Anthem

Submitted electronically via: publiccomments@icer-review.org

November 29th, 2016

Institute for Clinical and Economic Review (ICER)
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: ICER to Review Treatments for Atopic Dermatitis

To Whom It May Concern:

Anthem is working to transform health care with trusted and caring solutions. Our health plan companies deliver quality products and services that give their members access to the care they need. With over 73 million people served by its affiliated companies, including nearly 40 million enrolled in its family of health plans. For more information about Anthem's family of companies, please visit www.antheminc.com/companies.

In Anthem's role as a payer we share ICER's commitment to researching and evaluating drugs through a value-based lense. As such, Anthem offers services to address all facets of member care, including treatments to address atopic dermatitis, both mild-to-moderate and moderate-to-severe. Systemic treatments that have shown success for some patients but lack FDA approval, highlight the heterogeneity of patient populations and make the case for comparing the clinical effectiveness of crisaborole and dupilumab that much more essential.

The current ICER draft scoping document for review of treatments for atopic dermatitis notes *review populations* for dupilumab as "adults with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy" and *comparators* for dupilumab as "non-systemic therapy for moderate-to-severe atopic dermatitis (emollients with or without a topical corticosteroid or calcineurin inhibitor)".

Understandably, the pivotal trial evaluating dupilumab enrolled individuals with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy; however, phototherapy (although not widely utilized in the United States) is supported by atopic dermatitis guidelines[1]

[1] American Academy of Dermatology (2014); and European Academy of Allergy and Clinical Immunology/American Academy of Allergy, Asthma and Immunology Consensus Report (2006)

as second-line therapy for individuals with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy. Furthermore, documented systemic treatment for atopic dermatitis 6 months preceding trial enrollment was used as inclusion criteria in the pivotal trial (equivalent to inadequate response to topical treatments). For these reasons, we believe that ICER should consider the following:

- **For *review populations* for dupilumab**, consider adults with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, and/or phototherapy, and/or systemic treatment.
- **For *comparators* for dupilumab**, consider non-systemic therapy for moderate-to-severe atopic dermatitis (emollients with or without a topical corticosteroid or calcineurin inhibitor) and/or phototherapy, and/or systemic treatment.
- **Failing to consider populations and comparators** outside of the pivotal clinical trial inclusion criteria undermines the clinical utility of the ICER review, and limits interpretability for real-world clinical practice.

In conclusion, we would also seek to strongly encourage organizations like ICER to monitor the value of treatments for atopic dermatitis when monitoring the cost of new market entries to ensure that these drugs (both brand and generic) are not resetting the market in a way that causes untenable cost burdens on patients and payers (both public and private). And as a final thought, we would also respectfully request ICER strongly consider expanding evaluating comparative effectiveness with additional treatments for atopic dermatitis.

Sincerely,

Geoffrey B. Crawford, MD, MS

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Re: IEC Board of Directors Comment on ICER's Draft Scope for Atopic Dermatitis

We are writing as the Board of Directors of the International Eczema Council ("IEC"), the global nonprofit organization of dermatologist experts on Atopic Dermatitis (AD) from 20 countries. IEC is dedicated to increasing the understanding of AD and promoting its optimal management through research, education and patient/family care. Two components of the IEC mission are to disseminate evidence-based information about AD and its optimal management to health care professionals and the public, and to promote good practices in the care of patients with AD worldwide. As the only global organization of its kind dedicated solely to AD, the IEC would like to share its insights on:

- The high immediate and long-term burden of AD, including systemic comorbidities, which impacts patients, their families and society as a whole
- The lack of effect of topical therapies on most individuals with moderate-to-severe AD
- The limitations and dangers of currently available systemic immunosuppressants used for AD
- The need to compare dupilumab to the systemic therapies it will replace, not to ineffective topical therapies

Our Councilors, international leaders in AD care, have had personal experience in clinical trials with new topical and systemic medications for AD and are excited about their upcoming availability.

