

### **AbbVie Public Comment Submission: Psoriasis Condition Update.**

Given the rapidly changing landscape of psoriasis treatment, AbbVie supports ICER in its efforts to update its 2016 psoriasis report and improve the model to better reflect the realities of patient care. While no systematic model will ever capture real-world practice exactly, closing the current gap between clinical trial results and real-world experience would make the model results more useful for health care decision makers. The methods used in the draft report represent improvements from the previous report. Although the report presents a robust discussion of the issues and challenges in modeling psoriasis care, additional detail is necessary to understand how these factors were integrated into the model itself. We have focused our comments on ways that the model can be modified to better reflect real-world practice.

### **Network Meta Analysis**

#### ***Study inclusion***

The criteria for Phase 2 study inclusion are unclear. The draft report states that Phase 2 trials are only included when the trial uniquely adds to the Phase 3 study results in terms of results reported and/or study population. However, Appendix B Evidence Summary Tables includes Phase 2 trials that do not seem to meet such criteria. An example would be Gordon et al. 2015 X-PLORE for guselkumab (p106).

Additionally, the report cites the lack of available data in many instances where analyses are available in subsequent publications beyond the primary manuscript for the trial. The primary manuscript for key trials generally focuses on ranked endpoints of the trial, and subgroup analyses, such as bio-experienced or bio-failures, generally get published in subsequent manuscripts or conferences. Each trial may have many more publications that focus on additional analyses of the trial data beyond the ranked endpoints. These results can be important to include and could address some of the limitations currently referenced as having lack of available data.

#### ***Relevant patient-reported outcomes***

The draft report includes a discussion of the important patient-reported outcomes commonly included in psoriasis trials, such as quality of life (QoL), symptom control, and productivity. With respect to QoL, the report states that “mean change in DLQI were not measured in the risankizumab and tildrakizumab trials” (p36). Given the recent release of the trial results and the limited ability to include additional results beyond the ranked endpoints, perhaps a more accurate statement would be that the mean change in DLQI was not yet reported for risankizumab and tildrakizumab.

With respect to symptom control, two of the pivotal Phase 3 trials for risankizumab included a patient-reported measure of symptoms, the Psoriasis Symptom Scale (PSS).<sup>1</sup> The PSI, PSD, nor the PSSD are available in the public domain and are owned by the companies that developed the instruments for their research programs. The PSS was developed to measure symptoms that are important to patients and included input from the FDA.<sup>2</sup> The items on the PSS are similar to items on the other instruments referenced in the draft report. Given PSS results were ranked endpoints, they were reported with the clinical outcomes that were recently presented.

## Cost-Effectiveness Model

The current model attempts to address real-world practice differences from the clinical trials; however, in some instances, it is not clear how some of these factors influence the model, and in other areas, the topic is referenced but not integrated into the model itself.

### ***Discontinuation***

The draft report cites that drug-specific discontinuation is used in Year 1 of the model and presents a robust discussion of real-world discontinuation. It is unclear how real-world discontinuation is accounted for in the model as the drug-specific discontinuation in the model seems to include only the failure to meet PASI75 after the induction period based on clinical trial efficacy results. Some of the sensitivity analyses suggest that this could have a significant impact on the model results.

Similarly, Year 2 and subsequent years assume a 5% or 10% discontinuation rate. Based on published literature of discontinuation beyond year 1 cited in the report, these assumptions significantly underestimate discontinuation rates in year 2 and beyond.<sup>3</sup> This, along with the market basket approach to second and subsequent lines of therapy, significantly overestimates the time spent in PASI75 and above for some treatments and does not represent real-world treatment patterns.

### ***Choice of second and subsequent lines of therapy***

The previous report assumed an equal probability of choice of second line treatments across all products. This report uses a market basket approach to the choice of second-line treatment based on expert clinical input. However, this approach still does not reflect real-world treatment choices. The following represent common scenarios that highlight the limitations of the current market basket approach:

- ***Psoriatic arthritis (PsA)*** – Patients with PsA that are on an IL-17 only have the option of guselkumab as second-line treatment. Since guselkumab is not currently indicated to treat PsA, it is unlikely that physicians would choose guselkumab over a TNF for patients that fail an IL-17 since TNFs are indicated to treat PsA.
- ***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>8,9</sup> Therefore, a patient who fails guselkumab but has IBD is unlikely to be prescribed an IL-17 as a second or subsequent line of therapy. These patients are most likely prescribed a TNF in this scenario.
- ***Cardiovascular (CV) conditions*** – Several large, claims-based studies suggested that cumulative exposure to TNF inhibitors was associated with a reduced risk of major cardiovascular events.<sup>10,11</sup> Treatment decisions in psoriasis patients should consider the cardiovascular prevention profile, especially in high-risk patients. Therefore, in patients with a high-risk cardiovascular profile, physicians may prefer TNFs in subsequent lines of therapy.

- ***Use of TNFs beyond first line*** – Each of the previous scenarios represents realistic situations where TNFs may be used in a second or subsequent line of therapy. Moreover, market share data suggest that TNFs are significantly used beyond first-line therapy.<sup>12</sup>

Although sensitivity analysis was conducted using the previous approach of equal probability across all treatments showing minimal impact on model results, this method is limited in capturing real-world practice patterns for the reasons cited above. Thus, a more realistic market basket approach could better capture real-world treatment choice for second and subsequent lines.

### ***Effectiveness of second-line treatment***

The draft report cites the lack of RCT data on the efficacy in second-line treatment and uses a 5% reduction in efficacy for each PASI90 and PASI75 and a 5% increase in the remaining PASI groups. Sensitivity analyses suggest that in some instances, the effectiveness of second and subsequent lines of treatment can have a non-trivial impact on the results. While there are little to no actual RCTs of second-line treatment, subgroup analyses of Phase 3 trials for bio-experienced patients could serve as a reasonable proxy for second-line treatment effectiveness. This is a fairly standard subgroup analysis that is conducted on trial data. Although not always published as a manuscript, these analyses would be available through conference publications such as the American Academy of Dermatology (AAD) and the European Academy of Dermatology and Venereology (EADV) Annual Congresses. Review of these analyses would show significant variation in the differences in effectiveness from bio-naïve (“first line”) and bio-experienced/bio-failure (“second line”) across the various treatments included in the draft report.

### ***Dose escalation and reduction***

The draft report includes discussion of dose escalation and reduction, although it is unclear how such practices are accounted for in the model. 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 they do not capture the use of samples or free goods to achieve higher levels of doses. While there is some anecdotal evidence of this practice, it would be very difficult to systematically quantify the impact of such practices. Moreover, published rates of dose escalation, typically defined as a certain percentage higher than the FDA-approved dosing, does not fully capture dose escalation of weight-based dosing, such as ustekinumab, since dose escalation from the lower weight dosing to the higher weight dosing would not be included in most estimates. Given these challenges and likely underestimation of some published estimates, use of such estimates of dose escalation would be at least a starting point to attempt to capture real-world dosing in the model. The impact to the model results could be significant given the cost of such above-label dosing is high, with annual costs estimated at \$5,623,362, \$701,964, and \$1,304,790, for etanercept, adalimumab, and ustekinumab, respectively, for example.<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.

### ***Price threshold analysis of products not included in the model***

The analysis of the price needed to achieve various cost per QALY thresholds is a unique way of addressing the new or upcoming product for which a market price is not yet available. Given the

significant differences in comparative effectiveness between risankizumab and tildrakizumab from the NMA, the resulting differences in the threshold prices of these products does not seem accurate given the similarity in the dosing used in the Phase 3 trials. Since approximately 88% of patients achieve PASI75 or above with risankizumab compared to 61% for tildrakizumab (based on the NMA results), the value-based monthly maintenance prices for risankizumab should be higher than tildrakizumab since the assumptions used in the model due to lack of data for these products should be similar, such as discontinuation, etc.

## 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. While the draft report includes discussion of many of these factors, if and how they are actually integrated into the model still leaves a significant gap between the model scenarios and real-world practice. Without a model that reflects real-world practice patterns, the utility of the model will be limited. Thus, updating the model to more accurately capture real-world treatment patterns would prove to be more useful to health care decision makers.

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## **Amgen Response to ICER Draft Evidence Report for Moderate-to-Severe Plaque Psoriasis (Condition Update)**

Amgen appreciates the opportunity to comment on the ICER Draft Evidence Report “Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value (Condition Update).” We have been committed to helping adult and pediatric patients with psoriasis for over 20 years and understands the impact of the targeted immunomodulators in substantially changing the lives of patients.

Moderate-to-severe plaque psoriasis (PsO) is a chronic, systemic inflammatory disease associated with widespread skin involvement, significant comorbidities, and crippling physical, economic, emotional, and social consequences that accumulate over the course of a patient’s life.<sup>1</sup> Systemic biologic treatments are often the only effective option for patients with this hard-to-treat disease.<sup>2</sup> Biologic PsO treatments have transformed the outcome of this disease in life-altering ways that short-term trials fail to capture.

Etanercept (Enbrel) continues to bring good value to patients and the healthcare system, just as the 2016 ICER evidence report concluded.<sup>3</sup> The demonstrated value of all biologics for PsO reinforces the importance of preserving treatment choice for the patient as specific disease characteristics, clinical expertise/judgement, and patient preferences affect treatment choice.

After a careful review of the ICER PsO Draft Evidence Report for this Condition Update, we found the following issues warrant attention:

- Although ICER has made some advancements towards increased transparency, it remains an issue with this Draft Evidence Report. We ask ICER to make model inputs and detailed calculations available so that the model is reproducible.
- The Draft Evidence Report continues to use model inputs for non-targeted agents based on old data which biases the analyses against targeted biologics. We ask ICER to use current estimates of drug pricing and an updated basket of non-targeted therapies.
- The dose escalation analysis for etanercept uses a European study that incorrectly interprets Enbrel’s US dosing and should be excluded.
- The phase 3b LIBERATE study comparisons between apremilast and etanercept are based on a noncomparative design and should not be used as a direct comparison for determining clinical equivalency.
- Comorbidities in patients with moderate-to-severe PsO including the significant joint involvement from Psoriatic arthritis (PsA) need to be incorporated into ICER’s model.
- ICER should use a societal perspective as the primary analysis to fully capture the value of etanercept and other targeted biologic therapies.

**Although ICER has made some advancements towards increased transparency, it remains an issue with this Draft Evidence Report. We ask ICER to make model inputs and detailed calculations available so that the model is reproducible.**

Similar to our previous comments from 2016, transparency and reproducibility remain an issue with the current ICER model. In the spirit of transparency, a goal that ICER is committed to achieving, we ask that ICER make information available on the following: a) provide an explicit list of the non-targeted treatment active comparators as the report does not specifically mention

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which treatments are included in the PsO model. This is crucial, as the cost and magnitude of QALYs for the comparators are necessary to interpret the incremental cost effectiveness ratios as presented in the Draft Evidence Report. b) The modelling analysis plan does not explain how the incremental costs effectiveness ratios per month for achieving PASI scores of 75+ and 90+ are calculated. We ask ICER to be more transparent in the changes to pricing and estimation of QALY's for non-targeted treatments (i.e., the active comparators) so that its models can be independently reproduced and externally validated.

### **The Draft Evidence Report continues using model inputs for non-targeted agents based on old data which biases the analyses against targeted biologics. We ask ICER to use current estimates of drug pricing and an updated basket of non-targeted therapies.**

In 2016, we commented that the non-targeted therapy regimens and their costs are described vaguely in the Comparative Value section of the Draft Evidence Report. The acquisition costs provided are most likely a low estimate of their true costs as they do not capture the current basket of therapies available for moderate to severe PsO patients. The non-targeted therapy regimen costs should represent current US practice in patients with moderate to severe PsO. The current non-targeted therapies available to patients include multiple oral immunomodulators, systemic retinoids, phototherapy with and without chemotherapy, and a range of topical treatments with several different mechanisms of action. Some of these therapies have recently been made available to patients as novel agents or improved dosage forms. The non-targeted therapy and costs description is from a 2003 database analysis,<sup>4</sup> and does not include these newer therapies and dosage forms. This analysis also notes the limitation of not capturing all costs involved with these treatments, which would underestimate the total cost of the intervention that serves as the primary comparator for the cost-effectiveness analysis.

Additionally, the cost of the nontargeted therapy is based on a price from the pre-biologic practice era in 2003, inflated to 2017 costs. While the non-targeted therapy sensitivity analysis of the cost-effectiveness results attempts to address the low costs and outdated data, the large variation in results of the sensitivity analysis suggests the need for a more accurate portrayal and costing of these treatments based on today's standards. ICER needs to use updated non-targeted therapy costs based on true 2018 utilization and costs. ICER should survey databases, practitioners, and patients to best determine the prescribed therapies that are acceptable to patients with moderate to severe PsO. After establishing the new non-targeted therapy regimen, its cost should be derived to represent an accurate value comparison.

### **The dose escalation analysis for etanercept uses a European study that incorrectly interprets Enbrel's US dosing and should be excluded.**

The US label for etanercept in psoriasis states that Enbrel is to be administered "50 mg twice weekly for 3 months, followed by 50 mg once weekly".<sup>5</sup> The European label for Enbrel states that: "The recommended dose of Enbrel is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks."<sup>6</sup> The dose escalation analysis for etanercept presented in the Draft Evidence Report is based on a European study.<sup>7,8</sup> As

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previously noted, the labels on dosing for plaque psoriasis are different between the US and EU. This most likely explains the high dose escalation rate in the Egeberg *et al* study. The supplementary Table 3 of Egeberg *et al* shows the dosing for etanercept is well below 1800 mg for 24 weeks, the dose indicated in the US label. These different labels and practice patterns explain why some patients in the Egeberg *et al* paper have dose escalation. Given the limited validity of this data for the US Market and the fact that Enbrel patients did not experience dose escalation (i.e., dosing for these patients was consistent with US label), we ask that ICER exclude this data from the sensitivity analysis.

### **The phase 3b LIBERATE study comparisons between apremilast and etanercept are based on a noncomparative design and should not be used as a direct comparison for determining clinical equivalency.**

We reiterate our comment from the 2016 Draft Evidence Report response by recommending that the results from the Phase 3b LIBERATE study should not be used as a direct comparison for determining clinical equivalency. The Draft Evidence Report includes results from the LIBERATE study comparison between apremilast and etanercept that are flawed and compromise the validity of this analysis. In 2016, these results were deleted from the evaluation and as the study design has not changed, should continue to be deleted. Fundamentally, this study has a noncomparative design and was not powered to compare apremilast and etanercept.<sup>9,10</sup> Additionally, the etanercept dose used in the LIBERATE study is not the labeled starting dose. Instead, the study used the etanercept 50 mg weekly maintenance dose, which biases the comparison by reducing the efficacy results of etanercept.

