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

Draft Evidence Report

May 14, 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.

In the moderate-to-severe population, the four interventions all improved skin findings compared with placebo, and, where assessed, appeared to improve itch, sleep, and quality of life. Quantitative indirect comparisons across the new agents and dupilumab, as well as head-to-head comparisons between two of the agents (upadacitinib and abrocitinib) and dupilumab suggest that higher doses of updadacitinib and abrocitinib may be 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 JAK inhibitors when used for other conditions. Additionally, though, tralokinumab is a novel inhibitor of IL-13 and we have limited long-term safety data. Concerns about lack of long-term data for dupilumab, noted in ICER's 2017, have been alleviated over time based on published data and widespread use in clinical practice.[15]

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 concerns about long-term safety, especially for 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 net health benefit for abrocitinib and upadacitinib compared with dupilumab was also *insufficient* ("I"), and for baricitinib and tralokinumab with dupilumab was *comparable or inferior* ("C-").

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. For tralokinumab, we used the net price of dupilumab.

While abrocitinib numerically produced the highest effectiveness of therapies considered, it was not the most favorable in terms of cost effectiveness. Of the considered therapies with available

prices, the baricitinib base case is cost-effective at a $100,000/QALY threshold while the dupilumab base case is cost-effective at a $150,000/QALY threshold.

Table ES3. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per evLYG
Abrocitinib*	SoC	$167,000	$167,000
Baricitinib	SoC	$86,000	$86,000
Tralokinumab*	SoC	$147,000	$147,000
Upadacitinib	SoC	$275,000	$275,000
Dupilumab	SoC	$132,000	$132,000
Abrocitinib*	Dupilumab	$308,000	$308,000
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 and Less Effective)	Dominated (More Costly and Less Effective)

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.

In the mild-to-moderate population, topical ruxolitinib was more effective than placebo. While ruxolitinib 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 inadequate information on long-term safety of topical ruxolitinib. 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 consider the evidence on ruxolitinib cream compared to topical emollients to be *comparable or better* ("C++"). We consider the evidence on ruxolitinib cream compared to other topical medications to be *insufficient* ("I").

1. Background

Atopic dermatitis is a common, chronic skin condition with persistent or relapsing lesions that are itchy, inflamed, and dry. Commonly referred to as "eczema," atopic dermatitis affects both children and adults. Symptoms of itching and even pain vary in severity, but can affect sleep, cause psychological distress, and result in difficulty with performance at school or work.[1-3] The appearance of the skin can also lead to social embarrassment and isolation.[4] The net effect is that atopic dermatitis can have a profound effect on all aspects of patients' lives and those of their family and caregivers.[5,6,16] 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.[17,18] 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.[19] Atopic dermatitis frequently begins during childhood and persists into adulthood in about 50% of affected children.[20] 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.[21] 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.[19,22] Moderate or severe disease appears to be more common in adults.[23] The severity of atopic dermatitis can also vary by season and geographic region.[24] 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.[25] 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.[26] For those with atopic dermatitis not controlled with topical therapies, phototherapy or systemic immunomodulators are used.[27] 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.[28]

Despite available treatments, many individuals do not respond to multiple different topical and systemic therapies supporting the need for new treatment options.[29] This is especially true for children, where there is greater concern about the effects of topical and systemic corticosteroids.[30]

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.[31] 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.[32] 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.

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.[33]

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 48 references met our inclusion criteria for the moderate-to-severe population.[34-81] Of these, we identified five randomized controlled trials (RCTs) of abrocitinib (one phase II and four phase III),[34-36,39,41] five RCTs of baricitinib (one phase II and four phase III),[43,46,47,49] three RCTs of tralokinumab (two phase III),[65,66] five RCTs of upadacitinib (one phase II and four phase III),[71,74-76] and six RCTs of dupilumab (one phase II and five phase III) that met our inclusion criteria.[51,53-55,58] Of these trials, 21 enrolled adults, where 14 were placebo-controlled monotherapy trials and six were placebo-controlled combination trials that permitted background topical medication. Two head-to-head trials were identified, and these were one placebo- and active-controlled combination trial (JADE COMPARE) and one active-controlled monotherapy trial (Heads Up). Several trials solely enrolled children or adolescents, where one was a placebo-controlled monotherapy trial and two were placebo-controlled combination trials.

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

Only the FDA-approved dose of dupilumab was evaluated in adults (300 mg once every two weeks). Most of the trials have been published, while data for the pivotal trials of upadacitinib were obtained from press releases and the manufacturer as academic-in-confidence data.[73-77]

Evidence Tables D3.2-3.10 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 16 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 D2 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 TEEN	ABRO 100 mg + TCS ABRO 200 mg +TCS PBO + TCS	285	[redacted]	14.9	[redacted]	[redacted]
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	167	25.6	40.8	23.0[¥]	40.8

Trial	Arms	Sample Size (N)	EASI (Mean)	Mean age, y	Mean Disease Duration, y	IGA Score of 4 (%)
	PBO					
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 ¥	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¥	32.0	25.3	49.2
ECZTRA 3	TRA 300 mg + TCS PBO	380	25.5	36.0	26.0	46.3
Upadacitinib						
MEASURE UP 1*	UPA 15 mg UPA 30 mg PBO	847	29.5	34.0	NR	45.2
MEASURE UP 2*	UPA 15 mg UPA 30 mg PBO	836	29.1	33.6	NR	54.9
AD-UP	UPA 15 mg + TCS UPA 30 mg + TCS PBO + TCS	907	29.6	34.1	NR	52.9
Heads Up	DUP 300 mg UPA 30 mg	692	NR	NR	NR	NR
Guttman-Yassky 2018	UPA 7.5 mg** UPA **15 mg** UPA 30 mg PBO	167	25.6	40.8	23.0¥	40.8
Dupilumab						

Trial	Arms	Sample Size (N)	EASI (Mean)	Mean age, y	Mean Disease Duration, y	IGA Score of 4 (%)
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*	31.2[ɣ]	26.7[ɣ]	47.7
LIBERTY AD ADOL	DUP 200/ 300 mg Q2W DUP 300 mg Q4W PBO	251	35.5	14.5	12.2	53.8
LIBERTY AD PEDS	DUP 300 mg Q4W + TCS DUP 100/200 mg Q2W + TCS PBO	367	37.9	8.4	7.3	100.0
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, 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, [ɣ]median, **included in pooled values here, but not included in comparative clinical effectiveness evaluation.

Mild-to-Moderate Population

A total of 19 references met our inclusion criteria for the mild-to-moderate population.[82-100] Of these, we identified two phase III, placebo-controlled RCTs of ruxolitinib cream[85] and one phase IIb placebo- and active-controlled (topical triamcinolone acetonide) RCT of ruxolitinib cream.[83,84] These trials have been published.[83,84,94] 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.[92] 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 D3.53-3.56 contain the key study design and baseline characteristics of each trial, while a summary is presented below in Table 3.2 for the ruxolitinib trials. TRuE-AD1 and TRuE-AD2 were identical phase III multicenter, double-blind, 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 D2 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	PBO RUX 0.75% RUX 1.5%	631	8 weeks	7.8	31.8	16	75.8
	TRuE AD 2	PBO RUX 0.75% RUX 1.5%	618	8 weeks	8	34.2	16.1	74
	Phase II Kim 2020	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 D1 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.[34,35,41] 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.[36] 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 Evidence Tables D3.11-12).

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).[34,35,41] 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%).[36] 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.[34,35,101] 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.[102] One trial also measured Scoring Atopic Dermatitis (SCORAD), an instrument combining objective measures of area and intensity with subjective symptoms including itch and sleeplessness.[41] There were greater reductions from baseline with abrocitinib 200 mg (-70%) and abrocitinib 100 mg (-50%), compared to placebo (-29%; $p=0.002$ and $p<0.001$, respectively).[41] In one trial, mean reductions on the Hospital Anxiety and Depression Scale (HADS) were statistically significantly greater with abrocitinib 200 mg and 100 mg doses than placebo for both depression and anxiety.[34]

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).[40,101]

At the time of this report, long-term data for abrocitinib are limited but a post hoc analysis of two placebo-controlled monotherapy trials suggests maintenance of EASI 75, IGA response, and ≥4-point improvement on the patient reported PP-NRS at 48 weeks.[81]

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.[43,46] 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.[47,49] 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).[43,46] In one combination trial, more patients achieved a ≥4-point improvement with baricitinib 2 mg than placebo (38% vs. 20%).[47]

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.[43,46,101] 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.[102]. 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.[43] Results for HADS Anxiety and Depression from the monotherapy trials were not available.

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.[47,101] 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).[49]

At the time of this report, long-term data for baricitinib are limited but data submitted by the manufacturer as academic-in-confidence suggest maintenance of EASI 75 and IGA response at 68 weeks (see Report Supplement Table D2.1).[44,45]

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.[65] 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.[66] 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).[65] 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%).[66]

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).[65,101] 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).[65,101] 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.[102]. Similarly, in both trials, patients had greater reductions from baseline on SCORAD with tralokinumab than placebo (-25% to -28% vs. -14% to -15%; p<0.001). In both trials, patients had greater reductions from baseline in the weekly average of eczema-related sleep interference NRS with tralokinumab than placebo (-3 vs. -2; p=0.007).

Similar results were reported for the combination trial. For example, patients had greater reductions from baseline on the DLQI with tralokinumab than placebo (-12 vs. -9; p<0.001).[66,101]

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

At the time of this report, long-term data for tralokinumab are limited. Data from the 36-week maintenance periods of the two placebo-controlled monotherapy trials suggest maintenance of EASI 75 and IGA responses at 52 weeks, while similar results from the 32-week maintenance period of the placebo-controlled combination trial were also reported (see Report Supplement Tables D2.3

and D2.5).[65,66] Additionally, a lower dosing frequency of tralokinumab was evaluated among 16-week responders, and outcomes were similar but slightly worse than for those continued on the higher dose.[65]

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.[71,74,75] 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 preliminary reports from 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 numerically more patients achieved EASI 90.[72] 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.[76] 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).[71,74,75] More patients achieved a ≥4-point improvement with upadacitinib 30 mg than dupilumab (55% vs. 36%).[72] 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%).[76]

In two of the monotherapy trials, data submitted as academic-in-confidence by the manufacturer suggest that patients had greater reductions from baseline on the DLQI with upadacitinib 30 mg and 15 mg compared to placebo.[77] In one 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.[71,102] In that trial, patients had greater reductions from baseline on SCORAD with upadacitinib 30 mg and 15 mg compared to placebo (-60% and -47% vs. -12%; p<0.001 for both comparisons). At the time of this report, results for these outcomes from the trial versus placebo or in the trial that compared upadacitinib to placebo in patients receiving topical corticosteroids were unavailable. Further, results for HADS Anxiety and Depression were not reported in any trials of upadacitinib at the time of this Report.

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

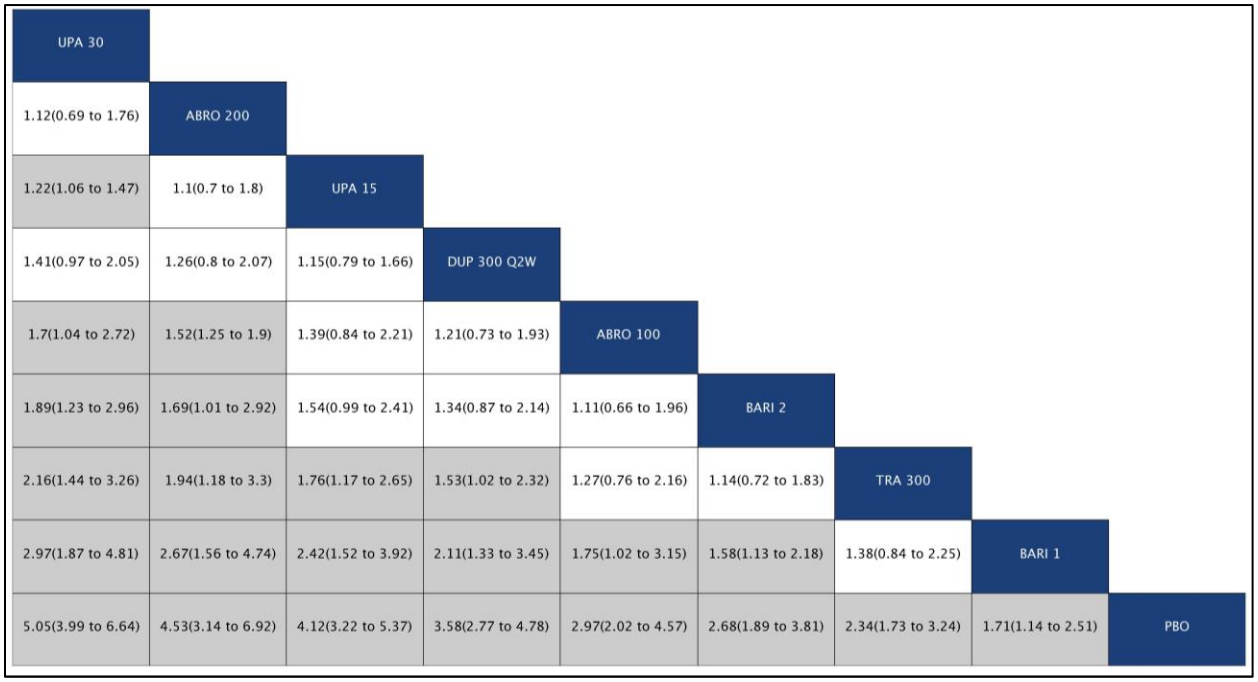
Network Meta-Analysis (NMA) Results of Placebo-controlled Monotherapy Trials

We feel that, for quantitative indirect comparisons, the monotherapy placebo-controlled trials of the agents provide results that are most comparable. Here, we present an NMA of EASI 75 from the monotherapy trials. NMAs of these trials for EASI 50, EASI 90, IGA response, and PP-NRS ≥4-point improvement are presented in the Report Supplement (see Figures D2.2-D2.5). NMAs from combination trials and NMAs of all trials are presented in the Report Supplement (see Figures D2.7-D2.9 and Figures D2.11-D2.13).

EASI 75

All interventions showed statistically significantly greater EASI 75 response compared to placebo, and almost all interventions showed a superior response compared to baricitinib 1 mg (Figure 3.1). There were no statistically significant differences with abrocitinib (both doses), baricitinib 2 mg, and upadacitinib (both doses) compared to dupilumab. In comparison, dupilumab showed a statistically significantly greater EASI 75 response than tralokinumab and baricitinib 1 mg.

Figure 3.1. NMA Results of EASI 75 in Placebo-controlled Monotherapy Trials in Adults



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 D2.6-2.9). 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.[32] Additionally, baricitinib and upadacitinib carry black box warnings for serious infections, malignancies, and thrombosis.[103,104] More information on the harms of the interventions is available in Evidence Tables D3.46-D3.51 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 D2.7 and D2.9 in the Report Supplement).[51,105]

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 subgroups of adolescent patients in those trials were provided by the manufacturers as academic-in-confidence data(see Report Supplement Tables D2.11-2.12).[39,42,77] 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,[54] which enrolled adolescent patients (see Report Supplement Tables D2.11-2.12).

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 D3.29, D3.31, D3.33, D3.35-38, D3.40, D3.42, and D3.44-45).[39,45,67] 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 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 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 use 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.

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,[106] few trials included a sizable number of

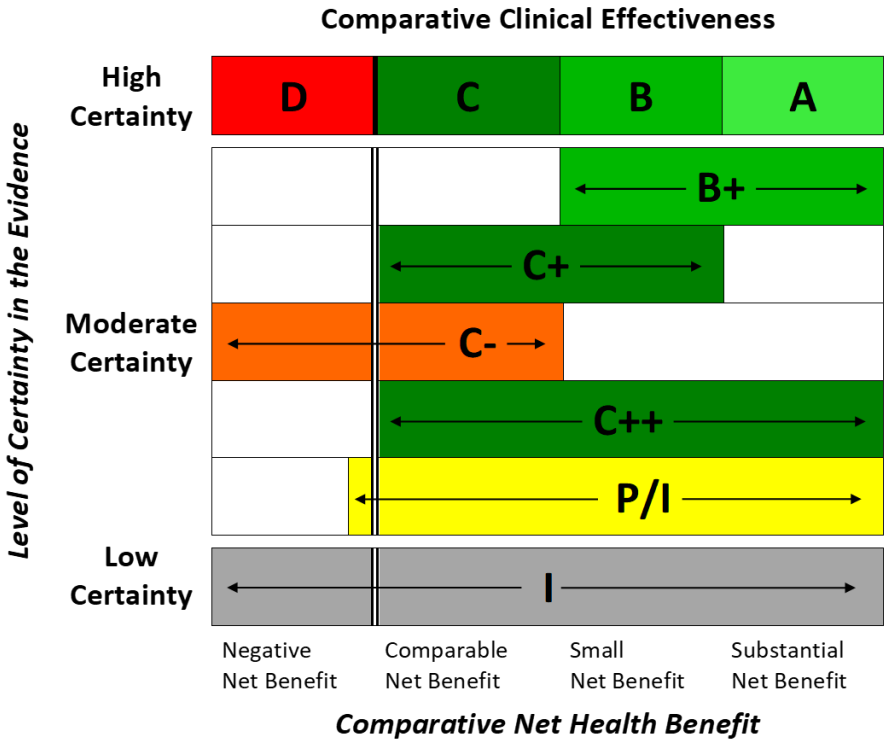
patients with darker skin complexions, and we are not aware of any trial that has reported outcomes among those with darker skin complexion.

Patients with atopic dermatitis often have other allergic conditions such as rhinitis and asthma. Dupilumab has been shown to be beneficial in a patient 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 dupilumab may not be as effective as higher doses of abrocitinib and upadacitinib and may be slightly more effective than baricitinib and tralokinumab. 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. 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. However, 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 lack of 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 JAK inhibitors. As such:

- We consider the evidence on abrocitinib, baricitinib, tralokinumab and upadacitinib compared to 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 on abrocitinib and upadacitinib compared to dupilumab to be "insufficient" (I), and baricitinib and tralokinumab compared to dupilumab to be "comparable or inferior" (C-), demonstrating moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior.
- We consider the evidence on abrocitinib, baricitinib, tralokinumab, and upadacitinib compared to 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 3.2. 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 D2.15-16 and Evidence Tables D3.57-3.64.

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 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.[107]

Ruxolitinib Cream

Ruxolitinib cream substantially increased the likelihood of achieving EASI 75, EASI 90, 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 topical corticosteroids, outcomes for ruxolitinib cream were better on reported measures. Results for adolescents were similar to adults. No long-term data was identified.

Two placebo-controlled monotherapy trials of ruxolitinib cream enrolled patients ≥12 years old, and most of the patients in these trials were ≥18 years old (80%-81%). One placebo- and active-controlled trial enrolled patients ≥18 years old.

In two placebo-controlled monotherapy trials that measured outcomes at week eight, 62% of patients achieved EASI 75 in the ruxolitinib cream 1.5% arms, compared with 14%-25% of patients in the placebo arms.[94] 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 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 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 placebo (51%-52% and 40%-43% vs. 15%-16%, respectively).

Other patient reported outcomes showed similar favorable results compared to 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 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.[96,101] Patients also had greater reductions from baseline on POEM with ruxolitinib cream 1.5% and 0.75% compared to 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.[96,102]. 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 placebo (22%-26% and 21% vs. 10%-19%%, respectively; $p<0.05$ for both comparisons).[108] Similarly, patients had greater reductions from baseline on SCORAD with ruxolitinib cream 1.5% and 0.75% dosing than 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 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.[83,84] However, no tests of statistical significance were reported (see Table D2.15 in the Report Supplement).

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

No long-term evidence was identified for ruxolitinib cream at the time of this Report.

Harms

All TEAEs were of mild-to-moderate severity (see Report Supplement Table D2.16). 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 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 Table D3.62 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) and disease severity (mild and moderate).

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 D3.63-66).[98]

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 D3.63-66).[94]

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. 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 in patients with darker skin complexions may be somewhat less, supporting the need for trials in broader populations.[98,107]

Summary and Comment

In two phase 3 trials of ruxolitinib cream versus topical emollients alone (placebo), patients receiving ruxolitinib had improved outcomes at the two doses studied. A single phase 2 trial of ruxolitinib included a topical steroid comparator. While outcomes appeared to favor ruxolitinib 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 placebo, though long-term safety remains uncertain. In summary:

- We consider the evidence on ruxolitinib cream compared to 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 on ruxolitinib cream compared to other topical medications to be "insufficient" (I).

4. Long-Term Cost Effectiveness

4.1. Methods Overview

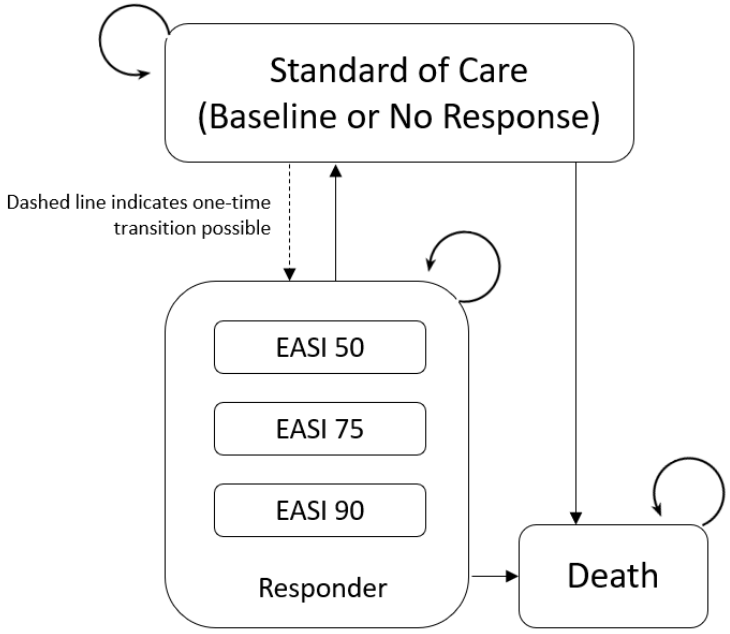
We adapted the Markov model from ICER's 2017 report on dupilumab for this evaluation, with the adaptation informed by key clinical trials and prior relevant economic models.[109] Costs and outcomes were discounted at 3% per year.

The model focused on an intention-to-treat analysis, with a hypothetical cohort of adult patients with moderate-to-severe AD 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.[110] 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 interventions of interest. Although patients may switch to additional active therapies in the real world, this switching was not anticipated to affect the estimated cost effectiveness of 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). Life-years and equal value life-years gained (evLYG) were calculated.
- Costs and outcomes were discounted annually at 3%.
- Change in peak pruritus numerical rating scale (PP-NRS) and impact on sleep items within the disease-specific patient-reported outcomes (POEM, SCORAD, and ADerm-IS), were assessed in the clinical review and were considered as part of a cost consequences analysis alongside the cost-effectiveness 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 AD in the U.S. being treated with abrocitinib, baricitinib, tralokinumab, and 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: 67% for abrocitinib, 48% for baricitinib, 47% for tralokinumab, 64% for upadacitinib, 60% for dupilumab, and 22% 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	9.5%	6.4%	5.9%	21.7%

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. 16-week 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, so data from a long-term extension study of upadacitinib in rheumatoid arthritis patients was used as a proxy.

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	9.14%	9.14%	NCT02720523
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 health state utilities for the non-responder and responder states by pooling utility estimates from manufacturer submitted data. We estimated weighted average utility values for each health state, combining estimates from all treatments with data available by health state. 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.

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 50		
EASI 75		
EASI 90		

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) and three measures for sleep (POEM, SCORAD, and ADerm-IS). These analyses were included if data were provided for the mean score at baseline and for each responder category. Data was available for baricitinib (PP-NRS, POEM, SCORAD) and upadacitinib (PP-NRS, Aderm-IS). The model output was the mean score and incremental mean score versus SoC over the model time horizon.

Table 4.5. Patient Reported Outcomes

	PP-NRS	PP-NRS	POEM (Sleep)	SCORAD (Sleep)	Aderm-IS (sleep)
Drug	**Tralokinumab**	**Upadacitinib**	**Tralokinumab**	**Tralokinumab**	**Upadacitinib**
Pooled Baseline*					
EASI50					
EASI75					
EASI90					
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
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

*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

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.[111]

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 published literature, updated to 2021 US dollars using the US Bureau of Labor Statistics CPI inflation calculator, which include all non-drug direct health care costs.[112,113] 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	$13,005.52	Drucker 2018[112]
Responder	$8,216.84	
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

Indirect Costs and Productivity Loss

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.[114]

Table 4.8. 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

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 AD who received a single treatment beyond emollients for up to 5 years, baricitinib had the lowest drug cost and total cost, $29,000 and $85,600, respectively, compared to upadacitinib at $113,000 and $168,000 as the highest drug and total costs, respectively. Abrocitinib generated the highest QALYs, 3.54, followed by dupilumab and upadacitinib, with 3.43 and 3.35, respectively. Abrocitinib's higher QALYs was due to having the highest percent of overall responders and a lower discontinuation rate versus comparators.

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

Treatment	Drug Cost	Total Cost	QALYs	Life Years	PP-NRS†	POEM (sleep)†	SCORAD (sleep)†	ADerm-IS (sleep)†
Abrocitinib*	$107,000	$158,000	3.54	4.85	NA	NA	NA	NA
Baricitinib	$29,000	$85,600	3.25	4.85	NA	NA	NA	NA
Tralokinumab*	$53,500	$109,000	3.29	4.85	-1.14	-0.54	-1.25	NA
Upadacitinib	$113,000	$168,000	3.35	4.85	-1.27	NA	NA	NA
Dupilumab	$69,000	$122,000	3.43	4.85	NA	NA	NA	-4.93
Standard of Care (Topicals)	$0	$61,800	2.97	4.85	-0.15	-0.08	-0.20	-0.56

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, SCORAD: Scoring Atopic Dermatitis

*Using a placeholder price

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

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.

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	$167,000	$-	$167,000
Baricitinib	SoC	$86,000	$-	$86,000
Tralokinumab*	SoC	$147,000	$-	$147,000
Upadacitinib	SoC	$275,000	$-	$275,000
Dupilumab	SoC	$132,000	$-	$132,000
Abrocitinib*	Dupilumab	$308,000	$-	$308,000
Baricitinib	Dupilumab	Less Costly, Less Effective	$-	Less Costly, Less Effective
Tralokinumab*	Dupilumab	Less Costly, Less Effective	$-	Less Costly, Less Effective
Upadacitinib	Dupilumab	Dominated	$-	Dominated

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.

Table 4.11 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 4.11. Incremental Cost-Consequence Results for the Base Case

Treatment	Comparator	Incremental Cost	Incremental QALYs gained	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)†
Abrocitinib*	SoC	$96,300	0.57	NA	NA	NA	NA
Baricitinib	SoC	$23,800	0.28	NA	NA	NA	NA
Tralokinumab*	SoC	$47,300	0.32	-0.98	-0.46	-1.06	NA
Upadacitinib	SoC	$106,000	0.38	-1.11	NA	NA	-3.81
Dupilumab	SoC	$60,400	0.46	NA	NA	NA	NA
Abrocitinib*	Dupilumab	$35,900	0.12	NA	NA	NA	NA
Baricitinib	Dupilumab	Less Costly	Less Effective	NA	NA	NA	NA
Tralokinumab*	Dupilumab	Less Costly	Less Effective	NA	NA	NA	NA
Upadacitinib	Dupilumab	$45,600	Less Effective	NA	NA	NA	NA

ADerm-IS: Atopic Dermatitis Impact Scale, NA: not available, POEM: Patient-Oriented Eczema Measure, QALY: quality-adjusted life year, PP-NRS: Peak Pruritis Numeric Rating Scale, SCORAD: Scoring Atopic Dermatitis

*Using a placeholder price

†Difference in average change in score from pooled baseline

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 4.12 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 4.12. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Each treatment versus SoC

Cost-Effectiveness Threshold	Abrocitinib*	Baricitinib	Tralokinumab*	Upadacitinib	Dupilumab
$50,000	0%	33%	10%	0%	0%
$100,000	1%	68%	34%	0%	19%
$150,000	34%	82%	58%	3%	67%
$200,000	72%	87%	71%	19%	86%

*Based on placeholder prices

Scenario Analyses

We conducted three scenario analyses for the draft report, and additional scenarios may be included in future versions of the report. First, we calculated a modified societal perspective by adding productivity loss associated with moderate-to-severe AD 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.

