733 Third Avenue
Suite 510
New York, NY 10017

212-685-3440
info@crohnscolitisfoundation.org
www.crohnscolitisfoundation.org

CROHN'S & COLITIS FOUNDATION

October 18, 2019

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

RE: Response to the Draft Scoping Document for Ulcerative Colitis

Dear Dr. Pearson,

Thank you for the opportunity to respond to the draft scoping document for the ulcerative colitis (UC) treatment review. I write on behalf of the Crohn's & Colitis Foundation (Foundation) to share our commentary on the proposed research methodology, and our views on low value services. The Foundation represents over 3.1[i] million individuals with Crohn's disease and ulcerative colitis living in the United States. Our mission is to cure these diseases, and to improve the quality of life of children and adults affected by these diseases.

As noted in our open comment submission to the Institute for Clinical and Economic Review (ICER), **ulcerative colitis (UC) is heterogeneous** and the needs of each patient is unique. UC is an immune-mediated condition which presents with both gastrointestinal and extra-intestinal manifestations[ii]. 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. The Foundation urges ICER to keep the heterogeneity and unique needs of UC patients in mind as it considers the value of the selected UC treatments.

The draft UC scoping document identified a step-up approach to treating UC, in which patients are stepped through certain medications before trying others. While this can be appropriate for some patients, recently updated UC management guidelines advise clinicians to consider an individual patient's **disease prognosis** upon presentation when choosing therapeutic strategies[iii]. In cases with a moderate-severe prognosis, patients may benefit from more aggressive initial therapy as opposed to standard therapy for mild to moderate disease. ICER must consider both the step-up approach and treatment by prognosis as it develops its assessment.

The Foundation supports ICER's stated intent to review **subpopulations** of UC patients that are naïve to biologics, as well as those who have previously used a biologic. In addition, we encourage ICER to consider subpopulations of patients that have been exposed to treatments by the class of the treatment. For example, the Foundation frequently encounters patients whose health plan requires them to fail two anti-TNFs despite the patient demonstrating a primary non-response to the first anti-TNF. In this scenario, the value of the second anti-TNF is greatly reduced and is not a medically reasonable approach to management. The effectiveness, and thus value, of any further treatment may be reduced as well because of subsequent disease progression due to undermanagement[iv].

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We understand that ICER's review emphasizes **comparator studies**, however, there is a lack of head-to-head trials among UC treatments. Further, such trials may be limited in their generalizability to the diversity of the UC patient community.

To date, there has only been one large, randomized, controlled, head-to-head trial comparing two biologics for the treatment of moderate to severe UC. In this trial, vedolizumab demonstrated significant improvements in long-term clinical remission and mucosal healing compared to adalimumab.[v] Further, while multiple classes of biologic and small molecule therapies are available for the treatment of UC, these therapies have variable efficacy and safety profiles. There are currently three clinical trials recruiting to study the efficacy and safety of therapies in head-to-head comparisons of vedolizumab/adalimumab (NCT03679546), golimumab/infliximab (NCT02878083), and adalimumab/ustekinumab (NCT03464136)[vi].

In addition, clinical trials frequently do not enroll racially and ethnically diverse populations, as well as moderate to severe UC patients with colectomies (23.3%), or prior treatment with infliximab (31.7%)[vii]. The trial inclusion and exclusion criteria may be so narrow that it raises questions regarding the external validity of therapeutic efficacy beyond the trial population.

ICER has stated it will review **network meta-analyses**. Meta/network analyses are important tools in assessing the relative effectiveness of therapies, however conclusions must be cautiously drawn to avoid inaccurate, invalid, or not clearly justified outcomes and potential bias[viii].

Much of our knowledge regarding potential positioning of therapies is generated from experiential and opinion-based treatment algorithms, real-world effectiveness data from large administrative claims[ix], network meta-analyses[x], and simulation models, such as decision analyses, cost-effectiveness models, and Markov simulation models. While each strategy is informative, significant knowledge gaps exist, and thus definitive statements regarding the positioning of therapies in clinical guidelines are difficult. These studies often make assumptions to account for knowledge gaps, which may negatively influence the accuracy of their findings.