### **Psoriatic arthritis (PsA) is a significant joint and skin comorbidity in patients with moderate-to-severe PsO that needs to be incorporated into ICER's model.**

We believe there is an opportunity to improve the current model by including significant comorbidities, such as those patients with Psoriatic Arthritis (PsA). As ICER notes in section 1.1., PsA affects 30% of the population, or almost 1 in 3 PsO patients.<sup>11</sup> PsA is an inflammatory arthritis that occurs in psoriasis patients and manifests in the joints and surrounding tendons and ligaments where pain, stiffness, tenderness and swelling occur. Though initially thought to be a variant of rheumatoid arthritis, it has emerged as a distinct clinical entity and comorbidity of many PsO patients. An ICER PsO model should include PsA as a comorbidity and take into account the progressive joint damage and associated conditions. PsA can contribute to differential effects on QALYs and costs as the targeted therapies have variable effectiveness for treating PsA. Therefore, an analysis that incorporates incremental disutilities for PsO patients with comorbidities would enhance ICER's model design and strengthen its conclusions.

### **ICER should use a societal perspective as the primary analysis to fully capture the value of etanercept and targeted biologic therapies.**

Given the feedback from the 2016 analysis, ICER should address heterogeneity in treatment responses, capture costs associated with significant comorbidities -such as PsA-, and use a societal perspective that includes work productivity estimates as the primary analysis to achieve a more patient-centric perspective.



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The report qualitatively addresses key patient issues unique to moderate-to-severe PsO in Section 1.4: Insights Gained from Discussions with Patients and Patient Groups of the Draft Evidence Report. The economic analysis should quantify these insights and the treatment benefits of avoiding the long-term cumulative economic, emotional, and social consequences of PsO. Short-term PsO clinical trials capture neither these cumulative life impairments nor the long-term benefits of therapeutic interventions. The burden of psoriasis on work productivity and other limitations have been well documented and quantified.<sup>12</sup> To represent the long-term PsO patient experience identified in the report in the economic model, ICER should integrate these concepts into the model and further show the value of these lifelong therapies beyond the standard clinical trial time horizon in its cost-effectiveness analysis.

As patients can often also achieve satisfactory responses based on their signs and symptoms that are not adequately captured by PASI scores, ICER should consider adjusting short-term trial-based utility with a long-term patient-based utility augmentation factor to test what omitting longer-term outcomes means for the base model.

The ICER model should employ a patient-centered approach by incorporating the varied individualized patient responses (i.e., by including heterogeneity in treatment responses in its model) and using a *societal perspective as the primary analysis in this patient centric disease*; including the effects from multiple comorbidities such as joint and cardiovascular complications; and factoring in the long-term safety profiles and efficacy and adherence data.

### **Conclusion**

With more than 20 years of clinical use, Enbrel has an established safety and efficacy profile in PsO, both in adult and pediatric indications, where Enbrel is currently the only biologic approved for use in pediatric patients with moderate to severe PsO as young as 4.

We encourage ICER to provide greater transparency and clarity in the use of data sources for the ICER PsO model and use appropriate cost data for non-targeted therapies. We have found the interpretation of some studies need to take into consideration an understanding of the US label and practice patterns for Enbrel. The Draft Evidence Report continues to use an economic model that relies heavily on short-term studies and would benefit from patient-specific impacts.

Despite its methodological shortcomings, the Draft Evidence Report shows that all biologics provide cost-effective value when including productivity costs and benefits in PsO. As PsO is a disease with societal-wide costs, ICER should ensure that the base case analysis for their economic model capture the full value of targeted biologic therapies. The model should account for the significant physically and emotionally life-altering patient factors associated with PsO, including productivity losses associated with this disease, over the lifetime of these patients and reflect U.S. culture and practice patterns that best represent the value of PsO treatments in the U.S.

As a patient-centered organization, Amgen believes in the importance of preserving choice across all PsO treatments based on patient-specific disease characteristics, clinician expertise and judgement, and patient preference. We believe that, by incorporating the comments outlined above, ICER's 2018 Draft Evidence Report will continue to conclude that all targeted biologic therapies for the treatment of psoriasis, including etanercept, showing good value to patients and the health care system, just as ICER concluded in its 2016 report.

## **Amgen Response to ICER Draft Evidence Report for Moderate-to-Severe Plaque Psoriasis (Condition Update)**

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Dear ICER Committee:

Thank you for the opportunity to offer our perspective on the draft report for targeted immunomodulators for moderate to severe plaque psoriasis (PsO). As we stated in our previous comments, at Celgene we recognize that value is a complex concept where multiple perspectives are not only needed, but should be encouraged. We strongly oppose a singular, monolithic quality-adjusted life year (QALY)-based view of value that, given its current shortcomings can at best mislead the consumers of this information, and at worst, contribute to imposing additional access barriers to needed medicines. This has been Celgene's consistent position in all of our communication with ICER. We believe that ICER's draft report on targeted immunomodulators includes many topics of scientific importance but overlooks or minimizes pragmatic elements of value, such as: the medicines' impacts on patient's quality of life while on treatment; the convenience of taking the medicine; and pragmatic insights gleaned from real world evidence and clinical experience.

Celgene has been engaged throughout the ICER review process and has provided specific input at every step of the process in the spirit of ensuring completeness of the apremilast data used in the evaluation, methodological rigor, and the appropriate interpretation of apremilast data. Specifically, Celgene has repeatedly questioned the following elements of ICER's methodologic approach:

- ICER's focus on PASI scores as the main driver of quality of life (e.g. QALYs) despite evidence suggesting otherwise
- ICER's reliance on assumptions about patient's duration of treatment (persistence) instead of actual real-world data
- ICER's minimization of the importance of patient preference for an oral product devoid of the administration challenges associated with injectable biologics.

Regrettably, ICER has either ignored or only partially addressed Celgene's concerns. All suggestions that Celgene has provided to ICER that currently remain unaddressed in the draft evidence report can be found in the Appendix to this letter. Additionally, we would like to reiterate our perspective on ICER's draft report in each of these three key areas.

### **1. ICER over reliance on PASI scores misses important elements of value**

While PASI score is the standard efficacy measure for regulatory approval, it is seldom used by dermatologists in clinical practice. ICER states that:

“Our review focused on key clinical outcomes common to plaque psoriasis trials, as well as symptoms and burdens of psoriasis that are not well-captured by standard trial outcomes.”

ICER goes on to provide a list of clinical benefits (trial outcomes and patients reported outcomes) and harms of interest. Nonetheless, the ICER evidence rating (Table 3.9), as well as the effectiveness inputs in the cost-effectiveness analysis, is based solely on PASI improvement and does not encompass the multitude of other patient-relevant aspects of value in PsO.

ICER notes that up to half of patients are dissatisfied with their psoriasis treatment<sup>1,2</sup>. ICER acknowledges that at an FDA meeting in 2017 on Patient-Focused Drug Development for Psoriasis, patients noted that simple body surface area (BSA) measurements of psoriasis involvement do not consider the greater effect that lesions in particular areas – such as the nails, genitals, scalp, face, flexural areas, palms, and soles of the feet— have on an individual’s quality of life, nor does it adequately account for the more significant impact of flaking/scaling and itching has compared to rash itself on their quality of life<sup>3</sup>.

Kerdel and Zaiac<sup>4</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; 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 several, e.g., enhanced quality of life, and improved patient satisfaction. Celgene recognizes the intra-patient variability in outcomes and measurements of treatment success and must rely on regulatory endpoints that make up our product label. However, we also constantly conduct and evaluate real-world-evidence studies to better understand the patient perspective. Celgene suggests that these data can be obtained through literature review, from the biopharmaceutical partners conducting these studies, and from patient advocacy groups who have the personal knowledge of the patient experience.

## **2. ICER relies on an arbitrary assumption that treatment duration is based solely on PASI improvement and does not consider real world data on patient persistence.**

First, it is not clear when patients are assumed to discontinue in Year 1. ICER states that:

“Patients with a PASI improvement of at least 75% after the initiation periods continued on first-line therapy after the initiation period. However, we applied a drug-specific discontinuation rate to each initial targeted drug which determines the rate of discontinuation due to all causes (e.g., loss of efficacy, development of adverse effects) after the end of the initiation period. This rate differed between the first and subsequent years of treatment.”

However, ICER then states that:

“All discontinuation in the first year is due to lack of effectiveness at the end of the initiation period, except for infliximab“ and then on pp.51 “year one discontinuation rates were determined by drug effectiveness - in the base-case, patients who do not achieve PASI 75 by the end of treatment induction discontinue first-line targeted therapy”.

These contradictions make it difficult to understand the assumed discontinuation rates in Year 1 and especially whether an additional discontinuation rule (beyond PASI-75 achievement) was assumed for infliximab.

Additionally, assuming that Year 1 discontinuations are driven by PASI-75 achievement, it is worth comparing the discontinuation rates assumed by ICER to those reported in real-world US studies<sup>5-12</sup>. Published real-world data from the US<sup>12</sup>, as well as our own data on file, has shown that persistency with apremilast is either no different or even superior to persistence with biologic therapy. As such, ICER’s use of a 72%

discontinuation/switch rate for apremilast in Year 1, while the rates used for etanercept and adalimumab are 40% and 39% discontinuation rates, respectively, is not credible considering available real-world evidence.

ICER partially tested this assumption in a scenario analysis, allowing 2% of individuals in the PASI 50-74 group per month to improve to PASI 75-89 in the first year after the initiation period, and 10% of patients per month to discontinue their first-line treatment. However, this scenario analysis is not the relevant one. As stated in the 2016 ICER review itself, other researchers and HTA bodies (i.e. NICE, INESSS) have assumed that a PASI of 50-74 is a clinically meaningful degree of improvement when accompanied with improvements in patient quality of life.<sup>13</sup> Therefore, it would be important to explicitly test the impact of patients achieving PASI 50 continuing on first-line treatment.

### **3. ICER does not fully capture patient preferences for an oral alternative**

Patient dissatisfaction can include dissatisfaction with therapeutic efficacy, tolerability, and/or anxiety and stress associated with medication administration (e.g., frequency of dosing, difficulty traveling with medication, needle phobia, etc.). Elliason *et al.*<sup>14</sup> performed a discrete choice experiment in adults from the United Kingdom with moderate-to-severe psoriasis, where 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.

Despite this evidence, ICER is vague in terms of describing what is known in terms of patient preferences, fails to mention likely adherence/persistency improvements due to apremilast's oral formulation (yet ICER highlights potential improvements in terms of subcutaneous versus intravenous administration)<sup>i</sup> and, even further, ICER does not incorporate the evidence that supports patient preference for oral formulations in any step of its evaluation.<sup>14</sup>

As the only oral alternative for patients suffering with moderate-to-severe plaque psoriasis, apremilast offers a unique option from the rest of the medicines evaluated in this report. Therefore, we believe that ICER should, at a minimum, explicitly acknowledge the importance of patient preference for an oral alternative and how the cost per QALY measure does not adequately capture this benefit. Preferably, ICER should recognize that as the only oral, non-biologic, medicine in this assessment, apremilast should be viewed separately and not as part of the broader category of "targeted immunomodulators."

At Celgene, we firmly believe that any construct of value should be focused on patient-centered elements. Given these important omissions in the ICER report, we suggest caution when interpreting these findings and restraint when drawing conclusions, especially when it comes to making decisions about patients having access to the medicines they need.

Our belief in the value that apremilast brings to patients is unwavering. We believe apremilast is an effective treatment for patients with moderate to severe plaque psoriasis and it meets the needs of many of these patients as evidenced by its rapid adoption and growth in the US, treating nearly 200,000 patients since its approval. We are fully committed to continue generating evidence that informs the safe and appropriate use of apremilast in clinical practice and investing and removing access barriers to ensure that every patient that can benefit from apremilast may have access to it.

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<sup>i</sup> ICER states: "All of the targeted immunomodulators are administered subcutaneously except for apremilast (oral) and infliximab (intravenous). Subcutaneous route of administration is less burdensome and has reduced complexity, which is likely to improve adherence as well as the ability for some patients with limited mobility to self-administer prophylaxis. Further, patients may favor the convenience of an oral drug like apremilast. Although infliximab has a relatively better efficacy in our evidence review, patients might be disinclined to use an intravenous medication that is associated with administration time and discomfort. In addition, patients could favor agents that need to be taken less frequently. The frequency of administration during maintenance is greatest for apremilast (twice a day). Other targeted immunomodulators are taken weekly (adalimumab, etanercept), every two weeks (brodalumab), every four weeks (secukinumab and ixekizumab), every 8 weeks (infliximab, guselkumab), and every 12 weeks (ustekinumab, tildrakizumab, risankizumab)."

We sincerely hope that by actively engaging in this process and providing concrete feedback on the current ICER draft report, we have contributed to a more accurate and balanced final report. More importantly, our greater aim remains in ensuring that patients continue to have access to the medicines they need.

Sincerely,



Richard H. Bagger

#### APPENDIX: ICER’s changes based on CELGENE comments

COMMENT / SUGGESTION	ADDRESSED BY ICER?
PASI 50, 75, and 90 responses were analyzed jointly in the model. Conduct scenario analysis by these groups to address issue of generalizability and differentiate moderate from severe patients.	<b>No changes made.</b> “Consistent with prior published methods, PASI 50,75 and 90 response outcomes from clinical trials were tabulated to create numbers of patients in mutually exclusive categories (i.e., <50, <75, 50-74,75-89, ≥90)”
Assess differences in demographics and comorbidities across trials	<b>No changes made.</b> “An adjusted model was specified with a covariate for placebo response rate which was assumed to be common across all treatments and provided a control for known and unknown differences between study populations”
Provide evidence-based justification for efficacy measures selected and undertake sensitivity analysis to understand what the impact would be if other measures beyond PASI had been chosen	<b>No changes made. Focus is PASI-75.</b>
The above-mentioned arguments suggest that the model assumption of all patients switching to second line if PASI 75 is not achieved in the induction period, may, <u>at the very least</u> , be evaluated in a sensitivity analysis and, ideally, the assumption removed.	<b>The assumption was not removed. A scenario analysis was included</b> but as discussed in the response to the draft report, it is not the relevant one.
For cost-effectiveness modelling purposes, efficacy is based on PASI alone while available evidence indicates that this is not reflective of clinical practice. Consider adding sensitivity analysis with other endpoints, namely patient satisfaction, DLQI, other relevant secondary Patient Reported Outcomes (PROs.)	<b>Not addressed.</b>
Persistency - Use available US analyses and based on those, consider no difference in discontinuation rates between apremilast and biologics.	<b>US real-world analyses were used</b> but ICER fails to include (or even mention) Feldman <i>et al.</i> <sup>12</sup> apremilast persistency data.
ICER considers, in essence, the induction period efficacy and takes this as the cost-effectiveness and comparative efficacy basis. Account for long-term evidence available, when available – such as the case of apremilast.	<b>Long-term data available is mentioned</b> but only if comparative in nature. As a result, apremilast PALACE-1 156 weeks in not mentioned.

