# JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Effectiveness and Value

**Evidence Report**

**July 9, 2021**

**Prepared for**

| ICER Staff and Consultants | The University of Washington Modeling Group |
|---|---|
| **Steven J. Atlas, MD, MPH**<br>Associate Professor of Medicine<br>Harvard Medical School, Boston<br>Director, Practice Based Research & Quality Improvement<br>Division of General Internal Medicine<br>Massachusetts General Hospital<br><br>**Grace E. Fox, PhD**<br>Research Lead<br>ICER<br><br>**Foluso Agboola, MBBS, MPH**<br>Vice President of Research<br>ICER<br><br>**Jon D. Campbell, PhD, MS**<br>Senior Vice President for Health Economics<br>ICER<br><br>**Steven D. Pearson, MD, MSc**<br>President<br>ICER<br><br>**David M. Rind, MD, MSc**<br>Chief Medical Officer<br>ICER | **Elizabeth Brouwer, PhD, MPH**<br>Research Scientist<br>The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute<br>Department of Pharmacy<br>University of Washington<br><br>**Josh J. Carlson, PhD, MPH**<br>Associate Professor<br>The CHOICE Institute<br>Department of Pharmacy<br>University of Washington<br><br>**Yilin Chen, MPH**<br>PhD Student<br>The CHOICE Institute<br>Department of Pharmacy<br>University of Washington<br><br>**Ryan N. Hansen, PharmD, PhD**<br>Associate Professor<br>The CHOICE Institute<br>Department of Pharmacy<br>University of Washington<br><br>*The role of The University of Washington is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of The University of Washington.* |



**DATE OF PUBLICATION:** July 9, 2021

**How to cite this document**: Atlas SJ, Brouwer E, Fox G, Carlson JJ, Campbell JD, Agboola F, Hansen RN, Pearson SD, Rind DM. JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, July 9, 2021. https://icer.org/assessment/atopic-dermatitis-2021/#timeline

**Acknowledgements:** Steven Atlas served as the lead author for the report and wrote the executive summary, background, patient and caregiver perspectives, uncertainty and controversies, summary and comment, potential other benefit and contextual considerations, definitions and oversaw the comparative clinical effectiveness sections in the main report and supplemental information. Grace Fox and Foluso Agboola led the systematic review and wrote the clinical effectiveness sections in collaboration with Steven Atlas. We would like to acknowledge the work of Serina Herron-Smith and Emily Nhan who contributed to the clinical effectiveness sections. Josh Carlson, Ryan Hansen, and Elizabeth Brouwer developed the economic model and authored the cost-effectiveness sections in collaboration with Yilin Chen. Jon Campbell provided methods guidance for the cost-effectiveness modeling and authored the budget impact analysis section. David Rind and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. We would like to thank Ashton Moradi for his contributions to the budget impact analysis. We also thank Maggie Houle, Liis Shea, and Zunelly Odhiambo for their contributions to this report.

## About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 21% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include: AbbVie, Eli Lilly, Incyte, Leo Pharma, Pfizer, Regeneron, and Sanofi. For a complete list of funders and for more information on ICER's support, please visit our independent funding webpage.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

## About New England CEPAC

The New England CEPAC – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The CEPAC Panel is an independent committee of medical evidence experts from across New England, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about CEPAC is available at https://icer.org/who-we-are/people/independent-appraisal-committees/new-england-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

*In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.*

*For a complete list of stakeholders from whom we requested input, please visit:* https://icer.org/wp-content/uploads/2021/01/ICER_Atopic-Dermatitis_Stakeholder-List_011521.pdf

## Expert Reviewers

**Wendy Smith Begolka, MBS**
**Vice President, Scientific and Clinical Affairs**
**National Eczema Association**
*Wendy is a salaried employee of the National Eczema Association which has received grants and sponsorship awards from a variety of industry partners.*

**Jonathan Silverberg, MD, PhD, MPH**
**Associate Professor of Dermatology**
**The George Washington University School of Medicine and Health Sciences**
*Dr. Silverberg has received honoraria as a consultant and/or advisory board member for AbbVie, Eli Lilly, Incyte, Leo Pharma, Pfizer, Regeneron, and Sanofi. He has also served as a speaker for Eli Lilly, Leo, Pfizer, and Regeneron.*

**Eric Simpson, MD, MCR**
**Professor of Dermatology**
**Oregon Health & Science University, School of Medicine**
*Dr. Simpson receives honoraria and grants from AbbVie, Eli Lilly, Incyte, Leo Pharma, Pfizer, Regeneron, and Sanofi.*

# Table of Contents

## List of Acronyms and Abbreviations Used in this Report

| | |
|---|---|
| **ADerm-IS** | **Atopic Dermatitis Impact Scale** |
| **AE** | **Adverse event** |
| **AHRQ** | **Agency for Healthcare Research and Quality** |
| **BSA** | **Body surface area** |
| **CDLQI** | **Children's Dermatology Life Quality Index** |
| **CPI** | **Consumer Price Index** |
| **DFI** | **Dermatitis Family Impact questionnaire** |
| **DLQI** | **Dermatology Life Quality Index** |
| **EASI** | **Eczema Area Severity Index** |
| **EQ-5D** | **EuroQol five-dimension questionnaire** |
| **FDA** | **Food and Drug Administration** |
| **HADS** | **Hospital Anxiety and Depression Scale** |
| **IGA** | **Investigator's Global Assessment** |
| **IL** | **Interleukin** |
| **JAK** | **Janus kinase** |
| **NICE** | **National Institutes for Health and Care Excellence** |
| **NMA** | **Network meta-analysis** |
| **PDE 4** | **Phosphodiesterase 4** |
| **PICOTS** | **Population, Intervention, Comparators, Outcomes, Timing, and Settings** |
| **POEM** | **Patient-Oriented Eczema Measure** |
| **PP-NRS** | **Peak Pruritus Numerical Rating Scale** |
| **PRISMA** | **Preferred Reporting Items for Systematic Reviews and Meta-Analyses** |
| **QALY** | **Quality-adjusted life-year** |
| **QoL** | **Quality of life** |
| **QW** | **Weekly dosing regimen** |
| **Q2W** | **Every two-week dosing regimen** |
| **RCT** | **Randomized controlled trial** |
| **SCORAD** | **Scoring Atopic Dermatitis** |
| **SLR** | **Systematic literature review** |
| **TCI** | **Topical calcineurin inhibitors** |
| **TCS** | **Topical corticosteroids** |
| **USPSTF** | **US Preventive Services Task Force** |
| **WPAI** | **Workplace Productivity and Activity Impairment** |
| **WTP** | **Willingness to pay** |

# Executive Summary

Atopic dermatitis is a common, chronic skin condition with persistent or relapsing lesions that are itchy, inflamed, and dry. Commonly referred to as "eczema," atopic dermatitis affects both children and adults. Symptoms of itching and even skin pain vary in severity, but can affect sleep, cause psychological distress, and result in difficulty with performance at school or work.[1-3] The appearance of the skin can also lead to social embarrassment and isolation.[4] The net effect is that atopic dermatitis can have a profound effect on all aspects of patients' lives and those of their family and caregivers.[5,6] In the United States (US), atopic dermatitis is estimated to affect around 11-15% of children and 7-10% of adults.[7-10] The overall costs associated with atopic dermatitis are estimated to be $5.3 billion dollars in the US, including over $1 billion in health care costs.[11,12] Atopic dermatitis also can lead to work and productivity loss.[5]

Patients and caregivers emphasized the importance of having measures of treatment outcomes that are most meaningful to them. Itching and pain were seen as the key outcomes, but their impact on sleep, increased distraction, worry, anxiety and other aspects of life varied according to an individual's particular circumstances. For example, some patients reflected that when they were adolescents, appearance was most important to them. As they got older, other issues such as the impact on the skin in terms of pain and infections became more important. Though all recognized atopic dermatitis as a chronic condition, the importance of flares and the need to break cycles of worsening disease was also emphasized. Since many individuals also are impacted by other conditions such as asthma and allergies, and some treatments improve these conditions as well, we heard about the importance of thinking broadly about the benefits of treatments. Since itching is the most bothersome symptom for most patients, the importance of measuring the impact of treatments on itch and associated issues such as sleep disruption are needed. The importance of comprehensive outcome measures that capture the diversity and impact of atopic dermatitis over time was emphasized.

ICER reviewed dupilumab for moderate-to-severe atopic dermatitis and topical crisaborole for mild-to-moderate atopic dermatitis in 2017. A number of new biologic therapies are available or being evaluated in patients with atopic dermatitis. Tralokinumab, a monoclonal antibody that blocks IL-13 receptor binding is given subcutaneously and is under investigation for patients with moderate-to-severe atopic dermatitis. Abrocitinib, baricitinib, and upadacitinib are oral Janus kinase (JAK) inhibitors that are also being evaluated for patients with moderate-to-severe atopic dermatitis. Concerns about the safety of oral JAK inhibitors that are approved for other conditions has led the U.S. Food and Drug Administration (FDA) to extend the review period for these drugs,[13] and tralokinumab received a Complete Response Letter from the FDA requesting additional data relating to a device component used to inject tralokinumab.[14] A topical JAK inhibitor, ruxolitinib

cream, is being evaluated for patients with mild-to-moderate atopic dermatitis, and its review period has also been extended by the FDA.[15]

In the moderate-to-severe population, the four interventions all improved skin findings compared with placebo, and, where assessed, appeared to improve itch, sleep, and quality of life. Quantitative indirect comparisons across the new agents and dupilumab, as well as head-to-head comparisons between two of the agents (upadacitinib and abrocitinib) and dupilumab suggest that higher doses of updadacitinib and possibly abrocitinib are somewhat more effective than dupilumab, while baricitinib (at the doses likely to be approved) and tralokinumab are likely somewhat less effective than dupilumab; however, there is substantial uncertainty in these comparisons. Resolution of itch may occur more quickly with higher-dose abrocitinib than with dupilumab.

Safety is an important consideration with biologic therapies and, as above there have been particular concerns about the safety of oral JAK inhibitors when used for other conditions. Concerns about lack of long-term data for dupilumab, noted in ICER's 2017 report, have been alleviated over time based on published data and widespread use in clinical practice.[16] Tralokinumab is a novel inhibitor of IL-13 that works through a mechanism more similar to dupilumab than the JAK inhibitors, but lacks the same long-term safety profile of dupilumab.

An additional consideration in comparing therapies is that many patients with atopic dermatitis have comorbid atopic conditions such as asthma, and dupilumab has proven efficacy in treating certain patients with asthma or chronic rhinosinusitis.

Taking into consideration the above information on short-term benefits seen in the trials but limited data and concerns about long-term safety, especially for oral JAK inhibitors, we concluded the evidence on net health benefit for abrocitinib, baricitinib, upadacitinib, and tralokinumab compared with topical therapies alone was *promising but inconclusive* ("P/I") and compared to each other was *insufficient* ("I"). We concluded that the evidence for net health benefit for abrocitinib and upadacitinib compared with dupilumab was also *insufficient* ("I"), and that the net health benefit of baricitinib and tralokinumab were *comparable or inferior* ("C-") when compared with dupilumab.

Since the baricitinib and tralokinumab trials only included adults and abrocitinib and upadacitinib trials enrolled small numbers of patients younger than age 18, there is greater uncertainty for adolescents with the new therapies.

We compared the cost and effectiveness of abrocitinib, baricitinib, tralokinumab and upadacitinib for moderate to severe atopic dermatitis to topical emollients (standard of care) and dupilumab, over a five-year time horizon taking a health system perspective.

Estimated net prices were used for baricitinib, upadacitinib and dupilumab that are currently marketed. For abrocitinib, we used the average of the net prices of baricitinib and upadacitinib as a placeholder. For tralokinumab, we used the net price of dupilumab as a placeholder.

Table ES1 presents the incremental results from the base case cost-effectiveness analysis. Given no modeled gains in life years across the evaluated therapies, the cost per life year gained is not reported.

**Table ES1. Incremental Cost-Effectiveness Ratios for the Base Case**

| Treatment | Comparator | Cost per QALY Gained | Cost per Life Year Gained | Cost per evLYG |
|---|---|---|---|---|
| **Abrocitinib*** | SoC | $148,300 | NA | $148,300 |
| **Baricitinib** | SoC | $71,600 | NA | $71,600 |
| **Tralokinumab*** | SoC | $129,400 | NA | $129,400 |
| **Upadacitinib** | SoC | $248,400 | NA | $248,400 |
| **Dupilumab** | SoC | $110,300 | NA | $110,300 |
| **Abrocitinib*** | Dupilumab | $303,400 | NA | $303,400 |
| **Baricitinib** | Dupilumab | Less Costly, Less Effective | NA | Less Costly, Less Effective |
| **Tralokinumab*** | Dupilumab | Less Costly, Less Effective | NA | Less Costly, Less Effective |
| **Upadacitinib** | Dupilumab | $1,912,200 | NA | $1,912,200 |

evLYG: equal-value life-year gained, QALY: quality-adjusted life-year, SOC: Standard of Care

*Using a placeholder price

Note: The cost per QALY and cost per evLYG ratios were the same given that the treatments have not been shown to lengthen life.

From the cost-effectiveness base case assuming the standard of care comparator, we estimated the Health Benefit Price Benchmarks (HBPBs) for each intervention. The HBPB range for abrocitinib is $30,600 to $41,800 (discounts not presented due to placeholder price); for baricitinib, $24,400 to $29,000 (16% discount to no discount from Wholesale Acquisition Cost (WAC) needed at the $150,000 threshold); for tralokinumab from $25,700 to $35,000 (discounts not presented due to placeholder price); for upadacitinib from $30,400 to $41,500 (discounts of 35% to 53% from WAC); and for dupilumab from $29,000 to $39,500 (discounts of 6% to 31% from WAC).

**Table ES2. Annual Cost-Effectiveness Health Benefit Price Benchmarks for Abrocitinib, Baricitinib, Tralokinumab, Upadacitinib, and Dupilumab versus Standard of Care**

| Health Benefit Measure | Annual WAC | Annual Price at $100,000 Threshold | Annual Price at $150,000 Threshold | Discount from WAC to Reach Threshold Prices |
|---|---|---|---|---|
| **Abrocitinib** | | | | |
| QALYs Gained | NA* | $30,600 | $41,800 | NA* |
| evLYG | NA* | $30,600 | $41,800 | NA* |
| **Baricitinib** | | | | |
| QALYs Gained | $29,000 | $24,400 | $33,300 | 0% to 16% |
| evLYG | $29,000 | $24,400 | $33,300 | 0% to 16% |
| **Tralokinumab** | | | | |
| QALYs Gained | NA* | $25,700 | $35,000 | NA* |
| evLYG | NA* | $25,700 | $35,000 | NA* |
| **Upadacitinib** | | | | |
| QALYs Gained | $64,300 | $30,400 | $41,500 | 35% to 53% |
| evLYG | $64,300 | $30,400 | $41,500 | 35% to 53% |
| **Dupilumab** | | | | |
| QALYs Gained | $41,800 | $29,000 | $39,500 | 6% to 31% |
| evLYG | $41,800 | $29,000 | $39,500 | 6% to 31% |

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

* Not applicable (NA) as placeholder prices were used

In the mild-to-moderate population, topical ruxolitinib cream was more effective than vehicle (placebo). While ruxolitinib cream also appeared to be more effective than a medium potency topical corticosteroid, it was not compared to more potent topical corticosteroids and differences in trial designs precluded quantitative indirect comparisons across topical therapies. There is currently limited information on long-term safety of ruxolitinib cream. As a topical JAK inhibitor therapy, safety concerns are likely not as great as with oral JAK inhibitors, but there still is systemic absorption of the topical agent. Topical corticosteroids have known harms both to the skin and, particularly with higher potency preparations in children, a risk for systemic harms. Topical calcineurin inhibitors carry a "black box" warning for a potential risk for causing malignancy, although many clinical experts feel the evidence does not warrant this concern.

We assess the net health benefit for ruxolitinib cream compared with topical emollients to be *comparable or better* ("C++"). We consider the evidence for the net health benefit for ruxolitinib cream compared with other topical medications to be *insufficient* ("I").

# 1. Background

Atopic dermatitis is a common, chronic skin condition with persistent or relapsing lesions that are itchy, inflamed, and dry. Commonly referred to as "eczema," atopic dermatitis affects both children and adults. Symptoms of itching and even pain vary in severity, but can affect sleep, cause psychological distress, and result in difficulty with performance at school or work.[1-3] The appearance of the skin can also lead to social embarrassment and isolation.[4] The net effect is that atopic dermatitis can have a profound effect on all aspects of patients' lives and those of their family and caregivers.[5,6,17] In the United States (US), atopic dermatitis is estimated to affect around 11-15% of children and 7-10% of adults.[7-10] The overall costs associated with atopic dermatitis are estimated to be $5.3 billion dollars in the US, including over $1 billion in health care costs.[11,12] Atopic dermatitis also can lead to work and productivity loss.[5]

Atopic dermatitis is thought to be caused by changes in the barrier properties of the skin and problems with the body's immune response.[18,19] Patients with atopic dermatitis often have a family history that can also include asthma and allergic rhinitis; atopic dermatitis is also associated with socioeconomic and environmental factors.[20] Atopic dermatitis frequently begins during childhood and persists into adulthood in about 50% of affected children.[21] Diagnosed primarily by its appearance, the skin lesions can be localized or widespread, varying in their location by age, and can come and go or be persistent.[22] When acute, the appearance is of red papules and vesicles with weeping, oozing and crusting. When subacute or chronic, lesions are dry, scaly, or excoriated with skin thickening, erosions, cracking and bleeding. Disease severity is difficult to consistently define because it is based upon the amount and location of skin involved, its appearance, and the subjective impact of symptoms.

Most children with atopic dermatitis have mild disease, with 12-26% having moderate and 4-7% having severe disease.[20,23] Moderate or severe disease appears to be more common in adults.[24] The severity of atopic dermatitis can also vary by season and geographic region.[25] For all patients with atopic dermatitis, treatment includes maintaining the skin barrier with moisturizers and emollients, avoiding triggers such as heat/cold, low humidity, and known allergens.[26] Topical corticosteroids are recommended for short-term, intermittent use, and long-term maintenance may include the topical calcineurin inhibitors, tacrolimus and pimecrolimus, or the phosphodiesterase 4 (PDE-4) inhibitor, crisaborole.[27] For those with atopic dermatitis not controlled with topical therapies, phototherapy or systemic immunomodulators are used.[28] Short-term use of systemic oral corticosteroids or cyclosporine can be used to more quickly control skin disease, while oral methotrexate, azathioprine or mycophenolate mofetil can be used for long-term control. Dupilumab, an IL-4 receptor antagonist, became available in 2017, is approved in the US for those

ages six and older, and is now a commonly used systemic immunomodulator for moderate- to-severe disease.[29]

Despite available treatments, many individuals do not respond to multiple different topical and systemic therapies supporting the need for new treatment options.[30] This is especially true for children, where there is greater concern about the effects of topical and systemic corticosteroids.[31]

A number of new biologic therapies are available or being evaluated in patients with atopic dermatitis. One new target for therapy is Interleukin (IL)-13.[32] Tralokinumab, a monoclonal antibody that blocks IL-13 receptor binding is given subcutaneously and is under investigation for patients with moderate-to-severe atopic dermatitis. It received a Complete Response Letter from the FDA requesting additional data relating to a device component used to inject tralokinumab.[14]

Janus kinases (JAKs), cytoplasmic protein tyrosine kinases that are critical for signal transduction to the cell nucleus, are other new targets for therapy.[33] Oral JAK inhibitors being evaluated for patients with moderate-to-severe atopic dermatitis include abrocitinib, baricitinib, and upadacitinib. Concerns about the safety of oral JAK inhibitors that are approved for other conditions has led the U.S. Food and Drug Administration (FDA) to extend the review period for these drugs.[13] A topical JAK inhibitor, ruxolitinib cream is being evaluated for patients with mild-to-moderate atopic dermatitis. The FDA has also extended the review period for ruxolitinib cream.[15]

**Table 1.1. Interventions of Interest**

| Intervention Generic Name (Brand Name) | Mechanism of Action | Delivery Route | Prescribing Information |
|---|---|---|---|
| **Abrocitinib** | JAK inhibitor | Oral | 100-200mg once daily |
| **Baricitinib (Olumiant)** | JAK inhibitor | Oral | 1-2mg once daily |
| **Upadacitinib (Rinvoq)** | JAK inhibitor | Oral | 15-30mg once daily |
| **Ruxolitinib Cream** | JAK inhibitor | Topical | 0.75-1.5% twice daily |
| **Tralokinumab** | IL-13 monoclonal antibody | Subcutaneous injection | 600mg initial dose then 300mg every 2 weeks |

JAK: Janus kinase, IL: interleukin

Note: There may be an option for dosing tralokinumab every four weeks in some patients.

# 2. Patient and Caregiver Perspectives

Discussions with individual patients, caregivers and patient advocacy groups identified important insights and perspectives. Common themes emphasized included: the considerable burden of this chronic condition on patients, caregivers and families; the diversity of the experience with atopic dermatitis especially at different times in one's life; the demands of current treatment and the need for better treatment options; the impact on all aspects of life including school, work and social/family relationships; the importance of measuring outcomes of care that are most meaningful to patients; and the high costs and affordability of care for patients and families.[34]

Though the majority of those with atopic dermatitis have a milder course that can be adequately managed with topical therapy, this perception may lead to an underappreciation of the profound effect that atopic dermatitis can have on all aspects of a patient's life. The considerable burden of atopic dermatitis reflects its chronic nature (often beginning in childhood and progressing through adolescence and into adulthood), and the unpredictability of disease flares. As such, it not only impacts the patient but also families, caregivers, friends, and relationships. The primary symptom of atopic dermatitis, itch, can lead to a host of additional problems including skin pain and infections as well as disrupting sleep and causing psychological distress including loss of self-esteem, anxiety, depression, and suicidal ideation. Because flares of the disease can lead individuals to search for some behavior or action to explain the worsening, there can be guilt, or it may lead others to blame the patient for the flare. The result is that atopic dermatitis can have a profound impact on life activities, interpersonal relationships and performance at school and work.

The impact of atopic dermatitis can vary depending on many factors, including the age of the patient, leading to a diversity of experiences. For children with atopic dermatitis, interpersonal effects can include bullying by other children and changes in family dynamics among parents and siblings associated with extra time and attention spent by caregivers focused on the patient, leading other children in a household to feel neglected. For adolescents, the impact of atopic dermatitis on appearance was emphasized, leading to self-isolation and insecurities, all affecting social interactions. Across all age groups, atopic dermatitis can impact life activities such as exercise and recreation due to their negative effects on the skin related to excessive sweating or cold/heat exposure. As an allergic condition, atopic dermatitis can also necessitate restrictions on diet that can be difficult.

As a result of the symptoms of atopic dermatitis that can lead to sleep disturbance and daytime fatigue, it can affect performance including that in school and work. For students it can affect school attendance and lead to distraction when in class, negatively impacting developmental milestones. Similarly, atopic dermatitis can affect work through missed days, decreased work

performance (presenteeism), missed promotions, limited career options, and even disability from one's chosen profession. The net result is a financial impact on individuals and families over the course of one's life in terms of educational and work advancement opportunities delayed or lost.

A wide range of deficiencies with currently available topical and systemic treatments for atopic dermatitis were noted. There was broad recognition that current therapies do not address all of the needs of patients with atopic dermatitis. The need for therapies that work quickly, provide sustained relief and are safe for long-term use were highlighted. Though some patients derive benefit from existing therapies, the considerable time and effort involved in applying topical moisturizers and wraps or traveling to and from phototherapy sessions is taxing on patients and their caregivers. Moreover, travel to receive care can be particularly demanding for patients in the US who live outside of large metropolitan areas. For those with mild to moderate disease, there is a need for new topical therapies. Topical steroids can damage skin with prolonged use, while topical calcineurin inhibitors carry a black box warning, and topical phosphodiesterase-4 (PDE-4) inhibitors have limited efficacy; these latter agents can also cause skin discomfort/burning.

For those with moderate to severe disease not adequately managed with topical therapies, oral corticosteroids are commonly used for short courses, but have well-recognized side effects, can have rebound flares when discontinued, and are avoided in younger patients. Other systemic therapies such as cyclosporin, methotrexate and other non-selective systemic immunomodulators have limited benefit and potentially serious side effects. Even dupilumab, the first biologic approved in the US for atopic dermatitis, takes time to begin working, does not help all individuals, and has side effects, such as conjunctivitis that result in some patients discontinuing use. Finally, patients and caregivers commented about the challenge of choosing therapies where the long-term effects are not completely known or may have uncommon but potentially serious side effects.

Patients and caregivers emphasized the importance of having measures of treatment outcomes that are most meaningful to them. Itching and skin pain were seen as the key outcomes, but their impact on sleep, increased distraction, worry and anxiety and other aspects of life varied according to an individual's particular circumstances. For example, some patients reflected that when they were adolescents, appearance was most important to them. As they got older, other issues such as the impact on the skin in terms of pain and infections became more important. Though all recognized atopic dermatitis as a chronic condition, the importance of flares and the need to break cycles of worsening disease was also emphasized. Since many individuals also are impacted by other conditions such as asthma and allergies, and some treatments improve these conditions as well, we heard about the importance of thinking broadly about the benefits of treatments. Since itching is the most burdensome symptom for most patients, the importance of measuring the impact of treatments on itch and associated issues such as sleep disruption are needed. The

importance of comprehensive outcome measures that capture the diversity and impact of atopic dermatitis over time was emphasized.

For many patients and parents, the high cost of care for atopic dermatitis was noted. Topical emollients and wraps are non-prescription and often not covered by health insurance. Even for those with health insurance, the affordability of care is a challenge for patients and families. The chronic nature of atopic dermatitis with copayments and deductibles for numerous doctor visits, multiple trials of different topical therapies, and phototherapy sessions add up quickly. Moreover, newer systemic therapies for atopic dermatitis are very expensive and patients and caregivers face the burden of negotiating insurance coverage policies and the potential for high out of pocket costs.

# 3. Comparative Clinical Effectiveness

## 3.1. Methods Overview

Procedures for the systematic literature review (SLR) assessing the evidence on abrocitinib, baricitinib, tralokinumab, and upadacitinib in moderate-to-severe atopic dermatitis and ruxolitinib cream in mild-to-moderate atopic dermatitis are described in Section D1 of the Report Supplement.

### Scope of Review

This SLR compares the clinical effectiveness of abrocitinib, baricitinib, tralokinumab, and upadacitinib to topical therapies, dupilumab, and each other for the treatment of moderate-to-severe atopic dermatitis in adolescents and adults. The SLR also compares ruxolitinib cream to topical therapies for the treatment of mild-to-moderate atopic dermatitis in adolescents and adults. The full PICOTS criteria are detailed in Section D1 of the Report Supplement.

### Evidence Base

#### *Moderate-to-Severe Population*

A total of 58 references met our inclusion criteria for the moderate-to-severe population.[35-84] Of these, we identified five randomized controlled trials (RCTs) of abrocitinib (one phase II and four phase III),[35-37,39,40,78,85] five RCTs of baricitinib (one phase II and four phase III),[42,45,46,48] three RCTs of tralokinumab (two phase III),[63,64] five RCTs of upadacitinib (one phase II and four phase III),[69-71,81-83] and six RCTs of dupilumab (one phase II and five phase III) that met our inclusion criteria.[50-53,56] Of these trials, 21 enrolled adults, where 14 were placebo-controlled monotherapy trials and six were placebo-controlled combination trials that permitted background topical medication. Two head-to-head trials were identified, and these were one placebo- and active-controlled combination trial (JADE COMPARE) and one active-controlled monotherapy trial (Heads Up). Several trials solely enrolled children or adolescents, where one was a placebo-controlled monotherapy trial and two were placebo-controlled combination trials.

Trials that enrolled adults are described first, followed by trials that solely enrolled children and adolescents.

Only the FDA-approved dose of dupilumab was evaluated in adults (300 mg once every two weeks). All the pivotal trials, except the Phase III head-to-head study of upadacitinib versus dupilumab

(HEAD UP), have been published. Data on the unpublished trial (HEADS UP) were obtained from a conference presentation and the manufacturer as academic-in-confidence data.[70,81]

Evidence Tables G1.3-1.7 contain the key study design and baseline characteristics of each trial, while a summary is presented below in Table 3.1. Please note that blacked out data represents academic-in-confidence data submissions. While most trials enrolled patients ≥18 years old, the pivotal trials for abrocitinib, JADE MONO-1 and JADE MONO-2, and the pivotal trials for upadacitinib, MEASURE UP 1, MEASURE UP 2, and AD-UP enrolled patients ≥12 years old. However, most patients in these trials were ≥18 years old, and we searched for evidence stratified by age. The primary endpoints of the abrocitinib trials, JADE MONO-1, JADE MONO-2, and JADE COMPARE, were measured at 12 weeks, while the remaining trials' primary endpoints were measured at 16 weeks. Trial populations were comparable with respect to age (31-41 years), duration of disease (21-28 years), and disease severity (32%-55% IGA of 4). Primary endpoints varied slightly among the trials but typically consisted of EASI 75 and/or IGA (IGA score of 0/1 or 0/1 and ≥2 points from baseline improvement).

RCTs that only enrolled children or adolescents were limited. LIBERTY AD ADOL enrolled patients 12-17 years and measured its co-primary endpoints of EASI 75 and IGA (IGA score of 0/1 and ≥2 points from baseline improvement) at 16 weeks. JADE TEEN also enrolled patients 12-17 years and measured its co-primary endpoints of EASI 75 and IGA (IGA score of 0/1 and ≥2 points from baseline improvement) at 12 weeks. In contrast, LIBERTY AD PEDS enrolled patients 6-11 years with severe atopic dermatitis and measured its primary endpoint of IGA (IGA score of 0/1) at 16 weeks.

Additional details are available in Section D3 of the Report Supplement.

**Table 3.1. Overview of Placebo-controlled Monotherapy and Combination Trials of Abrocitinib, Baricitinib, Tralokinumab, Upadacitinib, and Dupilumab in Adults**

| Trial | Arms | Sample Size (N) | EASI (Mean) | Mean age, y | Mean Disease Duration, y | IGA Score of 4 (%) |
|---|---|---|---|---|---|---|
| **Abrocitinib** | | | | | | |
| **JADE MONO-1*** | ABRO 100 mg<br>ABRO 200 mg<br>PBO | 387 | 30.2 | 32.4 | 23.4 | 40.7 |
| **JADE MONO-2*** | ABRO 100 mg<br>ABRO 200 mg<br>PBO | 391 | 28.5 | 35.1 | 21.0 | 32.2 |
| **JADE COMPARE** | ABRO 100 **mg + TCS**<br>ABRO 200 mg **+ TCS**<br>DUP 300 mg **+ TCS**<br>PBO + TCS | 837 | 30.9 | 37.7 | 22.7 | 35.4 |
| **Gooderham 2019** | ABRO 100 mg<br>ABRO 200 mg<br>PBO | 167 | 25.6 | 40.8 | 23.0[ɣ] | 40.8 |
| **Baricitinib** | | | | | | |
| **BREEZE-AD 1** | BARI 1 mg<br>BARI 2 mg<br>BARI 4 mg**<br>PBO | 624 | 31.0 | 35.7 | 25.7 | 41.8 |
| **BREEZE-AD 2** | BARI 1 mg<br>BARI 2 mg<br>BARI 4 mg**<br>PBO | 615 | 33.5 | 34.5 | 24.0 | 50.5 |
| **BREEZE-AD 5** | BARI 1 mg<br>BARI 2 mg<br>PBO | 440 | 27.1 | 39.7 | 23.7 | 41.7 |
| **BREEZE-AD 7** | BARI 2 mg + TCS<br>PBO + TCS | 329 | 29.57 | 33.8 | 24.03 | 45.0 |
| **Guttman-Yassky 2018** | BARI 4 mg + TCS**<br>BARI 2 mg + TCS<br>PBO + TCS | 104 | 21.23 [ɣ] | 36.5 | 22.03 | NR |
| **Tralokinumab** | | | | | | |
| **ECZTRA 1** | TRA 300 mg<br>PBO | 802 | 29.3 | 37.0 | 27.5 | 50.9 |
| **ECZTRA 2** | TRA 300 mg<br>PBO | 794 | 28.9[ɣ] | 32.0 | 25.3 | 49.2 |
| **ECZTRA 3** | TRA 300 mg + TCS<br>PBO + TCS | 380 | 25.5 | 36.0 | 26.0 | 46.3 |
| **Upadacitinib** | | | | | | |

| Trial | Arms | Sample Size (N) | EASI (Mean) | Mean age, y | Mean Disease Duration, y | IGA Score of 4 (%) |
|---|---|---|---|---|---|---|
| **MEASURE UP 1*** | UPA 15 mg<br>UPA 30 mg<br>PBO | 847 | 29.5 | 34.0 | 20.7 | 45.2 |
| **MEASURE UP 2*** | UPA 15 mg<br>UPA 30 mg<br>PBO | 836 | 29.1 | 33.6 | 24.3 | 54.9 |
| **AD-UP** | UPA 15 mg + TCS<br>UPA 30 mg + TCS<br>PBO + TCS | 907 | 29.6 | 34.1 | 23.4 | 52.9 |
| **Heads Up** | DUP 300 mg<br>UPA 30 mg | 692 | 29.8 | 36.7 | 24.2 | 50.1 |
| **Guttman-Yassky 2020** | UPA 7.5 mg**<br>UPA **15 mg**<br>UPA 30 mg<br>PBO | 167 | 25.6 | 40.8 | 23.0ʏ | 40.8 |
| **Dupilumab** | | | | | | |
| **LIBERTY AD SOLO 1** | DUP 300 mg Q2W<br>DUP 300 mg QW<br>PBO | 671 | 30.7 | 38.7 | 26.7 | 48.3 |
| **LIBERTY AD SOLO 2** | DUP 300 mg Q2W<br>DUP 300 mg QW<br>PBO | 708 | 29.4 | 34.7 | 24.8 | 48.3 |
| **LIBERTY AD CHRONOS** | DUP 300 mg QW + TCS *<br>DUP 300 mg + TCS<br>PBO + TCS | 740 | 29.8* | 31.2ʏ | 26.7ʏ | 47.7 |
| **Thaci 2016** | DUP 300 mg Q4W<br>DUP 300 mg Q2W<br>DUP 300 mg QW**<br>DUP 200 mg Q2W<br>DUP 100 mg Q4W**<br>PBO | 379 | 31.9 | 37.0 | 28.0 | 47.3 |

All values are pooled by ICER. All timepoints at 16 weeks except JADE MONO-1, JADE MONO-2, (12 weeks) and COMPARE (12/16 weeks). Bolded arms were included in the network meta-analyses. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, N: total number, NR: not reported, QW: weekly, Q2W: every two weeks, Q4W: every four weeks, TCS: topical corticosteroid, TRA: tralokinumab, UPA: upadacitinib, Y: year, %: percent. *pooled estimates from this trial were in patients 12 and older, ʏmedian, **included in pooled values here, but not included in comparative clinical effectiveness evaluation.

### *Mild-to-Moderate Population*

A total of 21 references met our inclusion criteria for the mild-to-moderate population.[74,75,86-104] Of these, we identified two phase III, placebo-controlled RCTs of ruxolitinib cream[98] and one phase IIb placebo- and active-controlled (topical triamcinolone acetonide) RCT of ruxolitinib cream.[87,88] While no new trials of crisaborole for this indication were identified since the prior ICER Report in 2017, two phase III RCTs of this agent met inclusion criteria in our previous review.[96] Differences in trial populations, outcome definitions, and length of follow-up do not permit us to quantitatively compare outcomes of trials of ruxolitinib cream with crisaborole or topical calcineurin inhibitors.

Evidence Tables G1.50-1.53 contain the key study design and baseline characteristics of each trial, while a summary is presented below in Table 3.2 for the ruxolitinib cream trials. TRuE-AD1 and TRuE-AD2 were identical phase III multicenter, double-blind, vehicle (placebo)-controlled RCTs conducted in North America and Europe among 631 and 618 patients ≥12 years old, respectively, while Kim 2020 was a phase IIb multicenter, double-blind, dosing-ranging RCT conducted in North America among 307 patients ≥18 years old. The trials had similar baseline characteristics (see Table 3.2.), and the primary endpoints of TRuE-AD1 and TRuE-AD-2 were the proportion of patients achieving IGA (score of 0/1 with ≥2-point improvement from baseline) at week eight. In contrast, the primary endpoint of Kim 2020 was the percentage change from baseline in EASI score at week four in patients treated with ruxolitinib cream 1.5% twice a day compared with placebo. Additional details are available in Section D3 of the Report Supplement.

**Table 3.2. Overview of Trials of Ruxolitinib Cream**

| Intervention | Trial | Arms | Sample Size (N) | Treatment Duration (Weeks) | EASI (Mean) | Median Age, y | Disease Duration, y | IGA Score of 3 (%) |
|---|---|---|---|---|---|---|---|---|
| **Ruxolitinib Cream** | TRuE AD 1 | Vehicle (PBO)<br>RUX 0.75%<br>RUX 1.5% | 631 | 8 weeks | 7.8 | 31.8 | 16 | 75.8 |
| | TRuE AD 2 | Vehicle (PBO)<br>RUX 0.75%<br>RUX 1.5% | 618 | 8 weeks | 8 | 34.2 | 16.1 | 74 |
| | Phase II Kim 2020 | Vehicle (PBO)<br>RUX 1.5% BID<br>TRI 0.1% | 307 | 8 weeks | 8.4 | 35.0 | 20.8 | NR |

TRuE-AD 1 and 2 enrolled patients 12 and older, while the phase II study enrolled patients 18 and older. BID: twice-daily, N: total number, NR: not reported, PBO: non-medicated cream, RUX: ruxolitinib, TRI: triamcinolone acetonide cream, Y: years, %: percent

## 3.2. Results for Moderate-to-Severe Population

The key clinical benefits and harms of abrocitinib, baricitinib, tralokinumab, and upadacitinib in moderate-to-severe atopic dermatitis as well as key network meta-analysis (NMA) results are described in Section 3.2. Data synthesis and quantitative analyses, such as additional NMAs, are described in Section D2 of the Report Supplement. Additional results are presented in Sections D2 and D3 of the Report Supplement.

### Clinical Benefits

#### *Abrocitinib*

**Abrocitinib substantially increased the likelihood of achieving EASI 75 and IGA response in a dose dependent manner compared to placebo. Results for other EASI thresholds and other patient reported outcomes were generally consistent with results for EASI 75 and IGA. In comparison with dupilumab, outcomes were similar on most measures, though outcomes with abrocitinib 200 mg were somewhat better and itch improved more at 2 weeks. Though few adolescents were included in these trials, they appeared to have similar outcomes compared to adults. Long-term data were limited.**

In three monotherapy trials of abrocitinib 200 mg, 61% to 65% of patients achieved EASI 75, compared with 10%-15% in the placebo arms of those trials.[35,36,40] EASI 75 was achieved by 40%-45% of patients with abrocitinib 100 mg. Tests of statistical significance comparing abrocitinib 200 mg and 100 mg dosing were not reported. EASI 90 was achieved by 38%-52% of patients with abrocitinib 200 mg, compared with 4%-10% of patients with placebo. EASI 90 was achieved by 19%-26% of patients with abrocitinib 100 mg. IGA response, defined as an IGA score of 0 or 1 *and* an improvement of 2 points or more from baseline, was achieved by 38%-44% of patients with abrocitinib 200 mg, compared to 6%-9% with placebo. In the abrocitinib 100 mg arms, IGA response was achieved by 24%-30% of patients.

One trial compared abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo in patients also treated with topical corticosteroids.[37] IGA response, as defined above, and EASI 75, both measured at week 12 were the co-primary outcomes. IGA response was achieved by 48% of patients with abrocitinib 200 mg, 37% with abrocitinib 100 mg, 37% with dupilumab, and 14% with placebo. The percentage of patients achieving EASI 75 with abrocitinib 200 mg was 70% compared with 59% with abrocitinib 100 mg, 58% with dupilumab, and 27% with placebo. Responses in the abrocitinib arms were statistically superior to placebo, but statistical significance was not reported compared to dupilumab at 12 weeks. However, at 16 weeks, there were no statistically significant differences in

EASI 75 and IGA response between the abrocitinib arms and dupilumab apart from the IGA response being greater for the abrocitinib 200 mg arm (see Report Supplement D3).

In the monotherapy trials, more patients experienced a ≥4-point improvement on the patient reported Peak Pruritus Numerical Rating Scale (PP-NRS), a measure of itching, with abrocitinib 200 mg and 100 mg than with placebo (55%-64% and 38%-50% vs. 12%-26%, respectively).[35,36,40] Concordant with the EASI and IGA results in the trial versus dupilumab, at week 16 more patients achieved a ≥4-point improvement with abrocitinib 200 mg, abrocitinib 100 mg, and dupilumab (63% and 48% and 55%), compared to placebo (29%).[37] Measurement of PP-NRS at two weeks was a key secondary outcome in this trial and abrocitinib 200 mg (49%), but not abrocitinib 100 mg (32%), was statistically superior to dupilumab (27%) for this outcome providing some evidence that resolution of itch may occur more quickly with abrocitinib 200 mg than dupilumab.

Other patient reported outcomes showed similar favorable results compared to placebo. In two monotherapy trials, patients had greater reductions from baseline on the Dermatology Life Quality Index (DLQI) with abrocitinib 200 mg (-9 to -10) and 100 mg (-7 to -8) than placebo (-4; p<0.05 for comparisons with both doses of abrocitinib), where a 4-point difference is considered to be clinically meaningful.[35,36,10]5 In those trials, patients had greater reductions from baseline on the Patient-Oriented Eczema Measure (POEM), a self-reported measure of symptom severity, with abrocitinib 200 mg (-11) and abrocitinib 100 mg (-7 to -9), compared with placebo (-4; p<0.05 for both comparisons with placebo), where a 3-4-point improvement is considered clinically meaningful.[106] The Scoring Atopic Dermatitis (SCORAD), an instrument combining objective measures of area and intensity with subjective symptoms including itch and sleeplessness, was also evaluated in the trials. Results showed there were greater reductions from baseline with abrocitinib 200 mg (-56% to -70%) and abrocitinib 100 mg (-46% to -50%), compared to placebo (-23% to -29%; p<0.002, for comparisons with both doses of abrocitinib).[4]0 [36] In addition, pooled analysis of the monotherapy trials showed that patients had greater numeric reductions from baseline on the Hospital Anxiety and Depression Scale (HADS) with abrocitinib 200 mg and 100 mg doses than placebo for both depression and anxiety (anxiety: − 2.0 and − 1.7 vs. − 1.0; depression: − 1.7 and − 1.3 vs. − 0.1; statistical significance not reported).[107]

Similar results on patient reported outcomes were reported for the trial that compared abrocitinib to dupilumab and placebo. For example, patients had greater improvements from baseline on the DLQI with abrocitinib 200 mg (-12; 95% CI: -12 to -11), abrocitinib 100 mg (-9; 95% CI: -10 to -8), and dupilumab (-11; 95% CI: -11 to -10) compared to placebo (-6; 95% CI: -7 to -5).[105]

At the time of this report, limited long-term data for abrocitinib suggest maintenance of EASI 75, IGA response, and ≥4-point improvement on the patient reported PP-NRS at 48 weeks (See Report Supplement D3).[77,108]

***Baricitinib***

**Baricitinib increased the likelihood of achieving EASI 75 and IGA response compared to placebo. Results for other EASI thresholds and other patient reported outcomes were generally consistent with results for EASI 75 and IGA. Differences compared to placebo were modest with baricitinib 1 mg and not always statistically significant. There are limited long-term data and baricitinib was not studied in adolescents.**

We do not report baricitinib 4 mg arm trial results because this dose is not anticipated to be used in the U.S. In three monotherapy trials of baricitinib 2 mg, 18%-30% of patients achieved EASI 75, compared with 6%-9% in the placebo arms of those trials.[42,45] EASI 75 was achieved by 13%-17% of patients with baricitinib 1 mg. Tests of statistical significance comparing baricitinib 2 mg and 1 mg were not reported. EASI 90 was achieved by 9%-21% of patients with baricitinib 2 mg, compared to 3%-5% of patients with placebo. In the baricitinib 1 mg arms of those trials, 6%-9% of patients achieved EASI 90. IGA response, defined as an IGA score of 0 or 1 *and* an improvement of 2 points or more from baseline, was achieved by 11%-24% in the baricitinib 2 mg arms, compared with 5% in the placebo arms. IGA response was achieved by 9%-13% of patients with baricitinib 1 mg.

Similar incremental improvements beyond placebo were reported in two trials that compared baricitinib 2 mg with placebo in patients also treated with topical corticosteroids.[46,48] For example, 30%-43% of patients achieved EASI 75 with baricitinib 2 mg compared to 20%-23% with placebo. IGA response, as defined above, was achieved by 22%-24% of patients with baricitinib 2 mg, compared with 8%-15% of patients with placebo.

In the monotherapy trials, more patients experienced a ≥4-point improvement on the patient reported PP-NRS with baricitinib 2 mg and baricitinib 1 mg than with placebo (12%-25% and 6%-16% vs. 5%-7%, respectively).[42,45] In addition, patients had greater improvements from baseline on nighttime awakenings due to itching, as measured by the atopic dermatitis sleep scale (ADSS), with baricitinib 2 mg than placebo (-1 to -1.2 vs. -0.4 to -0.8; statistical significance not reported).[49,109,110] In one combination trial, more patients achieved a PP-NRS ≥4-point improvement with baricitinib 2 mg than placebo (38% vs. 20%).[46]

In the monotherapy trials, patients had greater reductions from baseline on the DLQI with baricitinib 2 mg and 1 mg than placebo (-4 to -7 and -5 to -6 vs. -3 to -4, respectively; $p<0.05$ for both comparisons), where a 4-point difference is considered to be clinically meaningful.[42,45,105] In

these trials, patients had greater reductions from baseline on POEM with baricitinib 2 mg and 1 mg compared to placebo (-6 to -7 and -4 to -5 vs. -2 to -3, respectively; p<0.05 for both comparisons), where a 3-4-point improvement is considered clinically meaningful.[106]. Similarly, patients had greater reductions from baseline on SCORAD with baricitinib 2 mg than placebo in two trials that reported this outcome (-22% to -28% vs. -13%-14%, respectively; p<0.05); differences between baricitinib 1 mg and placebo were not statistically significant.[42] In addition, patients had greater numeric reductions from baseline on HADS Anxiety (-1.9 to -2.6 vs. 0.9 to 2.0) and HADS Depression (-1.0 to -1.7 vs. 0.3 to 1.3) with baricitinib 2 mg than placebo, although statistical significance was not reported.[49,109,110] Trial results also showed a greater improvement with baricitinib 2 mg on work productivity measures (absenteeism, presenteeism, work productivity loss, and activity impairment) than placebo. [49,109,110]

One combination trial reported a greater reduction from baseline on the DLQI with baricitinib 2 mg than placebo (-8 vs. -6, respectively; p=0.022), where a 4-point improvement is considered clinically meaningful.[46,105] The phase II trial reported a greater reduction in this outcome with baricitinib 2 mg compared to placebo that did not reach statistical significance (-6 vs. -7, respectively; p>0.05).[48]

At the time of this report, limited long-term data for baricitinib suggest maintenance of EASI 75 and IGA response at 52-68 weeks. [43,44,84] These are described in greater detail in Report Supplement D3.

***Tralokinumab***

**Tralokinumab increased the likelihood of achieving EASI 75 and IGA response compared to placebo. Results for other EASI thresholds and other patient reported outcomes were generally consistent with results for EASI 75 and IGA. There are limited long-term data and tralokinumab was not studied in adolescents.**

In two placebo-controlled monotherapy trials of tralokinumab, 25%-33% of patients achieved EASI 75, compared with 11%-13% of patients in the placebo arms of those trials.[63] EASI 90 was achieved by 15%-18% of patients with tralokinumab, compared with 4%-6% of patients with placebo. IGA response, defined as an IGA score of 0 or 1, was achieved by 16%-22% of patients in the tralokinumab arms, compared with 7%-11% in the placebo arms.

In a trial in patients treated with topical corticosteroids, tralokinumab was more effective than placebo.[64] For example, the percentage of patients achieving EASI 75 with tralokinumab was 56% compared with 36% with placebo. IGA response, also defined as an IGA score of 0 or 1, was 39% with tralokinumab compared with 26% with placebo.

In the placebo-controlled monotherapy trials, more patients experienced a ≥4-point improvement on the patient reported PP-NRS with tralokinumab than with placebo (20%-25% vs. 10%,

respectively).[63] Concordant with the EASI and IGA results in the combination trial, more patients achieved a ≥4-point improvement with tralokinumab than placebo (45% vs. 34%).[64]

In one of the monotherapy trials, patients had greater reductions from baseline on the DLQI with tralokinumab than placebo (-7 vs. -5; p=0.002); however, this difference is less than the difference considered clinically meaningful (4-point improvement).[63,105] In the other monotherapy trial, patients had greater reductions in this outcome with tralokinumab than placebo that also met this clinically meaningful difference (-9 vs. -5; p<0.001).[63,105] In both trials, patients had greater reductions from baseline on POEM with tralokinumab compared to placebo (-8 to -9 vs. -3 to -4; p<0.001), where a 3-4-point improvement is considered clinically meaningful.[106]. Similarly, in both trials, patients had greater reductions from baseline on SCORAD with tralokinumab than placebo (-25% to -28% vs. -14% to -15%; p<0.001). In both trials, patients had greater reductions from baseline in the weekly average of eczema-related sleep interference NRS with tralokinumab than placebo (-3 vs. -2; p=0.007).

Similar results were reported for the combination trial. For example, patients had greater reductions from baseline on the DLQI with tralokinumab than placebo (-12 vs. -9; p<0.001).[64,105]

Results for HADS Anxiety and Depression were not reported in any trials of tralokinumab at the time of this Report.

At the time of this report, long-term data for tralokinumab are limited. Data from the 36-week maintenance periods of the two placebo-controlled monotherapy trials suggest maintenance of EASI 75 and IGA responses at 52 weeks, while similar results from the 32-week maintenance period of the placebo-controlled combination trial were also reported (see Report Supplement D3 ).[63,64] Additionally, a lower dosing frequency of tralokinumab (300mg every 4 weeks) was evaluated among 16-week responders, and outcomes were similar but slightly worse than for those continued on the higher dose.[63]

***Upadacitinib***

**Upadacitinib substantially increased the likelihood of achieving EASI 75 and IGA response in a dose dependent manner compared to placebo. Results for other EASI thresholds and other patient reported outcomes were generally consistent with results for EASI 75 and IGA. Compared with dupilumab, outcomes for upadacitinib 30 mg were similar or somewhat better on reported measures. Though few adolescents were included in these trials, they appeared to have similar outcomes compared to adults. No long-term data were identified.**

In three monotherapy trials of upadacitinib 30 mg, 69%-80% of patients achieved EASI 75, compared with 10%-16% in the placebo arms of those trials.[69,82] In those same trials, 52%-70%

achieved EASI 75 with upadacitinib 15 mg. No tests of statistical significance comparing upadacitinib 30 mg to 15 mg dosing were reported in these trials. EASI 90 was achieved by 50%-66% of patients with upadacitinib 30 mg, compared with 2%-8% of patients with placebo. Further, EASI 90 was achieved by 26%-53% of patients with upadacitinib 15 mg. IGA response, defined as an IGA score of 0 or 1 *and* an improvement of 2 points or more from baseline, was achieved 50%-62% of patients with upadacitinib 30 mg, compared with 2%-8% of patients with placebo. In the upadacitinib 15 mg arms, 31%-48% achieved IGA response.

In a head-to-head monotherapy trial, more patients treated with upadacitinib 30 mg than dupilumab achieved EASI 75 (71% vs. 61%; p = 0.006) and EASI 90 (61% vs. 39%; p<0.001) at 16 weeks.[81] At the time of this Report, results for IGA response were not available.

In a trial that compared upadacitinib to placebo in patients also treated with topical corticosteroids, the percentage of patients achieving EASI 75 with upadacitinib 30 mg was 77% compared with 65% with upadacitinib 15 mg and 26% with placebo. [83] IGA response, as defined above, was achieved by 59% of patients with upadacitinib 30 mg, 40% with upadacitinib 15 mg, and 11% with placebo.

In the placebo-controlled monotherapy trials, more patients experienced a ≥4-point improvement on the patient reported PP-NRS with upadacitinib 30 mg and 15 mg than with placebo (53%-60% and 42%-59% vs. 6%-12%, respectively).[69,82] More patients achieved a ≥4-point improvement with upadacitinib 30 mg than dupilumab (55% vs. 36%).[70] Similarly, in the trial that compared upadacitinib to placebo in patients also treated with topical corticosteroids, more experienced achieved a ≥4-point improvement with upadacitinib 30 mg and 15 mg than placebo (64% and 52% vs. 15%).[83]

Other patient reported outcomes showed similar favorable results compared to placebo. In two of the monotherapy trials, DLQI response, defined as an improvement of 4-points or more from baseline, was achieved by 78%-82% of patients on upadacitinib 30 mg, 72%-75% of patients on upadacitinib 15 mg, compared with 28%-29% of patients on placebo. [82] In those trials, POEM response, defined as an improvement of 4-point or more from baseline, was achieved by 81%-84% of patients on upadacitinib 30 mg, 71%-75% of patients on upadacitinib 15 mg, compared with 23%-29% of patients on placebo. [82] In another trial, patients had greater reductions from baseline on POEM with upadacitinib 30 mg and 15 mg compared to placebo (-12 and -9 vs. -2, respectively; p≤0.001 for both comparisons), where a 3-4-point improvement is considered clinically meaningful.[69,106] Similarly, patients had greater reductions from baseline on SCORAD with upadacitinib 30 mg and 15 mg compared to placebo (-60% to -73% and -47% to -66% vs. -12% to -33%; p<0.001 for both comparisons). [69,82,106] In addition, greater proportions of patients achieved clinically meaningful improvement in HADS-anxiety and HADS-depression with upadacitinib 30 mg compared to placebo (49% to 56% vs. 11% to14%; p<0.0001). [82] Clinical meaningful improvement

was defined in those trials as a HADS anxiety or HADS depression score of <8, assessed in patients with HADS anxiety score of ≥8 or HADS depression score of ≥8 at baseline. [82] At the time of this report, these patient-reported outcomes were not reported in the trial that compared upadacitinib to placebo in patients receiving topical corticosteroids.

No long-term evidence was identified for upadacitinib at the time of this report.

### *Network Meta-Analysis (NMA) Results of Monotherapy Trials*

For quantitative indirect comparisons, the monotherapy placebo-controlled trials of the agents were felt to provide the most comparable results. Here, we present the NMA results of EASI 75 and EASI 90 from the monotherapy trials (15 trials). Refer to the Report Supplement D2 for more details on the methods and trials included and the results of NMA on other outcomes (EASI 50, IGA response, and PP-NRS ≥4-point improvement) on these trials. We also present information on the NMAs of combination trials (6 trials) in the Report Supplement (see Report Supplement D2).

*EASI 75 and EASI 90*

For the EASI NMA (15 trials), we present the results of the unadjusted random effect model, given its better fit for the model relative to the adjusted model (see Report Supplement D2). All interventions showed statistically significantly greater EASI 75 and EASI 90 responses than placebo and baricitinib 1 mg (Tables 3.4 and 3.5). Compared to placebo, interventions were 1.5 to 5.7 times more likely to achieve EASI 75 (Table 3.4) and 1.8 to 9.6 times more likely to achieve EASI 90 (Table 3.5). Updacitinib 30 mg was more likely to achieve EASI 75 and EASI 90 than the other interventions; however, upadacitinib 30 mg was not statistically better than abrocitinib 200 mg. Additionally, there were no statistically significant differences with abrocitinib (both doses) and upadacitinib 15 mg compared to dupilumab. In comparison, dupilumab showed statistically significantly greater EASI 75 and EASI 90 responses than tralokinumab and baricitinib (both doses).

Based on the NMA, the expected proportion of patients who achieved EASI 75 was 12% for placebo, 49% for dupilumab, 40% for abrocitinib 100 mg, 58% for abrocitinib 200 mg, 19% for baricitinib 1 mg, 29% for baricitinib 2 mg, 31% for tralokinumab, 55% for upadacitinib 15 mg, and 67% for updacitinib 30 mg (see Table 3.3).

**Table 3.3: NMA Results. Proportions of patients achieving EASI 50, 75, and 90 thresholds in Monotherapy RCTs.**

| Treatment | EASI 50 | EASI 75 | EASI 90 |
|---|---|---|---|
| | Median proportion (95% CrI) | | |
| **Placebo** | 0.21 (0.20 – 0.23) | 0.12 (0.1 -0.13) | 0.05 (0.04 - 0.06) |
| **Dupilumab 300 mg Q2W** | 0.64 (0.58 – 0.70) | 0.49 (0.42 – 0.55) | 0.32 (0.27 – 0.38) |
| **Abrocitinib 100 mg** | 0.55 (0.45 – 0.65) | 0.40 (0.30 -0.50) | 0.24 (0.17 – 0.33) |
| **Abrocitinib 200 mg** | 0.73 (0.64 – 0.81) | 0.58 (0.49 – 0.68) | 0.41 (0.32 -0.52) |
| **Baricitinib 1 mg** | 0.31 (0.25 – 0.39) | 0.19 (0.14 -0.25) | 0.09 (0.07 – 0.14) |
| **Baricitinib 2 mg** | 0.44 (0.36 – 0.52) | 0.29 (0.23 – 0.37) | 0.16 (0.12 – 0.22) |
| **Tralokinumab 300 mg** | 0.46 (0.38 – 0.53) | 0.31 (0.24 – 0.38) | 0.17 (0.13 – 0.23) |
| **Upadacitinib 15 mg** | 0.70 (0.64 – 0.76) | 0.55 (0.48 – 0.61) | 0.38 (0.31 – 0.45) |
| **Upadacitinib 30 mg** | 0.80 (0.75 – 0.84) | 0.67 (0.61 – 0.73) | 0.50 (0.44 -0.57) |

**Table 3.4. Relative Risks for EASI 75 in Monotherapy RCTs in Adults**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **UPA 30 mg** | | | | | | | | |
| 1.15 (0.97-1.40) | **ABRO 200 mg** | | | | | | | |
| 1.22 (1.10 -1.37) | 1.06 (0.86-1.28) | **UPA 15 mg** | | | | | | |
| 1.38 (1.23-1.56) | 1.20 (0.97-1.46) | 1.13 (0.97-1.32) | **DUP 300mg Q2W** | | | | | |
| 1.70 (1.34-2.23) | 1.47 (1.25-1.78) | 1.39 (1.08-1.85) | 1.23 (0.95-1.64) | **ABRO 100 mg** | | | | |
| 2.18 (1.77-2.77) | 1.89 (1.45-2.49) | 1.79 (1.42-2.29) | 1.58 (1.25-2.03) | 1.29 (0.93-1.76) | **TRA 300 mg** | | | |
| 2.28 (1.81-2.95) | 1.97 (1.50-2.62) | 1.86 (1.47-2.43) | 1.64 (1.28-2.15) | 1.34 (0.96-1.85) | 1.04 (0.77-1.41) | **BARI 2 mg** | | |
| 3.53 (2.65-4.79) | 3.06 (2.21-4.24) | 2.88 (2.14-3.95) | 2.54 (1.88-3.49) | 2.07 (1.42-2.98) | 1.61 (1.13-2.29) | 1.54 (1.20-2.01) | **BARI 1 mg** | |
| 5.71 (5.13-6.38) | 4.95 (4.11-5.85) | 4.67 (4.08-5.31) | 4.13 (3.60-4.70) | 3.36 (2.60-4.21) | 2.61 (2.09-3.18) | 2.50 (1.97-3.11) | 1.62 (1.22-2.12) | **PBO** |

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

**Table 3.5. Relative Risks for EASI 90 in Monotherapy RCTs in Adults**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **UPA 30 mg** | | | | | | | | |
| 1.23 (0.96-1.61) | **ABRO 200 mg** | | | | | | | |
| 1.33 (1.15-1.56) | 1.09 (0.81-1.43) | **UPA 15 mg** | | | | | | |
| 1.58 (1.35-1.87) | 1.29 (0.96-1.69) | 1.18 (0.96-1.47) | **DUP 300mg Q2W** | | | | | |
| 2.08 (1.51-2.98) | 1.70 (1.36-2.17) | 1.57 (1.11-2.28) | 1.32 (0.94-1.93) | **ABRO 100 mg** | | | | |
| 2.89 (2.19-3.95) | 2.36 (1.65-3.39) | 2.17 (1.60-3.0) | 1.83 (1.34-2.54) | 1.39 (0.91-2.09) | **TRA 300 mg** | | | |
| 3.05 (2.26-4.26) | 2.49 (1.72-3.61) | 2.29 (1.67-3.23) | 1.93 (1.39-2.71) | 1.47 (0.95-2.22) | 1.06 (0.71-1.55) | **BARI 2 mg** | | |
| 5.31 (3.69-7.79) | 4.32 (2.85-6.56) | 3.98 (2.72-5.9) | 3.35 (2.28-4.99) | 2.54 (1.57-4.04) | 1.83 (1.17-2.84) | 1.73 (1.26-2.42) | **BARI 1 mg** | |
| 9.60 (8.32-11.17) | 7.83 (6.05-9.87) | 7.21 (6.0-8.6) | 6.08 (5.08-7.22) | 4.61 (3.29-6.25) | 3.32 (2.5-4.27) | 3.14 (2.32-4.14) | 1.81 (1.27-2.54) | **PBO** |

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

## Harms

Most adverse events (AEs) and treatment-emergent adverse events (TEAEs) observed in the trials were of mild-to-moderate severity (see Report Supplement Tables D3.4-3.7). Included in the most commonly reported AEs with greater incidence than placebo were nausea, conjunctivitis, and herpetic infection. The incidence of discontinuation due to AEs or TEAEs and the incidence of serious adverse events (SAEs) were low and were generally similar among these agents.

Although the incidence of SAEs in the trials of JAK inhibitors for this indication was low, long-term data are limited and evidence from trials evaluating JAK inhibitors at longer time points for other indications suggest an increased risk of SAEs, such as reactivation of herpes zoster, malignancy, thromboembolic events, and cardiovascular events.[33] Additionally, baricitinib and upadacitinib carry black box warnings for serious infections, malignancies, and thrombosis.[111,112] More information on the harms of the interventions is available in Evidence Tables G1.42-1.47 of the Report Supplement.

At the time of the 2017 ICER Report, long-term safety for dupilumab were limited. Since then, long-term safety data over three years from an open-label extension were reported, and these results supporting the safety of dupilumab were consistent with trials of up to 52 weeks (see Tables D3.6 and D3.7 in the Report Supplement).[50,113]

## Subgroup Analyses and Heterogeneity

We examined outcomes among patient subgroups of interest based on age (children 6 to 11 years old, adolescents 12-17 years old, and adults greater than 18 years old) and disease severity (moderate and severe).

*Patient Age*

Trials of baricitinib and tralokinumab did not include patients younger than 18 years old. One trial of abrocitinib solely enrolled patients 12-17 years old, while several trials of abrocitinib and upadacitinib trials enrolled patients 12 years and older, and data on subgroups of adolescent patients in those trials were obtained from conference presentations or manufacturers as academic-in-confidence data(see Report Supplement Tables D3).[39,41,71,78] Results from these trials were qualitatively similar to results of patients greater than 18 years old in these trials and from the dupilumab trial, LIBERTY AD ADOL,[52] which enrolled adolescent patients (see Report Supplement Tables D3.8-3.11).

*Disease Severity*

Subgroup analyses based on disease severity at baseline mostly provided by manufacturers as academic-in-confidence suggest qualitatively better outcomes in patients with severe disease compared to those with moderate disease with abrocitinib, baricitinib, and tralokinumab (see Evidence Tables G1.25-1.42).[39,44,65] No evidence stratified by disease severity was identified for upadacitinib.

## Uncertainty and Controversies

There is no well-defined classification for "moderate-to-severe" atopic dermatitis and how it differs from those with "mild-to-moderate" disease. This results in differences in study populations among trials and the varying responses seen for those receiving placebo treatment.

Abrocitinib, baricitinib, tralokinumab, and upadacitinib are therapies with novel mechanisms of action affecting the body's immune system, and we lack adequate long-term safety data for patients with atopic dermatitis. Although SAEs were rare in the phase III atopic dermatitis trials of abrocitinib, baricitinib, and upadacitinib, worrisome side effects for oral JAK inhibitors approved and in use for other conditions have led the FDA to place boxed warnings on this class of agents. Presumably because of these concerns, the FDA announced in April 2021 that they are extending the review period for abrocitinib, baricitinib, and upadacitinib.[13]

Although patients with atopic dermatitis can have disease activity that flares and remits over time, suggesting that intermittent use of these therapies may be possible, clinical experts we spoke with felt that they will be used for long periods in patients with clinical response and tolerability.

Although tralokinumab is not a JAK inhibitor, lack of long-term data results in some concerns about safety for this novel IL-13 antagonist. Though dupilumab is an IL-4 receptor alpha antagonist, it inhibits IL-4 and IL-13 signaling and suggests that long-term safety data for dupilumab may also apply to tralokinumab.

We primarily used indirect quantitative methods (NMAs) to compare abrocitinib, baricitinib, tralokinumab, and upadacitinib to each other because there were no head-to-head studies. Such indirect analyses have more uncertainty than had the therapies been compared directly. Only two trials compared interventions to dupilumab (JADE COMPARE for abrocitinib and Heads Up for upadacitinib).

The pivotal phase II and III RCTs compared the active agents to placebo as monotherapy during the 16-week study periods (12 weeks for the abrocitinib trials). These trials represent the best evidence for the efficacy of the active therapies and were used in our primary NMA analyses. Other trials comparing these new drugs to placebo along with the use of topical steroids and/or calcineurin

inhibitors may better reflect benefit as used in routine practice since new therapy is often added to existing topical treatments. However, differences among trials that included the use of background topical therapy led us to consider these trials separately from the placebo trials in our NMA analyses. The choice of our primary NMA results using trials only with placebo and not with topical therapies likely reflects a best-case view of the benefit of these new therapies. This is supported by the lower risk ratios in the NMAs for trials that include topical therapies. We examined doses for the new therapies we anticipate may be approved for use including 1 mg of baricitinib that is recommended for rheumatoid arthritis patients with moderate renal impairment.

There is limited information available about the relative benefits and harms of these new therapies in important subgroups including patients with moderate versus severe atopic dermatitis and adolescents aged 12-17. Few trials have yet reported outcomes separately for patients with moderate versus severe atopic dermatitis at baseline, so it is uncertain whether the treatment benefit differs based upon baseline severity.

The onset of action may also differ among these drugs. Specifically, abrocitinib assessed its primary outcome at 12 weeks, whereas the other drugs used 16 weeks. In the JADE COMPARE trial of abrocitinib versus dupilumab, abrocitinib appeared to improve outcomes more quickly than dupilumab even though outcomes were similar by 16 weeks.

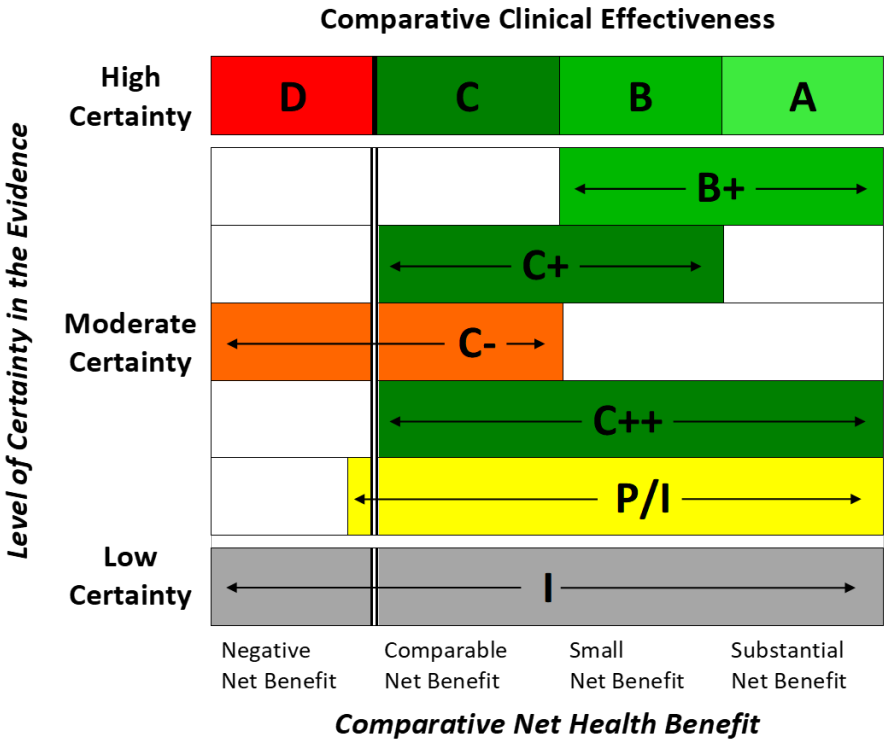
Given the large impact of atopic dermatitis in African-Americans and the importance of skin appearance on outcomes of treatment more broadly,[114] few trials included a sizable number of patients with darker skin complexions, and we are not aware of any trial that has reported outcomes among those with darker skin complexion.

Patients with atopic dermatitis often have other allergic conditions such as rhinitis and asthma. Dupilumab has been shown to be beneficial in patients with atopic dermatitis and these other conditions, but it is not known how abrocitinib, baricitinib, tralokinumab, and upadacitinib affect patients who also have allergic rhinitis or asthma.

## Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.2) is provided in Section D1 of the Report Supplement.

**Figure 3.2. ICER Evidence Rating Matrix**




***A = "Superior"*** *- High certainty of a substantial (moderate-large) net health benefit*
***B = "Incremental"*** *- High certainty of a small net health benefit*
***C = "Comparable"-*** *High certainty of a comparable net health benefit*
***D= "Negative"-*** *High certainty of an inferior net health benefit*
***B+= "Incremental or Better" –*** *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
***C+ = "Comparable or Incremental" -*** *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
***C- = "Comparable or Inferior" –*** *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
***C++ = "Comparable or Better" -*** *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
***P/I = "Promising but Inconclusive"*** *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
***I = "Insufficient" –*** *Any situation in which the level of certainty in the evidence is low*

Results from clinical trials and from our NMAs suggest that abrocitinib, baricitinib, tralokinumab, and upadacitinib improve outcomes of patients with atopic dermatitis compared to topical emollients alone (placebo). These outcomes included improving the severity of atopic dermatitis and patient reported itch and sleep. Similar favorable results for abrocitinib, baricitinib, tralokinumab, and upadacitinib are seen in trials that permitted use of topical medications. There

appear to be some differences among these medications in terms of their effectiveness, with abrocitinib and upadacitinib having more favorable outcomes than baricitinib and tralokinumab at the doses studied in the trials.

With regard to comparisons with dupilumab, direct comparisons with abrocitinib and upadacitinib and our NMAs suggest that higher doses of updadacitinib and possibly abrocitinib are somewhat more effective than dupilumab, while baricitinib (at the doses likely to be approved) and tralokinumab are likely somewhat less effective than dupilumab. When comparing therapies, other outcomes may also be important such as many patients with atopic dermatitis have comorbid atopic conditions and dupilumab has proven benefit in treating some patients with asthma.

Though abrocitinib, baricitinib, tralokinumab, and upadacitinib appeared to have few serious harms reported from the trials of atopic dermatitis, oral JAK inhibitors approved for other indications, including baricitinib and upadacitinib, have label warnings about potentially causing serious infections, blood vessel disorders, cancer and death, and serious harms are more common at the higher doses studied. Whether certain oral JAK inhibitors or their use in patients with atopic dermatitis is associated with fewer long-term harms remains uncertain. No similar risks have been reported with tralokinumab but while it works through a mechanism more similar to dupilumab than the JAK inhibitors it lacks the same long-term safety profile of dupilumab. Moreover, for all of these medications there is uncertainty about their relative benefit and safety caused by differences in the trials with regards to patient characteristics, outcomes assessed and their timing, the indirect nature of the NMAs, and limited long-term efficacy and safety data.

In summary, for adults and adolescents with moderate-to-severe atopic dermatitis inadequately controlled with topical or systemic therapies, or for whom topical or systemic therapies are not tolerated or are medically inadvisable, we identified benefits from short-term trials of these four agents but concerns about long-term safety, especially for the oral JAK inhibitors. As such:

- We consider the evidence for the net health benefit for abrocitinib, baricitinib, tralokinumab and upadacitinib compared with topical therapies alone to be *promising but inconclusive ("P/I")*, demonstrating a moderate certainty of a small or substantial net health benefit, with a small (but nonzero) likelihood of a negative net health benefit.
- We consider the evidence for the net health benefit for abrocitinib and upadacitinib compared with dupilumab to be *insufficient ("I")*, and that the net health benefit of baricitinib and tralokinumab were *comparable or inferior ("C-")* when compared with dupilumab, demonstrating moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior.

- We consider the evidence for the net health benefit for abrocitinib, baricitinib, tralokinumab, and upadacitinib compared with each other to be *insufficient ("I")*.

We also note that for the new therapies, we have greater uncertainties for adolescents given that baricitinib and tralokinumab trials only included adults and the randomized trials of abrocitinib and upadacitinib enrolled small numbers of patients younger than age 18.

**Table 3.6. Evidence Ratings**

| Treatment | Comparator | Evidence Rating |
|---|---|---|
| Abrocitinib | Topical therapies alone | P/I |
| Baricitinib | Topical therapies alone | P/I |
| Tralokinumab | Topical therapies alone | P/I |
| Upadacitinib | Topical therapies alone | P/I |
| Abrocitinib | Dupilumab | I |
| Baricitinib | Dupilumab | C- |
| Tralokinumab | Dupilumab | C- |
| Upadacitinib | Dupilumab | I |
| Abrocitinib, Baricitinib, Tralokinumab, Upadacitinib | To each other | I |

# 3.3. Results for Mild-to-Moderate Population

## Clinical Benefits

The key clinical benefits and harms of ruxolitinib cream in the mild-to-moderate population are described in Section 3.3. Additional evidence is presented in Sections D2 and D3 of the Report Supplement (see Report Supplement Tables D3.12-3.13 and Evidence Tables G1.48-1.64.)

Our 2017 Report found inadequate evidence to assess the relative efficacy of crisaborole with the other topical therapies for mild-to-moderate atopic dermatitis including topical calcineurin inhibitors and topical corticosteroids. Trials of crisaborole found modest improvement compared to vehicle (placebo). For example, in pooled analyses of two trials of crisaborole, Investigator's Static Global Assessment (ISGA) response, defined as an ISGA score of 0 or 1 *and* an improvement of 2 points or more from baseline, was moderately higher in the crisaborole arms, compared with the placebo arms at day 29 (32% vs. 22%). NMA results comparing crisaborole to pimecrolimus, a topical calcineurin inhibitor, showed a trend towards improvement in IGA response with pimecrolimus (risk ratio: 0.61; 95% CrI: 0.10 to 2.28). However, time periods and versions of IGA scales differed between the trials, and the credible interval was wide. Further, an SLR suggested pimecrolimus was less effective than topical tacrolimus or moderate potency topical corticosteroids.[115]

*Ruxolitinib Cream*

**Ruxolitinib cream substantially increased the likelihood of achieving EASI 75, EASI 90, and IGA response in a dose dependent manner compared to vehicle (placebo). Results for other EASI thresholds and other patient reported outcomes were generally consistent with results for EASI 75 and IGA. Compared with topical corticosteroids, outcomes for ruxolitinib cream were better on reported measures. Results for adolescents were similar to adults and long-term data were limited.**

We identified two monotherapy trials (TRuE-AD1 & TRuE-AD2) comparing ruxolitinib cream to vehicle (placebo). Both trials enrolled patients ≥12 years old; most of the patients were ≥18 years old (80%-81%). In addition, we identified a placebo- and active-controlled trial that enrolled patients ≥18 years old.

In TRuE-AD1 and 2, 62% of patients achieved EASI 75 in the ruxolitinib cream 1.5% arms, compared with 14%-25% of patients in the vehicle (placebo) arms at week eight.[98] EASI 75 was achieved by 52%-56% of patients with ruxolitinib cream 0.75%. EASI 90 was achieved by 43%-44% of patients in the ruxolitinib cream 1.5 arms, compared with 4%-10% of patients in the vehicle (placebo) arms. In the ruxolitinib cream 0.75% arms, 35%-38% of patients achieved this outcome. IGA response, defined as an IGA score of 0 or 1 and an improvement of 2 points or more from baseline, was achieved by 51%-54% of patients in the ruxolitinib cream 1.5% arms, compared with 8%-15% of patients in the vehicle (placebo) arms. IGA response was achieved by 39%-50% of patients with ruxolitinib cream 0.75%.

More patients experienced a ≥4-point improvement on the patient reported PP-NRS with ruxolitinib cream 1.5% and 0.75% dosing than with vehicle (placebo) (51%-52% and 40%-43% vs. 15%-16%, respectively).

Other patient reported outcomes showed similar favorable results compared to vehicle (placebo). In pooled analyses, patients had greater reductions from baseline on the DLQI with ruxolitinib cream 1.5% (-7) and ruxolitinib cream 0.75% (-7) than vehicle (placebo) (-3.1; $p<0.0001$ for comparisons with both doses of ruxolitinib cream), where a 4-point difference is considered to be clinically meaningful.[100,105] Patients also had greater reductions from baseline on POEM with ruxolitinib cream 1.5% and 0.75% compared to vehicle (placebo) (-11 and -11 to vs. –4.2, respectively; $p<0.0001$ for both comparisons), where a 3-4-point improvement is considered clinically meaningful.[100,106]. More patients experienced a ≥6-point improvement on the Patient Reported Outcomes Measurement Information System (PROMIS) Short Form-Sleep Disturbance Score with ruxolitinib cream 1.5% and 0.75% dosing than vehicle (placebo) (22%-26% and 21% vs. 10%-19%%, respectively; $p<0.05$ for both comparisons).[116] Similarly, patients had greater reductions

from baseline on SCORAD with ruxolitinib cream 1.5% and 0.75% dosing than vehicle (placebo) (-67% and -63% vs. -30.4%; p<0.0001).

In a monotherapy trial that compared ruxolitinib cream to topical triamcinolone acetonide (a medium potency topical corticosteroid) and vehicle (placebo), there were numerical improvements with ruxolitinib cream compared to triamcinolone acetonide cream for EASI 75, IGA response (as defined above), and change from baseline in itch NRS scores.[87,88] However, no tests of statistical significance were reported (see Table D3.12 in the Report Supplement).

Results for HADS Anxiety and Depression were not reported in any trials of ruxolitinib cream.

The 52-week long-term extension studies of TRuE-AD1 and TRuE-AD2, designed to primarily evaluate the long-term safety of ruxolitinib, suggest maintenance of IGA response at 52 weeks (see Report Supplement D3).[74]

## Harms

All TEAEs were of mild-to-moderate severity (see Report Supplement Table D3.13). The most commonly reported TEAEs included application site burning and pruritus, and the incidence of these TEAEs was lower in the ruxolitinib cream arms than vehicle (placebo). In contrast, the incidence of serious TEAEs was generally similar between the arms. Further, discontinuation incidence due to TEAEs was lower in the ruxolitinib cream arms compared to placebo and triamcinolone acetonide cream. More information on the harms of ruxolitinib cream is available in Evidence Tables G1.59-1.60 of the Report Supplement.

## Subgroup Analyses and Heterogeneity

We examined outcomes among patient subgroups of interest based on age (children 6 to 11 years old, adolescents 12-17 years old, and adults greater than 18 years old), disease severity (mild and moderate), and race.

*Patient Age*

No trials of ruxolitinib cream enrolled children. Subgroup analyses of adolescent patients from trials that enrolled patients 12 years and older suggest qualitatively similar results to the overall population, though the proportion of patients 12-17 years old in these trials was small (see Evidence Tables G1.61-1.64).[102]

*Disease Severity*

Subgroup analyses based on disease severity at baseline suggest qualitatively better outcomes in patients with moderate disease compared to those with mild disease (see Evidence Tables G1.61-1.64).[98]

*Race*

In a presentation of pooled data from two trials, IGA response with ruxolitinib appeared somewhat greater in white than black patients.[102] With the two doses (1.5% and 0.75%), the percentages of white patients who achieved IGA treatment success at week eight were 57.3% and 49.7% versus 12.2% with vehicle (placebo); in black patients, these results were 38.1% and 31.4% versus 11.5%. Results in Asians and other races appeared more similar to the results in white patients.

## Uncertainty and Controversies

Although ruxolitinib cream is a topical JAK inhibitor and concern for side effects may be lower, systemic absorption still occurs and its role for the long-term management of patients with mild-moderate atopic dermatitis, especially in children and adolescents, is uncertain and will also require long-term assessment of safety outcomes. Perhaps reflecting concerns about systemic JAK inhibitors and potential systemic absorption of topical JAK inhibitors, the FDA announced in June 2021 that they are extending the review period for ruxolitinib cream by three months.[15] Trial designs did not allow for quantitative indirect comparisons between topical ruxolitinib and other topical therapies. The only head-to-head trial was in comparison with a medium potency topical corticosteroid which would be expected to have lower efficacy than more potent topical therapies.

The effectiveness of ruxolitinib cream in patients with darker skin complexions may be somewhat less, supporting the need for trials in broader populations.[102]

## Summary and Comment

In two phase III trials of ruxolitinib cream versus topical emollients alone (placebo), patients receiving ruxolitinib cream had improved outcomes at the two doses studied. A single phase II trial of ruxolitinib cream included a topical steroid comparator. While outcomes appeared to favor ruxolitinib cream compared to topical triamcinolone acetonide, no tests of statistical significance were reported, and it was not compared with more potent topical corticosteroids. Side effects of ruxolitinib cream were similar to or better than vehicle (placebo), though long-term safety remains uncertain. In summary:

- We consider the evidence for the net health benefit for ruxolitinib cream compared with topical emollients to be *comparable or better ("C++")*, demonstrating a moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit.
- We consider the evidence for the net health benefit for ruxolitinib cream compared with other topical medications to be *insufficient ("I")*.

# 4. Long-Term Cost Effectiveness

## 4.1. Methods Overview

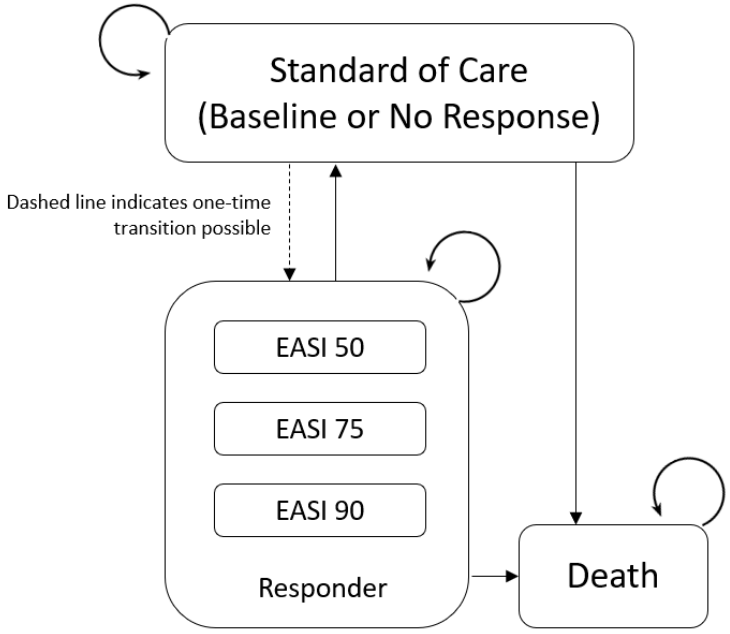
We adapted the Markov model from ICER's 2017 report on dupilumab for this evaluation, with the adaptation informed by key clinical trials and prior relevant economic models.[117] Costs and outcomes were discounted at 3% per year.

The model focused on an intention-to-treat analysis, with a hypothetical cohort of adult patients with moderate-to-severe atopic dermatitis being treated with abrocitinib, baricitinib, tralokinumab and upadacitinib compared to dupilumab, or emollients (representing standard of care). Model cycle length was 16 weeks based on common response evaluation time points, prior published economic models, and clinical data.

We developed a Markov model with health states based on treatment response. Treatment response was measured by the Eczema Area and Severity Index (EASI) score.[118] Health states were categorized by the percent decrease in EASI score from baseline after a patient begins an intervention: 50%-74% decrease (EASI 50), 75%-89% decrease (EASI 75), 90%-99% decrease (EASI 90), or less than 50% decrease (no response).

Patients enter the model in the non-responder state and then may remain in non-response or transition to a responder state (EASI 50-74, 75-89, or 90-100) in the first cycle. Once in a response state, patients were not allowed to transition between responder categories. Patients could transition back to the non-responder state as they discontinued treatment, for any reason. Patients could also transition from any health state to death. Patients remained in the model until the end of the time horizon of five years or death. We assumed that atopic dermatitis disease and treatment did not affect mortality.

**Figure 4.1. Model Structure**




EASI: Eczema Area Severity Index;
Schematic note: Standard of care indicates topical emollients only (not topical corticosteroids). Patients in the standard of care state, either at baseline or after discontinuing therapy, are assumed to have an EASI score of less than 50.

## 4.2. Key Model Choices and Assumptions

Below is a list of key model choices:

- Each therapy was included at one dosage, which is either the most commonly used dosage or the most effective dosage (if two doses have equal effects, we modeled the lower dose).
- We modeled one line of active therapy to focus the cost-effectiveness analyses on the available clinical data for the interventions of interest.
- The model used 16-week cycles and included a half-cycle correction for all cycles.
- Base case costs included direct medical costs by health state, drug costs, and any costs associated with administration or monitoring.
- Mortality in each health state was based on age- and gender-specific US mortality rates (all-cause).

- Due to no assumed differences in mortality across treatments and no assumed time variation on a treatment's benefits after the measurement of treatment response, we used a 5-year time horizon for the base case model and tested the horizon duration in a scenario analysis.
- All health states were weighted by a single set of health state utility values from pooled manufacturer data to derive quality-adjusted life-years (QALYs).
- Costs and outcomes were discounted annually at 3%.
- Change in peak pruritus numerical rating scale (PP-NRS), impact on sleep items within the disease-specific patient-reported outcomes (POEM, SCORAD, and ADerm-IS), and impact on anxiety/depression (HADS) were assessed in the clinical review and were considered as part of a cost consequences analysis alongside the cost-utility findings from the model.

