

## **Comments to ICER's Condition Update, Draft Background and Scope on Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value**

Given the rapidly changing landscape of psoriasis treatment, AbbVie applauds ICER for the update to its 2016 report. While we certainly understand the rationale for wanting to move forward with the same model structure as the previous report given how recently it was completed, we strongly encourage ICER to use the opportunity to improve the model for health care decision makers. There is a significant gap between the current model and real world practice. While no systematic model will ever capture real world practice exactly, closing the current gap would make the model results more useful for health care decision makers. Our comments will provide specific ways that this can be addressed. We have focused our comments on ways to address this gap and have only included comments for which we were also able to provide a specific recommendation to improve the current model to ensure it better reflects real world practice.

### **Choice of treatment**

The current model assumes an equal probability of the choice of biologic treatment, which is not the case in real world practice. Most notably, the presence of some co-morbidities drive the preference for some treatments over others. Specifically, the following co-morbidities can influence the choice of treatment:

- ***Psoriatic arthritis (PsA)*** – In patients with both psoriasis and PsA, the recommendations from both the European League Against Rheumatism (EULAR) and the British Association of Dermatologists (BAD) indicate that TNF inhibitors are the preferred first line biologic unless TNFs are contraindicated.<sup>1,2</sup> Expert opinion treatment algorithm on biologic therapy for patients with psoriasis with PsA also support the use of TNF inhibitors as first line, followed by IL-17 inhibitors and then by ustekinumab.<sup>3</sup>
- ***Irritable bowel disease (IBD) or other gastrointestinal (GI) symptoms*** – Research has shown an association between IL-17s and IBD exacerbations.<sup>4</sup> Moreover, both secukinumab and ixekizumab have warnings/precautions for use in patients with IBD,<sup>5,6</sup> and brodalumab is contraindicated in patients with Crohn's disease.<sup>7</sup> This is also reflected in guidelines and expert opinion treatment recommendations.<sup>2,3</sup>
- ***Depression or other behavioral health conditions*** – Several studies have shown an association between psoriasis and depression, suicidal ideation, and suicide attempts.<sup>8-10</sup> Brodalumab has a black box warning for suicide ideation and behavior, and healthcare professionals are advised to weigh the risks vs the benefits prior to use in patients with a depression.
- ***Multiple sclerosis*** – TNF inhibitors are contraindicated in psoriasis patients with multiple sclerosis.<sup>3</sup>
- ***Congestive heart failure (CHF)*** - It is recommended that TNF inhibitors be avoided in patients with New York Heart Association Class 3 or 4 Congestive Heart Failure.<sup>3</sup>
- ***Cardiovascular (CV) conditions*** – A large, claims-based study suggested that cumulative exposure to TNF inhibitors was associated with a reduced risk of major cardiovascular

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events.<sup>11</sup> Treatment decisions in psoriasis patients should consider the cardiovascular prevention profile, especially in high risk patients.

As discussed above, the utilization of particular biologics for the treatment of psoriasis are often based on patient comorbidities. Therefore, the probability of choosing a treatment is not equal across all options for these patients. In addition to co-morbidities, the long-term safety and durability of the treatment is also recommended to be considered when choosing a treatment.<sup>2</sup>

### **Real world dosing**

While the 2016 report acknowledges dose escalation that occurs in actual practice, it cites an abstract by Feldman et al. presented at the 2015 American Academy of Dermatology Annual Meeting as evidence that dose reductions occur at approximately the same rate as dose escalations and do not need to be accounted for in the model. Feldman et al. published a manuscript later in 2015 citing the 12 month dose escalation rate of 39.1% with specific rates as 41.0%, 36.6%, and 35.9% for etanercept, adalimumab, and ustekinumab, respectively.<sup>12</sup> The same paper cites dose reductions as 50.1% overall with 48.7%, 53.7%, and 37.4% for etanercept, adalimumab, and ustekinumab, respectively. For those patients who experienced a dose escalation, only 51% also experienced a dose reduction. Thus, the updated data published in the manuscript does not support the conclusion that dose reductions occur at the same rate as dose escalations and do not need to be accounted for in the model. Specific data on duration of reductions would also be needed to reach such a conclusion even if the rates were equivalent. Additionally, the BAD guidelines include recommendations for considering dose escalation.<sup>3</sup>

Furthermore, the cost of such above-label dosing is high and not equal across treatments. Feldman et al. extended this work with a 2017 paper showing that above label use of 20.0% for etanercept, 2.6% adalimumab, and 14.8% ustekinumab resulted in additional annual costs associated with the up dosing of \$5,623,362, \$701,964, and \$1,304,790, respectively.<sup>13</sup> Thus, accurately accounting for differences in real world dosing among the treatments is likely to have a significant effect on the model results.

It should also be noted that dose escalation is defined as dosing that is a certain percentage higher (typically 10-25%) than the FDA-approved dosing. Given the weight-based dosing of ustekinumab, dose escalation of patients  $\leq 100$ kg to the dosing intended for patients  $> 100$ kg would not be reflected in published studies. Therefore, the percentage of dose escalation for ustekinumab should also be applied to the distribution of dosing between 45mg and 90mg to account for such dose escalation to the higher FDA-approved dosing that is not reflected in published dose escalation studies.

Integrating the cost of real world dose escalation is an important improvement to the current model. The published rates of dose escalation are likely to be underestimates since these estimates do not capture the use of samples or free goods to achieve higher level of doses. While there is some anecdotal evidence of this practice, it would be very difficult to systematically quantify the impact of such practices. Use of the published estimates of dose escalation would be an essential starting point to capture real world dosing in the model.

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## **Discontinuation and switching**

The real world scenarios of discontinuation and switching can be quite complex. Durability of treatment in the real world has proven to be quite different than results from well-controlled clinical trial populations. While the simplification of these scenarios is necessary for the model, improvements can be made to better reflect real world practice. The current model uses discontinuation rates of 15% for all treatments except ustekinumab and the IL-17s, for which 5% is used. First, discontinuation rates are not equivalent across treatments.<sup>14-18</sup> Second, the discontinuation rates of IL-17s are typically higher than TNFs suggesting lower durability of clinical effectiveness.

Additionally, the model does include a cost in month 1 of the start of second line therapy to account for the cost of switching. However, the cost of switching is not equivalent across treatments. While literature is not conclusive on specific additional health resource utilization that occurs with switching, the literature is clear that patients in second line treatment go through the same induction period as with first line treatment.<sup>19</sup> Therefore, the cost of induction from the first line should also be applied in the second line.

Similarly with choice of first line therapy, the probability of specific second line treatments is not equivalent across therapies included in the model. Given the lack of specific data for this, a reasonable way to handle this in the model would be to use the modified probabilities of first line treatment as discussed above for the probability of second line treatment selection.

## **Inclusion of risankizumab**

One of the primary drivers of the psoriasis report update is the inclusion of the new IL-23 treatment class. While ICER has stated they are focusing on IL-23 treatments that have been approved or are expected to be approved in 2018, we would recommend inclusion of any treatments for which Phase 3 trial results have been made publicly available. The rationale is that dermatology KOLs look to the Phase 3 results that are available publicly in their assessment of the changing treatment landscape, and FDA approval dates can fluctuate. As such, it would be appropriate to include risankizumab in the model since Phase 3 trial results were released in late 2017.<sup>20,21</sup>

## **Conclusion**

With the frequent introduction of new therapeutic agents and new mechanisms of action, the treatment landscape of moderate-to-severe psoriasis is evolving rapidly. In this light, ICER has wisely undertaken the updating of its 2016 report. Recent literature suggests that real world practice of psoriasis treatment differs from clinical trial results, especially in terms of treatment selection, dosing, and durability. The model used in the 2016 report does not account for many of these differences. Without a model that reflects real world practice patterns, the utility of the model will be limited. Thus, updating the model to capture real world treatment patterns would prove to be more useful to health care decision makers.

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## **AMGEN'S RESPONSE TO ICER'S DRAFT SCOPING DOCUMENT ON TARGETED IMMUNOMODULATORS FOR THE TREATMENT OF MODERATE-TO-SEVERE PLAQUE PSORIASIS: EFFECTIVENESS AND VALUE (CONDITION UPDATE)**

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Amgen appreciates the opportunity to comment on ICER's draft scoping document on Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value (Condition Update). Amgen has been committed to helping patients with psoriasis for over 20 years and understands the impact of the targeted immunomodulators in substantially changing the lives of patients.

As ICER performs this Condition Update, Amgen is encouraged by and supports ICER's choice to utilize the previous methodology employed in the ICER's 2016 Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value Final Evidence Report. ICER's previous analysis demonstrated that targeted immunomodulators provide a "substantial net health benefit" and are "well aligned with commonly-accepted thresholds of cost-effectiveness." Using the same methodology will not only allow ICER to reconfirm the results of the previous analysis, but also, provide an opportunity for a comparison of the new results to the old, with the only variable being the update for new data.

In addition, we would also like to take this opportunity to highlight several areas which could be reinforced and improve the outcomes and modeling efforts based on the previous assessment. We believe that the consideration of these factors may allow ICER to capture the full value of these therapies. Specifically, ICER should employ a patient-centric approach as follows:

- Incorporate the varied individualized patient response and use a *societal perspective as the primary analysis in this patient centric disease*
- Include the effects from multiple comorbidities such as joint and cardiovascular complications
- Factor in the long-term safety profiles and efficacy and adherence data since psoriasis patients often develop severe disease early in life and remain on these agents for years

We hope that these enhancements will further incorporate the patient perspective in the assessment, reinforce the importance of greater therapeutic choices, and reconfirm the recommendation to insurers that step therapy should be limited or abolished.

