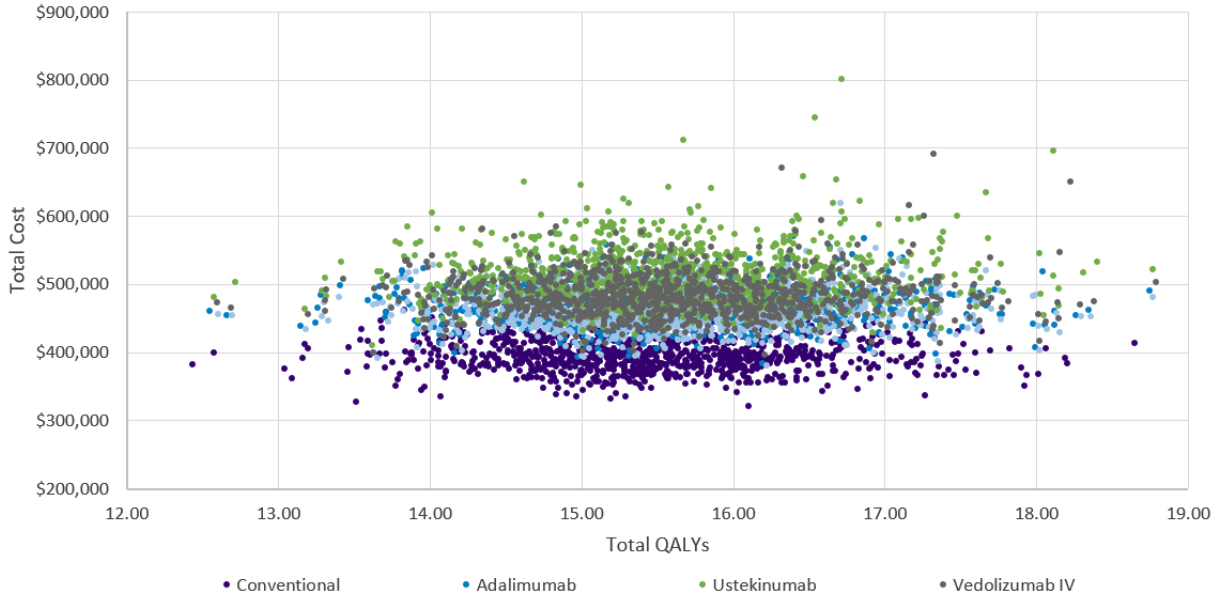
IV: intravenous, QALY: quality-adjusted life year

Table E11. Results of Probabilistic Sensitivity Analysis for TIMs versus Conventional Treatment: Biologic-Experienced

	TIM		Conventional Treatment		Incremental	
	Mean	95% Credible Range	Mean	95% Credible Range	Mean	95% Credible Range
Adalimumab						
Total Costs	$469,422	($416,569, $535,411)	$396,179	($351,693, $448,136)	$31,669	($22,189, $49,881)
Total QALYs	15.5	(13.9, 17.2)	15.4	(13.8, 17.0)	0.02	(0.00, 0.08)
ICER	--	--	--	--	$1,590,608	($643,519, -$11,824,398)
Tofacitinib						
Total Costs	$464,295	($412,153, $524,222)	$396,179	($351,693, $448,136)	$26,543	($17,516, $42,404)
Total QALYs	15.5	(14.0, 17.2)	15.4	(13.8, 17.0)	0.1	(0.02, 0.13)
ICER	--	--	--	--	$473,341	($338,730, $816,525)
Ustekinumab						
Total Costs	$522,911	($447,096, $611,399)	$396,179	($351,693, $448,136)	$85,159	($45,316, $147,519)
Total QALYs	15.6	(14.0, 17.2)	15.4	(13.8, 17.0)	0.08	(0.02, 0.16)
ICER	--	--	--	--	$1,135,016	($947,554, $1,956,180)
Vedolizumab						
Total Costs	$488,633	($431,764, $563,913)	$396,179	($351,693, $448,136)	$50,881	($34,891, $89,064)
Total QALYs	15.6	(14.0, 17.2)	15.4	(13.8, 17.0)	0.07	(0.02, 0.21)
ICER	--	--	--	--	$775,645	($421,194, $1,949,335)

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year, TIM: targeted immune modulator

Figure E10. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds: Biologic-Experienced



IV: intravenous, QALY: quality-adjusted life year

Table E12. Proportion of Patients in Each Health State at One, Five, and 10 Years: Biologic-Naïve

Adalimumab	Active UC	Response	Remission	Post-Colectomy	Dead
1 Year	35%	38%	26%	0%	0%
5 Years	76%	10%	9%	4%	1%
10 Years	76%	7%	5%	9%	3%
Golimumab	**Active UC**	**Response**	**Remission**	**Post-Colectomy**	**Dead**
1 Year	34%	38%	27%	0%	0%
5 Years	76%	10%	9%	4%	1%
10 Years	76%	7%	5%	9%	3%
Infliximab, Infliximab-dyyb, and Infliximab-dyyb	**Active UC**	**Response**	**Remission**	**Post-Colectomy**	**Dead**
1 Year	28%	36%	35%	0%	0%
5 Years	72%	11%	12%	3%	1%
10 Years	76%	7%	5%	9%	3%
Ustekinumab	**Active UC**	**Response**	**Remission**	**Post-Colectomy**	**Dead**
1 Year	27%	35%	38%	0%	0%
5 Years	68%	12%	16%	3%	1%
10 Years	75%	8%	6%	8%	3%
Vedolizumab	**Active UC**	**Response**	**Remission**	**Post-Colectomy**	**Dead**
1 Year	29%	36%	34%	0%	0%
5 Years	72%	11%	12%	3%	1%
10 Years	76%	7%	5%	9%	3%
Conventional Treatment	**Active UC**	**Response**	**Remission**	**Post-Colectomy**	**Dead**
1 Year	40%	39%	21%	0%	0%
5 Years	78%	9%	8%	4%	1%
10 Years	76%	7%	4%	10%	3%

UC: ulcerative colitis

Table E12. Proportion of Patients in Each Health State at One, Five, and 10 Years: Biologic-Experienced

Adalimumab	Active UC	Response	Remission	Post-Colectomy	Dead
1 Year	45%	36%	18%	0%	0%
5 Years	85%	5%	4%	5%	1%
10 Years	82%	3%	1%	11%	3%
Tofacitinib	**Active UC**	**Response**	**Remission**	**Post-Colectomy**	**Dead**
1 Year	37%	39%	23%	0%	0%
5 Years	83%	6%	5%	4%	1%
10 Years	83%	3%	1%	10%	3%
Ustekinumab	**Active UC**	**Response**	**Remission**	**Post-Colectomy**	**Dead**
1 Year	36%	40%	24%	0%	0%
5 Years	83%	6%	5%	4%	1%
10 Years	83%	3%	1%	10%	3%
Vedolizumab	**Active UC**	**Response**	**Remission**	**Post-Colectomy**	**Dead**
1 Year	39%	37%	23%	0%	0%
5 Years	82%	6%	6%	4%	1%
10 Years	82%	3%	1%	10%	3%
Conventional Treatment	**Active UC**	**Response**	**Remission**	**Post-Colectomy**	**Dead**
1 Year	49%	36%	15%	0%	0%
5 Years	86%	4%	3%	5%	1%
10 Years	82%	3%	1%	11%	3%

UC: ulcerative colitis

Appendix F. Network Meta-Analysis Supplemental Information

Network Meta-Analysis Methods

The comparative efficacy of the TIMs for patients living with moderate-to-severe UC was assessed by means of NMA, where feasible. Trials that were deemed sufficiently similar in terms of population, intervention type, duration, and outcome definitions were included in the NMAs.

NMAs focused on clinical response, clinical remission, and endoscopic improvement were conducted. Given the expected differences in the clinical efficacy of treatment in patients with and without prior biologic exposure, separate networks were developed for biologic-naïve and biologic-experienced populations. Clinical response and remission were analyzed as ordered categorical outcomes ("no response," "response without remission," and "remission") with a multinomial likelihood and a probit link. Endoscopic improvement was analyzed as a dichotomous outcome ("yes" or "no") with a binomial likelihood and log link.

Outcomes were analyzed separately for the induction phase (six to 14 weeks) and maintenance phase (52-60 weeks). All efficacy outcomes were analyzed in the induction phase (six to 14 weeks). In addition, clinical response and remission were analyzed in the maintenance phase (52-60 weeks). Trials included in the maintenance NMAs had a maintenance phase of at least 52 weeks. Therefore, some trials with a shorter maintenance phase (ACT 2, Jiang 2015, and Kobayashi 2016) were excluded from the maintenance evidence network. Endoscopic improvement was analyzed only during the induction phase due to limited data availability and trial design differences.