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 14 to 31% for the interventions and 51% 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 gained. Incremental cost-effectiveness ratios from the modified societal perspective versus the base case when applying the standard of care comparator decreased by 5% to 18% across the therapies

evaluated, but did not lead to therapies crossing cost-effectiveness thresholds (i.e., $50, $100, or $150,000 per QALY)

Table E4.5 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 11% to 27% 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 Supplementary Appendix 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 1.45% and 1%, respectively, and decrease ICER versus SoC and dupilumab by 1.5% and 3.7%, respectively. These outcomes are based on a placeholder price for Abrocitinib and will be updated.

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 4.14. We strongly caution the readers against assuming that the values provided in this section will approximate the health benefit price benchmarks (HBPBs) that will be presented in the next iteration of this report. These results may change substantially based on reviewer and public input, as well as manufacturer and internal model review.

Table 4.14. 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	$15,200	$26,400	$37,500
Baricitinib	$29,000	$19,400	$12,800	$22,000	$31,300
Tralokinumab	$41,800	$31,100	$13,000	$22,400	$31,700
Upadacitinib	$64,300	$63,400	$14,500	$25,400	$36,200
Dupilumab	$41,800	$31,100	$14,200	$24,600	$34,900

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

*Based on a Placeholder Price

Model Validation

We used several approaches to validate the model. First, 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. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area. The outputs from the model were validated against the trial/study data of the interventions and any relevant observational datasets.

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). Second, 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 AD, such as those with co-occurring asthma or chronic rhinosinusitis, which are not explicitly captured in the current model.

We also recognize that the ultimate dosing and utilization of these treatments will impact model outcomes. Specifically, tralokinumab dosing may include an option for every four week instead of every two-week dosing, which would lower treatment costs.

Fourth, 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, AD specific discontinuation rates were not available for upadacitinib and we therefore used discontinuation rates from another indication. 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.

Sixth, 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. Therefore, the incremental value of these treatments may not be generalizable to patients using topical steroids and/or calcineurin inhibitors. Furthermore, the NMA 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 (3.54) of therapies considered and baricitinib to produce the fewest (3.25). Compared to SoC with emollients only, baricitinib was cost-effective at a $100,000/QALY threshold, tralokinumab was cost-effective at a $150,000/QALY threshold (using a placeholder price), dupilumab was cost-effective at a $150,000/QALY threshold, abrocitinib would need to decrease its WAC per dose cost from $127.65 (placeholder price) to $102.73 in order to be cost-effective at $150,000/QALY threshold, and upadacitinib would need to decrease its WAC per dose cost from $176 to $99 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 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 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 on an initial every two seek schedule, tralokinumab dosing decreased to every four weeks in some patients could potentially affect real world adherence.
Health inequities	Not applicable The high costs of treatments for atopic dermatitis, especially newer agents, may exacerbate existing health inequities.
These interventions offer novel mechanisms of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	Abrocitinib, baricitinib, tralokinumab and upadacitinib represent new therapies that reflect translational research in which improved understanding of the mechanisms of disease have led to new therapies.

6. Health Benefit Price Benchmarks

ICER does not provide health benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmarks that will be presented in the next version of this Report.

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).

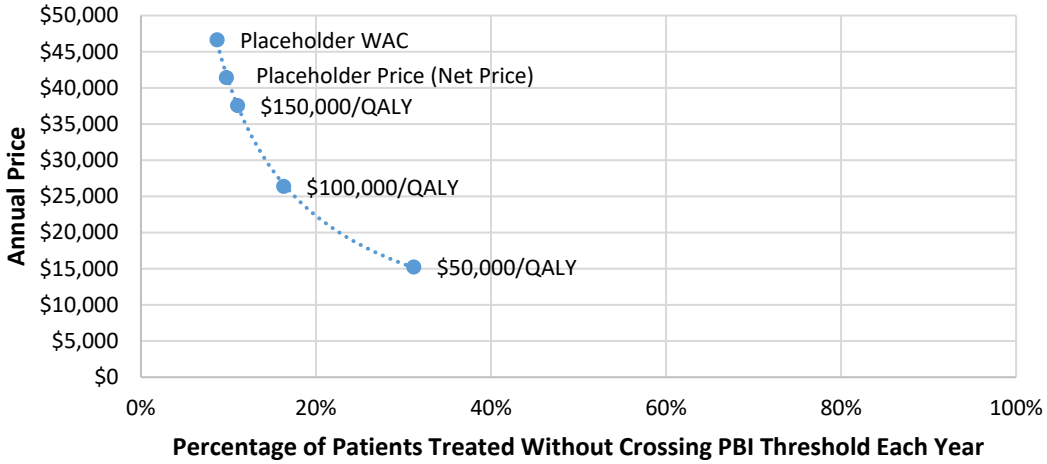
7.2. Results

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).

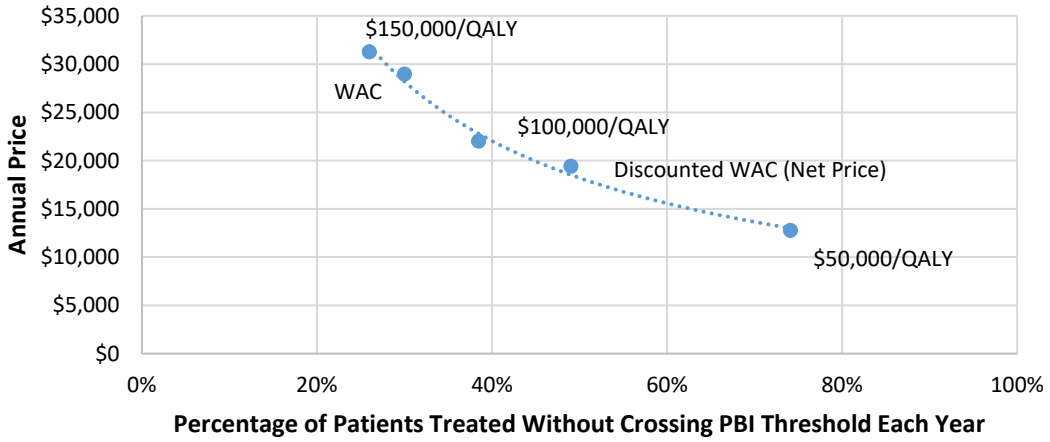
Upon removing the placeholder prices and across all four treatments, the range of the percentage of those treated without crossing the potential budget impact annual threshold was between 9% and 74% for all prices evaluated (WAC unit price to the maximum price to achieve $50,000 per QALY).

Figure 7.1. Budgetary Impact of Abrocitinib*



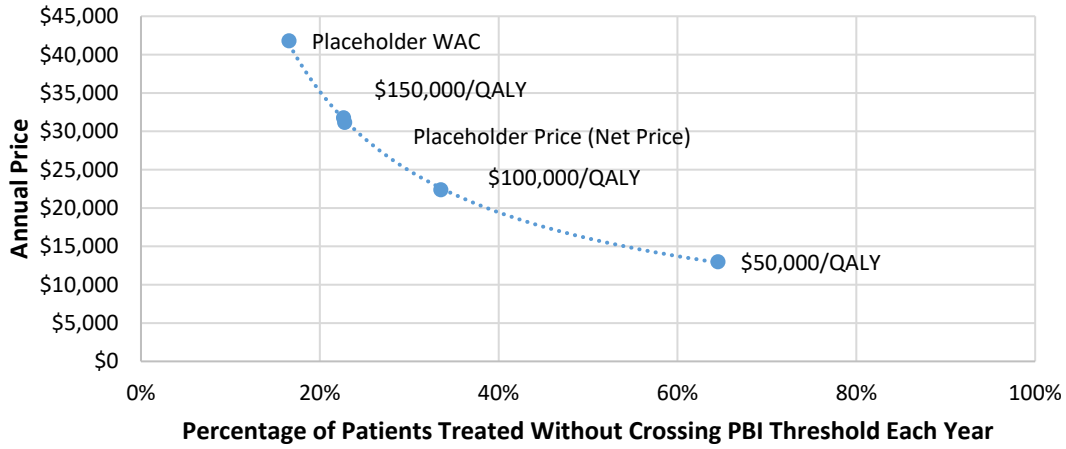
PBI: potential budget impact, QALY: quality-adjusted life-year, WAC: wholesale acquisition price
*Based on placeholder prices

Figure 7.2. Budgetary Impact of Baricitinib



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

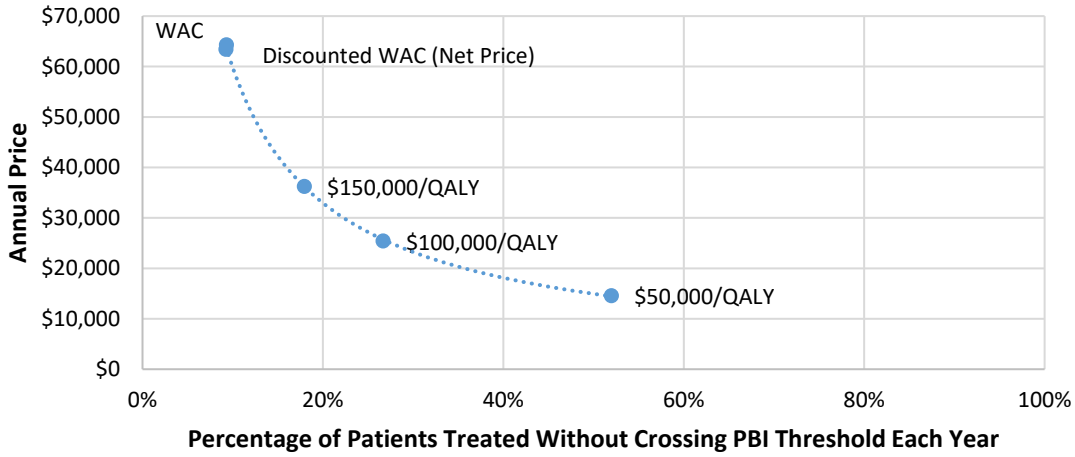
Figure 7.3. Budgetary Impact of Tralokinumab*



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

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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):***[115] 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):***[116] 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):***[117] 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):***[118] 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):***[119] 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):***[120] 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):***[102] 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, sleep disturbance. 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):***[121] 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 eight 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]".

9. ***Dermatitis Family Impact Questionnaire (DFI):***[122] 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):***[123] 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.

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[27]

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[124]

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[125]

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[125]

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 and 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 removed comparisons with methotrexate from 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.[126,127] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[128] 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., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

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

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

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

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

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

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

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

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

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

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

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

*Search last updated on January 27, 2021.

Table D1.4. Cochrane Database of Systematic Reviews*

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

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

*Search last updated on January 27, 2021.

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

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

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

*Search last updated on January 27, 2021.

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

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

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

*Search last updated on January 27, 2021.

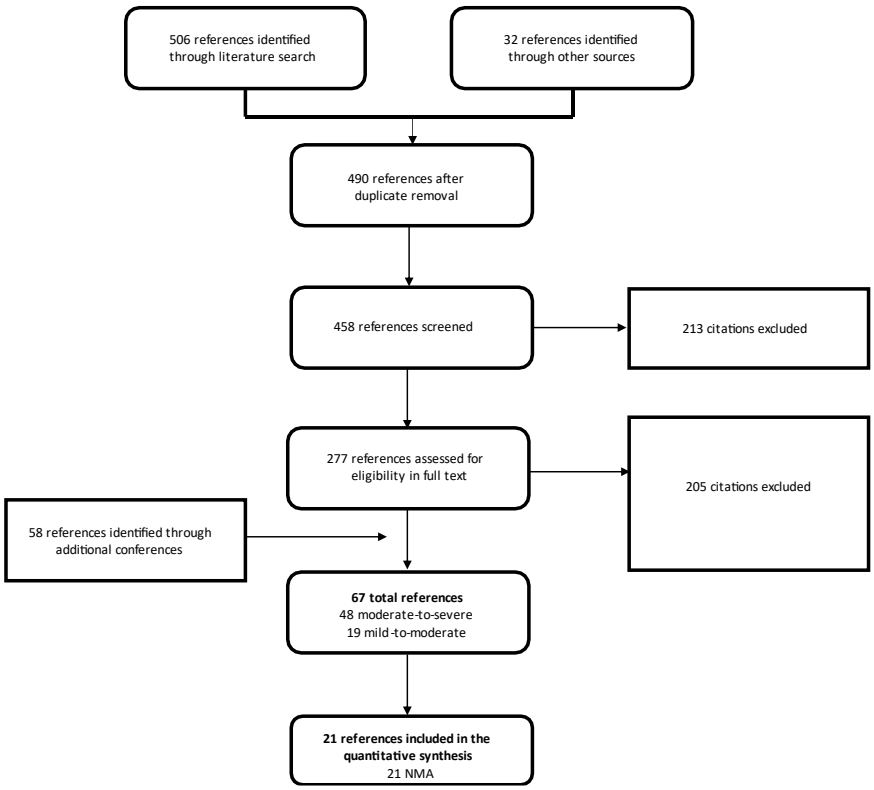
Table D1.7. Search Strategy of EMBASE SEARCH (Systematic Reviews)*

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

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

*Search last updated on January 27, 2021.

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



Study Selection

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

Data Extraction and Quality Assessment

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (Table D3.1 and D3.65.[129] 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).[130]

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 quantitatively and qualitatively in the body of the review. We evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcome assessment for each outcome of interest. Based on data availability, we created networks to compare IGA, EASI 50, EASI 75, EASI 90, and PP-NRS ≥4-point improvement at 12 and 16 weeks in trials of abrocitinib, baricitinib, upadacitinib, tralokinumab, and dupilumab. All network-meta-analyses (NMAs) were conducted in a Bayesian framework with random effects on the treatment parameters using the IndiRect NMA platform (CRG-EVERSANA, 2020™). The outcomes were analyzed using a binomial likelihood and log link. The goodness of fit of the analyses with and without adjustment for differences in placebo arm response was assessed. We presented the results of the adjusted NMA model where it provided a better fit of the data. League tables were presented for the treatment effects (RR of each drug versus each other and placebo, along with 95% credible intervals (95% CrI).

Due to inconsistent or limited data reporting, other outcomes are either described narratively or presented in tables.

D2. Additional Clinical Evidence

This section starts by providing additional clinical evidence for patients with moderate-to-severe atopic dermatitis in short-(≤16 weeks) and long-term (>16 weeks) placebo-controlled monotherapy and placebo-controlled combination trials (placebo plus topical medications). 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

Evidence Base

As stated in the report, we do not report data from the baricitinib 4 mg arm of the trials because this dose is not anticipated to be used in the U.S. Further, only the FDA-approved dose of dupilumab in adults was evaluated (300 mg once every two weeks).

Placebo-controlled Monotherapy and Combination Trials in Adults (Short-term)

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

Two placebo-controlled monotherapy trials of abrocitinib enrolled patients ≥12 years old, and most of the patients in these trials were ≥18 years old (74%-85%).[34,35] The remaining trials of abrocitinib enrolled patients ≥18 years old.[36,41]

While two placebo-controlled monotherapy trials and one placebo-controlled combination trial of upadacitinib enrolled patients ≥12 years old, most of the patients in these trials were ≥18 years old (85%-88%).[74,75] The head-to-head monotherapy trial and the remaining placebo-controlled monotherapy trial enrolled patients ≥18 years old.[71,72]

Placebo-controlled Monotherapy Trials in Adults (Long-term)

We identified one long-term trial of baricitinib,[44] two long-term trials of tralokinumab (two phase III),[65] and one long-term, phase III trial of dupilumab.[56] 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. 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. In LIBERTY AD SOLO-CONTINUE, 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).

While the trials of tralokinumab and dupilumab have been published, data for baricitinib were obtained from a press release and the manufacturer as academic-in-confidence data.[44,45]

Table D2.1. Overview of Placebo-controlled Monotherapy Trials in Adults (Long-term)

Trial	Arms	Sample Size (N)	EASI (Mean)	Mean Age, y	Mean Disease Duration, y	IGA Score of 4 (%)
Baricitinib						
BREEZE-AD3	BARI 2 mg	[redacted]		NR	[redacted]	
Tralokinumab						
ECZTRA 1	TRA 300 mg PBO	See Table 3.1 in the Report.				
ECZTRA 2	TRA 300 mg PBO					
Dupilumab						
LIBERTY AD SOLO-CONTINUE	DUP 300 mg Q2W or QW PBO	671	30.7	38.7	26.7	48.3

BARI: baricitinib, DUP: dupilumab, PBO: placebo, mg: milligram, N: total number, NR: not reported, QW: once weekly, Q2W: every two weeks, TRA: tralokinumab, Y: year, %: percent

Placebo-controlled Combinations Trials in Adults (Long-term)

ECZTRA 3 and LIBERTY AD CHRONOS also reported long-term results (see Table D2.5). After the 16-week initial treatment period of ECZTRA 3, 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 16 weeks.[66] In contrast, LIBERTY AD CHRONOS was a long-term trial that reported results at both 16 and 52 weeks.[51] Following the 52-week treatment period, patients were followed up for 12 weeks. Further, patients who completed the trial or discontinued the study drug but completed all trial visits were eligible to enter an OLE.

Results

Additional clinical evidence for short- and long-term placebo-controlled monotherapy and combination trials in adults is presented below, followed by a combined NMA of all the short-term trials.

Placebo-controlled Monotherapy Trials in Adults (Short-term)

Most results for the placebo-controlled monotherapy trials are described in Section 3.2 of the Report. Additional results for abrocitinib and upadacitinib, a table of key results, and results from NMAs are presented here.

Abrocitinib

In the two monotherapy trials that enrolled patients ≥12 years old, 61%-65% of patients ≥18 years old achieved EASI 75 with abrocitinib 200 mg, compared to 11%-12% in the placebo arms of those trials.[34,35] In this subgroup of patients, 39%-45% achieved EASI 75 with abrocitinib 100 mg. The percentages of patients achieving IGA response with abrocitinib 200 mg were 38%-48%, 23%-30% with abrocitinib 100 mg, and 7%-10% with placebo.

Upadacitinib

In the two monotherapy trials that enrolled patients ≥12 years old, data submitted by the manufacturer as academic-in-confidence for patients ≥18 years old suggests more patients achieved these outcomes with upadacitinib 30 mg and 15 mg than placebo (see Evidence Tables D3.30 and D3.32).[77]

Table D2.2. Key Outcomes in Placebo-controlled Monotherapy Trials in Adults

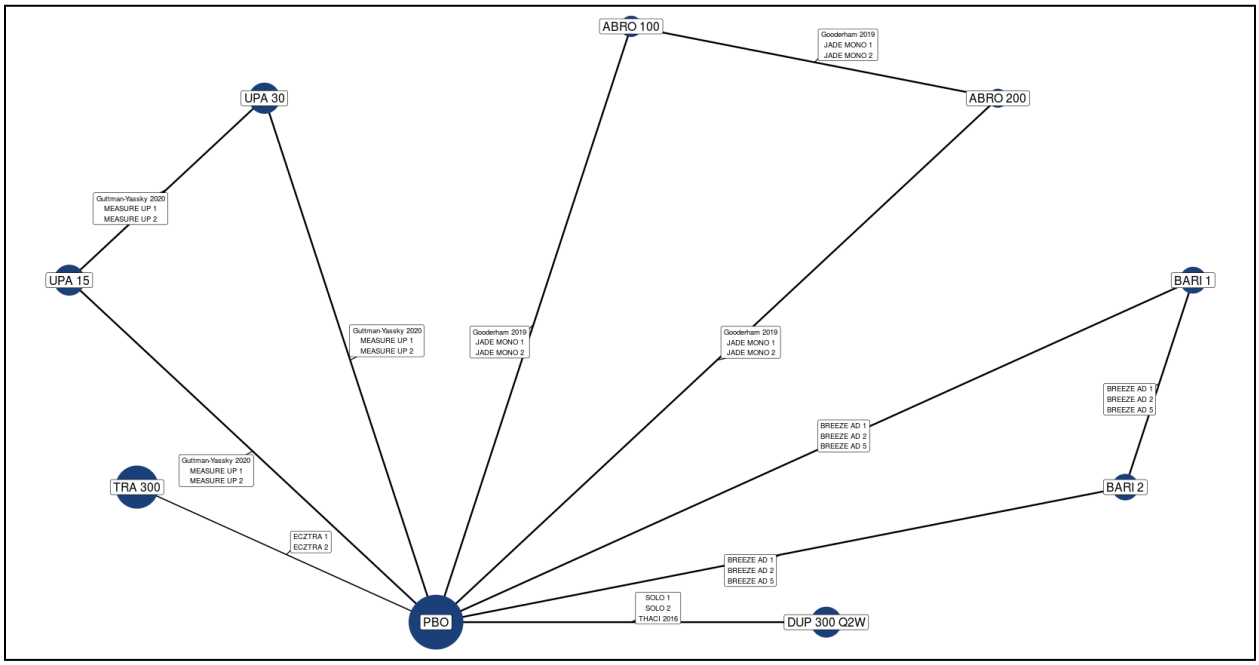
Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS†	SCORAD‡
Abrocitinib								
JADE MONO 1[γ]	ABRO 100 mg	12 weeks	58.0	40.0	19.0	24.0	38.0	NR
	ABRO 200 mg		76.0	63.0	39.0	44.0	57.2	NR
	PBO		22.0	12.0	5.0	8.0	15.0	NR
JADE MONO 2[γ]	ABRO 100 mg	12 weeks	68.4	44.5	23.9	28.4	45.2	NR
	ABRO 200 mg		79.9	61.0	37.7	38.1	55.3	NR
	PBO		19.5	10.4	3.9	9.1	11.5	NR
Gooderham 2019	ABRO 100 mg	16 weeks	55.6	40.7	25.9	29.6	50.0	-49.2
	ABRO 200 mg		79.2	64.6	52.1	43.8	63.6	-69.7
	PBO		26.9	15.4	9.6	5.8	25.5	-29.0
Baricitinib								
BREEZE-AD 1	BARI 1 mg	16 weeks	25.0	17.3	8.7	11.8	10.5	-18.9
	BARI 2 mg		30.1	18.7	10.6	11.4	12.0	-21.5

Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS[†]	SCORAD[‡]
	PBO		15.3	8.8	4.8	4.8	7.2	-13.4
BREEZE-AD 2	BARI 1 mg	16 weeks	18.4	12.8	6.4	8.8	6.0	-20.2
	BARI 2 mg		27.6	17.9	8.9	10.6	15.1	-27.8
	PBO		12.3	6.1	2.5	4.5	4.7	-13.4
BREEZE-AD 5	BARI 1 mg	16 weeks	19.7	12.9	7.5	12.9	15.9	NR
	BARI 2 mg		34.9	29.5	20.5	24.0	25.2	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[ɣ]	UPA 15 mg	16 weeks	NR	70.0	53.0	48.0	52.0	NR
	UPA 30 mg		NR	80.0	66.0	62.0	60.0	NR
	PBO		NR	16.0	8.0	8.0	12.0	NR
MEASURE UP 2[ɣ]	UPA 15 mg	16 weeks	NR	60.0	42.0	39.0	42.0	NR
	UPA 30 mg		NR	73.0	58.0	52.0	60.0	NR
	PBO		NR	13.0	5.0	5.0	9.0	NR
Phase II Guttmann-Yassky 2020	UPA 15 mg	16 weeks	71.4	52.4	26.2	31.0	59.4	-46.9
	UPA 30 mg		83.3	69.0	50.0	50.0	52.8	-60.4
	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
LIBERTY AD SOLO 2	DUP 300 mg Q2W	16 weeks	65.0	44.0	30.0	36.0	36.0	-51.1
	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.

Additional NMA Results

Figure D2.1. Network of Placebo-controlled Monotherapy Trials in Adults (Short-term)

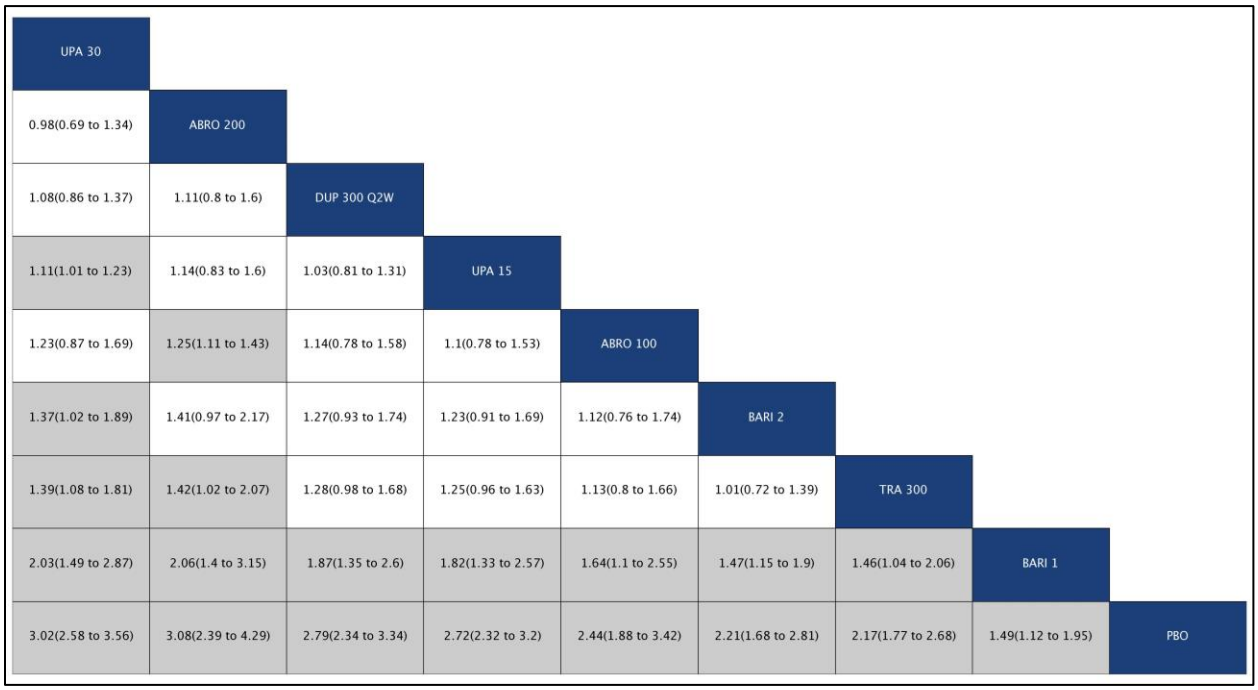


ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib.

EASI 50

All interventions showed statistically significantly greater EASI 50 responses than placebo and baricitinib 1 mg (Figure D2.2). There were no statistically significant differences with abrocitinib (both doses), baricitinib 2 mg, upadacitinib (both doses), and tralokinumab compared to dupilumab.

