Common Drug Review
Pharmacoeconomic Review Report

April 2017

Drug	Ustekinumab (Stelara)
Indication	For the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, loss of response to, or were intolerant to either immunomodulators or one or more tumour necrosis factor -alpha antagonists, or have had an inadequate response, intolerance or demonstrated dependence on corticosteroids.
Reimbursement request	As per indication.
Dosage form(s)	130 mg solution for intravenous infusion (for induction period) 90 mg solution for subcutaneous injection (for maintenance period)
NOC Date	December 12, 2016
Manufacturer	Janssen Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in gastroenterology who provided input on the conduct of the review and the interpretation of findings

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ABBREVIATIONS

CD	Crohn's disease
CDR	CADTH Common Drug Review
CUA	cost-utility analysis
FCTO	failure with conventional therapy only
ICUR	incremental cost-utility ratio
IPD	individual patient data
IV	intravenous
NMA	network meta-analysis
QALY	quality-adjusted life-year
TNF	tumour necrosis factor
WTP	willingness to pay

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Ustekinumab (Stelara)
Study Question	The objective of the analysis was to assess the cost utility of ustekinumab in the treatment of moderate-to-severe Crohn's disease (CD) in patients who have experienced a failure with conventional therapy only (FCTO), patients who have experienced a failure with anti–tumour necrosis factor (anti–TNF) biologics, and a mixed population of those who have experienced FCTO and failure with anti–TNF, compared with other biologics and with conventional therapy.
Type of Economic Evaluation	Cost-utility analysis (CUA)
Target Population	Adult patients with active CD (CDAI of ≥ 220 and ≤ 450), who have experienced either FCTO or failure with anti-TNF therapy
Treatment	**Ustekinumab:** • 6 mg/kg administered intravenously at induction • Subcutaneous doses of 90 mg/1.0 mL every 8 or 12 weeks at maintenance
Outcome	Quality-adjusted life-year (QALY)
Comparators	• **Biologics:** o Infliximab (and infliximab biosimilar): 5 mg/kg and 10 mg/kg at 0, 2, and 6 weeks, and every 8 weeks thereafter o Adalimumab: 160 mg at week 0 followed by 80 mg 2 weeks later, and then a maintenance dose of 40 mg every other week o Vedolizumab: 300 mg at 0, 2, and 6 weeks, then every 8 weeks thereafter • **Conventional therapies:** o Induction phase ▪ Oral steroid: a starting dose of 40 mg to 60 mg prednisolone daily, reduced by 5 mg per day at weekly intervals ▪ Oral azathioprine: 2 mg to 2.5 mg/kg/day o Maintenance phase ▪ Oral azathioprine: 2 mg to 2.5 mg/kg/day ▪ 6-mercaptopurine: 1.5 mg/kg/day
Perspective	Canadian public health care payer
Time Horizon	25 years
Results for Manufacturer Base Case	• **ICURs for ustekinumab vs. conventional therapy:** o $50,912 (q.12.w.) to $86,414 (q.8.w.) per QALY gained for population with FCTO o $38,764 (q.12.w.) to $83,535 (q.8.w.) per QALY gained for population with failure of anti-TNF therapy o $45,927 (q.12.w.) to $85,947 (q.8.w.) per QALY gained for mixed population • **In patients with FCTO:** o Most cost-effective: biosimilar infliximab with an ICUR of $32,045 per QALY compared with conventional therapy, followed by ustekinumab every 12 weeks with an ICUR of $65,368 per QALY when compared with biosimilar infliximab, then finally by ustekinumab every 8 weeks with an ICUR of $610,102 per QALY compared with ustekinumab every 12 weeks o Other biologics were either dominated or subjected to extended dominance. • **In the patients with failure of anti-TNF therapy:** o Most cost-effective: biosimilar infliximab with an ICUR of $8,730 per QALY compared with conventional therapy, followed by ustekinumab every 12 weeks with an ICUR of $103,621 per QALY compared with biosimilar infliximab, followed by ustekinumab mixed dosage with an ICUR of $911,556 per QALY and ustekinumab every 8 weeks

	with an ICUR of $1,025,500 per QALY. o Remaining biologic therapies (adalimumab, infliximab, and vedolizumab) were dominated or subjected to extended dominance.
Key Limitations	CDR identified the following key limitations: • Uncertainty with the transition probabilities: Important limitations were identified with the data from NMAs (heterogeneity across studies, carry-over effects from the induction phase to the maintenance phase) used to populate the model transition probabilities for the induction and maintenance phases of treatment. CDR could not test this limitation with enough certainty because of a lack of evidence. • Uncertainty of the clinical effectiveness of infliximab: Infliximab trials in patients with FCTO used a different definition of response, and data on patients with failure of anti-TNF therapy were not available, leading to the use of adalimumab data. This limits the cost-effectiveness assessment of infliximab. CDR could not test this limitation with enough certainty. • Utility values for model health states: There is inconsistency in how utility values were used by the manufacturer. This raises uncertainty about the results of the analysis. CDR conducted two scenario analyses: (1) applying utility values to the model based on the published study used by the manufacturer with more consistency, and (2) using an alternative set of utility values used in previous CADTH models in Crohn's disease. • Modelling error for the ustekinumab mixed dosage (every 8 weeks/every 12 weeks) treatment option: The model incorrectly calculated the weighted average QALY results for the ustekinumab mixed dosage (every 8 weeks/every 12 weeks) treatment by excluding the QALYs of the every 12 weeks dosage, which overestimated the ICUR results for the ustekinumab mixed dosage (every 8 weeks/every 12 weeks) treatment option, considering only the favourable every 8 weeks QALY benefits. This was corrected by CDR. • Adjustment of the maintenance-phase transition probabilities using real-world evidence: The manufacturer's approach is highly uncertain and increased the effect of treatments, which favours ustekinumab. CDR reanalysis excluded the impact of real-world evidence on the transition probabilities.
CDR Estimate(s)	• As described above, the health-state utility values and the effect of real-world evidence on the transition probabilities in the maintenance phase of the model were assessed in the CDR base case. CDR also corrected the error that overestimated the ICUR results for the mixed dosage. • CDR base case for ustekinumab when compared with conventional therapy in the population with FCTO resulted in an ICUR of $115,474 per QALY gained and, in the population with failure of anti-TNF therapy, $131,297 per QALY gained. For the mixed population with FCTO and with failure of anti-TNF therapy, ustekinumab resulted in an ICUR of $119,058 per QALY when compared with conventional therapy. • Among the available biologic therapies in patients with FCTO, ustekinumab every 12 weeks was the most cost-effective, with an ICUR of $115,474 per QALY, compared with conventional therapy, followed by ustekinumab mixed dosage every 8 weeks/every 12 weeks with an ICUR of $623,571 per QALY, when compared with ustekinumab every 12 weeks, then finally by ustekinumab every 8 weeks, with an ICUR of $658,533 per QALY compared with ustekinumab mixed dosage. Other biologics were either dominated or subjected to extended dominance. • In the patients with failure of anti-TNF therapy, the most cost-effective treatment was biosimilar infliximab, with an ICUR of $90,277 per QALY compared with conventional therapy, followed by ustekinumab every 12 weeks, with an ICUR of $228,571 per QALY compared with biosimilar infliximab, with the remaining ustekinumab (every 8 weeks and mixed dosage) regimens resulting in ICURs of more than $1 million per QALY. Remaining biologic therapies (adalimumab, infliximab, and vedolizumab) were also dominated or subjected to extended dominance.

	• Based on manufacturer correspondence indicating that the drug costs with the induction dose for ustekinumab would be reimbursed by the manufacturer, the ICURs for ustekinumab improve compared with conventional therapy and other biologic therapies, as expected. • A driving limitation of the CUA was the uncertainty associated with the comparative efficacy and safety of ustekinumab versus other biologic therapies.

CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; FCTO = failure with conventional therapy only; ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life-year; TNF = tumour necrosis factor; vs. = versus.

EXECUTIVE SUMMARY

Background

Ustekinumab (Stelara) is a human immunoglobulin G1 kappa monoclonal antibody, available as a pre-filled syringe of 90 mg/1 mL for subcutaneous injection at a unit price of $4,593 and as a single-use vial of 130 mg/26 mL solution for intravenous (IV) infusion at a unit price of $2,080. The current review of ustekinumab is for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response with, loss of response to, or intolerance to either conventional therapy, including corticosteroids or immunomodulators, or to one or more tumour necrosis factor-alpha (TNF) antagonists, or who are corticosteroid-dependent.[1]

Ustekinumab was previously reviewed by CADTH Common Drug Review (CDR) for psoriatic arthritis[2] and psoriasis.[3] For psoriatic arthritis, the CADTH Canadian Drug Expert Committee's final recommendation was that ustekinumab not be reimbursed.[2] In psoriasis, the former Canadian Expert Drug Advisory Committee had recommended that ustekinumab be reimbursed, subject to criteria or conditions.[3] CDR also reviewed infliximab, adalimumab, and, most recently, vedolizumab, for moderate-to-severe CD. All three were recommended for reimbursement, subject to criteria or conditions.[4-6]

The manufacturer submitted a cost-utility analysis (CUA) comparing ustekinumab with infliximab (brand and biosimilar), adalimumab, vedolizumab, and conventional therapy (including corticosteroids or immunomodulators) for the treatment of moderately to severely active CD. The analysis was conducted from a Canadian public-payer perspective over a 25-year time horizon. Two target populations were included: patients with moderately to severely active CD who had experienced a failure with conventional therapy only (FCTO), and those who had experienced a failure with anti-TNF therapy. The analysis also included a mixed population of the two. The CUA evaluated a dosage regimen of 90 mg every eight weeks or every 12 weeks for ustekinumab as well as a regimen reflecting the blend of the two dosages. The model structure consisted of a decision tree to model the induction-treatment phase and a Markov (cohort) structure to model maintenance treatment for the remainder of the time horizon. Model transition probabilities for the induction and the maintenance phases were based on network meta-analyses (NMAs) and the IM-UNITI trial assessing ustekinumab. The manufacturer's base-case analysis did not include a cost for the IV administration of ustekinumab in the induction phase.

Summary of Identified Limitations and Key Results

CDR identified several key limitations with the model submitted by the manufacturer: uncertainty with the model transition probabilities and the utility values used. The former was mainly due to significant limitations and uncertainty with the NMAs used to populate the model transition probabilities, and the latter was because of inconsistency in how the utility values from the publication used by the manufacturer were implemented in the CUA. Other limitations identified by CDR concerned the data used for assessing infliximab, the adjustment of long-term transition probabilities using real-world evidence which favoured ustekinumab, and the uncertainty of the analysis in the long-term extrapolation of clinical data.

In the revised base case, CDR varied the health-state utility values and excluded the effect of real-world evidence on the transition probabilities after one year in the model. CDR also corrected an error in calculating the weighted average quality-adjusted life-years (QALYs) for the ustekinumab mixed dosage (every eight weeks/every 12 weeks) treatment option. This error appeared to default to the every eight weeks dosage, excluding the every 12 weeks dosage, and resulting in an overestimate of the incremental cost-utility ratio (ICUR) results for the ustekinumab mixed dosage.

The CDR base case for ustekinumab when compared with conventional therapy in the population experiencing FCTO resulted in an ICUR of $115,474 per QALY gained and in the population experiencing failure of anti-TNF therapy, $131,297 per QALY gained. For the mixed population, ustekinumab resulted in an ICUR of $119,058 per QALY when compared with conventional therapy.

Among the available biologic therapies in patients experiencing FCTO, ustekinumab every 12 weeks was the most cost-effective, with an ICUR of $115,474 per QALY compared with conventional therapy, followed by ustekinumab mixed dosage every eight weeks/every 12 weeks, with an ICUR of $623,571 per QALY when compared with ustekinumab every 12 weeks, then finally by ustekinumab every eight weeks, with an ICUR of $658,533 per QALY compared with ustekinumab mixed dosage. Other biologics were either dominated or subjected to extended dominance. In the patients who had experienced a failure with anti-TNF therapy, the most cost-effective treatment was biosimilar infliximab, with an ICUR of $90,277 per QALY compared with conventional therapy, followed by ustekinumab every 12 weeks with an ICUR of $228,571 per QALY compared with biosimilar infliximab. The remaining ustekinumab regimens (every eight weeks and mixed dosage) resulted in ICURs of more than $1 million per QALY. Remaining biologic therapies (adalimumab, infliximab and vedolizumab) were also dominated or subjected to extended dominance.