The evidence base for the maintenance phase in the included trials is a combination of "treat-through" designs, where patients were randomized only at baseline and followed through until the end of maintenance, and "re-randomized" designs, where responders to treatment from one or two induction trials were re-randomized in the maintenance phase. In order to analyze all trials in comparable fashion in one network, results from treat-through trials were adjusted to more closely resemble results from re-randomized trials. Three maintenance trials included in the NMAs had a "treat-through" study design (ACT 1, ULTRA 2, and VARSITY);[8,90,93] of note, another one of the available trials also had a treat-through design (Suzuki 2014), but was not included in the maintenance NMA due to lack of data. Six maintenance trials had a "re-randomized" study design (PURSUIT-M, GEMINI 1, Motoya 2019, VISIBLE 1, OCTAVE SUSTAIN, and UNIFI);[9,77,92,94,99] of note, another available trial also had a re-randomized design (PURSUIT-J), but was not included in the maintenance NMA due to a lack of data.

Data were available for all TIMs (adalimumab, golimumab, infliximab, tofacitinib, ustekinumab, and vedolizumab) in the biologic-naïve population. We note, however, that use of tofacitinib is no longer feasible in a biologic-naïve population, based on an FDA-enforced label change (July 2019) that now requires that tofacitinib use be reserved for "…patients who have failed or do not tolerate tumor necrosis factor (TNF) blockers."[65] Based on this information, tofacitinib was not included in the NMAs for induction or maintenance within the biologic-naïve population. Data were available for adalimumab, tofacitinib, ustekinumab, and vedolizumab in the biologic-experienced population; data were not available for infliximab or golimumab, so we were unable to generate comparative efficacy estimates for these drugs.

Both random- and fixed-effects models were explored. We used fixed-effects models given the limited data available for each network. In addition, we explored adjusting for baseline risk given the differences in placebo response rates across trials.

The population of focus for this review included patients with moderate-to-severe UC who had inadequate response to conventional treatment. Despite this relatively narrow definition, trial populations may differ in terms of prior conventional therapies used, other demographic or clinical risk factors, timing of trial assessments, and other concerns. Adjusting for placebo response in an NMA design is frequently performed as means of controlling for differences in population characteristics and baseline risk; we considered placebo adjustment in situations where a) model fit and convergence was not compromised; and b) inclusion of such an adjustment materially changed model findings.

We attempted placebo adjustment for all four populations of interest in our NMAs. Material changes in findings were observed in both maintenance populations (i.e., biologic-naïve and biologic-experienced populations). However, results were highly unstable in the biologic-experienced maintenance NMA, regardless of the number of iterations attempted, in all likelihood due to the sparsity of the available network. We therefore included a placebo adjustment only in the maintenance NMA for the biologic-naïve population.

Table F1 lists the NMAs we conducted and the details of the model, and Table F2 lists the trials included in our NMAs as well as reasons for exclusion of trials. Finally, while different doses of some of the TIMs were studied in available trials, we found no statistically significant differences in rates of response or remission between doses in any relevant trial, so these data were pooled at the drug level for our NMAs. We conducted inconsistency tests for each of the NMA populations using the node-splitting approach. We found no statistical differences between direct and indirect estimates in any of our populations of interest (comparing indirect and direct evidence for vedolizumab and adalimumab: induction biologic-naive, p=0.67; induction biologic-experienced, p=0.08; maintenance biologic-naive, p=0.63 maintenance biologic-experienced, p=0.59).

All NMAs were conducted in a Bayesian framework in R. NMAs on clinical response and remission were conducted with JAGS using the R2jags package.[67] For our NMAs on clinical response and remission, we based out analysis on existing code.[176] NMAs on endoscopic improvement were conducted using the gemtc package.[66]

Table F1. NMAs Conducted to Inform Comparative Efficacy of TIMs

	Population	Model	Number of Trials
Induction Outcomes			
Clinical Response and Remission	a) Biologic-naïve b) Biologic-experienced	Multinomial with probit link	a) 12 b) 7
Endoscopic Improvement	a) Biologic-naïve b) Biologic-experienced	Binomial with log link	a) 11 b) 6
Maintenance Outcomes			
Clinical Response and Remission	a) Biologic-naïve b) Biologic-experienced	Multinomial with probit link	a) 8 b) 7

Table F2. Trials Included in NMAs Conducted to Inform Comparative Efficacy of TIMs

Trial	Induction NMAs				Maintenance NMAs	
	Response and Remission		Endoscopic Improvement		Response and Remission	
	Naïve	Experienced	Naïve	Experienced	Naïve	Experienced
VARSITY	✓	✓	X	X	✓	✓
ULTRA 1	✓	—	✓	—	—	—
ULTRA 2	✓	✓	✓	✓	✓	✓
Suzuki 2014	✓	—	✓	—	X	—
PURSUIT-SC	✓	—	✓	—	—	—
PURSUIT-M	—	—	—	—	✓	—
PURSUIT-J	—	—	—	—	X	—
ACT 1	✓	—	✓	—	✓	—
ACT 2	✓	—	✓	—	X	—
Kobayashi 2016	✓	—	✓	—	X	—
Jiang 2015	✓	—	✓	—	X	—
NCT01551290	X	—	X	—	X	—
OCTAVE 1	X	✓	X	✓	—	—
OCTAVE 2	X	✓	X	✓	—	—
OCTAVE SUSTAIN	—	—	—	—	X	✓
UNIFI	✓	✓	✓	✓	✓	✓
GEMINI 1	✓	✓	✓	✓	✓	✓
Motoya 2019	✓	✓	✓	✓	✓	✓
VISIBLE 1	—	—	—	—	✓	✓

NMA: network meta-analysis

In the table above, a check ("✓") indicates the trial was included in the specified NMA, while a cross mark ("X") indicates the trial was excluded from the NMA. A dash ("—") indicates that the trial was not designed to provide data for the specified NMA (i.e., the trial only included biologic-naïve patients [all infliximab and golimumab trials, ULTRA 1, and Suzuki 2014], or the trial included only a randomized induction phase [ULTRA 1, PURSUIT-SC, OCTAVE 1 & 2] or only a randomized maintenance phase [PURSUIT-M, PURSUIT-J, OCTAVE SUSTAIN, VISIBLE 1]). Below are the following reasons we excluded trials from our NMAs.

- VARSITY was excluded from the endoscopic improvement NMAs as data stratified by biologic exposure was not available.
- Suzuki 2014 and PURSUIT-J were excluded from the response and remission maintenance NMA due to a lack of data to achieve outcomes comparable to those in the other trials included in the network (more detailed provided in 'Inputs used in NMAs of Maintenance Outcomes').
- ACT 2, Kobayashi 2016, and Jiang 2015 were excluded from response and remission maintenance NMA as their maintenance phase was <52 weeks (as mentioned earlier).
- NCT01551290 was excluded from the NMAs as it was available only in grey literature.
- OCTAVE 1, 2, and SUSTAIN were excluded from the biologic-naïve NMAs due to tofacitinib's FDA-enforced label change.

Network Meta-Analysis Inputs

Inputs Used in Network Meta-Analyses of Induction Outcomes

Table F3. Inputs Used in NMA of Response and Remission in the Induction Phase, Biologic-Naïve

Trial	Wk	Arm*	Response			Remission		
			n	N	%	n	N	%
ACT 1	8	IFX 5 mg/kg	84	121	69.4	47	121	38.8
		IFX 10 mg/kg	75	122	61.5	39	122	32.0
		IFX pooled	159	243	65.4	86	243	35.4
		PBO	45	121	37.2	18	121	14.9
ACT 2	8	IFX 5 mg/kg	78	121	64.5	41	121	33.9
		IFX 10 mg/kg	83	120	69.2	33	120	27.5
		IFX pooled	161	241	66.8	74	241	30.7
		PBO	36	123	29.3	7	123	5.7
Jiang 2015	8	IFX 5 mg/kg	32	41	78.1	22	41	53.7
		PBO	15	41	36.6	9	41	21.9
Kobayashi 2016	8	IFX 5 mg/kg	57	104	54.8	21	104	20.2
		PBO	37	104	35.6	11	104	10.6
ULTRA 1	8	ADA 160/80 mg	71	130	54.6	24	130	18.5
		PBO	58	130	44.6	12	130	9.2
ULTRA 2	8	ADA 160/80 mg	89	150	59.3	32	150	21.3
		PBO	56	145	38.6	16	145	11.0
Suzuki 2014	8	ADA 160/80 mg	45	90	50.0	9	90	10.0
		PBO	34	96	35.4	11	96	11.5
PURSUIT-SC (Phase II & III Pooled)	6	GOL 200/100 mg	147	294	50.0	52	294	17.7
		GOL 400/200 mg	163	298	54.7	56	298	18.8
		GOL pooled	310	592	52.4	108	592	18.2
		PBO	89	292	30.5	20	292	6.8
GEMINI I	6	VEDO 300 mg	69	130	53.1	30	130	23.1
		PBO	20	76	26.3	5	76	6.6
Motoya 2019	10	VEDO 300 mg	42	79	53.2	22	79	27.8
		PBO	15	41	36.6	6	41	14.6
VARSITY	14	VEDO 300 mg	213	304	70.1	84	304	27.6
		ADA 160/80 mg	151	305	49.5	72	305	23.6
UNIFI	8	UST 6 mg/kg	104	156	66.7	29	156	18.6
		PBO	56	158	35.4	15	158	9.5

ADA: adalimumab, GOL: golimumab, IFX: infliximab, kg: kilogram, mg: milligram, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab, Wk: week

*Pooled doses used in primary NMA. Unpooled doses used in sensitivity analysis.