Figure D2.2. NMA Results of EASI 50 in Placebo-controlled Monotherapy Trials in Adults (Short-term)

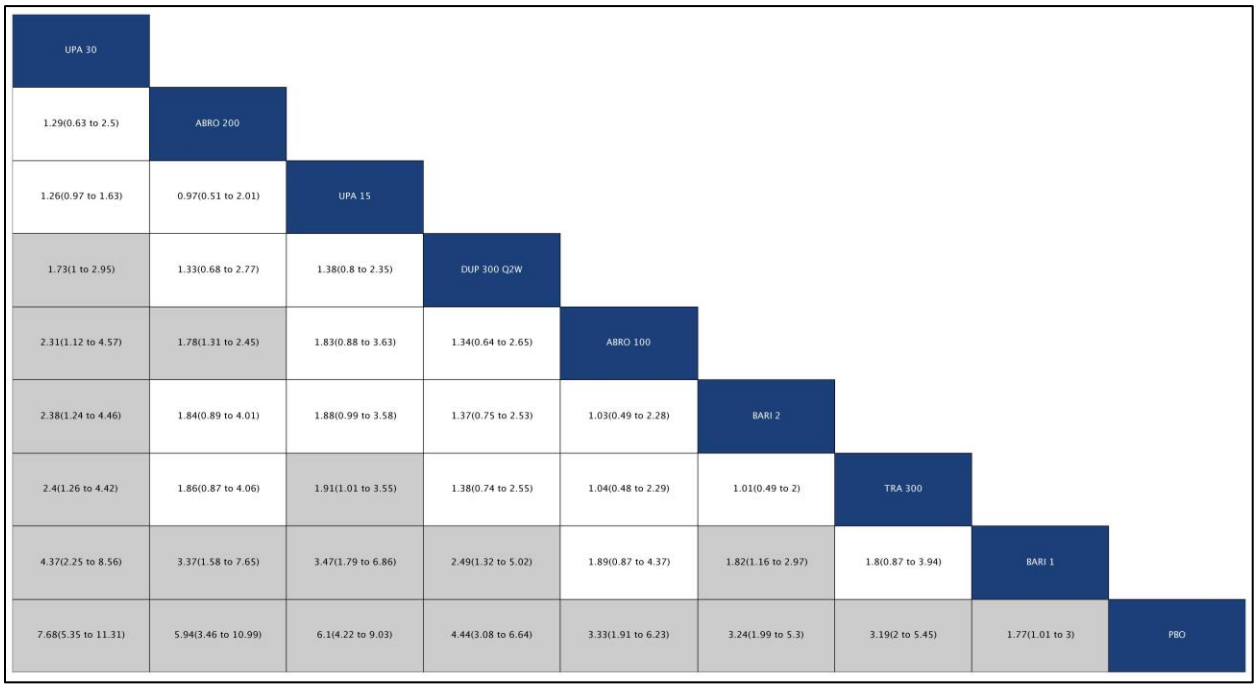


Each box represents the estimated risk ratio and 95% credible interval (CrI) for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% CrI does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: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

EASI 90

For EASI 90, all interventions showed statistically significantly greater response than placebo, while most interventions showed statistically significant results compared to baricitinib 1 mg (Figure D2.3). There were no statistically significant differences with abrocitinib (both doses), baricitinib 2 mg, tralokinumab, and upadacitinib 15 mg compared to dupilumab. However, upadacitinib 30 mg showed a greater EASI 90 response than dupilumab that was of borderline statistical significance (RR: 1.73; 95% CrI: 1.00 to 2.95).

Figure D2.3. NMA Results of EASI 90 in Placebo-controlled Monotherapy Trials in Adults (Short-term)

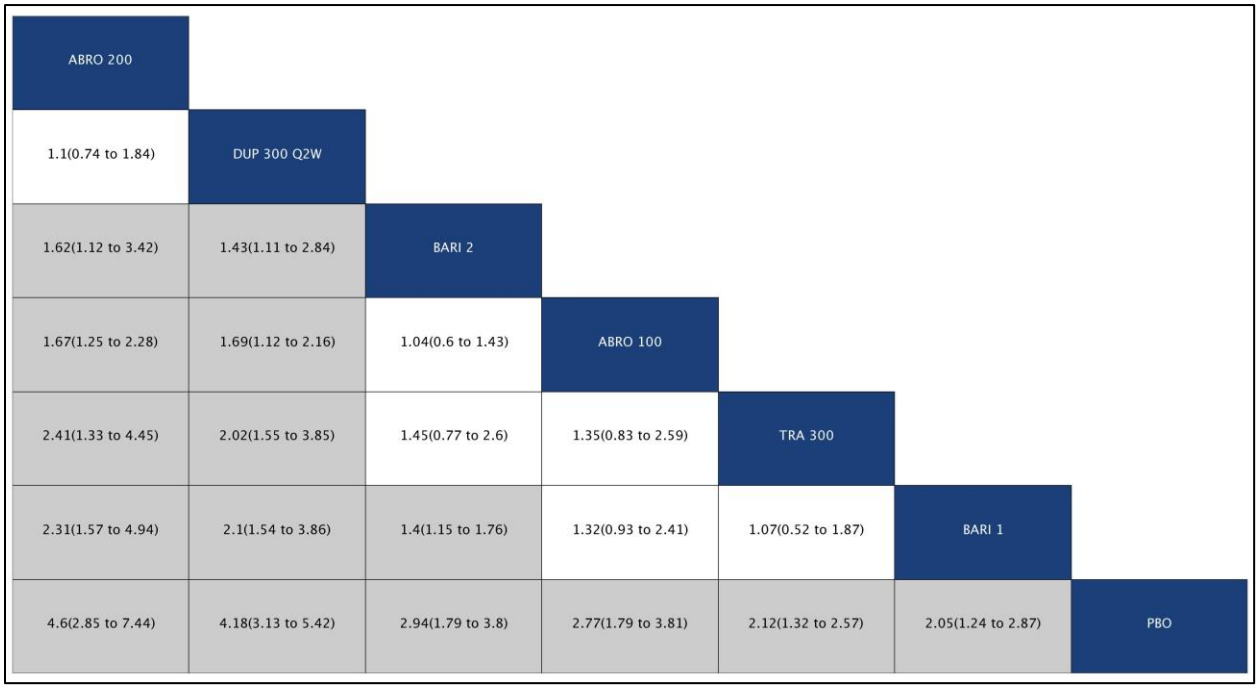


Each box represents the estimated risk ratio and 95% credible interval (CrI) for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% CrI does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: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

Investigator's Global Assessment (IGA)

Though IGA results in patients ≥18 years old for the pivotal trials of upadacitinib were unavailable at the time of this report, the remaining interventions showed statistically significantly higher efficacy on IGA, as defined in the trials, compared to placebo (Figure D2.4). Though there was no statistically significant difference with abrocitinib 200 mg compared to dupilumab, response rates were statistically significantly greater with dupilumab than the remaining interventions.

Figure D2.4. NMA Results of IGA in Placebo-controlled Monotherapy Trials in Adults

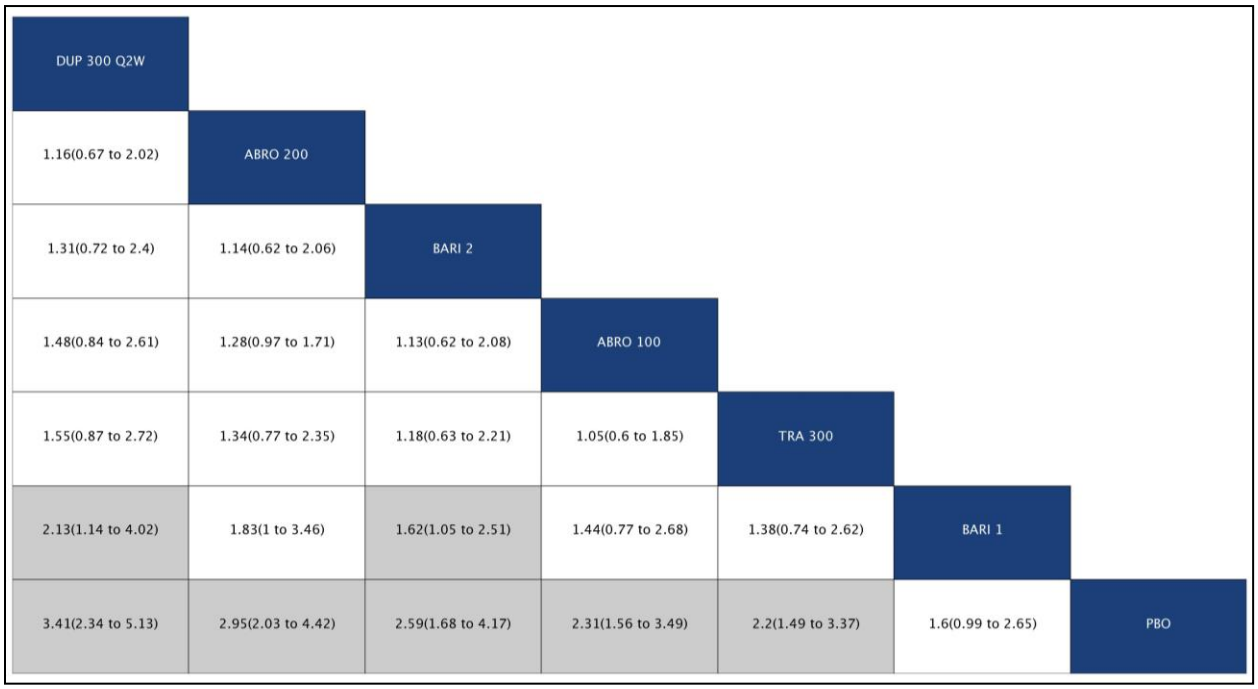


Each box represents the estimated risk ratios and 95% credible interval for the indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain 1. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks.

Peak Pruritus Numerical Rating Scale (PP-NRS) ≥4-point Improvement

While a clinically meaningful improvement in PP-NRS ranges from an improvement of 2-4-points,[117] 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 (Figure 2.5). Further, there were no statistically significant differences among the interventions, excluding baricitinib (both doses), compared to dupilumab. Though data for this outcome in patients ≥18 years old for the pivotal trials of upadacitinib were unavailable at the time of this report, PP-NRS ≥4-point improvement is correlated with an EASI 90 response.[117] Thus, results for patients ≥18 years old for the pivotal trials of upadacitinib may reflect those described above for EASI 90. (see Figure D2.3).

Figure D2.5. NMA Results of PP-NRS ≥4-point Improvement in Placebo-controlled Trials in Adults



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, Q2W: every two weeks.

Placebo-controlled Monotherapy Trials in Adults (Long-term)

Table D2.3. Key Outcomes in Placebo-controlled Monotherapy Trials in Adults (Long-term)

Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS[†]	SCORAD[‡]
Baricitinib								
BREEZE-AD3	BARI 2 mg	68 weeks	NR	[redacted]	NR	[redacted]	NR	NR
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
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

All values in the table are percentages. Includes trials only in adults 18 and older. DUP 300 mg Q8W and Q4W arms are not included in the table. BARI: baricitinib, DUP: dupilumab, PBO: placebo, mg: milligram, NR: not reported, QW: weekly, Q2W: every two weeks, Q4W: every four weeks, TRA: tralokinumab. [†]PP-NRS ≥4, [‡]LSM change from baseline, [§]maintenance period timepoint, [¶]reported LSM percentage change from baseline in SCORAD sleep loss.

Placebo-controlled Combination Trials in Adults (Short-term)

While most results for the placebo-controlled combination trials are described in Section 3.2 of the Report, additional results for abrocitinib and upadacitinib, a table of key results, and results from NMAs are presented here.

Abrocitinib

While results at 12 weeks are described in the Report, results at 16 weeks are presented here. In the trial that compared abrocitinib to dupilumab and placebo, EASI 75 response was reported in 71%, 60%, and 66%, and IGA response was reported in 48%, 35%, and 39% among abrocitinib 200 mg abrocitinib 100 mg, and dupilumab arms, respectively, and 16 weeks.[36] There were no statistically significant differences in EASI 75 and IGA response between the abrocitinib arms and dupilumab at 16 weeks with the exception of IGA response being greater for the abrocitinib 200 mg arm.

Upadacitinib

In the placebo-controlled combination trial, data submitted by the manufacturer as academic-in-confidence for patients ≥18 years old in this trial suggests more patients achieved these outcomes with upadacitinib 30 mg and 15 mg than placebo (see Evidence Tables D3.30 and D3.32).[77]

Table D2.4. Key Outcomes in Placebo-controlled Combination Trials in Adults (Short-term)

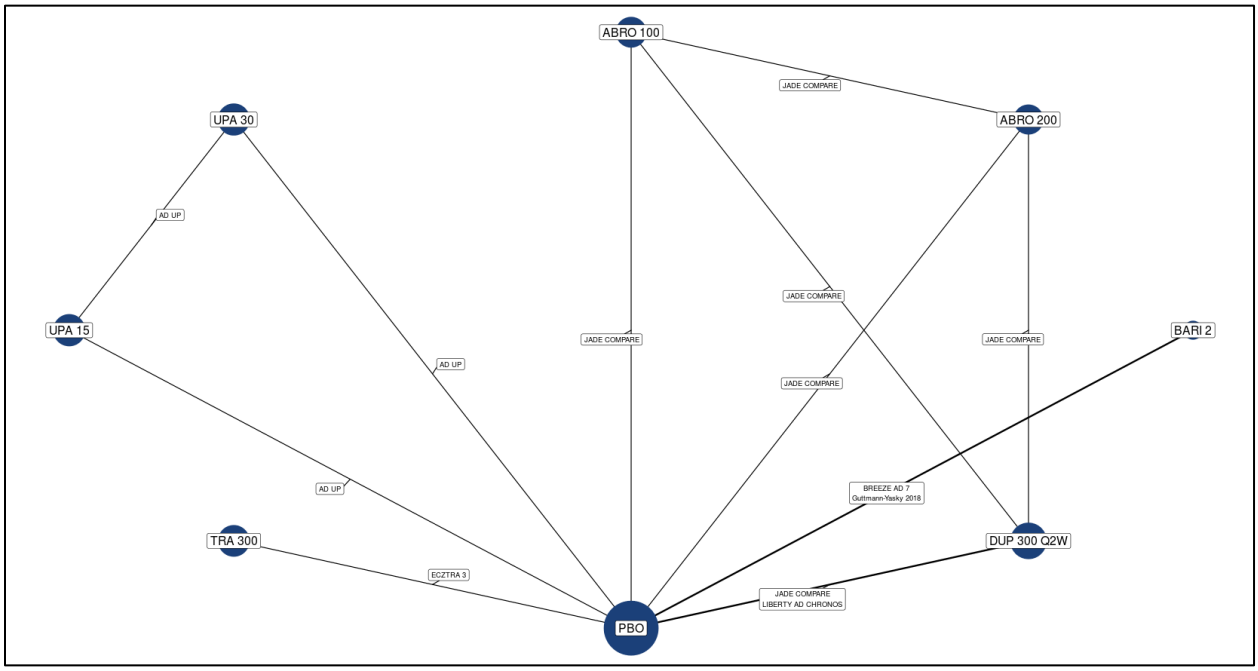
Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS[†]	SCORAD[‡]
Abrocitinib								
JADE COMPARE	ABRO 100 mg + TCS	16 weeks	81.2	60.3	38	34.8	47.0	NR
	ABRO 200 mg + TCS		87.3	71	48.9	47.5	62.8	NR
	DUP 300 mg + TCS		84.1	65.5	38.8	38.8	57.1	NR
	PBO + TCS		57.3	30.6	11.3	12.9	28.7	NR
Baricitinib								
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 15 mg +TCS	16 weeks	NR	65.0	NR	40.0	52.0	NR
	UPA 30 mg + TCS		NR	77.0	NR	59.0	64.0	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.

Additional NMA Results

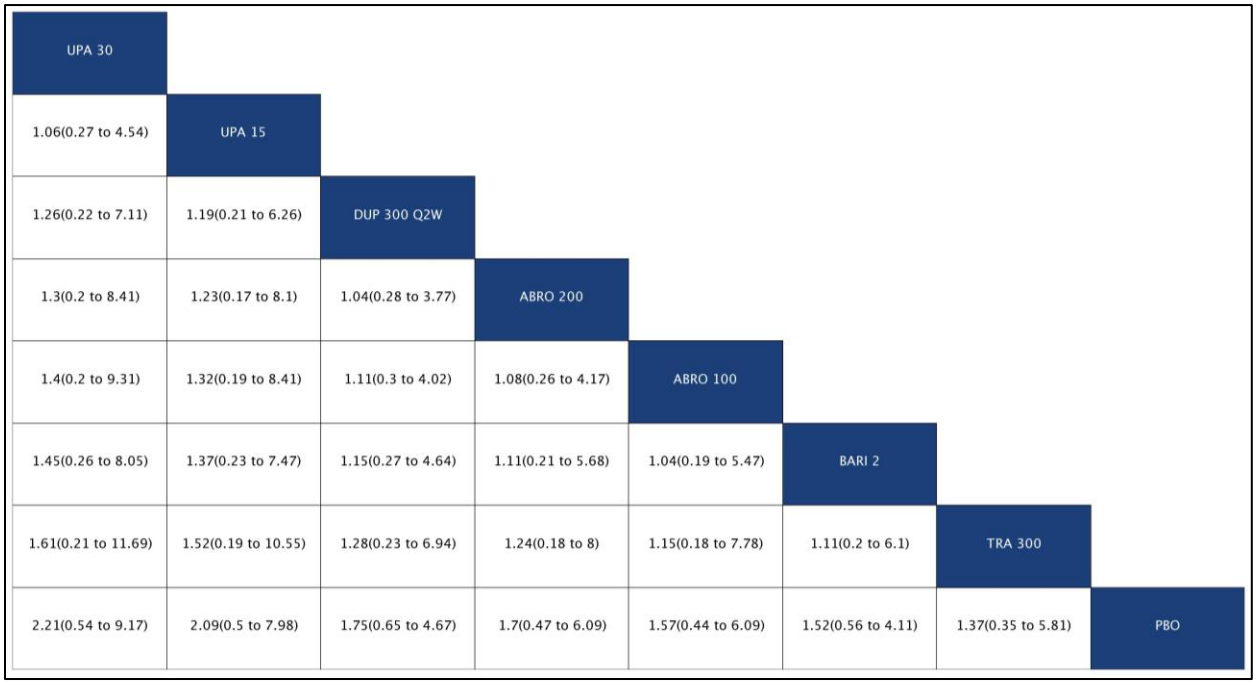
NMA results for EASI 50, 75, and 90 are shown in Figures D2.7-D2.9. Though all outcomes were better for each drug and dose compared to placebo, no differences were statistically significant due to the smaller effect size and smaller study populations. The one exception was dupilumab 300 mg Q2W compared to placebo for EASI 90 that was statistically significant.

Figure D2.6. Network of Placebo-controlled Combination Trials in Adults



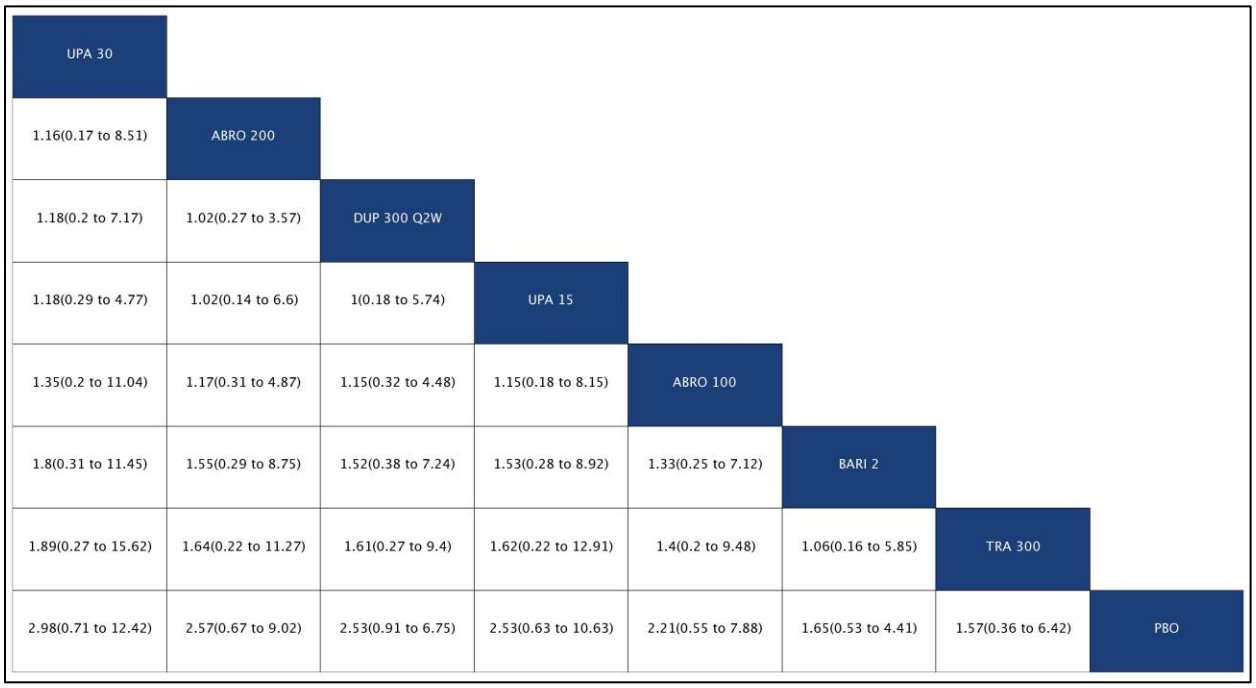
ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib.

Figure D2.7. NMA Results of EASI 50 in Placebo-controlled Combination Trials in Adults



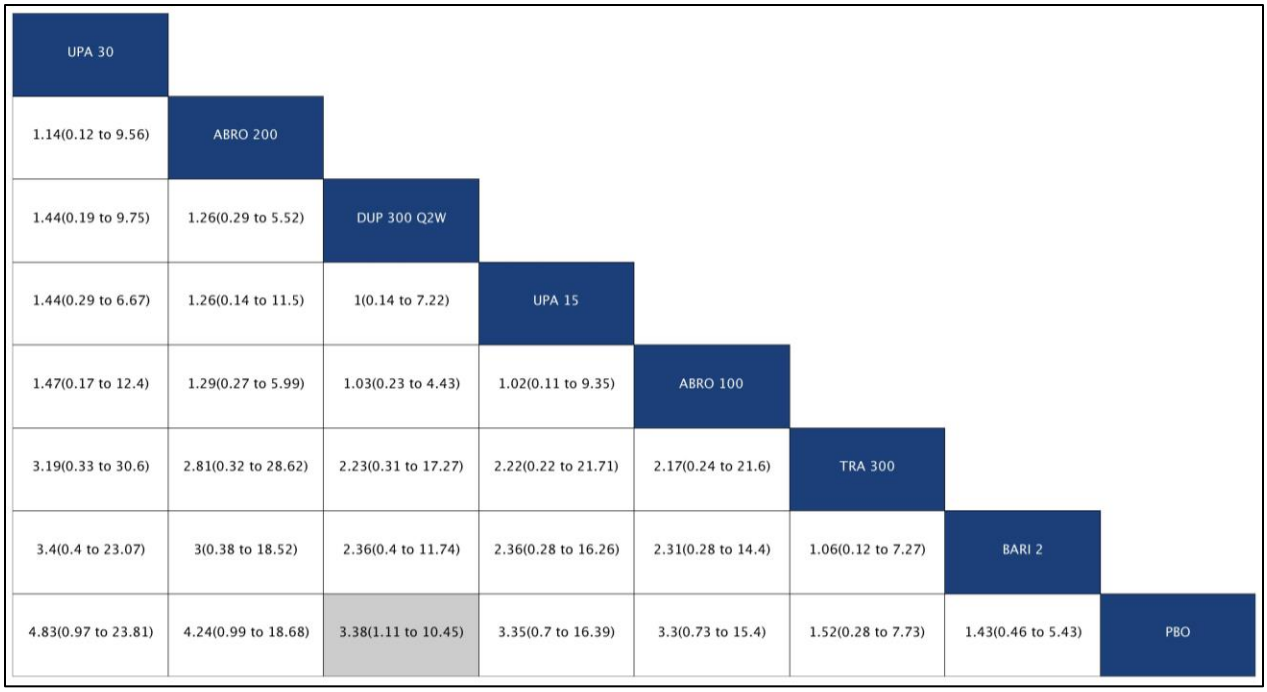
Each box represents the estimated risk ratios and 95% credible interval for the indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain 1. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib.

Figure D2.8. NMA Results of EASI 75 in Placebo-controlled Combination Trials in Adults



Each box represents the estimated risk ratios and 95% credible interval for the indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain 1. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib.

Figure D2.9. NMA Results of EASI 90 in Placebo-controlled Combination Trials in Adults



Each box represents the estimated risk ratios and 95% credible interval for the indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain 1. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib.

Placebo-controlled Combination Trials in Adults (Long-term)

Table D2.5. Key Outcomes in Placebo-controlled Combination Trials in Adults (Long-term)

Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS[†]	SCORAD[‡]
Tralokinumab								
ECZTRA 3	TRA 300 mg Q2W + TCS (non-responders)	Week 32	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[¶]								
LIBERTY AD CHRONOS	PBO + TCS	Week 52	30	22	16	13	13	-34.1
	DUP 300 mg + TCS Q2W		79	65	51	36	51	-66.2

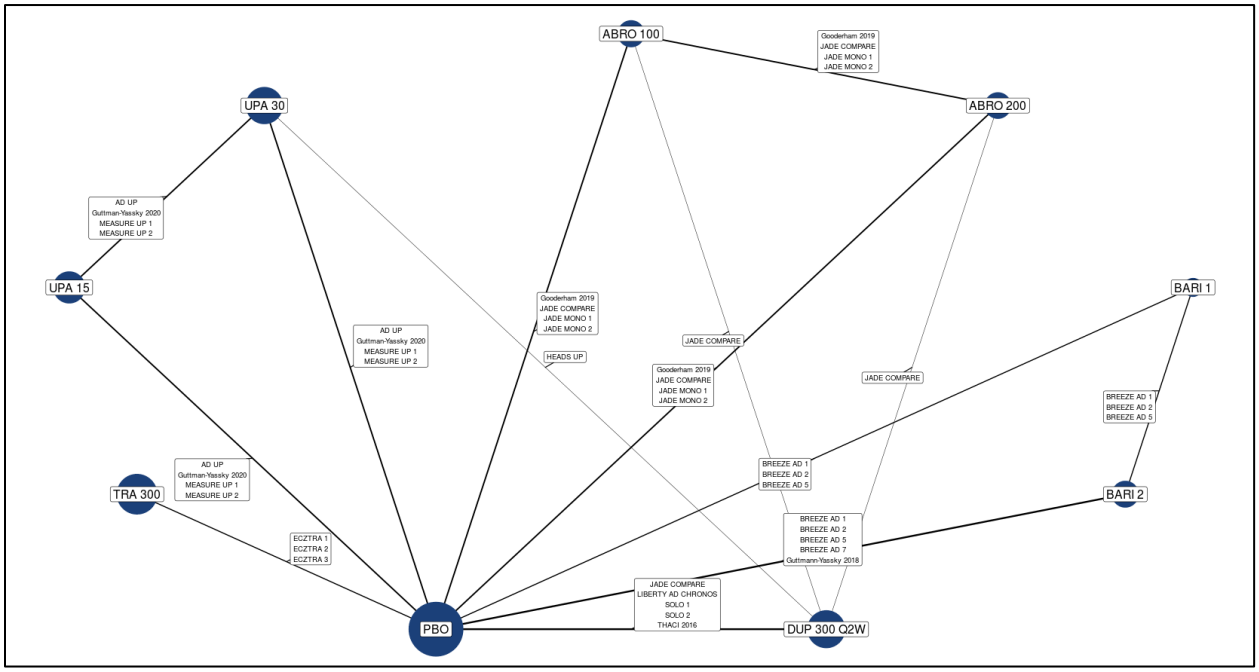
All values in the table are percentages. Includes trials only in adults 18 and older. DUP 300 mg QW + TCS dose was excluded from the table. DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, TCS: topical corticosteroids, TRA: tralokinumab. [†]PP-NRS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

Combined Placebo-controlled Monotherapy and Combination Trials in Adults (Short-term)

Additional NMA Results

On the assumption that background topical medication is not an important effect modifier, we included all trials in overall NMAs for EASI 50, 75, and 90 (Figures D2.11-D2.13). In general, these provided risk ratio results that were between NMA results for the placebo-controlled monotherapy alone trials and placebo-controlled combination alone trials.