Amgen will engage in the ICER Condition Update process as a patient-centered organization that is invested in continuing patient access. Since the new evidence has shown improved or similar efficacy, across the new and existing drugs, it would be expected that ICER's findings reinforce the previous results of the tremendous value to psoriasis patients. If this is the case, ICER will have the opportunity to strengthen its previous recommendations to open access to appropriate patients for these agents.

December 21, 2017

Subject: Celgene Comments on ICER's Psoriasis Scoping Document

Dear ICER Committee:

At Celgene, we believe that with collaboration and dialogue among patients, clinicians, payers and other relevant stakeholders, we will find constructive solutions to fulfill our aspiration of providing every patient with the medicine they need. Value is a fundamental part of that dialogue, and while it can be a difficult concept to measure, we firmly believe that any construct of value should be focused on patient-centered elements such as the patient's quality of life while on treatment, the convenience of taking the medicine as well as pragmatic insights gleaned from real world evidence and clinical experience.

We believe that cost per quality-adjusted life year (QALY) fails to accurately capture individual patient preferences. Similarly, constructs of value that rely solely on data generated in the controlled setting of clinical trials are inadequate to fully understand the real-life value of healthcare interventions. It is then with both a keen focus on patient-centered elements of value and an acknowledgement of the importance of real world clinical experience that we are pleased to submit our comments on the draft scoping document for the Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis analysis.

Our questions, concerns, and recommendations on the draft scoping document are detailed below for each of the main sections of the document.

### **Intervention Section**

- We would like to highlight that the clinical trial populations differ across pivotal trials, especially with regards to the proportion of patients with concomitant psoriatic arthritis and the proportion previously treated with a targeted immunomodulator differs among trials. As these key variables have been shown to significantly influence PASI-75, the primary outcome of interest in the comparative effectiveness assessment, we would therefore recommend considering a propensity-matched approach to the network meta-analysis to adjust for these between-trial differences.
- It is worth mentioning that the value of different treatment sequences in moderate-to-severe plaque psoriasis should take into account how products are used in clinical practice (reinforced by per label differences in target populations) and we would suggest an approach that evaluates the value of different treatment sequences, as opposed to the comparative evaluation of only first-line treatment options. Several analyses<sup>1</sup> in PsA have taken this approach, and demonstrated that incorporating apremilast (Otezla®) before biologics, as a first-line treatment option, delivers good value to payers.

## Outcomes Section

- Among others, Kerdel and Zaiac<sup>2</sup>, in their review paper, argue that patients and physicians often have very different expectations of the extent of disease control that will be achieved with treatment in moderate-to-severe plaque psoriasis; therefore, communication between patients and practitioners is essential to set agreed-on treatment goals. The authors go on to state that several measures of treatment success are available and that achieving maximum possible skin clearance is only one factor to be considered among, for example, enhanced quality of life, and improved patient satisfaction. Patient dissatisfaction can include dissatisfaction with therapeutic efficacy, tolerability, and/or medication administration (e.g., frequency of dosing, difficulty traveling with medication, etc.).
- With this in mind, we would like to reinforce the importance of patient preferences/satisfaction with treatment which is known to influence adherence and persistency in chronic conditions. Ellison et al<sup>3</sup> performed a discrete choice experiment, which is a type of methodology that asks patients to rank their preferences of a hypothetical drug profile, in adults from the United Kingdom with moderate-to-severe psoriasis. In that article, patients preferred a once weekly pill over all other routes of administration, followed by a twice daily pill, then injection bi-weekly, then weekly injections. This information clarifies the question raised in the ICER 2016 Report about the relative preference of more frequent oral mode of administration versus less frequent but injectable administration. The 2016 ICER Review report discusses this topic and its relevance, but does not explicitly incorporate this critical factor into their quantitative assessment of comparative and cost-effectiveness.
- We would like to better understand how the availability of real-world evidence is to be incorporated in the ICER's review. The relevance of qualitatively including this information is in contrast with the 2016 ICER report methodology which, considers, in essence, the induction period efficacy and takes that as a basis for comparative efficacy and cost-effectiveness analyses.

## Economic Models Focusing on Comparative Value Section

- We would also like to better understand how ICER's economic analysis will focus on patients with moderate-to-severe plaque psoriasis for whom topical therapies, older systemic therapies, or phototherapy have been ineffective, contraindicated, or not tolerated. This is relevant as:
  - (a) per label some comparators, such as apremilast, are indicated for patients with moderate to severe plaque psoriasis who **are** candidates for phototherapy or systemic therapy, and,
  - (b) the meta-analysis from which the comparative effectiveness is to be drawn for use in the economic model has no inclusion criteria restriction regarding ineligibility for topical therapies, older systemic therapies, or phototherapy.



- Additionally, we would like to better understand the rationale behind assuming that a switch to second line occurs for all patients who do not achieve an improvement in PASI of at least 75% at the end of the induction period. As noted above, Kerdel and Zaiac<sup>4</sup>, among others, argue that several measures of treatment success are available and that achieving maximum possible skin clearance is only one factor to be considered among many, e.g. enhanced quality of life, and improved patient satisfaction. Patient dissatisfaction can include dissatisfaction with therapeutic efficacy, tolerability, and/or medication administration (e.g., frequency of dosing, difficulty traveling with medication, etc.).
  - Along those lines, as stated in the 2016 ICER review, other peer-reviewed analyses have employed different assumptions; namely, the Villacorta *et al.*<sup>5</sup> cost-effectiveness analysis assumes that partial responders (PASI 50-74) continue treatment given that achieving PASI 50-74 can be considered a clinically meaningful degree of improvement for patients.
- We would like to highlight that in the 2016 ICER report, discontinuation rates during the first year after the initiation period were derived from a study by Feldman et al<sup>6</sup>, where, over the follow-up period, 35%, 27%, and 16% of etanercept, adalimumab, and ustekinumab patients discontinued therapy. ICER then assumed that the discontinuation rate for apremilast was the same as for etanercept (35%). However, Feldman et al. 2017<sup>7</sup> showed that at 12 months, patients receiving apremilast had treatment persistence rates higher than those receiving etanercept and similar to those receiving adalimumab, as such, the assumption of apremilast having a persistence identical to etanercept is not credible considering available evidence.
- The 2018 ICER review scope draft mentions that the cost per PASI 90 achieved will be included as an additional result in the economic analysis. We would like to better understand how this will be calculated, namely, will ICER consider the 10-year (base case time horizon) cost or 1 year cost difference? We would also request a rationale for selecting PASI 90 as an outcome of interest since PASI 75 is the primary endpoint in most RCTs.

Thank you again for the opportunity to offer our views on this draft scoping document. We look forward to further participation in this process.

Kind regards,

Richard H. Bagger

## References

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**RE: Response to ICER's "Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value—Draft Background and Scope" Document**

Eli Lilly and Company appreciates the opportunity to respond to ICER's Draft Background and Scope document entitled "Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value" which was posted December 4, 2017. There are several important issues listed below for ICER's consideration.

**1. Population.**

- a. The description of the population states that ICER may include patients with concomitant psoriasis types or psoriatic arthritis (PsA), and that outcomes for these patients will be assessed if possible. We agree and in addition we recommend that ICER also consider assessing outcomes for patient subpopulations of plaque psoriasis by body location (e.g., hands, palms, feet, scalp, face, genitals).

**2. Cost-effectiveness modeling by lines of therapy.**

- a. Under Key Findings of the 2016 Review, a recommendation for limiting or abolishing step-therapy is stated. We agree with ICER's recommendation. The FDA approval label for Taltz<sup>®</sup> (Ixekizumab) would support first line usage; however, in current practice insurers continue to impose step-therapy approaches to Taltz<sup>®</sup> and other, newer biologic therapies for psoriasis, independent of price and rebates of the new agents. Therefore, we suggest that ICER include additional analyses for treatments according to expected place in therapy since direct comparison of first-line therapies to second-line therapies may not be appropriate under current conditions.

**3. Economic Model and Value Assessment.**

- a. The document states that the "results will be expressed in terms of marginal cost per QALY gained per PASI 90 attainment." We agree that a PASI 90 goal attainment is appropriate and reflects the evolution of primary endpoints to higher levels of skin clearance. Please confirm that PASI 90 is the outcome for the base case analyses.
- b. Response rates associated with PASI 75, PASI 90 and PASI 100 are to be evaluated in this assessment along with PGA. We recommend that a health state for PASI 100 be added to the model.
- c. Non-Targeted Treatment costs and health utilities.
  - i. Any new data on non-targeted treatment related costs and health utilities should be included in the model, as the estimates for these inputs are critical drivers for the cost-effectiveness ratios. Extensive sensitivity analyses (one-way, probabilistic) should be conducted.
  - ii. Patients place a high value on total skin clearance [1-3]. Any new data on health utilities for PASI 100 should be included in the model, and extensive sensitivity analyses (one-way, probabilistic) should be conducted.
- d. The model uses incremental cost per QALY gained to measure economic value. Given the known limitations of the data and model structure, other approaches should also be applied to assess value. In particular, a Cost/NNT approach using number needed to treat (NNT) to achieve different levels of skin clearance is an important measure that should be considered in this assessment.
- e. Speed of onset and quick resolution of psoriasis symptoms within the induction or 'trial' phase of treatments (typically 12-16 weeks) is a valuable outcome measure. Recent studies have found that rapid clinical effects in terms of skin clearance based on PASI changes can lead to significant improvements in symptoms and quality of life [4,5]. However, these important, beneficial aspects of treatment are not

reflected in outcome measures at a single time point at the end of the induction period. An emerging approach to capture both the speed of onset and the *full* cumulative clinical benefit of a measure is the area-under-the-curve (AUC) approach [7]. Thus, we recommend that ICER conduct AUC analyses across different products as part of its assessment of clinical benefit and value.