Burden of AD

Atopic Dermatitis, commonly known as eczema, is a chronically relapsing skin disease which has profound impacts on patient and family quality of life (QoL).[1] It is also a very common disease affecting 11-20% and 7% of US children and adults, respectively.[2,3] Moreover, some estimates of the prevalence of AD are as high as 31.6 million patients in the US.[4] As AD is a disease that typically begins in childhood, but often continues or begins in adulthood, it clearly affects patients and their families throughout their lifetime. The patient and societal burden of AD is significant not only in terms of its impact on QoL, but also its social, academic, economic, and occupational consequences.[1]

The impacts on QoL include both physical aspects such as itching and scratching, sleep, pain, bleeding and dietary limitations, as well as emotional aspects, including behavioral problems, irritability, and crying.[5] Social isolation is prevalent in AD children[5], and generalized AD is second only to cerebral palsy regarding impact on QoL in children.[6] Parents are required to devote additional time to care for children with AD and exhibit issues related to lack of sleep.[7] Evidence shows that adults with AD also experience profound impact on QoL attributable to physical and social functioning. Adults with AD score lowered in mental health measures than patients with type 2 diabetes, hypertension and depression, and fared better only than those with clinical depression.[8] The economic toll of AD is also staggering, and includes direct costs, such as prescriptions, physician visits, and emergency and hospital costs as well as indirect costs including decreased productivity and absenteeism. Conservative estimates of direct costs are over $1 billion, while indirect costs are over $3 billion.[9]

In addition to the direct impact of AD on QoL, the list of comorbid disorders associated with AD is growing.[10,11] Bacterial and certain viral infections of skin are a well-recognized association that add to the burden of disease and have been linked to greater disease severity and poor control.[12, 13, 14] In particular, recurrent staphylococcal infections in patients with moderate-to-severe AD require frequent courses of oral antibiotic therapy. The risk of "marching" from early AD to other atopic disorders, including life-threatening asthma and food allergies, suggests that more aggressive early control of disease and improvement of the epidermal barrier could prevent the later development of asthma, as well as food allergies and allergic rhinitis. Attention deficit-hyperactivity disorder (ADHD) is now clearly linked to AD, and particularly more severe AD with sleep issues[15,16,17]; whether improvement

in disease severity and sleep directly reverses the ADHD once present vs. reducing the risk of ADHD by disease control during infancy and childhood as neurocognitive function develops is currently unknown. Depression, anxiety, and even suicidal ideation have clearly been linked to AD, particularly more severe AD,[18] suggesting that better disease control through therapeutic interventions lower the risk of these comorbid psychiatric disorders.[19,20,21,22] Finally, several emerging comorbidities – ranging from extracutaneous infections to cardiovascular disease [23,24,25,26,27,28] to lymphoma [29,30,31] have been associated with AD, further suggesting the importance of sustained disease control not only improving one's QoL, but also reducing the risk of systemic, even life-threatening diseases.

Currently available therapy and the emergence of new alternatives

Topical corticosteroids continue to be the main treatment for the majority of patients with AD, but their chronic use is complicated by the possibility of local side effects, particularly skin atrophy/ striae. With more extensive involvement of AD and widespread application of higher strength steroids, there is a risk of systemic side effects. Although these risks are very low, fear of their occurrence has led to a steroid phobia in patients, caregivers, and even physicians who are not as experienced in topical steroid utilization. Steroid phobia dramatically reduces the ability to use topical steroids effectively. While topical calcineurin inhibitors emerged 15 years ago as an alternative to topical steroids and have been shown to be safe and effective, the decision to place a black box warning for the theoretical risk of cancer (which never materialized in studies to date), coupled with their limited efficacy, sharply curtailed the availability of topical calcineurin inhibitors and led to phobia about their use as well. Therefore, <u>there continues to be a high unmet need for safe and effective topical treatments that are suitable for long-term use</u>, including in sensitive areas such as the face and groin, and are both embraced without phobia and accessible. Crisaborole, a topical phosphodiesterase 4 (PDE4) inhibitor, appears to be such an alternative and is approaching FDA approval. It has shown safety and proven efficacy in both adults and children.

We currently lack systemic treatments that are suitable for long term, chronic use in patients with moderate-to-severe AD, as the few available systemic treatments harbor significant side effects. Phototherapy is variably effective for AD, but requires 3 visits per week to a dermatologist, a regimen which is challenging for most patients. The most commonly used systemic medication for adults affected by AD is systemic corticosteroids, which is currently the only FDA-approved systemic intervention. However, use of both intramuscular triamcinolone and oral prednisone should be discouraged other than for short-term use prior to transition to other agents. Steroids tend to be quite effective, but virtually always end with rebound and acute AD flares upon discontinuation, in addition to the many long term side effects associated with their use (weight gain, cataracts, striae, osteoporosis, hypertension, etc). Cyclosporine A (CsA) has been shown to lead to permanent kidney damage after more than one year of use,[32, 33] in addition to its many other risks, particularly hypertension. Other systemic medications used in AD (azathioprine, mycophenolate mofetil, methotrexate) are slower to act than corticosteroids and CsA (often at least 6-8 weeks) and themselves have serious side effects (such bone marrow suppression, hepatitis, global immunosuppression). All of these agents require extremely close monitoring and regular (and costly) laboratory investigations to further ensure safety.