Figure D2.10. Network of Overall Trials in Adults



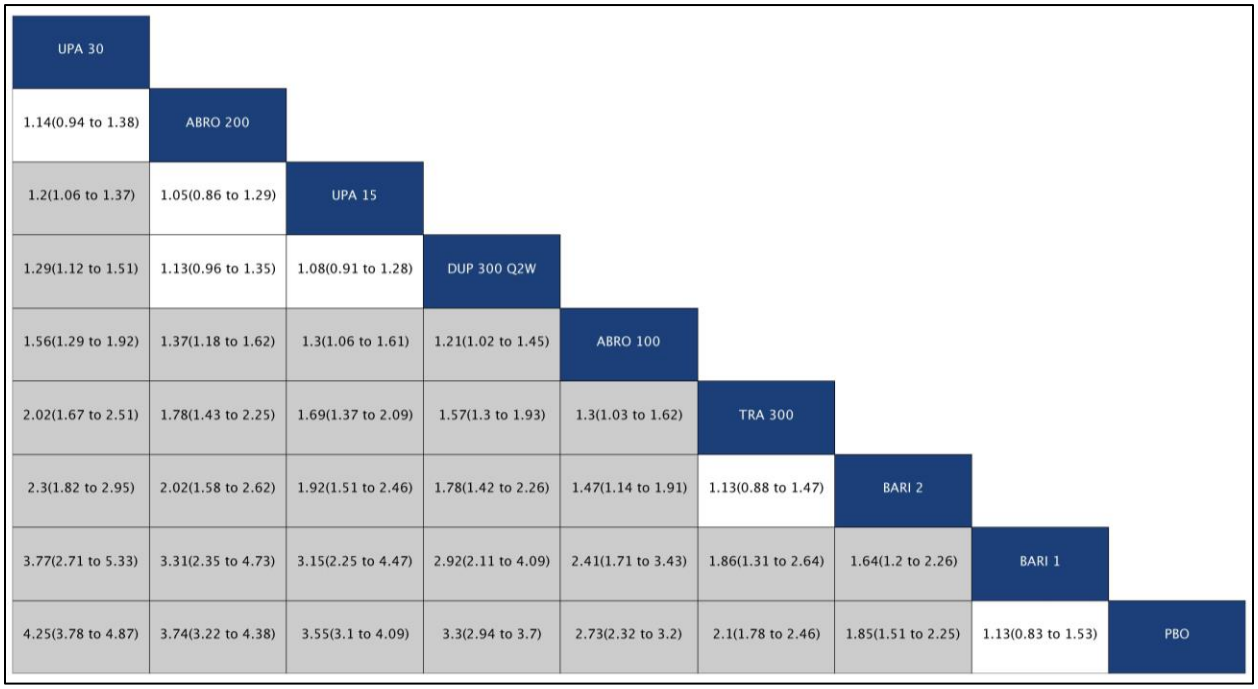
ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib.

Figure D2.11. NMA Results of EASI 50 in Overall Trials in Adults

UPA 30							
1.07(0.94 to 1.21)	ABRO 200						
1.09(1.01 to 1.19)	1.02(0.9 to 1.18)	UPA 15					
1.14(1.03 to 1.25)	1.06(0.96 to 1.19)	1.04(0.93 to 1.16)	DUP 300 Q2W				
1.26(1.11 to 1.44)	1.17(1.07 to 1.32)	1.15(1.01 to 1.32)	1.11(0.99 to 1.25)	ABRO 100			
1.47(1.3 to 1.69)	1.37(1.2 to 1.61)	1.35(1.18 to 1.55)	1.29(1.15 to 1.48)	1.17(1.01 to 1.36)	TRA 300		
1.7(1.46 to 2.02)	1.59(1.34 to 1.92)	1.56(1.33 to 1.85)	1.5(1.29 to 1.77)	1.35(1.14 to 1.62)	1.16(0.97 to 1.38)	BARI 2	
2.38(2.21 to 2.6)	2.22(2.02 to 2.49)	2.18(1.99 to 2.39)	2.1(1.95 to 2.27)	1.89(1.7 to 2.1)	1.62(1.45 to 1.8)	1.4(1.2 to 1.61)	PBO
2.75(2.14 to 3.53)	2.56(1.99 to 3.34)	2.51(1.95 to 3.24)	2.42(1.9 to 3.1)	2.18(1.68 to 2.82)	1.87(1.44 to 2.42)	1.61(1.28 to 2.04)	1.15(0.9 to 1.47)	BARI 1

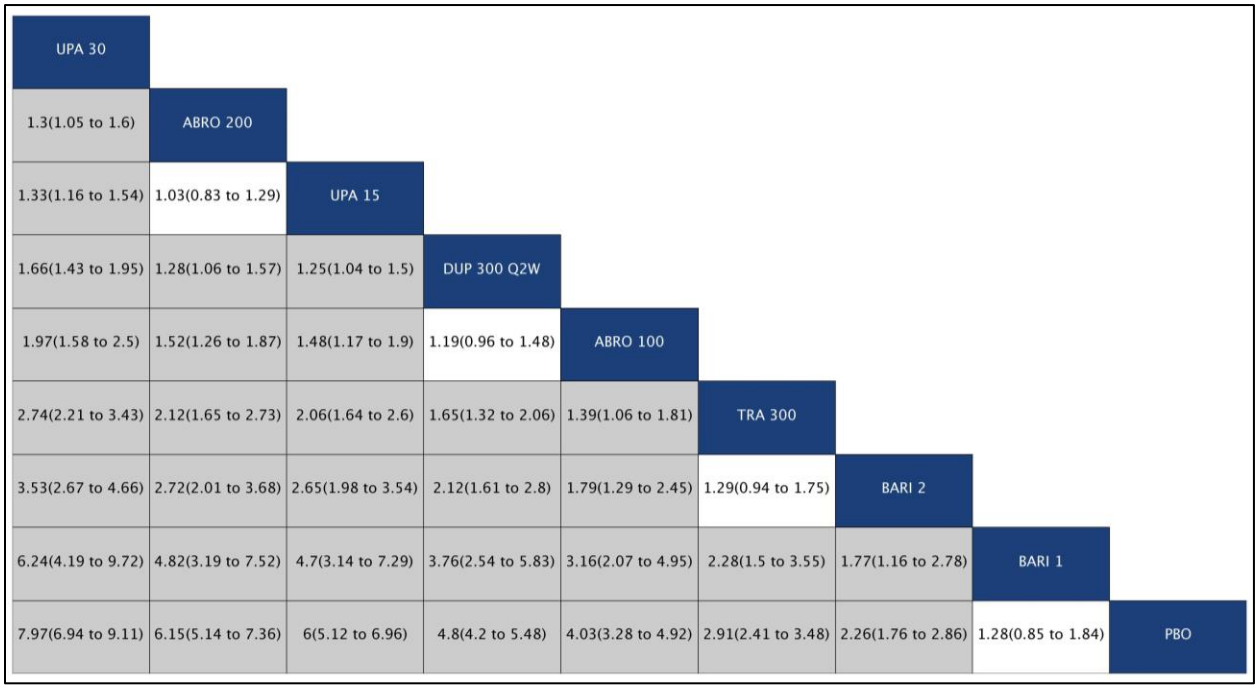
Each box represents the estimated risk ratios and 95% credible interval for the direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain 1. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib.

Figure D2.12. NMA Results of EASI 75 in Overall Trials in Adults



Each box represents the estimated risk ratios and 95% credible interval for the direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain 1. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib.

Figure D2.13. NMA Results of EASI 90 in Overall Trials in Adults



Each box represents the estimated risk ratios and 95% credible interval for the direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain 1. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib.

Harms

Placebo-controlled Monotherapy Trials in Adults (Short-term)

Summaries of the harms are provided in Section 3.2 of the Report. Tables presenting key harms from the trials are presented here.

Table D2.6. 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[§]	PBO	12 weeks	57	NR	9	4	0	3.0	1.3[¥]
	ABRO 100 mg		69	NR	6	3	2.6	9.0	4.5[¥]
	ABRO 200 mg		78	NR	6	3	2.6	20.0	3.9[¥]
JADE MONO 2[§]	PBO	12 weeks	NR	53.8	12.8	1.3	NR	2.6	1.3[#]
	ABRO 100 mg		NR	62.7	3.8	3.2	NR	7.6	1.3[#]
	ABRO 200 mg		NR	65.8	3.2	1.3	NR	14.2	1.3[#]
Gooderham 2019	PBO	16 weeks	NR	68.9	16.5	3.6	NR	1.8	2.8**
	ABRO 100 mg		NR			5.4	NR	1.8	3.6**
	ABRO 200 mg		NR			3.6	NR	14.5	0**
Baricitinib									
BREEZE-AD1	BARI 1 mg	16 weeks	NR	NR	1.6	0.8	0.8*	NR	5.5[††]
	BARI 2 mg		NR	NR	0.8	0	1.6*	NR	3.3[††]
	PBO		NR	NR	1.6	2.4	1.6*	NR	1.2[††]
BREEZE-AD2	BARI 1 mg	16 weeks	NR	NR	5.6	7.3	4.8*	NR	4.8[††]
	BARI 2 mg		NR	NR	2.4	2.4	1.6*	NR	5.7[††]
	PBO		NR	NR	0.8	3.7	0.8*	NR	4.5[††]
BREEZE-AD5	BARI 1 mg	16 weeks	NR	NR	2.7	0.7	NR	2.0	2.7[‡‡]
	BARI 2 mg		NR	NR	2.8	1.4	NR	3.4	1.4[‡‡]
	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 15 mg	16 weeks	NR	NR	NR	2.1	NR	3.5	4[¥¥]
	UPA 30 mg		NR	NR	NR	2.8	NR		
	PBO		NR	NR	NR	2.8	NR		0[¥¥]
MEASURE UP 2[§]	UPA 15 mg	16 weeks	NR	NR	NR	1.8	NR		1[¥¥]
	UPA 30 mg		NR	NR	NR	2.5	NR		2[¥¥]
	PBO		NR	NR	NR	2.9	NR		2[¥¥]
Phase II Guttmann-Yassky 2020	UPA 15 mg	16 weeks	63	NR	7.5	2.4	NR	2.5	0[¥¥]
	UPA 30 mg		76	NR	4.8	0	NR	7.1	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.

Placebo-controlled Monotherapy Trials in Adults (Long-term)

For responders in these trials re-randomized for long-term outcome assessment, 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.

Table D2.7. 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.

Placebo-controlled Combination Trials in Adults (Short-term)

Summaries of the harms are provided in Section 3.2 of the Report. Tables presenting the reported harms from the trials are presented here.

Table D2.8. 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 100 mg	16 weeks	50.8	NR	2.5	2.5	0.8	4.2	0.8
	ABRO 200 mg		61.9	NR	4.4	0.9	1.3	11.1	1.8
	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	20.8	11.1	0	5‡
	PBO + TCS		66.7	NR	0.8	3.2	3.2	0.79	6‡
Upadacitinib									
AD-UP	UPA 15 mg + TCS	16 weeks	NR	NR	0	2.3	NR	NR	1
	UPA 30 mg + TCS		NR	NR	0	1.3	NR	NR	1.3
	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.

Placebo-controlled Combination Trials in Adults (Long-term)

For patients in these trials, 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 D2.9. 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 Q4W +TCS (TRA responders)	Weeks 16-32	59.4	NR	1.4	0	1.4*	5.8	6‡
	TRA Q2W + TCS (TRA non-responders)		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‡
	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 Weeks	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 short-term placebo-controlled and combination trials in children and adolescents are presented below, followed by long-term combination trials. For adolescents, our literature search identified trials for abrocitinib, upadacitinib, and dupilumab. However, we did not identify any long-term evidence for abrocitinib and upadacitinib, while OLEs of dupilumab are presented below.

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.

Evidence Base

Placebo-controlled Monotherapy and Combination Trials in Adolescents (Short-term)

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

Though two placebo-controlled monotherapy trials of abrocitinib enrolled patients ≥12 years old, a small fraction of the patients in these trials were ≥12-17 years old (15%-26%).[34,35] One trial of abrocitinib solely enrolled patients 12-17 years old included use of topical medications in all arms.[39,42]

Two placebo-controlled monotherapy trials and one placebo-controlled combination trial of upadacitinib enrolled patients ≥12 years old; however, few patients in these trials were ≥12-17 years old (12%-15%).[74,75]

Placebo-controlled Combination Trials in Children and Adolescents (Long-term)

We identified one OLE of dupilumab in a subgroup in children with severe atopic dermatitis,[62] and one OLE of dupilumab in children with severe atopic dermatitis and adolescents with moderate-to-severe atopic dermatitis.[60,61] 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. Available baseline characteristics and results are presented in Tables D2.10 and D2.12.

Table D2.10. Overview of Placebo-controlled Combination Trials in Children and Adolescents (Short- and Long-term)

Population of Interest	Trial	Arms	Timepoint	Sample Size (N)	EASI (Mean)	Mean Age, y	Mean Disease Duration, y	IGA Score of 4 (%)
Dupilumab								
6-11 years*	LIBERTY AD PED OLE	DUP 2 mg/kg + TCS DUP 4 mg/kg + TCS	16 weeks and 52 weeks	33	26.5	8.5	7.5	37
6-11 years with severe AD*	Phase 2a AD-1412 Pediatric OL	DUP 2 mg/kg + TCS DUP 4 mg/kg + TCS	12 weeks	37	35.85	8.2	NR	97.2
12-17 years with moderate-to-severe AD*		DUP 2 mg/kg + TCS DUP 4 mg/kg + TCS	12 weeks	40	31.7	14.5	NR	52.5

All values are pooled by ICER. All trials had short-term timepoints at 12 or 16 weeks, and LIBERTY AD PED OLE additionally had a long-term time point of 52 weeks. There were no baseline data available in the adolescent subgroup of LIBERTY AD PED-OLE. ABRO: abrocitinib, AD: atopic dermatitis, AIC: academic-in-confidence, DUP: dupilumab, mg: milligram, N: total number, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, TCS: topical corticosteroids, y: year, %: percent. *subgroup of the trial population. †administered baseline weight-based dosing (DUP 100 mg for <30 kg weight, DUP 200 mg for ≥30 kg weight).

Results

Placebo-controlled Monotherapy Trials in Adolescents (Short-term)

While results for the placebo-controlled monotherapy trials in adolescents are briefly described in the Report, additional results and a table of key results are presented here.

Abrocitinib

In the two placebo-controlled monotherapy trials that enrolled patients ≥12 years old, 55%-60% of patients <18 years old achieved EASI 75, compared to 0%-13% in the placebo arms of those trials.[34,35] 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.

Data submitted from the manufacturer as academic-in-confidence showed improvements on EASI 90, a ≥4-point improvement on the patient-reported PP-NRS, and SCORAD with the abrocitinib arms, compared to the placebo arms of those trials.[39]

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

Upadacitinib

In the two placebo-controlled monotherapy trials that enrolled patients ≥12 years old, data submitted as academic-in-confidence from the manufacturer in patients <18 years old suggests improvements on EASI 75 and 90 in the upadacitinib arms, compared to the placebo arms.[77]

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

Table D2.11. 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 100 mg	12 weeks		44.1		26.5		
		ABRO 200 mg			54.5		27.3		
		PBO			12.5		12.5		
	JADE MONO-2*	ABRO 100 mg	12 weeks		43.8		12.5		
		ABRO 200 mg			60.0		40.0		
		PBO			0.0		0.0		
	Upadacitinib								
	MEASURE UP 1*	UPA 15 mg	16 weeks				NR	NR	NR
		UPA 30 mg					NR	NR	NR
		PBO					NR	NR	NR
	MEASURE UP 2*	UPA 15 mg	16 weeks				NR	NR	NR
		UPA 30 mg					NR	NR	NR
		PBO					NR	NR	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.

Placebo-controlled Combination Trials in Children and Adolescents (Short- and Long-term)

While results for the placebo-controlled combination trials in children and adolescents are briefly described in the report, additional results and a table of key results are presented here. As mentioned previously, no data for placebo-controlled combination trials of the interventions that enrolled children were identified.

Abrocitinib

In one placebo-controlled combination trial that enrolled adolescents, data submitted as academic-in-confidence from the manufacturer suggests improvements on EASI 75, EASI 90, a ≥4-point improvement on the patient-reported PP-NRS, and SCORAD with the abrocitinib arms, compared to the placebo arm.[39]

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

Table D2.12. 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 100/200 mg Q2W + TCS	16 weeks	82.8	67.2	30.3	29.5	58.3	-60.2¶
		DUP 300 mg Q4W + TCS		91	69.7	41.8	32.8	50.8	-62.4¶
		PBO + TCS		43.1	26.8	7.3	11.4	12.3	-29.8¶
	LIBERTY AD PED OLE*	DUP 2 mg/kg + TCS	16 weeks	94	59	41	35	53	-61
		DUP 4 mg/kg + TCS		93	73	33	40	69	-62
		DUP 2 mg/kg + TCS	52 weeks	94	94	71	76	65	-79
		DUP 4 mg/kg + TCS		94	75	44	25	69	-67
	Phase 2a AD-1412 Pediatric OL*	DUP 2 mg/kg + TCS	12 weeks	NR	NR	NR	16.7	NR	-57.5
		DUP 4 mg/kg + TCS		NR	NR	NR	21.1	NR	-46.9
12-17 years	**Abrocitinib**								
	JADE TEEN	ABRO 100 mg + TCS	12 weeks	[redacted]	68.5	[redacted]	41.6	52.6	[redacted]
		ABRO 200 mg + TCS			72		46.2	55.4	
		PBO +TCS			41.5		24.5	29.8	
	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 Pediatric OL*	DUP 2 mg/kg + TCS	12 weeks	NR	NR	NR	10	NR	-47.7
		DUP 4 mg/kg + TCS		NR	NR	NR	35	NR	-43.4

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

At the time of this report, no data for the harms of the interventions in children or adolescents were identified. Data for overall populations of trials that enrolled adolescents and adults are presented in Table D2.6.

Table D2.13. 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 D2.14. 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 100/200 mg Q2W + TCS	16 weeks	NR	67.2	1.6[†]	0[†]	14.8[‡]	NR	3.3[¶]
		DUP 300 mg Q4W + TCS		NR	65	0[†]	1.7[†]	6.7[‡]	NR	1.7[¶]
		PBO +TCS		NR	73.3	1.7[†]	1.7[†]	4.2[‡]	NR	5[¶]
	LIBERTY AD PED-OLE*	DUP 2 mg/kg + TCS	52 weeks	NR	94	0[†]	12[†]	5	NR	12
		DUP 4 mg/kg + TCS		NR	100	0[†]	19[†]	31	NR	50[#]
	Phase 2a AD-1412 Pediatric OL*	DUP 2 mg/kg + TCS	20 weeks	NR	NR	NR	0	0	0	5.56[§]
		DUP 4 mg/kg + TCS		NR	NR	NR	10.53	5.26	10.53	5.26[§]
12-17 years	**Abrocitinib**									
	JADE TEEN	ABRO 100 mg + TCS	12 weeks	NR	56.8	1.1	NR	NR	NR	NR
		ABRO 200 mg + TCS		NR	62.8	2.1	NR	NR	NR	NR
		PBO +TCS		NR	52.1	2.1	NR	NR	NR	NR
	Dupilumab									
	LIBERTY AD PED-OLE*	DUP 300 mg Q4W	52 weeks	NR	72.2	0[†]	3.8[†]	8.7[¥]	NR	NR
		DUP 200/300 mg Q2W		NR	74.4	0.9[†]	0.9[†]		NR	NR
	Phase 2a AD-1412 Pediatric OL*	DUP 2 mg/kg + TCS	20 weeks	NR	NR	NR	5	0	0	0[§]
		DUP 4 mg/kg + TCS		NR	NR	NR	5	0	0	5[§]

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

Results

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 2.15. Key Outcomes for Ruxolitinib Cream

Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS†	SCORAD‡
Ruxolitinib Cream								
TRuE AD 1	RUX 0.75%	8 weeks	NR	56.0	38.1	50.0	40.4	NR
	RUX 1.5%		NR	62.1	44.3	53.8	52.2	NR
	PBO		NR	24.6	9.5	15.1	15.4	NR
TRuE AD 2	RUX 0.75%	8 weeks	NR	51.5	35.1	39.0	42.7	-62.9**
	RUX 1.5%		NR	61.8	43.4	51.3	50.7	-67.3**
	PBO		NR	14.4	4.2	7.6	16.3	-30.4**
Phase II Kim 2020*	TRI 0.1%	4 weeks	NR	47.1	13.7	25.5	19.4	NR
	RUX 1.5%		NR	56.0	26.0	38.0	62.5	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 D3.57-D.66.

**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 D2.16. Key Harms for Ruxolitinib Cream

Trial	Arm	Timepoint	Any TEAE	Study Drug-Related TEAE	Serious TEAE	D/C Due to TEAEs	Application Site Burning	Application Site Pruritis
Ruxolitinib Cream								
TRuE AD 1	RUX 0.75%	8 weeks	29.4	6.0	0.4	1.2	0.0	0.8
	RUX 1.5%		28.9	5.5	0.8	1.2	0.8	0.0
	PBO		34.9	12.7	1.6	4.0	1.6	1.6
TruE AD 2	RUX 0.75%	8 weeks	29.4	3.2	1.2	0.4	0.8	0.8
	RUX 1.5%		23.6	4.5	0.4	0.0	0.8	0
	PBO		32.3	9.7	0.0	2.4	6.5	3.2
Phase II Kim 2020*	TAC 0.1%	8 weeks	33.3	2.0	NR	2.0	NR	NR
	RUX 1.5%		24	6.0	NR	0.0	NR	NR
	PBO		32.7	9.6	NR	1.9	NR	NR

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

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

D3. Evidence Tables

Moderate to Severe Population

Table D3.1. Study Quality Table[34-36,43,49,57,58,65-67,131]

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											
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

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

Table D3.2 Key Features

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
Abrocitinib						
Phase III JADE COMPARE[36-40] Bieber 2021 NEMJ, Pfizer Press release + Data submission	N= 837 Adults 18+ with moderate to severe atopic dermatitis DB, PC, RCT	•Abrocitinib (100 mg) + placebo Q2W (to Week 16)→abrocitinib (100 mg) (Week 20) •Abrocitinib (200 mg) + placebo Q2W (to Week 16) →abrocitinib (200 mg) (Week 20)	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	•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	•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 dysfunction, Q wave interval abnormalities, current or history of certain infections, cancer, lymphoproliferative disorders •Other active nonAD inflammatory skin diseases or conditions affecting skin	**Primary Endpoints Week 12:** •Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) response rate •Investigator's Global

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
		•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)	study. 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	screening) of inadequate 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	•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	Assessment (IGA) (score of 0 or 1 and ≥ 2 point from baseline improvement) response rate
Phase III JADE MONO-1[34,39] Simpson 2020 (additional: Pfizer 2019)	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	•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	•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	**Primary Endpoints at week 12:** •EASI-75 response rate •IGA response rate

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
			on stable regimen. •Prior drug/non-drug treatment, concomitant drug and non-drug treatment summarized according to CaPS	topical AD treatments or require systemic treatments for AD control		
Phase III JADE MONO-2[35,39] Silverberg 2020 JAMA Dermatology + Pfizer data on file	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	**Primary Endpoints at week 12**: •EASI-75 response rate •IGA response rate
Phase III JADE TEEN[39,42] Pfizer data on file + AAAI abstract	N=285 Ages 12-17 with moderate to severe atopic dermatitis	Once-daily oral administration in one of the following doses for 12 weeks: •Abrocitinib 200	**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	•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	**Co-primary endpoints at week 12**: •EASI-75 response rate •IGA response rate

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
	DB, PC, RCT	mg •Abrocitinib 100 mg •Placebo		to severe disease (≥ the following scores: BSA 10%, IGA 3, EASI 16, Pruritus NRS severity 4	•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 II[41] 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	Patients who had used topical corticosteroids or topical calcineurin inhibitors within 1 week of the first dose of study drug were excluded	**Primary endpoint at week 12:** Proportion of patients who achieved IGA score of 0 or 1

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
				to receive topical treatment within 12 months before the first dose of study drug because it was medically inadvisable		
Baricitinib						
Phase III BREEZE-AD1[43] Simpson 2020 BJD	Adults 18+ with moderate to severe AD DB, PC, RCT	Daily dose for 16 weeks: •Baricitinib 1 mg (Low) •Baricitinib 2 mg (Mid) •Baricitinib 4 mg (High) •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, lymphoproliferative disease or	**Primary Endpoint at week 16:** •IGA score of 0,1 response rate [**Secondary Endpoint at week 16**: •EASI-75 response rate

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
					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	Key Outcomes
Phase III BREEZE-AD2[43] Simpson 2020 BJD	Adults 18+ with moderate to severe AD DB, PC, RCT	Daily dose for 16 weeks: •Baricitinib 1 mg (Low) •Baricitinib 2 mg (Mid) •Baricitinib 4 mg (High) •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, lymphoproliferative disease or neuropsychiatric disorders •Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis.	**Primary Endpoint at week 16:** •IGA score of 0,1 response rate **Secondary Endpoint at week 16**: •EASI-75 response rate

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
BREEZE-AD3[44,45] (Press release, Eli Lilly Oct 31, 2020 + Data on file)	Adults 18+ with moderate to severe AD DB, PC, RCT	•Baricitinib 2 mg •Baricitinib 4 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.	**Primary Endpoint:** •IGA score of 0,1 response rate at week 16, 36, and 52

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
Phase III BREEZE-AD5[45,46] 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 1 mg (Low) •Baricitinib 2 mg (High) •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 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	**Primary Endpoint at week 16:** • EASI-75 response rate (high dose)

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
					• 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 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	Key Outcomes
Phase III BREEZE-AD7 Reich 2020[47,48] Reich 2020 JAMA	≥18 years of age, moderate-to-severe atopic dermatitis DB, PC, RCT	•Baricitinib 2 mg QD + TCS •Baricitinib 4 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	**Primary outcome:** proportion of patients achieving a validated IGA-AD score of 0 or 1, with a 2-point or greater improvement from baseline at week 16
Phase 2[49] Guttmann-Yassky 2018 JAAD	≥18 years of age, moderate-to-severe atopic dermatitis DB, PC, RCT	•Baricitinib 2 mg QD + TCS •Baricitinib 4 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 participation; certain vaccines	**Primary outcomes:** Proportion of patients achieving EASI 50 vs Placebo;
Dupilumab						

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
SOLO 1[53,57] Simpson 2016 NEMJ + data on file	≥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	**Primary outcomes at week 16**: IGA score of 0/1 and reduction of ≥2 from baseline

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
SOLO 2[53,57] Simpson 2016 NEMJ + data on file	≥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	**Primary outcomes at week 16**: IGA score of 0/1 and reduction of ≥2 from baseline

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
LIBERTY AD CHRONOS[51,52] Blauvelt et al 2017	≥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	**Primary Outcomes at week 16** •IGA score 0/1 and baseline reduction≥2 proportion •EASI-75 proportion

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
LIBERTY AD ADOL[54] Simpson et al 2020	N=251 Ages 12-17 adolescents with moderate to severe atopic dermatitis DB, PC, RCT, Parallel group	**Day 1 (Loading Dose)** •Dupilumab 400 mg (for patients <60kg)/Dupilumab 600 mg (for patients ≥60kg) •Placebo **After Day 1-Week 16:** •Dupilumab 200 mg (for patients <60kg)/Dupilumab 300 mg (for patients ≥60kg) Q2W •Dupilumab 300 mg Q4W •Placebo	**Permitted:** basic skin care, emollients (required as background treatment), topical anesthetics, antihistamines, topical and systemic anti-infective medications, meds used to treat chronic disease such as diabetes, hypertension, and asthma **Prohibited concomitant meds:** treatment with a live vaccine, an investigational drug (other than dupilumab), immunomodulating biologics, systemic nonsteroid immunosuppressant, systemic corticosteroids, TCS or TCI, crisaborole, Initiation of treatment of AD with prescription moisturizers, Major surgical procedures,	•adolescents ≥12 to <18 years of age •AD diagnosis (American Academy of Dermatology consensus criteria) •IGA ≥3 & EASI ≥16 •P-NRS average score for max itch intensity ≥4 •≥10% BSA of AD involvement at the screening and baseline visits •Recent history of inadequate response to topical AD med or for whom topical treatments is medically inadvisable	•Participation in a prior dupilumab clinical study •Treatment with TCS or TCI within 2 weeks before baseline visit •Used immunosuppressive/immunomodulating drugs within 4 weeks before the baseline visit •Body weight <30 kg at Baseline •Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the baseline visit •Known/suspected immunodeficiency, known history of HepB or HIV •History of malignancy before the baseline visit •Diagnosed high risk of active endoparasitic infections	**Primary Outcomes at week 16** •IGA score 0/1 and baseline reduction≥2 proportion •EASI-75 proportion

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
			tanning in a bed/booth, phototherapy			
Phase 2b AD-1021[57-59] Thaci et al 2016 (Additional: 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	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 at screening and baseline	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	**Primary Outcomes at week 16:** percentage change in EASI score from baseline to week 16

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
			drug other than dupilumab.			
LIBERTY AD PEDS Phase III[55] Paller et al 2020	n= 367 Children aged 6-11 years with severe AD inadequately controlled with topical therapies DB, PC, RCT	1:1:1 **Dupilumab + TCS every 2 weeks** (Q2W + TCS; weight-tiered: baseline weight 15 to <30 kg, 100 mg Q2W + TCS, 200 mg loading dose; baseline weight ≥30 kg, 200 mg Q2W + TCS, 400 mg loading dose) **Dupilumab + TCS every 4 weeks** (300 mg q4w + TCS; 600 mg loading dose regardless of weight) **Matching placebo + TCS**	All patients received concomitant once-daily medium-potency TCS starting 2 weeks before baseline.	- Children age 6-11 years with AD diagnosed >=1 year before screening; - IGA score of 4 - EASI score of >=21, - Affected BSA ≥15%, - Weekly averaged baseline worst itch score (PPNRS) >=4; - Weight >=15 kg; and - Documented history of inadequate response to topical AD medication within 6 months of baseline. -At least 11 (of a total of 14) applications of a stable dose of topical emollient (moisturizer) twice daily during the 7 consecutive days immediately before the baseline visit	-Participation in a prior dupilumab clinical study -Treatment with a systemic investigational drug before baseline visit or with a topical investigational drug, with crisabarole or with TCI within 2 weeks prior to the baseline visit -History of important side effects of medium potency TCS -used any of these treatments within 4 weeks before baseline visit, immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate, etc.) -Phototherapy for AD -Treatment with biologics: Any cell-depleting agents including rituximab within 6 months before baseline visit, or until lymphocyte and CD 19+ lymphocyte count returns to normal, Other biologics: within 5 half-lives or 16 weeks before baseline visit -Body weight <15 kg at baseline	**Primary outcomes:** Proportion of patients with an IGA score of 0 or 1 (clear or almost clear) at week 16; the co-primary endpoint in the European Union and EU reference countries was >=75% improvement in EASI (EASI-75) from baseline to week 16.

