Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value

Modeling Analysis Plan

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Institute for Clinical and Economic Review

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1. Approach

This analysis plan details our modeling approach and outcomes to be assessed for the economic evaluation of targeted immune modulators (TIMs) for ulcerative colitis (UC). Please refer to the Research Protocol for details on the systematic review of the clinical evidence on this topic.

The primary aim of this analysis will be to estimate the cost-effectiveness of TIMs for UC using a decision analytic model. The model will compare all eight treatments to each other and to conventional treatment. The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only), and a lifetime time horizon. Shorter time horizons may be considered as scenario analyses. A modified societal perspective, which considers the impact of UC on short-term disability, absenteeism, and presenteeism, will also be assessed as a scenario analysis. The model will be developed in Microsoft Excel 365.

2. Methods

2.1 Overview and Model Structure

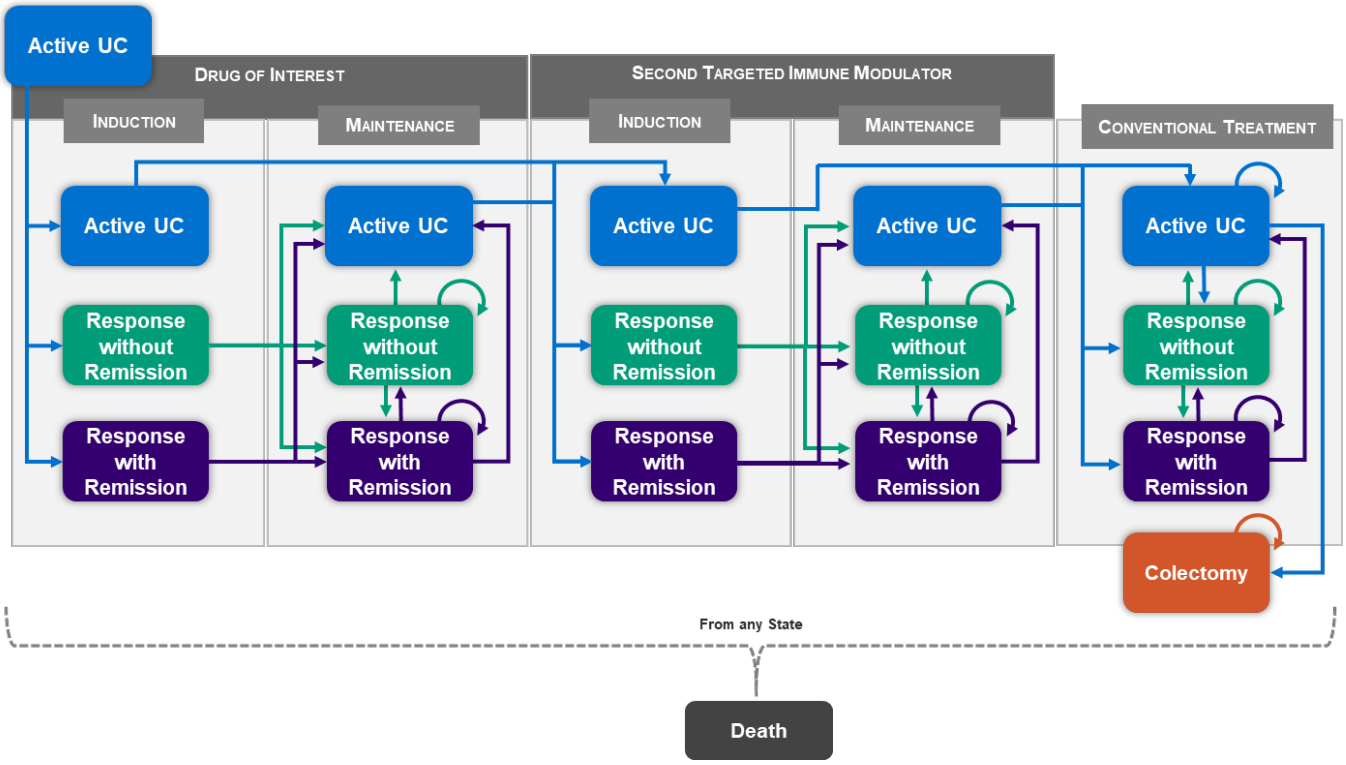
We will develop a decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models. The base-case analysis will take a health care sector perspective and thus focus on direct medical care costs only. Costs and outcomes will be discounted at 3% per year.

