

July 27, 2020

AbbVie supports an evidence-based value assessment paradigm that reflects the unique and diverse criteria of stakeholders impacted by the assessment and those making healthcare decisions, and that preserves shared decision-making between patients and their healthcare providers.

AbbVie has been a leader in the field of gastroenterology for more than ten years— we have since become a trusted partner for the gastroenterology community in advancing the quality of care for patients living with inflammatory bowel diseases (IBD). We are relentless in our quest to better understand the needs of people with IBD and will continue to work closely with patients and partners to advance research and the standard of care in this area. As such, AbbVie appreciates the opportunity to provide comments on the *Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value* Draft Evidence Report.

Ulcerative colitis (UC), a type of IBD, can be difficult to manage with symptoms that can have a significant physical and emotional toll in patients. A non-surgical cure for UC currently does not exist, and advancements in medicine, including the introduction and adoption of targeted immunomodulators (TIMs), have allowed many patients to get their often-debilitating symptoms under control and regain their quality of life without having to undergo a colectomy.

AbbVie respectfully disagrees with ICER's conclusion that all TIMs are not cost-effective. ICER's model does not reflect current clinical practice and does not account for the value of these important therapies beyond limited clinical outcomes, including value to society and improving patients' quality of life. ICER recognizes this as well, noting that "considerable uncertainty exists" in the model.

Below we offer recommendations for ICER's consideration in the development of the final report, to more accurately reflect real-world clinical practice.

## **Comparative Clinical Effectiveness**

### **Evidence Base**

- AbbVie would like to reiterate while a network meta-analysis can be an effective way to compare the efficacy of one drug relative to another, the high level of variability among UC clinical trials (including different patient populations, inclusion/exclusion criteria, study designs, and clinical endpoints) may yield inaccurate or invalid conclusions. The impact these variations may have on the true comparative clinical effectiveness are amplified when considering the small differences observed between the individual TIMs (QALY ranges from 15.97-16.04, a .07 maximum difference).
- The network meta-analysis (NMA) that ICER used to assess comparative efficacy of targeted immune modulators (TIMs) includes trials with meaningfully different clinical definitions of outcomes. For example, adalimumab trials used the worst rank method to measure Mayo scores, which ICER acknowledged may have underestimated effect sizes relative to the method of using average of the scores which most other trials did.
- The trials included in the ICER's NMA reported varying levels of placebo response and remission rates. This may indicate differences in the underlying patient populations across trials and across treatment arms which may lead to potential differences in treatment responses and disease prognosis. For example, authors in Motoya 2019 noted treatment group imbalances that may have resulted in the unusually high placebo response and remission rates.<sup>1</sup> This likely contributed to the lack of statistical difference in clinical response and remission rates between vedolizumab and placebo in the biologic-experienced population. It is worth to keep in mind that the response and

remission rates of placebo compared to adalimumab in ULTRA 2 are also notably high compared to the lower placebo response and remission rates in other trials, such as OCTAVE 1 & 2, UNIFI and GEMINI 1. This suggests trial heterogeneity which is not fully adjusted for in the ICER’s NMA model.

<b>Trial</b>	<b>Comparator</b>	<b>Placebo Response (%)</b>	<b>Placebo Remission (%)</b>
ULTRA 2	ADA 160/80 mg	28.7	6.9
OCTAVE 1 & 2	TOF 10 mg	23.4	0.8
UNIFI	UST 6 mg/kg	27.3	1.2
GEMINI 1	VEDO 300 mg	20.6	3.2
Motoya 2019	VEDO 300 mg	29.3	9.8

- Furthermore, we would like to note that in assessing the model fit of the ICER’s clinical effectiveness NMA, it is important to evaluate possible inconsistency between the direct and indirect trial evidence available. When comparing the indirect and direct estimates as reported in ICER’s clinical effectiveness results, there is some evidence of inconsistency that warrants further assessment. We recommend that ICER also take this evidence into consideration during model assessment and publish the results of their inconsistency tests if possible.<sup>2</sup>
- While the ICER’s CEA model is structured with eight-week cycles, it uses efficacy outcomes from trials with an induction phase ranging from 6-14 weeks without adjustment for difference in the induction duration. This could introduce potential bias for trials with shorter induction duration, as patients are allowed less time to respond to treatment compared to trials with a longer induction period. We recommend that ICER consider including a time-adjustment parameter within the base-case NMA to predict more accurate 8-week outcomes to be applied within the economic model. This can be incorporated by including a coefficient for time which specifies the average difference between 8 weeks and trial induction time points on the probit scale for clinical response and remission.

### **Data Synthesis and Statistical Analyses**

- The ICER’s model pools treatment dosages across trials for efficacy assessment. It includes treatment doses which are not approved by the U.S. Food and Drug Administration (FDA), such as infliximab 10 mg/kg, golimumab 400 mg, and vedolizumab maintenance q4w. Respectfully, we suggest that ICER reconsider this approach. Since these doses are not approved by the FDA, their use in clinical practice would be rare, if used at all, likely due to safety concerns. In addition, we see numerical differences in efficacy estimates between the unapproved (higher) doses and the approved doses. For example, golimumab 200/100 mg and golimumab 400/200 mg had clinical response rates of 51.0% and 54.9%, respectively, in its phase 3 trial (Section 4.3, Table 4.2). Therefore, including these unapproved higher doses in the data synthesis may be arbitrary in resulting in a better efficacy profile while not best representing the clinical profile of these treatments in the United States. We recommend that ICER only include treatments that have been approved by the FDA in data synthesis to enhance the validity of the clinical efficacy results.

Additionally, we noticed some discrepancies in ICER’s approach of data synthesis to derive efficacy inputs versus safety inputs. For example, while the efficacy estimates pooled all available doses of tofacitinib and infliximab, the safety estimates only included data for one selected dose of these treatments, despite the availability of safety data for other doses considered in the efficacy evaluation. We suggest that ICER apply a consistent pooling approach to the safety outcomes (i.e., adverse event rates) as the efficacy outcomes, and to leave out FDA unapproved doses in data synthesis for both outcomes.

**Long-term Cost Effectiveness**

**Model Structure**

- The current model structure is not consistent with routine clinical practice in the U.S. as patients who do not respond to the second TIM discontinue to conventional treatment. The assumption of 2nd-line TIM use as a “market basket” of other treatment options except the initial TIM may not sufficiently capture downstream costs for this patient population, as it is common in clinical practice for patients to cycle through more than two TIMs before discontinuing to conventional treatment. While we acknowledge the lack of empiric data to estimate more than two lines of TIM use, we suggest that ICER consider a longer duration of the 2<sup>nd</sup>-line TIM use to better reflect the additional cycles of TIMs patients would use in real-world practice. Modeling multi-line TIM use for a sufficiently long period may reduce the differences in long-term costs between treatment sequences.

**Clinical Inputs**

- In the current CEA model, the source that ICER uses to inform the post-colectomy utility value in its base case measures only the post-colectomy health state.<sup>3</sup> Without a broader spectrum of the UC health states considered together, a single utility value from one study may not accurately reflect the relative differences in utilities when considering pre-colectomy and post-colectomy health states. Therefore, it is difficult to assess whether the health state utilities for the pre-surgical and post-surgical health states in ICER’s model are entirely comparable. For example, the ICER’s model assumes that the utility of post-colectomy remission is higher than that of clinical response without remission (Section 5.2, Table 5.12). This assumption was not aligned with existing evidence which evaluated utility for both pre-surgical and post-surgical health states in the same model, and may overestimate the benefit of colectomy. Several health technology assessment (HTA) submissions used post-colectomy utility values from studies including both pre-surgical and post-surgical health state valuations, which showed that the utility value of response to treatment is higher than post-colectomy remission. For example, utility values reported in two sources cited in HTA submissions demonstrated 5.26-26.25% reduction in utility from clinical response without remission to post-colectomy,<sup>4,5</sup> which would result in a post-colectomy value between 0.58 and 0.74 using ICER’s current clinical response utility value. We recommend that ICER use a more reasonable utility value for post-colectomy in the base case.

<b>Study</b>	<b>ICER Draft Evidence Report</b>	<b>Woehl 2008<sup>4</sup></b>	<b>Swinburn 2012<sup>5</sup></b>
Sample Size	--	180	230
<b>Utility values</b>			
Remission	0.87	0.87	0.91
Response	0.78	0.76	0.80
Active UC	0.70	0.41	0.55
Post-Surgery	0.79	0.71-0.72	0.59

- The ICER’s CEA model does not consider long-term complications of colectomy other than chronic pouchitis. However, other long-term complications such as infertility and male sexual dysfunction can occur in patients who receive colectomy,<sup>6,7</sup> which can bear significant impacts on patients’ quality of life.<sup>8,9</sup> We recommend that ICER include these complications within the model by incorporating these events into the rate of long-term complications after colectomy. The HTA submission for adalimumab estimated the transition probability for chronic complication among patients who receive surgery as 19.19%,<sup>10</sup> which incorporated estimates for fertility<sup>11</sup> and male impotence<sup>12</sup> in addition to chronic pouchitis. Including the above-mentioned adverse events will allow ICER’s model to more accurately capture the impact associated with the colectomy procedure for the patient population of interest.

## **Economic Inputs**

- The ICER’s CEA model only considers serious infections to capture treatment-related adverse events, which may not reflect the larger impact of adverse events experienced by patients receiving treatments. Other adverse events noted by the FDA for various TIMs, including thrombotic events, cardiovascular mortality, and lymphoma, are also of relevance to this patient population. We recommend that ICER consider the above-mentioned adverse events within the modeled costs to best reflect resource use, patient disutility and mortality in the real-world patient population.
- Other costs of UC management, including hospitalization and outpatient visits, were included by health state. We recommend ICER also to consider differences in health resource utilization incurred by patients receiving infusion treatments vs. subcutaneous treatments given the reported differences between the two. A study comparing medical costs between patients receiving adalimumab and infliximab for Crohn’s disease reported significant differences in health care costs between patient groups. Average disease-related medical service costs, excluding drug costs, for the 6 months after treatment initiation were lower for patients receiving adalimumab (adalimumab: \$5,199 vs. infliximab: \$9,059,  $P < 0.0001$ ). The authors attribute much of this difference to “a decreased cost of outpatient office visits” for patients receiving adalimumab, and “infusion-related expenses for infliximab.”<sup>13</sup> Additionally, ICER should also consider differences in non-drug costs between patients receiving TIMs and patients receiving conventional treatment, as there is evidence that health resource utilization and annual medical service costs are higher among patients receiving conventional treatments compared to patients receiving anti-TNF therapies.<sup>14</sup> We suggest that ICER apply non-drug costs of UC management by treatment type to account for these differences in health resource utilization.