	ICER does mention that long-term results available suggest that initiation period results are generally maintained but then discussed the existence of waning effect which contradicts it.
Include other costs (e.g. hospitalization, drug administration cost, outpatient visit costs)	<b>Addressed.</b> Other costs are included in non-target therapy. For targeted therapy only drug + administration + monitoring costs are considered.
The above-mentioned arguments suggest that the model assumption of reduced efficacy/effectiveness in treatment experienced compared to treatment naïve is not solid and, may therefore, at the very least, be evaluated in a sensitivity analysis and, ideally, the assumption removed by assuming no efficacy reduction.	<b>Addressed.</b> Evidence was provided supporting the assumption of lower efficacy in second line.
Consider adverse events in the base case and explore not only respiratory infection but also other adverse events such as malignancies, and serious skin reactions.	<b>Not considered in the base case</b> and only in a very limited way in scenario analysis.
Results are presented versus non-target therapy as reference. Yet, no information on this (effectiveness or costs) is provided in the presentation and it is thus unclear what exactly is considered as reference. Provide detailed information regarding non-target therapy data, sources and assumptions.	<b>Provided.</b>
Sensitivity and scenario analysis. Consider real-world evidence when looking at the effect of dose escalation as part of sensitivity analysis.	<b>Included.</b>

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May 22, 2018

**RE: Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value Condition Update, Draft Evidence Report, April 27, 2018**

Eli Lilly and Company appreciates the opportunity to respond to ICER's Draft Evidence Report, "Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value Condition Update". Several comments are provided below for ICER's consideration:

**1. Comparative Clinical Effectiveness.**

- a. 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. Therefore, the use of efficacy data based on different induction period lengths may lead to unfair comparisons. Comparisons of clinical benefit within the same study duration at week 12 should be considered to minimize bias.

**2. Economic Model and Value Assessment.**

- a. We agree with ICER's use of additional measures of benefit beyond the QALY. In particular, the use of "time in PASI 90 and PASI 75" health states is an important step in the right direction towards assessing the true economic value of biologic therapies for psoriasis.
- b. The assumption of immediate time to onset was assessed whereby all treatments were examined for onset of effect at months 1, 2 and 3 (p. 61). However, time or speed of onset varies across treatments within the induction or 'trial' phase (typically 12-16 weeks). 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 [1,2]. 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 [3,4]. Thus, we recommend that ICER conduct new, supplemental AUC analyses across different products as part of its assessment of clinical benefit and value.
- c. We agree with ICER's conclusion that ixekizumab and other IL-17 drugs should be considered as first-line targeted therapies due to better efficacy and reasonable economic values versus step-therapy approaches that employ less effective and less expensive therapies ahead of the IL-17s (p.64). The FDA approved label for Taltz® (ixekizumab) would support first line usage. However, despite ICER's recommendation in its 2016 Final Evidence Report to remove step-therapy, in current practice insurers continue to impose step-therapy approaches to Taltz® and other, newer biologic therapies for psoriasis, independent of price and rebates for these new agents. In our experience, new biologic agents in Immunology, unlike other disease categories, are required to pay rebates to secure a place in the treatment algorithm - not based on the product's label or approved indication, but rather after patients are required to take the on-patent market leading product based on the insurer's formulary. Specifically, new biologic therapies pay rebates (which are sometimes significant) to compete for second line status behind the preferred, market leading product, so it is important for ICER to recognize this reality when considering its cost-effectiveness analyses and assessment of actual underlying value. The scenario in Appendix G changes the second-line market basket to be an average of all 10 targeted drugs, but this scenario does not reflect the typical mix of second-line treatments available to patients after having failed a TNF inhibitor. Therefore, we suggest that ICER include additional analyses for treatments according to expected place in therapy and further consider use of PASI responses from RCTs based on biologic-experienced or prior biologic failure or in inadequate responder patients as second-line effectiveness estimates.

### 3. Conclusions.

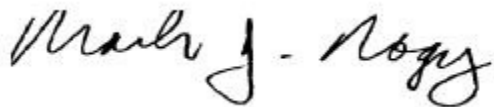
- a. Clarifications of conclusions are needed regarding place in therapy of IL-17s and in particular ixekizumab. On page 32 it states Ixekizumab has the highest relative effectiveness at every level (i.e., relative risk of achieving PASI 50, 75 or 90 response). On page 55, Section 4.3 Results, ICER concluded that ixekizumab and brodalumab are the most effective initial treatments and on page 63, section 4.4 Summary and Comment, ICER states the most effective treatment in this analysis start with ixekizumab with a 7.415 QALYs. Further, on page 72, Conclusions, ICER notes that initial treatment with either brodalumab, ixekizumab, secukinumab, or guselkumab is considerably more effective than initial (step) therapy with less effective agents. These findings seem to suggest that ixekizumab and other IL-17s provide the best overall value and should be recommended first line. However, the final paragraph in section 4.4 states that the IL-17 drugs have increased in price across the board, leading to less favorable value than in ICER's 2016 report. It should be noted that price increased for all agents in this analysis and in some cases were greater for tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) agents. This statement about price increases could create confusion for the reader, and mutes the outstanding clinical and economic findings. A clear explanation as to how this affects the conclusions should be provided, otherwise the statement should be removed. Further, ICER makes no mention that even with these findings, Appendix H, Health Plan coverage lists universal preference for TNFs followed by 46% preference for ustekinumab. IL-17s are relegated to 2<sup>nd</sup>, 3<sup>rd</sup> or 4<sup>th</sup> line access status, and with preferred access in only 3 small regional plans. On page 17, ICER notes a market shift in access for new entities; however, weighting these plans' coverage policies by total covered lives would show otherwise and more closely reflect the current situation. A significant access concern exists for IL-17s and other therapies – despite the documented clinical and economic value shown in the ICER report – as supported by over half of surveyed patients suggesting that they are dissatisfied with their psoriasis treatment (page 14). ICER should run the analysis by percentage of lives.

### 4. New data on Ixekizumab.

- a. Under the clinical benefit subsection “Sexual Function” on page 38, we request that ICER include important new data on ixekizumab and its effectiveness on sexual activity in patients with genital psoriasis (Ryan C., et al.; *J Sexual Medicine*, 2018; Ryan C. et al.; *British Journal of Dermatology*, 2018) [5,6]. In particular, the data from this randomized, placebo-controlled, clinical trial demonstrated that ixekizumab treatment led to significantly greater proportion of patients reporting that their genital psoriasis ‘never’ or ‘rarely’ limited their sexual activity based on the validated Genital Psoriasis Sexual Frequency Questionnaire (GenPs-SFQ [7]) at week 12 (ixekizumab: 78.4%, placebo: 21.4%,  $p < 0.001$ ). Furthermore, significant improvement with ixekizumab was observed as early as week 1 (ixekizumab: 21.6%, placebo: 4.8%,  $p = 0.036$ ). These results are now included in the updated Taltz USPI.

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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**Date:** May 24, 2018

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

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

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#### EXECUTIVE SUMMARY

- Janssen has replicated ICER's NMA and has identified a significant limitation that may have a significant impact on conclusions around comparative efficacy. ICER is assuming that the placebo response is uniform across levels of PASI response (50, 75, and 90), which is incorrect. Our analysis showed that assuming a single beta coefficient does not reflect the true efficacy of newer biologics. Additionally, the exclusion of a PASI 100 response rate further exacerbates this problem.
  - ICERs assumption that the relationship between placebo and PASI response is equivalent across PASI levels is not correct and creates a bias against newer more effective agents. Given the higher efficacy of the new agents, Janssen recommends that ICER include PASI 100 as a fourth level of response in the NMA and should include beta coefficients for PASI 50, 75, 90, and 100. We have determined that this is the most accurate approach based on external guidelines from HTA agencies.
  - At a minimum, Janssen strongly requests that ICER include three betas for each level of PASI response in the current NMA model (50, 75, and 90).
  - ICER should also perform individual NMAs for each PASI response level to assure that the NMA is internally consistent (meaning the simultaneous NMA and individual NMAs align). This is a common guideline from HTA agencies. Janssen's replication of ICERs NMA found that the simultaneous NMA does not align with individual NMAs for each level of PASI response (meaning the order of products from highest to lowest efficacy changed). This may lead to different conclusions around product efficacy, and thereby also impact long-term cost effectiveness results.
- Janssen also suggests that ICER emphasize that the highest efficacy products cannot be distinguished, as the credible intervals cross 1.
- Given the lack of publicly available discount data for guselkumab due to its' recent approval, Janssen suggests ICER apply an average of two of the newest IL-17s on the market (secukinumab and ixekizumab) of 41%, as opposed to an average discount across all products, since this would be a relevant representation of current competitive market dynamics.
- For ustekinumab, Janssen continues to recommend the Federal Supply Schedule (FSS) document as a publicly available resource for product discounts. Should ICER choose not to adopt this recommendation, Janssen recommends applying the 41% IL-17 average of the secukinumab and ixekizumab discount rates to ustekinumab as well.
- Janssen strongly disagrees with ICER's comment that guselkumab is likely one of the most expensive initial target treatments over 10 years (Section 4.3, bottom of page 56 and top of 57) for several reasons:
  - 1) Small variations in discounts have a dramatic impact on cost and cost effectiveness
  - 2) The lack of a

separate PASI 100 response threshold in the NMA, and 3) Other methodological limitations mentioned above.

- Current cost for ustekinumab in Table 4.4 is not accurate based on ICER's assumed discount rate of 27%. Janssen requests that ICER update ustekinumab costs in this table and ensure they are also accurately captured in the cost effectiveness model. Based on ICER's assumptions of a 70/30% dose mix for 45/90mg use and 27% discount assumptions (net cost for this dose mix would be \$9,767.25). First year cost should be \$48,836.25 (5 doses of ustekinumab). Second year cost should be \$39,069 (4 doses of ustekinumab) to be consistent with methodology used for other products. These costs will differ, and become more accurate, if ICER revises its' ustekinumab discount assumptions based on Janssen's recommendations.

## INTRODUCTION

- Page 5: Table 1.1: brodalumab loading dose is missing from "FDA Recommended Dosing" column (Siliq Prescribing Information)
- Page 6 (bottom): The statement "Head to head studies and registry studies for TNF-alpha therapy have shown that biosimilars can be interchanged with the reference biologic without losing effectiveness" is not accurate. No biosimilar manufacturers have completed studies to date establishing interchangeability of a biosimilar with an innovator based on draft FDA guidance (see Draft FDA Guidance link in references). Current biosimilar registration studies have established biosimilarity to innovators only, meaning most states will not permit the interchanging of a biosimilar for an innovator by pharmacists without the permission of the prescriber. Janssen recommends removing "interchanged" from this sentence to align with FDA draft interchangeability guidance.

## SUMMARY OF COVERAGE POLICIES & CLINICAL GUIDELINES

- Page 19: Note that the AAD guidelines published in 2011 do include ustekinumab, which was approved by the FDA in 2009; therefore, this statement should be corrected. These guidelines precede the approval of the newer agents in the ICER report such as guselkumab, brodalumab, ixekizumab, etc. (Menter 2011).
- Page 20: NICE reserves treatment with infliximab for patients with very severe plaque psoriasis after failure of first-line biologic treatment (a PASI>20 and a DLQI of more than 18).
- Page 20: Regarding the European Guideline on Systemic Treatment of Psoriasis Vulgaris, 2017 update, guselkumab, ixekizumab, and brodalumab were not included.

## COMPARATIVE CLINICAL EFFECTIVENESS

- Page 25: Included Studies: The guselkumab head-to-head studies were VOYAGE 1 and 2 (spelling error).
- Page 37: Table 3.6: DLQI 0/1 percentages for adalimumab and guselkumab for both VOYAGE 1 & 2 are transposed (should be 52% for guselkumab and 39% for adalimumab).
- Page 50: Janssen replicated ICERs simultaneous PASI NMA and also ran individual NMAs for each PASI response level (recommended by many HTA agencies) and found that the ICER results were internally inconsistent. This is not the case for Janssen's NMA. Namely, our simultaneous PASI NMA and individual NMA agreed. Janssen determined that ICER's use of a single common beta across PASI response levels, as well as not including a separate PASI 100 placebo response, are causing the inaccuracy. Namely:
  - Janssen's analysis shows that the relationship between placebo response and PASI response varies across PASI levels (50, 75, 90, and 100). Therefore, the assumption of a single beta coefficient masks these placebo response differences across PASI response levels and must be considered by ICER.
  - Additionally, the exclusion of PASI 100 as a discrete outcome further compounds this issue.

Janssen strongly requests that ICER consider at least one of the two options below given the importance of the NMA on subsequent models and conclusions.

- ICER should add PASI 100 and include four betas (PASI 50, 75, 90, and 100) in a simultaneous NMA, which is the most rigorous analysis from a methodological standpoint. This should also be checked against individual NMAs for each PASI response level to verify findings are consistent with those from the simultaneous model (Janssen's work suggests this would be the case).
- If the above suggestion is not accepted, ICER should run a simultaneous NMA with three betas (for PASI 50, 75, and 90) as the minimally acceptable option given the current cost effectiveness model structure.

Janssen suggests that ICER also consider the recent NICE review of guselkumab. The NICE appraisal of guselkumab showed that guselkumab is significantly better than secukinumab and comparable to ixekizumab, both findings in line with the Janssen NMA (Available at:

<https://www.nice.org.uk/guidance/gid-ta10232/documents/final-appraisal-determination-document>,

Section 3.4 page 6). Additionally, Janssen would like to make ICER aware of a recent favorable review of guselkumab by the German HTA agency GBA Available at: [https://www.g-ba.de/downloads/39-261-3315/2018-05-17\\_AM-RL-XII\\_Guselkumab\\_D-330.pdf](https://www.g-ba.de/downloads/39-261-3315/2018-05-17_AM-RL-XII_Guselkumab_D-330.pdf)

- It should also be noted that peak efficacy for guselkumab is achieved after induction. Some other products reach peak efficacy during induction (e.g. IL-17 products). Since plaque psoriasis is a chronic disease over a patient's lifetime, the use of only the induction data for the NMA should be highlighted as a major limitation.
- Page 49-50: ICER notes that there are no RCTs of second line targeted therapy and limited data on second line targeted therapy response in general. However, the NAVIGATE study can be informative for guselkumab used as a second line agent among ustekinumab inadequate responders. Additionally, NAVIGATE is not mentioned on page 50 of the summary of results for second line treatment (Langley 2017).