The model will focus on an intention-to-treat analysis, with a hypothetical cohort of patients with moderate-to-severe UC being treated with TIMs entering the model. Model cycle length will be eight weeks, based on a common point of assessment in clinical trials to mark the end of induction and beginning of maintenance treatment.

The model will consist of health states including active UC, response without remission, response with remission, post-colectomy health states (with and without complications), and death (Figure 2.1 on the following page). Moderate-to-severe UC patients enter the model upon initiation of a TIM. At the end of induction, patients with response will continue to receive the TIM. Those without response or those who discontinue after initial response will begin induction with a second TIM. The second TIM will be represented by a market basket of other treatment options except the initial TIM. The distribution of treatments options in the market basket will differ based on whether the initial TIM had an anti-TNF mechanism of action or other mechanism of action. For those with initial use of an anti-TNF, the market basket for the subsequent TIM will consist primarily of TIMs with other mechanisms of action. For those with initial use of non-anti-TNF agents, the market basket will consist of all treatment options except the initial TIM. At the end of induction of the second TIM, responders will continue to receive the second TIM. Patients who do not respond during the induction phase of the second TIM will discontinue treatment with TIMs and follow the transition probabilities of the conventional treatment arm (e.g., corticosteroids, other systemic immunomodulators) with a proportion of patients progressing to colectomy each cycle.

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 2.1. Model Schematic



2.2 Key Model Choices 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 induction and maintaining response without remission or response with remission will be informed by randomized controlled trials (RCTs) and results of the ICER network meta-analysis (NMA)
- Patients remaining in active UC at the end of induction will discontinue the TIM and initiate the next line of therapy
- Constant per-cycle rate of discontinuation based on RCTs
- Patients cycle through two TIMs before discontinuing to conventional treatment
- Constant per-cycle probability of elective colectomy only from the active UC in conventional treatment state
- Health state utilities based on a published meta-analysis
- Direct health state costs including hospitalization, emergency department visits, and outpatient visits, based on published claims analysis

- Mortality based on population mortality tables, with an elevated risk of mortality due to UC and colorectal cancer in UC applied to standard mortality tables and a one-time risk of mortality associated with colectomy
- Costs and disutility of serious infection with TIMs and complications of colectomy will be included

Our model includes several key assumptions stated below.

Assumption	Rationale
Conventional treatment will be represented by the control arm of RCTs.	In the real world and in controlled trials, background conventional treatment is taken in addition to TIMs.
Patients will cycle through two TIMs before discontinuing to conventional treatment and possible colectomy.	Based on clinician and patient group feedback, many pharmaceutical options are tried before consideration of surgical intervention.
Subsequent lines of therapy will be represented by a market basket with distribution based on whether the initial TIM was an anti-TNF agent, with efficacy, safety, and cost informed by a weighted average of treatments in the biologic-experienced population. Probabilities for any given patient to receive any given therapy in the market basket to be informed by market share data if available.	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.
Total lifetime probability of colectomy will be capped based on real-world observed rates.	Not all patients will opt for surgical intervention, even if pharmacologic interventions are unsuccessful.

2.3 Populations

The population of focus for the economic evaluation will include two subgroups of patients: 1) biologic-naïve and 2) biologic-experienced. These two subgroups are similar in age, gender, and weight[1] but have been shown to differ in clinical response to TIMs. The cost-effectiveness and threshold prices will be evaluated for both patient populations. If TIM efficacy data is not available for one of the subpopulations, that TIM will not be assessed in that subpopulation.