Table F4. Inputs Used in NMA of Response and Remission in the Induction Phase, Biologic-Experienced

Trial	Wk	Arm*	Response			Remission		
			n	N	%	n	N	%
ULTRA 2	8	ADA 160/80 mg	36	98	36.7	9	98	9.2
		PBO	29	101	28.7	7	101	6.9
GEMINI 1	6	VEDO 300 mg	32	82	39	8	82	9.8
		PBO	13	63	20.6	2	63	3.2
Motoya 2019	10	VEDO 300 mg	23	85	27.1	8	85	9.4
		PBO	12	41	29.3	4	41	9.8
VARSITY	14	VEDO 300 mg	44	79	55.7	18	79	22.8
		ADA 160/80 mg	26	81	32.1	10	81	12.3
OCTAVE 1 and 2 (Pooled)	8	TOF 10 mg	237	465	51.0	53	465	11.4
		PBO	29	124	23.4	1	124	0.8
UNIFI	8	UST 6 mg/kg	95	166	57.2	21	166	12.7
		PBO	44	161	27.3	2	161	1.2

ADA: adalimumab, kg: kilogram, mg: milligram, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab, Wk: week

Table F5. Inputs Used in NMA of Endoscopic Improvement in the Induction Phase, Biologic-Naïve and Biologic-Experienced

Trial	Wk	Arm	Biologic-Naïve			Biologic-Experienced		
			n	N	%	n	N	%
ACT 1	8	IFX pooled	147	243	60	*Not studied in biologic-experienced population*		
		PBO	41	121	34			
ACT 2	8	IFX pooled	147	241	61			
		PBO	38	123	31			
Jiang 2015	8	IFX pooled	24	41	59			
		PBO	10	41	24			
Kobayashi 2016	8	IFX pooled	48	104	46			
		PBO	29	104	28			
ULTRA 1	8	ADA 160 mg	61	130	47			
		PBO	54	130	42			
ULTRA 2	8	ADA 160 mg	74	150	49	28	98	28.6
		PBO	51	145	35	27	101	26.7
Suzuki 2014	8	ADA 160 mg	40	90	44	*Not studied in biologic-experienced population*		
		PBO	29	96	30			
GEMINI 1	6	VEDO 300 mg	64	130	49	25	82	30.5
		PBO	19	76	25	13	63	20.6
PURSUIT-SC (Phase II & III Pooled)	6	GOL pooled	256	592	43	*Not studied in biologic-experienced population*		
		PBO	82	292	28			
Motoya 2019	10	VEDO 300 mg	38	79	48	22	85	25.8
		PBO	13	41	32	12	41	29.2
UNIFI	8	UST 6 mg/kg	52	156	33	35	166	21.1
		PBO	33	158	21	11	161	6.8
OCTAVE 1 & 2 (Pooled)	8	TOF 10 mg	*Data not included in biologic-naive population*			112	488	22.9
		PBO				8	130	6.2

ADA: adalimumab, GOL: golimumab, IFX: infliximab, kg: kilogram, mg: milligram, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab, Wk: week

Inputs Used in Network Meta-Analyses of Maintenance Outcomes

In the section that follows, we describe the inputs used in our NMAs of response and remission in the maintenance phase. Throughout our review, we describe results for the key outcomes in the biologic-naïve and biologic-experienced populations as reported in the published trials (i.e., measures designated as primary and key secondary outcomes for the overall population). As discussed earlier, we adjusted the rates from the treat-through trials to more closely resemble results from re-randomized trials to enable comparisons in our NMA. Additionally, for some re-randomized trials, we preferred manufacturer-submitted inputs or other published secondary outcomes over published and key secondary outcomes as they provided us with more comparable

outcomes for our NMA (e.g., response *at* end of maintenance vs. response *through* the end of maintenance). The data inputs used in our response and remission maintenance NMA are provided in Table F6.

Adjusted Rates from Treat-Through Trials

As noted earlier, we adjusted the rates from the treat-through trials to more closely resemble results from re-randomized trials to enable comparisons in our NMA. Specifically, we adjusted rates from treat-through trials to reflect maintenance outcomes among induction responders. Responders to induction treatment (week six to 14) in the treat-through trials were assumed to enter the maintenance phase. The assumed denominator for the treat-through trials was the number of responders at the end of the induction phase. The numerator for clinical response was the number of sustained responders (i.e., having response at both beginning of induction and end of maintenance). The numerator for remission was the number of patients with remission at the end of maintenance among induction responders. To assist in these calculations, we have received adjusted rates from treat-through trials primarily from manufacturer data submissions. Trial specific adjustments included:

- VARSITY: Rate of response at week 52 among week-six responders (based on partial Mayo Score) submitted by manufacturer
- ULTRA 2**:** Rate of response at maintenance week 52 among week-eight responders reported in trial; rate of remission at week 52 among week-eight responders reported in conference abstract[102]
- ACT 1: Rate of response and remission at week 54 among eight-week responders submitted by manufacturer

Of note, in Suzuki 2014, the rate of response and remission among induction responders was available for the treatment (adalimumab) arm only; consequently, the lack of comparator arm data did not allow for inclusion in the maintenance NMA.

Alternative Endpoints Used for Re-Randomized Trials

For some re-randomized trials, we preferred manufacturer-submitted inputs or other published secondary outcomes over key outcomes as they provided us with more comparable outcomes for our NMA. Specifically, while many trials measured the rates of response *at* the end of maintenance, some trials used stricter criteria and measured the rates of response *through* the end of maintenance (PURSUIT-M, PURSUIT-J, and UNIFI). In addition, while most trials re-randomized patients who initially responded to six to ten-week induction treatment with the active agent, one trial also re-randomized patients who responded to placebo (OCTAVE SUSTAIN), and another trial re-randomized patients who did not respond to placebo but subsequently responded to the active agent after another eight weeks (UNIFI). Given the variation, we used manufacturer-submitted

inputs or other published secondary outcomes if they provided us with more comparable outcomes, where feasible. Below, we provide details for each trial.

PURSUIT-M

PURSUIT-M and PURSUIT-J measured the rates of maintaining response *through* the end of maintenance rather than measuring response *at* the end of maintenance. For PURSUIT-M, we included the rates of remission *at* the end of maintenance (i.e., *at* week 54) in our NMA. However, for PURSUIT-J, only the rate of remission at *both* weeks 30 and 54 was reported; therefore, we did not include PURSUIT-J in our analysis.

OCTAVE SUSTAIN

OCTAVE SUSTAIN re-randomized both tofacitinib- and placebo-induction responders in the maintenance phase. However, all other re-randomized trials included in our review re-randomized responders to the active agent only. Therefore, we included results from the modified full analysis set (mFAS) that only included tofacitinib induction responders in NMA. We obtained the rates of remission at week 52 in the mFAS from a conference abstract that reported the rates of remission among baseline remitters and baseline responders in the mFAS;[85] in order to obtain the rates among all responders (both remitters and responders without remission), we added the reported rates. The rates of response were not available from the mFAS.

UNFI

UNIFI measured the rate of response *through* the end of maintenance rather than measuring response *at* the end of maintenance. We received the rates of response at week 52 from manufacturer submissions. In addition, UNIFI re-randomized patients that did not respond to induction therapy with placebo but then responded to induction therapy with ustekinumab. Since no other trial re-randomized patients following a similar path, we used rates from analyses submitted by the manufacturer that excluded these patients.

VISIBLE 1

For VISIBLE 1, the rates of response at week 52 were submitted by the manufacturer.

Table F6. Inputs Used in the NMA of Response and Remission in Maintenance Phase*

Trial	Week	Arm*	Maintenance Outcomes Among Induction Responders											
			Biologic-Naïve						Biologic-Experienced					
			Response			Remission			Response			Remission		
			n	N	%	n	N	%	n	N	%	n	N	%
Treat-Through Trials														
VARSITY[1]	52	VEDO 300 mg q8w				NR						NR		
		ADA 40 mg												
ULTRA 2[2]	52	ADA 40 mg	44	89	49.4	34	89	38.2	15	36	41.7	10	36	27.8
		PBO	24	56	42.9	15	56	26.8	6	29	20.7	2	29	6.9
ACT 1[3]	54	IFX 5 mg/kg							N/A					
		IFX 10 mg/kg												
		IFX pooled												
		PBO												
Re-Randomized Trials														
PURSUIT-M[4]	54	GOL 100 mg	NR			51	151	33.8	N/A					
		PBO				34	154	22.1						
OCTAVE SUSTAIN[5]	52	TOF 5 mg	N/A						NR			16	76	21.1
		TOF 10 mg										28	78	35.9
		TOF pooled										44	154	28.6
		PBO										9	80	11.3
UNIFI[6]	52	UST 90 mg q8w												
		PBO												
GEMINI 1	52	VEDO 300 mg q4w	41	73	56.2	35	73	47.9	17	40	42.5	14	40	35
		VEDO 300 mg q8w	47	72	65.3	33	72	45.8	20	43	46.5	16	43	37.2
		VEDO pooled	88	145	60.7	68	145	46.9	37	83	44.6	30	83	36.1
		PBO	21	79	26.6	15	79	19.0	6	38	15.8	2	38	5.3
Motoya 2019	60	VEDO 300 mg q8w	16	24	66.7	13	24	54.2	11	17	64.7	10	17	58.8
		PBO	10	28	35.7	10	28	35.7	5	14	35.7	3	14	21.4
VISIBLE 1[7]	52	VEDO 300 mg q8w				17	32	53.1				6	22	27.3
		PBO				7	37	18.9				1	19	5.3

ADA: adalimumab, GOL: golimumab, IFX: infliximab, kg: kilogram, mg: milligram, NR: not reported, N/A: not applicable, PBO: placebo, q8w: every 4 weeks, q8w: every 8 weeks, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

*Pooled doses used in primary NMA. Unpooled doses used in sensitivity analysis.