Our model includes several assumptions stated below.

**Table 4.1. Key Model Assumptions**

| Assumption | Rationale |
|---|---|
| **Transitions to the response state occur after one cycle.** | Patients are typically evaluated for treatment response after approximately 16 weeks. |
| **Patients do not change response levels after the initial response while on treatment** | There are limited data on sustained changes between response levels. |
| **After transitioning off treatment, quality of life and costs are equivalent to a patient who was eligible for treatment but never treated** | There is limited evidence that treatment for atopic dermatitis alters the course of the condition after treatment has ceased |
| **Patients on only topical treatment who are responders (achieve ≥EASI50 after the first cycle) transition to non-response at a rate equivalent to discontinuation rates for placebo patients in the relevant clinical trials** | Patients in the placebo arms of the considered clinical trials were allowed to utilize emollients, and thus the recurrence rate in the placebo arms is expected to mirror that of patients treated with topicals. We did not consider discontinuation rates of trials where patients were allowed to use topical corticosteroids. |
| **Among responders, discontinuation rates do not vary by responder level** | There is limited evidence supporting differential discontinuation by response level or over time. |
| **Atopic dermatitis disease and treatments do not affect mortality** | There is limited evidence suggesting an effect on mortality. We assume the modeled patient population excludes patients for whom JAK inhibitors could affect mortality (those over 50 years of age with a cardiovascular risk factor). |

## Treatment Population

The modeled base case analysis utilized a hypothetical cohort of patients with moderate-to-severe atopic dermatitis in the U.S. being treated with abrocitinib, baricitinib, tralokinumab, or upadacitinib, compared to dupilumab or emollients (representing standard of care). We pooled trial data from these treatments to derive demographic details for the cohort, which included a mean age of 35.8 years and 44% of the cohort being female. The patient population is assumed to exclude patients over 50 with increased cardiovascular risk, as JAK inhibitors will likely not be approved in that population.

## Model Inputs

## Transition Probabilities

We utilized the results of the NMA of placebo-controlled monotherapy trials to inform the treatment-specific transitions to each responder health state in the first model cycle. The overall percentage of responders was as follows: 73% for abrocitinib, 44% for baricitinib, 46% for tralokinumab, 80% for upadacitinib, 64% for dupilumab, and 21% for standard of care.

**Table 4.2. Initial Response Health State Transition Probabilities**

| Drug | EASI 50-74 | EASI 75-99 | EASI 90+ | Total Responders |
|---|---|---|---|---|
| **Abrocitinib** | [redacted] | | | |
| **Baricitinib** | | | | |
| **Tralokinumab** | | | | |
| **Upadacitinib** | | | | |
| **Dupilumab** | | | | |
| **Standard of Care** | 9.6% | 6.5% | 5.3% | 21.4% |

EASI: Eczema Area Severity Index

We utilized treatment specific per-cycle treatment discontinuation rates for the first year after initial treatment and then for all subsequent years over the model time horizon where data was available. Per cycle discontinuation rates were derived from long-term follow-up data for patients who achieved a minimum of EASI 50 at their initial 16-week evaluation. Treatment discontinuation for any reason resulted in transitioning to the non-responder health state. Long-term discontinuation data for atopic dermatitis patients were not available for upadacitinib; in the absence of data provided on the discontinuation rate for responders after 16 weeks, we assumed a rate equal to the highest rate within the class.

**Table 4.3. Discontinuation Rates**

| Drug | Year 1 | Year 2+ | Source |
|---|---|---|---|
| **Abrocitinib** | [redacted] | | JADE COMPARE |
| **Baricitinib** | | | BREEZE-AD3 |
| **Tralokinumab** | 5.04% | 5.04% | ECZTRA 2 |
| **Upadacitinib** | [redacted] | | BREEZE-AD3 (proxy) |
| **Dupilumab** | 3.77% | 4.87% | LIBERTY AD-SOLO CONTINUE; LIBERTY AD OLE |
| **Standard of Care** | 25.40% | 25.40% | ECZTRA 1 & 2 |

EASI: Eczema Area Severity Index

## Health State Utilities

We derived pooled health state utilities for each health state (Baseline, <EASI 50, EASI 50-74, EASI 75-89, and EASI 90-100) from manufacturer submitted data. We estimated utility values for each health state by combining estimates from the treatments with disaggregated data by health state and weighting by the number of study participants. Utility data were not disaggregated by moderate and severe subpopulations. We considered therapy-specific health state utility values to capture benefit beyond EASI score, however the available evidence did not support differential utility scores by treatment. To capture the benefits during patients' first 16 weeks on therapy, the utilities in the first cycle were calculated as a weighted average with half the time assumed to be spent at baseline utility and the other half assumed to be in a responder state for those who transitioned in the subsequent cycle. Utility for the health state of EASI 0-49 was applied to only the first model cycle to represent patients who took the therapy during the initial 16-week trial period and may have derived some benefit from the therapy despite not reaching the responder status of EASI 50. It is assumed that after discontinuing therapy, patients return to the non-responder state utility.

**Table 4.4. Health State Utilities**

| Health State | Value | Source |
|---|---|---|
| **Non-responder** | [redacted] | ECZTRA 1 & 2, MEASURE UP 1 & 2, AD UP, SOLO 1 & 2 |
| **EASI 0-49** | | |
| **EASI 50-74** | | |
| **EASI 75-89** | | |
| **EASI 90-100** | | |

EASI: Eczema Area Severity Index

## Patient Reported Outcomes

Inputs in the cost-consequence analysis were derived from manufacturer submitted data, including one measure of itch (PP-NRS), three measures for sleep (POEM, SCORAD, and ADerm-IS), and one measure of anxiety/depression (HADS). These analyses were included if data were provided for the mean score at baseline and for each responder category. Data were available for tralokinumab (PP-NRS, POEM, SCORAD, HADS) and upadacitinib (PP-NRS, Aderm-IS). The model output was the mean score and incremental mean score versus SoC over the model time horizon. Measures of change in other patient reported outcomes were considered but ultimately not included in the cost-consequence modeling due to lack of data by health state.

**Table 4.5. Patient Reported Outcomes**

| | PP-NRS | PP-NRS | POEM (Sleep) | SCORAD (Sleep) | ADerm-IS (sleep) | HADS (anxiety/ depression) |
|---|---|---|---|---|---|---|
| **Drug** | **Tralokinumab** | **Upadacitinib** | **Tralokinumab** | **Tralokinumab** | **Upadacitinib** | **Tralokinumab** |
| **Pooled Baseline*** | | | | | | |
| **EASI 50** | | | | | | |
| **EASI 75** | | | | | | |
| **EASI 90** | | | | | | |
| **Source for pooled baseline** | ECZTRA 1, 2, MEASURE UP 1, 2, AD UP, BREEZE AD5, MONO1-2, COMPARE | ECZTRA 1, 2, MEASURE UP 1, 2, AD UP, BREEZE AD5, MONO1-2, COMPARE | ECZTRA 1, 2 | ECZTRA 1, 2 | Measure Up1, 2, and AD Up | LP0162-1326/1339/1325 |
| **Source for drug-specific scores** | ECZTRA 1, 2, | MEASURE UP 1, 2, and AD UP | ECZTRA 1, 2 | ECZTRA 1, 2 | Measure Up1, 2, and AD Up | LP0162-1326/1339/1325 |

*Pooled baseline estimates include all trials with a baseline estimate for each measure. Health state-specific measures are presented where data was available; drugs without health state specific PRO measures are not presented in this table.

ADerm-IS: Atopic Dermatitis Impact Scale, EASI: Eczema Area Severity Index, PP-NRS: Peak Pruritis Numeric Rating Scale, POEM, Patient-Oriented Eczema Measure, SCORAD: Scoring Atopic Dermatitis; HADS, hospital anxiety and depression scale;

## Mortality

Gender- and age-specific background mortality from the Centers for Disease Control and Prevention U.S.-specific tables was used for all-cause mortality rates, and was uniformly applied across all health states.[119]

## Cost Inputs

### *Drug Costs*

For included therapies that are currently marketed, we obtained net pricing estimates from SSR Health, LLC, which combine data on unit sales with publicly disclosed US sales figures that are net of discounts, rebates, patient assistance programs, and concessions to wholesalers and distributors, to derive a net price. We estimated net prices by comparing the four-quarter averages (i.e., 3rd quarter of year 2019 through 2nd quarter of 2020) of both net prices and wholesale acquisition cost (WAC) per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the most recent available WAC (Redbook accessed March 9, 2021) to arrive at an estimated net price per unit.

For abrocitinib, we used the average of the net prices of baricitinib and upadacitinib as a placeholder price. For tralokinumab, we used the net price of dupilumab as a placeholder price and assume that it is used every two weeks in the base case. No known corroborated analyst pricing is available for either abrocitinib or tralokinumab. Placeholder prices will be updated in future versions of the report as pricing information becomes available.

**Table 4.6. Drug Costs**

| Drug | WAC per Dose | Discount from WAC* | Net Price per Dose | Net Price per Year |
|---|---|---|---|---|
| **Abrocitinib (200 mg qd)†** | $127.65 | 17% | $113.34 | $41,397.44 |
| **Baricitinib (Olumiant™, 2 mg qd)** | $79.28 | 33% | $53.12 | $19,402.08 |
| **Tralokinumab (300 mg q2w)†** | $1,601.70 | 26% | $1,193.27 | $31,131.56 |
| **Upadacitinib (Rinvoq™, 30 mg qd)** | $176.02 | 1% | $173.56 | $63,392.79 |
| **Dupilumab (Dupixent®, 300 mg 2qw)** | $1,601.70 | 26% | $1,193.27 | $31,131.56 |

*SSR Health, LLC, was used for estimating discounts from wholesale acquisition cost
†Using placeholder prices

### *Non-Drug Costs*

*Direct Medical Costs*

We used annual direct medical cost estimates from manufacturer provided data derived from IBM Watson MarketScan claims database. Claims were analyzed from years 2011-2018, and costs were updated from 2018 to 2021 US dollars using the US Bureau of Labor Statistics CPI inflation calculator, which include all non-drug direct health care costs.[120] Subcutaneous injectables were assumed to also incur a one-time cost for self-injection training and monitoring. We did not find evidence of any serious adverse events occurring in >5% of subjects among any of the clinical trials, therefore we did not include adverse event costs in the model.

**Table 4.7. Direct Medical Health State Costs**

| | Value | Source |
|---|---|---|
| **Annual Health State Costs** | | |
| **Non-responder** | $18,588.62 | Data provided by manufacturer |
| **EASI 50-74** | $10,100.58 | |
| **EASI 75-89** | $8,910.17 | |
| **EASI 90+** | $8,595.68 | |
| **One-time SC Training and Monitoring Costs** | | |
| **Office visit/self-injection training** | $23.00 | CPT 99211 |
| **General practitioner visit** | $57.00 | CPT 99212 |
| **Blood panel** | $7.77 | CPT 85025 |

CPT: current procedural terminology codes, SC: subcutaneous
All costs in 2021 USD

## 4.3. Results

### Base Case Results

The total discounted costs, quality-adjusted life years (QALYs), life years (LYs), and equal value of life years gained (evLYG) over the five-year time horizon are presented in Table 4.9. We note that there are not currently available prices for abrocitinib and tralokinumab, and thus the cost estimates and incremental cost-effectiveness ratios are based on placeholder prices. In a cohort of patients with moderate-to-severe atopic dermatitis who received a single treatment beyond emollients for up to 5 years, baricitinib had the lowest drug cost and total cost, $26,900 and $105,300, respectively, compared to upadacitinib at $151,300 and $219,700 as the highest drug and total costs, respectively. Abrocitinib generated the highest QALYs, 3.59, followed by upadacitinib and dupilumab, with 3.51 and 3.47, respectively. Abrocitinib's higher QALYs was due to having the second highest percent of overall responders and a lower discontinuation rate versus comparators.

**Table 4.9. Discounted Results for the Base Case for each Treatment and Standard of Care**

| Treatment | Drug Cost | Total Cost | QALYs (same as evLYGs) | Life Years | PP-NRS† | POEM (sleep)† | SCORAD (sleep)† | ADerm-IS (sleep)† | HADS (depression and anxiety)† |
|---|---|---|---|---|---|---|---|---|---|
| **Abrocitinib*** | $113,200 | $178,400 | 3.59 | 4.85 | NA | NA | NA | NA | NA |
| **Baricitinib** | $26,900 | $105,300 | 3.23 | 4.85 | NA | NA | NA | NA | NA |
| **Tralokinumab*** | $51,700 | $127,700 | 3.29 | 4.85 | -1.11 | -0.52 | -1.23 | NA | -1.23 |
| **Upadacitinib** | $151,300 | $219,700 | 3.51 | 4.85 | -1.65 | NA | NA | -5.75 | NA |
| **Dupilumab** | $72,400 | $141,900 | 3.47 | 4.85 | NA | NA | NA | | NA |
| **Standard of Care (Topicals)** | $- | $87,800 | 2.98 | 4.85 | -0.15 | -0.08 | -0.19 | -0.55 | -0.19 |

ADerm-IS: Atopic Dermatitis Impact Scale, NA: not available, PP-NRS: Peak Pruritis Numeric Rating Scale, POEM: Patient-Oriented Eczema Measure, QALY: quality-adjusted life-year, evLYG: equal-value life-year gained, SCORAD: Scoring Atopic Dermatitis; HADS: hospital anxiety and depression scale;

*Using a placeholder price

†Average change in PRO score from pooled baseline over model time horizon

Results of the cost-consequence analysis, which reflect the average change in each patient reported outcome (PRO) score from a pooled baseline over the 5-year time horizon, are also reported in Table 4.9. Incremental results can be found in Supplement table E2.1.

Table 4.10 presents the incremental results from the base case analysis, which include incremental cost-effectiveness ratios for incremental cost per LY gained, incremental cost per QALY gained, and incremental cost per evLYG gained. Given no modeled gains in life years across the evaluated therapies, the cost per life year gained is not reported.

**Table 4.10. Incremental Cost-Effectiveness Ratios for the Base Case**

| Treatment | Comparator | Cost per QALY Gained | Cost per Life Year Gained | Cost per evLYG |
|---|---|---|---|---|
| **Abrocitinib*** | SoC | $148,300 | NA | $148,300 |
| **Baricitinib** | SoC | $71,600 | NA | $71,600 |
| **Tralokinumab*** | SoC | $129,400 | NA | $129,400 |
| **Upadacitinib** | SoC | $248,400 | NA | $248,400 |
| **Dupilumab** | SoC | $110,300 | NA | $110,300 |
| **Abrocitinib*** | Dupilumab | $303,400 | NA | $303,400 |
| **Baricitinib** | Dupilumab | Less Costly, Less Effective | NA | Less Costly, Less Effective |
| **Tralokinumab*** | Dupilumab | Less Costly, Less Effective | NA | Less Costly, Less Effective |
| **Upadacitinib** | Dupilumab | $1,912,200 | NA | $1,912,200 |

evLYG: equal-value life-year gained, QALY: quality-adjusted life-year, SOC: Standard of Care

*Using a placeholder price

Note: The cost per QALY and cost per evLYG ratios were the same given that the treatments have not been shown to lengthen life.

## Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Across all modeled comparisons, the health state utility values were identified as the most influential model parameters on the incremental cost-effectiveness ratios, followed by the drug cost, initial transition probabilities, non-responder direct costs, and discontinuation rates. The Report Supplement contains tornado diagrams for each of the modeled comparisons.

Probabilistic sensitivity analyses were also be performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results, contained in the Report Supplement. From the PSA simulations, we estimated the probability of a drug being cost-effective across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per QALY), presented in Table 4.11 versus standard of care. PSA results indicated that included therapies had 0% estimated probability of being cost-effective versus dupilumab at an ICER threshold of $200,000 or less. We also performed threshold analyses for drug costs across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per QALY), available in the Report Supplement.

**Table 4.11. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Each treatment versus SoC**

| Cost-Effectiveness Threshold | Abrocitinib* | Baricitinib | Tralokinumab* | Upadacitinib | Dupilumab |
|---|---|---|---|---|---|
| **$50,000** | 0% | 45% | 12% | 0% | 0% |
| **$100,000** | 3% | 74% | 43% | 0% | 38% |
| **$150,000** | 49% | 85% | 65% | 3% | 76% |
| **$200,000** | 82% | 90% | 75% | 25% | 92% |

*Based on placeholder prices

## Scenario Analyses

We conducted five scenario analyses for the report. First, we calculated a modified societal perspective by adding productivity loss associated with moderate-to-severe atopic dermatitis by health state. Second, we extended the time horizon to lifetime, but maintained the single line of treatment. Third, we adjusted the model for abrocitinib to be initially evaluated at 12-weeks rather than 16 weeks to reflect the JADE MONO-1 and -2 clinical trials. Fourth, we adjusted the model to reflect outcomes for combination therapy with topical corticosteroids. Finally, we adjusted the model for tralokinumab patients achieving EASI 75 or above after 16 initial weeks of therapy to reduce dosing frequency from every 2 weeks to every 4 weeks to reflect arms of the ECZTRA3 clinical trial.

The total discounted costs, quality-adjusted life years (QALYs), life years (LYs), and equal value of life years gained (evLYG) over the five-year time horizon under the modified societal perspective are presented in Table E4.2 in the Report Supplement. The drug costs and patient outcomes remained the same compared to the base case, and the table shows the base case total costs for comparison. The total cost from the modified societal perspective versus the base case increased by 10-26% for the interventions and 36% for standard of care.

Table E4.3 in the Report Supplement presents the incremental results from the modified societal perspective scenario analysis, which include incremental cost-effectiveness ratios for incremental cost per LY gained, incremental cost per QALY gained, and incremental cost per evLYG. Incremental cost-effectiveness ratios from the modified societal perspective versus the base case when applying the standard of care comparator decreased by 7% to 22% across the therapies evaluated, but did not lead to therapies crossing cost-effectiveness thresholds (i.e., $50, $100, or $150,000 per QALY), with the exception of dupilumab which became cost-effective at the $100,000 per QALY threshold.

Table E4.5 in the Report Supplement presents the incremental results from the lifetime time horizon scenario analysis, which include incremental cost-effectiveness ratios for incremental cost per LY gained, incremental cost per QALY gained, and incremental cost per evLYG gained. Incremental cost-effectiveness ratios from the lifetime time horizon versus the base case five-year horizon when applying the standard of care comparator decreased by 4% to 13% across the therapies evaluated, but did not lead to therapies crossing cost-effectiveness thresholds (i.e., $50, $100, or $150,000 per QALY).

Table E4.6 in the Report Supplement presents the effect of changing the initial model cycle for abrocitinib from 16-weeks to 12-weeks to better reflect the JADE MONO-1 and -2 clinical trials. This scenario had minimal effect on QALYs, life-years, or equal-value life-years. In a five-year time horizon, this switch would decrease drug cost and total costs by 1.4% and 0.9%, respectively, and decrease ICER versus SoC by 1%; ICER versus dupilumab would increase by 0.2%. These outcomes are based on a placeholder price for abrocitinib and will be updated.

Table E4.8 in the Report Supplement presents the total results for the combination therapy scenario analysis, which include drug costs, total costs, QALYs, life-years, and evLYG. Drug costs and total costs were higher in the combination therapy scenario for all therapies, with increases ranging from 6-36%. Total costs decreased by 2% for those on standard of care. QALYs increased 2-4% across all therapies and SoC in the combination therapy scenario. Incremental cost-effectiveness results (Table E4.9) were all nominally larger (9-14%) in the combination therapy scenario when compared to standard of care/placebo but remained in the same order of cost effectiveness. Abrocitinib was the only therapy to cross a cost-effectiveness threshold (exceeded $150,000 for combination therapy, assuming a placeholder price). When compared to dupilumab, both baricitinib and

tralokinumab remained less costly and less effective, however dupilumab switched to dominate upadacitinib (dupilumab being less costly and more effective than upadacitinib) in the combination therapy scenario.

Table E4.10 in the Report Supplement presents the results of scenario that allowed 50% of patients who achieved EASI 75 or above on tralokinumab to switch from Q2 to Q4 week dosing, which reflects data from the . This scenario had no effect on QALYs, life-years, or equal-value life-years. In a five-year time-horizon assuming concurrent TCS therapy in both arms, drug and total costs would decrease by 15% and 8%, respectively. The ICER would decrease by 20% compared to SoC, however tralokinumab would remain less costly and less effective when compared to dupilumab. Because the clinical trial informing the analysis allowed patients to use concurrent TCS therapy, these results are most comparable to the scenario analysis of combination therapy.

## Threshold Analyses

Annual prices necessary to reach cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY compared to standard of care are listed in Table 4.12.

**Table 4.12. QALY-Based Threshold Analysis Results**

| | Annual WAC | Annual Net Price | Annual Price to Achieve $50,000 per QALY | Annual Price to Achieve $100,000 per QALY | Annual Price to Achieve $150,000 per QALY |
|---|---|---|---|---|---|
| **Abrocitinib** | $46,600* | $41,400* | $19,400 | $30,600 | $41,800 |
| **Baricitinib** | $29,000 | $19,400 | $15,600 | $24,400 | $33,300 |
| **Tralokinumab** | $41,800* | $31,100* | $16,400 | $25,700 | $35,000 |
| **Upadacitinib** | $64,300 | $63,400 | $19,300 | $30,400 | $41,500 |
| **Dupilumab** | $41,800 | $31,100 | $18,400 | $29,000 | $39,500 |

QALY: quality-adjusted life-year, WAC: wholesale acquisition price

*Based on a Placeholder Price

## Model Validation

We used several approaches to validate the model. We provided preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. We varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. Specifically, we tested all mathematical functions in the model to ensure they were consistent with the report (and Report Supplement materials) and used extreme and null input values to ensure the model was producing findings

consistent with expectations. Finally, model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

## Uncertainty and Controversies

As with any modeling exercise, there are limitations to be considered when evaluating these findings. First, we extrapolated clinical trial efficacy beyond the length of time that the trials were conducted, which assumes continued effectiveness (along with adherence to treatment). Next, we assumed that levels of EASI response are associated with differences in health-related quality of life. However, there may be differential effects of the treatments modeled on conditions such as itch and sleep that are not completely captured by generic quality of life instruments. However, available data did not support the use of treatment specific utilities. Additionally, there may be incremental effects of some of these treatments on quality of life in sub-populations of people with atopic dermatitis, such as those with co-occurring asthma or chronic rhinosinusitis, which are not explicitly captured in the current model.

We only had discontinuation data beyond one year for dupilumab, and assumed that the discontinuation rates for the other treatments were the same as year 1 in years 2-5. However, we note that we selected a 5-year time horizon for the base case in part to reduce the impact of these assumptions. Further, atopic dermatitis specific discontinuation rates were not available for upadacitinib and we therefore assumed that the discontinuation rate was equal to the highest rate within the class. We also assumed that patient response to treatment was fixed after 16 weeks, allowing neither further improvement nor waning of efficacy, other than capturing discontinuation. This assumption was based on the lack of data demonstrating changes in either direction.

We excluded SAEs that occurred in less than 5% of the trial population. However, we note there are some rare SAEs from the phase III JAK inhibitor clinical trials that may impact both costs and patient health-related quality of life.

Finally, the NMA analyses that informed our effectiveness estimates in the model were derived from phase II and III RCTs that compared the treatments of interest to placebo with only the added use of topical emollients at 16 weeks. We provided results for the use of these products in combination with topical steroids as a scenario analysis. Furthermore, the NMA's produced estimates with wide confidence intervals and there may be additional uncertainty regarding the comparative effectiveness of these treatments.

## 4.4 Summary and Comment

Using a Markov model, we compared the cost and effectiveness of four emerging therapies for moderate to severe atopic dermatitis to skin emollients and an approved biologic, dupilumab, over a five-year time horizon taking a health system perspective. It is important to note that the JAK inhibitor class has been associated with some rare but serious clinical adverse events which are not captured in the current model but would carry the potential to impact both costs and outcomes in those patients who experience them.

While drug prices are not currently available for two therapies (abrocitinib and tralokinumab), we found abrocitinib to produce the most QALYs (3.59) of therapies considered and baricitinib to produce the fewest (3.23). Compared to SoC with emollients only, baricitinib was cost-effective at a $100,000/QALY threshold, abrocitinib and tralokinumab were cost-effective at a $150,000/QALY threshold (using placeholder prices), dupilumab was cost-effective at a $150,000/QALY threshold, and upadacitinib would need to decrease its WAC per dose cost from $176 to $113 in order to be cost-effective at $150,000/QALY threshold. Compared to dupilumab, baricitinib and tralokinumab were found to be less costly and less effective whereas abrocitinib (using a placeholder price) and upadacitinib did not meet commonly cited cost-effectiveness thresholds.

# 5. Contextual Considerations and Potential Other Benefits

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

**Table 6.1. Contextual Considerations**

| Contextual Consideration | Relevant Information |
|---|---|
| **Acuity of need for treatment of individual patients based on the severity of the condition being treated** | Patients, caregivers, advocacy groups and clinical experts all identified a need for new therapeutic options for patients with atopic dermatitis, especially those with more severe disease who are either unresponsive or intolerant of existing therapies. |
| **Magnitude of the lifetime impact on individual patients of the condition being treated** | Atopic dermatitis is a chronic condition that usually begins in childhood and can continue throughout the course of a patient's life broadly affecting physical, psychosocial, and emotional health. As such it can affect childhood development, school achievement and performance in the workplace. |
| **There is uncertainty about the long-term risk of serious side effects** | Though trials of abrocitinib, baricitinib and upadacitinib in atopic dermatitis showed few serious side effects, oral JAK inhibitors when used for other conditions include black box warnings for serious infections, malignancies, and clotting disorders. |

**Table 6.2. Potential Other Benefits or Disadvantages**

| Potential Other Benefit or Disadvantage | Relevant Information |
|---|---|
| **Patients' ability to achieve major life goals related to education, work, or family life** | New therapies for atopic dermatitis that improve the appearance, symptoms and complications of atopic dermatitis may help improve quality of life across a range of different outcomes including social interactions with family, friends and other relations, educational achievement, and work performance. However, it is uncertain whether abrocitinib, baricitinib, tralokinumab and upadacitinib will improve education or work outcomes. |
| **Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life** | For children and adolescents with atopic dermatitis, the care required often involves family members and other caregivers. The impact of atopic dermatitis and the demands of treatment fall not only on the patient, but also their caregivers. As such, new therapies for atopic dermatitis offer the possibility of improving the quality of life for the caregivers as well as for patients. |
| **Patients' ability to manage and sustain treatment given the complexity of regimen** | The potential of new oral therapies such as abrocitinib, baricitinib and upadacitinib to improve outcomes for patients with atopic dermatitis may also decrease the complexity of care. The need for topical therapies that are time-consuming to apply, phototherapies that require multiple treatment visits or medications that are delivered by injection all increase the complexity of care. Though oral JAK inhibitors are likely to be given along with topical therapies they are likely to reduce the complexity of a patient's regimen if effective.<br><br>For those responding to an initial every two week schedule, tralokinumab dosing decreased to every four weeks in some patients could potentially affect real world adherence. |
| **Health inequities** | The high costs of treatments for atopic dermatitis, especially newer agents, may exacerbate existing health inequities. |
| **These interventions offer novel mechanisms of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.** | Abrocitinib, baricitinib, tralokinumab and upadacitinib represent new therapies that reflect translational research in which improved understanding of the mechanisms of disease have led to new therapies. |

# 6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of treatment with the interventions when compared to standard of care alone are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLYG gained. Because of the assumption that atopic dermatitis and assessed therapies do not have an impact on mortality, calculated QALYs Gained and evLYGs are equal in this model. Using the broadest set of figures derived from these thresholds, we arrive at a HBPB for abrocitinib from $30,600 to $41,800; for baricitinib $24,400 (no discount needed at the $150,000 threshold); for tralokinumab, $25,700 to $35,000; for upadacitinib, $30,400 to $41,500; and for dupilumab, $29,000 to $39,500. Discounts from WAC to reach threshold prices for abrocitinib and tralokinumab are not applicable as they are currently based on placeholder WAC prices and should be updated when WAC pricing is established.

**Table 6.1. Annual Cost-Effectiveness Health Benefit Price Benchmarks for Abrocitinib, Baricitinib, Tralokinumab, Upadacitinib, and Dupilumab versus Standard of Care**

| Health Benefit Measure | Annual WAC | Annual Price at $100,000 Threshold | Annual Price at $150,000 Threshold | Discount from WAC to Reach Threshold Prices |
|---|---|---|---|---|
| **Abrocitinib** | | | | |
| **QALYs Gained** | NA* | $30,600 | $41,800 | NA* |
| **evLYG** | NA* | $30,600 | $41,800 | NA* |
| **Baricitinib** | | | | |
| **QALYs Gained** | $29,000 | $24,400 | $33,300 | 0% to 16% |
| **evLYG** | $29,000 | $24,400 | $33,300 | 0% to 16% |
| **Tralokinumab** | | | | |
| **QALYs Gained** | NA* | $25,700 | $35,000 | NA* |
| **evLYG** | NA* | $25,700 | $35,000 | NA* |
| **Upadacitinib** | | | | |
| **QALYs Gained** | $64,300 | $30,400 | $41,500 | 35% to 53% |
| **evLYG** | $64,300 | $30,400 | $41,500 | 35% to 53% |
| **Dupilumab** | | | | |
| **QALYs Gained** | $41,800 | $29,000 | $39,500 | 6% to 31% |
| **evLYG** | $41,800 | $29,000 | $39,500 | 6% to 31% |

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

* Not applicable (NA) as placeholder prices were used

# 7. Potential Budget Impact

## 7.1. Overview of Key Assumptions

ICER used results from the cost-effectiveness model to estimate the potential total budgetary impact of each drug that awaits US regulatory approval (abrocitinib, baricitinib, tralokinumab, and upadacitinib) for moderate-to-severe atopic dermatitis. We used the WAC, an estimate of net price, and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) for each drug in our estimates of budget impact. Consistent with the cost-effectiveness analysis, abrocitinib was assigned a placeholder net price equal to the average between baricitinib and upadacitinib's annual net prices. Similarly, tralokinumab was assigned a placeholder net price equal to dupilumab's annual net price. Placeholder prices will be updated in future versions of the report as actual pricing information becomes available.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

ICER's methods for estimating potential budget impact are described in detail in the Report Supplement Section F. For this analysis, we calculated the budget impact of new treatments (abrocitinib, baricitinib, tralokinumab, and upadacitinib) given these treatments' displacement of dupilumab plus usual care (assumed 10% mix) and usual care alone (90% mix) and by assigning 103,200 new individuals to each new treatment per year (for five years).

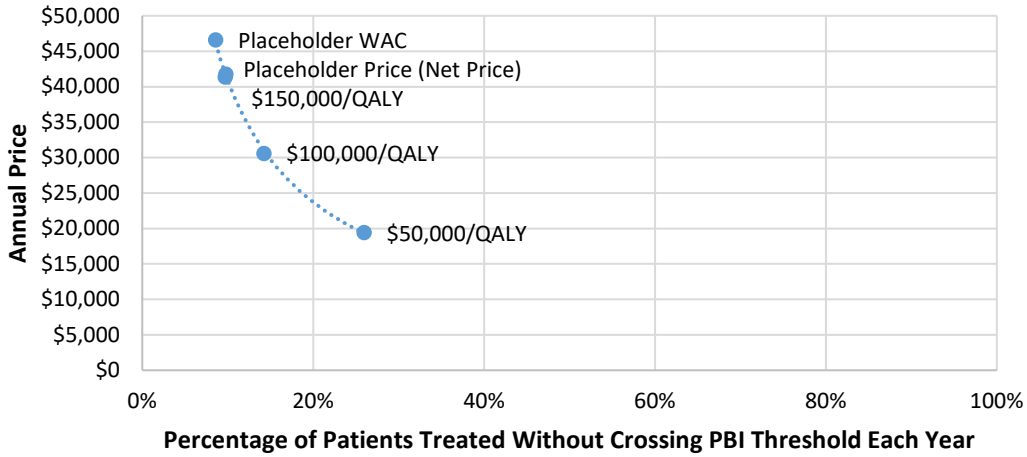
## 7.2. Results

Report Supplement Section F displays the average annual per patient budget impact findings across the five unit prices (WAC, discounted WAC, and the prices that achieve three different cost-effectiveness thresholds) for abrocitinib, baricitinib, tralokinumab, and upadacitinib. Further, Report Supplement Section F details the cumulative per-patient budget impact estimates for abrocitinib, baricitinib, tralokinumab, and upadacitinib.

Figures 7.1 – 7.4 illustrate the potential budget impact of abrocitinib, baricitinib, tralokinumab, and upadacitinib treatment of the eligible population, based on the respective five different unit prices (WAC, discounted WAC, and the prices that achieve three different cost-effectiveness thresholds). Upon removing the placeholder prices and across all four treatments, the range of the percentage of those treated without crossing the potential budget impact annual threshold was between 8%

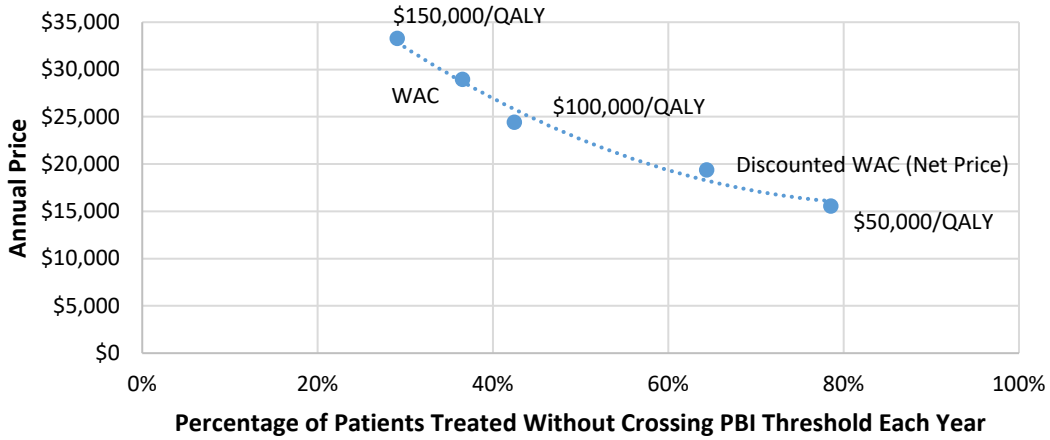
and 79% for all prices evaluated (WAC unit price to the maximum price to achieve $50,000 per QALY).

**Figure 7.1. Budgetary Impact of Abrocitinib***



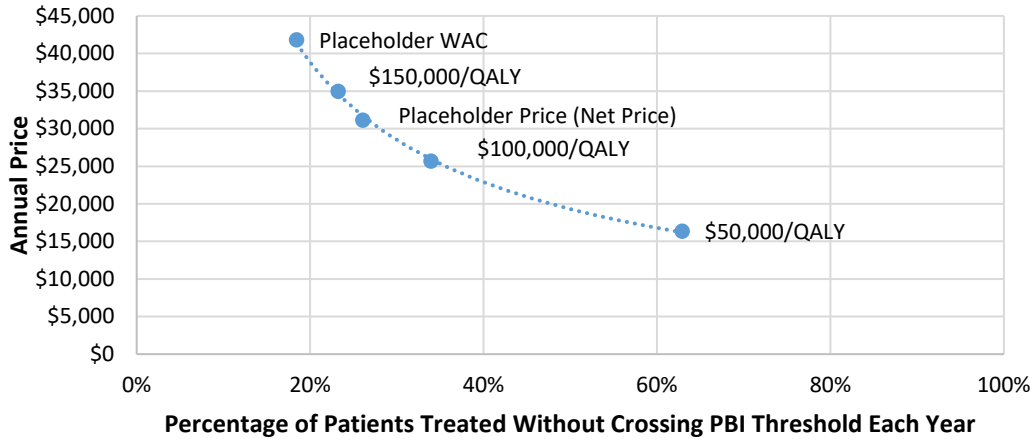

PBI: potential budget impact, QALY: quality-adjusted life-year, WAC: wholesale acquisition price
*Based on placeholder prices

**Figure 7.2. Budgetary Impact of Baricitinib**




PBI: potential budget impact, QALY: quality-adjusted life-year, WAC: wholesale acquisition price

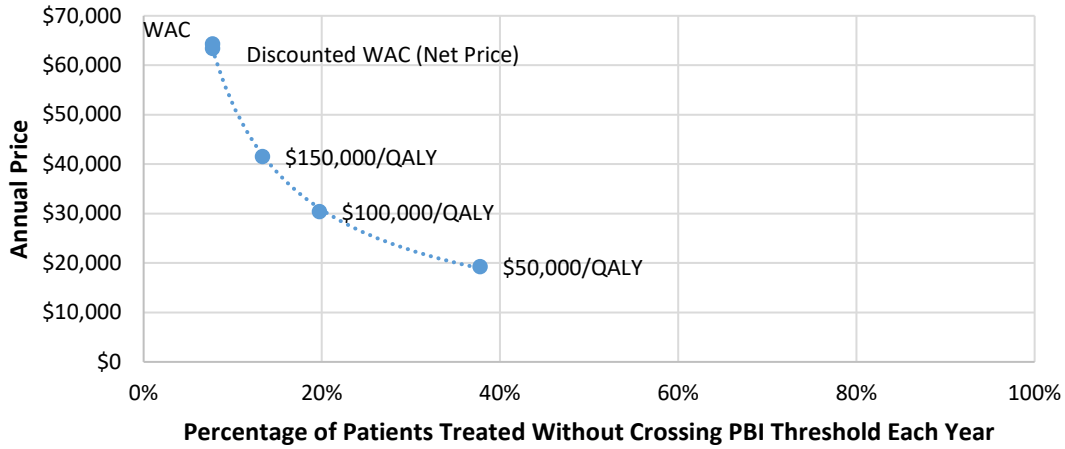
**Figure 7.3. Budgetary Impact of Tralokinumab***




PBI: potential budget impact, QALY: quality-adjusted life-year, WAC: wholesale acquisition price

*Based on placeholder prices

**Figure 7.4. Budgetary Impact of Upadacitinib**




PBI: potential budget impact, QALY: quality-adjusted life-year, WAC: wholesale acquisition price

# Supplemental Materials

# A. Background: Supplemental Information

## A1. Definitions

The primary outcomes in the pivotal trials studied include investigator assessed responses:

1. E***czema Area Severity Index score (EASI):***[121] This instrument represents a modification of the general schema used in the psoriasis area and severity index (PASI). The total score for the EASI ranges from 0 to a maximum of 72 with higher scores indicating greater severity. Total scores represent a sum of severity scores from four body regions (head and neck, upper extremities, trunk, and lower extremities). The score for each body region includes an assessment of severity for the four signs of erythema, induration/papulation/edema, excoriations, and lichenification. These are each assigned a score of 0 to 3 (None, mild, moderate, severe, respectively). These are added up for each anatomic region and multiplied by the percentage area involved and a proportionate body surface area assigned to each of the four body regions. The percentage area involved for each of the four body regions are assigned a proportional score from 0 to 6 (where 0= no eruption, 1 = ≤10%, 2 = 10-29%, 3 – 30-49%, 4 = 50-69%, 5= 70-89%, and 6 = 90-100%). The proportionate body surface areas assigned to adults are 10% for the head and neck (20% for children), 20% for the upper extremities (same for children), 30% for trunk (same for children) and 50% for lower extremities (30% for children). Outcomes are assessed as the change in EASI response from baseline and are categorized as the percent improvement as noted below. The EASI-75 response is most commonly used as the primary outcome end point.

- **EASI-50**: a percentage improvement of EASI score from baseline that is ≥ 50%
- **EASI-75**: a percentage improvement of EASI score from baseline that is ≥ 75%
- **EASI-90**: a percentage improvement of EASI score from baseline that is ≥ 90%

2. ***Investigator's Global Assessment (IGA):***[122] This clinician-reported outcome measure provides an overall assessment of the severity of a patient's atopic dermatitis at a specific time point. There are different versions of the instrument with the most common using a 5- or 6- point rating scale. The 5-point scale ranges from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe). The 6-point scale ranges from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), 4 (severe) to 5 (very severe). In many trials the primary response outcome or IGA response is defined as a score of 0 or 1 on the IGA. The IGA response can also include an improvement from baseline of ≥2 points. Other cutoffs used in studies include ≥3 or ≥4 points.

3. ***Peak Pruritus Numerical Rating Scale (PP-NRS):***[123] Itch (or pruritus) represents a key symptom for patients with atopic dermatitis and can be intense, persistent, and debilitating. This scale was developed to assess one dimension of pruritis, its severity. It is a single self-reported item designed to measure the severity of pruritis or peak pruritus, or 'worst' itch, over the previous 24 hours using an 11-point scale. The item asks: 'On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?' Improvement from baseline can be reported using a number of different cut points including, ≥2, ≥3, or ≥4 points

4. ***Scoring Atopic Dermatitis (SCORAD):***[124] Developed and validated by the European Task Force on Atopic Dermatitis, SCORAD is a composite severity index that combines objective symptoms (extent and intensity, and subjective criteria (pruritis and sleep loss). The extent of atopic dermatitis is expressed as the skin surface area involved. The intensity includes 6 specific symptoms: erythema, edema/papulation, oozing/crusts, excoriations, lichenification and dryness of the involved skin. These are rated from none (0), mild (1), moderate (2) or severe (3) for each item. The subjective symptoms are assessed using a visual analogue scale where 0 is no itch (or no sleeplessness) and 10 is the worst imaginable itch (or sleeplessness). The SCORAD index ranges from 0 to 103, with higher scores indicating worse severity.

5. ***Dermatology Life Quality Index (DLQI):***[125] The DLQI is a 10-item, validated dermatology specific quality of life assessment instrument used in clinical practice and clinical trials. It assesses six domains including: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and adverse effects of treatment. Nine items have four response options: "not at all," "a little," "a lot," and "very much." One item asks about whether work or study has been prevented, and then (if "yes") to what degree has the skin condition been a problem ("a lot," "a little," or "not at all"). Individual items are summed to obtain a total score that can range from 0 to 30, with higher scores indicating worse health-related quality of life. Suggested interpretation of DLQI score for 0-1 indicates no impact, 2-5 indicates small impact, 6-10 indicates moderate impact, 11-20 indicates large impact and 21-30 indicates an extremely large impact on health-related quality of life for the skin condition.

6. ***Children's Dermatology Life Quality Index (CLDQI):***[126] A version of the DLQI questionnaire designed to measure the impact of skin disease on the lives of children ages 4 to 16 years.

7. ***Patient-Oriented Eczema Measure (POEM):***[106] This simple, validated questionnaire assesses patient's symptoms and impact of atopic dermatitis in children and adults. It asks about symptoms over the prior week and includes seven questions about itch, sleep disturbance and whether the skin is weeping/oozing, cracked, flaking, dry/rough, or bleeding. These are rated from "no days," "1-2 days", "3-4 days", "5-6 days", or "every day". POEM scores range from 0 to 28 with higher

scores indicating worse disease severity and the minimal clinically important difference has been reported to be 3-4.

8. ***Atopic Dermatitis Impact Scale (ADerm-IS):***[127] It includes three items (difficulty falling asleep, level of impact on sleep, burden of waking up at night) to be completed daily, assessing impact on sleep over the previous 24 h, and seven items (limitations in household activities, physical activities, social activities, difficulty concentrating, feeling self-conscious, embarrassed, sad) completed weekly to assess overall impact over the past 7 days. Responses are on an 11-point numeric rating scale from 0 "not [present]" to 10 "extremely [present]".Responses are on an 11-point numeric rating scale from 0 "not [present]" to 10 "extremely [present]".

9. ***Dermatitis Family Impact Questionnaire (DFI):***[128] A disease-specific measure to assess the impact of atopic dermatitis on the quality of life of parents and family members of affected children.

10. ***Hospital Anxiety and Depression Scale (HADS):*** Likert scale used to detect states of anxiety and depression; anxiety and depression subscales each with 7 items.

11. ***Work Productivity and Activity Impairment for Atopic Dermatitis (WPAI-AD):***[129] The WPAI, a validated instrument is used to measure impairment in work productivity and daily activities. The questionnaire consists of six questions assessing the past 7 days: employment status (yes/no), work time missed due to atopic dermatitis (hours), work time missed due to other reasons (hours), actual work time (hours), impact of atopic dermatitis on work productivity while at work (0-10 point scale) and impact of atopic dermatitis on activities outside of work (0-10 point scale). Four scores are derived: absenteeism (percentage of time missed from work due to health), presenteeism (percentage of impairment while at work due to health), work productivity loss (aggregate of absenteeism and presenteeism) and activity impairment (percentage of impairment in daily activities due to health). Higher scores indicate a higher level of impairment. Higher scores indicate a higher level of impairment.

## A2. Potential Cost-Saving Measures in Atopic Dermatitis

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by therapies for atopic dermatitis (e.g., caregiver/family burden), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of atopic dermatitis beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with atopic dermatitis that could be reduced, eliminated, or made more efficient. No suggestions were received.

# B. Patient Perspectives: Supplemental Information

## B1. Methods

In developing and executing this report, we received valuable input from individual patients and patient advocacy groups throughout the scoping and evidence development process. We received public comments on our draft scoping document from the following patient advocacy organizations: the National Eczema Association, the International Eczema Council, and the Allergy and Asthma Network. We also conducted a focus group with three patients and three caregivers that was arranged through the National Eczema Association. These interviews with patients and caregivers helped to illustrate the diversity of experiences of patients living with atopic dermatitis, as well as highlighted the health outcomes that were most important to them.

# C. Clinical Guidelines

## American Academy of Dermatology

### *Guidelines of care for the management of atopic dermatitis*[28]

The American Academy of Dermatology issued updated and expanded clinical guidelines for the treatment of atopic dermatitis in 2014, based on the initial guidelines that were published in 2004. These guidelines were developed by a working group of experts in the field who used an evidence-based approach to discuss diagnosis, assessment, safety, and efficacy of available treatments for atopic dermatitis.

**Treatment with Topical Therapies**

Non-pharmacologic treatments are recommended to maintain and prevent flares. These interventions include moisturizers, bathing practices (i.e., limited use of non-soap cleansers, subsequent moisturization), and wet-wrap therapy for those with moderate-to-severe atopic dermatitis. Wet wrap therapy can also be used in conjunction with topical corticosteroids during flares. These methods serve to minimize the severity of atopic dermatitis and reduce the amount of pharmacologic intervention needed.

Topical pharmacologic treatments are recommended to treat atopic dermatitis in patients that do not respond to the above interventions. These include topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI), both of which are used for the treatment and management of adults and adolescent atopic dermatitis patients. TCS are recommended for both active and maintenance therapy in patients that have not had success in controlling symptoms with non-pharmacologic interventions. TCI are recommended as a second-line therapy if TCS has failed to control symptoms.

While other topical treatments exist for the maintenance of atopic dermatitis symptoms, they are not recommended lines of therapy. These topical therapies include antimicrobials, antiseptics, and antihistamines.

**Treatment with Phototherapy and Systemic Agents**

The American Academy of Dermatology recommends phototherapy as a second-line treatment for atopic dermatitis in children and adults, as well as maintenance therapy in cases of chronic disease. It can be used as monotherapy or in combination with other topical therapies. While it is considered a low-risk treatment, it is important to consider adverse events when used in

conjunction with other drugs. Phototherapy treatment is contingent on several patient factors, including availability, cost, skin type, and medical history.

The prescription of systemic agents for atopic dermatitis patients warrants several considerations related to disease contraindications, quality of life, and severity. Systemic treatment is recommended for patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled by topical regimens and phototherapy. The recommended off-label systemic therapies indicated by the guidelines include cyclosporine, azathioprine, and methotrexate. Mycophenolate mofetil and interferon gamma are also indicated as alternative off-label therapies for atopic dermatitis. The minimal effective dose of each systemic therapy should be used when treating patients. The guidelines also recommend against the use of systemic corticosteroids, as there are concerns with associated short- and long-term adverse events.

**Use of Adjunctive Therapies**

It is recommended that patient education always be included in conventional therapy. The use of TCS or TCI can also be used to prevent relapse after the disease has been stabilized.

## Joint Task Force on Practice Parameters for Allergy and Immunology

### *Atopic Dermatitis: A practice parameter update 2012*[130]

The Joint Task Force on Practice Parameters for Allergy and Immunology issued an update in 2012 to their 2004 treatment guidelines for atopic dermatitis. The task force was comprised of the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology. In these suggestions for practice, the joint task force presents recommendations for first line management and treatment of atopic dermatitis, as well as guidance for severe cases that are more difficult to treat.

### First Line Management and Treatment of Atopic Dermatitis

It is recommended that clinicians treat patients using a systematic approach, and the intensity of management and treatment should be determined by severity of the disease. Recommended treatments include skin hydration, topical anti-inflammatory medications, antipruritic therapy, antibacterial measures, and elimination of any environmental factors that may be exacerbating illness. Some of these common irritants include soaps, toiletries, wools, and chemicals that tend to trigger the itch-scratch cycle. Food allergies may also be considered as triggers for infants and children with atopic dermatitis.

Regardless of the severity of illness, it is imperative for clinicians to educate patients and family members on the chronic nature of the disease. Treating clinicians should review disease

exacerbating factors with their patients, as well as the safety and side effects of any prescribed medications.

### Treatment of Severe Cases of Atopic Dermatitis

For severe cases of atopic dermatitis, it is recommended that patients are treated with systemic immunomodulating agents, such as cyclosporine, mycophenolate mofetil, azathioprine, interferon gamma, and corticosteroids. Wet dressings can also be used in combination with topical corticosteroids. However, it is important to note the potential serious adverse events associated with these drugs, and the risks and benefits should be discussed with the patient. Phototherapy can also be utilized as a means of treatment, particularly narrow-band UBV, which has been proven to be most effective in the U.S. For extremely severe cases of atopic dermatitis, hospitalization is recommended, as this could potentially remove a patient from environmental allergens and lessen the effects of disease associated stressors, such as sleep deprivation.

Investigative approaches to treating and managing atopic dermatitis are not recommended, as there is currently insufficient data to prove effectiveness. Examples of these interventions include intravenous immunoglobin, omalizumab, and rituximab.

## National Institute for Health and Care Excellence (NICE)

### *Dupilumab for Treating Moderate to Severe: Recommendations*[131]

NICE released recommendations for use of dupilumab in 2018. Dupilumab is recommended as an option for treating moderate to severe atopic dermatitis in adults after not responding to at least one other systemic therapy such as cyclosporin, methotrexate, azathioprine, and mycophenolate, or if these are contraindicated or not tolerated. Response should be assessed at 16 weeks and therapy should be stopped if there has not been an adequate response. This is considered at least a 50% reduction in the EASI score (EASI 50) and at least a 4-point reduction in the DLQI, both compared to prior to starting treatment. The recommendation notes that skin color should be taken into account and clinical adjustments made if appropriate when assessing the EASI since it may affect the score. For the DLQI, adjustments can be made if appropriate to account for any physical, psychological, sensory, or learning disabilities, or communication difficulties that could affect patient responses.

### *Baricitinib for Treating Moderate to Severe: Recommendations*[131]

NICE released recommendations for use of baricitinib in March 2021. Baricitinib has similar recommendations as for dupilumab; adults with moderate to severe atopic dermatitis not responding to at least one other systemic therapy such as cyclosporin, methotrexate, azathioprine, and mycophenolate, or if these are contraindicated or not tolerated. Response should be assessed from 8 weeks and baricitinib should be stopped if there has not been an adequate response at 16 weeks, using the same criteria as for dupilumab.

# D. Comparative Clinical Effectiveness: Supplemental Information

## D1. Detailed Methods

### PICOTS

#### *Population*

The populations of focus for the review were:

1. Adults and children with moderate-to-severe atopic dermatitis whose disease has either not responded adequately to topical therapies or for whom topical therapies have not been tolerated or are medically inadvisable

2. Adults and children with mild-to-moderate atopic dermatitis

Additionally, based on the availability of data, we included evidence stratified by age (children: <12 years, adolescents: ≥12 years to <18 years, and adults: ≥18 years), duration (≤16 weeks and >16 weeks), and disease severity (mild, moderate, and severe).

#### *Interventions*

The interventions of interest included the following JAK inhibitors and monoclonal antibodies:

Moderate-to-severe atopic dermatitis (Population 1):

- Abrocitinib (Pfizer)
- Baricitinib (Olumiant©, Eli Lilly)
- Upadacitinib (Rinvoq©, AbbVie)
- Tralokinumab (Leo Pharma)

Note that each of these therapies may be used alone or with topical therapies (including emollients with or without a topical corticosteroid or calcineurin inhibitor)

Mild-to-moderate atopic dermatitis (Population 2):

- Ruxolitinib cream (Incyte)

***Comparators***

For moderate-to-severe atopic dermatitis (Population 1) we compared the interventions to:

- Dupilumab
- Each other
- Topical therapies (including emollients with or without a topical corticosteroid or calcineurin inhibitor)

We had initially included methotrexate as a comparator, but after additional input from clinical experts and other stakeholders we have not included comparisons with methotrexate in the report due to differences in study design, populations, and outcomes.

For mild-to-moderate atopic dermatitis (Population 2) we compared the intervention to:

- Topical emollient therapy alone
- Topical corticosteroids
- Topical calcineurin inhibitors
- Crisaborole cream

***Outcomes***

The outcomes of interest are described in the list below.

- Patient-reported pruritus or itching
- Eczema Area and Severity Index (EASI); 50, 75, and 90 or relative change from baseline
- Investigator's Global Assessment (IGA)
- Sleep
- Scoring Atopic Dermatitis (SCORAD) Score
- Patient-Oriented Eczema Measure (POEM)
- Dermatology Life Quality Index (DLQI)
- Children's Dermatology Life Quality Index (CDLQI)
- Anxiety and depression (e.g., Hospital Anxiety and Depression Scale [HADS])
- European Quality of Life-5 Dimensions (EQ-5D)
- Measures of productivity (e.g., Work Productivity and Activity Impairment Questionnaire [WPAI])
- Other patient-reported symptom and quality of life measures

- Safety
    - Adverse events (AEs)
    - Treatment-emergent adverse events (TEAEs)
    - Serious adverse events (SAEs)
    - Discontinuation due to AEs
    - Thrombotic events
    - Infections (serious, skin, herpetic)
    - Hematological abnormalities
    - Malignancy
        - Non-melanocytic skin cancer
    - All-cause mortality

***Timing***

Evidence on intervention effectiveness was derived from studies of at least four weeks duration.

## Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for atopic dermatitis followed established best research methods.[132,133] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[134] The PRISMA guidelines include a checklist of 27 items described further in Table D1.1.

**Table D1.1. PRISMA 2009 Checklist**

| Checklist Items | | |
|---|---|---|
| **TITLE** | | |
| **Title** | 1 | Identify the report as a systematic review, meta-analysis, or both. |
| **ABSTRACT** | | |
| **Structured summary** | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. |
| **INTRODUCTION** | | |
| **Rationale** | 3 | Describe the rationale for the review in the context of what is already known. |
| **Objectives** | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). |
| **METHODS** | | |
| **Protocol and registration** | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. |
| **Eligibility criteria** | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. |
| **Information sources** | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. |
| **Search** | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. |
| **Study selection** | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). |
| **Data collection process** | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. |
| **Data items** | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. |
| **Risk of bias in individual studies** | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. |
| **Summary measures** | 13 | State the principal summary measures (e.g., risk ratio, difference in means). |
| **Synthesis of results** | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. |

| | | |
|---|---|---|
| **Risk of bias across studies** | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). |
| **Additional analyses** | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. |
| **RESULTS** | | |
| **Study selection** | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. |
| **Study characteristics** | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. |
| **Risk of bias within studies** | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). |
| **Results of individual studies** | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. |
| **Synthesis of results** | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. |
| **Risk of bias across studies** | 22 | Present results of any assessment of risk of bias across studies (see Item 15). |
| **Additional analysis** | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). |
| **DISCUSSION** | | |
| **Summary of evidence** | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers). |
| **Limitations** | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). |
| **Conclusions** | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. |
| **FUNDING** | | |
| **Funding** | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. |

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from

conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer-review.org/use-of-in-confidence-data/).

**Table D1.2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (Interventions)***

| | |
|---|---|
| 1 | observational study.pt. |
| 2 | exp case-control studies/ |
| 3 | exp cohort studies/ |
| 4 | exp cross-over studies/ |
| 5 | exp matched-pair analysis/ |
| 6 | multicenter study.pt. |
| 7 | 1 or 2 or 3 or 4 or 5 or 6 |
| 8 | randomized controlled trial.pt. |
| 9 | controlled clinical trial.pt. |
| 10 | randomized.ab. |
| 11 | placebo.ab. |
| 12 | drug therapy.fs. |
| 13 | randomly.ab. |
| 14 | trial.ab. |
| 15 | groups.ab. |
| 16 | 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 |
| 17 | comparative study.pt. or compare.ab,ti. or compares.ab,ti. or compared.ab,ti. or comparing.ab,ti. or comparison.ab,ti. or comparison.ab,ti. or comparative.ab,ti. or effective.ab,ti. or effectiveness.ab,ti. or versus.ab,ti. or vs.ab,ti. |
| 18 | 7 and 17 |
| 19 | 16 or 18 |
| 20 | exp animals/ |
| 21 | humans.sh. |
| 22 | 20 not 21 |
| 23 | 19 not 22 |
| 24 | limit 23 to English language |
| 25 | (case reports or comment or congresses or editorial or letter or review).pt. |
| 26 | 24 not 25 |
| 27 | exp Eczema/ or eczema.mp. |
| 28 | exp Dermatitis, Atopic/ |
| 29 | neurodermatitis.mp. or exp Neurodermatitis/ |
| 30 | exp Dermatitis/ or dermatitis.mp. |
| 31 | 27 or 28 or 29 or 30 |

| | |
|---|---|
| 32 | Exp Abrocitinib/ or abrocitinib.mp. |
| 33 | (abrocitinib or "pf04965842" or pf04965842 or "pf 4965842" or pf4965842).ti,ab. |
| 34 | Exp baricitinib/ or baricitinib.mp. |
| 35 | (baricitinib or "incb 028050" or incb028050 or "incb 28050" or "ly 3009104" or ly3009104 or olumiant).ti,ab. |
| 36 | Exp upadacitinib/ or upadacitinib.mp. |
| 37 | (upadacitinib or "abt 494" or abt494 or rinvoq or "upadacitinib hemihydrate" or "upadacitinib hydrate" or "upadacitnib tartrate").ti,ab. |
| 38 | Exp tralokinumab/ or tralokinumab.mp. |
| 39 | (tralokinumab or "cat354" or cat354 or "cat-354").ti,ab. |
| 40 | Exp Ruxolitinib/ or ruxolitinib.mp. |
| 41 | (ruxolitinib or "incb 018424" or incb018424 or "incb 18424" or incb18424 or jakafi or jakavi or "ruxolitinib maleate" or "ruxolitinib phosphate").ti,ab. |
| 42 | 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 |
| 43 | 31 and 42 |
| 44 | 26 and 43 |

***Search last updated on January 27, 2021.**

**Table D1.3. Search Strategy Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (Comparators)***

| | |
|---|---|
| 1 | observational study.pt. |
| 2 | exp case-control studies/ |
| 3 | exp cohort studies/ |
| 4 | exp cross-over studies/ |
| 5 | exp matched-pair analysis/ |
| 6 | multicenter study.pt. |
| 7 | 1 or 2 or 3 or 4 or 5 or 6 |
| 8 | randomized controlled trial.pt. |
| 9 | controlled clinical trial.pt. |
| 10 | randomized.ab. |
| 11 | placebo.ab. |
| 12 | drug therapy.fs. |
| 13 | randomly.ab. |
| 14 | trial.ab. |
| 15 | groups.ab. |
| 16 | 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 |
| 17 | comparative study.pt. or compare.ab,ti. or compares.ab,ti. or compared.ab,ti. or comparing.ab,ti. or comparison.ab,ti. or comparison.ab,ti. or comparative.ab,ti. or effective.ab,ti. or effectiveness.ab,ti. or versus.ab,ti. or vs.ab,ti. |
| 18 | 7 and 17 |
| 19 | 16 or 18 |

| | |
|---|---|
| 20 | exp animals/ |
| 21 | humans.sh. |
| 22 | 20 not 21 |
| 23 | 19 not 22 |
| 24 | limit 23 to english language |
| 25 | (case reports or comment or congresses or editorial or letter or review).pt. |
| 26 | 24 not 25 |
| 27 | exp Eczema/ or eczema.mp. |
| 28 | exp Dermatitis, Atopic/ |
| 29 | neurodermatitis.mp. or exp Neurodermatitis/ |
| 30 | exp Dermatitis/ or dermatitis.mp. |
| 31 | 27 or 28 or 29 or 30 |
| 32 | dupilumab.mp. |
| 33 | (dupilumab or dupixent or "regn 668" or regn688 or "sar 231893" or sar231893).ti,ab |
| 34 | crisaborole.mp |
| 35 | (eucrisa or an2728 or 'an-2728').ti,ab |
| 36 | 32 or 33 or 34 or 35 |
| 37 | limit 38 to yr=2017-2021 |
| 38 | 31 and 37 |
| 39 | 26 and 38 |

*Search last updated on January 27, 2021.

**Table D1.4. Cochrane Database of Systematic Reviews***

| | |
|---|---|
| 1 | eczema.mp. |
| 2 | neurodermatitis.mp. |
| 3 | dermatitis.mp. |
| 4 | atopic dermatitis'.mp. |
| 5 | 1 or 2 or 3 or 4 |
| 6 | abrocitinib.mp. |
| 7 | (abrocitinib or "pf04965842" or pf04965842 or "pf 4965842" or pf4965842).ti,ab. |
| 8 | baricitinib.mp. |
| 9 | (baricitinib or "incb 028050" or incb028050 or "incb 28050" or "ly 3009104" or ly3009104 or olumiant).ti,ab. |
| 10 | upadacitinib.mp. |
| 11 | (upadacitinib or "abt 494" or abt494 or rinvoq or "upadacitinib hemihydrate" or "upadacitinib hydrate" or "upadacitnib tartrate").ti,ab. |
| 12 | tralokinumab.mp. |
| 13 | (tralokinumab or "cat354" or cat354 or "cat-354").ti,ab. |
| 14 | ruxolitinib.mp. |

| | |
|---|---|
| 15 | (ruxolitinib or "incb 018424" or incb018424 or "incb 18424" or incb18424 or jakafi or jakavi or "ruxolitinib maleate" or "ruxolitinib phosphate").ti,ab. |
| 16 | methotrexate.mp |
| 17 | (amethopterin or 'methotrexate hydrate' or mexate).ti,ab |
| 18 | 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 |
| 19 | dupilumab.mp. |
| 20 | (dupilumab or dupixent or "regn 668" or regn688 or "sar 231893" or sar231893).ti,ab |
| 21 | crisaborole.mp |
| 22 | (eucrisa or an2728 or 'an-2728').ti,ab |
| 23 | ('topical corticosteroid$' or 'topical emollient$' or 'topical therp$').mp |
| 24 | calcineurin inhibitor$'.mp. |
| 25 | 19 or 20 or 21 or 22 or 23 or 24 |
| 26 | limit 25 to dd=20200201-20210121 |
| 27 | 18 or 26 |
| 28 | 5 and 27 |

*Search last updated on January 27, 2021.

**Table D1.5. Search Strategy of EMBASE SEARCH (Interventions)***

| | |
|---|---|
| #1 | 'eczema'/exp OR eczema |
| #2 | 'atopic dermatitis'/exp OR 'atopic dermatitis' |
| #3 | 'neurodermatitis'/exp OR neurodermatitis |
| #4 | 'dermatitis'/exp OR dermatitis |
| #5 | #1 OR #2 OR #3 OR #4 |
| #6 | 'abrocitinib'/exp OR abrocitinib |
| #7 | abrocitinib:ti,ab OR 'pf 04965842':ti,ab OR pf04965842:ti,ab OR 'pf 4965842':ti,ab OR pf4965842:ti,ab |
| #8 | 'baricitinib'/exp OR baricitinib |
| #9 | baricitinib:ti,ab OR 'incb 028050':ti,ab OR 'incb 28050':ti,ab OR 'ly 3009104:ti,ab' OR olumiant:ti,ab |
| #10 | 'upadacitinib'/exp OR upadacitinib |
| #11 | upadacitinib:ti,ab OR 'abt 494':ti,ab OR rinvoq:ti,ab OR 'upadacitinib hemihydrate':ti,ab OR 'upadacitinib hydrate':ti,ab OR 'upadacitinib tartrate':ti,ab |
| #12 | 'tralokinumab'/exp OR tralokinumab |
| #13 | tralokinumab:ti,ab OR 'cat 354':ti,ab OR 'cat-354':ti,ab OR cat354:ti,ab |
| #14 | 'ruxolitinib'/exp OR ruxolitinib |
| #15 | ruxolitinib:ti,ab OR 'incb 018424':ti,ab OR 'incb 18424':ti,ab OR 'incb 424':ti,ab OR jakafi:ti,ab OR jakavi:ti,ab OR 'ruxolitinib maleate':ti,ab OR 'ruxolitinib phosphate':ti,ab |
| #16 | #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 |
| #17 | #5 AND #16 |
| #18 | random*:ti OR placebo*:ti OR 'single blind*':ti OR 'double blind*':ti OR 'triple blind*':ab,ti |
| #19 | 'cohort analysis'/de OR 'cohort analysis' |
| #20 | 'longitudinal study'/de OR 'longitudinal study' |

| | |
|---|---|
| #21 | 'prospective study'/de OR 'prospective study' |
| #22 | 'follow-up'/de OR 'follow-up' |
| #23 | 'case control study'/de OR 'case control study' |
| #24 | 'matched-pair analysis'/de OR 'matched-pair analysis' |
| #25 | 'cross-over study'/de OR 'cross-over study' |
| #26 | 'cohort*':ti,ab |
| #27 | 'case* and control*':ti,ab |
| #28 | #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 |
| #29 | 'compar*':ti,ab |
| #30 | 'effective*':ti,ab |
| #31 | 'versus':ti,ab |
| #32 | 'vs.':ti,ab |
| #33 | #29 OR #30 OR #31 OR #32 |
| #34 | #28 AND #33 |
| #35 | #18 OR #34 |
| #36 | #17 AND #35 |
| #37 | ('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp |
| #38 | #36 NOT #37 |
| #39 | #38 AND [english]/lim |
| #40 | #39 NOT [medline]/lim |

*Search last updated on January 27, 2021.

**Table D1.6. Search Strategy of EMBASE SEARCH (Comparators)***

| | |
|---|---|
| #1 | 'eczema'/exp OR eczema |
| #2 | 'atopic dermatitis'/exp OR 'atopic dermatitis' |
| #3 | 'neurodermatitis'/exp OR neurodermatitis |
| #4 | 'dermatitis'/exp OR dermatitis |
| #5 | #1 OR #2 OR #3 OR #4 |
| #6 | 'dupilumab'/exp OR dupilumab |
| #7 | dupilumab:ti,ab OR dupixent:ti,ab OR 'regn 668':ti,ab OR regn668:ti,ab OR 'sar 231893':ti,ab OR sar231893:ti,ab |
| #8 | 'crisaborole'/exp OR crisaborole |
| #9 | eucrisa:ti,ab OR staquis:ti,ab OR 'an 2728':ti,ab OR 'an-2728':ti,ab OR an2728:ti,ab |
| #10 | #6 OR #7 OR #8 OR #9 |
| #11 | #5 AND #10 |
| #12 | random*:ti OR placebo*:ti OR 'single blind*':ti OR 'double blind*':ti OR 'triple blind*':ab,ti |
| #13 | 'cohort analysis'/de OR 'cohort analysis' |
| #14 | 'longitudinal study'/de OR 'longitudinal study' |
| #15 | 'prospective study'/de OR 'prospective study' |
| #16 | 'follow-up'/de OR 'follow-up' |
| #17 | 'case control study'/de OR 'case control study' |
| #18 | 'matched-pair analysis'/de OR 'matched-pair analysis' |

| | |
|---|---|
| #19 | 'cross-over study'/de OR 'cross-over study' |
| #20 | 'cohort*':ti,ab |
| #21 | 'case* and control*':ti,ab |
| #22 | #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 |
| #23 | 'compar*':ti,ab |
| #24 | 'effective*':ti,ab |
| #25 | 'versus':ti,ab |
| #26 | 'vs.':ti,ab |
| #27 | #23 OR #24 OR #25 OR #26 |
| #28 | #22 AND #27 |
| #29 | #12 OR #28 |
| #30 | #11 AND #29 |
| #31 | #30 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) |
| #32 | #31 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp) |
| #33 | #32 AND [2017-2021]/py |
| #34 | #33 NOT [medline]/lim |
| #35 | #34 AND [english]/lim |

*Search last updated on January 27, 2021.

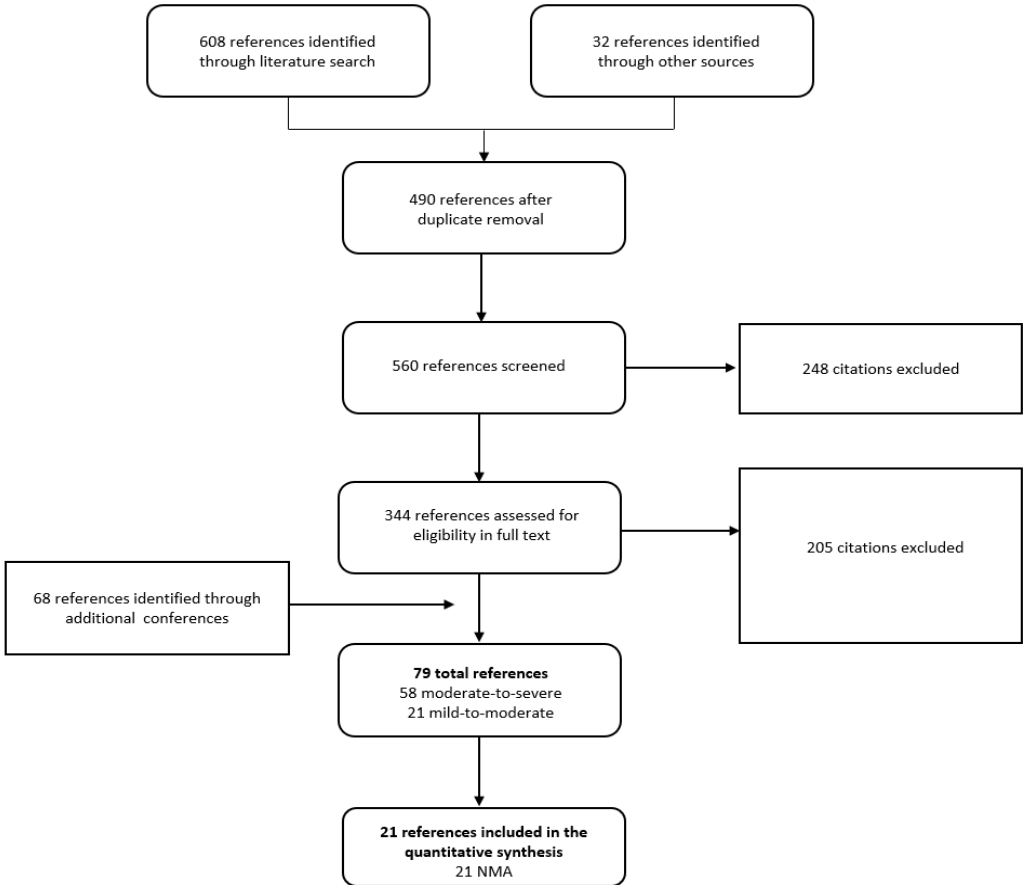
**Table D1.7. Search Strategy of EMBASE SEARCH (Systematic Reviews)***

| | |
|---|---|
| #1 | 'eczema'/exp OR 'eczema' OR 'eczema'/exp OR eczema |
| #2 | 'atopic dermatitis'/exp OR 'atopic dermatitis' |
| #3 | 'neurodermatitis'/exp OR neurodermatitis |
| #4 | 'dermatitis'/exp OR dermatitis |
| #5 | #1 OR #2 OR #3 OR #4 |
| #6 | 'abrocitinib'/exp OR abrocitinib |
| #7 | abrocitinib:ti,ab OR 'pf 04965842':ti,ab OR pf04965842:ti,ab OR 'pf 4965842':ti,ab OR pf4965842:ti,ab |
| #8 | baricitinib'/exp OR baricitinib |
| #9 | baricitinib:ti,ab OR 'incb 028050':ti,ab OR 'incb 28050':ti,ab OR 'ly 3009104:ti,ab' OR olumiant:ti,ab |
| #10 | 'upadacitinib'/exp OR upadacitinib |
| #11 | upadacitinib:ti,ab OR 'abt 494':ti,ab OR rinvoq:ti,ab OR 'upadacitinib hemihydrate':ti,ab OR 'upadacitinib hydrate':ti,ab OR 'upadacitinib tartrate':ti,ab |
| #12 | 'tralokinumab'/exp OR tralokinumab |
| #13 | tralokinumab:ti,ab OR 'cat 354':ti,ab OR 'cat-354':ti,ab OR cat354:ti,ab |
| #14 | 'ruxolitinib'/exp OR ruxolitinib |
| #15 | ruxolitinib:ti,ab OR 'incb 018424':ti,ab OR 'incb 18424':ti,ab OR 'incb 424':ti,ab OR jakafi:ti,ab OR jakavi:ti,ab OR 'ruxolitinib maleate':ti,ab OR 'ruxolitinib phosphate':ti,ab |
| #16 | 'methotrexate'/exp OR methotrexate |
| #17 | aminopterin:ti,ab OR mtx:ti,ab OR rasuvo:ti,ab OR otrexup:ti,ab OR xatmep:ti,ab OR trexall:ti,ab |
| #18 | #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 |
| #19 | 'dupilumab'/exp OR dupilumab |

| | |
|---|---|
| #20 | dupilumab:ti,ab OR dupixent:ti,ab OR 'regn 668':ti,ab OR regn668:ti,ab OR 'sar 231893':ti,ab OR sar231893:ti,ab |
| #21 | 'crisaborole'/exp OR crisaborole |
| #22 | eucrisa:ti,ab OR staquis:ti,ab OR 'an 2728':ti,ab OR 'an-2728':ti,ab OR an2728:ti,ab |
| #23 | 'calcineurin inhibitor$':ti,ab |
| #24 | steroid:ti,ab OR topical:ti,ab OR 'topical emollient$':ti,ab OR 'topical corticosteroid$':ti,ab |
| #25 | #19 OR #20 OR #21 OR #22 OR #23 OR #24 |
| #26 | #5 AND #25 |
| #27 | #26 AND [1-2-2020]/sd |
| #28 | #5 AND #18 |
| #29 | #27 OR #28 |
| #30 | #29 AND ([systematic review]/lim OR [meta analysis]/lim) |
| #31 | #30 AND [humans]/lim |
| #32 | #31 NOT [medline]/lim |

*Search last updated on January 27, 2021.

**Figure D1.1. PRISMA Flow Chart Showing Results of Literature Search for Abrocitinib, Baricitinib, Tralokinumab, Upadacitinib, and Ruxolitinib Cream**



## Study Selection

We performed screening at both the abstract and full-text levels. According to the inclusion and exclusion criteria described earlier, a single investigator screened all abstracts identified through electronic searches. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full-text appraisal. One investigator reviewed full papers and provided justification for the exclusion of each excluded study.

## Data Extraction and Quality Assessment

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (Table D3.1 and D3.6.[135] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

***Good:*** *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

***Fair:*** *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

***Poor:*** *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

## Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Figure 3.2 of the Report).[136]

## Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We performed an assessment of publication bias for abrocitinib, baricitinib, upadacitinib, tralokinumab, and ruxolitinib cream using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias.

## Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see section D3) and synthesized qualitatively in the body of the review. In addition, we evaluated the comparative efficacy of abrocitinib, baricitinib, upadacitinib, tralokinumab, and dupilumab for adults ≥ 18 years old with moderate-to-severe atopic dermatitis by means of network meta-analysis (NMA), where feasible. Based on data availability, our NMA evaluated IGA, EASI 50, EASI 75, EASI 90, and PP-NRS ≥4-point improvement outcomes at 12 and 16 weeks. Network Meta-Analysis Supplemental Information below (Section D2) contains a detailed description of the NMA methods. Due to inconsistent or limited data reporting, other outcomes were only described narratively in the body of the report or in Section D3 of the Report Supplement.

# D2. Network Meta-Analysis Supplemental Information

### *NMA Methods*

We evaluated the feasibility of conducting quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcome assessment for each outcome of interest. Trials deemed sufficiently similar in terms of population, intervention type, duration, and outcome definitions were included in the NMAs. While most trials that met the NMA eligibility criteria enrolled patients ≥18 years old, the pivotal trials of abrocitinib (JADE MONO-1 and JADE MONO-2) and the pivotal trials for upadacitinib (MEASURE UP 1, MEASURE UP 2, and AD-UP) enrolled patients ≥12 years old. In order to analyze all trials in a comparable fashion in a single network, we searched for subgroup evidence stratified by age on these trials. We received confidential data from the manufacturers for trials where the subgroup data by age were not publicly presented.

Based on data availability, we developed quantitative, indirect comparisons of abrocitinib, baricitinib, upadacitinib, tralokinumab, and dupilumab using a Bayesian network meta-analysis (NMA) for IGA, EASI 50, EASI 75, EASI 90, and PP-NRS ≥4-point improvement at 12 and 16 weeks in patients ≥18 years old. The primary endpoints of the abrocitinib trials, JADE MONO-1, JADE MONO-2, and JADE COMPARE, were measured at 12 weeks, while the remaining trials' primary endpoints were measured at 16 weeks. IGA and PP-NRS ≥4-point outcomes were analyzed as dichotomous outcomes ("yes" or "no") using a binomial likelihood and log link. EASI outcomes were analyzed as ordered categorical data with up to four distinct groups: i.e., EASI<50, EASI 50, EASI 75, and EASI 90, representing a reduction in the Eczema Area Severity Index (EASI) of less than 50%, at least 50%, at least 75%, and at least 90% respectively. Using the EASI outcomes reported in studies, we created mutually exclusive groups by re-classifying the data as <50, 50-74, 75-89, ≥90. Therefore, a multinomial likelihood model with a probit link with methods from the National Institute for Health and Clinical Excellence Decision Support Unit was used.[137]

Given the expected differences in the clinical efficacy of treatment in the monotherapy trials and combination trials, separate networks of the monotherapy trials and combination trials were developed. We explored both random- and fixed-effects models for each network and compared the goodness of fit to the data. We considered the model with the lowest deviance information criterion (DIC) to have the "best" fit to the data. We used fixed-effects models for the NMAs of the combination trials, given the limited data available for each network. Adjusting for placebo response in an NMA design is frequently performed to control for differences in population characteristics and baseline risk. We considered placebo adjustment for all NMAs and reported results where the adjusted NMA model provided a better fit of the data. The model with placebo

adjustment was considered a better fit if the regression coefficient was statistically significant and there was a reduction in between-trial heterogeneity.

Binomial NMAs were conducted using the IndiRect NMA platform (CRG-EVERSANA, 2020™). Multinomial NMAs were conducted using JAGS software (version 4.3.0) via R using the R2jags package. For all analyses, we used noninformative prior distributions for all model parameters. We initially discarded the first 50,000 iterations as "burn-in" and base inferences on an additional 50,000 iterations using three chains. Convergence of chains was through visual examination of the Brook–Gelman–Rubin diagnostic and historical plots. League tables were presented for the treatment effects (RR of each drug versus each other and placebo, along with 95% credible intervals (95% CrI). Table D2.1 lists the NMAs we conducted and the details of the model, and Table X lists the trials included in our NMAs as well as reasons for exclusion of trials.