The manufacturer provided correspondence to this report indicating that the drug costs for the induction dose of ustekinumab would be reimbursed by the manufacturer. Excluding the drug costs incurred from the induction dose appears to improve the ICUR for ustekinumab when compared with conventional therapy in a population experiencing FCTO, with an ICUR of $95,442 per QALY gained, and in a population experiencing failure with anti-TNF therapy, with an ICUR of $77,840 per QALY gained. For the mixed FCTO and anti-TNF population, ustekinumab resulted in an ICUR of $91,260 per QALY compared with conventional therapy.

Conclusions

The efficacy and safety of ustekinumab compared with conventional and other biologic therapy were based on an indirect comparison with noted limitations and heterogeneity across studies that raise uncertainty over the comparative efficacy and safety of ustekinumab in both the induction and maintenance phases. Other key limitations of the economic model pertain to the utility values included and the effects of real-world evidence on transition probabilities. In light of these limitations, CDR suggests that the ICUR for ustekinumab ranges from $115,474 to $189,403 per QALY when compared with conventional therapy, and from being dominant to $870,045 per QALY when compared with other biologic therapies.

At an induction dose of 6 mg/kg followed by 90 mg at week 8 and every eight weeks thereafter, the cost of ustekinumab in year 1 ($33,798) and subsequent years ($29,855) is higher than the cost of vedolizumab ($26,320 and $21,458, respectively), adalimumab ($23,099 and $20,019, respectively), and infliximab (brand: $31,602 and $25,765, respectively; biosimilar: $16,800 and $13,697, respectively). When ustekinumab is administered every 12 weeks in the maintenance phase, the costs for year 1 ($24,612) and subsequent years ($19,904) are lower than or comparable to the other biologics, with the exception of biosimilar infliximab.

If the drug costs associated with the induction dose for ustekinumab are reimbursed by the manufacturer, the ICURs for ustekinumab compared with conventional therapy and other biologic therapies tend to improve, as would be expected.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis that compared ustekinumab with infliximab, adalimumab, vedolizumab, and conventional therapy (including corticosteroids or immunomodulators) for the treatment of moderately to severely active Crohn's disease (CD). The analysis was conducted from a Canadian public-payer perspective over a 25-year time horizon. Two target populations were included: patients with moderately to severely active CD who had experienced failure with conventional therapy only (FCTO) and patients who had experienced failure with anti-TNF therapy. The analysis also included a mixed population of these, weighted based on the proportion of patient subpopulations in the phase III maintenance trial for ustekinumab, IM-UNITI. The cost-utility analysis evaluated a dosage regimen of every eight weeks and every 12 weeks for ustekinumab, as well as a regimen reflecting the blend of the two doses. The model structure consisted of a decision tree to model the induction-treatment phase and a Markov (cohort) structure to model maintenance treatment for the remainder of the time horizon.

Progression of disease and resulting transition probabilities between health states during the induction phase of treatment were based on a network meta-analysis (NMA) estimating relative treatment effect. For the maintenance phase, another NMA was performed to inform transition probabilities for biologics other than ustekinumab, and the IM-UNITI trial informed the transition probabilities for ustekinumab and conventional therapy. Long-term real-world evidence was used to inform transition probabilities beyond one year. The manufacturer justified the use of such evidence based on the lack of clinical trial data for each biologic treatment beyond approximately one year.

Patients were allocated to one of three outcomes at the end of induction treatment: remission, response, and no-response. The health states in the maintenance-phase Markov model consisted of "response," "remission," and "loss of response." The "loss of response" health state for four model cycles (representing 16 weeks) was classified as a "treatment failure." Patients experiencing a treatment failure could escalate the dosage as appropriate according to the product's label, remain in "loss of response" and transition to conventional therapy as appropriate, or undergo surgery. Patients who underwent surgery in the model entered a "post-surgical response" health state. Upon a secondary loss of response after surgery, patients were re-treated with their index biologic and re-entered the model in either the "response" or "loss of response" health state. An optional oral corticosteroid-sparing remission health state was included to reflect the improvement in quality of life and decrease in costs from the subset of patients with a remission who do not require management with oral corticosteroids.[1]

Data on health care resource utilization were collected by the manufacturer through a Delphi panel conducted with Canadian clinicians experienced in treating CD. Costs of medications were obtained from the Ontario Ministry of Health and Long-Term Care Exceptional Access Program formulary and from the Ontario Drug Benefit formulary.[7] Utility values were obtained from a Canadian study by Gregor et al. (1997) for the remission, response, nonresponse, surgery, and post-surgery health states.[8] Discount rates were applied to both costs and health benefits at a rate of 5%.[1] The manufacturer's base-case analysis did not include a cost for the intravenous (IV) administration of ustekinumab in the induction phase.

2. MANUFACTURER'S BASE CASE

The manufacturer's base-case results are summarized in Table 2. Among the available biologic therapies in patients experiencing an FCTO, biosimilar infliximab was the most cost-effective, with an incremental cost-utility ratio (ICUR) of $32,045 per quality-adjusted life-year (QALY) compared with conventional therapy, followed by ustekinumab every 12 weeks, with an ICUR of $65,368 per QALY when compared with biosimilar infliximab, then finally by ustekinumab every eight weeks, with an ICUR of $610,102 per QALY compared with ustekinumab every 12 weeks. Other biologics were either dominated or subjected to extended dominance. In the patients experiencing a failure with anti-TNF therapy, the most cost-effective treatment was also biosimilar infliximab, with an ICUR of $8,730 per QALY compared with conventional therapy, followed by ustekinumab every 12 weeks with an ICUR of $103,621 per QALY compared with biosimilar infliximab, with the ustekinumab mixed dosage following with an ICUR of $911,556 per QALY, and finally ustekinumab every eight weeks with an ICUR of $1,025,500 per QALY. Remaining biologic therapies (adalimumab, infliximab, and vedolizumab) were also dominated or subjected to extended dominance.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	ICUR ($/QALY)	
	Versus Conventional Therapy	**Sequential Analysis**
Population experiencing FCTO		
Biosimilar infliximab q.8.w.	$32,045	$32,045
Ustekinumab q.12.w.	$50,898	$65,368
Ustekinumab q.8.w.	$86,393	$610,102
Adalimumab q.2.w.	$51,077	Subject to extended dominance[a]
Ustekinumab mixed q.8.w./q.12.w.	$71,708	Subject to extended dominance[b]
Vedolizumab q.8.w.	$79,250	Dominated by adalimumab q.2.w.
Infliximab q.8.w.	$94,594	Dominated by biosimilar infliximab q.8.w., vedolizumab q.8.w., adalimumab q.2.w.
Population experiencing failure with anti-TNF therapy		
Biosimilar infliximab q.8.w.	$8,730	$8,730
Ustekinumab q.12.w.	$38,767	$103,621
Ustekinumab mixed q.8.w./q.12.w.	$74,883	$911,556
Ustekinumab q.8.w.	$83,544	$1,025,500
Adalimumab q.2.w.	$35,719	Dominated by biosimilar infliximab q.8.w.
Infliximab q.8.w.	$92,698	Dominated by adalimumab q.2.w., biosimilar infliximab q.8.w., ustekinumab q.12.w.
Vedolizumab q.8.w.	$129,431	Dominated by adalimumab q.2.w., biosimilar infliximab q.8.w.
IM-UNITI (mixed) population		
Biosimilar infliximab q.8.w.	$26,551	$26,551
Ustekinumab q.12.w.	$48,962	$69,280
Ustekinumab q.8.w.	$86,002	$651,000

	ICUR ($/QALY)	
	Versus Conventional Therapy	**Sequential Analysis**
Adalimumab q.2.w.	$47,998	Subject to extended dominance[c]
Ustekinumab mixed q.8.w./q.12.w.	$72,300	Subject to extended dominance[d]
Vedolizumab q.8.w.	$84,063	Dominated by biosimilar infliximab q.8.w., adalimumab q.2.w.
Infliximab q.8.w.	$94,156	Dominated by biosimilar infliximab q.8.w., adalimumab q.2.w.

ICUR = incremental cost-utility ratio; FCTO = failure with conventional therapy only; QALY = quality-adjusted life-years; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; TNF = tumour necrosis factor.

[a] Subject to extended dominance through conventional therapy and ustekinumab q.12.w., biosimilar infliximab q.8.w. and ustekinumab q.12.w., biosimilar infliximab q.8.w. and ustekinumab mixed, biosimilar infliximab q.8.w. and ustekinumab q.8.w.

[b] Subject to extended dominance through ustekinumab q.12.w. and ustekinumab q.8.w.

[c] Subject to extended dominance through biosimilar infliximab q.8.w. and ustekinumab q.12.w., biosimilar infliximab q.8.w. and ustekinumab mixed, biosimilar infliximab q.8.w. and ustekinumab q.8.w.

[d] Subject to extended dominance through ustekinumab q.12.w. and ustekinumab q.8.w.

Source: Adapted from manufacturer's pharmacoeconomic submission.[1]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

In the population experiencing an FCTO, base-case results for ustekinumab (every eight weeks and every 12 weeks) were sensitive to the proportion of patients with 16 weeks in the nonresponse health state who underwent surgery, to the remission and nonresponse utility values used, and finally to the efficacy of the additional induction dose. For results in the population experiencing a failure with anti-TNF therapy, the most sensitive parameters were the remission utility value, the efficacy of the additional induction dose, and the probability of surgery after 16 weeks in the nonresponse health state.

The manufacturer conducted a scenario analysis comparing ustekinumab with conventional therapy with alternative costing for ustekinumab medication costs, including such aspects as rebates, free induction dose, annual -patient expenditure caps, and free ustekinumab after loss of response after surgery (Appendix 3, Table 12).

The manufacturer did not present a sensitivity analysis for the mixed population.

4. KEY LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Uncertainty of the model's transition probabilities:** For the induction phase, the estimation of the relative efficacy of compared treatments was based on an NMA. For the maintenance phase, a second NMA was used for the efficacy of biologics other than ustekinumab, and the IM-UNITI trial informed the transition probabilities for ustekinumab and conventional therapy (using individual patient data [IPD]). The CADTH Common Drug Review (CDR) clinical review identified limitations of the available indirect comparisons and could not make any definitive conclusion regarding the comparative efficacy of ustekinumab versus infliximab, adalimumab, and vedolizumab for induction. The CDR clinical review also identified several serious limitations of the methodology (treatment-sequence analysis) and of the evidence base for the indirect comparisons of the maintenance phases of treatment and could not make any conclusion regarding the comparative efficacy of ustekinumab versus infliximab, adalimumab, and vedolizumab for that analysis. In

addition, the manufacturer highlighted in its submission that, if the NMA for the maintenance phase is considered inappropriate because of potential carry-over effects from the induction phase, then placebo response rates in the maintenance phase may vary across trials, thus influencing the relative treatment effects used as inputs for the analysis of the maintenance phase. Finally, use of IPD means there is no adjustment with a comparator when estimating treatment effect size. Since ustekinumab had the largest absolute treatment effect sizes, using IPD biases the results in favour of ustekinumab. CDR could not test the effect of this limitation on the uncertainty with the model's transition probabilities.