## **Key Model Assumptions**

- ICER applies an assumption that “*patients who discontinue conventional treatment after two TIMs will follow the biologic-naïve transition probabilities for the biologic-naïve population,*” while patients who begin in the biologic-experienced population and discontinue conventional treatment after two TIMs will follow the biologic-experienced transition probabilities. The assumptions applied in the biologic-naïve population could bias results in favor of treatments that do not have data among biologic-experienced population, specifically infliximab. Moreover, it is more realistic in clinical practice to consider patients after two TIMs as biologic-experienced. Therefore, we suggest that patients who discontinue conventional treatment in the TIM-treated arm follow the transitional probabilities for the biologic-experienced population.
- ICER’s model assigns a second TIM for patients with a different mechanism of action from the initial TIM in their market-basket approach. However, clinical practice suggests that it is possible for patients to be treated with a 2<sup>nd</sup>-line TIM with the same mechanism of action.<sup>15</sup> In fact, treatment guidelines published by the American College of Gastroenterology recommend that patients “with moderately to severely active UC who had an initial response but subsequently lost efficacy to one anti-TNF therapy” may transition to an alternative anti-TNF therapy.<sup>16</sup> Thus, we recommend that ICER allow the market basket to include all TIMs except the initial TIM.

## **Other Considerations**

- The CEA model currently considers a modified societal perspective as a scenario analysis. This includes indirect health care costs by the health state, but does not consider costs associated with different routes of administration. Given that there may be disruption to productivity and daily life for patients receiving IV therapies due to work loss because of infusion appointments and/or associated travel costs, we suggest that the model consider the

impact on indirect costs related to mode of administration. Furthermore, we recommend that ICER include additional indirect costs incurred by UC patients who undergo colectomy, as increased indirect costs among patients who receive UC-related surgery has been reported in the literature.<sup>17</sup>

- We suggest revising language in the ICER’s draft report which states that some TIMs “carry a black box warning in their FDA labels for an increased risk of lymphomas and other malignancies, based on clinical trials and real-world evidence for these TIMs when studied for other indications” (Section 4.3, “Harms”) to also acknowledge that the warning is primarily noted for adolescent and young-adult patients.
- We recommend that ICER publish additional interim clinical outcomes that are generated by the model to improve the transparency of the report. In particular, it would be helpful to report the distribution of the patients in each health state over time for each evaluated treatment separately.

### **Conclusion**

We appreciate the opportunity to provide comments and hope that these recommendations are seriously considered in the development of the final report, to truly and more accurately reflect the value that TIMs bring to the lives of UC patients. If additional clarity is needed on any of our comments, we welcome the opportunity to discuss these further with ICER.

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## Amgen Response to ICER Ulcerative Colitis Draft Evidence Report

### Summary Overview

Amgen appreciates the opportunity to comment on ICER's Targeted Immune Modulators for Ulcerative Colitis (UC) Assessment Draft Evidence Report, released 26 May 2020. As a science-based company, invested in robust methods and meaningful assessments, Amgen would like to provide the following comments and recommendations for consideration:

1. The high utility value assumed for the patients in active UC health states underestimates the patient burden of uncontrolled disease. **ICER should consider other utility estimates for the active UC health state that have been used in previous HTA assessments (e.g., Archer 2016).**
2. Despite the high estimates of indirect costs, the modified societal base case is reported only as a scenario analysis. Consistent with **ICER Value Assessment Framework, the modified societal perspective should be presented as a co-base case.**
3. The definition of the second line TIM market basket varies for each first line TIM and is not included in the conventional treatment (CT) arm. This limits the validity of the comparisons made. **ICER should revise the comparisons made to ensure they are appropriate and interpret these accurately.**
4. The per-cycle rate of colectomy and the cumulative colectomy rate are incompatible, meaning that the "cap" is reached before the end of the model. **ICER should calibrate the rate of colectomy to match the cumulative rate in the comparator arm.**

### Detailed Comments

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| <ol style="list-style-type: none"><li>1. The high utility value assumed for the active UC health state risks underestimating the quality of life burden of uncontrolled disease. <b>ICER should consider other utility estimates for active the UC health state that have been used in previous HTA assessments in UC.</b></li></ol> |
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The draft evidence report presents the significant impact the utility estimate for patients with active UC has on the model results in the deterministic sensitivity analysis (and is by far the most impactful parameter). The point estimate and upper bound assumed in the analysis risk overestimation of the quality of life of patients with moderate to severe UC who are not responding to treatment or are untreated. In particular, the upper bound is close to the general population utility value used by ICER to calculate evLYG (0.851), and the base case utility value for patients with moderate to severe UC in clinical remission is higher than this general population value.

The draft evidence reports cited an alternative source for utility estimates, previously used by NICE. (Archer, et al., 2016). This publication provides estimates for moderate to severe UC with values for active UC ranging between 0.41 and 0.66, all below the mean value adopted by ICER in this draft evidence report. The ICER draft evidence report notes that Archer 2016 has been used to inform previous cost-effectiveness evaluations in UC, which the primary source selected for the base case analysis has not. (Malinowski & Kawalec, 2016)

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The choice of the values (both mean and assumed distribution) used in the model should be based on the robustness of the evidence, and the selection should be justified. Additional consideration should be paid to the severity of disease for the patient population in the assessment, and potential differences in the utility of patients with active UC following the failure of prior biologic treatment, compared to those who are biologic-naive.

2. Despite the high estimates of indirect costs, the modified societal base case is reported only as a scenario analysis. **ICER should consider presenting the modified societal perspective as a co-base case.**

As stated in the 2020-2023 ICER Value Assessment Framework, when “*the societal costs of care for any disease are large relative to the direct health care costs, and that the impact of treatment on these costs is substantial (i.e., there are substantial differences in the cost-effectiveness findings between the two perspectives), the societal perspective is included as a co-base case, presented directly alongside the health care sector perspective analysis*”. (ICER, 2020)

Based on the results of the draft model and the scenario analysis included in the draft report, the above conditions appear to be met. The estimated indirect costs are almost as great as the estimated direct costs, so ICER should consider the inclusion of the modified societal perspective as a co-base case.

4. The definition of the second line TIM market basket varies for each first line TIM and is not included in the conventional treatment (CT) arm. This limits the validity of the comparisons made. **ICER should revise the comparisons made to ensure they are appropriate and interpret these accurately. HTA assessments in UC.**

The draft evidence report states that the second line TIM market basket is assumed to be made up of the treatment options other than the treatment received as first line therapy. This means that the second line treatment is different in each treatment arm, limiting the comparisons that can be made between them. Furthermore, the second line TIM is not included in the CT comparator arm, and so these comparisons are also invalidated by discrepancies in treatments received.

By defining the comparisons as they are stated in the draft evidence report, ICER is, in effect, modeling sequences of TIMs, but interpreting the results as if for a single first line treatment. Furthermore, the cost-effectiveness of any first line TIM is limited by the inclusion of the least cost-effective treatment in the second line basket. This penalizes the biologic treatments being assessed and introduces bias in favor of CT.

To include multiple treatment lines in the analysis, ICER should specify specific sequences of biologics and state the assumed sequences in the evidence report so that the sequence of treatments is clear when interpreting the cost-effectiveness results.



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5. The per-cycle rate of colectomy and the cumulative colectomy rate are incompatible, meaning that the “cap” is reached before the end of the model. **ICER should calibrate the rate of colectomy to match the cumulative rate in the comparator arm.**

When discontinuing a TIM, and at any time in the active UC health state on CT, patients have a probability of undergoing colectomy, incurring the costs and outcomes of the surgery procedure. The draft model contains a cap on colectomy incidence of 25.4%, and once this is reached, the probability of any future surgeries is set to 0. ICER should comment on the clinical validity of this assumption and provide greater detail on how the rate and cap were derived and applied.

ICER should consider calibrating the per-cycle probability of surgery, so that it is consistent with the cumulative colectomy incidence at 20 years as stated in the draft evidence report.

## **Amgen Response to ICER Ulcerative Colitis Draft Evidence Report**

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13 July 2020

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RE: Response to Draft Evidence Report - Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value

Baysient is thankful for the opportunity to provide comments on the Draft Evidence Report.

Baysient is a digital health company providing patented <sup>1, 2, 3</sup> decision support software as a service for therapeutic monoclonal antibodies used to treat IBD including infliximab, adalimumab, golimumab, vedolizumab, certolizumab pegol, and ustekinumab. The software may be used by health care providers to support individualized dosing (i.e. clinical decision support (CDS)) as well as by payors to individualized healthcare economic information for prior authorization decision support. Baysient has no economic interest in the distribution of any approved drug product.

Baysient recommends that the Final Evidence Report identify trending changes to the standard of care that have the potential to alter the analytical conclusions of the report within a 24 month timeframe.

These trends include the impact of:

- Increasing the application of therapeutic drug monitoring (TDM) combined with CDS as the standard of care.
- Filling “knowledge gaps” (i.e. the relationship between administered dose and trough concentration) in current clinical practice guidelines.<sup>4</sup>
- Providing sufficient evidence to recommend the routine use of TDM with TNF-alpha inhibitors.<sup>5</sup>
- Applying better-clinical-outcome-at-lower-cost alternative payment models to individualized infliximab therapy incorporating TDM combined with CDS.
- Changing the U.S. infliximab label making it consistent with monographs that include the use of TDM with infliximab.<sup>6</sup>
- Providing health care providers with scientifically appropriate and statistically sound dosing information derived from the laboratory assays provided by infliximab manufacturers or other licensed laboratories.

Data supporting these trends are included in the results of clinical validation studies that are currently moving through the process of publication.

The studies of interest are:

- Precision Dosing of Infliximab Versus Conventional Dosing of Infliximab (PRECISION), NCT02453776
- Precision IFX: Using a Dashboard to Individualize Infliximab Dosage, NCT02624037
- Optimization of infliximab therapy in inflammatory bowel disease using a dashboard approach – an Indian experience<sup>7</sup>
- Compassionate Use in Acute Severe IBD; Medical University of Vienna, Austria

Together these studies included both pediatric and adult patients. Severity encompassed moderate, severe, and acute severe disease. Clinical and economic outcomes were improved with the application of TDM combined with CDS to determine individualized dosing regimens.

The PRECISION study reported<sup>8</sup> a prospectively powered, randomized, open label study comparing standard of care versus CDS guided dosing in adult IBD patients in maintenance. This study reported a 70% lower rate of secondary non-response in adult patients treated with individualized dosing as compared to the population dosing standard of care arm.