#### **LONG-TERM COST EFFECTIVENESS**

- Page 48: Table 4.1: Medication Dosing Schedules: The FDA-approved dosing for ustekinumab is 90 mg for weight >100 kg for both initial dosing and maintenance dosing. Please correct the "≥" to ">" (STELARA Prescribing Information).
- Page 53: Table 4.4: Drug cost inputs table: The unit for infliximab is 100 mg, not 40 mg. Janssen suggests that ICER make this update (REMICADE Prescribing Information).
- Page 53: There are several inaccuracies in Table 4.4.
  - Janssen was not able to replicate the net price per unit using the discounts in the table for most of the products based on the ICER methods. Please verify these numbers and document in Table 4.4.
  - Ustekinumab costs, based on the current, yet inaccurate, discount rate of 27%, should be \$9767.25 net cost per unit. First year cost should be \$48,836.25 (5 doses of ustekinumab). The second-year cost should be \$39,069 (4 doses of ustekinumab) to be consistent with methodology used for other products.
  - The apremilast starter pack WAC is \$3383.09 per package for 55 tablets as of 4/4/18 and the 30mg tablet WAC as of 4/4/18 is \$52.72 (different than reported in the table). The starter pack takes patients through day 28, while the remainder of the 1<sup>st</sup> year requires 672 tablets and the second full year requires 730 tablets. Using a net price per starter pack of \$2560.81 and a net price per unit \$42.68 for the 30mg tablet based on the assumed discount, the first-year treatment cost would be \$31,241.77 and the second-year treatment cost would be \$31,156.40 (also different than reported in the table). Please correct these issues and ensure they align with what is used in the cost effectiveness model.
  - ICER seems to assume 15 doses for the 1<sup>st</sup> year of secukinumab. This should be at least 16 doses, to be consistent with methodology used for other products, which yields a first-year cost of \$47,746.88. Please correct this discrepancy and ensure it aligns with what is used in the cost effectiveness model.
- As stated earlier, Janssen recommends ICER consider our recommendations surrounding appropriate discounts as stated in the Executive Summary.

- Page 54: Table 4.5: Please correct the monitoring recommendations for infliximab, ustekinumab, and guselkumab aligning with the Prescribing Information (USPI) for each product (REMICADE Prescribing Information, STELARA Prescribing Information, and TREMFYA Prescribing Information).  
Corrections are as follows:
  - Tuberculosis (TB): patients should be evaluated for tuberculosis (TB) infection prior to treatment and monitored for signs and symptoms of active TB throughout therapy with infliximab, ustekinumab, and guselkumab. There is no recommendation for annual TB test for patients treated with infliximab in the USPI.
  - CBC: There are no recommendations regarding quarterly CBC for patients treated with either infliximab or ustekinumab per the USPI.
  - LFTs: There is no recommendation regarding quarterly LFTs for patients treated with infliximab per the USPI.
- Page 56-57: 4.3 Results section: Janssen requests that ICER include a statement referencing an assumed discount for guselkumab was used where it is stated that guselkumab is one of the most expensive initial targeted treatments (along with ixekizumab). The cost of etanercept as calculated by ICER is more expensive than both guselkumab and ixekizumab. Also, other corrections (such as accounting for the additional dose of secukinumab in the first year and correcting the ustekinumab cost as suggested above) puts numerous products close in cost for the first year.
- Page 57: Table 4.6: ICER should explain why the number of months spent in PASI 75 response numbers changed so dramatically from preliminary results.
- Page 57: Table 4.7: ICER should explain why the ustekinumab cost per QALY increased from the preliminary results since an additional 7% discount was applied.
- Page 63: Section 4.4 Summary and Comment section: Janssen suggests that ICER strike language that guselkumab is one of the most expensive treatments since flaws in the current NMA methodology, small variations in price/discounts, utilities, as well as uncertainty in the models have a dramatic impact on cost and cost effectiveness.

### **ADDITIONAL CONSIDERATIONS**

- Janssen suggests that ICER include factors such as productivity, and quality of life in the base case analysis of the long-term cost effectiveness model for determining the overall value of biologics. The current base case model does not provide a holistic understanding of the impact of plaque psoriasis on patients. For example, the model time horizon (10 years) and perspective (payer), underestimate the benefit of these products for a chronic condition with significant costs outside of the health care system (e.g. productivity, patient quality of life, anxiety and depression, etc.). This is evident from ICER's analysis that included productivity gains that further demonstrated the value of these products beyond what is shown in the base case.
- The discontinuation rate for guselkumab used in the ICER model is overestimated, as the timepoint for determining continuation on guselkumab based on PASI response is prior to when peak efficacy may be achieved. Janssen suggests that ICER clearly note this limitation of the model.
- Page 229: The FDA-approved maintenance dosage for brodalumab is 210 mg every two weeks (Siliq Prescribing Information).
- Page 229-239: Table G2, G4, G9, G10: Janssen suggests that ICER complete these tables with known available information for all products.
- Page 230: Table G3 Refer to the NICE review of guselkumab available at: <https://www.nice.org.uk/guidance/indevelopment/gid-ta10232/documents>.

## POTENTIAL BUDGET IMPACT

- Section 7: The ICER model assumes that 100% of incident cases with a BSA of >3% will receive guselkumab. This assumption is problematic for several reasons. First, many patients with moderate to severe plaque psoriasis are not treated with biologics. Second, most payers have fail first/step therapy edits for bio-naïve patients which prevent less severe patients from starting on newer biologics. Lastly, it is unrealistic to assume that physicians will start all new incident cases on guselkumab or any other biologic given the number of available products in the market. Janssen suggests that ICER revise the budget impact model methodology to consider the above issues to make it more realistic.

## APPENDICES

### Appendix B. Evidence Summary Tables

- Page 105: Blauvelt, 2016: Intervention Dosing Schedule: Patients on placebo crossed over to guselkumab at week 16 and continued to receive guselkumab through week 48; Outcomes: IGA 0/1, % 1)85.1
- Page 106: Reich, 2016: Intervention Dosing Schedule: Patients on placebo crossed over to guselkumab at week 16 and continued to receive guselkumab through week 48
- Page 107: Gordon, 2015: Intervention Dosing Schedule: 1) guselkumab a) 5 mg at weeks 0, 4 and every 12 weeks (41), b) 15 mg every 8 weeks (41), c) 50 mg at weeks 0, 4 and every 12 weeks (42)
- Page 163: Langley, 2015: Intervention Dosing Schedule: a) non-adjusters (n=544), b) adjusters (n=568); AEs at week 264 (2<sup>nd</sup> line) a)187 b)216 c)202; SAEs (1<sup>st</sup> line) 1)7.99 2)6.87 3)7.31; Infections (2<sup>nd</sup> line) a)73.9 b)83.4 c)78.9

### Appendix E. Comparative Clinical Effectiveness Supplemental Information

- Page 210-21, Table E1:
  - PASI 90 data from NAVIGATE are missing from Table E1 and is provided below. Note these data are at week 28 in patients who had an IGA  $\geq 2$  at week 16 and were randomized to either ustekinumab or guselkumab. The presented P value is versus ustekinumab (Langley 2017).

Treatment	Week	N	PASI 90 %	P value
guselkumab	28	135	48.1	$\leq 0.001$
ustekinumab	28	133	22.6	

- Page 213: Table E4: DLQI 0/1 percentages for adalimumab and guselkumab for both VOYAGE 1 & 2 are transposed (should be 52% for guselkumab and 39% for adalimumab).



## REFERENCES

Menter A, Korman NJ, Elmets CA, et al. American Academy of Dermatology guidelines of care for the management of psoriasis and psoriatic arthritis. *J Am Acad Dermatol*. 2011;65:137-74.

Considerations in demonstrating interchangeability with a reference product: guidance for industry. January 2017, available at:

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf> . Accessed May 9, 2018.

Siliq (brodalumab) Prescribing Information.

[STELARA \(ustekinumab\) Prescribing Information.](#)

Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol*. 2017;76(3):405-417.

- Correction published: *J Am Acad Dermatol*. 2017;76(6):1226.

Egeberg A, Ottosen MB, Gniadecki R, et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. *Br J Dermatol*. 2018;178(2):509-519.

Gordon K, Menter A, Ferris L, et al. Consistency of response (PASI 90 or 100 and IGA 0/1 or 0) in patients with moderate to severe psoriasis treated with guselkumab: results from the VOYAGE 1 and VOYAGE 2 trials. Poster presented at: 76th Annual Meeting of the American Academy of Dermatology; February 15-20, 2018; San Diego, CA

Langley RG, Tsai TF, Flavin S, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase 3 NAVIGATE trial. [published online ahead of print June 21, 2017]. *Br J Dermatol*. doi:10.1111/bjd.15750.

Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol*. 2017;76(3):418-431.

- Correction published: *J Am Acad Dermatol*. 2017;76(6):1226.

[REMICADE \(infliximab\) Prescribing Information.](#)

Taltz (ixekizumab) Prescribing Information.

[TREMFYA \(guselkumab\) Prescribing Information.](#)

Novartis appreciates the opportunity to provide feedback to ICER on the draft evidence report for the 2018 psoriasis review update. In this response, we summarize key benefits of secukinumab and provide recommendations to ensure this information is more accurately accounted for in the report.

Psoriasis, a lifelong systemic immune-mediated disease affecting approximately 7.5 million Americans, is a debilitating condition impacting patient well-being and quality of life.<sup>1</sup> In the U.S., secukinumab is approved for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Secukinumab is a fully human monoclonal antibody (mAb) that selectively binds to the interleukin-17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor.<sup>2</sup> Furthermore, secukinumab is also approved for adult patients with active ankylosing spondylitis (AS) and active psoriatic arthritis (PsA).<sup>2</sup> Novartis just initiated the 100<sup>th</sup> clinical trial studying secukinumab and over 140,000 patients have been treated to date.<sup>3</sup> Secukinumab's key benefits are supported by the vast body of evidence available:

- **Long Term Safety:** Secukinumab safety was compared to both placebo and etanercept over 52 weeks of treatment and has been carefully studied in 10 clinical trials in psoriasis.<sup>4</sup> Secukinumab has a consistent safety profile for up to five years, including low immunogenicity (<1%) & low injection site reactions (<1%) in the pivotal trials.<sup>5,6,7,8,9,10,12</sup>
- **Sustainable Efficacy:** Response rates for secukinumab were preserved for up to 5 years; Psoriasis Area Severity Index (PASI) 75/90/100 responses at Year 1 (88.9%, 68.5%, and 43.8% respectively) were sustained at Year 5 (88.5%, 66.4%, and 41%).<sup>6</sup>
- **Recapture of Response:** 95% of secukinumab patients recaptured PASI 75 response within 12 weeks when re-treated following treatment withdrawal.<sup>11</sup>
- **Comprehensive Treatment:** Novartis is committed to the treatment of the whole patient and thus has undertaken dedicated trials to demonstrate the efficacy of secukinumab in patients with moderate-to-severe psoriasis that are difficult to treat or of great interest to physicians.
  - **Clear skin:** In head to head, randomized clinical trials, secukinumab demonstrated superior efficacy to both etanercept and ustekinumab and showed an early impact on symptoms within 4 weeks.<sup>12,13</sup>
  - **Challenging to Treat Areas:** In three separate clinical studies of challenging to treat areas (nail, scalp, and palmoplantar), secukinumab demonstrated significantly greater response rates versus placebo at week 12.<sup>2,14</sup> These are the first three studies to demonstrate efficacy specifically and prospectively in challenging to treat patients, rather than relying on secondary analyses of subgroups captured within broader trials.
  - **Concomitant Active Psoriatic Arthritis and Disease Modification:** A majority of patients with psoriasis concomitant with active psoriatic arthritis achieved PASI 75 and PASI 90 at time points up to 52 weeks; with significantly more patients achieving PASI 75 and PASI 90 with secukinumab than with etanercept.<sup>15</sup> Additionally, in patients with active psoriatic arthritis, secukinumab has demonstrated significant improvements in radiographic progression, enthesitis, and joint damage, suggesting the potential to improve important aspects psoriatic disease.<sup>16</sup>

Below are recommendations for the draft report content, to further enhance the review and more accurately represent secukinumab's profile described above.

## *Comparative Clinical Effectiveness*

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**ICER should include the 16-week primary endpoint efficacy results for the CLEAR trial.** The CLEAR trial, comparing secukinumab directly to ustekinumab over a 52-week period, assessed its primary outcome at 16 weeks. Secukinumab achieved superior PASI 90 (79.0% vs 57.6%) and PASI 100 (44.3% vs 28.4%) than ustekinumab at week 16.<sup>13</sup> The PASI data provided in Table 3.1 in the draft report is from the CLEAR study; however, the 12-week data are reported, rather than the 16-week primary endpoint. Consistency should be applied when using the primary endpoint from clinical trials, as it impacts the network meta-analysis (NMA) results for secukinumab.

**The CLARITY trial should be included in the network meta-analysis.** Novartis has previously shared evidence from the CLARITY trial (head-to-head clinical trial of secukinumab vs. ustekinumab) with ICER<sup>17</sup>, but CLARITY was not included in the current network meta-analysis (NMA; Table 3.1; All Phase III Studies). Evidence from the grey literature was included for other drugs (specifically, risankizumab) in the NMA; therefore, grey literature data on CLARITY should also be included. With the addition of evidence from CLARITY, results in Table 3.9 (ICER Evidence Ratings for Available Head-to-Head Trials) should strengthen the evidence to A/B+ from C+ for secukinumab vs. ustekinumab. The NMA does not support the statistically significant difference between secukinumab and ustekinumab performance at 16 weeks. However, these non-significant results depend on the model choice and the focus on short-term outcomes in the NMA. Large, well-designed RCTs over longer-term time horizons such as CLEAR and CLARITY should be highly rated in the hierarchy of evidence. Additionally, data from the CLEAR<sup>7,13,18</sup> and CLARITY<sup>17</sup> head-to-head trials of secukinumab vs. ustekinumab, also previously shared with ICER, should be added to Table 3.6 (DLQI Outcomes Across Direct Comparative Trials).

**ICER should clarify the trials with active comparators in Table 3.1.** In the first section of Table 3.1 (All Phase III Studies), it would be helpful for payers, policymakers, and other stakeholders to better utilize this table if ICER would visually differentiate the trials with active comparators from the trials without active comparators. We recommend a simple revision to the table such as adding a footnote or italicizing the names of the trials with active comparators.

**The epidemiology of hard-to-treat areas of psoriasis should be described in the background section.** Hard-to-treat areas, such as scalp, nail involvement, and palmoplantar psoriasis, affect 47% of psoriasis patients and are particularly burdensome, impacting daily mental and physical well-being and affect overall quality of life.<sup>19,20,21</sup> Although treatments for these populations are not independently evaluated in ICER's report, we recommend that ICER highlight the epidemiologic information of these subpopulations of psoriasis patients in section 1.1 (Background) to draw attention to the potential severity of disease among psoriasis patients.

