Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value

Response to Public Comment on Draft Report

May 12, 2017

Prepared for

###	Commenter	Section	Comments on Atopic Dermatitis Draft	ICER Response
1	AAD	Clinical Effectiveness	We would argue that the comparative net health benefit of dupilumab over emollients is "superior" to emollients, not "incremental +" given the impressive reductions in disease severity…improvements in patient symptoms…and statistical and clinically-relevant...improvement in all other symptom scales, QOL scales, and mental health scales...	Dupilumab is clearly superior to emollients with regard to benefits. Net health benefit also includes harms, and there is uncertainty on net health benefits because of uncertainty in harms.
2	AAD	Clinical Effectiveness	It is true, that for many patients, topical steroids are a cost-effective therapy that can be highly effective and safely utilized. However, because AD is a chronic disease, non-steroidal approaches are often needed for long-term use or where topical steroids are ill advised...Although TCIs are labelled as "second-line" therapy, in reality they are less potent than many topical steroids. Thus they are incorporated most frequently as steroid-sparing agents for the treatment of areas of the body susceptible to steroid side effects...[because of the black box warning on TCIs] dermatologists have been in need of additional non-steroidal options to have in their arsenal for these clinical situations. While relative efficacy of crisaborole is an important question that needs answering, the relative efficacy is less important to our group than the ability to use a well-tolerated and effective therapy within a topical treatment regimen individualized for each patient to achieve the best and safest outcomes.	Thank you for your comment.

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3	IfPA	Clinical Effectiveness	“Data availability challenges” on long-term impact undermine dupilumab net health benefit grade. Put differently, the drug is new, therefore, no one has taken it long-term. Since there is no data on long-term impacts, the authors decided that a one letter-grade decrease in the clinical effectiveness of dupilumab was appropriate. The report provides no methodological reason why a one letter-grade decrease is a justifiable penalty. The reduction appears arbitrary at best.	This misinterprets how ICER grades evidence. We are not "penalizing" dupilumab, but reviewing the evidence. A B+ rating reflects certainty that dupilumab provides at least a small benefit, but some uncertainty as to whether dupilumab provides a substantial benefit given the lack of adequate evidence on harms.
4	Pfizer	Clinical Effectiveness	We further ask that ICER offer a stronger rationale for the comparison of the 5 versus 6 point scales used in the crisaborole and pimecrolimus trials, respectively. In the report, ICER offers no scientific rationale for the comparison of “clear” and “almost clear” categories on both scales. We recommend that ICER articulate the reliability and validity of this comparison in detail before publishing the final report.	When outcome measures are not the same, doctors and patients still need to make informed decisions. We are comparing two static IGA scales that both include ratings of clear and almost clear. We would be interested in additional data suggesting non-comparability, but absent such evidence we think our cautions about the evidence from the NMA are sufficiently stated.

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5	Pfizer	Clinical Effectiveness	Concern #2: On page 34 of the report, in discussing the limitations of the crisaborole network meta-analysis, the authors acknowledge that their approach to the pimecrolimus comparison is limited, noting that: "In addition to statistical uncertainty, the trials were performed in very different time periods and used different versions of static IGA scales... concerns that the pimecrolimus comparator vehicle can be irritating... Given the uncertainties, we cannot come to firm conclusions... Pimecrolimus appears to be less effective than tacrolimus or moderate potency topical corticosteroids." Yet on page 36, ICER states that "... crisaborole appeared unlikely to be as efficacious as higher potency topical corticosteroids or 0.1% tacrolimus." This contrasting statement is especially troubling given that the only reference to tacrolimus in the clinical efficacy review is a brief sentence (which appears at the end of the block quote above), citing, but not reviewing, a Cochrane study of pimecrolimus.	We have expanded the description of the results of the systematic review.
6	Pfizer	Clinical Effectiveness	* Statements which misrepresent crisaborole's potential use or value: "Trials of crisaborole…did not assess potentially important outcomes including psychologic and quality of life outcomes…" (page 37, emphasis added). > Note that crisaborole clinical trials did include quality of life outcomes, but these data were not included in the pivotal study publications. These data have been presented.	We appreciate the reference to these data (and the subsequent submission of the poster by the manufacturer). We have now included the data in the Evidence Report.