1 VARSITY: Rate of response at week 52 among week-six responders (based on partial Mayo Score) submitted by manufacturer.

2 ULTRA 2: Rate of response at week 52 among week-eight responders reported in trial; rate of remission at week 52 among week-eight responders reported in conference abstract.

3 ACT 1: Rate of response and remission at week 54 among eight-week responders submitted by manufacturer.

4 PURSUIT-M: Rate of remission at week 54 was reported in trial.

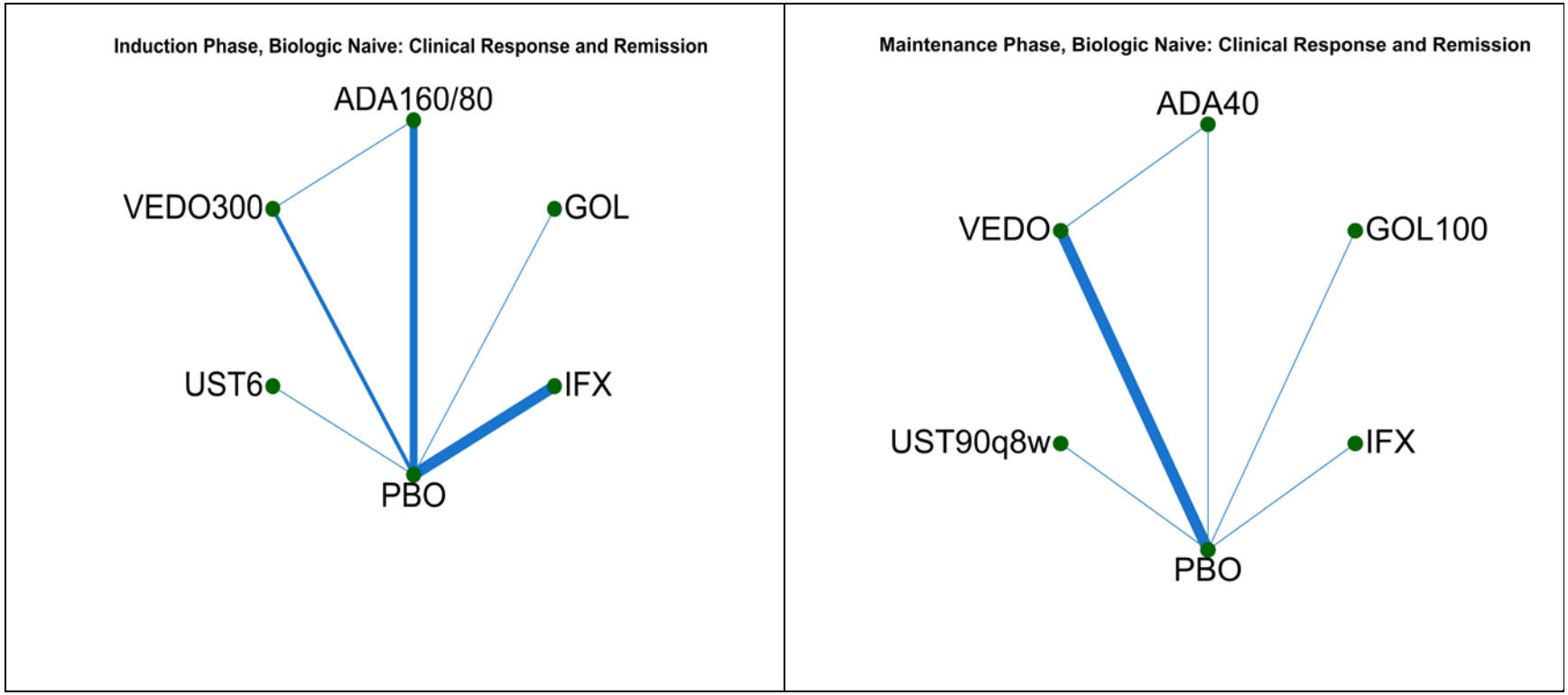
5 OCTAVE SUSTAIN: Rate of remission in the modified full analysis set obtained from conference abstract.

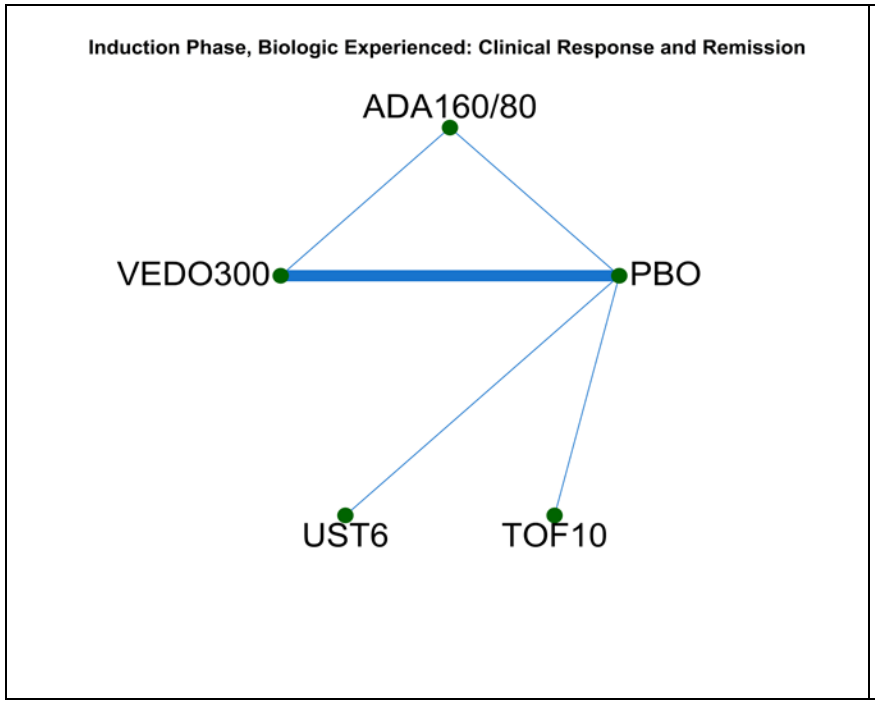
6 UNIFI: Rate of response and remission at maintenance week 52 among patients who initially responded to ustekinumab were submitted by the manufacturer.

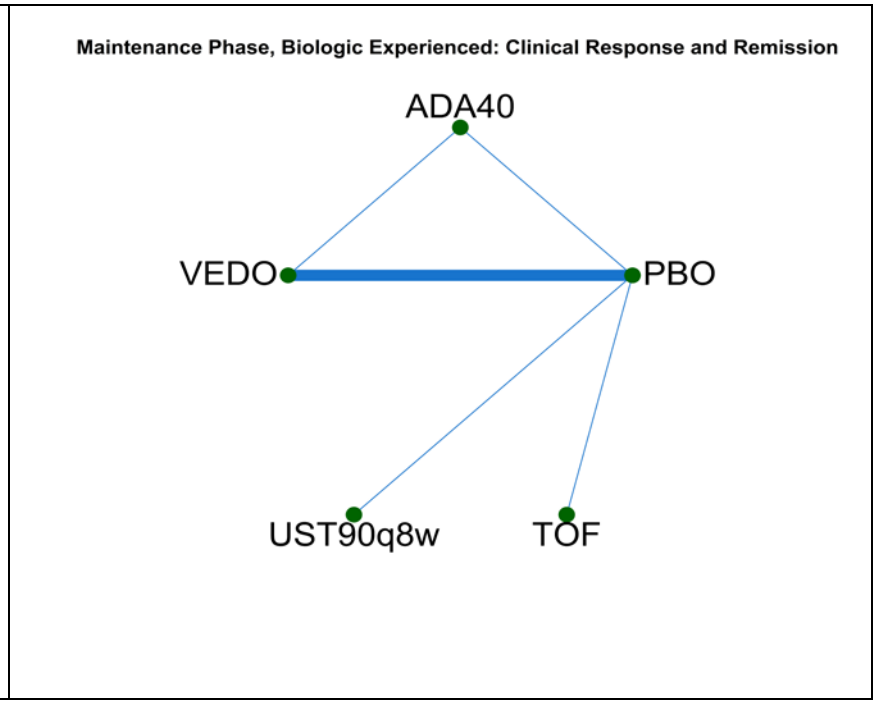
7 VISIBLE 1: Rate of response submitted by the manufacturer.