**Rates of injection site reactions should be reported.** Novartis has previously recommended that ICER include rates of adverse events (AEs) in the NMA. While we understand that ICER did not include infection or serious infection as AEs in the NMA due to similar rates amongst the most recently available treatments, we continue to recommend including injection site reaction rates in the evaluation of AEs in the NMA, as rates of injection site reactions vary. A recent analysis<sup>22</sup> compared AEs across Phase III placebo-controlled or head-to-head randomized controlled trials and found significant differences in injection site or infusion reaction rates by treatment (Table 2). For example, adalimumab, etanercept, infliximab, and ixekizumab all had rates in excess of 10%, while secukinumab, brodalumab, and apremilast (an oral treatment) had rates equal to or below 1%. We recommend that ICER incorporate the rates of injection site reaction according to this analysis in the NMA and report these rates in the body of the report.

## *Long-Term Cost Effectiveness*

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**The scenario analysis which incorporates productivity impacts should serve as the base case.** Novartis appreciates that ICER has taken steps to incorporate productivity into the evaluation of treatments for psoriasis. The academic literature has increasingly recognized the importance of including productivity in cost-effectiveness analysis.<sup>23,24</sup> Productivity is especially important to consider for patients with psoriasis, as increases in PASI response correspond to improvements in work productivity.<sup>18,25</sup> As such, we recommend that ICER use the inclusion of productivity costs and benefits scenario analysis as the base case in the final report (Table 4.9 Inclusion of Productivity Offsets).

**ICER should conduct a probabilistic sensitivity analysis.** Probabilistic sensitivity analyses (PSAs) permit an assessment of the overall level of uncertainty in cost-effectiveness models and are standard practice in cost-effectiveness analysis.<sup>26</sup> ICER has conducted PSAs for the last several product reviews (e.g., CAR-T, Voretigene, Neparvovec, Tardive Dyskinesia, low back pain). ICER indicated they would conduct a PSA in this review in the model analysis plan, but none was included in the draft evidence report. To align with the existing literature supporting PSAs in cost-effectiveness analysis and to maintain consistency across past and future evaluations, ICER should conduct a PSA for the psoriasis update and include the methodology and results in the final report.

There are two specific components of the deterministic results in the report that highlight the need for a PSA. First, the sensitivity analysis in which patients remained on IL therapy over a lifetime time horizon (Table G10; Results Comparing Each Drug to Non-Targeted Therapy Using A Lifetime Time Horizon). There are significant differences in rank order between the base case 10-year time horizon and the lifetime time horizon: specifically, secukinumab ranks 6<sup>th</sup> of 10 in the former, but 1<sup>st</sup> in the latter. This suggests that the results are highly sensitive to the choice of time horizon. Psoriasis is a lifetime chronic disease with the average age of onset ranging from 20 to 30 years. As such, we believe that a lifetime horizon would be more consistent with the epidemiology of the disease. However, if ICER maintains the 10-year time horizon, we request that ICER include a written justification of that choice for the base case.

Second and more generally, we observe that the base case cost per QALY estimates all occur in a tight band between \$100K and \$150K; this is particularly true for the therapies with the six lowest cost per QALY values. We believe that a high degree of uncertainty exists in the relative rankings of these therapies, and a PSA would permit a formal assessment of how much uncertainty exists in these rankings.

**ICER should expand the range of one-way sensitivity analyses.** Novartis appreciates that ICER tested the sensitivity of the results to many of the key model assumptions. However, there are two assumptions described in Table 4.2 (Key Model Assumptions) that have not yet been evaluated via one-way sensitivity analyses. The first is the assumption that 75% of patients discontinuing first line targeted drug therapy receive second line targeted therapy and the remainder of patients receive non-targeted therapy. The second is the assumption that second-line targeted treatments have a 10% lower probability of achieving PASI 75-100. We recommend that ICER perform these one-way sensitivity analyses for the final evidence report.

**The drug-specific dose calculations should be revised to correspond to the appropriate dosing schedules.** We believe that ICER has inconsistently reported the data in Table 4.4 (Drug Cost Inputs) according to the inputs from Table 4.1 (Medication Dosing Schedules). Specifically, it appears that the results of the calculations of “Cost of first year” and “Annual cost of year 2+” may have been obtained by converting the dosing schedules to approximate months, and then applying these dosing levels to the net price per unit as detailed in Table 4.4. We recommend that ICER revise the “Cost of first year” and “Annual cost of year 2+” to account for the exact weekly dosing schedule from Table 4.1, accounting for 52 weeks per year.

We assessed for this inconsistency by calculating the doses per year in year 1 and in years 2+ using three different methods. First, we utilized the data in Table 4.1. To determine the number of doses in year 1, we

divided the weeks per year by frequency of dose, subtracting the weeks included into the initial dose of the drug and adding the number of doses required during those weeks. Using secukinumab in an example, this would be 1 dose of 300 mg every 4 weeks after an initial period of 1 dose every week at weeks 0-4. This would amount to  $((52-4)/4)+5 = \mathbf{17 \text{ doses per year}}$ . In year 2+, using the maintenance dose, we divided the number of weeks per year by the frequency of dose. This would be  $52/4 = \mathbf{13 \text{ doses per year}}$  for secukinumab. Second, we calculated doses per year if we converted the weeks from Table 4.1 to months, assuming 4 weeks per month and 12 months per year. We converted the dosing schedule from weeks to months and calculated the doses per year, including the time and doses required for medication initiation. With this method, we calculate the secukinumab doses per year for year 1 as  $(12-1)+5 = \mathbf{16}$  and for years 2+ as  $\mathbf{12}$ . Finally, we calculated the doses per year based on cost data in Table 4.4. For both year 1 and years 2+, we divided the respective cost per year by the net price per unit. With secukinumab as the example, the number of doses in the first year was calculated as  $\$43825.13/\$2926.22 = \mathbf{15}$ ; the number of doses per year in years 2+ would be  $\$35060.11/\$2926.22 = \mathbf{12}$ . The three methods were applied to all the medications included in Tables 4.1 and 4.4, and results from our calculations can be found in Table 1 below. Based on these calculations, ICER has underestimated the number of doses per year for all 10 therapies.

We also recommend that ICER revise the certolizumab pegol maintenance dose in Table 4.1 from 400 mg per month to 400 mg every 4 weeks, as it appears on the FDA label (Food and Drug Administration, 2017). These adjustments will allow ICER to depict more accurate cost of individual treatments based on their respective approved dosing schedules.

### *Transparency of Net Price Changes*

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#### **There is limited transparency into how drug-based discounts were derived.**

We compliment ICER for continuously improving their methodology and trying to focus on net prices rather than using WAC. Using WAC is neither reflective of the actual price paid by payers nor the market place at large. As ICER moves from class-based discounts to drug-based discounts, however, weaknesses in the methodology used to calculate net prices become more apparent, which ICER is able to address by providing more clarity around how these discounts are formulated. In particular, the following issues below should be addressed, as they will impact net prices calculated at a drug level:

- ***Rebates vary by indication:*** For drugs with multiple indications, rebates can vary based on indication. If overall sales are used (and not sales by indication), this could lead to an average of rebates across all indications, not the true net price for a specific indication.
- ***Free drug programs are reported differently by companies:*** Different companies report their free drug programs differently and have changed their reporting of these programs over time. This could lead to incorrect estimations of total units distributed and would limit the validity when deriving net prices both at the class and drug level.
- ***Price protections are common in contracts:*** It is critical to disclose the time frame over which the rebates are being calculated as price protections are in place which shield payers from reported list price increases. Without knowing the time frame over which the net prices are being derived, it is hard to assess the accuracy of the net price calculations.
- ***Total covered lives not mentioned:*** ICER currently represents access by focusing on benefit design. It is important to also capture total covered lives in each tier by product. While we appreciate that the current net price is supposed to serve as a high-level population average, ICER should consider reporting the number of lives with access to each therapy to help contextualize the net price against total lives covered to ensure it has not been heavily distorted.

## *Effect of Net Price Changes*

### **Net price increase calculations between 2016 and 2018 are not directly comparable.**

There is limited validity to calculating the change in net price between 2016 and 2018 as these net prices were derived differently. The 2016 calculation was derived from class-based discounts, whereas 2018 was derived from drug-based discounts. It is not an accurate comparison based on the changes we are aware of (the change from class to drug based discounting) and providing additional transparency into the net price calculations (as mentioned above) would allow for better understanding on SSR Health's methodology used in the 2016 and 2018 report.

### **Increases in net price for drugs between 2016 and 2018 do not have face validity.**

Novartis is committed to providing psoriasis patients access to secukinumab and has been successful in increasing this access since launch. As written, the decrease in discounts and the increase in net price for secukinumab from the 2016 report to the 2018 report lack face validity as increase in access is not taken into account. This is the case because within highly competitive therapeutic areas with heavy competition for patient access, net drug prices were flat due to rebates for increased access, according to a 2017 report.<sup>27</sup> Thus, the decrease in net discount between 2016 and 2018 would not be realistic, as secukinumab made significant improvements in access within that time frame due to increased competition for first and second line patients (ICER report Table 2.1).

Table 1. Number of doses per year for year 1 and years 2+ for each therapy calculated using three methods

Drug	Doses per year Year 1 (Weeks)	Doses per year Year 2+ (Weeks)	Doses per year Year 1 (Months)	Doses per year Year 2+ (Months)	Doses per year Year 1 (Cost)	Doses per year Year 2+ (Cost)
Adalimumab	27	26	25	24	26	24
Apremilast	725	730	677	672	671	676
Brodalumab	28	26	26	24	25	24
Certolizumab pegol	15	13	14	12	14	12
Etanercept	66	52	64	48	60	48
Guselkumab	8	7	8	6	7	6
Infliximab	44	33	41	30	40	30
Ixekizumab	18	13	17	12	17	12
Secukinumab	17	13	16	12	15	12
Ustekinumab	6	4	6	4	7	5

*Calculations from independent Novartis analysis*

Table 2. Adverse events reported during the induction period of Phase III placebo-controlled or head-to-head RCTs

	adalimumab	etanercept	infliximab	ustekinumab	secukinumab	ixekizumab	brodalumab	apremilast	placebo
Any AE	65%	57%	71%	53%	58%	58%	58%	69%	52%
Injection site/infusion reactions	19%	14%	10%	4%	-	10%	1%	-	9%
Infection	32%	27%	36%	36%	29%	27%	-	-	25%
Headache	6%	7%	13%	7%	6%	4%	4%	6%	4%
Nausea	4%	2%	4%	-	5%	-	-	17%	4%
Serious AE	2%	2%	3%	1%	2%	2%	1%	2%	2%

*Table adapted from Loos et al, 2018.*

## References

Where legally able (as copyright and data embargos permit), Novartis is happy to share posters that are not available online after the conclusion of congresses.

1. Armstrong AW, Schupp C, Wu J, Bebo B. Quality of life and work productivity impairment among psoriasis patients: findings from the National Psoriasis Foundation survey data 2003–2011. *PloS one* 2012;7:e52935.
2. Cosentyx (secukinumab) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018.
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## **Sun Pharmaceutical: Public Comment on Psoriasis Condition Update**

Sun Pharmaceutical would like to thank ICER for the opportunity to provide input on the New England CEPAC draft evidence report on targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis.

We have the following three primary concerns regarding the ability of the report to reflect a full and fair evaluation:

1. Use of 12-week data significantly underestimates the benefit of tildrakizumab
2. Include the available long-term safety data for tildrakizumab
3. The ICER economic evaluation is highly sensitive to net price per unit – need to simulate additional discount rate scenarios for newer treatments

### **Use of 12-week data significantly underestimates the benefit of tildrakizumab**

The current use of 12-week efficacy data for tildrakizumab underestimates the benefits of tildrakizumab relative to its clinically demonstrated longer-term efficacy. In the reSURFACE 1 and 2 trials, week 12 is only 8 weeks after the 2<sup>nd</sup> dose – tildrakizumab was dosed at weeks 0 and 4, then every 12 weeks with the 3<sup>rd</sup> dose at week 16.[1] At 12 weeks, patients have not yet had the opportunity to be on treatment for a sufficient time to achieve maximal efficacy. Pooled data from reSURFACE 1 and reSURFACE 2 demonstrated that the efficacy of tildrakizumab improved continuously from week 12 to week 28. (Figure 1).[2] Only 8.3% of patients did not achieve at least PASI 50 by week 28. Starting from week 8, there was no overlap between the individual PASI categories. Patients consistently on tildrakizumab 100 mg between week 28 and week 52 demonstrated continuous and sustained PASI improvements over time, including those achieving PASI 50-74 at week 28 with an average of 76.5% PASI improvement at week 52 (Figure 2).[2] The majority of patients who achieved week-28 PASI $\geq$ 75 or PASI $\geq$ 90 maintained PASI $\geq$ 75 or PASI $\geq$ 90 at week 52, and more than half of partial responders (PASI 50-74) at week 28 eventually achieved PASI $\geq$ 75 and at least 1 in 5 achieved PASI $\geq$ 90 at week 52 (Figure 3).[3]

While the efficacy endpoint used for other treatments occurs at 12-16 weeks, most treatments are at or near their maximal efficacy at that point. For tildrakizumab, week 12 is too early for maximal efficacy (8 weeks at the 2<sup>nd</sup> dose), leading to significantly underestimated clinical benefits of tildrakizumab. Moreover, the use of a 12/16 week cut-off biases the results towards treatments that have more frequent initial doses and more frequent maintenance doses (i.e., every 2 or 4 weeks rather than every 12 weeks), but whose efficacy may not be sustained over long term.[4] Using short-term efficacy to evaluate the long term comparative effectiveness of treatments (such as a 10 year time horizon) has a serious limitation, as this does not take into account the sustainability of long-term efficacy, an important criterion when determining the optimal treatment options in psoriasis management.

Real world studies have demonstrated that psoriasis treatments have differential drug survival and can have high discontinuation rates. In a recent analysis of the DERMBIO registry that evaluated secukinumab, ustekinumab, adalimumab, etanercept, and infliximab, secukinumab (with the highest rate of early attainment of PASI 100) had the lowest drug survival and the highest likelihood of adverse events while ustekinumab (every 12 weeks of maintenance dosing) had the highest drug survival.[4] Similarly, in a retrospective observational claims database analysis recently presented at the Academy of Managed Care Pharmacy meeting, secukinumab had the highest discontinuation rate (54.6%) within 60 days of treatment initiation followed by adalimumab (42.1%), apremilast (31.4%), ustekinumab (18.7%), etanercept (17.3%), and infliximab (13.4%).[5] ICER used short-term efficacy (i.e., 12-16 weeks) to determine the discontinuation rate for the first-line treatments, which also

biases results in favor of drugs such as secukinumab and adalimumab which have high early rates of success but also high discontinuation rates and low drug survival, and against drugs such as ustekinumab and tildrakizumab which have lower very early response rates but longer drug survival and lower discontinuation rates.