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7	Pfizer	Clinical Effectiveness	Concern #1: On page 33 of the draft report, ICER notes a lack of study data comparing crisaborole to active treatment. The authors acknowledge that the two pimecrolimus studies use 6-point static Investigator Global Assessment (IGA) scales, while the two crisaborole trials utilized a 5 point static IGA scale. The authors then note that because "the severity of disease in the trials appeared to be reasonably similar with regard to baseline IGA score and percent body surface area involved", the authors felt comfortable undertaking "indirect comparisons using Bayesian network meta-analyses (NMAs), assuming "clear" and "almost clear" categories are similar on both scales". We disagree with ICER's assessment that the perceived similarities in baseline trial populations and IGA response scale structures allows for comparisons to be made across trials. While the discipline of meta-analysis offers powerful statistical tools that can help make comparisons across clinical trials, the results of any meta-analysis are directly a function of the assumptions made. We ask that ICER strengthen its report by offering a stronger rationale for the comparability of the crisaborole and pimecrolimus trial populations. Was the comparability of trials discussed with clinical experts? Did ICER consider what important differences there were in clinical trial design, such as potential differences in the pimecrolimus vehicles between trials, or formulations used in the two studies?	Issues of comparability and trial design were discussed with clinical experts before deciding to perform an NMA.

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8	Pfizer	Clinical Effectiveness	We also ask that ICER include additional background regarding the limitations and adverse effects associated with topical therapies. On page 35 of the report, ICER notes that adverse events with crisaborole were rare. However, safety events were not reported for the other topical agents considered, except for a brief a statement "that concerns about the safety of other topical agents may be greater than is warranted". We disagree with that statement, as side effects and limitations of use are well documented for the topical agents considered. For example: continuous use of topical steroids for long periods of time are not recommended, and use on thin skin areas should be limited. Similarly, use of topical calcineurin inhibitors is recommended only for short term and non-continuous chronic treatment, and safety concerns have led to the issuance of a black box warning label from the Food and Drug Administration.	Side effects of TCS and TCIs are discussed in the report, including on page 6.
9	Pfizer	Clinical Effectiveness	Even with the caveat of "uncertainty" raised above, ICER's comment regarding the relative efficacy of crisaborole compared to other treatments is clearly overstated and misleading to readers who may not have the scientific basis to understand the limitations of ICER's approach. We ask that ICER replace its statements regarding the relative efficacy of crisaborole with more factual language that simply acknowledges that comparative analyses are currently not possible given the lack of data at this time.	We believe we have fairly summarized the evidence and uncertainties comparing crisaborole and other topical therapies. We have removed the summative statements attempting to predict the likelihood of relative efficacy.

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10	Pfizer	Clinical Effectiveness	Further, in reading the report we note that there are a number of sentences that we believe misrepresent the state of the evidence and / or data available related to crisaborole. Given that they are not based in fact, such statements significantly reduce the scientific value of ICER's approach and findings and thus could confuse readers. We ask that ICER carefully review the entirety of its report to identify and remove these and any other potentially misleading statements made regarding the scientific data regarding crisaborole. These include (but are not limited to): * Broad statements made without scientific backing, such as: o "Mild-to-moderate disease can often be effectively controlled with existing topical therapies, but concerns about the side effects of those therapies inhibit treatment in many patients" (page 12, emphasis added). > ICER presents no scientific data supporting the statement that mild or moderate disease can be effectively controlled with existing therapies. o "Trials of crisaborole also did not assess effects on productivity, but crisaborole is used in patients with mild-to-moderate atopic dermatitis where productivity effects are likely to be less pronounced" (page 37, emphasis added). > ICER presents no evidence that productivity issues are less pronounced in this population, and there are studies that suggest that there may be significant indirect impacts of AD on families.	We added citations for control of mild to moderate disease. We believe the sentence about productivity is accurate and fair as written.