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
AD SOLO-CONTINUE[56] Worm 2019 JAMA	N= 422 re-randomized patients from SOLO to SOLO-CONTINUE Dupilumab-treated patients who has achieved IGA score of 0 or 1 or 75% or greater improvement l EASI at week 16 during the SOLO studies. DB, PC, RCT	Re-randomized 2:1:1:1 **Original regimen** (300 mg QW or Q2W) or **Less frequency** (300 mg Q4W or Q8W) or **Placebo**	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.	**Co-primary endpoint:** percentage of patients who maintained EASI75 at week 36, patients who maintained EASI response

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
Phase 2a - Pediatric OL (AD-1412)[57,60-62] Cork 2017 Abstract & Clinicaltrials.gov	Adolescents (12-17) with moderate-to-severe AD and Children (6-11) with severe AD N=78 (40 adolescents, 38 children) MC, OL, ascending dose, sequential-cohort study	Cohort 1: -Dupilumab 2 mg/kg single dose for first 8 weeks, then after week 8, weekly 2 mg/kg dose for 4 weeks Cohort 2: -Dupilumab 4 mg/kg single dose for first 8 weeks, then after week 8, weekly 2 mg/kg dose for 4 weeks	Not Reported	-Male or female patients ≥6 to <18 years of age -Atopic Dermatitis whose disease cannot be adequately controlled with topical medications -IGA = 3 or 4 in adolescents ≥12 to <18 year of age -IGA = 4 in children ≥6 to <12 years of age	-Recent treatment with systemic immunosuppressive agents -Any systemic infection requiring treatment within 4 weeks before the baseline visit -Superficial skin infections within 1 week before the baseline visit -Known history of HIV infection -History of HepB or HepC, clinical endoparasitosis (i.e., helminthic infection) within 12 months before the baseline visit, or high risk of helminthic infection -History of malignancy within 5 years before the baseline visit -Persistent (confirmed by repeated tests ≥2 weeks apart) elevated transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) more than 3 times the upper limit of normal (ULN) during the screening period -Presence of skin comorbidities that may interfere with study assessments	Primary: -PK Parameters

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
PHASE III LIBERTY AD PED-OLE (Pediatric 6-11 years subgroup analysis)[62] Cork 2020 BJD	Pediatric patients ages 6 months-17 years with AD (FOR THIS PUBLICATION: children ages 6-11; n=33) LT OLE	-Dupilumab 2 mg/kg -Dupilumab 4 mg/kg	TCS, TCI, systemic immunosuppressants	-Participated in a prior dupilumab study in pediatric patients with AD and adequately completed the visits and assessments required for both the treatment and follow-up periods, as defined in the prior study protocol Key	-Patients who, during their participation in a prior dupilumab study developed an AE or SAE related to study drug which could indicate that continued treatment with study drug may present an unreasonable risk for the patient -Treatment with an investigational drug, other than dupilumab, within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit -Having used immunosuppressive/immunomodulating drugs within 4 weeks before the baseline visit -Treatment with a live (attenuated) vaccine within 4 weeks before the baseline visit -Diagnosed active endoparasitic infections or at high risk of these infections -Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study	Primary: -dupilumab concentration -time profile -TEAEs
Tralokinumab						

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
Phase III ECZTRA 1[65,67] Wollenburg 2020 British Journal of Dermatology	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	**Primary endpoints at week 16:** •EASI-75 response rate •IGA score of 0 or 1 response rate

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
Phase III ECZTRA 2[65,67] Wollenburg 2020 British Journal of Dermatology	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	**Primary Endpoints at week 16:** •EASI-75 response rate •IGA score of 0 or 1 response rate

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
Phase III ECZTRA 3[66,67] (w/topical corticosteroids) Silverberg 2020 British Journal of Dermatology	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.	**Primary Endpoints at week 16:** •EASI-75 response rate •IGA score of 0 or 1 response rate
Upadacitinib						

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
Phase III AD-UP (with TCS)[76,77] (Press release) Abbvie 2020	N~901 Ages 12-75 with moderate to severe AD DB, PC, RCT	**Week 1-16** • Upadacitinib 15 mg + topical corticosteroids (TCS) • Upadacitinib 30 mg + TCS • Placebo + TCS **After Week 16:** • Upadacitinib 15 mg + TCS • Upadacitinib 30 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	**Primary Endpoints at week 16:** •EASI-75 response rate •IGA-AD score of 0 or 1 with ≥ 2 points reduction
Phase III MEASURE UP 1[74,77] (press release) Abbvie 2020	N= 847 Ages 12-75 years with moderate to severe AD DB, PC, RCT	**Week 1-16:** • Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo **After Week 16**: • Upadacitinib 15 mg • Upadacitinib 30 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	**Primary Endpoints at week 16:** •EASI-75 response rate •validated IGA-AD score of 0 or 1 with ≥ 2 points reduction response rate

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
Phase III MEASURE UP 2[75,77] (press release) Abbvie 2020	N= 836 Ages 12-75 years with moderate to severe AD DB, PC, RCT	**Week 1-16:** • Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo **After Week 16:** • Upadacitinib 15 mg • Upadacitinib 30 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	**Primary Endpoints at week 16:** •EASI-75 response rate •validated IGA-AD score of 0 or 1 with ≥ 2 points reduction response rate
Phase IIIb Heads Up[72,77] (Press release) AbbVie 2020	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	**Prohibited Medications:** JAK inhibitors, prior dupilumab use	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.	**Primary Endpoint at 16 weeks** EASI75

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria	Key Outcomes
Phase 2b[71] Guttman-Yassky 2020	N=167 Ages 18-75 years with moderate to severe AD DB, PC, RCT	**Week 1-16 (period 1):** •upadacitinib 7.5 mg QD •upadacitinib 15 mg QD •upadacitinib 30 mg QD •placebo **Week 16-88 (period 2 - rerandomization stratified by EASI 75 response at week 16):** •upadacitinib 7.5 mg QD •upadacitinib 15 mg QD •upadacitinib 30 mg QD •placebo	**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 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	•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. •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.	•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 (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	**Primary Endpoint at week 16:** •Mean % Change in EASI score

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, kg: kilogram, JAK: Janus kinase, LT: long-term, MACE: major adverse cardiovascular event, MC: multi-center, mg: milligram, MI: myocardial infarction n: number, N: total number, NR: not reported, NRS: numerical rating scale, 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 D3.3. Baseline Characteristics I[34-36,39,42-47,49,51,53-58,62-72,74-77,79,80]

Study Name	Arms	Sample Size (N)	Age (years)		Male		White		Weight (kg)	
			mean	SD	n	%	n	%	mean	SD
Abrocitinib										
JADE MONO-2	PBO	78	33.4	13.8	47	60.3	40	51.3	NR	NR
	ABRO 100 mg	158	37.4	15.8	94	59.5	101	63.9	NR	NR
	ABRO 200 mg	155	33.5	14.7	88	56.8	91	58.7	NR	NR
	Overall	391	35.1	15.1	229	58.6	232	59.3	NR	NR
JADE MONO-1	PBO	77	31.5	14.4	49	64	62	81	NR	NR
	ABRO 100 mg	156	32.6	15.4	90	58	113	72	NR	NR
	ABRO 200 mg	154	33	17.4	81	53	104	68	NR	NR
JADE COMPARE	PBO	131	37.4	15.2	77	58.8	87	66.4	NR	NR
	ABRO 100 mg	238	37.3	14.8	120	50.4	182	76.5	NR	NR
	ABRO 200 mg	226	38.8	14.5	104	46.0	161	71.2	NR	NR
	DUP 300 mg	242	37.1	14.6	108	44.6	176	72.7	NR	NR
	Total	837	37.7	14.7	409	48.9	606	72.4	NR	NR
JADE TEEN	PBO									
	ABRO 100 mg									
	ABRO 200 mg									
	Overall	285	14.9		145	50.9	160	56.1		
Phase 2 Gooderham 2019	PBO	56	42.6	15.1	21	37.5	40	71.4	NR	NR
	ABRO 100 mg	56	41.1	15.6	31	55.4	40	71.4	NR	NR
	ABRO 200 mg	55	38.7	17.6	28	50.9	37	67.3	NR	NR
Tralokinumab										
ECZTRA 1	PBO	199	Median: 37.0	IQR: 26.0 to 49.0	123	61.8	138	69.3	NR	NR
	TRA 300 mg	603	Median: 37.0	IQR: 27.0 to 48.0	351	58.2	426	70.6	NR	NR
ECZTRA 2	PBO	201	Median: 30.0	IQR: 23.0 to 46.0	114	56.7	123	61.2	NR	NR

Study Name	Arms	Sample Size (N)	Age (years)		Male		White		Weight (kg)	
			mean	SD	n	%	n	%	mean	SD
	TRA 300 mg	593	Median: 34.0	IQR: 25.0 to 48.0	359	60.5	374	63.1	NR	NR
ECZTRA 2 sub-analysis	PBO	91	38.9	15.9	46	50.5	46	50.5	NR	NR
	TRA 300 mg	270	40.2	15.7	147	54.4	148	54.8	NR	NR
ECZTRA 1 and 2 pooled LTE	PBO	400	37.2	14.8	237	59.3	NR	NR	NR	NR
	TRA 300 mg	1196	37.9	14.2	710	59.4	NR	NR	NR	NR
	Overall	1596	37.8	14.4	947	59.3	NR	NR	NR	NR
ECZTRA 3	PBO + TCS	127	Median: 34.0	IQR: 24.0 to 50.0	84	66.1	85	66.9	NR	NR
	TRA 300 mg + TCS	253	Median: 37.0	IQR: 28.0 to 52.0	125	49.4	203	80.2	NR	NR
	Overall	380	Median: 36.0	IQR: 27.0 to 51.0	209	55	288	75.8	NR	NR
Upadacitinib										
AD-UP	PBO + TCS	304	34.3	Range: 12 to 75	178	58.6	225	74	NR	NR
	UPA 15 mg + TCS	300	32.5	Range: 13 to 74	179	59.7	204	68	NR	NR
	UPA 30 mg + TCS	297	35.5	Range: 12 to 75	190	64	218	73.4	NR	NR
MEASURE UP 1	PBO	281	34.4	Range: 12 to 75	144	51.2	182	64.8	NR	NR
	UPA 15 mg	281	34.1	Range: 12 to 74	157	55.9	182	64.8	NR	NR
	UPA 30 mg	285	33.6	Range: 12 to 75	155	54.4	191	67	NR	NR
MEASURE UP 2	PBO	278	33.4	Range: 13 to 71	154	55.4	195	70.1	NR	NR
	UPA 15 mg	276	33.3	Range: 12 to 74	155	56.2	184	66.7	NR	NR

Study Name	Arms	Sample Size (N)	Age (years)		Male		White		Weight (kg)	
			mean	SD	n	%	n	%	mean	SD
	UPA 30 mg	282	34.1	RangeL 12 to 75	162	57.4	198	70.2	NR	NR
Phase 2b Guttman-Yassky 2020	PBO	41	39.9	17.5	24	58.5	28	68.3	26.2	6.8
	UPA 7.5 mg	42	41.5	15.4	28	66.7	24	57	27.9	6.3
	UPA 15 mg	42	38.5	15.2	30	71.4	21	50	27.4	6.7
	UPA 30 mg	42	39.9	15.3	22	52.4	23	55	27.4	6
Baricitinib										
BREEZE-AD1	PBO	249	35	12.6	148	59.4	147	59.5	73	15.7
	BARI 1 mg	127	36	12.4	78	61.4	74	58.3	74	17.2
	BARI 2 mg	123	35	13.7	82	66.7	75	61.0	75	17.7
	BARI 4 mg	125	37	12.9	83	66.4	70	56.5	74	17.2
BREEZE-AD2	PBO	244	35	13.0	154	63.1	169	69.3	72	15.5
	BARI 1 mg	125	33	10.0	80	64.0	85	68.0	75	16.6
	BARI 2 mg	123	36	13.2	65	52.8	85	69.1	72	14.7
	BARI 4 mg	123	34	14.1	82	66.7	82	66.7	74	14.9
BREEZE-AD3 (LTE)	BARI 2 mg	[redacted]					NR	NR	[redacted]	
BREEZE-AD3 sub-study	BARI 2 mg→PBO						NR	NR		
	BARI 2 mg→2 mg						NR	NR		
	Overall						NR	NR		
BREEZE-AD5	PBO	147	39	17	80	54	80	55		
	BARI 1 mg	147	40	17	75	51	86	59	NR	NR
	BARI 2 mg	146	40	15	69	47	85	58	[redacted]	

Study Name	Arms	Sample Size (N)	Age (years)		Male		White		Weight (kg)	
			mean	SD	n	%	n	%	mean	SD
BREEZE-AD7	PBO + TCS	109	33.7	13.2	71	65	46	42	73	15.8
	BARI 2 mg + TCS	109	33.8	12.8	70	64	50	46	72.4	15.5
	BARI 4 mg + TCS	111	33.9	11.4	75	68	54	49	73.3	17.8
Phase 2 Guttman-Yasky 2018	PBO + TCS	49	Median: 35	IQR: 28.0 to 48.0	24	49	23	47	NR	NR
	BARI 2 mg + TCS	37	Median: 42	IQR: 26.0 to 52.0	22	59	20	54	NR	NR
	BARI 4 mg + TCS	38	Median: 32.5	IQR: 26.0 to 48.0	22	58	18	47	NR	NR
Dupilumab										
SOLO 1	PBO	224	Median: 39	IQR: 27 to 50.5	118	53	146	65	NR	NR
	DUP 300 mg Q2W	224	Median: 38	IQR: 27.5 to 48.0	130	58	155	69	NR	NR
	DUP 300 mg QW	223	Median: 39	IQR: 27 to 51	142	64	149	67	NR	NR
SOLO 2	PBO	236	Median: 35	IQR: 25 to 47	132	56	156	66	NR	NR
	DUP 300 mg Q2W	233	Median: 34.0	IQR: 25 to 46	137	59	165	71	NR	NR
	DUP 300 mg QW	239	Median: 35	IQR: 25 to 46	139	58	168	70	NR	NR
LIBERTY AD CHRONOS	PBO + TCS	315	Median: 34.0	IQR: 25 to 45	193	61.0	208	66.0	NR	NR
	DUP 300 mg + TCS Q2W	106	Median: 40.5	IQR: 28 to 49	62	58.0	74	70.0	NR	NR
	DUP 300 mg + TCS QW	319	Median: 34.0	IQR: 26 to 45	191	60.0	208	65.0	NR	NR
	PBO	85	14.5	1.8	53	62.4	48	56.5	64.4	21.5

Study Name	Arms	Sample Size (N)	Age (years)		Male		White		Weight (kg)	
			mean	SD	n	%	n	%	mean	SD
LIBERTY AD ADOL	DUP 300 mg Q4W	84	14.4	1.6	52	61.9	55	65.5	65.8	20.1
	DUP 200/300 mg Q2W	82	14.5	1.7	43	52.4	54	65.9	65.6	24.5
	Overall	251	14.5	1.7	148	59	157	62.5	65.2	22
Phase 2b AD-1021 Thaci 2016	PBO	61	37.2	13.1	40	66	NR	NR	NR	NR
	DUP 200 mg Q2W	61	35.8	14.9	36	59	NR	NR	NR	NR
	DUP 300 mg Q2W	64	39.4	12.1	41	64	NR	NR	NR	NR
	DUP 300 mg Q4W	65	36.2	10.7	40	62	NR	NR	NR	NR
LIBERTY AD PEDS	**Overall**									
	PBO + TCS	123	8.3	1.8	61	49.6	77	62.6	31.5	10.8
	DUP 300 mg Q4W + TCS	122	8.5	1.7	57	46.7	89	73	31	9.4
	DUP 100/200 mg Q2W + TCS	122	8.5	1.7	65	53.3	88	72.1	32.1	10.8
	Baseline weight <30 kg									
	PBO + TCS	61	7.1	1.3	30	49.2	40	65.6	23.3	3.4
	DUP 300 mg Q4W + TCS	61	7.5	1.4	27	44.3	45	73.8	23.8	3
	DUP 100 mg Q2W + TCS	63	7.6	1.4	32	50.8	43	68.3	24.5	3.5
	Baseline weight ≥30 kg									
	PBO + TCS	62	9.5	1.3	31	50	37	59.7	39.5	9.5
	DUP 300 mg Q4W + TCS	61	9.5	1.5	30	49.2	44	72.1	38.1	8
	DUP 200 mg Q2W + TCS	59	9.5	1.4	33	55.9	45	76.3	40.2	10

Study Name	Arms	Sample Size (N)	Age (years)		Male		White		Weight (kg)	
			mean	SD	n	%	n	%	mean	SD
AD SOLO-CONTINUE	PBO	83	37	IQR: 27 to 46	51	61.4	54	65.1	NR	NR
	DUP 300 mg Q8W	84	35	IQR: 26 to 46.5	51	60.7	56	66.7	NR	NR
	DUP 300 mg Q4W	86	36	IQR: 24 to 49	43	50	64	74.4	NR	NR
	DUP 300 mg QW/Q2W	169	36	IQR: 26 to 48	82	48.5	124	73.4	NR	NR
Phase 2a AD-1412 Pediatric OL	DUP 2 mg/kg (Adolescents)	20	14.7	2.0	9	45	17	85	NR	NR
	DUP 2 mg/kg (Children)	18	8.2	1.6	9	50	17	94.4	NR	NR
	DUP 4 mg/kg (Adolescents)	20	14.3	1.7	9	45	15	75	NR	NR
	DUP 4 mg/kg (Children)	19	8.2	2.0	11	57.9	18	94.7	NR	NR
	Total	77	11.5	3.6	38	49.4	67	87	NR	NR
LIBERTY AD PED-OLE	Total						NR	NR		
LIBERTY AD PED-OLE (Children subgroup 1)	DUP 2 mg/kg	17	9	2	8	47	16	94	30.9	9
	DUP 4 mg/kg	16	8	2	9	56	15	94	29.3	8.6
LIBERTY AD PED-OLE (Children subgroup 2)	Overall	362*	8.6	1.7	176	48.6	263	72.7	32.5	10.9

None of these baseline characteristics were available in Heads Up. ABRO: abrocitinib, AIC: academic-in-confidence, 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. *sample size here is from initial pediatric trial.

Table D3.4 Baseline Characteristics II[34-36,39,42-47,49,51,53-58,62-72,74-77,79,80]

Study Name	Arms	Sample Size (N)	Disease duration (years)		Disease Severity, n (%)					
			mean	SD	Mild (IGA=2)		Moderate (IGA=3)		Severe (IGA=4)	
					n	%	n	%	n	%
Abrocitinib										
JADE MONO-2	PBO	78	21.7	14.3	NA	NA	52	66.7	26	33.3
	ABRO 100 mg	158	21.1	14.8	NA	NA	107	67.7	51	32.3
	ABRO 200 mg	155	20.5	14.8	NA	NA	106	68.4	49	31.6
	Overall	391	21	14.7	NA	NA	265	67.8	126	32.2
JADE MONO-1	PBO	77	22.5	14.4	NA	NA	46	60	31	40
	ABRO 100 mg	156	24.9	16.1	NA	NA	92	59	64	41
	ABRO 200 mg	154	22.7	14.5	NA	NA	91	59	63	41
JADE TEEN	PBO									
	ABRO 100 mg									
	ABRO 200 mg									
	Overall									
JADE COMPARE	PBO	131	21.4	14.4	NA	NA	88	67.2	43	32.8
	ABRO 100 mg	238	22.7	16.3	NA	NA	153	64.3	85	35.7
	ABRO 200 mg	226	23.4	15.6	NA	NA	138	61.1	88	38.9
	DUP 300 mg	242	22.8	14.8	NA	NA	162	66.9	80	33.1
	Total	837	22.7	15.4	NA	NA	541	64.6	296	35.4
Phase 2 Gooderham 2019	PBO	56	Median: 25.6	Range: 1.1 to 67.1	NA	NA	34	61.8	21	38.2
	ABRO 100 mg	56	Median: 23.8	Range: 1.1 to 66.7	NA	NA	29	52.7	26	47.3
	ABRO 200 mg	55	Median 19.6	Range: 1.9 to 68.8	NA	NA	34	63	20	37
Tralokinumab										
ECZTRA 1	PBO	199	Median: 28.0	IQR: 18.0 to 41.0	NA	NA	NR	NR	102	51.3

Study Name	Arms	Sample Size (N)	Disease duration (years)		Disease Severity, n (%)					
			mean	SD	Mild (IGA=2)		Moderate (IGA=3)		Severe (IGA=4)	
					n	%	n	%	n	%
	TRA 300 mg	603	Median: 27.0	IQR: 19.0 to 38.0	NA	NA	NR	NR	305	50.6
ECZTRA 2	PBO	201	Median: 25.0	IQR: 18.0 to 36.0	NA	NA	NR	NR	101	50.2
	TRA 300 mg	593	Median: 25.5	IQR: 17.0 to 39.0	NA	NA	NR	NR	286	48.2
ECZTRA 2 sub-analysis	PBO	91	30.2	16.8	NA	NA	52	57.1	39	42.9
	TRA 300 mg	270	29.7	16.4	NA	NA	153	56.7	117	43.3
ECZTRA 1 and 2 pooled LTE	PBO	400	28.5[†]	14.9	NA	NA	NR	NR	203	50.8
	TRA 300 mg	1196	28.1[‡]	15.2	NA	NA	NR	NR	519	49.4
	Overall	1596	28.2[¶]	15.2	NA	NA	NR	NR	794	49.7
ECZTRA 3	PBO + TCS	127	Median: 26.0	IQR: 18.0 to 39.0	NA	NA	66	52	60	47.2
	TRA 300 mg + TCS	253	Median: 27.0	IQR: 17.0 to 39.0	NA	NA	136	53.8	116	45.8
	Overall	380	Median: 26.0	IQR: 17.0 to 39.0	NA	NA	202	53.2	176	46.3
Upadacitinib										
AD-UP	PBO + TCS	304	[redacted]				141	46.4	163	53.6
	UPA 15 mg + TCS	300					143	47.7	157	52.3
	UPA 30 mg + TCS	297					140	47.1	157	52.9
MEASURE UP 1	PBO	281	NR	NR	NA	NA	156	55.5	125	44.5
	UPA 15 mg	281	NR	NR	NA	NA	154	54.8	127	45.2
	UPA 30 mg	285	NR	NR	NA	NA	154	54	131	46
MEASURE UP 2	PBO	278	NR	NR	NA	NA	125	45	153	55
	UPA 15 mg	276	NR	NR	NA	NA	126	45.7	150	54.3
	UPA 30 mg	282	NR	NR	NA	NA	126	44.7	156	55.3

Study Name	Arms	Sample Size (N)	Disease duration (years)		Disease Severity, n (%)					
			mean	SD	Mild (IGA=2)		Moderate (IGA=3)		Severe (IGA=4)	
					n	%	n	%	n	%
Phase 2b Guttman-Yassky 2020	PBO	41	26.8	18.8	NA	NA	18	44	23	56
	UPA 7.5 mg	42	30.4	18.1	NA	NA	29	69	13	31
	UPA 15 mg	42	22.6	15.8	NA	NA	19	45	23	55
	UPA 30 mg	42	24.2	13.6	NA	NA	31	74	11	26
Baricitinib										
BREEZE-AD1	PBO	249	26	15.5	NA	NA	NR	NR	105	42.2
	BARI 1 mg	127	27	14.9	NA	NA	NR	NR	53	41.7
	BARI 2 mg	123	25	14.6	NA	NA	NR	NR	52	42.3
	BARI 4 mg	125	25	14.9	NA	NA	NR	NR	51	40.8
BREEZE-AD2	PBO	244	25	13.9	NA	NA	NR	NR	121	49.6
	BARI 1 mg	125	24	12.7	NA	NA	NR	NR	63	50.8
	BARI 2 mg	123	24	13.8	NA	NA	NR	NR	62	50.4
	BARI 4 mg	123	23	14.8	NA	NA	NR	NR	63	51.2
BREEZE-AD3 (LTE)	BARI 2 mg	[redacted]	NR	NR	[redacted]					
BREEZE-AD3 sub-study	BARI 2 mg→PBO		NR	NR			NR	NR	NR	NR
	BARI 2 mg→2 mg		NR	NR			NR	NR	NR	NR
	Overall		NR	NR			NR	NR	NR	NR
BREEZE-AD5	PBO	147	23	17	NA	NA	86	59	61	41
	BARI 1 mg	147	24	17	NA	NA	85	58	62	42
	BARI 2 mg	146	24	16	NA	NA	85	58	61	42
BREEZE-AD7	PBO + TCS	109	22	12.2	NA	NA	NR	NR	48*	44
	BARI 2 mg + TCS	109	24.6	14.8	NA	NA	NR	NR	50	46
	BARI 4 mg + TCS	111	25.5	13.2	NA	NA	NR	NR	50	45
	PBO + TCS	49	Median: 17.7	IQR: 7.3 to 29.5	NA	NA	NR	NR	NR	NR