- f. The definition of the induction phase for psoriasis clinical trials varied from weeks 12 to 16 and most of the treatments may not reach their maximum benefit until week 16 or later. Comparison of clinical benefit within the same study duration at week 12 should be considered to minimize bias.

#### 4. New data on Ixekizumab.

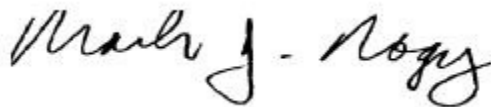
- a. New data on Ixekizumab has been published since the previous ICER assessment was conducted on psoriasis (see bibliography below). In particular, new data have been published on:
  - i. Efficacy of Ixekizumab by body locations.
  - ii. Impact of Ixekizumab on psoriasis symptoms and patient-reported outcomes.
  - iii. Impact of Ixekizumab on social/personal interactions.
  - iv. Ixekizumab's speed of onset.
  - v. Outcomes related to dosing patterns for Ixekizumab.
  - vi. Cost/NNT for Ixekizumab.
  - vii. Efficacy of Ixekizumab in patient sub-populations.
  - viii. Long-term of efficacy of Ixekizumab.
  - ix. Efficacy of Ixekizumab vs. Ustekinumab in a head-to-head trial.
  - x. Complete resolution outcomes for Ixekizumab.
  - xi. Safety of Ixekizumab.
  - xii. Indirect comparison of Ixekizumab to Secukinumab.

#### 5. New Disease State Data

- a. New publications on costs of psoriasis and real-world safety, efficacy and drug survival have been published and are included in the list below.

We appreciate efforts to create a transparent method for assessing value; however, we feel that consideration should be given to the issues we have raised to ensure a fair and balanced assessment of these treatments. We welcome the opportunity to discuss this in more detail with you if needed.

Sincerely,



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**BACKGROUND**

- **Page 1: Comment:** Suggest changing “Activated immune cells and inflammatory mediators lead to changes in and overgrowth of the surface layer of psoriatic skin.” to “Activated immune cells and inflammatory mediators lead to **thickening of the skin and other changes including reddening and scaling.**” to address other changes that occur in the skin.
- **Page 2:** TREMFYA™ should be changed to TREMFYA® throughout the document
- **Page 1 and 2:** A working model of the pathophysiology of psoriasis has been proposed where an initial triggering event activates innate immune cells to produce cytokines, which activate dendritic cells in the dermis.<sup>1</sup> The activated dendritic cells present antigens and secrete mediators, including interleukin(IL)-23, that play a key role in the development of plaque psoriasis.<sup>1-3</sup> IL-23 is formed from the pairing of a p40 subunit with a p19 subunit and is expressed by antigen-presenting cells such as dendritic cells. Interaction between IL-23 and its receptor drives the differentiation, proliferation, and survival of Th17 cells, which produce proinflammatory cytokines such as IL-17A, IL-17F, IL-22.<sup>1-4</sup> The IL-23/Th-17 pathway is thought to play an important role in the pathophysiology of psoriasis.<sup>1-3</sup>
- Guselkumab is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor.<sup>5</sup> Guselkumab inhibits the release of proinflammatory cytokines and chemokines.<sup>5</sup> Guselkumab reduced serum levels of IL-17A, IL-17F and IL-22 relative to pretreatment levels in evaluated subjects with psoriasis based on exploratory analysis of the pharmacodynamic markers.<sup>5</sup> The relationship between these pharmacodynamic markers and the mechanism(s) by which guselkumab exerts its clinical effects is not fully understood.<sup>5</sup>
- **Comment:** Please consider the heterogeneity of product profiles among drug classes and among products within the same class as it relates to efficacy and safety data, dosing considerations, and pharmacodynamic and pharmacokinetic characteristics.

**ANALYTICAL FRAMEWORK**

- **Page #3; Comment:** Within “Figure 1. Analytic Framework: Management of Moderate-to-Severe Chronic Plaque Psoriasis,” consider additional outcomes measures including:
  - Intermediate Outcomes**
    - IGA: Investigator Global Assessment
      - At a given time point, psoriatic lesions are graded by the investigator for induration, erythema, and scaling on a scale of 0-4: cleared (0), minimal (1), mild (2), moderate (3), or severe (4)
    - ss-IGA Scalp-Specific Investigator Global Assessment
      - Scalp lesions are assessed in terms of clinical signs of redness, thickness, and scaliness and are scored on a 5-point scale: 0 = absence of disease, 1 = very mild disease, 2 = mild disease, 3 = moderate disease, 4 = severe disease

## ICER SCOPING DOCUMENT -- RESPONSE TO REQUEST FOR PUBLIC COMMENTS

**Key Measures of Clinical benefit**

- PSSD: Psoriasis Symptoms and Signs Diary
  - Symptoms (i.e., itch, pain, stinging, burning, and skin tightness) and signs (skin dryness, cracking, scaling, shedding or flaking, redness, and bleeding) of psoriasis are graded (0-10 scale) by the patient in a daily diary. A higher score indicates more severe symptoms and signs of psoriasis
- DLQI: Dermatology Life Quality Index
  - Ten questions related to the effect of skin problems on aspects of life (ie, symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment) during the previous week are answered by the patient, for an overall score of 0-30. A higher score indicates more severe disease.

**POPULATIONS**

- **Page 5: Comment:** Consider incorporation of additional sub-groups based on 1) baseline demographic characteristics (including weight); 2) baseline plaque psoriasis disease characteristics; and 3) previous psoriasis treatments when evaluating outcomes for sub-analyses in subjects with moderate to severe plaque psoriasis

**OUTCOMES**

- **Page 5: Comment:** Consider evidence affecting additional domains captured in the PSSD (Psoriasis Symptoms and Signs Diary of Symptoms) assessment tool (i.e., itch, pain, stinging, burning, and skin tightness) and signs (skin dryness, cracking, scaling, shedding or flaking, redness, and bleeding) by the patient in a daily diary.
- **Page 7: Comment:** Consider including the IGA and ss-IGA when assessing **clinical trial and study outcomes**, PSSD, SF-36, WLQ, and HADS when assessing **patient reported outcomes**.
- **Page 7: Comment:** Regarding update of network meta-analysis, suggest considering the baseline-risk (or placebo-adjusted) multi-PASI NMA as the reference case analysis to avoid biasing clinical interpretation and CUAs. Additional information provided below supporting this suggestion.
- We conducted several NMA's based on PASI outcomes. Unadjusted NMAs on the relative scale clearly demonstrated that there was heterogeneity among comparisons (more detail available upon request). For example, our I<sup>2</sup> values exceeded 75% for some comparisons in the PASI 90 network. Further inspection of this important source of heterogeneity demonstrated that low placebo group response rates among studies might be biasing effect estimates. Even small differences in placebo response rates can have a large impact on results given placebo response is included in the denominator of relative risks and odds ratios (i.e., dividing by a small number can inflate relative effects).
- NMA's are not powered to adjust for more than one covariate at a time, and multiple clinical characteristics are clinically relevant in psoriasis. By considering baseline-risk (or placebo response), multiple potential effect modifiers are accounted for simultaneously. We have conducted various NMA analyses including key clinical characteristics in psoriasis recommended by clinical experts and the baseline risk (or placebo response) adjusted NMA has the best fit according to NICE Guidelines,<sup>6</sup> particularly for PASI outcomes when analyzed simultaneously as per original ICER Psoriasis Report – see Table 1 below.
- As per NICE guidelines<sup>6</sup>, when selecting models, one should assess whether the regression coefficient is statistically significant and whether there is a reduction in between-trial SD. The posterior mean of residual deviance and DIC can also be assessed, although the DIC is not a reliable criterion for assessing the fit of regression models.<sup>6</sup> As outlined in Table 1 below, all betas with the

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baseline-risk (or placebo response) adjusted NMA model are statistically significant, the SD is lower, and even the DIC detects an important difference ( $\geq 5$  points lower) between this model and other models. Importantly, the unadjusted NMA fits the data very poorly (highest standard deviation and DIC), suggesting it is not a robust NMA model to guide clinical interpretations.