Nonetheless, meta analyses for UC do exist and are cited in the references below. Of note, a 2016 meta-analysis comparing outcomes for patients with ulcerative colitis using infliximab and adalimumab showed no significant differences in UC-related hospitalizations or risk of serious infections. However, patients receiving infliximab used steroids significantly less and were more likely to stay on their drug longer than those receiving adalimumab[xi].

Given the limitations on both head-to-head studies and meta analyses, the decisions of positioning and sequencing therapies for UC should be patient and provider-driven decisions that are ultimately based on the best available evidence, followed by assessment of patient response to the therapy to affirm ongoing use of this strategy. This also means that health plans with restrictive formularies may fail to consider critical evidence when they fail to approve certain treatments.

Economic analysis and cost-effectiveness studies are an emerging area of research for the inflammatory bowel disease (IBD) community. A 2018 Canadian literature review evaluated the existing evidence supporting IBD treatments. In this study, the biologic treatments tended to be more cost-effective when compared with surgery, however, most of the UC studies compared

733 Third Avenue
Suite 510
New York, NY 10017

212-685-3440
info@crohnscolitisfoundation.org
www.crohnscolitisfoundation.org

biologic treatments to each other rather than surgery[xii]. The Canadian study concluded that a high proportion of the biologic therapies were cost-effective according to $CAD100,000/QALY[xiii].

The Foundation urges ICER to take into account the important knowledge gap regarding rewards estimates in value assessment models using the **Quality Adjusted Life Year (QALY).** For example, a study comparing infliximab, adalimumab, or golimumab to colectomy demonstrated that any of these biologic options were more likely to induce remission and response in patients, though colectomy may economically dominate such strategies[xiv]. From a clinical evaluation standpoint, many models use quality of life estimates that are derived from standard gamble or time trade-off analyses. These estimates often assume constant utility weights over time, and are scaled relative to perfect health, which may not be a realistic outcome in all disease states[xv]. Additionally, these estimates likely do not account for significant heterogeneity in patient preferences regarding medication benefits, risk tolerance, or desire for surgery. Recent research into developing novel reward estimates in Crohn's disease has highlighted these issues[xvi], and the impact they may have on patient quality of life[xvii]. In fact, the authors of the aforementioned analysis specifically highlight that surgical intervention may not be desirable for all patients in their discussion. Lastly, these simulations uniformly compare medical therapy options head-to-head. They do not account for sequencing of therapies, which is unfortunately common given response and remission rates in UC.

The Foundation applauds ICER's consideration of **low-value services** in the treatment of UC. Specifically, we offer as low-value services the repeated use of corticosteroids, insurance-mandated step therapy, and not taking patient perspectives into account in treatment decision-making. The repeat use of corticosteroids is a low-value service which most clinical guidelines for UC emphasize avoiding[iii]. Corticosteroids are associated with significant adverse effects including venous thromboembolism, fragility fracture, and infections[xviii]. Insurance-mandated step therapy protocols arguably also cost the health system. We note that an estimated 868.4 million hours are spent by physicians on prior authorization activities, valued at $69 billion[xix]. Further, 98 percent of formularies from the top 125 health plans in 2014 were not aligned with UC clinical guidelines[xx]. A December 2016 survey of our constituents found that nearly 40 percent of our patients knew they had been required to undergo insurance-required step therapy, and of those, 94 percent experienced step therapy as a barrier to timely and appropriate care[xxi]. Adverse events as a result of step therapy have been devastating for patients with UC[xxii]. Finally, there are several ways UC medications can be taken, including oral formulations, subcutaneous injections, and infused therapies[xxiii]. Not taking patient perspectives into account in treatment decision-making can impact adherence and reduce the value of the treatment.

In conclusion, there are significant gaps in the available information evaluating U.S. costs of UC treatment, including comparative studies of existing treatments, needed to inform appropriate, evidence-based approaches to management. As ICER embarks on its research, caution is recommended to ensure that any recommendations reflect the heterogeneity of UC, that analyses reflect the true diversity of the UC population, that longitudinal therapies are considered, and that choice between therapeutic options is ultimately decided by the patient and provider.

