INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis

Response to Public Comments on Draft Evidence Report

June 12

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#	Comment	Response/Integration
1.	***Manufacturers***	
2.	AbbVie	
3.	**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.**	We agree with you that the phase II X-plore trial does not meet our criteria. Our evidence table has been updated to exclude this study. In terms of presenting data on other endpoints, we included data from secondary publications and conference abstracts in our report. In fact, most of the data we have on the subgroup analyses are from secondary publications and conference abstracts. Finally, as part of our standard review process, we review abstracts that are presented at key conferences during our review to make sure all relevant data are captured.
4.	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.**	We have modified the statement to state that "we did not identify any data on mean change in DLQI for the new drugs"
5.	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). 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. The items on the PSS are similar to items on the other instruments referenced in the draft report. Given PSS results were ranked endpoints,	Thank you for your comment. As noted in our report, a variety of instruments have been used to assess symptom control. However, none of the identified presentations on risankizumab include any data on symptom control. We will be happy to update our findings if you provide us with the PSS data.

	they were reported with the clinical outcomes that were recently presented.	
6.	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. **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.**	As discussed in the report, we relied on data from RCTs for estimates of discontinuation due to lack of efficacy, rather than relying on observational data, for which we do not have consistent data for all drugs. The year 2 and beyond data are based on real-world observational findings, however. We believe this approach balances the use of higher-quality data from RCTs with the use of real-world data, which is subject to numerous limitations. We have explored uncertainty in these estimates in sensitivity and scenario analyses.
7.	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. Moreover, both secukinumab and ixekizumab have warnings/precautions for use in patients with IBD, and brodalumab is contraindicated in patients with Crohn's disease. This is also reflected in guidelines and expert opinion treatment recommendations. 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.	We have not studied specific patient sub-populations such as patients with PsA or IBD; our results are thus applicable to a general population as represented by the patients enrolled in RCTs. We agree that for these specific sub-populations, second-line therapy would likely be more specific. There are no high-quality, controlled, comparative data consistently showing an effect of these agents on CV risk, and these effects were thus not included in the analysis. Lastly, TNF use beyond first-line has not been uncommon, but based on input from clinical experts, we felt that given the plethora of treatment options, such use is less likely moving forward.

	• **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. 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 lin**e – 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. 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.	
8.	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.	Thank you for raising this issue. These data are discussed in the report, and we acknowledge, and highlight, this is an important data gap.

9.	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. Thus, accurately accounting for differences in real-world dosing among the treatments is likely to have a significant effect on the model results.	We have included dose variability for ustekinumab and certolizumab pegol in the base-case. We agree dose escalation has an important impact on results, but it should be recognized that correlating dose changes with effectiveness is challenging when data are lacking.
10.	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.	Thank you for this comment. We acknowledge that our original presentation of the threshold results could have been presented in a more straightforward manner and we have since modified this. Tildrakizumab was originally priced per-unit, while risankizumab was priced per-month. In order to facilitate comparison between drugs, we have changed all threshold prices to annual maintenance costs.

11.	Amgen	
12.	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 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 non-targeted treatment arm consists of a non-specific group of interventions as outlined in the study from which the cost estimates were derived. The costs and utilities of the non-targeted strategy are now provided in the report. Cost per incremental PASI month was calculated by dividing the difference in costs by the difference in time spent in PASI categories.

13.	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 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.**	We agree that updated costs for non-targeted therapy would be helpful, as well as effectiveness data. We note that while the cost of non-targeted therapy is influential in the model, including additional costly non-targeted treatments would also presumably increase the effectiveness of non-targeted treatment, offsetting to a degree the impact of increased cost.

14.	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". 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." The dose escalation analysis for etanercept presented in the Draft Evidence Report is based on a European study. **As 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.**	Thank you for this comment, and we agree that EU-centric data is not applicable to the US setting. We have deleted this scenario analysis.
15.	**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. 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.	Similar to the rationale described in the 2016 report, the PASI outcomes from the etanercept arm in LIBERATE were not included in the NMA because of the stated reasons. We only used the comparison of apremilast to placebo in our NMA. We have updated our report Section 3.3 to make this clear.