Given these side effect risks, the use of these global immunosuppressant medications is reserved only for the most severely affected patients, leaving many who need systemic intervention with only topical therapies, which have limited value in patients with moderate-to-severe AD. Thus, there is a <u>huge unmet need for a safe, and effective systemic long-term treatment</u> for the patients with moderate-to-severe AD. A decade ago, the armamentarium for treating psoriasis was similar, and the availability of targeted treatments has revolutionized psoriasis care, markedly lowering the risk for affected

individuals and improving outcomes, both in terms of efficacy and safety.

Dupilumab, a fully humanized monoclonal antibody directed against the interleukin 4 receptor, is the first targeted therapy available for AD, and its excellent efficacy and few side effects is reminiscent of that offered by the currently available biologic targeted agents for psoriasis. Dupilumab provides a safe medication with an efficacy that is equal if not higher than that of CsA, the most effective currently-available nonsteroidal medication for AD based on meta-analysis data. In these studies, CsA showed 55-70% efficacy vs. dupilumab showing >70% improvement in disease efficacy at 12 weeks.[34] Of course, CsA's dangers necessitate its discontinuation by 1 year after initiation, while dupilumab shows a very good safety profile.[35,36,37] We must also remember that when patients are on systemic immune suppressants such as CsA or prednisone, there needs to be constant monitoring for laboratory abnormalities and infections. This is not the case with dupilumab, which has to date shown no signal for concern about laboratory values, a trend towards decreased risk of cutaneous infections, and no increased risk of systemic infection.[35,36,37]

New systemic medications should be compared only with available systemic therapies

As a note, we were perplexed by the plan to compare dupilumab to non-systemic therapy, although we assume this plan was based on the fact that only systemic corticosteroids are approved by the FDA for use in AD. Nevertheless, since dupilumab and other systemic interventions in the future will be used in lieu of the more risky, currently available conventional systemic therapies for AD, these conventional systemic medications are the proper comparators. Treating patients with more severe AD with topical corticosteroids is not only ineffective, but is simply impractical and carries the high risk of systemic absorption. Furthermore, there is increasing evidence that AD in patients with moderate-to-severe disease is associated with systemic immune activation to a degree even higher than in psoriasis,[38] in which systemic immune activation has been linked to a high risk of metabolic/ cardiovascular disease. In fact, AD has also been associated with an atherosclerosis genomic profile[39]. Immune lymphocyte subsets and cytokine activation in blood correlates with disease severity,[40,41] and immune and barrier abnormalities are consistently observed in the uninvolved ("non-lesional") skin of AD patients, in contrast to the nonlesional skin of psoriasis, again correlating with disease severity.[42] Comparing dupilumab efficacy, risks and costs to topical treatments would not be as valuable as comparing dupilumab to conventional systemic immunosuppressants used for AD.

The need for new topical and systemic therapy

We are facing an exciting era in AD. After 15 years without any therapeutic advances in AD, the first new drugs will finally be available for treating AD: crisaborole for topical and dupilumab for systemic use. These treatments show great promise for efficacy of mild-to-moderate and moderate-to-severe AD, respectively. In addition, these agents lack the side effect risks associated with current treatments, particularly for the long term use required for AD patients. We strongly urge ICER to take into account the huge COSTS of currently available therapy – not just the more easily quantified costs of frequent physician visits for monitoring or intervention, laboratory testing, and lost work time of patients who actually are treated with immunosuppressant drug treatment, but also the real costs of poor control and persistent suppression of quality of life that result from NOT initiating immunosuppressant therapies when needed because of universal (and legitimate) fears from physicians and patients alike about potential side effects with long-term, chronic use of these conventional immunosuppressants.