The Precision-IFX study<sup>9</sup> is an open label one arm study of CDS guided dosing in adult and pediatric IBD patients initiating therapy with infliximab and following for a year of treatment. This study has related a primary non-response rate of 4% (7/180 patients).

The exploratory study manuscript, conducted in India, reports cost savings and an ability to restore remission in patients who were secondary non-responders.

The compassionate use study reported<sup>10</sup> a primary response rate of 80% (8/10 acute severe UC patients responding at week 14).

The TITRATE (induction for acute severe ulcerative colitis) study, NCT03937609, is an ongoing, prospectively powered, open label study of induction of infliximab in acute severe IBD patients. Other follow-on multicenter prospective trials are planned in North America, Europe, and Asia.

The CDS used in these studies combines a scientifically appropriate pharmacokinetic (PK) model with statistically sound Bayesian computation. Individual patient physical and laboratory data are used to estimate each respective patient's infliximab clearance. Once the clearance is estimated, suitable dosing regimens may be calculated to achieve the **trough concentration selected by the prescribing physician**.

During development, the PK model used in the CDS was qualified relative to infliximab labeling to ensure that drug exposures of the software-recommended individualized dosing regimens do not exceed the safe and effective limits established during infliximab licensure. "Exposure response information is at the heart of any determination of the safety and efficacy of drugs".<sup>11</sup> Then the qualified PK model was requalified using real world data. For example, the half-lives included in the infliximab label range from 7.7 to 9.5 days. However, in real world data they range from 2 to 15 days. By determining individual patient clearance and using the information to achieve a physician selected exposure target (e.g. trough concentration), CDS individualized

infliximab therapy is based upon patient drug exposure within the limits of safety and efficacy established during infliximab regulatory review and approval.

The software is regulated by Section 520(o), Regulation of Medical and Certain Decisions Support Software, of the Federal Food, Drug, and Cosmetic Act, which provides that when used by or under the supervision of a healthcare professional FDA clearance is not required.

However, “firms, who have an economic interest related to [drug] product distribution”<sup>12</sup> (i.e. drug companies) may have to meet requirements of the FDA framework for prescription drug-use-related software (PDURS).<sup>13, 14</sup>

The study results indicate that in clinical practice the combination of TDM and CDS can alter the status of less expensive infliximab to “biobetter”, relative to more expensive alternatives. Over the next 24 months additional scrutiny of the clinical data may verify factors to be added to the ICER models used to evaluate the effectiveness and value of targeted immune modulators.

Sincerely,

Steven A. Molnar, PhD  
Chief Executive Officer  
Baysient<sup>®</sup> LLC

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<https://www.ropesgray.com/en/newsroom/alerts/2018/12/Aiming-to-Foster-Innovation-FDA-Proposes-Regulatory-Framework-Specific-to-Prescription-Drug-Software>

July 29, 2020

Steven D. Pearson, MD, MSc  
President  
Institute for Clinical and Economic Review  
2 Liberty Square, 9th Floor  
Boston, MA 02109

RE: ICER Ulcerative Colitis Draft Evidence Report

Dear Dr. Pearson,

Thank you for the opportunity to comment on the draft evidence report for the Institute for Clinical and Economic Review (ICER) value assessment of certain ulcerative colitis (UC) treatments. The Crohn's & Colitis Foundation (Foundation) recognizes the goal of ICER to put a spotlight on drug pricing, and we share your concern that patients are subject to high costs and challenging insurance barriers to therapeutic access. While we support that goal, our comments focus on limitations we find in the methodology in the current value assessment for UC and the impact of these limitations on the ability to draw well-founded conclusions based on this model.

We note that the assumptions included in the draft evidence report rely upon limited real-world data (RWD), which impacts the reliability and external validity of ICER's findings. Our recommendations to improve the draft evidence report are as follows:

- Clarify the level of uncertainty around the cost-effectiveness values conclusions within the draft evidence report.
- Clarify recommendations to medical policy decision-makers on how to use the report given the lack of the degree of uncertainty.
- Provide greater transparency on how assumptions were developed for the draft evidence report.
- Further describe the barriers to care experienced by patients as a result of challenging and often confusing payer payment policies and their disconnect with evidence-based disease management guidelines.
- Recommend against insurance-mandated step therapy for UC patients.

The mission of the **Crohn's & Colitis Foundation** (the Foundation) is to cure Crohn's disease and ulcerative colitis (UC) and to improve the quality of life of children and adults affected by these diseases. Crohn's disease and UC are collectively known as inflammatory bowel disease (IBD) and affect approximately 3.1 million Americans. The Foundation is a leader in IBD research, sponsoring basic, translational, and clinical research, and is considered the definitive and most credible source of information, advocacy, and support for the IBD community.

The Foundation welcomes the chance to work with ICER to find better data to improve future value assessments on IBD treatments. We commend ICER for organizing a rich set of clinical

trial data and studies to support its UC treatment value assessment, however, it is clear that there is currently not enough information available for a strong assessment. Further, studies such as randomized controlled trials (RCTs) fall short of the real-world patient experience. The Foundation has developed IBD Plexus, a platform to gather RWD and encourage further research among the IBD research community. We have just begun to publish studies from Plexus and were unfortunately not able to provide this work in time for the ICER 2020 UC value assessment. IBD Plexus will be an important source of RWD for future assessments, and the Foundation would welcome the opportunity to partner with ICER using data derived from IBD Plexus on treatment-value assessments in UC and Crohn's disease in the future.

Below are specific findings of our review of the draft evidence report.

### ***Long-Term Cost Effectiveness – Patient Experience Model Assumptions***

The Foundation is concerned that the long-term cost effectiveness model is too disparate from the real-world patient experience to be a reliable source of cost-effectiveness information. We recommend ICER include verbiage around this uncertainty in the draft evidence report, and that ICER make recommendations for how health policy decision-makers should utilize the uncertain conclusions. Further, ICER could partner with organizations like the Foundation to identify information gaps and launch efforts to support the cultivation and use of more real-world data.

ICER's assumptions for biologic efficacy and use do not align well with real-world efficacy data. Per the model assumptions, the median patient is on the specific targeted immune modulator (TIM) for less than one year; and the average patient-duration on the specific TIM is less than 1.5 years.<sup>ii</sup> OPUS, a European registry, finds a median infliximab use duration of 19.8 months.<sup>iii</sup>

Furthermore, ICER's ongoing maintenance transition probabilities are "memoryless" – where the patient has the same probability of response failure each subsequent cycle. In the real world, treatment success often persists, with remission history begetting more continued response.

ICER's model does not consider infliximab as a treatment for biologically-experienced patients. Infliximab was the first biologic approved for ulcerative colitis (2005), and its FDA indication does not distinguish between biologically-experienced and naïve patients. However, infliximab is commonly used for biologically-experienced patients.<sup>iv</sup> ICER, in its primary model, should model infliximab and the newer infliximab bioequivalents as drugs for biologically-experienced patients. In the ICER sensitivity analysis, using infliximab after vedolizumab was a cost-effective strategy. For those with comorbidities or moderate disease severity, this may be a highly cost-effective sequence of therapies. This finding further questions the key assumptions of the primary model and reinforces the lack of external validity of the current ICER report and key findings.

Further, ICER assumptions for biologic efficacy and use do not align well with real-world biologic use. While ICER's assumptions for biologic discontinuation are too high, ICER underestimates that portion of discontinuations that are for reasons other than failure to respond to the drug. Non-response is one of many reasons for discontinuation; other reasons include drug



costs (patient cost sharing), health plan approvals and hassles, concerns over long-term safety, side effects, and pregnancy.

Finally, over a lifetime, patients may have more than two rounds of biologic drug use, which is not incorporated into the model. Patients, per the model, will spend less than two years of treatment on biologics and so nearly all of their 30+ year life expectancy on conventional treatment or with a colectomy. The concept that patients would undergo treatment with two TIMs and then be cycled on long-term steroids or immunomodulators is really not consistent with current clinical practice. The Foundation has found that patients may try several other TIMs along their disease journey as they seek to avoid surgery at all costs, and their health care providers seek to avoid long-term steroids.

### ***Long-Term Cost Effectiveness – Costs Model Assumptions***

Similar to the patient experience assumptions, ICER's cost estimates are inconsistent and not aligned with the costs to payers in the real world, which limits the reliability of ICER's findings. ICER should cite this uncertainty in its report and, given these uncertainties, recommend how the report can be leveraged by health policy decision-makers. Further, the Foundation encourages efforts to better understand the patient perspectives on UC health state utility values as ICER's assumptions do not align with a commonly held priority of patients to avoid surgery.

ICER's drug costs are manufacturer net revenues and not the average cost to payers, which impacts the relative cost effectiveness of some TIMs compared to others in the draft report. ICER's costs are estimates of the average manufacturer revenue for the drugs, net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs.<sup>v</sup> Payers instead pay a price that is marked-up by wholesalers, PBMs, and providers (pharmacies, physician offices, and hospital outpatient departments).<sup>vi</sup> Physician-administered drugs (paid for as a medical benefit) generally have higher markups than self-injected and oral drugs (paid for as a drug benefit), particularly if the drug is administered in a hospital outpatient setting.<sup>vii</sup> Including mark-ups in the cited drug costs will increase infliximab's cost relative to adalimumab, golimumab, tofacitinib, and ustekinumab and decrease its cost effectiveness advantage.

ICER's non-drug healthcare cost assumptions<sup>viii</sup> do not represent U.S. averages, have several gaps, and are poorly documented. Based on the forward of the draft evidence report, we expect to see healthcare cost assumptions that represent average costs for patients with commercial, Medicare, Medicaid, and other insurance. Instead we find a mix of costs. For example, some costs are pulled from Medicare but omit what commercial payers pay. Further, costs frequently do not take into account associated costs of key procedures and hospitalizations/outpatient care. These inconsistencies need to be addressed to strengthen the findings of the draft evidence report. Given space constraints, we are not including specific examples in this paper, and we can share more details upon request.

Additionally, per ICER's QALY assumptions and our calculations, colectomy by far dominates biologics for maximizing QALYs, implying that UC patients who are candidates for biologics should instead want an immediate colectomy. Since this is clearly not the case, we question the overall veracity of ICER's utility values and treatment efficacy assumptions. While biologics

provide a potential short-term boost in QALYs compared to conventional treatment, colectomy (per ICER's assumptions) produces a long-term boost for everyone except the 15% of the population who ICER assumes develop chronic pouchitis.<sup>ix</sup> We estimate that the net (of pouchitis) lifetime QALY boost from a colectomy, per ICER's assumptions, is a multiple of the 0.20 gain from biologics.<sup>x</sup> Yet, in the real world, patients who are candidates for biologics are not on the phone asking their payers for approval for colectomies. In fact, ICER estimates that only 18.9% of patients with conventionally-treated UC will get a colectomy over a period of 10 years.<sup>xi</sup> More work needs to be done to assess patient perspectives to inform accurate health-state utility values.