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11	Pfizer	Clinical Effectiveness	* Specific statements which belie the statistical significance (or lack thereof) of findings: o "The improvement rate was moderately higher in the crisaborole arm than in the placebo arm for each individual atopic dermatitis sign evaluated, including erythema (59% vs. 40%; p<0.001), exudation (40% vs. 30%; p<0.001), excoriation (60% vs. 48%; p<0.001), induration/papulation (55% vs. 48%; p=0.008), and lichenification (52% vs. 41%; p<0.001)" (page 33, emphasis added). > ICER's statement that improvement rates are "moderately higher" does not reflect the statistical significance of the findings; the qualitative statement is not applicable. o "There was a trend suggesting pimecrolimus was superior to crisaborole" (page 34, emphasis added). > ICER's statement regarding this "trend" does not acknowledge the actual lack of statistical significance in its findings.	The expression "moderately higher" reflects relative efficacy, not statistical significance, and is common usage. The next sentence after, "There was a trend suggesting pimecrolimus was superior to crisaborole" is: "However, there were wide credible intervals, and the findings were not statistically significant." This seems to adequately acknowledge the lack of statistical significance as written.
12	Pfizer	Clinical Effectiveness	* Statements made referencing commentary from unidentified "experts" that are not supported by other scientific data: o "We heard from experts that this response was greater than that seen in placebo arms of most trials of topicals and may reflect that comparator preparations in some older trials included compounds that could be irritating and induce dermatitis"(page 36, emphasis added). o "We have heard from experts and patient groups that concerns about the safety of the other topical agents may be greater than is warranted…" (page 36, emphasis added) > In both cases above, ICER makes general	The lists of groups with whom we discussed the information in the report is available online. Expert reviewers are listed in the body of the report. If there are concerns that these statements are inaccurate, they should be communicated to ICER.

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			statements attributed to “experts”, but does not reveal the names or qualifications of these individuals, making it difficult to interpret the veracity of the claims made.	
13	Pfizer	Clinical Effectiveness	Concern #3: ICER should clarify the differences between vehicles and placebo in AD treatment, and consider the impact of changes in vehicles over time: Throughout its report, ICER refers to the vehicles used in treatment of AD as placebo. It is important to note that scientific consensus has delineated a clear and important role for vehicles in the treatment of dermatologic conditions like AD, namely that vehicles should (a) efficiently deliver and release the drug to the skin, (b) sustain drug substance level in target tissue to provide pharmacological effect, and (c) be acceptable to the patient.	We already discuss this issue in multiple places in the report, including in the section on Controversies and Uncertainties.

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14	Pfizer	Clinical Effectiveness	Experts have also noted that: * the chemical and physical characteristics of individual ingredients determine performance of a product's formulation; * properties of vehicle formulations may influence drug delivery, efficacy, and tolerance profiles of topical medications; * excipients have more pronounced effects in the skin than previously considered and can improve clinical appearance and skin barrier function; * petrolatum has an immediate barrier-repairing effect in delipidized stratum corneum As such, we recommend that ICER clarify the role of vehicle in the treatment of AD, and consider how changes in vehicle over time may have impacted the results of clinical trials for AD treatments.	See #13.
15	Pfizer	Clinical Effectiveness	Concern #4: ICER should clarify its process for how patient input was gathered and considered as part of its report: While we appreciate ICER's efforts to improve its patient engagement, we note a clear lack of transparency around the process for how inputs on patient perspectives were gathered and ultimately, how these inputs impacted (or did not impact) the findings. Greater clarity is needed to help resolve a number of questions that we (and likely other) stakeholders have, including: * How many and which specific organization(s) did ICER engage? Is ICER confident that it has the full perspective of the entire AD patient community, which spans many different types of patient	ICER engaged with multiple organizations throughout the review process, including the National Eczema Association, the Asthma and Allergy Foundation of America and the International Eczema Council. One of these organizations stated: "We are pleased that ICER took every reasonable step to identify and quantify the impact of AD on patient quality of life." Through these organizations and our clinical experts, we were able to hear from patients experience a range of atopic dermatitis severity.

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			subgroups (e.g., based on age, disease severity, expected outcomes of treatment etc)?	
16	Pfizer	Clinical Effectiveness	* Did ICER speak to patients in addition to advocates (who, while knowledgeable, may not be AD patients themselves, and therefore may have a different set of perspectives)?	ICER spoke with multiple individual patients throughout the review process. For privacy reasons, we do not publicly post the names of patients with whom we speak.

