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

Final Evidence Report

August 17, 2021

Prepared for

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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

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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 upadacitinib 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").

Appraisal committee votes on questions of comparative effectiveness and value, along with key policy recommendations regarding pricing, access, and future research are included in the main report; several key policy themes are highlighted below:

- All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with atopic dermatitis are introduced in a way that will help reduce health inequities.

- Payers should only use step therapy when it provides adequate flexibility to meet the needs of the diverse range of patients with atopic dermatitis and when implementation can meet established standards of transparency and efficiency.

- Specialty societies should update treatment guidelines for patients with atopic dermatitis to reflect current treatment options in a form that is easy to interpret and use by clinicians, patients, and payers.

- Manufacturers, payers, and patient advocacy groups should support pricing and rebate reform efforts that will create better rewards for clinical and economic value while also helping patients afford access to the treatments they need.

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.[35-83] Of these, we identified five randomized controlled trials (RCTs) of abrocitinib (one phase II and four phase III),[35-37,39,40,77,84] 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),[69,70,80,81,83] 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. Of note, only the FDA-approved dose of dupilumab was evaluated in adults (300 mg once every two weeks).

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 ABRO 200 mg PBO	387	30.2	32.4	23.4	40.7
JADE MONO-2*	ABRO 100 mg ABRO 200 mg PBO	391	28.5	35.1	21.0	32.2
JADE COMPARE	ABRO 100 **mg + TCS** ABRO 200 mg **+ TCS** DUP 300 mg **+ TCS** PBO + TCS	837	30.9	37.7	22.7	35.4
Gooderham 2019	ABRO 100 mg ABRO 200 mg PBO	167	25.6	40.8	23.0[ɣ]	40.8
Baricitinib						
BREEZE-AD 1	BARI 1 mg BARI 2 mg BARI 4 mg** PBO	624	31.0	35.7	25.7	41.8
BREEZE-AD 2	BARI 1 mg BARI 2 mg BARI 4 mg** PBO	615	33.5	34.5	24.0	50.5
BREEZE-AD 5	BARI 1 mg BARI 2 mg PBO	440	27.1	39.7	23.7	41.7
BREEZE-AD 7	BARI 2 mg + TCS PBO + TCS	329	29.57	33.8	24.03	45.0
Guttman-Yassky 2018	BARI 4 mg + TCS** BARI 2 mg + TCS PBO + TCS	104	21.23 [ɣ]	36.5	22.03	NR
Tralokinumab						
ECZTRA 1	TRA 300 mg PBO	802	29.3	37.0	27.5	50.9
ECZTRA 2	TRA 300 mg PBO	794	28.9[ɣ]	32.0	25.3	49.2
ECZTRA 3	TRA 300 mg + TCS 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 UPA 30 mg PBO	847	29.5	34.0	20.7	45.2
MEASURE UP 2*	UPA 15 mg UPA 30 mg PBO	836	29.1	33.6	24.3	54.9
AD-UP*	UPA 15 mg + TCS UPA 30 mg + TCS PBO + TCS	901	29.6	34.1	23.4	52.9
Heads Up	DUP 300 mg UPA 30 mg	692	29.8	36.8	24.3	50.2
Guttman-Yassky 2020	UPA 7.5 mg** UPA **15 mg** UPA 30 mg PBO	167	25.6	40.8	23.0ʏ	40.8
Dupilumab						
LIBERTY AD SOLO 1	DUP 300 mg Q2W DUP 300 mg QW PBO	671	30.7	38.7	26.7	48.3
LIBERTY AD SOLO 2	DUP 300 mg Q2W DUP 300 mg QW PBO	708	29.4	34.7	24.8	48.3
LIBERTY AD CHRONOS	DUP 300 mg QW + TCS * DUP 300 mg + TCS PBO + TCS	740	29.8*	31.2ʏ	26.7ʏ	47.7
Thaci 2016	DUP 300 mg Q4W DUP 300 mg Q2W DUP 300 mg QW** DUP 200 mg Q2W DUP 100 mg Q4W** 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.[73,74,85-103] Of these, we identified two phase III, placebo-controlled RCTs of ruxolitinib cream[97] and one phase IIb placebo- and active-controlled (topical triamcinolone acetonide) RCT of ruxolitinib cream.[86,87] 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.[95] 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) RUX 0.75% RUX 1.5%	631	8 weeks	7.8	31.8	16	75.8
	TRuE AD 2	Vehicle (PBO) RUX 0.75% RUX 1.5%	618	8 weeks	8	34.2	16.1	74
	Phase II Kim 2020	Vehicle (PBO) RUX 1.5% BID 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.[35,36,104] 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.[105] 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).[40 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).[106]

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).[104]

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).[76,107]

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).[49,108,109] 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.[42,45,104] 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.[105]. 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.[49,108,109] 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. [49,108,109]

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.[46,104] 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. [43,44,82] 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).[63,104] 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).[63,104] 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.[105]. 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). In addition, data submitted as academic-in-confidence by the manufacturer suggest a greater reduction from baseline on HADS total score with tralokinumab compared to placebo; however, the difference was not statistically different in one trial.[65] 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).[64,104]

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.[69,80] 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.[83] 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. [81] 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).[69,80] More patients achieved a ≥4-point improvement with upadacitinib 30 mg than dupilumab (55% vs. 36%).[83] 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%).[81]

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. [80] 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. [80] 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.[69,105] 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). [69,80,105] 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). [80] 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. [80] 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). Upadacitinib 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 upadacitinib 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.[110,111] 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).[50,112]

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).[39,41,70,77] 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.

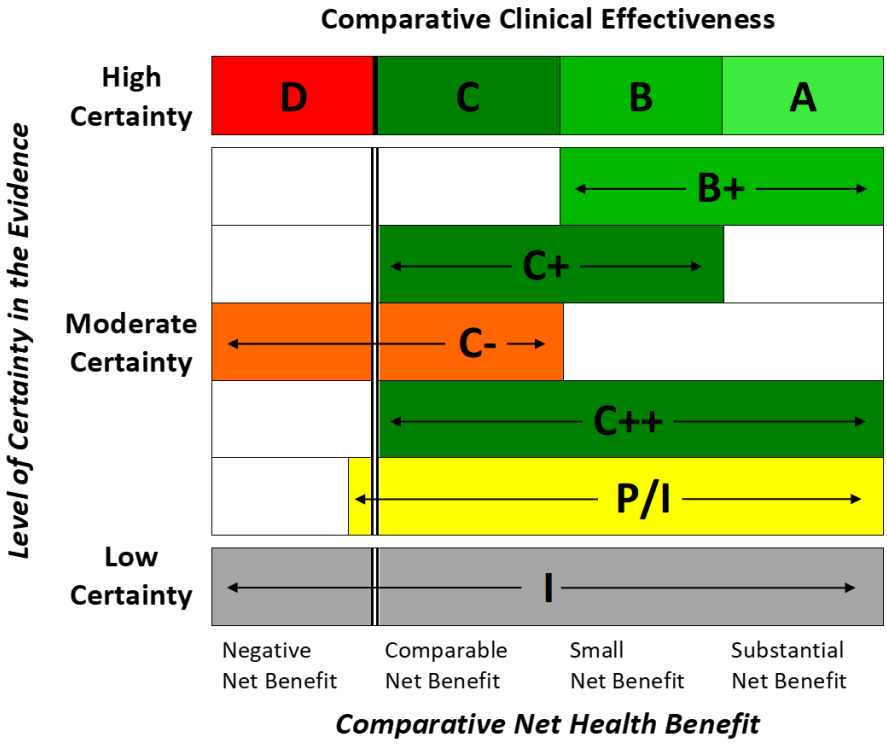
Given the large impact of atopic dermatitis in African-Americans and the importance of skin appearance on outcomes of treatment more broadly,[113] few trials included a sizable number of patients with darker skin complexions, and we are not aware of any trial that has reported outcomes among those with 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 upadacitinib 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.[114]

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.[97] 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.[99,104] 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.[99,105]. 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).[115] 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.[86,87] 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).[73]

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).[101]

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).[97]

Race

In a presentation of pooled data from two trials, IGA response with ruxolitinib appeared somewhat greater in white than black patients.[101] 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.[101]

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")*.

New England CEPAC Votes

Table 3.7. New England CEPAC Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
Patient Population for questions 1-4: *Adults 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. Usual care in such patients is defined as use of topical emollients and avoidance of exacerbating factors. Given the currently available evidence:*		
Is the evidence adequate to demonstrate that the net health benefit of **abrocitinib** added to usual care is superior to that provided by usual care alone?	8	5
Is the evidence adequate to demonstrate that the net health benefit of **baricitinib** added to usual care is superior to that provided by usual care alone?	7	6
Is the evidence adequate to demonstrate that the net health benefit of **upadacitinib** added to usual care is superior to that provided by usual care alone?	9	4
Is the evidence adequate to demonstrate that the net health benefit of **tralokinumab** added to usual care is superior to that provided by usual care alone?	11	2
Patient Population for Questions 5*: Adolescents and Adults with mild-to-moderate atopic dermatitis.*		
Given the currently available evidence, Is the evidence adequate to demonstrate that the net health benefit of **ruxolitinib cream** is superior to that provided by topical emollients alone?	12	1

Based on the evidence in the clinical trials and ongoing concerns about long-term safety with oral JAK inhibitors, the panel votes were split as to the net health benefit of abrocitinib, baricitinib, and upadacitinib in adults with moderate to severe atopic dermatitis. The panel voted that tralokinumab had adequate evidence of net health benefit in this setting.

For adolescent and adult patients with mild-to-moderate atopic dermatitis, the panel voted that ruxolitinib cream has adequate evidence of net health benefit compared with topical emollients alone. The panel focused on the clinical effectiveness and the safety profile of ruxolitinib cream.

4. Long-Term Cost Effectiveness

4.1. Methods Overview

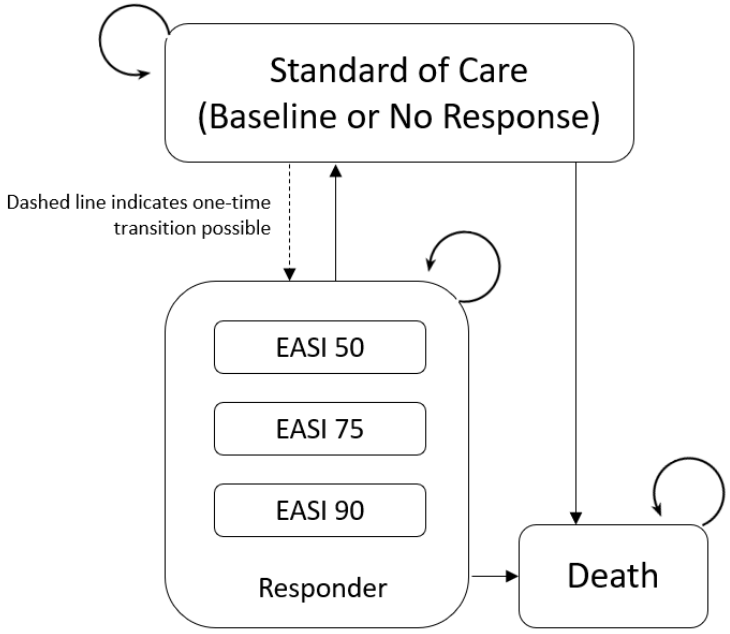
We adapted the Markov model from ICER's 2017 report on dupilumab for this evaluation, with the adaptation informed by key clinical trials and prior relevant economic models.[116] Costs and outcomes were discounted at 3% per year.

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.[117] 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.[118]

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.[119] 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. 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.

New England CEPAC Votes

At the public meeting, the New England CEPAC deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* effective treatment for atopic dermatitis, on the basis of the following contextual considerations:

Contextual Consideration	Very Low Priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on the severity of the condition being treated	0	0	6	6	1
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	3	9	1

For the acuity of need for treatment, the panel voted that any effective treatment should be given average or high priority due to the severity of the disease. The magnitude of lifetime impact on individual patients received a majority vote of "high priority;" the panel emphasized the chronic nature of atopic dermatitis which can start early in a person's life, often in adolescence.

For questions 8-12, considering the average effects of the new systemic therapies as a group, what are the relative effects of the new therapies versus usual care (use of topical emollients and avoidance of exacerbating factors) on the following outcomes that inform judgment of the overall long-term value for money.

Potential Other Benefit or Disadvantage	Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
Patients' ability to achieve major life goals related to education, work, or family life	0	0	0	4	9
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	0	6	7
Society's goal of reducing health inequities	0	1	7	4	1
What are the relative effects of the JAK inhibitors as a class versus dupilumab on patients' ability to manage and sustain treatment given the complexities of the regimens?	0	0	4	8	1
What are the relative effects of tralokinumab versus dupilumab on patients' ability to manage and sustain treatment given the complexities of the regimens?	0	0	8	5	0

The panel voted that the new systemic therapies would have a minor or major positive effect on both the patients' and their caregivers' quality of life. At the same time, the panel concluded that it is difficult to assess these therapies' impact on society's goal of reducing health inequities – high prices and any access limitations might negatively impact certain populations more severely than others. When talking about adherence and patients' ability to sustain a treatment given the complexities of the regimens, the panel voted that the oral JAK inhibitors may have a minor positive effect as oral therapies. When comparing tralokinumab and dupilumab, which are both given by subcutaneous injection, the panel voted that there would be no difference, or a minor positive difference, on the patients' ability to manage the treatments.

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

New England CEPAC Votes

Table 6.2. New England CEPAC Votes on Long-Term Value for Money at Current Prices

Question	Low long-term value for money at current prices	Intermediate long-term value for money at current prices	High long-term value for money at current prices
Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **baricitinib** versus usual care?	0	7	6
Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **upadacitinib** versus usual care?	10	3	0

The panel voted on two therapies which already have a known price as they are approved for other indications. The majority of the panel voted that baricitinib represents either an "intermediate" or "high" value for money at current prices. The incremental cost-effectiveness ratio for baricitinib was $71,600 per QALY gained.