733 Third Avenue
Suite 510
New York, NY 10017

212-685-3440
info@crohnscolitisfoundation.org
www.crohnscolitisfoundation.org

Sincerely,

Michael Osso
Chief Executive Officer
Crohn's & Colitis Foundation

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Simponi® (golimumab), Remicade® (infliximab), Stelara®(ustekinumab)

ICER Ulcerative Colitis DRAFT SCOPING DOCUMENT –
Response to Request for Public Comments

The enclosed information has been supplied to you in response to your unsolicited request. Information contained in this response is not intended as an endorsement or promotion of any usage. Stelara (ustekinumab) is currently not approved for the treatment of ulcerative colitis by the Food and Drug Administration (FDA) in the United States. For information on ongoing clinical trials for our products, please visit www.clinicaltrials.gov.

CONTACT INFORMATION

First Name	Shantel
Last Name	Gooden
Profession	PharmD
Organization	Janssen Scientific Affairs, LLC
City, State	Horsham, PA
Phone Number	215-325-2576
Email Address	sgooden2@its.jnj.com

Janssen appreciates the opportunity to provide comments on the ICER Draft Scoping Document for the Assessment of Treatments for Ulcerative Colitis.

SCOPE

Scope of Clinical Evidence Review

Design Considerations for Network Meta-Analysis (NMA) in UC:

- It is important to consider trial design differences between "treat-through" and "randomized withdrawal" design with ulcerative colitis (UC) indirect comparison.
    - In "randomized withdrawal" design trials, active drug induction responders are re-randomized to continue active drug or switch to placebo during maintenance. This addresses whether there is value of maintenance once patients respond to therapy.
    - Thus, "placebo" in randomized withdrawal maintenance trials is a reflection of durability of an effective induction with active drug.
        - High "placebo" rates in randomized withdrawal maintenance trials likely reflect good efficacy and durability of the drug's induction which may vary across products due to differences in "carry-over" effect of active drug across induction trials.
- Comparison of maintenance phases alone should not be done since entry into maintenance of randomized withdrawal trials is dependent on response to active drug during induction and due to the above mentioned differences in carry-over effects of active drug across induction trials.
- Consideration of Delayed Responders:
    - It is important that ICER consider delayed responders in the NMA for the following reasons:
        - A substantial portion of patients respond after the 8-week re-randomization point for entry into maintenance. For Stelara (ustekinumab), 58% of week 8 non-

responders from induction respond by week 16 after receiving one 90mg subcutaneous dose at week 8.

- Separate NMA for Bio-Naïve and Bio-Failure Populations for Base Case Analysis:
    - Janssen recommends that ICER perform separate NMAs for the bio-naïve and bio-failure populations for the following reasons:
        - Dramatic differences in response and remission were seen consistently in the two populations across products and trials
        - It is important to note that these are mutually exclusive and distinct clinical scenarios. For both clinical and payer applicability, patients will all start naïve then be failures [eventually]. Combining these scenarios fails to address either population adequately.
        - Analysis of both populations together as a mixed population would be biased by the proportion of bio-naïve and bio-failure patients which vary across trials.
        - In addition, there are differences in bio-failure populations across trials (ULTRA 2 excludes primary non responders to Remicade).[1] "Bio-experienced" or "Bio-exposed" patients are not the same as "Bio-failure" patients. Janssen recommends focusing on bio-naïve and bio-failure populations.

Scope of Comparative Value Analyses

Recommendations for Cost-Effectiveness Model:

- Janssen recommends using a societal perspective as the base case for the cost-effectiveness model since UC is associated with significant indirect burden (such as loss in work productivity) which is important to consider for a comprehensive assessment of the value associated with different treatments.
- Janssen disagrees with time horizons shorter than 10 years since UC is a chronic disease often requiring lifelong treatment and events such as hospitalizations and surgeries accumulate over time and are not given sufficient consideration when modeled over shorter time periods. Janssen agrees with use of a lifetime horizon.