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17	Pfizer	Clinical Effectiveness	* How knowledgeable were these organization(s) with respect to the intent and processes of value assessment? Did they understand what the objectives of the review were, and did they understand the underlying methodologies to be implemented? What were their expectations for how their inputs will be utilized? Were these expectations met?	ICER maintained an ongoing relationship with these organizations, provided orientations to our process, discussed preliminary results with them, and engaged in continuous communication to allow for any follow-up or clarifications, as needed.

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18	Pfizer	Clinical Effectiveness	* What kinds of questions were posed by ICER to the patient advocacy groups? Did ICER send surveys? Did ICER engage in open-ended dialogue?	ICER engaged in an ongoing dialogue with the patient advocacy groups, including several phone conversations, open-ended discussions about treatments and the disease, listening sessions with patients, and more pointed discussions around our preliminary results.
19	Pfizer	Clinical Effectiveness	* Were patient groups asked about patient experiences across the spectrum of disease severity? If so, how did this influence ICER's approach?	ICER sought out patient experiences that represented a range of experiences and is confident that the experiences of the patients attending and participating in the public meeting will provide insight into the spectrum of disease severity.

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20	Pfizer	Clinical Effectiveness	* Were patient groups asked about what outcomes matter most to patients – and if so, was that information being considered as part of the ICER review?	This is the first question that ICER asks of patients and patient groups. Outcomes identified by patients as mattering most were considered, and where data was available, were included in our analyses. Where data was not available, ICER noted this limitation in the review.
21	Sanofi Genzyme	Clinical Effectiveness	Adjustments should be made to the content related to the qualitative comparison of dupilumab and cyclosporine. First, the Evidence Report should clearly note that cyclosporine is not approved in the US for the treatment of AD and is only sparsely used. Based on the cyclosporine product label for other indications, serious side effects are associated with its use including, but not limited to, risks for malignancies, serious infection, hypertension, renal structural damages, and nephrotoxicity. Due to these long-term safety issues, physicians hesitate to prescribe cyclosporine for use in AD patients.	These points are all already in the Evidence Report. See, for instance, pages 7 and 24.

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22	Sanofi Genzyme	Clinical Effectiveness	Second, comparison of clinical utility between dupilumab and cyclosporine should be based on an integrated assessment of the benefit/risk profiles of these therapies rather than on separate and general comparisons of efficacy and safety, respectively. In particular, the Draft Evidence Report concludes on page 29 that: (i) "Dupilumab appears likely to be at least as effective as cyclosporine…", and (ii) "… short-term experience with dupilumab suggests it may be safer than cyclosporine." The above statements in ICER's Draft Evidence Report fail to clearly describe the distinctly more favorable benefit/risk profile of dupilumab compared with cyclosporine in the management of this chronic disease.	We cannot know more definitively about the relative benefit/risk profiles until more information is available on dupilumab, particularly with long-term use.
23	Sanofi Genzyme	Clinical Effectiveness	Additionally, the statement in the Draft Evidence Report on page 31 "Cyclosporine has important toxicities, and is generally not used for more than one year," is based on empirical clinical experience due to the lack of high quality RCTs evaluating its benefit/risk profile. However, demonstrating a therapy's favorable benefit/risk profile over a long study period (e.g., 1 year) is highly meaningful in the context of a chronic disease such as AD.	Even over one year, we have limited evidence on potential uncommon adverse events with dupilumab.

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24	Sanofi Genzyme	Clinical Effectiveness	In contrast with cyclosporine, there is a substantial amount of data from high quality RCTs evaluating the benefit/risk profile of dupilumab [2]. These RCTs, in which more than 2,000 patients were exposed to dupilumab, demonstrated that dupilumab has a favorable benefit/risk profile in adult patients with moderate-to-severe AD whose disease was not adequately controlled with topical prescription therapies or when those therapies were not advisable.	We disagree. We have far more evidence on the harms of cyclosporine based on its use in other populations.
25	Sanofi Genzyme	Clinical Effectiveness	Failure to highlight the favorable benefit/risk profile of dupilumab based on high quality clinical trial data relative to the lack of quality data for cyclosporine, undermines the potential long-term value of dupilumab to patients who are eligible for treatment with this drug.	We feel we have appropriately reflected the current uncertainty in the evidence.