**Table D2.1. NMAs Conducted & Presented**

| Outcome | Trial Type | Model | Number of trials |
|---|---|---|---|
| EASI | a) Monotherapy only<br>b) Combination only | Multinomial with probit link | a) 15<br>b) 6 |
| IGA | a) Monotherapy only<br>b) Combination only | Binomial with log link | a) 14<br>b) 6 |
| PP-NRS≥4-point | a) Monotherapy only<br>b) Combination only | Binomial with log link | a) 14<br>b) 5 |

**Table D2.2. Network Meta-Analysis Inputs for Monotherapy NMAs (All data inputs are in adults 18 and older)**

| Trial | Wk | Arm | IGA Response | | PP-NRS≥4 Response | | EASI Scores 50 | | 75 | | 90 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | n | N | n | N | n | N | n | N | n |
| JADE MONO-1 | 12 | ABRO 200 mg | 120 | 58 | 121 | 68 | | | 120 | 78 | | |
| | | ABRO 100 mg | 122 | 28 | 122 | 44 | | | 122 | 47 | | |
| | | PBO | 60 | 4 | 60 | 11 | | | 60 | 7 | | |
| JADE MONO-2 | 12 | ABRO 200 mg | 140 | 53 | 140 | 75 | | | 139 | 85 | | |
| | | ABRO 100 mg | 139 | 42 | 141 | 67 | | | 139 | 62 | | |
| | | PBO | 70 | 7 | 70 | 8 | | | 70 | 8 | | |
| Gooderham 2019 | 12 | ABRO 200 mg | 48 | 21 | 44 | 28 | 48 | 38 | 48 | 31 | 48 | 21 |
| | | ABRO 100 mg | 54 | 16 | 50 | 25 | 54 | 30 | 54 | 22 | 54 | 14 |
| | | PRO | 52 | 3 | 51 | 13 | 52 | 14 | 52 | 8 | 52 | 5 |
| ECZTRA 1 | 16 | TRA 300 mg | 601 | 95 | 594 | 119 | 601 | 250 | 601 | 150 | 601 | 87 |
| | | PBO | 197 | 14 | 194 | 20 | 197 | 42 | 197 | 25 | 197 | 8 |
| ECZTRA 2 | | TRA 300 mg | 591 | 131 | 575 | 144 | 591 | 295 | 591 | 196 | 591 | 108 |
| | 16 | PBO | 201 | 22 | 200 | 19 | 201 | 41 | 201 | 23 | 201 | 11 |
| MEASURE UP 1 | 16 | UPA 30 mg | 243 | 148 | 238 | 145 | | | 243 | 192 | | |
| | | UPA 15 mg | 239 | 119 | 234 | 125 | | | 239 | 166 | | |
| | | PBO | 241 | 21 | 233 | 26 | | | 241 | 43 | | |
| MEASURE UP 2 | 16 | UPA 30 mg | 247 | 125 | 246 | 150 | | | 247 | 180 | | |
| | | UPA 15 mg | 243 | 93 | 240 | 103 | | | 243 | 144 | | |
| | | PBO | 242 | 12 | 238 | 24 | | | 242 | 32 | | |
| Heads Up | 16 | UPA 30 mg | NR | NR | 336 | 120 | | | 348 | 247 | 348 | 211 |
| | | DUP 300 mg | NR | NR | 340 | 188 | | | 344 | 210 | 344 | 133 |
| Guttman-Yassky 2020 | 16 | UPA 30 mg | 42 | 21 | 36 | 19 | 42 | 35 | 42 | 29 | 42 | 21 |
| | | UPA 15 mg | 42 | 13 | 32 | 19 | 42 | 30 | 42 | 22 | 42 | 11 |
| | | PBO | 41 | 1 | 35 | 2 | 41 | 9 | 41 | 4 | 41 | 1 |
| BREEZE-AD 1 | 16 | BARI 2 mg | 123 | 14 | 100 | 12 | 123 | 37 | 123 | 23 | 123 | 13 |
| | | BARI 1 mg | 127 | 15 | 105 | 11 | 127 | 32 | 127 | 22 | 127 | 11 |
| | | PBO | 249 | 12 | 222 | 16 | 249 | 38 | 249 | 22 | 249 | 12 |
| BREEZE-AD 2 | | BARI 2 mg | 123 | 13 | 106 | 16 | 123 | 34 | 123 | 22 | 123 | 11 |
| | | BARI 1 mg | 125 | 11 | 100 | 6 | 125 | 23 | 125 | 16 | 125 | 8 |
| | 16 | PBO | 244 | 11 | 213 | 10 | 244 | 30 | 244 | 15 | 244 | 6 |
| BREEZE-AD 5 | | BARI 2 mg | 146 | 35 | 131 | 33 | 146 | 51 | 146 | 43 | 146 | 30 |
| | | BARI 1 mg | 147 | 19 | 132 | 21 | 147 | 29 | 147 | 19 | 147 | 11 |
| | 16 | PBO | 147 | 8 | 123 | 7 | 147 | 19 | 147 | 12 | 147 | 5 |
| SOLO 1 | | DUP 300 mg Q2W | 244 | 85 | 213 | 87 | 224 | 154 | 224 | 115 | 224 | 80 |
| | 16 | PBO | 224 | 23 | 212 | 26 | 224 | 55 | 224 | 33 | 224 | 17 |
| SOLO 2 | 16 | DUP 300 mg Q2W | 233 | 84 | 225 | 81 | 233 | 152 | 233 | 103 | 233 | 70 |

| Trial | Wk | Arm | IGA Response | | PP-NRS≥4 Response | | EASI Scores 50 | | 75 | | 90 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | n | N | n | N | n | N | n | N | n |
| | | PBO | 236 | 20 | 221 | 21 | 236 | 52 | 236 | 28 | 236 | 17 |
| THACI 2016 | 16 | DUP 300 mg Q2W | 64 | 19 | NR | NR | 64 | 50 | 64 | 34 | 64 | 19 |
| | | PBO | 61 | 1 | NR | NR | 61 | 18 | 61 | 7 | 61 | 2 |

ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, N: total number, NR: not reported, Q2W: every two weeks, TCS: topical corticosteroid, TRA: tralokinumab, UPA: upadacitinib, Wk: week

## Table D2.3. Network Meta-Analysis Inputs for Combination Therapy NMAs (All data inputs are in adults 18 and older)

| Trial | Wk | Arm | IGA Response | | PP-NRS≥4 Response | | EASI Scores 50 | | 75 | | 90 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | n | N | n | N | n | N | n | N | n |
| **JADE COMPARE*** | 16 | ABRO 200 mg | 221 | 105 | 172 | 108 | 221 | 193 | 221 | 157 | 221 | 108 |
| | | ABRO 100 mg | 230 | 80 | 168 | 79 | 229 | 186 | 229 | 138 | 229 | 87 |
| | | DUP 300 mg | 232 | 90 | 189 | 108 | 232 | 195 | 232 | 152 | 232 | 90 |
| | | PBO | 124 | 16 | 94 | 27 | 124 | 71 | 124 | 38 | 124 | 14 |
| **ECZTRA 3*** | 16 | TRA 300 mg + TCS | 252 | 98 | 249 | 113 | 252 | 200 | 252 | 141 | 252 | 83 |
| | | PBO + TCS | 126 | 33 | 126 | 43 | 126 | 73 | 126 | 45 | 126 | 27 |
| **AD-UP*** | 16 | UPA 30 mg + TCS | 260 | 150 | 258 | 168 | | | 260 | 201 | | |
| | | UPA 15 mg + TCS | 261 | 107 | 252 | 134 | | | 261 | 172 | | |
| | | PBO + TCS | 264 | 30 | 256 | 39 | | | 264 | 68 | | |
| **BREEZE-AD7*** | 16 | BARI 2 mg + TCS | 109 | 26 | 97 | 37 | 109 | 70 | 109 | 47 | 109 | 18 |
| | | PBO + TCS | 109 | 16 | 104 | 21 | 109 | 45 | 109 | 25 | 109 | 15 |
| **Guttman-Yassky 2018*** | 16 | BARI 2 mg + TCS | 37 | 8 | NR | NR | 37 | 21 | 37 | 11 | 37 | 7 |
| | | PBO + TCS | 49 | 4 | NR | NR | 49 | 18 | 49 | 10 | 49 | 3 |
| **LIBERTY AD CHRONOS*** | 16 | DUP 300 mg Q2W + TCS | 106 | 41 | 102 | 60 | 106 | 85 | 106 | 73 | 106 | 42 |
| | | PBO + TCS | 315 | 39 | 299 | 59 | 315 | 118 | 315 | 73 | 315 | 35 |

ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, N: total number, NR: not reported, Q2W: every two weeks, TCS: topical corticosteroid, TRA: tralokinumab, UPA: upadacitinib, Wk: week

**Figure D2.1. Network Figure. Monotherapy Trials**

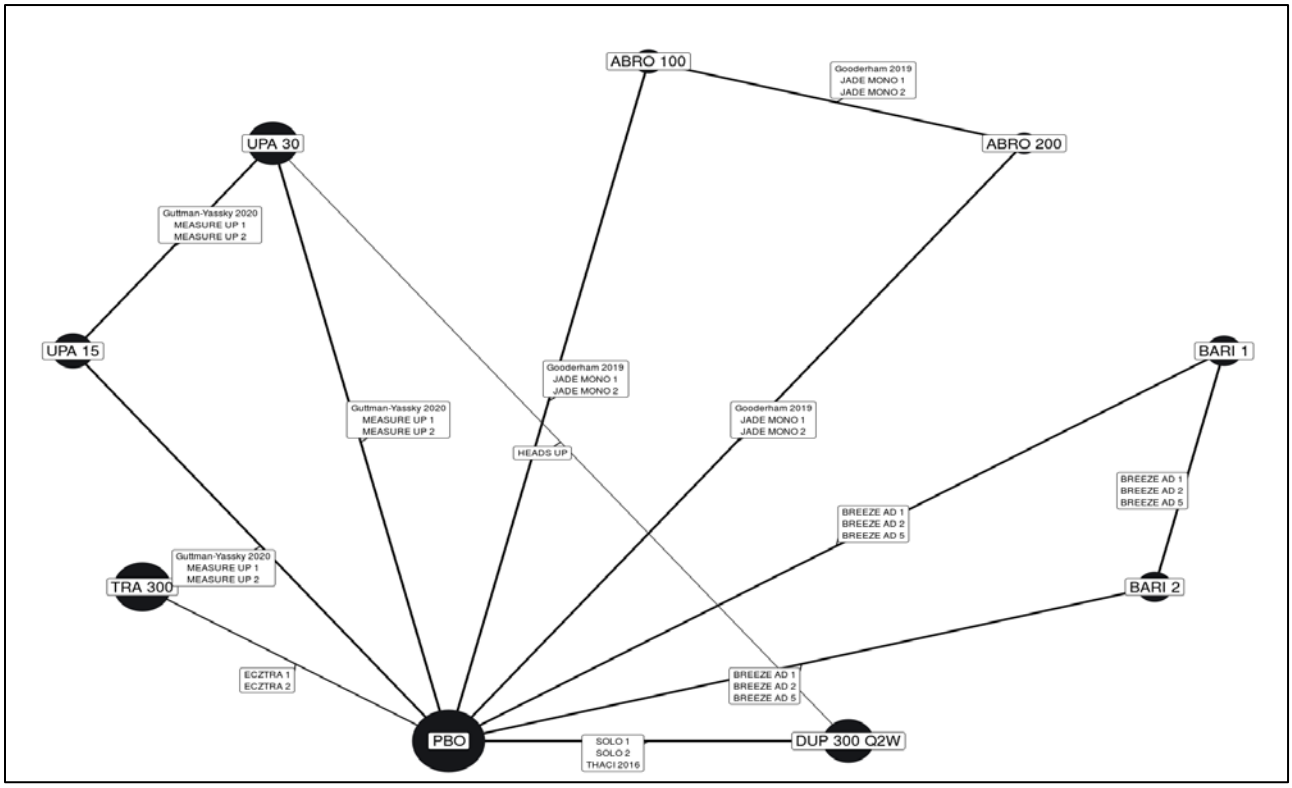
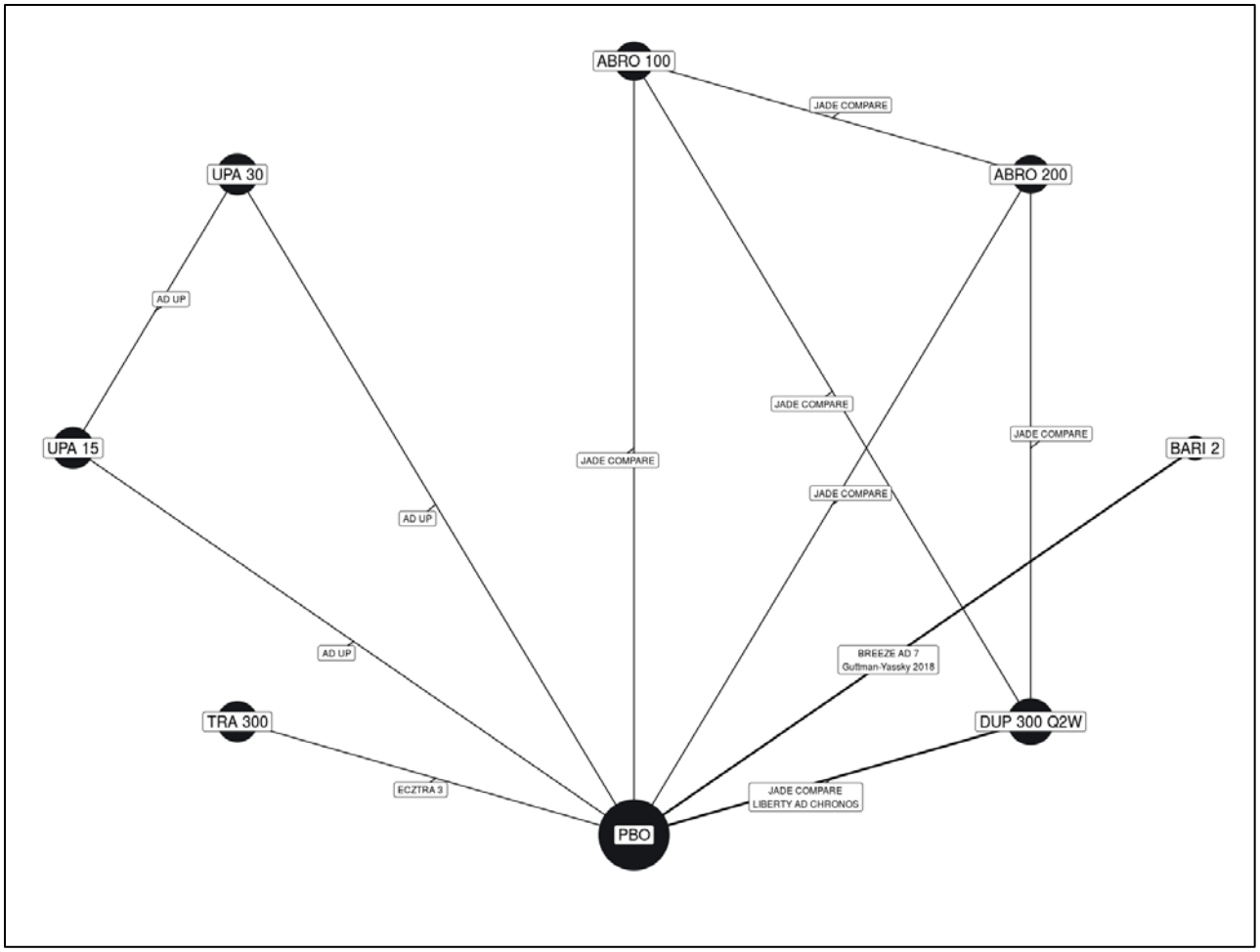


**Figure D2.2. Network Figure. Combination Trials**




***Network Meta-Analysis Results: Monotherapy RCTs***

For the EASI NMA, the unadjusted model (DIC: 195) was associated with improved fit compared to the adjusted model (DIC: 203); the estimated regression coefficient was not significant in the adjusted model (-0.33; 95% CrI: -1.18 to 0.54), and the interstudy SD with was increased in magnitude from 0.05 (95% CrI: 0.002–0.16) to 0.007 (95% CrI: 0.004–0.18) with placebo adjustment. For the IGA (DIC:231) and PP-NRS≥4-point improvement (DIC: 243) models, the unadjusted models were also associated with a better fit relative to the adjusted model (the interstudy SD followed a similar trend as presented for EASI model). Therefore, we presented the result of the unadjusted models for all outcomes.

*EASI 50 (15 trials):* Results were similar to EASI 75 and EASI 90 presented in the body of the report. All interventions showed statistically significantly greater EASI 50 responses than placebo and baricitinib 1 mg (Table D2.4). Updacitinib 30 mg was more likely to achieve EASI 50 compared to dupilumab. However, there were no statistically significant differences with abrocitinib (both

doses) and upadacitinib 15 mg compared to dupilumab. In comparison, dupilumab showed a statistically significantly greater EASI 50 response than tralokinumab and baricitinib (both doses).

*IGA (14 trials):* Results were similar to EASI responses. All interventions showed statistically significantly higher efficacy on IGA, as defined in the trials, compared to placebo (Table D2.5). Updacitinib 30 mg was more likely to achieve IGA response compared to all interventions. However, upadacitinib 30 mg was not statistically better than abrocitinib 200 mg. Additionally, there were no statistically significant differences with abrocitinib (both doses), upadacitinib 15 mg, and baricitinib 2 mg compared to dupilumab. In comparison, dupilumab showed statistically significantly greater IGA response compared to tralokinumab and baricitinib 1 mg.

*PP-NRS≥4-point improvement (14 trials):* While a clinically meaningful improvement in PP-NRS ranges from an improvement of 2-4-points, the available data for the interventions is almost entirely comprised of ≥4-point improvement. Apart from baricitinib 1 mg, the remaining interventions showed statistically significant responses compared to placebo (Table D2.6). Further, there was no statistically significant differences between abrocitinib (both doses), baricitinib 2mg, tralokinumab, updacitinib (both doses) compared to dupilumab.

### Table D2.4. Relative Risks for EASI 50 in Monotherapy RCTs in Adults

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| UPA 30 mg | | | | | | | | |
| 1.10 (0.98-1.26) | ABRO 200 mg | | | | | | | |
| 1.14 (1.07-1.24) | 1.04 (0.90-1.19) | UPA 15 mg | | | | | | |
| 1.25 (1.15-1.36) | 1.14 (0.98-1.30) | 1.09 (0.98-1.22) | DUP 300mg | | | | | |
| 1.45 (1.22-1.77) | 1.32 (1.17-1.52) | 1.27 (1.05-1.56) | 1.16 (0.97-1.44) | ABRO 100 mg | | | | |
| 1.75 (1.50-2.10) | 1.59 (1.31-1.95) | 1.53 (1.29-1.84) | 1.40 (1.18-1.69) | 1.21 (0.95-1.53) | TRA 300 mg | | | |
| 1.81 (1.53-2.20) | 1.64 (1.34-2.02) | 1.58 (1.32-1.93) | 1.45 (1.20-1.77) | 1.25 (0.97-1.59) | 1.03 (0.82-1.30) | BARI 2 mg | | |
| 2.54 (2.04-3.23) | 2.31 (1.80-2.98) | 2.22 (1.77-2.85) | 2.03 (1.61-2.60) | 1.75 (1.31-2.31) | 1.45 (1.10-1.91) | 1.40 (1.15-1.73) | BARI 1 mg | |
| 3.74 (3.46-4.05) | 3.40 (2.98-3.82) | 3.26 (2.97-3.58) | 2.99 (2.71-3.29) | 2.58 (2.12-3.04) | 2.14 (1.80-2.47) | 2.07 (1.72-2.43) | 1.47 (1.17-1.82) | PBO |

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

### Table D2.5. Relative Risks for IGA in Monotherapy RCTs in Adults

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| UPA 30 mg | | | | | | | | |
| 1.29 (1.09 -1.57) | UPA 15 mg | | | | | | | |
| 1.44 (0.95-2.26) | 1.12 (0.7-1.8) | ABRO 200 mg | | | | | | |
| 1.85 (1.28-2.64) | 1.43 (0.94-2.11) | 1.29 (0.77-2.06) | DUP 300mg | | | | | |
| 2.33 (1.4-3.98) | 1.8 (1.04-3.18) | 1.61 (1.21-2.19) | 1.26 (0.72-2.28) | ABRO 100 mg | | | | |
| 2.96-1.89-4.73) | 2.29 (1.41-3.72) | 2.06 (1.12-3.67) | 1.6 (0.97-2.75) | 1.28 (0.65-2.45) | BARI 2 mg | | | |
| 3.97 (2.54-6.31) | 3.07 (1.88-4.99) | 2.75 (1.54-4.94) | 2.15 (1.31-3.6) | 1.7 (0.89-3.28) | 1.34 (0.74-2.42) | TRA 300 mg | | |
| 4.08 (2.48-6.69) | 3.16 (1.86-5.29) | 2.83 (1.5-5.26) | 2.2 (1.28-3.89) | 1.75 (0.87-3.53) | 1.37 (0.92-2.06) | 1.03 (0.55-1.9) | BARI 1 mg | |
| 8.77 (6.81-11.17) | 6.78 (5.02-8.99) | 6.07 (3.89-9.14) | 4.72 (3.49-6.64) | 3.77 (2.21-6.23) | 2.95 (1.92-4.51) | 2.2 (1.47-3.3) | 2.16 (1.35-3.4) | PBO |

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

**Table D2.6. Relative Risks for PP-NRS≥4-point improvement in Placebo-controlled Monotherapy Trials in Adults**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| UPA 30 mg | | | | | | | | |
| 1.02 (0.71-1.56) | DUP 300mg | | | | | | | |
| 1.1 (0.78-1.56) | 1.08 (0.65-1.69) | UPA 15 mg | | | | | | |
| 1.19 (0.72-2.1) | 1.17 (0.67-2.04) | 1.09 (0.63-1.97) | ABRO 200 mg | | | | | |
| 1.68 (0.95-3.2) | 1.65 (0.88-3.11) | 1.53 (0.83-3.02) | 1.4 (0.92-2.23) | ABRO 100 mg | | | | |
| 1.87 (1.03-3.59) | 1.83 (0.96-3.53) | 1.7 (0.91-3.39) | 1.56 (0.79-3.16) | 1.11 (0.52-2.36) | BARI 2 mg | | | |
| 2.16 (1.14-4.58) | 2.12 (1.06-4.43) | 1.97 (1.01-4.28) | 1.81 (0.87-3.95) | 1.29 (0.58-2.94) | 1.16 (0.52-2.68) | TRA 300 | | |
| 2.94 (1.5-6.18) | 2.87 (1.4-6.03) | 2.67 (1.32-5.78) | 2.45 (1.14-5.38) | 1.75 (0.77-4.02) | 1.57 (0.88-2.86) | 1.35 (0.55-3.29) | BARI 1 mg | |
| 4.99 (3.5-6.85) | 4.89 (3.22-6.72) | 4.54 (2.99-6.58) | 4.18 (2.54-6.22) | 2.96 (1.66-4.83) | 2.66 (1.47-4.44) | 2.29 (1.17-4.08) | 1.69 (0.86-3.11) | PBO |

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

***Network Meta-Analysis Results: Combination RCTs***

*Choice of Model:* As noted above, we presented the results of the fixed-effect model for the combination therapy NMAs given the limited number of studies available for this network. Model fit information presented in Table D2.7 shows that the fixed effect models fit equally well or better compared to the random-effect model.

*NMA Results:* In general, the results for the combination therapy NMAs, provided more conservative estimates of the relative efficacies of these drugs versus placebo, although they followed a similar ranking order as the monotherapy NMAs. All interventions showed statistically significantly greater responses than placebo on all outcomes (Table D2.9 – D2.13). Table D2.8 presents the expected proportions of patients that achieved EASI 50,75 and 90 for each intervention.

**Table D2.7. Model fit information on Combination therapy NMAs**

| Model Fit | Fixed effect Model | Random effect Model |
|---|---|---|
| **EASI (multinomial model)** | | |
| Deviance Information Criterion (DIC) | 79.8 | 79.6 |
| Total Residual Deviance (vs. 60 data points) | 64.9 | 63.3 |
| **IGA (binomial model)** | | |
| Deviance Information Criterion (DIC) | 103.3 | 104.9 |
| Total Residual Deviance (vs. 15 data points) | 13.6 | 14.2 |
| **PP-NRS≥4-point improvement** | | |
| Deviance Information Criterion (DIC) | 96.8 | 96.8 |
| Total Residual Deviance (vs. 13 data points) | 14 | 14 |

**Table D2.8 NMA Results. Proportions of patients achieving EASI 50, 75, and 90 thresholds in Combination RCTs.**

| Treatment | EASI 50 | EASI 75 | EASI 90 |
|---|---|---|---|
| | Median proportion (95% CrI) | | |
| Placebo | 0.44 (0.41 – 0.47) | 0.24 (0.22 – 0.27) | 0.10 (0.09 – 0.12) |
| Dupilumab 300 mg Q2W | 0.79 (0.73 – 0.84) | 0.61 (0.54 – 0.68) | 0.39 (0.32 – 0.46) |
| Abrocitinib 100 mg | 0.75 (0.68 – 0.82) | 0.56 (0.47 – 0.65) | 0.34 (0.26 – 0.43) |
| Abrocitinib 200 mg | 0.83 (0.77 – 0.88) | 0.66 (0.58 – 0.74) | 0.44 (0.35 – 0.54) |
| Baricitinib 2 mg | 0.62 (0.52 -0.72) | 0.41 (0.31 – 0.52) | 0.21 (0.14 – 0.30) |
| Tralokinumab 300 mg | 0.63 (0.53 – 0.72) | 0.42 (0.33 – 0.52) | 0.22 (0.15 – 0.30) |
| Upadacitinib 15 mg | 0.83 (0.77 – 0.88) | 0.67 (0.59 – 0.74) | 0.44 (0.36 – 0.53) |
| Upadacitinib 30 mg | 0.91 (0.87 – 0.94) | 0.80 (0.73 – 0.85) | 0.60 (0.52 – 0.69) |

### Table D2.9. Relative Risks for EASI 50 in Combination RCTs in Adults

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| UPA 30 mg | | | | | | | |
| 1.10 (1.02-1.19) | ABRO 200 mg | | | | | | |
| 1.10 (1.05-1.16) | 1.00 (0.91-1.09) | UPA 15 mg | | | | | |
| 1.15 (1.07-1.25) | 1.05 (0.98-1.12) | 1.05 (0.96-1.14) | DUP 300mg | | | | |
| 1.21 (1.11-1.35) | 1.10 (1.02-1.20) | 1.10 (1.00-1.24) | 1.05 (0.98-1.14) | ABRO 100 mg | | | |
| 1.45 (1.27-1.71) | 1.32 (1.14-1.57) | 1.32 (1.15-1.57) | 1.26 (1.09-1.49) | 1.20 (1.02-1.43) | TRA 300 mg | | |
| 1.47 (1.27-1.76 | 1.33 (1.14-1.61) | 1.33 (1.15-1.61) | 1.27 (1.09-1.54) | 1.21 (1.02-1.48) | 1.01 (0.82-1.26) | BARI 2 mg | |
| 2.09 (1.96-2.25) | 1.91 (1.75-2.06) | 1.91 (1.77-2.06) | 1.82 (1.68-1.96) | 1.73 (1.56-1.90) | 1.44 (1.23-1.64) | 1.43 (1.20-1.65) | PBO |

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

### Table D2.10. Relative Risks for EASI 75 in Combination RCTs in Adults

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| UPA 30 mg | | | | | | | |
| 1.20 (1.05-1.38) | ABRO 200 mg | | | | | | |
| 1.20 (1.09-1.32) | 1.00 (0.85-1.17) | UPA 15 mg | | | | | |
| 1.30 (1.14-1.49) | 1.09 (0.97-1.22) | 1.09 (0.93-1.26) | DUP 300mg | | | | |
| 1.42 (1.21-1.69) | 1.18 (1.04-1.36) | 1.18 (0.99-1.43) | 1.09 (0.96-1.25) | ABRO 100 mg | | | |
| 1.90 (1.53-2.45) | 1.58 (1.25-2.07) | 1.58 (1.26-2.07) | 1.46 (1.15-1.90) | 1.34 (1.03-1.76) | TRA 300 mg | | |
| 1.93 (1.52-2.55) | 1.60 (1.25-2.15) | 1.61 (1.26-2.15) | 1.47 (1.15-1.97) | 1.36 (1.04-1.84) | 1.01 (0.73-1.42) | BARI 2 mg | |
| 3.26 (2.91-3.65) | 2.72 (2.35-3.11) | 2.72 (2.39-3.09) | 2.50 (2.21-2.83) | 2.30 (1.94-2.68) | 1.72 (1.35-2.11) | 1.69 (1.30-2.12) | PBO |

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

### Table D2.11. Relative Risks for EASI 90 in Combination RCTs in Adults

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| UPA 30 mg | | | | | | | |
| 1.36 (1.06-1.72) | ABRO 200 mg | | | | | | |
| 1.36 (1.17-1.60) | 1.00 (0.77-1.29) | UPA 15 mg | | | | | |
| 1.56 (1.25-1.94) | 1.14 (0.95-1.37) | 1.15 (0.90-1.45) | DUP 300mg | | | | |
| 1.77 (1.37-2.34) | 1.30 (1.07-1.61) | 1.30 (0.99-1.76) | 1.14 (0.93-1.41) | ABRO 100 mg | | | |
| 2.74 (1.98-3.97) | 2.01 (1.41-2.98) | 2.01 (1.43-2.96) | 1.76 (1.24-2.57) | 1.54 (1.05-2.31) | TRA 300 mg | | |
| 2.80 (1.97-4.20) | 2.05 (1.41-3.15) | 2.06 (1.42-3.11) | 1.79 (1.24-2.71) | 1.58 (1.06-2.45) | 1.02 (0.64- 1.66) | BARI 2 mg | |
| 5.82 (4.90-6.94) | 4.29 (3.43-5.27) | 4.29 (3.52-5.21) | 3.74 (3.09-4.51) | 3.28 (2.55-4.16) | 2.13 (1.51-2.88) | 2.08 (1.43-2.88) | PBO |

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

### Table D2.12. Relative Risks for IGA response in Combination RCTs in Adults

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| UPA 30 mg | | | | | | | |
| 1.26 (0.95-1.71) | ABRO 200 mg | | | | | | |
| 1.36 (1.15-1.63) | 1.08 (0.76-1.52) | UPA 15 mg | | | | | |
| 1.53 (1.15-2.04) | 1.21 (1-1.47) | 1.13 (0.8-1.57) | DUP 300mg | | | | |
| 1.7 (1.23-2.43) | 1.35 (1.09-1.7) | 1.25 (0.86-1.85) | 1.11 (0.89-1.42) | ABRO 100 mg | | | |
| 2.54 (1.62-4.08) | 2.01 (1.23-3.36) | 1.87 (1.13-3.12) | 1.66 (1.02-2.78) | 1.49 (0.87-2.59) | BARI 2 mg | | |
| 2.83 (1.9-4.27) | 2.24 (1.44-3.49) | 2.08 (1.35-3.25) | 1.85 (1.2-2.88) | 1.66 (1.02-2.68) | 1.11 (0.62-2.01) | TRA 300 mg | |
| 4.61 (3.68-5.75) | 3.65 (2.76-4.78) | 3.39 (2.57-4.42) | 3.02 (2.32-3.9) | 2.71 (1.94-3.69) | 1.82 (1.12-2.88) | 1.63 (1.11-2.35) | PBO |

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

### Table D2.13. Relative Risks for PP-NRS≥4-point improvement in Combination RCTs in Adults

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| UPA 30 mg | | | | | | | |
| 1.16 (1.04-1.31) | ABRO 200 mg | | | | | | |
| 1.24 (1.01-1.56) | 1.07 (0.85-1.37) | UPA 15 mg | | | | | |
| 1.32 (1.1-1.6) | 1.14 (0.91-1.41) | 1.06 (0.89-1.25) | DUP 300mg | | | | |
| 1.69 (1.3-2.26) | 1.46 (1.09-1.99) | 1.36 (1.1-1.71) | 1.28 (1.04-1.61) | ABRO 100 mg | | | |
| 1.81 (1.29-2.7) | 1.56 (1.08-2.35) | 1.45 (0.98-2.24) | 1.37 (0.94-2.09) | 1.07 (0.69-1.71) | BARI 2 mg | | |
| 2.37 (1.75-3.29) | 2.04 (1.47-2.89) | 1.91 (1.34-2.74) | 1.79 (1.28-2.55) | 1.4 (0.93-2.1) | 1.31 (0.8-2.1) | TRA 300 mg | |
| 3.36 (2.86-3.95) | 2.89 (2.39-3.48) | 2.7 (2.13-3.35) | 2.54 (2.09-3.07) | 1.99 (1.48-2.6) | 1.86 (1.23-2.66) | 1.42 (1.03-1.91) | PBO |

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

# D3. Additional Clinical Evidence

This section starts by providing additional clinical evidence for patients with moderate-to-severe atopic dermatitis presented by drug. Evidence is first presented for adults and then for adolescents and children. Next, we provide additional clinical evidence for patients with mild-to-moderate atopic dermatitis in short-term placebo-controlled trials of adults and adolescents. At the time of this report, no long-term evidence for ruxolitinib cream was identified.

## Moderate-to-Severe Population

## Adults

***Abrocitinib***

Two placebo-controlled monotherapy trials of abrocitinib enrolled patients ≥12 years old (JADE MONO-1 & 2). [35,36] Results of the subgroup of patients ≥18 years old in these trials (74%-85% of the trial population) showed that 61%-65% of patients achieved EASI 75 with abrocitinib 200 mg, compared to 11%-12% in the placebo arms of those trials. [35,36] [35,36] In this subgroup of patients, 39%-45% achieved EASI 75 with abrocitinib 100 mg. The percentages of patients in this subgroup that achieved IGA response with abrocitinib 200 mg were 38%-48%, 23%-30% with abrocitinib 100 mg, and 7%-10% with placebo.

As described in the report, one trial compared abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo in adult patients also treated with topical corticosteroids (JADE COMPARE). [37] While results at 12 weeks are described in the report, results at 16 weeks are presented here. The percentage of patients achieving EASI 75 with abrocitinib 200 mg was 71% compared with 60% with abrocitinib 100 mg, 66% with dupilumab, and 31% with placebo. [37] The percentage of patients achieving IGA with abrocitinib 200 mg was 48% compared with 35% with abrocitinib 100 mg, 39% with dupilumab, and 13% with placebo. [37] There were no statistically significant differences in EASI 75 and IGA response between the abrocitinib arms and dupilumab at 16 weeks. [37]

We identified one long-term trial of abrocitinib (JADE EXTEND).[77] JADE EXTEND is an ongoing, open-label extension study that evaluated continuous treatment with abrocitinib 100 mg or abrocitinib 200 mg in adults with moderate to severe atopic dermatitis who had participated in previous abrocitinib trials (JADE MONO-1, JADE MONO-2, JADE COMPARE). Results at week 48 showed the response rates on IGA (200 mg: 40%, 100 mg: 29%) and EASI 75 (200 mg: 62%, 100 mg: 46%) were sustained.

***Baricitinib***

We identified two long-term trials of baricitinib (BREEZE-AD3 and BREEZE-AD6). BREEZE-AD3 was a four-year blinded extension trial in which patients who achieved at least a partial response (IGA score of ≥2) at 16 weeks in originating trials were continued on baricitinib 2 mg for at least 52 weeks for a total of 68 weeks of continuous treatment. Week 68 results obtained from the manufacturer as academic-in-confidence suggest maintenance of EASI 75 and IGA response at 68 weeks. [43,44]

BREEZE-AD6 is an ongoing, 52-week, open-label, single-arm extension study that evaluated the long-term efficacy of continuous treatment with baricitinib 2 mg in adults with moderate to severe atopic dermatitis classified as non-responders or partial responders at week-16 in BREEZE-AD5 RCT.[84] The use of topical corticosteroids was permitted after Week 16 in BREEZE-AD5 and throughout BREEZE-AD6.[84] Results showed some improvement in EASI 75, IGA, and DLQI≤5 responses at 52 weeks (EASI: 49%, IGA:31%, DLQI≤5: 45% ) compared to week 16 (EASI: 40%, IGA:27%, DLQI≤5: 45%).[84]

***Tralokinumab***

In the two placebo-controlled monotherapy trials of tralokinumab (ECZTRA 1 and 2), patients were followed up for 52 weeks.[63] After the 16-week initial treatment periods of ECZTRA 1 and 2, patients who achieved response (IGA score of 0 or 1 or EASI 75) were rerandomized to tralokinumab 300 every two weeks or every four weeks, or placebo for a 36-week maintenance period. Results are presented in Table D3.3 below.

In ECZTRA 3, the placebo-controlled trial of tralokinumab conducted in patients treated with topical corticosteroids, patients were followed up for 32 weeks.[64] Similar to ECZTRA 1 and 2, patients who achieved response (IGA score of 0 or 1 or EASI 75) at 16 weeks in ECZTRA 3 were rerandomized and followed up to the end of the study. Results are presented in Table D3.3 below.

In addition, we identified one 268-week ongoing, open-label, single-arm extension study of tralokinumab (ECZTEND).[79] ECZTEND evaluated the efficacy of continuous treatment with tralokinumab in adults with moderate to severe atopic dermatitis who had participated in previous tralokinumab trials (ECZTRA 1, 2,3, and 5). Interim results at week 56 showed the response rates on IGA (41.7%), EASI 50 (79.7%), EASI 75 (68.4%), and EASI 90 (51.1%) were sustained.[79] Safety events were consistent with what was observed in the originating trials.

**Upadacitinib**

Two placebo-controlled monotherapy trials of upadacitinib (MEASURE UP 1 &2) and one placebo-controlled combination trial (AD-UP) of upadacitinib enrolled patients ≥12 years old. [83] [82] In the

monotherapy trials, the EASI and IGA responses in the subgroup of patients ≥18 years old were consistent with what was observed in the overall population. At week 16, 72%-79% of patients in the subgroup of patients ≥18 years old EASI 75 with upadacitinib 30 mg, compared to 13%-17% in the placebo arms of those trials.[80] In this subgroup of patients, 59%-69% achieved EASI 75 with upadacitinib 15 mg.[80] The percentages of patients in this subgroup that achieved IGA response with upadacitinib 30 mg were 51%-61%, 38%-50% with upadacitinib 15 mg, and 5%-9% with placebo.[80]

Similarly, in the combination trial that compared upadacitinib to placebo in patients also treated with topical corticosteroids, the EASI and IGA responses in the subgroup of patients ≥18 years old were consistent with what was observed in the overall population.[83] At week 16, the percentage of patients achieving EASI 75 in the subgroup of patients ≥18 years old with upadacitinib 30 mg was 77% compared with 66% with upadacitinib 15 mg and 26% with placebo.[80] IGA response was achieved by 58% of patients with upadacitinib 30 mg, 41% with upadacitinib 15 mg, and 11% with placebo.[80]

***Dupilumab***

We identified two long-term Phase III trials of dupilumab (LIBERTY AD SOLO-CONTINUE and LIBERTY AD CHRONOS). In LIBERTY AD SOLO-CONTINUE, dupilumab was compared to placebo. LIBERTY AD CHRONO is a combination trial that compared dupilumab plus topical corticosteroid to topical corticosteroid alone. In both trials, patients who achieved response (IGA score of 0 or 1 or EASI 75) at 16 weeks in the originating trials were rerandomized to dupilumab 300 mg weekly, every two weeks, every four weeks, or every eight weeks, or placebo for 36 weeks. After completion, patients were followed up for up to 12 weeks or enrolled in an open-label extension (OLE). Results of LIBERTY AD SOLO-CONTINUE and LIBERTY AD CHRONOS are presented in Table D3.3.

### *Additional Outcome Tables*

**Table D3.1 Key Outcomes in Placebo-controlled Monotherapy Trials in Adults**

| Trial | Arm | Timepoint | EASI 50 | EASI 75 | EASI 90 | IGA | PP-NRS[†] | SCORAD[‡] |
|---|---|---|---|---|---|---|---|---|
| **Abrocitinib** | | | | | | | | |
| JADE MONO-1[¥] | ABRO 200 mg | 12 weeks | 76.0 | 63.0 | 39.0 | 44.0 | 57.2 | NR |
| | ABRO 100 mg | | 58.0 | 40.0 | 19.0 | 24.0 | 38.0 | NR |
| | PBO | | 22.0 | 12.0 | 5.0 | 8.0 | 15.0 | NR |
| JADE MONO-2[¥] | ABRO 200 mg | 12 weeks | 79.9 | 61.0 | 37.7 | 38.1 | 55.3 | NR |
| | ABRO 100 mg | | 68.4 | 44.5 | 23.9 | 28.4 | 45.2 | NR |
| | PBO | | 19.5 | 10.4 | 3.9 | 9.1 | 11.5 | NR |
| Gooderham 2019 | ABRO 200 mg | 16 weeks | 79.2 | 64.6 | 52.1 | 43.8 | 63.6 | -69.7 |
| | ABRO 100 mg | | 55.6 | 40.7 | 25.9 | 29.6 | 50.0 | -49.2 |
| | PBO | | 26.9 | 15.4 | 9.6 | 5.8 | 25.5 | -29.0 |
| **Baricitinib** | | | | | | | | |
| BREEZE-AD 1 | BARI 2 mg | 16 weeks | 30.1 | 18.7 | 10.6 | 11.4 | 12.0 | -21.5 |
| | BARI 1 mg | | 25.0 | 17.3 | 8.7 | 11.8 | 10.5 | -18.9 |
| | PBO | | 15.3 | 8.8 | 4.8 | 4.8 | 7.2 | -13.4 |
| BREEZE-AD 2 | BARI 2 mg | 16 weeks | 27.6 | 17.9 | 8.9 | 10.6 | 15.1 | -27.8 |
| | BARI 1 mg | | 18.4 | 12.8 | 6.4 | 8.8 | 6.0 | -20.2 |
| | PBO | | 12.3 | 6.1 | 2.5 | 4.5 | 4.7 | -13.4 |
| BREEZE-AD 5 | BARI 2 mg | 16 weeks | 34.9 | 29.5 | 20.5 | 24.0 | 25.2 | NR |
| | BARI 1 mg | | 19.7 | 12.9 | 7.5 | 12.9 | 15.9 | NR |
| | PBO | | 12.9 | 8.2 | 3.4 | 5.4 | 5.7 | NR |
| **Tralokinumab*** | | | | | | | | |
| ECZTRA 1 | TRA 300 mg | 16 weeks | 41.6 | 25.0 | 14.5 | 15.8 | 20.0 | -25.2 |
| | PBO | | 21.3 | 12.7 | 4.1 | 7.1 | 10.3 | -14.7 |
| ECZTRA 2 | TRA 300 mg | 16 weeks | 49.9 | 33.2 | 18.3 | 22.2 | 25.0 | -28.1 |
| | PBO | | 20.4 | 11.4 | 5.5 | 10.9 | 9.5 | -14.0 |
| **Upadacitinib** | | | | | | | | |
| MEASURE UP 1[¥] | UPA 30 mg | 16 weeks | NR | 80.0 | 66.0 | 62.0 | 60.0 | NR |
| | UPA 15 mg | | NR | 70.0 | 53.0 | 48.0 | 52.0 | NR |
| | PBO | | NR | 16.0 | 8.0 | 8.0 | 12.0 | NR |
| MEASURE UP 2[¥] | UPA 30 mg | 16 weeks | NR | 73.0 | 58.0 | 52.0 | 60.0 | NR |
| | UPA 15 mg | | NR | 60.0 | 42.0 | 39.0 | 42.0 | NR |
| | PBO | | NR | 13.0 | 5.0 | 5.0 | 9.0 | NR |
| Heads Up | UPA 30 mg | 16 weeks | NR | 71 | 60.6 | NR | 55.2 | NR |
| | DUP 300 mg | | NR | 61.1 | 38.8 | NR | 35.9 | NR |
| Phase II Guttmann-Yassky 2020 | UPA 30 mg | 16 weeks | 83.3 | 69.0 | 50.0 | 50.0 | 52.8 | -60.4 |
| | UPA 15 mg | | 71.4 | 52.4 | 26.2 | 31.0 | 59.4 | -46.9 |
| | PBO | | 22.0 | 9.8 | 2.4 | 2.4 | 5.7 | -12.4 |
| **Dupilumab[¶]** | | | | | | | | |
| LIBERTY AD SOLO 1 | DUP 300 mg Q2W | 16 weeks | 69.0 | 51.0 | 36.0 | 38.0 | 41.0 | -57.7 |
| | PBO | | 25.0 | 15.0 | 8.0 | 10.0 | 12.0 | -29.0 |
| | DUP 300 mg Q2W | 16 weeks | 65.0 | 44.0 | 30.0 | 36.0 | 36.0 | -51.1 |

| Trial | Arm | Timepoint | EASI 50 | EASI 75 | EASI 90 | IGA | PP-NRS[†] | SCORAD[‡] |
|---|---|---|---|---|---|---|---|---|
| LIBERTY AD SOLO 2 | PBO | | 22.0 | 12.0 | 7.0 | 8.0 | 10.0 | -19.7 |
| Thaci 2016 | DUP 300 mg Q2W | 16 weeks | 78.0 | 52.8 | 29.8 | 30.0 | NR | -51.2 |
| | PBO | | 30.0 | 11.09 | 3.5 | 2.0 | NR | -13.8 |

All values in the table are percentages. BARI 4 mg, DUP 300 mg QW, DUP 200 mg, and DUP 100 mg doses were excluded from the network meta-analyses. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, TRA: tralokinumab, UPA: upadacitinib. [†]PP-NRS ≥4, [‡]LSM change from baseline, *reported adjusted mean change from baseline in SCORAD, [¶]reported LSM percentage change from baseline in SCORAD, [ɣ]data were from patients ages 12 and older.

### Table D3.2. Key Outcomes in Placebo-controlled Combination Trials in Adults (Short-term)

| Trial | Arm | Timepoint | EASI 50 | EASI 75 | EASI 90 | IGA | PP-NRS[†] | SCORAD[‡] |
|---|---|---|---|---|---|---|---|---|
| **Abrocitinib** | | | | | | | | |
| JADE COMPARE | ABRO 200 mg + TCS | 16 weeks | 87.3 | 71 | 48.9 | 47.5 | 62.8 | NR |
| | ABRO 100 mg + TCS | | 81.2 | 60.3 | 38 | 34.8 | 47.0 | NR |
| | DUP 300 mg + TCS | | 84.1 | 65.5 | 38.8 | 38.8 | 57.1 | NR |
| | PBO + TCS | | 57.3 | 30.6 | 11.3 | 12.9 | 28.7 | NR |
| **Baricitinib** | | | | | | | | |
| BREEZE-AD7 | BARI 2 mg + TCS | 16 weeks | 64.2 | 43.1 | 16.5 | 23.9 | 38.1 | -29.9 |
| | PBO + TCS | | 41.3 | 22.9 | 13.8 | 14.7 | 20.2 | -21.4 |
| Guttman-Yassky 2018 | BARI 2 mg + TCS | 16 weeks | 56.8 | 29.7 | 18.9 | 21.6 | NR | -23.87 |
| | PBO + TCS | | 36.7 | 20.4 | 6.1 | 8.2 | NR | -11.89 |
| **Tralokinumab** | | | | | | | | |
| ECZTRA 3 | TRA 300 mg + TCS | 16 weeks | 79.4 | 56.0 | 32.9 | 38.9 | 45.4 | -37.7 |
| | PBO + TCS | | 57.9 | 35.7 | 21.4 | 26.2 | 34.1 | -26.8 |
| **Upadacitinib** | | | | | | | | |
| AD-UP[§] | UPA 30 mg + TCS | 16 weeks | NR | 77.0 | NR | 59.0 | 64.0 | NR |
| | UPA 15 mg +TCS | | NR | 65.0 | NR | 40.0 | 52.0 | NR |
| | PBO + TCS | | NR | 26.0 | NR | 11.0 | 15.0 | NR |
| **Dupilumab** | | | | | | | | |
| LIBERTY AD CHRONOS | DUP 300 mg + TCS | 16 weeks | 80.0 | 69.0 | 40.0 | 39.0 | 59.0 | -62.1 |
| | PBO + TCS | | 37.0 | 23.0 | 11.0 | 12.0 | 20.0 | -31.8 |

All values in the table are percentages. BARI 4 mg, DUP 300 mg QW, DUP 200 mg, and DUP 100 mg doses were excluded from the NMA. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, TRA: tralokinumab, TCS: topical corticosteroids, UPA: upadacitinib. [†]PP-NRS ≥4, [‡]LSM change from baseline, *reported adjusted mean change from baseline in SCORAD, [§]results are from patients ages 12 and older, [¶]reported LSM percentage change from baseline in SCORAD.

**Table D3.3. Key Outcomes in Long-term Comparative Trials**

| Trial | Arm | Timepoint | EASI 50 | EASI 75 | EASI 90 | IGA | PP-NRS[†] | SCORAD[‡] |
|---|---|---|---|---|---|---|---|---|
| **Tralokinumab** | | | | | | | | |
| ECZTRA 1 | TRA 300 mg Q2W | 52 weeks[§] | NR | 59.6 | NR | 51.3 | NR | NR |
| | TRA 300 mg Q4W | | NR | 49.1 | NR | 38.9 | NR | NR |
| | PBO | | NR | 33.3 | NR | 47.4 | NR | NR |
| ECZTRA 2 | TRA 300 mg Q2W | 52 weeks[§] | NR | 55.8 | NR | 59.3 | NR | NR |
| | TRA 300 mg Q4W | | NR | 51.4 | NR | 44.9 | NR | NR |
| | PBO | | NR | 21.4 | NR | 25 | NR | NR |
| ECZTRA 3 | TRA 300 mg Q2W + TCS (non-responders) | 32 weeks | NR | 55.8 | NR | 30.5 | NR | NR |
| | TRA 300 mg Q2W +TCS (TRA responders) | | 98.6 | 92.5 | 72.5 | 89.6 | NR | NR |
| | TRA 300 mg Q4W + TCS (TRA responders) | | 91.3 | 90.8 | 63.8 | 77.6 | NR | NR |
| **Dupilumab** | | | | | | | | |
| AD SOLO 1-CONTINUE | DUP 300 mg Q2W or QW | 36 weeks | 39.8 | 30.4 | 18.2 | 14.3 | 12.8 | -2.7 |
| | PBO | | 73.4 | 71.6 | 64.7 | 54.0 | 49.1 | -4.3 |
| LIBERTY AD CHRONOS | DUP 300 mg + TCS Q2W | 52 weeks | 79 | 65 | 51 | 36 | 51 | -66.2 |
| | PBO + TCS | | 30 | 22 | 16 | 13 | 13 | -34.1 |

All values in the table are percentages. Includes trials only in adults 18 and older. DUP 300 mg QW + TCS dose was excluded from the table. DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, TCS: topical corticosteroids, TRA: tralokinumab. [†]PP-NRS ≥4, [‡]LSM change from baseline, [¶]reported LSM percentage change from baseline in SCORAD.

### *Harms*

Summaries of the harms are provided in Section 3.2 of the Report. Tables presenting key harms from the short-term RCTs are presented in Tables 3.4 and 3.5. For responders in re-randomized long-term monotherapy trials (Table D3.6), harms were uncommon though slightly more patients on active treatment discontinued therapy due to side effects. Additional reports of conjunctivitis and herpetic infections were similar among those receiving active therapy or placebo. For patients in long-term combination trials (Table D3.7), harms leading to discontinuation were uncommon and similar or slightly higher for patients receiving placebo. Other adverse effects were also similar among treatment arms.

**Table D3.4. Key Harms in Placebo-controlled Monotherapy Trials of Adults (Short-term)**

| Trial | Arm | Timepoint | Any AEs | TEAEs | D/C Due to AE | SAE | Conjunctivitis | Nausea | Herpetic Infection |
|---|---|---|---|---|---|---|---|---|---|
| **Abrocitinib** | | | | | | | | | |
| JADE MONO-1[§] | ABRO 200 mg | 12 weeks | 78 | NR | 6 | 3 | 2.6 | 20.0 | 3.9[¥] |
| | ABRO 100 mg | | 69 | NR | 6 | 3 | 2.6 | 9.0 | 4.5[¥] |
| | PBO | | 57 | NR | 9 | 4 | 0 | 3.0 | 1.3[¥] |
| JADE MONO-2[§] | ABRO 200 mg | 12 weeks | NR | 65.8 | 3.2 | 1.3 | NR | 14.2 | 1.3[#] |
| | ABRO 100 mg | | NR | 62.7 | 3.8 | 3.2 | NR | 7.6 | 1.3[#] |
| | PBO | | NR | 53.8 | 12.8 | 1.3 | NR | 2.6 | 1.3[#] |
| Gooderham 2019 | ABRO 200 mg | 16 weeks | NR | 68.9 | 16.5 | 3.6 | NR | 14.5 | 0** |
| | ABRO 100 mg | | NR | | | 5.4 | NR | 1.8 | 3.6** |
| | PBO | | NR | | | 3.6 | NR | 1.8 | 2.8** |
| **Baricitinib** | | | | | | | | | |
| BREEZE-AD1 | BARI 2 mg | 16 weeks | NR | NR | 0.8 | 0 | 1.6* | NR | 3.3[††] |
| | BARI 1 mg | | NR | NR | 1.6 | 0.8 | 0.8* | NR | 5.5[††] |
| | PBO | | NR | NR | 1.6 | 2.4 | 1.6* | NR | 1.2[††] |
| BREEZE-AD2 | BARI 2 mg | 16 weeks | NR | NR | 2.4 | 2.4 | 1.6* | NR | 5.7[††] |
| | BARI 1 mg | | NR | NR | 5.6 | 7.3 | 4.8* | NR | 4.8[††] |
| | PBO | | NR | NR | 0.8 | 3.7 | 0.8* | NR | 4.5[††] |
| BREEZE-AD5 | BARI 2 mg | 16 weeks | NR | NR | 2.8 | 1.4 | NR | 3.4 | 1.4[‡‡] |
| | BARI 1 mg | | NR | NR | 2.7 | 0.7 | NR | 2.0 | 2.7[‡‡] |
| | PBO | | NR | NR | 2.7 | 2.1 | NR | 2.1 | 0.6[‡‡] |
| **Tralokinumab** | | | | | | | | | |
| ECZTRA 1 | TRA 300 mg | 16 weeks | 76.4 | NR | 3.3 | 3.8 | 7.1[†] | NR | 0.5[¶¶] |
| | PBO | | 77 | NR | 4.1 | 4.1 | 2[†] | NR | 1[¶¶] |
| ECZTRA 2 | TRA 300 mg | 16 weeks | 61.5 | NR | 1.5 | 1.7 | 3[†] | NR | 0.3[¶¶] |
| | PBO | | 66 | NR | 1.5 | 2.5 | 1.5[†] | NR | 2.5[¶¶] |
| **Upadacitinib** | | | | | | | | | |
| MEASURE UP 1[§] | UPA 30 mg | 16 weeks | NR | NR | NR | 2.8 | NR | 3.5 | 4[¥¥] |
| | UPA 15 mg | | NR | NR | NR | 2.1 | NR | | |
| | PBO | | NR | NR | NR | 2.8 | NR | | 0[¥¥] |
| MEASURE UP 2[§] | UPA 30 mg | 16 weeks | NR | NR | NR | 2.5 | NR | | 2[¥¥] |
| | UPA 15 mg | | NR | NR | NR | 1.8 | NR | | 1[¥¥] |
| | PBO | | NR | NR | NR | 2.9 | NR | | 2[¥¥] |
| Phase II Guttmann-Yassky 2020 | UPA 30 mg | 16 weeks | 76 | NR | 4.8 | 0 | NR | 7.1 | 0[¥¥] |
| | UPA 15 mg | | 63 | NR | 7.5 | 2.4 | NR | 2.5 | 0[¥¥] |
| | PBO | | 79 | NR | 9.5 | 2.5 | NR | 1.4 | 0[¥¥] |
| **Dupilumab** | | | | | | | | | |

| Trial | Arm | Timepoint | Any AEs | TEAEs | D/C Due to AE | SAE | Conjunctivitis | Nausea | Herpetic Infection |
|---|---|---|---|---|---|---|---|---|---|
| LIBERTY AD SOLO 1 | DUP 300 mg Q2W | 16 weeks | 73 | NR | 2 | 3 | 4.8‡ | NR | 7## |
| | PBO | | 65 | NR | 1 | 5 | 0.9‡ | | 4## |
| LIBERTY AD SOLO 2 | DUP 300 mg Q2W | 16 weeks | 65 | NR | 1 | 13 | 3.8‡ | | 4## |
| | PBO | | 72 | NR | 2 | 2 | 0.4‡ | | 3## |
| Thaci 2016 | DUP 300 mg Q2W | 16 weeks | NR | 78 | 6 | NR | 5¶ | 2 | 8¥ |
| | PBO | | NR | 80 | 5 | NR | 3¶ | 7 | 2¥ |

All values in the table are percentages. AE: adverse event, D/C: discontinuation, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, SAE: serious adverse event, TEAE: treatment-emergent adverse event. §results are from patients ages 12 and older, *conjunctivitis/keratitis, †conjunctivitis, conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic, ‡conjunctivitis of unspecified cause, allergic, bacterial and viral conjunctivitis, and atopic keratoconjunctivitis, ¶conjunctival infections, irritations, and inflammation, ¥oral herpes, herpes simplex, eczema herpeticum, herpes virus infection, and herpes zoster, #eczema herpeticum and herpes zoster, **eczema herpeticum and treatment-emergent herpes simplex, ††herpes simplex, ‡‡herpes zoster and herpes simplex, ¶¶eczema herpeticum, ¥¥herpes zoster, ##herpes viral infection, including oral herpes, herpes simplex, eczema herpeticum, herpes virus infection, herpes zoster, ophthalmic herpes simplex, genital herpes, herpes ophthalmic, and herpes simplex otitis externa.

**Table D3.5. Key Harms in Placebo-controlled Combination Trials of Adults (Short-term)**

| Trial | Arm | Timepoint | Any AEs | TEAEs | D/C due to AEs/TEAEs | SAE | Conjunctivitis | Nausea | Herpetic Infection |
|---|---|---|---|---|---|---|---|---|---|
| **Abrocitinib** | | | | | | | | | |
| JADE COMPARE | ABRO 200 mg | 16 weeks | 61.9 | NR | 4.4 | 0.9 | 1.3 | 11.1 | 1.8 |
| | ABRO 100 mg | | 50.8 | NR | 2.5 | 2.5 | 0.8 | 4.2 | 0.8 |
| | DUP 300 mg | | 50 | NR | 3.3 | 0.8 | 6.2 | 2.9 | 0 |
| | PBO | | 53.4 | NR | 3.8 | 3.8 | 2.3 | 1.5 | 0 |
| **Baricitinib** | | | | | | | | | |
| BREEZE-AD7 | BARI 2 mg + TCS | 16 weeks | NR | 56 | 0 | 1.8 | NR | NR | 6.4 |
| | PBO + TCS | | NR | 38 | 0.9 | 3.7 | NR | NR | 3.7 |
| Guttman-Yassky 2018 | BARI 2 mg + TCS | 16 weeks | NR | 45.9 | 2.7 | NR | 0 | NR | 0 |
| | PBO + TCS | | NR | 49 | 10.2 | NR | 2 | NR | 0 |
| **Tralokinumab** | | | | | | | | | |
| ECZTRA 3 | TRA 300 mg + TCS | 16 weeks | 71.4 | NR | 2.4 | 0.8 | 11.1 | 0 | 5‡ |
| | PBO + TCS | | 66.7 | NR | 0.8 | 3.2 | 3.2 | 0.79 | 6‡ |
| **Upadacitinib** | | | | | | | | | |
| AD-UP | UPA 30 mg + TCS | 16 weeks | NR | NR | 0 | 1.3 | NR | NR | 1.3 |
| | UPA 15 mg + TCS | | NR | NR | 0 | 2.3 | NR | NR | 1 |
| | PBO + TCS | | NR | NR | 0 | 3 | NR | NR | NR |

All values in the table are percentages. No short-term safety data available for BREEZE-AD7, Guttman-Yassky 2018, AD-UP, and LIBERTY AD CHRONOS. ABRO: abrocitinib, AE: adverse event, BARI: baricitinib, D/C: discontinuation, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, SAE: serious adverse event, TCS: topical corticosteroids, TEAE: treatment-emergent adverse event, TRA: tralokinumab, UPA: upadacitinib. ‡eczema herpeticum.

**Table D3.6. Key Harms in Placebo-controlled Monotherapy Trials of Adults (Long-term)**

| Trial | Arm | Timepoint | Any AEs | TEAEs | D/C Due to AE | SAE | Conjunctivitis | Nausea | Herpetic Infection |
|---|---|---|---|---|---|---|---|---|---|
| **Baricitinib** | | | | | | | | | |
| BREEZE-AD3 | BARI 2 mg | NR | NR | NR | NR | NR | NR | NR | NR |
| **Tralokinumab** | | | | | | | | | |
| ECZTRA 1 | TRA 300 mg Q2W | 36 weeks | 79.4 | NR | 1.5 | 1.5 | 8.8* | NR | 0.0‡ |
| | TRA 300 mg Q4W | | 69.7 | NR | 1.3 | 3.9 | 6.6* | NR | 0.0‡ |
| | PBO | | 71.4 | NR | 0.0 | 0.0 | 5.7* | NR | 0.0‡ |
| ECZTRA 2 | TRA 300 mg Q2W | 36 weeks | 68.1 | NR | 2.2 | 0.0 | 8.8* | NR | 1.1‡ |
| | TRA 300 mg Q4W | | 62.9 | NR | 1.1 | 3.4 | 5.6* | NR | 0.0‡ |
| | PBO | | 69.6 | NR | 0.0 | 0.0 | 6.5* | NR | 0.0‡ |
| **Dupilumab** | | | | | | | | | |
| AD SOLO 1-CONTINUE | DUP 300 mg Q2W or QW | 36 weeks | NR | 81.7 | 3.7 | NR | 4.9† | NR | 6.1¶ |
| | PBO | | NR | 70.7 | 0.0 | NR | 5.4† | NR | 6.6¶ |

All values in the table are percentages. Includes trials only in adults 18 and older. Dupilumab 300 mg Q8W and Q4W doses were not included in the table. AE: adverse event, BARI: baricitinib, D/C: discontinuation, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, SAE: serious adverse event, TEAE: treatment-emergent adverse event, TRA: tralokinumab. *conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic, †conjunctivitis, conjunctivitis bacterial, conjunctivitis viral, conjunctivitis allergic, and atopic keratoconjunctivitis, ‡eczema herpeticum, ¶herpes simplex virus infection, oral herpes infection, ophthalmic herpes infection.

**Table D3.7. Key Harms in Placebo-controlled Combination Trials of Adults (Long-term)**

| Trial | Arm | Timepoint | Any AEs | TEAEs | D/C Due to AEs/TEAEs | SAE | Conjunctivitis | Nausea | Herpetic Infection |
|---|---|---|---|---|---|---|---|---|---|
| ECZTRA 3 | TRA Q2W + TCS (TRA non-responders) | 16-32 weeks | 65.3 | NR | 1.1 | 2.1 | 4.2* | 3.2 | 5‡ |
| | TRA 300 mg Q2W + TCS (TRA responders) | | 69.6 | NR | 0 | 4.3 | 4.3* | 4.3 | 4‡ |
| | TRA Q4W +TCS (TRA responders) | | 59.4 | NR | 1.4 | 0 | 1.4* | 5.8 | 6‡ |
| | PBO Q2W + TCS (PBO responders) | | 63.4 | NR | 2.4 | 2.4 | 2.4* | 0 | 2‡ |
| LIBERTY AD CHRONOS | DUP 300 mg Q2W + TCS | 52 2eeks | 88 | NR | 2 | 4 | 14† | NR | 7¶ |
| | PBO + TCS | | 84 | NR | 8 | 5 | 8† | NR | 8¶ |

All values in the table are percentages. AE: adverse event, D/C: discontinuation, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, SAE: serious adverse event, TEAE: treatment-emergent adverse event, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib. *conjunctivitis, conjunctivitis allergic, and conjunctivitis viral, conjunctivitis allergic, †conjunctivitis bacterial, atopic keratoconjunctivitis, and conjunctivitis, ‡oral herpes and eczema herpeticum, oral herpes, herpes simplex, herpes virus infection, herpes zoster, eczema herpeticum, genital herpes, ¶herpes ophthalmic, ophthalmic herpes simplex, and ophthalmic herpes zoster.

## Children and Adolescents

Additional clinical evidence for children and adolescents are presented below. For adolescents, our literature search identified trials for abrocitinib, upadacitinib, and dupilumab. Only trials of dupilumab were identified for children, and all of these included topical medications in all groups. Our literature search did not identify any baricitinib or tralokinumab trials in children or adolescents.

***Abrocitinib***

As noted in Section 3.2 of the Report, trials of abrocitinib included adolescents and adults.

Though two placebo-controlled monotherapy trials of abrocitinib enrolled patients ≥12 years old (JADE MONO-1 &2), a small fraction of the patients in these trials were ≥12-17 years old (15%-26%).[35,36] One trial of abrocitinib solely enrolled patients 12-17 years old and included use of

topical medications in all arms (JADE TEEN). [39,41,78] While results of these trials in adolescents are briefly described in the Report, additional results and a table of key results are presented here.

In the two placebo-controlled monotherapy trials that enrolled patients ≥12 years old (JADE MONO-1 &2), 55%-60% of patients <18 years old achieved EASI 75, compared to 0%-13% in the placebo arms of those trials. [35,36] In this subgroup of patients, 44% achieved EASI 75 with abrocitinib 100 mg. The percentages of patients achieving IGA response, defined as an IGA score of 0 or 1 and an improvement of 2 points or more from baseline, with abrocitinib 200 mg were 27%-40%, 13%-27% with abrocitinib 100 mg, and 0%-13% with placebo.

In the placebo-controlled combination trial that solely enrolled adolescents (JADE TEEN), more patients in the abrocitinib arms achieved EASI 75 and IGA response at 12 weeks compared to the placebo arm (see Table D3.9).[39,78]

At the time of this Report, no long-term data for abrocitinib in adolescents were identified.

***Upadacitinib***

As noted in Section 3.2 of the Report, trials of upadacitinib included adolescents and adults.

Two placebo-controlled monotherapy trials (MEASURE UP 1 &2) and one placebo-controlled combination trial (AD-UP) of upadacitinib enrolled patients ≥12 years old; however, few patients in these trials were ≥12-17 years old (12%-15%).[83] [82] While results of these trials in adolescents are briefly described in the Report, additional results and a table of key results are presented here.

In the two placebo-controlled monotherapy trials that enrolled patients ≥12 years old (MEASURE UP 1 &2), 75%-83% of patients <18 years old achieved EASI 75 on upadacitinib 30 mg, compared to 8%-13% in the placebo arms of those trials. [80] In this subgroup of patients, 67%-71% achieved EASI 75 with upadacitinib 15 mg. The percentages of patients achieving IGA response, defined as an IGA score of 0 or 1 and an improvement of 2 points or more from baseline, with upadacitinib 30 mg were 63%-69%, 38%-42% with upadacitinib 15 mg, and 3%-8% with placebo (See Table D3.8). [80]

In the combination trial that compared upadacitinib to placebo in patients also treated with topical corticosteroids (AD-UP), 77% of patients <18 years old achieved EASI 75 on upadacitinib 30 mg, compared to 30% in the placebo arms.[80] IGA response was achieved by 65% of patients with upadacitinib 30 mg, 31% with upadacitinib 15 mg, and 8% with placebo (See Table D3.9). [80]

At the time of this report, no long-term data for upadacitinib in adolescents were identified.

***Dupilumab***

We identified one OLE of dupilumab in a subgroup in children with severe atopic dermatitis,1[38] and one OLE of dupilumab in children with severe atopic dermatitis and adolescents with moderate-to-severe atopic dermatitis.5[8,59] At the time of this report, the OLE of dupilumab have been published. Results for the phase IIa OLE were obtained from a conference abstract and clinicaltrials.gov. Results are presented in Table D3.9.

***Additional Tables of Outcomes***

**Table D3.8. Key Outcomes in Placebo-controlled Monotherapy Trials in Adolescents (Short-term)**

| Population of Interest | Trial | Arm | Timepoint | EASI 50 | EASI 75 | EASI 90 | IGA | PP-NRS† | SCORAD‡ |
|---|---|---|---|---|---|---|---|---|---|
| 12-17 years | **Abrocitinib** | | | | | | | | |
| | JADE MONO-1* | ABRO 200 mg | 12 weeks | | 54.5 | | 27.3 | | |
| | | ABRO 100 mg | | | 44.1 | | 26.5 | | |
| | | PBO | | | 12.5 | | 12.5 | | |
| | JADE MONO-2* | ABRO 200 mg | 12 weeks | | 60.0 | | 40.0 | | |
| | | ABRO 100 mg | | | 43.8 | | 12.5 | | |
| | | PBO | | | 0.0 | | 0.0 | | |
| | **Upadacitinib** | | | | | | | | |
| | MEASURE UP 1* | UPA 30 mg | 16 weeks | | | | 69.0 | 54.8 | NR |
| | | UPA 15 mg | | | | | 38.1 | 45.0 | NR |
| | | PBO | | | | | 7.5 | 15.4 | NR |
| | MEASURE UP 2* | UPA 30 mg | 16 weeks | | | | 62.5 | 50.0 | NR |
| | | UPA 15 mg | | | | | 42.4 | 33.3 | NR |
| | | PBO | | | | | 2.8 | 2.8 | NR |
| | **Dupilumab** | | | | | | | | |
| | LIBERTY AD ADOL | DUP 200/300 mg Q2W | 16 weeks | 61 | 41.5 | 23.2 | 24.4 | 36.6 | -51.6¶ |
| | | DUP 300 mg Q4W | | 54.8 | 38.1 | 19.0 | 17.9 | 26.5 | -47.5¶ |
| | | PBO | | 12.9 | 8.2 | 2.4 | 2.4 | 4.8 | -17.6¶ |

All values in the table are percentages. No monotherapy trials were conducted in the children population. ABRO: abrocitinib, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, UPA: upadacitinib. *subgroup of the trial population, †PP-NRS ≥4, ‡mean change from baseline, ¶LSM percentage change from baseline.

**Table D3.9. Key Outcomes in Placebo-controlled Combination Trials of Children and Adolescents (Short- and Long-term)**

| Population of Interest | Trial | Arm | Timepoint | EASI 50 | EASI 75 | EASI 90 | IGA | PP-NRS† | SCORAD‡ |
|---|---|---|---|---|---|---|---|---|---|
| 6-11 years | **Dupilumab** | | | | | | | | |
| | LIBERTY AD PEDS | DUP 300 mg Q4W + TCS | 16 weeks | 91 | 69.7 | 41.8 | 32.8 | 50.8 | -62.4¶ |
| | | DUP 100/200 mg Q2W + TCS | | 82.8 | 67.2 | 30.3 | 29.5 | 58.3 | -60.2¶ |
| | | PBO + TCS | | 43.1 | 26.8 | 7.3 | 11.4 | 12.3 | -29.8¶ |
| | LIBERTY AD PED OLE* | DUP 4 mg/kg + TCS | 16 weeks | 93 | 73 | 33 | 40 | 69 | -62 |
| | | DUP 2 mg/kg + TCS | | 94 | 59 | 41 | 35 | 53 | -61 |
| | | DUP 4 mg/kg + TCS | 52 weeks | 94 | 75 | 44 | 25 | 69 | -67 |
| | | DUP 2 mg/kg + TCS | | 94 | 94 | 71 | 76 | 65 | -79 |
| | Phase 2a AD-1412* | DUP 4 mg/kg + TCS | 12 weeks | NR | NR | NR | 21.1 | NR | -46.9 |
| | | DUP 2 mg/kg + TCS | | NR | NR | NR | 16.7 | NR | -57.5 |
| 12-17 years | **Abrocitinib** | | | | | | | | |
| | JADE TEEN | ABRO 200 mg + TCS | 12 weeks | [redacted] | 72 | [redacted] | 46.2 | 55.4 | [redacted] |
| | | ABRO 100 mg + TCS | | | 68.5 | | 41.6 | 52.6 | |
| | | PBO +TCS | | | 41.5 | | 24.5 | 29.8 | |
| | **Upadacitinib** | | | | | | | | |
| | AD-UP | UPA 30 mg + TCS | 16 weeks | NR | 75.7 | NR | 64.9 | 54.5 | NR |
| | | UPA 15 mg + TCS | | NR | 56.4 | NR | 30.8 | 41.7 | NR |
| | | PBO + TCS | | NR | 30.0 | NR | 7.5 | 13.2 | NR |
| | **Dupilumab** | | | | | | | | |
| | LIBERTY AD PED-OLE* | **Baseline weight <60 kg** | | | | | | | |
| | | Overall | 52 weeks | NR | 86 | NR | 36.5 | NR | NR |
| | | **Baseline weight ≥60 kg** | | | | | | | |
| | | Overall | 52 weeks | NR | 76.5 | NR | 49 | NR | NR |
| | Phase 2a AD-1412* | DUP 4 mg/kg + TCS | 12 weeks | NR | NR | NR | 35 | NR | -43.4 |
| | | DUP 2 mg/kg + TCS | | NR | NR | NR | 10 | NR | -47.7 |

All values in the table are percentages. ABRO: abrocitinib, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, TCS: topical corticosteroids. *subgroup of the trial population, †PP-NRS ≥4, ‡mean percentage change from baseline, ¶LSM percentage change from baseline.

***Harms***

**Table D3.10. Key Harms in Placebo-controlled Monotherapy Trials of Adolescents**

| Population of Interest | Trial | Arm | Timepoint | Any AEs | TEAEs | D/C Due to AE | SAE | Conjunctivitis | Nausea | Herpetic Infection |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dupilumab** | | | | | | | | | | |
| 12-17 years | LIBERTY AD ADOL | DUP 200/300 mg Q2W | 16 weeks | NR | 72 | 0[†] | 0[†] | 9.8 | NR | 1.2[¶] |
| | | DUP 300 mg Q4W | | NR | 63.9 | 0[†] | 0[†] | 10.8 | NR | 4.8[¶] |
| | | PBO | | NR | 69.4 | 1.2[†] | 1.2[†] | 4.7 | NR | 3.5[¶] |

All values in the table are percentages. No placebo-controlled trials were conducted in the children population. **There were no available safety data for adolescent subgroups in JADE MONO-1, JADE MONO-2, MEASURE UP 1, and MEASURE UP 2.** ABRO: Abrocitinib, AE: adverse event, D/C: discontinuation, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, SAE: serious adverse event, TEAE: treatment-emergent adverse event, UPA: upadacitinib. *subgroup of the trial population, [†]based on TEAE, [¶]herpes viral infection.

**Table D3.11. Key Harms in Placebo-controlled Combination Trials of Children and Adolescents**

| Population of Interest | Trial | Arm | Timepoint | Any AEs | TEAEs | D/C Due to AE | SAE | Conjunctivitis | Nausea | Herpetic Infection |
|---|---|---|---|---|---|---|---|---|---|---|
| 6-11 years | **Dupilumab** | | | | | | | | | |
| | LIBERTY AD PEDS | DUP 300 mg Q4W + TCS | 16 weeks | NR | 65 | 0[†] | 1.7[†] | 6.7[‡] | NR | 1.7[¶] |
| | | DUP 100/200 mg Q2W + TCS | | NR | 67.2 | 1.6[†] | 0[†] | 14.8[‡] | NR | 3.3[¶] |
| | | PBO +TCS | | NR | 73.3 | 1.7[†] | 1.7[†] | 4.2[‡] | NR | 5[¶] |
| | LIBERTY AD PED-OLE* | DUP 4 mg/kg + TCS | 52 weeks | NR | 100 | 0[†] | 19[†] | 31 | NR | 50[#] |
| | | DUP 2 mg/kg + TCS | | NR | 94 | 0[†] | 12[†] | 5 | NR | 12 |
| | Phase 2a AD-1412* | DUP 4 mg/kg + TCS | 20 weeks | NR | NR | NR | 10.53 | 5.26 | 10.53 | 5.26[§] |
| | | DUP 2 mg/kg + TCS | | NR | NR | NR | 0 | 0 | 0 | 5.56[§] |
| 12-17 years | **Abrocitinib** | | | | | | | | | |
| | JADE TEEN | ABRO 200 mg + TCS | 12 weeks | NR | 62.8 | 2.1 | NR | NR | NR | NR |
| | | ABRO 100 mg + TCS | | NR | 56.8 | 1.1 | NR | NR | NR | NR |
| | | PBO +TCS | | NR | 52.1 | 2.1 | NR | NR | NR | NR |
| | **Dupilumab** | | | | | | | | | |
| | LIBERTY AD PED-OLE* | DUP 200/300 mg Q2W | 52 weeks | NR | 74.4 | 0.9[†] | 0.9[†] | 8.7[¥] | NR | NR |
| | | DUP 300 mg Q4W | | NR | 72.2 | 0[†] | 3.8[†] | | NR | NR |
| | Phase 2a AD-1412* | DUP 4 mg/kg + TCS | 20 weeks | NR | NR | NR | 5 | 0 | 0 | 5[§] |
| | | DUP 2 mg/kg + TCS | | NR | NR | NR | 5 | 0 | 0 | 0[§] |

All values in the table are percentages. ABRO: abrocitinib, AE: adverse event, D/C: discontinuation, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, SAE: serious adverse event, TCS: topical corticosteroids, TEAE: treatment-emergent adverse event. *subgroup of the trial population, [†]based on TEAE, [‡]conjunctivitis cluster, [¶]herpes viral infection, [#]herpes viral infection and herpes simplex, [§]herpes viral infection, herpes simplex, and oral herpes, [¥]treatment-emergent narrow conjunctivitis.

## Mild-to-Moderate Population

***Ruxolitinib Cream***

We identified two 52-week long-term trials of ruxolitinib conducted in patients with atopic dermatitis who had participated in TRuE-AD1 and TRuE-AD2 studies.[74] Patients were followed up for 8-weeks in TRuE-AD1 and TRuE-AD2 trials and followed up for additional 44 weeks in the extension studies.[74] Patients on ruxolitinib cream in the originating trials remained on their regimen during the long-term extension period, while patients in the vehicle (placebo) arms were re-randomized 1:1 to ruxolitinib cream 1.75% or ruxolitinib cream 1.75%.[74] During the extension studies, patients were instructed to stop treatment three days after clearance of atopic dermatitis lesions and restart treatment at the first sign of recurrence. At week 52, IGA response was achieved by 72%-80% and 60%-77% of patients on 1.5% and 0.75% ruxolitinib cream.[74]

### *Additional Table of Outcomes*

While most results for the ruxolitinib cream trials are described in Section 3.3 of the Report, a table of key results is presented here.

**Table D3.12. Key Outcomes for Ruxolitinib Cream[87,88,98]**

| Trial | Arm | Timepoint | EASI 50 | EASI 75 | EASI 90 | IGA | PP-NRS† | SCORAD‡ |
|---|---|---|---|---|---|---|---|---|
| **Ruxolitinib Cream** | | | | | | | | |
| TRuE AD 1 | RUX 1.5% | 8 weeks | NR | 62.1 | 44.3 | 53.8 | 52.2 | NR |
| | RUX 0.75% | | NR | 56.0 | 38.1 | 50.0 | 40.4 | NR |
| | PBO | | NR | 24.6 | 9.5 | 15.1 | 15.4 | NR |
| TRuE AD 2 | RUX 1.5% | 8 weeks | NR | 61.8 | 43.4 | 51.3 | 50.7 | -67.3** |
| | RUX 0.75% | | NR | 51.5 | 35.1 | 39.0 | 42.7 | -62.9** |
| | PBO | | NR | 14.4 | 4.2 | 7.6 | 16.3 | -30.4** |
| Phase II Kim 2020* | RUX 1.5% | 4 weeks | NR | 56.0 | 26.0 | 38.0 | 62.5 | NR |
| | TRI 0.1% | | NR | 47.1 | 13.7 | 25.5 | 19.4 | NR |
| | PBO | | NR | 17.3 | 5.8 | 7.7 | 11.1 | NR |

All values in the table are percentages. RUX: ruxolitinib cream, TRI: topical triamcinolone acetonide, NR: not reported, PBO: placebo.

*Results from additional RUX arms are presented in Evidence Tables G1.48-1.64.

**Results from a pooled analysis of TRuE AD 1 and 2.

***Harms***

Summaries of the harms are provided in Section 3.3 of the Report. A table presenting key harms from the trials are presented here.

**Table D3.13. Key Harms for Ruxolitinib Cream[87,88,98]**

| Trial | Arm | Timepoint | Any TEAE | Study Drug-Related TEAE | Serious TEAE | D/C Due to TEAEs | Application Site Burning | Application Site Pruritis |
|---|---|---|---|---|---|---|---|---|
| **Ruxolitinib Cream (short-term)** | | | | | | | | |
| TRuE AD 1 | RUX 1.5% | 8 weeks | 28.9 | 5.5 | 0.8 | 1.2 | 0.8 | 0.0 |
| | RUX 0.75% | | 29.4 | 6.0 | 0.4 | 1.2 | 0.0 | 0.8 |
| | PBO | | 34.9 | 12.7 | 1.6 | 4.0 | 1.6 | 1.6 |
| TRuE AD 2 | RUX 1.5% | 8 weeks | 23.6 | 4.5 | 0.4 | 0.0 | 0.8 | 0 |
| | RUX 0.75% | | 29.4 | 3.2 | 1.2 | 0.4 | 0.8 | 0.8 |
| | PBO | | 32.3 | 9.7 | 0.0 | 2.4 | 6.5 | 3.2 |
| Phase II Kim 2020* | RUX 1.5% | 8 weeks | 24 | 6.0 | NR | 0.0 | NR | NR |
| | TAC 0.1% | | 33.3 | 2.0 | NR | 2.0 | NR | NR |
| | PBO | | 32.7 | 9.6 | NR | 1.9 | NR | NR |
| **Ruxolitinib Cream (Long-term)** | | | | | | | | |
| TRuE AD 1 & 2 (Pooled) | RUX 1.5% | 52 weeks | 53.8 | 2.9 | 1.3 | 0 | 2.1 - 2.2/100 patient-years** | |
| | RUX 0.75% | | 60.1 | 4.7 | 2.3 | 2.1 | 3.5 - 4.7/100 patient-years** | |
| | PBO to RUX 1.5% | | 57.6 | 6.1 | 1.0 | 0 | NR | NR |
| | PBO to RUX 0.75% | | 53.5 | 2.0 | 5.0 | 0 | NR | NR |

All values in the table are percentages. D/C: discontinuation, NR: not reported, PBO: vehicle (placebo), RUX: ruxolitinib cream, TAC: topical triamcinolone acetonide, TEAE: treatment-emergent adverse event.

*The incidences of adverse events at four weeks were not reported.

**Presented as application site reactions

# D4. Ongoing Studies

### Figure D4.1. Ongoing Studies

| Title / Trial Sponsor | Study Design | Comparators | Patient Population | Primary Outcomes | Estimated Completion Dates |
|---|---|---|---|---|---|
| **Abrocitinib** | | | | | |
| Study of Abrocitinib Compared with Dupilumab in Adults with Moderate to Severe Atopic Dermatitis on Background Topical Therapy<br><br>Pfizer<br><br>NCT04345367 | Phase IIIb, randomized, double-blind, multi-center<br><br>N=600 | Arm 1<br>Abrocitinib 200 mg + TCS<br><br>Arm 2<br>Dupilumab 300 mg + TCS | **Inclusion**<br>18 years of age or older<br>Diagnosis of chronic atopic dermatitis for at least 6 months<br>Recent history of inadequate response to treatment with medicated topical therapy for AD or have required systemic therapies for control of their disease<br>**Exclusion**<br>Acute or chronic abnormality<br>Increased risk of developing thromboembolism<br>Unwilling to discontinue current medications<br>Prior treatment with JAK inhibitors or IL-4 or IL-13 | Change in PP-NRS4<br>Change in EASI-90 at week 4 | July 14th, 2021 |
| Study to Evaluate Efficacy and Safety of PF-04965842 With or Without Topical Medications in Subjects Aged 12 years and older with Moderate to Severe Atopic Dermatitis (JADE EXTEND)<br><br>Pfizer<br><br>NCT03422822 | Phase III, randomized, quadruple masking, Long-term extension study<br><br>N=3000 | Arm 1<br>Initial treatment period: Abrocitinib 100 mg<br><br>For patients, whose dose was changed from abrocitinib 100 mg to placebo, placebo was administered for remainder of study<br><br>Secondary treatment period: Abrocitinib 100 mg | **Inclusion**<br>Aged 12 and older<br>Must have completed a qualifying parent study<br><br>**Exclusion**<br>Other acute or chronic medical conditions<br>Currently have active forms of inflammatory diseases<br>Ongoing adverse event from parent study | Treatment-emergent adverse events<br>Serious adverse events | December 1, 2023 |

| Title / Trial Sponsor | Study Design | Comparators | Patient Population | Primary Outcomes | Estimated Completion Dates |
|---|---|---|---|---|---|
| | | Arm 2<br>Initial treatment period: Abrocitinib 200 mg<br><br>For patients, whose dose was changed from abrocitinib 200 mg to placebo, placebo was administered for remainder of study<br><br>Secondary treatment period: Abrocitinib 200 mg | | | |
| Study to Investigate Efficacy and Safety of PF-0465842 in Subjects Aged 12 Years and Older with Moderate to Severe Atopic Dermatitis with the Option of Rescue Treatment in Flaring Subjects<br><br>Pfizer<br><br>NCT03627767 | Phase III, randomized withdrawal, double-blind<br><br>N=1231 | Arm 1<br>Abrocitinib 100 mg<br><br>Arm 2<br>Abrocitinib 200 mg<br><br>Arm 3<br>Placebo | **Inclusion**<br>12 years or older with a minimum weight of 40kg<br>Diagnosed with atopic dermatitis<br>Recent history of inadequate response or inability to tolerate topical AD treatments<br><br>**Exclusion**<br>Prior treatment with JAKs<br>Other active non-AD inflammatory diseases | Loss of response (week 12 to 52) | October 2020 |
| Tralokinumab | | | | | |
| Effects of Tralokinumab Treatment of Atopic Dermatitis on Skin Barrier Function<br><br>Prof. Dr. Stephan Weidinger<br><br>NCT04556461 | Phase II, open-label, mono-center<br><br>N=16 | Tralokinumab 600 mg loading dose followed by 300 mg every 2 weeks | **Inclusion**<br>Aged 18 and older with atopic dermatitis<br>Subjects with a recent history of inadequate response to treatment with topical medications<br>EASI score >12 | Change in trans epidermal water loss (skin barrier function) | March 2022 |

| Title / Trial Sponsor | Study Design | Comparators | Patient Population | Primary Outcomes | Estimated Completion Dates |
|---|---|---|---|---|---|
| | | | **Exclusion**<br>Concurrent enrollment in another clinical trial<br>Previous enrollment in a tralokinumab trial<br>Subjects with mild atopic dermatitis | | |
| Long-term Extension Trial in Subjects with Atopic Dermatitis Who Participated in Previous Tralokinumab Trials (ECZTEND)<br><br>LEO Pharma<br><br>NCT03587805 | Phase III, open-label, long-term extension<br><br>N=1125 | Tralokinumab | **Inclusion**<br>Completed the treatment period(s) of one of the parent trials<br>Stable dose of emollient twice daily<br>**Exclusion**<br>Any condition requiring permeant discontinuation of the trial treatment<br>Patients who participated in a parent trial and experienced a serious adverse event related to the treatment | IGA score of 0 or 1<br>EASI 75 | September 13, 2021 |
| Tralokinumab in Combination with Topical Corticosteroids in Japanese Subjects with Moderate to Severe Atopic Dermatitis (ECZTRA 8)<br><br>LEO Pharma<br><br>NCT04587453 | Phase 3, randomized, double-blind<br><br>N=100 | Arm 1<br>Tralokinumab + topical corticosteroids<br><br>Arm 2<br>Placebo + topical corticosteroids | **Inclusion**<br>Japanese subject aged 18 years and above with AD for at least 1 year<br>AD involvement of 10% or more of body surface area<br>Applied a stable dose of emollient twice a day<br><br>**Exclusion**<br>Subjects who cannot take TCS<br>Concomitant conditions<br>Known primary immunodeficiency disorder<br>Previous treatment with systemic immunosuppressive drugs, JAKs, or TCS. | IGA score of 0 or 1<br>EASI 75 | September 2021 |
| **Upadacitinib** | | | | | |
| Open-Label Extension Study of Upadacitinib in Adult Patients | Phase IIIb, single group | Upadacitinib | **Inclusion** | Adverse Events | November 24, 2021 |

| Title / Trial Sponsor | Study Design | Comparators | Patient Population | Primary Outcomes | Estimated Completion Dates |
|---|---|---|---|---|---|
| with moderate to Severe Atopic Dermatitis<br><br>AbbVie<br><br>NCT04195698 | assessment, open-label<br><br>N=600 | | Successfully completed concomitant treatment in M16-046 study<br><br>**Exclusion**<br>Use of prohibited medications | | |
| Evaluation of Upadacitinib in Adolescent and Adult Patients with Moderate to Severe Atopic Dermatitis<br><br>AbbVie<br><br>NCT03569293 | Phase III, randomized, quadruple masked<br><br>N=912 | Arm 1<br>Upadacitinib dose A<br><br>Arm 2<br>Upadacitinib dose B<br><br>Arm 3<br>Placebo | **Inclusion**<br>Chronic atopic dermatitis<br>Moderate to severe AD<br>Candidate for systemic therapy<br><br>**Exclusion**<br>Prior exposure to JAK inhibitor<br>Other active skin disease | EASI 75<br>vIGA-AD score of 0 or 1 | May 24, 2023 |
| A Study to Evaluate Upadacitinib in Combination with Topical Steroids in Adolescent and Adult Participants with Moderate to Severe AD<br><br>AbbVie<br><br>NCT03568318 | Phase III, randomized, double-blind<br><br>N=969 | Arm 1<br>Upadacitinib A + topical corticosteroids<br><br>Arm 2<br>Upadacitinib B + topical corticosteroids<br><br>Arm 3<br>Placebo + corticosteroids | **Inclusion**<br>Chronic atopic dermatitis<br>Moderate to severe AD<br>Candidate for systemic therapy<br><br>**Exclusion**<br>Prior exposure to JAK inhibitor<br>Other active skin disease | EASI 75<br>vIGA-AD score of 0 or 1 | June 30, 2023 |
| A Study to Evaluate the Pharmacokinetics, Safety, and tolerability of Upadacitinib in Pediatric patients with Severe AD<br><br>AbbVie<br><br>NCT03646604 | Open-label<br><br>N=40 | Arm 1<br>Ages 6 to 12 on low dose UPA<br>Arm 2<br>Ages 6 to 12 on high dose UPA<br>Arm 3<br>Ages 2 to 6 on low dose UPA<br>Arm 4<br>Ages 2 to 6 on high dose UPA<br>Arm 5 | **Inclusion**<br>Ages 2 months to 12 years of age<br>Severe AD<br><br>**Exclusion**<br>Prior exposure to JAK | Maximum plasma concentration<br>Oral Clearance | November 28, 2024 |

| Title / Trial Sponsor | Study Design | Comparators | Patient Population | Primary Outcomes | Estimated Completion Dates |
|---|---|---|---|---|---|
| | | Ages 6 months to 2 years on low dose UPA<br>Arm 6<br>Ages 6 months to 2 years on high dose UPA | | | |
| A Study to Evaluate Upadacitinib in Adolescents and Adult Subjects with Moderate to Severe AD (Measure UP 2)<br><br>AbbVie<br><br>NCT03607422 | Phase III, randomized, double-blind<br><br>N=916 | Arm 1<br>UPA dose A<br>Arm 2<br>UPA dose B<br>Arm 3<br>Placebo | **Inclusion**<br>Moderate to severe AD<br>Chronic AD for at least 3 years<br>Ages 12 to 18<br>Documented history of inadequate response to topical corticosteroids or topical calcineurin inhibitor<br><br>**Exclusion**<br>Prior exposure to JAK inhibitor<br>Other skin disease<br>Unwilling to discontinue current medications | EASI75<br>vIGA-AD score of 0 or 1 | July 25, 2023 |
| A Study to Evaluate the Safety of Upadacitinib In Combination with Topical Steroids in Adolescent and Adult Participants with Moderate to Severe AD<br><br>AbbVie<br><br>NCT03661138 | Phase III, randomized, double-blind<br><br>N=272 | Arm 1<br>UPA dose A + topical corticosteroids<br>Arm 2<br>UPA dose B + topical corticosteroids<br>Arm 3<br>Placebo + topical corticosteroids | **Inclusion**<br>Active moderate to severe AD<br>Candidate for systemic therapy<br><br>**Exclusion**<br>Prior use of a JAK inhibitor<br>Unwilling to discontinue current medications | Adverse events | February 25, 2022 |

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies). There are no on-going trials for baricitinib or dupilumab.