Board of Directors, the International Eczema Council: Amy Paller, MS, MD, Emma Guttman-Yassky, MD, PhD, Lisa Beck, MD, Kevin Cooper, MD, Georg Stingl, MD, Carsten Flohr, FCRP, PhD, Kenji Kabashima, MD, PhD, and Robert Bissonnette, MD, MSc, FRCP

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December 9, 2016

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To Whom It May Concern:

On behalf of the National Eczema Association (NEA) and the Asthma and Allergy Foundation of America (AAFA), we wish to thank the Institute for Clinical and Economic Review (ICER) for taking up the challenge of evaluating the comparative clinical effectiveness of Crisaborole for the treatment of mild-to-moderate atopic dermatitis (AD) in children and adults; and the clinical effectiveness and value of Dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults. Our organizations are grateful to ICER for inviting us to provide a perspective on patient experiences with AD. We thank ICER for opening its evaluation process to public review and look forward to working with ICER to make sure that patient perspectives on quality of life, care, and treatment value are represented as this process moves forward.

This letter responds to ICER's draft background and scope document: "Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness, Value, and Value-Based Price Benchmarks." In general, our comments address our concerns about three broad aspects of the research plan: the outcomes considered by ICER as part of its review; the data that are used to support its analyses of those outcomes; and the model and methods that ICER will use to estimate value.

The proposed review does not capture the full range of outcomes that matter to patients and their families. The proposed scope identifies an important set of outcomes that are relevant to patients and families with AD. However, there are a number of others that are not mentioned: in particular, bullying; limitations on pursuing outside interests and social interactions; perception of health/well-being, restrictions on diet, exercise, and recreation; time taken to treat AD; intimacy; presenteeism for adults at work and children in school; unemployment and underemployment; and suicidal ideation. These additional outcomes may be especially important to consider, as the many of these may disproportionately affect underserved populations.

The proposed review does not address the potential impact of these treatments on co-morbid conditions—so, it may significantly underestimate their value. The association of AD with other chronic conditions is well documented. Recent studies have demonstrated that it is associated with a higher prevalence of asthma, allergic rhinitis, and food allergies in children, and that the severity of

AD is directly proportional to the severity of these comorbidities. Patients with AD are more likely to experience nasal polyps, hypertension, stroke, and obesity. These conditions can be very expensive to treat and the degree to which their prevalence and/or severity can be affected by one of these treatments should be considered.

This is particularly important with respect to Dupilumab. As we noted in our November 7 comments, Dupilumab may improve outcomes for two important comorbid conditions. Recent clinical studies confirm that Dupilumab is effective for the treatment of both asthma and nasal polyps. The clinical benefits associated with the use of Dupilumab in patients with these comorbidities should be explicitly considered in the analysis, as should the impact of those clinical benefits on other outcomes (health system utilization and cost of care, lost time at work/school, and so on) that tie to that clinical benefit.

The proposed approach does not consider costs as patients perceive them. The proposed simulation model appears to be anchored in economic models that drive off of direct (and, to a lesser extent, indirect) medical costs as accounted by health insurers and/or society. There is no doubt that these costs are important, but a patient-centered analysis of value requires consideration of the costs that patients face, and how these costs will affect their perceptions of "value" as consumers and their compliance as patients. If the intent is to limit the scope to assessments of "value" as payers perceive it, we think it important that ICER call that out specifically and explicitly as a limitation of the model.

The proposed approach does not consider—and will fail to capture—variations in value among patient groups. People with AD—as people with other chronic conditions—differ with respect to their preferences; there may be subgroups of individuals for whom certain outcomes are significantly more important than they are for the majority. And people with AD—as people with other chronic conditions—vary with respect to their ability or propensity to seek different types of therapies.

To the extent that these are true, the proposed approach—which is "population based" so that it estimates value "at the mean"—will fail to recognize groups for whom value may be extremely high. Such an approach does not drive toward true patient-centeredness, nor the promise of personalized medicine toward which the healthcare system aspires.

The proposed review does not consider the potential for long-term effects, particularly related to the potential for Dupilumab to modify the underlying atopic disease process. While the long-term impact of these agents—and particularly Dupilumab—on the underlying course of AD is not known, it may be important at least to consider in the analysis what the potential for disease modification may be, and what impact that would have long-term on clinical outcomes and cost. This impact may be either positive or negative; it is possible that, with therapy, the need for therapy (through disease modification) will be reduced. It is also possible that immunologic intervention may change the course of disease in a way that reduces the likelihood of remission over time. It may be appropriate to attempt to estimate these effects using reasonable assumptions, to understand potential additional benefits that will accrue over time.