Analytic Framework (Safety Outcomes)

Recommendations for Safety Comparisons:

- Janssen suggests looking at US FDA-approved labeling for each product. Some additional publications on safety for each Janssen product may also be considered (See references below).[2-12]

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October 18, 2019

Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston MA 02109 USA

RE: Draft Scoping Document for the Assessment of Targeted Immune Modulators for Ulcerative Colitis

Dear ICER Review Team:

Merck thanks ICER for the opportunity to provide comments on the draft scoping document for the assessment for targeted immune modulators for ulcerative colitis. Please see below Merck's brief comments for your consideration.

- Merck understands that ICER intends to compare all interventions including biosimilars to ongoing background therapy and against each other separately for efficacy and safety outcomes as described in the scope of clinical evidence review section. However, we think that the infliximab (Remicade) and its biosimilars (infliximab-dyyb (Inflectra) and infliximab-abda (Renflexis) should be combined as one therapy and then compared to other biologic therapies (e.g., adalimumab, vedolizumab, etc.) to evaluate the comparative clinical efficacy and safety. Below is our rationale:

    - FDA requires that biosimilar products demonstrate equivalence (i.e., biosimilarity) in safety (including immunogenicity) and efficacy, and no differences in purity and potency profiles between the originator and the biosimilar. FDA uses a "Totality of the Evidence approach", "including structural and functional characterization, nonclinical evaluation, human PK and PD data, clinical immunogenicity data, and comparative clinical study(ies) data." Once biosimilarity has been demonstrated and approval is granted, the label for the biosimilar is based on the originator label. (please see https://www.fda.gov/media/114574/download)

- Merck agrees with ICER's approach as described in the scope of comparative value analyses section. Comparisons for cost-effectiveness and budget impact analyses are proposed to be made across all treatment options separately including comparisons between originator and biosimilars as well as biosimilar to biosimilar. Merck would like to emphasize that the fundamental reason for development of biosimilars is to offer more affordable therapies to patients, physicians, and payers (i.e., potentially lower health care costs through competition).

Again, we appreciate the opportunity to provide input on the scoping document for the ICER review update. We look forward to engaging with ICER as this review moves forward.

Sincerely,

Fang Sun, M.D., Ph.D.
Director, Medical Policy, HTA & Value Assessment
The Center for Observational and Real-World Evidence (CORE)
Merck & Company, Inc.

Dear Institute for Clinical and Economic Review,

We have read with great interest the draft scoping document for the assessment of treatments for Ulcerative Colitis (UC) focusing on the effectiveness and value of the target immune modulator therapy. From the perspective of a pharmacy department in a large urban health system that utilizes these therapies on both inpatient and outpatient sides, we see a lot of value in such a pharmacoeconomic analysis of competing therapeutic strategies.

There is one additional area of a high interest to us that is not within the scope of the proposed report. Immunomodulation therapy has been used with increasing frequency as rescue/salvage therapy in steroid-refractory hospitalized patients for acute severe ulcerative colitis[1–4]. Additionally, some providers have been using infliximab as a first-line rescue therapy for acute ulcerative colitis flares without attempting initial therapy with intravenous corticosteroids[5,6]. This has been particularly prevalent in the pediatric populations with moderate-to-severe UC where clinicians desire corticosteroid sparing therapy, despite limited evidence for outcomes in this area.

Administering these medications to inpatients is extremely costly to health systems because inpatient doses do not generally get reimbursed by insurance. Furthermore, the slow onset of action (1-2 weeks) and increased fecal excretion of infliximab during severe UC episodes makes us doubtful that an inpatient infusion could lead to rapid improvement in symptoms needed to avoid surgical intervention[7,8]. As a result, we consider rescue infliximab infusion in an inpatient setting as a potential high-cost low-value therapy that is used without good evidence of improved short term or long term patient centered outcomes. There is also a general dearth of literature assessing the cost-effectiveness of this strategy.

In summary, we are requesting that the following analyses be considered for inclusion into your report:

- Cost-effectiveness of inpatient infliximab salvage therapy in hospitalized steroid-refractory patients with acute severe UC

- Cost-effectiveness of infliximab as a first-line medical therapy for acute severe UC, with or without adjunct corticosteroids

We appreciate your work in this important area and look forward to reading the final report.