## D5. Previous Systematic Reviews and Technology Assessments

We identified seven systematic literature reviews (SLRs) evaluating systemic treatments for patients with moderate-to-severe atopic dermatitis, three of which are summarized below. We did not identify any SLRs that assessed ruxolitinib in atopic dermatitis.

**Silverberg, J. I., et al. (2021). "Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis"** [139]

This systematic literature review and NMA evaluated the comparative efficacy and safety of several systemic therapies, including oral JAK inhibitors, IL-13 antagonists, and IL-31 antagonists, in adolescents and adults with moderate-to-severe atopic dermatitis. The medications assessed included abrocitinib, baricitinib, dupilumab, lebrikizumab, nemolizumab, tralokinumab and upadacitinib. Investigators identified 19 phase II and phase III RCTS, published before October 2019, to include in their analysis, which comprised of 11 monotherapy and 8 combination trials. Outcomes were analyzed separately for monotherapy and combination therapies (i.e., systemic therapies plus topical corticosteroids). For the monotherapy trials, upadacitinib 30 mg consistently had the highest response rate on all EASI measures, followed by abrocitinib 200 mg and upadacitinib 15 mg. Additionally, upadacitinib 30 mg and abrocitinib 200 mg demonstrated superiority over dupilumab 300 mg, both doses of baricitinib, and nemolizumab. A similar trend was observed for IGA response; however, no data were identified for upadacitinib for IGA response. For the combination therapy NMA, both doses of abrocitinib, dupilumab 300 mg, nemolizumab 30 mg, and lebikizumab 125 mg, had the highest response rates for all EASI measures. Additionally, abrocitinib 200 mg demonstrated superiority over baricitinib, tralokinumab, and dupilumab. On IGA, abrocitinib 200 mg, dupilumab 300 mg, nemolizumab 30 mg, and abrocitinib 100 mg, had the highest response rates. Upadacitinib was not included in the combination therapy NMA. For safety events, in the monotherapy and combination therapy RCTs, none of the treatments had adverse events that were statistically different from placebo; but most treatment arms had numerically higher probabilities of TEAEs than placebo arms. However, the probability of AE leading to discontinuation was generally lower in the treatment arms. There was no statistically significant difference between the active treatments on safety events.

**Drucker, A.M., et al. (2020). "Systemic Immunomodulatory Treatments for Patients with Atopic Dermatitis: A Systematic Review and Network Meta-analysis"**

Investigators conducted a systematic review assessing the efficacy and safety of systemic immunomodulatory treatments for patients with moderate-to-severe atopic dermatitis. 39 RCTs for 20 different medications, including abrocitinib, baricitinib, dupilumab, tralokinumab,

upadacitinib, methotrexate, and other immunosuppressants, antagonists, and monoclonal antibodies, were included in their network meta-analysis. A total of 6360 patients were included, the mean sample size for each RCT was 60 (4-319) patients, and the mean/median age ranged between 6 and 44 years. Eligibility criteria included patients with moderate-to-severe atopic dermatitis, a systemic immunomodulatory therapy as the treatment of focus, and an outcome assessment time point of eight weeks or more. An NMA was performed for each outcome, including change from baseline in EASI, POEM, DLQI, and itch, withdrawals due to adverse events, and frequency of serious adverse events. Data were pooled for trials with 8–16-week treatment timepoints, and trials with greater than 16-week treatment time points were not analyzed.

Multiple drug doses, including dupilumab 300 mg Q2W, baricitinib 2 mg and 4 mg daily, tralokinumab 150 mg Q2W, and 300 mg Q2W had a statistically significant reduction in EASI score compared to placebo, with dupilumab 300 mg Q2W having the highest amount of certainty (mean difference [MD]: -11.3; 95% CrI: 9.7 to 13.1).

When assessing changes in clinical signs of atopic dermatitis among drugs that are already used in clinical practice, it was found that all current drugs were more effective than placebo in clearing atopic dermatitis clinical signs, but with low certainty. When comparing these drugs, dupilumab 300 Q2W and cyclosporine high-dose were more effective in clearing atopic dermatitis signs than methotrexate and azathioprine.

Dupilumab 300 mg Q2W was the only drug that demonstrated clinically meaningful improvements in both POEM (MD: -7.5; 95% CrI: -11.6 to -3.6) and DLQI outcomes (MD: -4.8; 95% CrI: -5.8 to -3.7), with high certainty, while abrocitinib 100 mg and 200 mg, and upadacitinib 15 mg and 30 mg had significant improvements with lower certainty. Additionally, only dupilumab 300 mg Q2W had a statistically significant improvement in the mean change in PP-NRS, relative to placebo, with high certainty. Cyclosporine, dupilumab, methotrexate, and azathioprine could not be compared to each other for the itch outcome due to imprecise estimates.

Safety could not be robustly assessed due to the overall low rates of adverse events. Investigators identified potential limitations in their systematic review, including heterogeneity from incorporating trials that also used background topical medication therapy, using trials that varied in the definition of disease severity, and the lack of head-to-head trials in this analysis.

**Siegels, D., et al. (2020). "Systemic Treatments in the Management of Atopic Dermatitis: A Systematic Review and Meta-Analysis"**

An SLR and a MA were conducted to evaluate systemic treatments for moderate-to-severe atopic dermatitis. Investigators identified 50 RCTs for 13 different approved treatments in Europe, as of February 2020, to include in their meta-analysis. The medications included baricitinib, dupilumab,

methotrexate, upadacitinib, corticosteroids, and other monoclonal antibodies and immunosuppressants. The total patient population was 6681, a majority of which were in dupilumab trials (n=3529), and the average sample size for most trials was less than 100 patients. Thirty trials were conducted in adult populations. One trial was in adolescents, one trial assessed their treatment in children, and 18 trials had age groups inconsistent with the investigators' defined populations of focus.

Meta-analyses could be calculated only for dupilumab, azathioprine, baricitinib, and cyclosporine, as the other trials' evidence had higher risks of bias (RoB). Out of these treatments, dupilumab trials in adults with a dosage of 300 mg Q2W had the most robust and highest quality evidence due to the large number of trials and patients. All dupilumab doses in the trials demonstrated superiority to placebo in EASI 75 and mean change from baseline in EASI, SCORAD, PP-NRS, POEM, cDLQI (in adolescents), and DLQI (in adults). Cumulative safety data for dupilumab indicated that adverse events for dupilumab and placebo were equal and greater than 50% in incidence rates, with conjunctivitis and injection-site reactions being the most common concerns.

Investigators reported that uncertainty limited the evaluation of safety and efficacy of the other treatments' trials. Limitations included lack of published RCTs, most of the included RCTs having a high risk of bias, a relatively low number of patients in most trials, and inclusion of older trials.

# E. Long-Term Cost Effectiveness: Supplemental Information

## E1. Detailed Methods

**Table E.1. Impact Inventory**

| Sector | Type of Impact (Add additional domains, as relevant) | Included in This Analysis from […] Perspective? | | Notes on Sources (if quantified), Likely Magnitude & Impact (if not) |
|---|---|---|---|---|
| | | Health Care Sector | Societal | |
| **Formal Health Care Sector** | | | | |
| Health Outcomes | Longevity effects | X | X | |
| | Health-related quality of life effects | X | X | |
| | Adverse events | ☐ | ☐ | |
| Medical Costs | Paid by third-party payers | X | X | |
| | Paid by patients out-of-pocket | ☐ | ☐ | |
| | Future related medical costs | ☐ | ☐ | |
| | Future unrelated medical costs | ☐ | ☐ | |
| Informal Health Care Sector | | | | |
| Health-Related Costs | Patient time costs | NA | ☐ | |
| | Unpaid caregiver-time costs | NA | ☐ | |
| | Transportation costs | NA | ☐ | |
| Non-Health Care Sector | | | | |
| Productivity | Labor market earnings lost | NA | X | |
| | Cost of unpaid lost productivity due to illness | NA | X | |
| | Cost of uncompensated household production | NA | ☐ | |
| Consumption | Future consumption unrelated to health | NA | ☐ | |
| Social services | Cost of social services as part of intervention | NA | ☐ | |
| Legal/Criminal Justice | Number of crimes related to intervention | NA | ☐ | |
| | Cost of crimes related to intervention | NA | ☐ | |
| Education | Impact of intervention on educational achievement of population | NA | ☐ | |
| Housing | Cost of home improvements, remediation | NA | ☐ | |

| | | | | |
|---|---|---|---|---|
| Environment | Production of toxic waste pollution by intervention | NA | ☐ | |
| Other | Other impacts (if relevant) | NA | ☐ | |

NA: not applicable

Adapted from Sanders et al[140]

## Target Population

The target population for the economic evaluation is adult (aged 18 years or older) patients with moderate-to-severe atopic dermatitis. We pooled across treatment-specific population characteristics in order to estimate the population characteristics used within the model.

**Table E.2. Baseline Population Characteristics**

| | Pooled Population Used in Model |
|---|---|
| **Mean Age** | 36.5 |
| **Percent Female** | 43.7% |
| **Percent Severe Disease** | 45.9% |
| **Source** | Weighted averages from drug trials1[41-143] 69 63,6[4,144-146]Weighted averages from drug trials1[41-143] 69 63,6[4,144-146] |

## Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Abrocitinib (Pfizer)
- Baricitinib (Olumiant™, Eli Lilly)
- Upadacitinib (RINVOQ™, AbbVie)
- Tralokinumab (LEO Pharma)

### Comparators

Each intervention of interest is compared pairwise with each comparator. The comparators for these interventions were expected to be:

- Dupilumab (Dupixent™, Sanofi)
- Topical therapies (including emollients, with or without topical corticosteroid or calcineurin inhibitor)

Topical therapies, including emollients, topical corticosteroids, and calcineurin inhibitors, are a commonly used treatment for atopic dermatitis. Dupilumab was approved for treating moderate-to-severe atopic dermatitis in 2017, becoming the only approved alternative treatment for patients beyond the topical therapies. These two groups represent the predominantly used available treatment options for patients with moderate-to-severe atopic dermatitis.

## E2. Results

Table E2.1. presents the incremental costs and benefits of each therapy compared to standard of care and dupilumab as measured by the Peak Pruritis Numerical Rating Scale (PP-NRS), and the sleep scores for the POEM, SCORAD, and ADerm-IS measures. The average incremental change in score over the five-year time horizon is presented where data was available by health state, as no commonly meaningful threshold or translation for these measurements was identified.

**Table E2.1. Incremental Cost-Consequence Results for the Base Case**

| Treatment | Comparator | Incremental Cost | Incremental QALYs gained (same as evLYG) | Incremental Gain in Average PP-NRS† | Incremental Gain in Average POEM (Sleep)† | Incremental Gain in Average SCORAD (Sleep)† | Incremental Gain in Average ADerm-IS (Sleep)† | Incremental Gain in Average HADS (Anxiety and Depression)† |
|---|---|---|---|---|---|---|---|---|
| **Abrocitinib*** | SoC | $90,600 | 0.61 | NA | NA | NA | NA | NA |
| **Baricitinib** | SoC | $17,500 | 0.26 | NA | NA | NA | NA | NA |
| **Tralokinumab*** | SoC | $39,900 | 0.32 | -0.96 | -0.44 | -1.04 | NA | -1.04 |
| **Upadacitinib** | SoC | $131,800 | 0.53 | -1.50 | NA | NA | -5.21 | NA |
| **Dupilumab** | SoC | $54,000 | 0.50 | NA | NA | NA | NA | NA |
| **Abrocitinib*** | Dupilumab | $36,500 | 0.12 | NA | NA | NA | NA | NA |
| **Baricitinib** | Dupilumab | Less Costly | Less Effective | NA | NA | NA | NA | NA |
| **Tralokinumab*** | Dupilumab | Less Costly | Less Effective | NA | NA | NA | NA | NA |
| **Upadacitinib** | Dupilumab | $77,800 | 0.03 | NA | NA | NA | NA | NA |

ADerm-IS: Atopic Dermatitis Impact Scale, NA: not available, POEM: Patient-Oriented Eczema Measure, QALY: quality-adjusted life year, evLYG: equal-value life-year gained, PP-NRS: Peak Pruritis Numeric Rating Scale, SCORAD: Scoring Atopic Dermatitis; HADS, hospital anxiety and depression scale;

*Using a placeholder price

†Difference in average change in score from pooled baseline

## Description evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy. [147]

2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).

3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.

4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.

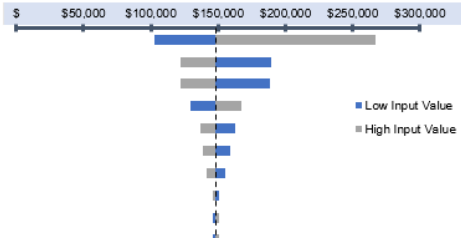
6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

## E3. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per addition QALY for each modeled treatment. Across all modeled comparisons, the health state utility values were identified as the most influential model parameters on the incremental cost-effectiveness ratios, followed by the initial transition probabilities, non-responder direct costs, and discontinuation rates. Figures E3.1 to E3.9 display the results of the one-way sensitivity analyses performed on each modeled comparison.

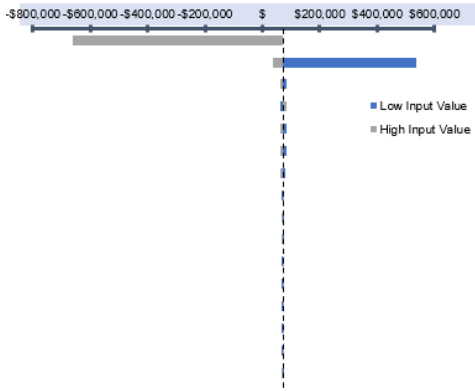
**Figure E3.1 Tornado Diagram for Abrocitinib versus Standard of Care**




| Parameter | Low Input Value | ligh Input Valu | Low Result | High Result |
|---|---|---|---|---|
| Utility of non-responder state (off treatment) - Soc/Placebo | 0.54 | 0.66 | 102666 | 267228 |
| Utility of achieving EASI 90 (on treatment) - Abrocitinib | 0.79 | 0.97 | 189226.2 | 121984.8 |
| Utility of non-responder state (off treatment) - Abrocitinib | 0.54 | 0.66 | 188868.9 | 122133.7 |
| Cost per dose - Net price - Abrocitinib | 102.01 | 124.67 | 129802 | 166881 |
| Utility of achieving EASI 75 (on treatment) - Abrocitinib | 0.76 | 0.93 | 162375.5 | 136540.0 |
| Utility of achieving EASI 50 (on treatment) - Abrocitinib | 0.72 | 0.88 | 159272.1 | 138814.4 |
| Annual Direct Cost - Non-Responder | 16729.76 | 20447.48 | 155469 | 141214 |
| Probability of initial transition EASI 90 - Abrocitinib | 0.37 | 0.45 | 151079.3 | 145951.5 |
| Utility of achieving EASI 50 (on treatment) - Soc/Placebo | 0.72 | 0.88 | 146058 | 150697 |
| Annual Direct Cost - EASI 90 | 7736.11 | 9455.25 | 146360 | 150323 |

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

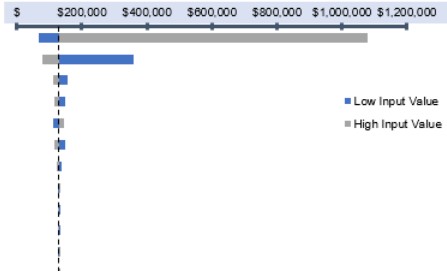
**Figure E3.2 Tornado Diagram for Baricitinib versus Standard of Care**




| Parameter | Low Input Value | ligh Input Valu | Low Result | High Result |
|---|---|---|---|---|
| Utility of non-responder state (off treatment) - Soc/Placebo | 0.54 | 0.66 | 33943 | -662224 |
| Utility of non-responder state (off treatment) - Baricitinib | 0.54 | 0.66 | 535387.4 | 38338.9 |
| Utility of achieving EASI 90 (on treatment) - Baricitinib | 0.79 | 0.97 | 86237.5 | 61143.1 |
| Cost per dose - Net price - Baricitinib | 47.81 | 58.43 | 60597 | 82510 |
| Utility of achieving EASI 50 (on treatment) - Baricitinib | 0.72 | 0.88 | 82992.1 | 62886.6 |
| Utility of achieving EASI 75 (on treatment) - Baricitinib | 0.76 | 0.93 | 82147.8 | 63380.2 |
| Annual Direct Cost - Non-Responder | 16729.76 | 20447.48 | 79034 | 64074 |
| Utility of achieving EASI 50 (on treatment) - Soc/Placebo | 0.72 | 0.88 | 68873 | 74452 |
| Risk of discontinuation - SoC | 0.23 | 0.28 | 74281.2 | 69354.5 |
| Probability of initial transition EASI 90 - Baricitinib | 0.15 | 0.18 | 73729.6 | 69598.7 |
| Utility of achieving EASI 75 (on treatment) - Soc/Placebo | 0.76 | 0.93 | 69608 | 73611 |
| Utility of achieving EASI 90 (on treatment) - Soc/Placebo | 0.79 | 0.97 | 69916 | 73270 |
| Annual Direct Cost - EASI 90 | 7736.11 | 9455.25 | 70148 | 72959 |
| Risk of discontinuation - Baricitinib | 0.07 | 0.08 | 70303.4 | 72833.6 |
| Utility of achieving <EASI 50 (first cycle) - Soc/Placebo | 0.64 | 0.78 | 70325 | 72827 |
| Probability of initial transition EASI 75 - Baricitinib | 0.12 | 0.14 | 72830.6 | 70368.6 |
| Annual Direct Cost - EASI 50 | 9090.52 | 11110.64 | 70324 | 72784 |

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

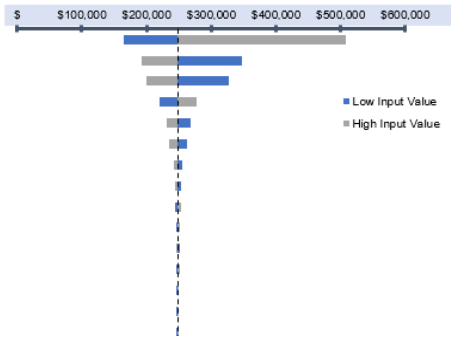
**Figure E3.3 Tornado Diagram for Tralokinumab versus Standard of Care**




| Parameter | Low Input Value | high Input Valu | Low Result | High Result |
|---|---|---|---|---|
| Utility of non-responder state (off treatment) - Soc/Placebo | 0.54 | 0.66 | 68843 | 1079007 |
| Utility of non-responder state (off treatment) - Tralokinuma | 0.54 | 0.66 | 357713.6 | 79007.4 |
| Utility of achieving EASI 90 (on treatment) - Tralokinumab | 0.79 | 0.97 | 155284 | 110953 |
| Utility of achieving EASI 50 (on treatment) - Tralokinumab | 0.72 | 0.88 | 148596.3 | 114640.3 |
| Cost per dose - Net price - Tralokinumab | 1073.94 | 1312.6 | 112694 | 146162 |
| Utility of achieving EASI 75 (on treatment) - Tralokinumab | 0.76 | 0.93 | 147472 | 115318 |
| Annual Direct Cost - Non-Responder | 16729.76 | 20447.48 | 136914 | 121943 |
| Utility of achieving EASI 50 (on treatment) - Soc/Placebo | 0.72 | 0.88 | 125547 | 133557 |
| Risk of discontinuation - SoC | 0.23 | 0.28 | 132707.8 | 126759.3 |
| Probability of initial transition EASI 90 - Tralokinumab | 0.16 | 0.19 | 132463.2 | 126694.9 |
| Utility of achieving EASI 75 (on treatment) - Soc/Placebo | 0.76 | 0.93 | 126617 | 132367 |
| Utility of achieving EASI 90 (on treatment) - Soc/Placebo | 0.79 | 0.97 | 127065 | 131881 |

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

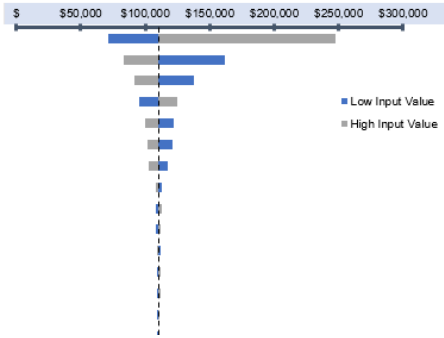
**Figure E3.4 Tornado Diagram for Upadacitinib versus Standard of Care**




| Parameter | Low Input Value | high Input Valu | Low Result | High Result |
|---|---|---|---|---|
| Utility of non-responder state (off treatment) - Soc/Placebo | 0.54 | 0.66 | 164320 | 508651 |
| Utility of non-responder state (off treatment) - Upadacitinib | 0.54 | 0.66 | 348031 | 193112 |
| Utility of achieving EASI 90 (on treatment) - Upadacitinib | 0.79 | 0.97 | 327231 | 200171 |
| Cost per dose - Net price - Upadacitinib | 156.2 | 190.92 | 219899 | 276893 |
| Utility of achieving EASI 75 (on treatment) - Upadacitinib | 0.76 | 0.93 | 269098 | 230652 |
| Utility of achieving EASI 50 (on treatment) - Upadacitinib | 0.72 | 0.88 | 262915 | 235396 |
| Annual Direct Cost - Non-Responder | 16729.76 | 20447.48 | 255371 | 241421 |
| Probability of initial transition EASI 90 - Upadacitinib | 0.45 | 0.55 | 253352.4 | 244135.9 |
| Utility of achieving EASI 50 (on treatment) - Soc/Placebo | 0.72 | 0.88 | 244010 | 252943 |
| Utility of achieving EASI 75 (on treatment) - Soc/Placebo | 0.76 | 0.93 | 245231 | 251644 |
| Risk of discontinuation - SoC | 0.23 | 0.28 | 251620.2 | 245733.1 |
| Utility of achieving EASI 90 (on treatment) - Soc/Placebo | 0.79 | 0.97 | 245738 | 251112 |
| Annual Direct Cost - EASI 90 | 7736.11 | 9455.25 | 246203 | 250589 |
| Utility of achieving <EASI 50 (first cycle) - Soc/Placebo | 0.64 | 0.78 | 246407 | 250417 |
| Risk of discontinuation - Upadacitinib | 0.07 | 0.08 | 246855.9 | 249958.5 |
| Probability of initial transition EASI 50 - Placebo/SoC | 0.09 | 0.11 | 247140.9 | 249662.1 |

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

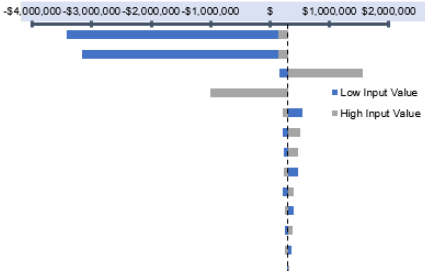
**Figure E3.5 Tornado Diagram for Dupilumab versus Standard of Care**




| Parameter | Low Input Value | high Input Valu | Low Result | High Result |
|---|---|---|---|---|
| Utility of non-responder state (off treatment) - Soc/Placebo | 0.54 | 0.66 | 70958 | 247334 |
| Utility of non-responder state (off treatment) - Dupilumab | 0.54 | 0.66 | 162211 | 83534 |
| Utility of achieving EASI 90 (on treatment) - Dupilumab | 0.79 | 0.97 | 137503 | 92052 |
| Cost per dose - Net price - Dupilumab | 1073.94 | 1312.6 | 95522 | 125034 |
| Utility of achieving EASI 75 (on treatment) - Dupilumab | 0.76 | 0.93 | 122434 | 100318 |
| Utility of achieving EASI 50 (on treatment) - Dupilumab | 0.72 | 0.88 | 120731 | 101491 |
| Annual Direct Cost - Non-Responder | 16729.76 | 20447.48 | 117519 | 103037 |
| Probability of initial transition EASI 90 - Dupilumab | 0.29 | 0.35 | 112654.0 | 108180.7 |
| Utility of achieving EASI 50 (on treatment) - Soc/Placebo | 0.72 | 0.88 | 108172 | 112468 |
| Annual Direct Cost - EASI 90 | 7736.11 | 9455.25 | 108493 | 112063 |
| Risk of discontinuation - SoC | 0.23 | 0.28 | 112095.9 | 108779.6 |
| Utility of achieving EASI 75 (on treatment) - Soc/Placebo | 0.76 | 0.93 | 108758 | 111842 |
| Utility of achieving EASI 90 (on treatment) - Soc/Placebo | 0.79 | 0.97 | 109002 | 111585 |
| Utility of achieving <EASI 50 (first cycle) - Soc/Placebo | 0.64 | 0.78 | 109323 | 111251 |
| Annual Direct Cost - EASI 75 | 8019.15 | 9801.19 | 109396 | 111161 |

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

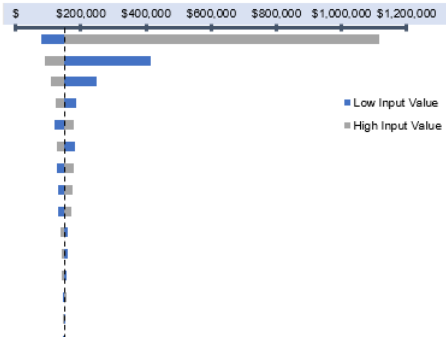
**Figure E3.6. Tornado Diagram for Abrocitinib versus Dupilumab**




| Parameter | Low Input Value | high Input Valu | Low Result | High Result |
|---|---|---|---|---|
| Utility of non-responder state (off treatment) - Abrocitinib | 0.54 | 0.66 | -3429419.6 | 145252.0 |
| Utility of achieving EASI 90 (on treatment) - Abrocitinib | 0.79 | 0.97 | -3160624.7 | 144730.6 |
| Utility of achieving EASI 90 (on treatment) - Dupilumab | 0.79 | 0.97 | 167938 | 1566339 |
| Utility of non-responder state (off treatment) - Dupilumab | 0.54 | 0.66 | 131674 | -998458 |
| Utility of achieving EASI 75 (on treatment) - Abrocitinib | 0.76 | 0.93 | 540174.9 | 210892.9 |
| Utility of achieving EASI 75 (on treatment) - Dupilumab | 0.76 | 0.93 | 216010 | 509275 |
| Utility of achieving EASI 50 (on treatment) - Dupilumab | 0.72 | 0.88 | 224275 | 468562 |
| Utility of achieving EASI 50 (on treatment) - Abrocitinib | 0.72 | 0.88 | 465353.1 | 225018.0 |
| Cost per dose - Net price - Abrocitinib | 102.01 | 124.67 | 209310 | 397395 |
| Probability of initial transition EASI 90 - Abrocitinib | 0.37 | 0.45 | 404543.7 | 254010.4 |
| Probability of initial transition EASI 90 - Dupilumab | 0.29 | 0.35 | 257092.0 | 380996.8 |
| Cost per dose - Net price - Dupilumab | 1073.94 | 1312.6 | 363445 | 243259 |
| Probability of initial transition EASI 75 - Dupilumab | 0.15 | 0.18 | 280553.4 | 332178.1 |

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

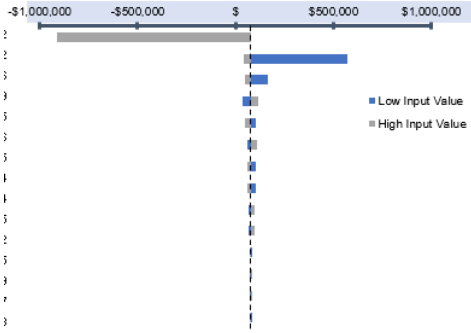
## Figure E3.7 Tornado Diagram for Baricitinib versus Dupilumab




| Parameter | Low Input Value | high Input Valu | Low Result | High Result |
|---|---|---|---|---|
| Utility of non-responder state (off treatment) - Baricitinib | 0.54 | 0.66 | 79830.1 | 1117767.5 |
| Utility of non-responder state (off treatment) - Dupilumab | 0.54 | 0.66 | 414433 | 90840 |
| Utility of achieving EASI 90 (on treatment) - Dupilumab | 0.79 | 0.97 | 246744 | 106741 |
| Utility of achieving EASI 75 (on treatment) - Dupilumab | 0.76 | 0.93 | 185949 | 124325 |
| Cost per dose - Net price - Dupilumab | 1073.94 | 1312.6 | 119500 | 178535 |
| Utility of achieving EASI 50 (on treatment) - Dupilumab | 0.72 | 0.88 | 180232 | 127019 |
| Utility of achieving EASI 90 (on treatment) - Baricitinib | 0.79 | 0.97 | 127328.9 | 179611.5 |
| Utility of achieving EASI 50 (on treatment) - Baricitinib | 0.72 | 0.88 | 130961.1 | 172849.2 |
| Utility of achieving EASI 75 (on treatment) - Baricitinib | 0.76 | 0.93 | 131989.3 | 171090.0 |
| Cost per dose - Net price - Baricitinib | 47.81 | 58.43 | 159978 | 138057 |
| Probability of initial transition EASI 90 - Dupilumab | 0.29 | 0.35 | 159612.2 | 140767.3 |
| Annual Direct Cost - Non-Responder | 16729.76 | 20447.48 | 156020 | 142015 |
| Probability of initial transition EASI 90 - Baricitinib | 0.15 | 0.18 | 143133.7 | 155565.2 |
| Risk of discontinuation - Baricitinib | 0.07 | 0.08 | 153807.7 | 144859.3 |
| Probability of initial transition EASI 75 - Baricitinib | 0.12 | 0.14 | 145055.2 | 153285.7 |

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

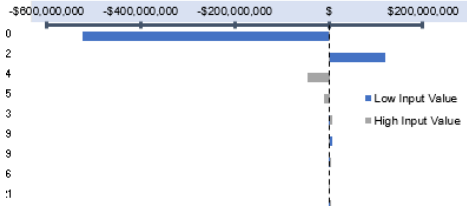
## Figure E3.8 Tornado Diagram for Tralokinumab versus Dupilumab




| Parameter | Low Input Value | high Input Valu | Low Result | High Result |
|---|---|---|---|---|
| Utility of non-responder state (off treatment) - Tralokinuma | 0.54 | 0.66 | 37274.5 | -913850.5 |
| Utility of non-responder state (off treatment) - Dupilumab | 0.54 | 0.66 | 573516 | 41684 |
| Utility of achieving EASI 90 (on treatment) - Dupilumab | 0.79 | 0.97 | 167005 | 50643 |
| Cost per dose - Net price - Dupilumab | 1073.94 | 1312.6 | 37875 | 117563 |
| Cost per dose - Net price - Tralokinumab | 1073.94 | 1312.6 | 106170 | 49268 |
| Utility of achieving EASI 90 (on treatment) - Tralokinumab | 0.79 | 0.97 | 60571 | 108410 |
| Utility of achieving EASI 75 (on treatment) - Dupilumab | 0.76 | 0.93 | 106188 | 61288 |
| Utility of achieving EASI 50 (on treatment) - Dupilumab | 0.72 | 0.88 | 101432 | 62993 |
| Utility of achieving EASI 50 (on treatment) - Tralokinumab | 0.72 | 0.88 | 63739.7 | 99552.9 |
| Utility of achieving EASI 75 (on treatment) - Tralokinumab | 0.76 | 0.93 | 64335 | 98134 |
| Annual Direct Cost - Non-Responder | 16729.76 | 20447.48 | 84545 | 70893 |
| Annual Direct Cost - EASI 90 | 7736.11 | 9455.25 | 75313 | 80125 |
| Probability of initial transition EASI 50 - Dupilumab | 0.14 | 0.17 | 75673.6 | 79540.6 |
| Probability of initial transition EASI 50 - Tralokinumab | 0.13 | 0.16 | 79431.2 | 75810.3 |
| Utility of achieving <EASI 50 (first cycle) - Tralokinumab | 0.64 | 0.78 | 76469.4 | 79010.2 |

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

**Figure E3.9 Tornado Diagram for Upadacitinib versus Dupilumab**




| Parameter | Low Input Value | high Input Valu | Low Result | High Result |
|---|---|---|---|---|
| Utility of achieving EASI 75 (on treatment) - Upadacitinib | 0.76 | 0.93 | -523407060 | 954356 |
| Probability of initial transition EASI 90 - Upadacitinib | 0.45 | 0.55 | 120218472.8 | 1056211.4 |
| Utility of achieving EASI 50 (on treatment) - Dupilumab | 0.72 | 0.88 | 936001 | -44526563 |
| Utility of achieving EASI 75 (on treatment) - Dupilumab | 0.76 | 0.93 | 870749 | -9754196 |
| Probability of initial transition EASI 90 - Dupilumab | 0.29 | 0.35 | 1125055.9 | 7402901.6 |
| Utility of achieving EASI 50 (on treatment) - Upadacitinib | 0.72 | 0.88 | 6840672 | 1111442 |
| Risk of discontinuation - Upadacitinib | 0.07 | 0.08 | 1349859.0 | 3386682.9 |
| Utility of achieving EASI 90 (on treatment) - Dupilumab | 0.79 | 0.97 | 564887 | -1380550 |
| Probability of initial transition EASI 75 - Dupilumab | 0.15 | 0.18 | 1443250.2 | 2875866.7 |

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

**Table E.3. Results of Probabilistic Sensitivity Analysis for Interventions versus Standard of Care and Dupilumab**

| PSA Results: Credible Ranges for the Incremental Cost-Effectiveness Ratios | | | | | | |
|---|---|---|---|---|---|---|
| | Intervention | | Comparator | | Incremental | |
| | Mean | Credible Range | Mean | Credible Range | Mean | Credible Range |
| **Abrocitinib vs SoC** | | | | | | |
| **Total Costs** | $184,796.41 | ($171,640 - $199,554) | $87,294.14 | ($78,966 - $95,735) | $97,502.27 | ($92,674 - $103,819) |
| **Total QALYs** | 3.63 | (3.44 - 3.82) | 2.99 | (2.72 - 3.26) | 0.65 | (0.71 - 0.56) |
| **ICER** | | | | | $150,587.32 | ($129,766 - $185,250) |
| **Baricitinib vs SoC** | | | | | | |
| **Total Costs** | $102,520.36 | ($94,665 - $110,261) | $87,294.14 | ($78,966 - $95,735) | $15,226.22 | ($15,699 - $14,525) |
| **Total QALYs** | 3.18 | (2.93 - 3.41) | 2.99 | (2.72 - 3.26) | 0.19 | (0.21 - 0.15) |
| **ICER** | | | | | $80,212.86 | ($76,177 - $100,000) |
| **Tralokinumab vs SoC** | | | | | | |
| **Total Costs** | $119,605.79 | ($111,474 - $128,004) | $87,294.14 | ($78,966 - $95,735) | $32,311.65 | ($32,508 - $32,268) |
| **Total QALYs** | 3.22 | (3.00 - 3.45) | 2.99 | (2.72 - 3.26) | 0.23 | (0.27 - 0.18) |
| **ICER** | | | | | $138,765.04 | ($118,531 - $174,722) |
| **Upadacitinib vs SoC** | | | | | | |
| **Total Costs** | $225,978.46 | ($208,645 - $243,601) | $87,294.14 | ($78,966 - $95,735) | $138,684.31 | ($129,679 - $147,866) |
| **Total QALYs** | 3.56 | (3.31 - 3.76) | 2.99 | (2.72 - 3.26) | 0.57 | (0.59 - 0.50) |
| **ICER** | | | | | $244,292.28 | ($220,579 - $296,778) |
| **Dupilumab vs SoC** | | | | | | |

| PSA Results: Credible Ranges for the Incremental Cost-Effectiveness Ratios | | | | | | |
|---|---|---|---|---|---|---|
| **Total Costs** | $145,143.99 | ($135,673 - $154,619) | $87,294.14 | ($78,966 - $95,735) | $57,849.84 | ($56,707 - $58,884) |
| **Total QALYs** | 3.51 | (3.30 - 3.70) | 2.99 | (2.72 - 3.26) | 0.52 | (0.57 - 0.44) |
| **ICER** | | | | | $111,171.08 | ($98,772 - $133,717) |
| **Abrocitinib vs Dupilumab** | | | | | | |
| **Total Costs** | $184,796.41 | ($171,640 - $199,554) | $145,143.99 | ($135,673 - $154,619) | $39,652.42 | ($35,968 - $44,934) |
| **Total QALYs** | 3.63 | (3.44 - 3.82) | 3.51 | (3.30 - 3.70) | 0.13 | (0.14 - 0.12) |
| **ICER** | | | | | $311,948.32 | ($256,828 - $374,276) |
| **Baricitinib vs Dupilumab** | | | | | | |
| **Total Costs** | $102,520.36 | ($94,665 - $110,261) | $145,143.99 | ($135,673 - $154,619) | -$42,623.63 | (-$41,007 - -$44,359) |
| **Total QALYs** | 3.18 | (2.93 - 3.41) | 3.51 | (3.30 - 3.70) | -0.33 | (-0.37 - -0.30) |
| **ICER** | | | | | Less Costly, Less Effective | Less Costly, Less Effective |
| **Tralokinumab vs Dupilumab** | | | | | | |
| **Total Costs** | $119,605.79 | ($111,474 - $128,004) | $145,143.99 | ($135,673 - $154,619) | -$25,538.19 | (-$24,199 - -$26,616) |
| **Total QALYs** | 3.22 | (3.00 - 3.45) | 3.51 | (3.30 - 3.70) | -0.29 | (-0.30 - -0.26) |
| **ICER** | | | | | Less Costly, Less Effective | Less Costly, Less Effective |
| **Upadacitinib vs Dupilumab** | | | | | | |
| **Total Costs** | $225,978.46 | ($208,645 - $243,601) | $145,143.99 | ($135,673 - $154,619) | $80,834.47 | ($72,973 - $88,981) |
| **Total QALYs** | 3.56 | (3.31 - 3.76) | 3.51 | (3.30 - 3.70) | 0.05 | (0.01 - 0.06) |
| **ICER** | | | | | $1,707,871.35 | ($5,293,659 - $1,537,610) |

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life-year, SoC: standard of care

**Figure E3.4. Results of Probabilistic Sensitivity Analysis for Cost Effectiveness at Different Thresholds**

| | Vs SoC | | | | |
|---|---|---|---|---|---|
| **Cost-Effectiveness Threshold** | **Abrocitinib*** | **Baricitinib** | **Tralokinumab*** | **Upadacitinib** | **Dupilumab** |
| $50,000 | 0% | 45% | 12% | 0% | 0% |
| $100,000 | 3% | 74% | 43% | 0% | 38% |
| $150,000 | 49% | 85% | 65% | 3% | 76% |
| $200,000 | 82% | 90% | 75% | 25% | 92% |
| | **Vs Dupilumab** | | | | |
| **Cost-Effectiveness Threshold** | **Abrocitinib*** | **Baricitinib** | **Tralokinumab*** | **Upadacitinib** | |
| $50,000 | 0% | 0% | 0% | 0% | |
| $100,000 | 0% | 0% | 0% | 0% | |
| $150,000 | 0% | 0% | 0% | 0% | |
| $200,000 | 0% | 0% | 0% | 0% | |

SoC: standard of care

# E4. Scenario Analyses

## Scenario Analysis 1 – Modified Societal Perspective

We included productivity loss due to moderate-to-severe AD as indirect costs by health state. We derived estimates by health state using responses to the Workplace Productivity and Activity Impairment (WPAI) questionnaire, collected in the upadacitinib clinical trials. The work productivity loss percentage scores were multiplied by the average annual US wages from the US Social Security Administration and adjusted to per-cycle values.[148]

**Table E4.1. Scenario Analysis Inputs – Productivity Loss**

| Health State | Value | Source |
|---|---|---|
| **Non-responder** | [redacted] | MEASURE UP 1 & 2 |
| **EASI 50** | | |
| **EASI 75** | | |
| **EASI 90** | | |

EASI: Eczema Area Severity Index, SE: standard error

The total discounted costs, quality-adjusted life years (QALYs), life years (LYs), and equal value of life years gained (evLYG) over the five-year time horizon under the modified societal perspective are presented in Table E4.2 The drug costs and patient outcomes remained the same compared to the base case, and the table shows the base case total costs for comparison. The total cost from the modified societal perspective versus the base case increased by 10-26% for the interventions and 36% for standard of care.

**Table E4.2. Results for the Modified Societal Perspective Scenario Analysis**

| Treatment | Base Case Total Cost | Scenario Total Cost | QALYs | Life Years | evLYGs |
|---|---|---|---|---|---|
| **Abrocitinib*** | $178,400 | $199,700 | 3.59 | 4.85 | 3.59 |
| **Baricitinib** | $105,300 | $132,800 | 3.23 | 4.85 | 3.23 |
| **Tralokinumab*** | $127,700 | $154,200 | 3.29 | 4.85 | 3.29 |
| **Upadacitinib** | $219,700 | $242,100 | 3.51 | 4.85 | 3.51 |
| **Dupilumab** | $141,900 | $165,300 | 3.47 | 4.85 | 3.47 |
| **Standard of Care** | $87,800 | $119,100 | 2.98 | 4.85 | 2.98 |

*Using a placeholder price

Table E4.3 presents the incremental results from the modified societal perspective scenario analysis, which include incremental cost-effectiveness ratios for incremental cost per LY gained, incremental cost per QALY gained, and incremental cost per evLYG gained. Incremental cost-effectiveness ratios from the modified societal perspective versus the base case when applying the standard of care comparator decreased by 7% to 22% across the therapies evaluated.

**Table E4.3. Incremental Cost-Effectiveness Ratios for the Modified Societal Perspective Analysis**

| Treatment | Comparator | Cost per QALY Gained | Cost per Life Year Gained | Cost per evLYG |
|---|---|---|---|---|
| **Abrocitinib*** | SoC | $133,900 | $- | $133,900 |
| **Baricitinib** | SoC | $58,100 | $- | $58,100 |
| **Tralokinumab*** | SoC | $115,900 | $- | $115,900 |
| **Upadacitinib** | SoC | $233,700 | $- | $233,700 |
| **Dupilumab** | SoC | $96,200 | $- | $96,200 |
| **Abrocitinib*** | Dupilumab | $287,700 | $- | $287,700 |
| **Baricitinib** | Dupilumab | Less Costly, Less Effective | $- | Less Costly, Less Effective |
| **Tralokinumab*** | Dupilumab | Less Costly, Less Effective | $- | Less Costly, Less Effective |
| **Upadacitinib** | Dupilumab | $1,890,300 | $- | $1,890,300 |

SOC: Standard of Care; QALY: quality adjusted life-year; evLYG: equal value life year gained;

*Using a placeholder price

## Scenario Analysis 2 – Lifetime Time Horizon

We extended the model time horizon from 5 years to lifetime in this scenario to capture longer term value, though we note that only one line of treatment was modeled in order to focus on the comparisons of interest.

**Table E4.4. Results for the Lifetime Time Horizon Scenario**

| Treatment | Drug Cost | Total Cost | QALYs | Life Years | evLYGs |
|---|---|---|---|---|---|
| **Abrocitinib*** | $200,631 | $585,944 | 15.82 | 24.31 | 15.82 |
| **Baricitinib** | $34,302 | $448,118 | 15.01 | 24.31 | 15.01 |
| **Tralokinumab*** | $77,924 | $485,329 | 15.19 | 24.31 | 15.19 |
| **Upadacitinib** | $195,831 | $597,035 | 15.39 | 24.31 | 15.39 |
| **Dupilumab** | $112,250 | $509,336 | 15.49 | 24.31 | 15.49 |
| **Standard of Care** | $0 | $426,060 | 14.67 | 24.31 | 14.67 |

eVLYG: equal-value life-years gained, QALY: quality-adjusted life-year

*Using a placeholder price

**Table E4.5. Incremental Cost-Effectiveness Ratios for the Lifetime Time Horizon Scenario**

| Treatment | Comparator | Cost per QALY Gained | Cost per Life Year Gained | Cost per evLYG |
|---|---|---|---|---|
| **Abrocitinib*** | SoC | $136,784 | $- | $136,784 |
| **Baricitinib** | SoC | $63,159 | $- | $63,159 |
| **Tralokinumab*** | SoC | $113,150 | $- | $113,150 |
| **Upadacitinib** | SoC | $237,668 | $- | $237,668 |
| **Dupilumab** | SoC | $100,408 | $- | $100,408 |
| **Abrocitinib*** | Dupilumab | $224,072 | $- | $224,072 |
| **Baricitinib** | Dupilumab | Less Costly, Less Effective | $- | Less Costly, Less Effective |
| **Tralokinumab*** | Dupilumab | Less Costly, Less Effective | $- | Less Costly, Less Effective |
| **Upadacitinib** | Dupilumab | Dominated | $- | Dominated |

SOC: Standard of Care

*Using a placeholder price

Table E4.5 presents the incremental results from the lifetime time horizon scenario analysis, which include incremental cost-effectiveness ratios for incremental cost per LY gained, incremental cost per QALY gained, and incremental cost per evLYG gained. Incremental cost-effectiveness ratios from the lifetime time horizon versus the base-case five-year horizon when applying the standard of care comparator decreased by 4% to 13% across the therapies evaluated. Compared to dupilumab, upadacitinib became dominated in the lifetime scenario.

## Scenario Analysis 3 – Abrocitinib with a 12-week Initial Cycle

In phase III trials JADE MONO-1 and 2, Abrocitinib and placebo arms were evaluated at 12-weeks rather than 16-weeks (therapies were evaluated at 16 weeks in JADE COMPARE and in every other trial for included AD therapies). In the base-case model, Abrocitinib's initial impact on patients was evaluated at the end of the first 16-week cycle. To test the impact of this assumption, we built a scenario where Abrocitinib patients were evaluated at 12 weeks. Decreasing the initial cycle from 16-weeks to 12-weeks had no effect on total QALYs or life-years; changes in drug costs drove changes in total costs and ICERs by small amounts presented in table E4.6.

**Table E4.6. Effect of 12-week Initial Cycle on Dupilumab Costs**

| Abrocitinib Outcomes | Base Case (16-week initial cycle) | Alternative Scenario (12-week initial cycle) | % Difference |
|---|---|---|---|
| **Drug Cost** | $113,174 | $111,631 | -1.4% |
| **Total Cost** | $178,362 | $176,762 | -0.9% |
| **ICER vs SoC** | $148,341 | $146,927 | -1.0% |
| **ICER vs Dupilumab** | $303,352 | $302,661 | -0.2% |

ICER: incremental cost-effectiveness ratio, SoC: standard of care

## Scenario Analysis 4 – Combination therapy with topical corticosteroids

Several clinical trials for emerging atopic dermatitis therapies allowed patients to use topical corticosteroids (TCS) in combination with the therapies being assessed, including JADE COMPARE, ECZTRA 3, AD UP, BREEZE AD 7, LIBERTY AD CHRONOS, and Guttmann-Yassky (2018). The use of TCS changes clinical outcomes and is therefore assessed in a scenario analysis separate from the base case analysis. Initial response health state transition probabilities, reported in Table E4.7, were derived from a fixed effects network meta-analysis using data from the aforementioned studies. In addition to differential initial health state transitions, we assumed that patients would use one 60 ml tube of over-the-counter mometasone furoate (a common brand of TCS) per 16-week cycle, whose average wholesale price was $57 (NDC 68462-0385-02)[149].

Drug costs and total costs were higher in the combination therapy scenario for all therapies, with increases ranging from 6-36%. Total costs decreased by 2% for those on standard of care plus TCS. QALYs increased 2-4% across all therapies and SoC in the combination therapy scenario.

Incremental cost-effectiveness results were all nominally larger (9-14%) in the combination therapy scenario when compared to standard of care/placebo but remained in the same order of cost effectiveness. No therapies changed relationship to a cost-effectiveness threshold. When compared to dupilumab, both baricitinib and tralokinumab remained less costly and less effective, however dupilumab switches to dominate upadacitinib in the combination therapy scenario.

**Table E4.7. Initial Response Health State Transition Probabilities from the Network Meta-Analysis of Combination Therapy Trials**

| Treatment | EASI<50 | EASI 50-74 | EASI 75-89 | EASI 90-100 |
|---|---|---|---|---|
| Placebo | 56% | 19% | 14% | 10% |
| Abrocitinib 200 mg | [redacted] | | | |
| Baricitinib 2 mg | | | | |
| Tralokinumab 300 mg | | | | |
| Upadacitinib 30 mg | | | | |
| Dupilumab 300 mg Q2W | | | | |

**Table E4.8. Results for the Combination Therapy Scenario**

| Treatment | Drug Cost† | Total Cost | QALYs | Life Years | evLYGs |
|---|---|---|---|---|---|
| **Abrocitinib*** | $128,700 | $191,200 | 3.7 | 4.8 | 3.7 |
| **Baricitinib** | $36,500 | $111,200 | 3.3 | 4.8 | 3.3 |
| **Tralokinumab*** | $69,000 | $140,800 | 3.4 | 4.8 | 3.4 |
| **Upadacitinib** | $171,600 | $237,600 | 3.6 | 4.8 | 3.6 |
| **Dupilumab** | $88,300 | $153,800 | 3.6 | 4.8 | 3.6 |
| **Standard of Care** | $- | $86,300 | 3.0 | 4.8 | 3.0 |

eVLYG: equal-value life-years gained, QALY: quality-adjusted life-year

*Using a placeholder price; †TCS included as a health state cost, not a drug cost

**Table E4.9. Incremental Cost-Effectiveness Ratios for the Combination Therapy Scenario**

| Treatment | Comparator | Cost per QALY Gained | Cost per Life Year Gained | Cost per evLYG |
|---|---|---|---|---|
| **Abrocitinib** | SoC | $163,400 | $- | $163,400 |
| **Baricitinib** | SoC | $81,800 | $- | $81,800 |
| **Tralokinumab** | SoC | $142,600 | $- | $142,600 |
| **Upadacitinib** | SoC | $270,600 | $- | $270,600 |
| **Dupilumab** | SoC | $120,600 | $- | $120,600 |
| **Abrocitinib** | Dupilumab | $452,900 | $- | $452,900 |
| **Baricitinib** | Dupilumab | Less Costly, Less Effective | $- | Less Costly, Less Effective |
| **Tralokinumab** | Dupilumab | Less Costly, Less Effective | $- | Less Costly, Less Effective |
| **Upadacitinib** | Dupilumab | Dominated (More Costly, Less Effective) | $- | Dominated (More Costly, Less Effective) |

SOC: Standard of Care

*Using a placeholder price

## Scenario Analysis 5 – A portion of responding patients on Tralokinumab switch from q2w to q4w

In a double-blind, placebo+TCS controlled phase III trial (ECZTRA3), patients who achieved EASI 75 and/or clear or almost clear skin after 16 weeks of treatment with tralokinumab every two weeks plus TCS were able to switch to dosing every four weeks. As the cost of treatment would decrease for those taking tralokinumab therapy less frequently, we employed a scenario analysis to assess the potential impact of this dosing schedule on cost-effectiveness estimates.

In ECZTRA3 clinical trial, patients who achieved IGA score of 0 or 1 and/or a minimum of an EASI75 score at the end of the 16-week trial period were rerandomized to receive an equal tralokinumab dose every 4 weeks (Q4W) or every 2 weeks (Q2W). In this scenario analysis, we assume no differential outcomes between the two dosing arms in the model as treatment response at week 32 was comparable between the two dosing arms (92.5% maintained a minimum EASI75 in the Q2W trial arm compared to 90.8% in the Q4W trial arm). We assume in this scenario analysis that 50% of patients achieving EASI75 or higher will switch to Q4W dosing; we make this assumption based on the manufacturer's analysis of the clinical trial data recognizing this is an estimate pending real world data. Because the clinical trial informing the analysis allowed patients to use concurrent TCS therapy, these results are only comparable to the scenario analysis of combination therapy.

The result for this scenario, where all patients achieving EASI75 or higher after the initial 16-week trial period switch to a Q4W dosing regimen, resulted in a 15% decrease in drug costs over a 5-year time horizon and an 8% decrease in total costs. Versus standard of care, tralokinumab's ICER decreased 20% to $115,000 per additional QALY gained, however the therapy was still less effective and less costly than dupilumab. There were no changes in cost-effectiveness threshold categorization.

**Table E4.10. Effect of dosing change on Tralokinumab costs**

| Tralokinumab Outcomes | Base Case (all patients Q2W +TCS) | Alternative Scenario (all patients ≥EASI75 Q4W +TCS)* | % Difference |
|---|---|---|---|
| **Drug Cost** | $69,044 | $58,401 | -15% |
| **Total Cost** | $140,776 | $130,132 | -8% |
| **ICER vs SoC** | $142,646 | $114,765 | -20% |
| **ICER vs Dupilumab** | Less Costly, Less Effective | Less Costly, Less Effective | NA |

Q2W: dosed once every two weeks; Q4W: dosed once every four weeks;

*Switch to Q4W in scenario occurs after initial 16-week trial period and is dependent on their response at 16 weeks

## E5. Prior Economic Models

The results of the cross validation showed that our model results were similar to other available atopic dermatitis models. We identified two published economic evaluations of dupilumab for treatment of moderate to severe atopic dermatitis.[150,151] No prior economic evaluations of abrocitinib, baricitinib, upadacitinib, or tralokinumab were found.

Researchers in the US developed a 16-week decision tree linked to a Markov model estimating a price range in which dupilumab plus emollients would be considered cost-effective compared to emollients only (SOC) in adult patients with moderate to severe AD, using efficacy data form SOLO trials.[150] Their analysis used a US payer perspective over a lifetime horizon. The model included two health states, with patients who achieved ≥EASI 75 improvement after 16-week trial continuing on dupilumab, and non-responders switching to and remaining on SOC. After 4-month cycles, dupilumab patients could either continue to respond or transition to SOC or die. They applied utility values change from baseline in the model, with 0.21 for patients on dupilumab, 0.03 for patients on SOC, and 0.25 for non-responders. They found that dupilumab produced 1.12 more QALYs than SOC (15.95 vs 14.83) and $32,089 additional non-dupilumab drug costs ($299,449 vs $331,538). Although their model did not generate an incremental cost-effectiveness ratio, the QALYs and lifetime non-dupilumab drug costs estimates are similar to ours.

Costanzo and colleagues estimated the cost effectiveness of dupilumab plus SOC vs SOC in the Italian adult population with severe AD, using a 1-year decision tree followed by a lifetime horizon Markov model.[151] Their analysis adopted the Italian National Health Service perspective, with utility values of 0.66 at baseline for both groups, 0.95 for dupilumab and 0.78 for SOC after week 16, and 0.78 for non-responder group. They found that dupilumab generated 2.42 more QALYs than SOC (16.96 vs 14.57), with an incremental cost-effectiveness ratio of € 33,263 per QALY gained. The results from their analyses are not directly comparable to the results of the cost-effectiveness analysis presented in this report, due to different severity of disease in two populations. However, it is interesting to note that the utility values of dupilumab used in their study are slightly higher than values used in our model. Whereas we used same utility values to dupilumab and SOC, ranging from 0.81 to 0.89 for responders and 0.60 for non-responder.

In the 2017 ICER report, we estimated the cost effectiveness of dupilumab for moderate-to-severe AD compared to usual care over a lifetime horizon from a US health system perspective.[117] We found that dupilumab produced 1.91 more QALYs than usual care (16.28 vs 14.37), with an incremental cost-effectiveness ratio of $101,830 per QALY gained. The model results in this analysis were similar to the prior ICER report.

# F. Potential Budget Impact: Supplemental Information

## Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapies (i.e., usual care, dupilumab) for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we used inputs from the US market leading biologic therapy, dupilumab, across the following age categories (12-17 years old; and 18 and older).[152] We note that limitations exist in using cost-effectiveness model findings within the adult population for estimating the potential budget impact within younger ages but consider those limitations to be outweighed by a comprehensive approach that includes all eligible age categories. For adults (18 years and older), evidence suggests 1,675,000 US individuals have moderate-to-severe uncontrolled disease and are eligible for treatment.[152] For adolescents (age 12-17), evidence suggests 389,000 US individuals have moderate-to-severe uncontrolled disease and are eligible for treatment.[152] For the purposes of this analysis, we summed across the two age categories and assumed that 20% of these patients would initiate new treatments in each of the five years, or 412,800 patients per year.

Consistent with the ICER Reference Case, we calculated the budget impact of new treatments (abrocitinib, baricitinib, tralokinumab, and upadacitinib) given these treatments' displacement of dupilumab and usual care. We assigned an equal distribution of annually eligible individuals for each of the four treatments (abrocitinib, baricitinib, tralokinumab, and upadacitinib) = 412,800 / 4 = 103,200 new individuals per treatment per year (for five years). Per the ICER Reference Case, we assumed that all the dupilumab users switch over to each of the four new treatments in the potential budget impact analyses. We assumed that approximately 2.5% of those adolescents and adults eligible in the US are currently taking dupilumab (approximately 51,600) based on reports that over 100,000 US patients have started dupilumab.[153] This assumption results in a 10% mix of dupilumab and 90% mix of usual care alone upon which each new treatment is evaluated.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[154,155] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

The five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $819 million per year for new drugs for 2019-2020.

## Results

Table F.1 illustrates the per-patient budget impact results in more detail, for:

- Abrocitinib WAC ($46,600* per year), discounted WAC ($41,400* per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY ($41,800, $30,600, and $19,400 per year, respectively) compared to usual care;
- Baricitinib WAC ($29,000 per year), discounted WAC ($19,400 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY ($33,300, $24,400, and $15,600 per year, respectively) compared to usual care;
- Tralokinumab WAC ($41,800*per year), discounted WAC ($31,100* per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY ($35,000, $25,700, and $16,400 per year, respectively) compared to usual care and;
- Upadacitinib WAC ($64,300 per year), discounted WAC ($63,400 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY ($41,500, $30,400, and $19,300 per year, respectively) compared to usual care.

* Based on placeholder prices that were assumed for abrocitinib and tralokinumab. Interpret findings with caution.

We note that dupilumab is considered a part of usual care and therefore not displayed as a standalone result.

**Table F1. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon**

| | Average Annual Per Patient Budget Impact | | | | |
|---|---|---|---|---|---|
| | **WAC*** | **Discounted WAC*** | **$150,000/QALY** | **$100,000/QALY** | **$50,000/QALY** |
| **Abrocitinib vs. usual care** | $31,200 | $27,600 | $27,300 | $18,800 | $10,300 |
| **Baricitinib vs. usual care** | $8,600 | $5,000 | $10,700 | $7,400 | $4,100 |
| **Tralokinumab vs. usual care** | $16,500 | $11,700 | $13,100 | $9,100 | $5,000 |
| **Upadacitinib vs. usual care** | $38,300 | $38,400 | $22,400 | $15,200 | $8,100 |

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

* Placeholder prices were assumed for abrocitinib and tralokinumab. Interpret findings with caution.

Figures F.1-F.4 illustrate the cumulative per-patient budget impact calculations for abrocitinib, baricitinib, tralokinumab, and upadacitinib compared to usual care (including 10% of patients treated with dupilumab), based on the net prices used within the cost-effectiveness analysis. We suggest caution in interpreting the potential budget impact of abrocitinib and tralokinumab due to the placeholder annual net prices assumed. We observed the general trend of decreasing year over year per treated patient potential budget impacts due to treatment discontinuation over time. Year 4 in the cost-effectiveness model included an additional model cost cycle compared to the other years . The same year 4 method was applied across evaluated treatments and for usual care and therefore, we did not smooth over the year-by-year cumulative findings.

**Figure F1. Cumulative Net Cost Per Patient Treated with Abrocitinib for Five Years at Placeholder $41,400 per Year Price***


* Placeholder prices were assumed. Interpret findings with caution.

**Figure F2. Cumulative Net Cost Per Patient Treated with Baricitinib for Five Years at $19,400 per Year Price**

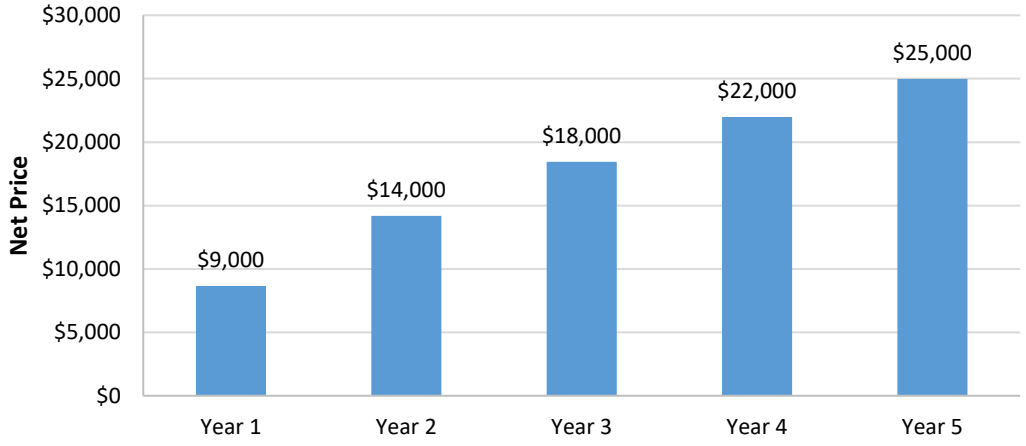
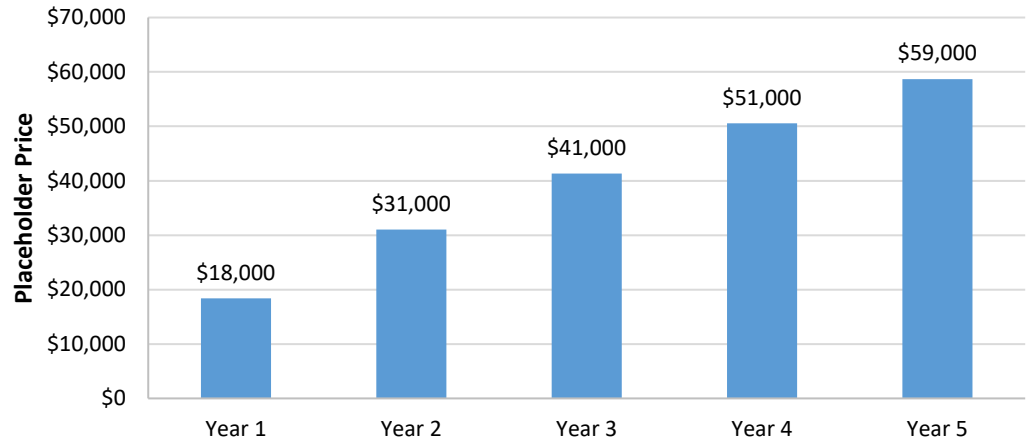
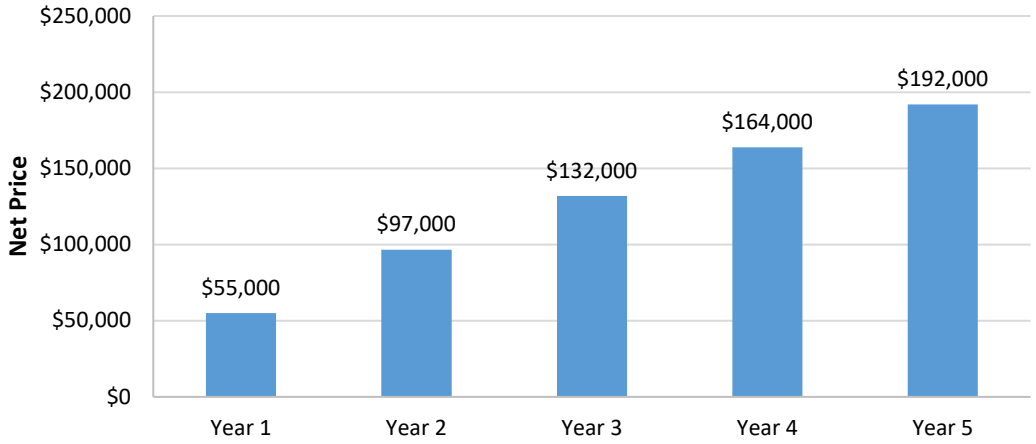


**Figure F3. Cumulative Net Cost Per Patient Treated with Tralokinumab for Five Years at Placeholder $31,100 per Year Price***




* Placeholder prices were assumed. Interpret findings with caution.

**Figure F4. Cumulative Net Cost Per Patient Treated with Upadacitinib for Five Years at $63,400 per Year Price**



# G. Additional Evidence Tables

*Moderate to Severe Population*

**Table G1.1. Study Quality Table**[35-37,40,42,45,46,48,50,51,56,63,64,69,82,83]

| Trial | Comparable Groups | Non-differential Follow-up | Patient/ Investigator Blinding | Clear Definition of Intervention | Clear Definition of Outcomes | Selective Outcome Reporting | Measurements Valid | Intention-to-treat Analysis | Approach to Missing Data | USPSTF Rating |
|---|---|---|---|---|---|---|---|---|---|---|
| **Abrocitinib** | | | | | | | | | | |
| **JADE MONO-1** | Yes | Yes | Yes | Yes | Yes | No | Yes | No | MI | Good |
| **JADE MONO-2** | Yes | No | Yes | Yes | Yes | No | Yes | No | MI | Good |
| **JADE COMPARE** | Yes | Yes | Yes | Yes | Yes | No | Yes | No | NRI | Good |
| **Gooderham 2019** | Yes | No | Yes | Yes | Yes | No | Yes | No | MI* | Fair |
| **Baricitinib** | | | | | | | | | | |
| **BREEZE-AD1** | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | MI and NRI | Good |
| **BREEZE-AD2** | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | MI and NRI | Good |
| **BREEZE-AD5** | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | MM** | Good |
| **BREEZE-AD7** | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | MM | Good |
| **Guttman-Yassky 2018** | Yes | No | Yes | Yes | Yes | No | Yes | Yes | MM | Good |
| **Tralokinumab** | | | | | | | | | | |
| **ECZTRA 1** | Yes | Yes | Yes | Yes | Yes | No | Yes | No | NRI and MI | Good |
| **ECZTRA 2** | Yes | Yes | Yes | Yes | Yes | No | Yes | No | NRI and MI | Good |
| **ECZTRA 3** | Yes | Yes | Yes | Yes | Yes | No | Yes | No | NRI and MI | Good |

| Trial | Comparable Groups | Non-differential Follow-up | Patient/ Investigator Blinding | Clear Definition of Intervention | Clear Definition of Outcomes | Selective Outcome Reporting | Measurements Valid | Intention-to-treat Analysis | Approach to Missing Data | USPSTF Rating |
|---|---|---|---|---|---|---|---|---|---|---|
| **Upadacitinib** | | | | | | | | | | |
| **MEASURE Up 1** | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | NRI and MM | Good |
| **MEASURE Up 2** | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | NRI and MM | Good |
| **AD-UP** | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | NRI and MM | Good |
| **Guttman-Yassky 2020** | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | LOCF and NRI | Good |
| **Dupilumab** | | | | | | | | | | |
| **LIBERTY AD SOLO 1** | Yes | Yes | Yes | Yes | Yes | No | Yes | No | MI, LOCF and NRI | Good |
| **LIBERTY AD SOLO 2** | Yes | Yes | Yes | Yes | Yes | No | Yes | No | MI, LOCF and NRI | Good |
| **LIBERTY AD CHRONOS** | Yes | Yes | Yes | Yes | Yes | No | Yes | No | MI | Good |
| **Thaci 2016** | Yes | Yes | Yes | Yes | Yes | No | Yes | No | LOCF and NRI | Good |

Includes only published RCTs. LOCF: last observation carried forward, MI: multiple imputation, MM: mixed-effects model, NRI: non-responder imputation.
*Mixed-effects model repeated measure and generalized linear mixed model assumption, **Mixed-effects model repeated measure.

**Table G1.2 Key Features**

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| **Abrocitinib** | | | | | |
| Phase III JADE MONO-1[35,76,156]<br><br>Simpson 2020 Lancet + Simpson 2021 RAD Abstract | N= 387<br><br>Ages 12+ with moderate to severe atopic dermatitis<br><br>DB, PC, RCT | Once-daily oral administration in one of the following doses for 12 weeks:<br><br>•Abrocitinib 200 mg<br>•Abrocitinib 100 mg<br>•Placebo | **Prohibited medication:** concomitant topical therapies (corticosteroids, calcineurin inhibitors, tars, antibiotic creams, and topical antihistamines)<br><br>•If receiving non-AD related concomitant medications, must be on stable regimen.<br>•Prior drug/non-drug treatment, concomitant drug and non-drug treatment summarized according to CaPS | •Age: ≥ 12 years with minimum body weight of 40 kg<br>•Diagnosis of atopic dermatitis (AD) for at ≥1 year and current status of moderate to severe disease (≥ the following scores: BSA 10%, IGA 3, EASI 16, Pruritus NRS severity 4<br>• Inability to tolerate topical AD treatments or require systemic treatments for AD control | •Unwilling to discontinue current AD medications prior to study or require treatment with prohibited medications during study<br>•Prior treatment with JAK inhibitors<br>•Other active non-AD skin diseases<br>•Medical history including thrombocytopenia, coagulopathy, or platelet dysfunction, current or history of certain infections, cancer, lymphoproliferative disorders |
| Phase III JADE MONO-2[36,76,157]<br><br>Silverberg 2020 JAMA Dermatology | N=391<br><br>Ages 12+ with moderate to severe atopic dermatitis<br><br>DB, PC, RCT | Once-daily oral administration in one of the following doses for 12 weeks:<br><br>•Abrocitinib 200 mg<br>•Abrocitinib 100 mg<br>•Placebo | **Permitted medication: O**ral antihistamines and topical non-medicated emollients<br><br>**Prohibited medication:** Concomitant use of topical (corticosteroids, calcineurin inhibitors, tars, antibiotic creams, or topical antihistamines) or systemic therapies for AD | •Age: ≥12 years with minimum body weight of 40 kg<br>•Diagnosis of atopic dermatitis (AD) for at ≥1 year and current status of moderate to severe disease (≥ the following scores: BSA 10%, IGA 3, EASI 16, Pruritus NRS severity 4<br>•Recent history of inadequate response or inability to tolerate topical AD treatments or require systemic treatments for AD control | •Unwilling to discontinue current AD medications prior to study or require treatment with prohibited medications during study<br>•Prior treatment with JAK inhibitors<br>•Other active non-AD skin diseases<br>•Medical history including thrombocytopenia, coagulopathy, or platelet dysfunction, current or history of certain infections, cancer, lymphoproliferative disorders |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| Phase III JADE TEEN[39,41,78,85]<br><br>Pfizer data on file + Eichenfield 2021 AAAI Abstract + Eichenfield 2021 RAD Abstract | N=285<br>Ages 12-17 with moderate to severe atopic dermatitis<br><br>DB, PC, RCT | Once-daily oral administration in one of the following doses for 12 weeks:<br><br>•Abrocitinib 200 mg<br>•Abrocitinib 100 mg<br>•Placebo | **Permitted medication:** background topical therapy<br><br>**Permitted medication:** NR | •Age: ≥12-17 years with minimum body weight of 40 kg<br>•Diagnosis of atopic dermatitis (AD) for at ≥1 year and current status of moderate to severe disease (≥ the following scores: BSA 10%, IGA 3, EASI 16, Pruritus NRS severity 4 | •Acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation<br>•Unwilling to discontinue current AD medications prior to the study or require treatment with prohibited medications during the study<br>•Prior treatment with JAK inhibitors<br>•Other active non-AD inflammatory skin diseases or conditions affecting skin<br>•Medical history including thrombocytopenia, coagulopathy or platelet dysfunction, malignancies, current or history of certain infections, lymphoproliferative disorders, and other medical conditions at the discretion of the investigator |
| Phase III JADE COMPARE[37,39]<br><br>Bieber 2021 NEMJ + Pfizer data on file | N= 837<br><br>Adults 18+ with moderate to severe atopic dermatitis<br><br>DB, PC, RCT | •Abrocitinib (200 mg) + placebo Q2W ( to Week 16)→abrocitinib (200 mg) (Week 20)<br>•Abrocitinib (100 mg) + placebo Q2W (to Week | Permitted/provided: non-medicated emollients at least twice a day and medicated topical therapy such as corticosteroids, calcineurin inhibitors, or PDE4 inhibitors, as per protocol guidance, to treat active lesions during study. | •18+ diagnosed with AD for ≥1 year and current status of moderate to severe disease (≥ the following scores: BSA 10%, IGA 3, EASI 16, Pruritus NRS severity 4)<br>•Documented recent history (within 6 months before screening) of inadequate | •Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior<br>•Medical history including thrombocytopenia, coagulopathy or platelet |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| | | 16) →abrocitinib (100 mg) (Week 20)<br>•Dupilumab (300 mg; with a 600 mg loading dose at baseline) + placebo once-daily to Week 16) →placebo once-daily (Week 20)<br>•Placebo + dupilumab Q2W (to Week 16) →abrocitinib (100 mg) (Week 20)<br>•Placebo + dupilumab Q2W (to Week 16) →abrocitinib (200 mg) (Week 20)<br>Placebo (to week 16) → placebo (week 20) | If receiving concomitant medications for any reason other than AD, must be on a stable regimen prior to Day 1 and through the duration of the study | response to treatment with medicated topical therapy for AD for at least 4 weeks, or who have required systemic therapies for control of their disease.<br>•Must be willing and able to comply with standardized background topical therapy | dysfunction, Q wave interval abnormalities, current or history of certain infections, cancer, lymphoproliferative disorders<br>•Other active nonAD inflammatory skin diseases or conditions affecting skin<br>•Prior treatment with JAK inhibitors<br>•Previous treatment with dupilumab<br>•Unwilling to discontinue current AD medications prior to study or require treatment with prohibited medications during study |
| Phase III JADE EXTEND[77,108]<br><br>Reich 2021 Abstract and Shi 2021 Abstract | N=1116<br><br>Ages 12+ moderate to severe AD | •Abrocitinib 200-mg<br>•Abrocitinib 100-mg | NR | •Patients ages 12+ and meets minimum body weight<br>•Must have completed full treatment period or the full rescue treatment period of a qualifying Parent study OR must have completed the full open-label run-in period in B7451014 and did not meet | •Other acute or chronic medical or psychiatric condition including recent (within the past year) or behavior or laboratory abnormality that may interfere with the study<br>•Currently have active forms of other inflammatory |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| | | | | the protocol-specified response criteria at Week 12<br>•Must avoid prolonged exposure to the sun, tanning booths, sun lamps or other ultraviolet light sources | skin diseases, i.e., not AD or have evidence of skin conditions (e.g., psoriasis, seborrheic dermatitis, Lupus)<br>•Discontinued from treatment early in a qualifying Parent study OR triggered a discontinuation criterion at any point during the qualifying Parent study which in the opinion of the investigator, or sponsor, is an ongoing safety concern<br>•Ongoing AE in the qualifying Parent study that is an ongoing safety concern |
| Phase IIb[40,158]<br><br>Gooderham 2019 | N= 267<br><br>Ages 18 to 75 with a clinical diagnosis of moderate to severe atopic dermatitis | Abrocitinib 10 mg<br>Abrocitinib 30 mg<br>**Abrocitinib 100 mg**<br>**Abrocitinib 200 mg**<br>**Placebo** | **Permitted medication:** oral antihistamines and nonmedicated emollient (CeraVe lotion [CeraVe]; or Aquaphor [Beiersdorf Inc]) and sunscreen (both provided by the sponsor)<br><br>**Prohibited:** systemic or topical medication | Adults aged 18 to 75 years with a clinical diagnosis of moderate to severe AD (percentage of affected body surface area [%BSA] ≥10; Investigator's Global Assessment [IGA] score ≥3; and Eczema Area and Severity Index [EASI] score ≥12) for 1 year or more before day 1 of the study and inadequate response to topical medications (topical corticosteroids or topical calcineurin inhibitors) for 4 weeks or more (based on investigator's judgment) or inability to receive topical | Patients who had used topical corticosteroids or topical calcineurin inhibitors within 1 week of the first dose of study drug were excluded |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| | | | | treatment within 12 months before the first dose of study drug because it was medically inadvisable | |
| **Baricitinib** | | | | | |
| Phase III BREEZE-AD1[42,109]<br><br>Simpson 2020 BJD | Adults 18+ with moderate to severe AD<br><br>DB, PC, RCT | Daily dose for 16 weeks:<br><br>•Baricitinib 4 mg (High)<br>•Baricitinib 2 mg (Mid)<br>•Baricitinib mg (Low)<br>•Placebo | **Provided/required:** emollient<br><br>**Prohibited:** intra-articular corticosteroid injection, parenteral corticosteroids, JAK inhibitor treatment, monoclonal antibody | • Diagnosed with moderate to severe Atopic Dermatitis for ≥ 12 months<br>• Inadequate response or intolerance to existing topical medications within 6 months of screening<br>• Willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period)<br>• Agree to use emollients daily | •History of other concomitant skin conditions, skin disease or eczema herpeticum<br>•Currently experiencing a skin infection or illness that requires or is being treated with topical or systemic antibiotics or corticosteroids<br>•Prior treatment of: oral JAK inhibitor, parenteral corticosteroids injection, or intra-articular corticosteroid injection, within 2 weeks prior to study entry or 6 weeks prior to randomization<br>•Have high blood pressure<br>•Had major surgery within the past 8 weeks<br>•Have experienced any of the following within 12 weeks of screening: VTE, myocardial infarction (MI), unstable ischemic heart disease, stroke, heart failure. |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| | | | | | •Have a history of recurrent (≥ 2) VTE or are considered at high risk of VTE<br>•Have a history or presence of cardiovascular, respiratory, hepatic, liver, gastrointestinal, endocrine, hematological, neurological, lymphoproliferative disease or neuropsychiatric disorders<br>•Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis. |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| Phase III BREEZE-AD2[42,110]<br><br>Simpson 2020 BJD | Adults 18+ with moderate to severe AD<br><br>DB, PC, RCT | Daily dose for 16 weeks:<br><br>•Baricitinib 4 mg (High)<br>•Baricitinib 2 mg (Mid)<br>•Baricitinib 1 mg (Low)<br>•Placebo | **Provided/required:** emollient<br><br>**Prohibited:** intra-articular corticosteroid injection, parenteral corticosteroids, JAK inhibitor treatment, monoclonal antibody | • Diagnosed with moderate to severe Atopic Dermatitis for ≥ 12 months<br>• Inadequate response or intolerance to existing topical medications within 6 months of screening<br>• Willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period)<br>• Agree to use emollients daily | •History of other concomitant skin conditions, skin disease or eczema herpeticum<br>•Currently experiencing a skin infection or illness that requires or is being treated with topical or systemic antibiotics or corticosteroids<br>•Prior treatment of: oral JAK inhibitor, parenteral corticosteroids injection, or intra-articular corticosteroid injection, within 2 weeks prior to study entry or 6 weeks prior to randomization<br>•Have high blood pressure<br>•Had major surgery within the past 8 weeks<br>•Have experienced any of the following within 12 weeks of screening: VTE, myocardial infarction (MI), unstable ischemic heart disease, stroke, heart failure.<br>•Have a history of recurrent (≥ 2) VTE or are considered at high risk of VTE<br>•Have a history or presence of cardiovascular, respiratory, hepatic, liver, gastrointestinal, endocrine, hematological, neurological, |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| | | | | | lymphoproliferative disease or neuropsychiatric disorders<br>•Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis. |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| Phase III BREEZE-AD3[43,44]<br><br>Eli Lilly Oct 31, 2020 (Press release) + Eli Lilly data on file | Adults 18+ with moderate to severe AD<br><br>DB, PC, RCT | •Baricitinib 4 mg<br>•Baricitinib 2 mg<br>•Placebo | **Not reported** | • Have completed the final active treatment visit for an originating study eligible to enroll participants directly into study BREEZE-AD3<br><br>OR<br><br>• Meet criteria for NCT03334396 or NCT03334422. | • Had investigational product permanently discontinued at any time during a previous baricitinib study.<br>• Had temporary investigational product interruption continue at the final study visit of a previous baricitinib study and, in the opinion of the investigator, this poses an unacceptable risk for the participant's participation in the study. |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| Phase III BREEZE-AD5[44,45,49]<br><br>Simpson 2021 JAAD + Eli Lilly data on file | N=440<br><br>Adults 18+ with moderate to severe AD<br><br>DB, PC, RCT | Daily dose for 16 weeks:<br><br>•Baricitinib 2 mg (Mid)<br>•Baricitinib 1 mg (Low)<br>•Placebo | Not reported | • Diagnosed with moderate to severe Atopic Dermatitis for ≥12 months, including all of the following:<br>• EASI score ≥16<br>• IGA score of ≥3<br>• ≥10% of BSA involvement<br>• Inadequate response or intolerance to existing topical medications within 6 months of screening<br>• Willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period)<br>• Agree to use emollients daily | • Currently experiencing or have a history of other concomitant skin conditions (e.g., psoriasis or lupus erythematosus), or a history of erythrodermic, refractory, or unstable skin disease that requires frequent hospitalizations and/or intravenous treatment for skin infections<br>• History of eczema herpeticum within 12 months, and/or a history of 2 or more episode of eczema herpeticum in the past<br>• Participants who are currently experiencing a skin infection that requires treatment, or is currently being treated, with topical or systemic antibiotics<br>• Any serious illness that is anticipated to require the use of systemic corticosteroids or otherwise interfere with study participation or require active frequent monitoring (e.g., unstable chronic asthma)<br>• Treated with the following therapies:<br>• Monoclonal antibody |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| | | | | | for less than 5 half-lives before randomization<br>• Received prior treatment with any oral JAK inhibitor less than 4 weeks before randomization<br>• Received any parenteral corticosteroid administered by IM or IV injection within 6 weeks of planned randomization or are anticipated to require parenteral injection of corticosteroids during the study<br>• Have had an intra-articular corticosteroid injection within 6 weeks of planned randomization<br>• Probenecid at the time of randomization that cannot be discontinued for the duration of the study<br>• Have high blood pressure<br>• Had major surgery within the past 8 weeks<br>• Have experienced any of the following within 12 weeks of screening: MI, unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure<br>• Have a history of VTE, or are considered at high risk |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| | | | | | for VTE<br>• Have a history or presence of cardiovascular, respiratory, hepatic, chronic liver disease gastrointestinal, endocrine, hematological, neurological, lymphoproliferative disease or neuropsychiatric disorders or any other serious and/or unstable illness<br>• Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis. |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| Phase III BREEZE-AD6[84]<br><br>Simpson 2021 RAD Abstract | Adults 18+ with moderate to severe AD who completed the first 16 weeks of BREEZE-AD5 | Baricitinib 2 mg QD + TCS | TCS permitted | • Have not participated in a Study JAIW (NCT03435081)<br>• Have moderate to severe AD, including all of the following: EASI score ≥16, IGA score of ≥3, 10%- 50% BSA involvement<br>• Have had inadequate response or intolerance to existing topical (applied to the skin) medications within 6 months preceding screening.<br>• Are willing to discontinue certain treatments for eczema (such as systemic and topical treatments)<br>• Agree to use emollients daily. | •Are currently experiencing or have a history of other concomitant skin conditions (e.g., psoriasis or lupus erythematosus)<br>•A history of eczema herpeticum within 12 months<br>•Skin infection requiring treatment with topical or systemic antibiotics.<br>•Have been treated with the following therapies: monoclonal antibody for less than 5 half-lives before randomization, any oral JAK inhibitor less than 4 weeks before randomization, any parenteral corticosteroid administered by intramuscular or intravenous injection within 6 weeks of planned randomization<br>•Have high blood pressure characterized by a repeated systolic blood pressure >160 millimeters of mercury (mm Hg) or diastolic blood pressure >100 mm Hg.<br>•Have experienced any of the following within 12 weeks of screening: myocardial infarction (MI), unstable ischemic heart |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| | | | | | disease, stroke, or NYHA Stage III/IV heart failure<br>•Have a history of VTE, cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematological, neurological, lymphoproliferative disease or neuropsychiatric disorders<br>•Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis |
| Phase III<br>BREEZE-AD7<br>Reich 2020[46,47]<br><br>Reich 2020<br>JAMA | ≥18 years of age, moderate-to-severe atopic dermatitis<br><br>DB, PC, RCT | •Baricitinib 4 mg QD + TCS<br>•Baricitinib 2 mg QD + TCS<br>•Placebo QD + TCS | All patients received moderate- and/or low potency TCS (such as 0.1% triamcinolone cream and 2.5% hydrocortisone ointment, respectively) for active lesions; topical calcineurin inhibitors and/or crisaborole, in countries where approved, could be used in place of TCS, with guidance to limit use to areas considered inadvisable for TCS | ≥18 years of age, moderate-to-severe atopic dermatitis (IGA 3 or 4), inadequately controlled by topical treatment or medically inadvisable, AD ≥1 year | ~VTE or MACE w/I 12 weeks of screening; history of recurrent or high risk VTE; serious comorbid condition requiring systemic corticosteroids; history of alcohol or drug abuse; laboratory abnormalities |
| Phase II[48]<br><br>Guttmann-Yassky 2018<br>JAAD | ≥18 years of age, moderate-to-severe atopic dermatitis<br><br>DB, PC, RCT | •Baricitinib 4 mg QD + TCS<br>•Baricitinib 2 mg QD + TCS<br>•Placebo QD + TCS | Triamcinolone was used throughout the study according to the labeling or as recommended by the investigator | ≥18 years of age; moderate-to-severe atopic dermatitis; EASI ≥12; BSA ≥10%; disease duration ≥2 years; Inadequate response to emollients, TCS, systemic corticosteroids, or immunosuppressants; study conducted in US and Japan | History of TB, HIV, HepC, HepB; Pregnant or nursing females; participants not agreeing to use adequate contraception; serious comorbid condition that could interfere with study |

| Trial | Patient Population | Interventions | Concomitant Therapy | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|---|---|
| | | | | | participation; certain vaccines |

| Tralokinumab | | | | | |
|---|---|---|---|---|---|
| Phase III ECZTRA 1[63,65]<br><br>Wollenburg 2020 British Journal of Dermatology + LeoPharma data on file | N= 802<br><br>Adults 18+ with moderate to severe atopic dermatitis | **Pre-initial treatment (day 0):**<br>• Tralokinumab 600 mg loading dose<br><br>**Initial treatment period (16 weeks):**<br>• Tralokinumab 300 mg injection (2 injections of 150 mg each) Q2W<br>• Placebo Q2W<br><br>**Maintenance treatment period (36 weeks):**<br>• Tralokinumab 300 mg injection Q2W<br>• Tralokinumab 300 mg injection Q4W<br>• Placebo | **Provided:** patients instructed to use emollient twice daily | •Age 18+<br>•Diagnosis of AD for ≥1 year<br>•Subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable.<br>•AD involvement of ≥10% body surface area at screening and baseline.<br>•EASI≥12 screening, ≥16 at baseline<br>•IGA≥3<br>•Applied a stable dose of emollient twice daily for at least 14 days before randomization | •Active dermatologic conditions that may confound the diagnosis of AD.<br>•Use of tanning beds or phototherapy 6 weeks prior to randomization.<br>•Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomization.<br>•Treatment with TCS and/or TCI within 2 weeks prior to randomization.<br>•Active skin infection within 1 week prior to randomization.<br>•Clinically significant infection 4 weeks prior to randomization.<br>•A helminth parasitic infection within 6 months prior study entry.<br>•Tuberculosis requiring treatment within the 12 months prior to screening.<br>•Known primary immunodeficiency disorder.<br>•Positive HepB or HepC |