### ***Long-Term Cost Effectiveness – Transparency***

ICER should reframe the lifetime-horizon data point. A casual reader of the cost-effectiveness summary and tables might reasonably, yet incorrectly, conclude that ICER modeled the costs of a patient receiving a single biologic drug for the remainder for their life vs. the cost of the patient receiving conventional treatment. Section 5.4, Summary and Content, starts with “*We estimated the cost effectiveness of TIMs over a lifetime horizon...*” and the data tables name single biologics. As noted above, per ICER's model, the median patient is on the specified (first) biologic for less than one year and the mean patient is on for less than 1.5 years. If the patient fails the induction phase of the first biologic, the patient receives a second biologic, which the patient will also most likely be on for a very short time. The modeled patient will therefore have biologic treatment for less than 10% of their expected 30+ year life expectancy and the biologic costs reported by ICER for the specified biologic include the costs for both the first and, when applicable, second biologic drug.

ICER should share its pathways from cited sources to the assumptions used in the modeling. Most of the assumptions are not straight “pick-ups” from the cited paper(s) into the model, and it is clear that some degree of transformative judgment and blending of papers was required. The transformations are as critical to assumption soundness as the underlying citation, yet they are described in only the most general terms, if at all. NMA workpapers would fill-in the missing information. Without access to these models, we and other stakeholders cannot fully understand the dynamics of the modeling or check for potential errors.

### ***Coverage Policies and Clinical Guidelines***

ICER's review of payer drug-approval policies ignores/understates payer-approval complexities and the lack of alignment with clinical guidelines. The Coverage Policies and Clinical Guidelines section presents *default commercial* payer coverage policies for 17 of the largest U.S. national and regional commercial medical payers. While ICER finds an inconsistent jumble of policies that often do not align with clinical guidelines, the reality is worse. For example, UnitedHealthcare has separate policies for the use of infliximab for commercial insurance and Medicare Advantage<sup>xii</sup> and the language within both policies makes it clear that numerous exceptions exist. Payer policy is further complicated when a patient has prescription drug benefits via a PBM whose benefits are not integrated with the patient's medical benefits. Divergent health plan and PBM policies are particularly stressful to UC patients as some UC drugs (those that require physician administration) are typically paid for as a medical benefit and

other UC drugs are paid for under the prescription drug benefit. PBMs set their own benefit policies and their policies vary by health plan, self-insured employer, and state.

Finally, we will short-change our patients if we do not note that patients and their physicians often have to navigate multiple policies as patients move between health plans and health plans modify their payment policies. We further note that it is estimated that 98% of top health plan formularies are not aligned with the American Gastroenterological Association's (AGA) UC clinical guidelines<sup>xiii</sup>, further complicating access to appropriate and needed care.

### ***Policy Recommendations***

ICER should recommend against the use of insurance-mandated step therapy among the UC patient population, particularly for moderate to severe patients, in its final policy recommendations paper. For decades, the Foundation has invested in medical research and has played a part in the discovery of every recent therapy brought to market so that UC patients have many options to treat the unique manifestation of their condition. Despite these advancements in research, high pharmaceutical costs and insurance-mandated medical management limit patient access to the full suite of available treatments. The draft evidence report notes there are currently limited head to head studies and sequencing information, therefore, providers and patients must make the best decision based on clinical guidelines, the provider's experience, and the patient's known characteristics, treatment preferences, and medical history. It is impossible for an insurance-mandated step therapy protocol to take all of these factors into account. Further, the consequences of undertreatment are quick and devastating for UC patients – many patients who do not receive adequate treatment in time experience irreversible damage to their large intestine and can degrade so far as to need a colectomy. It is often thought – though difficult to prove – that the colectomy could have been avoided if the patient had access to the right treatment at the right time. Further, ICER notes the high cost per QALY of every assessed TIM. Requiring patients to step through inappropriate treatments reduces the value of the payer's-preferred TIM that is unlikely to work. Therefore, the Crohn's & Colitis Foundation strongly urges ICER to recommend against the use of step therapy among UC patients.

ICER should encourage pharmaceutical companies and insurance plans to work together to improve fair patient access at affordable prices. Even if many of the TIM prices referenced in Table 5.17 Cost of Induction and Maintenance were slashed in half, many UC patients would still be unable to afford their out-of-pocket treatment costs. Insurance coverage is a must for patients to access the therapies they need to thrive. While the Foundation recognizes the purpose of the UC Value Assessment is to assess whether the TIM drug prices meet the usual standards for cost effectiveness, ICER must acknowledge the critical lifeline these treatments present for patients, and urge manufacturers and payers to come together to ensure that patients can afford their treatments and maintain consistent, regular therapy without undue formulary burdens.

As stated above, while ICER plays an important lead role in advancing the use of value assessments in the American healthcare system, ICER should recognize the limitations of its comparisons and valuations, and encourage further studies leveraging RWD. Better study inputs, such as carefully gathered RWD, would improve the validity and usefulness of the value

assessments. The Foundation will continue to develop and promote IBD Plexus as a platform for RWD that can support better pricing and formulary decision making.

Thank you for your consideration of our views. For additional information, please contact Sarah Buchanan, Director of Advocacy, at [sbuchanan@crohnscolitisfoundation.org](mailto:sbuchanan@crohnscolitisfoundation.org).

Sincerely,



Michael Osso  
President & Chief Executive Officer  
Crohn's & Colitis Foundation

- 
- i Draft Evidence Report, Tables 5.3, 5.4, 5.5, 5.6, and 5.10: per our calculations, using the assumptions from these tables, substantially less than 50% of patients are experiencing clinical remission or clinical response at the end of a year
  - ii Draft Evidence Report, Tables 5.17 and 5.21: comparison of “Initial TIM Drug Cost” to “Net Price per Eight Week Induction”+“Net Price per Maintenance Year”
  - iii Panes, <https://pubmed.ncbi.nlm.nih.gov/30809631/>
  - iv Example: UnitedHealthcare’s Remicade policy does not distinguish between the biologically experience and naïve: <https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/infliximab-remicade-inflectra.pdf>, pg. 7
  - v Draft Evidence Report, Drug Acquisition Costs, pg. 79
  - vi <https://www.healthaffairs.org/doi/10.1377/hblog20180726.670593/full/>; <http://www.themoranccompany.com/wp-content/uploads/2019/07/Hospital-Charges-Report-July-2019.pdf>
  - vii <https://www.healthcarefinancenews.com/news/hospitals-keep-91-percent-profit-physician-administered-drugs>
  - viii Draft Evidence Report, pages 81-82
  - ix Draft Evidence Report, Tables 5.12 and 5.13
  - x Draft Evidence Report, Table 5.21; note: LYs and QALYs are discounted 3% and therefore are less than a straight sum of LYs and QALYs
  - xi Draft Evidence Report, Clinical Inputs, page 74
  - xii <https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/infliximab-remicade-inflectra.pdf>,  
<https://www.uhcprovider.com/content/dam/provider/docs/public/policies/medadv-coverage-sum/medicare-part-b-step-therapy-programs.pdf>
  - xiii <https://pubmed.ncbi.nlm.nih.gov/28509816/>

July 29, 2020

Institute for Clinical and Economic Review (ICER)  
2 Liberty Square  
Boston, MA 02109

Dear ICER Review Panel:

Genentech appreciates the opportunity to provide feedback on ICER's "*Targeted Immune Modulators for Ulcerative Colitis [UC]: Effectiveness and Value; Draft Evidence Report*" during this public comment period. Genentech has a deep-seated commitment to innovation and ensuring a patient-centric approach to access. We encourage ICER to refine their assessment to better reflect both current clinical practice in UC and best practice methodologies for cost-effectiveness analysis. Therefore, we provide the following recommendations to further enhance the relevance of the report and better inform health care decision-making:

- 1. Use infliximab or adalimumab as the base case model comparator instead of “conventional therapy” (CT).**
- 2. Update the definition of “conventional therapy” and acknowledge the high uncertainty of this comparator given the inconsistency in background therapy across randomized clinical trials (RCT).**
- 3. Perform a scenario analysis removing the artificial cap limiting colectomy within the model.**
- 4. Derive adverse event model inputs from relative risks via a safety network meta-analysis (NMA) rather than using an absolute percentage selected from individual RCTs.**

- 1. Use infliximab or adalimumab as the base case model comparator instead of “conventional therapy” (CT)**

The use of conventional therapy (CT), defined as corticosteroids for induction followed by azathioprine or mercaptopurine, as a baseline comparator is not appropriate in moderate-to-severe UC. American Gastroenterological Association (AGA) and American College of Gastroenterology (ACG) guidelines cite a stronger grade of evidence for the use of targeted immune modulators (TIM) in the induction and remission of moderate-to-severe UC population over CT<sup>1-2</sup>. Instead, we recommend following a guidelines-based approach supplemented by real-world practice, of which infliximab and adalimumab have most prevalent usage<sup>3</sup>. Adopting

this approach will ensure that the base case represents the appropriate relative value of treatment in the moderate-severe UC population.

**2. Update the definition of “conventional therapy” and acknowledge the high uncertainty of this comparator given the inconsistency in background therapy across randomized clinical trials (RCTs).**

We recommend ICER update the definition of CT to denote the placebo arm of RCTs rather than the current definition of “*corticosteroids for induction followed by maintenance with 50:50 split of azathioprine and mercaptopurine*”<sup>4</sup>. The current CT definition is flawed, as there is significant heterogeneity within the placebo arms of each RCT, and thus may not accurately reflect ICER’s definition of CT<sup>5-13</sup>. For example, the range of corticosteroid use in the baseline placebo group from UC clinical trials ranges from 38.9% in GEMINI I<sup>12</sup> to 65.3% in PURSUIT-SC<sup>8</sup>. The use of immunomodulators such as thiopurines in placebo is reported as 12.1% in GEMINI I<sup>12</sup> to 43.8% in ACT I<sup>13</sup>. Some trials, such as the OCTAVE I, II, and SUSTAIN cohorts, do not report immunomodulator use<sup>10-11</sup>. As such, we encourage ICER to further acknowledge the uncertainty of using CT as a comparator due to its high heterogeneity. This will ensure the report provides the relevant context that is necessary for correct interpretation of any conclusions or comparisons made concerning the usage of CT in UC.