Table 2.1. Baseline Population Characteristics

	Mean Age	Percent Male	Weight	Source
Biologic-Naïve	40 years	59%	74.3 kg	GEMINI 1[2]
Biologic-Experienced	40 years	59%	74.3 kg	GEMINI 1[2]

kg: kilogram

2.4 Interventions

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

- Adalimumab (Humira®, AbbVie)
- Golimumab (Simponi®, Janssen Biotech)
- Infliximab (Remicade®, Janssen Biotech)
- Infliximab-dyyb (Inflectra®, Pfizer)
- Infliximab-abda (Renflexis®, Merck)
- Tofacitinib (Xeljanz®, Pfizer)
- Ustekinumab (Stelara®, Janssen Biotech)
- Vedolizumab (Entyvio®, Takeda Pharmaceuticals)*

*Only the intravenous (IV) formulation of vedolizumab will be included in the model given the Food and Drug Administration's recent complete response letter regarding the subcutaneous formulation.[3]

Comparators

Interventions will be compared to conventional treatment and to each other.

- Conventional treatment (corticosteroids for induction followed by azathioprine or mercaptopurine)

2.5 Input Parameters

Clinical Inputs

Efficacy and safety data will be 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 placebo used as a proxy for conventional treatment.

Transition Probabilities

For each of the biologic-naïve and biologic-experienced subpopulations separately, a set of transition probabilities will be 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 will calculate the probability of achieving response (with and without remission) at the end of induction. Conditional upon achieving response entering the maintenance phase, we will calculate the probability of

maintaining response with remission, response without remission, or losing response. If maintenance phase transition probabilities are only available at longer timepoints than our cycle length (e.g., one year), transition probabilities will be converted to shorter cycle lengths using standard approaches.

Based on the results of the NMAs, risk ratios for each TIM relative to placebo will be calculated and applied to the transition probabilities of conventional treatment.

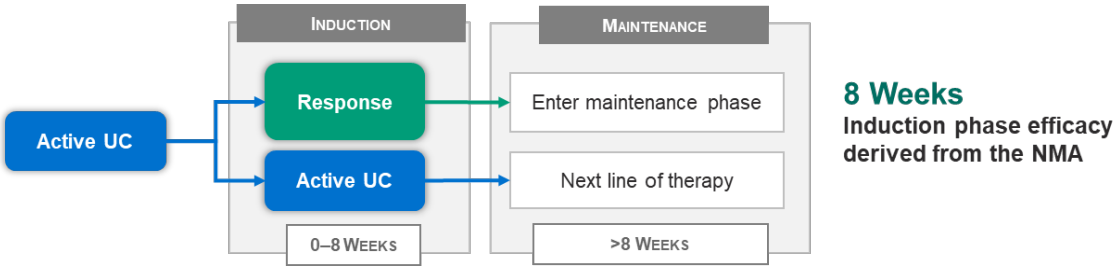
From the conventional treatment health state, patients with active UC will have a constant per-cycle risk of elective colectomy. Colectomy is assumed to induce remission of UC, but at a lower utility compared to drug-induced remission because of the health consequences of removing the colon and the potential for long-term complications and adverse events. The per-cycle probability of colectomy will be based on a cumulative rate of 18.9% at 10 years (95% CI, 14.4% to 23.2%) from UC diagnosis observed from a cohort of UC patients in Olmstead County, Minnesota from 1997 to 2004, converted to an annual probability of 2.1% (or 0.32% per eight week cycle).[4] This sample represents a cohort treated before TIMs became available on the market, and may therefore be reflective of surgery rates for patients on conventional treatment after discontinuation of TIMs. Some patients may never opt for colectomy or are ineligible for the procedure. Therefore, the total number of colectomy procedures will be capped at 25.4% at 20 years (95% CI, 19.8% to 30.8%) over the lifetime time horizon based on the 20-year cumulative probability of colectomy in the Olmstead County cohort.