The proposed review should include gray literature in its synthesis of the available evidence to support conclusions regarding the symptoms and burden of AD. The proposed approach appropriately recognizes many important outcomes have not been adequately addressed in randomized trials. We appreciate that ICER is committed to looking for evidence where available, and reiterate our commitment to working with and supporting ICER's investigators in this effort.

ICER's stated policy is "to evaluate the grey literature as part of its assessment of the potential for publication or reporting bias, but not to include such sources in its synthesis of the available evidence." It provides exceptions for situations in which the evidence base is deemed to be "rapidly evolving" such that grey literature represents a significant portion of the available evidence. We believe that this

is a situation in which ICER ought to be prepared to seek and include evidence from that broader literature.

Given that, we want to note that NEA launched a survey series called "In Your Words" in 2016, to learn more about the challenges that confront people affected by AD, which includes not only patients, but their caretakers and providers, experience with the disease. To this point, NEA has conducted surveys that evaluate patient satisfaction and the role of doctors in the treatment of AD, how AD impacts school-age children and their families, and how AD affects the lives of adults with the disease. We are eager to make these results available to ICER

And we want again to note that NEA and AAFA have underway a large and potentially very relevant research project. Modeled after AAFA's landmark "Anaphylaxis in America Study," "AD in America" involves surveys of adults (both with, and without, AD) and of physicians (allergists, dermatologists, and internists) to evaluate the impact of AD on the lives of those with the condition, and to assess awareness, knowledge, and behaviors related to AD. Data collection is underway and will proceed through the end of 2016. We expect to have insights from the work in the first quarter of 2017.

We are eager to explore with ICER how those insights can help inform the proposed report; at a minimum, we believe that AD in America can be very important to establishing to what extent the ICER analysis aligns with current patient perceptions of value, as well as establishing baselines against which the effects of Dupilumab and Crisaborole can be compared in the future.

Again, we want very clearly and directly to communicate our interest in further conversation with ICER, regarding the potential for AD in America—and the understanding of patient voice that will emerge from it—to assist ICER to understand the challenges and opportunities that exist to increase value for Americans with AD.

Finally, ICER should solicit public comment on its proposed economic simulation model once the model is detailed in its final scoping document. Per the draft paper, ICER will develop an economic simulation model to the assess the cost-effectiveness of Dupilumab versus a non-systemic therapy, like the one advanced in Hjelmgren et al. Unfortunately, the draft plan does not provide enough detail concerning the methodological appropriateness of using this model to compare a systemic with a topical treatment or address the question of why Crisoborole is not considered in the model.

Thank you again for ICER's efforts to incorporate the input of AD patients into its analysis of these drugs. We are grateful that your office reached out to us and look forward to working with ICER as this study takes shape. If you have any questions about what we have written here or about patient perspectives on any aspect of this analysis, please feel free to contact us.

Regards;

Julie Block
President and CEO
NEA

Cary Sennett, MD, PhD, FACP
President and CEO
AAFA

Sanofi Genzyme and Regeneron Pharmaceuticals welcome the opportunity to provide comments to the Institute for Clinical and Economic Review (ICER) on the Atopic Dermatitis: Draft Scoping Document. We recommend that the key points below be strongly considered. The order below tracks the Analytic Framework in ICER's November 7 Atopic Dermatitis Draft Background and Scope:

1. Prevalence
    - The scoping document indicates that atopic dermatitis (AD) affects 3%-7% of the US adult population. In fact, these prevalence estimates include mild, moderate and severe AD patients. In the US, the prevalence of adults with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies (i.e. the proposed dupilumab label population in the US) is approximately 0.7% (about 1.6 million patients).[1] To estimate the size of the dupilumab-treated patient population over the first five years on the market, we recommend assuming a biologic uptake pattern that is similar to that reported for psoriasis. Data reported to date suggests a low biologic drug uptake pattern. In 2011, seven years following the introduction of the first biologic indicated for the treatment of psoriasis, the proportion of patients receiving biologics for the treatment of moderate-to-severe psoriasis was only about 16%;[2] thus, we estimate the number of biologic-treated psoriasis patients in the US to be under 250,000. By extension, the number of dupilumab-treated patients would likely follow a similar low uptake pattern in the first 5 years after launch and would include a small fraction of the estimated 1.6 million adult patients in the US.