Partial responders to tildrakizumab improve in efficacy over time, so it is inappropriate to assume that patients achieving PASI 50-74 percent improvement discontinue after first-line initiation (Figures 1-3).[2, 3] In a real-world setting, physicians will likely maintain treatment for “partial responders” (who achieve PASI 50-74 improvement from baseline) at week 12 for tildrakizumab. For tildrakizumab, ICER should consider using PASI 50 achievement as the threshold for discontinuation rather than PASI 75. According to a European consensus, "treatment success is defined as a decrease in PASI score of 75% or greater that allows for treatment continuation; treatment failure is defined as a decrease in PASI score of less than 50% that necessitates a change in treatment regimen. An intermediate response of decrease in PASI score of 50% or greater but less than 75% with DLQI score 5 or less can lead to continuing current treatment, whereas a decrease in PASI score of 50% or greater but less than 75% with DLQI score greater than 5 warrants modifying treatment regimen." [6] This issue is further compounded when the first-year discontinuation rates cited by ICER (37.7% for tildrakizumab) are based on 12-16 week efficacy data in the NMA. This becomes a significant issue for tildrakizumab as its efficacy, particularly amongst early partial responders, improves over the course of the first year. If ICER were to use tildrakizumab's efficacy beyond week 12, the discontinuation rate for tildrakizumab could be as low as 8.3% for patients not achieving PASI 50 at week 28. Due to these reasons, the induction period listed 12 weeks for tildrakizumab in Table 3.1 of the ICER draft evidence report is misleading.

### **Include the available long-term safety data for tildrakizumab**

Tildrakizumab has a demonstrated improved long-term safety profile based on a pooled analysis of 3 randomized controlled studies (1 phase 2: P05495, and 2 phase 3: reSURFACE 1 and reSURFACE 2).[7] The following safety data for tildrakizumab should be included in the ICER report. Over 52 weeks (P05495 and reSURFACE 2) or 64 weeks (reSURFACE 1), exposure adjusted rates showed that patients on tildrakizumab 100 mg experienced fewer treatment-emergent adverse events (TEAEs) (77.0 per 100 person-years vs. 153.5 and 148.6, respectively) than placebo and etanercept (ETN) (Table 1).[7] Tildrakizumab also had significantly fewer treatment-related AEs, serious AEs, treatment related serious AEs, and discontinuation due to TEAE than etanercept.[7] Safety is an important factor for patients in making treatment decisions. The cost of adverse events should be included in the quantitative evaluation in the base case, not just as scenario analyses. Without accounting for adverse events, the economic evaluation of these treatments becomes primarily a price-driven exercise for the drug alone.

### **The ICER economic evaluation is highly sensitive to net price per unit – need to simulate additional discount rate scenarios for newer treatments**

Because the ICER economic evaluation is highly sensitive to net price per unit, the discount rates applied to the treatments evaluated have a significant impact on the cost-effectiveness results. Currently, for treatments that have not been on market sufficiently long to have calculable discounts, ICER used an average of the discounts for the other treatments. This is arbitrary as the report identifies how heterogeneous the discounts are. Additionally, applying the average discount necessarily disadvantages newer treatments compared to older treatments as the ICER cost-effectiveness results are extremely sensitive to the net price per unit (after price discount is applied) which determines the total net cost over 10 years. To help account for this bias, ICER should: 1)

provide results using a spectrum of discount estimates in the base analysis when there is no reasonable assumption that can be made to determine a more precise discount rate; and 2) update the scenario analysis using WAC pricing in table G9 to reflect inputs and assumptions of the current analysis, not the original 2016 numbers, and add the results for guselkumab and certolizumab pegol. Generally, the appendix should be reviewed to ensure all tables and scenario analyses have been updated to the current analysis.

### **Additional Corrections**

- Table 3.2: PASI 90 for tildrakizumab should be 35-39
- Network Meta-Analysis of PASI Results
  - Page 32: “These agents were followed by ustekinumab 45/90 mg, adalimumab, tildrakizumab, certolizumab and apremilast, respectively” - Ustekinumab 45/90 mg, adalimumab, tildrakizumab, and certolizumab were not statistically different for PASI 75 comparisons, and all were significantly superior to etanercept and apremilast (see Table 3.5). Please update the report accordingly.
  - 70/30 split for ustekinumab 45 mg and 90 mg: does not reflect the real world utilization as this was based on its early clinical trial setting.

We would also recommend the following changes to improve the ability of the evaluation to reflect real world treatment practices.

### **Transparently describe the parameters, assumptions, and inputs used for the threshold pricing calculation for tildrakizumab and risankizumab.**

Currently, the parameters, assumptions, and inputs used to calculate the threshold price for tildrakizumab and risankizumab are not included in the report due to unavailability of a WAC price. However, this makes it difficult to assess the accuracy of these elements and therefore the resultant calculated outcomes. We recommend including all the components for the calculation alongside the other drugs.

### **List the threshold price for one cycle on the regimen for all treatments.**

Providing the per unit threshold price for most drugs and the monthly threshold price for risankizumab makes it difficult to interpret the threshold prices for each treatment. We recommend providing the threshold prices calculated for a comparable regimen across all treatments, allowing for apples-to-apples comparisons of the threshold price estimates.

### **Include the cost of dose escalation in the base case**

Currently dose escalation is only included as a scenario analysis. However, to reflect real-world practices, it is important to include dose escalation costs as part of the base case. Many products have real-world dose escalation, as noted in ICER’s 2016 psoriasis review. Feldman et al 2017 showed that 20%, 2.6%, and 14.8% of patients treated with etanercept, adalimumab, or ustekinumab respectively had extended above or beyond label use in terms of dose escalation ( $\geq 180$  days over a 12-month follow up) that increased costs per day (etanercept: \$69; adalimumab: \$68; ustekinumab: \$64).[8] This resulted in additional annual costs per patient: \$19,458, \$18,972, and \$21,045 for etanercept, adalimumab, and ustekinumab.[8] In a recent analysis of the DERMBIO registry, 35%, 39%, 22.7%, and 20% of patients were treated with a higher dose of adalimumab, etanercept, infliximab, and ustekinumab than the EMA-label dose during the first 24 weeks of therapy (including the induction dose), and the EMA-label dose was exceeded in 0.9%, 35.1%, 56.7% and 46.2% of patients in the maintenance period (weeks 25-52), respectively.[4]

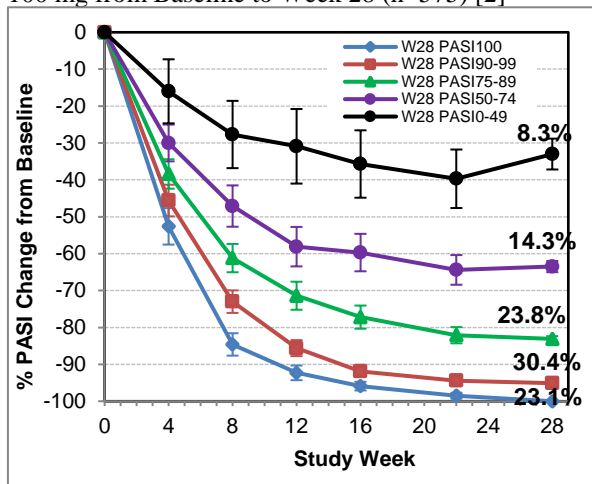
**An NMA without placebo-adjusted results should be presented as a sensitivity analysis.**

Placebo-response adjustments remedy increasing placebo-response over time, but introduce risks. Placebo-response is influenced by both effect modifiers (which change the relative efficacy of treatments, such as prior treatment experience) and prognostic factors (which affect outcomes, but not relative treatment effects). It is unclear what factors are being adjusted for, and over-correction and the introduction of new bias may occur. Further, eligibility creep is more acute for rheumatic diseases than psoriasis. It is thus vital that an NMA without adjustment be included alongside these analytical results so that readers can understand the impact of the assumptions and modelling decisions that have been made.

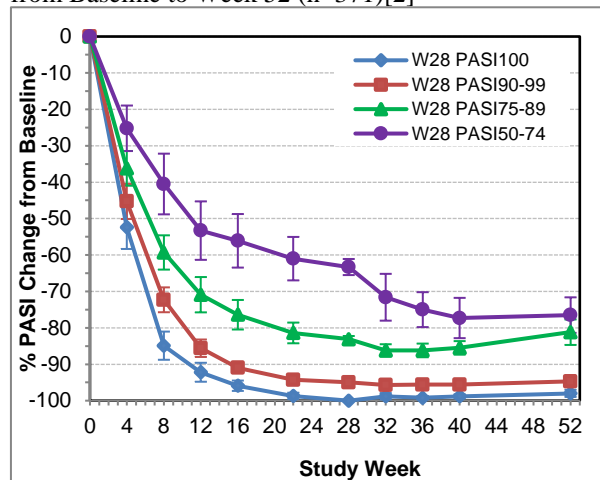
**Adjust parameter values for inflation.**

A few parameter values, including hospitalization for pneumonia and productivity improvement, were taken from the 2016 review. These values should be adjusted for inflation.

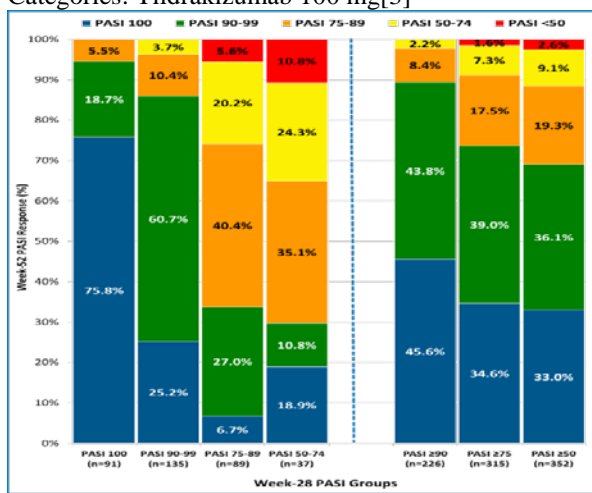
**Figure 1:** % PASI Change from Baseline by Week-28  
 PASI Categories: Patients Consistently on Tildrakizumab 100 mg from Baseline to Week 28 (n=575) [2]



**Figure 2:** % PASI Change from Baseline by Week-28 PASI Categories: Patients Consistently on Tildrakizumab 100 mg from Baseline to Week 52 (n=371)[2]



**Figure 3:** Week-52 PASI Responses by Week-28 PASI Categories: Tildrakizumab 100 mg[3]



NOTE for Figures 1-3. Pooled data from reSURFACE1 and reSURFACE2 for patients consistently on tildrakizumab 100mg from baseline to week 28. Mutually exclusive groups were created based on patients' week 28 PASI responses.



**Table 1. Summary of adverse events in the placebo-controlled and full-trial periods (all patients as treated)[7]**

	Placebo-Controlled Period, n (%)				Full-trial period, Exposure-Adjusted Rate (Patients/100 Patient Years [95% CI])			
	TIL 100 mg (n=705)	TIL 200 mg (n=708)	Placebo (n=355)	ETN 50 mg (n=313)	TIL 100 mg (n=1083)	TIL 200 mg (n=1041)	Placebo (n=588)	ETN 50 mg (n=313)
TEAE	340 (48.2)	399 (47.9)	191 (53.8)	169 (54.0)	77.0 (74.0, 79.9)	79.3 (76.1, 82.4)	153.5 (142.5, 164.4)	148.6 (137.8, 158.5)
Treatment-related AE	104 (14.8)	99 (14.0)	47 (13.2)	92 (29.4)	23.3 (20.7, 26.1)	25.5 (22.4, 28.2)	37.9 (30.6, 4.2)	73.0 (62.2, 84.4)
Serious AE	10 (1.4)	16 (2.3)	6 (1.7)	7 (2.2)	5.8 (4.4, 7.5)	7.2 (5.6, 9.1)	6.4 (3.5, 10.6)	13.0 (8.1, 19.8)
Treatment-related serious AE	0	3 (0.4)	0	2 (0.6)	0.3 (0.1, 0.9)	1.0 (0.4, 1.8)	0.9 (0.1, 3.3)	3.3 (1.1, 7.5)
Discontinued due to TEAE	4 (0.6)	9 (1.3)	4 (1.1)	6 (1.9)	2.2 (1.4, 3.3)	2.2 (1.3, 3.3)	2.3 (0.7, 5.3)	5.9 (2.7, 11.0)
Discontinued due to treatment-related AE	1 (0.1)	3 (0.4)	2 (0.6)	4 (1.3)	0.8 (0.3, 1.6)	0.9 (0.4, 1.7)	0.9 (0.1, 3.3)	2.6 (0.7, 6.6)

NOTE AE, adverse event; ETN, etanercept; TEAE, treatment-emergent adverse event; TIL, tildrakizumab. These results are based on pooled analysis from 3 randomized controlled studies: P05495 (52 weeks), reSURFACE 1 (64 weeks), and reSURFACE2 (52 weeks).

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May 25, 2018

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**RE: Comments on Draft Evidence Report** (*submitted electronically via: c-segel@icer-review.org*)

Good Afternoon Celia,

We would like to thank the ICER team on the opportunity to comment and provide feedback on the ongoing psoriasis condition update. Please find below UCB comments on the draft evidence report.

### **Major comments and questions**

1. (Page 69) UCB would like to raise the following concerns regarding the methods and assumptions used in the budget impact analysis.
  - UCB questions the assumption that certolizumab pegol would displace non-biologics. In the current healthcare landscape, use of non-biologic therapies are often required prior to biologic approval. It is thus more likely that certolizumab pegol will be initiated in psoriasis patients for which non-biologic therapies are no longer effective, contraindicated, or not tolerated, or will displace market share of other biologics where the clinical determination that a biologic (whether first or second-line) is needed. UCB thus considers that the budget impact estimates from the ICER report are inflating the budgetary impact of certolizumab pegol and would caution their use in any decision-making process.
  - UCB suggests expanding the candidate psoriasis population from the incident population alone to a mixed population of incident and prevalent psoriasis patients. This is aligned with the comment above regarding the displacement assumptions for certolizumab pegol and in acknowledging that anti-TNF therapy is still a common treatment option among current biologic patients.
  - Can ICER provide clarification on how the CEA results were used in the budget impact model? Were any assumptions used in the CEA such as discontinuation, displacement, treatment sequences, etc. applied directly or indirectly to the budget impact analysis?
2. (Page 65) In the concluding paragraphs of the ICER report, phrases such as ‘similar effectiveness’, ‘highest effectiveness’, and ‘considerably more effective’ are used without any clear definition of how these parameters are being defined. Several questions arise as to what effectiveness metric is being compared (QALY, cost/QALY, months in PASI90+/75+) but more importantly, the differences between agents that constitute them to be similar or not. Furthermore, the metrics being considered are limited to certain outcomes, and do not capture all the clinical benefits of some agents, including certolizumab pegol, benefits which are not captured in the analysis conducted by ICER. UCB considers that these statements ultimately



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introduce bias toward some agents by implying that they are not effective, which is not consistent with the clinical results, nor the ICER analysis of these agents. Consequently, UCB suggests that the referred statements are revised and contextualized, to provide an unbiased view of the efficacy of all agents. This is especially important as panelists will later vote on the comparative effectiveness of the biologics available for the treatment of psoriasis.