**3. Perform a scenario analysis removing the artificial cap limiting colectomy within the model.**

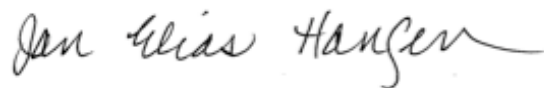
The justification for a surgery cap references a small study sample of 369 patients within one county in the United States<sup>14</sup>. As such, we caution on its generalizability to a national real-world population. Furthermore, it is unclear from the reference whether these patients are moderate-to-severe UC patients or inclusive of all severity states, which may underestimate the true cumulative rate of surgery. By capping surgery rates, this potentially biases the outcomes for weaker comparators as they may have a higher cost and disutility burden of surgery that is removed from the model due to the artificial cap. Therefore, to improve model transparency and show the impact of this artificial construct, we recommend a scenario analysis removing the cap limiting colectomy within the model.

**4. Derive adverse event model inputs from relative risks via a safety network meta-analysis (NMA) rather than using an absolute percentage selected from individual RCTs.**

Per the International Society for Pharmacoeconomics and Outcomes (ISPOR) Good Research Practices Task force, it is recommended that parameter estimates follow evidence-based medicine principles, e.g. “*seek to incorporate all evidence, rather than selectively picking a single source.*”<sup>15</sup> Current adverse event rates for TIMs within the model are selected from a single source using an absolute incidence, which could bias the disutility and costs of certain TIMs due to the heterogeneity of each RCT. A more robust approach would be to utilize relative risks and adjusted probabilities from ICER’s NMA. For example, a recent NMA by Singh et al. and Jairath et al. found significant differences in serious adverse events and infection rates of TIMs.<sup>16-17</sup>

We believe that the incorporation of these recommendations will enhance the accuracy and utility of the report and more appropriately reflect real-world treatment patterns. In turn, Genentech believes this will ensure a more robust value assessment of treatments in this complex landscape, and will help support appropriate patient access to UC therapies. We would be eager to further discuss our recommendations and answer any questions.

Sincerely,

A handwritten signature in black ink that reads "Jan Elias Hansen". The signature is written in a cursive, flowing style.

Jan Elias Hansen, Ph.D.  
Vice President, Evidence for Access Medical Unit  
U.S. Medical Affairs  
Genentech, Inc.

**Date:** July 29, 2020

**RE:** ICER Ulcerative Colitis Draft Evidence Report – Response to Request for Public Comment

*The following information is provided in response to request for public comment and is not intended as an endorsement of any usage not contained in the Prescribing Information. For complete information, please refer to the full Prescribing Information for each product, including the following sections: INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, AND ADVERSE REACTIONS.*

#### CONTACT INFORMATION

Name	Shantel Gooden, PharmD
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City, State	Horsham, PA
Email Address	sgooden2@its.jnj.com

#### EXECUTIVE SUMMARY

Janssen appreciates the opportunity to provide comments on the ICER Draft Evidence Report given the positive impact of our medicines for patients living with Ulcerative Colitis (UC). Upon review of this draft, Janssen is compelled to reiterate our concerns with ICER’s methodological approach, specifically regarding the Network Meta-Analysis (NMA) and subsequent Cost-Effectiveness Model results.

Janssen looks forward to ICER’s response to the concerns outlined below. These considerations are critical in determining the accuracy and relevance of this report.

#### Network Meta-Analysis:

The NMA should appropriately account for differences between re-randomized maintenance placebo rates across trials. These placebo rates are statistically different across re-randomized maintenance trials. The differences observed can be explained by the varying rates of carry-over effects patients experience when they receive active treatment in induction trials, and are subsequently re-randomized to receive placebo in maintenance trials. (Figure 1: “Placebo” rates across re-randomized maintenance arms in the maintenance phase<sup>1</sup>) Therefore, placebo is **not** a common comparator as reported across re-randomized maintenance trials, and cannot appropriately be used to conduct an NMA without further adjustment.

- Notably, placebo efficacy rates in the Stelara UNIFI re-randomized maintenance trial are significantly higher than the placebo efficacy rates reported in other re-randomized maintenance trials. (Figure 1)<sup>1</sup> This is due to the prolonged efficacy of Stelara following a single intravenous (IV) dose during the induction trial. All patients entering the maintenance trial received Stelara during the induction trial, the effect of which carries over into the maintenance trial, and continues to benefit patients who are re-randomized to placebo in the maintenance trial. Evidence of this carryover effect at a molecular level was presented by Li et al.<sup>2</sup>
- This difference in placebo efficacy across re-randomized maintenance trials cannot be attributed to heterogeneity across patient populations in the trials since clinical response for placebo arms at end of induction were similar across trials.

The methods ICER has employed for this analysis result in:

1. Substantial underestimation of efficacy for Stelara in ICER’s maintenance NMA



2. Overestimation of efficacy for conventional treatment, which particularly impacts clinical response in maintenance trials
3. Overestimation of efficacy for products that have a more rapid decrease in efficacy following induction (i.e. treatments which lack a carry-over effect). This particularly impacts clinical response in maintenance trials

**NMA Summary and Conclusion:** Placebo arms across the UC maintenance trials are **not** a common comparator. Examining these trials independent of induction trials and converting treat-through maintenance trials to randomized withdrawal trials results in flawed NMA results. ICER's analysis violates the homogeneity assumption, rendering it invalid, and making it contrary to guidelines issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) for how to appropriately conduct indirect treatment comparisons.<sup>3</sup>

**Welty et al. NMA:** An NMA with Janssen authors recently published by Welty et al, utilized alternative methodology that attempted to correct for the variation in placebo efficacy rates across maintenance trials.<sup>4</sup>

### **Cost-Effectiveness Model:**

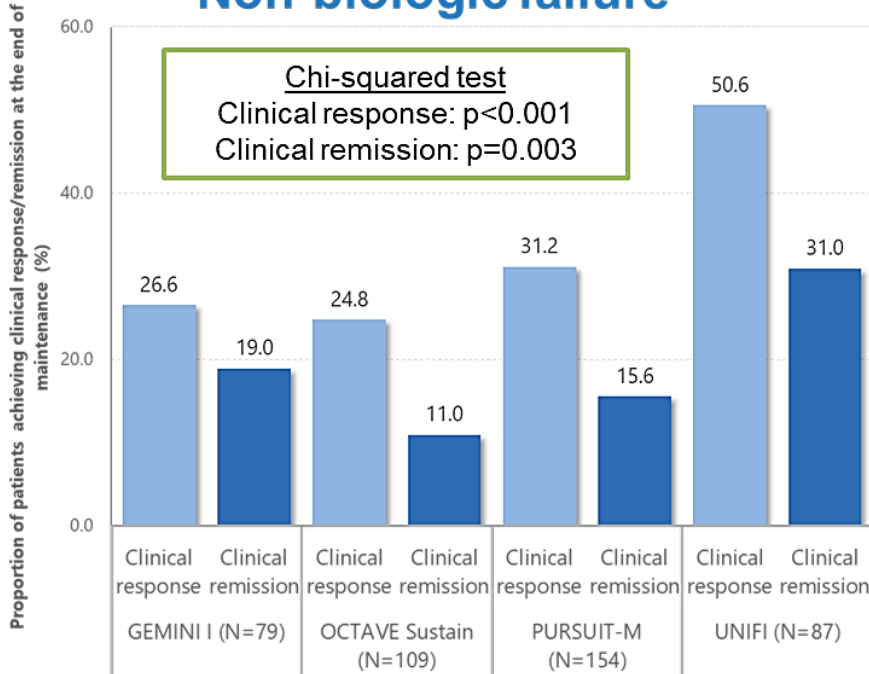
ICER's cost effectiveness model results are misleading, and undervalue the benefit of advanced therapies to patients who have not been sufficiently managed with conventional treatments for the following reasons:

- **Flawed Maintenance NMA Analysis:** As described above
- **Stelara Net Cost Assumptions:** The SSR Health net cost assumptions used in ICER's base-case cost-effectiveness model does not account for rebates that differ between Stelara doses used for UC (90 mg syringe) and those used in other indications (45 mg syringe). Additionally, SSR Health net prices lag behind those relevant in the current market.
- **Limitations of QALYs in assessing product value in UC:** Janssen fundamentally disagrees with the use of quality adjusted life year (QALY) alone to determine the value of a medication for patients and the healthcare system, as QALY rates the value of human life relative to a subjective standard of perfect health. QALYs and cost/QALY results are highly sensitive to utility assumptions which are themselves subjective measures of health and may not adequately capture variability in UC disease severity. This is evident from the results showing low QALYs gained relative to conventional treatment and costs/QALY vs. conventional therapy that are higher than the \$150K/QALY threshold for all advanced therapies.

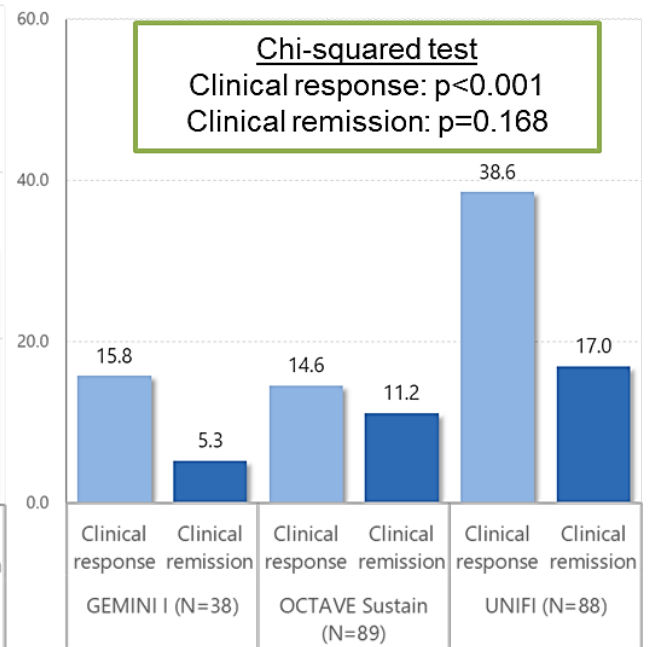
In closing, Janssen asks that ICER consider and address these important methodological limitations to ensure an accurate and relevant analysis in the final report.