The majority of the panel voted that upadacitinib represents a "low" value for money at current prices. The incremental cost-effectiveness ratio for upadacitinib was $248,400 per QALY gained.

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).

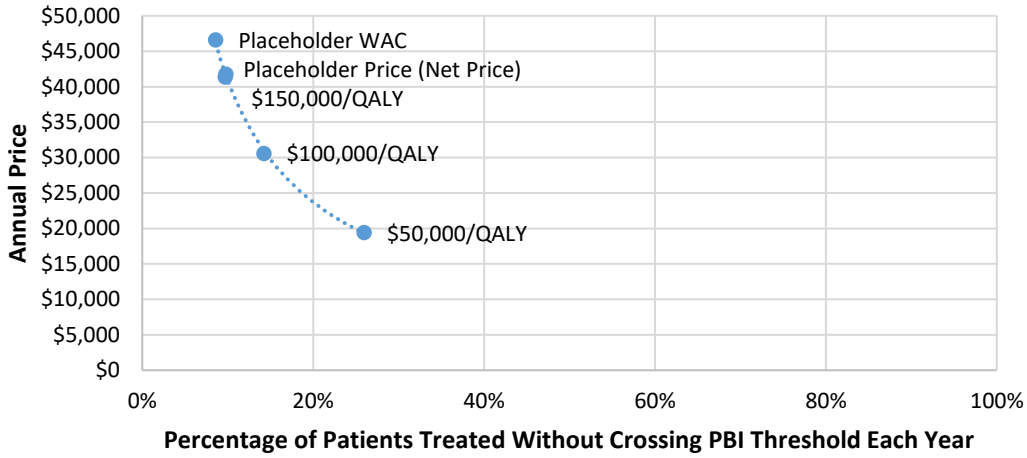
7.2. Results

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%

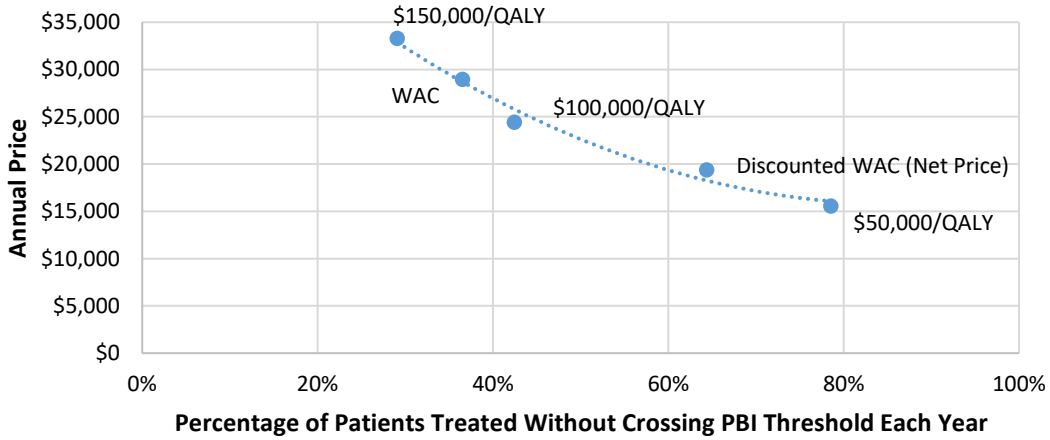
and 79% for all prices evaluated (WAC unit price to the maximum price to achieve $50,000 per QALY).

Figure 7.1. Budgetary Impact of Abrocitinib*



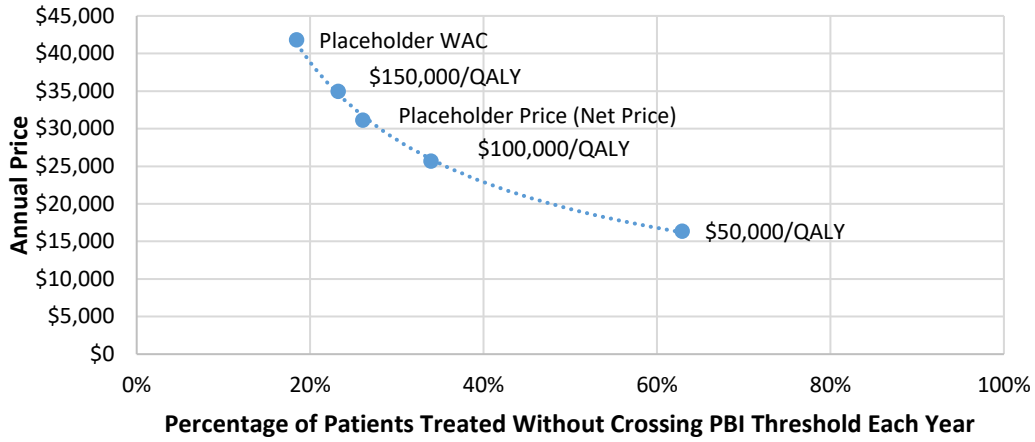
PBI: potential budget impact, QALY: quality-adjusted life-year, WAC: wholesale acquisition price
*Based on placeholder prices

Figure 7.2. Budgetary Impact of Baricitinib



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

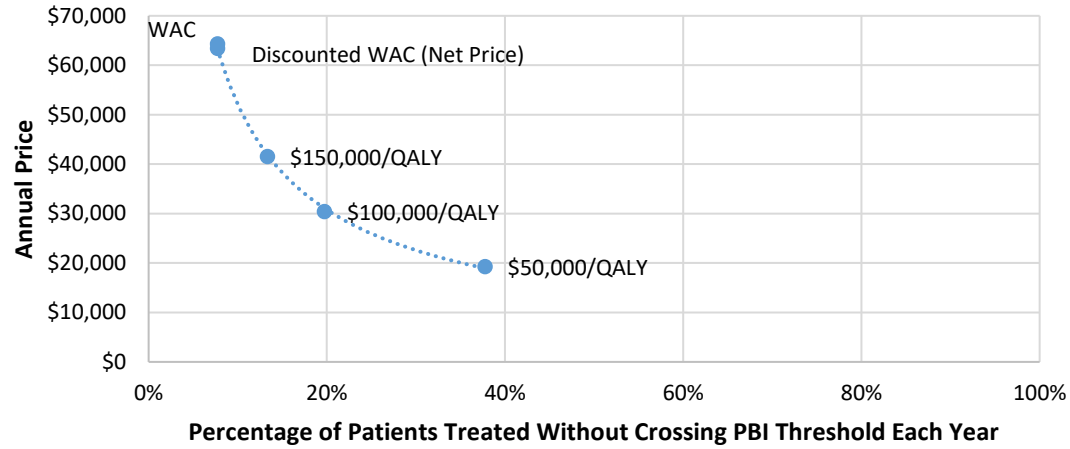
Figure 7.3. Budgetary Impact of Tralokinumab*



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

8. Policy Recommendations

Following its deliberation on the evidence, the Comparative Effectiveness Public Advisory Council engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of oral abrocitinib, baricitinib, and upadacitinib, topical ruxolitinib cream, and subcutaneous tralokinumab. The policy roundtable members included three patient advocates, two clinical experts, two payers, and three representatives from the drug maker(s). The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

All Stakeholders

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with atopic dermatitis are introduced in a way that will help reduce health inequities.

Safe and effective treatment for atopic dermatitis, especially for those with moderate to severe disease, remains a significant unmet health care need. Efforts are needed to ensure that new therapies for atopic dermatitis such as oral abrocitinib, baricitinib, and upadacitinib, topical ruxolitinib cream, and subcutaneous tralokinumab, improve the health of patients and families and do not aggravate existing health inequities. Clinical experts and patients highlighted that the high cost of new therapies may worsen disparities in accessing care. This may be due to lack of health insurance that limits access to specialists and the new therapies that they prescribe, or high deductible payments even for those with insurance may result in steep out of pocket costs. The cost of care is not the only factor that may contribute to health inequities. Our clinical experts noted that the appearance of the skin is a key contributor to measures of disease severity, and individuals with darker skin types may be assessed as having less severe skin involvement. Since educational materials often include photos of individuals with atopic dermatitis who have lighter skin types, those with darker skin may be more likely to be misdiagnosed.

To address these concerns:

<u>Manufacturers should take the following actions:</u>

- Follow the precedent of responsible pricing set by Sanofi/Regeneron with dupilumab and set the price for new treatments for atopic dermatitis in fair alignment with added benefits for patients.

- Take steps necessary to include a more diverse patient population in clinical trials, including adequate number of patients with ethnic and racial backgrounds who have darker skin types.

Payers should take the following actions:

- Ensure that benefit designs developed in conjunction with employers and other plan sponsors do not create requirements for out-of-pocket spending that create major barriers to appropriate access for vulnerable patients

Clinical specialty societies should take the following actions:

- Develop and disseminate educational materials and create measurable goals to demonstrate that clinicians are aware of the challenges of diagnosing atopic dermatitis in patients with darker skin types.

Payers

The large number of patients with varying levels of severity of atopic dermatitis, combined with the potential for side effects and the high annual prices for newer generation treatments, will lead payers to develop prior authorization criteria and to consider other limits on utilization.

Perspectives on specific elements of cost sharing and coverage criteria for oral abrocitinib, baricitinib, and upadacitinib, topical ruxolitinib cream, and subcutaneous tralokinumab within insurance coverage policy are discussed below.

Coverage Criteria

- **Age:** Age criteria are likely to follow the FDA label for each drug and will not be expanded to cover earlier ages in the case of drugs not approved for adolescents or children. Similarly, although there may be greater uncertainty in outcomes for younger patients, it seems unlikely that payers will use clinical trial eligibility criteria to narrow coverage if the FDA approval includes treatment of adolescents. Payers should have efficient mechanisms for clinicians to seek coverage exceptions for patients with serious unmet need who are near the cutoff for the age necessary for coverage.

- **Clinical eligibility**: There is no clear consensus on how to operationalize a definition of the FDA indication for treatment of patients with "moderate to severe" atopic dermatitis. The severity of atopic dermatitis can vary substantially over time and, from a patient's perspective, can include a complex combination of intensity of itch, location, body surface

area involvement, and degree of skin impairment. Some payers will allow clinician attestation, whereas others will adopt criteria based on clinical trial eligibility. Given the variability of patient phenotype and lack of familiarity among clinicians with scoring systems used in clinical trials, it is advisable for payers to create a broad, clinically relevant definition inclusive of multiple specific measures of disease intensity, e.g. "any of the following: BSA ≥ 10%, IGA ≥ 3, EASI ≥ 16," or "affected BSA ≥ 10% OR involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g. hands, feet, face, neck, scalp, genitals/groin, skin folds) or severe itch that has been unresponsive to topical therapies."

- In addition to a definition of severity, payers are likely to require that patients have received an adequate trial of topical therapy, e.g. a 30-day trial of prescription topical corticosteroid and/or topical calcineurin inhibitor OR the use of these medications is not medically advisable (as occurs with eyelid involvement). Payers should not require that this trial of topical agent(s) be immediately prior to the requested prescription; medical records indicating prior trial of topical therapy be sufficient.

- Potential criteria requiring prior use of phototherapy or systemic off-label treatment with agents like methotrexate is covered in the section on step therapy below.

- Ruxolitinib cream, if approved by the FDA, will likely have an indication for treatment of "mild to moderate" atopic dermatitis. The clinical criteria for coverage may be based on clinical trial eligibility (BSA ≥ 3% excluding scalp OR IGA 2-3) but will also likely require prior use of topical corticosteroids or calcineurin inhibitors. Another indication could be allowing the use of ruxolitinib cream in patients with severe atopic dermatitis for areas that do not clear adequately with systemic therapies.

- **Exclusion criteria**: There are no special medical comorbidities at this time that would serve as exclusion criteria for these treatments.

- **Duration of coverage and renewal criteria**: Initial coverage will likely be for a period of six to 12 months, which is long enough for dose titration, assessment of side effects, or disease progression.

- Clinical experts and payers felt that it would be appropriate to require attestation for continuation of therapy. The timing of such renewal may depend to some extent upon the specific therapy. For example, oral JAK inhibitors appear to have a quicker onset of action than biologics such as dupilumab or tralokinumab. Patients and clinicians felt that requiring submission of outcome measures to support continuation was not needed. For biologics that are given by injection, patients reported that they would not want to continue use in

the absence of improvement. For JAK inhibitors, given the potential for uncommon but serious side effects, long-term use in the absence of considerable benefit may also be unlikely. Most clinical experts suggested a three- to six-month period prior to renewal to be appropriate.

- **Provider restrictions**: Clinical experts agreed that it is reasonable to restrict prescriptions for dupilumab, abrocitinib, baricitinib, tralokinumab and upadacitinib to dermatologists or allergy specialists. Some payers may consider allowing prescription by generalist physicians able to work in consultation with specialists. The new therapies for moderate to severe atopic dermatitis require knowledge about evaluating and treating patients that most primary care clinicians are unlikely to have. Specialty clinicians are better suited to identify patients who are most likely to benefit, provide sufficient information for patients to make a well-informed decision, and monitor for response and side effects. Ruxolitinib cream may be covered with less restrictions on prescriber qualifications, but because it may be used in younger patients some payers may still wish to limit prescribing, at least initially, to specialists or generalist clinicians working in consultation with specialists.

Step Therapy

Payers should only use step therapy when it provides adequate flexibility to meet the needs of diverse patients and when implementation can meet high standards of transparency and efficiency.