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26	Sanofi Genzyme	Clinical Effectiveness	Modify characterization of comparative clinical effectiveness of dupilumab and cyclosporine to reflect the discussion above.	See #25.
27	Sanofi Genzyme	Clinical Effectiveness	Remove Voting Question 3 in the Draft Voting Questions document as it is not feasible to perform an evidence-based assessment of the long-term value of cyclosporine compared with non-systemic treatment or dupilumab.	The voting question will allow the MW CEPAC to vote on the state of the evidence.

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28	AAD	Cost Effectiveness	While the ICER health economics model for dupilumab falls within generally-accepted thresholds for cost-effectiveness, as treating clinicians we feel the therapeutic value of dupilumab is even greater than the model suggests. The additional benefit, not included in the model include...: cost of improper treatment...the side effects of poor adherence to standard treatments, the opportunity costs and risk of unproven alternative treatments and potential consequences of systemic corticosteroid overuse.	The benefits from costs of improper treatment are implicitly included in the model, because the cost and quality of life data inputs included patients with varying levels of adherence. Longer term effects/harms such as those seen with long-term effects of systemic corticosteroid overuse may not have been fully captured and we have added this to the section on "Other Benefits and Disadvantages".
29	AAD	Cost Effectiveness	While the ICER health economics model for dupilumab falls within generally-accepted thresholds for cost-effectiveness, as treating clinicians we feel the therapeutic value of dupilumab is even greater than the model suggests. The additional benefit, not included in the model include...: infection...Skin infections are an ever-present problem for AD patients necessitating multiple antibiotic or antiviral courses. Skin infections cause pain and flares of AD and may result in hospitalization. In addition to the concerns of drug resistance, antibiotics come with a host of potential side effects. Another study...found adult patients with AD have a higher incidence of systemic infection, with some of these being related to skin...may have broader implication on overall health.	We agree that skin infections are an important part of AD. This is captured implicitly in the model. The data for health costs as well as data for quality-of-life include patients with many health outcomes, including infections. These data are representative of average patients, many of whom would have had infections. Text has been added to the report to further explain these data sources.

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30	AAD	Cost Effectiveness	While the ICER health economics model for dupilumab falls within generally-accepted thresholds for cost-effectiveness, as treating clinicians we feel the therapeutic value of dupilumab is even greater than the model suggests. The additional benefit, not included in the model include...: comorbidities. The impact of dupilumab on the well-described comorbid atopic diseases, especially asthma, was not captured in your economic model. Up to 40% of patients with moderate-to-severe AD have concomitant asthma; thus a medication treating multiple conditions in the same patient provides higher value. Dupilumab is also being developed for other atopic diseases found more common in this population such as nasal polyposis and eosinophilic esophagitis. Another comorbid condition dupilumab positively affects are mental health conditions...[anxiety and depression].	The model captured the economic effects of dupilumab on co-morbid diseases such as asthma, with the exception of the potential reduction in costs from stopping other medications for asthma. This is likely only relevant if substantial numbers of patients are stopping expensive therapies such as omalizumab, and this issue is raised in "Other Benefits or Disadvantages".
31	IfPA	Cost Effectiveness	"Data availability challenges" leave the report's impact on patients in question. [W]e have concerns regarding the timing of the ICER report...the analysis presents a hypothetical result that may, or may not, be applicable to dupilumab depending upon its final price. Yet the ICER methodology creates a cost-effectiveness value with an implied precision that is clearly inappropriate for a drug that has not yet been sold on the market. Moreover, the impact of this report on patient access if dupilumab either assumes a higher initial price, or rises over time to reach a higher price, than $30,000 remains unclear.	The draft report made it clear that $30K was a placeholder value. The report now relies on a net price informed by information from Sanofi-Regeneron.