Sincerely,

Pavel Goriacko, PharmD, MPH, BCPS
Dhara D. Shah, PharmD

On behalf of

The Center for Pharmacotherapy Research and Quality
Department of Pharmacy, Division of Pharmacotherapy
Montefiore Medical Center
111 East 210th Street
Bronx, NY 10467

References:

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Pfizer Inc
235 East 42nd Street
New York, NY 10017

October 18th, 2019

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

RE: Targeted Immune Modulators Ulcerative Colitis: Effectiveness and Value. *Draft Background and Scope*

Dear Dr. Pearson,

On behalf of Pfizer Inc., thank you for the opportunity to comment on the draft scoping document for the Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value**.** Pfizer is committed to discovering medicines and vaccines that enhance the health of patients, their families, and society. At the same time Pfizer is committed to identifying solutions for creating a more effective, efficient, and equitable health care system in the US. In reviewing the UC draft scoping document, we have identified several areas of concern that will lead to unobjective and biased assesment. Within, you will find our concerns and suggested modifications for the following areas:

Definition: We recommend ICER to replace the term "Targeted Immune Modulators" with Advanced Therapies and include in the title the fact that the report will focus on moderate to severely active UC.

Inclusion of biosimilars in clinical and economic analysis: We would like to ask ICER whether they can confirm that the biosimilar review will be performed both in terms of clinical effectiveness and evidence grading as well as economic assessment. The U.S. FDA approval of INFLECTRA was based on the totality of evidence to demonstrate that there are no clinically meaningful differences to the reference product, Remicade® (infliximab) in terms of safety, purity, and potency. There is robust evidence from randomized, controlled clinical data with Inflectra but this is limited to patients with Ankylsoing spondylitis, Rheumatoid Arthritis or Crohn's disease. There are no randomized controlled clinical trial data evaluating efficacy and safety of Inflectra to Remicade in patients with moderate to severely active UC. There are a substantial number of real-world data studies on the use of Inflectra in patients with IBD including UC (including single cohort and switching non-interventional prospective studies a at least one retrospective database analysis comparing outcomes in UC for CT-P13 vs originator infliximab). Inflectra is approved for all indications of Remicade due to extrapolation. Biosimilar extrapolation occurs from the reference biologic to the biosimilar, when scientifically justified, based on all available data—not from the indication(s) studied with the biosimilar to other indications **Recommendation:** Clinical effectiveness: the main analysis should focus only on the originators for consistency. A subsequent clinical analysis can compare evidence for each biosimilar versus its originator and among biosimilars. Cost-effectiveness: If ICER will assume biosimilars have the same expected efficacy and safety, we recommend that ICER separates the originators models from the biosimilars model: (i) Cost-effectiveness model for the originators (ii) Cost-minimization for the biosimilars vs originators

Heterogeneity in trial designs: We are concerned about the approach ICER will select for the direct and indirect (NMA) comparison of advanced therapies given the large differences in clinical trial

design in the UC population. As ICER is aware not all advanced therapies have data for adults naïve and exposed (missing in exposed to biologics are IFX and GOL) and for the induction and maintenance phases. We are happy to provide below the list of advanced therapies available for indirect comparison in each subpopulation and treatment phase.

Induction		Maintenance	
Naïve to biologic therapy	**Exposed to biologic therapy**	**Naïve to biologic therapy**	**Exp**
ADA (ULTRA 1, ULTRA 2) GOL (PURSUIT-SC) IFX (ACT 1, ACT 2) TOFACITINIB10mg (OCTAVE 1, OCTAVE 2) UST 130mg (UNIFI) UST 6 mg/kg (UNIFI) VDO (GEMINI 1)	ADA (ULTRA 2) TOFACITINIB10mg (OCTAVE 1, OCTAVE 2) UST 130mg (UNIFI) UST 6 mg/kg (UNIFI) VDO (GEMINI 1)	ADA (ULTRA 2, Suzuki 2014) GOL 50mg (PURSUIT-M) GOL 100mg (PURSUIT-M, PURSUIT-J) IFX (ACT 1) TOFACITINIB10mg (OCTAVE Sustain) TOFACITINIB5mg (OCTAVE Sustain) UST 130mg (UNIFI) UST 6 mg/kg (UNIFI) VDO Q8W (GEMINI 1, Motoya 2019) VDO Q4W (GEMINI 1) VDO SC (VISIBLE 1)	ADA (TOFA Sustain TOFA Sustain UST 1 UST 6 VDO (2019) VDO (VDO S