Clinical experts and patient representatives stated that delayed and restricted access to treatment due to step therapy requirements for patients with moderate to severe atopic dermatitis is common. While it is possible to tailor step therapy in a clinically responsible fashion, it is often administered with documentation burdens and inadequate procedures for exceptions that make step therapy a source of great frustration and the cause of poor outcomes for some patients due to the discontinuation of medicine/missed doses. A particular area of concern raised by patients involved requirements to re-step through previously failed therapies when insurance changed.

Payers establishing step therapy with less expensive, off-label systemic agents and/or phototherapy should allow patients and clinicians to choose from multiple options rather than require patients to try multiple options.

Currently available specialty society guidelines are out of date and updated versions are expected in the coming year that may help shape policies regarding appropriate step therapy. Clinical experts at the ICER meeting stated that it may be reasonable for payers to require patients to step through a less expensive off-label systemic therapy, but these therapies have well-known adverse effects

and limited efficacy data that make it clinically inappropriate to require patients to attempt trials with all options prior to obtaining coverage for one of the newer agents. Prior agents include cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and interferon gamma. Cyclosporine may be a reasonable first-line agent for some patients, but the risk of renal toxicity requires patients to switch to another treatment after 6-12 months, so patients should not be required to try this agent after having an inadequate response to another systemic agent such as methotrexate that may be used for longer term use.

It is reasonable to include phototherapy as an option for first-step therapy, but lack of availability in many locations makes it inappropriate for payers to require patients to try phototherapy before receiving coverage for other options. The only exception would be a health plan/system that can provide good access to phototherapy at an out-of-pocket expense comparable to medication treatment options.

If multiple agents for severe atopic dermatitis are approved, payers should make available at least one biologic (dupilumab and/or tralokinumab) and at least one oral JAK inhibitor given how different these classes are in their onset of action and their risk profile. Clinician experts emphasized that the heterogeneity of atopic dermatitis and the challenges in defining and measuring disease severity support the need for having access to a range of different therapies. Specifically, clinical experts did not feel it would be appropriate to use step therapy that makes only one treatment available as the first step agent across biologics and oral JAK inhibitors. Some patients only have severe disease on a seasonal basis, making continual biologic treatment potentially less desirable than periodic use of a JAK inhibitor. Similarly, patients with asthma or more year-round severity are better candidates for biologic treatment. Clinical experts therefore strongly urged that at least one agent from both classes be available within any step therapy policy.

For ruxolitinib cream use in patients with mild to moderate atopic dermatitis, policy round table participants felt that stepping through other topical therapies such as a corticosteroid or calcineurin inhibitor was reasonable. Some clinical experts felt that since ruxolitinib cream may be used for younger patients as a steroid sparing medication, requiring stepping through a more potent topical steroid may not be appropriate. Manufacturers, Payers and Patient Advocacy Groups

Support pricing and rebate reform efforts that will create better rewards for clinical and economic value while also helping patients access and afford the treatments they need

It is widely recognized that the high prices of new prescription medications limit access to patients who may benefit from their use. Current pricing for medications is complex and the practice of using rebates and other methods to obscure the price of a therapy makes it difficult to assess whether the price being paid is in line with its effectiveness. Manufacturers and payers during the policy round table highlighted the potential impact of value-based pricing as helping to promote

transparency, affordability and promote access to new therapies. For example, upadacitinib has a much higher price after estimated rebates than other treatments, and it is possible that this drug can compete with a higher price largely because its manufacturer can tie formulary placement to rebates provided by other drugs made by that same manufacturer. This phenomenon, commonly known as "rebate walls," may in some cases provide an overall lower net cost to the payer, but it may only drive up the bubble between the list price and the net price for the benefit of pharmacy benefit managers and/or wholesalers, and it also creates true barriers to competition for new agents that have fewer indications or which are not made by companies that have other products whose rebates can be bundled together in negotiation. Unfortunately, there are no easy solutions to the role of rebates in the current system, but policy round table participants agreed that the federal government, plan sponsors, and other policy makers should work together to try to develop new approaches, such as indication-specific pricing, that can be piloted to create a pathway toward an end to the dominant role of bundled rebates.

Specialty Societies

Update treatment guidelines for patients with atopic dermatitis to reflect current treatment options in a form that is easy to interpret and use by clinicians, patients, and payers

Clinical societies should update their practice guidelines for managing patients with mild to moderate and moderate to severe atopic dermatitis to include newer therapies such as abrocitinib, baricitinib, dupilumab, tralokinumab and upadacitinib. Payers base their coverage decisions and integration of utilization tools to a great extent on clinical guidelines. The American Academy of Dermatology last updated it guidelines for the treatment of atopic dermatitis in 2014. The Joint Task Force on Practice Parameters for Allergy and Immunology, 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 issued updated treatment guidelines for atopic dermatitis in 2012. Current guidelines do not include newer approved agents for patients with atopic dermatitis such as dupilumab, approved by the FDA in 2017 or crisaborole cream, approved by the FDA in 2016; guidelines also do not discuss newer therapies that have not yet received FDA approval, such as IL-13 receptor antagonists and JAK inhibitors.

Policy round table participants highlighted that guidelines should not only provide information on options to be used by clinicians and patients for shared decision making, but also offer pragmatic advice about how to select specific therapies for specific subgroups. Payers expressed the need for updated guidelines from clinical societies with detailed guidance to permit meaningful stepped therapy approaches that permit reasonable clinical exceptions. For example, guidelines should distinguish use of agents in adolescents versus adults where there may be differences in the willingness to accept small but potentially serious risks and the need for rapid onset of

improvement.

Manufacturers and Researchers

Establish long-term registries that can be used to assess the benefits and harms of chronic use of oral JAK inhibitors for patients with atopic dermatitis

Concerns about uncommon but potentially serious risks of oral JAK inhibitors such as serious infections, cancer, blood clots and cardiovascular events when used for other conditions have led to boxed warnings. Whether these harms will also be seen when used in patients with moderate to severe atopic dermatitis requires larger, long-term follow-up studies that assess not only the durability of response but these infrequent risks among individuals using oral JAK inhibitors versus other biologic therapies such as dupilumab. Even the topical JAK inhibitor, ruxolitinib cream, has topical absorption and may warrant long-term follow-up, especially since it may be used in younger individuals. Even if it is not associated with systemic toxicity, topical ruxolitinib cream use might increase the risk of skin cancers.

Conduct research that directly compares real-world treatment options and sequential treatment effectiveness

Multiple stakeholders expressed concerns about the lack of information directly comparing new treatments and the need for active comparator trials. With the potential for having multiple newer therapeutic options that work through different mechanisms for patients with mild to moderate and moderate to severe atopic dermatitis, there is a great need for pragmatic research trials that compare different medications as they will be used by patients and clinicians in real world settings. Appropriate head-to-head trials would inform decision making by patients and clinicians. Trials that compare multiple treatment options, sequences and combinations are needed to identify comparative effectiveness, durability of benefit, and adverse effects. For example, trials should compare the net benefits of different oral JAK inhibitors or the tolerability and acceptance of oral versus injectable therapies for patients with moderate to severe disease.

Support the development of improved measures of disease severity and outcomes that are meaningful to patients

Clinical experts identified the lack of standard definitions of disease severity in atopic dermatitis as a challenge to identifying homogeneous patient populations for inclusion in clinical trials. We also heard from patient advocacy groups that endpoints used in clinical trials do not always measure what is most important to patients and families. For example, many endpoint measures focus on the appearance of the skin, something that may be important for an adolescent or young adult, but

may be less important for older patients. Though there are measures of itch, sleep, and interference in quality of life, these outcomes are not yet combined in ways that reflect the heterogeneity needed. Moreover, they are rarely translated into utility measures that can be incorporated into cost effectiveness analyses. Patient groups can take a leading role in collecting real-world data, as well as collaborating with researchers, manufacturers, and regulators to define a core set of severity and outcome measures and then in promoting their use in all clinical trials.

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):***[120] 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):***[121] 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):***[122] 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):***[123] 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):***[124] 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):***[125] 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):***[105] 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):***[126] 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):***[127] 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):***[128] 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[129]

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[130]

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[130]

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.[131,132] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[133] 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 May 26, 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 May 26, 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 May 26, 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 May 26, 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 May 26, 2021.**

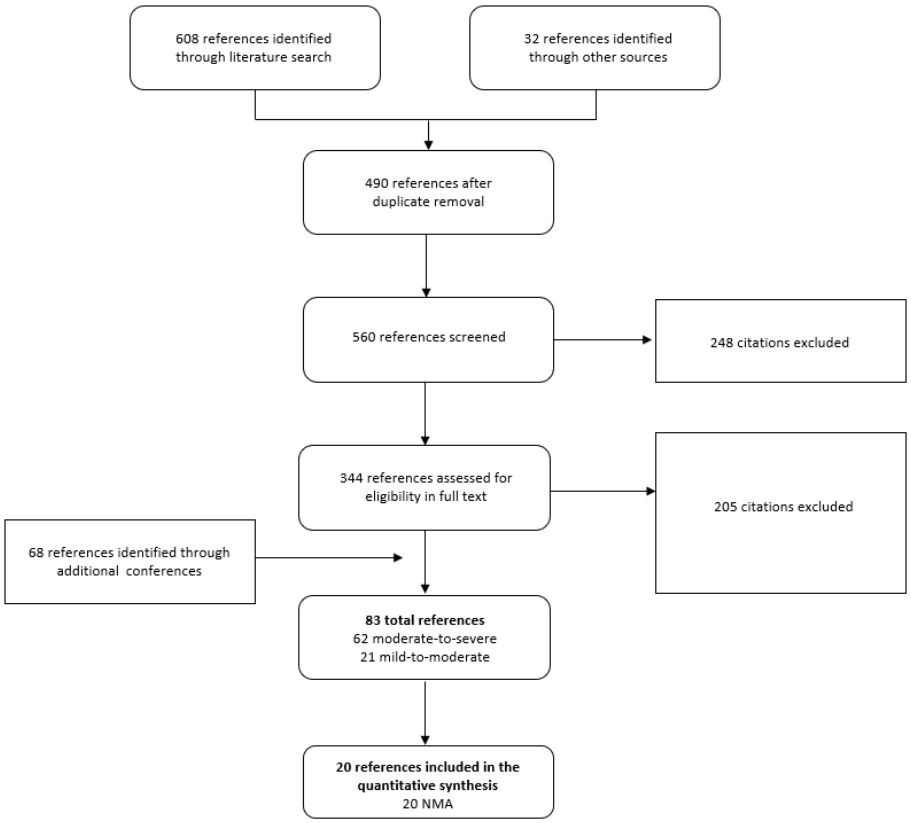
Table D1.7. Search Strategy of EMBASE SEARCH (Systematic Reviews)*

#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 May 26, 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.[134] 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).[135]

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.[136]

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 b) Combination only	Multinomial with probit link	a) 15 b) 6
IGA	a) Monotherapy only b) Combination only	Binomial with log link	a) 14 b) 6
PP-NRS≥4-point	a) Monotherapy only b) Combination only	Binomial with log link	a) 14 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	16	TRA 300 mg	591	131	575	144	591	295	591	196	591	108
		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	340	188			348	247	348	211
		DUP 300 mg	NR	NR	336	120			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	16	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
		PBO	244	11	213	10	244	30	244	15	244	6
BREEZE-AD 5	16	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
		PBO	147	8	123	7	147	19	147	12	147	5
SOLO 1	16	DUP 300 mg Q2W	244	85	213	87	224	154	224	115	224	80
		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