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32	IfPA	Cost Effectiveness	Inattention to subjective factors such as quality of life benefits artificially deflates the value of these therapies to patients with atopic dermatitis. These benefit impacts are particularly important because, based on the assumed price of $30,000, dupilumab meets ICER's typical QALY cost thresholds. Therefore, if the assumed price is correct, then the value of dupilumab is much greater than ICER is acknowledging. Consequently, it is vital that the ICER report incorporate reasonable estimates of these subjective costs. Many behavioral economic studies provide methodologies designed to create cost proxies for subjective assessments. While applying these methodologies will be difficult, and care must be taken to ensure a correct estimate is used, ignoring the costs from subjective benefits create a serious bias against any medicine that is developed to address diseases with harder-to-quantify impacts.	Quality of life is explicitly included in the model. We applied utility values between 0 (death) and 1 (perfect health, depending on the treatment and responder state. See Table 15 for values used.
33	IfPA	Cost Effectiveness	Value estimates based on pricing assumptions and incomplete data could ultimately undermine access to treatment for patients with atopic dermatitis. To the extent that health plans use cost-effectiveness data to determine how accessible a treatment will be for patients, ICER's determination that dupilumab and crisaborole are cost effective may bode well for atopic dermatitis patients' ability to access treatment. That access retains an element of uncertainty, however, because of the tentative nature of the data used in calculating the therapies' value – in particular, the cost and long-term effectiveness of dupilumab. Tentative findings are vulnerable to reversal, leaving patients who find	Thank you for your comment.

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			stable treatment with dupilumab at risk of later losing access or facing non-medical switching attempts by their health plans.	
34	NEA/AAFA	Cost Effectiveness	It is unfortunate that the effectiveness of dupilumab for treating comorbidities, like asthma, was not captured in the ICER cost-benefit analysis. As the report concedes, “the overall benefit to quality of life of treating patients with dupilumab who also have other atopic diseases such as asthma and nasal polyposis should have been captured in [the] analyses.” The reason given in the report for not considering the cost offsets is a lack of data on the potential benefits of stopping other expensive therapies used to treat them. This is unfortunate. Dupilumab’s potential efficacy in treating atopic comorbidities could yield significant cost savings. These savings may positively affect dupilumab’s value estimate and provide a more accurate picture of its cost-effectiveness.	The model captured the economic effects of dupilumab on co-morbid diseases such as asthma, with the exception of the potential reduction in costs from stopping other medications for asthma. This is likely only relevant if substantial numbers of patients are stopping expensive therapies such as omalizumab, and this issue is raised in "Other Benefits or Disadvantages".

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35	NEA/AAFA	Cost Effectiveness	We would appreciate a clearer, more detailed, description of the ICER process used to develop cost estimates. For example, it would be useful to know if direct costs due to hospitalization can be linked to known AD comorbidities such as infection.	Text has been added to the report to further describe the cost data.
36	NEA/AAFA	Cost Effectiveness	We are pleased that ICER took every reasonable step to identify and quantify the impact of AD on patient quality of life…The final report would benefit from incorporating a broader spectrum of benefits and costs than what are captured in most clinical studies and cost-benefit analyses.	The benefits and costs included in the model do capture a wide spectrum, and the data sources used were from patients with varying levels of disease and comorbidities. Any benefits that could not be directly incorporated in the model are described in the 'other benefits and disadvantages' section.
37	Sanofi Genzyme	Cost Effectiveness	The cost-effectiveness analysis should be presented for the full moderate-to-severe AD population only without stratification by AD disease severity. Measuring disease severity in clinical trials based on Investigator's Global Assessment (IGA) at isolated time points (such as at study entry/baseline) is not necessarily indicative of what patients may experience during the course of their disease, since AD is a chronic disease where the severity of signs and symptoms wax and wane with a high degree of fluctuation.	We feel it is helpful to see the cost-effectiveness stratified by disease severity.