Induction and Delayed Response

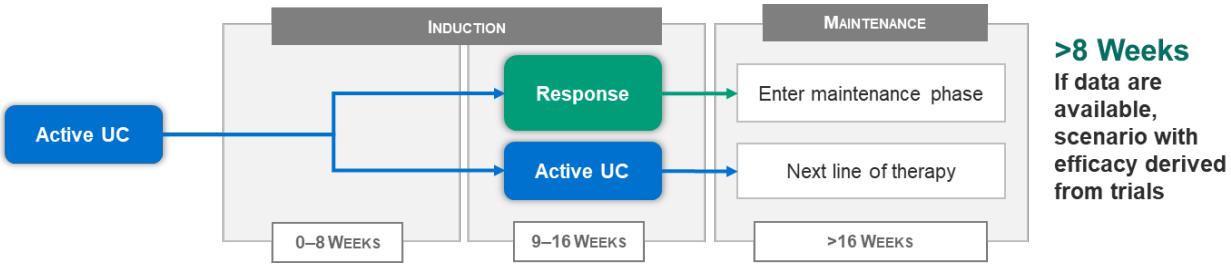
Evidence exists for a few TIMs that some additional patients achieve response if the induction period is extended beyond eight weeks. Furthermore, clinicians engaged during the scoping period of this review also commented that it is not uncommon in clinical practice to wait longer than eight weeks to determine response and non-response to TIMs. Therefore, delayed response will be explored in scenario analyses for TIMs with available data through a 16-week induction period in combination with dose escalation for a proportion of patients to mirror real-world practice patterns (Figure 2.2 on the following page).

Figure 2.2. Schematic of Induction Phase

Base Case



Scenario Analysis Considering Delayed Response



Discontinuation

At the end of the induction period, patients who remain in active UC will discontinue treatment with the TIM and initiate the next line of therapy. In the maintenance phase, the model will assume that patients who revert to active UC will discontinue treatment with a TIM. The model will also consider discontinuation for reasons other than loss of efficacy. For those response states, a per-cycle probability of discontinuation will be applied based on rates observed in RCTs or long-term extension studies (Table 2.2 on the following page). Discontinuation will be based on rates of discontinuation for reasons other than loss of efficacy and converted to a per-cycle probability.

Table 2.2. Discontinuation

Parameter	Discontinuation	Per-Cycle Discontinuation	Source
Adalimumab	31/254 (12.2%) had discontinued at 52 weeks	1.98%	ULTRA 2[5]
Golimumab	23/154 (14.9%) had discontinued at 54 weeks	2.37%	PURSUIT[6]
Infliximab	59/229 (25.7%) had discontinued at 152 weeks	1.56%	ACT-1 and ACT-2[7]
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[8]
Ustekinumab	*Academic-in-confidence data*		Manufacturer
Vedolizumab	14/122 (11.5%) had discontinued at 52 weeks	1.86%	GEMINI 1[2]

Mortality and Colorectal Cancer

Gender- and age-specific mortality will be sourced from the Human Mortality Database's US-specific tables.[9] In addition, an elevated risk of mortality will be assumed among patients with UC based on a published NMA, which showed slightly elevated risk of mortality among patients with UC.[10]

UC has been associated with increased risk of colorectal cancer and colorectal cancer death in large epidemiologic studies.[10,11] The exact pathology of excess colorectal cancer risk is unknown but may be linked to mucosal inflammation.[12,13] The impact of TIMs on risk of colorectal cancer incidence and mortality is unknown and early research does not suggest a clear beneficial effect.[14] 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.[15]

To capture excess colorectal cancer deaths within the model, a mortality multiplier for colorectal cancer-related mortality will be applied for all patients with a colon (i.e., without colectomy) to SEER colorectal cancer-related death rates by age.[16] As a scenario analysis, we will apply a risk of mortality in UC, which excludes colorectal cancer-related mortality to patients in the remission health state to capture a potential long-term benefit effect of mucosal healing. No impact of TIMs on non-colorectal cancer related mortality will be assumed, as evidence to date does not provide conclusive evidence of impact. [17]