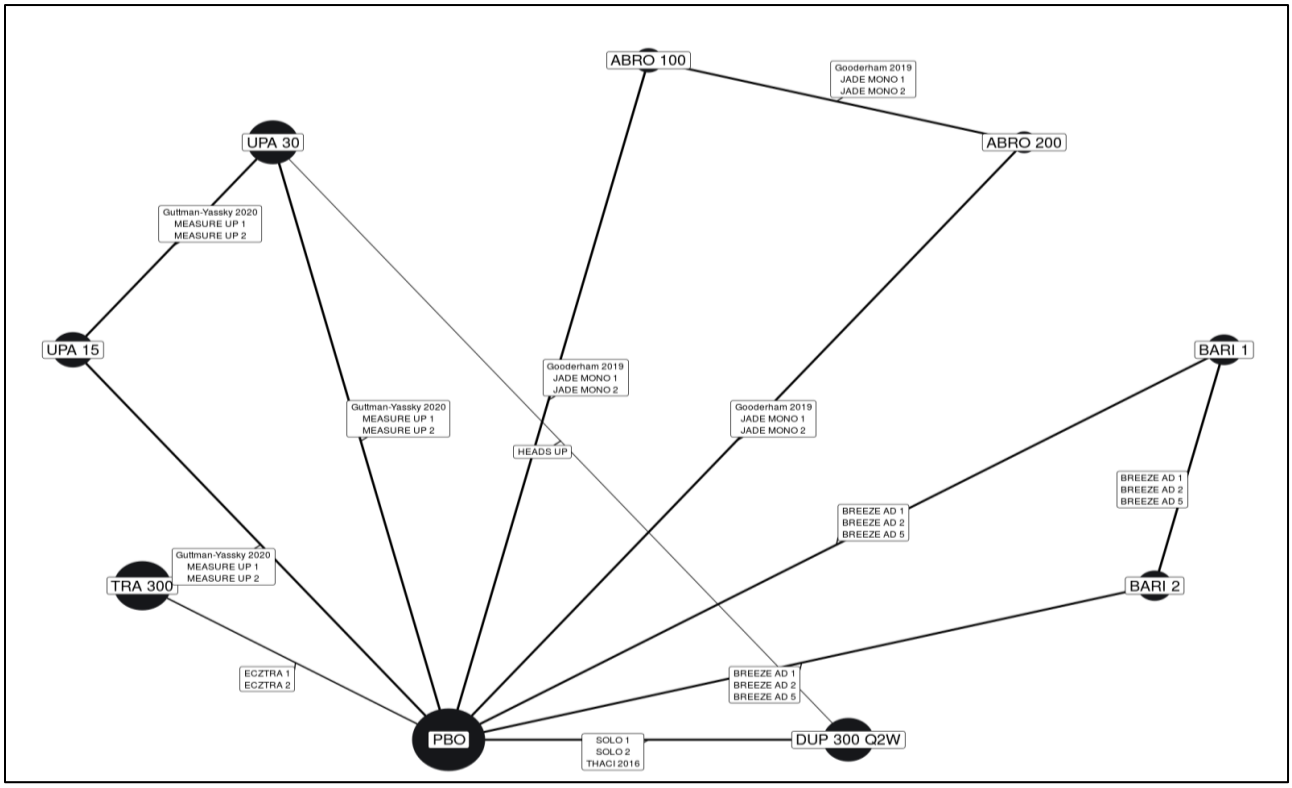
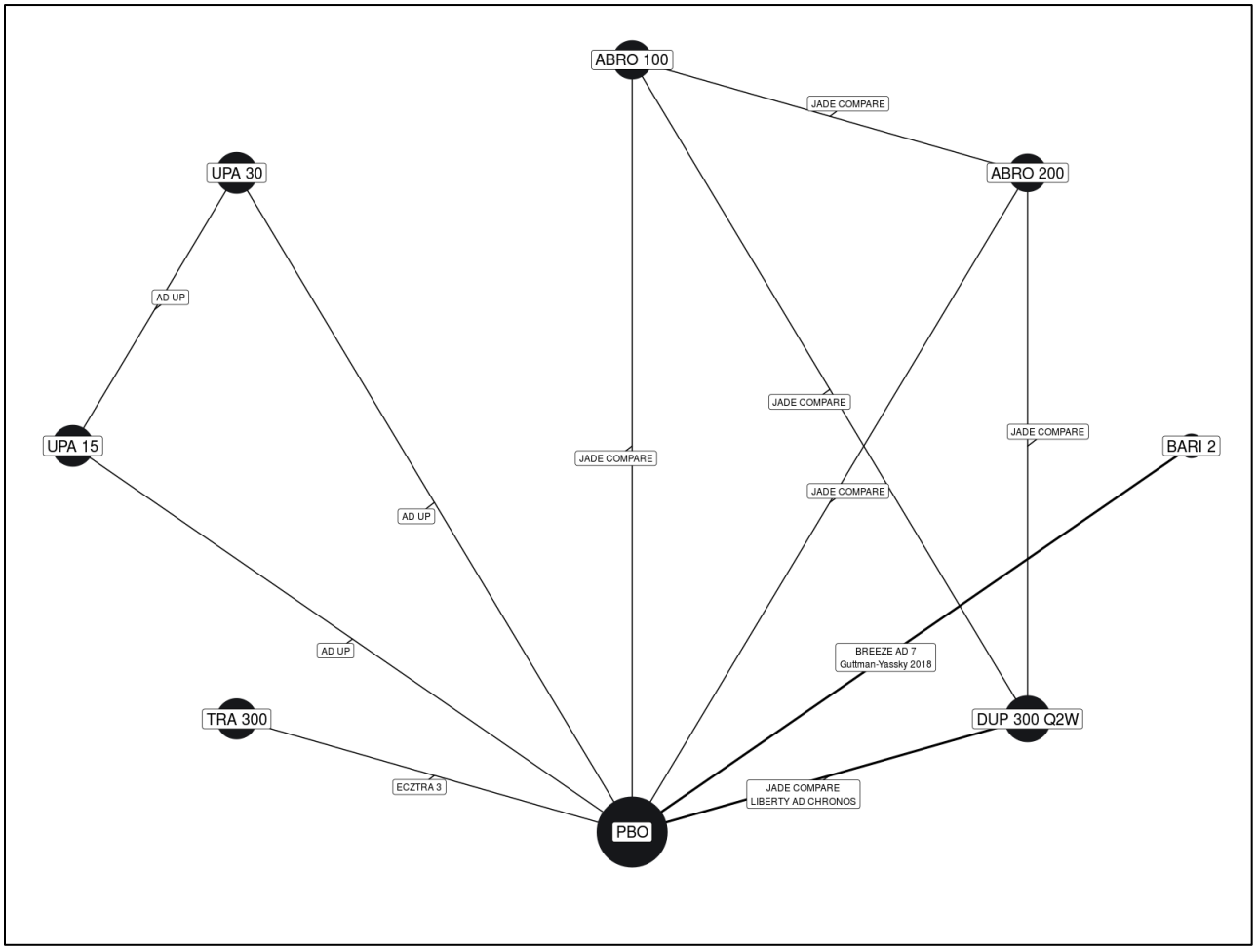


Figure D2.2. Network Figure. Combination Trials



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). Upadacitinib 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). Upadacitinib 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, upadacitinib (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).[76] 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.[82] The use of topical corticosteroids was permitted after Week 16 in BREEZE-AD5 and throughout BREEZE-AD6.[82] 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%).[82]

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).[78] 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.[78] 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. [81] [80] 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.[79] In this subgroup of patients, 59%-69% achieved EASI 75 with upadacitinib 15 mg.[79] 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.[79]

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.[81] 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.[79] IGA response was achieved by 58% of patients with upadacitinib 30 mg, 41% with upadacitinib 15 mg, and 11% with placebo.[79]

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	55.3	NR
	DUP 300 mg		NR	61.1	38.7	NR	35.7	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). [39,41,77] 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).[39,77]

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%).[81] [80] 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. [79] 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). [79]

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.[79] 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). [79]

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,[137] and one OLE of dupilumab in children with severe atopic dermatitis and adolescents with moderate-to-severe atopic dermatitis.[58,59] 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.[73] 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.[73] 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%.[73] 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.[73]

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[86,87,97]

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[86,87,97]

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 Pfizer NCT04345367	Phase IIIb, randomized, double-blind, multi-center N=600	Arm 1 Abrocitinib 200 mg + TCS Arm 2 Dupilumab 300 mg + TCS	**Inclusion** 18 years of age or older Diagnosis of chronic atopic dermatitis for at least 6 months Recent history of inadequate response to treatment with medicated topical therapy for AD or have required systemic therapies for control of their disease **Exclusion** Acute or chronic abnormality Increased risk of developing thromboembolism Unwilling to discontinue current medications Prior treatment with JAK inhibitors or IL-4 or IL-13	Change in PP-NRS4 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) Pfizer NCT03422822	Phase III, randomized, quadruple masking, Long-term extension study N=3000	Arm 1 Initial treatment period: Abrocitinib 100 mg For patients, whose dose was changed from abrocitinib 100 mg to placebo, placebo was administered for remainder of study Secondary treatment period: Abrocitinib 100 mg	**Inclusion** Aged 12 and older Must have completed a qualifying parent study **Exclusion** Other acute or chronic medical conditions Currently have active forms of inflammatory diseases Ongoing adverse event from parent study	Treatment-emergent adverse events Serious adverse events	December 1, 2023

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
		Arm 2 Initial treatment period: Abrocitinib 200 mg For patients, whose dose was changed from abrocitinib 200 mg to placebo, placebo was administered for remainder of study 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 Pfizer NCT03627767	Phase III, randomized withdrawal, double-blind N=1231	Arm 1 Abrocitinib 100 mg Arm 2 Abrocitinib 200 mg Arm 3 Placebo	**Inclusion** 12 years or older with a minimum weight of 40kg Diagnosed with atopic dermatitis Recent history of inadequate response or inability to tolerate topical AD treatments **Exclusion** Prior treatment with JAKs 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 Prof. Dr. Stephan Weidinger NCT04556461	Phase II, open-label, mono-center N=16	Tralokinumab 600 mg loading dose followed by 300 mg every 2 weeks	**Inclusion** Aged 18 and older with atopic dermatitis Subjects with a recent history of inadequate response to treatment with topical medications 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 Concurrent enrollment in another clinical trial Previous enrollment in a tralokinumab trial Subjects with mild atopic dermatitis		
Long-term Extension Trial in Subjects with Atopic Dermatitis Who Participated in Previous Tralokinumab Trials (ECZTEND) LEO Pharma NCT03587805	Phase III, open-label, long-term extension N=1125	Tralokinumab	**Inclusion** Completed the treatment period(s) of one of the parent trials Stable dose of emollient twice daily **Exclusion** Any condition requiring permeant discontinuation of the trial treatment Patients who participated in a parent trial and experienced a serious adverse event related to the treatment	IGA score of 0 or 1 EASI 75	September 13, 2021
Tralokinumab in Combination with Topical Corticosteroids in Japanese Subjects with Moderate to Severe Atopic Dermatitis (ECZTRA 8) LEO Pharma NCT04587453	Phase 3, randomized, double-blind N=100	Arm 1 Tralokinumab + topical corticosteroids Arm 2 Placebo + topical corticosteroids	**Inclusion** Japanese subject aged 18 years and above with AD for at least 1 year AD involvement of 10% or more of body surface area Applied a stable dose of emollient twice a day **Exclusion** Subjects who cannot take TCS Concomitant conditions Known primary immunodeficiency disorder Previous treatment with systemic immunosuppressive drugs, JAKs, or TCS.	IGA score of 0 or 1 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 AbbVie NCT04195698	assessment, open-label N=600		Successfully completed concomitant treatment in M16-046 study **Exclusion** Use of prohibited medications		
Evaluation of Upadacitinib in Adolescent and Adult Patients with Moderate to Severe Atopic Dermatitis AbbVie NCT03569293	Phase III, randomized, quadruple masked N=912	Arm 1 Upadacitinib dose A Arm 2 Upadacitinib dose B Arm 3 Placebo	**Inclusion** Chronic atopic dermatitis Moderate to severe AD Candidate for systemic therapy **Exclusion** Prior exposure to JAK inhibitor Other active skin disease	EASI 75 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 AbbVie NCT03568318	Phase III, randomized, double-blind N=969	Arm 1 Upadacitinib A + topical corticosteroids Arm 2 Upadacitinib B + topical corticosteroids Arm 3 Placebo + corticosteroids	**Inclusion** Chronic atopic dermatitis Moderate to severe AD Candidate for systemic therapy **Exclusion** Prior exposure to JAK inhibitor Other active skin disease	EASI 75 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 AbbVie NCT03646604	Open-label N=40	Arm 1 Ages 6 to 12 on low dose UPA Arm 2 Ages 6 to 12 on high dose UPA Arm 3 Ages 2 to 6 on low dose UPA Arm 4 Ages 2 to 6 on high dose UPA Arm 5	**Inclusion** Ages 2 months to 12 years of age Severe AD **Exclusion** Prior exposure to JAK	Maximum plasma concentration 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 Arm 6 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) AbbVie NCT03607422	Phase III, randomized, double-blind N=916	Arm 1 UPA dose A Arm 2 UPA dose B Arm 3 Placebo	**Inclusion** Moderate to severe AD Chronic AD for at least 3 years Ages 12 to 18 Documented history of inadequate response to topical corticosteroids or topical calcineurin inhibitor **Exclusion** Prior exposure to JAK inhibitor Other skin disease Unwilling to discontinue current medications	EASI75 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 AbbVie NCT03661138	Phase III, randomized, double-blind N=272	Arm 1 UPA dose A + topical corticosteroids Arm 2 UPA dose B + topical corticosteroids Arm 3 Placebo + topical corticosteroids	**Inclusion** Active moderate to severe AD Candidate for systemic therapy **Exclusion** Prior use of a JAK inhibitor 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" [138]

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[139]

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 trials[140-142 69 63,64,143-145]Weighted averages from drug trials[140-142 69 63,64,143-145]

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. [146]

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.

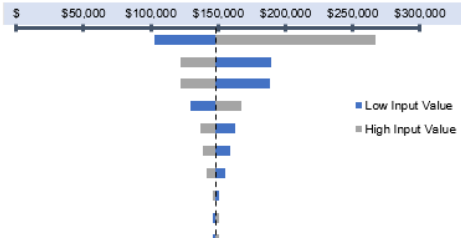
6. We use the same calculations in the comparator arm to derive its evLY.

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.

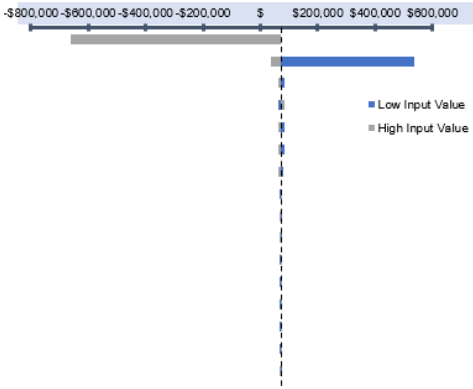
Figure E3.1 Tornado Diagram for Abrocitinib versus Standard of Care



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.

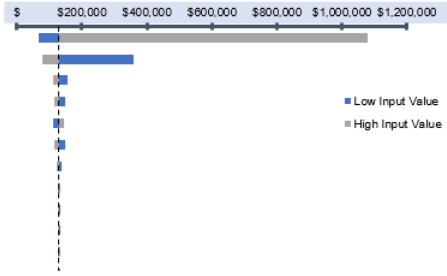
Figure E3.2 Tornado Diagram for Baricitinib versus Standard of Care



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.

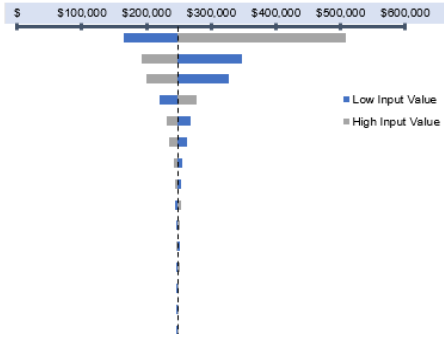
Figure E3.3 Tornado Diagram for Tralokinumab versus Standard of Care



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.