Study Name	Arms	Sample Size (N)	Disease duration (years)		Disease Severity, n (%)					
			mean	SD	Mild (IGA=2)		Moderate (IGA=3)		Severe (IGA=4)	
					n	%	n	%	n	%
Phase 2 Guttman-Yasky 2018	BARI 2 mg + TCS	37	Median: 26.4	IQR: 18.3 to 40.5	NA	NA	NR	NR	NR	NR
	BARI 4 mg + TCS	38	Median: 22.0	IQR: 6.4 to 30.7	NA	NA	NR	NR	NR	NR
Dupilumab										
SOLO 1	PBO	224	Median: 28	IQR: 19 to 40	NA	NA	NR	NR	110	49
	DUP 300 mg Q2W	224	Median: 26	IQR: 17 to 40	NA	NA	NR	NR	108	48
	DUP 300 mg QW	223	Median: 26	IQR: 16 to 42	NA	NA	NR	NR	106	48
SOLO 2	PBO	236	Median: 26	IQR: 18 to 39	NA	NA	NR	NR	115	49
	DUP 300 mg Q2W	233	Median: 24.5	IQR: 18 to 36	NA	NA	NR	NR	115	49
	DUP 300 mg QW	239	Median: 24	IQR: 17 to 37	NA	NA	NR	NR	112	47
LIBERTY AD CHRONOS	PBO + TCS	315	Median: 26	IQR: 17 to 38	NA	NA	168	53	147	47
	DUP 300 mg + TCS Q2W	106	Median: 28	IQR: 20 to 44	NA	NA	53	50	53	50
	DUP 300 mg + TCS QW	319	Median: 26	IQR: 18 to 39	NA	NA	172	54	147	46
LIBERTY AD ADOL	PBO	85	12.3	3.4	NA	NA	39	45.9	46	54.1
	DUP 300 mg Q4W	84	11.9	3.2	NA	NA	38	45.2	46	54.8
	DUP 200/300 mg Q2W	82	12.5	3	NA	NA	39	47.6	43	52.4
	Overall	251	12.2	3.2	NA	NA	116	46.2	135	53.8
Phase 2b AD-1021 Thaci 2016	PBO	61	29.8	13.5	NA	NA	32	53	29	48
	DUP 200 mg Q2W	61	25.2	12.8	NA	NA	31	51	30	49
	DUP 300 mg Q2W	64	30.5	15.8	NA	NA	34	53	30	47

Study Name	Arms	Sample Size (N)	Disease duration (years)		Disease Severity, n (%)					
			mean	SD	Mild (IGA=2)		Moderate (IGA=3)		Severe (IGA=4)	
					n	%	n	%	n	%
	DUP 300 mg Q4W	65	26.5	11.4	NA	NA	37	57	28	43
LIBERTY AD PEDS	**Overall**									
	PBO + TCS	123	7.2	2.2	NA	NA	NA	NA	123	100
	DUP 300 mg Q4W + TCS	122	7.4	2.4	NA	NA	NA	NA	122	100
	DUP 100/200 mg Q2W + TCS	122	7.2	2.3	NA	NA	NA	NA	122	100
	Baseline weight <30 kg									
	PBO + TCS	61	6.3	1.7	NA	NA	NA	NA	61	100
	DUP 300 mg Q4W + TCS	61	6.8	1.7	NA	NA	NA	NA	61	100
	DUP 100 mg Q2W + TCS	63	6.4	2.1	NA	NA	NA	NA	63	100
	Baseline weight ≥30 kg									
	PBO + TCS	62	8	2.2	NA	NA	NA	NA	62	100
	DUP 300 mg Q4W + TCS	61	8	2.9	NA	NA	NA	NA	61	100
	DUP 200 mg Q2W + TCS	59	8.1	2.3	NA	NA	NA	NA	59	100
AD SOLO-CONTINUE	PBO	83	NR	NR	19	22.9	1	1.2	0	0
	DUP 300 mg Q8W	84	NR	NR	18	21.4	2	2.4	0	0
	DUP 300 mg Q4W	86	NR	NR	12	14	6	7	0	0
	DUP 300 mg QW/Q2W	169	NR	NR	37	21.9	3	1.8	0	0
Phase 2a AD-1412 Pediatric OL	DUP 2 mg/kg (Adolescents)	20	NR	NR	NR	NR	8	40	12	60
	DUP 2 mg/kg (Children)	18	NR	NR	NR	NR	1	5.6	17	94.4

Study Name	Arms	Sample Size (N)	Disease duration (years)		Disease Severity, n (%)					
			mean	SD	Mild (IGA=2)		Moderate (IGA=3)		Severe (IGA=4)	
					n	%	n	%	n	%
	DUP 4 mg/kg (Adolescents)	20	NR	NR	NR	NR	11	55	9	45
	DUP 4 mg/kg (Children)	19	NR	NR	NR	NR	0	0	19	100
	Total	77	NR	NR	NR	NR	20	26	57	74
LIBERTY AD PED-OLE	Total		NR	NR	NR	NR				
LIBERTY AD PED-OLE (Children subgroup 1)	DUP 2 mg/kg	17	7	3	3	18	9	53	4	24
	DUP 4 mg/kg	16	8	2	1	6	7	44	8	50
LIBERTY AD PED-OLE (Children subgroup 2)	Overall	362[¥]	7.4	2.2	118	32.6	108	29.8	71	19.6

None of these baseline characteristics were available in Heads Up. ABRO: abrocitinib, AIC: academic-in-confidence, BARI: baricitinib, DUP: dupilumab, IQR: interquartile range, LTE: long-term extension, 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, Q8W: every eight weeks, SD: standard deviation, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *N=108, [†]N=399, [‡]N=1195, [¶]N=1594, [¥]sample size here is from initial pediatric trial.

Table D3.5 Baseline Characteristics III[34-36,39,42-47,49,51,53-58,62-72,74-77,79,80]

Study Name	Arms	Sample Size (N)	EASI score		% BSA affected		SCORAD		Itch or PP-NRS	
			mean	SD	mean	SD	mean	SD	mean	SD
Abrocitinib										
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 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 TEEN	PBO									
	ABRO 100 mg									
	ABRO 200 mg									
	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
Phase 2 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
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

Study Name	Arms	Sample Size (N)	EASI score		% BSA affected		SCORAD		Itch or PP-NRS	
			mean	SD	mean	SD	mean	SD	mean	SD
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 sub-analysis	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
ECTRA 1 and 2 pooled LTE	PBO	400	32.72[†]	13.86	53.6[¥]	25.3	71.07[†]	12.38	7.84[§]	1.37
	TRA 300 mg	1196	32.15[‡]	14.01	52.7	24.8	70.16[‡]	13.19	7.79[ɣ]	1.45
	Overall	1596	32.29[¶]	13.97	52.9[#]	24.9	70.39[¶]	13	7.81**	1.43
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
Upadacitinib										
AD-UP	PBO + TCS	304	30.3	13	48.6	23.1	NR	NR	NR	NR
	UPA 15 mg + TCS	300	29.2	11.8	46.7	21.6	NR	NR	NR	NR
	UPA 30 mg + TCS	297	29.7	11.8	48.5	23.1	NR	NR	NR	NR
MEASURE UP 1	PBO	281	28.8	12.6	45.7	21.6	NR	NR	7.5	1.8
	UPA 15 mg	281	30.6	12.8	48.5	22.2	NR	NR	7.4	1.8
	UPA 30 mg	285	29	11.1	47	22	NR	NR	7.5	1.7
MEASURE UP 2	PBO	278	29.1	12.1	47.6	22.7	NR	NR	7.5	1.9
	UPA 15 mg	276	28.6	11.7	45.1	22.4	NR	NR	7.2	1.8
	UPA 30 mg	282	29.7	12.2	47	23.2	NR	NR	7.4	1.7
Phase 2b 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

Study Name	Arms	Sample Size (N)	EASI score		% BSA affected		SCORAD		Itch or PP-NRS	
			mean	SD	mean	SD	mean	SD	mean	SD
	UPA 30 mg	42	28.2	11.6	42.1	20.4	NR	NR	6.3	2.1
Baricitinib										
BREEZE-AD1	PBO	249	32	13	53	23.1	68	14.0	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	13.0	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-AD3 sub-study	BARI 2 mg→PBO									
	BARI 2 mg→2 mg									
	Overall									
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-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 2 Guttman-Yasky 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
Dupilumab										

Study Name	Arms	Sample Size (N)	EASI score		% BSA affected		SCORAD		Itch or PP-NRS	
			mean	SD	mean	SD	mean	SD	mean	SD
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
LIBERTY AD ADOL	PBO	85	35.5	14	56.4	24.1	70.4	13.3	7.7	1.6
	DUP 300 mg Q4W	84	35.8	14.8	56.9	23.5	69.8	14.1	7.5	1.8
	DUP 200/300 mg Q2W	82	35.3	13.8	56	21.4	70.6	13.9	7.5	1.5
	Overall	251	35.5	14.2	56.5	23	70.3	13.7	7.6	1.7
Phase 2b AD-1021 Thaci 2016	PBO	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
LIBERTY AD PEDS	**Overall**									
	PBO + TCS	123	39	12	60.2	21.5	72.9	12	7.7	1.5
	DUP 300 mg Q4W + TCS	122	37.4	12.5	54.8	21.6	75.6	11.7	7.8	1.6

Study Name	Arms	Sample Size (N)	EASI score		% BSA affected		SCORAD		Itch or PP-NRS	
			mean	SD	mean	SD	mean	SD	mean	SD
	DUP 100/200 mg Q2W + TCS	122	37.3	10.9	57.8	20	72.3	10.8	7.8	1.5
	Baseline weight <30 kg									
	PBO + TCS	61	38.9	12.6	62	20.9	73	12.6	7.6	1.6
	DUP 300 mg Q4W + TCS	61	36.9	12.4	54.6	21.9	75.5	12.6	7.9	1.5
	DUP 100 mg Q2W + TCS	63	37.5	10	61.5	19.4	73.3	10.4	7.9	1.5
	Baseline weight ≥30 kg									
	PBO + TCS	62	39	11.5	58.4	22.1	72.8	11.5	7.8	1.5
	DUP 300 mg Q4W + TCS	61	37.8	12.6	54.9	21.4	75.8	10.9	7.7	1.7
	DUP 200 mg Q2W + TCS	59	37.1	11.8	53.9	20.2	71.2	11.3	7.6	1.5
AD SOLO-CONTINUE	PBO	83	2.5	2.3	8.1	8.2	16.8	10.0	2.8	2.1
	DUP 300 mg Q8W	84	2.3	2.3	7.9	9.0	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	9.0	17.1	10.5	2.8	1.9
Phase 2a AD-1412 Pediatric OL	DUP 2 mg/kg (Adolescents)	20	34.8	17	52.2	24.8	68	13.2	6.1	2.5
	DUP 2 mg/kg (Children)	18	32.9	15.5	59	22.5	66.4	13.1	6.4	2.2
	DUP 4 mg/kg (Adolescents)	20	28.6	14.7	45.9	25.3	63	14.4	6.9	2.21
	DUP 4 mg/kg (Children)	19	38.8	18.6	62.3	30.3	72.7	13.0	6.7	2.4
	Total	77	33.7	16.6	54.6	26.2	67.5	13.6	6.5	2.3
LIBERTY AD PED-OLE	DUP 2 mg/kg	17	21	18	37	27	52	17	6	3
	DUP 4 mg/kg	16	32	20	50	31	67	18	6	2

Study Name	Arms	Sample Size (N)	EASI score		% BSA affected		SCORAD		Itch or PP-NRS	
			mean	SD	mean	SD	mean	SD	mean	SD
(Children subgroup 1)										
LIBERTY AD PED-OLE (Children subgroup 2)	Overall	362[††]	15.6	15.8	28.5	25.4	41.9	22.4	NR	NR

None of these baseline characteristics were available in Heads Up. ABRO: abrocitinib, AIC: academic-in-confidence, 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, [†]N=398, [‡]N=1192, [¶]N=1590, [¥]N=399, [#]N=1595, [§]N=395, [ɣ]N=1182, **N=1577, [††]sample size here is from initial pediatric trial.

Table D3.6. Baseline Characteristics IV[34-36,39,42-47,49,51,53-58,62-72,74-77,79,80]

Study Name	Arms	Sample Size (N)	DLQI			CDLQI			POEM	
			N	mean	SD	N	mean	SD	mean	SD
Abrocitinib										
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 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 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

Study Name	Arms	Sample Size (N)	DLQI			CDLQI			POEM	
			N	mean	SD	N	mean	SD	mean	SD
	Total	837	837	15.7	6.6	NR	NR	NR	21.1	5.5
JADE TEEN	PBO	[redacted]	NA	NA	NA	[redacted]				
	ABRO 100 mg		NA	NA	NA					
	ABRO 200 mg		NA	NA	NA					
	Overall		NA	NA	NA					
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 sub-analysis	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
ECTRA 1 and 2 pooled LTE	PBO	400	394	17.45	6.98	NA	NA	NA	NA	NA
	TRA 300 mg	1196	1178	17.25	7.12	NA	NA	NA	NA	NA
	PBO	1596	1572	17.3	7.08	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
Upadacitinib										
AD-UP	PBO + TCS	304	NR	16.3	7	NR	NR	NR	21.5	5.1

Study Name	Arms	Sample Size (N)	DLQI			CDLQI			POEM	
			N	mean	SD	N	mean	SD	mean	SD
	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
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
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
	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-AD3 sub-study	BARI 2 mg→PBO					NA	NA	NA		
	BARI 2 mg→2 mg					NA	NA	NA		
	Overall					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-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

Study Name	Arms	Sample Size (N)	DLQI			CDLQI			POEM	
			N	mean	SD	N	mean	SD	mean	SD
	BARI 4 mg + TCS	111	111	14.7	7.9	NA	NA	NA	21.4	6
Phase 2 Guttman-Yasky 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
Dupilumab										
SOLO 1	PBO	224	224	Median: 14.0	IQR: 9.0 to 20.0	NR	NR	NR	Median: 21.0	IQR: 16.0-25.0
	DUP 300 mg Q2W	224	224	Median: 13.0	IQR: 8.0 to 19.0	NR	NR	NR	Median: 21.0	IQR: 16.0 to 25.0
	DUP 300 mg QW	223	223	Median: 14.0	IQR: 8.0 to 20.0	NR	NR	NR	Median: 22.0	IQR: 17.0 to 26.0
SOLO 2	PBO	236	236	Median: 15.0	IQR: 9.0 to 22.0	NR	NR	NR	Median: 23.0	IQR: 17.0 to 26.0
	DUP 300 mg Q2W	233	233	Median: 15.0	IQR: 10.0 to 21.0	NR	NR	NR	Median: 21.0	IQR: 18.0 to 25.0
	DUP 300 mg QW	239	239	Median: 16.0	IQR: 10.0 to 22.0	NR	NR	NR	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
LIBERTY AD ADOL	PBO	85	NA	NA	NA	85	13.1	6.7	21.1	5.4
	DUP 300 mg Q4W	84	NA	NA	NA	84	14.8	7.4	21.1	5.5
	DUP 200/300 mg Q2W	82	NA	NA	NA	82	13	6.2	21.0	5.0
	Overall	251	NA	NA	NA	251	13.6	6.8	21.0	5.3

Study Name	Arms	Sample Size (N)	DLQI			CDLQI			POEM	
			N	mean	SD	N	mean	SD	mean	SD
Phase 2b AD-1021 Thaci 2016	PBO	61	61	12.8	6.2	NR	NR	NR	NR	NR
	DUP 200 mg Q2W	61	61	15	7.1	NR	NR	NR	NR	NR
	DUP 300 mg Q2W	64	64	14.5	7.2	NR	NR	NR	NR	NR
	DUP 300 mg Q4W	65	65	13.3	7.3	NR	NR	NR	NR	NR
LIBERTY AD PEDS	**Overall**									
	PBO + TCS	123	NA	NA	NA	123	14.6	7.4	20.7	5.5
	DUP 300 mg Q4W + TCS	122	NA	NA	NA	122	16.2	7.9	21.3	5.5
	DUP 100/200 mg Q2W + TCS	122	NA	NA	NA	122	14.5	6.8	20.5	5.5
	Baseline weight <30 kg									
	PBO + TCS	61	NA	NA	NA	61	16.1	6.9	21.1	4.9
	DUP 300 mg Q4W + TCS	61	NA	NA	NA	61	16.9	8.1	21.5	6
	DUP 100 mg Q2W + TCS	63	NA	NA	NA	63	16	7	21.1	5.6
	Baseline weight ≥30 kg									
	PBO + TCS	62	NA	NA	NA	62	13.2	7.7	20.4	6
	DUP 300 mg Q4W + TCS	61	NA	NA	NA	61	15.5	7.7	21.1	5.1
	DUP 200 mg Q2W + TCS	59	NA	NA	NA	59	13	6.3	19.9	5.3
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
LIBERTY AD PED-OLE	DUP 2 mg/kg	17	NA	NA	NA	17	12	8	17	8
	DUP 4 mg/kg	16	NA	NA	NA	16	12	4	20	5

Study Name	Arms	Sample Size (N)	DLQI			CDLQI			POEM	
			N	mean	SD	N	mean	SD	mean	SD
(Children subgroup 1)										
LIBERTY AD PED-OLE (Children subgroup 2)	Overall	362*	NA	NA	NA	362	7.1	6.7	NR	NR

None of these baseline characteristics were available in Phase 2 Gooderham 2019, Heads Up, Phase 2b Guttman-Yassky 2020, and Phase 2a AD-1412 Pediatric OL. ABRO: abrocitinib, AIC: academic-in-confidence, 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. *sample size here is from initial pediatric trial.

Table D3.7. Baseline Characteristics V[34-36,39,43-47,49,51,53-58,62,65-68,71,72,74-77]

Study Name	Arms	Sample Size (N)	PSAAD			Total HADS		HADS Anxiety		HADS Depression	
			N	mean	SD	mean	SD	mean	SD	mean	SD
Abrocitinib											
JADE MONO-2	PBO	78	77	5.1	2.1	NR	NR	6	3.7	4.4	3.3
	ABRO 100 mg	158	156	5.4	2.1	NR	NR	5.5	4.2	4.1	4
	ABRO 200 mg	155	155	5.2	2	NR	NR	5.9	3.9	4	3.7
	Overall	391	388	5.2	2.1	NR	NR	5.7	4	4.1	3.8
JADE MONO-1	PBO	77	NR	5.5	2	NR	NR	NR	NR	NR	NR
	ABRO 100 mg	156	NR	5.3	2.3	NR	NR	NR	NR	NR	NR
	ABRO 200 mg	154	NR	5.4	2.1	NR	NR	NR	NR	NR	NR
JADE COMPARE	PBO	131	[redacted]			NR	NR	NR	NR	NR	NR
	ABRO 100 mg	238				NR	NR	NR	NR	NR	NR
	ABRO 200 mg	226				NR	NR	NR	NR	NR	NR
	DUP 300 mg	242				NR	NR	NR	NR	NR	NR
	Total	837				NR	NR	NR	NR	NR	NR

Study Name	Arms	Sample Size (N)	PSAAD			Total HADS		HADS Anxiety		HADS Depression	
			N	mean	SD	mean	SD	mean	SD	mean	SD
JADE TEEN	PBO					NR	NR	NR	NR	NR	NR
	ABRO 100 mg					NR	NR	NR	NR	NR	NR
	ABRO 200 mg					NR	NR	NR	NR	NR	NR
	Overall					NR	NR	NR	NR	NR	NR
Baricitinib											
BREEZE-AD3 (LTE)	BARI 2 mg	NR	NR	NR	NR	NR	NR				
BREEZE-AD3 sub-study	BARI 2 mg→PBO	NR	NR	NR	NR	NR	NR				
	BARI 2 mg→2 mg	NR	NR	NR	NR	NR	NR				
	Overall	NR	NR	NR	NR	NR	NR				
BREEZE-AD5	PBO	147	NR	NR	NR	NR	NR				
	BARI 1 mg	147	NR	NR	NR	NR	NR	NR	NR	NR	NR
	BARI 2 mg	146	NR	NR	NR	NR	NR				
BREEZE-AD7	PBO + TCS	109	NR	NR	NR	NR	NR	6.8	4.3	5.8	4.3
	BARI 2 mg + TCS	109	NR	NR	NR	NR	NR	6.4	4	5.3	3.7
	BARI 4 mg + TCS	111	NR	NR	NR	NR	NR	6.7	4.4	5.5	4.1
Dupilumab											
SOLO 1	PBO	224	NR	NR	NR	Median:12	IQR: 6.0 to 17.0	NR	NR	NR	NR
	DUP 300 mg Q2W	224	NR	NR	NR	Median: 11	IQR: 6.0 to 17.0	NR	NR	NR	NR
	DUP 300 mg QW	223	NR	NR	NR	Median: 12	IQR: 6.0 to 17.5	NR	NR	NR	NR
SOLO 2	PBO	236	NR	NR	NR	Median: 12	IQR: 7.0 to 19.0	NR	NR	NR	NR
	DUP 300 mg Q2W	233	NR	NR	NR	Median: 13	IQR: 8.0 to 19.0	NR	NR	NR	NR
	DUP 300 mg QW	239	NR	NR	NR	Median: 14	IQR: 8.0 to 20.0	NR	NR	NR	NR
LIBERTY AD CHRONOS	PBO + TCS	315	NR	NR	NR	Median: 11	IQR:6.0 to 18.0	NR	NR	NR	NR

Study Name	Arms	Sample Size (N)	PSAAD			Total HADS		HADS Anxiety		HADS Depression	
			N	mean	SD	mean	SD	mean	SD	mean	SD
	DUP 300 mg + TCS Q2W	106	NR	NR	NR	Median: 12.5	IQR: 7.0 to 18.0	NR	NR	NR	NR
	DUP 300 mg + TCS QW	319	NR	NR	NR	Median: 12.0	IQR:7.0 to 18.0	NR	NR	NR	NR
LIBERTY AD ADOL	PBO	85	NR	NR	NR	11.6	2.8	NR	NR	NR	NR
	DUP 300 mg Q4W	84	NR	NR	NR	13.3	8.2	NR	NR	NR	NR
	DUP 200/300 mg Q2W	82	NR	NR	NR	12.6	8.0	NR	NR	NR	NR
	Overall	251	NR	NR	NR	12.5	8.0	NR	NR	NR	NR
LIBERTY AD PEDS	**Overall**										
	PBO + TCS	123	NR	NR	NR	NR	NR	57.3*	11.6	55[†]	12.1
	DUP 300 mg Q4W + TCS	122	NR	NR	NR	NR	NR	59.8*	13.7	58.1[†]	12.8
	DUP 100/200 mg Q2W + TCS	122	NR	NR	NR	NR	NR	58.6*	11.3	56.3[†]	11.2
	Baseline weight <30 kg										
	PBO + TCS	61	NR	NR	NR	NR	NR	58.9*	11.8	54.4[†]	12.3
	DUP 300 mg Q4W + TCS	61	NR	NR	NR	NR	NR	60.3*	13.6	58.8[†]	13.1
	DUP 100 mg Q2W + TCS	63	NR	NR	NR	NR	NR	60.6*	10.5	57.8[†]	10.6
	Baseline weight ≥30 kg										
	PBO + TCS	62	NR	NR	NR	NR	NR	55.8*	11.4	55.6[†]	11.9
	DUP 300 mg Q4W + TCS	61	NR	NR	NR	NR	NR	59.3*	13.8	57.4[†]	12.5
	DUP 200 mg Q2W + TCS	59	NR	NR	NR	NR	NR	56.5*	11.8	54.7[†]	11.7
AD SOLO-CONTINUE	PBO	83	NR	NR	NR	5.9	6.4	NR	NR	NR	NR
	DUP 300 mg Q8W	84	NR	NR	NR	7.1	6.9	NR	NR	NR	NR
	DUP 300 mg Q4W	86	NR	NR	NR	7.3	7.5	NR	NR	NR	NR

Study Name	Arms	Sample Size (N)	PSAAD			Total HADS		HADS Anxiety		HADS Depression	
			N	mean	SD	mean	SD	mean	SD	mean	SD
	DUP 300 mg QW/Q2W	169	NR	NR	NR	6.4	5.9	NR	NR	NR	NR

None of these baseline characteristics were available in Phase 2 Gooderham 2019, ECZTRA 1, ECZTRA 2, ECZTRA 3, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, Phase 2 Guttman-Yassky 2018, Phase 2b AD-1021 Thaci 2016, Phase 2a AD-1412 Pediatric OL, and LIBERTY AD PED-OLE. ABRO: abrocitinib, AIC: academic-in-confidence, 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. *assessed via PROMIS anxiety scale, †assessed via PROMIS depression scale.

Table D3.8. Baseline Characteristics: Previous Treatments I[34-36,47,55,65,66,69]

Study Name	Arms	Sample Size (N)	Previous Treatment(s)							
			Any previous treatment		Antibiotics		Topical corticosteroids		Topical calcineurin inhibitors	
			n	%	n	%	n	%	n	%
Abrocitinib										
JADE MONO-2	PBO	78	78	100	NR	NR	NR	NR	NR	NR
	ABRO 100 mg	158	157	99.4	NR	NR	NR	NR	NR	NR
	ABRO 200 mg	155	153	98.7	NR	NR	NR	NR	NR	NR
	Overall	391	388	99.2	NR	NR	NR	NR	NR	NR
JADE MONO-1	PBO	77	77	100	NR	NR	NR	NR	NR	NR
	ABRO 100 mg	156	155	99	NR	NR	NR	NR	NR	NR
	ABRO 200 mg	154	154	100	NR	NR	NR	NR	NR	NR
JADE COMPARE	PBO	131	[redacted]		NR	NR	NR	NR	NR	NR
	ABRO 100 mg	238			NR	NR	NR	NR	NR	NR
	ABRO 200 mg	226			NR	NR	NR	NR	NR	NR
	DUP 300 mg	242			NR	NR	NR	NR	NR	NR
	Total	837			NR	NR	NR	NR	NR	NR
Tralokinumab										
ECZTRA 1	PBO	199	197	99	NR	NR	195	98	103	51.8

Study Name	Arms	Sample Size (N)	Previous Treatment(s)							
			Any previous treatment		Antibiotics		Topical corticosteroids		Topical calcineurin inhibitors	
			n	%	n	%	n	%	n	%
	TRA 300 mg	603	598	99.2	NR	NR	591	98	298	49.4
ECZTRA 2	PBO	201	201	100	NR	NR	200	99.5	98	48.8
	TRA 300 mg	593	591	99.7	NR	NR	584	98.5	271	45.7
ECZTRA 2 sub-analysis	PBO	91	NR	NR	NR	NR	91	100	32	35.2
	TRA 300 mg	270	NR	NR	NR	NR	269	99.6	90	33.3
ECZTRA 3	PBO + TCS	127	127	100	45	35.4	122	96.1	NR	NR
	TRA 300 mg + TCS	253	253	100	107	42.3	251	99.2	NR	NR
	Overall	380	380	100	152	40	373	98.2	NR	NR
Baricitinib										
BREEZE-AD7	PBO + TCS	109	NR	NR	NR	NR	101	93	63	58
	BARI 2 mg + TCS	109	NR	NR	NR	NR	100	92	60	55
	BARI 4 mg + TCS	111	NR	NR	NR	NR	103	93	64	58
Dupilumab										
LIBERTY AD PEDS	PBO + TCS	123	NR	NR	NR	NR	17*	14.2	NR	NR
	DUP 300 mg Q4W + TCS	122	NR	NR	NR	NR	25*	20.8	NR	NR
	DUP 100/200 mg Q2W + TCS	122	NR	NR	NR	NR	30†	24.6	NR	NR

None of these baseline characteristics were available in Phase 2 Gooderham 2019, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5, Phase 2 Guttman-Yassky 2018, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, LIBERTY AD SOLO-CONTINUE, Phase 2a AD-1412 Pediatric OL, and LIBERTY AD PED-OLE. No trials reported on previous treatment use with crisaborole. ABRO: abrocitinib, AIC: academic-in-confidence, 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.
*N=120, †N=122.