Table 2.3. Mortality Inputs

Parameter	Value	Source
All-Cause Mortality[18]	Gender- and age-specific	US Life Tables
Standardized Mortality Ratio for UC[10]	1.19 (95% CI 1.06-1.35)	Bewtra 2013
Standardized Mortality Ratio for Colorectal Cancer-Related Death in UC[10]	2.82 (95% CI 1.30-1.63)	Bewtra 2013
One-Time Probability of Mortality Among Patients Undergoing Laparoscopic Colectomy[19]	0.2%	Causey 2013
One-Time Probability of Mortality Among Patients Undergoing Open Colectomy Procedure[19]	1.7%	Causey 2013

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

Adverse Events

Disutility associated with serious infections with TIMs (e.g., respiratory infections, gastrointestinal infections, sepsis), early complications of colectomy, and late complications (chronic pouchitis) will be included (Table 2.4). The rate of serious infection will be informed by the ICER safety NMA, which will cover both the biologic-naïve and biologic-experienced populations. A disutility of 52% will be assumed for the duration of the cycle with a serious infection event.

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 2.4 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 2.4. Adverse Events

Parameter	Value	Source	Utility	Source
Serious Infection	Varies by TIM	Varies	-0.520 disutility	NICE STA342[20]
Early Complications of Colectomy (Open Procedure)	25.3% incidence	Zogg 2016[21]	0.49	Arseneau 2006[22]
Early Complications of Colectomy (Laparoscopic)	17.3% incidence	Zogg 2016[21]	0.49	Arseneau 2006 [22]
Chronic Pouchitis	15.5% prevalence	Zogg 2016 [21]	0.40	Arseneau 2006[22]

TIM: targeted immune modulator

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.[23] However, long-term studies have not consistently demonstrated an elevated risk, and the comparative risk across agents is unknown.[24-26] Therefore, risk of malignancy will not be included in the base case.

Health State Utilities

Health state utilities will be derived from a published systematic literature review and meta-analysis of utility values in UC and applied to health states of active UC, response without remission, and remission (Table 2.5). We will use consistent health state utility values across treatments evaluated in the model. Utility for the post-colectomy health state will be 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.[27] Disutility associated with short-term complications of colectomy and chronic pouchitis will be captured separately (see Table 2.4). Other long-term complications and long-term impact of colectomy is assumed to be captured within the utility score applied to the post-colectomy health state.

Table 2.5. Health State Utilities

Parameter	Value (95% CI)	Source
Active UC	0.6992 (0.5847, 0.8136)	Malinowski 2016[28]
Response without Remission*	0.7834 (0.7265, 0.8403)	Malinowski 2016[28]
Remission	0.8726 (0.8457, 0.8995)	Malinowski 2016[28]
Post-Colectomy	0.79 (0.77, 0.81)	Brown 2015[27]

CI: confidence interval, UC: ulcerative colitis

*Response without remission utility value represented by mild UC cohort in Malinowski et al. 2016.

Drug Utilization

Table 2.6 outlines inputs that will be used to model drug utilization and associated costs in TIMs. Conventional treatment will be 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[29] (assuming a 50:50 split between mercaptopurine and azathioprine).

Table 2.6. Treatment Regimen Recommended Dosage

Generic Name	Adalimumab	Golimumab	Infliximab	Infliximab-dyyb	Infliximab-abda	Tofacitinib	Ustekinumab	Vedolizumab
Brand Name	Humira	Simponi	Remicade	Inflectra	Renflexis	Xeljanz	Stelara	Entyvio
Manufacturer	AbbVie	Janssen	Janssen	Pfizer	Merck	Pfizer	Janssen	Takeda
Route of Administration	SC	SC	IV	IV	IV	Oral	SC	IV
Dosing	160 mg on day 1 or split over 2 consec-utive days, then 80 mg 2 weeks later, then 40 mg every other week after	200 mg at week 0, 100 mg at week 2, then 100 mg every 4 weeks thereafter	5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks thereafter	5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks thereafter	5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks thereafter	10 mg twice daily for 8 weeks, then 5 mg twice daily thereafter	90 mg at 0 and 4 weeks, then 90 mg every 12 weeks thereafter	300 mg at 0, 2, and 6 weeks, then every 8 weeks thereafter