16.	**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. 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.**	We agree that the impact of targeted treatments on PsA is important. Our analysis inherently includes this effect to an extent, as a proportion of patients enrolled in the RCTs had PsA, and the benefits of treatment on patients' health-related quality of life would be reflected in the correlations between EQ-5D and PASI response, which were derived from these RCTs.
17.	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.** 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. 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	We have included productivity effects in a scenario analysis, per standard ICER protocol. We agree this is a potentially important effect. While a suggestion to include a 'long-term patient-based utility augmentation factor' is interesting, such a factor should be based on high-quality data given its potential impact. We are unaware of such data at the time of the analysis.

	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.**	
18.	Celgene	
19.	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.**	We considered other coprimary and major secondary outcomes such as Physician Global Assessment (PGA) or Investigators Global Assessment (IGA) response and Dermatology Life Quality Index (DLQI) outcome in our evidence ratings, but note that these findings tracked quite closely with PASI performance. In addition, our evidence rating is based on net health benefit, which includes any considerations related to potential harms. We have updated the section on the evidence ratings to make this clear.
20.	ICER notes that up to half of patients are dissatisfied with their psoriasis treatment. 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.	Thank you for your comment. We feel that these are important patient-centered concerns to highlight.

21.	Kerdel and Zaiac, 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.**	ICER has conducted a systematic review and used the available data for assessing the comparative clinical effectiveness, as described in the report. During the scoping process, we documented multiple outcomes of interest, but are limited in drawing conclusions based on the data actually collected in the studies of interest. In addition, we have engaged with multiple individual patients as well as the National Psoriasis Foundation to understand the impact of the disease and treatment on multiple aspects of patients' lives. The insights gained are highlighted in our report.
22.	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.**	Discontinuation in this model can be thought of as occurring in three phases. The first phase is a single point in time immediately after the end of each drug's initiation period, wherein any patient not achieving PASI 75 or better discontinues their first-line targeted drug. The second phase occurs between the end of the initiation period and the end of the first year; this includes discontinuation for any cause (e.g., loss of effectiveness, adverse events, etc.) and occurs gradually over the remainder of the first year. In practice, only infliximab patients discontinue during this period because infliximab is the only drug we found whose discontinuation rate exceeded its rate of non-response at the end of its initiation period. The third period occurs from the start of year 2 until the end of the model and again accounts for discontinuation due to any cause. We have clarified our approach in the report.

23.	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 studies5-12. Published real-world data from the US12, 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.**	We assessed the impact of continuing therapy in the first year for patients in the PASI 50-75 response group in a scenario analysis; this scenario is most impactful for apremilast, as it has the poorest response rate of all drugs studied, but the overall conclusions of the study are relatively unchanged. It is important to note that high-quality, comparative data on the impact of such continued treatment are lacking.
24.	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. Therefore, it would be important to explicitly test the impact of patients achieving PASI 50 continuing on first-line treatment.	This scenario analysis does explicitly test the impact of patients achieving PASI 50 continuing on first-line treatment through year one. We did not assume patients with PASI 50-74 continued beyond year one given the lack of high-quality comparative data and the plethora of other treatment options.
25.	**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) and, even further, ICER does not incorporate the evidence that supports patient preference for oral formulations in any step of its evaluation.**	Section 5 on additional considerations mentions that patients may favor the convenience of an oral drug like apremilast. The additional considerations are an integral part of the report and are important in the overall assessment of the available evidence. We also note that, across multiple diseases, the literature is anything but conclusive on patient utility for specific formulations or route of administration; if specific references in plaque psoriasis can be provided, we would be glad to consider them.
26.	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**	We note in the report that apremilast is the only oral targeted agent, which may be more important than effectiveness for some patients. We do not agree, however, that route of delivery alone excludes comparison with other drugs to treat plaque psoriasis.

	should be viewed separately and not as part of the broader category of "targeted immunomodulators."	
27.	Eli Lilly	
28.	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.	The primary outcome in the trials was assessed at the end of the induction period (between 10 and 16 weeks after initiation, depending on agent) , after which treatment crossover was typically allowed. Because of this, we could only confidently compare the comparative efficacy of targeted immunomodulators at the end of the induction period. Since the agents have different dosing frequency, we generally used what was defined as the primary endpoint in the trials in order to minimize bias.
29.	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. **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. **Thus, we recommend that ICER conduct new, supplemental AUC analyses across different products as part of its assessment of clinical benefit and value.**	We assessed the impact of time to achieving response in a scenario analysis, but found that it had a relatively minor influence, likely because a difference in timing of several weeks is small relative to a 10-year time-frame.
30.	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	We have included drug rebates and other concessions, as well as the uncertainty around them, in the analysis. The mix of treatments after TNF failure is changing with the rapid introduction of new drug treatments; our assumptions are based on input from multiple clinical experts. We recognize that benefit design might influence how patients step through therapy, but these designs vary, and our intent was to model the effects of these treatments as considered for first line use – indeed, it would be results like ours that plans might consider in altering their step-therapy protocols. Lastly, we did account for differences in PASI response with biologic exposed (or failure) versus biologic naive in estimating second-line targeted therapy effectiveness, as described in the report.