3. (Page 18, Table 2.1) Since certolizumab pegol is not currently approved for psoriasis and Table 2.1. summarizes the benefit design for treating moderate-to-severe plaque psoriasis, can ICER provide further clarification on how this assessment was completed? Aligned with risankizumab and tildrakizumab it seems more appropriate to provide a statement for certolizumab pegol acknowledging that coverage for psoriasis is currently unknown. UCB recommends that the information mentioned in Table 2.1 for certolizumab pegol is replaced by “Formulary status currently unknown.”
4. (Page 29) In the CIMPACT study, as per the study protocol, the initial treatment for etanercept was through week 12 and for certolizumab pegol the initial treatment continued through week 16. All patients were re-randomized at week 16. Can ICER confirm that week 16 efficacy response rates were used from the CIMPACT in the ICER analysis, as recommended in the UCB response that included the CIMPACT trial data? UCB suggests utilizing the 16-week efficacy data for certolizumab pegol from CIMPACT, to ensure consistency with the efficacy data to be used from the other two pivotal studies, CIMPASI 1 and 2.
5. (Page 29) In the last statement, UCB suggests including the results for certolizumab pegol 400mg Q2W dose, for which the data was provided. Also, for consistency we recommend that it is included with the results included on page 30, which indicated statistically significantly higher PASI 75 response for certolizumab pegol 400mg Q2W compared to etanercept.
6. (Page 31, Table 3.3) UCB would like to note that the certolizumab pegol data from the CIMPACT study is inaccurate. The PASI 75 response rates are swapped for etanercept and certolizumab pegol. The text should indicate 53% for etanercept and 61% certolizumab pegol.
7. (Page 43) UCB would like to note that in the CIMPACT study, both certolizumab pegol doses have been compared to etanercept. For consistency with the study design and to accurately reflect the results, the statistically significant results of CZP 400mg Q2W compared to etanercept should also be mentioned. UCB thus suggests making note of the improved outcomes achieved with the CZP 400mg dose compared to etanercept.
8. (Page 48, Table 4.1) UCB would like to note that certolizumab pegol is currently under review with FDA and the target posology includes two dosing regimens for CZP.
  - Consequently, UCB requests the addition of certolizumab pegol 400mg Q2W dose in the maintenance dose, alongside the existing dose.



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- UCB would also like to note that the existing text in Table 4.1 for the maintenance dose of CZP (“400mg once a month”) is inaccurate as it does not reflect the submitted posology. UCB requests that the text is revised to “200mg Q2W” for consistency with the submitted posology.

## **Other comments and questions**

### Section 3.3 - Results

9. (Page 32) In the interpretation of the results, the ICER report labels certain biologics as being “top performers”. UCB considers this terminology to be misleading. While the results indicate that some of these agents may have had the highest proportion of patients reaching different PASI thresholds, differences in RR listed in Table 3.4 were nominal, raising the question if any clinically meaningful differences would be expected. Furthermore, as per the ICER report (page 30), given that most of the PASI 50 data was missing, it is not clear how these comparisons were made. Lastly, at this juncture in the report, it is still unknown how these agents compare in the cost-effectiveness analysis, from a cost/QALY standpoint, thus it is quite premature to draw any conclusions regarding the ranking of these agents. UCB thus suggests that the report is revised to allow the data to drive the discussion without the use of terminology that may lead to bias.
10. (Page 40, Table 3.7) UCB suggests the addition of a clear context to accompany this table summarizing the adverse events. Given the difference between the study designs, in terms of duration of the initial placebo-controlled phase, definitions (especially how adverse events were defined across the different trials) and methodologies related to the assessment of safety events, it is important that the table also captures information regarding the drug exposure and length of the study period. We also recommend including the total number of patients assessed and number of adverse events in addition to the percentages provided.
11. (Page 45, Table 3.9) UCB would like to seek clarity on why certain grades in this table were bolded, as this is not provided in the report.
12. (Page 53, Table 4.4) Previous reports have assumed flat discount rates for agents within the same biologic class, however the current discount levels seem to differ among biologics. Could ICER provide clarity on how were the discount rates in the draft evidence report determined?
13. (Page 57) UCB considers that conclusions derived based on ‘initial treatments’ are misleading and should be removed. As indicated in the ICER report, “The results below should be interpreted not as treatments with a single targeted drug, but as sequences of targeted drugs.”, thus in an evaluation of psoriasis therapies over a 10-year period, all lines of therapies ultimately influence differences in overall QALYs. While we acknowledge the importance of choosing the most optimal first-line therapy to increase the odds of treatment durability, specific assumptions were made regarding the selection of second-line therapies, which were not consistent across all agents, thus not all possible sequences (i.e. consecutive anti-TNF use), that is used in real-world clinical practice, have been assessed.





**UCB, Inc.** - 1950 Lake Park Drive - Smyrna, Georgia 30080

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

Sincerely,

*Mohamed Yassine*

Mohamed Yassine, MD  
Head of US Medical Immunology  
UCB, Inc.  
770.970.8858  
Mohamed.Yassine@ucb.com

Dear Sirs:

I am writing to comment on the update of your psoriasis report. I am a past president of the American Academy of Dermatology, past chairman of the Medical Board of the National Psoriasis Foundation, and current chairman of the Department of Dermatology at the Icahn School of Medicine at Mount Sinai where we perform numerous clinical trials supported by most of the companies that make psoriasis products.

I am writing to ask you to reconsider your placement of apremilast in a different category than biologic therapies for psoriasis. Unlike biologics, apremilast is an oral therapy that offers a different kind of therapeutic option for our patients. It is not a biologic; is not administered by injection; and requires no laboratory monitoring.

Indeed it could be compared to the other oral agents available for psoriasis, all of which have significant drawbacks. Cyclosporine has numerous side effects including hypertension and kidney damage, in fact, nephrosclerosis occurs in 100% of patients who are administered cyclosporine for two years. For that reason, the United States guideline and package insert recommend that it not be used for more than a year total. Methotrexate has numerous black box warnings and requires frequent laboratory monitoring and even liver biopsy. It is hepatotoxic, but most of the deaths associated with it are due to bone marrow toxicity. In one study of patients enrolled in controlled clinical trials of methotrexate for rheumatoid arthritis, the frequency of pancytopenia or death was 1.4%. Acitretin is only modestly effective for psoriasis, and is associated with numerous mucocutaneous effects including hair loss which occurs in a significant proportion of patients. Of the four oral drugs available for psoriasis, only methotrexate is affordable by most patients, as the others all cost thousands of dollars. Cyclosporine and acitretin do not have widely used patient assistance programs, but apremilast is often provided at little or no cost by the pharmaceutical manufacturer, thus making it the only safe option for many of our patients.

It is important that the psoriasis report look at apremilast in the correct context – i.e. a safe oral therapy for psoriasis.

Sincerely,

Mark Lebwohl, MD



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

May 25, 2018

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

**RE: ICER Psoriasis Condition Update Draft Evidence Report**

Dear Dr. Pearson,

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 Evidence Report* released on April 27, 2018. We offer the following comments as part of the National Psoriasis Foundation's commitment to ensuring the perspective of individuals living with psoriatic disease are properly considered and reflected in discussions regarding the value of therapies. Included in our comments is also a discussion of soon to be released coverage trend data gathered earlier this year to understand – among other access issues – the impact of the 2016 ICER review on access to the systemic psoriasis therapies. We urge ICER to consider this information and future access conditions as part of these value assessments.

***Background on Psoriasis, Patient Insights and Continued Challenges in this Review Measures***

The NPF has reiterated consistently in teleconferences, comment letters, and public dialogues (including the November 2016 ICER public meeting on this topic) the serious nature of psoriasis and the associated significant morbidity and increased mortality.<sup>i,ii</sup> Significant attention has also been dedicated in NPF comments to the widespread prevalence of disease, and way in which it “significantly decreases health-related quality of life.” While the NPF appreciates that ICER has given greater attention to these issues in this condition update evidence report as compared to the 2016 review, on behalf of the patient community we continue to stress the challenge of measuring a chronic disease such as psoriasis with the measures (QALY, PASI, BSA, etc) and tools available today.

We have previously commented on the limitation of each of the aforementioned measures. ICER itself noted PASI limitations (p. 64) in this report. During a payer and pharmacy benefit manager roundtable hosted by the NPF in April 2018, these limitations were a large focus of discussion. Roundtable participants – payer and pharmacy benefit manager representatives – raised several concerns around Psoriasis Area and Severity Index (PASI) 75 scale, including its lack of application in clinical practice outside of academic settings, challenges in understanding the potential clinical improvement associated with a medication and an increasing lack of relevance given newer therapies able to obtain higher levels of clearance. Participants even questioned the applicability for formulary decisions of an ICER assessment with a focus on PASI 75 if a PASI 90 is

achievable. Separately, NPF medical experts have also questioned the appropriateness of including Otezla in this review, as they did in 2016, given the nature of the cost-effectiveness model and that it is the only non-biologic in the review.

#### *Subpopulations & Additional Considerations*

We were pleased to see greater discussion given in this report to the disconnect between individual patient frustrations and the focus of various outcome measures. As ICER noted, the March 2016 FDA Patient Focused Drug Development (PFDD) meeting provided great insight into the significant quality of life impacts of this disease and the challenges in trying to manage each of the symptoms – including itch and pain – that often accompany moderate to severe disease. We were pleased that the model inputs in the condition update continued 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 noted the addition of ‘satisfaction with treatment’ was new to this 2018 condition update among the domains considered.

Nonetheless, while we were pleased to see these additions, section **3.4 Summary and Comment** and **Table 3.9. ICER Evidence Ratings for Available Head-to-Head Comparisons** (included therein) do not include measures that speak to those patient perspectives. Limited mention is also given in **5. Additional Considerations** to several issues discussed during the 2016 review including patient perspectives on the route of administration of certain therapies (e.g. favoring oral therapies or preference for self-administered versus infused therapies) and frequency of administration. It is unclear to us how ICER has factored these patient preferences in to the cost-effectiveness model.

In earlier comments, the NPF urged ICER to keep individuals living with psoriatic disease at the forefront and specifically encouraged the importance of examining sub-populations in greater detail to ensure the model appropriately reflects the nuances of treating the disease for complex patients. ICER did include a limited number of items related to subgroups of individuals living with psoriasis (Asian population, patients with previous biologic therapy exposure and patients with psoriatic arthritis), and as well as disparities experienced by racial and ethnic minorities (including delayed diagnosis, more severe disease, more common misdiagnosis, and more frequent non-treatment, reduced representation in clinical trials, and lower use of biologics in Medicare compared to white patients). However, there are many more subpopulations of individuals living with psoriasis that may have been examined. Given the unique nature of the individual subpopulations of individuals living with psoriasis, and the noted lack of robust data about treatment patterns and discontinuation rates, the NPF continues to encourage ICER and those informed by this condition update to avoid treating the community as a homogenous population for which a single standard first or second line treatment decision model can be easily imposed.

#### *Policy Considerations*

The 2016 economic analyses resulted in incremental cost-effectiveness ratios across all agents that were well-aligned with commonly-accepted thresholds for cost-effectiveness. This finding of “good value” for all reviewed treatments was accompanied by 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.

In spring 2018, the National Psoriasis Foundation in collaboration with the State Access to Innovative Medicines (SAIM) coalition commissioned a study by Avalere Health to examine patient access to a select

group of therapies across public and private healthcare plans. The NPF was eager to see whether the 2016 ICER assessment that found all of the eight reviewed therapies to be “of good value” had a positive impact on patient access to these therapies. Avalere analyzed a total of 15 therapies used to treat plaque psoriasis, Crohn’s disease, arthritis, and ulcerative colitis – including all ten of the on the market treatments included in this condition update – Humira, Enbrel, Remicade, Cimzia, Stelara, Tremfya, Cosentyx, Taltz, Siliq, and Otezla. The analysis examined coverage trends including changes to formularies, tier placement, cost sharing, step therapy and other utilization management tools over a three year period (2015-2017). The plans included in the review were representative of all major health insurance markets—employer, ACA exchange, Medicare, and Medicaid.

The study findings raise concern for the NPF about the impact of the 2016 assessment.<sup>iii</sup> Among the key findings:

- Over the three years included in the study, the percentage of drugs covered by health insurers dropped in all health insurance markets.
- Newer biologic drugs are commonly placed on the highest drug tier, where cost sharing with the member is the least generous. The migration of covered biologics to the specialty tier was evident across three the years of the study.
- Health insurers are also increasingly relying on utilization management tools, e.g., step therapy and prior authorization, to limit access to covered drugs. This is true across all insurance markets, but particularly true in the employer market where only 18 percent of health plans relied on both step therapy and prior authorization in 2015, but 60 percent did in 2017.
- Partly as a result of formulary tier placement, cost sharing responsibilities on plan members can be very high. Among 2017 silver plans on the health insurance exchanges, 50 percent of biologic drugs are either uncovered or subject to very high coinsurance payments (40 percent or greater).

It is unfortunate that it appears the “access problem” may have gotten worse for individuals living with psoriasis. In many ways, there is no better time to be diagnosed with psoriasis than today given the many safe and effective therapies available. Our hope would be that individuals living with psoriasis be able to work with their provider choose the most appropriate treatment for them given their individual disease. As ICER completes this review, the NPF encourages consideration be given to recommendations that may positively improve patient access to therapies. One example may be that shared recently by Express Scripts during a panel talk on “Defining Value” hosted by The Atlantic on *The State of Care: Patient Access & Affordability*. These remarks touched new contracting procedures at Express Scripts that have created easy access for patients and given physician access to all the reviewed psoriasis therapies “in the toolbox.”<sup>iv</sup>

### ***Cost Saving Measures***

New to this update, ICER has requested information on wasteful or lower-value services in the same clinical area that may be reduced or eliminated to create budget headroom. Such recommendations are hard to identify in a chronic disease such as psoriasis. As is noted in the draft report, to date no suggestions have been received or professional society recommendations been identified. While this information is worth capturing, the NPF would reiterate the individual, personal benefits of treating moderate to severe psoriasis appropriately that – while hard to quantify – deliver significant long term individual and societal benefits. For an individual living with moderate to severe psoriasis who is under treating their disease with a topical cream, for example, to begin treating up to the standard of care would not save the system resources from a wasteful standpoint but would likely result in significant quality of life improvements and thereby likely reduce some of the indirect costs of psoriasis such as worker absenteeism or presentism.

### ***Future Considerations: Updated Guidelines***

The NPF appreciates ICER's goal of developing reports that translate evidence into decisions. Nonetheless, the timing of this update is disappointing in that it, too, will fail to include updated guidelines currently in development by the National Psoriasis Foundation and American Academy of Dermatology. As you may know, the development of guidelines is a rigorous process following an established methodology and administrative regulations. We believe that, once released, these guidelines will be highly informative to payers, providers, and patients alike. Were they available for this review, they would likely have also brought additional considerations forward for this update. It is unfortunate that timing of this update occurred so soon after the initial review such that these guidelines are not yet complete. (The NPF would additionally recommend that the use of the word "guidelines" on page 19 of the report in the discussion of the NPF Medical Board JAAD paper on treatment targets would be more accurate as "recommendations").