Moreover, as ICER is aware, there are two distinct trial design approaches to evaluate maintenance in UC: (1) Treat-through trials (ACT 1, ULTRA 2 and Suzuki 2014). In trials with a treat-through design patients are randomized at baseline and outcomes are measured at the end of an induction phase and at the end of a maintenance phase. (2) Re-randomized responder trials (OCTAVE Sustain, GEMINI 1, Motoya 2019, PURSUIT-M, PURSUITJ, VISIBLE 1, UNIFI). In re-randomized responder trials responders to the induction phase are re-randomized to placebo or to a maintenance dose of the active treatment. Outcomes are measured at the end of a maintenance phase strictly among patients who achieved clinical response during induction. There are also differences in how endpoints are defined such remission. These endpoints are based predominantly on the mayo scoring system utilizing locally read endoscopic scores. Only a few (stelara and tofa) used a central reader (more conservative). Endpoints are becoming more stringently defined over time. For example, the definition of remission was more stringently defined as a total Mayo score ≤2, with no individual subscore >1, and rectal bleeding subscore of 0. The way the remission composite score is defined in the trial influences efficacy level. Finally, some RTCs allow the use of concomitant therapies, such as azathioprine and 6-mercaptopurine while others do not, and again this impact efficacy and safety. Therefore, the quantitative evaluation of maintenance related outcomes and the cost-effectiveness results will be highly impacted by the approach ICER decides to take to design an NMA to address this large heterogeneity in RCTs. **Recommendation:** We recommend ICER to carefully evaluate which trials and which treatment to include in the overall analysis (combination of naïve and exposed data, trial design, endpoints definitions, and use of concomitant therapy), as the efficacy outcomes will clearly be different. Pfizer recommend that ICER consider the method described by Thorlund 2015, which extrapolates/imputes the re-randomized responder trial data to better match a treat-through design. Due to differences in design, simply combining the reported maintenance phase outcomes from treat-through trials and re-randomized responder trials would violate the similarity and homogeneity assumptions necessary for NMA. We also recommend ICER to remove from the main analysis medications that have only data (or limited data) on naïve or exposed and only run subgroup analysis.

Analytical framework and outcomes: It would be very useful if ICER could provide more details on the PROs they are planning to use for measuring "functional outcomes" and which "other patient-reported outcomes" they are planning to include. Moreover, we would like to inquire whether ICER is indeed planning to include "pain relief" under efficacy outcomes as pain has been tracked in trials under adverse events and not as an efficacy endpoint (e.g., OCTAVE trials). For PROs, we suggest ICER to consider partial Mayo score (focus on these 3 main domains: physician's global assessment, rectal bleeding and stool frequencies) at 2 weeks and daily diary data at 3 days on stool frequency and rectal bleeding. We also suggest using IBDQ, EQ5D, and SF36v2 as PROs.

Population: As per the draft scoping document: 'the population of focus for the review is adults with moderate-to-severely active UC, whose disease has either inadequate response or intolerance to conventional therapy, such as corticosteroids, azathioprine, or mercaptopurine. Additionally, based on the availability of data, we intend to include evidence on children ages six to 17 years old with moderate-to-severely active UC. Data permitting, we intend to examine subpopulations including but not limited to: 1) Patients who are naïve to biologic therapy; 2) Patients who have previously used biologic therapy. We would like ICER to note that for tofacitinib and inflectra we do not have any data in the pediatric population. **Recommendation:** as per above we recommend ICER to remove from the main cost-effectiveness analysis (looking at general population in adults) medications that have only data (or limited data) on naïve or exposed and only run subgroup analysis.