Table D3.9. Baseline Characteristics: Previous Treatments II[34-36,47,55,65,66,69]

Study Name	Arms	Sample Size (N)	Previous Treatment(s)							
			Topical agents alone		Systemic steroids		Mycophenolate		Cyclosporine	
			n	%	n	%	n	%	n	%
Abrocitinib										
JADE MONO-2	PBO	78	46	59	NR	NR	NR	NR	NR	NR
	ABRO 100 mg	158	87	55.1	NR	NR	NR	NR	NR	NR
	ABRO 200 mg	155	93	60	NR	NR	NR	NR	NR	NR
	Overall	391	226	57.8	NR	NR	NR	NR	NR	NR
JADE MONO-1	PBO	77	34*	44	NR	NR	NR	NR	NR	NR
	ABRO 100 mg	156	69*	44	NR	NR	NR	NR	NR	NR
	ABRO 200 mg	154	82*	53	NR	NR	NR	NR	NR	NR
JADE COMPARE	PBO	131	[redacted]		NR	NR	NR	NR	NR	NR
	ABRO 100 mg	238			NR	NR	NR	NR	NR	NR
	ABRO 200 mg	226			NR	NR	NR	NR	NR	NR
	DUP 300 mg	242			NR	NR	NR	NR	NR	NR
	Total	837			NR	NR	NR	NR	NR	NR
Tralokinumab										
ECZTRA 1	PBO	199	NR	NR	119	59.8	9	4.5	65	32.7
	TRA 300 mg	603	NR	NR	357	59.2	27	4.5	227	37.6
ECZTRA 2	PBO	201	NR	NR	125	62.2	14	7	65	32.3
	TRA 300 mg	593	NR	NR	410	69.1	37	6.2	204	34.4
ECZTRA 2 sub-analysis	PBO	91	NR	NR	54	59.3	7	7.7	9	9.9
	TRA 300 mg	270	NR	NR	173	64.1	11	4.1	34	12.6
ECZTRA 3	PBO + TCS	127	NR	NR	86	67.7	5	3.9	43	33.9
	TRA 300 mg + TCS	253	NR	NR	148	58.5	7	2.8	75	29.6
	Overall	380	NR	NR	234	61.6	12	3.2	118	31.1
Baricitinib										
BREEZE-AD7	PBO + TCS	109	NR	NR	59	54	NR	NR	39	36
	BARI 2 mg + TCS	109	NR	NR	50	46	NR	NR	35	32

Study Name	Arms	Sample Size (N)	Previous Treatment(s)							
			Topical agents alone		Systemic steroids		Mycophenolate		Cyclosporine	
			n	%	n	%	n	%	n	%
	BARI 4 mg + TCS	111	NR	NR	47	42	NR	NR	33	30
Dupilumab										
LIBERTY AD ADOL	PBO	85	NR	NR	NR	NR	0	0	12	14.1
	DUP 300 mg Q4W	84	NR	NR	NR	NR	1	1.2	6	7.2
	DUP 200/300 mg Q2W	82	NR	NR	NR	NR	2	2.4	14	17.1
	Overall	251	NR	NR	NR	NR	3	1.2	32	12.8
LIBERTY AD PEDS	PBO + TCS	123	NR	NR	NR	NR	2[†]	1.7	12/120	10
	DUP 300 mg Q4W + TCS	122	NR	NR	NR	NR	2[†]	1.7	17[‡]	14.2
	DUP 100/200 mg Q2W + TCS	122	NR	NR	NR	NR	1[‡]	0.8	11[‡]	9

None of these baseline characteristics were available in Phase 2 **Gooderham 2019, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5, Phase 2 Guttman-Yassky 2018, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, Phase 2b AD-1021 Thaci 2016, LIBERTY AD SOLO-CONTINUE, Phase 2a AD-1412 Pediatric OL, and LIBERTY AD PED-OLE. Previous treatment use with crisaborole. ABRO: abrocitinib, AIC: academic-in-confidence, 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. *topical agents include corticosteroids and calcineurin inhibitors, [†]N=120, [‡]N=122.**

Table D3.10. Baseline Characteristics: Previous Treatments III[34-36,54,55,65,66,69]

Study Name	Arms	Sample Size (N)	Previous Treatment(s)									
			Methotrexate		Azathioprine		Other immunosuppressant		Dupilumab		Systemic agents	
			n	%	n	%	n	%	n	%	n	%
Abrocitinib												
JADE MONO-2	PBO	78	NR	NR	NR	NR	NR	NR	2	2.6	32	41
	ABRO 100 mg	158	NR	NR	NR	NR	NR	NR	7	4.4	70	44.3
	ABRO 200 mg	155	NR	NR	NR	NR	NR	NR	5	3.2	60	38.7
	Overall	391	NR	NR	NR	NR	NR	NR	14	3.6	162	41.4
JADE MONO-1	PBO	77	NR	NR	NR	NR	NR	NR	8	10	41	53
	ABRO 100 mg	156	NR	NR	NR	NR	NR	NR	13	8	78	50
	ABRO 200 mg	154	NR	NR	NR	NR	NR	NR	9	6	68	44
JADE COMPARE	PBO	131	NR	NR	NR	NR	NR	NR	NR	NR	[redacted]	
	ABRO 100 mg	238	NR	NR	NR	NR	NR	NR	NR	NR		
	ABRO 200 mg	226	NR	NR	NR	NR	NR	NR	NR	NR		
	DUP 300 mg	242	NR	NR	NR	NR	NR	NR	NR	NR		
	Total	837	NR	NR	NR	NR	NR	NR	NR	NR		
Tralokinumab												
ECZTRA 1	PBO	199	26	13.1	7	3.5	11	5.5	NR	NR	NR	NR
	TRA 300 mg	603	77	12.8	39	6.5	29	4.8	NR	NR	NR	NR
	Overall	802	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ECZTRA 2	PBO	201	38	18.9	25	12.4	10	5	NR	NR	NR	NR
	TRA 300 mg	593	127	21.4	72	12.1	31	5.2	NR	NR	NR	NR
	Overall	794	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ECZTRA 2 sub-analysis	PBO	91	14	15.4	3	3.3	6	6.6	NR	NR	NR	NR
	TRA 300 mg	270	45	16.7	10	3.7	26	9.6	NR	NR	NR	NR
ECZTRA 3	PBO + TCS	127	30	23.6	12	9.4	0	0	10	7.9	NR	NR
	TRA 300 mg + TCS	253	29	11.5	13	5.1	6	2.4	14	5.5	NR	NR
	Overall	380	59	15.5	25	6.6	6	1.6	24	6.3	NR	NR

Study Name	Arms	Sample Size (N)	Previous Treatment(s)									
			Methotrexate		Azathioprine		Other immunosuppressant		Dupilumab		Systemic agents	
			n	%	n	%	n	%	n	%	n	%
Dupilumab												
LIBERTY AD ADOL	PBO	85	6	7.1	1	1.2	0	0	NA	NA	33	38.8
	DUP 300 mg Q4W	84	10	12	1	1.2	1	1.2	NA	NA	38	45.8
	DUP 200/300 mg Q2W	82	10	12.2	0	0	2	2.4	NA	NA	35	42.7
	Overall	251	26	10.4	2	0.8	3	1.2	NA	NA	106	42.4
LIBERTY AD PEDS	**Overall**											
	PBO + TCS	123	11*	9.2	0	0	22*	18.3	NA	NA	36*	30
	DUP 300 mg Q4W + TCS	122	7*	5.8	2/120	1.7	23*	19.2	NA	NA	42*	35
	DUP 100/200 mg Q2W + TCS	122	3†	2.5	2/122	1.6	16†	13.1	NA	NA	40†	32.8

None of these baseline characteristics were available in Phase 2 Gooderham 2019, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, Phase 2b AD-1021 Thaci 2016, LIBERTY AD SOLO-CONTINUE, Phase 2a AD-1412 Pediatric OL, and LIBERTY AD PED-OLE. ABRO: abrocitinib, AIC: academic-in-confidence, DUP: dupilumab, 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, TCS: topical corticosteroids, TRA: tralokinumab, %: percent. *topical agents include corticosteroids and calcineurin inhibitors, †N=120, †N=122.

Table D3.11. Short-Term Efficacy Outcomes: IGA Response Rates[34-36,39,42-47,49,51,53-58,62,65-69,71,72,74-77,80]

Study Name	Arms	Sample Size (N)	IGA response					
			n	N	%	Diff from PBO	95% CI	p value
Abrocitinib								
JADE MONO-2	**Week 12**							
	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 MONO-1	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 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
	Week 12							
JADE TEEN	PBO	[redacted]			24.5	[redacted]		REF
	ABRO 100 mg				41.6			<0.05
	ABO 200 mg				46.2			<0.05
Phase 2 Gooderham 2019	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

Tralokinumab								
ECZTRA 1	**Week 16**							
	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 sub-analysis	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								
AD-UP	**Week 16**							
	PBO + TCS	304	33	304	11	NR	NR	REF
	UPA 15 mg + TCS	300	120	300	40	NR	NR	<0.001
	UPA 30 mg + TCS	297	175	297	59	NR	NR	<0.001
MEASURE UP 1	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
Heads UP	DUP 300 mg	344	NR	NR	NR	NR	NR	NR
	UPA 30 mg	348	NR	NR	NR	NR	NR	NR
Phase 2b 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
Baricitinib								
BREEZE-AD1	**Week 16**							
	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 2 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
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

LIBERTY AD ADOL	PBO	85	2	85	2.4	REF	REF	REF
	DUP 300 mg Q4W	84	15	84	17.9	15.5	6.7 to 24.3	<0.001
	DUP 200/300 mg Q2W	82	20	82	24.4	22	12.2 to 31.9	<0.001
Phase 2b AD-1021 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
LIBERTY AD PEDS	**Overall**							
	PBO + TCS	123	14	123	11.4	NR	NR	REF
	DUP 300 mg Q4W + TCS	122	40	122	32.8	NR	NR	<0.0001
	DUP 100/200 mg Q2W + TCS	122	36	122	29.5	NR	NR	<0.001
	Baseline weight <30 kg							
	PBO + TCS	61	8	61	13.1	NR	NR	REF
	DUP 300 mg Q4W + TCS	61	18	61	29.5	NR	NR	<0.05
	DUP 100 mg Q2W + TCS	63	13	63	20.6	NR	NR	NR
	Baseline weight ≥30 kg							
	PBO + TCS	62	6	62	9.7	NR	NR	REF
	DUP 300 mg Q4W + TCS	61	22	61	36.1	NR	NR	<0.001
	DUP 200 mg Q2W + TCS	59	23	59	39	NR	NR	<0.001

Short-term data on IGA were not available in Heads Up. ABRO: abrocitinib, AIC: academic-in-confidence, 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.

Table D3.12. Short-Term Efficacy Outcomes: EASI75[34-36,39,42-47,49,51,53-58,62,65-69,71,72,74-77]

Study Name	Arms	Sample Size (N)	EASI 75					
			n	N	%	Diff from PBO	95% CI	p value
Abrocitinib								
JADE MONO-2	**Week 12**							
	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 MONO-1	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 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
JADE TEEN	**Week 12**							
	PBO	NR	[redacted]		41.5	NR	NR	REF
	ABRO 100 mg	NR			68.5	NR	NR	<0.01
	ABO 200 mg	NR			72	NR	NR	<0.01
	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

Study Name	Arms	Sample Size (N)	EASI 75					
			n	N	%	Diff from PBO	95% CI	p value
Phase 2 Gooderham 2019	ABRO 200 mg	48	31	48	64.6	9.51	4.3 to 21.2	NR
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 sub-analysis	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								
AD-UP	**Week 16**							
	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
MEASURE UP 1	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
HEADS UP	DUP 300 mg	344	210	344	61	NR	NR	REF
	UPA 30 mg	348	248	348	71	NR	NR	0.006
	Week 8							

Study Name	Arms	Sample Size (N)	EASI 75					
			n	N	%	Diff from PBO	95% CI	p value
Phase 2b Guttman-Yassky 2020	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
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
Phase 2 Guttman-Yassky 2018	PBO + TCS	49	10	49	20.4	REF	NR	REF
	BARI 2 mg + TCS	37	11	37	29.7	9.3	NR	0.319
	BARI 4 mg + TCS	38	13	38	34.2	13.8	NR	0.148
Dupilumab								

Study Name	Arms	Sample Size (N)	EASI 75					
			n	N	%	Diff from PBO	95% CI	p value
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
LIBERTY AD ADOL	PBO	85	7	85	8.2	REF	REF	REF
	DUP 300 mg Q4W	84	32	84	38.1	29.9	17.9 to 41.8	<0.001
	DUP 200/300 mg Q2W	82	34	82	41.5	33.2	21.1 to 45.4	<0.001
Phase 2b AD-1021 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
LIBERTY AD PEDS	**Overall**							
	PBO + TCS	123	33	123	26.8	NR	NR	REF
	DUP 300 mg Q4W + TCS	122	85	122	69.7	NR	NR	<0.0001
	DUP 100/200 mg Q2W + TCS	122	82	122	67.2	NR	NR	<0.0001
	Baseline weight <30 kg							
	PBO + TCS	61	17	61	27.9	NR	NR	REF

Study Name	Arms	Sample Size (N)	EASI 75					
			n	N	%	Diff from PBO	95% CI	p value
	DUP 300 mg Q4W + TCS	61	46	61	75.4	NR	NR	<0.0001
	DUP 100 mg Q2W + TCS	63	38	63	60.3	NR	NR	<0.001
	Baseline weight ≥30 kg							
	PBO + TCS	62	16	62	25.8	NR	NR	REF
	DUP 300 mg Q4W + TCS	61	39	61	63.9	NR	NR	<0.0001
	DUP 200 mg Q2W + TCS	59	44	59	74.6	NR	NR	<0.0001

ABRO: abrocitinib, AIC: academic-in-confidence, 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.

Table D3.13. Short-Term Efficacy Outcomes: EASI 50 and 90[34-36,39,43-47,49,51,53-58,62,65-68,71,72,74-77]

Study Name	Arms	Sample Size (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-2	**Week 12**													
	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 MONO-1	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 COMPARE	PBO	131	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ABRO 100 mg	238	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ABRO 200 mg	226	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	DUP 300 mg	242	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Week 16													
	PBO	131	71	124	57.3	NR	NR	NR	14	124	11.3	NR	NR	NR
	ABRO 100 mg + PBOàABRO 100 mg	238	186	229	81.2	NR	NR	NR	87	229	38	NR	NR	NR
	ABRO 200 mg + PBOàABRO 200 mg	226	193	221	87.3	NR	NR	NR	108	221	48.9	NR	NR	NR
	DUP 300 mg + Oral PBOàPBO	242	195	232	84.1	NR	NR	NR	90	232	38.8	NR	NR	NR
JADE TEEN	**Week 12**													
	PBO	NR	[redacted]			NR	NR	NR	[redacted]			NR	NR	NR

Study Name	Arms	Sample Size (N)	EASI 50						EASI 90					
			n	N	%	Diff from PBO	95% CI	p value	n	N	%	Diff from PBO	95% CI	p value
	ABRO 100 mg	NR				NR	NR	NR				NR	NR	NR
	ABO 200 mg	NR				NR	NR	NR				NR	NR	NR
Phase 2 Gooderham 2019	PBO	52	14	52	26.9	REF	REF	NR	5	52	9.6	REF	REF	NR
	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
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														
AD-UP	**Week 16**													
	PBO + TCS	304	124	304	40.9	NR	NR	REF				NR	NR	REF
	UPA 15 mg + TCS	300	244	300	81.4	NR	NR	≤0.001				NR	NR	<0.001
	UPA 30 mg + TCS	297	262	297	88.1	NR	NR	≤0.001				NR	NR	<0.001
MEASURE UP 1	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
	PBO	278	79	278	28.4	NR	NR	REF	14	278	5	NR	NR	- REF

Study Name	Arms	Sample Size (N)	EASI 50						EASI 90					
			n	N	%	Diff from PBO	95% CI	p value	n	N	%	Diff from PBO	95% CI	p value
MEASURE UP 2	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
Heads Up	DUP 300 mg	344	[redacted]			NR	[redacted]		135	344	39	NR	NR	REF
	UPA 30 mg	348				NR	NR	NR	213	348	61	NR	NR	<0.001
Phase 2b 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
Baricitinib														
BREEZE-AD1	**Week 16**													
	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

Study Name	Arms	Sample Size (N)	EASI 50						EASI 90					
			n	N	%	Diff from PBO	95% CI	p value	n	N	%	Diff from PBO	95% CI	p value
	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
Phase 2 Guttman-Yassky 2018	PBO + TCS	49	18	49	36.7	REF	NR	REF	3	49	6.1	REF	NR	REF
	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
Dupilumab														
	Week 16													
SOLO 1	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	Sample Size (N)	EASI 50						EASI 90					
			n	N	%	Diff from PBO	95% CI	p value	n	N	%	Diff from PBO	95% CI	p value
LIBERTY AD ADOL	PBO	85	11	85	12.9	REF	REF	REF	2	85	2.4	REF	REF	REF
	DUP 300 mg Q4W	84	46	84	54.8	41.8	29.0 to 54.6	<0.001	16	84	19	16.7	7.7 to 25.7	<0.001
	DUP 200/300 mg Q2W	82	50	82	61	48	35.3 to 60.8	<0.001	19	82	23.2	20.8	11.1 to 30.5	<0.001
Phase 2b AD-1021 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
LIBERTY AD PEDS	**Overall**													
	PBO + TCS	123	53	123	43.1	NR	NR	REF	9	123	7.3	NR	NR	REF
	DUP 300 mg Q4W + TCS	122	111	122	91	NR	NR	<0.0001	51	122	41.8	NR	NR	<0.0001
	DUP 100/200 mg Q2W + TCS	122	101	122	82.8	NR	NR	<0.0001	37	122	30.3	NR	NR	<0.0001
	Baseline weight <30 kg													
	PBO + TCS	61	26	61	42.6	NR	NR	REF	4	61	6.6	NR	NR	REF
	DUP 300 mg Q4W + TCS	61	58	61	95.1	NR	NR	<0.0001	28	61	45.9	NR	NR	<0.0001
	DUP 100 mg Q2W + TCS	63	50	63	79.4	NR	NR	<0.0001	16	63	25.4	NR	NR	<0.01
	Baseline weight ≥30 kg													
	PBO + TCS	62	27	62	43.5	NR	NR	REF	5	62	8.1	NR	NR	REF
	DUP 300 mg Q4W + TCS	61	53	61	86.9	NR	NR	<0.0001	23	61	37.7	NR	NR	<0.0001
	DUP 200 mg Q2W + TCS	59	51	59	86.4	NR	NR	<0.0001	21	59	35.6	NR	NR	<0.001

ABRO: abrocitinib, AIC: academic-in-confidence, 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 D3.14. Short-Term Efficacy Outcomes: PP-NRS ≥4-Point Change [34-36,39,42-47,49,51,53-58,62,65-69,71,72,74-77,80]

Study Name	Arms	Sample Size (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-2	**Week 12**									
	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 MONO-1	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 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	[redacted]	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
JADE TEEN	**Week 12**									
	PBO	NR	[redacted]		29.8	[redacted]	NR	NR	NR	NR
	ABRO 100 mg	NR			52.6		NR	NR	NR	NR

Study Name	Arms	Sample Size (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	NR			55.4		NR	NR	NR	NR
Phase 2 Gooderham 2019	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
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 sub-analysis	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										
AD-UP	**Week 16**									
	PBO + TCS	304	46	304	15	LSM: 25.1*	SE: 3.4†	REF	REF	REF
	UPA 15 mg + TCS	300	156	300	52	LSM: 58.1*	SE: 3.4†	36.8	29.7 to 43.8	≤0.001
	UPA 30 mg + TCS	297	190	297	64	LSM: 66.9*	SE: 2.91†	49	41.9 to 55.7	≤0.001
MEASURE UP 1	PBO	281	34	281	12	LSM: 26.1*	SE: 5.24†	REF	REF	REF
	UPA 15 mg	281	146	281	52	LSM: 62.8*	SE: 4.37†	40.4	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	278	9	LSM: 17*	SE: 2.81†	REF	REF	REF
	UPA 15 mg	276	116	276	42	LSM: 51.2*	SE: 2.34†	32.7	25.8 to 39.4	≤0.001
	UPA 30 mg	282	169	282	60	LSM: 66.5*	SE: 2.34†	50.5	43.8 to 57.1	≤0.001
Heads Up	DUP 300 mg	344	121	336	36	-49*	NR	NR	NR	REF
	UPA 30 mg	348	187	340	55	-67*	NR	NR	NR	<0.001

Study Name	Arms	Sample Size (N)	Itch or PP-NRS (≥4-point improvement from baseline)							
			n	N	%	Change from baseline	SD	Diff from PBO	95% CI	p value
Phase 2b 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
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
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
	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

Study Name	Arms	Sample Size (N)	Itch or PP-NRS (≥4-point improvement from baseline)							
			n	N	%	Change from baseline	SD	Diff from PBO	95% CI	p value
Phase 2 Guttman-Yassky 2018	BARI 4 mg + TCS	38	NR	NR	NR	LSM: -2.22	SE: 0.46	NR	NR	NR
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
LIBERTY AD ADOL	PBO	85	4	85	4.8	LSM: -19*	SE: 4.1	REF	REF	REF
	DUP 300 mg Q4W	84	22	84	26.5	LSM: -45.5*	SE: 3.5	21.7	11.2 to 32.3	<0.001
	DUP 200/300 mg Q2W	82	30	82	36.6	LSM: -47.9*	SE: 3.4	31.8	20.5 to 43.2	<0.001
Phase 2b AD-1021 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
	DUP 300 mg Q4W	65	NR	NR	NR	LSM: -32.6*	SE: 4.5	NR	NR	NR
LIBERTY AD PEDS	**Overall**									
	PBO + TCS	123	15	122	12.3	LSM: -25.9*	SE: 2.9	NR	NR	REF
	DUP 300 mg Q4W + TCS	122	61	120	50.8	LSM: -54.6*	SE: 2.9	NR	NR	<0.0001

Study Name	Arms	Sample Size (N)	Itch or PP-NRS (≥4-point improvement from baseline)							
			n	N	%	Change from baseline	SD	Diff from PBO	95% CI	p value
	DUP 100/200 mg Q2W + TCS	122	70	120	58.3	LSM: -57*	SE: 2.8	NR	NR	<0.0001
	Baseline weight <30 kg									
	PBO + TCS	61	7	60	11.7	LSM: -27*	SE: 4.2	NR	NR	REF
	DUP 300 mg Q4W + TCS	61	33	61	54.1	LSM: -55.1*	SE: 3.9	NR	NR	<0.0001
	DUP 100 mg Q2W + TCS	63	35	63	55.6	LSM: -56.1*	SE: 3.9	NR	NR	<0.0001
	Baseline weight ≥30 kg									
	PBO + TCS	62	8	62	12.9	LSM: -25*	SE: 4	NR	NR	REF
	DUP 300 mg Q4W + TCS	61	28	59	47.5	LSM: -54.3*	SE: 4.2	NR	NR	<0.0001
	DUP 200 mg Q2W + TCS	59	35	57	61.4	LSM: -58.2*	SE: 4	NR	NR	<0.0001

ABRO: abrocitinib, AIC: academic-in-confidence, 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.

Table D3.15. Short-Term Efficacy Outcomes: SCORAD[34-36,39,43-47,49,51,53-58,62,65-69]

Study Name	Arms	Sample Size (N)	SCORAD					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
Abrocitinib								
JADE MONO-1	**Week 12**							
	PBO	77	NR	NR	NR	NR	NR	NR
	ABRO 100 mg	156	NR	NR	NR	NR	NR	NR
	ABRO 200 mg	154	NR	NR	NR	NR	NR	NR
JADE COMPARE	PBO	131	128	NR	95% CI: 2.1 to 10.4	NR	NR	NR
	ABRO 100 mg	238	234	NR	95% CI: 20.0 to 31.2	NR	NR	NR
	ABRO 200 mg	226	224	NR	95% CI: 32.9 to 45.7	NR	NR	NR
	DUP 300 mg	242	238	NR	95% CI: 20.5 to 31.6	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
JADE TEEN	**Week 12**							
	PBO	NR	[redacted]		NR	NR	NR	NR
	ABRO 100 mg	NR			NR	NR	NR	NR
	ABO 200 mg	NR			NR	NR	NR	NR
Phase 2 Gooderham 2019	PBO	52	52	-29	-36.6 to -21.3	NR	NR	REF
	ABRO 100 mg	54	54	-49.2	-56.4 to -42.0	NR	NR	0.002
	ABRO 200 mg	48	48	-69.7	-76.9 to -62.5	NR	NR	<0.001
Tralokinumab								

Study Name	Arms	Sample Size (N)	SCORAD					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
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 sub-analysis	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								
Phase 2b 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
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

Study Name	Arms	Sample Size (N)	SCORAD					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
	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 2 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
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
LIBERTY AD ADOL	PBO	85	85	LSM: -17.6*	SE: 3.8	REF	REF	REF
	DUP 300 mg Q4W	84	84	LSM: -47.5*	SE: 3.2	-29.9	-40.0 to -19.8	<0.001
	DUP 200/300 mg Q2W	82	82	LSM: -51.6*	SE: 3.2	-34	-43.4 to -24.6	<0.001
Phase 2b AD-1021 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

Study Name	Arms	Sample Size (N)	SCORAD					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
LIBERTY AD PEDS	**Overall**							
	PBO + TCS	123	123	LSM: -29.8*	SE: 2.3	NR	NR	REF
	DUP 300 mg Q4W + TCS	122	122	LSM: -62.4*	SE: 2.1	NR	NR	<0.0001
	DUP 100/200 mg Q2W + TCS	122	122	LSM: -60.2*	SE: 2.1	NR	NR	<0.0001
	Baseline weight <30 kg							
	PBO + TCS	61	61	LSM: -28.9*	SE: 3.1	NR	NR	REF
	DUP 300 mg Q4W + TCS	61	61	LSM: -65.3*	SE: 2.9	NR	NR	<0.0001
	DUP 100 mg Q2W + TCS	63	63	LSM: -58.1*	SE: 2.8	NR	NR	<0.0001
	Baseline weight ≥30 kg							
	PBO + TCS	62	62	LSM: -30.7*	SE: 3.3	NR	NR	REF
	DUP 300 mg Q4W + TCS	61	61	LSM: -59.3*	SE: 3.1	NR	NR	<0.0001
	DUP 200 mg Q2W + TCS	59	59	LSM: -62.7*	SE: 3.1	NR	NR	<0.0001

Short-term data on SCORAD were not available in JADE MONO-2, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, and BREEZE-AD5. ABRO: abrocitinib, AIC: academic-in-confidence, 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.