IV: intravenous, kg: kilogram, mg: milligram, SC: subcutaneous

Dose escalation will be considered in a scenario as an additional cost through a higher dose and/or frequency of administration for a proportion of patients.[30] Dose escalation will be applied across all TIMs equally with the exception of tofacitinib, with dose escalation for up to 44% of patients remaining on treatment for 36 months.[31]

Table 2.7. Assumptions for Dose Escalation

Generic Name	Adalimumab	Golimumab	Infliximab	Infliximab-dyyb	Infliximab-abda	Tofacitinib	Ustekinumab	Vedolizumab
Standard Maintenance Dosing	40 mg every other week	100 mg every 4 weeks	5 mg/kg every 8 weeks	5 mg/kg every 8 weeks	5 mg/kg every 8 weeks	5 mg twice daily	90 mg every 12 weeks	300 mg every 8 weeks
Common Escalated Maintenance Dosing	80 mg every 2 weeks or 40 mg every week	200 mg every 4 weeks	5 mg/kg every 4-6 weeks or 10 mg/kg every 8 weeks	5 mg/kg every 4-6 weeks or 10 mg/kg every 8 weeks	5 mg/kg every 4-6 weeks or 10 mg/kg every 8 weeks	10 mg twice daily	90 mg every 4-6 weeks*	300 mg every 4 weeks
Source	Gemayel 2019[30]	Gemayel 2019[30]	Gemayel 2019[30]	Assumption	Assumption	Assumption	Ma 2017[32]	Gemayel 2019[30]

kg: kilogram, mg: milligram

*Based on escalated dosing in Crohn's disease.

Cost Inputs

Drug Costs

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 distributors, and patient assistance programs, to derive a net price.[33] The average discount was not available for infliximab-abda and was instead assumed to be equivalent to infliximab-dyyb. 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 (January 10, 2020) to arrive at an estimated net price per unit.

Table 2.8. Drug Costs

Drug	WAC per Dose[34]	Discount from WAC[33]	SSR/Net Price per Dose	Net Price per Year (Maintenance)
Adalimumab	$6,727.65	35.2%	$1,676.41	$43,706
Golimumab	$5,530.40	43.8%	$3,108.08	$40,516
Infliximab	$1,167.82	62.0%	$1,628.64	$10,615
Infliximab-dyyb	$946.28	42.0%	$2,014.25	$13,129
Infliximab-abda	$753.39	N/A	$1,603.67	$10,452
Tofacitinib	$4,700.18	37.9%	$48.65	$33,853
Ustekinumab	$22,004.61	39.1%	$13,400.81	$58,230
Vedolizumab	$6,727.65	18.3%	$5,496.49	$34,448
6-Mercaptopurine	$6.34	N/A	$6.34	$2,314
Azathioprine	$1.35	N/A	$1.35	$493

N/A: not applicable, WAC: wholesale acquisition cost

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

Non-Drug Costs

In addition to drug costs, the model will include cost of administration, direct health state costs, cost of colectomy, and cost of treating adverse events. As a scenario analysis, we will adopt a modified societal perspective to include the indirect cost of lost productivity.

Administration Costs

Administration costs will be 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).[35] The average non-facility price for CPT 96366 ($21.98) will be added for infliximab,

infliximab-dyyb, and infliximab-abda to account for a second hour of infusion time per product labeling.[36]

Cost of Colectomy Procedure

A cost of $33,871 per admission for colectomy will be used in the model, 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.[37-39]

Cost of Adverse Events

Costs associated with serious infections with TIMs, early complications of colectomy, and late complications (chronic pouchitis) will be included (Table 2.9). Serious infection events will be 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.[40] Table 2.9 also presents the cost per short-term complication in open and laparoscopic colectomy procedures, as well as chronic pouchitis.