| | | | | | |
|---|---|---|---|---|---|
| Phase III ECZTRA 2[63,65]<br><br>Wollenburg 2020 British Journal of Dermatology + LeoPharma data on file | N= 794<br><br>Adults 18+ with moderate to severe atopic dermatitis<br><br>DB, PC, RCT | **Pre-initial treatment (day 0):**<br>• tralokinumab 600 mg loading dose<br><br>**Initial treatment period (16 weeks):**<br>• tralokinumab 300 mg injection (2 injections of 150 mg each) Q2W<br>• placebo Q2W<br><br>**Maintenance treatment period (36 weeks):**<br>• tralokinumab 300 mg injection Q2W<br>• tralokinumab 300 mg injection Q4W<br>• placebo | **Provided:** patients instructed to use emollient twice daily | •Age 18+<br>•Diagnosis of AD for ≥1 year<br>•Subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable.<br>•AD involvement of ≥10% body surface area at screening and baseline.<br>•EASI≥12 screening, ≥16 at baseline<br>•IGA≥3<br>•Applied a stable dose of emollient twice daily for at least 14 days before randomization | •Active dermatologic conditions that may confound the diagnosis of AD.<br>•Use of tanning beds or phototherapy 6 weeks prior to randomization.<br>•Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomization.<br>•Treatment with TCS and/or TCI within 2 weeks prior to randomization.<br>•Active skin infection within 1 week prior to randomization.<br>•Clinically significant infection 4 weeks prior to randomization.<br>•A helminth parasitic infection within 6 months prior study entry.<br>•Tuberculosis requiring treatment within the 12 months prior to screening.<br>•Known primary immunodeficiency disorder.<br>•Positive HepB or HepC |

| | | | | | |
|---|---|---|---|---|---|
| Phase III ECZTRA 3 (with TCS)[64,65]<br><br>Silverberg 2020 British Journal of Dermatology + LeoPharma data on file | N=380<br><br>Adults 18+ with moderate-to-severe atopic dermatitis<br><br>DB, PC, RCT | **Pre-initial treatment (day 0):**<br>•tralokinumab 600 mg injection<br><br>**Initial treatment period (16 weeks)**<br>•tralokinumab 300 mg injection Q2W + optional TCS<br>•placebo Q2W + optional TCS<br><br>**Maintenance treatment period (32 weeks)**<br>•tralokinumab 300 mg injection Q2W + optional TCS<br>•tralokinumab 300 mg injection Q4W + optional TCS<br>•placebo Q2W + TCS | **permitted/provided:** TCS, emollient | •Age 18+<br>•Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD.<br>•History of AD for ≥1 year.<br>•Subjects who have a recent history of inadequate response to treatment with topical medications.<br>•AD involvement of ≥10% body surface area at screening and baseline.<br>•Stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomization. | •Subjects for whom TCS are medically inadvisable<br>•Active dermatologic conditions that may confound AD diagnosis<br>•Use of tanning beds or phototherapy within 6 weeks prior to randomization.<br>•Treatment with systemic immunosuppressive/immunomodulating drugs or systemic corticosteroid within 4 weeks prior to randomization.<br>•Treatment with TCS, topical calcineurin inhibitors (TCI), or topical phosphodiesterase 4 (PDE-4) inhibitor within 2 weeks prior to randomization.<br>•Receipt of any marketed biological therapy including dupilumab or investigational biologic agents.<br>•Active skin infection within 1 week prior to randomization.<br>•Helminth parasitic infection within 6 months prior to study start<br>•Tuberculosis requiring treatment within the 12 months prior to screening.<br>•Known primary immunodeficiency disorder. |

| | | | | | |
|---|---|---|---|---|---|
| Phase III ECZTEND[79]<br><br>Blauvelt 2021 RAD Abstract | N=1175<br><br>Patients 18+ who participated in previous tralokinumab clinical trials | Tralokinumab 300 mg Q2W | Optional TCS | • Completed the treatment period(s) of one of the parent trials: LP0162-1325, -1326, -1339, -1341 or -1342<br>• Able and willing to self-administer tralokinumab treatment (or have it administered by a caregiver) at home after the initial 3 injection visits at the trial site<br>• Stable dose of emollient twice daily (or more, as needed) for at least 14 days before baseline | • More than 20 weeks have elapsed since the subject received the last injection of investigational medicinal product (IMP) in the parent trial<br>• Subjects who, during the parent trial, developed an AE or SAE related to tralokinumab that led to temporary discontinuation of trial treatment<br>• Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to baseline<br>• Treatment with topical phosphodiesterase 4 inhibitors within 2 weeks prior to baseline<br>• A helminth parasitic infection<br>• Tuberculosis requiring treatment within 12 months prior to screening |
| **Upadacitinib** | | | | | |
| Phase III MEASURE UP 1[72,82]<br><br>Guttman-Yassky 2021 Lancet + Simpson 2021 AAD VMX Abstract | N= 847<br><br>Ages 12-75 years with moderate to severe AD<br><br>DB, PC, RCT | **Week 1-16:**<br>• Upadacitinib 30 mg<br>• Upadacitinib 15 mg<br>• Placebo<br><br>**After Week 16**:<br>• Upadacitinib 30 mg<br>• Upadacitinib 15 mg | **Prohibited medications:** UV light therapy, JAK inhibitors, systemic or topical, bleach baths (if more than 2x/week during study), topical treatments for AD | • Active moderate to severe atopic dermatitis defined by EASI, IGA, BSA, and pruritus<br>• Candidate for systemic therapy or have recently required systemic therapy for atopic dermatitis | • Prior exposure to any JAK inhibitor<br>• Unable or unwilling to discontinue current AD treatments prior to study<br>• Requirement of prohibited medications during the study<br>• Other active skin diseases/infections requiring systemic treatment or would interfere with appropriate assessment of atopic dermatitis lesions |

| | | | | | |
|---|---|---|---|---|---|
| Phase III MEASURE UP 2[72,82]<br><br>Guttman-Yassky 2021 Lancet + Simpson 2021 AAD VMX Abstract | N= 836<br><br>Ages 12-75 years with moderate to severe AD<br><br>DB, PC, RCT | **Week 1-16:**<br>• Upadacitinib 30 mg<br>• Upadacitinib 15 mg<br>• Placebo<br><br>**After Week 16:**<br>• Upadacitinib 30 mg<br>• Upadacitinib 15 mg | **Prohibited medications:** UV light therapy, JAK inhibitors, systemic or topical, bleach baths (if more than 2x/week during study), topical treatments for AD | • Active moderate to severe atopic dermatitis defined by EASI, IGA, BSA, and pruritus<br>• Candidate for systemic therapy or have recently required systemic therapy for atopic dermatitis | • Prior exposure to any JAK inhibitor<br>• Unable or unwilling to discontinue current AD treatments prior to study<br>• Requirement of prohibited medications during the study<br>• Other active skin diseases/infections requiring systemic treatment or would interfere with appropriate assessment of atopic dermatitis lesions |
| Phase III AD-UP (with TCS)[72,83]<br><br>Reich 2021 Lancet + Simpson 2021 AAD VMX Abstract | N~901<br><br>Ages 12-75 with moderate to severe AD<br><br>DB, PC, RCT | **Week 1-16**<br>• Upadacitinib 30 mg + topical corticosteroids (TCS)<br>• Upadacitinib 15 mg + TCS<br>• Placebo + TCS<br><br>**After Week 16:**<br>• Upadacitinib 30 mg + TCS<br>• Upadacitinib 15 mg + TCS | **TCS**<br><br>prohibited meds, no details | • Active moderate to severe atopic dermatitis defined by EASI, IGA, BSA, and pruritus<br>• Candidate for systemic therapy or have recently required systemic therapy for atopic dermatitis<br>• Able to tolerate topical corticosteroids for atopic dermatitis lesions | • Prior exposure to any JAK inhibitor<br>• Unable or unwilling to discontinue current AD treatments prior to study<br>• Requirement of prohibited medications during the study<br>• Other active skin diseases/infections requiring systemic treatment or would interfere with appropriate assessment of atopic dermatitis lesions |

| | | | | | |
|---|---|---|---|---|---|
| Phase IIIb Heads Up[70,71,81]<br><br>AbbVie 2020 (Press release) + Blauvelt 2021 RAD Abstract + AbbVie data on file | N= 692<br><br>Adults 18 and older with moderate to severe AD<br><br>MC, RCT, DB, DD, AC | **Dose for 24 weeks**<br>*Arm 1*<br>Upadacitinib 30 mg daily (oral)<br>Placebo<br><br>*Arm 2*<br>Dupilumab 300 mg every other week (subcutaneous)<br>Placebo | **Prohibited Medications:** JAK inhibitors, prior dupilumab use | Patients 18 and older with moderate to severe AD<br><br>Participant has active moderate to severe atopic dermatitis (AD) defined by Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), Body Surface Area (BSA) and pruritus.<br><br>Participant is a candidate for systemic therapy or have recently required systemic therapy for AD. | Participant has prior exposure to Janus Kinase (JAK) inhibitor.<br>Participant has prior exposure to dupilumab.<br>Participant is unable or unwilling to discontinue current AD treatments prior to the study.<br>Participant has requirement of prohibited medications during the study.<br>Participant has other active skin diseases or skin infections requiring systemic treatment or would interfere with appropriate assessment of AD lesions.<br>Female participant who is pregnant, breastfeeding, or considering pregnancy during the study. |
| Phase IIb[69,159]<br><br>Guttman-Yassky 2020 Allergy and Immunology + Reich 2021 RAD Abstract | N=167<br><br>Ages 18-75 years with moderate to severe AD<br><br>DB, PC, RCT | **Week 1-16 (period 1):**<br>•upadacitinib 30 mg QD<br>•upadacitinib 15 mg QD<br>•upadacitinib 7.5 mg QD<br>•placebo<br><br>**Week 16-88 (period 2 - rerandomization stratified by EASI** | **Permitted:** emollient, orally administered antibiotics for superficial skin infections<br><br>**Prohibited medications:** Concomitant medications for the treatment of AD, JAK inhibitors (other than upadacitinib) and other non-biologic systemic treatments for AD; all biologic therapies, corticosteroids, phototherapy, extensive | •Atopic dermatitis with a diagnosis confirmed by a dermatologist and onset of symptoms at least 1 year prior to Baseline.<br>•Moderate to severe atopic dermatitis defined by EASI≥16, BSA≥10% and IGA score≥ 3 at the Baseline visit. | •Prior exposure to any systemic or topical Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, ruxolitinib, and filgotinib).<br>•Treatment with topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin within 10 days prior to the Baseline visit.<br>•Prior exposure to dupilumab or exposure to systemic therapies for AD including corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 |

| | | | | | |
|---|---|---|---|---|---|
| | | **75 response at week 16):**<br>•upadacitinib 30 mg QD<br>•upadacitinib 15 mg QD<br>•upadacitinib 7.5 mg QD<br>•placebo | light exposure that could have affected study outcomes; all topical therapies, investigational drugs, live vaccines, cannabis, and strong inducers and inhibitors of cytochrome P450 3A; and traditional Chinese medicine | •Documented history (within 1 year prior to the screening visit) of inadequate response to treatment with topical corticosteroids (TCS), or topical calcineurin inhibitors (TCI), or for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).<br>•Twice daily use of an additive-free, bland emollient for at least 7 days prior to Baseline. | (PDE4)-inhibitors and mycophenolate mofetil within 4 weeks prior to Baseline.<br>•Prior exposure to any investigational systemic treatment within 30 days or 5 half-lives (whichever is longer) of the Baseline visit |

| Dupilumab | | | | | |
|---|---|---|---|---|---|
| Phase III LIBERTY AD SOLO 1[51]<br><br>Simpson 2016 NEMJ | ≥18 years of age, moderate-to-severe atopic dermatitis<br><br>DB, PC, RCT | **Dosing until week 16:**<br><br>Dupilumab monotherapy 300 mg/wk, s.c.(n=223)<br>dupilumab 300 mg s.c. every other week alternating with placebo (n=224)<br>Placebo (n=224) | **Prohibited:** Prohibited concomitant medications included topical glucocorticoids and calcineurin inhibitors, immunomodulating biologic agents, systemic glucocorticoids, and nonsteroidal systemic immunosuppressants.<br><br>Also prohibited procedures: Phototherapy, tanning bed or booth, and major elective surgeries<br><br>**Permitted/allowed**: Concomitant topical glucocorticoids and calcineurin inhibitors were allowed only as rescue therapy | ≥18 years of age, moderate-to-severe atopic dermatitis (IGA 3 or 4), inadequately controlled by topical treatment or medically inadvisable, AD ≥3 years | • Treatment with an investigative drug within 8 weeks or within 5 half-lives<br>• Treatment with immunosuppressive/immunomodulatory drugs or phototherapy for atopic dermatitis within 4 weeks of baseline<br>• Treatment with topical corticosteroids or topical calcineurin inhibitors within 1 week of baseline<br>• Regular use (>2 visits per week) of a tanning booth/parlor within 4 weeks of the baseline visit<br>• Planned or anticipated use of any prohibited medications and procedures during study treatment<br>• Known or suspected history of immunosuppression, including history of invasive opportunistic infections, HIV, HepC or presence of any condition listed as criteria for discontinuation of drug and history of malignancies<br>• Presence of skin comorbidities that may interfere with study assessments |

| | | | | | |
|---|---|---|---|---|---|
| Phase III LIBERTY AD SOLO 2[51]<br><br>Simpson 2016 NEMJ | ≥18 years of age, moderate-to-severe atopic dermatitis<br><br>DB, PC, RCT | **Dosing until week 16:**<br><br>Dupilumab monotherapy 300 mg/wk, s.c.(n=239)<br>Dupilumab 300 mg s.c. every other week alternating with placebo (n=233)<br>Placebo (n=236) | **Prohibited:** Prohibited concomitant medications included topical glucocorticoids and calcineurin inhibitors, immunomodulating biologic agents, systemic glucocorticoids, and nonsteroidal systemic immunosuppressants.<br><br>Also prohibited procedures: Phototherapy, tanning bed or booth, and major elective surgeries<br><br>**Permitted/allowed**: Concomitant topical glucocorticoids and calcineurin inhibitors were allowed only as rescue therapy | ≥18 years of age, moderate-to-severe atopic dermatitis (IGA 3 or 4), inadequately controlled by topical treatment or medically inadvisable, AD ≥3 years | same as SOLO 1 |

| | | | | | |
|---|---|---|---|---|---|
| Phase III LIBERTY AD CHRONOS[50]<br><br>Blauvelt 2017 Lancet | ≥18 years of age, moderate-to-severe atopic dermatitis<br><br>DB, PC, RCT | **Day 1 (Loading dose)**<br>•Dupilumab 600 mg<br>•placebo<br><br>**Day 1-Week 16**<br>•Dupilumab 300 mg QW + TCS<br>•Dupilumab 300 mg Q2W + TCS<br>•Placebo QW + TCS | **provided during study:** TCS (medium/low potency) w/ or w/o TCIs (where inadvisable for TCS)<br><br>**Permitted concomitant meds:** any medications other than those that were prohibited<br><br>**Prohibited concomitant medications:** live (attenuated) vaccine, immunomodulating biologics, investigational drugs, wet wraps, any omed for AD interfering with efficacy outcomes or affect evaluation for AD severity, major elective surgical procedures, or tanning in a bed/booth. | •Chronic atopic dermatitis (AD) present for 3+ years before screening<br>•Documented recent history (within 6 months before the screening visit) of inadequate response to a sufficient course of outpatient treatment with topical AD meds<br>•IGA score ≥3, on the IGA scale of 0–4, BSA affected ≥10%, EASI score of ≥16, PP-NRS average score ≥3<br>•Applied moisturizers at least twice daily for the 7 days before randomization | •Participation in a prior dupilumab clinical trial<br>•Important side effects of topical medication (e.g., intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects)<br>•Used any of these treatments within 4 weeks before baseline, or condition likely to require treatment during first 2 weeks of study treatment: Immunosuppressive/immunomodulating drugs (e.g., systemic steroids, cyclosporine, mycophenolate-mofetil, Janus kinase inhibitors, IFN-γ, azathioprine, methotrexate, etc., Phototherapy for AD<br>•Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit<br>•History or current positive HIV<br>•Positive HepB or HepC antibody at the screening visit<br>•Active or acute infection requiring systemic treatment within 2 weeks before baseline visit<br>•Known or suspected history of immunosuppression |
| Phase III AD SOLO-CONTINUE[54]<br><br>Worm 2019 JAMA | N= 422 re-randomized patients from SOLO to SOLO-CONTINUE<br><br>Dupilumab-treated patients who has achieved IGA score of 0 or | Re-randomized 2:1:1:1<br><br>**Original regimen** (300 mg QW or Q2W)<br>or<br>**Less frequency** (300 mg Q4W or Q8W) | Patients were required to apply moisturizers 2 or more times daily throughout the study. | Received dupilumab in the SOLO studies and achieved IGA 0/1 or EASI75 at week 16. | Did not completed SOLO study or did not achieve primary endpoint. |

| | | | | | |
|---|---|---|---|---|---|
| | 1 or 75% or greater improvement I EASI at week 16 during the SOLO studies.<br><br>DB, PC, RCT | or<br>**Placebo** | | | |
| Phase IIb Thaci 2016[56,57]<br><br>Thaci 2016 Lancet + Simpson 2016 JAAD | 18 and older with moderate to severe atopic dermatitis<br><br>N= 380<br><br>DB, PC, RCT, dose ranging | Dupilumab 300 mg once a week (n = 63)<br>**Dupilumab 300 mg every 2 weeks (n= 64)**<br>**Dupilumab 200 mg every 2 weeks (n = 61)**<br>**Dupilumab 300 mg every 4 weeks (n= 65)**<br>Dupilumab 100 mg every 4 weeks (n = 65)<br>**Placebo once a week (n = 61)** | **Prohibited concomitant medications**: topical calcineurin inhibitors, topical corticosteroids, prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin, systemic corticosteroids, systemic treatment for AD with an immunosuppressive /immunomodulating agent (e.g., cyclosporin, mycophenolate-mofetil, azathioprine, methotrexate, interferon-gamma, or other biologics); allergen immunotherapy; live (attenuated vaccine); or investigational drug other than dupilumab. | adults (aged ≥18 years) diagnosed with moderate-to-severe atopic dermatitis for at least 3 years not adequately controlled by topical treatments, or for whom topical treatment was inadvisable, Eczema Area and Severity Index (EASI), score 12 or higher at screening and 16 or higher at baseline; Investigator's Global Assessment (IGA) score of 3 or higher at screening and baseline; atopic dermatitis involvement of 10% or more of body surface area | previous treatment with dupilumab; active acute or chronic infections; use of topical treatments for atopic dermatitis (other than bland emollients) within 1 week of baseline; systemic immunosuppressive or immunomodulating drugs within 4 weeks of baseline; or significant comorbidities or laboratory abnormalities |

| | | | | | |
|---|---|---|---|---|---|
| | | | | at screening and baseline | |

AC: active controlled, AD: atopic dermatitis, AE: adverse event, BSA: body surface area, CD19: Cluster of Differentiation 19, DB: double-blind, DD: double dummy, HepB: hepatitis B, HepC: hepatitis C, HIV: human immunodeficiency virus, IFN-γ: interferon gamma, IMP: investigational medicinal product, kg: kilogram, JAK: Janus kinase, LT: long-term, MACE: major adverse cardiovascular event, MC: multi-center, mg: milligram, MI: myocardial infarction n: number, mm Hg: millimeter of mercury, N: total number, NR: not reported, NRS: numerical rating scale, NYHA: New York Heart Association Functional Classification, OL: open-label, OLE: open-label extension, PC: placebo-controlled, PDE4: Phosphodiesterase-4, QD: once daily, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, RCT: randomized control trial, s.c.: subcutaneous, TB: tuberculosis, TCI: topical calcineurin inhibitors, TCS: topical corticosteroids, VTE: venous thromboembolism.

**Table G1.3. Baseline Characteristics I** [35-37,39,40,42,44-48,50,51,54,56,63,64,67,69,77-79,81-85,108]

| Study Name | Arms | N | Age (years) | | Male | | White | | Disease duration (years) | | Disease Severity, n (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Moderate | | Severe | |
| | | | mean | SD | n | % | n | % | Mean | SD | n | % | n | % |
| **Abrocitinib** | | | | | | | | | | | | | | |
| JADE MONO-1 | PBO | 77 | 31.5 | 14.4 | 49 | 64 | 62 | 81 | 22.5 | 14.4 | 46 | 60 | 31 | 40 |
| | ABRO 100 mg | 156 | 32.6 | 15.4 | 90 | 58 | 113 | 72 | 24.9 | 16.1 | 92 | 59 | 64 | 41 |
| | ABRO 200 mg | 154 | 33 | 17.4 | 81 | 53 | 104 | 68 | 22.7 | 14.5 | 91 | 59 | 63 | 41 |
| JADE MONO-2 | PBO | 78 | 33.4 | 13.8 | 47 | 60.3 | 40 | 51.3 | 21.7 | 14.3 | 52 | 66.7 | 26 | 33.3 |
| | ABRO 100 mg | 158 | 37.4 | 15.8 | 94 | 59.5 | 101 | 63.9 | 21.1 | 14.8 | 107 | 67.7 | 51 | 32.3 |
| | ABRO 200 mg | 155 | 33.5 | 14.7 | 88 | 56.8 | 91 | 58.7 | 20.5 | 14.8 | 106 | 68.4 | 49 | 31.6 |
| | Overall | 391 | 35.1 | 15.1 | 229 | 58.6 | 232 | 59.3 | 21 | 14.7 | 265 | 67.8 | 126 | 32.2 |
| JADE TEEN | PBO | 96 | Median: 14 | IQR: 13.5 to 16.5 | 44 | 45.8 | 56.0 | 58.3 | 10.5 | 4.8 | 57 | 59.4 | 39 | 40.6 |
| | ABRO 100 mg | 95 | Median: 16 | IQR: 14 to 17 | 45 | 47.4 | 52.0 | 54.7 | 9.8 | 5.4 | 57 | 60 | 38 | 40 |
| | ABRO 200 mg | 94 | Median: 15 | IQR: 13 to 16 | 56 | 59.6 | 52.0 | 55.3 | 9.7 | 5.3 | 61 | 64.9 | 33 | 35.1 |
| | Overall | 285 | 14.9 | | 145 | 50.9 | 160 | 56.1 | | | | | | |
| JADE COMPARE | PBO | 131 | 37.4 | 15.2 | 77 | 58.8 | 87 | 66.4 | 21.4 | 14.4 | 88 | 67.2 | 43 | 32.8 |
| | ABRO 100 mg | 238 | 37.3 | 14.8 | 120 | 50.4 | 182 | 76.5 | 22.7 | 16.3 | 153 | 64.3 | 85 | 35.7 |
| | ABRO 200 mg | 226 | 38.8 | 14.5 | 104 | 46 | 161 | 71.2 | 23.4 | 15.6 | 138 | 61.1 | 88 | 38.9 |
| | DUP 300 mg | 242 | 37.1 | 14.6 | 108 | 44.6 | 176 | 72.7 | 22.8 | 14.8 | 162 | 66.9 | 80 | 33.1 |
| | Total | 837 | 37.7 | 14.7 | 409 | 48.9 | 606 | 72.4 | 22.7 | 15.4 | 541 | 64.6 | 296 | 35.4 |
| JADE EXTEND Subgroup 1[†] | ABRO 100 mg | 595 | Median: 32 | Range: 12-83 | 340 | 57.1 | NR | NR | 22.7 | 15.2 | 384 | 64.5 | 211 | 35.5 |
| | ABRO 200 mg | 521 | Median: 32 | Range: 12-80 | 277 | 53.2 | NR | NR | 22.3 | 15 | 322 | 61.8 | 199 | 38.2 |
| JADE EXTEND Subgroup 2[‡] | ABRO 100 mg | 130 | NR | NR | NR | NR | NR | NR | 24.2 | 15 | 87 | 66.9 | 43 | 33.1 |
| | ABRO 200 mg | 73 | NR | NR | NR | NR | NR | NR | 23.6 | 15.6 | 47 | 64.4 | 26 | 35.6 |

| Study Name | Arms | N | Age (years) | | Male | | White | | Disease duration (years) | | Disease Severity, n (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Moderate | | Severe | |
| | | | mean | SD | n | % | n | % | Mean | SD | n | % | n | % |
| Phase IIb Gooderham 2019 | PBO | 56 | 42.6 | 15.1 | 21 | 37.5 | 40 | 71.4 | Median: 25.6 | Range: 1.1 to 67.1 | 34 | 61.8 | 21 | 38.2 |
| | ABRO 100 mg | 56 | 41.1 | 15.6 | 31 | 55.4 | 40 | 71.4 | Median: 23.8 | Range: 1.1 to 66.7 | 29 | 52.7 | 26 | 47.3 |
| | ABRO 200 mg | 55 | 38.7 | 17.6 | 28 | 50.9 | 37 | 67.3 | Median 19.6 | Range: 1.9 to 68.8 | 34 | 63 | 20 | 37 |
| **Baricitinib** | | | | | | | | | | | | | | |
| BREEZE-AD1 | PBO | 249 | 35 | 12.6 | 148 | 59.4 | 147 | 59.5 | 26 | 15.5 | NR | NR | 105 | 42.2 |
| | BARI 1 mg | 127 | 36 | 12.4 | 78 | 61.4 | 74 | 58.3 | 27 | 14.9 | NR | NR | 53 | 41.7 |
| | BARI 2 mg | 123 | 35 | 13.7 | 82 | 66.7 | 75 | 61 | 25 | 14.6 | NR | NR | 52 | 42.3 |
| | BARI 4 mg | 125 | 37 | 12.9 | 83 | 66.4 | 70 | 56.5 | 25 | 14.9 | NR | NR | 51 | 40.8 |
| BREEZE-AD2 | PBO | 244 | 35 | 13 | 154 | 63.1 | 169 | 69.3 | 25 | 13.9 | NR | NR | 121 | 49.6 |
| | BARI 1 mg | 125 | 33 | 10 | 80 | 64 | 85 | 68 | 24 | 12.7 | NR | NR | 63 | 50.8 |
| | BARI 2 mg | 123 | 36 | 13.2 | 65 | 52.8 | 85 | 69.1 | 24 | 13.8 | NR | NR | 62 | 50.4 |
| | BARI 4 mg | 123 | 34 | 14.1 | 82 | 66.7 | 82 | 66.7 | 23 | 14.8 | NR | NR | 63 | 51.2 |
| BREEZE-AD3 (LTE) | BARI 2 mg | | | | | | NR | NR | NR | NR | | | | |
| BREEZE-AD5 | PBO | 147 | 39 | 17 | 80 | 54 | 80 | 55 | 23 | 17 | 86 | 59 | 61 | 41 |
| | BARI 1 mg | 147 | 40 | 17 | 75 | 51 | 86 | 59 | 24 | 17 | 85 | 58 | 62 | 42 |
| | BARI 2 mg | 146 | 40 | 15 | 69 | 47 | 85 | 58 | 24 | 16 | 85 | 58 | 61 | 42 |
| BREEZE-AD6 | BARI 2 mg | 146 | 39.7 | 15 | 69 | 47.3 | 85 | 58.2 | 23.9 | 15.9 | 85 | 58.2 | 61 | 41.8 |
| BREEZE-AD7 | PBO + TCS | 109 | 33.7 | 13.2 | 71 | 65 | 46 | 42 | 22 | 12.2 | NR | NR | 48* | 44 |
| | BARI 2 mg + TCS | 109 | 33.8 | 12.8 | 70 | 64 | 50 | 46 | 24.6 | 14.8 | NR | NR | 50 | 46 |
| | BARI 4 mg + TCS | 111 | 33.9 | 11.4 | 75 | 68 | 54 | 49 | 25.5 | 13.2 | NR | NR | 50 | 45 |
| Phase II Guttman-Yassky 2018 | PBO + TCS | 49 | Median: 35 | IQR: 28.0 to 48.0 | 24 | 49 | 23 | 47 | Median: 17.7 | IQR: 7.3 to 29.5 | NR | NR | NR | NR |
| | BARI 2 mg + TCS | 37 | Median: 42 | IQR: 26.0 to 52.0 | 22 | 59 | 20 | 54 | Median: 26.4 | IQR: 18.3 to 40.5 | NR | NR | NR | NR |

| Study Name | Arms | N | Age (years) | | Male | | White | | Disease duration (years) | | Disease Severity, n (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Moderate | | Severe | |
| | | | mean | SD | n | % | n | % | Mean | SD | n | % | n | % |
| | BARI 4 mg + TCS | 38 | Median: 32.5 | IQR: 26.0 to 48.0 | 22 | 58 | 18 | 47 | Median: 22.0 | IQR: 6.4 to 30.7 | NR | NR | NR | NR |
| **Tralokinumab** | | | | | | | | | | | | | | |
| ECZTRA 1 | PBO | 199 | Median: 37.0 | IQR: 26.0 to 49.0 | 123 | 61.8 | 138 | 69.3 | Median: 28.0 | IQR: 18.0 to 41.0 | NR | NR | 102 | 51.3 |
| | TRA 300 mg | 603 | Median: 37.0 | IQR: 27.0 to 48.0 | 351 | 58.2 | 426 | 70.6 | Median: 27.0 | IQR: 19.0 to 38.0 | NR | NR | 305 | 50.6 |
| ECZTRA 2 | PBO | 201 | Median: 30.0 | IQR: 23.0 to 46.0 | 114 | 56.7 | 123 | 61.2 | Median: 25.0 | IQR: 18.0 to 36.0 | NR | NR | 101 | 50.2 |
| | TRA 300 mg | 593 | Median: 34.0 | IQR: 25.0 to 48.0 | 359 | 60.5 | 374 | 63.1 | Median: 25.5 | IQR: 17.0 to 39.0 | NR | NR | 286 | 48.2 |
| ECZTRA 2 Subgroup[¶] | PBO | 91 | 38.9 | 15.9 | 46 | 50.5 | 46 | 50.5 | 30.2 | 16.8 | 52 | 57.1 | 39 | 42.9 |
| | TRA 300 mg | 270 | 40.2 | 15.7 | 147 | 54.4 | 148 | 54.8 | 29.7 | 16.4 | 153 | 56.7 | 117 | 43.3 |
| ECZTRA 3 | PBO + TCS | 127 | Median: 34.0 | IQR: 24.0 to 50.0 | 84 | 66.1 | 85 | 66.9 | Median: 26.0 | IQR: 18.0 to 39.0 | 66 | 52 | 60 | 47.2 |
| | TRA 300 mg + TCS | 253 | Median: 37.0 | IQR: 28.0 to 52.0 | 125 | 49.4 | 203 | 80.2 | Median: 27.0 | IQR: 17.0 to 39.0 | 136 | 53.8 | 116 | 45.8 |
| | Overall | 380 | Median: 36.0 | IQR: 27.0 to 51.0 | 209 | 55 | 288 | 75.8 | Median: 26.0 | IQR: 17.0 to 39.0 | 202 | 53.2 | 176 | 46.3 |
| ECZTEND | Overall | 1174 | Median: 38 | IQR: 27 to 50 | 675 | 57.5 | NR | NR | Median: 27.0 | IQR: 18 to 40 | NR | NR | NR | NR |
| **Upadacitinib** | | | | | | | | | | | | | | |
| MEASURE UP 1 | PBO | 281 | 34.4 | Range: 12 to 75 | 144 | 51.2 | 182 | 64.8 | 21.3 | 15.3 | 156 | 55.5 | 125 | 44.5 |
| | UPA 15 mg | 281 | 34.1 | Range: 12 to 74 | 157 | 55.9 | 182 | 64.8 | 20.5 | 15.9 | 154 | 54.8 | 127 | 45.2 |
| | UPA 30 mg | 285 | 33.6 | Range: 12 to 75 | 155 | 54.4 | 191 | 67 | 20.4 | 14.3 | 154 | 54 | 131 | 46 |
| MEASURE UP 2 | PBO | 278 | 33.4 | Range: 13 to 71 | 154 | 55.4 | 195 | 70.1 | 21.1 | 13.6 | 125 | 45 | 153 | 55 |

| Study Name | Arms | N | Age (years) | | Male | | White | | Disease duration (years) | | Disease Severity, n (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Moderate | | Severe | |
| | | | mean | SD | n | % | n | % | Mean | SD | n | % | n | % |
| | UPA 15 mg | 276 | 33.3 | Range: 12 to 74 | 155 | 56.2 | 184 | 66.7 | 25.8 | 5.6 | 126 | 45.7 | 150 | 54.3 |
| | UPA 30 mg | 282 | 34.1 | Range: 12 to 75 | 162 | 57.4 | 198 | 70.2 | 25.9 | 5.8 | 126 | 44.7 | 156 | 55.3 |
| AD-UP | PBO + TCS | 304 | 34.3 | Range: 12 to 75 | 178 | 58.6 | 225 | 74 | 24.3 | 15.2 | 141 | 46.4 | 163 | 53.6 |
| | UPA 15 mg + TCS | 300 | 32.5 | Range: 13 to 74 | 179 | 59.7 | 204 | 68 | 22.9 | 13.9 | 143 | 47.7 | 157 | 52.3 |
| | UPA 30 mg + TCS | 297 | 35.5 | Range: 12 to 75 | 190 | 64 | 218 | 73.4 | 23.1 | 16.1 | 140 | 47.1 | 157 | 52.9 |
| Heads Up | DUP 300 mg | 344 | 36.9 | Range: 18 to 76 | 194 | 56.4 | NR | NR | 25 | 14.8 | 171 | 49.7 | 173 | 50.3 |
| | UPA 30 mg | 348 | 36.6 | Range: 18 to 76 | 183 | 52.6 | NR | NR | 23.5 | 14.7 | 174 | 50 | 174 | 50 |
| Phase IIb Guttman-Yassky 2020 | PBO | 41 | 39.9 | 17.5 | 24 | 58.5 | 28 | 68.3 | 26.8 | 18.8 | 18 | 44 | 23 | 56 |
| | UPA 7.5 mg | 42 | 41.5 | 15.4 | 28 | 66.7 | 24 | 57 | 30.4 | 18.1 | 29 | 69 | 13 | 31 |
| | UPA 15 mg | 42 | 38.5 | 15.2 | 30 | 71.4 | 21 | 50 | 22.6 | 15.8 | 19 | 45 | 23 | 55 |
| | UPA 30 mg | 42 | 39.9 | 15.3 | 22 | 52.4 | 23 | 55 | 24.2 | 13.6 | 31 | 74 | 11 | 26 |
| **Dupilumab** | | | | | | | | | | | | | | |
| SOLO 1 | PBO | 224 | Median: 39 | IQR: 27 to 50.5 | 118 | 53 | 146 | 65 | Median: 28 | IQR: 19 to 40 | NR | NR | 110 | 49 |
| | DUP 300 mg Q2W | 224 | Median: 38 | IQR: 27.5 to 48.0 | 130 | 58 | 155 | 69 | Median: 26 | IQR: 17 to 40 | NR | NR | 108 | 48 |
| | DUP 300 mg QW | 223 | Median: 39 | IQR: 27 to 51 | 142 | 64 | 149 | 67 | Median: 26 | IQR: 16 to 42 | NR | NR | 106 | 48 |
| SOLO 2 | PBO | 236 | Median: 35 | IQR: 25 to 47 | 132 | 56 | 156 | 66 | Median: 26 | IQR: 18 to 39 | NR | NR | 115 | 49 |

| Study Name | Arms | N | Age (years) | | Male | | White | | Disease duration (years) | | Disease Severity, n (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Moderate | | Severe | |
| | | | mean | SD | n | % | n | % | Mean | SD | n | % | n | % |
| | DUP 300 mg Q2W | 233 | Median: 34.0 | IQR: 25 to 46 | 137 | 59 | 165 | 71 | Median: 24.5 | IQR: 18 to 36 | NR | NR | 115 | 49 |
| | DUP 300 mg QW | 239 | Median: 35 | IQR: 25 to 46 | 139 | 58 | 168 | 70 | Median: 24 | IQR: 17 to 37 | NR | NR | 112 | 47 |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | Median: 34.0 | IQR: 25 to 45 | 193 | 61 | 208 | 66 | Median: 26 | IQR: 17 to 38 | 168 | 53 | 147 | 47 |
| | DUP 300 mg + TCS Q2W | 106 | Median: 40.5 | IQR: 28 to 49 | 62 | 58 | 74 | 70 | Median: 28 | IQR: 20 to 44 | 53 | 50 | 53 | 50 |
| | DUP 300 mg + TCS QW | 319 | Median: 34.0 | IQR: 26 to 45 | 191 | 60 | 208 | 65 | Median: 26 | IQR: 18 to 39 | 172 | 54 | 147 | 46 |
| AD SOLO-CONTINUE | PBO | 83 | 37 | IQR: 27 to 46 | 51 | 61.4 | 54 | 65.1 | NR | NR | 1 | 1.2 | 0 | 0 |
| | DUP 300 mg Q8W | 84 | 35 | IQR: 26 to 46.5 | 51 | 60.7 | 56 | 66.7 | NR | NR | 2 | 2.4 | 0 | 0 |
| | DUP 300 mg Q4W | 86 | 36 | IQR: 24 to 49 | 43 | 50 | 64 | 74.4 | NR | NR | 6 | 7 | 0 | 0 |
| | DUP 300 mg QW/Q2W | 169 | 36 | IQR: 26 to 48 | 82 | 48.5 | 124 | 73.4 | NR | NR | 3 | 1.8 | 0 | 0 |
| Phase IIb Thaci 2016 | PBO QW | 61 | 37.2 | 13.1 | 40 | 66 | NR | NR | 29.8 | 13.5 | 32 | 53 | 29 | 48 |
| | DUP 200 mg | 61 | 35.8 | 14.9 | 36 | 59 | NR | NR | 25.2 | 12.8 | 31 | 51 | 30 | 49 |
| | DUP 300 mg | 64 | 39.4 | 12.1 | 41 | 64 | NR | NR | 30.5 | 15.8 | 34 | 53 | 30 | 47 |
| | DUP 300 mg | 65 | 36.2 | 10.7 | 40 | 62 | NR | NR | 26.5 | 11.4 | 37 | 57 | 28 | 43 |

ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, IQR: interquartile range, kg: kilogram, LTE: long-term extension, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, SD: standard deviation, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *N=108, †JADE MONO-1 & 2 and JADE COMPARE subgroup, ‡JADE COMPARE dupilumab nonresponder subgroup, ¶North American subgroup.

**Table G1.4 Baseline Characteristics III**[35-37,39,40,42,44-48,50,51,54,56,63,64,67,69,77-79,81-85,108]

| Study Name | Arms | N | EASI score | | % BSA affected | | SCORAD | | Itch or PP-NRS | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | mean | SD | mean | SD | mean | SD | mean | SD |
| **Abrocitinib** | | | | | | | | | | |
| JADE MONO-1 | PBO | 77 | 28.7 | 12.5 | 47.4 | 22.7 | 64.5 | 13.2 | 7 | 1.8 |
| | ABRO 100 mg | 156 | 31.3 | 13.6 | 50.8 | 23.4 | 67.1 | 13.7 | 6.9 | 2 |
| | ABRO 200 mg | 154 | 30.6 | 14.1 | 49.9 | 24.4 | 64.3 | 13.1 | 7.1 | 1.9 |
| JADE MONO-2 | PBO | 78 | 28 | 10.2 | 48.2 | 20.8 | 64.3 | 12.4 | 6.7 | 1.9 |
| | ABRO 100 mg | 158 | 28.4 | 11.2 | 48.7 | 21.4 | 63.8 | 11.4 | 7.1 | 1.6 |
| | ABRO 200 mg | 155 | 29 | 12.4 | 47.7 | 22.3 | 64.1 | 13.1 | 7 | 1.6 |
| | Overall | 391 | 28.5 | 11.5 | 48.2 | 21.6 | 64 | 12.3 | 7 | 1.7 |
| JADE TEEN | PBO | 96 | 29.2 | 12.7 | 45.8 | 22.4 | | | 7.2 | 1.7 |
| | ABRO 100 mg | 95 | 31 | 12.8 | 51.2 | 21.7 | | | 7 | 1.8 |
| | ABRO 200 mg | 94 | 29.5 | 12.2 | 48.7 | 21.7 | | | 6.8 | 2 |
| | Overall | | | | | | | | | |
| JADE COMPARE | PBO | 131 | 31 | 12.6 | 48.9 | 24.9 | 67.9 | 12 | 7.1 | 1.8 |
| | ABRO 100 mg | 238 | 30.3 | 13.5 | 48.1 | 23.1 | 66.8 | 13.8 | 7.1 | 1.7* |
| | ABRO 200 mg | 226 | 32.1 | 13.1 | 50.8 | 23 | 69.3 | 12.7 | 7.6 | 1.5 |
| | DUP 300 mg | 242 | 30.4 | 12 | 46.5 | 22.1 | 67.9 | 11.4 | 7.3 | 1.7* |
| | Total | 837 | 30.9 | 12.8 | 48.5 | 23.1 | 67.9 | 12.6 | 7.3 | 1.7 |
| JADE EXTEND Subgroup 1[†] | ABRO 100 mg | 595 | 29.6 | 12.4 | 48.6 | 22.8 | NR | NR | 48.6 | 22.8 |
| | ABRO 200 mg | 521 | 30.9 | 13.2 | 49.5 | 23.4 | NR | NR | 49.5 | 23.4 |
| JADE EXTEND Subgroup 2[‡] | ABRO 100 mg | 130 | 29.6 | 11.2 | 45.4 | 21.2 | NR | NR | 7.4 | 1.7 |
| | ABRO 200 mg | 73 | 31.2 | 12.4 | 47.9 | 22.9 | NR | NR | 7.2 | 1.6 |
| Phase IIb Gooderham 2019 | PBO | 56 | 25.4 | 12.9 | 40.1 | 22.3 | 65 | 12.1 | 7.6 | 1.8 |
| | ABRO 100 mg | 56 | 26.7 | 11.8 | 41.9 | 22.3 | 65.4 | 13.7 | 7.4 | 2.2 |
| | ABRO 200 mg | 55 | 24.6 | 13.5 | 38 | 23.3 | 62.7 | 13.7 | 6.9 | 2.7 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Baricitinib** | | | | | | | | | | |
| BREEZE-AD1 | PBO | 249 | 32 | 13 | 53 | 23.1 | 68 | 14 | NR | NR |
| | BARI 1 mg | 127 | 29 | 11.8 | 47 | 21.2 | 66 | 14.4 | NR | NR |
| | BARI 2 mg | 123 | 31 | 11.7 | 50 | 22.1 | 68 | 13 | NR | NR |
| | BARI 4 mg | 125 | 32 | 12.7 | 52 | 21.8 | 68 | 12.9 | NR | NR |
| BREEZE-AD2 | PBO | 244 | 33 | 12.8 | 52 | 21.7 | 68 | 12.7 | NR | NR |
| | BARI 1 mg | 125 | 33 | 12.7 | 55 | 21.9 | 67 | 12.9 | NR | NR |
| | BARI 2 mg | 123 | 35 | 16 | 55 | 26.1 | 69 | 13.3 | NR | NR |
| | BARI 4 mg | 123 | 33 | 12.7 | 54 | 21.5 | 68 | 13.6 | NR | NR |
| BREEZE-AD3 (LTE) | BARI 2 mg | | | | | | | | | |
| BREEZE-AD5 | PBO | 147 | 27 | 11 | 41.5 | 23 | | | 7 | 2.4 |
| | BARI 1 mg | 147 | 27.7 | 12 | 41.4 | 23 | NR | NR | 7.2 | 2 |
| | BARI 2 mg | 146 | 26.6 | 11 | 39.7 | 22 | | | 7.3 | 2.1 |
| BREEZE-AD6 | BARI 2 mg | 146 | 26.6 | 11.4 | NR | NR | 6.5 | 3.1 | 7.7[¥] | 2.1 |
| BREEZE-AD7 | PBO + TCS | 109 | 28.5 | 12.3 | 48.1 | 24.4 | 66.6 | 13.8 | 7.4 | 1.7 |
| | BARI 2 mg + TCS | 109 | 29.3 | 11.9 | 50.6 | 21.6 | 66.8 | 14 | 7 | 2.1 |
| | BARI 4 mg + TCS | 111 | 30.9 | 12.6 | 52.1 | 23.3 | 68.3 | 13.2 | 7 | 2 |
| Phase II Guttman-Yassky 2018 | PBO + TCS | 49 | Median: 22.1 | IQR: 15.3 to 28.0 | NR | NR | Median: 55 | IQR: 44.9 to 63.8 | Median: 7 | IQR: 6 to 8 |
| | BARI 2 mg + TCS | 37 | Median: 22.1 | IQR: 16.8 to 32.3 | NR | NR | Median: 53.3 | IQR: 49.9 to 61.1 | Median: 6 | IQR: 5 to 8 |
| | BARI 4 mg + TCS | 38 | Median: 19.5 | IQR: 13.7 to 25.9 | NR | NR | Median: 57.6 | IQR: 49.5-64.9 | Median: 6.5 | IQR: 4 to 8 |
| **Tralokinumab** | | | | | | | | | | |
| ECZTRA 1 | PBO | 199 | Median: 30.3 | IQR: 22.0 to 41.5 | Median: 52.5 | IQR: 31.0 to 77.0 | Median: 70.8 | IQR: 63.8 to 81.0 | Median: 7.9 | IQR: 6.9 to 8.7 |
| | TRA 300 mg | 603 | Median: 28.2 | IQR: 21.3 to 40.0 | Median: 50.0 | IQR: 33.0 to 70.0 | Median: 69.2 | IQR: 61.5 to 79.1 | Median: 7.9 | IQR: 6.7 to 8.9 |
| | Overall | 802 | NR | NR | NR | NR | NR | NR | NR | NR |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ECZTRA 2 | PBO | 201 | Median: 29.6 | IQR: 20.6 to 41.4 | Median: 50.0 | IQR: 31.0 to 74.0 | Median: 69.9 | IQR: 61.9 to 79.1 | Median: 8.1 | IQR: 7.1 to 9.0 |
| | TRA 300 mg | 593 | Median: 28.2 | IQR: 19.8 to 40.8 | Median: 50.0 | IQR: 31.0 to 74.0 | Median: 69.5 | IQR: 60.5 to 79.1 | Median: 8.0 | IQR: 7.0 to 9.0 |
| | Overall | 794 | NR | NR | NR | NR | NR | NR | NR | NR |
| ECZTRA 2 Subgroup¶ | PBO | 91 | 29.9 | 13.1 | 45.2 | 23.6 | 69 | 11.8 | 8.1 | 1.3 |
| | TRA 300 mg | 270 | 27.9 | 11.8 | 43.5 | 23.5 | 67.1 | 11.3 | 8 | 1.5 |
| ECZTRA 3 | PBO | 127 | Median: 26.5 | IQR: 19.9 to 39.3 | Median: 40.0 | IQR: 26.0 to 74.0 | Median: 67.9 | IQR: 59.4 to 79.0 | Median: 8.0 | IQR: 7.0 to 9.0 |
| | TRA 300 mg | 253 | Median: 24.7 | IQR: 18.4 to 35.9 | Median: 41.0 | IQR: 30.0 to 63.0 | Median: 66.2 | IQR: 57.6 to 76.3 | Median: 8.0 | IQR: 6.6 to 8.7 |
| | Overall | 380 | Median: 25.5 | IQR: 19.2 to 37.1 | Median: 41.0 | IQR: 28.0 to 69.5 | Median: 66.5 | IQR: 57.9 to 77.6 | Median: 8.0 | IQR: 6.6 to 8.9 |
| ECZTEND | Overall | 1174 | Median: 4.7 | IQR: 1.8 to 11.7 | Median: 44.5 | IQR: 30 to 67 | Median: 30.2 | IQR: 18.7 to 45 | NR | NR |
| **Upadacitinib** | | | | | | | | | | |
| MEASURE UP 1 | PBO | 281 | 28.8 | 12.6 | 45.7 | 21.6 | 66.1 | 12.9 | 7.5 | 1.8 |
| | UPA 15 mg | 281 | 30.6 | 12.8 | 48.5 | 22.2 | 68.2 | 12.6 | 7.4 | 1.8 |
| | UPA 30 mg | 285 | 29 | 11.1 | 47 | 22 | 67.3 | 12.5 | 7.5 | 1.7 |
| MEASURE UP 2 | PBO | 278 | 29.1 | 12.1 | 47.6 | 22.7 | 67.9 | 12.1 | 7.5 | 1.9 |
| | UPA 15 mg | 276 | 28.6 | 11.7 | 45.1 | 22.4 | 66.6 | 12.5 | 7.2 | 1.8 |
| | UPA 30 mg | 282 | 29.7 | 12.2 | 47 | 23.2 | 66.7 | 13 | 7.4 | 1.7 |
| AD-UP | PBO + TCS | 304 | 30.3 | 13 | 48.6 | 23.1 | NR | NR | 7.1 | 1.6 |
| | UPA 15 mg + TCS | 300 | 29.2 | 11.8 | 46.7 | 21.6 | NR | NR | 7.1 | 1.8 |
| | UPA 30 mg + TCS | 297 | 29.7 | 11.8 | 48.5 | 23.1 | NR | NR | 7.4 | 1.6 |
| Heads Up | DUP 300 mg | 344 | 28.8 | 11.5 | 44.4 | 22.8 | NR | NR | 7.5 | 1.7 |
| | UPA 30 mg | 348 | 30.8 | 12.5 | 48.2 | 24 | NR | NR | 7.5 | 1.6 |
| Phase IIb Guttman-Yassky 2020 | PBO | 41 | 32.6 | 14.5 | 45.7 | 22.8 | NR | NR | 6.5 | 1.9 |
| | UPA 7.5 mg | 42 | 31.4 | 15.8 | 46.9 | 24.9 | NR | NR | 6.8 | 1.8 |
| | UPA 15 mg | 42 | 31.4 | 12.3 | 50.6 | 21.5 | NR | NR | 6.4 | 1.7 |
| | UPA 30 mg | 42 | 28.2 | 11.6 | 42.1 | 20.4 | NR | NR | 6.3 | 2.1 |
| **Dupilumab** | | | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| SOLO 1 | PBO | 224 | Median: 31.8 | IQR:22.2 to 43.8 | Median: 57 | IQR: 37.4 to 77 | Median: 67.0 | IQR: 58.0 to 77.6 | Median: 7.7 | IQR: 6.2 to 8.6 |
| | DUP 300 mg Q2W | 224 | Median: 30.4 | IQR: 21.5 to 40.8 | Median: 53.4 | IQR: 37.4 to 72.5 | Median: 65.1 | IQR: 56.5 to 77.4 | Median: 7.6 | IQR: 5.9 to 8.7 |
| | DUP 300 mg QW | 223 | Median: 29.8 | IQR: 22.0 to 41.2 | Median: 54.5 | IQR: 39.0 to 73 | Median: 65.9 | IQR: 57.2 to 75.8 | Median: 7.7 | IQR: 6.0 to 8.7 |
| SOLO 2 | PBO | 236 | Median: 30.5 | IQR: 22.1 to 41.7 | Median: 53.3 | IQR: 34.0 to 72.8 | Median: 68.9 | IQR: 58.6 to 78.5 | Median: 7.7 | IQR: 6.5 to 9.0 |
| | DUP 300 mg Q2W | 233 | Median: 28.6 | IQR: 21.0 to 40.1 | Median: 50.0 | IQR: 36.0 to 68.0 | Median: 67.8 | IQR: 57.3 to 76.7 | Median: 7.8 | IQR: 6.7 to 8.9 |
| | DUP 300 mg QW | 239 | Median: 29.0 | IQR: 21.2 to 41.8 | Median: 50.0 | IQR: 34.0 to 69.0 | Median: 67.4 | IQR: 58.4 to 77.9 | Median: 7.8 | IQR: 6.3 to 8.9 |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | Median: 29.6 | IQR: 22.2 to 40.8 | Median: 55.0 | IQR: 40 to 75 | Median: 64.1 | IQR: 55.9 to 76.1 | Median: 7.6 | IQR: 6.3 to 8.6 |
| | DUP 300 mg + TCS Q2W | 106 | Median: 30.9 | IQR: 22.3 to 41.6 | Median: 58.8 | IQR: 43.5 to 78.5 | Median: 69.7 | IQR: 60.4 to 79.8 | Median: 7.7 | IQR: 6.6 to 8.5 |
| | DUP 300 mg + TCS QW | 319 | Median: 29.0 | IQR: 21.6 to 40.7 | Median: 52.0 | IQR: 36 - 71.5 | Median: 65.3 | IQR: 55.2 to 76.3 | Median: 7.4 | IQR: 6.0 to 8.6 |
| AD SOLO-CONTINUE | PBO | 83 | 2.5 | 2.3 | 8.1 | 8.2 | 16.8 | 10 | 2.8 | 2.1 |
| | DUP 300 mg Q8W | 84 | 2.3 | 2.3 | 7.9 | 9 | 17.1 | 9.4 | 2.7 | 2.3 |
| | DUP 300 mg Q4W | 86 | 2.8 | 3.3 | 9.3 | 10.5 | 17.5 | 10.6 | 3.1 | 2.2 |
| | DUP 300 mg QW/Q2W | 169 | 2.6 | 2.9 | 7.9 | 9 | 17.1 | 10.5 | 2.8 | 1.9 |
| Phase IIb Thaci 2016 | PBO QW | 61 | 32.9 | 13.8 | 51.1 | 24 | 67.1 | 13.6 | 6.34 | 1.83 |
| | DUP 200 mg Q2W | 61 | 32.9 | 15.5 | 50.8 | 23 | 68.3 | 14.0 | 6.98 | 2.32 |
| | DUP 300 mg Q2W | 64 | 33.8 | 14.5 | 53.2 | 25 | 68.5 | 12.6 | 6.74 | 2.07 |
| | DUP 300 mg Q4W | 65 | 29.4 | 11.5 | 48.7 | 24 | 67.2 | 12.3 | 6.84 | 1.85 |

ABRO: abrocitinib, BARI: baricitinib, BSA: body surface area, DUP: dupilumab, IQR: interquartile range, kg: kilogram, LTE: long-term extension, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, SD: standard deviation, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *N=241, [†]JADE MONO-1 & 2 and JADE COMPARE subgroup, [‡]JADE COMPARE dupilumab nonresponder subgroup, [¶]North American subgroup, [¥]SCORAD pruritus.

**Table G1.5. Baseline Characteristics IV**[35-37,39,40,42,44-48,50,51,54,56,63,64,67,78,79,82-85]

| Study Name | Arms | N | DLQI | | | CDLQI | | | POEM | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | mean | SD | N | mean | SD | mean | SD |
| **Abrocitinib** | | | | | | | | | | |
| JADE MONO-1 | PBO | 77 | NR | 13.9 | 7.3 | NR | 13.6 | 7 | 19.9 | 6.1 |
| | ABRO 100 mg | 156 | NR | 14.6 | 6.5 | NR | 11.7 | 6.6 | 19.5 | 6.5 |
| | ABRO 200 mg | 154 | NR | 14.6 | 6.8 | NR | 13.2 | 5.5 | 19.6 | 5.9 |
| JADE MONO-2 | PBO | 78 | 70 | 15 | 7.1 | 8 | 10.1 | 3.8 | 19.2 | 5.5 |
| | ABRO 100 mg | 158 | 140 | 15.4 | 7.3 | 16 | 13.8 | 5.8 | 20.9 | 5.7 |
| | ABRO 200 mg | 155 | 139 | 14.8 | 6 | 15 | 12.9 | 5.7 | 19.7 | 5.7 |
| | Overall | 391 | 349 | 15 | 6.8 | 39 | 12.7 | 5.4 | 20.1 | 5.7 |
| JADE TEEN | PBO | 96 | NA | NA | NA | | | | | |
| | ABRO 100 mg | 95 | NA | NA | NA | | | | | |
| | ABRO 200 mg | 94 | NA | NA | NA | | | | | |
| | Overall | 285 | NA | NA | NA | | | | | |
| JADE COMPARE | PBO | 131 | 131 | 15.2 | 6.9 | NR | NR | NR | 20.4 | 6.1 |
| | ABRO 100 mg | 238 | 238 | 15.5 | 6.4 | NR | NR | NR | 20.9 | 5.5 |
| | ABRO 200 mg | 226 | 226 | 16.3 | 6.6 | NR | NR | NR | 21.5 | 5.3 |
| | DUP 300 mg | 242 | 242 | 15.6 | 6.7 | NR | NR | NR | 21.1 | 5.5 |
| | Total | 837 | 837 | 15.7 | 6.6 | NR | NR | NR | 21.1 | 5.5 |
| **Baricitinib** | | | | | | | | | | |
| BREEZE-AD1 | PBO | 249 | 249 | 14 | 7.4 | NA | NA | NA | 21 | 5.6 |
| | BARI 1 mg | 127 | 127 | 13 | 6.8 | NA | NA | NA | 20 | 5.6 |
| | BARI 2 mg | 123 | 123 | 13 | 7.7 | NA | NA | NA | 21 | 5.6 |
| | BARI 4 mg | 125 | 125 | 14 | 7.1 | NA | NA | NA | 21 | 5.6 |
| BREEZE-AD2 | PBO | 244 | 244 | 15 | 8.1 | NA | NA | NA | 21 | 6.3 |
| | BARI 1 mg | 125 | 125 | 15 | 8.1 | NA | NA | NA | 20 | 6.5 |

| Study Name | Arms | N | DLQI | | | CDLQI | | | POEM | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | mean | SD | N | mean | SD | mean | SD |
| | BARI 2 mg | 123 | 123 | 14 | 7.7 | NA | NA | NA | 21 | 6 |
| | BARI 4 mg | 123 | 123 | 14 | 8.4 | NA | NA | NA | 20 | 6.3 |
| BREEZE-AD3 (LTE) | BARI 2 mg | | | | | NA | NA | NA | | |
| BREEZE-AD5 | PBO | 147 | 147 | 15 | 7 | NA | NA | NA | | |
| | BARI 1 mg | 147 | 147 | 15 | 7 | NA | NA | NA | NR | NR |
| | BARI 2 mg | 146 | 146 | 15 | 8 | NA | NA | NA | | |
| BREEZE-AD6 | BARI 2 mg | 146 | 146 | 15 | 7.6 | NA | NA | NA | NR | NR |
| BREEZE-AD7 | PBO + TCS | 109 | 109 | 15 | 7.9 | NA | NA | NA | 20.9 | 6.7 |
| | BARI 2 mg + TCS | 109 | 109 | 15 | 7.7 | NA | NA | NA | 21 | 6.3 |
| | BARI 4 mg + TCS | 111 | 111 | 14.7 | 7.9 | NA | NA | NA | 21.4 | 6 |
| Phase II Guttman-Yassky 2018 | PBO + TCS | 49 | 49 | Median: 15.0 | IQR: 10.0 to 19.0 | NA | NA | NA | Median: 20.0 | IQR: 17.0 to 23.0 |
| | BARI 2 mg + TCS | 37 | 37 | Median: 10.0 | IQR: 7.0 to 17.0 | NA | NA | NA | Median: 17.0 | IQR: 12.0 to 25.0 |
| | BARI 4 mg + TCS | 38 | 38 | Median: 11.0 | IQR: 8.0 to 17.0 | NA | NA | NA | Median: 20.5 | IQR: 11.0 to 26.0 |
| **Tralokinumab** | | | | | | | | | | |
| ECZTRA 1 | PBO | 199 | NR | Median: 16.0 | IQR: 13.0 to 22.0 | NA | NA | NA | Median: 24.0 | IQR: 20.0 to 27.0 |
| | TRA 300 mg | 603 | NR | Median: 17.0 | IQR: 12.0 to 22.0 | NA | NA | NA | Median: 24.0 | IQR: 20.0 to 27.0 |
| | Overall | 802 | NR | NR | NR | NA | NA | NA | NR | NR |
| ECZTRA 2 | PBO | 201 | NR | Median: 18.0 | IQR: 12.5 to 24.0 | NA | NA | NA | Median: 24.0 | IQR: 20.0 to 27.5 |
| | TRA 300 mg | 593 | NR | Median: 18.0 | IQR: 13.0 to 23.0 | NA | NA | NA | Median: 24.0 | IQR: 20.0 to 27.0 |
| | Overall | 794 | NR | NR | NR | NA | NA | NA | NA | NA |
| ECZTRA 2 Subgroup* | PBO | 91 | NR | 17.3 | 7.8 | NA | NA | NA | NA | NA |
| | TRA 300 mg | 270 | NR | 17.5 | 7.2 | NA | NA | NA | NA | NA |
| ECZTRA 3 | PBO + TCS | 127 | 125 | Median: 18.0 | IQR: 12.0 to 23.0 | NA | NA | NA | Median: 24.0 | IQR: 20.0 to 27.0 |
| | TRA 300 mg + TCS | 253 | 250 | Median: 18.0 | IQR: 12.0 to 23.0 | NA | NA | NA | Median: 23.0 | IQR: 20.0 to 26.0 |
| | Overall | 380 | 375 | Median: 18.0 | IQR: 12.0 to 23.0 | NA | NA | NA | Median: 23.0 | IQR: 20.0 to 27.0 |
| ECZTEND | Overall | 1174 | 1174 | Median: 5 | IQR: 2 to 10 | NA | NA | NA | Median: 12 | IQR: 6 to 18 |

| Study Name | Arms | N | DLQI | | | CDLQI | | | POEM | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | mean | SD | N | mean | SD | mean | SD |
| **Upadacitinib** | | | | | | | | | | |
| MEASURE UP 1 | PBO | 281 | NR | 17 | 6.8 | NR | NR | NR | 21.5 | 5.3 |
| | UPA 15 mg | 281 | NR | 16.2 | 7 | NR | NR | NR | 21.2 | 4.8 |
| | UPA 30 mg | 285 | NR | 16.4 | 7 | NR | NR | NR | 21.4 | 5.1 |
| MEASURE UP 2 | PBO | 278 | NR | 17.1 | 7.2 | NR | NR | NR | 21.9 | 5.2 |
| | UPA 15 mg | 276 | NR | 16.9 | 7 | NR | NR | NR | 21.2 | 5.1 |
| | UPA 30 mg | 282 | NR | 16.7 | 6.9 | NR | NR | NR | 21.8 | 4.8 |
| AD-UP | PBO + TCS | 304 | NR | 16.3 | 7 | NR | NR | NR | 21.5 | 5.1 |
| | UPA 15 mg + TCS | 300 | NR | 16.4 | 7.2 | NR | NR | NR | 21 | 5 |
| | UPA 30 mg + TCS | 297 | NR | 17.1 | 7 | NR | NR | NR | 21.5 | 5.3 |
| **Dupilumab** | | | | | | | | | | |
| SOLO 1 | PBO | 224 | 224 | Median: 14.0 | IQR: 9.0 to 20.0 | NA | NA | NA | Median: 21.0 | IQR: 16.0-25.0 |
| | DUP 300 mg Q2W | 224 | 224 | Median: 13.0 | IQR: 8.0 to 19.0 | NA | NA | NA | Median: 21.0 | IQR: 16.0 to 25.0 |
| | DUP 300 mg QW | 223 | 223 | Median: 14.0 | IQR: 8.0 to 20.0 | NA | NA | NA | Median: 22.0 | IQR: 17.0 to 26.0 |
| SOLO 2 | PBO | 236 | 236 | Median: 15.0 | IQR: 9.0 to 22.0 | NA | NA | NA | Median: 23.0 | IQR: 17.0 to 26.0 |
| | DUP 300 mg Q2W | 233 | 233 | Median: 15.0 | IQR: 10.0 to 21.0 | NA | NA | NA | Median: 21.0 | IQR: 18.0 to 25.0 |
| | DUP 300 mg QW | 239 | 239 | Median: 16.0 | IQR: 10.0 to 22.0 | NA | NA | NA | Median: 21.0 | IQR: 18.0 to 26.0 |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | 315 | Median: 14 | IQR: 9 to 20 | NA | NA | NA | Median: 20 | IQR: 16 to 25 |
| | DUP 300 mg + TCS Q2W | 106 | 106 | Median: 13.5 | IQR: 8 to 20 | NA | NA | NA | Median: 21 | IQR: 16 to 25 |
| | DUP 300 mg + TCS QW | 319 | 319 | Median: 14 | IQR: 8 to 20 | NA | NA | NA | Median: 20 | IQR: 16 to 25 |
| AD SOLO-CONTINUE | PBO | 83 | NR | 3.4 | 4.3 | NA | NA | NA | 6.1 | 5.4 |
| | DUP 300 mg Q8W | 84 | NR | 3 | 3.8 | NA | NA | NA | 6.8 | 5.9 |
| | DUP 300 mg Q4W | 86 | NR | 3.2 | 3.9 | NA | NA | NA | 6.1 | 5.1 |
| | DUP 300 mg QW/Q2W | 169 | NR | 3.4 | 4.2 | NA | NA | NA | 6.4 | 5.3 |

| Study Name | Arms | N | DLQI | | | CDLQI | | | POEM | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | mean | SD | N | mean | SD | mean | SD |
| Phase IIb Thaci 2016 | PBO QW | 61 | 61 | 12.8 | 6.2 | NA | NA | NA | NR | NR |
| | DUP 200 mg Q2W | 61 | 61 | 15 | 7.1 | NA | NA | NA | NR | NR |
| | DUP 300 mg Q2W | 64 | 64 | 14.5 | 7.2 | NA | NA | NA | NR | NR |
| | DUP 300 mg Q4W | 65 | 65 | 13.3 | 7.3 | NA | NA | NA | NR | NR |

None of these baseline characteristics were available in JADE EXTEND, Phase IIb Gooderham 2019, Heads Up, and Phase IIb Guttman-Yassky 2020. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, IQR: interquartile range, kg: kilogram, LTE: long-term extension, mg: milligram, N: total number, NA: not applicable, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, SD: standard deviation, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib. *North American subgroup.

**Table G1.6. Baseline Characteristics V**[36,44-47,50,51,54,82]

| Study Name | Arms | N | Total HADS | | HADS Anxiety | | HADS Depression | |
|---|---|---|---|---|---|---|---|---|
| | | | mean | SD | mean | SD | mean | SD |
| **Abrocitinib** | | | | | | | | |
| JADE MONO-2 | PBO | 78 | NR | NR | 6 | 3.7 | 4.4 | 3.3 |
| | ABRO 100 mg | 158 | NR | NR | 5.5 | 4.2 | 4.1 | 4 |
| | ABRO 200 mg | 155 | NR | NR | 5.9 | 3.9 | 4 | 3.7 |
| | Overall | 391 | NR | NR | 5.7 | 4 | 4.1 | 3.8 |
| **Baricitinib** | | | | | | | | |
| BREEZE-AD3 (LTE) | BARI 2 mg | NR | NR | NR | | | | |
| BREEZE-AD5 | PBO | 147 | NR | NR | | | | |
| | BARI 1 mg | 147 | NR | NR | NR | NR | NR | NR |
| | BARI 2 mg | 146 | NR | NR | | | | |
| BREEZE-AD7 | PBO + TCS | 109 | NR | NR | 6.8 | 4.3 | 5.8 | 4.3 |
| | BARI 2 mg + TCS | 109 | NR | NR | 6.4 | 4 | 5.3 | 3.7 |
| | BARI 4 mg + TCS | 111 | NR | NR | 6.7 | 4.4 | 5.5 | 4.1 |

| Study Name | Arms | N | Total HADS | | HADS Anxiety | | HADS Depression | |
|---|---|---|---|---|---|---|---|---|
| | | | mean | SD | mean | SD | mean | SD |
| **Upadacitinib** | | | | | | | | |
| MEASURE UP 1 | PBO | 281 | NR | NR | 7.2 | 4.4 | 5 | 4 |
| | UPA 15 mg | 281 | NR | NR | 7.5 | 4 | 5.2 | 3.9 |
| | UPA 30 mg | 285 | NR | NR | 7.4 | 4.4 | 5.2 | 4.2 |
| MEASURE UP 2 | PBO | 278 | NR | NR | 7.5 | 4.3 | 5.8 | 4.1 |
| | UPA 15 mg | 276 | NR | NR | 7.2 | 4.2 | 5.3 | 4.2 |
| | UPA 30 mg | 282 | NR | NR | 7.6 | 4.3 | 5.9 | 4.1 |
| **Dupilumab** | | | | | | | | |
| SOLO 1 | PBO | 224 | Median:12 | IQR: 6.0 to 17.0 | NR | NR | NR | NR |
| | DUP 300 mg Q2W | 224 | Median: 11 | IQR: 6.0 to 17.0 | NR | NR | NR | NR |
| | DUP 300 mg QW | 223 | Median: 12 | IQR: 6.0 to 17.5 | NR | NR | NR | NR |
| SOLO 2 | PBO | 236 | Median: 12 | IQR: 7.0 to 19.0 | NR | NR | NR | NR |
| | DUP 300 mg Q2W | 233 | Median: 13 | IQR: 8.0 to 19.0 | NR | NR | NR | NR |
| | DUP 300 mg QW | 239 | Median: 14 | IQR: 8.0 to 20.0 | NR | NR | NR | NR |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | Median: 11 | IQR:6.0 to 18.0 | NR | NR | NR | NR |
| | DUP 300 mg + TCS Q2W | 106 | Median: 12.5 | IQR: 7.0 to 18.0 | NR | NR | NR | NR |
| | DUP 300 mg + TCS QW | 319 | Median: 12.0 | IQR:7.0 to 18.0 | NR | NR | NR | NR |
| | PBO | 83 | 5.9 | 6.4 | NR | NR | NR | NR |

| Study Name | Arms | N | Total HADS | | HADS Anxiety | | HADS Depression | |
|---|---|---|---|---|---|---|---|---|
| | | | mean | SD | mean | SD | mean | SD |
| AD SOLO-CONTINUE | DUP 300 mg Q8W | 84 | 7.1 | 6.9 | NR | NR | NR | NR |
| | DUP 300 mg Q4W | 86 | 7.3 | 7.5 | NR | NR | NR | NR |
| | DUP 300 mg QW/Q2W | 169 | 6.4 | 5.9 | NR | NR | NR | NR |

None of these baseline characteristics were available in JADE MONO-1, JADE TEEN, JADE COMPARE, JADE EXTEND, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEEZE-AD6, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, AD-UP, Heads Up, Phase IIb Guttman-Yassky 2020, and Phase IIb Thaci 2016. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, IQR: interquartile range, LTE: long-term extension, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, SD: standard deviation, TCS: topical corticosteroids.

**Table G1.7. Baseline Characteristics: Previous Treatments**[35-37,46,63,64,67]

| Study Name | Arms | N | Previous Treatment(s) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Any previous treatment | | Topical corticosteroids | | Topical agents alone | | Systemic agents | |
| | | | n | % | n | % | n | % | n | % |
| **Abrocitinib** | | | | | | | | | | |
| JADE MONO-1 | PBO | 77 | 77 | 100 | NR | NR | 34 | 44 | 41 | 53 |
| | ABRO 100 mg | 156 | 155 | 99 | NR | NR | 69 | 44 | 78 | 50 |
| | ABRO 200 mg | 154 | 154 | 100 | NR | NR | 82 | 53 | 68 | 44 |
| JADE MONO-2 | PBO | 78 | 78 | 100 | NR | NR | 46 | 59 | 32 | 41 |
| | ABRO 100 mg | 158 | 157 | 99.4 | NR | NR | 87 | 55.1 | 70 | 44.3 |
| | ABRO 200 mg | 155 | 153 | 98.7 | NR | NR | 93 | 60 | 60 | 38.7 |
| | Overall | 391 | 388 | 99.2 | NR | NR | 226 | 57.8 | 162 | 41.4 |
| JADE COMPARE | PBO | 131 | | | NR | NR | | | | |
| | ABRO 100 mg | 238 | | | NR | NR | | | | |
| | ABRO 200 mg | 226 | | | NR | NR | | | | |
| | DUP 300 mg | 242 | | | NR | NR | | | | |

| Study Name | Arms | N | Previous Treatment(s) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Any previous treatment | | Topical corticosteroids | | Topical agents alone | | Systemic agents | |
| | | | n | % | n | % | n | % | n | % |
| | Total | 837 | | | NR | NR | | | | |
| **Baricitinib** | | | | | | | | | | |
| BREEZE-AD7 | PBO + TCS | 109 | NR | NR | 101 | 93 | NR | NR | NR | NR |
| | BARI 2 mg + TCS | 109 | NR | NR | 100 | 92 | NR | NR | NR | NR |
| | BARI 4 mg + TCS | 111 | NR | NR | 103 | 93 | NR | NR | NR | NR |
| **Tralokinumab** | | | | | | | | | | |
| ECZTRA 1 | PBO | 199 | 197 | 99 | 195 | 98 | NR | NR | NR | NR |
| | TRA 300 mg | 603 | 598 | 99.2 | 591 | 98 | NR | NR | NR | NR |
| ECZTRA 2 | PBO | 201 | 201 | 100 | 200 | 99.5 | NR | NR | NR | NR |
| | TRA 300 mg | 593 | 591 | 99.7 | 584 | 98.5 | NR | NR | NR | NR |
| ECZTRA 2 Subgroup* | PBO | 91 | NR | NR | 91 | 100 | NR | NR | NR | NR |
| | TRA 300 mg | 270 | NR | NR | 269 | 99.6 | NR | NR | NR | NR |
| ECZTRA 3 | PBO + TCS | 127 | 127 | 100 | 122 | 96.1 | NR | NR | NR | NR |
| | TRA 300 mg + TCS | 253 | 253 | 100 | 251 | 99.2 | NR | NR | NR | NR |
| | Overall | 380 | 380 | 100 | 373 | 98.2 | NR | NR | NR | NR |
| **Upadacitinib** | | | | | | | | | | |
| AD-UP | PBO + TCS | 304 | 157 | 52 | NR | NR | NR | NR | NR | NR |
| | UPA 15 mg + TCS | 300 | 171 | 57 | NR | NR | NR | NR | NR | NR |
| | UPA 30 mg + TCS | 297 | 172 | 58 | NR | NR | NR | NR | NR | NR |

None of these baseline characteristics were available in JADE TEEN, JADE EXTEND, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5, BREEZE-AD6, Phase II Guttman-Yassky 2018, ECZTEND, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase IIb Guttman-Yassky 2020, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD SOLO-CONTINUE, and Phase IIb Thaci 2016. No trials reported on previous treatment use with crisaborole. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, TCS: topical corticosteroids, TRA: tralokinumab, %: percent. *North American subgroup.

**Table G1.8. Short-Term Efficacy Outcomes: IGA Response Rates**[35-37,40,42,45,46,48,50,51,56,63,64,67,69,82,83,85]

| Study Name | Arms | N | IGA response | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | | |
| | PBO | 77 | 6 | 76 | 8 | REF | REF | REF |
| | ABRO 100 mg | 156 | 37 | 156 | 24 | 15.8 | 6.8 to 24.8 | 0.0037 |
| | ABRO 200 mg | 154 | 67 | 153 | 44 | 36 | 26.2 to 45.7 | <0.0001 |
| JADE MONO-2 | PBO | 78 | 7 | 77 | 9.1 | REF | REF | REF |
| | ABRO 100 mg | 158 | 44 | 155 | 28.4 | 19.3 | 9.6 to 29.0 | 0.0008 |
| | ABRO 200 mg | 155 | 59 | 155 | 38.1 | 28.7 | 18.6 to 38.8 | <0.0001 |
| JADE TEEN | PBO | 96 | 23 | 94 | 24.5 | REF | REF | REF |
| | ABRO 100 mg | 95 | 37 | 89 | 41.6 | 16.7 | 3.5 to 29.9 | 0.0147 |
| | ABO 200 mg | 94 | 43 | 93 | 46.2 | 20.6 | 7.3 to 33.9 | 0.003 |
| JADE COMPARE | PBO | 131 | 18 | 129 | 14 | REF | REF | REF |
| | ABRO 100 mg | 238 | 86 | 235 | 36.6 | 23.1 | 14.7 to 31.4 | <0.001 |
| | ABRO 200 mg | 226 | 106 | 219 | 48.4 | 34.8 | 26.1 to 43.5 | <0.001 |
| | DUP 300 mg | 242 | 88 | 241 | 36.5 | 22.5 | 14.2 to 30.9 | NR |
| | **Week 16** | | | | | | | |
| | PBO | 131 | 16 | 124 | 12.9 | REF | REF | REF |
| | ABRO 100 mg + PBO→ABRO 100 mg | 238 | 80 | 230 | 34.8 | 22.1 | 13.7 to 30.5 | <0.001 |
| | ABRO 200 mg + PBO→ABRO 200 mg | 226 | 105 | 221 | 47.5 | 35 | 26.3 to 43.7 | <0.001 |
| | DUP 300 mg + Oral PBO→PBO | 242 | 90 | 232 | 38.8 | 25.6 | 17.1 to 34.1 | NR |
| Phase IIb Gooderham 2019 | **Week 12** | | | | | | | |
| | PBO | 52 | 3 | 52 | 5.8 | REF | 0.0 to 12.1 | REF |
| | ABRO 100 mg | 54 | 16 | 54 | 29.6 | NR | 17.5 to 41.8 | <0.001 |
| | ABRO 200 mg | 48 | 21 | 48 | 43.8 | NR | 29.7 to 57.8 | <0.001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Baricitinib** | | | | | | | | |
| | **Week 16** | | | | | | | |
| BREEZE-AD1 | PBO | 249 | 12 | 249 | 4.8 | REF | NR | REF |
| | BARI 1 mg | 127 | 15 | 127 | 11.8 | 7.0 | 7.3 to 18.6 | 0.014 |
| | BARI 2 mg | 123 | 14 | 123 | 11.4 | 6.6 | 6.9 to 18.2 | 0.02 |
| | BARI 4 mg | 125 | 21 | 125 | 16.8 | 12.0 | 11.3 to 24.3 | <0.001 |
| BREEZE-AD2 | PBO | 244 | 11 | 244 | 4.5 | REF | 2.5 to 7.9 | REF |
| | BARI 1 mg | 125 | 11 | 125 | 8.8 | 4.3 | 5.0 to 15.1 | 0.108 |
| | BARI 2 mg | 123 | 13 | 123 | 10.6 | 6.1 | 6.3 to 17.2 | 0.042 |
| | BARI 4 mg | 123 | 17 | 123 | 13.8 | 9.3 | 8.8 to 21.0 | 0.003 |
| BREEZE-AD5 | PBO | 147 | 8 | 147 | 5.4 | NR | NR | NR |
| | BARI 1 mg | 147 | 19 | 147 | 12.9 | NR | NR | NR |
| | BARI 2 mg | 146 | 35 | 146 | 24 | NR | NR | ≤0.001 |
| BREEZE-AD7 | PBO + TCS | 109 | 16 | 109 | 14.7 | REF | REF | NR |
| | BARI 2 mg + TCS | 109 | 26 | 109 | 23.9 | 9.2 | NR | NR |
| | BARI 4 mg + TCS | 111 | 34 | 111 | 30.6 | 15.9 | NR | NR |
| Phase II Guttman-Yassky 2018 | PBO + TCS | 49 | 4 | 49 | 8.2 | REF | NR | REF |
| | BARI 2 mg + TCS | 37 | 8 | 37 | 21.6 | 13.4 | NR | 0.115 |
| | BARI 4 mg + TCS | 38 | 8 | 38 | 21.1 | 12.9 | NR | 0.118 |
| **Tralokinumab** | | | | | | | | |
| | **Week 16** | | | | | | | |
| ECZTRA 1 | PBO | 197 | 14 | 197 | 7.1 | REF | REF | REF |
| | TRA 300 mg | 601 | 95 | 601 | 15.8 | 8.6 | 4.1 to 13.1 | 0.002 |
| ECZTRA 2 | PBO | 201 | 22 | 201 | 10.9 | REF | REF | REF |
| | TRA 300 mg | 591 | 131 | 591 | 22.2 | 11.1 | 5.8 to 16.4 | <0.001 |
| ECZTRA 2 Subgroup[†] | PBO | 91 | 13 | 91 | 14.3 | REF | REF | REF |
| | TRA 300 mg | 270 | 70 | 270 | 25.9 | RD: 11.7 | 3.0 to 20.4 | 0.021 |
| ECZTRA 3 | PBO + TCS | 126 | 33 | 126 | 26.2 | REF | REF | REF |
| | TRA 300 mg + TCS | 252 | 98 | 252 | 38.9 | 12.4 | 2.9 to 21.9 | 0.015 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Upadacitinib** | | | | | | | | |
| MEASURE UP 1 | **Week 16** | | | | | | | |
| | PBO | 281 | 22 | 281 | 8 | NR | NR | REF |
| | UPA 15 mg | 281 | 135 | 281 | 48 | NR | NR | <0.001 |
| | UPA 30 mg | 285 | 177 | 285 | 62 | NR | NR | <0.001 |
| MEASURE UP 2 | PBO | 278 | 14 | 278 | 5 | NR | NR | REF |
| | UPA 15 mg | 276 | 108 | 276 | 39 | NR | NR | <0.001 |
| | UPA 30 mg | 282 | 147 | 282 | 52 | NR | NR | <0.001 |
| AD-UP | PBO + TCS | 304 | 33 | 304 | 11 | REF | REF | REF |
| | UPA 15 mg + TCS | 300 | 120 | 300 | 40 | 28.5 | 22.1 to 34.9 | <0.001 |
| | UPA 30 mg + TCS | 297 | 175 | 297 | 59 | 47.6 | 41.1 to 54.0 | <0.001 |
| Phase IIb Guttman-Yassky 2020 | **Week 8** | | | | | | | |
| | PBO | 41 | 0 | 41 | 0* | NR | NR | NR |
| | UPA 7.5 mg | 42 | 7 | 42 | 16.7* | NR | NR | NR |
| | UPA 15 mg | 42 | 10 | 42 | 23.4* | NR | NR | NR |
| | UPA 30 mg | 42 | 22 | 42 | 52.2* | NR | NR | NR |
| | **Week 16** | | | | | | | |
| | PBO | 41 | 1 | 41 | 2.4 | NR | NR | REF |
| | UPA 15 mg | 42 | 13 | 42 | 31 | NR | NR | <0.001 |
| | UPA 30 mg | 42 | 21 | 42 | 50 | NR | NR | <0.001 |
| **Dupilumab** | | | | | | | | |
| SOLO 1 | **Week 16** | | | | | | | |
| | PBO | 224 | 23 | 224 | 10 | NR | NR | NR |
| | DUP 300 mg Q2W | 224 | 85 | 224 | 38 | NR | NR | NR |
| | DUP 300 mg QW | 223 | 83 | 223 | 37 | NR | NR | NR |
| SOLO 2 | PBO | 236 | 20 | 236 | 8 | NR | NR | NR |
| | DUP 300 mg Q2W | 233 | 84 | 233 | 36 | NR | NR | NR |
| | DUP 300 mg QW | 239 | 87 | 239 | 36 | NR | NR | NR |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | 39 | 315 | 12 | REF | REF | REF |
| | DUP 300 mg + TCS Q2W | 106 | 41 | 106 | 39 | 26 | 16.3 to 36.3 | <0.0001 |
| | DUP 300 mg + TCS QW | 319 | 125 | 319 | 39 | 27 | 20.3 to 33.3 | <0.0001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Phase IIb Thaci 2016 | PBO QW | 61 | 1 | 61 | 2 | REF | REF | REF |
| | DUP 200 mg Q2W | 61 | 17 | 61 | 28 | 26.2 | 14.5 to 37.9 | <0.0001 |
| | DUP 300 mg Q2W | 64 | 19 | 64 | 30 | 28 | 16.4 to 39.7 | <0.0001 |
| | DUP 300 mg Q4W | 65 | 14 | 65 | 22 | 19.9 | 9.4 to 30.4 | 0.0004 |

Short-term data on IGA were not available in Heads Up. ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, NS: not significant, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, RD: risk difference, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *digitized estimate, †North American subgroup.