- **Uncertainty of the effectiveness of infliximab:** There were limitations on assessing infliximab for two reasons. In the case of the population with an FCTO, there were different definitions of response used in clinical trials comparing ustekinumab with other biologics. In the case of the population with a failure of anti-TNF therapy, there was a lack of data in this population, given that infliximab was the first approved biologic. The manufacturer's submission instead used data from adalimumab for the population with a failure of anti-TNF therapy, although the patients' baseline characteristics in these clinical trials differed from those in the ustekinumab trials. CDR could not test this limitation with enough certainty.
- **Utility values for model's health states:** The manufacturer assumed utility values from a Canadian study that asked a cohort of patients with CD to rate three hypothetical disease states representing mild (0.82), moderate (0.73), and severe disease (0.54) using a standard gamble approach.[8] The publication also reported utility values for remission (0.88), chronically active therapy–responsive (0.86), and therapy-resistant (0.74). For the manufacturer's model, the remission, response, and no-response health states were assigned utilities of 0.88, 0.73, and 0.54, respectively. There is inconsistency in how the utility values from the publication were used in the manufacturer's model, which raises uncertainty with regard to the results of the analysis. CDR conducted two scenario analyses, one applying more appropriately to the model the utilities from the Canadian study used by the manufacturer, and the other using an alternative source of utility values (Table 13).
- **Overestimation of QALYs for ustekinumab mixed dosage (every eight weeks/every 12 weeks):** The submitted model indicated that a weighted average for costs and QALYs for every eight weeks and every 12 weeks dosages was applied to estimate the results for the mixed-dosage regimen. On verification, the model did not apply the weighted average for QALYs but appeared to default to the every eight weeks QALYs, which were more favourable than the every 12 weeks QALY results. This error overestimated the ICUR results for the mixed dose. This was corrected by CDR.
- **Adjustment of the maintenance-phase transition probabilities using real-world evidence: The** manufacturer acknowledged that adjusting these transition probabilities to real data was challenging because of limited real-world evidence. The manufacturer also recognized that a limitation of the approach was its application to the transition at one year, at the end of the trials, at which time point the approach resulted in an "uptick" effect. The manufacturer argued that the uptick meant that the proportions of patients in remission and response in the final cycles of year 1 were artificially low and that the uptick was simply a correction.[1] However, this favoured ustekinumab. The manufacturer's argument for the relevance of this approach with regard to its uncertainty is not convincing. CDR reanalysis excluded the impact of real-world evidence on the transition probabilities.
- **Time horizon:** The submitted model used a time horizon of 25 years. Although CD is a chronic condition, the limitation with a long time horizon is that a significant proportion of patients are expected to experience a waning efficacy of therapy over 25 years. Therefore, the benefits in long-term survival may bias against the disutility in those who lose response more rapidly. CDR conducted an exploratory analysis testing a time horizon of 10 years (Appendix 3).

5. CADTH COMMON DRUG REVIEW REANALYSES

As described above, the CDR base case varied the model time horizon and health-state utility values (using two scenarios), as well as assessing the impact of excluding the effect of real-world evidence on the transition probabilities after one year in the maintenance phase of the model. CDR also corrected the error that overestimated the ICUR results for the mixed dosage. One-way and multi-way reanalyses were performed varying these model components (Appendix 3). The model was particularly sensitive to variations in health-state utility values and to the exclusion of real-world evidence when estimating transition probabilities.

The CDR base case for ustekinumab when compared with conventional therapy in the population experiencing an FCTO resulted in an ICUR of $115,474 per QALY gained and, in the population experiencing a failure of anti-TNF therapy, $131,297 per QALY gained. For the mixed population, ustekinumab resulted in an ICUR of $119,058 per QALY when compared with conventional therapy.

Among the available biologic therapies in patients who had experienced an FCTO, ustekinumab every 12 weeks was the most cost-effective, with an ICUR of $115,474 per QALY compared with conventional therapy, followed by ustekinumab mixed dosage (every eight weeks/every 12 weeks), with an ICUR of $623,571 per QALY when compared with ustekinumab every 12 weeks, then finally by ustekinumab every eight weeks with an ICUR of $658,533 per QALY compared with ustekinumab mixed dosage. Other biologics were either dominated or subjected to extended dominance. In the patients with a failure of anti-TNF therapy, the most cost-effective treatment was biosimilar infliximab, with an ICUR of $90,277 per QALY compared with conventional therapy, followed by ustekinumab every 12 weeks with an ICUR of $228,571 per QALY compared with biosimilar infliximab, with the remaining ustekinumab regimens (every eight weeks and mixed dosage) resulting in ICURs of more than $1 million per QALY. Remaining biologic therapies (adalimumab, infliximab, and vedolizumab) were also dominated or subjected to extended dominance.

The manufacturer provided correspondence to this report indicating that the drug costs with the induction dose for ustekinumab would be reimbursed by the manufacturer. Excluding the drug costs incurred from the induction dose appears to improve the ICUR for ustekinumab when compared with conventional therapy in a population experiencing an FCTO, with an ICUR of $95,442 per QALY gained, and in a population experiencing a failure of anti-TNF therapy, with an ICUR of $77,840 per QALY gained. For the mixed population, ustekinumab resulted in an ICUR of $91,260 per QALY compared with conventional therapy. Additional information is provided in APPENDIX 3.

TABLE 3: RESULTS OF CDR MULTI-WAY ANALYSIS USING HEALTH STATE UTILITY FROM CDR MODELS

	ICUR ($/QALY)	
	Versus Conventional Therapy	**Sequential Analysis**
Population experiencing FCTO		
Ustekinumab q.12.w.	$115,474	$115,474
Ustekinumab mixed q.8.w./q.12.w.	$147,517	$623,571
Ustekinumab mixed q.8.w.	$169,543	$658,533
Biosimilar infliximab q.8.w.	$143,062	Subject to extended dominance[a]
Adalimumab q.2.w.	$164,583	Subject to extended dominance[b]

	ICUR ($/QALY)	
	Versus Conventional Therapy	**Sequential Analysis**
Vedolizumab q.8.w.	$271,363	Dominated by adalimumab q.2.w.
Infliximab q.8.w.	$342,856	Dominated by biosimilar infliximab q.8.w., vedolizumab q.8.w., adalimumab q.2.w.
Population experiencing failure with anti-TNF therapy		
Biosimilar infliximab q.8.w.	$90,277	$90,277
Ustekinumab q.12.w.	$131,297	$228,571
Ustekinumab mixed q.8.w./q.12.w.	$189,403	$1,332,167
Ustekinumab q.8.w.	$203,880	$1,999,000
Adalimumab q.2.w.	$134,373	Dominated by biosimilar infliximab q.8.w.
Infliximab q.8.w.	$284,904	Dominated by adalimumab q.2.w., biosimilar infliximab q.8.w., ustekinumab q.12.w., ustekinumab mixed
Vedolizumab q.8.w.	$500,920	Dominated by adalimumab q.2.w., biosimilar infliximab q.8.w.
IM-UNITI (mixed) population		
Ustekinumab q.12.w.	$119,058	$119,058
Ustekinumab q.8.w.	$177,093	$744,826
Biosimilar infliximab q.8.w.	$120,923	Subject to extended dominance[c]
Adalimumab q.2.w.	$154,194	Subject to extended dominance[d]
Ustekinumab mixed q.8.w./q.12.w.	$157,268	Subject to extended dominance[e]
Vedolizumab q.8.w.	$311,328	Dominated by biosimilar infliximab q.8.w., adalimumab q.2.w.
Infliximab q.8.w.	$317,945	Dominated by biosimilar infliximab q.8.w., adalimumab q.2.w., ustekinumab q.12.w.

FCTO = failure with conventional therapy only; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; TNF = tumour necrosis factor.

[a] Subject to extended dominance through conventional therapy and ustekinumab q.12.w.

[b] Subject to extended dominance through conventional therapy and ustekinumab q.12.w., biosimilar infliximab q.8.w. and ustekinumab q.12.w., conventional therapy and ustekinumab mixed, biosimilar infliximab q.8.w. and ustekinumab mixed, biosimilar infliximab q.8.w. and ustekinumab q.8.w.

[c] Subject to extended dominance through conventional therapy and ustekinumab q.12.w.

[d] Subject to extended dominance through conventional therapy and ustekinumab q.12.w., biosimilar infliximab q.8.w. and ustekinumab q.12.w., biosimilar infliximab q.8.w. and ustekinumab mixed, biosimilar infliximab q.8.w. and ustekinumab q.8.w.

[e] Subject to extended dominance through ustekinumab q.12.w. and ustekinumab q.8.w.

6. ISSUES FOR CONSIDERATION

Ustekinumab is currently indicated for plaque psoriasis and psoriatic arthritis. There is potential for ustekinumab to be used off-label as a treatment option for ulcerative colitis, thus leading to increased overall costs for this class of treatments. Also, ustekinumab is the only available biologic that requires IV infusions for the induction phase, followed by subcutaneous administration for the maintenance phase. Costing discrepancies between these modes of administration may affect the overall cost of treatment and budgets for jurisdictions. The manufacturer provided a response confirming that administration costs of the IV dose for ustekinumab would be reimbursed by the manufacturer under the same program that supports the administration of the IV doses of infliximab (Remicade).

7. PATIENT INPUT

Input was received from the Gastrointestinal (GI) Society and Crohn's and Colitis Canada. According to the input, subcutaneous administration for treatment maintenance was seen as appealing and would reduce the need to travel to infusion centres. Patients also described the expected improvements in quality of life and the ability of the drug to provide patients with a more normal and stable life without the effects of CD. The manufacturer's economic submission captured quality of life while patients receive ustekinumab but did not model administration costs or all adverse events associated with biologics therapy except serious infections.

8. CONCLUSIONS

The efficacy and safety of ustekinumab compared with conventional and other biologic therapy were based on an indirect comparison with noted limitations and heterogeneity across studies that raise uncertainty concerning the comparative efficacy and safety of ustekinumab in both the induction and maintenance phases. Other key limitations of the economic model pertain to the utility values included and the effects of real-world evidence on transition probabilities, despite the lack of supportive data. In light of these limitations, CDR suggests that the ICUR for ustekinumab ranges from $115,474 to $189,403 per QALY when compared with conventional therapy, and from being dominant to $870,045 per QALY when compared with other biologic therapy.

At an induction dose of 6 mg/kg followed by 90 mg at week 8 and every eight weeks thereafter, the cost of ustekinumab in year 1 ($33,798) and subsequent years ($29,855) is higher than the cost of vedolizumab ($26,320 and $21,458, respectively), adalimumab ($23,099 and $20,019, respectively), and infliximab (brand: $31,602 and $25,765, respectively; biosimilar: $16,800 and $13,697 respectively). When ustekinumab is administered every 12 weeks in the maintenance phase, the costs for year 1 ($24,612) and subsequent years ($19,904) are lower than or comparable to the other biologics, with the exception of biosimilar infliximab.

If the drug costs associated with the induction dose for ustekinumab are reimbursed by the manufacturer, the ICURs for ustekinumab compared with conventional therapy and other biologic therapies tend to improve, as would be expected.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 4 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice, rather than actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Existing product reimbursement agreements are not reflected in the table; as a result, prices may not represent the actual costs to public drug plans.