Supplemental Network Meta-Analysis Results

Network Diagrams for the Primary Network Meta-Analyses




Induction Phase, Biologic Experienced: Clinical Response and Remission
ADA160/80
VEDO300
PBO
UST6
TOF10


Maintenance Phase, Biologic Experienced: Clinical Response and Remission
ADA40
VEDO
PBO
UST90q8w
TOF

Sensitivity Analyses

Unpooled Doses

We conducted a sensitivity analysis using unpooled doses. Results were generally consistent with the primary analysis results, with the exception of results for tofacitinib in the maintenance biologic-experienced NMA. Results from the sensitivity analysis showed tofacitinib 10 mg had statistically higher rates of response and remission compared to placebo, but tofacitinib 5 mg did not differ from placebo. When the doses were pooled in the primary analysis, tofacitinib had statistically higher rates of response and remission compared to placebo.

Table F7. Sensitivity Analysis Using Unpooled Doses, Induction Biologic-Naïve: Risk Ratios versus Placebo

Treatment	Response	Response without Remission	Remission
PBO	--	--	--
VEDO 300	1.76 (1.54, 2)	1.37 (1.23, 1.54)	2.8 (2.18, 3.56)
IFX 5	1.9 (1.68, 2.17)	1.39 (1.22, 1.6)	3.3 (2.64, 4.13)
IFX 10	1.83 (1.58, 2.11)	1.38 (1.22, 1.58)	3.04 (2.32, 3.94)
ADA 160/80	1.38 (1.21, 1.57)	1.24 (1.14, 1.36)	1.75 (1.38, 2.21)
GOL 200/100	1.58 (1.36, 1.84)	1.32 (1.2, 1.48)	2.28 (1.7, 2.99)
GOL 400/200	1.68 (1.46, 1.94)	1.35 (1.22, 1.52)	2.55 (1.97, 3.31)
UST 6	1.71 (1.43, 2.04)	1.36 (1.21, 1.54)	2.65 (1.88, 3.68)

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab

Table F8. Sensitivity Analysis Using Unpooled Doses, Maintenance Biologic-Naïve: Risk Ratios versus Placebo

	Response	Response without Remission	Remission
PBO	---	---	---
VEDO 300 q8w	1.7 (1.25, 2.12)	1.1 (0.93, 1.23)	2.04 (1.35, 2.77)
VEDO 300 q4w	1.58 (1.04, 2.07)	1.1 (0.9, 1.24)	1.84 (1.05, 2.68)
IFX 5	1.56 (1.03, 2.27)	1.1 (0.86, 1.22)	1.8 (1.04, 3.08)
IFX 10	1.67 (1.14, 2.35)	1.09 (0.82, 1.22)	1.99 (1.2, 3.25)
ADA 40	1.39 (0.98, 1.81)	1.11 (0.98, 1.23)	1.54 (0.98, 2.2)
GOL 100	1.28 (0.83, 1.74)	1.09 (0.89, 1.22)	1.38 (0.79, 2.09)
UST 90 q8w	1.78 (1.24, 2.49)	1.06 (0.69, 1.21)	2.18 (1.32, 3.56)

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, q4w: every 4 weeks, q8w: every 8 weeks, UST: ustekinumab, VEDO: vedolizumab

Table F9. Sensitivity Analysis Using Unpooled Doses, Maintenance Biologic-Experienced: Risk Ratios versus Placebo

Treatment	Response	Response without Remission	Remission
PBO	---	---	---
VEDO 300 q8w	2.5 (1.91, 3.17)	1.49 (1.21, 1.78)	3.64 (2.45, 5.21)
VEDO 300 q4w	2.39 (1.58, 3.25)	1.47 (1.18, 1.76)	3.37 (1.85, 5.45)
ADA 40	2.2 (1.48, 2.98)	1.47 (1.21, 1.74)	3 (1.69, 4.75)
TOF 10	2.27 (1.57, 3.05)	1.47 (1.24, 1.76)	3.14 (1.84, 4.86)
TOF 5	1.57 (0.9, 2.38)	1.32 (0.93, 1.61)	1.84 (0.88, 3.35)
UST 90 q8w	1.95 (1.44, 2.59)	1.44 (1.23, 1.69)	2.51 (1.65, 3.76)

ADA: adalimumab, GOL: golimumab, PBO: placebo, q4w: every 4 weeks, q8w: every 8 weeks, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Multinational Trials Only

We conducted another sensitivity analysis assessing multinational trials separately by excluding trials conducted exclusively in Asian populations (Suzuki 2014, Jiang 2015, Kobayashi 2016, and Motoya 2019). We were unable to conduct this sensitivity analysis for our maintenance biologic-naïve NMA as removal of Motoya 2019 led to a sparser network and the results from the model with placebo adjustment were unstable. We noted that risk ratios were higher when removing the Asian studies, with the largest effect on risk ratios observed for vedolizumab in the induction biologic-experienced NMA.

Table F10. Sensitivity Analysis with Multinational Trials Only, Induction Biologic-Naïve: Risk Ratios versus Placebo

Treatment	Response	Response without Remission	Remission
PBO	--	--	--
VEDO 300	1.84 (1.59, 2.13)	1.4 (1.24, 1.6)	3.1 (2.33, 4.03)
IFX Pooled	1.96 (1.72, 2.25)	1.41 (1.23, 1.63)	3.54 (2.77, 4.52)
ADA 160/80	1.44 (1.24, 1.66)	1.27 (1.16, 1.42)	1.91 (1.47, 2.46)
GOL Pooled	1.64 (1.42, 1.88)	1.35 (1.23, 1.52)	2.43 (1.89, 3.12)
UST 6	1.73 (1.43, 2.07)	1.37 (1.23, 1.57)	2.71 (1.89, 3.79)

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, UST: ustekinumab, VEDO: vedolizumab

Table F11. Sensitivity Analysis with Multinational Trials Only, Induction Biologic-Experienced: Risk Ratios versus Placebo

Treatment	Response	Response without Remission	Remission
PBO	--	--	--
VEDO Pooled	1.99 (1.46, 2.56)	1.72 (1.37, 2.09)	3.66 (2.01, 6.21)
ADA 160/80	1.2 (0.84, 1.64)	1.17 (0.85, 1.51)	1.38 (0.74, 2.46)
TOF 10	2.16 (1.74, 2.67)	1.81 (1.53, 2.17)	4.35 (2.79, 6.63)
UST 6	2.17 (1.75, 2.68)	1.82 (1.54, 2.16)	4.42 (2.83, 6.73)

ADA: adalimumab, PBO: placebo, TOF: tofacitinib, UST: ustekinumab, VEDO: vedolizumab

Table F12. Sensitivity Analysis with Multinational Trials Only, Maintenance Biologic-Experienced: Risk Ratios versus Placebo

Treatment	Response	Response without Remission	Remission
PBO	---	---	---
VEDO Pooled	2.56 (1.92, 3.29)	1.55 (1.26, 1.87)	3.86 (2.48, 5.76)
ADA 40	2.25 (1.49, 3.09)	1.52 (1.26, 1.82)	3.16 (1.73, 5.12)
TOF	1.97 (1.34, 2.73)	1.48 (1.22, 1.76)	2.6 (1.49, 4.24)
UST 90 q8w	2 (1.4, 2.73)	1.49 (1.24, 1.77)	2.66 (1.59, 4.18)

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, q8w: every 8 weeks, UST: ustekinumab, VEDO: vedolizumab

Additional Analyses

As noted earlier, we included placebo adjustment in the maintenance biologic-naïve NMA. Below, we provide results without placebo adjustment, as previously reported as our primary analysis in our Draft Evidence Report.