Table 2.9. Cost of Adverse Events

Parameter	Cost	Source
Serious Infection	$10,238	AHRQ[41]
Early Complications of Colectomy (Open Procedure)	$11,435*	Zogg 2016[21]
Early Complications of Colectomy (Laparoscopic)	$8,293*	Zogg 2016[21]
Chronic Pouchitis	$1,581/month*	Park 2012[42]

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.

Direct Health State Costs

Non-drug costs of UC management will include the average cost of hospitalization, emergency department visits, and outpatient visits by health state. Direct healthcare utilization costs will be calculated based on previously published estimates of mean unadjusted annual costs among privately-insured employed people with UC and a matched cohort without UC.[43] The active UC health state will be 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 response without remission health state will be informed by the overall UC study population, which includes all patients with at least two diagnoses of UC. Finally, the remission health state will be informed by the non-UC control cohort.

Table 2.10. Annual Direct Healthcare Costs*

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[43]
Response without Remission†	$4,461 ($23,436)	$410 ($1,436)	$7,506 ($14,561)	Cohen 2015[43]
Remission‡	$969 ($8,137)	$223 ($992)	$2,722 ($8,266)	Cohen 2015[43]

CI: confidence interval, UC: ulcerative colitis

*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.

Indirect Health State Costs

A modified societal perspective including indirect costs of disability, medical-related absenteeism, and presenteeism will be included as a scenario analysis. Days of disability and medical-related absenteeism will be 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).[43,44] For presenteeism, Work Productivity and Activity Impairment Questionnaire (WPAI) presenteeism estimates from a US patient survey will be combined with US Bureau of Labor Statistics average working hours per week (38.6) and average hourly wage ($28.18) (Table 2.11). ENREF 43[44-46]

Table 2.11. Annual Indirect Healthcare Costs

Parameter	Disability	Medical-Related Absenteeism	Presenteeism	Total Indirect Costs per Year	Source
Active UC	$2,773	$2,593	$13,694	$19,059	Cohen 2015[43], Ding 2019[46]; US Bureau of Labor Statistics[44], OECD.Stat[45]
Response without Remission	$1,781†	$1,916†	$7,843†	$11,540*	
Response with Remission	$1,014‡	$1,195‡	$3,056	$5,266	

UC: ulcerative colitis

*Response without remission utility value represented by mild UC cohort.

†Informed by overall UC population.

‡Informed by non-UC control group.

2.6 Model Outcomes

Model outcomes will include total costs, life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal value of life-years gained (evLYG), and a potential cost consequence measure such as time in remission or colectomies performed for each intervention over a lifetime time horizon. Costs and QALYs will also be reported by the health state to understand the contribution of different costs elements. All the costs and QALYs will be reported as discounted values, using a discount rate of 3% per annum.

2.7 Model Analysis

Cost-effectiveness will be estimated using incremental cost-effectiveness ratios, with incremental analyses comparing TIMs to conventional treatment from a health sector perspective in the base-case analyses. Additionally, we will present a cost per evLYG, cost per year in remission, and cost per colectomy avoided.

Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be 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 will also perform threshold analyses for drug costs across a range of incremental cost-effectiveness ratios (from $50,000 to $150,000 per QALY).

Scenario Analyses

If data allow, we will consider conducting scenario analyses that include:

1) Dose escalation
2) Delayed response and dose escalation
3) Modified societal perspective that includes productivity losses
4) Reduced risk of colorectal cancer death for patients in remission state
5) Shorter time horizons

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for

model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we will also share the model with the manufacturers for external verification around the time of publishing the Draft Evidence Report for this review. Finally, we will compare the results to other cost-effectiveness models in this therapy area. The outputs from the model will be validated against the trial/study data of the interventions and also any relevant observational datasets.

References

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