➤ **Table 1:** Model fit stats for simultaneous multi-PASI NMA analyses\* for psoriasis NMA based on 45 RCTs

	Beta	Standard deviation	DIC	Resdev
Unadjusted	NA	0.13 (0.08 to 0.20)	2246.28	732 vs. 430 data points
<b>Baseline-Risk Adjusted</b>	<b>4/4 stats sig betas</b>	<b>0.10 (0.05 to 0.16)</b>	<b>2133.99</b>	<b>610 vs. 430 data points</b>
Baseline PASI	0/4 stats sig betas	0.12 (0.07 to 0.19)	2139.83	617.70 vs. 430 data points
Weight	0/4 stats sig betas	0.14 (0.06 to 0.20)	2147.35	626.04 vs. 430 data points
Previous Biologic Use	2/4 stats sig betas	0.13 (0.06 to 0.18)	2143.35	622.27 vs. 430 data points

\* Please note that multiple betas for each PASI must be considered given different relationships between covariates and various PASI outcomes

- The above table unequivocally demonstrates that the baseline-risk (or placebo-adjusted) NMA clearly fits the data best for the multi-PASI NMA. Given all betas are statistically significant, this means that NMAs failing to account for differences in placebo rates will bias NMA and CEA results against treatments with higher placebo response rates and in favor of treatments with lower rates. Similar findings were reported for individual PASI outcomes. Not surprisingly, HTA bodies and experts worldwide recommend baseline-risk (or placebo) adjusted NMAs.<sup>6,7,8</sup> Indeed, NICE<sup>6</sup> provides an analogous NMA example and concludes: “...it clearly suggests a relation between efficacy and baseline risk that needs to be incorporated into CEA models (p45).”
- Based on this, we suggest consideration of baseline-risk (or placebo-adjusted) NMA as the reference case analysis to adhere to best practices<sup>6</sup> and not bias the clinical interpretation and CUA analyses. Additional information is provided in the figures below, and can be further discussed with Janssen and Chris Cameron, MSc, PhD (one of the key informants provided by Janssen in the Open Input Comment submission).

**ECONOMIC MODELS FOCUSING ON COMPARATIVE VALUE**

- Page 8: Comment: Regarding lack of sufficient data to consider mortality effects from psoriasis treatment; while this is true, psoriasis may have an impact on mortality either directly or through comorbidities.<sup>9,10</sup>
- It should be explicitly noted that the model used in the 2016 review is not reflective of current treatment patterns for many reasons. First, patients that discontinue their initial biologic typically move onto a second, third, and even fourth biologic. Additionally, there is limited evidence to support the assumption that half of patients in the model will go to non-targeted/best supportive care after discontinuing their first biologic. Finally, there is growing evidence that there are differences in the probability of discontinuing IL17 therapy compared to other biologics.<sup>11,12</sup> We would request that as part of the conditional update that the underlying model structure and all assumptions are reviewed and updated to reflect real-world utilization of these therapies.

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Merck appreciates this opportunity to provide feedback to ICER on the scoping document for the plaque psoriasis review update. Merck is dedicated to improving the lives of those with psoriasis and ensuring patient access to treatment. Tildrakizumab is a humanized IgG1k monoclonal antibody that specifically binds the IL-23p19 protein subunit. Research has shown that IL-23 has a critical role in the immunopathogenesis of psoriasis.<sup>1</sup> We recommend the following be considered in the scoping document finalization and review development process.

**Focusing on long-term efficacy and safety:** Due to the chronic nature of psoriasis, long-term efficacy balanced with long-term safety is critical. We suggest ICER focus on clinically-demonstrated efficacy and safety outcomes at longer time-points, rather than only focusing on week 12-16 efficacy and safety, which were the primary endpoints included in phase-3 registration trials. In the two phase-3, double-blind, randomized controlled trials (reSURFACE 1 and reSURFACE 2), tildrakizumab 200 mg or 100 mg were administered at weeks 0 and 4, and then every 12 weeks. The proportion of patients treated with tildrakizumab or etanercept (reSURFACE 2) achieving PASI 75 improved from week 12 to week 28 (Figure 1)<sup>2</sup>. Consistently, greater proportion of PASI75 responders than etanercept was achieved with either tildrakizumab 100 mg or 200 mg at both week 12 and week 28 (week 12 PASI 75: 61% and 66% vs. 48%; week 28 PASI 75: 73% and 73% vs. 54%, all p<0.001; Table 1)<sup>2</sup>.

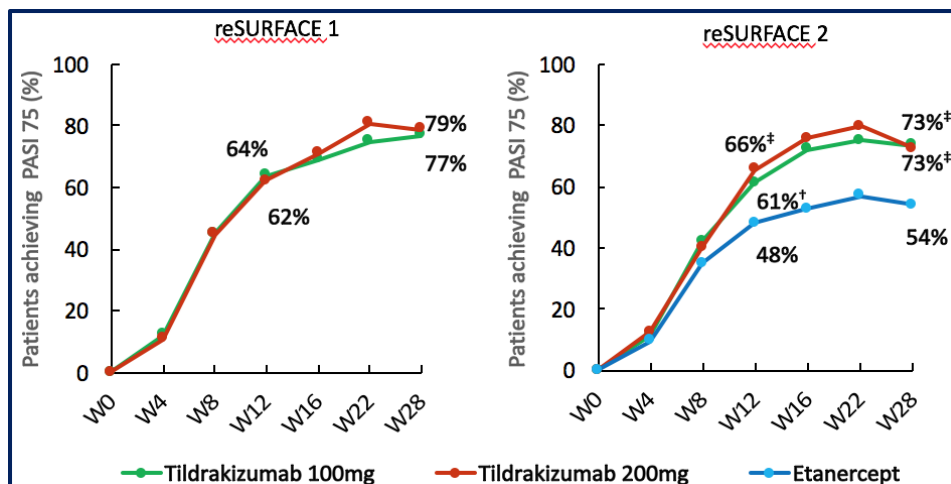


Figure 1: Efficacy over time through Week 28<sup>2</sup> (non-responder imputation)  
Significance in reSURFACE 2 relative to etanercept indicated by †p<0.005 ‡p<0.0001, p values not adjusted for multiplicity

Table 1: Primary and secondary efficacy endpoints at Weeks 12 and 28 in reSURFACE 2<sup>2</sup>(non-responder imputation)

Responders	Week 12			Week 28		
	TIL 100 (n=307)	TIL 200 (n=314)	ETN (n=313)	TIL 100 (n=294)	TIL 200 (n=299)	ETN (n=289)
PASI 75, n (%)	188 (61)***	206 (66) ***	151 (48)	216 (73) ***	217 (73) ***	155 (54)
PASI 90, n (%)	119 (39)***	115 (37) ***	67 (21)	161 (55) ***	169 (57) ***	85 (29)
PASI 100, n (%)	38 (12) ***	37 (12) **	15 (5)	66 (22) ***	79 (26) ***	31 (11)
PGA, n (%)	168 (55)	186 (59) *	149 (48)	190 (65) ***	207 (69) ***	131 (45)

TIL 100: tildrakizumab 100 mg; TIL 200: tildrakizumab 200 mg. ETN: etanercept. Difference vs etanercept: \*\*\* p<0.001; \*\* p<0.01; \* p<0.05. Non responder imputation. p values not adjusted for multiplicity

PASI 75 responses to tildrakizumab were well-maintained through completion of both phase-3 studies (Week 64, re-SURFACE 1; Week 52, reSURFACE 2), indicating long-term durability

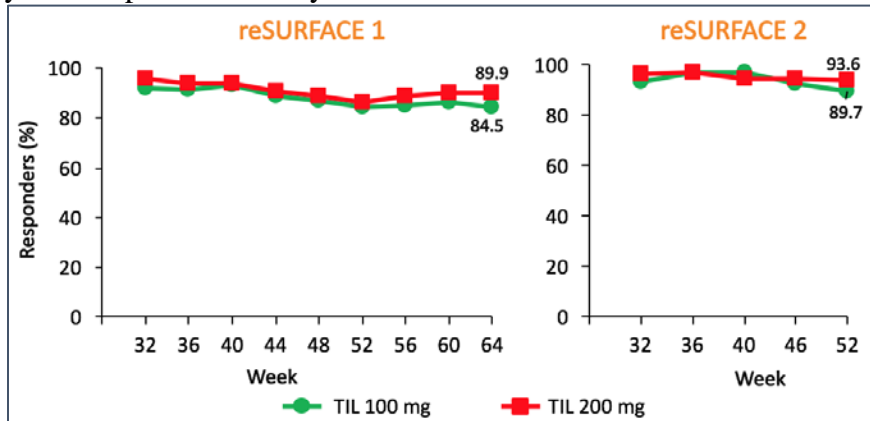




(Figure 2)<sup>2</sup>. Additional long-term analyses and publications for tildrakizumab are in development and should be incorporated by ICER upon availability.

Figure 2: PASI 75 Maintenance Through Week 52 or 64: Week 28 PASI 75 Responders Continuing Same Dose<sup>2</sup>

Responders=patients achieving PASI 75 at Week 28. Full Analysis Set (FAS) population, non-responder imputation.



**Outcomes – account for key adverse events:** Balanced and appropriate characterization of the cost-effectiveness of therapies for psoriasis requires comprehensive consideration of adverse events (AEs), including estimates of AE frequency among different treatment regimens, and the associated real-world costs. Both doses of tildrakizumab were well-tolerated. In reSURFACE 2, through Week 12, tildrakizumab had a comparable safety profile to placebo (Table 2)<sup>2</sup>. For example, the rates of serious AEs for tildrakizumab 100mg and 200mg were similar to placebo through 12 weeks (1%, 2% vs. 3%, respectively) of treatment, and numerically lower than that of etanercept during Part 2 of the study (3%, 2% vs. 5%, respectively, Table 2)<sup>2</sup>.