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38	Sanofi Genzyme	Cost Effectiveness	In the clinical setting, disease severity is determined based on a subjective assessment by physicians, which integrates AD signs, the patient's symptoms and their duration, response to current treatment, and the impact of the disease on quality-of-life (QoL). As indicated in the Draft Evidence Report on page 6, "Disease severity is not consistently defined and frequently involves patient/parent self-report in epidemiologic studies, and global clinical assessments used in trials (such as the Investigator's Global Assessment [IGA]). However, even with global clinical assessment measures, there are many variations used in studies." In fact, severity scales used in clinical trials, such as the IGA, do not necessarily correlate with the intensity of patient symptoms or degree of impact on QoL. Our clinical trial data suggest that there are no clinically meaningful differences in patient-assessed symptoms and QoL between patients with severe (IGA=4) and moderate (IGA=3) AD. For example, the minimal clinically important differences (MCID) for the pruritus numeric rating scale (NRS), Patient Oriented Eczema Measure (POEM) and Dermatology Life Quality Index (DLQI) are 3, 4, and 4, respectively. The differences in the pruritus NRS, POEM and DLQI between patients with baseline IGA=4 and patients with baseline IGA=3, were 0.53, 3.1, and 2.5, respectively, which are all below the MCIDs for the respective measures.	Utility data supplied by Sanofi Regeneron show substantial differences in baseline QOL between patients with moderate and severe disease. We expect that clinicians, patients, and payors will be interested in the differential effects in these populations. We understand these populations are heterogeneous and this is one of the reasons we have ranges around our estimates.

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39	Sanofi Genzyme	Cost Effectiveness	A patient's need for dupilumab treatment is not defined by clear demarcation of moderate versus severe disease as measured by IGA, but relies on a dichotomized assessment of whether or not patients with moderate-to-severe AD warrant such therapy because their disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Thus, the reported individual cost-effectiveness analyses of dupilumab based on baseline IGA scores of 4 versus 3 are of limited clinical utility. These may be interpreted to imply that stakeholders such as physicians should follow treatment plans solely based on the severity of skin signs without considering patients' symptoms and QoL.	We believe the discussion at the public meeting will be able to address and inform such issues.
40	Sanofi Genzyme	Cost Effectiveness	Finally, ICER's assessment of the effectiveness and value for the treatment of other indications such as psoriasis did not include separate cost-effectiveness assessments of moderate versus severe psoriasis. A similar approach should be taken for ICER's assessment of dupilumab for the treatment of atopic dermatitis.	See #39.
41	Sanofi Genzyme	Cost Effectiveness	Assess the value of dupilumab as per the clinical trial design for the integrated moderate-to-severe population whose disease is not adequately controlled with topical prescription therapies or for whom topical therapies are not advisable. In particular, results for cost-effectiveness on page 44 in the Draft Evidence Report should not be stratified by disease severity.	See #39.

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42	Sanofi Genzyme	Cost Effectiveness	Combine the voting questions on long-term value and pose the question as follows: "Given the available evidence on comparative clinical effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, in adults with moderate-to-severe atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment? (Low, Intermediate, High)"	See #39.
43	Sanofi Genzyme	Budget Impact	More details should be included in the report to facilitate replication of the budget impact analysis by stakeholders. In particular, additional explanation for the calculations leading to the results presented in Table 21 on page 50 of the Draft Evidence Report would be valuable. Also, clarifying if the uptake results are annual or cumulative over 5 years would be helpful.	The results are updated, and we have added more explanation.

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44	Sanofi Genzyme	Budget Impact	Finally, the titles/description of the tables noted in the text on pages 48-50 do not match the titles of the respective table numbers.	Updated, thank you.
45	Patients for Affordable Drugs	Overall	Input from certain patient groups must be scrutinized in light of their funding. *The New England Journal of Medicine* recently reported that 83 percent of patient groups in the U.S. receive funding from pharma. *The New York Times* has documented the chilling effect that pharma funding can have on patient groups' positions on pricing. Sadly, there are groups that go further and attack ICER's steps to curb unfair prices. Many of these groups represent drug corporations over patients. We hope that ICER will not be influenced by groups that are funded by and operate on behalf of drug corporations."	ICER appreciates this comment. We take steps to ensure that any pertinent conflicts of interest are identified and disclosed publicly. Clinical experts, policy roundtable participants, public commenters, and the voting panel all are required to disclose their conflicts publicly.