TABLE 4: COST-COMPARISON TABLE OF BIOLOGICS FOR THE TREATMENT OF CROHN'S DISEASE

Drug / Comparator	Strength	Dosage Form	Price	Recommended Dose	Drug Cost in Year 1	Average Drug Cost Subsequent Years
Ustekinumab (Stelara)	**130 mg/26 mL** **90 mg/1.0 mL**	**Vial for IV infusion** **Single-use pre-filled syringe for SC injection**	**$2,079.84[a]** **$4,593.15[a]**	**6 mg/kg IV injection for induction at week 0, followed by 90 mg SC injection at week 8, and every 8 weeks or every 12 weeks thereafter**	**$33,798[b]** **$24,612[c]**	**$29,855[b]** **$19,904[c]**
Vedolizumab (Entyvio)	300 mg	Vial for IV infusion	$3,290.00[d]	300 mg at weeks 0, 2, and 6, followed by every 8 weeks thereafter	$26,320	$21,458
Anti-TNF Alpha Therapies						
Adalimumab (Humira)	40 mg	Pen for SC injection	$769.97	160 mg week 0, 80 mg week 2, 40 mg week 4, and every 2 weeks thereafter	$23,099	$20,019
Infliximab (Remicade)	100 mg	Vial for IV infusion	$987.56	5 mg/kg at weeks 0, 2, and 6, then every 8 weeks thereafter. May be increased to 10 mg/kg every 8 weeks in patients who have lost response	$31,602 to $46,415	$25,765 to $45,088
Infliximab (Inflectra)	100 mg	Vial for IV infusion	$525.00[e]	5 mg/kg at weeks 0, 2, and 6, then every 8 weeks thereafter. May be increased to 10 mg/kg every 8 weeks in patients who have lost response	$16,800 to $24,675	$13,697 to $23,970

IV = intravenous; SC = subcutaneous; TNF = tumour necrosis factor.
All prices are from the Ontario Drug Benefit Formulary Exceptional Access Program (July 2016) unless otherwise indicated.[7]
All weight-based dosage is based on an average weight of 69.8 kg as in the manufacturer's economic submission.[1]
[a] Manufacturer's submitted and current market price.[1]
[b] Based on receiving a dose once every 8 weeks.
[c] Based on receiving a dose once every 12 weeks.
[d] CADTH Canadian Drug Expert Committee Final Recommendation for vedolizumab (Entyvio) for ulcerative colitis (October 28, 2015).[9]
[e] Ontario Drug Benefit Formulary list price.[10]

TABLE 5: COST-COMPARISON TABLE OF OTHER DRUG CLASSES FOR TREATMENT OF CROHN'S DISEASE

Drug / Comparator	Strength	Dosage Form	Price	Recommended Dose[c]	Average Daily Cost	Average Annual Cost
Immunomodulators						
Methotrexate	2.5 mg	Tab	$0.6325	Maintenance therapy only: 12.5 to 22.5 mg weekly	$0.45 to $0.81	$164 to $296
	50 mg/ 2 mL 20 mg/ 2 mL	Injection Injection	$8.9200 $12.5000	25 mg IM/SC weekly for 16 weeks to induce remission, then 15 mg weekly IM/SC	Induction dose: $0.64 Maintenance dose: $1.79	Induction alone: $71 Induction + maintenance therapy: $521
Azathioprine (Imuran and generics)	50 mg	Tab	$0.2405	2 to 3.5 mg/kg daily	$0.72 to $1.20	$263.35 to $438.91
6-mercaptopurine (Purinethol)	50 mg	Tab	$2.8610	1 to 2.5 mg/kg daily	$4.29 to $10.01	$1,566 to $3,655
Cyclosporine (Neoral)	25 mg 50 mg 100 mg	Capsule	$0.9952 $1.9400 $3.8815	5 to 7.5 mg/kg daily divided every 12 hours	$13.58 to $20.40	$4,958 to $7,447
Corticosteroids						
Betamethasone enema (Betnesol)	5 mg/ 100 mL	Enema	$10.7314	5 mg nightly	$10.73	$3,917
Budesonide (Entocort)	0.02 mg/mL	Enema	$8.8900[b]	2 mg nightly for 8 weeks	$8.89	$498
Hydrocortisone enema (Hycort/Cortenema) (Cortifoam)	100 mg/ 60 mL 15 g/pk (14 doses)	Enema Rectal aerosol	$7.2711 $94.99	60 mL nightly or every other night One dose nightly or every other night	$3.64 to $7.27 $3.39 to $6.79	$1,327 to $2,654 $1,238 to $2,477
Hydrocortisone (generic)	100 mg 250 mg 500 mg 1000 mg	vial	$2.5585[b] $4.3494[b] $6.5244[b] $11.0019[b]	300 to 400 mg IV daily	$7.68 to $10.23	N/A

Drug / Comparator	Strength	Dosage Form	Price	Recommended Dose[c]	Average Daily Cost	Average Annual Cost
Methylprednisone (generic)	40 mg/mL 80 mg/mL 100 g/5 mL	Injection suspension	$5.6388 $10.8160 $12.6271	40 mg to 60 mg IV daily	$5.64 to $8.46	N/A
Prednisone (generic)	1 mg 5 mg 50 mg	Tablet	$0.1066 $0.0220 $0.1735	40 mg to 60 mg daily to induce remission; then lower dose	$0.18 to $0.22	$64 to $79 or lower
Aminosalicylates						
5-ASA (Asacol, Asacol 800)	400 mg	Tablet	$0.3951	Active: 0.8 to 3 g daily in divided doses Maintenance: 1.6 g daily in divided doses	$0.79 to $4.74 $1.58	$288 to $1,731 $577
	800 mg	Ent. Tab	$1.0938	4.8 g daily in divided doses	$6.56	$2,395
5-ASA (Mesasal)	500 mg	Ent. Tab	$0.6559	Active: 1.5 to 3 g tabs daily in divided doses Maintenance: 1.5 g daily in divided doses	$1.97 to $3.94 $1.97	$718 to $1,436 $718
5-ASA (Pentasa)	500 mg	Delayed-release Tab	$0.5569	2 to 4 g daily in divided doses	$2.23 to $4.46	$813 to $1,626
	1,000 mg 1 g/100 mL 4 g/100 mL	Suppository Enema Enema	$1.6000 $3.7000 $4.4600	Suppository: 1g daily Enema: 1 to 4 g daily	$1.60 $3.70 to $4.46	$584 $1,351 to $1,628
5-ASA (Salofalk)	500 mg	Ent. Tab	$0.5991	3 to 4 g daily in divided doses	$3.59 to $4.79	$1,312 to $1,749
	500 mg 1,000 mg	Suppository Suppository	$1.3243 $1.9453	Suppository: 1 to 1.5 g daily	$1.95 to $3.97	$712 to $1,449
	2 g/100 mL 4 g/100 mL	Rectal Suspension	$3.9967[b] $7.0351	Active: 4 g nightly Maintenance: 2 g nightly or 4 g every two nights	$7.04 $3.52 to $4.00	$2,568 $1,222 to $1,387
Sulfasalazine (Salazopyrin and generics)	500 mg 500 mg	Tab Ent Tab	$0.1804 $0.2816	Active: 1 to 2 g three to four times daily Maintenance: 1 g two to three times daily	$1.08 to $4.51 $0.72 to $1.69	$395 to $1,645 $263 to $617

Drug / Comparator	Strength	Dosage Form	Price	Recommended Dose[c]	Average Daily Cost	Average Annual Cost
Olsalazine (Dipentum)	250 mg	Capsule	0.5330	Active: 1 to 3 g daily in divided doses Maintenance: 1 g daily in divided doses	$2.13 to $6.40 $2.13	$778 to $2,335 $778

Ent. = enteric; IV = intravenous; SC = subcutaneous; Tab = tablet.
All prices are from the Ontario Drug Benefit Formulary (November 2016) unless otherwise indicated.[10]
All weight-based dosage is based on an average weight of 69.8 kg as in the manufacturer's economic submission.[1]

APPENDIX 2: ADDITIONAL INFORMATION

TABLE 6: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

TABLE 7: AUTHORS' INFORMATION

Authors of the pharmacoeconomic evaluation submitted to CDR			
☐ Adaptation of global model/Canadian model done by the manufacturer ☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

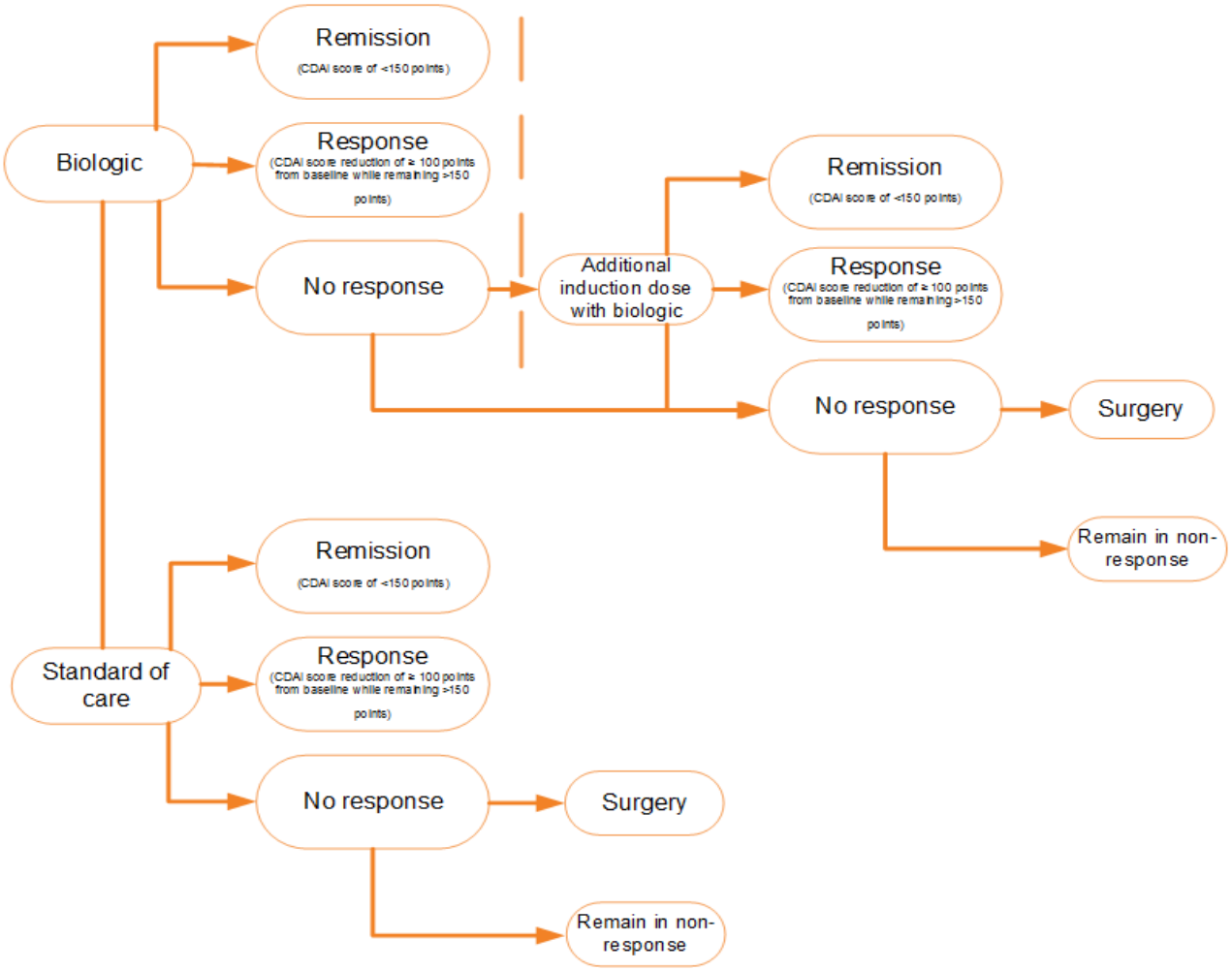
APPENDIX 3: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The model estimates disease progression through a series of health states, classifying patients with Crohn's disease (CD) based on Crohn's Disease Activity Index (CDAI) score as well as the occurrence of surgery and the subsequent loss of response following surgery. The model structure consisted of a decision tree to model the induction-treatment phase and a Markov (cohort) structure to model maintenance treatment for the remainder of the time horizon.