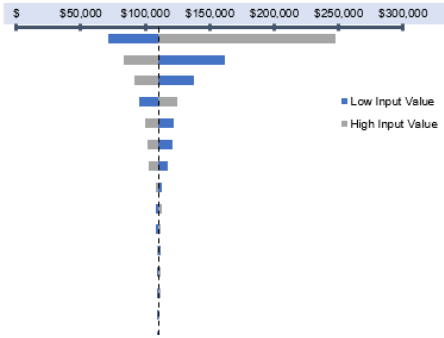
Figure E3.4 Tornado Diagram for Upadacitinib versus Standard of Care



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.

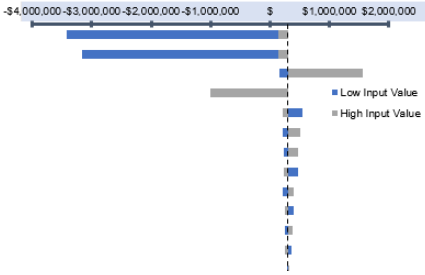
Figure E3.5 Tornado Diagram for Dupilumab versus Standard of Care



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.

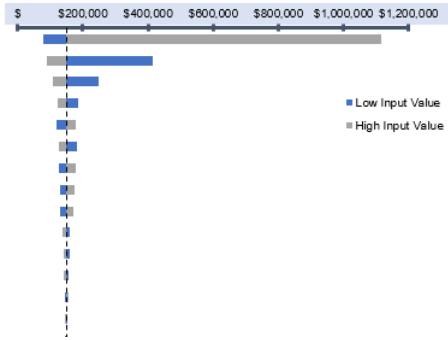
Figure E3.6. Tornado Diagram for Abrocitinib versus Dupilumab



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.

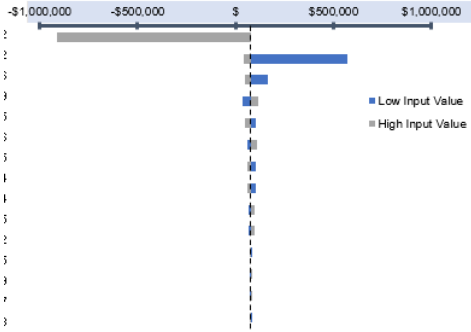
Figure E3.7 Tornado Diagram for Baricitinib versus Dupilumab



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.

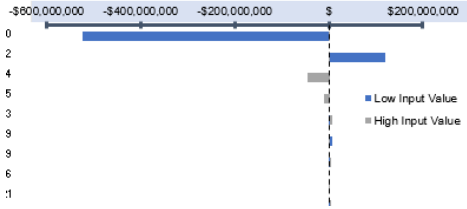
Figure E3.8 Tornado Diagram for Tralokinumab versus Dupilumab



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	(0.56 - 0.71)
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	(0.15 - 0.21)
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	($32,268 - $32,508)
Total QALYs	3.22	(3.00 - 3.45)	2.99	(2.72 - 3.26)	0.23	(0.18 - 0.27)
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	(0.50 - 0.59)
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	(0.44 - 0.57)
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	(0.12 - 0.14)
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	(-$44,359 - -$41,007)
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	(-$26,616 - -$24,199)
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.[147]

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)[148].

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.[149,150] 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.[149] 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.[150] 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.[116] 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).[151] 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.[151] For adolescents (age 12-17), evidence suggests 389,000 US individuals have moderate-to-severe uncontrolled disease and are eligible for treatment.[151] 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.[152] 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.[153,154] 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

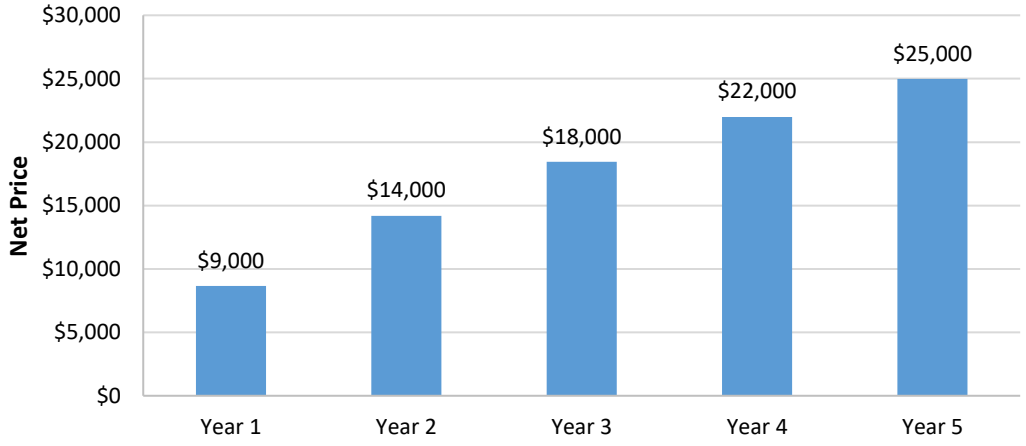
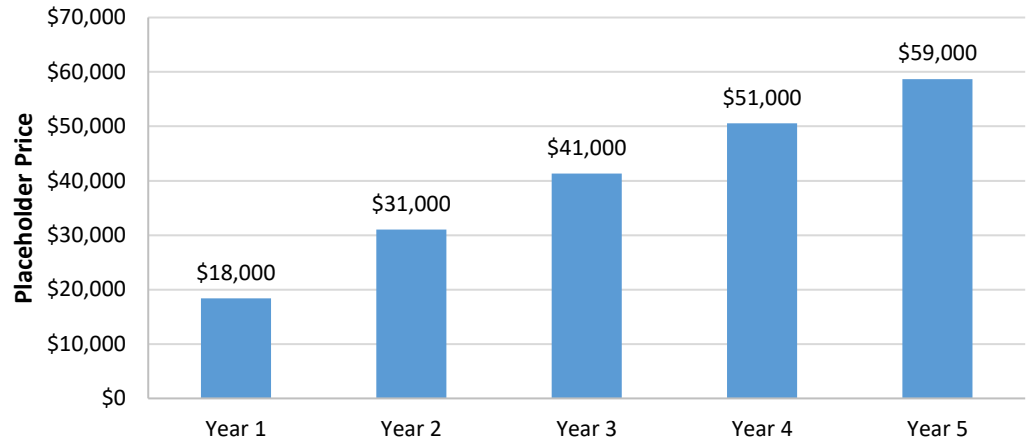
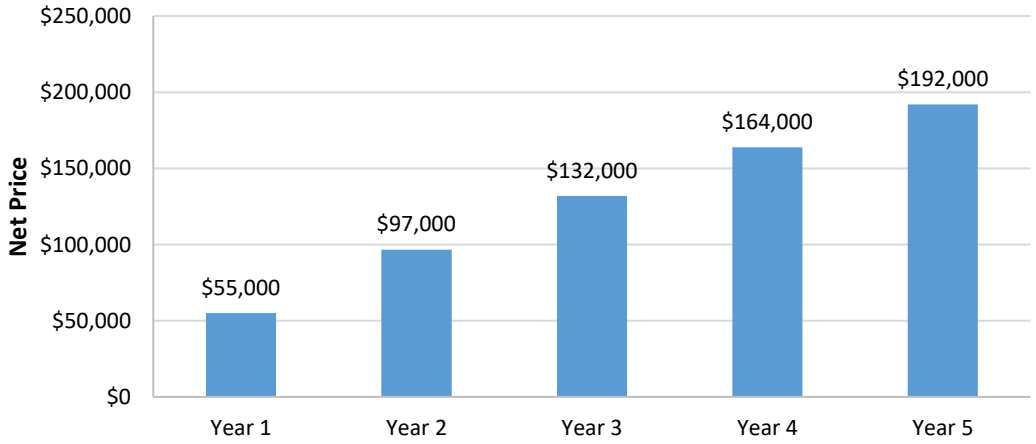


Figure F3. Cumulative Net Cost Per Patient Treated with Tralokinumab for Five Years at Placeholder $31,100 per Year Price*



* 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[35-37,40,42,45,46,48,50,51,56,63,64,69,80,81]

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[35,75,155] Simpson 2020 Lancet + Simpson 2021 RAD Abstract	N= 387 Ages 12+ with moderate to severe atopic dermatitis DB, PC, RCT	Once-daily oral administration in one of the following doses for 12 weeks: •Abrocitinib 200 mg •Abrocitinib 100 mg •Placebo	**Prohibited medication:** concomitant topical therapies (corticosteroids, calcineurin inhibitors, tars, antibiotic creams, and topical antihistamines) •If receiving non-AD related concomitant medications, must be on stable regimen. •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 •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 • 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 •Prior treatment with JAK inhibitors •Other active non-AD skin diseases •Medical history including thrombocytopenia, coagulopathy, or platelet dysfunction, current or history of certain infections, cancer, lymphoproliferative disorders
Phase III JADE MONO-2[36,75,156] Silverberg 2020 JAMA Dermatology	N=391 Ages 12+ with moderate to severe atopic dermatitis DB, PC, RCT	Once-daily oral administration in one of the following doses for 12 weeks: •Abrocitinib 200 mg •Abrocitinib 100 mg •Placebo	**Permitted medication: O**ral antihistamines and topical non-medicated emollients **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 •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 •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 •Prior treatment with JAK inhibitors •Other active non-AD skin diseases •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[39,41,77,84] Pfizer data on file + Eichenfield 2021 AAAI Abstract + Eichenfield 2021 RAD Abstract	N=285 Ages 12-17 with moderate to severe atopic dermatitis DB, PC, RCT	Once-daily oral administration in one of the following doses for 12 weeks: •Abrocitinib 200 mg •Abrocitinib 100 mg •Placebo	**Permitted medication:** background topical therapy **Permitted medication:** NR	•Age: ≥12-17 years with minimum body weight of 40 kg •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 •Unwilling to discontinue current AD medications prior to the study or require treatment with prohibited medications during the study •Prior treatment with JAK inhibitors •Other active non-AD inflammatory skin diseases or conditions affecting skin •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] Bieber 2021 NEMJ + Pfizer data on file	N= 837 Adults 18+ with moderate to severe atopic dermatitis DB, PC, RCT	•Abrocitinib (200 mg) + placebo Q2W (to Week 16)→abrocitinib (200 mg) (Week 20) •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) •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 •Medical history including thrombocytopenia, coagulopathy or platelet

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
		16) →abrocitinib (100 mg) (Week 20) •Dupilumab (300 mg; with a 600 mg loading dose at baseline) + placebo once-daily to Week 16) →placebo once-daily (Week 20) •Placebo + dupilumab Q2W (to Week 16) →abrocitinib (100 mg) (Week 20) •Placebo + dupilumab Q2W (to Week 16) →abrocitinib (200 mg) (Week 20) 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. •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 •Other active nonAD inflammatory skin diseases or conditions affecting skin •Prior treatment with JAK inhibitors •Previous treatment with dupilumab •Unwilling to discontinue current AD medications prior to study or require treatment with prohibited medications during study
Phase III JADE EXTEND[76,107] Reich 2021 Abstract and Shi 2021 Abstract	N=1116 Ages 12+ moderate to severe AD	•Abrocitinib 200-mg •Abrocitinib 100-mg	NR	•Patients ages 12+ and meets minimum body weight •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 •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 •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) •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 •Ongoing AE in the qualifying Parent study that is an ongoing safety concern
Phase IIb[40,157] Gooderham 2019	N= 267 Ages 18 to 75 with a clinical diagnosis of moderate to severe atopic dermatitis	Abrocitinib 10 mg Abrocitinib 30 mg **Abrocitinib 100 mg** **Abrocitinib 200 mg** **Placebo**	**Permitted medication:** oral antihistamines and nonmedicated emollient (CeraVe lotion [CeraVe]; or Aquaphor [Beiersdorf Inc]) and sunscreen (both provided by the sponsor) **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[42,108] Simpson 2020 BJD	Adults 18+ with moderate to severe AD DB, PC, RCT	Daily dose for 16 weeks: •Baricitinib 4 mg (High) •Baricitinib 2 mg (Mid) •Baricitinib mg (Low) •Placebo	**Provided/required:** emollient **Prohibited:** intra-articular corticosteroid injection, parenteral corticosteroids, JAK inhibitor treatment, monoclonal antibody	• Diagnosed with moderate to severe Atopic Dermatitis for ≥ 12 months • Inadequate response or intolerance to existing topical medications within 6 months of screening • Willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period) • Agree to use emollients daily	•History of other concomitant skin conditions, skin disease or eczema herpeticum •Currently experiencing a skin infection or illness that requires or is being treated with topical or systemic antibiotics or corticosteroids •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 •Have high blood pressure •Had major surgery within the past 8 weeks •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 •Have a history or presence of cardiovascular, respiratory, hepatic, liver, gastrointestinal, endocrine, hematological, neurological, lymphoproliferative disease or neuropsychiatric disorders •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[42,109] Simpson 2020 BJD	Adults 18+ with moderate to severe AD DB, PC, RCT	Daily dose for 16 weeks: •Baricitinib 4 mg (High) •Baricitinib 2 mg (Mid) •Baricitinib 1 mg (Low) •Placebo	**Provided/required:** emollient **Prohibited:** intra-articular corticosteroid injection, parenteral corticosteroids, JAK inhibitor treatment, monoclonal antibody	• Diagnosed with moderate to severe Atopic Dermatitis for ≥ 12 months • Inadequate response or intolerance to existing topical medications within 6 months of screening • Willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period) • Agree to use emollients daily	•History of other concomitant skin conditions, skin disease or eczema herpeticum •Currently experiencing a skin infection or illness that requires or is being treated with topical or systemic antibiotics or corticosteroids •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 •Have high blood pressure •Had major surgery within the past 8 weeks •Have experienced any of the following within 12 weeks of screening: VTE, myocardial infarction (MI), unstable ischemic heart disease, stroke, heart failure. •Have a history of recurrent (≥ 2) VTE or are considered at high risk of VTE •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 •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] Eli Lilly Oct 31, 2020 (Press release) + Eli Lilly data on file	Adults 18+ with moderate to severe AD DB, PC, RCT	•Baricitinib 4 mg •Baricitinib 2 mg •Placebo	**Not reported**	• Have completed the final active treatment visit for an originating study eligible to enroll participants directly into study BREEZE-AD3 OR • Meet criteria for NCT03334396 or NCT03334422.	• Had investigational product permanently discontinued at any time during a previous baricitinib study. • 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] Simpson 2021 JAAD + Eli Lilly data on file	N=440 Adults 18+ with moderate to severe AD DB, PC, RCT	Daily dose for 16 weeks: •Baricitinib 2 mg (Mid) •Baricitinib 1 mg (Low) •Placebo	Not reported	• Diagnosed with moderate to severe Atopic Dermatitis for ≥12 months, including all of the following: • EASI score ≥16 • IGA score of ≥3 • ≥10% of BSA involvement • Inadequate response or intolerance to existing topical medications within 6 months of screening • Willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period) • 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 • History of eczema herpeticum within 12 months, and/or a history of 2 or more episode of eczema herpeticum in the past • Participants who are currently experiencing a skin infection that requires treatment, or is currently being treated, with topical or systemic antibiotics • 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) • Treated with the following therapies: • Monoclonal antibody