Model structure and endpoints: Regarding the model structure we would like to understand if modeling mucosal healing will also be included as an efficacy outcome in the cost-effectiveness model. Moreover, upon discontinuation of advanced therapies, will ICER be modeling a subsequent TIM of a different class or will patients proceed directly to conventional therapy? Will you be differentiating the treatment sequence by whether patients are either naïve or exposed to biologics? We are looking forward to finding more information in the analytical plan. **Recommendations:** Data permitting, we suggest that the model base analysis account for dose escalation or extended induction to better reflect real world treatment practices. Biologic agents were studied with dosages that may differ from doses used in clinical practice that relies on active therapeutic monitoring and dose escalation with substantial costs for the health care system and patients. We acknowledge that publicly available data may be limited to inform efficacy associated with dose escalation or extended induction, but at least a scenario analysis based on clinically reasonable assumptions could give some insights to the potential limitation of a base case analysis that does not include dose escalation or extended induction. W also suggest using the methodology of the recently published cost effectiveness model by Lohan in 2019.

Sincerely,

Cristina Masseria, MSc PhD
Patient and Health Impact (PHI) Methods & Capabilities Lead, Chief Business Office
Pfizer Inc. 235 E. 42nd street, New York, NY 10017
Tel: 212-733-5377
Cristina.Masseria@pfizer.com

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

October 18, 2019

RE: Takeda Response to the Draft Background and Scope for the Institute for Clinical and Economic Review (ICER) Evaluation "Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value"

Dear Dr. Pearson:

Takeda Pharmaceutical Company Limited (Takeda) is committed to bringing better health and a brighter future to patients by translating science into highly innovative medicines. Recognizing the unmet need for managing chronic gastrointestinal diseases, Takeda has developed Entyvio® (vedolizumab), a humanized monoclonal antibody that is an α4β7 integrin receptor antagonist indicated for the treatment of adult patients (biologic naïve or with TNFα antagonist failure) with moderately to severely active ulcerative colitis (UC) and Crohn's disease (CD).[1] Entyvio® (vedolizumab) was approved by the US FDA in 2014 and is now approved in more than 60 countries.

Given ICER's ongoing evaluation of treatment options in UC, Takeda would like to contribute to the development of a solid modeling framework and use of the most relevant data. Therefore, Takeda presents important information for ICER's consideration regarding the review and evaluation of the draft scoping document.

1. Entyvio® (vedolizumab) should be considered as a 1st line (1L) biologic option (IV or SC (under FDA review), as appropriate). Vedolizumab has illustrated its clinical impact in pivotal randomized-controlled clinical trials, real world effectiveness studies, and the first ever head-to-head study versus adalimumab post failure with conventional therapy in patients with active UC who failed conventional therapies.[2] The American College of Gastroenterology (ACG) 2019 guidelines listed vedolizumab among the therapies for induction as well as maintenance of remission in patients with moderately to severely active UC.[3,4] Vedolizumab as a first line therapy has demonstrated proven efficacy and potentially two administration routes, intravenous and, under FDA review, subcutaneous administration. Efficacy and route of administration are concerns of patient advocacy organizations.

The efficacy of vedolizumab is supported by the results of the GEMINI clinical trial program.[5] Vedolizumab induction treatment resulted in significantly higher rates of clinical response (47.1% vs 25.5%), clinical remission (16.9% vs 5.4%), and mucosal healing (40.9% vs 24.8%) compared to placebo. Compared to placebo, vedolizumab maintenance treatment was also associated with significantly higher rates for all secondary end points, including durable clinical response, durable clinical remission, mucosal healing, and glucocorticoid-free remission in patients receiving glucocorticoids at baseline.[5]

In a head-to-head clinical trial (VARSITY), vedolizumab IV was superior to adalimumab in achieving clinical remission (31.3% versus 22.5%, respectively) in the overall UC population, higher rates of remission in the anti-TNF naïve UC populations (34.2% vs 24.3%, respectively), and superiority on the clinical endpoint endoscopic mucosal healing in comparison to adalimumab (39.7% vs 27.7%, respectively) at week 52.[2,6] No statistically significant difference was observed between vedolizumab and adalimumab in corticosteroid-free clinical remission at 52 weeks. Finally, comparative analysis from the VICTORY consortium showed that compared to TNFα antagonists, vedolizumab use led to higher 12-month rates of clinical remission (54% vs 37%).[7]

The VISIBLE 1 trial evaluated the efficacy of vedolizumab SC and the results showed that vedolizumab patients achieved superior clinical remission compared to patients receiving placebo (46.2% vs. 14.3%; $p<0.001$) at week 52. A similar rate of clinical remission was observed in the vedolizumab IV 300 mg reference arm (42.6%) at week 52.[8] This data is under review by the FDA.