**Table G1.9. Short-Term Efficacy Outcomes: EASI75**[35-37,40,42,45,46,48,50,51,56,63,64,67,69,81-83,85]

| Study Name | Arms | N | EASI 75 | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | | |
| | PBO | 77 | 9 | 76 | 12 | REF | REF | REF |
| | ABRO 100 mg | 156 | 62 | 156 | 40 | 27.9 | 17.4 to 38.3 | <0.0001 |
| | ABRO 200 mg | 154 | 96 | 153 | 63 | 51 | 40.5 to 61.5 | <0.0001 |
| JADE MONO-2 | PBO | 78 | 8 | 77 | 10.4 | REF | REF | REF |
| | ABRO 100 mg | 158 | 69 | 155 | 44.5 | 33.9 | 23.3 to 44.4 | <0.0001 |
| | ABRO 200 mg | 155 | 94 | 154 | 61 | 50.5 | 40.0 to 60.9 | <0.0001 |
| JADE TEEN | PBO | 96 | 66 | 94 | 41.5 | REF | REF | REF |
| | ABRO 100 mg | 95 | 78 | 89 | 68.5 | 26.5 | 13.1 to 39.8 | 0.0002 |
| | ABO 200 mg | 94 | 81 | 93 | 72 | 29.4 | 16.3 to 42.5 | <0.0001 |
| JADE COMPARE | PBO | 131 | 35 | 129 | 27.1 | REF | REF | REF |
| | ABRO 100 mg | 238 | 138 | 235 | 58.7 | 31.9 | 22.2 to 41.6 | <0.001 |
| | ABRO 200 mg | 226 | 154 | 219 | 70.3 | 43.2 | 33.7 to 52.7 | <0.001 |
| | DUP 300 mg | 242 | 140 | 241 | 58.1 | 30.9 | 21.1 to 40.6 | REF |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Week 16** | | | | | | | |
| | PBO | 131 | 38 | 124 | 30.6 | REF | REF | REF |
| | ABRO 100 mg + PBO→ABRO 100 mg | 238 | 138 | 229 | 60.3 | 29.7 | 19.5 to 39.9 | <0.001 |
| | ABRO 200 mg + PBO→ABRO 200 mg | 226 | 157 | 221 | 71 | 40.4 | 30.4 to 50.4 | <0.001 |
| | DUP 300 mg + Oral PBO→PBO | 242 | 152 | 232 | 65.5 | 34.7 | 24.6 to 44.8 | NR |
| Phase IIb Gooderham 2019 | **Week 12** | | | | | | | |
| | PBO | 52 | 8 | 52 | 15.4 | REF | REF | NR |
| | ABRO 100 mg | 54 | 22 | 54 | 40.7 | 3.86 | 1.8 to 8.4 | NR |
| | ABRO 200 mg | 48 | 31 | 48 | 64.6 | 9.51 | 4.3 to 21.2 | NR |
| **Baricitinib** | | | | | | | | |
| BREEZE-AD1 | **Week 16** | | | | | | | |
| | PBO | 249 | 22 | 249 | 8.8 | REF | REF | REF |
| | BARI 1 mg | 127 | 22 | 127 | 17.3 | 8.5 | 11.7 to 24.8 | 0.0032 |
| | BARI 2 mg | 123 | 23 | 123 | 18.7 | 9.9 | 12.8 to 26.5 | 0.006 |
| | BARI 4 mg | 125 | 31 | 125 | 24.8 | 16.0 | 18.1 to 33.0 | <0.001 |
| BREEZE-AD2 | PBO | 244 | 15 | 244 | 6.1 | REF | 3.8 to 9.9 | REF |
| | BARI 1 mg | 125 | 16 | 125 | 12.8 | 6.7 | 8.0 to 19.8 | 0.046 |
| | BARI 2 mg | 123 | 22 | 123 | 17.9 | 11.8 | 12.1 to 25.6 | <0.001 |
| | BARI 4 mg | 123 | 26 | 123 | 21.1 | 15.0 | 14.9 to 29.2 | <0.001 |
| BREEZE-AD5 | PBO | 147 | 12 | 147 | 8.2 | NR | NR | REF |
| | BARI 1 mg | 147 | 19 | 147 | 12.9 | NR | NR | NS |
| | BARI 2 mg | 146 | 43 | 146 | 29.5 | NR | NR | ≤0.001 |
| BREEZE-AD7 | PBO + TCS | 109 | 25 | 109 | 22.9 | REF | NR | NR |
| | BARI 2 mg + TCS | 109 | 47 | 109 | 43.1 | 20.2 | NR | NR |
| | BARI 4 mg + TCS | 111 | 53 | 111 | 47.7 | 24.8 | NR | NR |
| | PBO + TCS | 49 | 10 | 49 | 20.4 | REF | NR | REF |
| | BARI 2 mg + TCS | 37 | 11 | 37 | 29.7 | 9.3 | NR | 0.319 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Phase II Guttman-Yassky 2018 | BARI 4 mg + TCS | 38 | 13 | 38 | 34.2 | 13.8 | NR | 0.148 |
| **Tralokinumab** | | | | | | | | |
| ECZTRA 1 | **Week 16** | | | | | | | |
| | PBO | 197 | 25 | 197 | 12.7 | REF | REF | REF |
| | TRA 300 mg | 601 | 150 | 601 | 25 | 12.1 | 6.5 to 17.7 | <0.001 |
| ECZTRA 2 | PBO | 201 | 23 | 201 | 11.4 | REF | REF | REF |
| | TRA 300 mg | 591 | 196 | 591 | 33.2 | 21.6 | 15.8 to 27.3 | <0.001 |
| ECZTRA 2 Subgroup† | PBO | 91 | 14 | 91 | 15.4 | REF | REF | REF |
| | TRA 300 mg | 270 | 109 | 270 | 40.4 | RD: 25.0 | 15.6 to 34.4 | <0.001 |
| ECZTRA 3 | PBO + TCS | 126 | 45 | 126 | 35.7 | REF | REF | REF |
| | TRA 300 mg + TCS | 252 | 141 | 252 | 56 | 20.2 | 9.8 to 30.6 | <0.001 |
| **Upadacitinib** | | | | | | | | |
| MEASURE UP 1 | **Week 16** | | | | | | | |
| | PBO | 281 | 45 | 281 | 16 | NR | NR | REF |
| | UPA 15 mg | 281 | 197 | 281 | 70 | NR | NR | <0.001 |
| | UPA 30 mg | 285 | 228 | 285 | 80 | NR | NR | <0.001 |
| MEASURE UP 2 | PBO | 278 | 36 | 278 | 13 | NR | NR | REF |
| | UPA 15 mg | 276 | 166 | 276 | 60 | NR | NR | <0.001 |
| | UPA 30 mg | 282 | 206 | 282 | 73 | NR | NR | <0.001 |
| AD-UP | PBO + TCS | 304 | 79 | 304 | 26 | NR | NR | REF |
| | UPA 15 mg + TCS | 300 | 195 | 300 | 65 | NR | NR | <0.001 |
| | UPA 30 mg + TCS | 297 | 229 | 297 | 77 | NR | NR | <0.001 |
| Heads Up | DUP 300 mg | 344 | 210 | 344 | 61.1 | REF | NR | REF |
| | UPA 30 mg | 348 | 247 | 348 | 71 | 10 | NR | 0.006 |
| Phase IIb Guttman-Yassky 2020 | **Week 8** | | | | | | | |
| | PBO | 41 | 3 | 41 | 7.3 | NR | NR | REF |
| | UPA 7.5 mg | 42 | 13 | 42 | 31 | NR | NR | 0.004 |
| | UPA 15 mg | 42 | 22 | 42 | 52.4 | NR | NR | <0.001 |
| | UPA 30 mg | 42 | 34 | 42 | 81 | NR | NR | <0.001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Week 16** | | | | | | | |
| | PBO | 41 | 4 | 41 | 9.8 | NR | NR | REF |
| | UPA 15 mg | 42 | 22 | 42 | 52.4 | NR | NR | <0.001 |
| | UPA 30 mg | 42 | 29 | 42 | 69 | NR | NR | <0.001 |
| **Dupilumab** | | | | | | | | |
| SOLO 1 | **Week 16** | | | | | | | |
| | PBO | 224 | 33 | 224 | 15 | NR | NR | NR |
| | DUP 300 mg Q2W | 224 | 115 | 224 | 51 | NR | NR | NR |
| | DUP 300 mg QW | 223 | 117 | 223 | 52 | NR | NR | NR |
| SOLO 2 | PBO | 236 | 28 | 236 | 12 | NR | NR | NR |
| | DUP 300 mg Q2W | 233 | 103 | 233 | 44 | NR | NR | NR |
| | DUP 300 mg QW | 239 | 115 | 239 | 48 | NR | NR | NR |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | 73 | 315 | 23 | REF | REF | REF |
| | DUP 300 mg + TCS Q2W | 106 | 73 | 106 | 69 | 46 | 35.7 to 55.7 | <0.0001 |
| | DUP 300 mg + TCS QW | 319 | 204 | 319 | 64 | 41 | 33.7 to 47.8 | <0.0001 |
| Phase IIb Thaci 2016 | PBO QW | 61 | 7 | NR | 11.09* | NR | NR | 0.147 |
| | DUP 200 mg Q2W | 61 | 34 | NR | 55.5* | NR | NR | <0.0001 |
| | DUP 300 mg Q2W | 64 | 34 | NR | 52.8* | NR | NR | <0.0001 |
| | DUP 300 mg Q4W | 65 | 32 | NR | 48.6* | NR | NR | <0.0001 |

ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, NS: not significant, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, RD: risk difference, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *digitized estimate, †North American subgroup.

**Table G1.10. Short-Term Efficacy Outcomes: EASI 50 and 90**[35-37,40,42,45,46,48,50,51,56,63,64,69,71,72,81-83,85]

| Study Name | Arms | N | EASI 50 | | | | | | EASI 90 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value | n | N | % | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | | | | | | | | |
| | PBO | 77 | 17 | 76 | 22 | REF | REF | NR | 4 | 76 | 5 | REF | REF | NR |
| | ABRO 100 mg | 156 | 90 | 156 | 58 | 35.3 | 23.3 to 47.4 | NR | 29 | 156 | 19 | 13.3 | 5.4 to 21.2 | NR |
| | ABRO 200 mg | 154 | 116 | 153 | 76 | 53.5 | 42.0 to 65.0 | NR | 59 | 153 | 39 | 33.4 | 24.3 to 42.5 | NR |
| JADE MONO-2 | PBO | 78 | 15 | 77 | 19.5 | REF | REF | NR | 3 | 77 | 3.9 | REF | REF | REF |
| | ABRO 100 mg | 158 | 106 | 155 | 68.4 | 48.7 | 37.2 to 60.1 | NR | 37 | 155 | 23.9 | 20.1 | 11.9 to 28.3 | ≤0.0001 |
| | ABRO 200 mg | 155 | 123 | 154 | 79.9 | 60.1 | 49.1 to 71.0 | NR | 58 | 154 | 37.7 | 33.5 | 24.6 to 42.5 | ≤0.0001 |
| JADE TEEN | PBO | 96 | 66 | 94 | 69.1 | NR | NR | NR | 17 | 94 | 18.1 | NR | NR | NR |
| | ABRO 100 mg | 95 | 78 | 89 | 87.6 | NR | NR | NR | 37 | 89 | 41.6 | NR | NR | NR |
| | ABO 200 mg | 94 | 81 | 93 | 87.1 | NR | NR | NR | 46 | 93 | 49.5 | NR | NR | NR |
| JADE COMPARE | **Week 16** | | | | | | | | | | | | | |
| | PBO | 131 | 71 | 124 | 57.3 | NR | NR | NR | 14 | 124 | 11.3 | NR | NR | NR |
| | ABRO 100 mg + PBO→ABRO 100 mg | 238 | 186 | 229 | 81.2 | NR | NR | NR | 87 | 229 | 38 | NR | NR | NR |
| | ABRO 200 mg + PBO→ABRO 200 mg | 226 | 193 | 221 | 87.3 | NR | NR | NR | 108 | 221 | 48.9 | NR | NR | NR |
| | DUP 300 mg + Oral PBO→PBO | 242 | 195 | 232 | 84.1 | NR | NR | NR | 90 | 232 | 38.8 | NR | NR | NR |
| | **Week 12** | | | | | | | | | | | | | |
| | PBO | 52 | 14 | 52 | 26.9 | REF | REF | NR | 5 | 52 | 9.6 | REF | REF | NR |

| Study Name | Arms | N | EASI 50 | | | | | | EASI 90 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value | n | N | % | Diff from PBO | 95% CI | p value |
| Phase IIb Gooderham 2019 | ABRO 100 mg | 54 | 30 | 54 | 55.6 | 3.8 | OR: 1.7 to 6.5 | NR | 14 | 54 | 25.9 | 3.2 | 1.3 to 7.9 | NR |
| | ABRO 200 mg | 48 | 38 | 48 | 79.2 | 9.7 | OR: 4.5 to 20.9 | NR | 21 | 48 | 43.8 | 9.3 | 3.8 to 22.5 | NR |
| **Baricitinib** | | | | | | | | | | | | | | |
| | **Week 16** | | | | | | | | | | | | | |
| BREEZE-AD1 | PBO | 249 | 38 | 249 | 15.3 | REF | NR | REF | 12 | 249 | 4.8 | REF | REF | REF |
| | BARI 1 mg | 127 | 32 | 127 | 25.0 | 9.7 | NR | <0.05 | 11 | 127 | 8.7 | 3.9 | NR | NS |
| | BARI 2 mg | 123 | 37 | 123 | 30.1 | 14.8 | NR | <0.001 | 13 | 123 | 10.6 | 5.8 | NR | <0.05 |
| | BARI 4 mg | 125 | 52 | 125 | 41.6 | 26.3 | NR | <0.001 | 20 | 125 | 16.0 | 11.2 | NR | <0.001 |
| BREEZE-AD2 | PBO | 244 | 30 | 244 | 12.3 | REF | NR | REF | 6 | 244 | 2.5 | REF | 1.1 to 5.3 | REF |
| | BARI 1 mg | 125 | 23 | 125 | 18.4 | 6.1 | NR | NS | 8 | 125 | 6.4 | 3.9 | 3.3 to 12.1 | 0.053 |
| | BARI 2 mg | 123 | 34 | 123 | 27.6 | 15.3 | NR | <0.001 | 11 | 123 | 8.9 | 6.4 | 5.1 to 15.3 | 0.007 |
| | BARI 4 mg | 123 | 36 | 123 | 29.3 | 17.0 | NR | <0.001 | 16 | 123 | 13.0 | 10.5 | 8.2 to 20.1 | <0.001 |
| BREEZE-AD5 | PBO | 147 | 19 | 147 | 12.9 | NR | 8.4 to 19.3 | NR | 5 | 147 | 3.4 | NR | 1.5 to 7.7 | NR |
| | BARI 1 mg | 147 | 29 | 147 | 19.7 | NR | 14.1 to 26.9 | NS | 11 | 147 | 7.5 | NR | 4.2 to 12.9 | NR |
| | BARI 2 mg | 146 | 51 | 146 | 34.9 | NR | 27.7 to 43 | ≤0.001 | 30 | 146 | 20.5 | NR | 14.8 to 27.8 | <0.001 |
| BREEZE-AD7 | PBO + TCS | 109 | 45 | 109 | 41.3 | REF | NR | REF | 15 | 109 | 13.8 | REF | NR | NR |
| | BARI 2 mg + TCS | 109 | 70 | 109 | 64.2 | 22.9 | NR | NR | 18 | 109 | 16.5 | 2.7 | NR | NR |
| | BARI 4 mg + TCS | 111 | 78 | 111 | 70.3 | 29 | NR | NR | 27 | 111 | 24.3 | 10.5 | NR | NR |
| | PBO + TCS | 49 | 18 | 49 | 36.7 | REF | NR | REF | 3 | 49 | 6.1 | REF | NR | REF |

| Study Name | Arms | N | EASI 50 | | | | | | EASI 90 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value | n | N | % | Diff from PBO | 95% CI | p value |
| Phase II Guttman-Yassky 2018 | BARI 2 mg + TCS | 37 | 21 | 37 | 56.8 | 20.1 | NR | 0.065 | 7 | 37 | 18.9 | 12.8 | NR | 0.092 |
| | BARI 4 mg + TCS | 38 | 23 | 38 | 60.5 | 23.8 | NR | 0.027 | 8 | 38 | 21.1 | 15 | NR | 0.052 |
| **Tralokinumab** | | | | | | | | | | | | | | |
| ECZTRA 1 | **Week 16** | | | | | | | | | | | | | |
| | PBO | 197 | 42 | 197 | 21.3 | REF | REF | REF | 8 | 197 | 4.1 | REF | REF | REF |
| | TRA 300 mg | 601 | 250 | 601 | 41.6 | 20.1 | 13.3 to 26.8 | <0.001 | 87 | 601 | 14.5 | 10.3 | 6.4 to 14.1 | <0.001 |
| ECZTRA 2 | PBO | 201 | 41 | 201 | 20.4 | REF | REF | REF | 11 | 201 | 5.5 | REF | REF | REF |
| | TRA 300 mg | 591 | 295 | 591 | 49.9 | 29.3 | 22.5 to 36.1 | <0.001 | 108 | 591 | 18.3 | 12.7 | 8.3 to 17.0 | <0.001 |
| ECZTRA 3 | PBO + TCS | 126 | 73 | 126 | 57.9 | REF | REF | REF | 27 | 126 | 21.4 | REF | REF | REF |
| | TRA 300 mg + TCS | 252 | 200 | 252 | 79.4 | 21.3 | 11.3 to 31.3 | <0.001 | 83 | 252 | 32.9 | 11.4 | 2.1 to 20.7 | 0.022 |
| **Upadacitinib** | | | | | | | | | | | | | | |
| MEASURE UP 1 | **Week 16** | | | | | | | | | | | | | |
| | PBO | 281 | 83 | 281 | 29.6 | NR | NR | REF | 22 | 281 | 8 | NR | NR | REF |
| | UPA 15 mg | 281 | 217 | 281 | 77.2 | NR | NR | ≤0.001 | 149 | 281 | 53 | NR | NR | <0.001 |
| | UPA 30 mg | 285 | 244 | 285 | 85.6 | NR | NR | ≤0.001 | 188 | 285 | 66 | NR | NR | <0.001 |
| MEASURE UP 2 | PBO | 278 | 79 | 278 | 28.4 | NR | NR | REF | 14 | 278 | 5 | NR | NR | - REF |
| | UPA 15 mg | 276 | 206 | 276 | 74.6 | NR | NR | ≤0.001 | 116 | 276 | 42 | NR | NR | <0.001 |
| | UPA 30 mg | 282 | 232 | 282 | 82.1 | NR | NR | ≤0.001 | 163 | 282 | 58 | NR | NR | <0.001 |
| AD-UP | PBO + TCS | 304 | 124 | 304 | 40.9 | NR | NR | REF | 40 | 304 | 13.2 | REF | 9.4 to 17.0 | REF |
| | UPA 15 mg + TCS | 300 | 244 | 300 | 81.4 | NR | NR | ≤0.001 | 128 | 300 | 42.8 | 28.5 | 22.1 to 34.9 | <0.001 |
| | UPA 30 mg + TCS | 297 | 262 | 297 | 88.1 | NR | NR | ≤0.001 | 187 | 297 | 63.1 | 49.9 | 43.3 to 56.4 | <0.001 |

| Study Name | Arms | N | EASI 50 | | | | | | EASI 90 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value | n | N | % | Diff from PBO | 95% CI | p value |
| Heads Up | DUP 300 mg | 344 | [redacted] | | | NR | [redacted] | | 133 | 344 | 38.8 | REF | NR | REF |
| | UPA 30 mg | 348 | | | | NR | NR | NR | 211 | 348 | 60.6 | 21.8 | NR | <0.001 |
| Phase IIb Guttman-Yassky 2020 | **Week 8** | | | | | | | | | | | | | |
| | PBO | 41 | 9 | 41 | 22 | NR | NR | REF | 0 | 41 | 0 | NR | NR | REF |
| | UPA 7.5 mg | 42 | 23 | 42 | 54.8 | NR | NR | <0.001 | 4 | 42 | 9.5 | NR | NR | 0.051 |
| | UPA 15 mg | 42 | 30 | 42 | 71.4 | NR | NR | <0.001 | 11 | 42 | 26.2 | NR | NR | <0.001 |
| | UPA 30 mg | 42 | 39 | 42 | 92.9 | NR | NR | <0.001 | 19 | 42 | 45.2 | NR | NR | <0.001 |
| | **Week 16** | | | | | | | | | | | | | |
| | PBO | 41 | 9 | 41 | 22 | NR | NR | REF | 1 | 41 | 2.4 | NR | NR | REF |
| | UPA 15 mg | 42 | 30 | 42 | 71.4 | NR | NR | <0.001 | 11 | 42 | 26.2 | NR | NR | <0.01 |
| | UPA 30 mg | 42 | 35 | 42 | 83.3 | NR | NR | <0.001 | 21 | 42 | 50 | NR | NR | <0.001 |
| **Dupilumab** | | | | | | | | | | | | | | |
| SOLO 1 | **Week 16** | | | | | | | | | | | | | |
| | PBO | 224 | 55 | 224 | 25 | NR | NR | NR | 17 | 224 | 8 | NR | NR | NR |
| | DUP 300 mg Q2W | 224 | 154 | 224 | 69 | NR | NR | NR | 80 | 224 | 36 | NR | NR | NR |
| | DUP 300 mg QW | 223 | 136 | 223 | 61 | NR | NR | NR | 74 | 223 | 33 | NR | NR | NR |
| SOLO 2 | PBO | 236 | 52 | 236 | 22 | NR | NR | NR | 17 | 236 | 7 | NR | NR | NR |
| | DUP 300 mg Q2W | 233 | 152 | 233 | 65 | NR | NR | NR | 70 | 233 | 30 | NR | NR | NR |
| | DUP 300 mg QW | 239 | 146 | 239 | 61 | NR | NR | NR | 73 | 239 | 31 | NR | NR | NR |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | 118 | 315 | 37 | REF | REF | REF | 35 | 315 | 11 | REF | REF | REF |
| | DUP 300 mg + TCS Q2W | 106 | 85 | 106 | 80 | 43 | 33.5 to 52.0 | <0.0001 | 42 | 106 | 40 | 29 | 18.6 to 38.5 | <0.0001 |
| | DUP 300 mg + TCS QW | 319 | 249 | 319 | 78 | 41 | 33.6 to 47.6 | <0.0001 | 138 | 319 | 43 | 32 | 25.7 to 38.6 | <0.0001 |

| Study Name | Arms | N | EASI 50 | | | | | | EASI 90 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value | n | N | % | Diff from PBO | 95% CI | p value |
| Phase IIb Thaci 2016 | PBO QW | 61 | 18 | 61 | 30 | NR | NR | REF | 2 | 61 | 3.5* | NR | NR | 0.0242 |
| | DUP 200 mg Q2W | 61 | 38 | 61 | 62 | NR | NR | 0.0003 | 19 | 61 | 31.1* | NR | NR | <0.0001 |
| | DUP 300 mg Q2W | 64 | 50 | 64 | 78 | NR | NR | <0.0001 | 19 | 64 | 29.8* | NR | NR | <0.0001 |
| | DUP 300 mg Q4W | 65 | 46 | 65 | 71 | NR | NR | <0.0001 | 19 | 65 | 28.8* | NR | NR | <0.0001 |

Short-term data on EASI 50 and EASI 90 were not available in JADE COMPARE at 12 weeks. ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, NS: not significant, OR: odds ratio, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *digitized estimate.

**Table G1.11. Short-Term Efficacy Outcomes: PP-NRS ≥4-Point Change** [35-37,39,40,42,45,46,48,50,51,56,63,64,69,71,72,81-83,85]

| Study Name | Arms | N | Itch or PP-NRS (≥4-point improvement from baseline) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | | | | |
| | PBO | 77 | 11 | 74 | 15 | NR | NR | REF | REF | REF |
| | ABRO 100 mg | 156 | 55 | 147 | 38 | NR | NR | 22.5 | 10.3 to 34.8 | 0.0003 |
| | ABRO 200 mg | 154 | 84 | 147 | 57.2 | NR | NR | 41.7 | 29.6 to 53.9 | <0.0001 |
| JADE MONO-2 | PBO | 78 | 9 | 76 | 11.5 | NR | NR | REF | 4.1 to 19.0 | REF |
| | ABRO 100 mg | 158 | 71 | 156 | 45.2 | NR | NR | 33.7 | 22.8 to 44.7 | <0.0001 |
| | ABRO 200 mg | 155 | 85 | 153 | 55.3 | NR | NR | 43.9 | 32.9 to 55.0 | <0.0001 |
| JADE TEEN | PBO | 96 | 25 | 84 | 29.8 | [redacted] | NR | REF | REF | REF |
| | ABRO 100 mg | 95 | 40 | 76 | 52.6 | [redacted] | NR | 22.8 | 8 to 37.7 | 0.0035 |

| Study Name | Arms | N | Itch or PP-NRS (≥4-point improvement from baseline) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| | ABRO 200 mg | 94 | 41 | 74 | 55.4 | | NR | 25.6 | 10.6 to 40.6 | 0.0013 |
| JADE COMPARE | PBO | 131 | 35 | 121 | 29 | NR | NR | NR | NR | NR |
| | ABRO 100 mg | 238 | 105 | 221 | 48 | NR | NR | NR | NR | NR |
| | ABRO 200 mg | 226 | 137 | 217 | 63 | NR | NR | NR | NR | NR |
| | DUP 300 mg | 242 | 122 | 224 | 54 | NR | NR | NR | NR | NR |
| | **Week 16** | | | | | | | | | |
| | PBO | 131 | 27 | 94 | 28.7 | | NR | NR | NR | NR |
| | ABRO 100 mg | 238 | 79 | 168 | 47.0 | | NR | 17.9 | 9.5 to 26.3 | 0.0002 |
| | ABRO 200 mg | 226 | 108 | 172 | 62.8 | | NR | 34.9 | 26 to 43.7 | <.0001 |
| | DUP 300 mg | 242 | 108 | 189 | 57.1 | | NR | 5.2 | -2.9 to 13.4 | 0.2084 |
| Phase IIb Gooderham 2019 | **Week 12** | | | | | | | | | |
| | PBO | 52 | 13 | 51 | 25.5 | NR | NR | REF | REF | NR |
| | ABRO 100 mg | 54 | 25 | 50 | 50 | NR | NR | OR: 2.8 | 1.4 to 5.8 | NR |
| | ABRO 200 mg | 48 | 28 | 44 | 63.6 | NR | NR | OR: 5.1 | 2.4 to 10.8 | NR |
| **Baricitinib** | | | | | | | | | | |
| BREEZE-AD1 | **Week 16** | | | | | | | | | |
| | PBO | 249 | 16 | 222 | 7.2 | NR | NR | REF | 1.2 to 5.8 | REF |
| | BARI 1 mg | 127 | 11 | 105 | 10.5 | NR | NR | 3.3 | 6.0 to 17.8 | 0.246 |
| | BARI 2 mg | 123 | 12 | 100 | 12.0 | NR | NR | 4.8 | 7.0 to 19.8 | 0.169 |
| | BARI 4 mg | 125 | 23 | 107 | 21.5 | NR | NR | 14.3 | 14.8 to 30.2 | <0.001 |
| BREEZE-AD2 | PBO | 244 | 10 | 213 | 4.7 | NR | NR | REF | 2.6 to 8.4 | REF |
| | BARI 1 mg | 125 | 6 | 100 | 6.0 | NR | NR | 1.3 | 2.8 to 122.5 | 0.505 |
| | BARI 2 mg | 123 | 16 | 106 | 15.1 | NR | NR | 10.4 | 9.5 to 23.1 | 0.002 |
| | BARI 4 mg | 123 | 20 | 107 | 18.7 | NR | NR | 14.0 | 12.4 to 27.1 | <0.001 |
| BREEZE-AD5 | PBO | 147 | 7 | 123 | 5.7 | NR | NR | NR | NR | REF |
| | BARI 1 mg | 147 | 21 | 132 | 15.9 | NR | NR | NR | NR | ≤0.05 |
| | BARI 2 mg | 146 | 33 | 131 | 25.2 | NR | NR | NR | NR | ≤0.001 |

| Study Name | Arms | N | Itch or PP-NRS (≥4-point improvement from baseline) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| BREEZE-AD7 | PBO + TCS | 109 | 21 | 104 | 20.2 | LSM: -27* | SE: 3.4 | REF | NR | REF |
| | BARI 2 mg + TCS | 109 | 37 | 97 | 38.1 | LSM: -43.4* | SE: 3.3 | 17.9 | NR | 0.002 |
| | BARI 4 mg + TCS | 111 | 44 | 100 | 44 | LSM: -51.2* | SE: 3.3 | 23.8 | NR | <0.001 |
| Phase II Guttman-Yassky 2018 | PBO + TCS | 49 | NR | NR | NR | LSM: -1.72 | SE: 0.44 | NR | NR | NR |
| | BARI 2 mg + TCS | 37 | NR | NR | NR | LSM: -2.61 | SE: 0.47 | NR | NR | NR |
| | BARI 4 mg + TCS | 38 | NR | NR | NR | LSM: -2.22 | SE: 0.46 | NR | NR | NR |
| **Tralokinumab** | | | | | | | | | | |
| ECZTRA 1 | **Week 16** | | | | | | | | | |
| | PBO | 197 | 20 | 194 | 10.3 | -1.7 | SE: 0.21 | REF | REF | REF |
| | TRA 300 mg | 601 | 119 | 594 | 20 | -2.6 | SE: 0.11 | 9.7 | 4.4 to 15.0 | 0.002 |
| ECZTRA 2 | PBO | 201 | 19 | 200 | 9.5 | -1.6 | SE: 0.21 | REF | REF | REF |
| | TRA 300 mg | 591 | 144 | 575 | 25 | -2.9 | SE: 0.11 | 15.6 | 10.3 to 20.9 | <0.001 |
| ECZTRA 2 Subgroup‡ | PBO | 91 | 13 | 90 | 14.4 | -1.9† | SE: 0.3† | REF | REF | REF |
| | TRA 300 mg | 270 | 77 | 264 | 29.2 | -3.1† | SE: 0.2† | RD: 14.9 | 5.9 to 23.9 | 0.005 |
| ECZTRA 3 | PBO + TCS | 126 | 43 | 126 | 34.1 | -2.9 | SE: 0.21 | REF | REF | REF |
| | TRA 300 mg + TCS | 252 | 113 | 249 | 45.4 | -4.1 | SE: 0.15 | 11.3 | 0.9 to 21.6 | 0.037 |
| **Upadacitinib** | | | | | | | | | | |
| MEASURE UP 1 | **Week 16** | | | | | | | | | |
| | PBO | 281 | 32 | 272 | 11.8 | LSM: 26.1* | SE: 5.24† | REF | REF | REF |
| | UPA 15 mg | 281 | 143 | 274 | 52.2 | LSM: 62.8* | SE: 4.37† | 40.5 | 33.5 to 47.5 | ≤0.001 |
| | UPA 30 mg | 285 | 171 | 285 | 60 | LSM: 72* | SE:4.37† | 48.2 | 41.3 to 55.0 | ≤0.001 |
| MEASURE UP 2 | PBO | 278 | 25 | 274 | 9.1 | LSM: 17* | SE: 2.81† | REF | REF | REF |
| | UPA 15 mg | 276 | 113 | 270 | 41.9 | LSM: 51.2* | SE: 2.34† | 32.6 | 25.8 to 39.4 | ≤0.001 |
| | UPA 30 mg | 282 | 167 | 280 | 59.6 | LSM: 66.5* | SE: 2.34† | 50.4 | 43.8 to 57.1 | ≤0.001 |
| AD-UP | PBO + TCS | 304 | 44 | 294 | 15 | 25.1 | SE: 3.4 | REF | 10.9 to 19.0 | REF |
| | UPA 15 mg + TCS | 300 | 149 | 288 | 51.7 | 58.1 | SE: 3.4 | 36.8 | 29.7 to 43.8 | ≤0.001 |
| | UPA 30 mg + TCS | 297 | 186 | 291 | 63.9 | 66.9 | SE: 2.91 | 48.8 | 41.9 to 55.7 | ≤0.001 |

| Study Name | Arms | N | Itch or PP-NRS (≥4-point improvement from baseline) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| Heads Up | DUP 300 mg | 344 | 120 | 336 | 35.9 | -49 | 1.9 | REF | NR | REF |
| | UPA 30 mg | 348 | 188 | 340 | 55.2 | -66.9 | 1.9 | 19.3 | NR | <0.001 |
| Phase IIb Guttman-Yassky 2020 | **Week 8** | | | | | | | | | |
| | PBO | 41 | 2 | 37 | 5.5† | LSM: -6.7* | SE: 7.5 | NR | NR | REF |
| | UPA 7.5 mg | 42 | 13 | 40 | 32.1† | LSM: -35.5* | SE: 7.3 | NR | NR | 0.002 |
| | UPA 15 mg | 42 | 22 | 37 | 58.8† | LSM: -45.1* | SE: 7.3 | NR | NR | <0.001 |
| | UPA 30 mg | 42 | 27 | 42 | 63.7† | LSM: -73.1* | SE: 7.1 | NR | NR | <0.001 |
| | **Week 16** | | | | | | | | | |
| | PBO | 41 | 2 | 35 | 5.7 | LSM: -9.7* | SE: 8.3 | NR | NR | REF |
| | UPA 15 mg | 42 | 19 | 32 | 59.4 | LSM: -48* | SE: 8.1 | NR | NR | <0.001 |
| | UPA 30 mg | 42 | 19 | 36 | 52.8 | LSM: -68.9* | SE: 7.8 | NR | NR | <0.001 |
| **Dupilumab** | | | | | | | | | | |
| SOLO 1 | **Week 16** | | | | | | | | | |
| | PBO | 224 | 26 | 212 | 12 | LSM: -26.1* | SE: 3 | NR | NR | NR |
| | DUP 300 mg Q2W | 224 | 87 | 213 | 41 | LSM: -51* | SE: 2.5 | NR | NR | NR |
| | DUP 300 mg QW | 223 | 81 | 201 | 40 | LSM: -48.9* | SE: 2.6 | NR | NR | NR |
| SOLO 2 | PBO | 236 | 21 | 221 | 10 | LSM: -15.4* | SE: 3 | NR | NR | NR |
| | DUP 300 mg Q2W | 233 | 81 | 225 | 36 | LSM: -44.3* | SE: 2.3 | NR | NR | NR |
| | DUP 300 mg QW | 239 | 89 | 228 | 39 | LSM: -48.3* | SE: 2.4 | NR | NR | NR |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | 59 | 299 | 20 | LSM: -2.1 | SE: 0.1 | REF | REF | REF |
| | DUP 300 mg + TCS Q2W | 106 | 60 | 102 | 59 | LSM: -4.1 | SE: 0.2 | 39 | 28.5 to 49.7 | <0.0001 |
| | DUP 300 mg + TCS QW | 319 | 150 | 295 | 51 | LSM: -4.1 | SE: 0.1 | 31 | 23.8 to 38.4 | <0.0001 |
| Phase IIb Thaci 2016 | PBO QW | 61 | NR | NR | NR | LSM: -5.2* | SE: 4.8 | NR | NR | NR |
| | DUP 200 mg Q2W | 61 | NR | NR | NR | LSM: -34.1* | SE: 4.7 | NR | NR | NR |
| | DUP 300 mg Q2W | 64 | NR | NR | NR | LSM: -40.1* | SE: 4.5 | NR | NR | NR |

| Study Name | Arms | N | Itch or PP-NRS (≥4-point improvement from baseline) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| | DUP 300 mg Q4W | 65 | NR | NR | NR | LSM: -32.6* | SE: 4.5 | NR | NR | NR |

ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, LSM: least squares mean, mg: milligram, n: number, N: total number, NR: not reported, OR: odds ratio, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, RD: risk difference, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *percent change, †digitized estimate, ‡North American subgroup.

**Table G1.12. Short-Term Efficacy Outcomes: SCORAD** [35-37,39,40,42,45,46,48,50,51,56,63,64,69,71,72,81-83,85,156,157]

| Study Name | Arms | N | SCORAD | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | | |
| | PBO | 77 | 75 | LSM: -13.6 | 95% CI: -18.3 to -9 | REF | REF | REF |
| | ABRO 100 mg | 156 | 150 | LSM: -27 | 95% CI: -30.2 to -23.7 | -13.3 | -19 to -7.7 | <0.0001 |
| | ABO 200 mg | 154 | 151 | LSM: -35.5 | 95% CI: -38.7 to -32.3 | -21.9 | -27.5 to -16.3 | <0.0001 |
| JADE MONO-2 | PBO | 78 | 78 | LSM: -22.7 | 95% CI: -30.4 to -15.1 | REF | REF | REF |
| | ABRO 100 mg | 158 | 158 | LSM: -45.8 | 95% CI: -50.9 to -40.7 | -23.1 | -32.3 to -13.9 | <0.0001 |
| | ABO 200 mg | 155 | 155 | LSM: -56.2 | 95% CI: -61.2 to -51.1 | -33.4 | -42.6 to -24.3 | <0.0001 |
| JADE TEEN | PBO | 96 | 96 | LSM: -30.2 | 95% CI: -33.9 to -26.4 | NR | NR | NR |
| | ABRO 100 mg | 95 | 95 | LSM: -40.9 | 95% CI: -44.7 to -37.2 | NR | NR | NR |
| | ABO 200 mg | 94 | 93 | LSM: -42.9 | 95% CI: -46.7 to -39.1 | NR | NR | NR |
| JADE COMPARE | PBO | 131 | 131 | LSM: -23 | NR | NR | NR | NR |
| | ABRO 100 mg | 238 | 238 | LSM: -36.6 | NR | NR | NR | NR |
| | ABRO 200 mg | 226 | 226 | LSM: -44.9 | NR | NR | NR | NR |
| | DUP 300 mg | 242 | 242 | LSM: -39.7 | NR | NR | NR | NR |
| | **Week 16** | | | | | | | |
| | PBO | 131 | 123 | NR | 95% CI: 5.1 to 16.0 | NR | NR | NR |
| | ABRO 100 mg + PBO→ABRO 100 mg | 238 | 228 | NR | 95% CI:21.0 to 32.5 | NR | NR | NR |
| | ABRO 200 mg + PBO→ABRO 200 mg | 226 | 221 | NR | 95% CI: 33.8 to 46.7 | NR | NR | NR |
| | DUP 300 mg + Oral PBO→PBO | 242 | 231 | NR | 95% CI:23.6 to 35.3 | NR | NR | NR |
| Phase II Gooderham 2019 | **Week 12** | | | | | | | |
| | PBO | 52 | 52 | -29 | 95% CI: -36.6 to -21.3 | NR | NR | REF |
| | ABRO 100 mg | 54 | 54 | -49.2 | 95% CI: -56.4 to -42.0 | NR | NR | 0.002 |
| | ABRO 200 mg | 48 | 48 | -69.7 | 95% CI: -76.9 to -62.5 | NR | NR | <0.001 |

| Study Name | Arms | N | SCORAD | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| **Baricitinib** | | | | | | | | |
| BREEZE-AD1 | **Week 16** | | | | | | | |
| | PBO | 249 | 249 | LSM: -13.5 | SE: 2 | REF | REF | REF |
| | BARI 1 mg | 127 | 127 | LSM: -18.9 | SE: 2.5 | -9.1 | -11.6 to 0.9 | 0.093 |
| | BARI 2 mg | 123 | 123 | LSM: -21.5 | SE: 2.4 | -12.7 | -14.0 to -1.9 | 0.01 |
| | BARI 4 mg | 125 | 125 | LSM: -28.3 | SE: 2.1 | -23.0 | -20.5 to -9.1 | <0.001 |
| BREEZE-AD2 | PBO | 244 | 244 | LSM: -13.4 | SE: 2.3 | REF | REF | REF |
| | BARI 1 mg | 125 | 125 | LSM: -20.2 | SE: 2.8 | -11.3 | -14 to 0.3 | 0.059 |
| | BARI 2 mg | 123 | 123 | LSM: -27.8 | SE: 2.6 | -21.6 | -21.3 to -7.6 | <0.001 |
| | BARI 4 mg | 123 | 123 | LSM: -27.5 | SE: 2.4 | -22.7 | -20.7 to -7.6 | <0.001 |
| BREEZE-AD7 | PBO + TCS | 109 | 109 | LSM: -21.4 | SE: 1.9 | REF | REF | REF |
| | BARI 2 mg + TCS | 109 | 109 | LSM: -29.9 | SE: 1.9 | -8.5 | -13.7 to -3.2 | 0.002 |
| | BARI 4 mg + TCS | 111 | 111 | LSM: -35.8 | SE: 1.8 | -14.8 | -19.6 to -9.1 | <0.001 |
| Phase II Guttman-Yassky 2018 | PBO + TCS | 49 | 49 | LSM: -11.9 | SE: 2.9 | REF | NR | REF |
| | BARI 2 mg + TCS | 37 | 37 | LSM: -23.9 | SE: 3.0 | -23 | NR | <0.01 |
| | BARI 4 mg + TCS | 38 | 38 | LSM: -26.5 | SE: 3.0 | -31 | NR | <0.001 |
| **Tralokinumab** | | | | | | | | |
| ECZTRA 1 | **Week 16** | | | | | | | |
| | PBO | 197 | NR | -14.7 | SE: 1.8 | REF | REF | REF |
| | TRA 300 mg | 601 | NR | -25.2 | SE: 0.9 | -10.4 | -14.4 to -6.5 | <0.001 |
| ECZTRA 2 | PBO | 201 | NR | -14 | SE: 1.8 | REF | REF | REF |
| | TRA 300 mg | 591 | NR | -28.1 | SE: 0.9 | -14 | -18 to -10.1 | <0.001 |
| ECZTRA 2 Subgroup[†] | PBO | 91 | NR | -16 | NR | REF | REF | REF |
| | TRA 300 mg | 270 | NR | -29 | NR | LSM: -13.7 | -19.3 to -8.0 | <0.001 |
| ECZTRA 3 | PBO + TCS | 126 | NR | -26.8 | SE: 1.8 | REF | REF | REF |
| | TRA 300 mg + TCS | 252 | NR | -37.7 | SE: 1.3 | -10.9 | -15.2 to -6·6 | <0.001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Upadacitinib** | | | | | | | | |
| MEASURE UP 1 | **Week 16** | | | | | | | |
| | PBO | 281 | 125 | -32.7 | 95% CI: -37.3 to -28.1 | REF | REF | REF |
| | UPA 15 mg | 281 | 239 | -65.7 | 95% CI: -69.2 to -62.2 | -33.0 | -38.4 to -27.6 | <0.001 |
| | UPA 30 mg | 285 | 253 | -40.4 | 95% CI: -76.5 to -69.7 | -40.4 | -45.8 to -35.0 | <0.001 |
| MEASURE UP 2 | PBO | 278 | 142 | -28.4 | 95% CI: -33.3 to -23.5 | REF | REF | REF |
| | UPA 15 mg | 276 | 246 | -29.5 | 95% CI: -61.8 to '54.0 | -29.5 | -35.2 to -23.7 | <0.001 |
| | UPA 30 mg | 282 | 250 | -68.4 | 95% CI: -72.4 to ;64.4 | -40.0 | -45.8 to -34.2 | <0.001 |
| Phase IIb Guttman-Yassky 2020 | **Week 8** | | | | | | | |
| | PBO | 41 | 33 | LSM: -7* | SE: 5.8 | NR | NR | REF |
| | UPA 7.5 mg | 42 | 39 | LSM: -35.4* | SE: 5.5 | NR | NR | <0.001 |
| | UPA 15 mg | 42 | 36 | LSM: -44.1* | SE: 5.7 | NR | NR | <0.001 |
| | UPA 30 mg | 42 | 40 | LSM: -65.3* | 5.5 | NR | NR | <0.001 |
| | **Week 16** | | | | | | | |
| | PBO | 41 | 33 | LSM: -12.4* | SE: 6.0 | NR | NR | REF |
| | UPA 15 mg | 42 | 36 | LSM: -46.9* | SE: 5.8 | NR | NR | <0.001 |
| | UPA 30 mg | 42 | 40 | LSM: -60.4* | SE: 5.7 | NR | NR | <0.001 |
| **Dupilumab** | | | | | | | | |
| SOLO 1 | **Week 16** | | | | | | | |
| | PBO | 224 | NR | LSM: -29* | SE: 3.2 | NR | NR | NR |
| | DUP 300 mg Q2W | 224 | NR | LSM: -57.7* | SE: 2.1 | NR | NR | NR |
| | DUP 300 mg QW | 223 | NR | LSM: -57* | SE: 2.1 | NR | NR | NR |
| SOLO 2 | PBO | 236 | NR | LSM: -19.7* | SE: 2.5 | NR | NR | NR |
| | DUP 300 mg Q2W | 233 | NR | LSM: -51.1* | SE: 2 | NR | NR | NR |
| | DUP 300 mg QW | 239 | NR | LSM: -53.5* | SE: 2 | NR | NR | NR |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | 315 | LSM: -31.8* | SE: 1.55 | NR | NR | REF |
| | DUP 300 mg + TCS Q2W | 106 | 106 | LSM: -62.1* | SE: 2.61 | NR | NR | <0.0001 |
| | DUP 300 mg + TCS QW | 319 | 319 | LSM: -63.3* | SE: 1.53 | NR | NR | <0.0001 |
| Phase IIb Thaci 2016 | PBO QW | 61 | 61 | LSM: -13.8* | SE: 4.1 | REF | REF | REF |
| | Dupilumab 200 mg Q2W | 61 | 61 | LSM: -46.0* | SE: 4.1 | -32.2 | -42.9 to -21.6 | <0.0001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | DUP 300 mg Q2W | 64 | 64 | LSM: -51.2* | SE: 4.1 | -37.4 | -47.9 to -26.9 | <0.0001 |
| | DUP 300 mg Q4W | 65 | 65 | LSM: -48.8* | SE: 4.0 | -35.0 | -45.4 to -24.6 | <0.0001 |

Short-term data on SCORAD were not available in BREEZE-AD5, AD-UP, and Heads Up. ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, REF: reference, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, SD: standard deviation, SE: standard error, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib. *percent change, †North American subgroup.

**Table G1.13. Short-Term Efficacy Outcomes: DLQI and CDLQI**[35-37,39,40,42,45,46,48,50,51,56,63,64,69,71,72,81-83,85]

| Study Name | Arms | N | DLQI | | | | | | CDLQI | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value | N | Change from baseline | 95% CI | p value |
| **Abrocitinib** | | | | | | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | | | | | | |
| | PBO | 77 | 60 | LSM: -4.2 | 95% CI: -5.9 to -2.5 | REF | REF | NR | 16 | LSM: -3.9 | REF | NR |
| | ABRO 100 mg | 156 | 121 | LSM: -7 | 95% CI: -8.1 to -5.8 | –2·8 | -4.8 to -0.8 | NR | 32 | LSM: -6.4 | -5.2 to 0.1 | NR |
| | ABRO 200 mg | 154 | 119 | LSM: -9.1 | 95% CI: -10.3 to -8.0 | –4·9 | -6.9 to -2.9 | NR | 32 | LSM: -7.5 | -6.2 to -0.9 | NR |
| JADE MONO-2 | PBO | 78 | 70 | LSM: -3.9 | NR | REF | -5.3 to -2.4 | NR | 8 | LSM: -2.7 | -6.1 to 0.8 | NR |
| | ABRO 100 mg | 158 | 140 | LSM: -8.3 | NR | −4.4 (−6.2 to −2.7) | -9.3 to -7.3 | NR | 16 | LSM: -4.8 | -7.2 to -2.5 | NR |
| | ABRO 200 mg | 155 | 139 | LSM: -9.8 | NR | −5.9 (−7.7 to −4.2) | -10.7 to -8.8 | NR | 15 | LSM: -9.7 | -12.1 to -7.4 | NR |
| JADE TEEN | PBO | 96 | NA | NA | NA | NA | NA | NA | 96 | LSM: -6.3 | -7.4 to -5.3 | NR |
| | ABRO 100 mg | 95 | NA | NA | NA | NA | NA | NA | 95 | LSM: -8.6 | -9.6 to -7.5 | NR |
| | ABO 200 mg | 94 | NA | NA | NA | NA | NA | NA | 94 | LSM: -8.7 | -9.7 to -7.6 | NR |
| JADE COMPARE | PBO | 131 | 131 | LSM: -6.2 | 95% CI: -7.1 to -5.3 | NR | NR | NR | NA | NA | NA | NA |
| | ABRO 100 mg | 238 | 238 | LSM: -8.7 | 95% CI: -9.4 to -8 | NR | NR | NR | NA | NA | NA | NA |
| | ABRO 200 mg | 226 | 226 | LSM: -11 | 95% CI: -11.7 to -10.3 | NR | NR | NR | NA | NA | NA | NA |

| Study Name | Arms | N | DLQI | | | | | | CDLQI | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value | N | Change from baseline | 95% CI | p value |
| | DUP 300 mg | 242 | 241 | LSM: -9.9 | 95% CI: -10.6 to -9.2 | NR | NR | NR | NA | NA | NA | NA |
| | **Week 16** | | | | | | | | | | | |
| | PBO | 131 | 131 | LSM: -6.2 | 95% CI: -7.1 to -5.2 | NR | NR | NR | NA | NA | NA | NA |
| | ABRO 100 mg + PBO→ABRO 100 mg | 238 | 238 | LSM: -9 | 95% CI: -9.7 to -8.4 | NR | NR | NR | NA | NA | NA | NA |
| | ABRO 200 mg + PBO→ABRO 200 mg | 226 | 226 | LSM: -11.7 | 95% CI:-12.4 to -11.1 | NR | NR | NR | NA | NA | NA | NA |
| | DUP 300 mg + Oral PBO→PBO | 242 | 241 | LSM: -10.8 | 95% CI: -11.4 to -10.1 | NR | NR | NR | NA | NA | NA | NA |
| **Baricitinib** | | | | | | | | | | | | |
| BREEZE-AD1 | **Week 16** | | | | | | | | | | | |
| | PBO | 249 | 249 | -2.5 | NR | REF | NR | REF | NA | NA | NA | NA |
| | BARI 1 mg | 127 | 127 | -4.6 | NR | -2.1 | NR | <0.05 | NA | NA | NA | NA |
| | BARI 2 mg | 123 | 123 | -4.3 | NR | -1.8 | NR | <0.05 | NA | NA | NA | NA |
| | BARI 4 mg | 125 | 125 | -6.8 | NR | -4.3 | NR | <0.001 | NA | NA | NA | NA |
| BREEZE-AD2 | PBO | 244 | 244 | -3.4 | NR | REF | NR | REF | NA | NA | NA | NA |
| | BARI 1 mg | 125 | 125 | -5.1 | NR | -1.7 | NR | NS | NA | NA | NA | NA |
| | BARI 2 mg | 123 | 123 | -7.4 | NR | -4.0 | NR | <0.001 | NA | NA | NA | NA |
| | BARI 4 mg | 123 | 123 | -7.6 | NR | -4.2 | NR | <0.001 | NA | NA | NA | NA |
| BREEZE-AD5 | PBO | 147 | 28 | -4.0 | 1.0 | NR | NR | NR | NA | NA | NA | NA |
| | BARI 1 mg | 147 | 47 | -5.5 | 0.8 | NR | -3.9 to 0.9 | NR | NA | NA | NA | NA |
| | BARI 2 mg | 146 | 63 | -7.5 | 0.7 | NR | -5.8 to -1.2 | <0.001 | NA | NA | NA | NA |
| BREEZE-AD7 | PBO + TCS | 109 | 89 | LSM: -5.6 | SE: 0.6 | REF | REF | REF | NA | NA | NA | NA |
| | BARI 2 mg + TCS | 109 | 99 | LSM: -7.5 | SE: 0.6 | -1.9 | -3.6 to -0.3 | 0.022 | NA | NA | NA | NA |

| Study Name | Arms | N | DLQI | | | | | | CDLQI | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value | N | Change from baseline | 95% CI | p value |
| | BARI 4 mg + TCS | 111 | 99 | LSM: -8.9 | SE: 0.9 | -3.3 | -4.9 to -1.7 | <0.001 | NA | NA | NA | NA |
| Phase II Guttman-Yassky 2018 | PBO + TCS | 49 | 49 | -6.3 | 0.8 | NR | NR | REF | NA | NA | NA | NA |
| | BARI 2 mg + TCS | 37 | 37 | -6.9 | 0.9 | NR | NR | NS | NA | NA | NA | NA |
| | BARI 4 mg + TCS | 38 | 38 | -8.0 | 0.9 | NR | NR | NS | NA | NA | NA | NA |
| **Tralokinumab** | | | | | | | | | | | | |
| ECZTRA 1 | **Week 16** | | | | | | | | | | | |
| | PBO | 197 | 197 | -5 | SE: 0.6 | REF | REF | REF | NA | NA | NA | NA |
| | TRA 300 mg | 601 | 601 | -7.1 | SE: 0.3 | -2.1 | -3.4 to -0.8 | 0.002 | NA | NA | NA | NA |
| ECZTRA 2 | PBO | 201 | 201 | -4.9 | SE: 0.6 | REF | REF | REF | NA | NA | NA | NA |
| | TRA 300 mg | 591 | 591 | -8.8 | SE: 0.3 | -3.9 | -5.2 to -2.6 | <0.001 | NA | NA | NA | NA |
| ECZTRA 2 Subgroup* | PBO | 91 | NR | -5 | NR | REF | REF | REF | NA | NA | NA | NA |
| | TRA 300 mg | 270 | NR | -9 | NR | LSM: -3.9 | -5.8 to -2.0 | <0.001 | NA | NA | NA | NA |
| ECZTRA 3 | PBO + TCS | 126 | 126 | -8.8 | SE: 0.6 | REF | REF | REF | NA | NA | NA | NA |
| | TRA 300 mg + TCS | 252 | 252 | -11.7 | SE: 0.4 | -2.9 | -4.3 to -1.6 | <0.001 | NA | NA | NA | NA |
| **Upadacitinib** | | | | | | | | | | | | |
| MEASURE UP 1 | **Week 16** | | | | | | | | | | | |
| | PBO | 281 | [redacted] | | NR | NR | NR | NR | NR | NR | NR | NR |
| | UPA 15 mg | 281 | | | NR | NR | NR | NR | NR | NR | NR | NR |
| | UPA 30 mg | 285 | | | NR | NR | NR | NR | NR | NR | NR | NR |
| MEASURE UP 2 | PBO | 278 | | | NR | NR | NR | NR | NR | NR | NR | NR |
| | UPA 15 mg | 276 | | | NR | NR | NR | NR | NR | NR | NR | NR |
| | UPA 30 mg | 282 | | | NR | NR | NR | NR | NR | NR | NR | NR |
| **Dupilumab** | | | | | | | | | | | | |
| SOLO 1 | **Week 16** | | | | | | | | | | | |

| Study Name | Arms | N | DLQI | | | | | | CDLQI | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value | N | Change from baseline | 95% CI | p value |
| | PBO | 224 | 224 | -5.3 | 0.5 | NR | NR | NR | NA | NA | NA | NA |
| | DUP 300 mg Q2W | 224 | 224 | -9.3 | 0.4 | NR | NR | NR | NA | NA | NA | NA |
| | DUP 300 mg QW | 223 | 223 | -9 | 0.4 | NR | NR | NR | NA | NA | NA | NA |
| SOLO 2 | PBO | 236 | 236 | -3.6 | 0.5 | NR | NR | NR | NA | NA | NA | NA |
| | DUP 300 mg Q2W | 233 | 233 | -9.3 | 0.4 | NR | NR | NR | NA | NA | NA | NA |
| | DUP 300 mg QW | 239 | 239 | -9.5 | 0.4 | NR | NR | NR | NA | NA | NA | NA |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | 315 | LSM: -5.3 | SE: 0.3 | NR | NR | REF | NA | NA | NA | NA |
| | DUP 300 mg + TCS Q2W | 106 | 106 | LSM: -9.7 | SE: 0.5 | NR | NR | <0.0001 | NA | NA | NA | NA |
| | DUP 300 mg + TCS QW | 319 | 319 | LSM: -10.5 | SE: 0.3 | NR | NR | <0.0001 | NA | NA | NA | NA |
| Phase IIb Thaci 2016 | PBO QW | 61 | 61 | 2.6 | SE: 7.3 | REF | REF | REF | NA | NA | NA | NA |
| | Dupilumab 200 mg Q2W | 61 | 61 | -43.3 | SE: 7.2 | -45.9 | -64.6 to -27.2 | <0.0001 | NA | NA | NA | NA |
| | DUP 300 mg Q2W | 64 | 64 | -39.6 | SE: 7.0 | -42.3 | -60.6 to -23.9 | <0.0001 | NA | NA | NA | NA |
| | DUP 300 mg Q4W | 65 | 65 | -37.4 | SE: 6.9 | -40.1 | -58.3 to -21.9 | <0.0001 | NA | NA | NA | NA |

Short-term data on DLQI and CDLQI were not available in Phase IIb Gooderham 2019, AD-UP, Heads Up, and Phase IIb Guttman-Yassky 2020. ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, LSM: least squares mean, mg: milligram, N: total number, NA: not applicable, NR: not reported, NS: not significant, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib. *North American subgroup.

**Table G1.14. Short-Term Efficacy Outcomes: POEM**[35-37,39,40,42,45,46,48,50,51,56,63,64,69,71,72,81-83,85]

| Study Name | Arms | Sample Size (N) | POEM | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | | |
| | PBO | 77 | 77 | -3.7 | 95% CI: -5.5 to -1.9 | NR | NR | REF |
| | ABRO 100 mg | 156 | 153 | -6.8 | 95% CI: -8.0 to -5.6 | -3.1 | -5.2 to -0.9 | NR |
| | ABRO 200 mg | 154 | 153 | -10.6 | 95% CI: -11.8 to -9.4 | -6.9 | -9.0 to -4.7 | NR |
| JADE MONO-2 | PBO | 78 | 78 | -3.6 | 95% CI: -5.3 to -1.9 | NR | -5.3 to -1.9 | REF |
| | ABRO 100 mg | 158 | 156 | -8.7 | 95% CI: -9.9 to -7.5 | -5.1 (-7.2 to -3.1) | -9.9 to -7.5 | NR |
| | ABRO 200 mg | 155 | 154 | -11 | 95% CI: -12.1 to -9.8 | -7.4 (-9.5 to -5.3) | -12.1 to -9.8 | NR |
| JADE COMPARE | PBO | 131 | 131 | -5.1 | 95% CI: -6.3 to -3.9 | NR | NR | NR |
| | ABRO 100 mg | 238 | 238 | -9.6 | 95% CI: -10.1 to -8.6 | NR | NR | NR |
| | ABRO 200 mg | 226 | 226 | -12.6 | 95% CI: -13.6 to -11.7 | NR | NR | NR |
| | DUP 300 mg | 242 | 241 | -10.8 | 95% CI: -11.7 to -9.9 | NR | NR | NR |
| | **Week 16** | | | | | | | |
| | PBO | 131 | 131 | -5 | 95% CI: -6.3 to -3.8 | NR | NR | NR |
| | ABRO 100 mg + PBO→ABRO 100 mg | 238 | 238 | -9.2 | 95% CI: -10.1 to -8.2 | NR | NR | NR |
| | ABRO 100 mg + PBO→ABRO 100 mg | 226 | 226 | -12.5 | 95% CI:-13.4 to -11.6 | NR | NR | NR |
| | DUP 300 mg + Oral PBO→PBO | 242 | 241 | -10.8 | 95% CI:-11.8 to -9.9 | NR | NR | NR |
| **Baricitinib** | | | | | | | | |
| BREEZE-AD1 | **Week 16** | | | | | | | |
| | PBO | 249 | 72 | -2.7 | SE: 0.8 | NR | NR | REF |
| | BARI 1 mg | 127 | 53 | -5.3 | SE: 0.9 | -2.6 | NR | <0.05 |
| | BARI 2 mg | 123 | 52 | -6.3 | SE: 0.9 | -3.6 | NR | <0.01 |
| | BARI 4 mg | 125 | 70 | -7.8 | SE: 0.8 | -5.1 | NR | <0.001 |

| Study Name | Arms | Sample Size (N) | POEM | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| BREEZE-AD2 | PBO | 244 | 52 | -1.5 | NR | REF | | REF |
| | BARI 1 mg | 125 | 34 | -3.9 | NR | -2.4 | NR | NS |
| | BARI 2 mg | 123 | 40 | -7.1 | NR | -5.6 | NR | <0.001 |
| | BARI 4 mg | 123 | 48 | -7.6 | NR | -6.1 | NR | <0.001 |
| BREEZE-AD5 | PBO | 147 | 147 | -2.7 | NR | NR | NR | NR |
| | BARI 1 mg | 147 | 147 | -4.6 | NR | NR | -4.9 to 1.1 | NR |
| | BARI 2 mg | 146 | 146 | -7.4 | NR | NR | -7.7 to -1.8 | <0.001 |
| BREEZE-AD7 | PBO + TCS | 109 | 109 | -5.6 | 0.8 | REF | REF | REF |
| | BARI 2 mg + TCS | 109 | 109 | -8.5 | 0.7 | -2.9 | -5.0 to -0.8 | 0.006 |
| | BARI 4 mg + TCS | 111 | 111 | -10.8 | 0.7 | -5.2 | -7.3 to -3.2 | <0.001 |
| Phase II Guttman-Yassky 2018 | PBO + TCS | 49 | 49 | -3.5 | NR | NR | NR | REF |
| | BARI 2 mg + TCS | 37 | 37 | -6.4 | NR | NR | NR | NS |
| | BARI 4 mg + TCS | 38 | 38 | -7.5 | NR | NR | NR | <0.01 |
| **Tralokinumab** | | | | | | | | |
| ECZTRA 1 | **Week 16** | | | | | | | |
| | PBO | 197 | 197 | -3 | 0.66 | REF | REF | REF |
| | TRA 300 mg | 601 | 601 | -7.6 | 0.35 | -4.5 | -6.0 to -3.1 | <0.001 |
| ECZTRA 2 | PBO | 201 | 201 | -3.7 | 0.66 | REF | REF | REF |
| | TRA 300 mg | 591 | 591 | -8.8 | 0.33 | -5.1 | -6.5 to -3.6 | <0.001 |
| ECZTRA 3 | PBO + TCS | 126 | 126 | -7.8 | 0.66 | REF | REF | REF |
| | TRA 300 mg + TCS | 252 | 252 | -11.8 | 0.46 | -0.4 | -5.6 to -2.4 | <0.001 |
| **Upadacitinib** | | | | | | | | |
| Phase IIb Guttman-Yassky 2020 | **Week 16** | | | | | | | |
| | PBO | 41 | 41 | 1.6 | 1.4 | NR | NR | REF |
| | UPA 15 mg | 42 | 42 | 8.6 | 1.4 | NR | NR | ≤0.001 |
| | UPA 30 mg | 42 | 42 | 12.3 | 1.4 | NR | NR | ≤0.001 |

| Study Name | Arms | Sample Size (N) | POEM | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| **Dupilumab** | | | | | | | | |
| SOLO 1 | **Week 16** | | | | | | | |
| | PBO | 224 | 224 | -5.1 | 0.7 | NR | NR | NR |
| | DUP 300 mg Q2W | 224 | 224 | -11.6 | 0.5 | NR | NR | NR |
| | DUP 300 mg QW | 223 | 223 | -11 | 0.5 | NR | NR | NR |
| SOLO 2 | PBO | 236 | 236 | -3.3 | 0.6 | NR | NR | NR |
| | DUP 300 mg Q2W | 233 | 233 | -10.2 | 0.5 | NR | NR | NR |
| | DUP 300 mg QW | 239 | 239 | -11.3 | 0.5 | NR | NR | NR |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | 315 | -4.7 | 0.4 | NR | NR | REF |
| | DUP 300 mg + TCS Q2W | 106 | 106 | -12.4 | 0.6 | NR | NR | <0.0001 |
| | DUP 300 mg + TCS QW | 319 | 319 | -12.5 | 0.4 | NR | NR | <0.0001 |
| Phase IIb AD-1021 | PBO QW | 61 | 61 | LSM: -1.1 | SE: 0.9 | NR | NR | REF |
| | Dupilumab 200mg Q2W | 61 | 61 | LSM: -10.4 | SE: 0.9 | NR | NR | <0.0001 |
| | DUP 300mg Q2W | 64 | 64 | LSM: -9.8 | SE: 0.9 | NR | NR | <0.0001 |
| | DUP 300mg Q4W | 65 | 65 | LSM: -9.9 | SE: 0.9 | NR | NR | <0.0001 |

Short-term data on POEM were not available in JADE TEEN, Phase IIb Gooderham 2019, MEASURE UP 1, MEASURE UP 2, AD-UP, and Heads Up. ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, NS: not significant, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib.

**Table G1.15. Short-Term Efficacy Outcomes: Total HADS**[42-46,48,50-56,60,64-66,71,156]

| Study Name | Arms | N | Total HADS | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | | |
| | PBO | 77 | 77 | LSM: -0.2 | -0.8 to 0.4 | REF | REF | REF |
| | ABRO 100 mg | 156 | 156 | LSM: -1.4 | -1.8 to -0.9 | -1.1 | -19 to -0.4 | 0.0028 |
| | ABRO 200 mg | 154 | 154 | LSM: -1.8 | -2.2 to -1.4 | -1.6 | -2.3 to -0.9 | <0.001 |
| **Baricitinib** | | | | | | | | |
| BREEZE-AD7 | **Week 16** | | | | | | | |
| | PBO + TCS | 109 | 109 | LSM: -3.2 | 0.6 | REF | REF | REF |
| | BARI 2 mg + TCS | 109 | 109 | LSM: -4.8 | 0.5 | -1.6 | -3.1 to -0.1 | 0.042 |
| | BARI 4 mg + TCS | 111 | 111 | LSM: -5.1 | 0.5 | -1.9 | -3.5 to -0.4 | 0.011 |
| **Dupilumab** | | | | | | | | |
| SOLO 1 | **Week 16** | | | | | | | |
| | PBO | 224 | 224 | -3 | 0.7 | NR | NR | NR |
| | DUP 300 mg Q2W | 224 | 224 | -5.2 | 0.5 | NR | NR | NR |
| | DUP 300 mg QW | 223 | 223 | -5.2 | 0.5 | NR | NR | NR |
| SOLO 2 | PBO | 236 | 236 | -0.8 | 0.4 | NR | NR | NR |
| | DUP 300 mg Q2W | 233 | 233 | -5.1 | 0.4 | NR | NR | NR |
| | DUP 300 mg QW | 239 | 239 | -5.8 | 0.4 | NR | NR | NR |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | 315 | -3.6 | 0.34 | NR | NR | REF |
| | DUP 300 mg + TCS Q2W | 106 | 106 | -4.9 | 0.56 | NR | NR | 0.03 |
| | DUP 300 mg + TCS QW | 319 | 319 | -5.2 | 0.33 | NR | NR | 0.0004 |
| | PBO QW | 61 | 61 | LSM: 0 | SE: 0.8 | NR | NR | REF |

| Study Name | Arms | N | Total HADS | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| Phase IIb Thaci 2016 | DUP 200 mg Q2W | 61 | 61 | LSM: -4 | SE: 0.8 | NR | NR | 0.0002 |
| | DUP 300 mg Q2W | 64 | 64 | LSM: -4.3 | SE: 0.8 | NR | NR | <0.0001 |
| | DUP 300 mg Q4W | 65 | 65 | LSM: -2.7 | SE: 0.8 | NR | NR | 0.0103 |

Short-term data on total HADS were not available in JADE MONO 2, JADE TEEN, JADE COMPARE, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, MEASURE UP 1, MEASURE UP 2, Heads Up, AD-UP, and Phase IIb Guttman-Yassky 2020. BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids.

**Table G1.16. Short-Term Efficacy Outcomes: HADS Anxiety**[35-37,39,46,50-56,60,63-66,69,85,156,158]

| Study Name | Arms | HADS Anxiety | | | | | |
|---|---|---|---|---|---|---|---|
| | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | |
| | PBO | 76 | LSM: -1 | 95% CI: -1.7 to -0.4 | REF | REF | REF |
| | ABRO 100 mg | 152 | LSM: -1.6 | 95% CI: -2.0 to -1.1 | -0.5 | -1.3 to 0.2 | 0.1675 |
| | ABRO 200 mg | 152 | LSM: -2.1 | 95% CI: -2.5 to -1.6 | -1 | -1.8 to -0.3 | 0.0085 |
| JADE MONO-2 | PBO | 78 | LSM: −0.6 | 95% CI: −1.3 to 0.2 | REF | REF | REF |
| | ABRO 100 mg | 156 | LSM: −1.6 | 95% CI: −2.1 to −1.1 | -1.0 | -1.9 to -0.1 | NR |
| | ABRO 200 mg | 153 | LSM: −1.7 | 95% CI: −2.2 to −1.2 | -1.1 | -2.0 to -0.2 | NR |
| JADE TEEN | PBO | 96 | LSM: -2.1 | 95% CI: -2.7 to -1.5 | NR | NR | NR |
| | ABRO 100 mg | 95 | LSM: -2 | 95% CI: -2.6 to -1.4 | NR | NR | NR |
| | ABRO 200 mg | 94 | LSM: -2.4 | 95% CI: -3 to -1.8 | NR | NR | NR |
| JADE COMPARE | PBO | 131 | LSM: -0.4 | 95% CI: -0.9 to 0.1 | REF | REF | REF |
| | ABRO 100 mg | 238 | LSM: -1.2 | 95% CI: -1.5 to -0.8 | -0.7 | -1.4 to -0.1 | NR |
| | ABRO 200 mg | 226 | LSM: -1.6 | 95% CI: -2.0 to -1.2 | -1.2 | -1.8 to -0.5 | NR |
| | DUP 300 mg | 241 | LSM: -1.4 | 95% CI: -1.7 to -1.0 | -1 | -1.6 to -0.3 | NR |
| | **Week 16** | | | | | | |

| Study Name | Arms | HADS Anxiety | | | | | |
|---|---|---|---|---|---|---|---|
| | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| | PBO | 131 | LSM: -0.4 | 95% CI: -0.9 to 0.1 | NR | NR | NR |
| | ABRO 100 mg | 238 | LSM: -1.2 | 95% CI: -1.6 to -.8 | NR | NR | NR |
| | ABRO 200 mg | 226 | LSM: -2.0 | 95% CI: -2.4 to -1.6 | NR | NR | NR |
| | DUP 300 mg | 241 | LSM: -1.5 | 95% CI: -1.9 to -1.1 | NR | NR | NR |
| Gooderham 2019 | **Week 12** | | | | | | |
| | PBO | 36 | -2.6 | 3.01 | NR | NR | NR |
| | ABRO 100 mg | 43 | -2.8 | 3.71 | NR | NR | NR |
| | ABRO 200 mg | 46 | -2.5 | 3.51 | NR | NR | NR |
| **Baricitinib** | | | | | | | |
| BREEZE-AD7 | **Week 16** | | | | | | |
| | PBO + TCS | 109 | -1.9 | 0.3 | REF | REF | REF |
| | BARI 2 mg + TCS | 109 | -2.7 | 0.3 | -0.8 | -1.6 to 0 | 0.051 |
| | BARI 4 mg + TCS | 111 | -2.8 | 0.3 | -0.9 | -1.7 to -0.1 | 0.028 |
| **Dupilumab** | | | | | | | |
| SOLO 1 | **Week 16** | | | | | | |
| | PBO | NR | NR | 0.7 | NR | NR | NR |
| | DUP 300 mg Q2W | NR | NR | 0.5 | NR | NR | NR |
| | DUP 300 mg QW | NR | NR | 0.5 | NR | NR | NR |
| SOLO 2 | PBO | NR | NR | 0.4 | NR | NR | NR |
| | DUP 300 mg Q2W | NR | NR | 0.4 | NR | NR | NR |
| | DUP 300 mg QW | NR | NR | 0.4 | NR | NR | NR |
| Phase IIb Thaci 2016 | PBO QW | 61 | LSM: -0.4 | SE: 0.4 | NR | NR | REF |
| | DUP 200 mg Q2W | 61 | LSM: -1.9 | SE: 0.4 | NR | NR | 0.0062 |
| | DUP 300 mg Q2W | 64 | LSM: -2.2 | SE: 0.4 | NR | NR | 0.0011 |
| | DUP 300 mg Q4W | 65 | LSM: -1.3 | SE: 0.4 | NR | NR | 0.0808 |

Short-term data on HADS Anxiety were not available in BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, MEASURE UP 1, MEASURE UP 2, AD-UP, Heads Up, Phase IIb Guttman-Yassky 2020, and LIBERTY AD CHRONOS. ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids.

**Table G1.17. Short-Term Efficacy Outcomes: HADS Depression**[35-37,39,46,50-56,60,63-67,85,156,158]

| Study Name | Arms | HADS Depression | | | | | |
|---|---|---|---|---|---|---|---|
| | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | |
| | PBO | 76 | LSM: -0.2 | 95% CI: -0.8 to 0.4 | REF | REF | REF |
| | ABRO 100 mg | 152 | LSM: -1.4 | 95% CI: -1.8 to -0.9 | -1.1 | -1.9 to -0.4 | 0.0028 |
| | ABRO 200 mg | 152 | LSM: -1.8 | 95% CI: -2.2 to -1.4 | -1.6 | -2.3 to -0.9 | <0.0001 |
| JADE MONO-2 | PBO | 78 | 0.3 | 95% CI: -0.3 to 0.9 | REF | REF | REF |
| | ABRO 100 mg | 156 | -1.0 | 95% CI: -1.5 to -0.6 | -1.3 | -2.1 to -0.6 | NR |
| | ABRO 200 mg | 153 | -1.4 | 95% CI: -1.8 to -1.0 | -1.7 | -2.5 to -0.9 | NR |
| JADE TEEN | PBO | 96 | 96 | LSM: -1 | 95% CI: -1.5 to -0.5 | NR | NR |
| | ABRO 100 mg | 95 | 95 | LSM: -1.4 | 95% CI: -1.9 to -0.8 | NR | NR |
| | ABRO 200 mg | 94 | 94 | LSM: -1.2 | 95% CI: -1.7 to -0.6 | NR | NR |
| JADE COMPARE | PBO | 131 | LSM: -0.3 | 95% CI: -0.7 to 0.2 | REF | REF | REF |
| | ABRO 100 mg | 238 | LSM: -1.3 | 95% CI: -1.6 to -0.9 | -1 | -1.6 to -0.4 | NR |
| | ABRO 200 mg | 226 | LSM: -1.6 | 95% CI: -1.9 to -1.2 | -1.3 | -1.9 to -0.7 | NR |
| | DUP 300 mg | 241 | LSM: -1.3 | 95% CI: -1.6 to -0.9 | -1 | -1.6 to -0.4 | NR |
| | **Week 16** | | | | | | |
| | PBO | 131 | LSM: -0.3 | 95% CI: -0.8 to 0.2 | NR | NR | NR |
| | ABRO 100 mg | 238 | LSM: -1 | 95% CI: -1.4 to -0.7 | NR | NR | NR |
| | ABRO 200 mg | 226 | LSM: -1.6 | 95% CI: -1.9 to -1.2 | NR | NR | NR |
| | DUP 300 mg | 241 | LSM: -1.2 | 95% CI: -1.5 to -0.8 | NR | NR | NR |
| Gooderham 2019 | **Week 12** | | | | | | |
| | PBO | 36 | -0.9 | 3.96 | NR | NR | NR |
| | ABRO 100 mg | 43 | -2.4 | 3.74 | NR | NR | NR |
| | ABRO 200 mg | 46 | -1.8 | 3.9 | NR | NR | NR |
| **Baricitinib** | | | | | | | |
| BREEZE-AD7 | PBO + TCS | 109 | -1.3 | 0.3 | REF | REF | REF |
| | BARI 2 mg + TCS | 109 | -2.1 | 0.3 | -0.7 | -1.6 to 0.1 | 0.083 |

| Study Name | Arms | HADS Depression | | | | | |
|---|---|---|---|---|---|---|---|
| | | N | Change from baseline | SD | Diff from PBO | 95% CI | p value |
| | BARI 4 mg + TCS | 111 | -2.3 | 0.3 | -1 | -1.0 to -0.2 | 0.016 |
| **Dupilumab** | | | | | | | |
| Phase IIb Thaci 2016 | **Week 16** | | | | | | |
| | PBO QW | 61 | LSM: 0.4 | SE: 0.5 | NR | NR | REF |
| | DUP 200 mg Q2W | 61 | LSM: -2 | SE: 0.5 | NR | NR | <0.0001 |
| | DUP 300 mg Q2W | 64 | LSM: -2 | SE: 0.4 | NR | NR | <0.0001 |
| | DUP 300 mg Q4W | 65 | LSM: -1.4 | SE: 0.4 | NR | NR | 0.0036 |

Short-term data on HADS Depression were not available in BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, MEASURE UP 1, MEASURE UP 2, AD-UP, Heads Up, Phase IIb Guttman-Yassky 2020, LIBERTY AD SOLO 1 and SOLO 2, and LIBERTY AD CHRONOS.
ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids.

**Table G1.18. Long-Term Efficacy Outcomes: IGA Response Rates**[43,44,50,54,55,63-65,77,79,84,108,159,160]

| Study Name | Arms | N | IGA response | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | |
| JADE EXTEND Subgroup 1* | **Week 48** | | | | | | | |
| | ABRO 100 mg | 595 | 84 | 287 | 29.1 | NR | NR | NR |
| | ABRO 200 mg | 521 | 99 | 250 | 39.5 | NR | NR | NR |
| | **Week 48 (Responders)** | | | | | | | |
| | ABRO 100 mg | NR | 49 | 92 | 53.3 | NR | NR | NR |
| | ABRO 200 mg | NR | 78 | 136 | 57.4 | NR | NR | NR |
| | **Week 24 (Nonresponders)** | | | | | | | |
| | ABRO 100 mg | NR | 65 | 290 | 22.4 | NR | NR | NR |
| | ABRO 200 mg | NR | 59 | 221 | 26.7 | NR | NR | NR |
| | **Week 48 (Nonresponders)** | | | | | | | |
| | ABRO 100 mg | NR | 49 | 224 | 21.9 | NR | NR | NR |
| | ABRO 200 mg | NR | 47 | 172 | 27.3 | NR | NR | NR |
| JADE EXTEND Subgroup 2† | **Week 32** | | | | | | | |
| | ABRO 100 mg | 130 | 25 | 71 | 35.2 | NR | NR | NR |
| | ABRO 200 mg | 73 | 17 | 36 | 47.2 | NR | NR | NR |
| **Baricitinib** | | | | | | | | |
| BREEZE-AD3 | **Week 32** | | | | | | | |
| | BARI 2 mg | [redacted] | | | | NR | NR | NR |
| | **Week 40** | | | | | | | |
| | BARI 2 mg | [redacted] | | | | NR | NR | NR |
| | **Week 68** | | | | | | | |
| | BARI 2 mg | [redacted] | | | | NR | NR | NR |
| BREEZE-AD6 | **Week 16** | | | | | | | |
| | BARI 2 mg | 146 | 39 | 146 | 27 | NR | NR | NR |
| | **Week 32** | | | | | | | |

| Study Name | Arms | N | IGA response | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| | BARI 2 mg | 146 | 56 | 146 | 38.2 | NR | NR | NR |
| | **Week 52** | | | | | | | |
| | BARI 2 mg | 146 | 46 | 146 | 31.3 | NR | NR | NR |
| **Tralokinumab** | | | | | | | | |
| ECZTRA 1 | **Week 52 (Maintenance Period)** | | | | | | | |
| | PBO | 35 | 9 | 19 | 47.4 | REF | REF | REF |
| | TRA 300 mg Q2W | 68 | 20 | 39 | 51.3 | 6 | -21.8 to 33.7 | 0.68 |
| | TRA 300 mg Q4W | 76 | 14 | 36 | 38.9 | -9.5 | -37.1 to 18.0 | 0.50 |
| ECZTRA 2 | PBO | 46 | 7 | 28 | 25 | REF | REF | REF |
| | TRA 300 mg Q2W | 91 | 32 | 54 | 59.3 | 34.1 | 13.4 to 54.9 | 0.004 |
| | TRA 300 mg Q4W | 89 | 22 | 49 | 44.9 | 19.9 | -1.2 to 40.9 | 0.084 |
| ECZTRA 1 and 2 OLE (Initial nonresponders) | TRA 300 mg Q2W + TCS | 686 | 138 | 686 | 20.1 | NR | NR | NR |
| | TRA 300 mg Q2W + TCS (no response at week 24 group) | NR | NR | NR | 13.9 | NR | NR | NR |
| ECZTRA 3 | **Week 32 (Maintenance Period)** | | | | | | | |
| | TRA 300 mg Q2W + TCS (TRA nonresponders) | 95 | NR | NR | 30.5 | NR | 22.2 to 40.4 | NR |
| | TRA 300 mg Q2W + TCS (TRA responders) | 69 | NR | NR | 89.6 | NR | 77.8 to 99.5 | NR |
| | TRA 300 mg Q4W + TCS (TRA responders) | 69 | NR | NR | 77.6 | NR | 64.1 to 87.0 | NR |
| ECZTEND | **Week 56** | | | | | | | |
| | TRA 300 mg Q2W (Week 56 Cohort) | 612 | 255‡ | 612 | 41.7 | NR | NR | NR |
| | TRA 300 mg Q2W (2-year Cohort) | 345 | NR | NR | NR | NR | NR | NR |
| **Upadacitinib** | | | | | | | | |
| Phase IIb Guttman-Yassky 2020 | **Week 16** | | | | | | | |
| | PBO→PBO | 8 | 0 | 8 | 0 | NR | NR | NR |
| | UPA 7.5 mg→PBO | 13 | 3 | 13 | 7.7 | NR | NR | NR |
| | UPA 15 mg→PBO | 17 | 11 | 17 | 47.1 | NR | NR | NR |

| Study Name | Arms | N | IGA response | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| | UPA 30 mg→PBO | 13 | 10 | 13 | 61.5 | NR | NR | NR |
| | PBO→UPA 30 mg | 1 | 0 | 1 | 0 | NR | NR | NR |
| | UPA 7.5 mg→UPA 7.5 mg | 11 | 1 | 11 | 9.1 | NR | NR | NR |
| | UPA 15 mg→UPA 15 mg | 12 | 3 | 12 | 25 | NR | NR | NR |
| | UPA 30 mg→UPA 30 mg | 3 | 0 | 3 | 0 | NR | NR | NR |
| | **START OF RESCUE W/ UPA 30mg** | | | | | | | |
| | PBO→PBO | 8 | 0 | 8 | 0 | NR | NR | NR |
| | UPA 7.5 mg→PBO | 13 | 0 | 13 | 0 | NR | NR | NR |
| | UPA 15 mg→PBO | 17 | 0 | 17 | 0 | NR | NR | NR |
| | UPA 30 mg→PBO | 13 | 0 | 13 | 0 | NR | NR | NR |
| | PBO→UPA 30 mg | 1 | 0 | 1 | 0 | NR | NR | NR |
| | UPA 7.5 mg→UPA 7.5 mg | 11 | 0 | 11 | 0 | NR | NR | NR |
| | UPA 15 mg→UPA 15 mg | 12 | 0 | 12 | 0 | NR | NR | NR |
| | UPA 30 mg→UPA 30 mg | 3 | 0 | 3 | 0 | NR | NR | NR |
| | **8 WEEKS POST-RESCUE** | | | | | | | |
| | PBO→PBO | 8 | 4 | 8 | 50 | NR | NR | NR |
| | UPA 7.5 mg→PBO | 12 | 7 | 12 | 58.3 | NR | NR | NR |
| | UPA 15 mg→PBO | 16 | 15 | 16 | 93.8 | NR | NR | NR |
| | UPA 30 mg→PBO | 13 | 9 | 13 | 69.2 | NR | NR | NR |
| | PBO→UPA 30 mg | 1 | 0 | 1 | 0 | NR | NR | NR |
| | UPA 7.5 mg→UPA 7.5 mg | 10 | 1 | 10 | 10 | NR | NR | NR |
| | UPA 15 mg→UPA 15 mg | 9 | 2 | 9 | 22.2 | NR | NR | NR |
| | UPA 30 mg→UPA 30 mg | 3 | 0 | 3 | 0 | NR | NR | NR |
| **Dupilumab** | | | | | | | | |
| LIBERTY AD CHRONOS | **Week 52** | | | | | | | |
| | PBO + TCS | 264 | 33 | 264 | 13 | REF | REF | REF |
| | DUP 300 mg + TCS Q2W | 89 | 32 | 89 | 36 | 24 | 12.7 to 34.2 | <0.0001 |

| Study Name | Arms | N | IGA response | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| | DUP 300 mg + TCS QW | 270 | 108 | 270 | 40 | 28 | 20.4 to 34.6 | <0.0001 |
| AD SOLO-CONTINUE | **Week 36** | | | | | | | |
| | PBO | 83 | 9 | 63 | 14.3 | NR | NR | NR |
| | DUP 300 mg Q8W | 84 | 21 | 64 | 32.8 | NR | NR | NR |
| | DUP 300 mg Q4W | 86 | 29 | 66 | 43.9 | NR | NR | NR |
| | DUP 300 mg QW/Q2W | 169 | 68 | 126 | 54 | NR | NR | NR |

Long-term data on IGA were not available in Heads Up long-term outcomes. BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, LTE: long-term extension, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, TCS: topical corticosteroids, TRA: tralokinumab, %: percent. *JADE MONO-1 & 2 and JADE COMPARE subgroup, †JADE COMPARE dupilumab nonresponder subgroup, ‡Non-responder imputation.