Table F13. Sensitivity Analysis without Placebo Adjustment, Maintenance Biologic-Naïve: Risk Ratios versus Placebo

Treatment	Response	Response without Remission	Remission
PBO	---	---	---
VEDO Pooled	1.76 (1.52, 2.02)	1.05 (0.87, 1.2)	2.14 (1.74, 2.58)
IFX Pooled	1.46 (1.06, 1.87)	1.09 (0.96, 1.2)	1.66 (1.08, 2.31)
ADA 40	1.43 (1.15, 1.71)	1.1 (1.01, 1.19)	1.6 (1.2, 2.04)
GOL 100	1.35 (1.05, 1.65)	1.09 (1, 1.18)	1.48 (1.07, 1.97)
UST 90 q8w	1.58 (1.16, 1.98)	1.08 (0.91, 1.2)	1.84 (1.21, 2.52)

ADA: adalimumab, GOL: golimumab, IFX: infliximab, PBO: placebo, q8w: every 8 weeks, UST: ustekinumab, VEDO: vedolizumab

Network Meta-Analysis Code

Model (Fixed Effects)

```
model <- function() { # *** PROGRAM STARTS
 for(i in 1:ns){ # LOOP THROUGH STUDIES
  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(eff>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
    z.index[i,j,k]<- C[i,(j+1)]-1 # index the cut point
    theta[i,k,j] <- mu[i] + d[t[i,k]] - d[t[i,1]] + z[z.index[i,j,k]] # 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)]) )
   }
  }
  resdev[i] <- sum(dev[i,(1:na[i])]) # summed residual deviance contribution for this trial
 }
 z[1] <- 0 # set zRs=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)
 for (k in 1:nt) {
  # calculate prob of achieving  >=2, >=3 on treat k
  for (j in 1: (Cmax-1)) { T[j,k] <- 1 - phi(A + d[k] + z[j])}
  # calculate prob of achieving ranges [1,2), [2,3), [3, Inf) on treat k
  T1[k] <- phi(A + d[k] + z[1])
  T2[k] <- phi(A + d[k] + z[2])-T1[k]
  T3[k] <- 1-phi(A + d[k] + z[2])
 }

 # calculate risk ratios
 for (k in 1:(nt-1)){
  for (kk in (k+1):nt){
   rr1[kk,k] <- T[1,kk]/T[1,k]
   rr2[kk,k] <- T[2,kk]/T[2,k]
   rr1_exc[kk,k] <- T2[kk]/T2[k]

   rr1[k,kk] <- T[1,k]/T[1,kk]
   rr2[k,kk] <- T[2,k]/T[2,kk]
   rr1_exc[k,kk] <- T2[k]/T2[kk]

  }
 }
}
```

Analysis

```
NMAresults <- jags(data=datalist, inits=jaginits, parameters.to.save = c("d", "z", "T1", "T2", "T3",
"rr1", "rr2", "rr1_exc"), model.file = model, n.iter = 100000)
```

Appendix G. Public Comments

This section includes summaries of the public comments prepared for the CTAF Public Meeting on September 24. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Three speakers did not submit summaries of their public comments.

A video recording of all comments can be found here. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Maria T. Abreu, MD, University of Miami Miller School of Medicine
Professor of Medicine

Thank you for the opportunity to provide my comments during the California Technology Assessment Forum (CTAF) meeting on September 24, 2020 regarding the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report assessing the comparative clinical effectiveness and value of treatments for ulcerative colitis (UC).

The AGA urges CTAF to consider the unique needs of UC patients and the nature of the disease when making decisions regarding coverage and treatment. Because each patient responds differently to UC treatments, it is important that physicians can tailor the best treatment for each patient. Like many other experts who delivered comments, we urge CTAF not to incorporate step therapy treatment into its model. There is no evidence that step therapy improves health outcomes and it is not supported by guidelines from AGA, ACG, or ASGE.

We would like to comment on the Long-Term Cost Effectiveness section of the report. Although we respect the financial analysis performed and accept the data as presented, we question the use of discounted drug prices as shown in the Drug Acquisition Costs section on page 79. The report states: "For all TIMs, we obtained net pricing estimates from SSR Health, LLC, which combines data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributor, and patient assistance programs to derive a net price."

As shown in Table 5.16, Drug Unit Costs of the report, discounts from WAC range from 18.3% to 62%. The significant range of discounts significantly favors the use of infliximab against use of all of its competitors. Furthermore, since these discounts are not transparent to either the provider space or the patient space, the following results occur:

- Value-based care contracts with providers, which are based on shared savings, do not reflect these nontransparent discounts provided to the payer by the manufacturer.

- Even in fee for service contracts, nontransparent discounts provided from manufacturers to payers result in the use of brand-named drugs over the use of biosimilars. Although this is financially favorable for the payer, patients suffer. As a result of use of a more expensive drug, patients are paying higher copays.
- Patient copays and deductibles do not take these rebates into consideration. Therefore, patients are paying copays and deductibles against the "non-net" payment.
- These discounts vary from payer to payer depending on their contractual relationship and are not transparent.
- Self-administered drug discounts and rebates vary by the Pharmacy Benefit Manager

We would have preferred a standardized payment to be used across all TIMs which would normalize these discounts. Medicare payment rates could be used as a proxy.

A second issue is site of service. Due to contractual agreements, TIMs provided in an office setting are significantly less expensive than those administered in hospital outpatient departments. The current analysis does not incorporate site of service contractual differences. Again, a standardized payment would correct for this.

A third issue concerns patient preference, which is trending away from infused TIMs to the self-administered drugs. This is due both to drug development as well as patient preference. The administration costs of infused drugs as well as the lost time from work/school must be considered.

In conclusion, I urge CTAF to consider the unique needs of UC patients and the nature of the disease when making decisions regarding coverage and treatment, to reject step therapy as it conflicts with AGA, ACG, and ASGE guidelines on treatment of patients with UC, and to consider data from payor sources as you make your determination.

Dr. Abreu is a grant/research support consultant.

Ed Barnes, MD, MPH, UNC School of Medicine
Assistant Professor of Medicine

When considering the care of patients with ulcerative colitis (UC) and in particular treatment decisions for patients with UC, I think that it is critical to remember the heterogeneity that is present in both patients with UC and their individual disease presentations. This heterogeneity and diversity may present in multiple different ways including disease severity (and prognosis), comorbidities, and patient preferences, each of which can have direct impacts on the therapy decisions that a patient and their physician or other providers ultimately consider.

Given the diversity that is present in these treatment choices, it is critical to avoid prescribed or forced "step therapy" where providers and patients are forced into algorithmic programs.

Certainly, as physicians and particularly inflammatory bowel disease specialists, we strive to practice evidence-based medicine. We seek to incorporate all best available evidence into treatment decisions. However, the forced use of sub-standard or non-advised therapies because of payer or other entity recommendations should not be factored into the ultimate shared decision-making process of a patient and their provider. This shared decision-making process is the backbone of the current practice of medicine in the care of patients with UC. Future treatment decisions will always need to incorporate the heterogeneity present in the disease processes, as well as our own knowledge that there is no universally outstanding agent for all patients with UC (to date).

In reviewing the current analyses presented by ICER, it is also notable that while based in much of the available evidence, there are gaps in our published literature that do not reflect real-world clinical trial practice. For example, infliximab has not been included in randomized controlled trials after failure of other biologic (or specifically anti-TNF) therapies. This leaves large knowledge gaps in modeling, particularly with relatively common scenarios such as the use of vedolizumab as a first-line therapy (as recommended by the American Gastroenterological Association and other societies) followed by infliximab in the setting of non-response or loss of response to vedolizumab.

Additionally, many of the modeled colectomy outcomes may not match patient preferences or the expected outcomes over the lifetime/disease course after an ileal pouch-anal anastomosis. Although it is important to include outcomes such as chronic pouchitis, it may be difficult to fully capture the impact of having a chronic inflammatory condition of the pouch with respect to quality of life as this is a major area of ongoing research and work. This is particularly problematic with a clinical condition that was not modeled such as Crohn's-like disease of the pouch, which affects 10% of patients after IPAA for UC. The impact of a chronic inflammatory condition of the pouch, or even a new Crohn's-like disease process despite the preoperative diagnosis of UC, is difficult to quantify in these models. Similarly, future use of biologics or small molecule therapies for chronic inflammatory conditions of the pouch would further complicate these models.

I appreciate the opportunity to participate in this process, and hope that there will be a continued focus on the heterogeneity and diversity in presentations of UC among individual patients with UC that ultimately affect treatment decisions.

Dr. Ed Barnes is a consultant for AbbVie, Takeda, Gilead, Pfizer, and Target RWE.

Sarah Buchanan, Crohn's & Colitis Foundation
Director of Advocacy

The Crohn's & Colitis Foundation (Foundation) is concerned about patient-borne medical costs and supports efforts to develop value-based assessments for Crohn's disease and ulcerative colitis (UC)

treatments. The Foundation recognizes the efforts by the Institute for Clinical and Economic Review (ICER) to embark on a UC treatment cost-effective assessment.

Crohn's disease and UC are chronic conditions of the gastrointestinal tract and impact as many as 3.1 million Americans. These conditions are collectively known as inflammatory bowel disease (IBD). IBD is complex and disease progression is irreversible. As such, patients require individualized treatment and timely access to care. Treatment seeks to improve symptoms, induce clinical remission, and ultimately lead to mucosal healing (that is, no evidence of disease activity seen during a colonoscopy) and histologic remission (that is, no disease activity at the tissue-biopsy level). Because UC is a complex, heterogeneous condition, a one-size approach to treatment will not work. For this reason, the Foundation opposes the application of insurance-mandated step therapy for UC patients. Insurance-mandated step therapy has led to severe and irreversible negative health consequences for patients. There are far too many stories of patients who have required urgent surgery, including total colectomies, because the treatment selected by the patient and their provider was denied, and the patient's disease progressed during the time it took to prove failure of the insurer-preferred treatment. Step therapy interrupts the patient-provider shared decision-making relationship, which is critical for ensuring the unique patient's needs are addressed in the treatment plan. Further, insurance-mandated step therapy protocols are often based on rebate deals or other cost considerations, and not based on clinical guidelines and available medical science. The Foundation urges ICER to include in its public policy report a robust discussion on the harms of insurance-mandated step therapy for UC patients and to recommend against its use in the UC population.