## APPENDICES

### Non-biologic failure



### Biologic failure



## REFERENCES

1. Welty M, Mesana L, Padhiar A, et al. Indirect Treatment Comparison Of The 1 Year Efficacy For Ustekinumab Versus Other Advanced Therapies In Moderate To Severe Ulcerative Colitis. Poster presented at: American College of Gastroenterology, October 25-30, 2019, San Antonio, TX, Poster P2285.
2. Li K, Yang F, Hayden K, et al. Clinical and molecular characterization of patients with durable response to ustekinumab induction therapy: results from the UNIFI phase 3 studies in moderate-to-severe ulcerative colitis. Poster presented at: Digestive Disease Week, May 26-29, 2020.
3. Hoaglin D C, Hawkins N, Jansen J P, et al. (2011) Conducting indirect-treatment-comparisons and network-meta-analysis studies: Report of the ISPOR task force on indirect treatment comparisons good research practices: Part 2. Value in Health, Vol. 14, 429-437.
4. Welty M, Mesana L, Padhiar A, et al. Efficacy of ustekinumab vs. advanced therapies for the treatment of moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. Curr Med Res Opin. 2020:1-12.

July 29, 2020

Dr. Steven D. Pearson  
President  
Institute for Clinical and Economic Review  
Two Liberty Square, Ninth Floor  
Boston, MA 02109

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report regarding treatments for Ulcerative Colitis. Ulcerative Colitis (UC) is a painful and, at times debilitating, chronic illness that does not currently have a cure. UC patients are more likely than people without UC to experience other health conditions like cardiovascular disease and arthritis. Given the complications and comorbidities associated with UC, it is imperative to deliver more options of efficacious treatments to patients. With this in mind, PIPC asks ICER to consider the following comments:

### **ICER neglects to account for heterogeneity of patient population**

UC is a highly heterogeneous condition. The presentation of symptoms and disease course can vary substantially among patients. In some, the disease course may reflect periods of active disease and remission, while in others the symptoms are persistent despite increased use of medical therapy. In addition, there are noted but currently poorly understood differences in how racial and ethnic minorities experience UC. The Crohn's & Colitis Foundation highlighted this heterogeneity in their initial letter to ICER, noting that treatment needs may vary greatly based on the specific patient's presentation of the disease: "UC is heterogeneous and the needs of each patient unique...Because each patient is unique and UC is a chronic and generally progressive disease, optimal care for the UC patient requires timely access to the full suite of treatments currently available."

Though ICER acknowledges the reality that UC patients are heterogeneous in their report, they neglect to represent this in their base case for cost-effectiveness and continue to base these judgements off of an "average" patient. Reliance on averages in cost-effectiveness analyses has shown to be illogical<sup>i</sup> and unscientific.<sup>ii</sup> It also results in very real harm for many patients whose experiences do not sit conveniently close to the averages portrayed in these sampling-based summaries of widely varying sets of outcomes.<sup>iii</sup> As a result, new therapies that are likely to have significant impacts on the lives of patients with life-altering levels of discomfort and pain will not be made available – or will have their access restricted – simply because other patients deemed to fall into the same disease category experience far less of such pain and discomfort, or experience it infrequently rather than constantly, diluting the effects of the former group.

## **ICER's use of the QALY is inappropriate**

PIPC would like to reiterate the point it has made to ICER in past comment letters that the use of the Quality-Adjusted Life Year (QALY) is inappropriate in assessing treatments for chronic illnesses. For many UC patients, incremental improvements in health without having to undergo surgery are significantly beneficial to their quality of life, even if they never achieve “perfect health.”

ICER's use of the QALY in this report is particularly concerning because the utility weights used vary considerably from other published estimates.

ICER uses utility weights for active UC, clinical response without remission, and clinical remission of 0.69, 0.78 and 0.87 respectively.<sup>iv</sup> Other published estimates of the utility weight of time spent in active UC not only vary considerably from the figure used in the base case for ICER's report, but they also tend to have multiple figures describing various levels of severity of active disease. For example, Wohel et al<sup>v</sup> and Tsai et al<sup>vi</sup> estimate mild active UC at 0.72, but for moderate and severe disease the utility is estimated at 0.42. Similar estimates have been used in numerous UC treatment models in the last decade.<sup>vii</sup> This is also the estimate of utility for severe disease that was suggested by the Evidence Review Group of NICE in recent submissions for amongst others vedolizumab.<sup>viii</sup>

ICER's choice to use a single “active disease” utility weight that represents an average across all patients with the disease, rather than one which represents the population with moderate to severe disease for which these drugs are indicated, is concerning. As mentioned previously, UC is a disease of significant heterogeneity in terms of severity.<sup>ix</sup> It is inevitable that the utility weights for patients suffering moderate or severe disease will be lower, as their suffering is more extreme,<sup>x</sup> and the use of an artificially higher utility weight for active disease will underestimate the value of any effective treatment as ICER's model uses the utility weight as the most impactful input variable.

## **ICER omits outcomes that matter to patients**

Patient advocacy groups have voiced concerns to ICER about the narrow scope of symptoms collected in clinical trials, which omit outcomes important to patients, like pain, fatigue, and depression. Published studies confirm the need to incorporate this data. One recent study of nearly 300 Crohn's and UC patients found that 40% of respondents met criteria for chronic pain and nearly 20% reported opioid use,<sup>xi</sup> and much of this pain was not directly explained by rate of incidence of disease activity. Despite this consistent message from patient groups and researchers, it does not appear that these outcomes were incorporated into ICER's economic model.

ICER defines only three health states for the disease: active UC, response without remission, and response with remission. Even if we assume that a generic patient-reported outcomes (PRO) tool, like the EQ-5D or SF-36, effectively captures all the components of utility in UC including pain,

fatigue, anxiety and depression, the fact that many of these will not be directly correlated with disease activity, and that they will vary considerably with severity of active disease, means that ICER's simplistic representation of the disease will have a negative impact across a considerably heterogeneous patient population who are known to show wide variance in terms of treatment effect. That heterogeneous group is currently represented by just one health state when in active disease, which has the detrimental outcome of failing to capture health gains properly for patients with more severe UC.

### **ICER missed an opportunity to evaluate true “value” to patients**

Vedolizumab is a gut-selective biologic agent that is recommended as a potential first-line treatment for both induction and maintenance in UC but is often not covered by insurance until failure of other treatment options. In some cases, patients must try and fail at least two TNF inhibitors before vedolizumab is considered medically necessary and ultimately covered by payers, even despite clinical evidence that many patients do not respond to this biologic class. Patient advocacy organizations highlighted to ICER that one of patients' primary concerns around access to treatment is step-therapy.

ICER's assessments are frequently considered by insurers as they develop arduous step therapy guidelines. Step therapy is primarily used by payers as a utilization management tool to help contain costs, and there is no evidence to suggest the use of step therapy improves health outcomes. Given that ICER's stated goal is to determine true clinical and cost-effectiveness of treatments, and to optimize value in the United States healthcare system, this would have been an opportunity to evaluate the impact of step therapy on clinical outcomes in UC patients. It is a worthy question to determine whether there is any long term 'value' in the payer community's reliance on step therapy,<sup>xii</sup> which has been shown to result in very real harm to patients.<sup>xiii</sup> This could have been easily modeled through a scenario analysis to assess the value of treatment pathways with and without step-therapy.

There is evidence that in the case of ulcerative colitis, the vast majority of insurance medical policies around prescribing for UC are incompatible with current American Gastroenterological Association (AGA) clinical pathway recommendations.<sup>xiv</sup> ICER's UC assessment represents a missed opportunity to develop a comprehensive modeling exercise comparing step therapy to a system where patients are prescribed the most effective treatment indicated for them based on their physician's expert diagnosis, disease progression, individual patient characteristics, and relevant clinical society guidelines. ICER's decision not to capitalize on this opportunity contradicts its previously stated goal to determine the true value of treatments and is another missed attempt to better account for outcomes that matter most to patients.

### **Conclusion**

UC is a condition that impacts a very heterogeneous patient population, and treatment can vary greatly from patient to patient. For this reason, it is imperative that ICER account for this heterogeneity within its model and consider improving its methods.

Sincerely,



Tony Coelho  
Chairman  
Partnership to Improve Patient Care

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# UNIVERSITY OF MINNESOTA

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28 July 2020

TO: Dr. S Pearson, CEO  
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Two Liberty Square, Ninth Floor  
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Email: [publiccomments@ICER-review.org](mailto:publiccomments@ICER-review.org)

Dr. Pearson

**REF: Draft Evidence Report for Ulcerative Colitis**

Recent commentaries, including my own, have made the case that the QALY is an impossible construct <sup>1</sup>  
<sup>2</sup>. The reason is quite straightforward: utilities (e.g., EQ-5D-3L) are clearly ordinal scales as they are the  
product of aggregation over symptom specific ordinal scales <sup>3 4</sup>. Multiplying ordinal ranks by preference  
weights only produces an ordinal scale. This follows from the axioms of fundamental measurement  
where an ordinal scale has identity and magnitude in an ordered relation but with unknown distances  
between the ranks. This means the scale is capable of generating medians and modes, and the  
application of nonparametric statistics. It cannot support multiplication. To create QALYs you need a  
ratio scale (which you do not have) to multiply time by a utility score. If this is the objective, putting to  
one side the imaginary lifetime models, then a utility 'instrument' has to be designed to have ratio  
properties. The EQ-5D-3L and similar instruments were not designed to achieve this objective.

Given that the centerpiece of ICER's value assessment rests on a reference case model where evidence  
to support incremental cost-per-QALY claims is created from discounted lifetime QALYs, the concern  
must be that if the QALY is an impossible mathematical construct, as it clearly is, then how can ICER  
support lifetime QALY models and value assessment claims? Clearly, if the utilities are on an ordinal  
scale, then it is impossible to multiply time spent in a disease state by an ordinal utility to create a QALY.  
The ulcerative colitis QALYs are, therefore, mathematically impossible constructs. This needs to be made  
clear to the respective manufacturers and health decision makers.

I realize, of course, that ICER may take refuge in the argument that this construction of mathematically  
impossible QALYs is a standard in health technology assessment <sup>5 6</sup>. In short, irrespective of  
considerations of fundamental measurement, the reference case cost-per-QALY is a valid (?)

methodology. Truth is by consensus. This is not, of course, a satisfactory response; it begs the question. It is imperative, therefore, from the perspective of those who may consider introducing your ulcerative colitis recommendations in formulary decisions and treatment practice that ICER makes quite clear why it continues to use cost-utility as the basis for value assessment.

If ICER persists with constructing reference case, as appears to be the case, then ICER must be able to defend its position though proof. Nothing else will suffice if ICER is to retain its credibility. This applies not only to ulcerative colitis but to all ICER evidence reports.