Table 2: Safety through week 28 reSURFACE 2<sup>2</sup>

Adverse Event Rates n, (%)	Part 1 (12 weeks)				Part 2 (16 weeks)				
	PBO	TIL100	TIL200	ETN	TIL100	TIL200	PBO/TIL 100	PBO/TIL 200	ETN
n	156	307	314	313	294	299	69	72	289
≥1 AE	86 (55)	136 (44)	155 (49)	169 (54)	135 (46)	135 (45)	37 (54)	31 (43)	164 (57)
Serious AEs	4 (3)	4 (1)	6 (2)	7 (2)	9 (3)	6 (2)	1 (1)	2 (3)	14 (5)
Discontinued owing to AEs	2 (1)	3 (1)	3 (1)	6 (2)	1 (<1)	1 (<1)	1 (1)	0	3 (1)
Upper respiratory tract infection	0	0	0	0	5 (2)	6 (2)	0	0	7 (2)
AEs of special interest									
Severe infections <sup>a</sup>	1 (1)	0	1 (<1)	0	1 (<1)	2 (1)	0	0	3 (1)
Malignancies <sup>b</sup>	0	1 (<1)	1 (<1)	1 (<1)	0	0	1 (1)	1 (1)	3 (1)
Nonmelanoma skin cancer	0	1 (<1)	1 (<1)	1 (<1)	0	0	1 (1)	1 (1)	1 (<1)
Confirmed MACE <sup>c</sup>	0	0	0	0	0	0	0	0	0
Drug-related hypersensitivity reaction	1 (1)	1 (<1)	0	0	0	0	2 (3)	0	0

AE adverse event; MACE major adverse cardiovascular event; PBO: placebo; TIL 100: tildrakizumab 100 mg; TIL 200: tildrakizumab 200 mg. ETN: etanercept. All values are n (%). <sup>a</sup>Defined as infection meeting the regulatory definition of an SAE, or any infection requiring IV antibiotics whether or not reported as an SAE, as per the regulatory definition; <sup>b</sup>Excluding carcinoma in situ of the cervix; <sup>c</sup>Includes nonfatal myocardial infarction, nonfatal stroke, and CV deaths confirmed as "cardiovascular" or "sudden."

**Account for heterogeneous factors between trial designs:** Heterogeneity in study design should be adequately addressed in the ICER review. Patient inclusion and exclusion criteria varied by trial (e.g., prior biologic use, depression, concomitant therapies use, baseline body surface area and PASI). Some trials included all patients (intent-to-treat) in the maintenance phase rather than only responders from the induction period or per-protocol patients.

Tildrakizumab trials did not allow for concomitant topical steroid use, phototherapy, or systemic therapy and included all patients through week 28. Trials also differed in baseline characteristics, especially on proportion of patients with prior biologic use and the type of biologic used. All

differences need to be considered, especially when comparing efficacy across trials. In this regard, we note that relevant tildrakizumab data are available for ICER's subgroup analysis comparing biologic experienced versus naïve patients.

**Network meta-analysis (NMA):** Because ICER proposed to use NMA to inform the cost-effectiveness analysis, decisions related to the NMA may have significant impact on the final conclusions of the review. The principal challenge in the NMA will be timing. Placebo-controlled psoriasis trials typically switch non-responders on placebo to active treatment at 12-16 weeks. Despite a growing number of trials with active comparators,<sup>2-10</sup> there remains a lack of network connectivity following removal of placebo arms when using later time-points. In 2016, ICER used the last time point prior to partial crossover for analyses. This approach assumes that relative treatment effects at 12-16 weeks are sustained over long periods. In this regard, reSURFACE 2 trial results clearly demonstrated an increasing disparity between tildrakizumab and etanercept efficacy over time,<sup>2</sup> with larger differences at week 28 versus week 12 (Figure 1). With a simple assumption regarding the placebo group (such as carrying forward the last observation or relative difference), a NMA could potentially be conducted at later time-points (e.g. 28 weeks). We suggest ICER use longer-term outcomes, which would align better with ICER's statement "*Timing: Because psoriasis is a chronic condition with no cure, we are particularly interested in evidence of durability of response to medications, as well as long-term safety.*"

Other concerns around the proposed NMA are model choice and sensitivity analyses. The 2016 ICER Review correctly used a conditional binomial likelihood with probit link functions. This approach should be replicated as it allows for simultaneous modeling of all PASI thresholds, and strengthens analyses at individual thresholds. The draft scoping document specifies that the NMA will be conducted on PASI 75 scores and NMA for PASI 90 and PASI 100 will only be conducted if data permits. This suggests a change in the analytical approach. We suggest ICER conduct NMA simultaneously on PASI 50, PASI 75 and PASI 90 and include PASI 100 when data are sufficient. For sensitivity analyses, it is well-documented that newer biologics are disadvantaged due to study population differences over time. This phenomenon, termed eligibility creep, leads to increasing placebo-effects over time.<sup>11</sup> For example, early trials had low (10-15%) or nonexistent prior biologic use, while current trials typically have prior biologic use around 25%, and up to 50%. Notably, guselkumab allowed prior use of IL-23 and IL 12/23 antagonist, which may affect efficacy relative to trials for other therapies. A placebo-response adjusted sensitivity analysis should be performed to ensure optimal comparison of new agents to older therapies.

**Cost-effectiveness analysis should reflect regulatory standards and real-world practices**

ICER proposed to use cost per PASI 90 response as well as cost per QALY as a primary cost-effectiveness result. However, PASI 75 remains the more familiar treatment goal in real-world practice, has consistently been the primary endpoint for FDA approval of psoriasis treatments, and is typically considered the standard criterion to define treatment responders. PASI 90 has only recently been reported in clinical trials as a primary outcome. Therapies approved based on older trial data may not have reported PASI 90.



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Novartis appreciates this opportunity to provide feedback to ICER on the scoping document for plaque psoriasis. Below, we recommend the following key criteria to include for scoping document finalization and model development.

When defining “moderate-to-severe” plaque psoriasis, ICER should request feedback from patients about what constitutes a significant reduction/improvement in quality of life. Certain localizations can affect a patient’s quality of life very differently and a single measure may not always adequately capture these impacts. It is important to obtain the patient perspective on what they value most from a biologic treatment and how that may change based on their own personal treatment targets.

Prior biologic experience is likely an effect modifier leading to reduced comparative incremental benefits relative to biologic-naïve patients. Given the growing proportion of biologic-experienced patients included in trial *populations*, ICER should conduct sub-group analyses on biologic-naïve (i.e., 1<sup>st</sup> line therapy) patients as well as the mixed-population analysis. In addition to the proposed inclusion of psoriasis patients with psoriatic arthritis, nail involvement, palmoplantar psoriasis, and scalp psoriasis should be included among the subgroup analyses.

ICER should detail a plan to account for *study design* and targeted population differences. Trials vary in inclusion/exclusion criteria (e.g., prior biologic use, baseline severity index, use of rescue medication and allowed medications, and depression), which will require adjustments in assessing clinical effectiveness. Clinical trials also differ in allowed concomitant therapies that are effective in improving psoriasis symptoms. This needs to be taken into consideration, especially when comparing efficacy data across clinical trials. Finally, some trials included all patients (intent-to-treat) in the maintenance phase rather than only responders from the induction period or per-protocol patients. Secukinumab trials did not allow for concomitant topical steroid use and included all patients in the maintenance phase regardless of their responder status. Beyond differences in study designs, trials differed with respect to baseline characteristics.

ICER needs to account for cross-trial differences in efficacy measurement. Secukinumab pivotal trials used the Investigator’s Global Assessment mod 2011 (IGA) score, which is more methodologically rigorous than the Physician’s Global Assessment (PGA).<sup>1</sup> PGA itself varies across trials with respect to Likert scale and anchor.<sup>2-4</sup> Secukinumab achieved consistently higher IGA 0/1 responses versus ustekinumab at each assessed time point throughout 16 weeks of treatment in the CLEAR study (week 12: 80.8% vs. 65.1%; week 16: 82.9% vs. 67.5%, both  $p < 0.0001$ ; Figure 1),<sup>5</sup> and higher response versus etanercept at week 12 (62.5% vs. 27.2%,  $p < 0.001$ ) and maintenance of IGA 0/1 responses from weeks 12-52 (79.7% vs. 56.8%,  $p < 0.001$ ; Table 1) in the FIXTURE study.<sup>6</sup>

Moreover, *patient-reported outcomes* (PROs) should include psoriasis-related pain, itching, scaling, and complete relief of these symptoms. Significant improvements in itching, pain, and scaling were demonstrated with secukinumab vs. etanercept in the FIXTURE study at Week 12 (-4.93 vs. -3.80, -4.48 vs. -3.48, -4.93 vs. -3.74, all  $p < 0.001$ )<sup>6</sup> and complete relief of these symptoms

vs. ustekinumab were observed in the CLEAR study at week 16 (49.7% vs. 36.7%, 69.1% vs. 56.7%, 61.0% vs. 42.4%; all  $p < 0.05$ ; Figure 2).<sup>7</sup>