2. Long term safety considerations should be prioritized to capture a complete picture of clinical effect and benefit-risk profile. UC is associated with considerable burden for individual patients, the overall population, and the healthcare system due to its onset in early adulthood, chronicity, associated morbidity and disability, frequent need for hospitalization and surgery, and effects on quality of life.[9] As a result, long-term safety is important in characterizing the downstream implications, which should be included when assessing benefit and value of treatments.

The GEMINI long term safety study demonstrated that patients who responded to vedolizumab induction and persisted on vedolizumab for 104 weeks and 152 weeks had remission rates of 88% and 96%, respectively.[10]

Real-world effectiveness and safety were assessed via the VICTORY consortium, which is a multicenter collaborative effort among US hospitals to prospectively maintain a registry of real-world outcomes of IBD patients treated with biologics. In addition to the demonstrated effectiveness in achieving clinical remission (54% vs 37%, HR: 1.54) and endoscopic healing (50% vs 42%, HR: 1.73), evidence from the VICTORY consortium confirmed the safety profile of vedolizumab compared to TNFα antagonists in adult patients with moderately to severely active UC and CD.[11,12] Other real-world practice trials have observed treatment benefits and safety profile for vedolizumab in adult patients with moderately to severely active UC.[13-15]

Vedolizumab is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to vedolizumab or any of its excipients. Hypersensitivity reactions, including anaphylaxis, have been observed. Additionally, treatment with vedolizumab is not recommended in patients with active, severe infections until the infections are controlled. Although no cases have been observed in clinical trials, JCV infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in patients treated with another integrin receptor antagonist. A risk of PML cannot be ruled out.

3. Gut-selective therapies are recommended by the ACG guidelines before use of systemic treatments in UC subpopulations susceptible to therapy side effects. Vedolizumab is a gut-selective humanized monoclonal antibody which, in alignment with ACG's recommendations, is preferred for use in vulnerable patients before the use of systemic therapies. The gut-selectivity of vedolizumab in combination with its gastrointestinal tropism of α4β7 integrin function, research suggests it may confer an improved benefit-risk profile for patients with IBD,[16] and may be of particular value to subgroups of older age, at higher risk of comorbidities, and with previous malignancies. Thus, characterizing the patient populations most relevant for each therapy in ICER's evaluation will be important.

4. Comparison between other therapies may be hampered by factors such as heterogeneity in patient population and duration of follow-up across individual trials and thus must be evaluated carefully. In relation to the chronic nature of the disease and the importance of long-term safety in evaluating the value of treatment, trials of short duration may not capture the full picture. Although ICER indicated that efficacy and safety data will be used for treatments with at least 6 weeks of exposure, use of evidence generated solely over a short-term induction period may misrepresent long-term outcomes, including durability of effect and safety. Maintenance benefits of vedolizumab are apparent as shown in trials of 52-week duration or longer.[5] Data from long-term follow-up will result in a more meaningful evaluation of treatment value, and priority should therefore be given to comparison of long-term evidence.

5. Mucosal healing (MH) is a critical endpoint in modeling efficacy based upon the association between MH and long-term resource use and quality of life implications. MH has been identified as an independent predictor of colectomy-free survival, while in multivariate analysis, it was found that the absence of MH was the only factor associated with colectomy.[17,18] In an analysis conducted in a UC population in Norway, it was found that MH at one year follow-up is strongly predictive for less surgery in UC.[19] This clinical outcome will therefore be an important element of evaluating long-term cost-effectiveness of UC treatment, due to its impact on downstream costs and potential improvement in quality of life outcomes associated with disease-related intervention offsets.

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 term of follow-up. We appreciate the opportunity to share insights and welcome further discussions.

Kind regards,

Phil Naughten, Pharm D
VP, US HEOR,
Takeda Pharmaceuticals USA
philip.naughten@takeda.com

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