2. Populations
    - For dupilumab, we recommend the following modification to the proposed population: adults with moderate-to-severe AD inadequately controlled with topical therapy, *or for whom topical therapies are medically inadvisable.*

3. Interventions
    - We agree with ICER's proposed scope of Interventions

4. Comparators
    - We agree with ICER's proposed scope of Comparators

5. Outcomes
    - We agree in principle, but we would like to confirm the specific measure of health-related quality of life instrument ICER is proposing to use as a Key Measure of Clinical Benefit. Other health economic (HE) models developed in inflammatory skin conditions, such as psoriasis, utilized changes in the Euroqol-5D (EQ-5D) among treatment responders to inform improvements in health related quality of life. The EQ-5D has also been included in the dupilumab Phase 3 program and we recommend using it in the ICER model when evaluating the cost-effectiveness of dupilumab in adult patients with moderate-to-severe AD.

6. Timing
    - We agree with ICER's proposed scope of Timing

7. Settings
    - Dupilumab is intended to be supplied in single-dose prefilled syringes. It is intended for subcutaneous injection in an out-patient setting.

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- Dupilumab is intended to be administered by the patient or a caregiver after receiving adequate training from a healthcare provider.

8. Simulation Models Focusing on Comparative Value
    - We believe it is inappropriate to base the dupilumab HE model structure on previously published economic models aimed at assessing treatments for moderate-to-severe AD, such as the study published by Hjelmgren et al.[3] This study assessed the cost-effectiveness of tacrolimus ointment versus standard therapy in a similar population of patients with moderate and severe AD. However, tacrolimus is indicated for "the short-term and non-continuous chronic treatment of moderate-to-severe atopic dermatitis."[4] As a result, the Hjelmgren model utilizes a relatively short follow-up time of 12 months during which patients cycle in between several health states (i.e. severe, moderate, and virtually cleared). While such a model structure is appropriate for a topical medicine intended for short-term use, it is not appropriate for the assessment of a systemic therapy, such as dupilumab, which is currently under investigation for the long-term treatment of adult patients with moderate-to-severe AD. In addition, patients in the Hjelmgren model are assumed to continue on therapy for the entire model duration of 12 months. While this assumption may be reasonable for a treatment such as tacrolimus, it would be inappropriate to assume that patients who do not respond to dupilumab would continue on the therapy, and incur the cost of dupilumab, over the entire duration of a 10-year or lifetime model.

      Rather than base the current model on the one published by Hjelmgren, we strongly recommend a model structure adapted from cost-effectiveness models of biologic therapies also indicated for long-term chronic use in similar inflammatory skin conditions, such as psoriasis. Many published HE models and health technology assessment (HTA) submissions of biologic psoriasis therapies are based on a model developed at the University of York.[5] This model utilizes data from published randomized clinical trials to define treatment response after an initial treatment period. Patients who respond to therapy after the initial treatment period are assumed to continue on therapy, while patients who do not respond are assumed to discontinue and transition to non-targeted therapy or supportive care. Allowing for treatment discontinuation upon non-response is a core element of HE models in various other immunological conditions,[6,7] but this concept had not been previously incorporated into the short-term HE models in AD.[3,8] The York model also allows for extrapolation of clinical and economic outcomes over a 10-year or even lifetime horizon.

      The most recent cost-effectiveness model conducted by the New England CEPAC was also based on the York model.[9] However, in contrast with psoriasis, where multiple classes of biologic treatment options are available and eight individual drugs were included in the ICER model, it may be necessary to adapt the AD model. This can be done by eliminating the transition to second-line therapy following treatment with dupilumab, and transition non-responding patients immediately to non-systemic therapy.

      Finally, we would like to reiterate our position regarding the relevant cost-effectiveness threshold. Given the substantial burden of disease and unmet need in AD patients with moderate-to-severe disease who are candidates for systemic therapies, the lack of safe and effective treatment options, and the overall favorable risk-benefit profile of dupilumab, we believe dupilumab constitutes potentially high 'care value'. We therefore recommend that ICER employ a cost-effectiveness threshold at the upper end of the range stated in the current ICER framework, (*i.e.* $150k/QALY gained), as a benchmark to assess the cost-effectiveness of dupilumab. This would also be in line with World Health Organization recommendations.[10]

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