	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.**	
31.	**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.** 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.	Our conclusions have been refined based on results from the PSA. We do not believe that these conclusions are inconsistent at all – namely, that value across the board is less favorable than in 2016 (due in large part to price increases), but certain agents in the 2018 view "rise to the top" in our analysis.
32.	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 2nd, 3rd or 4th 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.**	Unfortunately, we are unable to obtain information on covered lives at the payer level in individual markets in each state, as public reporting requirements vary by state. Still, we acknowledge that this is an important point, and have now highlighted that this plan survey does not necessarily present a weighted representation of drug availability for members on individual market plans in New England. Still, we think it is important for the reader to understand how both big and small regional plans may design their formularies differently-- with different prescribing requirements, step protocols and preferred access-- based on their ability to leverage membership. As our readership consists of individual members, purchasers, payers, and drug manufacturers, we hope this can inform their understanding of variances between big and small regional plans.

33.	**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.** 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).	Thank you for your comment. We did not include data from this trial because the trial population was limited to patients with only genital psoriasis. Studies conducted in patients with psoriasis specific to a location were excluded (e.g. genital psoriasis, nail psoriasis). We have updated the section of the report describing our exclusion criteria to make this clear to the reader.
34.	Janssen	
35.	**Page 5: Table 1.1: brodalumab loading dose is missing from "FDA Recommended Dosing" column (Siliq Prescribing Information)**	Thank you. This has been corrected.
36.	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.	Thank you for your comment. The wording has been adjusted from "that biosimilars can be interchanged with the reference biologic without losing effectiveness" to "that biosimilars can replace the reference biologic without losing effectiveness"
37.	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).	Thank you. We have corrected this statement in the updated report.
38.	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).	Thank you for this clarification. We have added DLQI to the definition of 'severe psoriasis,' based on the NICE definition, in the updated reported.

39.	Page 20: Regarding the European Guideline on Systemic Treatment of Psoriasis Vulgaris, 2017 update, guselkumab, ixekizumab, and brodalumab **were not included.**	Thank you for this clarification. We have made this change accordingly in the report.
40.	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).	Thank you. This has now been corrected.
41.	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: o 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. o Additionally, the exclusion of PASI 100 as a discrete outcome further compounds this issue.	We conducted a sensitivity analysis with three distinct "betas" for the placebo adjustment as suggested. The results from this analysis were similar and did not have any meaningful impact on the ranking of the drugs. In addition, the DIC (as assessment of model fit) measures for the two models were very similar. As such, we use the standard placebo-adjustment model (one beta) as our base case, which is consistent with other published models. We present the result of the NMA model with three betas as a sensitivity analysis in Appendix F of our report.
42.	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.	We opted not to include PASI 100 in our NMA, as our analysis assumes a continuous distribution with defined cutpoints and an estimated probability of achieving a ***range*** of results between cutpoints (i.e.,<49, 50-74, 75-89, 90+). With this approach, the probability of achieving a ***single*** result (like 100) is zero. We also note that separate utilities for PASI 90-99 and 100 were estimated in a sensitivity analysis in our 2016 review, without any material change in cost-effectiveness findings. However, we have integrated your suggestion on multiple betas into a new sensitivity analysis. See comment 41 above.
43.	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	Thank you for your comment. We reviewed the NICE appraisal comment as suggested. We will first note that our NMA model with placebo adjustment matches that specified in the NICE appraisal. In addition, the analysis included fewer drugs (7 drugs vs. 12 drugs evaluated in the ICER NMA), and a different set of studies. Still, we believe the conclusion of the NICE appraisal was similar with ours: "Although guselkumab appeared to be