Psoriasis trials have partial crossover periods at which non-responders in the placebo group are switched to active treatment, typically at 12-16 weeks. Although psoriasis requires long-term treatment, it is critical that the *network meta-analysis* (NMA) be conducted using data that conserve randomization. The NMA should use trial-specific last time points prior to partial crossover. ICER should detail how the meta-analysis will be conducted for long-term outcomes, given that networks will be disconnected following crossover. In the SCULPTURE extension study, patients treated with secukinumab 300 mg every 4 weeks sustained efficacy through 5 years (PASI 75: 88.5%, PASI 90: 66.4%, Figure 3).<sup>8</sup> Additionally, in the CLEAR study, a significantly higher proportion of patients treated with secukinumab achieved PASI 90 response vs. ustekinumab at week 52 (PASI 90: 76.2% vs. 60.6%;  $p < 0.0001$ , Figure 4).<sup>9</sup> Furthermore, in the FIXTURE study, a significantly higher proportion of patients treated with secukinumab achieved IGA 0/1, PASI 75/90/100 responses vs. etanercept at week 52 (IGA 0/1: 67.8% vs. 37.2%, PASI 75: 78.6% vs. 55.4%, PASI 90: 65.0% vs. 33.4%, PASI 100: 36.2% vs. 9.9%; all  $p < 0.0001$ , Figure 5).<sup>6,10</sup> ICER's NMA should make adjustments for eligibility creep, which leads to consistently increasing placebo-effects over time, to avoid underestimating the benefit of biologics versus placebo.<sup>11</sup> Finally, as ICER models treatment discontinuation and movement through lines of therapy, they should consider the impact on efficacy and recapture of response for later lines of therapy. Drug holidays are common in this population which can impact adherence and thus clinical outcomes. Secukinumab has unique data demonstrating recapture of response in patients following an interruption of treatment. 94.5% of patients who had previously achieved a PASI score of 100 were able to reach PASI 75 within 16 weeks after initiation of retreatment (Figure 6).<sup>12</sup>

We recommend the York model as a basis for the *simulation model*, which conventionally includes a 10-year time horizon.<sup>13</sup> Additionally, ICER should ensure that utility values are consistent in the model across PASI thresholds and uniformly applied across regimens. ICER should also include indirect costs due to work productivity and quality-of-life reductions, which have been estimated to equal up to 2/3 of psoriasis burden.<sup>14</sup> Failing to model these outcomes ignores critical ways in which psoriasis treatments improve day-to-day patient wellbeing, associated costs, and long-term impacts.

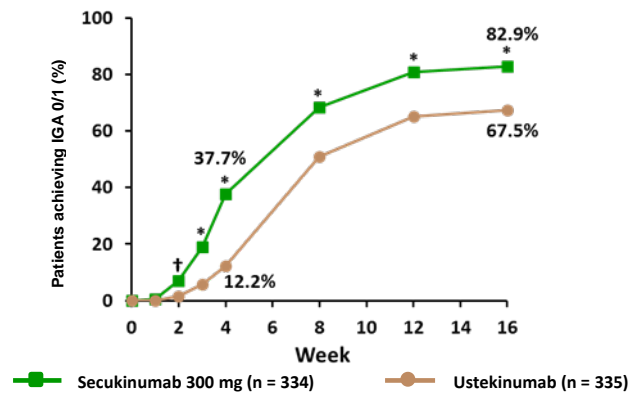
ICER states in the scoping document that the long-term durability of effect is important when assessing the value of the interventions of interest. Novartis agrees and would strongly encourage ICER to appropriately weight and score the evidence for the interventions under review as not all will have longer-term data at the time the report is finalized. In the evidence report, it will be critical to highlight the availability of studies with longer-term follow-up for each intervention. In addition, ICER should also focus on the long-term safety of these interventions and appropriately weight and score long-term safety data for each intervention. Both long-term durability of effect and safety are important, particularly since these inventions have an immunomodulatory effect.

**Table 1.** Efficacy Response Rates in FIXTURE<sup>6</sup>

Efficacy Endpoint	Secukinumab 300mg	Etanercept	P value
<b>Coprimary efficacy end points at week 12 — no./total no. (%)</b>			
PASI 75	249/323 (77.1)	142/323 (44.0)	†
IGA 0/1	202/323 (62.5)	88/323 (27.2)	†
<b>Key secondary efficacy end points — no./total no. (%)</b>			
PASI 90	175/323 (54.2)	67/323 (20.7)	†
Maintenance of PASI 75 from week 12 to week 52	210/249 (84.3)	103/142 (72.5)	†
Maintenance of IGA 0/1 from week 12 to week 52	161/202 (79.7)	50/88 (56.8)	†
<b>Other efficacy end point</b>			
PASI 100 at wk 12 — no./total no. (%)	78/323 (24.1)	14/323 (4.3)	†

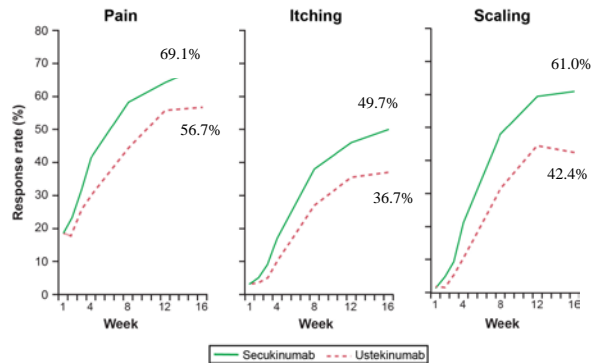
IGA: Investigator’s Global Assessment mod 2011; PASI: Psoriasis Area and Severity Index score; PASI 75, PASI 90, and PASI 100 responses indicate reductions from baseline in the PASI score of 75% or more, 90% or more, and 100%, respectively. † p<0.001 for the comparison with etanercept.

**Figure 1.** Efficacy over time to week 16 (CLEAR)<sup>5</sup>



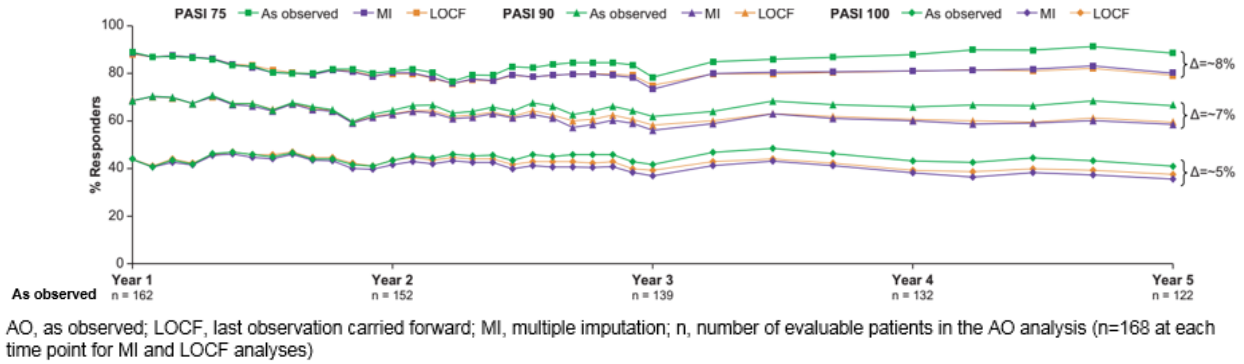
\*p < 0.0001; †p < 0.01; .Missing values for IGA 0/1 response were imputed as nonresponses (non-responder imputation).

**Figure 2.** Complete Relief Rates of Pain, Itching, and Scaling: Week 1-Week 16 (CLEAR)<sup>7</sup>

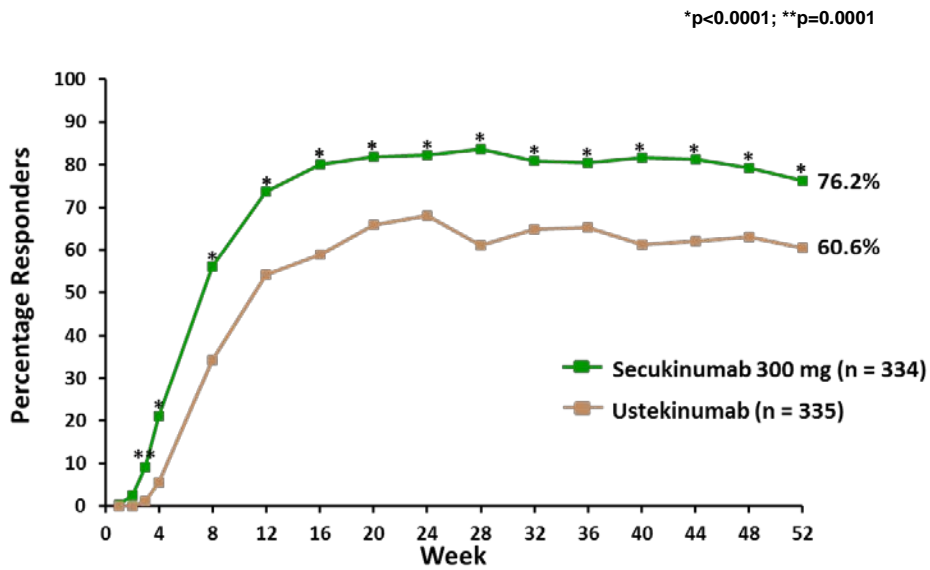


Secukinumab rates were significantly greater than ustekinumab (p<0.05), starting at Week 4 (except for pain at Week 12).