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
					for less than 5 half-lives before randomization • Received prior treatment with any oral JAK inhibitor less than 4 weeks before randomization • 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 • Have had an intra-articular corticosteroid injection within 6 weeks of planned randomization • Probenecid at the time of randomization that cannot be discontinued for the duration of the study • Have high blood pressure • Had major surgery within the past 8 weeks • 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 • Have a history of VTE, or are considered at high risk

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
					for VTE • 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 • 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[82] 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) • Have moderate to severe AD, including all of the following: EASI score ≥16, IGA score of ≥3, 10%- 50% BSA involvement • Have had inadequate response or intolerance to existing topical (applied to the skin) medications within 6 months preceding screening. • Are willing to discontinue certain treatments for eczema (such as systemic and topical treatments) • Agree to use emollients daily.	•Are currently experiencing or have a history of other concomitant skin conditions (e.g., psoriasis or lupus erythematosus) •A history of eczema herpeticum within 12 months •Skin infection requiring treatment with topical or systemic antibiotics. •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 •Have high blood pressure characterized by a repeated systolic blood pressure >160 millimeters of mercury (mm Hg) or diastolic blood pressure >100 mm Hg. •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 •Have a history of VTE, cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematological, neurological, lymphoproliferative disease or neuropsychiatric disorders •Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis
Phase III BREEZE-AD7 Reich 2020[46,47] Reich 2020 JAMA	≥18 years of age, moderate-to-severe atopic dermatitis DB, PC, RCT	•Baricitinib 4 mg QD + TCS •Baricitinib 2 mg QD + TCS •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/l 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] Guttmann-Yassky 2018 JAAD	≥18 years of age, moderate-to-severe atopic dermatitis DB, PC, RCT	•Baricitinib 4 mg QD + TCS •Baricitinib 2 mg QD + TCS •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] Wollenburg 2020 British Journal of Dermatology + LeoPharma data on file	N= 802 Adults 18+ with moderate to severe atopic dermatitis	**Pre-initial treatment (day 0):** • Tralokinumab 600 mg loading dose **Initial treatment period (16 weeks):** • Tralokinumab 300 mg injection (2 injections of 150 mg each) Q2W • Placebo Q2W **Maintenance treatment period (36 weeks):** • Tralokinumab 300 mg injection Q2W • Tralokinumab 300 mg injection Q4W • Placebo	**Provided:** patients instructed to use emollient twice daily	•Age 18+ •Diagnosis of AD for ≥1 year •Subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable. •AD involvement of ≥10% body surface area at screening and baseline. •EASI≥12 screening, ≥16 at baseline •IGA≥3 •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. •Use of tanning beds or phototherapy 6 weeks prior to randomization. •Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomization. •Treatment with TCS and/or TCI within 2 weeks prior to randomization. •Active skin infection within 1 week prior to randomization. •Clinically significant infection 4 weeks prior to randomization. •A helminth parasitic infection within 6 months prior study entry. •Tuberculosis requiring treatment within the 12 months prior to screening. •Known primary immunodeficiency disorder. •Positive HepB or HepC

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

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

Phase III ECZTEND[78] Blauvelt 2021 RAD Abstract	N=1175 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 • 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 • 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 • Subjects who, during the parent trial, developed an AE or SAE related to tralokinumab that led to temporary discontinuation of trial treatment • Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to baseline • Treatment with topical phosphodiesterase 4 inhibitors within 2 weeks prior to baseline • A helminth parasitic infection • Tuberculosis requiring treatment within 12 months prior to screening
Upadacitinib					
Phase III MEASURE UP 1[71,80] Guttman-Yassky 2021 Lancet + Simpson 2021 AAD VMX Abstract	N= 847 Ages 12-75 years with moderate to severe AD DB, PC, RCT	**Week 1-16:** • Upadacitinib 30 mg • Upadacitinib 15 mg • Placebo **After Week 16**: • Upadacitinib 30 mg • 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 • Candidate for systemic therapy or have recently required systemic therapy for atopic dermatitis	• Prior exposure to any JAK inhibitor • Unable or unwilling to discontinue current AD treatments prior to study • Requirement of prohibited medications during the study • Other active skin diseases/infections requiring systemic treatment or would interfere with appropriate assessment of atopic dermatitis lesions

Phase III MEASURE UP 2[71,80] Guttman-Yassky 2021 Lancet + Simpson 2021 AAD VMX Abstract	N= 836 Ages 12-75 years with moderate to severe AD DB, PC, RCT	**Week 1-16:** • Upadacitinib 30 mg • Upadacitinib 15 mg • Placebo **After Week 16:** • Upadacitinib 30 mg • 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 • Candidate for systemic therapy or have recently required systemic therapy for atopic dermatitis	• Prior exposure to any JAK inhibitor • Unable or unwilling to discontinue current AD treatments prior to study • Requirement of prohibited medications during the study • Other active skin diseases/infections requiring systemic treatment or would interfere with appropriate assessment of atopic dermatitis lesions
Phase III AD-UP (with TCS)[71,81] Reich 2021 Lancet + Simpson 2021 AAD VMX Abstract	N~901 Ages 12-75 with moderate to severe AD DB, PC, RCT	**Week 1-16** • Upadacitinib 30 mg + topical corticosteroids (TCS) • Upadacitinib 15 mg + TCS • Placebo + TCS **After Week 16:** • Upadacitinib 30 mg + TCS • Upadacitinib 15 mg + TCS	**TCS** prohibited meds, no details	• Active moderate to severe atopic dermatitis defined by EASI, IGA, BSA, and pruritus • Candidate for systemic therapy or have recently required systemic therapy for atopic dermatitis • Able to tolerate topical corticosteroids for atopic dermatitis lesions	• Prior exposure to any JAK inhibitor • Unable or unwilling to discontinue current AD treatments prior to study • Requirement of prohibited medications during the study • Other active skin diseases/infections requiring systemic treatment or would interfere with appropriate assessment of atopic dermatitis lesions

Phase IIIb Heads Up[70,83] Blauvelt 2021 JAMA Dermatology + AbbVie data on file	N= 692 Adults 18 and older with moderate to severe AD MC, RCT, DB, DD, AC	**Dose for 24 weeks** *Arm 1* Upadacitinib 30 mg daily (oral) Placebo *Arm 2* Dupilumab 300 mg every other week (subcutaneous) Placebo	**Permitted:** topical emollients **Prohibited Medications:** JAK inhibitors, prior dupilumab use, TCS, TCIs	Patients 18 and older with moderate to severe AD 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. Participant is a candidate for systemic therapy or have recently required systemic therapy for AD.	Participant has prior exposure to Janus Kinase (JAK) inhibitor. Participant has prior exposure to dupilumab. Participant is unable or unwilling to discontinue current AD treatments prior to the study. Participant has requirement of prohibited medications during the study. Participant has other active skin diseases or skin infections requiring systemic treatment or would interfere with appropriate assessment of AD lesions. Female participant who is pregnant, breastfeeding, or considering pregnancy during the study.
Phase IIb[69,158] Guttman-Yassky 2020 Allergy and Immunology + Reich 2021 RAD Abstract	N=167 Ages 18-75 years with moderate to severe AD DB, PC, RCT	**Week 1-16 (period 1):** •upadacitinib 30 mg QD •upadacitinib 15 mg QD •upadacitinib 7.5 mg QD •placebo **Week 16-88 (period 2 - rerandomization stratified by EASI**	**Permitted:** emollient, orally administered antibiotics for superficial skin infections **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. •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). •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. •Prior exposure to dupilumab or exposure to systemic therapies for AD including corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4

		75 response at week 16): •upadacitinib 30 mg QD •upadacitinib 15 mg QD •upadacitinib 7.5 mg QD •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). •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. •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] Simpson 2016 NEMJ	≥18 years of age, moderate-to-severe atopic dermatitis DB, PC, RCT	**Dosing until week 16:** Dupilumab monotherapy 300 mg/wk, s.c.(n=223) dupilumab 300 mg s.c. every other week alternating with placebo (n=224) Placebo (n=224)	**Prohibited:** Prohibited concomitant medications included topical glucocorticoids and calcineurin inhibitors, immunomodulating biologic agents, systemic glucocorticoids, and nonsteroidal systemic immunosuppressants. Also prohibited procedures: Phototherapy, tanning bed or booth, and major elective surgeries **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 • Treatment with immunosuppressive/immunomodulatory drugs or phototherapy for atopic dermatitis within 4 weeks of baseline • Treatment with topical corticosteroids or topical calcineurin inhibitors within 1 week of baseline • Regular use (>2 visits per week) of a tanning booth/parlor within 4 weeks of the baseline visit • Planned or anticipated use of any prohibited medications and procedures during study treatment • 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 • Presence of skin comorbidities that may interfere with study assessments

Phase III LIBERTY AD SOLO 2[51] Simpson 2016 NEMJ	≥18 years of age, moderate-to-severe atopic dermatitis DB, PC, RCT	**Dosing until week 16:** Dupilumab monotherapy 300 mg/wk, s.c.(n=239) Dupilumab 300 mg s.c. every other week alternating with placebo (n=233) Placebo (n=236)	**Prohibited:** Prohibited concomitant medications included topical glucocorticoids and calcineurin inhibitors, immunomodulating biologic agents, systemic glucocorticoids, and nonsteroidal systemic immunosuppressants. Also prohibited procedures: Phototherapy, tanning bed or booth, and major elective surgeries **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] Blauvelt 2017 Lancet	≥18 years of age, moderate-to-severe atopic dermatitis DB, PC, RCT	**Day 1 (Loading dose)** •Dupilumab 600 mg •placebo **Day 1-Week 16** •Dupilumab 300 mg QW + TCS •Dupilumab 300 mg Q2W + TCS •Placebo QW + TCS	**provided during study:** TCS (medium/low potency) w/ or w/o TCIs (where inadvisable for TCS) **Permitted concomitant meds:** any medications other than those that were prohibited **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 •Documented recent history (within 6 months before the screening visit) of inadequate response to a sufficient course of outpatient treatment with topical AD meds •IGA score ≥3, on the IGA scale of 0–4, BSA affected ≥10%, EASI score of ≥16, PP-NRS average score ≥3 •Applied moisturizers at least twice daily for the 7 days before randomization	•Participation in a prior dupilumab clinical trial •Important side effects of topical medication (e.g., intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects) •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 •Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit •History or current positive HIV •Positive HepB or HepC antibody at the screening visit •Active or acute infection requiring systemic treatment within 2 weeks before baseline visit •Known or suspected history of immunosuppression
Phase III AD SOLO-CONTINUE[54] Worm 2019 JAMA	N= 422 re-randomized patients from SOLO to SOLO-CONTINUE Dupilumab-treated patients who has achieved IGA score of 0 or	Re-randomized 2:1:1:1 **Original regimen** (300 mg QW or Q2W) or **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. DB, PC, RCT	or **Placebo**			
Phase IIb Thaci 2016[56,57] Thaci 2016 Lancet + Simpson 2016 JAAD	18 and older with moderate to severe atopic dermatitis N= 380 DB, PC, RCT, dose ranging	Dupilumab 300 mg once a week (n = 63) **Dupilumab 300 mg every 2 weeks (n= 64)** **Dupilumab 200 mg every 2 weeks (n = 61)** **Dupilumab 300 mg every 4 weeks (n= 65)** Dupilumab 100 mg every 4 weeks (n = 65) **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 [35-37,39,40,42,44-48,50,51,54,56,63,64,67,69,76-78,80-84,107]

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	14.1	194	56.4	NR	NR	25	14.8	171	49.7	173	50.3
	UPA 30 mg	348	36.6	14.6	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
	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

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 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 II[35-37,39,40,42,44-48,50,51,54,56,63,64,67,69,76-78,80-84,107]

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	7.4	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 III[35-37,39,40,42,44-48,50,51,54,56,63,64,67,77,78,80-82,84]

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 IV[36,44-47,50,51,54,80]

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[35-37,40,42,45,46,48,50,51,56,63,64,67,69,80,81,84]

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[35-37,40,42,45,46,48,50,51,56,63,64,67,69,80,81,83,84]

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[35-37,40,42,45,46,48,50,51,56,63,64,69-71,80,81,83,84]

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	38.7	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 [35-37,39,40,42,45,46,48,50,51,56,63,64,69-71,80,81,83,84]