		statistically significantly better than secukinumab in terms of PASI 75 response in the NMA, the difference might not be clinically meaningful. As a result, NICE concluded that guselkumab was likely to provide similar benefits to secukinumab and ixekizumab in clinical practice. The finding in our NMA also suggest there is no significant difference between guselkumab and secukinumab.
44.	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).	Thank you for pointing out this study - we have now included it in our discussion of second-line effectiveness. This study indicates that response to guselkumab is likely lower (48% PASI 90 at 12 weeks vs. 70-73% PASI 90 at 16 weeks in the VOYAGER studies) in patients who fail a targeted therapy, and is thus supportive of our assumption that second-line targeted therapy is less effective than first-line targeted therapy.
45.	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).**	We have corrected this table.
46.	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).**	Thank you for pointing out this mislabeling. We have confirmed that it was an error in the table only and was not incorrect in the model.
47.	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.**	The rebate percentage was calculated based on observed rebates and other concessions as publicly disclosed by manufacturers, then applied to the WAC prices gathered from REDBOOK. The percentages displayed have been rounded for ease of reading and the discrepancies seen between calculated price and displayed price are due solely to this rounding.
48.	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.	Thank you, we have updated our method of calculating doses and have double checked our calculations.

49.	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 1st 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.**	We were not able to access rebate percentages for the two separate apremilast products (the starter pack and the tablets). We have therefore priced apremilast on a per-tablet basis.
50.	ICER seems to assume 15 doses for the 1st 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.**	Thank you for this comment and others; we have comprehensively changed our dose calculation method. Our new method calculates average daily dose, then multiplies it by 30.44 (average days per month) to arrive at the mean per-cycle (i.e., monthly) dose. This should correct the inconsistency you have pointed out with secukinumab.
51.	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). **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.	Thank you for the comment. We have revised the monitoring parameters accordingly.
52.	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.	We appreciate the uncertainty around the discount for guselkumab and have added a qualifier to the text.
53.	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.**	There was an error in the preliminary results that caused "Months spent in PASI 75" to be reported as the sum of months spent in PASI 75 and months spent in PASI 90. This was corrected for the draft report.

54.	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.**	Due to feedback received after the presentation of preliminary results, we reconsidered the utility weights used in this model and have settled on an average of utility weights from five studies as presented in Pickard, 2017. The change in ustekinumab outcomes is attributable to this change in utility weights, which affected all drugs.
55.	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.	We have added a qualifier about uncertainty in the price due to uncertainty in the discount, as noted above.
56.	**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.	Productivity effects are included in a scenario analysis, per current ICER methods.
57.	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.**	This is a potential limitation that applies to all drugs due to design of the clinical trials (limited follow-up during randomization period); we have noted this in the report.
58.	Page 229: The FDA-approved maintenance dosage for brodalumab is 210 mg every two weeks (Siliq Prescribing Information).	We have ensured that the brodalumab dosage is calculated correctly in the model and will ensure that it is correctly communicated in the report.
59.	Page 229-239: Table G2, G4, G9, G10: **Janssen suggests that ICER complete these tables with known available information for all products.**	Thank you for pointing this out. These tables were inadvertently included in the draft report.

60.	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.**	ICER's model does not assume that 100% of eligible incident cases will receive guselkumab. (As in our 2016 report, we used incidence rather than prevalence because we were interested only in patients who were taking a biologic for the first time.) The intent of our budgetary impact analysis is not to predict the percent of incident cases that will receive a given treatment, but to document the percentage of incident patients that *could* be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.
61.	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	Thank you. This has been updated.
62.	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	Thank you. This has been updated.
63.	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)	Thank you. This has been updated.
64.	Page 163: Langley, 2015: Intervention Dosing Schedule: a) non-adjusters (n=544), b) adjusters (n=568); AEs at week 264 (2nd line) a)187 b)216 c)202; SAEs (1st line) 1)7.99 2)6.87)7.31; Infections (2nd line) a)73.9 b)83.4 c78.9	Thank you. This has been updated.
65.	PASI 90 data from NAVIGATE are missing from Table E1. Note these data are at week 28 in patients who had an IGA ≥2 at week 16 and were randomized to either ustekinumab or guselkumab. The presented P value is versus ustekinumab (Langley 2017).	Thank you. This has been updated.
66.	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).	Thank you. This has been updated.