Please respond to the following questions:

1. When a QALY is constructed time spent in a disease state is multiplied by a utility score on a range 0 = death to 1 = perfect health. Would ICER agree that this requires the utility score to have ratio properties?
2. Ratio property means that the measurement scale must have a true zero. This means that the EQ-5D-3L should have a true zero. In fact, EQ-5D-3L utilities can take negative values (with a range -0.59 to 1). Would ICER agree that this means the EQ-5D-3L is not a ratio scale?
3. In respect of Q2, if ICER believes that the EQ-5D-3L instrument has, despite negative values, a true zero, could ICER provide a proof?
4. It appears to be commonly assumed that the EQ-5D-3L (in common with other generic instruments) meets the axioms for invariance of comparisons. That is, it has interval scoring properties. Would ICER agree?
5. In respect of Q4, if ICER believes that the EQ-5D-3L has interval properties, could ICER provide a proof?
6. If ICER cannot provide a proof that the EQ-5D-3L has interval properties, how does ICER justify the creation of QALYs as responses to therapy?
7. Over the past 20 years commentaries from measurement theory specialists have made the case that instruments such as the EQ-5D-3L, in fact the majority of patient reported outcomes instruments, have lacked ratio (and interval) properties. Is ICER aware of this literature and would ICER care to comment? <sup>3 4</sup>
8. In respect of the draft evidence report for TIMs in ulcerative colitis, the utility scores appear to be an amalgam over different generic instruments (the Malinowski & Kawalec paper). How does ICER justify this given the differences that exist between the various instruments?
9. Table 5.12 in the draft evidence report provides 95% confidence intervals for four disease states. As the various scales, on which these are based, are ordinal how are these justified? If ICER believes these are justified could ICER demonstrate that the consequent utility scale has the required measurement properties to support confidence intervals? Given the 95% confidence intervals overlap, can you claim that the utility scores are significantly different? At what level? Does this mean there are only two disease stages that yield significantly different utilities (clinical remission vs. other three)? Should the model be reworked for two utility measures?
10. Again, in respect of Table 5.12, could you detail: (i) the attributes captured by the utility scale (i.e., symptoms); (ii) the ordinal response levels for each attribute; and (iii) the preference



weights or values for each response level by symptom attribute? Or is this impossible given the meta-analytical basis for aggregating over quite different utility systems? Do these utility scores have ratio properties? Can ICER demonstrate that this is the case?

11. If the EQ-5D-3L (or other generic utility scale) cannot be shown to have ratio (and interval) properties why does ICER persist in creating lifetime cost-per-QALY claims? As the utility scale is ordinal then the QALY is an impossible construct? Would ICER agree?
12. If, given that the QALY is mathematically impossible, would ICER inform its audience that it recognizes this but insists that there is still merit in constructing imaginary value assessments on imaginary QALYS to create imaginary claims information?

I am sure you agree that if ICER is to have any credibility in value assessment, these are pertinent questions. If you require further elaboration on measurement axioms and the ordinal nature of multiattribute utility scales, please let me know.

Sincerely

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**Pfizer Inc**  
235 East 42nd Street  
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July 29<sup>th</sup>, 2020

Steven D. Pearson, MD, MSc  
President  
Institute for Clinical and Economic Review  
Two Liberty Square, Ninth Floor, Boston, MA 02109  
*Submitted via email: [publiccomments@icer-review.org](mailto:publiccomments@icer-review.org)*

**RE: Targeted Immune Modulators Ulcerative Colitis: Effectiveness and Value. *Draft Evidence Report***

Dear Dr. Pearson and ICER UC team,

On behalf of Pfizer Inc., thank you for the opportunity to comment on the Targeted Immune Modulators (TIM) UC draft evidence report. In reviewing the report, we noted incorporation of our earlier suggestions into the methodology and approach, which is sincerely appreciated. We have identified 5 additional areas for recommended revisions to eliminate biased conclusions. They are listed in order of priority:

1. *Choice of conventional treatment as a comparator in the bio-experienced population*
2. *Infliximab price assumption and net pricing input*
3. *Errors in the model*
4. *Implications of Modelling Second TIMs*
5. *Dose escalation price inputs for Tofacitinib*

1. *Choice of conventional treatment as a comparator in the bio-experienced population:*

We appreciate ICER's choice to compare the TIMs to Adalimumab in biologic-experienced patients in their base case analysis. However, ICER's threshold analysis/conclusions on cost effectiveness is based mostly on the analyses of TIMs compared to conventional treatment (corticosteroids, mercaptopurine, azathioprine) alone.

We recommend the selection of conventional treatment in the bio-experienced population as a comparator. Cost-effectiveness of new interventions should be made from comparison to

standard of care based on clinical guidelines. It is debatable whether conventional treatment alone is considered standard of care for patients that already failed a biologic. Instead, we believe that long-established TIMs, like Adalimumab, represent standard of care for these patients.

To substantiate our request, we want to highlight recommendations from the latest American College of Gastroenterology (ACG) guidelines. In the key concept statement section ACG specifically identifies Vedolizumab, and Tofacitinib (Ustekinumab is not included in the guidelines because it was not yet approved for moderate to severe UC) as recommended treatment options for induction and maintenance of remission in patients who fail a TNF blocker (pasted below).

*"In patients with moderately to severely active UC who have previously failed anti-TNF therapy, we recommend vedolizumab for induction of remission (strong recommendation, moderate quality of evidence)"*

*"In patients with moderately to severely active UC who have previously failed anti-TNF therapy, we recommend tofacitinib for induction of remission (strong recommendation, moderate quality of evidence)."*

ACG makes no mention of steroids and or 5-ASA in moderate to severe UC patients who have failed a TNF blocker. It is important to note that the guidelines do not state that azathioprine or 6-monotherapy for the maintenance of remission are appropriate therapeutic options for patients who have failed TNF blockers. In addition, systemic steroids are not recommended for maintenance of remission either. Also, budesonide MMX has not been studied for maintenance of remission of previously moderately to severely active UC. Finally, treatment with 5-ASA therapy has been shown to be efficacious and safe as monotherapy for induction of moderately but not severely active UC, therefore, it may not be appropriate to consider 5-ASA therapy in moderate to severe UC patients.

We strongly recommend ICER to compare the TIMs to Adalimumab *only* in biologic-experienced patients and estimate economically justifiable price of TIMs versus Adalimumab (and not conventional therapy). At the minimum, we recommend that ICER include in their "limitations" discussion about the uncertainty of whether standard of care should be represented by commonly used TIM (Adalimumab) or conventional treatment given the US guidelines recommended use of TIMs in bio-experienced population

2. *Infliximab price assumption and net pricing approach*

We support ICER’s decision to use SSR Health pricing for pharmacy benefit products (orals, self-injectables), since there is no publicly available source for net price.

However, for products dispensed through medical benefit (infusions), e.g. Infliximab, Infliximab-dyyb, Infliximab-abda, CMS published ASP values are the most transparent source of net pricing, since these include discounts to providers and reflects how payers reimburse as well. ASP values for Medical benefit products are updated every quarter and publicly available.

In this case, we strongly recommend using the actual price data from CMS rather than estimating price using SSR data. ASP is a market-based price that reflects the weighted average of all manufacturer sales prices and includes all rebates and discounts that are privately negotiated between manufacturers and purchasers (with the exception of Medicaid and certain federal discounts and rebates). This methodology mirrors reimbursement for physician-administered drugs in the commercial market. A manufacturer’s ASP must be calculated by the manufacturer every calendar quarter and submitted to CMS within 30 days of the close of the quarter. Since ASP is accurate enough to be the official determinant physician’s actual reimbursement, it should also be the basis for ICER’s assessment of cost-effectiveness. Below are the ASP and SSR based cost tables that we propose to be used to replace the SSR values in the cost effectiveness analysis. We have provided costs for all infliximab molecules for transparency and completeness

	<b>WAC Per Vial</b>	<b>SSR Net Costs</b>	<b>SSR Discounts</b>	<b>CMS payment Per Vial</b>	<b>ASP Discount</b>	<b># of Vials Per Patient per Year</b>	<b>Annual Net Costs at SSR</b>	<b>Annual Net Cost at ASP</b>
Inflectra	\$946.28	\$548.84	-42%	\$471.26	-50%	28	\$15,367.52	\$13,195
Remicade	\$1,167.82	\$443.77	-62%	\$512.00	-56%		\$12,425.56	\$14,336
Renflexis	\$753.39	\$436.97	-42%	\$486.37	-35%		\$12,235.16	\$13,618

3. *Errors in the Model*

A. Calculation of disease-specific and general population mortality: We observed that mortality resulting from UC without colorectal cancer (CRC) was higher than UC with CRC. This can be observed from the mortality estimates in the “Inputs sheet” of the model where the estimates in cells P357 to P457 (average mortality rates for UC without CRC) are higher than those in cells M357 to M457 (average mortality rates for UC with

CRC). We believe mortality resulting from UC with CRC should be higher than mortality resulting from UC without CRC.

- B. Discounting: We do not believe the formula for discounting costs and benefits implemented in the model is correct. The correct formula (and widely used) is the following:

$$\frac{(\text{Undiscounted costs or benefits})}{(1 + (\text{Discount Rate}))^{\text{Time}}}$$

4. *Implications of Modelling second TIM sequence: i.e. first TIM, followed by second TIM, followed by conventional treatment sequence*

The model structure assumes that patients that discontinue their assigned TIM are switched to a second TIM, represented by a market basket of other treatment options. While multiple biologics are used following treatment failure and the inclusion of a second TIM would be reflective of clinical practice, the inclusion of subsequent treatments introduces additional uncertainty into interpreting model results.

Inclusion of a second TIM convolutes the cost-effectiveness ratio of the initial TIM because the benefit and costs are attributed in part to the second TIM. The ICER analysis as it stands therefore deviates from the intended health-economic question about the cost-effectiveness of the initial TIM, and instead estimates the cost-effectiveness of the treatment sequence.

The basket of second TIMs modelled also possesses some limitations due to limitations in data, which further introduces uncertainty in the cost-effectiveness ratios of the initial TIM. For example, in the draft evidence report on page 95, it states that, “No RCT data was identified for infliximab or infliximab biosimilars in a biologic-experienced population, so these therapies were excluded from the market basket of second TIMs...”. These assumptions strongly influence the cost-effectiveness ratio. If there is uncertainty in the 2L TIM basket, then this translates to uncertainty in the final cost-effectiveness ratio. You can see this effect in Table 5.40 of the report. Replacing the 2LTIM basket with just infliximab lowered the cost-effectiveness ratio by 18%.