**Table G1.19. Long-Term Efficacy Outcomes: EASI 75**[43,44,50,54,55,63-65,77,79,81,84,108,159,160]

| Study Name | Arms | N | EASI 75 | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | |
| JADE EXTEND Subgroup 1* | **Week 48** | | | | | | | |
| | ABRO 100 mg | 595 | 132 | 289 | 45.9 | NR | NR | NR |
| | ABRO 200 mg | 521 | 155 | 252 | 61.7 | NR | NR | NR |
| | **Week 48 (Responders)** | | | | | | | |
| | ABRO 100 mg | NR | 106 | 153 | 69.3 | NR | NR | NR |
| | ABRO 200 mg | NR | 147 | 208 | 70.7 | NR | NR | NR |
| | **Week 24 (Nonresponders)** | | | | | | | |
| | ABRO 100 mg | NR | 91 | 203 | 44.8 | NR | NR | NR |
| | ABRO 200 mg | NR | 68 | 126 | 54 | NR | NR | NR |
| | **Week 48 (Nonresponders)** | | | | | | | |
| | ABRO 100 mg | NR | 58 | 165 | 35.2 | NR | NR | NR |
| | ABRO 200 mg | NR | 48 | 101 | 47.5 | NR | NR | NR |
| JADE EXTEND Subgroup 2† | **Week 32** | | | | | | | |
| | ABRO 100 mg | 130 | 21 | 31 | 67.7 | NR | NR | NR |
| | ABRO 200 mg | 73 | 16 | 20 | 80 | NR | NR | NR |
| **Baricitinib** | | | | | | | | |
| BREEZE-AD3 | **Week 32** | | | | | | | |
| | BARI 2 mg | [redacted] | | | | NR | NR | NR |
| | **Week 40** | | | | | | | |
| | BARI 2 mg | [redacted] | | | | NR | NR | NR |
| | **Week 68** | | | | | | | |
| | BARI 2 mg | [redacted] | | | | NR | NR | NR |
| BREEZE-AD6 | **Week 16** | | | | | | | |
| | BARI 2 mg | 146 | 58 | 146 | 40 | NR | NR | NR |

| Study Name | Arms | N | EASI 75 | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| | **Week 32** | | | | | | | |
| | BARI 2 mg | 146 | 75 | 146 | 51.4 | NR | NR | NR |
| | **Week 52** | | | | | | | |
| | BARI 2 mg | 146 | 71 | 146 | 48.6 | NR | NR | NR |
| **Tralokinumab** | | | | | | | | |
| ECZTRA 1 | **Week 52 (Maintenance period)** | | | | | | | |
| | PBO | 35 | 10 | 30 | 33.3 | REF | REF | REF |
| | TRA 300 mg Q2W | 68 | 28 | 47 | 59.6 | 21.2 | -0.2 to 42.6 | 0.056 |
| | TRA 300 mg Q4W | 76 | 28 | 57 | 49.1 | 11.7 | -8.7 to 32.0 | 0.27 |
| ECZTRA 2 | PBO | 46 | 9 | 42 | 21.4 | REF | REF | REF |
| | TRA 300 mg Q2W | 91 | 43 | 77 | 55.8 | 33.7 | 17.3 to 50.0 | <0.001 |
| | TRA 300 mg Q4W | 89 | 37 | 74 | 51.4 | 30 | 13.7 to 46.4 | 0.001 |
| ECZTRA 1 and 2 OLE (Initial nonresponders) | 686 | 294 | 686 | 42.9 | NR | NR | NR | NR |
| | NR | NR | NR | 25.7 | NR | NR | NR | NR |
| ECZTRA 3 | **Week 32 (Maintenance period)** | | | | | | | |
| | TRA 300 mg Q2W + TCS (TRA nonresponders) | 95 | NR | NR | 55.8 | NR | 45.8 to 65.4 | NR |
| | TRA 300 mg Q2W + TCS (TRA responders) | 69 | NR | NR | 92.5 | NR | 83.7 to 96.8 | NR |
| | TRA 300 mg Q4W + TCS (TRA responders) | 69 | NR | NR | 90.8 | NR | 81.5 to 95.7 | NR |
| ECZTEND | **Week 56** | | | | | | | |
| | TRA 300 mg Q2W (Week 56 Cohort) | 612 | 425‡ | 612 | 69.4 | NR | NR | NR |
| | TRA 300 mg Q2W (2-year Cohort) | 345 | 272‡ | 345 | 78.8 | NR | NR | NR |
| **Upadacitinib** | | | | | | | | |
| Heads Up | **Week 24** | | | | | | | |
| | DUP 300 mg | 344 | NR | NR | 59.5 | NR | NR | NR |
| | UPA 30 mg | 348 | NR | NR | 64.2 | NR | NR | NR |
| Phase IIb Guttman-Yassky 2020 | **Week 16** | | | | | | | |

| Study Name | Arms | N | EASI 75 | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| | PBO→PBO | 8 | 0 | 8 | 0 | NR | NR | NR |
| | UPA 7.5 mg→PBO | 13 | 3 | 13 | 23.1 | NR | NR | NR |
| | UPA 15 mg→PBO | 17 | 11 | 17 | 64.7 | NR | NR | NR |
| | UPA 30 mg→PBO | 13 | 10 | 13 | 76.9 | NR | NR | NR |
| | PBO→UPA 30 mg | 1 | 0 | 1 | 0 | NR | NR | NR |
| | UPA 7.5 mg→UPA 7.5 mg | 11 | 1 | 11 | 9.1 | NR | NR | NR |
| | UPA 15 mg→UPA 15 mg | 12 | 6 | 12 | 50 | NR | NR | NR |
| | UPA 30 mg→UPA 30 mg | 3 | 2 | 3 | 66.7 | NR | NR | NR |
| | **START OF RESCUE W/ UPA 30 mg** | | | | | | | |
| | PBO→PBO | 8 | 0 | 8 | 0 | NR | NR | NR |
| | UPA 7.5 mg→PBO | 13 | 0 | 13 | 0 | NR | NR | NR |
| | UPA 15 mg→PBO | 17 | 0 | 17 | 0 | NR | NR | NR |
| | UPA 30 mg→PBO | 13 | 0 | 13 | 0 | NR | NR | NR |
| | PBO→UPA 30 mg | 1 | 0 | 1 | 0 | NR | NR | NR |
| | UPA 7.5 mg→UPA 7.5 mg | 11 | 0 | 11 | 0 | NR | NR | NR |
| | UPA 15 mg→UPA 15 mg | 12 | 0 | 12 | 0 | NR | NR | NR |
| | UPA 30 mg→UPA 30 mg | 3 | 0 | 3 | 0 | NR | NR | NR |
| | **8 WEEKS POST-RESCUE** | | | | | | | |
| | PBO→PBO | 8 | 4 | 8 | 50 | NR | NR | NR |
| | UPA 7.5 mg→PBO | 12 | 7 | 12 | 58.3 | NR | NR | NR |
| | UPA 15 mg→PBO | 16 | 15 | 16 | 93.8 | NR | NR | NR |
| | UPA 30 mg→PBO | 13 | 9 | 13 | 69.2 | NR | NR | NR |
| | PBO→UPA 30 mg | 1 | 1 | 1 | 100 | NR | NR | NR |
| | UPA 7.5 mg→UPA 7.5 mg | 10 | 3 | 10 | 30 | NR | NR | NR |
| | UPA 15 mg→UPA 15 mg | 9 | 5 | 9 | 55.6 | NR | NR | NR |
| | UPA 30 mg→UPA 30 mg | 3 | 1 | 3 | 33.3 | NR | NR | NR |
| **Dupilumab** | | | | | | | | |

| Study Name | Arms | N | EASI 75 | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| LIBERTY AD CHRONOS | **Week 52** | | | | | | | |
| | PBO + TCS | 264 | 57 | 264 | 22 | REF | REF | REF |
| | DUP 300 mg + TCS Q2W | 89 | 58 | 89 | 65 | 44 | 32.5 to 54.7 | <0.0001 |
| | DUP 300 mg + TCS QW | 270 | 173 | 270 | 64 | 43 | 34.9 to 50.1 | <0.0001 |
| AD SOLO-CONTINUE | **Week 36** | | | | | | | |
| | PBO | 83 | 24 | 79 | 30.4 | NR | NR | NR |
| | DUP 300 mg Q8W | 84 | 45 | 82 | 54.9 | NR | NR | NR |
| | DUP 300 mg Q4W | 86 | 49 | 84 | 58.3 | NR | NR | NR |
| | DUP 300 mg QW/Q2W | 169 | 116 | 162 | 71.6 | NR | NR | NR |

BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, LTE: long-term extension, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *JADE MONO-1 & 2 and JADE COMPARE subgroup, [†]JADE COMPARE dupilumab nonresponder subgroup, [‡]non-responder imputation (NRI).

**Table G1.20. Long-Term Efficacy Outcomes: EASI 50 and 90**[50,54,55,64,65,77,79,81,108]

| Study Name | Arms | N | EASI 50 | | | | | | EASI 90 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value | n | N | % | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | | | | | | | |
| JADE EXTEND Subgroup 1* | **Week 48** | | | | | | | | | | | | | |
| | ABRO 100 mg | 595 | NR | NR | NR | NR | NR | NR | 84 | 289 | 29.2 | NR | NR | NR |
| | ABRO 200 mg | 521 | NR | NR | NR | NR | NR | NR | 103 | 252 | 40.7 | NR | NR | NR |
| JADE EXTEND Subgroup 2† | **Week 32** | | | | | | | | | | | | | |
| | ABRO 100 mg | 130 | NR | NR | NR | NR | NR | NR | 27 | 68 | 39.7 | NR | NR | NR |
| | ABRO 200 mg | 73 | NR | NR | NR | NR | NR | NR | 22 | 37 | 59.5 | NR | NR | NR |
| **Tralokinumab** | | | | | | | | | | | | | | |
| ECZTRA 3 | **Week 32 (Maintenance period)** | | | | | | | | | | | | | |
| | TRA 300 mg Q2W + TCS (TRA nonresponders) | 95 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | TRA 300 mg Q2W + TCS (TRA responders) | 69 | NR | NR | 98.6 | NR | NR | NR | NR | NR | 72.5 | NR | NR | NR |
| | TRA 300 mg Q4W + TCS (TRA responders) | 69 | NR | NR | 91.3 | NR | NR | NR | NR | NR | 63.8 | NR | NR | NR |
| ECZTEND | **Week 56** | | | | | | | | | | | | | |
| | TRA 300 mg Q2W (Week 56 Cohort) | 612 | 488‡ | 612 | 79.6 | NR | NR | NR | 313 | 612 | 51.1 | NR | NR | NR |
| | TRA 300 mg Q2W (2-year Cohort) | 345 | 314‡ | 345 | 91 | NR | NR | NR | 195 | 345 | 56.5 | NR | NR | NR |
| **Upadacitinib** | | | | | | | | | | | | | | |
| Heads Up | **Week 24** | | | | | | | | | | | | | |
| | DUP 300 mg | 344 | NR | NR | NR | NR | NR | NR | NR | NR | 47.6 | NR | NR | NR |

| Study Name | Arms | N | EASI 50 | | | | | | EASI 90 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value | n | N | % | Diff from PBO | 95% CI | p value |
| | UPA 30 mg | 348 | NR | NR | NR | NR | NR | NR | NR | NR | 55.6 | NR | NR | NR |
| **Dupilumab** | | | | | | | | | | | | | | |
| LIBERTY AD CHRONOS | **Week 52** | | | | | | | | | | | | | |
| | PBO + TCS | 264 | 79 | 264 | 30 | REF | REF | REF | 41 | 264 | 16 | REF | REF | REF |
| | DUP 300 mg + TCS Q2W | 89 | 70 | 89 | 79 | 49 | 38.6 to 58.9 | <0.0001 | 45 | 89 | 51 | 35 | 23.8 to 46.3 | <0.0001 |
| | DUP 300 mg + TCS QW | 270 | 189 | 270 | 70 | 40 | 32.3 to 47.9 | <0.0001 | 137 | 270 | 51 | 35 | 27.8 to 42.6 | <0.0001 |
| AD SOLO-CONTINUE | **Week 36** | | | | | | | | | | | | | |
| | PBO | 83 | 33 | 83 | 39.8 | NR | NR | NR | 10 | 55 | 18.2 | NR | NR | NR |
| | DUP 300 mg Q8W | 84 | 46 | 84 | 54.8 | NR | NR | NR | 16 | 49 | 32.7 | NR | NR | NR |
| | DUP 300 mg Q4W | 86 | 52 | 86 | 60.5 | NR | NR | NR | 33 | 56 | 58.9 | NR | NR | NR |
| | DUP 300 mg QW/Q2W | 169 | 124 | 169 | 73.4 | NR | NR | NR | 75 | 116 | 64.7 | NR | NR | NR |

Long-term data on EASI 50 and EASI 90 were not available for the following long-term trials: BREEZE-AD3, BREEZE-AD6, ECZTRA 1, ECZTRA 2, and Phase IIb Guttman-Yassky 2020. CI: confidence interval, Diff: difference, DUP: dupilumab, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, %: percent. *JADE MONO-1 & 2 and JADE COMPARE subgroup, †JADE COMPARE dupilumab nonresponder subgroup, ‡last observation carried forward (LOCF).

**Table G1.21. Long-Term Efficacy Outcomes: PP-NRS ≥4-Point Change**[50,54,77,81,108,159]

| Study Name | Arms | N | Itch or PP-NRS (≥4 point improvement from baseline) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | |
| JADE EXTEND Subgroup 1* | **Week 48** | | | | | | | |
| | ABRO 100 mg | 595 | 105 | 280 | 37.6 | NR | NR | NR |

| Study Name | Arms | N | Itch or PP-NRS (≥4 point improvement from baseline) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| | ABRO 200 mg | 521 | 125 | 246 | 50.9 | NR | NR | NR |
| | **Week 48 (Responders)** | | | | | | | |
| | ABRO 100 mg | NR | 63 | 122 | 51.6 | NR | NR | NR |
| | ABRO 200 mg | NR | 116 | 168 | 69 | NR | NR | NR |
| | **Week 24 (Nonresponders)** | | | | | | | |
| | ABRO 100 mg | NR | 63 | 195 | 32.3 | NR | NR | NR |
| | ABRO 200 mg | NR | 57 | 138 | 41.4 | NR | NR | NR |
| | **Week 48 (Nonresponders)** | | | | | | | |
| | ABRO 100 mg | NR | 38 | 142 | 26.8 | NR | NR | NR |
| | ABRO 200 mg | NR | 31 | 101 | 30.7 | NR | NR | NR |
| JADE EXTEND Subgroup 2[†] | **Week 32** | | | | | | | |
| | ABRO 100 mg | 130 | 17 | 45 | 37.8 | NR | NR | NR |
| | ABRO 200 mg | 73 | 17 | 22 | 77.3 | NR | NR | NR |
| **Upadacitinib** | | | | | | | | |
| Heads Up | **Week 24** | | | | | | | |
| | DUP 300 mg | 344 | NR | NR | 41.9 | NR | NR | NR |
| | UPA 30 mg | 348 | NR | NR | 50.2 | NR | NR | NR |
| Phase IIb Guttman-Yassky 2020 | **Week 16** | | | | | | | |
| | PBO→PBO | 8 | 0 | 6 | 0 | NR | NR | NR |
| | UPA 7.5 mg→PBO | 13 | 3 | 12 | 25 | NR | NR | NR |
| | UPA 15 mg→PBO | 17 | 9 | 14 | 64.3 | NR | NR | NR |
| | UPA 30 mg→PBO | 13 | 9 | 10 | 90 | NR | NR | NR |
| | PBO→UPA 30 mg | 1 | 0 | 1 | 0 | NR | NR | NR |
| | UPA 7.5 mg→UPA 7.5 mg | 11 | 3 | 11 | 27.3 | NR | NR | NR |
| | UPA 15 mg→UPA 15 mg | 12 | 7 | 10 | 70 | NR | NR | NR |
| | UPA 30 mg→UPA 30 mg | 3 | 0 | 3 | 0 | NR | NR | NR |

| Study Name | Arms | N | Itch or PP-NRS (≥4 point improvement from baseline) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| | **START OF RESCUE W/ UPA 30mg** | | | | | | | |
| | PBO→PBO | 8 | 0 | 6 | 0 | NR | NR | NR |
| | UPA 7.5 mg→PBO | 13 | 3 | 13 | 23.1 | NR | NR | NR |
| | UPA 15 mg→PBO | 17 | 0 | 14 | 0 | NR | NR | NR |
| | UPA 30 mg→PBO | 13 | 0 | 10 | 0 | NR | NR | NR |
| | PBO→UPA 30 mg | 1 | 1 | 1 | 100 | NR | NR | NR |
| | UPA 7.5 mg→UPA 7.5 mg | 11 | 3 | 11 | 27.3 | NR | NR | NR |
| | UPA 15 mg→UPA 15 mg | 12 | 5 | 10 | 50 | NR | NR | NR |
| | UPA 30 mg→UPA 30 mg | 3 | 0 | 3 | 0 | NR | NR | NR |
| | **8 WEEKS POST-RESCUE** | | | | | | | |
| | PBO→PBO | 8 | 4 | 6 | 66.7 | NR | NR | NR |
| | UPA 7.5 mg→PBO | 12 | 7 | 12 | 58.3 | NR | NR | NR |
| | UPA 15 mg→PBO | 16 | 12 | 14 | 85.7 | NR | NR | NR |
| | UPA 30 mg→PBO | 13 | 8 | 10 | 80 | NR | NR | NR |
| | PBO→UPA 30 mg | 1 | 1 | 1 | 100 | NR | NR | NR |
| | UPA 7.5 mg→UPA 7.5 mg | 10 | 5 | 11 | 45.4 | NR | NR | NR |
| | UPA 15 mg→UPA 15 mg | 9 | 8 | 10 | 80 | NR | NR | NR |
| | UPA 30 mg→UPA 30 mg | 3 | 2 | 3 | 66.7 | NR | NR | NR |
| **Dupilumab** | | | | | | | | |
| LIBERTY AD CHRONOS | **Week 52** | | | | | | | |
| | PBO + TCS | 264 | 32 | 249 | 13 | REF | REF | REF |
| | DUP 300 mg + TCS Q2W | 89 | 44 | 86 | 51 | 38 | 27.0 to 49.7 | <0.0001 |
| | DUP 300 mg + TCS QW | 270 | 97 | 249 | 39 | 26 | 18.8 to 33.5 | <0.0001 |
| AD SOLO-CONTINUE | **Week 36** | | | | | | | |
| | PBO | 83 | 10 | 78 | 12.8 | NR | NR | NR |
| | DUP 300 mg Q8W | 84 | 21 | 79 | 26.6 | NR | NR | NR |

| Study Name | Arms | N | Itch or PP-NRS (≥4 point improvement from baseline) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | N | % | Diff from PBO | 95% CI | p value |
| | DUP 300 mg Q4W | 86 | 27 | 82 | 32.9 | NR | NR | NR |
| | DUP 300 mg QW/Q2W | 169 | 78 | 159 | 49.1 | NR | NR | NR |

Long term data on PP-NRS were not available for the following long-term trials: BREEZE-AD3, BREEZE-AD6, ECZTRA 1, ECZTRA 2, ECZTRA 3, and ECZTEND. CI: confidence interval, Diff: difference, DUP: dupilumab, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, REF: reference, TCS: topical corticosteroids, %: percent. *JADE MONO-1 & 2 and JADE COMPARE subgroup, †JADE COMPARE dupilumab nonresponder subgroup.

**Table G1.22. Long-Term Efficacy Outcomes: SCORAD**[50,54]

| Study Name | Arms | N | SCORAD | | | |
|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | p value |
| **Dupilumab** | | | | | | |
| LIBERTY AD CHRONOS | **Week 52** | | | | | |
| | PBO + TCS | 264 | NR | LSM: -34.1* | SE: 1.88 | REF |
| | DUP 300 mg + TCS Q2W | 89 | NR | LSM: -66.2* | SE: 3.14 | <0.0001 |
| | DUP 300 mg + TCS QW | 270 | NR | LSM: -66.1* | SE: 1.85 | <0.0001 |
| LIBERTY AD SOLO-CONTINUE | **Week 36** | | | | | |
| | PBO | 83 | NR | -2.7† | 0.3 | NR |
| | DUP 300 mg Q8W | 84 | NR | -3.3† | 0.3 | NR |
| | DUP 300 mg Q4W | 86 | NR | -4.2† | 0.2 | NR |
| | DUP 300 mg QW/Q2W | 169 | NR | -4.3† | 0.2 | NR |

Long-term data on SCORAD were not available for the following long-term trials: JADE EXTEND, BREEZE-AD3, BREEZE-AD6, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, Heads Up, and Phase IIb Guttman-Yassky 2020. There were no Difference vs. placebo or 95% confidence intervals available for long-term SCORAD. CI: confidence interval, Diff: difference, DUP: dupilumab, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids. *percent change, †SCORAD sleep loss.

**Table G1.23. Long-Term Efficacy Outcomes: DLQI**[50,54,64]

| Study Name | Arms | N | DLQI | | | |
|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | p value |
| **Tralokinumab** | | | | | | |
| ECZTRA 3 | **Week 32 (Maintenance period)** | | | | | |
| | TRA 300 mg Q2W + TCS (TRA nonresponders) | 95 | 95 | -9.81 | 0.94* | NR |
| | TRA 300 mg Q2W + TCS (TRA responders) | 69 | 69 | -14.2 | 1.16* | NR |
| | TRA 300 mg Q4W + TCS (TRA responders) | 69 | 69 | -13.64 | 1.13* | NR |
| **Dupilumab** | | | | | | |
| LIBERTY AD CHRONOS | **Week 52** | | | | | |
| | PBO + TCS | 264 | 264 | LSM: -5.6 | SE: 0.36 | REF |
| | DUP 300 mg + TCS Q2W | 89 | 89 | LSM: -10.9 | SE: 0.59 | <0.0001 |
| | DUP 300 mg + TCS QW | 270 | 270 | LSM: -10.7 | SE: 0.36 | <0.0001 |
| AD SOLO-CONTINUE | **Week 36** | | | | | |
| | PBO | 83 | NR | -3.1 | 0.52 | NR |
| | DUP 300 mg Q8W | 84 | NR | -1.5 | 0.46 | NR |
| | DUP 300 mg Q4W | 86 | NR | -0.3 | 0.48 | NR |
| | DUP 300 mg QW/Q2W | 169 | NR | 0.2 | 0.33 | NR |

Long-term data on DLQI were not available for the following long-term trials: JADE EXTEND, BREEZE-AD3, BREEZE-AD6, ECZTRA 1, ECZTRA 2, ECZTEND, Heads Up, and Phase IIb Guttman-Yassky 2020. There were data available for CDLQI and no Difference vs. placebo or 95% confidence interval data available for long-term DLQI. DUP: dupilumab, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids, TRA: tralokinumab. *digitized estimate.

**Table G1.24. Long-Term Efficacy Outcomes: POEM**[50,54]

| Study Name | Arms | N | POEM | | | |
|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | p value |
| **Dupilumab** | | | | | | |
| LIBERTY AD CHRONOS | **Week 52** | | | | | |
| | PBO + TCS | 264 | 264 | LSM: -5.3 | SE: 0.5 | REF |
| | DUP 300 mg + TCS Q2W | 89 | 89 | LSM: -13.7 | SE: 0.8 | <0.0001 |
| | DUP 300 mg + TCS QW | 270 | 270 | LSM: -12.7 | SE: 0.5 | <0.0001 |
| LIBERTY AD SOLO-CONTINUE | **Week 36** | | | | | |
| | PBO | 83 | NR | -7 | 0.9 | NR |
| | DUP 300 mg Q8W | 84 | NR | -2.8 | 0.8 | NR |
| | DUP 300 mg Q4W | 86 | NR | -0.8 | 0.7 | NR |
| | DUP 300 mg QW/Q2W | 169 | NR | 0.3 | 0.6 | NR |

Long-term data on DLQI were not available for the following long-term trials: JADE EXTEND, BREEZE-AD3, BREEZE-AD6, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, Heads Up, and Phase IIb Guttman-Yassky 2020. CI: confidence interval, Diff: difference, DUP: dupilumab, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids.

**Table G1.25. Outcomes by subgroup: IGA stratified by age**[35,36,39,53,60,80]

| Study Name | Arms | Category | IGA | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | n | % | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | | |
| | PBO | <18 years | 16 | 2 | 12.5 | NR | NR | NR |
| | ABRO 100 mg | | 34 | 9 | 26.5 | NR | NR | NR |
| | ABRO 200 mg | | 33 | 9 | 27.3 | NR | NR | NR |
| | PBO | ≥18 years | 60 | 4 | 6.7 | NR | NR | NR |
| | ABRO 100 mg | | 122 | 28 | 23 | NR | NR | NR |
| | ABRO 200 mg | | 120 | 58 | 48.3 | NR | NR | NR |
| JADE MONO-2 | PBO | <18 years | 7 | 0 | 0 | REF | REF | NR |
| | ABRO 100 mg | | 16 | 2 | 12.5 | 12.5 | -11.7 to 36.7 | NR |
| | ABRO 200 mg | | 15 | 6 | 40 | 40 | 9.4 to 70.6 | NR |
| | PBO | ≥18 years | 70 | 7 | 10 | REF | REF | NR |
| | ABRO 100 mg | | 193 | 42 | 30.2 | 20.2 | 9.8 to 30.6 | NR |
| | ABRO 200 mg | | 140 | 53 | 37.9 | 27.9 | 17.2 to 38.5 | NR |
| **Upadacitinib** | | | | | | | | |
| MEASURE UP 1 | **Week 16** | | | | | | | |
| | PBO | Adults | 241 | 21 | 8.6 | NR | NR | REF |
| | UPA 15 mg | | 239 | 119 | 49.9 | NR | NR | <0.001 |
| | UPA 30 mg | | 243 | 148 | 60.8 | NR | NR | <0.001 |
| | PBO | Adolescents | 40 | 3 | 7.5 | NR | NR | REF |
| | UPA 15 mg | | 42 | 16 | 38.1 | NR | NR | <0.001 |
| | UPA 30 mg | | 42 | 29 | 69 | NR | NR | <0.001 |
| MEASURE UP 2 | PBO | Adults | 242 | 12 | 5 | NR | NR | REF |
| | UPA 15 mg | | 243 | 93 | 38.3 | NR | NR | <0.001 |
| | UPA 30 mg | | 247 | 125 | 50.5 | NR | NR | <0.001 |

| Study Name | Arms | Category | IGA | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | n | % | Diff from PBO | 95% CI | p value |
| | PBO | Adolescents | 36 | 1 | 2.8 | NR | NR | REF |
| | UPA 15 mg | | 33 | 14 | 42.4 | NR | NR | <0.001 |
| | UPA 30 mg | | 35 | 22 | 62.5 | NR | NR | <0.001 |
| AD-UP | PBO + TCS | Adults | 264 | 30 | 11.4 | NR | NR | REF |
| | UPA 15 mg + TCS | | 261 | 107 | 40.9 | NR | NR | <0.001 |
| | UPA 30 mg + TCS | | 260 | 150 | 57.7 | NR | NR | <0.001 |
| | PBO + TCS | Adolescents | 40 | 3 | 7.5 | NR | NR | REF |
| | UPA 15 mg + TCS | | 39 | 12 | 30.8 | NR | NR | <0.01 |
| | UPA 30 mg + TCS | | 37 | 24 | 64.9 | NR | NR | <0.001 |

Data on IGA stratified by age were not available in JADE TEEN, JADE COMPARE, JADE EXTEND, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5,BREEZE-AD6, BREEZE-AD7, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, Heads Up, Phase IIb Guttman-Yassky 2020, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD SOLO-CONTINUE, and Phase IIb Thaci 2016. ABRO: abrocitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, %: percent.

**Table G1.26. Outcomes by subgroup: IGA stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[39,44,65]

**Table G1.27. Outcomes by subgroup: EASI 75 Stratified by Age**[35,36,60-62,80]

| Study Name | Arms | Category | N | EASI 75 | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | N | n | % | Diff from PBO | 95% CI | p value |
| **Abrocitinib** | | | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | | | |
| | PBO | <18 years | 8 | 16 | 2 | 12.5 | NR | NR | NR |
| | ABRO 100 mg | | 17 | 34 | 15 | 44.1 | NR | NR | NR |
| | ABRO 200 mg | | 15 | 33 | 18 | 54.5 | NR | NR | NR |
| | PBO | ≥18 years | 70 | 60 | 7 | 11.7 | NR | NR | NR |
| | ABRO 100 mg | | 141 | 122 | 47 | 38.5 | NR | NR | NR |
| | ABRO 200 mg | | 140 | 120 | 78 | 65 | NR | NR | NR |
| JADE MONO 2 | PBO | <18 years | 17 | 7 | 0 | 0 | REF | REF | NR |
| | ABRO 100 mg | | 34 | 16 | 7 | 43.8 | 43.8 | 13.5 to 74.0 | NR |
| | ABRO 200 mg | | 33 | 15 | 9 | 60 | 60 | 29.4 to 90.6 | NR |
| | PBO | ≥18 years | 60 | 70 | 8 | 11.4 | REF | REF | NR |
| | ABRO 100 mg | | 122 | 139 | 62 | 44.6 | 33.2 | 22.0 to 44.3 | NR |
| | ABRO 200 mg | | 121 | 193 | 85 | 61.2 | 49.7 | 38.7 to 60.7 | NR |
| **Upadacitinib** | | | | | | | | | |
| MEASURE UP 1 | **Week 16** | | | | | | | | |
| | PBO | Adults | 241 | 241 | 43 | 17.7 | NR | NR | REF |
| | UPA 15 mg | | 239 | 239 | 166 | 69.3 | NR | NR | <0.001 |
| | UPA 30 mg | | 243 | 243 | 192 | 79.1 | NR | NR | <0.001 |
| | PBO | Adolescents | 40 | 40 | 3 | 8.3 | NR | NR | REF |
| | UPA 15 mg | | 42 | 42 | 30 | 71.4 | NR | NR | <0.001 |

| Study Name | Arms | Category | N | EASI 75 | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | N | n | % | Diff from PBO | 95% CI | p value |
| | UPA 30 mg | | 42 | 42 | 35 | 83.3 | NR | NR | <0.001 |
| MEASURE UP 2 | PBO | Adults | 242 | 242 | 32 | 13.2 | NR | NR | REF |
| | UPA 15 mg | | 243 | 243 | 144 | 59.3 | NR | NR | <0.001 |
| | UPA 30 mg | | 247 | 247 | 180 | 72.7 | NR | NR | <0.001 |
| | PBO | Adolescents | 36 | 36 | 5 | 13.9 | NR | NR | REF |
| | UPA 15 mg | | 33 | 33 | 22 | 66.7 | NR | NR | <0.001 |
| | UPA 30 mg | | 35 | 35 | 26 | 74.5 | NR | NR | <0.001 |
| AD-UP | PBO + TCS | Adults | 264 | 264 | 68 | 25.9 | NR | NR | REF |
| | UPA 15 mg + TCS | | 261 | 261 | 172 | 65.8 | NR | NR | <0.001 |
| | UPA 30 mg + TCS | | 260 | 260 | 201 | 77.3 | NR | NR | <0.001 |
| | PBO + TCS | Adolescents | 40 | 40 | 12 | 30 | NR | NR | REF |
| | UPA 15 mg + TCS | | 39 | 39 | 22 | 56.4 | NR | NR | <0.05 |
| | UPA 30 mg + TCS | | 37 | 37 | 28 | 75.7 | NR | NR | <0.001 |

Data on EASI 75 stratified by age were not available in JADE TEEN, JADE COMPARE, JAD EXTEND, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5, BREEZE-AD6, BREEZE-AD7, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, Heads Up, Phase IIb Guttman-Yassky 2020, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD SOLO-CONTINUE, and Phase IIb Thaci 2016. ABRO: abrocitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, UPA: upadacitinib, %: percent.

**Table G1.28. Outcomes by subgroup: EASI 75 Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[39,44,55,65]

**Table G1.29. Outcomes by subgroup: EASI 50 and 90 Stratified by Age**[39,55,65,76]

| Study Name | Arms | Category | EASI 50 | | | | EASI 90 | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | n | % | p value | N | n | % | p value |
| **Abrocitinib** | | | | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | | | | |
| | PBO | <18 years | [redacted] | | | | | | 12.5 | NR |
| | ABRO 100 mg | | | | | | | | 20.6 | NR |
| | ABRO 200 mg | | | | | | | | 30.3 | NR |
| | PBO | ≥18 years | | | | | | | 3.3 | NR |
| | ABRO 100 mg | | | | | | | | 18 | NR |
| | ABRO 200 mg | | | | | | | | 40.8 | NR |
| JADE MONO-2 | PBO | <18 years | | | | | | | 0 | NR |
| | ABRO 100 mg | | | | | | | | 12.5 | NR |
| | ABRO 200 mg | | | | | | | | 33.3 | NR |
| | PBO | ≥18 years | | | | | | | 4.3 | NR |
| | ABRO 100 mg | | | | | | | | 25.2 | NR |
| | ABRO 200 mg | | | | | | | | 38.1 | NR |
| **Upadacitinib** | | | | | | | | | | |
| MEASURE UP 1 | **Week 16** | | | | | | | | | |
| | PBO | Adults | [redacted] | | | | | | | |
| | UPA 15 mg | | | | | | | | | |
| | UPA 30 mg | | | | | | | | | |
| | PBO | Adolescents | | | | | | | | |
| | UPA 15 mg | | | | | | | | | |
| | UPA 30 mg | | | | | | | | | |
| MEASURE UP 2 | PBO | Adults | | | | | | | | |
| | UPA 15 mg | | | | | | | | | |
| | UPA 30 mg | | | | | | | | | |

| Study Name | Arms | Category | EASI 50 | | | | EASI 90 | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | n | % | p value | N | n | % | p value |
| | PBO | Adolescents | | | | | | | | |
| | UPA 15 mg | | | | | | | | | |
| | UPA 30 mg | | | | | | | | | |
| AD-UP | PBO + TCS | Adults | | | | | | | | |
| | UPA 15 mg + TCS | | | | | | | | | |
| | UPA 30 mg + TCS | | | | | | | | | |
| | PBO + TCS | Adolescents | | | | | | | | |
| | UPA 15 mg + TCS | | | | | | | | | |
| | UPA 30 mg + TCS | | | | | | | | | |

Data on EASI 50 and EASI 90 stratified by age were not available for JADE TEEN, JADE COMPARE, JADE EXTEND, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5, BREEZE-AD6, BREEZE-AD7, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, Heads Up, Phase IIb Guttman-Yassky 2020, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD SOLO-CONTINUE, and Phase IIb Thaci 2016. ABRO: abrocitinib, CI: confidence interval, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, UPA: upadacitinib, %: percent.

**Table G1.30. Outcomes by subgroup: EASI 50 and 90 Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[39,44,55,65]

**Table G1.31. Outcomes by subgroup: PP-NRS Change from Baseline and ≥3- or ≥4-Point Change Stratified by Age**[39,53,55,76,81]

| Study Name | Arms | Category | Itch or PP-NRS Change from Baseline | | | PP-NRS ≥4-point Change | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | N | ≥4-point Change | |
| | | | N | Change from baseline | SD | | n | % |
| **Abrocitinib** | | | | | | | | |
| JADE MONO-1 | **Week 12** | | | | | | | |
| | PBO | <18 years | NR | [redacted] | NR | [redacted] | | 7.1 |
| | ABRO 100 mg | | NR | | NR | | | 33.3 |
| | ABRO 200 mg | | NR | | NR | | | 47.8 |
| | PBO | ≥18 years | NR | | NR | | | 19.1 |
| | ABRO 100 mg | | NR | | NR | | | 36.4 |
| | ABRO 200 mg | | NR | | NR | | | 56.4 |
| JADE MONO-2 | PBO | <18 years | NR | | NR | | | 12.5 |
| | ABRO 100 mg | | NR | | NR | | | 20 |
| | ABRO 200 mg | | NR | | NR | | | 84.6 |
| | PBO | ≥18 years | NR | | NR | | | 11.1 |
| | ABRO 100 mg | | NR | | NR | | | 47.6 |
| | ABRO 200 mg | | NR | | NR | | | 52.9 |
| **Upadacitinib** | | | | | | | | |
| MEASURE UP 1 | **Week 16** | | | | | | | |
| | PBO | Adults | 241 | NR | NR | 233 | 26 | 11.2 |
| | UPA 15 mg | | 239 | NR | NR | 234 | 125 | 53.4 |
| | UPA 30 mg | | 243 | NR | NR | 238 | 145 | 60.9 |
| | PBO | Adolescents | 40 | NR | NR | 39 | 6 | 15.4 |
| | UPA 15 mg | | 42 | NR | NR | 40 | 18 | 45 |
| | UPA 30 mg | | 42 | NR | NR | 42 | 23 | 54.8 |
| MEASURE UP 2 | PBO | Adults | 242 | NR | NR | 238 | 24 | 10.1 |
| | UPA 15 mg | | 243 | NR | NR | 240 | 103 | 42.9 |

| Study Name | Arms | Category | Itch or PP-NRS Change from Baseline | | | PP-NRS ≥4-point Change | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Change from baseline | SD | N | ≥4-point Change | |
| | | | | | | | n | % |
| | UPA 30 mg | | 247 | NR | NR | 246 | 150 | 61 |
| | PBO | Adolescents | 36 | NR | NR | 36 | 1 | 2.8 |
| | UPA 15 mg | | 33 | NR | NR | 30 | 10 | 33.3 |
| | UPA 30 mg | | 35 | NR | NR | 34 | 17 | 50 |
| AD-UP | PBO + TCS | Adults | 264 | NR | NR | 256 | 39 | 15.2 |
| | UPA 15 mg + TCS | | 261 | NR | NR | 252 | 134 | 53.2 |
| | UPA 30 mg + TCS | | 260 | NR | NR | 258 | 168 | 65.1 |
| | PBO + TCS | Adolescents | 40 | NR | NR | 38 | 5 | 13.2 |
| | UPA 15 mg + TCS | | 39 | NR | NR | 15 | 36 | 41.7 |
| | UPA 30 mg + TCS | | 37 | NR | NR | 33 | 18 | 54.5 |

Data on PP-NRS change from baseline and ≥4-point change stratified by age were not available in JADE TEEN, JADE COMPARE, JADE EXTEND, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5, BREEZE-AD6, BREEZE-AD7, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, Heads Up, Phase IIb Guttman-Yassky 2020, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD SOLO-CONTINUE, and Phase IIb Thaci 2016. No data on PP-NRS≥3 or p-values were reported. ABRO: abrocitinib, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, SD: standard deviation, %: percent.

**Table G1.32. Outcomes by subgroup: PP-NRS Change from Baseline Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[39,44,65]

**Table G1.33. Outcomes by subgroup: PP-NRS ≥2-Point Change Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[44,65]

**Table G1.34. Outcomes by subgroup: PP-NRS ≥3-Point Change Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[44]

**Table G1.35. Outcomes by subgroup: PP-NRS ≥4-Point Change Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[39,44,65]

**Table G1.36. Outcomes by subgroup: SCORAD, DLQI and CDLQI Stratified by Age (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[39,58,59]

**Table G1.37. Outcomes by subgroup: SCORAD Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[39,44,65]

**Table G1.38. Outcomes by subgroup: DLQI and CDLQI Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[39,44,65]

**Table G1.39. Outcomes by subgroup: POEM Stratified by Age (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[39]

**Table G1.40. Outcomes by subgroup: POEM Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[39,44,65]

**Table G1.41. Outcomes by subgroup: HADS Anxiety, HADS Depression and EQ-5D Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)**[44]

**Table G1.42. Short-Term Safety I**[35-37,39,41-46,48,50-56,58-60,63-67,69-71,78]

| Study Name | Arms | N | Timepoint | Any AE | | TEAE | | Study Drug-Related AEs | | D/C due to AE | | Serious AE | | Serious TEAE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % | n | % | n | % |
| **Abrocitinib** | | | | | | | | | | | | | | | |
| JADE MONO-1 | PBO | 77 | 12 weeks | 44 | 57 | NR | NR | 0* | 0 | 7 | 9 | 3 | 4 | NR | NR |
| | ABRO 100 mg | 156 | | 108 | 69 | NR | NR | 1* | 1 | 9 | 6 | 5 | 3 | NR | NR |
| | ABRO 200 mg | 154 | | 120 | 78 | NR | NR | 1* | 1 | 9 | 6 | 5 | 3 | NR | NR |
| JADE MONO-2 | PBO | 78 | 12 weeks | NR | NR | 42 | 53.8 | NR | NR | 10 | 12.8 | 1 | 1.3 | 2 | 2.6 |
| | ABRO 100 mg | 158 | | NR | NR | 99 | 62.7 | NR | NR | 6 | 3.8 | 5 | 3.2 | 2 | 1.3 |
| | ABRO 200 mg | 155 | | NR | NR | 102 | 65.8 | NR | NR | 5 | 3.2 | 2 | 1.3 | 0 | 0 |
| JADE TEEN | PBO | 96 | 12 weeks | NR | NR | 50 | 52.1 | NR | NR | 2 | 2.1 | 2 | 2.1 | | |
| | ABRO 100 mg | 95 | | NR | NR | 54 | 56.8 | NR | NR | 1 | 1.1 | 0 | 0 | | |
| | ABRO 200 mg | 94 | | NR | NR | 59 | 62.8 | NR | NR | 2 | 2.1 | 1 | 1.1 | | |
| JADE COMPARE | PBO | 131 | 16 weeks | 70 | 53.4 | NR | NR | NR | NR | 5 | 3.8 | 5 | 3.8 | NR | NR |
| | ABRO 100 mg | 238 | | 121 | 50.8 | NR | NR | NR | NR | 6 | 2.5 | 6 | 2.5 | NR | NR |
| | ABRO 200 mg | 226 | | 140 | 61.9 | NR | NR | NR | NR | 10 | 4.4 | 2 | 0.9 | NR | NR |
| | DUP 300 mg | 242 | | 121 | 50 | NR | NR | NR | NR | 8 | 3.3 | 2 | 0.8 | NR | NR |
| Phase II Gooderham 2019 | PBO | 56 | 16 weeks | NR | NR | 184 | 68.9 | 64 | 24 | 44 | 16.5 | NR | NR | 9 | 3.4 |
| | ABRO 100 mg | 56 | | NR | NR | | | | | | | NR | NR | | |
| | ABRO 200 mg | 55 | | NR | NR | | | | | | | NR | NR | | |
| **Baricitinib** | | | | | | | | | | | | | | | |
| BREEZE-AD1 | PBO | 249 | 16 weeks | NR | NR | 135 | 54.2 | NR | NR | 4 | 1.6 | 6 | 2.4 | 7† | 2.8 |
| | BARI 1 mg | 127 | | NR | NR | 69 | 54.3 | NR | NR | 2 | 1.6 | 1 | 0.8 | 5† | 3.9 |
| | BARI 2 mg | 123 | | NR | NR | 71 | 57.7 | NR | NR | 1 | 0.8 | 0 | 0 | 3† | 2.4 |
| | BARI 4 mg | 125 | | NR | NR | 73 | 58.4 | NR | NR | 1 | 0.8 | 2 | 1.6 | 2† | 1.6 |
| | PBO | 244 | 16 weeks | NR | NR | 137 | 56.1 | NR | NR | 2 | 0.8 | 9 | 3.7 | 9† | 3.7 |

| Study Name | Arms | N | Timepoint | Any AE | | TEAE | | Study Drug-Related AEs | | D/C due to AE | | Serious AE | | Serious TEAE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % | n | % | n | % |
| BREEZE-AD2 | BARI 1 mg | 125 | | NR | NR | 66 | 53.2 | NR | NR | 7 | 5.6 | 9 | 7.3 | 6[†] | 4.8 |
| | BARI 2 mg | 123 | | NR | NR | 71 | 57.7 | NR | NR | 3 | 2.4 | 3 | 2.4 | 5[†] | 4.1 |
| | BARI 4 mg | 123 | | NR | NR | 66 | 53.7 | NR | NR | 2 | 1.6 | 1 | 0.8 | 3[†] | 2.4 |
| BREEZE-AD5 | PBO | 146 | 16 weeks | NR | NR | 72 | 49 | NR | NR | 4 | 2.7 | 3 | 2.1 | 6[†] | 4 |
| | BARI 1 mg | 147 | | NR | NR | 79 | 54 | NR | NR | 4 | 2.7 | 1 | 0.7 | 0[†] | 0 |
| | BARI 2 mg | 145 | | NR | NR | 74 | 51 | NR | NR | 4 | 2.8 | 2 | 1.4 | 1[†] | 0.7 |
| BREEZE-AD7 | PBO + TCS | 108 | 16 weeks | NR | NR | 41 | 38 | NR | NR | 1 | 0.9 | 4 | 3.7 | 3[†] | 2.8 |
| | BARI 2 mg + TCS | 109 | | NR | NR | 61 | 56 | NR | NR | 0 | 0 | 2 | 1.8 | 6[†] | 5.5 |
| | BARI 4 mg + TCS | 111 | | NR | NR | 64 | 57.7 | NR | NR | 5 | 4.5 | 4 | 3.6 | 6[†] | 5.4 |
| Phase II Guttman-Yassky 2018 | PBO + TCS | 49 | 16 weeks | NR | NR | 24 | 49 | NR | NR | 5[‡] | 10.2 | NR | NR | 0 | 0 |
| | BARI 2 mg + TCS | 37 | | NR | NR | 17 | 45.9 | NR | NR | 1[‡] | 2.7 | NR | NR | 0 | 0 |
| | BARI 4 mg + TCS | 38 | | NR | NR | 27 | 71.1 | NR | NR | 5[‡] | 13.2 | NR | NR | 1 | 2.6 |
| **Tralokinumab** | | | | | | | | | | | | | | | |
| ECZTRA 1 | PBO | 196 | 16 weeks | 151 | 77 | | | NR | NR | 8 | 4.1 | 8 | 4.1 | | |
| | TRA 300 mg | 602 | | 460 | 76.4 | | | NR | NR | 20 | 3.3 | 23 | 3.8 | | |
| ECZTRA 2 | PBO | 200 | 16 weeks | 132 | 66 | | | NR | NR | 3 | 1.5 | 5 | 2.5 | | |
| | TRA 300 mg | 592 | | 364 | 61.5 | | | NR | NR | 9 | 1.5 | 10 | 1.7 | | |
| ECZTRA 2 Subgroup[¶] | Placebo | 91 | 16 weeks | 57 | 62.6 | 26 | 28.6 | NR | NR | 0 | 0 | 0 | 0 | NR | NR |
| | TRA 300 mg | 270 | | 151 | 55.9 | 52 | 19.3 | NR | NR | 4 | 1.5 | 4 | 1.5 | NR | NR |
| ECZTRA 3 | PBO + TCS | 126 | 16 weeks | 84 | 66.7 | | | NR | NR | 1 | 0.8 | 4 | 3.2 | | |
| | TRA 300 mg + TCS | 252 | | 180 | 71.4 | | | NR | NR | 6 | 2.4 | 2 | 0.8 | | |
| **Upadacitinib** | | | | | | | | | | | | | | | |
| MEASURE UP 1 | PBO | 281 | 16 weeks | NR | NR | 166 | 59.1 | NR | NR | 12 | 4.3 | 8 | 2.8 | NR | NR |
| | UPA 15 mg | 281 | | NR | NR | 176 | 62.6 | NR | NR | 4 | 1.4 | 6 | 2.1 | NR | NR |

| Study Name | Arms | N | Timepoint | Any AE | | TEAE | | Study Drug-Related AEs | | D/C due to AE | | Serious AE | | Serious TEAE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % | n | % | n | % |
| | UPA 30 mg | 285 | | NR | NR | 209 | 73.3 | NR | NR | 11 | 3.9 | 8 | 2.8 | NR | NR |
| MEASURE UP 2 | PBO | 278 | 16 weeks | NR | NR | 146 | 52.5 | NR | NR | 12 | 4.3 | 8 | 2.9 | NR | NR |
| | UPA 15 mg | 276 | | NR | NR | 166 | 60.1 | NR | NR | 11 | 4 | 5 | 1.8 | NR | NR |
| | UPA 30 mg | 282 | | NR | NR | 173 | 61.3 | NR | NR | 7 | 2.5 | 7 | 2.5 | NR | NR |
| AD-UP | PBO + TCS | 304 | 16 weeks | NR | NR | 190 | 62.7 | NR | NR | 7 | 2.3 | 9 | 3 | NR | NR |
| | UPA 15 mg + TCS | 300 | | NR | NR | 200 | 66.7 | NR | NR | 4 | 1.3 | 7 | 2.3 | NR | NR |
| | UPA 30 mg + TCS | 297 | | NR | NR | 215 | 72.4 | NR | NR | 4 | 1.3 | 4 | 1.3 | NR | NR |
| Heads Up | DUP 300 mg | 344 | 16 weeks | NR | NR | NR | NR | NR | NR | NR | NR | 4 | 1.2 | NR | NR |
| | UPA 30 mg | 348 | | NR | NR | NR | NR | NR | NR | NR | NR | 10 | 2.9 | NR | NR |
| Phase IIb Guttman-Yassky 2020 | PBO | 40 | 16 weeks | 25 | 63 | NR | NR | NR | NR | 3 | 7.5 | 1 | 2.5 | NR | NR |
| | UPA 7.5 mg | 42 | | 31 | 74 | NR | NR | NR | NR | 4 | 9.5 | 2 | 4.8 | NR | NR |
| | UPA 15 mg | 42 | | 32 | 76 | NR | NR | NR | NR | 2 | 4.8 | 1 | 2.4 | NR | NR |
| | UPA 30 mg | 42 | | 33 | 33 | NR | NR | NR | NR | 4 | 9.5 | 0 | 0 | NR | NR |
| **Dupilumab** | | | | | | | | | | | | | | | |
| SOLO 1 | PBO | 224 | 16 weeks | 145 | 65 | NR | NR | NR | NR | 2 | 1 | 11 | 5 | NR | NR |
| | DUP 300 mg Q2W | 224 | | 167 | 73 | NR | NR | NR | NR | 4 | 2 | 7 | 3 | NR | NR |
| | DUP 300 mg QW | 223 | | 150 | 69 | NR | NR | NR | NR | 4 | 2 | 2 | 1 | NR | NR |
| SOLO 2 | PBO | 236 | 16 weeks | 168 | 72 | NR | NR | NR | NR | 5 | 2 | 13 | 6 | NR | NR |
| | DUP 300 mg Q2W | 233 | | 154 | 65 | NR | NR | NR | NR | 2 | 1 | 4 | 2 | NR | NR |
| | DUP 300 mg QW | 239 | | 157 | 66 | NR | NR | NR | NR | 3 | 1 | 8 | 3 | NR | NR |
| Phase IIb Thaci 2016 | PBO QW | 61 | 16 weeks | NR | NR | 49 | 80 | 49 | 80 | 3‡ | 5 | NR | NR | 4 | 7 |
| | DUP 200 mg Q2W | 61 | | NR | NR | 46 | 75 | 46 | 75 | 3‡ | 5 | NR | NR | 1 | 2 |
| | DUP 300 mg Q2W | 64 | | NR | NR | 50 | 78 | 50 | 78 | 4‡ | 6 | NR | NR | 2 | 3 |
| | DUP 300 mg Q4W | 65 | | NR | NR | 56 | 86 | 56 | 86 | 3‡ | 5 | NR | NR | 3 | 5 |

None of these short-term safety outcomes were available in LIBERTY AD CHRONOS. ABRO: abrocitinib, AE: adverse event, BARI: baricitinib, D/C: discontinuation, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, TCS: topical corticosteroids, TEAE: treatment-emergent adverse event, TRA: tralokinumab, UPA: upadacitinib, %: percent. *treatment-related serious AE, †severe TEAE, ‡discontinuation due to TEAE, ¶North American subgroup.

**Table G1.43. Short-Term Safety II**[35-37,41-43,45,46,48,51,56,63,64,66,67,69,70,85]

| Study Name | Arms | N | Timepoint | Fatal TEAE | | All-cause Mortality | | Major Adverse Cardiovascular Event | | Venous Thromboembolism | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % |
| **Abrocitinib** | | | | | | | | | | | |
| JADE MONO-1 | PBO | 77 | 12 weeks | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| | ABRO 100 mg | 156 | | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| | ABRO 200 mg | 154 | | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| JADE MONO-2 | PBO | 78 | 12 weeks | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| | ABRO 100 mg | 158 | | NR | NR | 1 | 0.6 | 0 | 0 | 0 | 0 |
| | ABRO 200 mg | 155 | | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| JADE TEEN | PBO | 96 | 12 weeks | NR | NR | 0 | 0 | NR | NR | NR | NR |
| | ABRO 100 mg | 95 | | NR | NR | 0 | 0 | NR | NR | NR | NR |
| | ABRO 200 mg | 94 | | NR | NR | 0 | 0 | NR | NR | NR | NR |
| JADE COMPARE | PBO | 131 | 16 weeks | NR | NR | 0 | 0 | NR | NR | NR | NR |
| | ABRO 100 mg | 238 | | NR | NR | 0 | 0 | NR | NR | NR | NR |
| | ABRO 200 mg | 226 | | NR | NR | 0 | 0 | NR | NR | NR | NR |
| | DUP 300 mg | 242 | | NR | NR | 0 | 0 | NR | NR | NR | NR |
| Phase II Gooderham 2019 | PBO | 56 | 16 weeks | 0 | 0 | 0 | 0 | NR | NR | 0* | 0 |
| | ABRO 100 mg | 56 | | 0 | 0 | 0 | 0 | NR | NR | 0* | 0 |
| | ABRO 200 mg | 55 | | 0 | 0 | 0 | 0 | NR | NR | 1* | 1.8 |
| **Baricitinib** | | | | | | | | | | | |
| BREEZE-AD1 | PBO | 249 | 16 weeks | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| Study Name | Arms | N | Timepoint | Fatal TEAE | | All-cause Mortality | | Major Adverse Cardiovascular Event | | Venous Thromboembolism | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % |
| | BARI 1 mg | 127 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | BARI 2 mg | 123 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | BARI 4 mg | 125 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| BREEZE-AD2 | PBO | 244 | 16 weeks | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | BARI 1 mg | 125 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | BARI 2 mg | 123 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | BARI 4 mg | 123 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| BREEZE-AD5 | PBO | 146 | 16 weeks | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| | BARI 1 mg | 147 | | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| | BARI 2 mg | 145 | | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| BREEZE-AD7 | PBO + TCS | 108 | 16 weeks | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0[†] |
| | BARI 2 mg + TCS | 109 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0[†] |
| | BARI 4 mg + TCS | 111 | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1[†] |
| Phase II Guttman-Yassky 2018 | PBO + TCS | 49 | 16 weeks | 0 | 0 | NR | NR | NR | NR | NR | NR |
| | BARI 2 mg + TCS | 37 | | 0 | 0 | NR | NR | NR | NR | NR | NR |
| | BARI 4 mg + TCS | 38 | | 0 | 0 | NR | NR | NR | NR | NR | NR |
| **Upadacitinib** | | | | | | | | | | | |
| MEASURE UP 1 | PBO | 281 | 16 weeks | NR | NR | 0 | 0 | 0 | 0 | [redacted] | |
| | UPA 15 mg | 281 | | NR | NR | 0 | 0 | 0 | 0 | | |
| | UPA 30 mg | 285 | | NR | NR | 0 | 0 | 0 | 0 | | |
| MEASURE UP 2 | PBO | 278 | 16 weeks | NR | NR | 0 | 0 | 0 | 0 | | |
| | UPA 15 mg | 276 | | NR | NR | 0 | 0 | 0 | 0 | | |
| | UPA 30 mg | 282 | | NR | NR | 0 | 0 | 0 | 0 | | |
| AD-UP | PBO + TCS | 304 | 16 weeks | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| | UPA 15 mg + TCS | 300 | | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |

| Study Name | Arms | N | Timepoint | Fatal TEAE | | All-cause Mortality | | Major Adverse Cardiovascular Event | | Venous Thromboembolism | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % |
| | UPA 30 mg + TCS | 297 | | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| Heads Up | DUP 300 mg | 344 | 16 weeks | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| | UPA 30 mg | 348 | | NR | NR | 1 | 0.3 | 0 | 0 | 0 | 0 |
| Phase IIb Guttman-Yassky 2020 | PBO | 40 | 16 weeks | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| | UPA 7.5 mg | 42 | | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| | UPA 15 mg | 42 | | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| | UPA 30 mg | 42 | | NR | NR | 0 | 0 | 0 | 0 | 0 | 0 |
| **Dupilumab** | | | | | | | | | | | |
| SOLO 1 | PBO | 224 | 16 weeks | NR | NR | 0 | 0 | NR | NR | NR | NR |
| | DUP 300 mg Q2W | 224 | | NR | NR | 0 | 0 | NR | NR | NR | NR |
| | DUP 300 mg QW | 223 | | NR | NR | 0 | 0 | NR | NR | NR | NR |
| SOLO 2 | PBO | 236 | 16 weeks | NR | NR | 0 | 0 | NR | NR | NR | NR |
| | DUP 300 mg Q2W | 233 | | NR | NR | 1 | <1 | NR | NR | NR | NR |
| | DUP 300 mg QW | 239 | | NR | NR | 1 | <1 | NR | NR | NR | NR |

None of these short-term safety outcomes were available in ECZTRA 1, ECZTRA 2, ECZTRA 3, LIBERTY AD CHRONOS, and Phase IIb Thaci 2016. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, TCS: topical corticosteroids, TEAE: treatment-emergent adverse event, UPA: upadacitinib, %: percent. *pulmonary embolism, †deep vein thrombosis and pulmonary embolism.

**Table G1.44. Short-Term Safety III**[35-37,41-43,45,46,48,51,53,56,63-66,69-71,80,85]

| Study Name | Arms | N | Timepoint | Injection Site RXN | | Skin Infection | | Herpetic Infection | | Serious Infection | | Malignancy | | Non-Melanocytic Skin Cancer | | Conjunctivitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| **Abrocitinib** | | | | | | | | | | | | | | | | | |
| JADE MONO-1 | PBO | 77 | 12 weeks | NR | NR | 0 | 0 | 2* | 2.6 | NR | NR | 0 | 0 | NR | NR | 0 | 0 |
| | ABRO 100 mg | 156 | | NR | NR | 2 | 1 | 2* | 1.3 | NR | NR | 0 | 0 | NR | NR | 1 | 1 |
| | ABRO 200 mg | 154 | | NR | NR | 1 | 1 | 0* | 0 | NR | NR | 0 | 0 | NR | NR | 1 | 1 |
| JADE MONO-2 | PBO | 78 | 12 weeks | NR | NR | NR | NR | 1* | 1.3 | 1 | 1.3 | 0 | 0 | NR | NR | 0 | 0 |
| | ABRO 100 mg | 158 | | NR | NR | NR | NR | 7* | 4.4 | 3 | 1.9 | 0 | 0 | NR | NR | 4 | 3 |
| | ABRO 200 mg | 155 | | NR | NR | NR | NR | 4* | 2.6 | 0 | 0 | 0 | 0 | NR | NR | 4 | 3 |
| JADE TEEN | PBO | 96 | 12 weeks | NR | NR | NR | NR | 0 | 0 | NR | NR | NR | NR | NR | NR | NR | NR |
| | ABRO 100 mg | 95 | | NR | NR | NR | NR | 1 | 1.1 | NR | NR | NR | NR | NR | NR | NR | NR |
| | ABRO 200 mg | 94 | | NR | NR | NR | NR | 2 | 2.1 | NR | NR | NR | NR | NR | NR | NR | NR |
| JADE COMPARE | PBO | 131 | 16 weeks | 0† | 0 | 1 | 0.8 | 0‡ | 0 | NR | NR | NR | NR | NR | NR | 3 | 2.3 |
| | ABRO 100 mg | 238 | | 2† | 0.01 | 1 | 0.4 | 2‡ | 0.8 | NR | NR | NR | NR | NR | NR | 2 | 0.8 |
| | ABRO 200 mg | 226 | | 2† | 0.01 | 1 | 0.4 | 4‡ | 1.8 | NR | NR | NR | NR | NR | NR | 3 | 1.3 |
| | DUP 300 mg | 242 | | 3† | 0.01 | NR | NR | 0‡ | 0 | NR | NR | NR | NR | NR | NR | 15 | 6.2 |
| Phase II Gooderham 2019 | PBO | 56 | 16 weeks | NR | NR | NR | NR | 2¶ | 3.6 | NR | NR | 0¥ | 0 | NR | NR | NR | NR |
| | ABRO 100 mg | 56 | | NR | NR | NR | NR | 2¶ | 3.6 | NR | NR | 0¥ | 0 | NR | NR | NR | NR |
| | ABRO 200 mg | 55 | | NR | NR | NR | NR | 0¶ | 0 | NR | NR | 0¥ | 0 | NR | NR | NR | NR |
| **Baricitinib** | | | | | | | | | | | | | | | | | |
| BREEZE-AD1 | PBO | 249 | 16 weeks | NA | NA | 11§ | 4.4 | 3** | 1.2 | NR | NR | NR†† | NR†† | NR | NR | 4‡‡ | 1.6 |
| | BARI 1 mg | 127 | | NA | NA | 1§ | 0.8 | 7 | 5.5 | NR | NR | 0 | 0 | NR | NR | 1‡‡ | 0.8 |
| | BARI 2 mg | 123 | | NA | NA | 6§ | 4.9 | 4 | 3.3 | NR | NR | 0 | 0 | NR | NR | 2‡‡ | 1.6 |
| | BARI 4 mg | 125 | | NA | NA | 4§ | 3.2 | 9 | 7.2 | NR | NR | 0 | 0 | NR | NR | 1‡‡ | 0.8 |
| BREEZE-AD2 | PBO | 244 | 16 weeks | NA | NA | 19 | 7.8 | 11 | 4.5 | NR | NR | NR†† | NR†† | NR | NR | 2 | 0.8 |

| Study Name | Arms | N | Timepoint | Injection Site RXN | | Skin Infection | | Herpetic Infection | | Serious Infection | | Malignancy | | Non-Melanocytic Skin Cancer | | Conjunctivitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| | BARI 1 mg | 125 | | NA | NA | 6 | 4.8 | 6 | 4.8 | NR | NR | 0 | 0 | NR | NR | 6 | 4.8 |
| | BARI 2 mg | 123 | | NA | NA | 9 | 7.3 | 7 | 5.7 | NR | NR | 0 | 0 | NR | NR | 2 | 1.6 |
| | BARI 4 mg | 123 | | NA | NA | 6 | 4.9 | 5 | 4.1 | NR | NR | 0 | 0 | NR | NR | 0 | 0 |
| BREEZE-AD5 | PBO | 146 | 16 weeks | NR | NR | 7¶¶ | 5 | 1¥¥ | 0.6 | 1 | 0.7 | 0 | 0 | NR | NR | NR | NR |
| | BARI 1 mg | 147 | | NR | NR | 6¶¶ | 4 | 4¥¥ | 2.7 | 0 | 0 | 0 | 0 | NR | NR | NR | NR |
| | BARI 2 mg | 145 | | NR | NR | 6¶¶ | 4 | 2¥¥ | 1.4 | 1 | 0.7 | 0 | 0 | NR | NR | NR | NR |
| BREEZE-AD7 | PBO + TCS | 108 | 16 weeks | NA | NA | NR | NR | 4## | 3.7 | 2 | 1.9 | 0§§ | 0 | NR | NR | NR | NR |
| | BARI 2 mg + TCS | 109 | | NA | NA | NR | NR | 7## | 6.4 | 0 | 0 | 0§§ | 0 | NR | NR | NR | NR |
| | BARI 4 mg + TCS | 111 | | NA | NA | NR | NR | 7## | 6.3 | 0 | 0 | 0§§ | 0 | NR | NR | NR | NR |
| Phase II Guttman-Yassky 2018 | PBO + TCS | 49 | 16 weeks | NA | NA | 0 | 0 | 0** | 0 | NR | NR | NR | NR | NR | NR | 1¥¥ | 2 |
| | BARI 2 mg + TCS | 37 | | NA | NA | 0 | 0 | 0** | 0 | NR | NR | NR | NR | NR | NR | 0¥¥ | 0 |
| | BARI 4 mg + TCS | 38 | | NA | NA | 1 | 3 | 1** | 3 | NR | NR | NR | NR | NR | NR | 0¥¥ | 0 |
| **Tralokinumab** | | | | | | | | | | | | | | | | | |
| ECZTRA 1 | PBO | 196 | 16 weeks | NR | NR | 3 | 1.5 | 2 | 1 | NR | NR | 0# | 0 | NR | NR | 4¥ | 2 |
| | TRA 300 mg | 602 | | | | 6 | 1 | 3 | 0.5 | NR | NR | 0# | 0 | NR | NR | 43¥ | 7.1 |
| ECZTRA 2 | PBO | 200 | 16 weeks | NR | NR | 11 | 5.5 | 5 | 2.5 | NR | NR | 0# | 0 | NR | NR | 3¥ | 1.5 |
| | TRA 300 mg | 592 | | | | 12 | 2 | 2 | 0.3 | NR | NR | 1# | 0.2 | NR | NR | 18¥ | 3 |
| ECZTRA 2 Subgroup¶¶¶ | Placebo | 91 | 16 weeks | NR | NR | 8§ | 8.8 | NR | NR | NR | NR | NR | NR | NR | NR | 3 | 2.2 |
| | TRA 300 mg | 270 | | NR | NR | 5§ | 1.9 | 1### | 0.4 | NR | NR | NR | NR | NR | NR | 6 | 2.2 |
| ECZTRA 3 | PBO + TCS | 126 | 16 weeks | 0 | 0 | 7§ | 5.6 | 1 | 0.8 | NR | NR | 0# | 0 | NR | NR | 4 | 3.2 |
| | TRA 300 mg + TCS | 252 | | 17 | 6.7 | 4§ | 1.6 | 1 | 0.4 | NR | NR | 0# | 0 | NR | NR | 28 | 11.1 |
| **Upadacitinib** | | | | | | | | | | | | | | | | | |

| Study Name | Arms | N | Timepoint | Injection Site RXN | | Skin Infection | | Herpetic Infection | | Serious Infection | | Malignancy | | Non-Melanocytic Skin Cancer | | Conjunctivitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| MEASURE UP 1 | PBO | 281 | 16 weeks | NR | NR | NR | NR | | | 0 | 0 | 0 | 0 | 0 | 0 | NR | NR |
| | UPA 15 mg | 281 | | NR | NR | NR | NR | | | 2 | 1 | 0 | 0 | 1 | 1 | NR | NR |
| | UPA 30 mg | 285 | | NR | NR | NR | NR | | | 3 | 1 | 2 | 1 | 0 | 0 | NR | NR |
| MEASURE UP 2 | PBO | 278 | 16 weeks | NR | NR | NR | NR | | | 2 | 1 | 0 | 0 | 0 | 0 | NR | NR |
| | UPA 15 mg | 276 | | NR | NR | NR | NR | | | 1 | 1 | 0 | 0 | 2 | 1 | NR | NR |
| | UPA 30 mg | 282 | | NR | NR | NR | NR | | | 2 | 1 | 1 | 1 | 0 | 0 | NR | NR |
| AD-UP | PBO + TCS | 304 | 16 weeks | NR | NR | NR | NR | | | 3 | 1 | | | | | NR | NR |
| | UPA 15 mg + TCS | 300 | | NR | NR | NR | NR | | | 3 | 1 | | | | | NR | NR |
| | UPA 30 mg + TCS | 297 | | NR | NR | NR | NR | | | 0 | 0 | | | | | NR | NR |
| Heads Up | DUP 300 mg | 344 | 16 weeks | NR | NR | NR | NR | NR | NR | 2 | 0.6 | NR | NR | 1 | 0.3 | NR | NR |
| | UPA 30 mg | 348 | | NR | NR | NR | NR | NR | NR | 4 | 1.1 | 0 | 0 | 0 | 0 | NR | NR |
| Phase IIb Guttman-Yassky 2020 | PBO | 40 | 16 weeks | NR | NR | 0 | 0 | 0‡ | 0 | 0 | 0 | 0 | 0 | NR | NR | NR | NR |
| | UPA 7.5 mg | 42 | | NR | NR | 1 | 2.4 | 0‡ | 0 | 2 | 4.8 | 0 | 0 | NR | NR | NR | NR |
| | UPA 15 mg | 42 | | NR | NR | 0 | 0 | 0‡ | 0 | 1 | 2.4 | 0 | 0 | NR | NR | NR | NR |
| | UPA 30 mg | 42 | | NR | NR | 0 | 0 | 0‡ | 0 | 0 | 0 | 0 | 0 | NR | NR | NR | NR |
| **Dupilumab** | | | | | | | | | | | | | | | | | |
| SOLO 1 | PBO | 224 | 16 weeks | 13 | 6 | 18 | 8 | 9*** | 4 | NR | NR | NR | NR | NR | NR | 2 | 0.9 |
| | DUP 300 mg Q2W | 224 | | 19 | 8 | 13 | 6 | 15*** | 7 | NR | NR | NR | NR | NR | NR | 11 | 4.8 |
| | DUP 300 mg QW | 223 | | 41 | 19 | 14 | 6 | 9*** | 4 | NR | NR | NR | NR | NR | NR | 7 | 3.2 |
| SOLO 2 | PBO | 236 | 16 weeks | 15 | 6 | 26 | 11 | 8 | 3 | NR | NR | NR | NR | NR | NR | 1 | 0.4 |
| | DUP 300 mg Q2W | 233 | | 32 | 14 | 13 | 6 | 10 | 4 | NR | NR | NR | NR | NR | NR | 9 | 3.8 |
| | DUP 300 mg QW | 239 | | 31 | 13 | 15 | 6 | 12 | 5 | NR | NR | NR | NR | NR | NR | 9 | 3.8 |

| Study Name | Arms | N | Timepoint | Injection Site RXN | | Skin Infection | | Herpetic Infection | | Serious Infection | | Malignancy | | Non-Melanocytic Skin Cancer | | Conjunctivitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| Phase IIb Thaci 2016 | PBO QW | 61 | 16 weeks | 2 | 3 | NR | NR | 1[†††] | 2 | NR | NR | NR | NR | NR | NR | 2[‡‡‡] | 3 |
| | DUP 200 mg Q2W | 61 | | 4 | 7 | NR | NR | 6[†††] | 10 | NR | NR | NR | NR | NR | NR | 6[‡‡‡] | 10 |
| | DUP 300 mg Q2W | 64 | | 3 | 5 | NR | NR | 5[†††] | 8 | NR | NR | NR | NR | NR | NR | 3[‡‡‡] | 5 |
| | DUP 300 mg Q4W | 65 | | 5 | 8 | NR | NR | 4[†††] | 6 | NR | NR | NR | NR | NR | NR | 4[‡‡‡] | 6 |

None of these short-term safety outcomes were available in LIBERTY AD CHRONOS. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NA: not applicable, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, RXN: reaction, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *herpes simplex, herpes zoster, oral herpes, and eczema herpeticum, [†]injection site erythema, oedema, pain, swelling, [‡]herpes zoster, [¶]herpes simplex, herpes zoster, and eczema herpecitum, [¥]malignant melanoma, [#]malignancies diagnosed after randomization, [§]skin infection requiring systemic treatment, [ɣ]conjunctivitis, conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic, **herpes simplex, [††]2 malignancies were reported in patients on placebo, but publication doesn't distinguish which trial's patients experienced these (either BREEZE-AD1 or BREEZE-AD2), [‡‡]conjunctivitis/keratitis, [¶¶]skin infection requiring antibiotics, [¥¥]herpes zoster and herpes simplex, [##]oral herpes virus infection, herpes simplex virus infection, and herpes zoster virus infection, [§§]malignant tumors other than NMSC and NMSC, [ɣɣ]conjunctivitis viral, ***herpes viral infection include oral herpes, herpes simplex, eczema herpeticum, herpes virus infection, herpes zoster, ophthalmic herpes simplex, genital herpes, herpes ophthalmic, herpes simplex otitis externa, [†††]herpes viral infections include oral herpes, herpes simplex, eczema herpeticum, herpes virus infection, and herpes zoster, [‡‡‡]conjunctival infections, irritations, and inflammation, [¶¶¶]North American subgroup.

**Table G1.45. Long-Term Safety I**[50,53,54,60-64,67,77,79,81,108]

| Study Name | Arms | N | Timepoint | Any AE | | TEAE | | Study Drug-Related AEs | | D/C due to AE | | Serious AE | | Serious TEAE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % | n | % | n | % |
| **Abrocitinib** | | | | | | | | | | | | | | | |
| JADE EXTEND Subgroup 1‡ | ABRO 100 mg | 595 | 48 weeks | NR | NR | NR | NR | NR | NR | 37 | 6.2 | NR | NR | NR | NR |
| | ABRO 200 mg | 521 | | NR | NR | NR | NR | NR | NR | 45 | 8.6 | NR | NR | NR | NR |
| JADE EXTEND Subgroup 2¶ | ABRO 100 mg | 130 | 32 weeks | NR | NR | 54 | 41.5 | NR | NR | 1¥ | 0.8 | NR | NR | 3 | 2.3 |
| | ABRO 200 mg | 73 | | NR | NR | 37 | 50.7 | NR | NR | 1¥ | 1.4 | NR | NR | 1 | 1.4 |
| **Tralokinumab** | | | | | | | | | | | | | | | |
| ECZTRA 1 | PBO | 35 | 36 weeks | 25 | 71.4 | NR | NR | NR | NR | 0 | 0 | 0 | 0 | NR | NR |
| | TRA 300 mg Q2W | 68 | | 54 | 79.4 | NR | NR | NR | NR | 1 | 1.5 | 1 | 1.5 | NR | NR |
| | TRA 300 mg Q4W | 76 | | 53 | 69.7 | NR | NR | NR | NR | 1 | 1.3 | 3 | 3.9 | NR | NR |
| ECZTRA 2 | PBO | 46 | 36 weeks | 32 | 69.6 | NR | NR | NR | NR | 0 | 0 | 0 | 0 | NR | NR |
| | TRA 300 mg Q2W | 91 | | 62 | 68.1 | NR | NR | NR | NR | 2 | 2.2 | 0 | 0 | NR | NR |
| | TRA 300 mg Q4W | 89 | | 56 | 62.9 | NR | NR | NR | NR | 1 | 1.1 | 3 | 3.4 | NR | NR |
| ECZTRA 3 | TRA 300 mg Q2W + TCS (PBO nonresponders) | 79 | 16-32 weeks | 55 | 69.6 | NR | NR | NR | NR | 2 | 2.5 | 0 | 0 | NR | NR |
| | PBO Q2W + TCS (PBO responders) | 41 | | 26 | 63.4 | NR | NR | NR | NR | 1 | 2.4 | 1 | 2.4 | NR | NR |
| | TRA 300 mg Q2W + TCS (TRA responders) | 69 | | 48 | 69.6 | NR | NR | NR | NR | 0 | 0 | 3 | 4.3 | NR | NR |
| | TRA 300 mg Q4W + TCS (TRA responders) | 69 | | 41 | 59.4 | NR | NR | NR | NR | 1 | 1.4 | 0 | 0 | NR | NR |
| | TRA 300 mg Q2W + TCS (TRA nonresponders) | 95 | | 62 | 65.3 | NR | NR | NR | NR | 1 | 1.1 | 2 | 2.1 | NR | NR |

| Study Name | Arms | N | Timepoint | Any AE | | TEAE | | Study Drug-Related AEs | | D/C due to AE | | Serious AE | | Serious TEAE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % | n | % | n | % |
| ECZTEND | TRA 300 mg Q2W | 1174 | 56 weeks | 844 | 71.9 | NR | NR | NR | NR | 19 | 1.6 | 55 | 4.7 | NR | NR |
| **Upadacitinib** | | | | | | | | | | | | | | | |
| Heads Up | DUP 300 mg | 344 | 24 weeks | 230 | 66.9 | NR | NR | 129 | 37.5 | 4 | 1.2 | 7 | 2 | NR | NR |
| | UPA 30 mg | 348 | | 270 | 77.6 | NR | NR | 170 | 48.9 | 11 | 3.2 | 14 | 4 | NR | NR |
| Phase IIb Guttman-Yassky 2020 | PBO→PBO | 10 | 32 weeks | 1 | 10.0 | NR | NR | 1* | 10.0 | 0 | 0.0 | 0 | 0.0 | NR | NR |
| | PBO→UPA 30 mg | 10 | | 7 | 70.0 | NR | NR | 5* | 50.0 | 1 | 10.0 | 2 | 20.0 | NR | NR |
| | UPA 7.5 mg→PBO | 15 | | 1 | 6.7 | NR | NR | 1* | 6.7 | 0 | 0.0 | 0 | 0.0 | NR | NR |
| | UPA 7.5 mg→UPA 7.5 mg | 16 | | 4 | 25.0 | NR | NR | 1* | 6.3 | 0 | 0.0 | 0 | 0.0 | NR | NR |
| | UPA 15 mg→PBO | 19 | | 5 | 26.3 | NR | NR | 3* | 15.8 | 0 | 0.0 | 0 | 0.0 | NR | NR |
| | UPA 15 mg→UPA 15 mg | 18 | | 5 | 27.8 | NR | NR | 3* | 16.7 | 0 | 0.0 | 0 | 0.0 | NR | NR |
| | UPA 30 mg→PBO | 19 | | 7 | 36.8 | NR | NR | 3* | 15.8 | 0 | 0.0 | 0 | 0.0 | NR | NR |
| | UPA 30 mg→UPA 30 mg | 19 | | 8 | 42.1 | NR | NR | 4* | 21.1 | 1 | 5.3 | 0 | 0.0 | NR | NR |
| **Dupilumab** | | | | | | | | | | | | | | | |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | 52 weeks | 266 | 84 | NR | NR | NR | NR | 24 | 8 | 16 | 5 | NR | NR |
| | DUP 300 mg + TCS Q2W | 110 | | 97 | 88 | NR | NR | NR | NR | 2 | 2 | 4 | 4 | NR | NR |
| | DUP 300 mg + TCS QW | 315 | | 261 | 83 | NR | NR | NR | NR | 9 | 3 | 9 | 3 | NR | NR |
| AD SOLO-CONTINUE | PBO | 82 | 36 weeks | NR | NR | 67 | 81.7 | 1† | 1.2 | 3 | 3.7 | NR | NR | NR | NR |
| | DUP 300 mg Q8W | 84 | | NR | NR | 63 | 75 | 3† | 3.6 | 0 | 0 | NR | NR | NR | NR |
| | DUP 300 mg Q4W | 87 | | NR | NR | 64 | 73.6 | 4† | 4.6 | 2 | 2.3 | NR | NR | NR | NR |

| Study Name | Arms | N | Timepoint | Any AE | | TEAE | | Study Drug-Related AEs | | D/C due to AE | | Serious AE | | Serious TEAE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % | n | % | n | % |
| | DUP 300 mg QW/Q2W | 167 | | NR | NR | 118 | 70.7 | 6[†] | 3.6 | 0 | 0 | NR | NR | NR | NR |

None of these long-term safety data were available in BREEZE-AD3 and BREEZE-AD6. AE: adverse event, D/C: discontinuation, DUP: dupilumab, kg: kilogram, LTE: long-term extension, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, RXN: reaction, TEAE: treatment-emergent adverse event, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent.*AE possibly related to drug, [†]treatment-emergent SAE, [‡]JADE MONO-1 & 2 and JADE COMPARE subgroup, [¶]JADE COMPARE dupilumab nonresponder subgroup, [¥]discontinuation due to TEAE.

**Table G1.46. Long-Term Safety II**[50,53,54,60,63,64,69,81,108]

| Study Name | Arms | N | Timepoint | All-cause Mortality | | Major Adverse Cardiovascular Event | | Venous Thromboembolism | | Nausea | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % |
| **Abrocitinib** | | | | | | | | | | | |
| JADE EXTEND Subgroup 2* | ABRO 100 mg | 130 | 32 weeks | NR | NR | NR | NR | NR | NR | 0 | 0 |
| | ABRO 200 mg | 73 | | NR | NR | NR | NR | NR | NR | 6 | 8.2 |
| **Tralokinumab** | | | | | | | | | | | |
| ECZTRA 3 | TRA 300 mg Q2W + TCS (PBO nonresponders) | 79 | 16-32 weeks | NR | NR | NR | NR | NR | NR | 1 | 1.3 |
| | PBO 300 mg Q2W + TCS (PBO responders) | 41 | | NR | NR | NR | NR | NR | NR | 0 | 0 |
| | TRA 300 mg Q2W + TCS (TRA responders) | 69 | | NR | NR | NR | NR | NR | NR | 3 | 4.3 |
| | TRA 300 mg Q4W + TCS (TRA responders) | 69 | | NR | NR | NR | NR | NR | NR | 4 | 5.8 |
| | TRA 300 mg Q2W + TCS (TRA nonresponders) | 95 | | NR | NR | NR | NR | NR | NR | 3 | 3.2 |
| **Upadacitinib** | | | | | | | | | | | |
| Heads Up | DUP 300 mg | 344 | 24 weeks | 0 | 0 | NR | NR | NR | NR | NR | NR |
| | UPA 30 mg | 348 | | 1 | 0.3 | NR | NR | NR | NR | NR | NR |
| Phase IIb Guttman-Yassky 2020 | PBO→PBO | 10 | 32 weeks | NR | NR | 0 | 0 | 0 | 0 | NR | NR |
| | PBO→UPA 30 mg | 10 | | NR | NR | 0 | 0 | 0 | 0 | NR | NR |
| | UPA 7.5 mg →PBO | 15 | | NR | NR | 0 | 0 | 0 | 0 | NR | NR |
| | UPA 7.5 mg →UPA 7.5 mg | 16 | | NR | NR | 0 | 0 | 0 | 0 | NR | NR |
| | UPA 15 mg→ PBO | 19 | | NR | NR | 0 | 0 | 0 | 0 | NR | NR |
| | UPA 15 mg→ UPA 15 mg | 18 | | NR | NR | 0 | 0 | 0 | 0 | NR | NR |
| | UPA 30 mg→ PBO | 19 | | NR | NR | 0 | 0 | 0 | 0 | NR | NR |
| | UPA 30 mg→ UPA 30 mg | 19 | | NR | NR | 0 | 0 | 0 | 0 | NR | NR |
| **Dupilumab** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LIBERTY AD CHRONOS | PBO + TCS | 315 | 56 weeks | 0 | 0 | NR | NR | NR | NR | NR | NR |
| | DUP 300 mg + TCS Q2W | 110 | | 0 | 0 | NR | NR | NR | NR | NR | NR |
| | DUP 300 mg + TCS QW | 315 | | 1 | <1 | NR | NR | NR | NR | NR | NR |
| AD SOLO-CONTINUE | PBO | 82 | 36 weeks | 0 | 0 | NR | NR | NR | NR | NR | NR |
| | DUP 300 mg Q8W | 84 | | 0 | 0 | NR | NR | NR | NR | NR | NR |
| | DUP 300 mg Q4W | 87 | | 1 | 1.1 | NR | NR | NR | NR | NR | NR |
| | DUP 300 mg QW/Q2W | 167 | | 0 | 0 | NR | NR | NR | NR | NR | NR |

None of these long-term safety data were available in BREEZE-AD3, BREEZE-AD6, ECZTRA 1, ECZTRA 2, and ECZTEND. There were no long-term data on Fatal TEAE's available. DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, TCS: topical corticosteroids, TEAE: treatment-emergent adverse event, TRA: tralokinumab, UPA: upadacitinib, %: percent. *JADE COMPARE dupilumab nonresponder subgroup.

**Table G1.47. Long-Term Safety III**[50,53-55,60-64,67,79,81]

| Study Name | Arms | N | Timepoint | Injection Site RXN | | Skin Infection | | Herpetic Infection | | Serious Infection | | Malignancy | | Non-Melanocytic Skin Cancer | | Conjunctivitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| **Tralokinumab** | | | | | | | | | | | | | | | | | |
| ECZTRA 1 | PBO | 35 | 36 weeks | 1 | 2.9 | 0* | 0 | 0[†] | 0 | NR | NR | 0[‡] | 0 | NR | NR | 2[¶] | 5.7 |
| | TRA 300 mg Q2W | 68 | | 5 | 7.4 | 2* | 2.9 | 0[†] | 0 | NR | NR | 0[‡] | 0 | NR | NR | 6[¶] | 8.8 |
| | TRA 300 mg Q4W | 76 | | 7 | 9.2 | 2* | 2.6 | 0[†] | 0 | NR | NR | 0[‡] | 0 | NR | NR | 5[¶] | 6.6 |
| ECZTRA 2 | PBO | 46 | 36 weeks | 0 | 0 | 1* | 2.2 | 0[†] | 0 | NR | NR | 0[‡] | 0 | NR | NR | 3[¶] | 6.5 |
| | TRA 300 mg Q2W | 91 | | 4 | 4.4 | 2* | 2.2 | 1[†] | 1.1 | NR | NR | 0[‡] | 0 | NR | NR | 8[¶] | 8.8 |
| | TRA 300 mg Q4W | 89 | | 4 | 4.5 | 1* | 1.1 | 0[†] | 0 | NR | NR | 1[‡] | 1.1 | NR | NR | 5[¶] | 5.6 |
| ECZTRA 3 | TRA 300 mg Q2W + TCS (PBO non-responders) | 79 | 16-32 weeks | 2 | 2.5 | 2* | 2.5 | 3[¥] | 4 | NR | NR | 0[‡] | 0 | NR | NR | 6[#] | 7.6 |
| | PBO Q2W + TCS (PBO responders) | 41 | | 0 | 0 | 0* | 0 | 1[¥] | 2 | NR | NR | 1[‡] | 2.4 | NR | NR | 1[#] | 2.4 |
| | TRA 300 mg Q2W + TCS (TRA responders) | 69 | | 5 | 7.2 | 0* | 0 | 3[¥] | 4 | NR | NR | 0[‡] | 0 | NR | NR | 3[#] | 4.3 |
| | TRA 300 mg Q4W + TCS (TRA responders) | 69 | | 4 | 5.8 | 0* | 0 | 4[¥] | 6 | NR | NR | 1[‡] | 1.4 | NR | NR | 1[#] | 1.4 |
| | TRA 300 mg Q2W + TCS (TRA non-responders) | 95 | | 5 | 5.3 | 1* | 1.1 | 5[¥] | 5 | NR | NR | 0[‡] | 0 | NR | NR | 4[#] | 4.2 |
| ECZTEND | TRA 300 mg Q2W | 1174 | Week 56 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | 65[¶] | 5.9 |
| **Upadacitinib** | | | | | | | | | | | | | | | | | |
| Heads Up | DUP 300 mg | 344 | 24 weeks | NR | NR | NR | NR | 4[##] | 1.2 | 2 | 0.6 | 0 | 0 | 1 | 0.3 | 35 | 10.2 |
| | UPA 30 mg | 348 | | NR | NR | NR | NR | 12[##] | 3.4 | 4 | 1.1 | 1 | 0.3 | 0 | 0 | 5 | 1.4 |
| Phase IIb | PBO→PBO | 10 | 32 weeks | NR | NR | NR | NR | NR | NR | 0 | 0 | 0 | 0 | 0[§] | 0 | NR | NR |
| | PBO→UPA 30 mg | 10 | | NR | NR | NR | NR | NR | NR | 1 | 10 | 1 | 10 | 1[§] | 10 | NR | NR |

| Study Name | Arms | N | Timepoint | Injection Site RXN | | Skin Infection | | Herpetic Infection | | Serious Infection | | Malignancy | | Non-Melanocytic Skin Cancer | | Conjunctivitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| Guttman-Yassky 2020 | UPA 7.5 mg→ PBO | 15 | | NR | NR | NR | NR | NR | NR | 0 | 0 | 0 | 0 | 0[§] | 0 | NR | NR |
| | UPA 7.5 mg→ UPA 7.5 mg | 16 | | NR | NR | NR | NR | NR | NR | 0 | 0 | 0 | 0 | 0[§] | 0 | NR | NR |
| | UPA 15 mg→PBO | 19 | | NR | NR | NR | NR | NR | NR | 0 | 0 | 0 | 0 | 0[§] | 0 | NR | NR |
| | UPA 15 mg→ UPA 15 mg | 18 | | NR | NR | NR | NR | NR | NR | 0 | 0 | 0 | 0 | 0[§] | 0 | NR | NR |
| | UPA 30 mg→ PBO | 19 | | NR | NR | NR | NR | NR | NR | 0 | 0 | 0 | 0 | 0[§] | 0 | NR | NR |
| | UPA 30 mg→ UPA 30 mg | 19 | | NR | NR | NR | NR | NR | NR | 0 | 0 | 0 | 0 | 0[§] | 0 | NR | NR |
| **Dupilumab** | | | | | | | | | | | | | | | | | |
| LIBERTY AD CHRONOS | PBO + TCS | 315 | 52 weeks | 24 | 8 | 56[¥] | 18 | 25** | 8 | NR | NR | NR | NR | NR | NR | 25[††] | 8 |
| | DUP 300 mg + TCS Q2W | 110 | | 16 | 15 | 12[¥] | 11 | 8** | 7 | NR | NR | NR | NR | NR | NR | 15[††] | 14 |
| | DUP 300 mg + TCS QW | 315 | | 60 | 19 | 26[¥] | 8 | 22** | 7 | NR | NR | NR | NR | NR | NR | 61[††] | 19 |
| AD SOLO-CONTINUE | PBO | 82 | 36 weeks | 7 | 8.5 | 8[¥] | 9.8 | 5[‡‡] | 6.1 | NR | NR | 0[¶¶] | 0 | 0 | 0 | 4[¥¥] | 4.9 |
| | DUP 300 mg Q8W | 84 | | 6 | 7.1 | 5[¥] | 6 | 10[‡‡] | 11.9 | NR | NR | 2[¶¶] | 2.4 | 2 | 2.4 | 3[¥¥] | 3.6 |
| | DUP 300 mg Q4W | 87 | | 6 | 6.9 | 1[¥] | 1.1 | 3[‡‡] | 3.4 | NR | NR | 1[¶¶] | 1.1 | 1 | 1.1 | 4[¥¥] | 4.6 |
| | DUP 300 mg QW/Q2W | 167 | | 18 | 10.8 | 4[¥] | 2.4 | 11[‡‡] | 6.6 | NR | NR | 0[¶¶] | 0 | 0 | 0 | 9[¥¥] | 5.4 |
| | DUP 4 mg/kg (Children) | 19 | | 2[##] | 10.5 | 0[¥¥] | 0 | 1[§§] | 5.3 | NR | NR | NR | NR | NR | NR | 1*** | 5.3 |

None of these long-term safety data were available in JADE EXTEND, BREEZE-AD3, and BREEZE-AD6. DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, RXN: reaction, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *skin infection requiring systemic treatment, [†]eczema herpeticum, [‡]malignancies diagnosed after randomization, [¶]conjunctivitis, conjunctivitis bacterial, conjunctivitis viral, and conjunctivitis allergic, [¥]oral herpes and eczema herpeticum, [#]conjunctivitis, conjunctivitis allergic, and conjunctivitis viral, [§]non-melanoma skin cancer, [¥]non-herpetic skin infection, **oral herpes, herpes simplex, herpes virus infection, herpes zoster, eczema herpeticum, genital herpes, herpes ophthalmic, ophthalmic herpes simplex, and ophthalmic herpes

zoster, [††]conjunctivitis allergic, conjunctivitis bacterial, atopic keratoconjunctivitis, and conjunctivitis, [‡‡]herpes simplex virus infection, oral herpes infection, ophthalmic herpes infection, [¶¶]basal cell carcinoma, [¥¥]conjunctivitis, conjunctivitis bacterial, conjunctivitis viral, conjunctivitis allergic, and atopic keratoconjunctivitis, [##]herpes zoster.