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	35.7	-49	2	REF	NR	REF
	UPA 30 mg	348	188	340	55.3	-66.9	1.9	-17.8	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 [35-37,39,40,42,45,46,48,50,51,56,63,64,69-71,80,81,84,155,156]

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[35-37,39,40,42,45,46,48,50,51,56,63,64,69-71,80,81,84]

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[35-37,39,40,42,45,46,48,50,51,56,63,64,69-71,80,81,84]

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[42-46,48,50-56,60,64-66,70,155]

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
ECZTRA 1	**Week 16**							
	PBO	197	197	[redacted]				
	TRA 300 mg	601	601					
ECZTRA 2	PBO	201	201					
	TRA 300 mg	591	591					
ECZTRA 3	PBO + TCS	126	126					
	TRA 300 mg + TCS	252	252					
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

Study Name	Arms	N	Total HADS					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
	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
Phase IIb Thaci 2016	PBO QW	61	61	LSM: 0	SE: 0.8	NR	NR	REF
	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[35-37,39,46,50-56,60,63-66,69,84,155,157]

Study Name	Arms	HADS Anxiety					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
Abrocitinib							
	Week 12						
JADE MONO-1	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

Study Name	Arms	HADS Anxiety					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
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						
	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

Study Name	Arms	HADS Anxiety					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
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[35-37,39,46,50-56,60,63-67,84,155,157]

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

Study Name	Arms	HADS Depression					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
	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
	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[43,44,50,54,55,63-65,76,78,82,107,158,159]

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[43,44,50,54,55,63-65,76,78,82,83,107,158,159]

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	205	344	59.5	NR	NR	NR
	UPA 30 mg	348	223	348	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[50,54,55,64,65,76,78,83,107]

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	164	344	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	193	348	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[50,54,76,83,107,158]

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	**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
Subgroup 1*	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	141	336	41.9	NR	NR	NR
	UPA 30 mg	348	171	340	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[35,36,39,53,60,79]

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[35,36,60-62,79]

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[39,55,65,75]

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[39,53,55,75]

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	%
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[35-37,39,41-46,48,50-56,58-60,63-67,69,70,77,83]

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	216	62.8	NR	NR	122	35.3	4	1.2	4	1.2	NR	NR
	UPA 30 mg	348		249	71.6	NR	NR	153	44	7	2	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[35-37,41-43,45,46,48,51,56,63,64,66,67,69,83,84]

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	0	0	0	0	0	0	0	0
	UPA 30 mg	348		1	0.3	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[35-37,41-43,45,46,48,51,53,56,63-66,69,70,79,83,84]

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	3‡	0.9	2	0.6	0	0	1	0.3	29	8.4
	UPA 30 mg	348		NR	NR	NR	NR	7‡	2	4	1.1	0	0	0	0	5	1.4
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[50,53,54,60-64,67,76,78,83,107]

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[50,53,54,60,63,64,69,83,107]

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	0	0	0	0	NR	NR
	UPA 30 mg	348		1	0.3	0	0	0	0	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[50,53-55,60-64,67,78,83]

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[92,95]

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 TRuE-AD1 (poster)[85,88,89] Papp, K. 2020	N~600 DB, PC, RCT Adolescents aged 12-17 and adults aged 18+ with mild-to-moderate AD	Applied twice daily for 8 weeks: • ruxolitinib cream 1.5% • ruxolitinib cream 0.75% • vehicle (placebo) cream 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. • Participants with AD for ≥ 2 years. • Participants with an IGA score of 2 to 3 at screening and 0 to 4 at Week 8 • Participants with % BSA (excluding scalp) of AD involvement of 3% to 20% at screening and 0% to 20% at Week 8 • Participants who agree to discontinue all agents used to treat AD during trial • Willingness to avoid pregnancy or fathering of children	Primary Endpoint at week 8: •IGA-TS response rate Secondary Endpoints at week 8: •EASI-75 response rate •Itch NRS 4-point improvement response rate •PROMIS Short Form-Sleep Disturbance 6-point improvement response rate •SCORAD, mean change from baseline
Phase III TRuE-AD2 (Poster)[85,88,89] Papp, K. 2020	N~600 DB, PC, RCT Adolescents aged 12-17 and adults aged 18+ with mild-to-moderate AD	Applied twice daily for 8 weeks: • ruxolitinib cream 1.5% • ruxolitinib cream 0.75% • vehicle (placebo) cream 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. • Participants with AD for ≥ 2 years. • Participants with an IGA score of 2 to 3 at screening and 0 to 4 at Week 8 • Participants with % BSA (excluding scalp) of AD involvement of 3% to 20% at screening and 0% to 20% at Week 8 • Participants who agree to discontinue all agents used to treat AD during trial • Willingness to avoid pregnancy or fathering of children	Primary Endpoint at week 8: •IGA-TS response rate Secondary Endpoints at week 8: •EASI-75 response rate •Itch NRS 4-point improvement response rate •PROMIS Short Form-Sleep Disturbance 6-point improvement response rate •SCORAD, mean change from baseline

Trial	Patient Population	Interventions	Inclusion Criteria	Key Outcomes
Phase II[86,87] Kim 2020, Kim 2019	N= 307 randomized, dose-ranging Adults 18 to 70 with active atopic dermatitis	Vehicle BID (n=52) Triamcinolone 0.1% BID (n=51) RUX 0.15% QD (n= 51) RUX 0.5% QD (n=51) RUX 1.5% QD (n=52) RUX 1.5 % BID (n=50) Prohibited concomitant therapy: systemic and topical treatments	• Patients aged 18–70 years with active atopic dermatitis • History of AD >2 years • IGA of 2 or 3 • BSA involvement of 3%–20%	Primary endpoint: mean percentage change from baseline EASI score at week 4 Secondary Endpoints: responder rates (IGA and EASI), itch NRS score, and safety
Crisaborole				
Phase III[95] AD 301	N=763 RCT, MC, DB, vehicle-controlled phase III studies Patients 2 and older with mild to moderate AD	Crisaborole or Vehicle cream 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) 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 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[95] AD 302	N= 764 RCT, MC, DB, vehicle-controlled phase III studies Patients 2 and older with mild to moderate AD			
Phase III AD 303 Long-term safety study[90] Eichenfield 2017	Patients 2 and older with mild to moderate AD MC, OL, LTE safety study N= 517	Crisaborole 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 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[91,93,94,96]	*Same as AD 301/302*	*Same as AD 301/302*	*Same as AD 301/302*	QoL
Phase IV CrisADe CARE 1[92] Schlessinger 2020	N= 137 MC, PK, OL, single arm 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 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[86-96]

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[86-89,91-96,98-100,102]

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[86-96,98-100,102]

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[86-97]

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[73,74]

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[86-90,97,98,100,102]

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[86-89,97,100,102]

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[88,89]

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[91,92,94,96,98]

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[85-96,98,102]

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[73,74]

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[101,103]

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[101,103]

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[101,103]

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[101,103]

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.

H. Public Comments

This section includes summaries of the public comments prepared for the New England CEPAC Public Meeting on July 23, 2021. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. One speaker did not submit a summary of their public comments.

A video recording of all comments can be found here. Conflict of interest disclosures are included at the bottom of each statement for each speaker.

Andrew J. Thorpe, PhD, Pfizer Inc.
Senior Medical Director, US Dermatology Team Leader
North America Medical Affairs, Inflammation, and Immunology

Pfizer would like to acknowledge the ICER staff and consultants, and the numerous stakeholders who have contributed to the review of "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis (AD)."

Pfizer is dedicated to the development of breakthrough therapies that change patients' lives, including those living with AD. Abrocitinib is an oral, once-daily, small molecule that selectively inhibits JAK 1 and is under investigation for the treatment of moderate-to-severe AD. Over the course of our work, we have heard directly from patients, families, advocacy groups and healthcare providers about the profound clinical, humanistic, and economic impact of AD. We have incorporated these perspectives into our activities, particularly in selecting trial outcomes that are meaningful to patients.

Pfizer has announced positive results from our phase 2 and 3 clinical trial program, where abrocitinib has demonstrated significant improvements in AD measures, including rapid itch relief (for example, within 2 days for some patients as seen in pooled monotherapy studies[1]), with a consistent safety and tolerability profile. In addition to the four trials included in ICER's network meta-analyses, we have also reported positive results from our adolescent phase 3 study (NCT03796676) and results from a responder-enriched, randomized withdrawal study (NCT03627767). We believe this body of evidence, inclusive of 20 distinct patient reported outcomes, coupled with longer-term safety data beyond 48 weeks, demonstrates the holistic value of abrocitinib and a favorable risk-benefit profile for patients who suffer from moderate-to-severe AD.

We appreciate that ICER has addressed many of the points Pfizer raised throughout the review process and highlight below elements of our recommended elevation of abrocitinib's Evidence Rating.

1. When considering the comparison of abrocitinib with standard of care, defined as "topical emollients," Pfizer recommends a change from "P/I" to B+, an "incremental or better" rating.

    - Our monotherapy studies[2-5] demonstrated abrocitinib's significant improvement across IGA, EASI, itch and additional validated patient-reported outcomes compared with placebo. The monotherapy trials permitted the use of topical non-medicated emollients.

    - Confirming ICER's network meta-analysis, a recently published and peer-reviewed network meta-analysis by Silverberg and colleagues[6] showed that abrocitinib was estimated to have a greater than 98% probability of superiority over placebo with respect to IGA and itch response.

2. When considering the Evidence Rating of abrocitinib compared with dupilumab, we recommend an elevation from "I" to B+, an "incremental or better" rating.
    - In the JADE (JAK1 Atopic Dermatitis Efficacy and Safety) COMPARE phase 3 clinical trial (NCT03720470)[7], when compared to dupilumab, statistical superiority of abrocitinib 200 mg, and numerically higher response of abrocitinib 100 mg was achieved on the key secondary itch response at week 2.
    - In addition to patient-centered trial endpoints, patient preference is an important consideration not traditionally captured in network meta-analyses or economic models. A recently published patient preference study of systemic AD treatment attributes among 320 moderate-to-severe AD patients found that patients significantly preferred an oral daily administration over a biweekly subcutaneous injection and also preferred treatments with rapid onset of itch relief.[8] We believe both of these characteristics of abrocitinib should be considered as part of the net health benefit rating compared with dupilumab.

3. ICER explained that a primary reason for not elevating abrocitinib's current Ratings centers around existing boxed warnings for oral JAK inhibitors for other indications. We fully recognize that safety is a critical consideration and component of a treatment's risk-benefit profile and ICER's Evidence Rating. The continuous assessment and reporting of the safety profile of our medicines is a priority and abrocitinib's long-term extension study, whose primary endpoint is safety, is ongoing. We are confident in the benefit-risk profile of abrocitinib as a treatment for moderate-to-severe atopic dermatitis.

In summary, Pfizer respectfully believes that the Evidence Rating of abrocitinib compared to standard of care and to dupilumab merits elevation as supported by the points highlighted here and in our prior Public Comments to ICER's Draft Evidence Report, posted on July 9, 2021.

Though we have some remaining concerns with the assessment, we acknowledge the efforts to seek and incorporate input from diverse stakeholders, especially considering a number of investigational agents are under active regulatory review. We believe that methods assessing the value of medicines

should continue improving, especially in their ability to capture patient-centered outcomes and preferences. Pfizer is dedicated to advancing such methodologies and is committed to working with stakeholders to identify solutions for creating a more effective, efficient, and equitable health care system for patients.

Dr. Thorpe is a full-time employee of Pfizer.

Meghan Feely, MD, FAAD, Eli Lilly
Senior Medical Advisor, U.S. Medical Affairs, Bio-Medicines

Today, most patients with moderate-to-severe AD live a life of compromise, where topical therapies are no longer able to manage their AD. In patients with moderate-to-severe AD, a review of existing treatment patterns indicate that the use of topical regimens is followed by an inadequate response, leading to the use of short-term systemic therapies to attempt to control patients' worsening symptoms, but without achieving good disease control. After completion of short courses of conventional immunosuppressants or systemic corticosteroids, topical regimens are then resumed. This cycle fails to provide appropriate management of symptoms, but still few patients advance in their care to using dupilumab. Dupilumab is presently the only novel systemic agent approved for the treatment moderate-to-severe AD.[1] There is a significant unmet need in AD for moderate-to-severe patients who are failing topical treatments, but who are not willing to commit to indefinite treatment with an injectable biologic.

At this time, baricitinib is not FDA approved for the treatment of moderate-to-severe atopic dermatitis, though discussions with the FDA are ongoing. Lilly believes that Olumiant (baricitinib) is uniquely placed to serve patients with moderate-to-severe AD where short-term systemics and topical regimens are inadequately controlling disease, adding an additional treatment option for patients suffering from moderate-to-severe atopic dermatitis.

The BREEZE-AD5 clinical trial of baricitinib 2 mg in moderate-to-severe atopic dermatitis is a North American study that best represents the US population of patients impacted by this disease.[2] In this trial, baricitinib 2 mg met the primary endpoint with 30% of patients with moderate-to-severe atopic dermatitis achieving at least a 75% or greater change from baseline in their Eczema Area and Severity Index (EASI) at week 16 compared to 8% of those taking placebo ($P < .001$ for 2 mg vs. placebo).[2] In addition, adults with moderate-to-severe atopic dermatitis receiving baricitinib 2 mg monotherapy experienced improvements in skin inflammation, skin pain, itch, sleep disturbance due to itch and quality of life versus placebo-treated patients.[2]

The safety profile in BREEZE-AD5 was consistent with the known safety findings of baricitinib in atopic dermatitis across the BREEZE-AD clinical trial program. The most common treatment-emergent adverse events included upper respiratory tract infections, nasopharyngitis, and diarrhea. No venous thromboembolic events or deaths were reported in the trial.[2] The drug was generally well tolerated with low rates of nausea (2.3%, adjusted percentage) and diarrhea (2.0%, adjusted percentage) reported in the 16-week placebo-controlled period across BREEZE-AD1 through BREEZE-AD6.[3] Lilly submitted data on the lowest efficacious dose of baricitinib in atopic dermatitis to the FDA at 2 mg.[2, 4-6]

We remain confident in the positive benefit-risk profile of Olumiant in this supplemental New Drug Application for the AD population and are committed to continuing to investigate its potential across the different indications being studied. There are more than 13,000 patient years and more than 8.4 years of exposure to Olumiant in rheumatoid arthritis clinical trials with no new safety concerns identified. We have ongoing Phase 3 programs in AD, alopecia areata, systemic lupus erythematosus and COVID-19 and have just recently published pooled safety data from eight clinical trials in AD collected for 2,531 patients who were given baricitinib for 2,247 patient-years (median duration 310 days). Lilly is committed to transparency about the clinical profile of baricitinib 2 mg in patients with moderate-to-severe AD, including its safety and tolerability.