We also note that because of some of these limitations, the results of the base case analysis are inconsistent with the results of the EJP, which excludes the second TIM in its calculation.

We recommend removing the second TIM from the base case analysis or at the very least running a scenario analysis that excludes the second TIM. Alternately, we also recommend addressing the uncertainty created by the inclusion of the second TIM in the limitations section.

#### 5. *Drug Pricing for Tofacitinib in Dose Escalation Scenario*

For the biologic-experienced population, the scenario analysis of dose escalation showed the cost per QALY gained for tofacitinib increased (**Table 5.32** of ICER's report). This is surprising because the cost of 10 mg and 5 mg are the same (flat pricing) and we would expect the overall cost to remain the same. We recommend ICER to check the price and efficacy used for 5mg and 10mg BID dose.

Thank you for your attention on our remaining concerns and for the opportunity to provide additional feedback.

Sincerely,



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#### References

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July 29, 2020

**RE: Takeda Response to the Draft Evidence Report during the Institute for Clinical and Economic Review (ICER) Evaluation of the Comparative Clinical Effectiveness and Value of Therapies for Ulcerative Colitis (UC)**

Submitted electronically via: [publiccomments@icer-review.org](mailto:publiccomments@icer-review.org)

Dear Dr. Pearson:

Takeda Pharmaceutical Company Limited (Takeda) appreciates the opportunity to provide feedback to ICER's Draft Evidence Report on "Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value" posted on May 26th, 2020. Given ICER's ongoing evaluation of treatment options in UC, Takeda would like to contribute to the development of a solid assessment framework and use of the most relevant data. Therefore, we would like to offer the following feedback for your consideration:

**1. Replace utility data:**

Given that the health state utilities (HSU) associated with the active disease state have by far the greatest impact on the final cost per QALY in the draft ICER report, it is important to ensure that these estimates are valid and reliable for meaningful interpretation of results.

- ICER's univariate sensitivity analyses upper bound range for active disease HSU (0.814) results in a higher HSU value than the base case HSU value for the response health state (0.727), undermining the value of obtaining clinical successes with treatment.
- Malinowski and Kawalec (M&K)<sup>1</sup> should not be used as the base case source for HSU values, as it lacks robust validity in several ways, making it inappropriate for use:
  - M&K do not explicitly state how they aggregated studies with different health states.
  - M&K included 'active' as a health state but 'active' disease as defined in the included publications<sup>2-4</sup> do not align with the definition of the population to be modeled by ICER, "moderate-to-severe UC being treated with TIMs".
  - M&K did not include the most cited sources for HSU values in their meta-analysis (MA), some of which were available to them at the time of their analysis.<sup>5</sup>
  - Face validity is limited. Moderate-severely active disease HSU (0.7977) is greater than the HSU for moderate (0.6969) and mild (0.7834) disease. Active disease HSU (0.6992) also has a lower utility preference than moderate-severe (0.7977) and severe (0.7059). Normally, an approximate linear relationship between severity and utilities is to be expected. Higher quality of life for those with more severe disease highlights the danger of combining studies with differing methodologies.



- M&K state their MA revealed a significant heterogeneity among studies and warn that their results should be interpreted with caution. Cochrane's Q test and  $I^2$  illustrate this significant heterogeneity.

Recommendation:

- The limitations of the M&K study make it inappropriate as the base case utility values. We therefore recommend that ICER conduct an MA to generate HSU using inclusion criteria that would better reflect the population being modeled.
- If conducting a targeted MA is not an option, it may also be appropriate to use HSU values from Woehl et al.<sup>6</sup> or Arseneau et al.<sup>2</sup> for the base case and use M&K (and/or other updated sources) as a scenario analysis. This reflects a more appropriate population and would decrease uncertainty around interpretation of the results.

**2. Include relevant long-term clinical data of vedolizumab:**

While the therapeutic area is still developing, therapeutic goals have evolved from relief of IBD-related symptoms to the “treat-to-target” approach of endoscopic improvement. Long-term studies are particularly effective in identifying durability of treatment.<sup>7-10</sup> A network meta-analysis (NMA) conducted in 2017<sup>7</sup> explored endoscopic improvement data separately over the short-term, using eight short-term studies, and after longer follow-up using five long-term studies.

- Because of the lack of optimal incorporation of long-term mucosal healing data, overall cost-savings associated with mucosal healing's clinical and economic benefit, such as colectomy-free survival and reduced colectomy, are undermined in the ICER model.
- The ICER evaluation anchors analysis on RCTs and thus does not adequately capture long-term real-world outcomes.

Recommendation:

- A similar NMA augmented by the VARSITY trial's long-term endoscopic healing outcome scores<sup>11</sup> should be performed to ensure that the ICER analysis accurately reflects long-term endoscopic/mucosal healing.
- Alternatively, both the VICTORY consortium data<sup>12</sup> as well as the EVOLVE study<sup>13</sup> should be considered for inclusion in ICER's evaluation to supplement the current deficiency in long-term clinical projections for vedolizumab.

**3. Update market distribution in 2nd line:**

In the cost-effectiveness model, the rationale for the ICER assumption in creating a 2<sup>nd</sup> line market basket is not clear.





- In the base case analysis, adalimumab is the sole TNF $\alpha$  therapy included for 2<sup>nd</sup> line following vedolizumab, ustekinumab, or tofacitinib, despite its lack of indication in TNF $\alpha$  failure population, poorer efficacy and higher cost than some alternatives. This is contradictory to real-world data that indicates patients often switch to other TNF $\alpha$ s, as evidenced by some plans which require a double step of two non-TNF $\alpha$  prior to switching to biologic therapies, leading to malapportioned 2<sup>nd</sup> line market baskets. Likely the exclusion of infliximab from 2<sup>nd</sup> line will introduce bias and produce inflated cost per QALY estimates for all other products.

#### **4. Exclude - ex-US regional trials with poor population alignment or quality:**

ICER leverages the NMA of available multinational randomized clinical trials, as well as clinical trials with local/regional populations. Including regional trials in the base case model analysis could introduce bias in the meaningful interpretation of data for the US population.

- Jiang 2015, Motoya 2017, Suzuki 2014, Kobayashi 2016 and NCT01551290 trials introduce variance in population outcomes through underlying patient demographics. Diagnosis criteria, treatment patterns, background treatment and therapeutic access are different from the US healthcare system. In addition, this could be through predisposition to comorbid conditions, nutritional intake, or control on AE reporting which is illustrated by the AE of tuberculosis featured in Suzuki 2014 and the lack of any serious infections in any of their associated trials. The ICER report specifically states that imbalances in key disease characteristics in the Motoya et al. RCT population bias results in placebo favorability, especially in the biologic-experienced group, thus potentially diminishing the relative efficacy of vedolizumab. With major study limitations and heterogeneity in study design, including this study in the NMA risks invalidating its interpretation.

#### **Recommendation:**

- We suggest that the base case analysis in both the NMA and the cost-effectiveness model focus on high-quality and appropriately generalizable evidence, including well-designed trials in populations that align with ICER's target population, and real-world studies in the US healthcare system. Clinical trials with unbalanced arms or with population characteristics that limit appropriate comparison should be reserved for sensitivity analysis.

#### **5. Utilize most appropriate induction period clinical data of vedolizumab:**

When evaluating the induction clinical outcomes of vedolizumab, week 6 data from the GEMINI trial should be replaced with week 14 data in the base case induction NMA.



- In comparison to week 6 data that is currently used, week 14 data more appropriately matched the clinically relevant assessment period for vedolizumab, and still falls within the timepoint range (6-14 weeks) established for the base case induction period.

Recommendation:

- Using week 14 GEMINI data in place of week 6 data will align most appropriately with vedolizumab induction usage while remaining consistent with ICER's stated approach.

**6. Ensure appropriate comparator choice:**

Although ICER compared each therapy to "conventional" non-biologic therapy, it may no longer be considered clinically appropriate for long-term use in patients with moderate to severe UC.

- Long-term treatment over a year or more with conventional therapy such as steroids are known to cause serious adverse events that require additional medical attention and costs that are not accounted for in the ICER model.

Recommendation:

- Follow the 2019 ACG<sup>14</sup> and the 2020 AGA guidelines<sup>15</sup> recommendations of using advanced therapy for the management of moderate to severe UC to reflect reference comparator.

**7. Acknowledge limitation of cost data:**

Net prices estimated from SSR database cannot be validated, are often inaccurate and do not reflect real-world costs of drugs in UC paid by various plans. Cost-effectiveness analysis based on such strong assumptions possess enormous uncertainties and conclusions from CEA models cannot be generalized and can be mis-leading.

Recommendation:

- ICER should be transparent that this is a major limitation when making conclusions of comparative cost-effectiveness in the report and be extremely cautious in making policy recommendations based on such analysis.

**8. Correct reporting errors:**

- Vedolizumab indication is stated incorrectly (Section 3.1, page 16). Vedolizumab is indicated for adult patients with moderately to severely active UC, similar to ustekinumab.
- FDA sent Takeda a Complete Response Letter (CRL) in response to Takeda's Biologics License Agreement (BLA) supporting the use of subcutaneous (SC) vedolizumab as



maintenance treatment in patients with moderately to severely active UC. Takeda is assessing the details of the CRL, gathering information needed to resolve the FDA's questions, and will work closely with the FDA on a path to approval.

- Report internal inconsistencies:
  - Annual drug costs reported in Table 1.1 do not match those reported in Table 5.16
  - Golimumab recommended dosage differs between Table 1.1 and Table 5.14 (correct in Table 5.14)
  - Ustekinumab recommended dosage differs between Table 1.1 and Table 5.14 (correct in Table 1.1)
  - Table 4.20 – Tofacitinib and ustekinumab estimates for AEs leading to discontinuation need to be reviewed and revised.

Takeda Pharmaceutical Company Limited (Takeda) is committed to bringing better health and a brighter future to patients by translating science into highly innovative medicines. Takeda believes that UC is a chronic and heterogeneous condition that requires a personalized approach to treatment. It is important to preserve access to all therapeutic options for patients and guide treatment selection with solid evidence that is based on sufficient follow-up. We appreciate the opportunity to share insights and welcome further discussions.

We believe the information provided can help lead to a fully scientific approach that is well-accepted across all relevant stakeholders. Ultimately, we seek to see all products assessed according to their full holistic value to patients and society. We support analyses that incorporate elements that are important to patients and reflect real-world clinical practice.

Kind Regards,

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