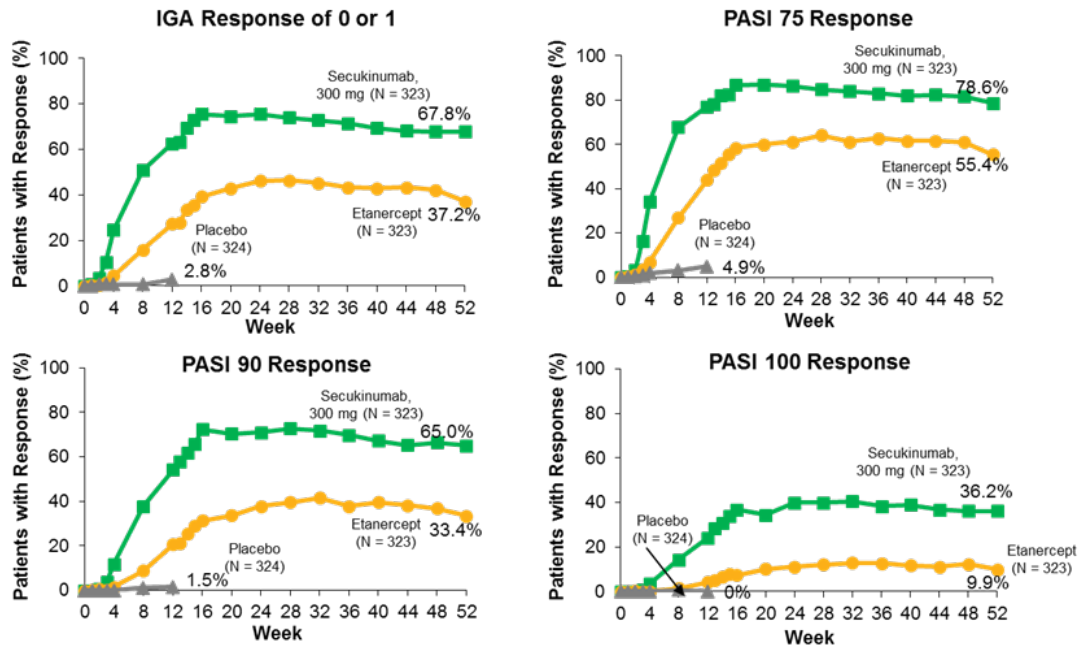
**Figure 3.** Secukinumab 300mg treatment sustained high PASI 75/90/100 response rates through year 5 (SCULPTURE)<sup>8</sup>



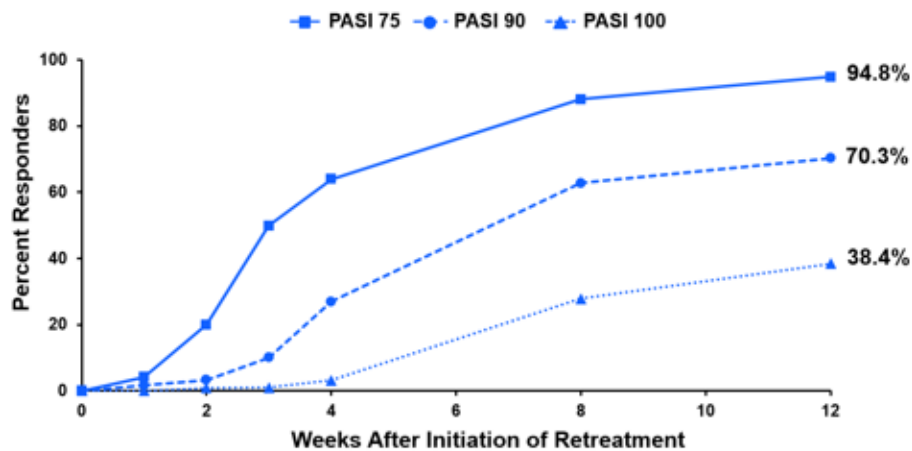
**Figure 4.** Sustainability of PASI 90 Response through Week 52 (CLEAR)<sup>9</sup>



**Figure 5. Efficacy over Time (FIXTURE)<sup>6</sup>**



**Figure 6. PASI Response 16 weeks after Retreatment with Secukinumab 300mg in Prior PASI 100 Responders who Replaced with Placebo (FIXTURE, ERASURE Pooled Analysis)<sup>12</sup>**



In the core studies, subjects were randomized 1:1:1 to secukinumab 300mg, 150mg, or matching placebo or etanercept 50mg (FIXTURE only). Treatments were administered at Baseline, Wk. 1, 2, 3, and then every 4 weeks from Wk. 4 until end of study (week 208) or discontinuation. At Wk. 12 placebo group subjects who did not achieve a PASI 75 response were re-randomized to receive secukinumab 300mg or 150mg.

PASI, Psoriasis Area Severity Index; Missing data were handled using multiple imputation. Subjects who had relapsed late and had not reached Week 16 post relapse are not included in Week 16 analysis. Prior PASI90 and 100 responders are included within PASI75 response groups, PASI90 responders within PASI100 response groups.

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Our Mission: To drive efforts to cure psoriatic disease and improve the lives of those affected.

December 22, 2017

Matt Seidner  
Program Manager  
Institute for Clinical and Economic Review  
2 Liberty Square, 9th Floor  
Boston, MA 02109

**RE: ICER Psoriasis Condition Update Scoping Document Public Comment**

Dear Mr. Seidner,

On behalf of the National Psoriasis Foundation, and the more than 8 million individuals living with psoriatic disease, I write to you today to offer public comment on the Institute for Clinical and Economic Review (ICER) *Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value Condition Update Draft Background and Scope* released on December 4, 2017. The National Psoriasis Foundation appreciates the opportunity to again offer the insights of our patient and provider experts to ICER as you undertake this psoriasis condition update.

***Rationale for the ICER psoriasis condition update***

The NPF understands from the scoping document and discussions with ICER staff, that the Institute is conducting this first-of-its-kind condition update due to the approval of two new drugs since the psoriasis report was released in December 2016 and the expected 2018 approval of two additional therapies. We also understand that part of the rationale is the emergence of new evidence for “many” of the treatments originally assessed. We look forward to learning more about the new evidence to which ICER is referring, as well as understanding the outlook and timing for future reviews given that the psoriasis pipeline is robust and several other new therapies are anticipated in the coming years. The NPF hopes ICER also intends to look at evidence regarding the degree to which the 2016 report’s policy recommendations – including expanded access to these therapies – have been adopted.

***Key Findings of 2016 Review***

As is noted in the scoping document, the 2016 assessment concluded all eight of the reviewed therapies to be of good value. The NPF was pleased that based on the evidence reviewed and input offered – including the data and patient perspectives submitted by the National Psoriasis Foundation – ICER and the New England CEPAC concluded that therapy costs were reasonably aligned with the benefits they provided to patients. Additionally, we appreciated that factors considered important by a variety of stakeholders including method of administration, frequency of dosing during maintenance, and rapidity of effect were considered during the review.

Beyond the economic analyses that resulted in incremental cost-effectiveness ratios across all agents that were well-aligned with commonly-accepted thresholds for cost-effectiveness, the report also made a number of policy recommendations. Recommendations included encouraging payers to abolish or limit the use of step



therapy for these treatments; basing co-payment and/or co-insurance for therapies on prices net of discounts and rebates instead of list price; and updating treatment guidelines for patients with moderate-to-severe chronic plaque psoriasis in a form that is easy to understand and easy-to-use by payers, clinicians, and patients. While the NPF appreciates ICER's goal of developing reports that translate evidence into decisions, the timing of this report so soon after the 2016 assessment unfortunately means that the updated guidelines begun by the National Psoriasis Foundation and American Academy of Dermatology in the spring of 2016 are still in development and will not be published until after the conclusion of this condition update. We agree that these will be helpful to payers, providers, and patients alike and look forward to promoting them upon their completion.

The National Psoriasis Foundation also calls ICER's attention to an effort of our medical board mentioned briefly in the 2016 report – a consensus paper published in the Journal of the American Academy of Dermatology (JAAD) in November 2016 on treatment targets that we again encourage ICER to review as part of this condition update.<sup>i</sup> This paper sets specific treatment goals that will make achieving clear or almost clear skin the new standard of care for psoriasis. In this treatment strategy, known as “Treat to Target,” a patient and their health care provider set specific targets or goals for improved health outcomes. The goals are meant to reduce the severity of plaque psoriasis so that it covers 1 percent or less of a person's body within three months after starting a treatment.

### ***Scope of the Assessment***

The National Psoriasis Foundation appreciates that the proposed scope for the update will generally follow the approach adopted for the prior review. Given the time and resources put in to contributing to the 2016 review by our organization, other stakeholders, patients and providers, it is reasonable for ICER to adopt the same methodology thereby ensuring prior contributions and findings are both relevant to this update and produce comparable results.

### ***Analyses, Populations, and Considerations***

As the NPF has reiterated recently during teleconferences with ICER staff and throughout our engagement in the 2016 ICER psoriasis treatment review, psoriasis is a serious chronic disease associated with significant morbidity and increased mortality.<sup>ii,iii</sup> As is noted in the scoping document, beyond the widespread prevalence of disease, it is also a disease that “significantly decreases health-related quality of life.” As ICER conducts this condition update we are pleased that model inputs will continue to extend beyond disease-specific measures such as the PASI, to include symptom improvement, treatment-related adverse events, health-related quality of life, and systemic manifestations, as well as data for evidence about the comparative effectiveness of targeted immunomodulators in affecting domains such as itch, scaling, pain, quality of life, work productivity, and satisfaction with treatment. We appreciate the steps ICER has taken over the last few years to refine the model in an effort to more accurately capture all the important elements that ought to factor in to these analyses. We continue to encourage you to explore novel approaches to assessing value in such a complex disease state.