67.	Novartis	
68.	**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 16.13 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.	Thank you for your comment. We have now updated our report, using the week 16 data in the CLEAR trial for our NMA.
69.	**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 ICER17, 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 and CLARITY 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).	We have now included CLARITY in our NMA, and the evidence ratings have been updated accordingly.
70.	**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	Thank you for your comment. This has been clarified with a footnote.

	table such as adding a footnote or italicizing the names of the trials with active comparators.	
71.	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. 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.	Thank you for your comment. We have added this information.
72.	**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 analysis22 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.	Thanks for your comment. We did not include injection site reaction as an outcome in the NMA because it was not consistently reported across trials. However, we presented the weighted average across trials in Appendix E, Table E5.
73.	**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. Productivity is especially important to consider for patients with psoriasis, as increases in PASI response correspond to improvements in work productivity.18,25 As such, we recommend that ICER use the inclusion of productivity costs and	We have followed current ICER methodology and included productivity in a scenario analysis. Our approach to considering societal impacts as a "base case" is reserved for ultra-rare diseases only (a classification for which plaque psoriasis does not qualify).

	benefits scenario analysis as the base case in the final report (Table 4.9 Inclusion of Productivity Offsets).	
74.	**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.26 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.	We have conducted a PSA for this review, and agree it is important for interpreting results under conditions of uncertainty.
75.	**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.	Thank you, we have added the parameter of loss of effectiveness in second line to our one-way sensitivity analyses. The percentage of patients receiving targeted versus non-targeted therapy in second line is currently in the one-way sensitivity analysis, labeled as "d/c % to 2L"
76.	**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 appreciate this suggestion and have modified our cost calculations accordingly.
77.	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	See the comment above.

	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 = 17 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 = 13 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 = 16 and for years 2+ as 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 = 15; the number of doses per year in years 2+ would be $35060.11/$2926.22 = 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.**	

78.	There is limited transparency into how drug-based discounts were derived. 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 proving 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.	We agree there are important uncertainties in drug-specific rebates and have included these uncertainties in our analyses.
79.	**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	We agree and have modified this scenario analysis accordingly. Namely, we have applied drug-specific rebates available from 2016 to 2016 WAC prices to calculate the net prices used in this scenario analysis and allow direct comparability with the 2018 results.

	calculations (as mentioned above) would allow for better understanding on SSR Health's methodology used in the 2016 and 2018 report.	
80.	**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.27 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).	Please see comment above.
81.	Sun Pharmaceuticals	
82.	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 2nd 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. 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.**	We recognize this limitation. However, because the primary outcome in the trials was assessed at the end of the induction period (between 10 and 16 weeks after initiation, depending on agent), after which treatment crossover was typically allowed we could only confidently compare the comparative efficacy of these agents at the end of the induction period. We noted this as a general limitation of our evaluation in the Controversies and Uncertainties Section of the report.
83.	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.	Follow-up data on drug survival is complex, heterogenous, and strongly influenced by dose changes (increases). We thus rely on data from RCTs to assess response and lack thereof, leading to treatment discontinuation. We acknowledge limitations in the design of the key RCTs - short duration of follow-up during the randomization period – potentially hampers assessment of the value of these drugs, but note that similar challenges exist

		in using real-world rates of discontinuation without robust estimates of real-world effectiveness.
84.	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). 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." **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.**	We have included a scenario analysis assessing the impact of continued treatment for PASI 50-74 patients. We note that such analyses are not based on comparative, randomized data because such data are lacking. We also note that any evaluation of effectiveness beyond the primary endpoint in a trial, and after randomization is broken, is based on observational, often non-comparative, data.
85.	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). **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).	We have now added the data on long term safety of tildrakizumab.

	Tildrakizumab also had significantly fewer treatment-related AEs, serious AEs, treatment related serious AEs, and discontinuation due to TEAE than etanercept. Safety is an important factor for patients in making treatment decisions.	
86.	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 impact of the cost of adverse events has not been found to be influential in our analyses, or any other previous analysis, that we are aware of in plaque psoriasis. The statement that "Without accounting for adverse events, the economic evaluation of these treatments becomes primarily a price-driven exercise for the drug alone" is incorrect for obvious reasons given the other important parameters included in our analysis.
87.	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.**	We agree there is uncertainty in the discounts used, particularly for newer agents; we have accounted for this in our sensitivity analyses. We have reviewed the Appendix tables for accuracy and made necessary corrections and/or deletions - thank you for the suggestion.
88.	Table 3.2: PASI 90 for tildrakizumab should be 35-39	Thank you. This has now been updated in the report
89.	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.	We have updated our report to reflect that ustekinumab, adalimumab, tildrakizumab, certolizumab were significantly better than etanercept and apremilast in the NMA.