### ***Conclusion***

Throughout the 2016 and 2018 ICER reviews, the NPF has acknowledged 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 again believe the assessment is improved by our meaningful contributions to this condition update.

As we have previously stated, we believe 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. And to achieve that goal, we are going to need to engage every stakeholder who has an interest in the psoriatic disease community from value modelers, to payers, to pharmacy benefit managers, to physicians, to patients themselves in this dialogue. 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> Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, Treatment Trends, and Treatment Dissatisfaction Among Patients With Psoriasis and Psoriatic Arthritis in the United States: Findings From the National Psoriasis Foundation Surveys, 2003-2011. *JAMA Dermatol.* 2013;149(10):1180-1185. doi:10.1001/jamadermatol.2013.5264.

<sup>ii</sup> Gelfand, Joel M., et al. "The risk of mortality in patients with psoriasis: results from a population-based study." *Archives of Dermatology* 143.12 (2007): 1493-1499.

<sup>iii</sup> Study documents are expected to be released online the first week of June. Note: The findings presented above are not weighted by the enrollment of the plans in the analysis. The findings pertaining to coverage are based on a percentage of available drugs, and are not adjusted to reflect new drugs coming into the market. This creates a possibility that the same number of covered drugs might result in a lower percentage of covered drugs. The findings do not consider coverage permitted through off-formulary exceptions processes and appeals as this is not easily accessible data.

<sup>iv</sup> [https://youtu.be/-jY\\_16eOGJI?t=1h28m10s](https://youtu.be/-jY_16eOGJI?t=1h28m10s)



May 25, 2018

Steven D. Pearson, MD, MSc, FRCP  
President  
Institute for Clinical and Economic Review  
One State Street, Suite 1050  
Boston, MA 02109 USA

RE: Draft Evidence Report “Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value Condition Update”

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Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with life-threatening conditions and chronic diseases. We seek to improve access to treatments and services, which is a matter of survival for those patients, and a requirement for them to have better and more productive lives.

We are committed to engaging all stakeholders by analyzing information and publicly communicating those analyses to address patient barriers of affordability, insurance coverage, and physical access through realistic, patient-centered, solution-oriented discussions. By amplifying patients’ collective voices, our goal is to advance a balanced dialogue that illuminates the truth about health care in a just and equitable manner.

We appreciate the opportunity to provide our comments on ICER’s April 27, 2018 draft evidence report, “Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value Condition Update”

Treatment for psoriasis is complicated because of multiple therapeutic options, the systemic nature of the disease, the variability in its manifestations across a patient population, (i.e., areas of the skin, types of involvement, and other systemic presentations such as arthritis), and the diversity of patients’ goals and needs. Thus, successful care for people with psoriasis requires close collaboration between a patient and their clinical team to determine the best therapeutic plan for them – including when and if to consider increasing doses or switching medicines, either within a class or to a medicine in a new class. As ICER’s draft report found “...loss of effect over time is a very common problem with these drugs. In fact, switching treatment is generally expected among patients.”<sup>i</sup>

As is widely recognized, additional layers of complexity are added by insurance coverage parameters (that may require step-therapy, fail-first policies, or prior authorization), and by people changing insurance plans when they change jobs, move, or during their annual election period. And as the draft evidence report illustrates in Table 2.1 and Appendix H, there are clearly differences in how individual insurance plans (both private and Medicaid in New England) direct and manage access to different medicines for psoriasis.

This is the reality of the health care in the United States – and we expect that if ICER had extended its analysis beyond the New England states, and to private payers outside of the ACA Marketplace plans, ICER would have found even greater variability of coverage and degrees of restrictions to access. We make this point to illustrate the limitations of all economically based analyses within the inherently multi-payer, public/private, and State/Federal multiplexed U.S. health care system.

All those factors of patient heterogeneity related to biology, care delivery, and insurance coverage are important to consider, and ICER’s draft report touches upon all of them. Within that context, Patients Rising Now provides comments about ICERs current draft report in the following areas: Patient Perspectives and Outcomes, Modeling Unapproved Therapies and Interchangeability of Biologics, Cost-Effectiveness, and Budget Impact.

### **Patient Perspectives and Outcomes**

We are concerned that ICER continues to not conduct a balanced analysis and presents skewed conclusions because its process does not adequately weigh patients’ perspectives – particularly about the importance and value of quality of life. Below are some statements from the draft report that show ICER recognizes the importance of patient perspectives, but we find that the report’s main conclusions still fail to incorporate that important information:

- “Patients also pointed out that average treatment responses described in clinical trials may not capture individual patient variability.”<sup>ii</sup>
- “For all patients, treatments for plaque psoriasis may be challenging. It can be difficult to apply topical therapies, especially when the affected area involves the scalp or covers a large part of the body. Therapies can also be inconvenient to use; some require multiple injections on a daily or weekly basis, especially initially, during induction. Patients need to consider time and travel for administration of phototherapy and infused therapy. Psoriasis is a chronic disease that requires management over a lifetime, potentially during the treatment of other chronic conditions, including cancer.”<sup>iii</sup>
- “Plaque psoriasis has both psychological and emotional effects. The psychological impact of severe psoriasis is comparable to that of diabetes or depression.”<sup>iv</sup>
- “Data from clinical effectiveness shows that the use of targeted immunomodulators offers patients better treatment potential in regard to greater skin clearance and overall improved quality of life. Although we have very limited data on the evaluating the effect of these drugs on patients’ quality of life, there is reason to believe that for some patients with psoriasis, targeted immunomodulators may make many aspects of day-to-day living easier.”<sup>v</sup>

Overall, based on those and other sections of the report, we conclude that ICER has heard the concerns and perspectives of patients but has chosen not to adequately listen. For example, ICER notes that patient oriented outcomes were reported in 25 of 52 trials it evaluated for this draft report, but that “not all trials used the same standard of measurement, and other scales were not uniformly employed.”<sup>vi</sup> Because this type of data does not meet the standardized rigor of other data from the clinical trials, ICER has decided to not equally incorporate it into it’s analysis - other than noting that quality of life data was “generally consistent” with that of skin clearance data for some treatments.<sup>vii</sup>



As the rest of the US health care system is expanding its consideration of patient-focused perspectives and outcomes, ICER (and anyone else attempting to influence care or coverage decisions) must appropriately recognize patient perspectives and incorporate them into their work in a fully meaningful way.

Therefore, we strongly urge that aspects of value important to patients be given considerable discussion at the July 12<sup>th</sup> Public Meeting and during the voting by the New England Comparative Effectiveness Public Advisory Council (New England CEPAC) – and specifically related to final question under Contextual Considerations/Other Benefits i.e., “There are additional contextual considerations that should have an important role in judgments of the value of this intervention: \_\_\_\_\_.”

### **Modeling Unapproved Therapies and Interchangeability of Biologics**

In this draft report ICER compares and contrasts new and potential (i.e., yet to be approved) medicines with longer-standing therapies. ICER also makes projections about the interchangeability of biologic medicines, which is still a theoretical construct since the FDA has yet to even finalize rules on how that could happen.<sup>viii</sup> Both of those are troubling since they are essentially imagining future occurrences and including them into models for current action.

For example, the draft report illustrates the diversity of different plans for coverage of newer therapies.<sup>ix</sup> As we noted previously, most patients are expected to need to switch medicines as their current regimen loses effectiveness for them. This clearly demonstrates the challenges of modeling usage and uptake of new medicines – particularly in a disease like psoriasis where there are multiple therapeutic options that span several classes with different biological effects. And similarly, we are concerned that ICER appears to imply that interchangeability is already something that is occurring or can occur with this statement: “Head to head studies and registry studies for TNF- $\alpha$  therapy have shown that biosimilars can be **interchanged** with the reference biologic without losing effectiveness.”<sup>x</sup> [Emphasis added]

### **Cost-Effectiveness**

Patients Rising Now believes that the most important factor in understanding cost-effectiveness is the perspective being evaluated. In other words, is cost-effectiveness being evaluated from the perspective of the payer, the clinician, or the patient? Each has their own direct and indirect - and objective and subjective - criteria regarding cost-effectiveness, and those criteria may conflict with those of other stakeholders. For example, therapeutic options that have time and convenience benefits for a clinician may have negative time and convenience implications for patients. And of course, what may be less expensive (and thus more cost-effective) for a payor, could have greater costs and be less “cost-effectiveness” for a patient simply because of the benefits and coverage structure of their insurance plan.

Thus, cost-effectiveness is a very stakeholder specific individualized concept that is complicated by the multifaceted payer and provider environment that is rapidly evolving with mergers, consolidations, and seismic shifts from paying for volume to “value”. As ICER accurately states, “Patients are frustrated that they are being forced to start treatment with less efficacious medications due to insurance requirements for “step therapy” that mandates use of “preferred

medications” first. Patients are also frustrated by a lack of clarity in the exception process and timing in many plans, reporting that their physicians are not always sure how to get through a step therapy process even when that patient is an appropriate candidate to move on to a more advanced treatment. In addition, switching insurance or within-plan coverage changes might require movement to another step therapy approach, which often requires patients to “start over” with previously-tried medications.”<sup>xi</sup>

Some more technical notes and questions we have about ICER’s cost-effectiveness process in this draft report are summarized below:

- Footnote 129 indicates that the York Model is the basis for the cost-effectiveness modeling. However, in the referenced paper, it states that this model was created because the U.S. focus of a previous paper “give it limited relevance to UK practice,”<sup>xii</sup> which was the focus for the York Model. Therefore, we are interested in how ICER adjusted the York Model for the US health care environment and practice settings – particularly given the very extensive diversity of provider settings and reimbursement mechanisms in which U.S. clinicians deliver care. And we noted that ICER recognizes a similar limitation of its own analysis that “While we have some data from psoriasis registries in other countries, the choice of what drug to switch to is largely determined by policies unique to each locale.”<sup>xiii</sup>
- Additional issues with the York Model that we would appreciate ICER’s insights about are:
  - “The focus of the York Model is to establish the most cost-effective **sequence** of therapies based on alternative threshold values for cost-effectiveness.” Therefore, did ICER adopt the input parameters of the York Model for the U.S., e.g., hospital costs of non-responders.<sup>xiv</sup>
  - The York Model analysis gives ranges for costs per QALY.<sup>xv</sup> Why doesn’t ICER do that?
- In Appendix H, coverage and access parameters for marketplace silver and Medicaid plans in NE states are presented.<sup>xvi</sup> However, the date that this data was acquired is not given. Presumably it was in 2018 for the 2018 coverage year but given how significantly some plans change coverage from year to year, it would be good if ICER provided that information. Similarly, ICER’s draft report does not indicate how this data was acquired, i.e., from plan websites or documents, or in person or with phone calls. Given that plans have a history of problems accurately updating their coverage documents and websites – particularly related to provider networks, but also involving formularies – we believe ICER should disclose its data acquisition methodology for this information since it is presented as primary data in the draft report.

### **Budget Impact**

We have previously expressed our concerns about ICER’s Budget Impact calculations, but now want to emphasize how those impact assessment curves do not adequately account for patient perspectives. Specifically, since the Budget Impact curves – such as Figures 7.1 and 7.2 in the draft report – are based upon QALY numbers that are derived with only limited quality of life aspects of treatments, then from patients’ perspectives, those curves are too high. If more realistic patient QALYs gained with each treatment option were used in those calculations, then the curves would be shifted down and to the left. Thus, under ICER’s budget limit scenarios, more people would benefit from each of those therapies before the curve would cross ICER’s

self-determined and arbitrary budget impact threshold.

### **Conclusions & Recommendations**

We believe patients' voices need to be a part of defining and assessing the value of their treatment plans along with the cost of all aspects of their care – including patient's direct out of pocket costs and indirect costs related to patients' ability to work, etc. Analyses designed to support patients and clinicians – across the range of clinical decision making, benefit design, reimbursement policies, and coverage choices or limitation – need to encompass real patient's choices and goals, the spectrum of financial implications for new therapies, and practical options for increasing value for patients within the pluralistic U.S. health care system.

Within that context Patients Rising Now believes that ICER's draft report on psoriasis therapies inadequately reflects patients' perspectives about quality of life and the complexity of treatments – particularly concerning combination therapy and the need for patients to switch medicines as their response diminishes.

Sincerely,



Terry Wilcox

Co-Founder & Executive Director, Patients Rising Now

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- <sup>i</sup> ICER April 2018 Draft Evidence Report on Targeted Immunomodulators for the Treatment of Psoriasis, p. 67
- <sup>ii</sup> ICER April 2018 Draft Evidence Report on Targeted Immunomodulators for the Treatment of Psoriasis, p. 14
- <sup>iii</sup> ICER April 2018 Draft Evidence Report on Targeted Immunomodulators for the Treatment of Psoriasis, p. 15
- <sup>iv</sup> ICER April 2018 Draft Evidence Report on Targeted Immunomodulators for the Treatment of Psoriasis, p. 15
- <sup>v</sup> ICER April 2018 Draft Evidence Report on Targeted Immunomodulators for the Treatment of Psoriasis, pp. 66-67
- <sup>vi</sup> ICER April 2018 Draft Evidence Report on Targeted Immunomodulators for the Treatment of Psoriasis, p. 42
- <sup>vii</sup> ICER April 2018 Draft Evidence Report on Targeted Immunomodulators for the Treatment of Psoriasis, p. 35 & 36
- <sup>viii</sup> <http://www.centerforbiosimilars.com/contributor/sonia-oskouei/04/2018/biosimilar-interchangeability-9-things-to-consider>
- <sup>ix</sup> ICER April 2018 Draft Evidence Report on Targeted Immunomodulators for the Treatment of Psoriasis, p. 18
- <sup>x</sup> ICER April 2018 Draft Evidence Report on Targeted Immunomodulators for the Treatment of Psoriasis, pp. 6-7
- <sup>xi</sup> ICER April 2018 Draft Evidence Report on Targeted Immunomodulators for the Treatment of Psoriasis, pp. 15-16
- <sup>xii</sup> Woolacott, et al. "Etanercept and efalizumab for the treatment of psoriasis: a systematic review. Health technology assessment" (Winchester, England). 2006;10(46), p. xv and 73
- <sup>xiii</sup> ICER April 2018 Draft Evidence Report on Targeted Immunomodulators for the Treatment of Psoriasis, p. 64.
- <sup>xiv</sup> Woolacott, et al., op. cit., p. 76
- <sup>xv</sup> Woolacott, et al., op. cit., p. 76
- <sup>xvi</sup> ICER April 2018 Draft Evidence Report on Targeted Immunomodulators for the Treatment of Psoriasis, p. 243