As the condition update progresses, the NPF urges ICER to keep individuals living with psoriatic disease at the forefront. Examining sub-populations, for example, in greater detail to ensure the model appropriately reflects the nuances of treating the disease for complex patients. As we discussed during recent teleconferences, and highlighted in the prior assessment, we urge ICER to consider (1) the significant impact that psoriasis has on quality of life - particularly when the disease is present on the face, genitals, hands and feet; (2) the impact of additional comorbid conditions including psoriatic arthritis, cardiovascular disease, diabetes, suicidality, emotional and mental health conditions, among others; (3) limitation using short-term clinical trial outcomes to measure the impact of psoriasis treatments on comorbidity and other long-term costs and measures that do not capture patient satisfaction or dissatisfaction or the realities of managing a chronic disease over a lifetime; and (4) real-life prescribing challenges of this population.

**Conclusion**

As ICER moves ahead with this condition update, we again acknowledge the benefit of bringing forward sound science and evidence that informs patients and providers about treatment options. We thank ICER for including the perspective of individuals living with psoriatic disease in the 2016 review, and stand ready to meaningfully contribute again to this condition update.

We have a shared goal – to reduce the 55% of patients with moderate to severe psoriasis who are not being treated to the appropriate standards of care. On behalf of National Psoriasis Foundation, thank you for your consideration of these comments which we hope will positively inform this review. We again invite you to call upon us, our Medical Board, and our patient community as you move forward. Please contact Leah Howard, JD, NPF's Chief Operating Officer at [lhoward@psoriasis.org](mailto:lhoward@psoriasis.org) with any questions.

Sincerely,



Randy Beranek  
President & CEO

Cc: Abby Van Voorhees, M.D., Chair, National Psoriasis Foundation Medical Board  
Celia S. Segel, MPP, Program Manager, ICER

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<sup>i</sup> From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis. Armstrong, April W. et al. *Journal of the American Academy of Dermatology* , Volume 76 , Issue 2 , 290 - 298

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**RE: Draft Scoping Document for the Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value Condition Update**

UCB appreciates the opportunity to provide comments on the **Draft Scoping Document for the Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value Condition Update**. UCB is a global biopharmaceutical company, with North American headquarters located in Atlanta, Georgia. We have consistently demonstrated our commitment to creating value for patients, investing about a quarter of total revenues into research and development for new therapies over the past several years. Our focus is on innovating new medicines to treat chronic, severe diseases in neurology, immunology and bone disorders.

As the manufacturer of certolizumab pegol (CIMZIA®), we are committed to improving the health and quality of life of patients affected by the chronic conditions for which CIMZIA® is currently approved to treat, including Crohn's disease, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. At UCB we understand that there is no such thing as an “average patient,” especially for the complex and heterogeneous conditions that are the focus of our innovation. As such, we are concerned about the timing of this update for several reasons. Per the draft scoping document, CIMZIA® is currently under FDA review but has not yet been approved to treat the indication in question. Thus, key clinical information and proposed pricing that can inform this evaluation may not yet be available. In addition to potentially critical information gaps, we are concerned that payers have not had enough time to implement and assess the impact of ICER’s 2016 recommendations. However, if ICER plans to move forward with this review, we recommend ICER consider postponing the evaluation of CIMZIA® in psoriasis until the indication and label posology is confirmed by the FDA.

Regarding the draft scoping document, below, we provide several comments pertaining to the evaluation of long-term outcomes relevant to both patients and providers, measures that account for heterogeneous real-world and special populations, and clarification of pricing and cost-effectiveness analyses. Although ICER’s overall framework discusses the evaluation of long-term benefits, it does not adequately account for factors that UCB considers to be of high importance to patients when evaluating the cost and utility of treatment options – particularly durability, or maintenance of treatment effect, and dose escalation.<sup>1,2,3</sup> Further, dose escalation is common for many therapies and often utilized to maintain treatment effectiveness and may potentially hide issues with durability.



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### **Evaluation of Outcomes**

We recommend that ICER include durability as a factor that determines the overall utility and cost-effectiveness of treatments. Previous and current scoping documents recognized the importance of “evidence of durability in response to medications,” however, it was not explicitly incorporated into the 2016 analysis. Poorly controlled psoriasis can be debilitating and have severe physical, social, and emotional impacts on daily life.<sup>4</sup> Patients have expressed fear that treatments will lose effectiveness and frustration with treatments that are no longer effective.<sup>5</sup> Thus, we believe that data addressing the uncertainty of long-term effectiveness should be incorporated when assessing the overall utility of the treatment in question. These data are more readily available and models that do not consider durability are inherently limited in their ability to assess the value of psoriasis treatment options. In addition to poor patient and physician reported outcomes, durability is also a factor that is associated with treatment-switching and poor adherence which can lead to increased costs. Models that aim to look at long-term outcomes should include variables that determine a treatment’s ability to sustain PASI and DLQI responses over time.<sup>6,7,8,9,10,11,12,13</sup>

UCB also strongly recommends ICER consider dose escalation (DE) in its evaluation. We note that the 2016 report did not consider DE due to poor characterization in the scientific literature. However, DE is a fundamental aspect of treating chronic conditions and a reality for patients living with psoriasis. One study found that 33% of psoriasis patients experienced a DE of their biologic agent with most occurring within the first 6 months; cost studies using claims databases have shown that dose escalation is highly prevalent, and most often sustained for long durations.<sup>14</sup> This is associated with substantial costs and increased economic burden.<sup>15</sup> We therefore recommend ICER consider DE for all agents, including the duration of the DE prior to dose reduction and discontinuation.

Finally, we support ICER’s intent to perform a network meta-analysis using PASI 90 and PASI 100, and support the inclusion of the treatments ability to achieve and sustain a DLQI score of 0/1. DLQI captures important patient-reported outcomes such as itchiness, soreness, pain, and stinging, symptoms that tend to have the most significant impact on daily life for psoriasis patients but are not fully captured in a PASI score.<sup>16,17</sup> As such, while achieving PASI thresholds are important in assessing dermal symptoms, DLQI assesses additional symptoms critical to the wellness of psoriasis patients.<sup>18</sup>

### **Economic Evaluation**

Despite QALYs being a more commonly used measure of cost-effectiveness in other countries, it is neither widely accepted nor applicable in US healthcare settings. For example, PCORI is statutorily prohibited from considering cost-effectiveness; CMS is similarly restricting from using of any adjusted life year measure in coverage and reimbursement decisions because of concerns about this metric.<sup>19</sup> Although QALYs provide a standard method for measuring cost-effectiveness across multiple therapeutic areas, inherent limitations in its methodology, including derivation and calculation of utility scores, alongside the numerous assumptions that have to be made, makes for a difficult task for decision-makers to interpret and implement.

Additionally, in the 2016 report, the PASI and EQ-5D data from secukinumab trials were used to derive utility scores, and then applied to all therapies included in the analysis. Going forward, we strongly recommend ICER identify an externally validated method to calculate utility scores and



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encourage the use of quality of life measures from individual studies where available. We do support ICER's decision to consider other measures of cost effectiveness, such as cost-per-patient achieving a minimally important difference (MID) in the Dermatology Life Quality Index (DLQI) and the cost-per-patient achieving a 75% improvement in the Psoriasis Area Severity Index (PASI-75).<sup>20,21,22</sup>

### **Population**

Given previously mentioned concerns about accurate dosing for effective response maintenance, ICER should stratify the percentage of ustekinumab patients by  $\geq 100$  kg vs.  $\leq 100$  kg in its evaluation. Importantly, for patients in non-trial settings, patients who require higher doses may face higher costs. Additionally, we support ICER's intent to conduct subgroup analyses for certain comorbid conditions. However, we recommend ICER expand its stratification approach and consider the clinical and cost impact of products in treating concomitant conditions. Patients living with psoriasis are often affected by other closely-linked conditions, including joint pain, Crohn's disease, spondyloarthritis, and rheumatoid arthritis. Many products included in this analysis are indicated to treat one or more of these conditions. ICER should therefore include comorbid disease as a clinically-relevant consideration, as patients suffering from multiple conditions may often derive additional benefit from a product that treats comorbid conditions.

It is also recommended that data evaluating the use of therapies in special populations be included in the updated report. Specifically, the Pregnancy and Lactation Labeling Rule went into effect on June 30, 2015 and will ultimately lead to the removal of pregnancy categories.<sup>23</sup> For therapies included in this review, we recommend a section that summarizes the robustness of data available regarding pregnancy, lactation, and females and males of reproductive potential.

### **Other Pricing Considerations**

We recommend ICER provide clarification on its approaches to the pricing analysis. First, ICER should discuss a proposed approach to regularly update WAC prices for agents included in the analysis. Given that prices are not static, an evaluation that only obtains prices at one point in time may generate inaccurate results, particularly for those products that experience price changes after the update. Second, ICER should also note the limitations associated with its approach for calculating rebates. Rebates can vary widely in how they are applied (e.g. portfolio-based, volume-based, agent-specific, etc.). ICER's method of calculating rebate averages at the drug class level may not accurately reflect actual rebates, and should be appropriately caveated and discussed in the report.

UCB respectfully appreciates this opportunity to comment. Please direct any questions to Edward Lee, Head of Health Economics & Outcomes Research, at 770.970.8393; Edward.Lee@ucb.com.

Sincerely,

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