In addition, the Foundation is concerned that ICER's cost-effectiveness model does not include real-world evidence (RWE) and is therefore inadequate to reflect the value of UC treatments accurately for the range of patients affected. In order to be taken up by the UC community, value-based assessments must reflect the full range of patient experience. The Foundation has built an infrastructure and resources to gather real-world data and evidence. We welcome the opportunity to continue to engage with ICER to design value-based assessments that can address cost-effectiveness and patient-centered questions in a meaningful way for the IBD community.

The Foundation thanks ICER for its consideration of our views. We look forward to engaging with ICER and other stakeholders on these critical discussions related to treatment costs and value in order to improve the ability of patients to access and afford appropriate care.

No financial conflicts to disclose.

Emily Morgan
Patient Expert

- Diagnosed at age 13.
- Days were consumed by school and competitive swimming. First, I battled mono for a few months and then it seemed like my energy never got back to how it was beforehand. Severe cramping after meals and urgent bathroom visits with blood resulted in me getting a colonoscopy and there was no question as to what was going on- it was UC. Fast forward three years- I had been on four different medications, each of them failing, which meant I had to take prednisone to get the inflammation back under control. Finally, after being hospitalized the two weeks leading up to my 16th birthday, my doctor and I (along w my family) decided it was time to speak to a surgeon. Knowing that there was a procedure that could make it all go away made me excited and nervous. Being 16, I'm not sure that I truly knew the magnitude of the two-step procedure. But what I did know was that I would NOT miss my colon.
- After a bit more time and consult, I ultimately decided to have a colectomy- a two-step surgery- during the summer between 10th and 11th grade. It wasn't easy but, for me, having surgery was the best decision I have ever made. Since that summer, I have never been hospitalized for my UC. It hasn't been a totally smooth ride but my overall quality of life is significantly better than it ever was, I have found balance in my disease, and it's important to me to use my voice and experience to advocate for others.

That's just the thing…. Others haven't had the same experience as me. As you all have heard and been researching- UC is heterogeneous- no two patients (that I know of) are the same. We even have different symptoms sometimes and different food triggers is VERY common in my experience.

For example, one of my very close UC friends had surgery a few years back and is unfortunately still struggling to reach her desired quality of life. It's frustrating and confusing.

And so with that- I really want to focus on the topic of colectomy. ICER's report seems to indicate that a colectomy is more cost- effective than the studied treatments. That's great; however, I know for a fact that each patient's goals and preferences are different. Not everyone bounces back after surgery and lives their "best life."

As you know, I did opt for a colectomy, but for others, it's the last resort. And not to mention this was over 10 years ago. Now- there are even more approved therapies on the market for UC patients. I sometimes wonder if I would've been that ready and willing had there been more options to try.

I wouldn't go back and change my decision, but surgery brings its own set of barriers and considerations. For me- it's scars and body image battles and then, most recently- the topic of conception and pregnancy.

I speak to about four to five patients/year- connected via my gastroenterologist to discuss my experience with a colectomy. I've heard firsthand about other patient's fears, concerns, and treatment goals. No two patients are ever the same.

The obvious and ugly truth is that there is no cure for UC. So as a result, patients are having to figure out what is most important to them- how they can best manage their disease and still live a life as close as possible to the one they desire.

For some, that may be completing an Iron Man, some it's being able to build a family and have children, and for others it's being able to attend their niece and nephews sporting events on an 85-degree weekend without having to run to the bathroom or take a nap afterward.

To conclude, as a UC patient I think that it is imperative that health plans should not steer patients towards treatment strategies based on cost effectiveness data--- much less data that isn't nuanced enough to reflect the patient experience or perspective, but rather a patient's plan should allow patients to make treatment decisions with their provider and loved ones.

Emily Morgan is a full-time health behavior medical writer for IQVIA.

Rosanne Mottola, Crohn & Colitis Foundation Volunteer
Patient Expert

Thank you to the ICER for inviting me to speak today and for ensuring that ulcerative colitis patients are heard during this critical meeting.

My name is Rosanne Mottola, and I am 35 years old. I am a public affairs director for a NYC hospital, I'm a volunteer with the Crohn's and Colitis foundation and – most importantly – I am a wife and a mother to my two young children Ryan and Abigail. 14 years ago, I did not think any of these things would've been possible. I was 21 years old when I was diagnosed with Ulcerative Colitis. I was a few months away from graduating college and I was deathly ill and incredibly scared. I was housebound and in excruciating pain at one of the most important times of my life. My doctor at the time, who claimed I had only a mild case, would put me on high doses of steroids every few months which had devastating side effects and impacted both my physical and mental well-being.

My health quickly deteriorated and I was hospitalized for the entirety of fall 2006. I had to medically withdraw from my first semester of graduate school at NYU. At this time, I met my current gastroenterologist who worked alongside me in exploring treatment options. The most

frustrating part about fighting UC is the fact that no two patients are the same. There is no roadmap. There is trial and error, and time is critical. No two patients react to medications the same way, have the same food sensitivities, and no two patients' journeys are identical. We must treat ulcerative colitis patients individually.

Therefore, I was put on a number of different biologics and dealt with the pain and stress of trying new therapies. At the same time, I was planning my wedding and trying to hold down a job to remain on my health insurance. That's when my health took a turn for the worse and I was facing a colectomy.

There's a lot of differing opinions on colectomies among the members of the UC patient community. Through my advocacy work with the CCF I know a lot of patients who are leading healthy lives post colectomy. However, I also know many patients who have had difficulties post-colectomy and whose symptoms have manifested elsewhere. All of these patients are warriors and I'm proud to call them my friends. However, cost of treatments should not be the determining factor in an UC patient's decision to have a colectomy. Almost every UC patient I've met were diagnosed during their formative years. If there are medications that can be tried and a patient is willing to try them, then they shouldn't be forced in any way to choose a colectomy because of cost. Plus, we shouldn't pretend that colectomies are cheap either: the surgery itself is outrageously expensive, and lifelong ostomy supplies are too.

Personally, I was in my early 20s and was terrified at the thought of a colectomy and wanted to exhaust all of my options first. While I met with surgeons, my gastroenterologist - who is my partner in my care - put in a last-ditch effort. By prescribing an immunomodulator and a double dosage of an infusion biologic, I finally found the mix of medications that worked for me and kept me in remission until this day.

Through this magical mix that has worked so well for me, I was able to finish graduate school, travel with my husband, advance my career, and deliver two healthy babies. All on the same biologic I started on a decade ago. I often think of what my life would be like if my doctor had continued to treat me with courses of steroids or jumped the gun on performing a colectomy.

Today, please let me leave you with these two thoughts:

1. When considering the voting questions, please remember the age of diagnosis of most ulcerative colitis patients and how these decisions impact the quality of rest of their lives.

2. In a lot of cases (like mine) finding the right mix of medications is key to proper treatment, and with proper treatment ulcerative colitis patients can avoid costly surgeries, hospitalizations and future complications.

Thank you to the Crohn's and Colitis Foundation and ICER for giving me the opportunity to speak today once again and for your time and attention.

No financial conflicts of interest to disclose.

Phil Naughten, PharmD, Takeda Pharmaceuticals
Vice President, HEOR

Takeda is committed to bringing better health and a brighter future to patients by translating science into highly innovative medicines. We are dedicated to achieving this objective through pricing responsibly and working with stakeholders to ensure patient access. Recognizing the unmet need for managing chronic gastrointestinal diseases, Takeda has developed vedolizumab, a humanized monoclonal antibody, α4β7 integrin receptor antagonist, indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) and Crohn's disease (CD). It is the only gut-selective treatment option that provides a favorable benefit-risk profile for moderate to severe UC patients, as well as unique benefits to the US health care system. I would like to underscore the broad evidence from both RCT and RWE that have demonstrated the efficacy, safety, and real-world effectiveness of vedolizumab IV.

The efficacy and safety of vedolizumab is supported by the results of the pivotal GEMINI clinical trial program, where significant and durable improvements in response and remission, and better mucosal healing were observed among bio-naive and bio-experienced patients. Data from the GEMINI long-term safety (LTS) study (up to nine years follow-up) demonstrated that vedolizumab was safe, well-tolerated, and continued to achieve favorable clinical outcomes for long-term IBD treatment.

In the first and only head-to-head IBD clinical trial of biologics, VARSITY, which was published in the NEJM in September 2019, vedolizumab was superior to adalimumab in achieving clinical remission and endoscopic mucosal healing in the overall and anti-TNF Naïve UC Populations.