*Mild to Moderate Population*

**Table G1.48 Study Quality**[93,96]

| Trial | Comparable Groups | Non-differential Follow-up | Patient/ Investigator Blinding (Double-blind) | Clear Definition of Intervention | Clear Definition of Outcomes | Selective Outcome Reporting | Measurements Valid | Intention-to-treat Analysis | Approach to Missing Data | USPSTF Rating |
|---|---|---|---|---|---|---|---|---|---|---|
| **Ruxolitinib Cream** | | | | | | | | | | |
| **TRuE AD-1** | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | NRI | Good |
| **TRuE AD-2** | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | NRI | Good |
| **Crisaborole** | | | | | | | | | | |
| **AD301/302** | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Unclear | Good |
| **CrisADe CARE 1** | NA | Yes | NA | Yes | Yes | No | Yes | NA | NA | Fair |

Includes on published phase II RCTs. NA: not applicable, NRI: non-responder imputation,

**Table G1.49. Key Features**

| Trial | Patient Population | Interventions | Inclusion Criteria | Key Outcomes |
|---|---|---|---|---|
| **Ruxolitinib Cream** | | | | |
| Phase III<br>TRuE-AD1<br>(poster)[86,89,90]<br><br>Papp, K. 2020 | N~600<br>DB, PC, RCT<br><br>Adolescents aged 12-17 and adults aged 18+ with mild-to-moderate AD | Applied twice daily for 8 weeks:<br><br>• ruxolitinib cream 1.5%<br>• ruxolitinib cream 0.75%<br>• vehicle (placebo) cream<br><br>Prohibited concomitant therapy: UV light therapy, JAK inhibitors (systemic/topical), bleach baths (diluted sodium hypochlorite) more than 2x/week | • Adolescents aged 12 to 17 years, inclusive, and adults aged ≥ 18 years.<br>• Participants with AD for ≥ 2 years.<br>• Participants with an IGA score of 2 to 3 at screening and 0 to 4 at Week 8<br>• Participants with % BSA (excluding scalp) of AD involvement of 3% to 20% at screening and 0% to 20% at Week 8<br>• Participants who agree to discontinue all agents used to treat AD during trial<br>• Willingness to avoid pregnancy or fathering of children | Primary Endpoint at week 8:<br>•IGA-TS response rate<br><br>Secondary Endpoints at week 8:<br>•EASI-75 response rate<br>•Itch NRS 4-point improvement response rate<br>•PROMIS Short Form-Sleep Disturbance 6-point improvement response rate<br>•SCORAD, mean change from baseline |
| Phase III<br>TRuE-AD2<br>(Poster)[86,89,90]<br><br>Papp, K. 2020 | N~600<br><br>DB, PC, RCT<br><br>Adolescents aged 12-17 and adults aged 18+ with mild-to-moderate AD | Applied twice daily for 8 weeks:<br><br>• ruxolitinib cream 1.5%<br>• ruxolitinib cream 0.75%<br>• vehicle (placebo) cream<br><br>Prohibited concomitant therapy: UV light therapy, JKA inhibitors (systemic/topical), bleach baths (diluted sodium hypochlorite) more than 2x/week | • Adolescents aged 12 to 17 years, inclusive, and adults aged ≥ 18 years.<br>• Participants with AD for ≥ 2 years.<br>• Participants with an IGA score of 2 to 3 at screening and 0 to 4 at Week 8<br>• Participants with % BSA (excluding scalp) of AD involvement of 3% to 20% at screening and 0% to 20% at Week 8<br>• Participants who agree to discontinue all agents used to treat AD during trial<br>• Willingness to avoid pregnancy or fathering of children | Primary Endpoint at week 8:<br>•IGA-TS response rate<br><br>Secondary Endpoints at week 8:<br>•EASI-75 response rate<br>•Itch NRS 4-point improvement response rate<br>•PROMIS Short Form-Sleep Disturbance 6-point improvement response rate<br>•SCORAD, mean change from baseline |

| Trial | Patient Population | Interventions | Inclusion Criteria | Key Outcomes |
|---|---|---|---|---|
| Phase II[87,88]<br><br>Kim 2020, Kim 2019 | N= 307<br><br>randomized, dose-ranging<br><br>Adults 18 to 70 with active atopic dermatitis | Vehicle BID (n=52)<br>Triamcinolone 0.1% BID (n=51)<br>RUX 0.15% QD (n= 51)<br>RUX 0.5% QD (n=51)<br>RUX 1.5% QD (n=52)<br>RUX 1.5 % BID (n=50)<br><br>Prohibited concomitant therapy: systemic and topical treatments | • Patients aged 18–70 years with active atopic dermatitis<br>• History of AD >2 years<br>• IGA of 2 or 3<br>• BSA involvement of 3%–20% | Primary endpoint: mean percentage change from baseline EASI score at week 4<br><br>Secondary Endpoints: responder rates (IGA and EASI), itch NRS score, and safety |
| **Crisaborole** | | | | |
| Phase III[96]<br>AD 301 | N=763<br><br>RCT, MC, DB, vehicle-controlled phase III studies<br><br>Patients 2 and older with mild to moderate AD | Crisaborole or Vehicle cream<br><br>Prohibited concomitant therapy: biologic or systemic therapy or TCS or TCI | Patients to be aged 2 years or older and have a clinical diagnosis of AD according to Hanifin and Rajka34 criteria, 5% or more treatable body surface area involvement, and a baseline Investigator's Static Global Assessment (ISGA) score of mild (2) or moderate (3)<br>Patients were also allowed to use acceptable bland emollients to manage dry skin areas around, but not overlapping, the treatable AD-involved areas. | Primary Endpoint: success of ISGA score at 29 days<br><br>Secondary endpoint: Proportion of patients with an ISGA score of clear or almost clear at 29 days, time to success in ISGA score, pruritus severity, signs of AD |
| Phase III[96]<br>AD 302 | N= 764<br><br>RCT, MC, DB, vehicle-controlled phase III studies<br><br>Patients 2 and older with mild to moderate AD | | | |
| Phase III<br>AD 303 Long-term safety study[91]<br><br>Eichenfield 2017 | Patients 2 and older with mild to moderate AD<br><br>MC, OL, LTE safety study<br><br>N= 517 | Crisaborole<br><br>Prohibited concomitant therapy: TCS or TCI | Patients eligible for AD-303 must have completed the pivotal study (AD-301, AD-302) without experiencing a crisaborole treatment-related AE or<br>a serious AE (SAE) that precluded further treatment with crisaborole ointment; they could enroll in the extension study within 8 days of day 36 of the pivotal studies. | Safety |

| Trial | Patient Population | Interventions | Inclusion Criteria | Key Outcomes |
|---|---|---|---|---|
| Post Hoc Analyses of AD 301/302[92,94,95,97] | *Same as AD 301/302* | *Same as AD 301/302* | *Same as AD 301/302* | QoL |
| Phase IV CrisADe CARE 1[93]<br><br>Schlessinger 2020 | N= 137<br><br>MC, PK, OL, single arm<br><br>Infants aged 3 <24 months with mild-to-moderate AD | Crisaborole | aged 3 to < 24 months with a diagnosis of AD per Hanifin and Rajka criteria [10], mild (2) or moderate (3) AD per ISGA [6], and a percentage of treatable body surface area (%BSA) ≥ 5, excluding the scalp. | Primary Endpoint: the incidence of TEAEs<br><br>Secondary Endpoints: ISGA success, ISGA clear or almost clear at day 29, percent change in EASI, POEM |

AD: atopic dermatitis, AE: adverse event, BID: twice daily, BSA: body surface area, DB: double-blind, LTE: long-term extension, MC: multicenter, N: total number, OL: open-label, PC: placebo-controlled, PK: pharmacokinetic, QD: once daily, RCT: randomized controlled trial, QoL: quality of life, RUX: ruxolitinib, SAE: serious adverse event, TCS: topical corticosteroid, TCI: topical corticoinhibitor, TEAE: treatment-emergent adverse event.

**Table G1.50. Baseline Characteristics I**[87-97]

| Study Name | Arms | N | Age (years) | | Male | | White | | Disease duration (years) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | mean | SD | n | % | n | % | mean | SD |
| **Ruxolitinib Cream** | | | | | | | | | | |
| TRuE AD 1 | Vehicle cream | 126 | Median: 31.5 | Range: 12 to 82 | 47 | 37.3 | 85 | 67.5 | Median: 17.9 | Range: 1.9 to 79.1 |
| | RUX 0.75% | 252 | Median: 34.0 | Range: 12 to 85 | 98 | 38.9 | 171 | 67.9 | Median: 14.1 | Range: 1.0 to 68.8 |
| | RUX 1.5% | 253 | Median: 30.0 | Range: 12 to 77 | 95 | 37.5 | 175 | 69.2 | Median: 16.0 | Range: 0 to 69.2 |
| TRuE AD 2 | Vehicle cream | 124 | Median: 37.5 | Range: 12 to 82 | 44 | 35.5 | 84 | 67.7 | Median: 15.9 | Range: 0.8 to 70.7 |
| | RUX 0.75% | 248 | Median: 33.0 | Range: 12 to 81 | 98 | 39.5 | 174 | 70.2 | Median: 15.9 | Range: 0.1 to 68.6 |
| | RUX 1.5% | 246 | Median: 32.0 | Range: 12 to 85 | 96 | 39 | 178 | 72.4 | Median: 16.6 | Range: 0 to 68.8 |
| Subgroup Analysis – Partial response | Vehicle cream | 174 | Median: 34.5 | Range: 12 to 82 | 57 | 35.1 | 117 | 67.2 | Median: 15.5 | Range: 0.8 to 79.1 |
| | RUX 0.75% | 213 | Median: 37.0 | Range: 12 to 85 | 96 | 45.1 | 138 | 64.8 | Median: 14.0 | Range: 1.8 to 68.6 |
| | RUX 1.5% | 197 | Median: 28.0 | Range: 12 to 84 | 70 | 35.5 | 124 | 62.9 | Median: 14.9 | Range: 0.2 to 69.2 |
| | Total | 584 | Median 33.0 | Range: 12 to 85 | 227 | 38.9 | 379 | 64.9 | Median: 14.9 | Range: 0.2 to 79.1 |
| Subgroup Analysis – BSA >10, EASI > 16 | Vehicle cream | 13 | Median: 41.0 | Range: 12 to 63 | 6 | 46.2 | 11 | 84.6 | Median: 17.0 | Range: 2.1 to 60.1 |
| | RUX 0.75% | 36 | Median 45.5 | Range: 12 to 75 | 12 | 33.3 | 27 | 75 | Median: 18.2 | Range: 1.9 to 55.8 |
| | RUX 1.5% | 32 | Median: 26.5 | Range: 13 to 85 | 15 | 46.9 | 27 | 84.4 | Median: 18.1 | Range: 1.9 to 60.1 |
| | Total | 81 | Median: 34.0 | Range: 12 to 85 | 33 | 40.7 | 65 | 80.2 | Median: 17.0 | Range: 2.1 to 60.1 |
| Phase II Kim 2020 | Vehicle cream | 52 | Median 31.5 | Range: 18 to 69 | 20 | 38.5 | 27 | 51.9 | Median: 19.5 | Range: 2.2 to 65.3 |
| | RUX 1.5% | 50 | Median: 35.5 | Range: 18 to 70 | 24 | 52 | 33 | 66 | Median: 21.2 | Range: 0.1 to 64.8 |
| | TAC 0.1% | 51 | Median: 35.0 | Range: 18 to 69 | 23 | 45.1 | 28 | 54.9 | Median: 24.8 | Range: 2.3 to 62.2 |
| | Total | 307 | Median: 35.0 | Range: 18 to 70 | 139 | 45.3 | 172 | 56 | Median: 20.8 | Range: 0.1 to 66.1 |
| **Crisaborole** | | | | | | | | | | |
| AD 301 | CRIS | 503 | 12 | NR | 219 | 43.5 | 308 | 61.2 | NR | NR |
| | Vehicle cream | 256 | 12.4 | NR | 113 | 44.1 | 162 | 63.3 | NR | NR |
| AD 302 | CRIS | 513 | 12.6 | NR | 231 | 45 | 309 | 60.2 | NR | NR |
| | Vehicle cream | 250 | 11.8 | NR | 112 | 44.8 | 144 | 57.6 | NR | NR |

| Study Name | Arms | N | Age (years) | | Male | | White | | Disease duration (years) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | mean | SD | n | % | n | % | mean | SD |
| Post-Hoc AD 301/302 | CRIS | 1016 | 12.3 | 12.2 | 450 | 44.3 | 617 | 60.7 | NR | NR |
| | Vehicle cream | 506 | 12.1 | 11.7 | 225 | 44.5 | 306 | 60.5 | NR | NR |
| AD 303 | 2-11 years | 308 | 6.1 | 2.8 | 131 | 42.5 | 189 | 61.4 | NR | NR |
| | 12-17 years | 146 | 14 | 1.5 | 61 | 41.8 | 94 | 64.4 | NR | NR |
| | >18 years | 63 | 34 | 13.4 | 19 | 30.2 | 32 | 50.8 | NR | NR |
| | Total | 517 | 11.7 | 10.4 | 211 | 40.8 | 315 | 60.9 | NR | NR |
| CrisADe CARE 1 | Non-PK | 116 | 13.7 | 6.4 | 75 | 64.7 | 71 | 61.2 | 10.4 | 6.4 |
| | PK | 21 | 12.7 | 6.6 | 13 | 61.9 | 13 | 61.9 | 9.1 | 5.5 |
| | Total | 137 | 13.6 | 6.4 | 88 | 64.2 | 84 | 61.3 | 10.2 | 6.3 |

None of these baseline characteristics were available in the ruxolitinib pooled analysis. No trials reported on weight (kg) at baseline. CRIS: crisaborole, n: number, N: total number, NR: not reported, PK: pharmacokinetic, RUX: ruxolitinib, SD: standard deviation, TAC: triamcinolone acetonide cream, %: percent.
*for these baseline data, N=250, †for these baseline data, N=500, ‡for these baseline data, N=499.

**Table G1.51. Baseline Characteristics II**[87-90,92-97,99-101,103]

| Study Name | Arms | N | Disease Severity, n (%) | | | | | | EASI score | | % BSA affected | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mild | | Moderate (3) | | Severe (4) | | mean | SD | mean | SD |
| | | | n | % | n | % | n | % | | | | |
| **Ruxolitinib Cream** | | | | | | | | | | | | |
| TRuE AD 1 | Vehicle cream | 126 | 31 | 24.6 | 95 | 75.4 | NA | NA | 7.4 | 4.3 | 9.2 | 5.1 |
| | RUX 0.75% | 252 | 61 | 24.2 | 191 | 75.8 | NA | NA | 8.2 | 4.8 | 9.9 | 5.4 |
| | RUX 1.5% | 253 | 60 | 23.7 | 193 | 76.3 | NA | NA | 7.9 | 4.6 | 9.3 | 5.2 |
| TRuE AD 2 | Vehicle cream | 124 | 33 | 26.6 | 91 | 73.4 | NA | NA | 8.2 | 5.2 | 10.1 | 5.8 |
| | RUX 0.75% | 248 | 64 | 25.8 | 184 | 74.2 | NA | NA | 8.1 | 5.0 | 10.1 | 5.3 |
| | RUX 1.5% | 246 | 63 | 25.6 | 183 | 74.4 | NA | NA | 7.8 | 4.9 | 9.9 | 5.4 |
| Subgroup analysis – Partial response | Vehicle cream | 174 | 55 | 31.6 | 119 | 68.4 | NA | NA | 7.9 | 4.9 | 9.3 | 5.3 |
| | RUX 0.75% | 213 | 83 | 39 | 130 | 61 | NA | NA | 7.8 | 5.3 | 9.9 | 5.2 |
| | RUX 1.5% | 197 | 80 | 40.6 | 117 | 59.4 | NA | NA | 7.2 | 4.7 | 9.1 | 5.1 |
| | Total | 584 | 218 | 37.3 | 366 | 62.7 | NA | NA | 7.6 | 5 | 9.5 | 5.2 |
| Subgroup analysis – BSA >10 EASI > 16 | Vehicle cream | 13 | 0 | 0 | 13 | 100 | NA | NA | 20.2 | 2.9 | 17.7 | 3.3 |
| | RUX 0.75% | 36 | 3 | 8.3 | 33 | 91.7 | NA | NA | 19.4 | 3.4 | 16.6 | 3 |
| | RUX 1.5% | 32 | 0 | 0 | 32 | 100 | NA | NA | 19.3 | 2.9 | 18 | 1.9 |
| | Total | 81 | 3 | 3.7 | 78 | 96.3 | NA | NA | 19.5 | 3.1 | 17.3 | 2.7 |
| Phase II Kim 2020 | Vehicle cream | 52 | 15 | 28.8 | 36 | 69.2 | NA | NA | 8.6 | 5.1 | 9.5 | 5 |
| | RUX 1.5% | 50 | 14 | 28 | 36 | 72 | NA | NA | 8.4 | 4.7 | 10.5 | 5.2 |
| | TAC 0.1% | 51 | 18 | 35.3 | 33 | 64.7 | NA | NA | 8.4 | 4.7 | 9.9 | 5.5 |
| | Total | 307 | 95 | 30.9 | 210 | 68.4 | NA | NA | 8.4 | 4.7 | 9.6 | 5.4 |
| **Crisaborole** | | | | | | | | | | | | |
| AD 301 | CRIS | 503 | 196 | 39 | 307 | 61 | NA | NA | NR | NR | 18.8 | Range: 5 to 95 |
| | Vehicle cream | 256 | 93 | 36.3 | 163 | 63.7 | NA | NA | NR | NR | 18.6 | Range: 5 to 90 |
| AD 302 | CRIS | 513 | 197 | 38.4 | 316 | 61.6 | NA | NA | NR | NR | 17.9 | Range: 5 to 95 |

| Study Name | Arms | N | Disease Severity, n (%) | | | | | | EASI score | | % BSA affected | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mild | | Moderate (3) | | Severe (4) | | mean | SD | mean | SD |
| | | | n | % | n | % | n | % | | | | |
| | Vehicle cream | 250 | 100 | 40 | 150 | 60 | NA | NA | NR | NR | 17.7 | Range: 5 to 90 |
| Post-Hoc AD 301/302 | CRIS | 1016 | 393 | 38.7 | 623 | 61.3 | NA | NA | NR | NR | 18.3 | 18.0 |
| | Vehicle cream | 506 | 193 | 38.1 | 313 | 61.9 | NA | NA | NR | NR | 18.1 | 17.3 |
| CrisADe CARE 1 | Non-PK | 116 | 52 | 44.8 | 64 | 55.2 | 0 | 0 | 10.4 | 8.2 | 23.5 | 20.1 |
| | PK | 21 | 0 | 0 | 20 | 95.2 | 1 | 4.8 | 19.8 | 4.4 | 53.5 | 12.6 |
| | Total | 137 | 52 | 38 | 84 | 61.3 | 1 | 0.7 | 11.8 | 8.4 | 28.1 | 22 |

None of these baseline characteristics were available in the ruxolitinib pooled analysis, Simpson 2021, and AD 303. BSA: body surface area, CRIS: crisaborole, n: number, N: total number, NA: not applicable, NR: not reported, PK: pharmacokinetic, RUX: ruxolitinib, SD: standard deviation, TAC: triamcinolone acetonide cream, %: percent. *for these baseline data, N=250, †for these baseline data, N=500, ‡for these baseline data, N=499.

**Table G1.52. Baseline Characteristics III**[87-97,99-101,103]

| Study Name | Arms | N | Itch or PP-NRS | | DLQI | | POEM | | CDLQI | | Previous Treatments | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | mean | SD | mean | SD | mean | SD | mean | SD | Topical corticosteroids | | Topical calcineurin inhibitors | | Systemic steroids | |
| | | | | | | | | | | | n | % | n | % | n | % |
| **Ruxolitinib Cream** | | | | | | | | | | | | | | | | |
| **Week 8** | | | | | | | | | | | | | | | | |
| TRuE AD 1 | Vehicle cream | 126 | 5.1 | 2.5 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | RUX 0.75% | 252 | 5.1 | 2.3 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | RUX 1.5% | 253 | 5.2 | 2.5 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| TRuE AD 2 | Vehicle cream | 124 | 5.1 | 2.4 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | RUX 0.75% | 248 | 5.2 | 2.5 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | RUX 1.5% | 246 | 4.9 | 2.5 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Simpson 2021 | RUX pooled | 1249 | 5.1 | 2.4 | NR | NR | NR | NR | NR | NR | 408* | 32.7 | 269 | 21.5 | 218.6 | 17.5 |

| Study Name | Arms | N | Itch or PP-NRS | | DLQI | | POEM | | CDLQI | | Previous Treatments | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | mean | SD | mean | SD | mean | SD | mean | SD | Topical corticosteroids | | Topical calcineurin inhibitors | | Systemic steroids | |
| | | | | | | | | | | | n | % | n | % | n | % |
| **Weeks 4/8/12** | | | | | | | | | | | | | | | | |
| Phase II Kim 2020 | Vehicle cream | 52 | 6 | 2.1 | NR | NR | NR | NR | NA | NA | NR | NR | NR | NR | NR | NR |
| | RUX 1.5% | 50 | 5.9 | 2.3 | NR | NR | NR | NR | NA | NA | NR | NR | NR | NR | NR | NR |
| | TAC 0.1% | 51 | 5.2 | 2.2 | NR | NR | NR | NR | NA | NA | NR | NR | NR | NR | NR | NR |
| | Total | 307 | 6 | 2.1 | NR | NR | NR | NR | NA | NA | NR | NR | NR | NR | NR | NR |
| **Crisaborole** | | | | | | | | | | | | | | | | |
| **Week 4/Day 29** | | | | | | | | | | | | | | | | |
| Post-Hoc AD 301/302 | CRIS | 1016 | NR | NR | 9.7[†¥] | 6.3 | NR | NR | 9.3[‡§] | 6.0 | NR | NR | NR | NR | NR | NR |
| | Vehicle cream | 506 | NR | NR | 9.3[†#] | 6.6 | NR | NR | 9[‡**] | 6.0 | NR | NR | NR | NR | NR | NR |
| CrisADe CARE 1 | Non-PK | 116 | NR | NR | NR | NR | 13.9 | 5.9 | NR | NR | 63 | 54.3 | 2 | 1.7 | NR | NR |
| | PK | 21 | NR | NR | NR | NR | 19.7 | 5.2 | NR | NR | 9 | 49.2 | 0 | 0 | NR | NR |
| | Total | 137 | NR | NR | NR | NR | 14.8 | 6.1 | NR | NR | 72 | 52.6 | 2 | 1.5 | NR | NR |

None of these baseline characteristics were available in the ruxolitinib pooled analysis, AD 301, AD 302, and AD303. No trials reported on previous treatment use with antibiotics, crisaborole, topical agents alone, mycophenolate, cyclosporine, methotrexate, azathioprine, systemic agents, or dupilumab. Baseline data on SCORAD, PSSAD, total HADS, HADS anxiety, and HADS depression were not reported in any trials. CRIS: crisaborole, n: number, N: total number, NR: not reported, PK: pharmacokinetic, RUX: ruxolitinib, SD: standard deviation, TAC: triamcinolone acetonide cream, %: percent. *high potency topical corticosteroids, [†]population reported here is adolescents and adults ages ≥16 years, [‡]population reported here is children ages 2-15 years, [¥]N=201, [#]N=94, [§]N=815, **N=412, [††]for these baseline data, N=250, [‡‡]for these baseline data, N=500, [¥¥]for these baseline data, N=499.

**Table G1.53. Efficacy Outcomes: IGA Response Rates**[87-98]

| Study Name | Arm | N | IGA response | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | n | % | Diff from PBO | 95% CI | p value |
| **Ruxolitinib Cream** | | | | | | | | |
| **Week 8** | | | | | | | | |
| TRuE AD 1 | Vehicle cream | 126 | 126 | 20 | 15.1 | REF | REF | REF |
| | RUX 0.75% | 252 | 252 | 126 | 50.0 | 34.9 | 26.1 to 43.7 | <0.0001 |
| | RUX 1.5% | 253 | 253 | 137 | 53.8 | 38.7 | 29.9 to 47.4 | <0.0001 |
| TRuE AD 2 | Vehicle cream | 124 | 124 | 10 | 7.6 | REF | REF | REF |
| | RUX 0.75% | 248 | 248 | 97 | 39.0 | 31.3 | 23.4 to 39.2 | <0.0001 |
| | RUX 1.5% | 246 | 246 | 127 | 51.3 | 43.7 | 35.6 to 51.8 | <0.0001 |
| Subgroup analysis – partial response | Vehicle cream | 174 | 174 | 75 | 43.1 | NR | NR | REF |
| | RUX 0.75% | 213 | 213 | 153 | 71.8 | NR | NR | <0.0001 |
| | RUX 1.5% | 197 | 197 | 140 | 71.1 | NR | NR | <0.0001 |
| Subgroup analysis – BSA > 10, EASI > 16 | Vehicle cream | 13 | 13 | 0 | 0 | NR | NR | NR |
| | RUX 0.75% | 36 | 36 | 18 | 50 | NR | NR | NR |
| | RUX 1.5% | 32 | 32 | 19 | 59.4 | NR | NR | NR |
| **Week 4** | | | | | | | | |
| Phase II Kim 2020 | Vehicle cream | 52 | 52 | 4 | 7.7 | NR | NR | REF |
| | TAC 0.1% BID | 51 | 51 | 13 | 25.5 | NR | NR | NS |
| | RUX 1.5% BID | 50 | 50 | 20 | 38 | NR | NR | <0.001 |
| | **Week 8** | | | | | | | |
| | Vehicle cream | 52 | 52 | 5 | 9.6 | NR | NR | REF |
| | TAC 0.1% BID | 40 | 40 | 8 | 20 | NR | NR | NR |
| | RUX 1.5% BID | 50 | 50 | 24 | 48 | NR | NR | <0.0001 |
| | **Week 12** | | | | | | | |
| | Vehicle cream | 52 | 36 | 19 | 52.8 | NR | NR | NR |
| | TAC 0.1% BID | 39 | 39 | 26 | 66.7 | NR | NR | NR |
| | RUX 1.5% BID | 50 | 41 | 24 | 58.5 | NR | NR | NR |
| **Crisaborole** | | | | | | | | |

| Study Name | Arm | N | IGA response | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | n | % | Diff from PBO | 95% CI | p value |
| **Week 4/Day 29** | | | | | | | | |
| AD 301 | CRIS | 503 | 503 | 260 | 51.7 | NR | NR | 0.005 |
| | Vehicle cream | 256 | 256 | 104 | 40.6 | NR | NR | REF |
| AD 302 | CRIS | 513 | 513 | 249 | 48.5 | NR | NR | <0.001 |
| | Vehicle cream | 250 | 250 | 74 | 29.7 | NR | NR | REF |
| CrisADe CARE 1 | Overall population | 137 | 129 | 61 | 47.3 | NR | NR | NR |

Data on IGA were not available in the Post-Hoc Analysis for AD 301/302. BID: twice daily, CI: confidence interval, CRIS: crisaborole, Diff: difference, n: number, N: total number, NR: not reported, NS: not significant, PBO: placebo, REF: reference, RUX: ruxolitinib cream, SE: standard error, TAC: triamcinolone acetonide cream, %: percent.

### Table G1.54. Long term Efficacy Outcomes: IGA Response Rates[74,75]

| Study Name | Arm | N | IGA response | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | n | % | Diff from PBO | 95% CI | p value |
| **Ruxolitinib Cream** | | | | | | | | |
| **Week 52** | | | | | | | | |
| TRuE AD 1 | Vehicle cream to 0.75% RUX | NR | 38 | 29 | 76.3 | NR | NR | NR |
| | Vehicle cream to 1.5% RUX | NR | 38 | 28 | 73.7 | NR | NR | NR |
| | RUX 0.75% | NR | 173 | 133 | 76.9 | NR | NR | NR |
| | RUX 1.5% | NR | 171 | 129 | 75.4 | NR | NR | NR |
| TRuE AD 2 | Vehicle cream to 0.75% RUX | NR | 34 | 27 | 79.4 | NR | NR | NR |
| | Vehicle cream to 1.5% RUX | NR | 43 | 32 | 74.4 | NR | NR | NR |
| | RUX 0.75% | NR | 150 | 115 | 76.7 | NR | NR | NR |
| | RUX 1.5% | NR | 171 | 137 | 80.1 | NR | NR | NR |
| Subgroup Analysis—more severe | RUX 0.75% | 39 | 30 | 20 | 66.7 | NR | NR | NR |
| | RUX 1.5% | 36 | 23 | 18 | 78.3 | NR | NR | NR |

There were no long-term data on IGA available in any of the crisaborole trials. CI: confidence interval, Diff: difference, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, RUX: ruxolitinib cream, %: percent.

**Table G1.55. Efficacy Outcomes: EASI Response Rates**[87-91,98,99,101,103]

| Study Name | Arms | EASI 50 | | EASI 75 | | | | | EASI 90 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | n/N | % | n/N | % | Diff from PBO | 95% CI | p value | n/N | % |
| **Ruxolitinib Cream** | | | | | | | | | | |
| **Week 8** | | | | | | | | | | |
| TRuE AD 1 | Vehicle cream | NR | NR | 31/126 | 24.6 | REF | REF | REF | 12/126 | 9.5 |
| | RUX 0.75% | NR | NR | 142/252 | 56.0 | 31.4 | 21.7 to 41.1 | <0.0001 | 96/252 | 38.1 |
| | RUX 1.5% | NR | NR | 158/253 | 62.1 | 37.5 | 27.8 to 47.1 | <0.0001 | 112/253 | 44.3 |
| TRuE AD 2 | Vehicle cream | NR | NR | 18/124 | 14.4 | REF | REF | REF | 5/118 | 4.2 |
| | RUX 0.75% | NR | NR | 128/248 | 51.5 | 37.1 | 28.1 to 46.2 | <0.0001 | 81/231 | 35.1 |
| | RUX 1.5% | NR | NR | 153/246 | 61.8 | 47.4 | 38.5 to 56.4 | <0.0001 | 99/228 | 43.4 |
| Subgroup analysis – partial response | Vehicle cream | 67/174 | 38.5 | NR | NR | NR | NR | NR | NR | NR |
| | RUX 0.75% | 136/213 | 63.8 | NR | NR | NR | NR | NR | NR | NR |
| | RUX 1.5% | 128/197 | 65 | NR | NR | NR | NR | NR | NR | NR |
| Subgroup analysis – BSA > 10, EASI > 16 | Vehicle cream | 5/13 | 38.5 | 1/13 | 7.7 | NR | NR | NR | 1/13 | 7.7 |
| | RUX 0.75% | 29/36 | 80.6 | 27/36 | 75 | NR | NR | NR | 19/36 | 52.8 |
| | RUX 1.5% | 25/32 | 78.1 | 23/32 | 71.9 | NR | NR | NR | 15/32 | 46.9 |
| Phase II Kim 2020 | **Week 4** | | | | | | | | | |
| | Vehicle cream | 41/52 | 78 | 9/52 | 17.3 | NR | NR | REF | 3/52 | 5.8 |
| | TRI 0.1% BID | 34/51 | 66.7 | 24/51 | 47.1 | NR | NR | NR | 7/51 | 13.7 |
| | RUX 1.5% BID | 12/50 | 23.1 | 28/50 | 56 | 48.6 | NR | <0.001 | 13/50 | 26 |
| | **Week 12** | | | | | | | | | |
| | Vehicle cream | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | TRI 0.1% BID | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | RUX 1.5% BID | 37/39 | 95.1 | 22/30 | 73.2 | NR | NR | NR | 14/50 | 56.1 |

Data on EASI 50 and EASI 90 were not available in Phase II Kim 2020 at 8 weeks and crisaborole trials AD 301, AD 302, Post-Hoc AD 301/302, and CrisADe CARE 1. There were no Difference vs. placebo, 95% confidence intervals, or p-values available for EASI 50 and EASI 75 responses. BID: twice daily, CI: confidence

interval, CRIS: crisaborole, n: number, Diff: difference, N: total number, NR: not reported, NS: not significant, PBO: placebo, REF: reference, RUX: ruxolitinib, SE: standard error, TAC: Triamcinolone acetonide cream, %: percent.

**Table G1.56. Efficacy Outcomes: PP-NRS Response Rates**[87-90,98,101,103]

| Study Name | Arms | N | Itch or PP-NRS (≥4-point improvement from baseline) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n/N | % | SD | Diff from PBO | 95% CI | p value |
| **Ruxolitinib Cream** | | | | | | | | |
| **Week 8** | | | | | | | | |
| TRuE AD 1 | Vehicle cream | 126 | 20/126 | 15.4 | SE: 4.1 | REF | REF | REF |
| | RUX 0.75% | 252 | 102/252 | 40.4 | SE: 3.9 | 25 | 13.9 to 36.1 | <0.001 |
| | RUX 1.5% | 253 | 133/253 | 52.2 | SE: 3.9 | 36.8 | 25.7 to 47.9 | <0.0001 |
| TRuE AD 2 | Vehicle cream | 124 | 21/124 | 16.3 | SE: 4.1 | REF | REF | REF |
| | RUX 0.75% | 248 | 106/248 | 42.7 | SE: 4.0 | 26.4 | 15.2 to 37.6 | <0.0001 |
| | RUX 1.5% | 246 | 125/246 | 50.7 | SE: 4.1 | 34.4 | 23.0 to 45.9 | <0.0001 |
| Subgroup analysis – BSA > 10, EASI > 16 | Vehicle cream | 13 | 3/11 | 27.3 | NR | NR | NR | NR |
| | RUX 0.75% | 36 | 13/26 | 50 | NR | NR | NR | NR |
| | RUX 1.5% | 32 | 11/16 | 61.1 | NR | NR | NR | NR |
| Phase II Kim 2020 | **Week 4** | | | | | | | |
| | Vehicle cream | 52 | 4/36 | 11.1* | NR | NR | NR | REF |
| | TAC 0.1% BID | 51 | 6/31 | 19.4* | NR | NR | NR | NS |
| | RUX 1.5% BID | 50 | 25/40 | 62.5* | NR | NR | NR | <0.001 |
| | **Week 8** | | | | | | | |
| | Vehicle cream | 52 | 5/35 | 14.3* | NR | NR | NR | REF |
| | TAC 0.1% BID | 40 | 10/31 | 32.3* | NR | NR | NR | NS |
| | RUX 1.5% BID | 50 | 22/38 | 57.9* | NR | NR | NR | <0.001 |

Data on PP-NRS were not available in the subgroup analysis on partial responders, Phase II Kim 2020 at 12 weeks and crisaborole trials AD 301, AD 302, Post-Hoc AD 301/302. BID: twice daily, CI: confidence interval, Diff: difference, n: number, N: total number, NR: not reported, NS: not significant, PBO: placebo, REF: reference, RUX: ruxolitinib, SD: standard deviation, SE: standard error, TAC: Triamcinolone acetonide cream, %: percent. *marked as clinically relevant improvements

**Table G1.57. SCORAD**[89,90]

| Agent(s) | | Ruxolitinib Cream | | |
|---|---|---|---|---|
| Timepoint | | Week 8 | | |
| Study Name | | Pooled Analysis | | |
| Arms | | Vehicle cream | RUX 0.75% | RUX 1.5% |
| SCORAD | N | 244 | 483 | 481 |
| | Change from baseline | -30.4 | -62.9 | -67.3 |
| | SD | NR | NR | NR |
| | Diff from PBO | NR | NR | NR |
| | 95% CI | NR | NR | NR |
| | p value | REF | <0.0001 | <0.0001 |

Data on SCORAD were available only in the ruxolitinib pooled analysis. CI: confidence interval, Diff: difference, N: total number, NR: not reported, PBO: placebo, REF: reference, RUX: ruxolitinib, SD: standard deviation.

**Table G1.58. DLQI, CLDQI, POEM**[92,93,95,97,99]

| Agent(s) | | Ruxolitinib Cream | | | Crisaborole | | |
|---|---|---|---|---|---|---|---|
| Timepoint | | Week 8 | | | Week 4/Day 29 | | |
| Study Name | | Pooled Analysis | | | Post-Hoc AD 301/302 | | CrisADe CARE 1 |
| Arms | | Vehicle cream | RUX 0.75% | RUX 1.5% | CRIS | Vehicle cream | Overall |
| DLQI | N | 169 | 355 | 386 | 180 | 82 | 137 |
| | Change from baseline | -3.1 | -7.2 | -7.1 | -5.2 | -3.5 | NR |
| | SD | NR | NR | NR | NR | NR | NR |
| | p value | REF | <0.001 | <0.001 | 0.015 | REF | NR |
| CDLQI | N | 27 | 66 | 53 | 750* | 355* | NR |
| | Change from baseline | -2.3 | -5.3 | -6 | -4.6 | -3 | NR |
| | SD | NR | NR | NR | NR | NR | NR |
| | p value | NR | NR | NR | <0.001 | REF | NR |
| POEM | N | 197 | 422 | 438 | NR | NR | 130 |
| | Change from baseline | -4.2 | -10.5 | -11 | NR | NR | -8.5 |
| | SD | NR | NR | NR | NR | NR | 0.51 |
| | p value | REF | <0.001 | <0.001 | NR | NR | NR |

Data on DLQI, CDLQI, and POEM were available on in Post-Hoc AD 301/302 and CrisADe CARE 1. No trials reported on HADS, HADS Anxiety or HADS Depression. CRIS: crisaborole, N: total number, NR: not reported, REF: reference, SD: standard deviation. *population reported here is children ages 2-15.

**Table G1.59. Safety**[86-97,99,103]

| Trial | Arms | N | TEAE | | Study Drug-Related AEs | | D/C due to AE | | Serious TEAE | | Application Site Pain | | Application Site Burning | | Application Site Pruritus | | Skin Infection | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| TRuE AD 1 | **Week 8** | | | | | | | | | | | | | | | | | |
| | Vehicle cream | 126 | 44 | 34.9 | 16* | 12.7 | 5† | 4 | 2 | 1.6 | NR | NR | 2 | 1.6 | 2 | 1.6 | NR | NR |
| | RUX 0.75% | 252 | 74 | 29.4 | 15* | 6.0 | 3† | 1.2 | 1 | 0.4 | NR | NR | 0 | 0 | 2 | 0.8 | NR | NR |
| | RUX 1.5% | 253 | 73 | 28.9 | 14* | 5.5 | 3† | 1.2 | 2 | 0.8 | NR | NR | 2 | 0.8 | 0 | 0 | NR | NR |
| TRuE AD 2 | Vehicle cream | 124 | 40 | 32.3 | 12* | 9.7 | 3† | 2.4 | 0 | 0 | NR | NR | 8 | 6.5 | 4 | 3.2 | NR | NR |
| | RUX 0.75% | 248 | 73 | 29.4 | 8* | 3.2 | 1† | 0.4 | 3 | 1.2 | NR | NR | 2 | 0.8 | 2 | 0.8 | NR | NR |
| | RUX 1.5% | 246 | 58 | 23.6 | 11* | 4.5 | 0† | 0 | 1 | 0.4 | NR | NR | 2 | 0.8 | 0 | 0 | NR | NR |
| Subgroup – BSA > 10, EASI > 16 | Vehicle cream | 13 | 6 | 46.2 | 5 | 38.5 | 1† | 7.7 | 1 | 7.7 | 2 | 15.4 | NR | NR | NR | NR | NR | NR |
| | RUX 0.75% | 36 | 14 | 38.9 | 1 | 2.8 | 0† | 0 | 0 | 0 | 0 | 0 | NR | NR | NR | NR | NR | NR |
| | RUX 1.5% | 32 | 10 | 31.3 | 3 | 9.4 | 0† | 0 | 0 | 0 | 0 | 0 | NR | NR | NR | NR | NR | NR |
| Phase II Kim 2020 | Vehicle cream | 52 | 17 | 32.7 | 5* | 9.6 | 1† | 1.9 | 0 | 0 | 2 | 3.8 | NR | NR | NR | NR | NR | NR |
| | TAC 0.1% | 51 | 17 | 33.3 | 1* | 2 | 1† | 2 | 1 | 2 | 0 | 0 | NR | NR | NR | NR | NR | NR |
| | RUX 1.5% | 50 | 12 | 24 | 3* | 6 | 0† | 0 | 0 | 0 | 1 | 2 | NR | NR | NR | NR | NR | NR |
| | **Week 12** | | | | | | | | | | | | | | | | | |
| | Vehicle cream | 41 | 5 | 12.2 | 0* | 0 | 0† | 0 | 0 | 0 | NR | NR | NR | NR | NR | NR | NR | NR |
| | TAC 0.1% | 40 | 11 | 227.5 | 0* | 0 | 0† | 0 | 0 | 0 | NR | NR | NR | NR | NR | NR | NR | NR |
| | RUX 1.5% | 43 | 17 | 39.5 | 0* | 0 | 0† | 0 | 0 | 0 | NR | NR | NR | NR | NR | NR | NR | NR |
| Pooled AD 301/302 | **Week 4** | | | | | | | | | | | | | | | | | |
| | CRIS | 1012 | 954 | 94.3 | 217 | 21.4 | 12 | 1.2 | NR | NR | 45 | 4.4 | NR | NR | 5 | 0.5 | 1‡ | 0.1 |
| | Vehicle | 499 | 484 | 96.9 | 79 | 15.8 | 6 | 1.2 | NR | NR | 6 | 1.2 | NR | NR | 6 | 1.2 | 5‡ | 1 |
| AD 303 | **Week 48** | | | | | | | | | | | | | | | | | |

| Trial | Arms | N | TEAE | | Study Drug-Related AEs | | D/C due to AE | | Serious TEAE | | Application Site Pain | | Application Site Burning | | Application Site Pruritus | | Skin Infection | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| | 2-11 | 308 | NR | NR | 53 | 10.3 | 9 | 1.7 | NR | NR | 6 | 1.9 | NR | NR | 1 | 0.3[¶] | 12[¥] | 3.9 |
| | 12-17 | 146 | | | | | | | NR | NR | 5 | 3.4 | NR | NR | 0 | 0[¶] | 3[¥] | 2.1 |
| | >18 | 63 | | | | | | | NR | NR | 1 | 1.6 | NR | NR | 1 | 1.6[¶] | 0[¥] | 0 |
| | Total | 517 | | | | | | | NR | NR | 12 | 2.3 | NR | NR | 2 | 0.4[¶] | 15 | 2.9 |
| CrisADe CARE 1 | **Week 8** | | | | | | | | | | | | | | | | | |
| | Overall | 137 | 88 | 64.2 | 22 | 16.1 | 4 | 2.9 | NR | NR | 5 | 3.6 | 4[#] | 2.9 | NR | NR | 1[§] | 0.7 |

None of these safety data were available in the ruxolitinib pooled analysis and Simpson 2021. No trials reported on safety data related to any AEs, Serious AE, MACE, venous thromboembolism, herpes infection, serious infection, malignancy, non-melanocytic skin cancer. AD301/302 and 303 reported no deaths across all arms. Only CrisADe CARE 1 reported conjunctivitis (3.6%). AE: adverse event, CRIS: crisaborole, D/C: discontinuation, n: number, N: total number, NR: not reported, RUX: ruxolitinib cream, TAC: Triamcinolone acetonide cream, TEAE: treatment-emergent adverse event, %: percent. *study drug-related TEAE, [†]discontinuation due to TEAE, [‡]staphylococcal skin infection, [¶]application site dermatitis, [¥]infections and infestations, [#]discomfort, [§]skin irritation.

**Table G1.60. Long Term Safety**[74,75]

| Trial | Arms | N | TEAE | | Study Drug-Related AEs | | D/C due to AE | | Serious TEAE | | Application Site Pain | | Application Site Burning | | Application Site Pruritus | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| **Week 52** | | | | | | | | | | | | | | | | |
| TRuE AD 1 | Vehicle cream to 0.75% RUX | 101 | 54 | 53.5 | 2 | 2 | 0 | 0 | 5 | 5 | NR | NR | 101 | 54 | 53.5 | 2 |
| | Vehicle cream to 1.5% RUX | 99 | 57 | 57.6 | 6 | 6.1 | 0 | 0 | 1 | 1 | NR | NR | 99 | 57 | 57.6 | 6 |
| | RUX 0.75% | 426 | 256 | 60.1 | 20 | 4.7 | 9 | 2.1 | 10 | 2.3 | NR | NR | 426 | 256 | 60.1 | 20 |
| | RUX 1.5% | 446 | 240 | 53.8 | 13 | 2.9 | 0 | 0 | 6 | 1.3 | NR | NR | 446 | 240 | 53.8 | 13 |
| TRuE AD 2 | Vehicle cream to 0.75% RUX | 39 | 28 | 71.8 | 6 | 15.4 | 0 | 0 | 1 | 2.6 | 1 | 2.6 | 39 | 28 | 71.8 | 6 |
| | Vehicle cream to 1.5% RUX | 36 | 24 | 66.7 | 6 | 16.7 | 0 | 0 | 1 | 2.8 | 2 | 5.6 | 36 | 24 | 66.7 | 6 |
| | RUX 0.75% | 101 | 54 | 53.5 | 2 | 2 | 0 | 0 | 5 | 5 | NR | NR | 101 | 54 | 53.5 | 2 |
| | RUX 1.5% | 99 | 57 | 57.6 | 6 | 6.1 | 0 | 0 | 1 | 1 | NR | NR | 99 | 57 | 57.6 | 6 |
| | RUX 0.75% | 426 | 256 | 60.1 | 20 | 4.7 | 9 | 2.1 | 10 | 2.3 | NR | NR | 426 | 256 | 60.1 | 20 |
| Subgroup Analysis—more severe | RUX 0.75% | 446 | 240 | 53.8 | 13 | 2.9 | 0 | 0 | 6 | 1.3 | NR | NR | 446 | 240 | 53.8 | 13 |
| | RUX 1.5% | 39 | 28 | 71.8 | 6 | 15.4 | 0 | 0 | 1 | 2.6 | 1 | 2.6 | 39 | 28 | 71.8 | 6 |

No trials reported on safety data related to any AEs, Serious AE, MACE, venous thromboembolism, herpes infection, serious infection, malignancy, non-melanocytic skin cancer. D/C: discontinuation, n: number, N: total number, NR: not reported, RUX: ruxolitinib cream, TEAE: treatment-emergent adverse event, %: percent

**Table G1.61. Efficacy Outcomes by Subgroup: IGA**[102,104]

| Study | Arm | Category | N | IGA response | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | N | % | Diff from PBO | 95% CI | p value |
| **Ruxolitinib** | | | | | | | | | |
| Pooled Analysis | Vehicle cream | Ages 12 to 17 | 250 | 6 | 43 | 14 | NR | NR | NR |
| | RUX 0.75% | | 500 | 50 | 106 | 47.2 | NR | NR | NR |
| | RUX 1.5% | | 499 | 44 | 87 | 50.6 | NR | NR | NR |
| | Vehicle cream | Ages 18 to 64 | 250 | 18 | 175 | 10.3 | NR | NR | NR |
| | RUX 0.75% | | 500 | 150 | 327 | 45.9 | NR | NR | NR |
| | RUX 1.5% | | 499 | 186 | 356 | 52.2 | NR | NR | NR |
| | Vehicle cream | >65 | 250 | 4 | 26 | 15.4 | NR | NR | NR |
| | RUX 0.75% | | 500 | 16 | 50 | 32 | NR | NR | NR |
| | RUX 1.5% | | 499 | 23 | 38 | 60.5 | NR | NR | NR |
| | Vehicle cream | IGA 2 | 250 | 1 | 64 | 1.6 | NR | NR | NR |
| | RUX 0.75% | | 500 | 24 | 125 | 19.2 | NR | NR | NR |
| | RUX 1.5% | | 499 | 31 | 123 | 25.2 | NR | NR | NR |
| | Vehicle cream | IGA 3 | 250 | 27 | 180 | 15 | NR | NR | NR |
| | RUX 0.75% | | 500 | 192 | 358 | 53.6 | NR | NR | NR |
| | RUX 1.5% | | 499 | 222 | 358 | 62 | NR | NR | NR |
| **Crisaborole** | | | | | | | | | |
| Yosipovitch 2018 | CRIS | Mild | 1016 | NR | NR | 71.4 | NR | NR | 0.0024 |
| | | Moderate | | NR | NR | 36.7 | NR | NR | <0.001 |
| | Vehicle cream | Mild | 506 | NR | NR | 56.7 | NR | REF | NR |
| | | Moderate | | NR | NR | 22.3 | NR | REF | NR |
| | CRIS | 2 to <7 | 506 | NR | NR | 30.5 | NR | NR | 0.064 |
| | | 7 to <12 | 436 | NR | NR | 36.6 | NR | NR | 0.0037 |
| | | 12 to <18 | 371 | NR | NR | 30.3 | NR | NR | 0.026 |
| | | 18+ | 209 | NR | NR | 29.7 | NR | NR | 0.46 |
| | Vehicle cream | 2 to <7 | 506 | NR | NR | 21.8 | NR | NR | REF |
| | | 2 to <12 | 436 | NR | NR | 22.9 | NR | NR | REF |
| | | 12 to <18 | 371 | NR | NR | 19.4 | NR | NR | REF |
| | | 18+ | 209 | NR | NR | 24.7 | NR | NR | REF |
| Eichenfield 2020 (ages 2-17) | CRIS | Mild | 874 | NR | NR | 72.3 | NR | NR | <0.05 |
| | | Moderate | | NR | NR | 37.1 | NR | NR | REF |
| | Vehicle cream | Mild | 439 | NR | NR | 55.9 | NR | NR | <0.0001 |
| | | Moderate | | NR | NR | 21.4 | NR | NR | REF |

CI: confidence interval, CRIS: crisaborole, Diff: difference, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, RUX: ruxolitinib, %: percent.

**Table G1.62. Efficacy Outcomes by Subgroup: EASI 50**[102,104]

| Study | Arm | Category | N | EASI 50 | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | N | % | Diff from PBO | 95% CI | p value |
| **Ruxolitinib** | | | | | | | | | |
| Pooled Analysis | Vehicle cream | Ages 12 to 17 | 250 | 21 | 43 | 48.8 | NR | NR | NR |
| | RUX 0.75% | | 500 | 79 | 106 | 74.5 | NR | NR | NR |
| | RUX 1.5% | | 499 | 73 | 87 | 83.9 | NR | NR | NR |
| | Vehicle cream | Ages 18 to 64 | 250 | 64 | 175 | 36.6 | NR | NR | NR |
| | RUX 0.75% | | 500 | 239 | 327 | 73.1 | NR | NR | NR |
| | RUX 1.5% | | 499 | 274 | 356 | 77 | NR | NR | NR |
| | Vehicle cream | >65 | 250 | 10 | 26 | 38.5 | NR | NR | NR |
| | RUX 0.75% | | 500 | 32 | 50 | 64 | NR | NR | NR |
| | RUX 1.5% | | 499 | 32 | 38 | 84.2 | NR | NR | NR |
| | Vehicle cream | IGA 2 | 250 | 27 | 64 | 42.2 | NR | NR | NR |
| | RUX 0.75% | | 500 | 81 | 125 | 64.8 | NR | NR | NR |
| | RUX 1.5% | | 499 | 88 | 123 | 71.5 | NR | NR | NR |
| | Vehicle cream | IGA 3 | 250 | 68 | 180 | 37.8 | NR | NR | NR |
| | RUX 0.75% | | 500 | 269 | 358 | 75.1 | NR | NR | NR |
| | RUX 1.5% | | 499 | 291 | 358 | 81.3 | NR | NR | NR |

Subgroup data on this outcome were not available in any of the crisaborole trials. CI: confidence interval, Diff: difference, n: number, N: total number, NR: not reported, PBO: placebo, RUX: ruxolitinib, %: percent.

**Table G1.63. Efficacy Outcomes by Subgroup: EASI 75 and EASI 90**[102,104]

| Study name | Arm | Category | N | EASI 75 | | | | EASI 90 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | N | % | p value | n | N | % | p value |
| **Ruxolitinib** | | | | | | | | | | | |
| Pooled Analysis | Vehicle cream | Ages 12 to 17 | 250 | 15 | 43 | 34.9 | NR | 3 | 43 | 7 | NR |
| | RUX 0.75% | | 500 | 58 | 106 | 54.7 | NR | 44 | 106 | 41.5 | NR |
| | RUX 1.5% | | 499 | 53 | 87 | 60.9 | NR | 34 | 87 | 39.1 | NR |
| | Vehicle cream | Ages 18 to 64 | 250 | 29 | 175 | 16.6 | NR | 13 | 175 | 7.4 | NR |
| | RUX 0.75% | | 500 | 180 | 327 | 55 | NR | 120 | 327 | 36.7 | NR |
| | RUX 1.5% | | 499 | 217 | 356 | 61 | NR | 158 | 356 | 44.4 | NR |
| | Vehicle cream | >65 | 250 | 4 | 26 | 15.4 | NR | 1 | 26 | 3.8 | NR |
| | RUX 0.75% | | 500 | 22 | 50 | 44 | NR | 13 | 50 | 26 | NR |
| | RUX 1.5% | | 499 | 28 | 38 | 73.7 | NR | 19 | 38 | 50 | NR |
| | Vehicle cream | IGA 2 | 250 | 11 | 64 | 17.2 | NR | 7 | 64 | 10.9 | NR |
| | RUX 0.75% | | 500 | 57 | 125 | 45.6 | NR | 36 | 125 | 28.8 | NR |
| | RUX 1.5% | | 499 | 61 | 123 | 49.6 | NR | 41 | 123 | 33.3 | NR |
| | Vehicle cream | IGA 3 | 250 | 37 | 180 | 20.6 | NR | 10 | 180 | 5.6 | NR |
| | RUX 0.75% | | 500 | 203 | 358 | 56.7 | NR | 141 | 358 | 39.4 | NR |
| | RUX 1.5% | | 499 | 237 | 358 | 66.2 | NR | 170 | 358 | 47.5 | NR |

Subgroup data on these outcomes were not available in any of the crisaborole trials. There were no Difference vs. placebo or 95% confidence intervals available for EASI 75 or EASI 90. n: number, N: total number, NR: not reported, RUX: ruxolitinib, %: percent.

**Table G1.64. Efficacy Outcomes by Subgroup: PP-NRS ≥4**[102,104]

| Study | Arm | Category | N | Itch or PP-NRS (≥4-point improvement from baseline) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | N | % | Change from baseline | SD | p value |
| **Ruxolitinib** | | | | | | | | | |
| Pooled Analysis | Vehicle cream | Ages 12 to 17 | 250 | 4 | 23 | 17.4 | NR | NR | NR |
| | RUX 0.75% | | 500 | 24 | 58 | 41.4 | NR | NR | NR |
| | RUX 1.5% | | 499 | 25 | 48 | 52.1 | NR | NR | NR |
| | Vehicle cream | Ages 18 to 64 | 250 | 18 | 118 | 15.3 | NR | NR | NR |
| | RUX 0.75% | | 500 | 93 | 219 | 42.5 | NR | NR | NR |
| | RUX 1.5% | | 499 | 119 | 233 | 51.1 | NR | NR | NR |
| | Vehicle cream | >65 | 250 | 3 | 17 | 17.6 | NR | NR | NR |
| | RUX 0.75% | | 500 | 13 | 36 | 36.1 | NR | NR | NR |
| | RUX 1.5% | | 499 | 14 | 26 | 53.8 | NR | NR | NR |
| | Vehicle cream | IGA 2 | 250 | 4 | 38 | 10.5 | NR | NR | NR |
| | RUX 0.75% | | 500 | 17 | 70 | 24.3 | NR | NR | NR |
| | RUX 1.5% | | 499 | 32 | 75 | 42.7 | NR | NR | NR |
| | Vehicle cream | IGA 3 | 250 | 21 | 120 | 17.5 | NR | NR | NR |
| | RUX 0.75% | | 500 | 113 | 243 | 46.5 | NR | NR | NR |
| | RUX 1.5% | | 499 | 126 | 232 | 54.3 | NR | NR | NR |
| **Crisaborole** | | | | | | | | | |
| Yosipovitch 2018 | CRIS | Mild | 1016 | NR | 209 | 70.2 | NR | NR | 0.05 |
| | | Moderate | | NR | 385 | 53.8 | NR | NR | 0.01 |
| | Vehicle cream | Mild | 506 | NR | 105 | 58.1 | NR | NR | REF |
| | | Moderate | | NR | 188 | 39.1 | NR | NR | REF |

CRIS: crisaborole, n: number, N: total number, NR: not reported, RUX: ruxolitinib, SD: standard deviation, %: percent.

# References


1. Sherry H Yu HA, Phyllis Zee, Jonathan I Silverberg. . Burden of Sleep and Fatigue in US Adults With Atopic Dermatitis. *Dermatitis.* 2016;27(2):50-58.
2. Ramirez FD CS, Langan SM, Prather AA, McCulloch CE, Kidd SA, Cabana MD, Chren MM, Abuabara K. Association of Atopic Dermatitis With Sleep Quality in Children. *JAMA Pediatr.* 2019;173(5)::e190025.
3. Silverberg J. Comorbidities and the impact of atopic dermatitis. *Ann Allergy Asthma Immunol.* 2019;123(2):144-151.
4. Holm JG AT, Clausen ML, Thomsen SF. Quality of life and disease severity in patients with atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2016;30(10):1760-1767.
5. Eckert L GS, Amand C, Gadkari A, Mahajan P, Gelfand JM. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: An analysis using the National Health and Wellness Survey. *J Am Acad Dermatol.* 2017;77(2):274-279.
6. Ramirez FD CS, Langan SM, Prather AA, McCulloch CE, Kidd SA, Cabana MD, Chren MM, Abuabara K. Assessment of Sleep Disturbances and Exhaustion in Mothers of Children With Atopic Dermatitis. *JAMA Dermatol.* 2019;155(5):556-563.
7. Shaw TE CG, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermtol.* 2010;131(1):67-73.
8. McKenzie C SJ. The prevalence and persistence of atopic dermatitis in urban United States children. *Ann Allergy Asthma Immunol.* 2019;123(2):173-178.e171.
9. Silverberg JI HJ. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol.* 2013;132(5):1132-1138.
10. Silverberg JI GN, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol.* 2014;135(1):56-66.
11. D.R. Bickers HWL, D. Margolis, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol.* 2006;55:490-500.
12. Drucker AM WA, Li WQ, Sevetson E, Block JK, Qureshi AA. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *J Invest Dermatol.* 2017;137(1):26-30.
13. Brennan Z. Series of JAK inhibitor delays may signal an upcoming FDA adcomm. *Endpoints News.* 2021.
14. LeoPharma. Update on U.S. FDA review of LEO Pharma's Biologics License Application for tralokinumab for the treatment of adults with moderate-to-severe atopic dermatitis. 2021.
15. Incyte Announces U.S. FDA Has Extended the New Drug Application Review Period for Ruxolitinib Cream for the Treatment of Atopic Dermatitis [press release]. Business Wire2021.
16. Beck LT, D. Deleuran, M. Blauvelt, A. Bissonnette, R. de Bruin-Weller, M. Hide, M. Sher, L. Hussain, I. Chen, Z. Khokhar, FA. Beazley, B. Ruddy, M. Patel, N. Graham, NMH. Ardeleanu, M. Shumel. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. *American Journal of Clinical Dermatology* 2020.

17. Cheng B, Silverberg, JI. Association of pediatric atopic dermatitis and psoriasis with school absenteeism and parental work absenteeism: A cross-sectional United States population-based study. *Journal of the American Academy of Dermatology.* 2021.
18. Boguniewicz M LD. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev.* 2011;242(1):233-246.
19. Guttman-Yassky E WA, Ahluwalia J,Ong PY, Eichenfield LF. . Atopic dermatitis: pathogenesis. *Semin Cutan Med Surg.* 2017;36(3):100-103.
20. Silverberg JI SE. Associations of childhood eczema severity: a US population-based study. *Dermatitis.* 2014;25(3):107-114.
21. Mortz CG AK, Dellgren C, Barington T, Bindslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. *Allergy.* 2015;70(7):836-845.
22. Silverberg JI MD, Boguniewicz M, Fonacier L, Grayson MH, Ong PY, Chiesa Fuxench ZC, Simpson EL, Gelfand JM. . Distribution of atopic dermatitis lesions in United States adults. *J Eur Acad Dermatol Venereol.* 2019;33(7):1341-1348.
23. Ballardini N KI, Söderhäll C, Lilja G, Wickman M, Wahlgren CF. Eczema severity in preadolescent children and its relation to sex, filaggrin mutations, asthma, rhinitis, aggravating factors and topical treatment: a report from the BAMSE birth cohort. *Br J Dermatol.* 2013;168(3):588-594.
24. Simpson EL ea. Association of Inadequately Controlled Disease and Disease Severity With Patient-Reported Disease Burden in Adults With Atopic Dermatitis. *JAMA Dermatol.* 2018.
25. Jr. ABF. Atopic dermatitis: the relationship to temperature and seasonality in the United States. *International Journal of Dermatology.* 2019.
26. Weidinger S, Novak N. Atopic dermatitis. *Lancet (London, England).* 2016;387(10023):1109-1122.
27. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol.* 2014;71(2):327-349.
28. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014;71(1):116-132.
29. Gooderham MJ, Hong HC, Eshtiaghi P, Papp KA. Dupilumab: A review of its use in the treatment of atopic dermatitis. *J Am Acad Dermatol.* 2018;78(3 Suppl 1):S28-s36.
30. Moyle M, Cevikbas F, Harden JL, Guttman-Yassky E. Understanding the immune landscape in atopic dermatitis: The era of biologics and emerging therapeutic approaches. *Experimental dermatology.* 2019;28(7):756-768.
31. Ghamrawi R, Bell KA, Balogh EA, Strowd LC, Feldman SR. Current and emerging biologics for the treatment of pediatric atopic dermatitis. *Expert opinion on biological therapy.* 2020:1-11.
32. Hamann CR, Thyssen JP. Monoclonal antibodies against interleukin 13 and interleukin 31RA in development for atopic dermatitis. *J Am Acad Dermatol.* 2018;78(3 Suppl 1):S37-s42.
33. He H, Guttman-Yassky E. JAK Inhibitors for Atopic Dermatitis: An Update. *American journal of clinical dermatology.* 2019;20(2):181-192.
34. Allergy & Asthma Association AaAFoA, Global Parents for Eczema Research, International Topical Steroid Awareness Network, National Eczema Association. More Than Skin Deep Report. 2020.
35. Simpson EL, Sinclair R, Forman S, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-

blind, randomised, placebo-controlled, phase 3 trial. *Lancet (London, England).* 2020;396(10246):255-266.
36. Silverberg JI, Simpson EL, Thyssen JP, et al. Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA Dermatology.* 2020;156(8):863-873.
37. Bieber T, Simpson EL, Silverberg JI, et al. Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. *New England Journal of Medicine.* 2021;384(12):1101-1112.
38. Pfizer. Abrocitinib Data Request for ICER Assessment of "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis"2021.
39. Pfizer. Data on File2020.
40. Gooderham MJ, Forman SB, Bissonnette R, et al. Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: a Phase 2 Randomized Clinical Trial. *JAMA dermatology.* 2019;155(12):1371-1379.
41. Eichenfield L, Flohr C, Sidbury R. Efficacy and Safety of Abrocitinib in Adolescent Patients With Moderate-to-Severe Atopic Dermatitis (AD): Results From the Phase 3 JADE TEEN study. Paper presented at: American Academy of Allergy Asthma & Immunology Virtual Annual Meeting2021.
42. Simpson EL, Lacour JP, Spelman L, et al. Baricitinib in Patients with Moderate-to-Severe Atopic Dermatitis and Inadequate Response to Topical Corticosteroids: results from Two Randomised Monotherapy Phase 3 Trials. *British journal of dermatology.* 2020.
43. EADV 2020: Lilly and Incyte Showcase New Data for Baricitinib for the Treatment of Moderate to Severe Atopic Dermatitis [press release]. 2020.
44. Lilly E. Data on File2021.
45. Simpson EL, Forman S, Silverberg JI, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis: Results from a randomized monotherapy phase 3 trial in the United States and Canada (BREEZE-AD5). *Journal of the American Academy of Dermatology.* 2021.
46. Reich K, Kabashima K, Peris K, et al. Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: a Randomized Clinical Trial. *JAMA dermatology.* 2020.
47. Clinicaltrials.gov. A Study of Baricitinib (LY3009104) in Combination With Topical Corticosteroids in Adults With Moderate to Severe Atopic Dermatitis (BREEZE-AD7). Published 2020. Accessed.
48. Guttman-Yassky E, Silverberg JI, Nemoto O, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *Journal of the American Academy of Dermatology.* 2019;80(4):913-921.e919.
49. Clinicaltrials.gov. A Study of Baricitinib (LY3009104) in Adult Participants With Moderate to Severe Atopic Dermatitis (BREEZE-AD5). Published 2021. Accessed.
50. Blauvelt A, e Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet (London, England).* 2017;389(10086):2287-2303.
51. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *New England Journal of Medicine.* 2016;375(24):2335-2348.
52. Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: a Phase 3 Randomized Clinical Trial. *JAMA dermatology.* 2020;156(1):44-56.

53. Paller AS, Siegfried EC, Thaci D, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial. *Journal of the American Academy of Dermatology.* 2020.
54. Worm M, Simpson EL, Thaci D, et al. Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis: a Randomized Clinical Trial. *JAMA dermatology.* 2020;156(2):131-143.
55. Sanofi-Regeneron. Sanofi-Regeneron Academic-in-Confidence Data Submission Table 2.1.2.1.2021.
56. Thaçi D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *The Lancet.* 2016;387(10013):40-52.
57. Simpson EL, Gadkari A, Worm M, et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): A phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). *Journal of the American Academy of Dermatology.* 2016;75(3):506-515.
58. Cork M, Thaçi D, Davis JD, et al. Pharmacokinetics, safety and efficacy of dupilumab in a pediatric population with moderate-to-severe atopic dermatitis: Results from an open-label phase 2A trial. *Pediatric Dermatology.* 2017;34:S32.
59. Clinicaltrials.gov. A Study to Determine the Safety and Tolerability of Dupilumab (REGN668/SAR231893) in Patients Aged ≥6 to <18 Years With Atopic Dermatitis (Eczema). Published 2020. Accessed.
60. Cork MJ, Thaci D, Eichenfield LF, et al. Dupilumab provides favourable long-term safety and efficacy in children aged >= 6 to < 12 years with uncontrolled severe atopic dermatitis: results from an open-label phase IIa study and subsequent phase III open-label extension study. *British journal of dermatology.* 2020.
61. Blauvelt A, Guttman-Yassky E, Paller A. Efficacy and Safety of Dupilumab for up to 1 Year in a Phase 3 Open-Label Extension (OLE) Trial (LIBERTY AD PED-OLE) in Adolescents With Moderate-to-Severe Atopic Dermatitis (AD). Paper presented at: American Academy of Dermatology Association Virtual Meeting Experience2021.
62. Cork M, Thaci D, Eichenfield L. Long-Term Efficacy and Safety Data for Dupilumab in a Phase 3, Open-Label Extension Trial (LIBERTY AD PED-OLE) in Patients Aged ≥ 6 to < 12 Years With Uncontrolled, Moderate-to-Severe Atopic Dermatitis (AD). Paper presented at: American Academy of Dermatology Association Virtual Meeting Experience2021.
63. Wollenberg A, Blauvelt A, Guttman-Yassky E, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *British journal of dermatology.* 2020.
64. Silverberg JI, Toth D, Bieber T, et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. *British journal of dermatology.* 2020.
65. LeoPharma. Data on File2021.
66. LEO Pharma Presents Data for Tralokinumab on Pooled Safety, S. aureus Colonization Reduction and Impact on Vaccine Response Rates at the 29th Annual European Academy of Dermatology and Venereology (EADV) Virtual Congress [press release]. 2020.
67. Wiseman M, Armstrong AW, Soung J. Efficacy and safety of tralokinumab monotherapy in North American adult patients with moderate-to-severe atopic dermatitis: A subanalysis of the ECZTRA

2 trial. Paper presented at: American Academy of Dermatology Association Virtual Meeting Experience2021.
68. Blauvelt A, Wollenberg A, Pink A, Worm M. Assessing Long-term Maintenance of Efficacy With Tralokinumab Monotherapy in Patients With Moderate-to-severe Atopic Dermatitis: Combined Results From Two Phase 3, Randomized, Double-blind, Placebo-controlled Trials (ECZTRA 1 and 2). Paper presented at: American Academy of Dermatology Association Virtual Meeting Experience2021.
69. Guttman-Yassky E, Thaci D, Pangan AL, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *Journal of allergy and clinical immunology.* 2020;145(3):877-884.
70. RINVOQ™ (upadacitinib) Achieved SuperiorityVersus DUPIXENT® (dupilumab) For Primaryand All Ranked Secondary Endpoints in Phase3b Head-to-Head Study in Adults with AtopicDermatitis [press release]. 2020.
71. AbbVie. Data on File. 2021.
72. Simpson EL, Warren RB, Eichenfield LF. Rapid Skin Improvement With Upadacitinib With or Without Topical Corticosteroids (TCS) in Moderate-to-Severe Atopic Dermatitis (AD): Results From 3 Phase 3 Studies (Measure Up 1, Measure Up 2, and AD Up). Paper presented at: American Academy of Dermatology Association Virtual Meeting Experience2021.
73. Kristian Reich MdB-W, Mette Sondergaard Deleuran, Lisa Beck, Kim A. Papp,, Thomas Werfel NK, Saleem Farooqui, Pinaki Biswas, Ricardo Rojo, Marco Dibonaventura,, Claire Clibborn UK. Abrocitinib Efficacy and Safety as Monotherapy Over 48 Weeks: Results From a Long-Term Extension Study. Paper presented at: European Academy of Dermatology and Venereology Virtual Congress2020.
74. Papp J. Long-Term Safety and Disease Control With Ruxolitinib Cream in Atopic Dermatitis: Results From Two Phase 3 Studies. Revolutionizing Atopic Dermatitis (RAD) Virtual Conference; 2021.
75. EL S. Long-Term Safety and Disease Control With Ruxolitinib Cream in Patients With More Severe Atopic Dermatitis: Pooled Results From Two Phase 3 Studies. Revolutionizing Atopid Dermatitis (RAD) Virtual Conference; 2021.
76. Simpson EL. Efficacy and Safety of Abrocitinib in Adolescent Patients With Moderate-to-Severe Atopic Dermatitis: Stratified Analysis Across 3 Clinical Trials. Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
77. Reich J. Long-Term Management of Moderate-to-Severe Atopic Dermatitis With Abrocitinib: A Phase 3 Extension Study (JADE EXTEND). Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
78. Eichenfield L. Efficacy and Safety of Abrocitinib in Adolescents With Moderate-to-Severe Atopic Dermatitis From the JADE Clinical Trial Program. Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
79. Blauvelt A. Long-term Improvements Observed in Tralokinumab-treated Patients With Moderate-to-severe Atopic Dermatitis: An ECZTEND Interim Analysis. Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
80. Paller A. Efficacy and Safety of Upadacitinib in Adult and Adolescent Subgroups With Moderate-to-Severe Atopic Dermatitis: An Analysis of the Measure Up 1, Measure Up 2, and AD Up Phase 3 Clinical Trials. Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.

81. Blauvelt A. Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: Analysis of the Heads Up Phase 3 Trial. Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
82. Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *The Lancet (British edition).* 2021;397(10290):2151-2168.
83. Reich K, Teixeira HD, de Bruin-Weller M, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet (British edition).* 2021;397(10290):2169-2181.
84. Simpson E. Long-term Efficacy of Baricitinib 2-mg for the Treatment of Atopic Dermatitis in North America. Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
85. Clinicaltrials.gov. JAK1 Inhibitor With Medicated Topical Therapy in Adolescents With Atopic Dermatitis (JADE TEEN). Published 2021. Accessed2021.
86. Simpson E, Lee M, Brar K, et al. Disease Characteristics and Burden in Patients With Atopic Dermatitis: Insights From Two Phase 3 Studies of Ruxolitinib Cream. *Journal of allergy and clinical immunology.* 2021;147(2):AB35-AB35.
87. Kim BS, Sun K, Papp K, Venturanza M, Nasir A, Kuligowski ME. Effects of ruxolitinib cream on pruritus and quality of life in atopic dermatitis: Results from a phase 2, randomized, dose-ranging, vehicle- and active-controlled study. *Journal of the American Academy of Dermatology.* 2020;82(6):1305-1313.
88. Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. *Journal of allergy and clinical immunology.* 2020;145(2):572-582.
89. Papp K, Szepietowski JC. Efficacy and Safety of Ruxolitinib Cream for the Treatment of Atopic Dermatitis: Results From Two Phase 3, Randomized Double-Blind Studies. 2nd Annual Revolutionizing Atopic Dermatitis Conference; 2020; Chicago, IL.
90. Pooled Results from Incyte's TRuE-AD1 and TRuE-AD2 Atopic Dermatitis Studies of Ruxolitinib Cream Show Clinically Meaningful Improvements in Patient- Reported Quality of Life Assessments [press release]. Incyte.com: Incyte2020.
91. Eichenfield L, Call R, Forsha D, et al. Long-term safety of crisaborole ointment in children, adolescents, and adults with mild to moderate atopic dermatitis. *Pediatric dermatology Conference: 13th world congress of pediatric dermatology United states.* 2017;34:S32-S33.
92. Eichenfield LF, Yosipovitch G, Stein Gold LF, et al. Improvement in disease severity and pruritus outcomes with crisaborole ointment, 2%, by baseline atopic dermatitis severity in children and adolescents with mild-to-moderate atopic dermatitis. *Pediatric dermatology.* 2020.
93. Schlessinger J, Shepard JS, Gower R, et al. Safety, Effectiveness, and Pharmacokinetics of Crisaborole in Infants Aged 3 to < 24 Months with Mild-to-Moderate Atopic Dermatitis: A Phase IV Open-Label Study (CrisADe CARE 1). *American journal of clinical dermatology.* 2020;21(2):275-284.
94. Simpson EL, Paller AS, Boguniewicz M, et al. Crisaborole Ointment Improves Quality of Life of Patients with Mild to Moderate Atopic Dermatitis and Their Families. *Dermatology and therapy.* 2018;8(4):605-619.

95. Yosipovitch G, Gold LF, Lebwohl MG, Silverberg JI, Tallman AM, Zane LT. Early Relief of Pruritus in Atopic Dermatitis with Crisaborole Ointment, A Non-steroidal, Phosphodiesterase 4 Inhibitor. *Acta Derm Venereol.* 2018;98(5):484-489.
96. Paller ASMSMD, Tom WLMD, Lebwohl MGMD, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *Journal of the American Academy of Dermatology.* 2016;75(3):494-503.e496.
97. Paller AS. Crisaborole ointment improves global atopic dermatitis severity: pooled results from two phase 3 clinical trials. *Journal of investigative dermatology.* 2018;Conference: 47th Annual Meeting of the European Society for Dermatological Research, ESDR 2017. Austria. 137(10 Supplement 2):S193.
98. Papp K, Szepietowski JC, Kircik L, et al. Efficacy and Safety of Ruxolitinib Cream for the Treatment of Atopic Dermatitis: Results From Two Phase 3, Randomized, Double-Blind Studies. *Journal of the American Academy of Dermatology.* 2021.
99. Blauvelt A, Eichenfield L. Efficacy of Ruxolitinib Cream Among Patients With Atopic Dermatitis Based on Previous Medication History: Pooled Results From Two Phase 3 Studies. Paper presented at: American Academy of Dermatology Virtual Meeting Experience2021.
100. EL. S, Augustin M, Thaçi D. Patient-Reported Outcomes of Ruxolitinib Cream for the Treatment of Atopic Dermatitis: Pooled Results From Two Phase 3 Studies. Paper presented at: American Academy of Dermatology Virtual Meeting Experience2021.
101. L SE, Kircik L, Blauvelt A. Efficacy of Ruxolitinib Cream in Patients With Atopic Dermatitis Who Demonstrated Partial Responses: Pooled Analysis From Two Randomized Phase 3 Studies. Paper presented at: American Academy of Dermatology Virtual Experience2021.
102. Papp K, Szepietowski JC. Efficacy of Ruxolitinib Cream for the Treatment of Atopic Dermatitis by Baseline Patient Demographics: Pooled Subgroup Analysis From Two Randomized Phase 3 Studies. American Academy of Dermatology Virtual Meeting Experience; 2021.
103. Simpson EL, Kircik L, Blauvelt A. Effects of Ruxolitinib Cream in Patients With Atopic Dermatitis With Baseline Body Surface Area ≥10% and Eczema Area and Severity Index Score ≥16: Pooled Results From Two Phase 3 Studies. Paper presented at: American Academy of Dermatology Virtual Meeting Experience2021.
104. Papp K, Szepietowski JC, Kircik L. Efficacy of Ruxolitinib Cream for the Treatment of Atopic Dermatitis by Baseline Clinical Characteristics: Pooled Subgroup Analysis From Two Randomized Phase 3 Studies. Paper presented at: American Academy of Dermatology Virtual Meeting Experience2021.
105. Basra MKA, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the Minimal Clinically Important Difference and Responsiveness of the Dermatology Life Quality Index (DLQI): Further Data. *Dermatology.* 2015;230(1):27-33.
106. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol.* 2004;140(12):1513-1519.
107. Silverberg JI, Thyssen JP, Simpson EL, et al. Impact of Oral Abrocitinib Monotherapy on Patient-Reported Symptoms and Quality of Life in Adolescents and Adults with Moderate-to-Severe Atopic Dermatitis: A Pooled Analysis of Patient-Reported Outcomes. *American journal of clinical dermatology.* 2021;22(4):541-554.

108. Shi N. Abrocitinib in the Treatment of Moderate-to-Severe Atopic Dermatitis Refractory to Dupilumab Treatment: An Analysis of JADE-EXTEND, a Phase 3 Long-Term Extension Study. Paper presented at: REvolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
109. Clinicaltrials.gov. A Study of Baricitinib (LY3009104) in Patients With Moderate to Severe Atopic Dermatitis (BREEZE-AD1). U.S National Library of Medicine. Published 2018. Accessed.
110. Clinicaltrials.gov. Study of Baricitinib (LY3009104) in Patients With Moderate to Severe Atopic Dermatitis (BREEZE-AD2). Published 2018. Accessed.
111. Lilly E. Baricitinib Package Insert. 2018.
112. Abbvie. Upadacitinib Package Insert. 2019.
113. Beck LA, Thaçi D, Deleuran M, et al. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. *American journal of clinical dermatology.* 2020;21(4):567-577.
114. Fu T KE, Linos E, et al. Eczema and sensitization to common allergens in the United States: a multiethnic, population-based study. *Pediatric Dermatology.* 2014.
115. Ashcroft DM, Chen LC, Garside R, Stein K, Williams HC. Topical pimecrolimus for eczema. *Cochrane Database Syst Rev.* 2007(4):Cd005500.
116. Buysse DJ, Yu L, Moul DE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep.* 2010;33(6):781-792.
117. Zimmermann M, Rind D, Chapman R, Kumar V, Kahn S, Carlson J. Economic Evaluation of Dupilumab for Moderate-to-Severe Atopic Dermatitis: A Cost-Utility Analysis. *Journal of drugs in dermatology: JDD.* 2018;17(7):750-756.
118. Schmitt J, Langan S, Williams HC. What are the best outcome measurements for atopic eczema? A systematic review. *Journal of Allergy and Clinical Immunology.* 2007;120(6):1389-1398.
119. Arias E, Xu J. *United States life tables, 2018.* Hyattsville, MD: National Center for Health Statistics;2020.
120. National Economic Accounts. 2018. Accessed August 10, 2018.
121. Hanifin JT, M. Omoto, M. Cherill, R. Tofte, SJ. Graeber, M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. 2001.
122. Futamura ML, YA. Thomas, KS. Nankervis, H. Williams, HC. Simpson, EL. . A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: many options, no standards. *Journal of the American Academy of Dermatology.*
123. Yosipovitch G, Reaney M, Mastey V, et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. *British journal of dermatology (1951).* 2019;181(4):761-769.
124. Kunz BO, AP. Labrèze, L. Stalder, JF. Ring, J. Taïeb, A. . Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. 1997.
125. Barrett AH-P, J. Kragh, N. Evans, E. Gnanasakthy, A. . Patient-Reported Outcome Measures in Atopic Dermatitis and Chronic Hand Eczema in Adults. 2019.
126. Salek MJ, S. Brincat-Ruffini, LA. et al. . Clinical experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995-2012. *The British journal of dermatology.* 2013.
127. Foley CT, N. Simpson, E. Teixeira, HD. Litcher-Kelly, L. Bodhani, A. . Development, and content validity of new patient-reported outcome questionnaires to assess the signs and symptoms and impact of atopic dermatitis: the Atopic Dermatitis Symptom Scale (ADerm-SS) and the Atopic Dermatitis Impact Scale (ADerm-IS). 2019.

128. Dodington SB, MK. Finlay, AY. Salek, MS. . The Dermatitis Family Impact questionnaire: a review of its measurement properties and clinical application. *The British journal of dermatology.* 2013.
129. Reilly MZ, AS. Dukes, EM. . The validity and reproducibility of a work productivity and activity impairment instrument. . *Pharmacoeconomics.* 1993.
130. Schneider LT, S. Lio, P. Boguniewicz, M. Beck, L. LeBovidge, J. Novak, N. Atopic dermatitis: A practice parameter update 2012. *American Academy of Allergy, Asthma & Immunology.* 2013.
131. Ting S, Elsada A, Hayre J, Powell J. *Dupilumab for treating moderate to severe atopic dermatitis : Technology appraisal guidance (TA534).* National Institute for Health and Care Excellence (NICE); 1 August 2018 2018.
132. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
133. Higgins JP. Cochrane Collaboration Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. 2008.
134. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8(5):336-341.
135. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. Published 2008. Accessed.
136. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. . Published 2020. Updated January 31, 2020. Accessed.
137. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE Decision Support Unit Technical Support Documents. In: *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials.* London: National Institute for Health and Care Excellence (NICE)Copyright © 2014 National Institute for Health and Clinical Excellence, unless otherwise stated. All rights reserved.; 2014.
138. Cork MJ, Eckert L, Simpson EL, et al. Dupilumab improves patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related quality of life in moderate-to-severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2. *Journal of dermatological treatment.* 2020;31(6):606-614.
139. Silverberg JI, Thyssen JP, Fahrbach K, et al. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis. *Journal of the European Academy of Dermatology and Venereology.* 2021;n/a(n/a).
140. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.
141. Simpson EL, Sinclair R, Forman S, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet (London, England).* 2020;396(10246):255-266.
142. Silverberg JI, Simpson EL, Thyssen JP, et al. Efficacy and Safety of Abrocitinib in Patients with Moderate-to-Severe Atopic Dermatitis: a Randomized Clinical Trial. *JAMA dermatology.* 2020.
143. Thaçi D, Bieber T, Simpson EL, et al. A Phase 3 Study to Investigate the Efficacy and Safety of Abrocitinib and Dupilumab in Comparison With Placebo in Adults With Moderate-to-Severe Atopic Dermatitis.
144. Thaci D, L. Simpson E D, M K, et al. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). *Journal of Dermatological Science.*94(2):266-275.

145. Wollenberg A, Boguniewicz M, Travers J, et al. Efficacy of Baricitinib in Patients with Atopic Dermatitis and Atopic Comorbidities: Results of Pooled Data from 2 Phase 3 Monotherapy Randomized, Double-Blind, Placebo-Controlled 16-week Trials (BREEZE-AD1 and BREEZE-AD2). *Journal of Allergy and Clinical Immunology.* 2020;145(2):AB190.
146. Simpson EL, Forman S, Silverberg JI, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis: Results from a randomized monotherapy Phase 3 trial in the United States and Canada (BREEZE-AD5). *Journal of the American Academy of Dermatology.* 2021.
147. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2019;22(8):931-941.
148. Measures of Central Tendency for Wage Data. In. United States Social Security Administration2019.