Atopic Dermatitis is a heterogenous disease. As such, Dermatologists need more options available to connect the appropriate treatment to the appropriate patient. With so few treatments approved, there is room for more treatment options to help patients with a range of AD symptoms. ICER's assessment of potential novel treatment options for patients with moderate-to-severe AD has shed light on the variety of mechanisms and delivery systems that may soon be available with varying benefit and risk profiles. Lilly encourages ICER to acknowledge the need for treatment options for patients with atopic dermatitis in their final report for this disease state. Similarly, Lilly encourages ICER to recognize the clinical, economic, patient access, and equity implications of tactics such as non-evidence-based step therapy restrictions and rebate walls. It is essential for patients with atopic dermatitis to have access to a range of treatment options that best reflect the complex nature of their disease state, response to treatment, tolerance of side effects, and individual quality of life considerations.[7]

Dr. Feely is a full-time employee of Eli Lilly.

Kyle Hvidsten, MPH, Sanofi
Vice President, Head of Global Health Economics and Value Assessment

Good morning to our colleagues from ICER and members of the CEPAC. My name is Kyle Hvidsten and I am the Head of the Sanofi Genzyme Health Economics and Value Assessment Group. I am joined by my colleague Dr Ana Rossi who is a Dermatologist and a member of the Sanofi Genzyme Medical Organization. We are both pleased to participate in today's discussion.

We first engaged with ICER in 2017 during their review of dupilumab for moderate to severe atopic dermatitis (AD). At that time, ICER established a range of value-based prices. Independently of this process, Sanofi Genzyme, in collaboration with Regeneron, and taking into consideration patient needs, determined dupilumab's price according to Sanofi's Pricing Policy; the resulting price happened to fall within ICER's range.

I'd like to note that a company's pricing decision rarely aligns so well with ICER's recommendation. We feel that this demonstrates how we follow our stated principles for responsible pricing and our commitment to achieving affordable access for patients who need our medicines. Dupilumab's price was viewed by some analysts as "lower than it should have been" based on its transformative value.

Despite how well dupilumab's price aligned with ICER's recommendation, our discussions with payers have been dominated by rebates. This situation, which continues to exist, is based on a set of mixed incentives where companies are encouraged to set prices to enable substantial rebates. As stated in our Policy, we establish a clear rationale for our launch prices that includes a holistic assessment of our medicine's value and affordable access for patients.

Since dupilumab's launch we have only made modest and predictable price increases in line with our Policy. This is reflected in the fact that dupilumab, or any other Sanofi medicine, has never been included in ICER's annual list of products that have taken "unsubstantiated price increases."

ICER's 2017 review noted several important questions that could not be answered at that time. Recognizing that managing AD requires long-term treatment, we shared ICER's desire to learn more about this important medicine and initiated many studies to understand the difference it is making in the lives of patients. This included several independent registries and the largest pediatric registry in moderate to severe AD.

Our evaluation of long-term data has established that dupilumab is not an immunosuppressant. Pooled results of clinical trials including adults, adolescents and children have demonstrated that patients treated with dupilumab have lower rates of infections, serious infections, and herpetic infections compared to placebo. Dupilumab is also associated with reduced rates and duration of "all cause" and "AD-related" hospitalizations.

Additionally, a three-year open label extension study demonstrated dupilumab's favorable safety and sustained efficacy. Safety data from this study were consistent with one-year trials and the rate of infections at three years was even lower than at one year. Furthermore, the signs and symptoms of AD showed sustained improvements over three years.

As we all know, no medicine will help patients suffering from a chronic condition like AD if they do not take it consistently. Analyses of healthcare data have shown a very high rate of persistency with dupilumab over twelve months and an independent registry showed dupilumab's persistency to be over 80% after 2 years of treatment. We are encouraged by these findings as they suggest that patients who persist are probably receiving meaningful value from their treatment and thereby managing their chronic disease.

We appreciate that ICER has taken a holistic approach to its comparison of clinical effectiveness where all forms of evidence were considered. Dupilumab is the only systemic therapy with established long-term safety and effectiveness data. We appreciate how ICER acknowledged that unanswered questions from the 2017 review have been addressed with long-term evidence.

Thank you again for the opportunity to participate in today's meeting and in the important process that began last December. Both Dr Rossi and I look forward to answering your questions.

Kyle is a full-time employee of Sanofi.

Ahmad Naim, MD, Incyte
Vice President, Medical Affairs

As the manufacturer of ruxolitinib cream, Incyte Corporation appreciated the opportunity to provide oral comment at the public meeting held on July 23, 2021.

We are summarizing our oral statements and sharing our feedback on ICER's comparative clinical evaluation and assessment of ruxolitinib cream vs emollients in mild to moderate atopic dermatitis.

TrueAD 1 and 2 (Phase 3) studies of ruxolitinib cream were designed with input from clinical experts to reflect real world clinical management of AD patients. Over 90% of patients enrolled had prior experience with AD topical and/or systemic treatment and were inadequately controlled at the time of enrollment. Results from these Phase 3 studies have demonstrated superior clinical efficacy compared to vehicle (topical emollients):

- Significantly more patients treated with either ruxolitinib cream regimen achieved the primary endpoint of Investigator Global Assessment (IGA) treatment success at week 8 (44.7% and 52.6% for 0.75% and 1.5% ruxolitinib cream, respectively) versus vehicle (11.5%; all $p < 0.0001$).

- Eczema Area and Severity Index (EASI) 75 (75% improvement in EASI score from baseline) at week 8 was achieved by 53.8% and 62.0% of patients who applied 0.75% ruxolitinib cream and 1.5% ruxolitinib cream, respectively, versus 19.7% on vehicle (all $p < 0.0001$).

- Statistically significant itch reduction was observed within approximately 12 hours of first ruxolitinib cream application (mean change from baseline: –0.4 and –0.5 for 0.75% ruxolitinib and 1.5% ruxolitinib) versus vehicle (–0.1; all $p < 0.02$). At week 8, more patients who applied ruxolitinib cream achieved a four-point improvement from baseline on the Itch Numeric Rating Scale (Itch NRS4) (41.5% and 51.5% for 0.75% ruxolitinib cream and 1.5% ruxolitinib cream, respectively) versus vehicle (15.8%; all $p < 0.0001$).

- Ruxolitinib cream was well-tolerated as demonstrated with <1% of patients reporting application site burning and less than 5% reporting TEAEs.

- No adverse events indicative of systemic activity of ruxolitinib cream were observed and no ruxolitinib cream-related serious adverse events were reported.

Ruxolitinib cream was purposefully designed to be a topical JAK inhibitor from its inception, acting locally to reduce systemic absorption. Published pharmacokinetics of Phase 3 studies have shown that plasma ruxolitinib concentrations after treatment with topical ruxolitinib cream (mean bioavailability of 6.2-7.7%) is not expected to lead to systemic plasma concentrations that may be

associated with adverse effects commonly associated with oral JAK inhibitors. The AE profile observed in Phase 3 studies were consistent with negligible systemic absorption.

In June 2021, the Food and Drug Administration (FDA) extended its review of ruxolitinib cream to allow time to review additional analyses of previously submitted data. Ruxolitinib cream was well tolerated in clinical trials. Specifically, clinically meaningful trends in hematologic parameters were not observed.

Based on the aforementioned results and characteristics, we request ICER consider ruxolitinib cream as a novel topical JAK inhibitor and review it separately from oral JAK inhibitors.

We believe ruxolitinib cream provides a beneficial treatment option for patients suffering from mild to moderate atopic dermatitis. In closing, ruxolitinib cream has demonstrated superior evidence against topical emollients with high certainty of substantial net health benefit.

Dr. Naim is a full-time employee of Incyte.

I. Conflict of Interest Disclosures

Tables I1 through I3 contain conflict of interest (COI) disclosures for all participants at the July 23, 2021, Public meeting of the New England CEPAC.

Table I1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Foluso Agboola, MBBS, MPH, Vice President of Research, ICER*	**Serina Herron-Smith**, BA, Senior Research Assistant, Evidence Synthesis, ICER*
Steven J. Atlas, MD, MPH, Associate Professor of Medicine, Harvard Medical School, Director, Practice Based Research & Quality Improvement, Division of General Internal Medicine, MGH*	**Maggie Houle**, BS, Program and Event Coordinator, ICER*
Elizabeth Brouwer, PhD, MPH, Research Scientist, The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, Department of Pharmacy, University of Washington*	**Emily Nhan,** BA, Research Assistant, ICER*
Jon D. Campbell, PhD, MS, Senior Vice President for Health Economics, ICER*	**Steven D. Pearson,** MD, MSc, President, ICER*
Josh J. Carlson, PhD, MPH, Associate Professor, The CHOICE Institute, Department of Pharmacy, University of Washington*	**David M. Rind,** MD, MSc, Chief Medical Officer, ICER*
Yilin Chen, MPH, PhD Student, The CHOICE Institute, Department of Pharmacy, University of Washington*	**Liis Shea**, MA, Program Director, ICER*
Ryan N. Hansen, PharmD, PhD, Associate Professor, The CHOICE Institute, Department of Pharmacy, University of Washington*	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table I2. New England CEPAC Panel Member Participants and COI Disclosures

Participating Members of CEPAC	
Robert Aseltine, PhD, Professor and Chair, Division of Behavioral Sciences and Community Health, UCONN Health*	**Kimberly Lenz**, PharmD, FAMCP, Director of Clinical and Operational Pharmacy, University of Massachusetts Medical School*
Kelly Buckland, MS, Executive Director, National Council on Independent Living*	**Greg Low**, RPh, PhD, Director, MGPA Pharmacy Quality and Utilization Program, Massachusetts General Hospital*
Austin Frakt, PhD, Director, Partnered Evidence-Based Policy Resource Center, VA Boston Healthcare System*	**Eleftherios Mylonakis,** MD, PhD, FIDSA, Professor of Infectious Disease, Chief of Infectious Disease, Brown University*
Christopher Jones, PhD, MSc, Director, Ventures Investments, UVM Health Network*	**Leslie Ochs,** PharmD, PhD, MSPH, Associate Professor and Department Chair, University of New England School of Pharmacy*
Rebecca Kirch, JD, Executive Vice President of Policy and programs, National Patient Advocate Foundation*	**Jeanne Ryer,** MSc, EdD, Director, NH Citizens Health Initiative*
Stephen Kogut, PhD, MBA, RPh, Professor, University of Rhode Island College of Pharmacy*	**Jason L. Schwartz,** PhD, Associate Professor of Health Policy, Yale School of Public Health*
Donald M. Kreis, MS, JD, Consumer Advocate, New Hampshire Office of the Consumer Advocate*	**Jason Wasfy**, MD, MPhil, Medical Director, Mass General Physician's Organization[†]
Tara Lavelle, PhD, Assistant Professor, Tufts Medical Center*	**Albert Whitaker,** MA, MPH, Director of Community Impact, American Heart Association*

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

[†]Dr. Wasfy did not participate as a voting member of the New England CEPAC during this meeting.

Table I3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Samantha Bittner, Patient Ambassador, National Eczema Association	No financial conflicts to disclose.
Thomas Brownlie, MS, Senior Director, Pfizer Inc.	Thomas is a full-time employee of Pfizer Inc.
Jeffrey Casberg, MS, RPh, Vice President of Pharmacy, IPD Analytics	Jeffrey is a full-time employee of IPD Analytics.
Michele Guadalupe, MPH, Associate Director of Advocacy and Access, National Eczema Association	The National Eczema Association has received grants and sponsorship awards from a variety of industry partners, including Pfizer, AbbVie, Sanofi, Regeneron, Incyte, and LEO Pharma.
Catherine Herren, PharmD, MS, Advisor, Value Development, Eli Lilly, and Company	Dr. Catherine Herren is a full-time employee of Eli Lilly and Company.
Kyle Hvidsten, MPH, Vice President, Head of Global Health Economics and Value Assessment, Sanofi	Kyle is a full-time employee of Sanofi.
Erik Schindler, PharmD, Director, Emerging Therapeutics and Outcome-Based Contracting, UnitedHealthcare Pharmacy	Dr. Erik Schindler is a full-time employee of UnitedHealthcare Pharmacy.
Elaine Siegfried, MD, Professor of Pediatrics and Dermatology, Saint Louis University School of Medicine	Dr. Elaine Siegfried has received consulting fees and honoraria from industry partners, including Incyte, Regeneron, Sanofi, LEO Pharma, Pfizer, and AbbVie for participation in clinical trials as a PI. She also received funding from Pfizer to support a two-year fellowship position at Saint Louis University.
Jonathan Silverberg, MD, PhD, MPH, Associate Professor, George Washington University School of Medicine and Health Sciences	Dr. Jonathan Silverberg has received funding from industry partners, including AbbVie, Eli Lilly, Incyte, LEO Pharma, Regeneron, and Sanofi.

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