90.	Network Meta-Analysis of PASI Results: 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.	Observational studies have shown that ustekinumab dose increases are common, and labeled dosing is weight-based.
91.	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.**	The only parameter missing from these calculations are lab monitoring parameters, which we have not included in the calculation. We did not include any assumptions about monitoring in the threshold price calculation.
92.	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.**	We agree and now report all threshold prices using the same time period.
93.	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 (≥ 180 days over a 12-month follow up) that increased costs per day (etanercept: $69; adalimumab: $68; ustekinumab: $64). This resulted in additional annual costs per patient: $19,458, $18,972, and $21,045 for etanercept, adalimumab, and ustekinumab. 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.	The limitations of real-world data on drug survival/discontinuation and dose changes (and corresponding changes in effectiveness) are extensively discussed in the report. It is important to note that the Feldman 2015 study found about as many dose decreases as increases; EU dosing for etanercept is different than US (mean dose in Egeberg study was within labeled US dosing), and the Feldman 2017 study accounted for dose increases, but not dose decreases, nor did the authors provide information on mean doses.

94.	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.	Thank you for your comment. We believe the placebo adjusted model is more appropriate than the unadjusted one in this case because the placebo arm response rate (which is a proxy for baseline risks) varies across trials. Therefore, an unadjusted model will result in significant bias in cross-trial comparisons of treatment outcomes. Our approach is consistent with what has been done in previous published models. We present the results of the unadjusted model as a sensitivity analysis in Appendix F of our report.
95.	A few parameter values, including hospitalization for pneumonia and productivity improvement, were taken from the 2016 review. These values should be adjusted for inflation.	The productivity and hospitalization scenario analyses have been updated to reflect updated prices.
96.	UCB Pharma	
97.	**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.**	Our potential budget impact analysis included the entire candidate population for treatment, which in our model included adults with moderate to severe plaque psoriasis who are taking a biologic agent for psoriasis for the first time. To estimate the size of the potential candidate population for treatment, we based our estimates on incidence of psoriasis in the U.S., rather than prevalent cases that had failed prior treatment. We did not restrict the population to those who have failed non-biologic therapies because the label indication for each drug is "treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy," not only those who have failed such treatments. We do not estimate market share in our budget impact analyses, but decision-makers who wish to do so can take this into account when considering the percent uptake in Figures 7.1 and 7.2 in the report.
98.	**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.	See above.

99.	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?	We used results from the CEA model to estimate total potential budgetary impact, calculated as incremental health care costs (including drug costs) minus any offsets in these costs from averted health care events. Any assumptions used in the CEA would apply directly to the budget impact analysis, although over an undiscounted 5-year time horizon.
100.	(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 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.**	We appreciate this comment, and have refined our statements, in part based on results of the PSA, which help account for uncertainty in the value comparisons.
101.	(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."**	We agree with your comment and have updated the report accordingly. We did look at certolizumab pegol coverage in order to understand its comparative placement in existing indications in relation to other drugs within the same class.

102.	(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.**	Although we generally used the primary endpoints specified in trials for our NMA, we were limited by the design issue in this trial. As noted in Table E1, Appendix E of our report, we used the 12-week data for certolizumab and etanercept in the CIMPACT trial. This is because only the 12-week data was reported for etanercept, and felt that direct comparative evidence collected at the same timepoint would represent a more fair comparison.
103.	(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.**	We have now included the results for certolizumab pegol 400mg Q2W dose.
104.	(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.	Thank you for your comment. This has now been changed.
105.	(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.**	We have now included the results for certolizumab pegol 400mg Q2W dose compared to etanercept.
106.	(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.** • 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.**	We have included the 400mg dose as requested and updated the dose schedule. We have assumed that half of patients use the 400mg dose and half use the 200mg dose.

107.	(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.**	Thank you for your comment. The wording in this section has now been updated to be more specific to the results of the NMA.
108.	(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.**	Thank you for your comment. This table has now been updated.
109.	(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.	The bolded ratings are the new ratings that are added to or updated from the 2016 report. We have clarified this in the table.
110.	(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 the discount rates in the draft evidence report were determined?	Our 2016 report on psoriasis treatments used class-specific discounts, but our subsequent reports have used drug-specific discounts. Discounts were estimated using data from SSR Health, which combines public data on net US dollar sales with information on unit sales to derive net pricing at the unit level across all payer types.