In addition to the clinical trial programs, substantial real-world data documents the effectiveness and safety of vedolizumab through both the VICTORY consortium and EVOLVE study. VICTORY is a multicenter collaborative effort among US institutions to prospectively maintain a registry of real-world outcomes of IBD patients treated with biologics. Results from VICTORY demonstrated effectiveness in achieving clinical remission, endoscopic healing, and favorable safety profile of vedolizumab vs. anti-TNF therapies. EVOLVE, a real-world retrospective medical chart review study evaluating the long-term outcomes (up to 24 months) in biologic-naïve vedolizumab patients with IBD, also demonstrated real-world effectiveness, persistence, and safety of vedolizumab.

Taken together, these data not only complement recent published literature, but also have been recognized and incorporated into guideline recommendations. Vedolizumab's gut-selective

mechanism of action is well aligned with the 2019 ACG recommendation of starting with organ-selective biologic treatments before the use of systemic therapies, and the 2020 AGA guidelines suggested using vedolizumab as one of the first-line biologic therapies over adalimumab among adult biologic-naïve patients.

Additionally, I would like to make a few comments on the analysis itself. Several limitations of this analysis impact interpretation of value, and we hope that CTAF will be able to take these details into consideration.

1. The base-case comparator considered in this assessment was conventional therapy, which may include immunomodulators and/or immunosuppressants. The assumption that conventional therapy is a potential option for treating moderate-to-severe UC patients contradicts 2020 AGA and 2019 ACG clinical guidelines. Additionally, payers considering formulary placement of new biologics usually compare their value against existing biologics. Representing the current state of clinical management for UC is a critical part of assessing the value of therapies.

2. Health state utilities are important variables in the model, and despite a change to ICER's original data sources, the model now relies on data from one single Australian study that does not align with values used in prior HTA submissions. This data source now minimizes the differences between active UC, response, and remission health states. In addition, with no adjustment to the post-colectomy utility source, the model input suggested that the quality of life among patients living with remission is nearly equivalent compared to those with colectomy. The revised model inputs therefore continue to underrepresent the importance of improving the health of patients living with UC, including avoiding the need for surgery.

3. ICER's review was solely based on RCT data. In UC management with biologics, outcomes such as mucosal healing and its associated benefits are well captured in real-world data. Indeed, due to the long-term nature of therapy in UC as well as change in effects of therapies with long-term use, inclusion of real-world data would likely improve modeled insights.

I urge CTAF to keep these limitations of ICER's assumptions and inputs in mind while deliberating on the value of biologics such as vedolizumab IV.

Ultimately, we seek to see all products assessed according to their full holistic value to patients and society, and Takeda supports appropriate analyses that incorporate elements that are important to patients and reflect real-world clinical practice.

Phil Naughten, PharmD, is a full-time employee of Takeda.

Jordan Wilson
Patient Expert

I'm a 37-year-old Realtor out here in southern California, indoor cycling instructor and most importantly, a patient advocate for the IBD community. My journey with ulcerative colitis started just over ten years ago. After showing minor symptoms I was diagnosed with UC back in 2010. Luckily, I was put into remission rather quickly following my diagnosis.

That all changed about 18 months later when my symptoms came back and I went into a flare, which my gastroenterologist said was the worst he'd seen in five years.

I went from living a "normal life" to not being able to eat, not being able to sleep, exercise, or work. My colon went from having only a minor case of ulcers, to the entire organ being diseased and inflamed, all in less than two years. For a year and a half, I was on and off steroids, biologics, immunomodulators, and unfortunately nothing seemed to work for me. I was hospitalized several times and actually almost died from complications of ulcerative colitis twice.

I was referred to a second GI and she suggested surgery. I was explained what a colectomy was and how a j-pouch is constructed. With my back against the wall and viewing this option as truly a last resort, I decided to go through with the procedure. I'm beyond grateful to say that I am one of the lucky ones, even after going through everything I just mentioned. I have been living with a relatively healthy j-pouch since 2013. Unfortunately, that can't be said for everyone. Through my advocacy work I have met numerous patients who, while having the same procedure as me, aren't having the same success.

These varied responses to medication and surgeries just confirm what we already know, ulcerative colitis is such an individual disease and no two patients react to treatments the same way. No matter how positive I try to remain, there are very different opinions on colectomies throughout the patient community. There are stories of the disease reappearing, chronic pouchitis, or having to remove the j-pouch and go back to living with an ostomy. Quality of life and the efficacy of treatments should be the main consideration when treating an ulcerative colitis patient, not cost. Since each patient is different, each treatment will have to be as well.

No financial conflicts of interest to disclose.

Appendix H. Conflict of Interest Disclosures

Tables H1 through H3 contain conflict of interest (COI) disclosures for all participants at the CTAF September 24 public meeting.

Table H1. ICER Staff and Consultants and COI Disclosures

Name	Organization	Disclosures
Lisa Bloudek, PharmD, MS	Senior Research Scientist, University of Washington	*
Pamela Bradt, MD, MPH	Chief Scientific Officer, ICER	*
Josh J. Carlson, PhD, MPH	Associate Professor, Department of Pharmacy, University of Washington	*
Rick Chapman, PhD, MS	Director of Health Economics, ICER	*
Laura Cianciolo	Program Manager, ICER	*
Katherine Fazioli	(Former) Research Lead, Evidence Synthesis, ICER	*
Monica Frederick	Program and Event Coordinator, ICER	*
Daniel A. Ollendorf, PhD	Director, Value Measurement & Global Health Initiatives, Center for the Evaluation of Value and Risk in Health, Tufts University Medical Cent	*
Rajshree Pandey, PhD, MPH	Research Lead, Evidence Synthesis, ICER	*
Steven D. Pearson, MD, MSc	President, ICER	*

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table H2. CTAF Panel Member Participants and COI Disclosures

Name	Organization	Disclosures
Ralph G. Brindis, MD, MPH, MACC, FSCAI, FAHA	Clinical Professor of Medicine, UCSF	*
Felicia Cohn, PhD	Bioethics Director, Kaiser Permanente, Orange County	*
Rena K. Fox, MD	Professor of Medicine, UCSF	*
Paul Heidenreich, MD, MS (Chair)	Professor and Vice-Chair for Quality, Clinical Affairs, and Analytics, Stanford University	*
Jeffrey Hoch, PhD	Associate Director, Center for Healthcare Policy and Research, UC Davis	*
Jeff Klingman, MD	Chief of Neurology, The Permanente Medical Group	*
Annette Langer-Gould, MD, PhD	Regional Lead for Clinical and Translational Neuroscience, Southern California Permanente Medical Group, Kaiser Permanente	*
Elizabeth J. Murphy, MD, DPhil	Professor of Clinical Medicine, UCSF; Chief, Division of Endocrinology and Metabolism, Zuckerberg San Francisco General Hospital	*
Kathryn A. Phillips, PhD	Professor of Health Economics and Health Services Research; Director and Founder, UCSF Center for Translational and Policy Research on Personalized Medicine; Department of Clinical Pharmacy/School of Pharmacy, UCSF Institute for Health Policy Studies, and UCSF Comprehensive Cancer Center	*

Ann Raldow, MD, MPH	Assistant Professor, Department of Radiation Oncology, UCLA David Geffen School of Medicine	*
Rita F. Redberg, MD, MSc, FACC	Professor, UCSF School of Medicine	*
Sei Lee, MD	Associate Professor of Medicine, University of California San Francisco	*
Alexander Smith, MD, MPH	Associate Professor of Medicine, UCSF	*
Joanna Smith, LCSW, MPH, CHA	Chief Executive Officer, Healthcare Liaison, Inc.	*
Anthony Sowry	Patient Advocate and Lead Volunteer, California, National Patient Advocate Foundation; Senior Vice President, Maritime Container Shipping (Retired)	*

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table H3. Policy Roundtable Participants and COI Disclosures

Name	Organization	Disclosures
Thomas Brownlie, PhD, MS	Senior Director, US Payer Policy, Pfizer	Full-time employee of Pfizer.
Deborah Gan, MBA	Leader, US Payer Marketing, Primary Care, Merck	Full-time employee of Merck.
Patrick Gleason, PharmD	Assistant Vice President, Health Outcomes, Prime Therapeutics	Full-time employee of Prime Therapeutics.
Bruce Sands, MD, MS	Professor of Medicine and Chief, Division of Gastroenterology, Mount Sinai	Dr. Sands has consulted for AbbVie, Janssen (service on a scientific advisory board), Pfizer (service on a scientific advisory board), and Takeda (honoraria for speaking in a CME program).
Siddharth Singh, MD	Assistant Professor of Medicine, UC San Diego School of Medicine; Gastroenterologist, UC San Diego Health	Dr. Singh has received research grants from AbbVie, and consulting fees from AbbVie, Takeda, Pfizer, AMAG Pharmaceuticals.
Megan Starshak	Patient Advocate	No conflicts of interest to disclose.
Fernando Velayos, MD	Director, Inflammatory Bowel Disease Program, Kaiser Permanente Northern California	Dr. Velayos' spouse has received honoraria in consulting fees.
Laura Wingate	Senior Vice President, Education, Support, and Advocacy, Crohn's & Colitis Foundation	No conflicts of interest to disclose.