The model structure of the induction phase is based on a decision tree that allocates patients to one of three outcomes following the end of induction treatment: remission, response, and no-response. Patients allocated to the remission or response outcomes move to the maintenance phase based on relative efficacy data for induction (versus conventional therapy) estimated in a network meta-analysis (NMA) conducted by the manufacturer. Patients receiving conventional therapy who do not demonstrate response to the induction treatment are classified as having experienced a treatment failure, and can undertake surgery or remain indefinitely in a state of nonresponse. Patients initiating biologic therapy who do not achieve response after the standard assessment of induction can either receive an additional induction dose, undergo surgery, or remain in a nonresponse state, receiving conventional therapy but not undergoing surgery later (Figure 1).[1]

FIGURE 1: MODEL STRUCTURE — INDUCTION

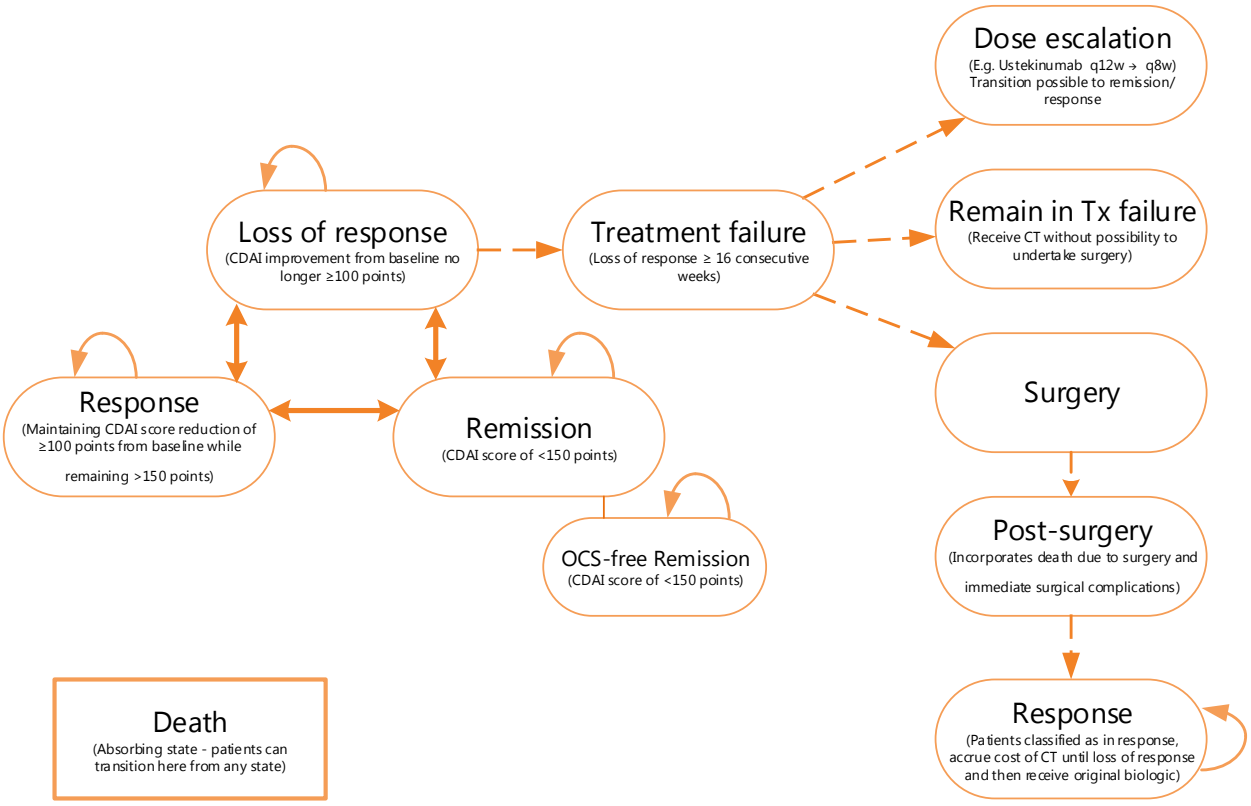


CDAI = Crohn's Disease Activity Index.
Source: Manufacturer's pharmacoeconomic submission.[1]

The maintenance phase is modelled using discrete cycles corresponding to the four-week frequency of the assessment of response in the ustekinumab trials. Maintenance is driven by three health states: remission (CDAI < 150), response (CDAI maintained more than 100 points less than baseline CDAI), and loss of response. The base case uses the 100-point definition of CDAI improvement, which was derived from the primary end points of the adalimumab and vedolizumab trials. The infliximab trials used a 70-point definition to assess response, rather than CDAI-100, which requires infliximab results to be interpreted with caution, as its rate of response relative to the comparators would be overestimated.

Oral corticosteroid (CS)-free remission is presented in the diagram as a separate health state, although patients in this health state were assumed to progress based on the same transition probabilities as the remission health state but with lower disease management costs and improved quality of life.[1]

FIGURE 2: MODEL STRUCTURE — MAINTENANCE



CDAI = Crohn's Disease Activity Index; CT = conventional therapy; OCS = oral corticosteroid; q8w = every 9 weeks; q12w = every 12 weeks; Tx = therapy.
Source: Manufacturer's pharmacoeconomic submission.[1]

TABLE 8: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy in induction phase	The efficacy of comparators in the induction phase was estimated from an NMA conducted by the manufacturer (2015).[12] ORs were estimated from the NMA, analyzing the relative risks of achieving response and remission versus the placebo group from the UNITI-1 and UNITI-2 trials for each treatment of interest (adalimumab, infliximab, vedolizumab) and stratified by treatment experience.[12]	The CDR clinical review concluded that there were several limitations with the available indirect comparisons and heterogeneity across studies; as a result, the comparative efficacy of ustekinumab against infliximab, adalimumab, and vedolizumab is uncertain for both the induction and maintenance phases of treatment. The manufacturer mentioned in its submission that it considered the NMA for the maintenance phase to be inappropriate because potential carry-over effects from the induction phase
Efficacy of additional induction doses	Ustekinumab – Based on patient responses in the UNITI-1 and UNITI-2 trials. Adalimumab – From the CHARM study among patients who were not in response at week 4 and who received additional doses into the maintenance phase[13] Vedolizumab – Based on the GEMINI II trial patients who failed to demonstrate response at week 6 to doses of vedolizumab 300 mg at week 0 and week 2 and were	

Data Input	Description of Data Source	Comment
	retained in the study and received additional doses every four weeks[14]	can drive maintenance placebo response rates to vary across trials and influence the relative treatment effects used as inputs for the analysis of the maintenance phase.
Efficacy in maintenance phase	For ustekinumab, the proportions of patient in response, remission, and nonresponse at the beginning and end of maintenance treatment were retrieved from the q.8.w. and q.12.w. arms in IM-UNITI trial.[15] Patients who did not receive biologic treatment at any time during the UNITI trials were considered as a proxy for patients on conventional therapy to week 52.[16,17] For adalimumab, vedolizumab, and infliximab, the proportions of patients in response, remission, and nonresponse at 52 weeks were obtained from an NMA considering the CHARM, GEMINI-II and ACCENT I (at 56 weeks) trials, respectively.[13,14,18]	
Patient baseline characteristics	The cohort was assumed to be 36 years old and to weigh 69 kg, based on baseline data from the active treatment arms of the ustekinumab induction and maintenance clinical trials (UNITI-1, UNITI-2, and IM-UNITI).[15-17]	Acceptable
Utilities	The manufacturer indicated that utility values were obtained from a published Canadian study by Gregor et al.(1997) for the remission, response, nonresponse, surgery, and post-surgery health states.[8] The study estimated utility values based on the responses of 180 Canadian patients with CD to the time trade-off, visual analogue scale, and standard gamble methods of health state valuation. A separate publication was used to derive the utility benefit of being in the steroid-free remission health state (Greenberg et al.).[19]	The utility value used by the manufacturer for the remission health state (0.88) was higher than the value cited in Gregor et al.[29] for the remission health state (0.82). This biases the results in favour of ustekinumab.
Resource use		
Adverse events	Adverse events associated with conventional or biologics treatments were not included (except serious infections).	Acceptable
Mortality	Background mortality is based on the reported Canadian mortality risk by age and sex.[1]	Acceptable
Costs		
Drug	Costs of medications were obtained from the Ontario Ministry of Health and Long-Term Care Exceptional Access Program formulary[7] and from the Ontario Drug Benefit formulary.[10]	Drug wastage and vial-sharing were integrated in the model.
Administration	Not included in the base case	Provided a value of $367 per IV administration for use in sensitivity analyses; this was based on a published study on administration costs of IV biologics for rheumatoid arthritis in Finland.[20] These cost data are very limited for use in a Canadian perspective, but the results of the analysis are not sensitive to varying this data.

Data Input	Description of Data Source	Comment
Routine management	Costs of management by disease stage were calculated based on health care resource use estimated from an unpublished Delphi panel conducted by Janssen Inc.[1] and using costs obtained from the Ontario Schedule of Benefits Physician Services [21] and the Ontario Schedule of Laboratory Fees.[22]	The manufacturer's Delphi panel is associated with uncertainty, especially as it involves a small sample of physicians. This raises uncertainty concerning the included management costs in the model and ultimately the results of the analysis.
Serious infections	Costs of serious infections while patients are receiving biologic treatment were included, based on data from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) registry on rates of serious infections in patients with IBD who were treated for psoriasis with ustekinumab and other biologic therapies[23] and using costs of treatment of infections obtained from the Ontario Case Costing Initiative Database.[1]	Acceptable
Surgery	Based on the published Canadian study on hospitalizations and operations for Crohn's disease by Bernstein et al. (2012).[24] Health care resource use 6 months before and following surgery was based on the Delphi panel (see *Routine management*)	The costs of complications of surgery have not been included, given that the management of these short-term complications are assumed to be covered in the cost of surgery.

CD = Crohn's disease; CDR = CADTH Common Drug Review; IBD = inflammatory bowel disease; IV = intravenous; NMA = network meta-analysis; OR = odds ratio; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks.

TABLE 9: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
The efficacy of infliximab was assumed to be equivalent to that of adalimumab in the population experiencing failure with anti-TNF therapy	Appropriate, as infliximab was the first anti-TNF treatment introduced.
Drug-administration costs were not included in the base-case analysis, as treatments were subcutaneous and therefore self-administered	Although ustekinumab requires IV administration in the induction phase, a patient may self-administer in the maintenance phase if a physician determines that it is appropriate after proper training in subcutaneous injection technique. The manufacturer did not mention providing patient management for IV administration at the induction phase. Infliximab and vedolizumab are administered intravenously in both the induction and the maintenance phases, and the manufacturer of these therapies provides patient management for IV administration.
Time horizon set at 25 years	Although Crohn's disease is a chronic and lifelong condition, efficacy of the treatments is expected to wane over a 25-year period. The manufacturer's model included the waning effects based on real-world evidence.
Beyond 1 year, the maintenance transition matrices based on 1-year clinical trial data were adjusted to align with the results of the Chaparro et al. study evaluating	This approach favours the results for ustekinumab.

Assumption	Comment
the long-term response of adalimumab in patients withCD.[25]	
For patients in the "loss of response" health state for 16 consecutive weeks, 30% were assumed to undergo immediate surgery.	Based on expert opinion, the percentage of patients undergoing surgery depends on their treatment history: in those who have had resistance to conventional therapies, the percentage will be lower, whereas in those with resistance to previous anti-TNF therapy, the percentage will be higher. However, when the two populations are pooled, the 30% assumption by the manufacturer seems appropriate.
Patients maintain post-surgery response based on a median time to loss of response of 24 months.	Despite the lack of long-term evidence to support this assumption, the feedback from the clinical expert suggests it may be appropriate.
94% of patients respond to re-initiation of biologic treatment post-surgery, of which 55% are assumed to be in remission. This was based on the results of a prospective study of patients with IBD that evaluated the rate of response to retreatment after discontinuation of anti-TNF treatments in patients with IBD in deep remission.[26]	The manufacturer stated that the included study was not comparable to the target population in the model, given that it assessed IBD patients in deep remission who discontinued biologic treatment and then re-started it.
Upon a secondary loss of response after surgery, patients were re-treated with their index biologic drug and re-entered the model in either the "response" or "loss of response" health state. An optional oral corticosteroid-sparing remission health state was included to reflect the improvement in quality of life and decrease in costs from the subset of patients in remission who do not require management with oral corticosteroids.	Although the submitted model included a steroid-free remission health state, the manufacturer did not use it in the base-case analysis. The manufacturer justified this on the basis of the challenge of quantifying the benefit of steroid-free remission with a utility, due to the lack of data. Also, the manufacturer acknowledged the difficulty in estimating the proportion of patients who could achieve steroid-free remission for all of the comparators. This leads to uncertainty of the analysis.
The manufacturer assumed that patients remain in a state of response following second surgery, accruing costs and QALYs corresponding to the response health state.	This assumption is limited by the lack of long-term data, including long-term efficacy of biologic drugs post-surgery, as well as disease progression following two total operations.

CD = Crohn's disease; IBD = inflammatory bowel disease; IV = intravenous; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.