111.	(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.	The point made here was not clear. If all conclusions based on what treatment was selected as first-line treatment were removed, decision makers would have no information to inform the policy decisions they face.
112.	***Clinical Experts***	
113.	Mark Lebwohl, MD, Chairman, Department of Dermatology, Icahn School of Medicine at Mount Sinai	
114.	**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. Methotrexate has numerous black box warnings and requires frequent laboratory monitoring and even liver biopsy. 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.**	Our report includes apremilast as part of immunomodulating agents based on its method of action. The difference between apremilast as a small molecule and the biologics is clearly indicated the report. As the commenter likely appreciates, providing the drug at "little or no cost" describes benefit to the patient, but does not represent the price paid by the insurer for the drug. Our net price estimates include all concessions provided by the manufacturer, including copay assistance programs.

	It is important that the psoriasis report look at apremilast in the correct context – i.e. a safe oral therapy for psoriasis.	
115.	***Patient Organizations***	
116.	Randy Beranek, President & CEO, National Psoriasis Foundation	
117.	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.	The policy recommendations of the 2016 report stress the importance of including patient relevant outcomes in the design of clinical trials and also the importance of data on disease-specific quality of life. The present condition update report will provide a new look at the 2016 policy recommendations.
118.	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.	Patient preferences for treatment outcomes (PASI response) are an inherent component of the cost-effectiveness model. We did not include patient preferences for route of administration, given the high degree of variability in the literature regarding the findings of such preference studies.
119.	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.	We included the subpopulations as indicated, but our assessment is limited by the available evidence. This is definitely an area for further research and we invite comment on this point at the public meeting.
120.	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	Your comment is very important. The present condition update report will provide a new look on the 2016 policy recommendations and we invite comment on this point at the public meeting.

	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. The study findings raise concern for the NPF about the impact of the 2016 assessment. 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).	
121.	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	Your comment is very important. The present condition update report will provide a new look on the 2016 policy recommendations and we invite comment on this point at the public meeting.

	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."	
122.	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.	In the update to ICER's value assessment framework in 2017, we added a new section to our reports based on feedback to identify "low-value" care that could be eliminated to create headroom in health care budgets for higher value innovative services. The goal of this section is to highlight for policy makers the opportunities for reallocating resources as new innovations enter the market. These low-value services are ones that would not be directly affected by targeted immunomodulators (e.g., reduced hospitalizations, improved productivity, etc.), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of moderate-severe plaque psoriasis beyond the potential offsets that arise from a new intervention.
123.	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	The wording has been changed as suggested. Our report provides an assessment of currently available therapeutics, including the new class of IL-23 inhibitors to help with the immediate decision-making required by patients, clinicians, and payers. This information may also prove useful for development or refinement of evidence-based guidelines.

	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").	
124.	Terry Wilcox, Co-Founder & Executive Director, Patients Rising Now	
125.	**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. 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 12th 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: _____."	As per standard practice at ICER, the considerations listed will be considered at length at our public meeting, including in deliberation by our CEPAC.
126.	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. Both of those are troubling since they are essentially imagining future occurrences and including them into models for current action.	Thank you for your comment. In order to avoid any confusion, the wording has been adjusted from "that biosimilars can be interchanged with the reference biologic without losing effectiveness" to "that biosimilars can replace the reference biologic without losing effectiveness"

127.	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," 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."	The structure of the model was originally based on the York model; the data used, however, are reflective of the US setting.
128.	"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.** The York Model analysis gives ranges for costs per QALY. **Why doesn't ICER do that?**	See comment above. A PSA was conducted to assess uncertainty (ranges) in the results.
129.	In Appendix H, coverage and access parameters for marketplace silver and Medicaid plans in NE states are presented. 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.**	Thank you for your comment. We identified 2-3 lowest cost silver level plans on the individual marketplace in each New England state in March 2018. In order to acquire information on formulary design, we identified online formularies corresponding to the 2018 plan selected. If plans required prior authorization, we found online documentation of prior authorization criteria connected to the formulary to understand step protocols or prescriber requirements. We supplemented this primary research with conversations with payers and patient groups to ensure takeaways were directionally valid. We have clarified this approach in our updated report.

130.	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.	Our budget impact analyses use estimated net health care costs (calculated as incremental health care costs minus any cost offsets from averted health care events) to estimate the potential impact of new treatments on the health care sector's budget. As such, they are not based upon QALY estimates, and the inclusion of any additional quality of life effects would not alter the budget impact analysis unless they directly impacted health care costs for these patients.