Manufacturer's Results

For patients experiencing a failure of conventional therapy only (FCTO), ustekinumab at both doses was associated with the highest number of quality-adjusted life-years (QALYs) versus all other comparators. Compared with conventional therapy, ustekinumab every eight weeks had an incremental cost-utility ratio (ICUR) of $86,424 per QALY, after which ustekinumab every 12 weeks had an ICUR of $50,912 per QALY, followed by the mixed every 12 weeks/every eight weeks ustekinumab group with an ICUR of $69,575 per QALY. Biosimilar infliximab every two weeks had the lowest ICUR compared with conventional therapy, at $32,032 per QALY (Table 10).

TABLE 10: MANUFACTURER BASE-CASE RESULTS COMPARED WITH CONVENTIONAL THERAPY

	Total costs ($)	Incremental Costs Vs. Conventional Therapy	Total QALYs	Incremental QALYs Vs. Conventional Therapy	Incremental Cost Per QALY Vs. Conventional Therapy
In population experiencing FCTO					
Conventional therapy	$147,462	0	8.170	0	0
Infliximab q.8.w.	$218,975	$71,513	8.926	0.756	$94,555
Biosimilar infliximab q.8.w.	$171,688	$24,226	8.926	0.756	$32,032
Vedolizumab q.8.w.	$213,715	$66,253	9.006	0.836	$79,242
Adalimumab q.2.w.	$194,810	$47,349	9.097	0.927	$51,072
Ustekinumab q.12.w.	**$236,075**	**$88,614**	**9.911**	**1.740**	**$50,912**
Ustekinumab q.8.w.	**$308,067**	**$160,605**	**10.029**	**1.859**	**$86,414**
Ustekinumab mixed q.8.w./q.12.w.	**$277,110**	**$129,649**	**9.978**	**1.808**	**$71,716**
In population experiencing failure with anti-TNF therapy					
Conventional therapy	$313,745	0	8.060	0	0
Infliximab q.8.w.	$340,164	$26,419	8.345	0.285	$92,676
Biosimilar infliximab q.8.w.	$316,233	$2,488	8.345	0.285	$8,727
Vedolizumab q.8.w.	$327,853	$14,107	8.169	0.109	$129,112
Adalimumab q.2.w.	$323,925	$10,180	8.345	0.285	$35,711
Ustekinumab q.12.w.	**$329,911**	**$16,166**	**8.477**	**0.417**	**$38,764**
Ustekinumab q.8.w.	**$350,421**	**$36,676**	**8.499**	**0.439**	**$83,535**
Ustekinumab mixed q.8.w./q.12.w.	**$346,319**	**$32,574**	**8.495**	**0.435**	**$74,944**
IM-UNITI (mixed) population					
Conventional therapy	$222,289	0	8.121	0	0
Infliximab q.8.w.	$273,510	$51,221	8.665	0.544	$94,112
Biosimilar infliximab q.8.w.	$236,733	$14,444	8.665	0.544	$26,539
Vedolizumab q.8.w.	$265,077	$42,788	8.630	0.509	$84,059
Adalimumab q.2.w.	$252,912	$30,623	8.759	0.638	$47,984
Ustekinumab q.12.w.	**$278,301**	**$56,012**	**9.265**	**1.144**	**$48,921**
Ustekinumab q.8.w.	**$327,126**	**$104,837**	**9.340**	**1.219**	**$85,947**
Ustekinumab mixed q.8.w./q.12.w.	**$308,254**	**$85,965**	**9.310**	**1.189**	**$72,247**

FCTO = failure with conventional therapy only; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; QALY = quality-adjusted life-year, TNF = tumour necrosis factor; vs. = versus.
Source: Manufacturer's pharmacoeconomic submission.[1]

In the anti-TNF failure subpopulation, biosimilar infliximab every eight weeks had the lowest ICUR of $8,727 per QALY compared with conventional treatments, after which ustekinumab every 12 weeks resulted in an ICUR of $38,764 per QALY, followed by the mixed ustekinumab every eight weeks/every

12 weeks with an ICUR of $74,192 per QALY, and ustekinumab every eight weeks with an ICUR of $83,535 per QALY (Table 10).

The results of the analyses comparing ustekinumab and other biologics with each other are presented in Table 11.

TABLE 11: MANUFACTURER BASE-CASE RESULTS COMPARED WITH OTHER BIOLOGICS

	ICUR ($/QALY) versus			
	Biosimilar Infliximab q.8.w.	**Vedolizumab q.8.w.**	**Adalimumab q.2.w.**	**Ustekinumab q.12.w.**
Population experiencing FCTO				
Infliximab q.8.w.	-	Dominated	Dominated	$17,375[a]
Biosimilar infliximab q.8.w.	-	$526,846[a]	$135,392[a]	$65,421[a]
Vedolizumab q.8.w.	$526,846	-	Dominated	$24,723[a]
Adalimumab q.2.w.	$135,392	Dominant	-	$50,730[a]
Ustekinumab q.12.w.	$65,421	$24,723	$50,730	-
Ustekinumab q.8.w.	$123,728	$92,278	$121,589	$609,866
Ustekinumab mixed q.8.w./q.12.w.	$100,260	$65,241	$93,448	$609,866
Population experiencing failure with anti-TNF therapy				
Infliximab q.8.w.	-	$70,031	Dominated	Dominated
Biosimilar infliximab q.8.w.	-	Dominant	Dominant	$103,654[a]
Vedolizumab q.8.w.	Dominated	-	Dominated	$6,688[a]
Adalimumab q.2.w.	-	Dominant	-	$45,360[a]
Ustekinumab q.12.w.	$103,654	$6,688	$45,360	-
Ustekinumab q.8.w.	$222,031	$68,435	$172,074	$931,326
Ustekinumab mixed q.8.w./q.12.w.	$201,144	$56,754	$149,717	$931,326
IM-UNITI (mixed) population				
Infliximab q.8.w.	-	$239,321	Dominated	Dominated
Biosimilar infliximab q.8.w.	-	Dominant	$172,244[a]	$65,421[a]
Vedolizumab q.8.w.	Dominated	-	Dominated	$12,262[a]
Adalimumab q.2.w.	$172,244	Dominant	-	42,993[a]
Ustekinumab q.12.w.	$69,200	$20,796	$50,101	-
Ustekinumab q.8.w.	$133,811	$87,300	$127,604	$652,436
Ustekinumab mixed q.8.w./q.12.w.	$110,778	$63,416	$100,313	$666,583

FCTO = failure with conventional therapy only; ICUR = incremental cost-utility ratio; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; QALY = quality-adjusted life-year, TNF = tumour necrosis factor.
[a] Treatment results in lower costs and lower benefits than comparator.
Source: Manufacturer's pharmacoeconomic submission.[1]

Manufacturer's Sensitivity Analyses

The manufacturer conducted several deterministic sensitivity analyses varying model parameters in the following manner (with results presented in tornado diagrams):

- Baseline characteristics (age, sex, body weight) were varied by ± 10%.
- Proportion undergoing surgery was varied based on low/high rates reported in the literature.[1]
- Time to loss of response post-surgery was based on low/high estimates reported in the literature.
- Response to induction treatment was varied using the 95% credible intervals per treatment and by population versus conventional therapy estimated in the NMA.[1]
- Probabilities of response and remission associated with conventional therapy, to which odds ratios were applied to obtain probabilities of response and remission for biologic drugs, were varied by ± 10%, as were the probabilities of response and remission to additional induction doses following initial nonresponse to induction.[1]
- For the proportion of patients in CS-free remission, low/high values of 10%/30% were chosen.
- Proportions of patients in whom the dosage was escalated, per treatment, were set to 100% in a deterministic sensitivity analysis to assess the impact of systematic escalation of patients' dosage, which was also a means to vary the definition of treatment failure, as patients need to demonstrate nonresponse for an additional 16 weeks before their dosage is escalated.[1]
- All cost inputs other than medication costs were varied by ± 10%, and the management costs increase factor applied to anti-TNF failure patients was set between 1.0 (i.e., no increase) and 1.5, corresponding to the highest estimate of increased costs for these patients obtained through the Delphi panel.

- Utility values were varied by ± 10% to prevent health-state utility values in more severe health states from exceeding the utility values in less severe health states.
- Discount rates were set to 3% and 6%.

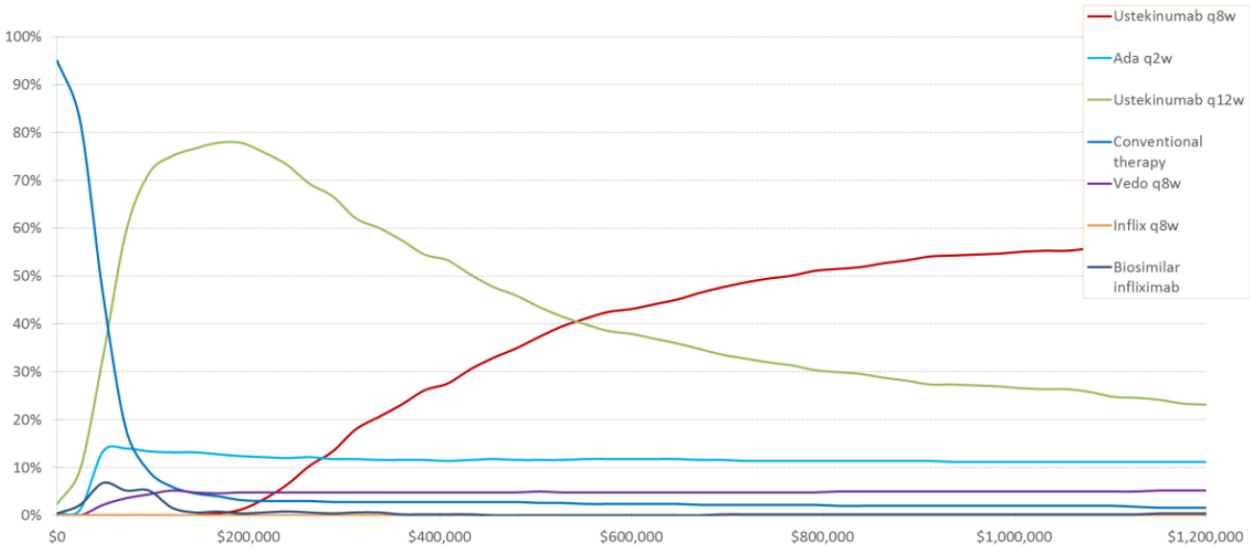
Results of the deterministic sensitivity analyses for ustekinumab every eight weeks for the FCTO showed that the base-case results were most sensitive to the proportion undergoing surgery as well as to remission and nonresponse utility values, followed by the efficacy of an additional induction dose. In the population experiencing failure with anti-TNF therapy, the most sensitive parameters were the remission utility value, the efficacy of an additional induction dose, the probability of surgery after 16 weeks in nonresponse, and the cost increase factor for patients experiencing failure with anti-TNF therapy.

Manufacturer's Probabilistic Sensitivity Analysis

The manufacturer conducted a probabilistic sensitivity analysis (PSA) based on a Monte Carlo simulation in which the model was run for 500 simulations. In each simulation, parameter values were randomly selected based on statistical distributions, simultaneously for all varied parameters. In results using the population experiencing an FCTO, and across all willingness-to-pay thresholds (WTP) up to $1,200,000, ustekinumab every eight weeks and every 12 weeks had the highest net monetary benefit (NMB) in 58.5% and 23.2% of the 500 PSA simulations, respectively. At a WTP of $120,000, ustekinumab every 12 weeks generated the highest NMB in 75.0% of the 500 simulations, followed by adalimumab every two weeks, which generated the highest NMB in 13.2% of the 500 simulations (Figure 3). In the population experiencing failure with anti-TNF therapy, ustekinumab every eight weeks and every 12 weeks had the highest NMB, in 54.1% and 36.3% of the 500 PSA simulations, respectively. Adalimumab every two weeks had the highest NMB in 4.2% of the simulations across all WTP values. At a WTP of $120,000, ustekinumab every 12 weeks generated the highest NMB in 76.2% of the 500 simulations, followed by

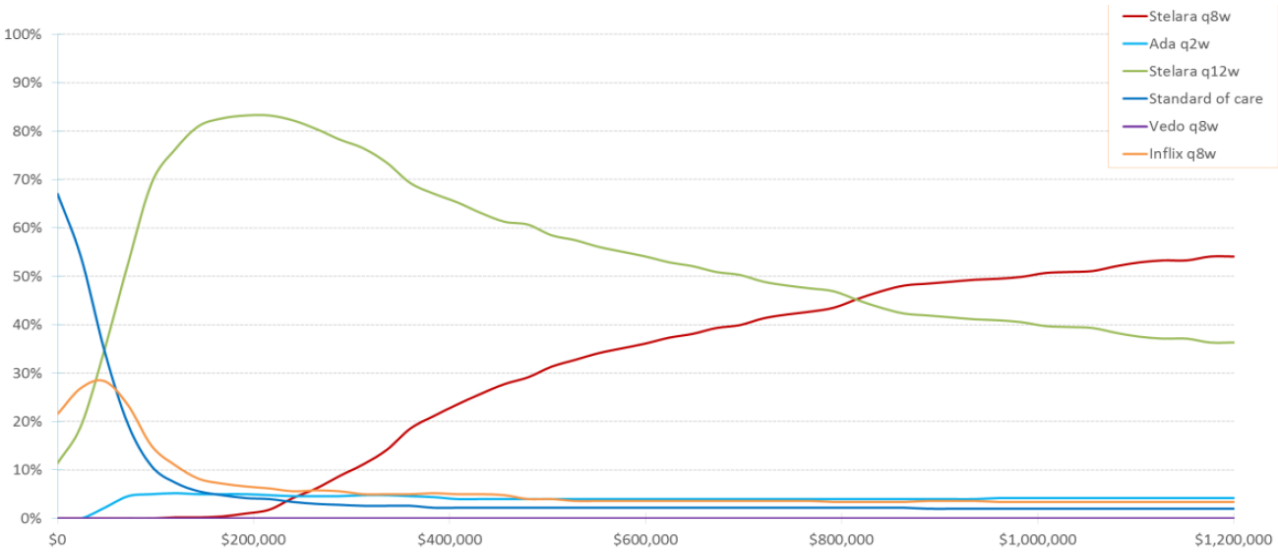
infliximab every eight weeks, which generated the highest NMB in 11.0% of the 500 simulations (Figure 4).

FIGURE 3: COST-EFFECTIVENESS ACCEPTABILITY CURVE — FAILURE WITH CONVENTIONAL THERAPY ONLY POPULATION



Ada = adalimumab; Inflix = infliximab; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; Vedo = vedolizumab.
Source: Manufacturer's pharmacoeconomic submission.[1]

FIGURE 4: COST-EFFECTIVENESS ACCEPTABILITY CURVE — POPULATION EXPERIENCING FAILURE WITH ANTI-TNF THERAPY



Ada = adalimumab; Inflix = infliximab; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; Vedo = vedolizumab; TNF = tumour necrosis factor.
Source: Manufacturer's pharmacoeconomic submission.[1]

Manufacturer's Alternative Costing Scenarios

The manufacturer conducted scenario analyses to assess alternative costing scenarios that varied the assumptions related to ustekinumab medication costs (Table 12):

- Offering the IV induction dose for free
- Including rebates of varying amounts (5%, 10%, 15%, 20%) on ustekinumab
- Implementing a number of annual per-patient expenditure caps ($20,000, $18,000, $16,000, $14,000; capping ustekinumab every eight weeks at $20,000 annually effectively assumes the cost of every 12 weeks dosage for the every eight weeks regimen)
- Providing ustekinumab at no cost after re-initiating therapy after surgery.

TABLE 12: RESULTS OF MANUFACTURER'S SCENARIO ANALYSIS WITH ALTERNATIVE COSTING

	FCTO		Failure With Anti-TNF Therapy	
	Ustekinumab q.8.w.	**Ustekinumab q.12.w.**	**Ustekinumab q.8.w.**	**Ustekinumab q.12.w.**
Base case	$86,414	$50,912	$83,535	$38,764
Free IV induction dose	$78,638	$42,827	$73,835	$25,152
Ustekinumab rebate				
5%	$75,336	$41,428	$77,256	$31,571
10%	$69,557	$37,384	$69,242	$25,896
15%	$63,777	$33,339	$61,229	$20,222
20%	$57,998	$29,295	$53,215	$14,547
Annual per-patient expenditure caps				
$20,000	$40,543	$40,943	$29,014	$30,890

	FCTO		Failure With Anti-TNF Therapy	
	Ustekinumab q.8.w.	**Ustekinumab q.12.w.**	**Ustekinumab q.8.w.**	**Ustekinumab q.12.w.**
$18,000	$32,683	$32,935	$18,116	$19,654
$16,000	$24,823	$23,656	$7,217	$6,637
$14,000	$16,963	$16,942	Dominating	Dominating
Free cost of ustekinumab after re-initiating therapy after surgery	$77,487	$42,950	$68,304	$25,445

FCTO = failure with conventional therapy only; IV = intravenous; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; TNF = tumour necrosis factor.
Source: Manufacturer's pharmacoeconomic submission.[1]

The manufacturer conducted a PSA using 500 simulations. In results using the patient population experiencing FCTO, and across all WTP thresholds up to $1,200,000, ustekinumab every eight weeks and every 12 weeks had generally the highest NMB. It had the highest NMB in 58.5% and 23.2% of the 500 PSA simulations, respectively, for the WTP of $1,200,000. At a WTP of $120,000, ustekinumab every 12 weeks generated the highest NMB in 75.0% of the 500 simulations, followed by adalimumab every two weeks, which generated the highest NMB in 13.2% of the 500 simulations.

In the patient population experiencing failure with anti-TNF therapy, ustekinumab every eight weeks and every 12 weeks had the highest NMB in 54.1% and 36.3% of the 500 PSA simulations, respectively, for the WTP of $1,200,000. Adalimumab every two weeks had the highest NMB in 4.2% of the simulations across all WTP values. At a WTP of $120,000, ustekinumab every 12 weeks generated the highest NMB in 76.2% of the 500 simulations, followed by infliximab every eight weeks, which generated the highest NMB in 11.0% of the 500 simulations.

CADTH Common Drug Review Reanalyses

Utility values for model health states: The manufacturer assumed utility values from a Canadian study (Gregor et al. [1997]) that asked a cohort of patients with CD to rate three hypothetical disease states representing mild (0.82), moderate (0.73), and severe disease (0.54) using a standard gamble approach.[8] The study also reported utility values for remission (0.88), chronically active therapy–responsive (0.86), and therapy-resistant (0.74). The manufacturer indicated that utility values from the study were used in published models as part of CADTH technical reports.[27] For the manufacturer's model, the remission, response, and no-response health states were assigned utilities of 0.88, 0.73, and 0.54, respectively. CDR conducted scenario analyses that applied utility values exclusively from each publication (Table 13).

TABLE 13: SUMMARY OF CDR UTILITY VALUES FOR THE REANALYSES

Health State	Manufacturer Values Used[1]	Range Used by CDR	
		Values From Gregor et al. (1997)[8]	Values Used in CADTH Models[27]
Remission	0.888	0.88	0.820
Response	0.730	0.86	0.730
Nonresponse	0.540	0.74	0.540
Surgery	0.540	0.74	0.540
Post-surgery	0.730	0.860	0.730
CS-free remission benefit	0.100		

CDR = CADTH Common Drug Review; CS = corticosteroid.

Results of the scenario analyses show the ICUR for ustekinumab compared with conventional therapy and other biologics in FCTO, failure with anti-TNF therapy, and mixed FCTO/failure with anti-TNF therapy (Table 14 and Table 15).

TABLE 14: CDR REANALYSES USING PUBLISHED HEALTH STATE UTILITY VALUES BY GREGOR ET AL. (1997)

	ICUR ($/QALY) Versus				
	Conventional Therapy	**Infliximab q.8.w.**	**Biosimilar Infliximab q.8.w.**	**Vedolizumab q.8.w.**	**Adalimumab q.2.w.**
Population experiencing FCTO					
Ustekinumab q.12.w.	119,652	44,765	168,552	58,256	125,859
Ustekinumab q.8.w.	207,746	214,942	329,026	226,633	314,293
Ustekinumab mixed q.8.w./q.12.w.	170,789	145,149	263,212	157,563	237,598
Population experiencing failure with anti-TNF therapy					
Ustekinumab q.12.w.	87,936	Dominant	252,978	14,814	110,706
Ustekinumab q.8.w.	192,207	168,018	560,025	154,652	434,020
Ustekinumab mixed q.8.w./q.12.w.	171,967	103,183	504,364	127,765	375,411
IM-UNITI (mixed) population					
Ustekinumab q.12.w.	114,298	20,438	177,314	48,329	124,058
Ustekinumab q.8.w.	205,135	205,135	353,869	210,590	328,868
Ustekinumab mixed q.8.w./q.12.w.	197,708	170,989	289,406	150,795	254,618

FCTO = failure with conventional therapy only; ICUR = incremental cost-utility ratio; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.
Note: Based on utility values from Gregor et al. (1997).[8]

TABLE 15: CDR REANALYSES USING PUBLISHED HEALTH STATE UTILITY VALUES USED IN CADTH MODELS

	ICUR ($/QALY) Versus				
	Conventional Therapy	**Infliximab q.8.w.**	**Biosimilar Infliximab q.8.w.**	**Vedolizumab q.8.w.**	**Adalimumab q.2.w.**
Population experiencing FCTO					
Ustekinumab q.12.w.	61,486	21,734	81,834	29,882	62,558
Ustekinumab q.8.w.	105,301	102,309	156,611	113,364	152,302
Ustekinumab mixed q.8.w./q.12.w.	87,067	69,649	126,301	79,626	116,324
Population experiencing failure with anti-TNF therapy					
Ustekinumab q.12.w.	46,220	Dominant	127,088	7,889	55,615
Ustekinumab q.8.w.	100,171	82,717	275,706	81,382	213,673
Ustekinumab mixed q.8.w./q.12.w.	89,770	50,983	249,208	67,386	185,492
IM-UNITI (mixed) population					
Ustekinumab q.12.w.	58,957	9,958	86,389	25,000	61,740
Ustekinumab q.8.w.	104,459	100,264	169,038	106,513	159,670
Ustekinumab mixed q.8.w./q.12.w.	87,516	67,674	139,307	76,936	124,797

FCTO = failure with conventional therapy only; ICUR = incremental cost-utility ratio; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.
Note: Based on utility values from published models as part of CADTH technical reports.[27-29]

Excluding real-world evidence to adjust transition probabilities: The manufacturer acknowledged that adjusting the transition probabilities to real data was challenging because of lack of data available to make the calculations. The manufacturer's approach, associated with significant uncertainty, favours ustekinumab. CDR conducted a reanalysis that excluded the impact of real-world evidence on the transition probabilities. The results for ustekinumab compared with conventional therapy and other biologics are presented in Table 16.

TABLE 16: CDR REANALYSIS EXCLUDING REAL-WORLD EVIDENCE FROM TRANSITION PROBABILITIES

	ICUR ($/QALY) Versus				
	Conventional Therapy	**Infliximab q.8.w.**	**Biosimilar Infliximab q.8.w.**	**Vedolizumab q.8.w.**	**Adalimumab q.2.w.**
Population experiencing FCTO					
Ustekinumab q.12.w.	95,933	10,269	82,073	33,260	68,063
Ustekinumab q.8.w.	139,550	81,178	142,287	105,009	137,049
Ustekinumab mixed q.8.w./q.12.w.	122,049	53,453	118,743	77,145	110,387
Population experiencing failure with anti-TNF therapy					
Ustekinumab q.12.w.	108,587	Dominant	187,540	26,901	101,726
Ustekinumab q.8.w.	168,490	35,874	351,167	108,937	279,716
Ustekinumab mixed q.8.w./q.12.w.	157,059	Dominant	322,975	93,489	249,050

	ICUR ($/QALY) Versus				
	Conventional Therapy	**Infliximab q.8.w.**	**Biosimilar Infliximab q.8.w.**	**Vedolizumab q.8.w.**	**Adalimumab q.2.w.**
IM-UNITI (mixed) population					
Ustekinumab q.12.w.	98,933	Dominant	94,150	31,577	73,350
Ustekinumab q.8.w.	146,102	75,889	166,674	105,976	155,264
Ustekinumab mixed q.8.w./q.12.w.	130,210	46,644	143,273	81,339	128,710

FCTO = failure with conventional therapy only; ICUR = incremental cost-utility ratio; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.

Model time horizon reduced: The manufacturer's base-case analysis used a 25-year time horizon, based on a conservative assumption that CD is a chronic and lifelong disease and that patients initiating a biologic therapy would survive at least 25 more years. However, there is a lack of long-term data to support the assumption that the effects of biologic therapy would be sustained without waning over time. CDR conducted an exploratory analysis using a time horizon of 10 years (Table 17).

TABLE 17: CDR REANALYSIS USING A TIME HORIZON OF 10 YEARS

	ICUR ($/QALY) Versus				
	Conventional Therapy	**Infliximab q.8.w.**	**Biosimilar Infliximab q.8.w.**	**Vedolizumab q.8.w.**	**Adalimumab q.2.w.**
Population experiencing FCTO					
Ustekinumab q.12.w.	60,310	103	68,473	24,606	49,686
Ustekinumab q.8.w.	98,373	74,239	135,440	98,436	130,453
Ustekinumab mixed q.8.w./q.12.w.	82,569	44,355	108,447	68,742	98,290
Population experiencing failure with anti-TNF therapy					
Ustekinumab q.12.w.	57,129	Dominant	112,328	12,503	45,935
Ustekinumab q.8.w.	105,397	60,519	245,219	81,211	187,984
Ustekinumab mixed q.8.w./q.12.w.	96,113	31,717	221,657	68,189	162,799
IM-UNITI (mixed) population					
Ustekinumab q.12.w.	59,636	Dominant	74,409	21,302	49,095
Ustekinumab q.8.w.	99,847	72,320	150,790	93,895	139,656
Ustekinumab mixed q.8.w./q.12.w.	85,447	42,560	124,525	68,592	36,113

FCTO = failure with conventional therapy only; ICUR = incremental cost-utility ratio; IV = intravenous; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.

Multi-way CDR reanalyses: CDR conducted multi-way scenario reanalyses that varied the health-state utility values and were based on a 25-year time horizon that excluded real-world evidence (Table 18 and Table 19).

TABLE 18: CDR MULTI-WAY REANALYSES USING HEALTH STATE UTILITY VALUES FROM CADTH ANALYSES

	ICUR ($/QALY) Versus				
	Conventional Therapy	**Infliximab q.8.w.**	**Biosimilar Infliximab q.8.w.**	**Vedolizumab q.8.w.**	**Adalimumab q.2.w.**
Population experiencing FCTO					
Ustekinumab q.12.w.	115,474	12,850	102,699	39,714	84,516
Ustekinumab q.8.w.	169,543	102,352	179,400	127,284	171,820
Ustekinumab mixed q.8.w./q.12.w.	147,517	67,195	149,271	92,964	137,879
Population experiencing failure with anti-TNF therapy					
Ustekinumab q.12.w.	130,322	Dominant	227,687	31,652	123,503
Ustekinumab q.8.w.	203,406	44,242	433,080	129,305	344,962
Ustekinumab mixed q.8.w./q.12.w.	189,394	Dominant	397,231	110,786	306,309
IM-UNITI (mixed) population					
Ustekinumab q.12.w.	118,969	Dominant	117,399	37,558	89,580
Ustekinumab q.8.w.	177,265	95,434	209,600	127,789	194,246
Ustekinumab mixed q.8.w./q.12.w.	157,459	58,481	179,630	97,594	160,436

FCTO = failure with conventional therapy only; ICUR = incremental cost-utility ratio; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.

TABLE 19: CDR MULTI-WAY REANALYSES USING HEALTH STATE UTILITY VALUES FROM PUBLISHED STUDY

	ICUR ($/QALY) Versus				
	Conventional Therapy	**Infliximab q.8.w.**	**Biosimilar Infliximab q.8.w.**	**Vedolizumab q.8.w.**	**Adalimumab q.2.w.**
Population experiencing FCTO					
Ustekinumab q.12.w.	223,776	26,446	211,366	75,944	171,651
Ustekinumab q.8.w.	333,339	213,379	374,005	248,993	354,621
Ustekinumab mixed q.8.w./q.12.w.	288,959	139,377	309,621	180,233	282,787
Population experiencing failure with anti-TNF therapy					
Ustekinumab q.12.w.	249,887	Dominant	446,416	59,179	242,146
Ustekinumab q.8.w.	392,077	88,882	870,045	244,811	693,019
Ustekinumab mixed q.8.w./q.12.w.	361,323	Dominant	794,607	209,248	612,730
IM-UNITI (mixed) population					
Ustekinumab q.12.w.	228,957	Dominant	240,216	71,386	181,091
Ustekinumab q.8.w.	345,819	198,067	435,012	247,922	399,490
Ustekinumab mixed q.8.w./q.12.w.	305,585	120,756	370,915	187,918	327,940

FCTO = failure with conventional therapy only; ICUR = incremental cost-utility ratio; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.

Multi-way CDR reanalyses excluding induction costs: Based on correspondence from the manufacturer indicating that the drug costs for the induction dose of ustekinumab would be reimbursed by the manufacturer, CDR ran the multi-way scenario reanalysis excluding costs of the induction dose (Table 18).

TABLE 20: RESULTS OF CDR MULTI-WAY ANALYSIS USING HEALTH STATE UTILITY FROM CADTH MODELS EXCLUDING DRUG COSTS FOR THE INDUCTION DOSE

	ICUR ($/QALY)		ICUR ($/QALY) Excluding Cost of Induction Dose		
	Versus Conventional Therapy	**Sequential Analysis**		**Versus Conventional Therapy**	**Sequential Analysis**
Population experiencing FCTO					
Ustekinumab q.12.w.	$115,474	$115,474	Ustekinumab q.12.w.	$95,442	$95,442
Ustekinumab mixed q.8.w./q.12.w.	$147,517	$623,571	Ustekinumab q.8.w.	$151,633	$641,045
Ustekinumab q.8.w.	$169,543	$658,533	Ustekinumab mixed q.8.w./q.12.w.	$128,955	Subject to extended dominance[f]
Biosimilar infliximab q.8.w.	$143,062	Subject to extended dominance[a]	Biosimilar infliximab q.8.w.	$143,909	Subject to extended dominance[g]
Adalimumab q.2.w.	$164,583	Subject to extended dominance[b]	Adalimumab q.2.w.	$165,251	Subject to extended dominance[h]
Vedolizumab q.8.w.	$271,363	Dominated by adalimumab q.2.w.	Vedolizumab q.8.w.	$271,689	Dominated by adalimumab q.2.w.
Infliximab q.8.w.	$342,856	Dominated by biosimilar infliximab q.8.w., vedolizumab q.8.w., adalimumab q.2.w., ustekinumab q.12.w.	Infliximab q.8.w.	$344,875	Dominated by biosimilar infliximab q.8.w., vedolizumab q.8.w., adalimumab q.2.w., ustekinumab q.12.w.
Population experiencing failure with anti-TNF therapy					
Biosimilar infliximab q.8.w.	$90,277	$90,277	Ustekinumab q.12.w.	$77,840	$77,840
Ustekinumab q.12.w.	$131,297	$228,571	Ustekinumab mixed q.8.w./q.12.w.	$139,081	$1,559,521
Ustekinumab mixed q.8.w./q.12.w.	$189,403	$1,332,167	Ustekinumab q.8.w.	$153,608	$1,559,521
Ustekinumab q.8.w.	$203,880	$1,999,000	Biosimilar infliximab q.8.w.	$89,469	Subject to extended dominance[i]
Adalimumab q.2.w.	$134,373	Dominated by biosimilar infliximab q.8.w.	Adalimumab q.2.w.	$133,183	Dominated by biosimilar infliximab q.8.w., ustekinumab q.12.w.
Infliximab q.8.w.	$284,904	Dominated by adalimumab q.2.w., biosimilar infliximab q.8.w., ustekinumab q.12.w., ustekinumab mixed	Infliximab q.8.w.	$282,365	Dominated by adalimumab q.2.w., biosimilar infliximab q.8.w., ustekinumab q.12.w., ustekinumab mixed, ustekinumab q.8.w.
Vedolizumab q.8.w.	$500,920	Dominated by adalimumab q.2.w., biosimilar infliximab q.8.w.	Vedolizumab q.8.w.	$499,971	Dominated by adalimumab q.2.w., biosimilar infliximab q.8.w., ustekinumab q.12.w.

	ICUR ($/QALY)		ICUR ($/QALY) Excluding Cost of Induction Dose		
	Versus Conventional Therapy	**Sequential Analysis**		**Versus Conventional Therapy**	**Sequential Analysis**
IM-UNITI (mixed) population					
Ustekinumab q.12.w.	$119,058	$119,058	Ustekinumab q.12.w.	$91,260	$91,260
Ustekinumab q.8.w.	$177,093	$744,826	Ustekinumab q.8.w.	$152,083	$758,251
Biosimilar infliximab q.8.w.	$120,923	Subject to extended dominance[c]	Biosimilar infliximab q.8.w.	$121,295	Subject to extended dominance[j]
Adalimumab q.2.w.	$154,194	Subject to extended dominance[d]	Ustekinumab mixed q.8.w./q.12.w.	$131,322	Subject to extended dominance[k]
Ustekinumab mixed q.8.w./q.12.w.	$157,268	Subject to extended dominance[e]	Adalimumab q.2.w.	$153,566	Subject to extended dominance[l]
Vedolizumab q.8.w.	$311,328	Dominated by biosimilar infliximab q.8.w., adalimumab q.2.w.	Vedolizumab q.8.w.	$309,918	Dominated by biosimilar infliximab q.8.w., adalimumab q.2.w., ustekinumab q.12.w.
Infliximab q.8.w.	$317,945	Dominated by biosimilar infliximab q.8.w., adalimumab q.2.w., ustekinumab q.12.w.	Infliximab q.8.w.	$318,909	Dominated by biosimilar infliximab q.8.w., adalimumab q.2.w., ustekinumab q.12.w.

FCTO = failure with conventional therapy only; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks.

[a] Subject to extended dominance through conventional therapy and ustekinumab q.12.w.

[b] Subject to extended dominance through conventional therapy and ustekinumab q.12.w., biosimilar infliximab q.8.w. and ustekinumab q.12.w., conventional therapy and ustekinumab mixed, biosimilar infliximab q.8.w. and ustekinumab mixed, biosimilar infliximab q.8.w. and ustekinumab q.8.w.

[c] Subject to extended dominance through conventional therapy and ustekinumab q.12.w.

[d] Subject to extended dominance through conventional therapy and ustekinumab q.12.w., biosimilar infliximab q.8.w. and ustekinumab q.12.w., biosimilar infliximab q.8.w. and ustekinumab mixed, biosimilar infliximab q.8.w. and ustekinumab q.8.w.

[e] Subject to extended dominance through ustekinumab q.12.w. and ustekinumab q.8.w.

[f] Subject to extended dominance through ustekinumab q.12.w. and ustekinumab q.8.w.

[g] Subject to extended dominance through conventional therapy and ustekinumab q.12.w., conventional therapy and ustekinumab mixed.

[h] Subject to extended dominance through conventional therapy and ustekinumab q.12.w., biosimilar infliximab q.8.w. and ustekinumab q.12.w., conventional therapy and ustekinumab mixed, biosimilar infliximab q.8.w. and ustekinumab mixed, conventional therapy and ustekinumab q.8.w., biosimilar infliximab q.8.w. and ustekinumab q.8.w.

[i] Subject to extended dominance through conventional therapy and ustekinumab q.12.w.

[j] Subject to extended dominance through conventional therapy and ustekinumab q.12.w.

[k] Subject to extended dominance through ustekinumab q.12.w. and ustekinumab q.8.w.

[l] Subject to extended dominance through conventional therapy and ustekinumab q.12.w., biosimilar infliximab q.8.w. and ustekinumab q.12.w., conventional therapy and ustekinumab mixed, biosimilar infliximab q.8.w. and ustekinumab mixed, conventional therapy and ustekinumab q.8.w., biosimilar infliximab q.8.w. and ustekinumab q.8.w.

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