Table D3.16. Short-Term Efficacy Outcomes: DLQI and CDLQI[34-36,39,43,44,46,47,49-51,53-55,58,65,66,68,69,71,72,74-77]

Study Name	Arms	Sample Size (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-2	**Week 12**											
	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 MONO-1	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 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
	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

Study Name	Arms	Sample Size (N)	DLQI						CDLQI			
			N	Change from baseline	SD	Diff from PBO	95% CI	p value	N	Change from baseline	95% CI	p value
	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
JADE TEEN	**Week 12**											
	PBO	NR	NA	NA	NA	NA	NA	NA	NR	[redacted]	NR	NR
	ABRO 100 mg	NR	NA	NA	NA	NA	NA	NA	NR	[redacted]	NR	NR
	ABO 200 mg	NR	NA	NA	NA	NA	NA	NA	NR	[redacted]	NR	NR
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 sub-analysis	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

Study Name	Arms	Sample Size (N)	DLQI						CDLQI			
			N	Change from baseline	SD	Diff from PBO	95% CI	p value	N	Change from baseline	95% CI	p value
	UPA 30 mg	282	[redacted]		NR	NR	NR	NR	NR	NR	NR	NR
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
	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 2 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
Dupilumab												
SOLO 1	**Week 16**											
	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

Study Name	Arms	Sample Size (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 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
LIBERTY AD ADOL	PBO	85	NA	NA	NA	NA	NA	NA	85	LSM: -5.1	NR	REF
	DUP 300 mg Q4W	84	NA	NA	NA	NA	NA	NA	84	LSM: -8.8	NR	<0.001
	DUP 200/300 mg Q2W	82	NA	NA	NA	NA	NA	NA	82	LSM: -8.5	NR	<0.001
Phase 2b AD-1021 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
LIBERTY AD PEDS	**Overall**											
	PBO + TCS	123	NA	NA	NA	NA	NA	NA	123	LSM: -6.4	SE: 0.5	REF
	DUP 300 mg Q4W + TCS	122	NA	NA	NA	NA	NA	NA	122	LSM: -10.6	SE: 0.5	<0.0001
	DUP 100/200 mg Q2W + TCS	122	NA	NA	NA	NA	NA	NA	122	LSM: -10.7	SE: 0.5	<0.0001

Study Name	Arms	Sample Size (N)	DLQI						CDLQI			
			N	Change from baseline	SD	Diff from PBO	95% CI	p value	N	Change from baseline	95% CI	p value
	Baseline weight <30 kg											
	PBO + TCS	61	NA	NA	NA	NA	NA	NA	61	LSM: -7.2	SE: 0.8	REF
	DUP 300 mg Q4W + TCS	61	NA	NA	NA	NA	NA	NA	61	LSM: -11.5	SE: 0.7	<0.0001
	DUP 100 mg Q2W + TCS	63	NA	NA	NA	NA	NA	NA	63	LSM: -11.6	SE: 0.7	<0.0001
	Baseline weight ≥30 kg											
	PBO + TCS	62	NA	NA	NA	NA	NA	NA	62	LSM: -5.6	SE: 0.7	REF
	DUP 300 mg Q4W + TCS	61	NA	NA	NA	NA	NA	NA	61	LSM: -9.7	SE: 0.6	<0.0001
	DUP 200 mg Q2W + TCS	59	NA	NA	NA	NA	NA	NA	59	LSM: -9.8	SE: 0.6	<0.0001

Short-term data on DLQI and CDLQI were not available in Phase 2 Gooderham 2019, AD-UP, Heads Up, and Phase 2b Guttman-Yassky 2020. ABRO: abrocitinib, AIC: academic-in-confidence, 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.

Table D3.17. Short-Term Efficacy Outcomes: POEM[34-36,39,43-47,49,51,53-58,62,65-68]

Study Name	Arms	Sample Size (N)	POEM					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
Abrocitinib								
JADE MONO-2	**Week 12**							
	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 MONO-1	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 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
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 2b 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
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
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 2 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
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
LIBERTY AD ADOL	PBO	85	85	-3.8	NR	REF	REF	REF
	DUP 300 mg Q4W	84	84	-9.5	0.9	-5.7	-8.2 to -3.2	<0.001
	DUP 200/300 mg Q2W	82	82	-10.1	0.8	-6.3	-8.6 to -4.0	<0.001
Phase 2b AD-1021 Thaci 2016	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
LIBERTY AD PEDS	**Overall**							
	PBO + TCS	123	123	-5.3	SE: 0.7	NR	NR	REF
	DUP 300 mg Q4W + TCS	122	122	-13.6	SE: 0.7	NR	NR	<0.0001
	DUP 100/200 mg Q2W + TCS	122	122	-13.4	SE: 0.7	NR	NR	<0.0001
	Baseline weight <30 kg							
	PBO + TCS	61	61	-5.9	SE: 1	NR	NR	REF
	DUP 300 mg Q4W + TCS	61	61	-14	SE: 1	NR	NR	<0.0001

	DUP 100 mg Q2W + TCS	63	63	-13.3	SE: 0.9	NR	NR	<0.0001
	Baseline weight ≥30 kg							
	PBO + TCS	62	62	-4.7	SE: 0.9	NR	NR	REF
	DUP 300 mg Q4W + TCS	61	61	-13.2	SE: 0.9	NR	NR	<0.0001
	DUP 200 mg Q2W + TCS	59	59	-13.6	SE: 0.9	NR	NR	<0.0001

Short-term data on POEM were not available in Phase 2 Gooderham 2019, AD-UP, MEASURE UP 1, MEASURE UP 2, 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. *digitized estimate.

Table D3.18. Short-Term Efficacy Outcomes: Total HADS[43-47,49,51,53-58,62,65-68,77]

Study Name	Arms	Sample Size (N)	Total HADS					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
Baricitinib								
BREEZE-AD7	**Week 16**							
	PBO + TCS	109	109	LSM: -3.2	0.6	REF	REF	REF
	BARI 2 mg + TCS	109	109	LSM: -4.8	0.5	-1.6	-3.1 to -0.1	0.042
	BARI 4 mg + TCS	111	111	LSM: -5.1	0.5	-1.9	-3.5 to -0.4	0.011
Dupilumab								
SOLO 1	**Week 16**							
	PBO	224	224	-3	0.7	NR	NR	NR
	DUP 300 mg Q2W	224	224	-5.2	0.5	NR	NR	NR
	DUP 300 mg QW	223	223	-5.2	0.5	NR	NR	NR
SOLO 2	PBO	236	236	-0.8	0.4	NR	NR	NR
	DUP 300 mg Q2W	233	233	-5.1	0.4	NR	NR	NR
	DUP 300 mg QW	239	239	-5.8	0.4	NR	NR	NR
LIBERTY AD CHRONOS	PBO + TCS	315	315	-3.6	0.34	NR	NR	REF
	DUP 300 mg + TCS Q2W	106	106	-4.9	0.56	NR	NR	0.03
	DUP 300 mg + TCS QW	319	319	-5.2	0.33	NR	NR	0.0004
LIBERTY AD ADOL	PBO	85	85	LSM: -2.5	0.8	REF	REF	REF
	DUP 300 mg Q4W	84	84	LSM: -5.2	0.7	-2.7	-4.8 to -0.6	0.01
	DUP 200/300 mg Q2W	82	82	LSM: -3.8	0.7	-1.3	-3.3 to 0.8	0.22
Phase 2b AD-1021 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 COMPARE, JADE MONO 1, JADE MONO 2, BREEZE AD3, ECZTRA 1, ECZTRA 2, ECZTRA 3, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, Phase 2 Guttman-Yassky 2018, and LIBERTY AD PEDS. 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 D3.19. Short-Term Efficacy Outcomes: HADS Anxiety[34-36,39,47,51,53-58,62,65-68,71]

Study Name	Arms	HADS Anxiety					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
Abrocitinib							
JADE MONO-2	**Week 12**						
	PBO	NR	−0.6 (−1.3 to 0.2)	NR	REF	-1. to 0.2	REF
	ABRO 100 mg	NR	−1.6 (−2.1 to −1.1)	NR	-1.0 (-1.9 to -0.1)	-2.1 to -1.1	NR
	ABRO 200 mg	NR	−1.7 (−2.2 to −1.2)	NR	-1.1 (-2.0 to -0.2)	2.2 to -1.2	NR
JADE COMPARE	**Week 16**						
	PBO	131	-0.4	95% CI: -0.9 to 0.1	NR	NR	NR
	ABRO 100 mg	238	-1.2	95% CI: -1.6 to -.8	NR	NR	NR
	ABRO 200 mg	226	-2.0	95% CI: -2.4 to -1.6	NR	NR	NR
	DUP 300 mg	241	-1.5	95% CI: -1.9 to -1.1	NR	NR	NR
Phase 2 Gooderham 2019	PBO	NR	NR	NR	NR	NR	NR
	ABRO 100 mg	NR	NR	NR	NR	NR	NR
	ABRO 200 mg	NR	NR	NR	NR	NR	NR
Baricitinib							
BREEZE-AD7	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

Study Name	Arms	HADS Anxiety					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
	DUP 300 mg QW	NR	NR	0.4	NR	NR	NR
Phase 2b AD-1021 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
LIBERTY AD PEDS	**Overall**						
	PBO + TCS	123	LSM: -10.2*	SE: 0.9	NR	NR	REF
	DUP 300 mg Q4W + TCS	122	LSM:-13.2*	SE: 0.9	NR	NR	<0.05
	DUP 100/200 mg Q2W + TCS	122	LSM: -13.5*	SE: 0.9	NR	NR	<0.01

Short-term data on HADS **Anxiety were not available in JADE MONO 1, JADE COMPARE at 12 weeks, ECZTRA 1, ECZTRA 2, ECZTRA 3, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, Phase 2 Guttman-Yassky 2018, LIBERTY AD CHRONOS, and LIBERTY AD ADOL. 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. *assessed via PROMIS anxiety score.**

Table D3.20. Short-Term Efficacy Outcomes: HADS Depression[34-36,39,47,51,53-58,62,65-69]

Study Name	Arms	HADS Depression					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
Abrocitinib							
JADE MONO-2	**Week 12**						
	PBO	NR	0.3	NR	REF	-0.3 to .9	NR
	ABRO 100 mg	NR	-1	NR	-1.3 (-2.1 to -0.6)	-1.5 to -0.6	NR
	ABRO 200 mg	NR	-1.4	NR	-1.7 (-2.5 to -0.9)	-1.8 to -1.0	NR
JADE COMPARE	**Week 16**						
	PBO	131	-0.3	95% CI: -0.8 to 0.2	NR	NR	NR
	ABRO 100 mg	238	-1	95% CI: -1.4 to -0.7	NR	NR	NR
	ABRO 200 mg	226	-1.6	95% CI: -1.9 to -1.2	NR	NR	NR
	DUP 300 mg	241	-1.2	95% CI: -1.5 to -0.8	NR	NR	NR
Phase 2 Gooderham 2019	PBO	NR	NR	NR	NR	NR	NR
	ABRO 100 mg	NR	NR	NR	NR	NR	NR
	ABRO 200 mg	NR	NR	NR	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							
SOLO 1	**Week 16**						
	PBO	NR	NR	NR	NR	NR	NR
	DUP 300 mg Q2W	NR	NR	NR	NR	NR	NR
	DUP 300 mg QW	NR	NR	NR	NR	NR	NR
SOLO 2	PBO	NR	NR	NR	NR	NR	NR
	DUP 300 mg Q2W	NR	NR	NR	NR	NR	NR
	DUP 300 mg QW	NR	NR	NR	NR	NR	NR
	PBO QW	61	LSM: 0.4	SE: 0.5	NR	NR	REF

Study Name	Arms	HADS Depression					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
Phase 2b AD-1021 Thaci 2016	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
LIBERTY AD PEDS	**Overall**						
	PBO + TCS	123	LSM: -7.4*	SE: 0.8	NR	NR	REF
	DUP 300 mg Q4W + TCS	122	LSM: -12.8*	SE: 0.8	NR	NR	<0.0001
	DUP 100/200 mg Q2W + TCS	122	LSM: -11.9*	SE: 0.8	NR	NR	<0.0001

Short-term data on HADS Depression were not available in JADE MONO 1, JADE COMPARE at 12 weeks, ECZTRA 1, ECZTRA 2, ECZTRA 3, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, Guttman-Yassky 2018, LIBERTY AD CHRONOS, and LIBERTY AD ADOL. 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. *assessed via PROMIS depression score.

Table D3.21. Long-Term Efficacy Outcomes: IGA Response Rates[44,45,51,56,57,65-67,70]

Study Name	Arms	Sample Size (N)	IGA response					
			n	N	%	Diff from PBO	95% CI	p value
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 pooled LTE	TRA 300 mg Q2W→PBO	81	16	47	34	NR	NR	REF
	TRA 300 mg Q2W→TRA 300 mg Q2W	159	52	93	55.9	NR	NR	0.013
	TRA 300 mg Q2W→TRA 300 mg Q4W	165	36	85	42.4	NR	NR	0.38
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
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
	Week 52							

BREEZE-AD3 sub-study	BARI 2 mgàPBO	[redacted]				NR	NR	NR
	BARI 2 mgàBARI 2 mg					NR	NR	NR
	Week 56							
	BARI 2 mgàPBO	[redacted]						
	BARI 2 mgàBARI 2 mg							
	Week 68							
	BARI 2 mgàPBO	[redacted]						
	BARI 2 mgàBARI 2 mg							
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
	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 long-term trial Phase 2b Guttman-Yassky 2020. AIC: academic-in-confidence, 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.

Table D3.22. Long-Term Efficacy Outcomes: EASI 75[44,45,51,56,57,65-67,78]

Study Name	Arms	Sample Size (N)	EASI 75					
			n	N	%	Diff from PBO	95% CI	p value
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 pooled LTE	TRA 300 mg Q2W→PBO	81	19	72	26.4	NR	NR	REF
	TRA 300 mg Q2W→TRA 300 mg Q2W	159	71	124	57.3	NR	NR	<0.001
	TRA 300 mg Q2W→TRA 300 mg Q4W	165	66	131	50.4	NR	NR	0.002
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
Upadacitinib								
Phase 2b Guttman-Yassky 2020	**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
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-AD3 sub-study	**Week 52**							
	BARI 2 mg→PBO	[redacted]				NR	NR	NR
	BARI 2 mg→BARI 2 mg	[redacted]				NR	NR	NR
	Week 56							
	BARI 2 mg→PBO	[redacted]						
	BARI 2 mg→BARI 2 mg	[redacted]						
	Week 68							
	BARI 2 mg→PBO	[redacted]						
	BARI 2 mg→BARI 2 mg	[redacted]						
Dupilumab								
	Week 52							

LIBERTY AD CHRONOS	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

AIC: academic-in-confidence, 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.

Table D3.23. Long-Term Efficacy Outcomes: EASI 50 and 90[51,56,57,66,67]

Study Name	Arms	Sample Size (N)	EASI 50						EASI 90					
			n	N	%	Diff from PBO	95% CI	p value	n	N	%	Diff from PBO	95% CI	p value
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
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: ECZTRA 1, ECZTRA 2, and Phase 2b 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.

Table D3.24. Long-Term Efficacy Outcomes: PP-NRS ≥4-Point Change[51,56]

Study Name	Arms	Sample Size (N)	Itch or PP-NRS (≥4 point improvement from baseline)					
			n	N	%	Diff from PBO	95% CI	p value
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
	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: ECZTRA 1, ECZTRA 2, and ECZTRA 3. 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.

Table D3.25. Long-Term Efficacy Outcomes: SCORAD[51,56]

Study Name	Arms	Sample Size (N)	SCORAD					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
Dupilumab								
LIBERTY AD CHRONOS	**Week 52**							
	PBO + TCS	264	NR	LSM: -34.1*	SE: 1.88	REF	REF	REF
	DUP 300 mg + TCS Q2W	89	NR	LSM: -66.2*	SE: 3.14	NR	NR	<0.0001
	DUP 300 mg + TCS QW	270	NR	LSM: -66.1*	SE: 1.85	NR	NR	<0.0001
AD SOLO-CONTINUE	**Week 36**							
	PBO	83	NR	-2.7†	0.3	NR	NR	NR
	DUP 300 mg Q8W	84	NR	-3.3†	0.3	NR	NR	NR
	DUP 300 mg Q4W	86	NR	-4.2†	0.2	NR	NR	NR
	DUP 300 mg QW/Q2W	169	NR	-4.3†	0.2	NR	NR	NR

Long-term data on SCORAD were not available for the following long-term trials: ECZTRA 1, ECZTRA 2, ECZTRA 3, and Phase 2b 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. *percent change, †SCORAD sleep loss.

Table D3.26. Long-Term Efficacy Outcomes: DLQI[51,56,66,67]

Study Name	Arms	Sample Size (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: ECZTRA 1, ECZTRA 2, and Phase 2b Guttman-Yassky 2020. There were no applicable populations for CDLQI. There were no Difference vs. placebo or 95% confidence interval data available for 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 D3.27. Long-Term Efficacy Outcomes: POEM[51,56]

Study Name	Arms	Sample Size (N)	POEM					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
Dupilumab								
LIBERTY AD CHRONOS	**Week 52**							
	PBO + TCS	264	264	LSM: -5.3	SE: 0.5	NR	NR	REF
	DUP 300 mg + TCS Q2W	89	89	LSM: -13.7	SE: 0.8	NR	NR	<0.0001
	DUP 300 mg + TCS QW	270	270	LSM: -12.7	SE: 0.5	NR	NR	<0.0001
AD SOLO-CONTINUE	**Week 36**							
	PBO	83	NR	-7	0.9	NR	NR	NR
	DUP 300 mg Q8W	84	NR	-2.8	0.8	NR	NR	NR
	DUP 300 mg Q4W	86	NR	-0.8	0.7	NR	NR	NR
	DUP 300 mg QW/Q2W	169	NR	0.3	0.6	NR	NR	NR

Long-term data on DLQI were not available for the following long-term trials: ECZTRA 1, ECZTRA 2, ECZTRA 3, and Phase 2b 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 D3.28. Outcomes by subgroup: IGA stratified by age[34,35,39,55,62]

Study Name	Arms	Category	IGA					
			N	n	%	Diff from PBO	95% CI	p value
Abrocitinib								
JADE MONO-2	**Week 12**							
	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
JADE MONO-1	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
Dupilumab								
Phase 2a AD-1412 Pediatric OL	**Week 12**							
	DUP 2 mg/kg	12-17 years	20	2	10	NR	NR	NR
	DUP 4 mg/kg		20	7	35	NR	NR	NR
	DUP 2 mg/kg	6-11 years	18	3	16.7	NR	NR	NR
	DUP 4 mg/kg		19	4	21.1	NR	NR	NR
LIBERTY AD PED-OLE (Children subgroup 1)	**Week 16**							
	DUP 2 mg/kg	6-11 years	17	6	35	NR	NR	NR
	DUP 4 mg/kg		15	6	40	NR	NR	NR
	Week 52							
	DUP 2 mg/kg	6-11 years	17	13	76	NR	NR	NR

	DUP 4 mg/kg		16	4	25	NR	NR	NR
LIBERTY AD PED-OLE (Children subgroup 2)	Overall	6-11 years	34	15	44.1	NR	NR	NR
LIBERTY AD PED-OLE (Adolescent subgroup)	**Baseline weight <60 kg**							
	Overall	12-17 years	52	19	36.5	NR	NR	NR
	Baseline weight ≥60 kg							
	Overall	12-17 years	51	25	49	NR	NR	NR

Data on IGA stratified by age were not available in Phase 2 Gooderham 2019, ECZTRA 1, ECZTRA 2, ECZTRA 3, AD-UP MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, and LIBERTY AD PEDS. 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 D3.29. Outcomes by subgroup: IGA stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)[39,45,67]

Table D3.30. Outcomes by subgroup: EASI 75 Stratified by Age[34,35,62-64,74-76]

Study Name	Arms	Category	Sample Size (N)	EASI 75					
				N	n	%	Diff from PBO	95% CI	p value
Abrocitinib									
JADE MONO-2	**Week 12**								
	PBO	<18 years	NR	7	0	0	REF	REF	NR
	ABRO 100 mg		NR	16	7	43.8	43.8	13.5 to 74.0	NR
	ABRO 200 mg		NR	15	9	60	60	29.4 to 90.6	NR
	PBO	≥18 years	NR	70	8	11.4	REF	REF	NR
	ABRO 100 mg		NR	139	62	44.6	33.2	22.0 to 44.3	NR
	ABRO 200 mg		NR	193	85	61.2	49.7	38.7 to 60.7	NR
JADE MONO-1	PBO	<18 years	NR	16	2	12.5	NR	NR	NR
	ABRO 100 mg		NR	34	15	44.1	NR	NR	NR

	ABRO 200 mg		NR	33	18	54.5	NR	NR	NR
	PBO	≥18 years	NR	60	7	11.7	NR	NR	NR
	ABRO 100 mg		NR	122	47	38.5	NR	NR	NR
	ABRO 200 mg		NR	120	78	65	NR	NR	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								
	PBO	Adolescents							
	UPA 15 mg								
	UPA 30 mg								
AD UP	PBO	Adults							
	UPA 15 mg								
	UPA 30 mg								
	PBO	Adolescents							
	UPA 15 mg								
	UPA 30 mg								
Dupilumab									
LIBERTY AD PED-OLE (Children subgroup 1)	**Week 16**								
	DUP 2 mg/kg	6-11 years	17	17	10	59	NR	NR	NR
	DUP 4 mg/kg		16	15	11	73	NR	NR	NR
	Week 52								
	DUP 2 mg/kg	6-11 years	17	17	16	94	NR	NR	NR
	DUP 4 mg/kg		16	16	12	75	NR	NR	NR

LIBERTY AD PED-OLE (Children subgroup 2)	Overall	6-11 years	362*	34	27	79.4	NR	NR	NR
LIBERTY AD PED-OLE (Adolescent subgroup)	**Baseline weight <60 kg**								
	Overall	12-17 years	146	50	43	86	NR	NR	NR
	Baseline weight ≥60 kg								
	Overall	12-17 years	148	51	39	76.5	NR	NR	NR

Data on EASI 75 stratified by age were not available in ECZTRA 1, ECZTRA 2, ECZTRA 3, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, LIBERTY AD PEDS, and Phase 2a AD-1412 Pediatric OL. ABRO: abrocitinib, AIC: academic-in-confidence, 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. *sample size here is from initial pediatric trial.

Table D3.31. Outcomes by subgroup: EASI 75 Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)[39,45,57,67]

Table D3.32. Outcomes by subgroup: EASI 50 and 90 Stratified by Age[39,57,67]

Study Name	Arms	Category	EASI 50				EASI 90			
			N	n	%	p value	N	n	%	p value
Abrocitinib										
JADE MONO-2	**Week 12**									
	PBO	<18 years	[redacted]							NR
	ABRO 100 mg									NR
	ABRO 200 mg									NR
	PBO	≥18 years								NR
	ABRO 100 mg									NR
	ABRO 200 mg									NR
JADE MONO-1	PBO	<18 years								NR
	ABRO 100 mg									NR
	ABRO 200 mg									NR
	PBO	≥18 years								NR
	ABRO 100 mg									NR
	ABRO 200 mg									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									
	PBO	Adolescents								
	UPA 15 mg									

	UPA 30 mg		[redacted]							
AD-UP	PBO	Adults								
	UPA 15 mg									
	UPA 30 mg									
	PBO	Adolescents								
	UPA 15 mg									
	UPA 30 mg									
Dupilumab										
Phase 2a AD-1412 Pediatric OL	**Week 12**									
	DUP 2 mg/kg	12-17 years	NR	NR	NR	NR	NR	NR	NR	NR
	DUP 4 mg/kg		NR	NR	NR	NR	NR	NR	NR	NR
	DUP 2 mg/kg	6-11 years	NR	NR	NR	NR	NR	NR	NR	NR
	DUP 4 mg/kg		NR	NR	NR	NR	NR	NR	NR	NR
LIBERTY AD PED-OLE (Children subgroup 1)	**Week 16**									
	DUP 2 mg/kg	6-11 years	17	16	94	NR	17	7	41	NR
	DUP 4 mg/kg		15	14	93	NR	15	5	33	NR
	Week 52									
	DUP 2 mg/kg	6-11 years	17	16	94	NR	17	12	71	NR
	DUP 4 mg/kg		16	15	94	NR	16	7	44	NR

Data on EASI 50 and EASI 90 stratified by age were not available for JADE COMPARE, ECZTRA 1, ECZTRA 2, ECZTRA 3, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, and LIBERTY AD PEDS. ABRO: abrocitinib, AIC: academic-in-confidence, CI: confidence interval, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, UPA: upadacitinib, %: percent.

Table D3.33. Outcomes by subgroup: EASI 50 and 90 Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)[39,45,57,67]

Table D3.34. Outcomes by subgroup: PP-NRS Change from Baseline and ≥3- or ≥4-Point Change Stratified by Age[39,55,57]

Study Name	Arms	Category	Itch or PP-NRS Change from Baseline			PP-NRS ≥3-point Change			PP-NRS ≥4-point Change		
						N	≥3-point Change		N	≥4-point Change	
			N	Change from baseline	SD		n	%		n	%
Abrocitinib											
JADE MONO-2	**Week 12**										
	PBO	<18 years	NR	[redacted]	NR	NR	NR	NR	[redacted]		
	ABRO 100 mg		NR		NR	NR	NR	NR			
	ABRO 200 mg		NR		NR	NR	NR	NR			
	PBO	≥18 years	NR		NR	NR	NR	NR			
	ABRO 100 mg		NR		NR	NR	NR	NR			
	ABRO 200 mg		NR		NR	NR	NR	NR			
JADE MONO-1	PBO	<18 years	NR		NR	NR	NR	NR			
	ABRO 100 mg		NR		NR	NR	NR	NR			
	ABRO 200 mg		NR		NR	NR	NR	NR			
	PBO	≥18 years	NR		NR	NR	NR	NR			
	ABRO 100 mg		NR		NR	NR	NR	NR			
	ABRO 200 mg		NR		NR	NR	NR	NR			
Dupilumab											
Phase 2a AD-1412 Pediatric OL	**Week 12**										
	DUP 2 mg/kg	12-17 years	20	-30.8*	68.4	NR	NR	NR	NR	NR	NR
	DUP 4 mg/kg		20	-37.6*	34.4	NR	NR	NR	NR	NR	NR
	DUP 2 mg/kg	6-11 years	18	-41.6*	35.3	NR	NR	NR	NR	NR	NR
	DUP 4 mg/kg		19	-39.6*	40.9	NR	NR	NR	NR	NR	NR
LIBERTY AD PED-OLE (Children subgroup 1)	**Week 16**										
	DUP 2 mg/kg	6-11 years	17	-50*	42	17	11	65	17	9	53
	DUP 4 mg/kg		16	-51*	44	16	11	69	16	11	69
	Week 52										

	DUP 2 mg/kg	6-11 years	17	-70*	32	17	14	82	17	11	65
	DUP 4 mg/kg		16	-58*	33	16	11	69	16	11	69

Data on PP-NRS change from baseline, ≥3-point change, and ≥4-point change stratified by age were not available in JADE COMPARE, ECZTRA 1**, ECZTRA 2, ECZTRA 3, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, and LIBERTY AD PEDS. No p-values were reported. ABRO: abrocitinib, AIC: academic-in-confidence, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, SD: standard deviation, %: percent. *percent change.**

Table D3.35. 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)[39,45,67]

Table D3.36. 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)[45,67]

Table D3.37. 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)[45]

Table D3.38. 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)[39,45,67]

Table D3.39. Outcomes by subgroup: SCORAD, DLQI and CDLQI Stratified by Age[39,60,61]

Study Name	Arms	Category	SCORAD				DLQI				CDLQI				
			N	Change from baseline	SD	p value	n	Change from baseline	SD	p value	n	N	Change from baseline	SD	p value
Abrocitinib															
JADE MONO-2	**Week 12**														
	PBO	<18 years	NR	[redacted]	NR	NR	NR	[redacted]	NR	NR	[redacted]			NR	NR
	ABRO 100 mg		NR		NR	NR	NR		NR	NR				NR	NR
	ABRO 200 mg		NR		NR	NR	NR		NR	NR				NR	NR
	PBO	≥18 years	NR		NR	NR	NR		NR	NR				NR	NR
	ABRO 100 mg		NR		NR	NR	NR		NR	NR				NR	NR
	ABRO 200 mg		NR		NR	NR	NR		NR	NR				NR	NR
JADE MONO-1	PBO	<18 years	NR		NR	NR	NR		NR	NR				NR	NR
	ABRO 100 mg		NR		NR	NR	NR		NR	NR				NR	NR
	ABRO 200 mg		NR		NR	NR	NR		NR	NR				NR	NR
	PBO	≥18 years	NR		NR	NR	NR		NR	NR				NR	NR
	ABRO 100 mg		NR		NR	NR	NR		NR	NR				NR	NR
	ABRO 200 mg		NR		NR	NR	NR		NR	NR				NR	NR
Dupilumab															
Phase 2a AD-1412 Pediatric OL	**Week 12**														
	DUP 2 mg/kg	12-17 years	20	-47.7*	27.3	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
	DUP 4 mg/kg		20	-43.4*	25.4	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
	DUP 2 mg/kg	6-11 years	18	-57.5*	23.1	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
	DUP 4 mg/kg		19	-46.9*	24.3	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR

LIBERTY AD PED-OLE (Children subgroup 1)	**Week 16**														
	DUP 2 mg/kg	6-11 years	17	-61*	31	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
	DUP 4 mg/kg		15	-62*	18	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
	Week 52														
	DUP 2 mg/kg	6-11 years	17	-79*	16	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
	DUP 4 mg/kg		16	-67*	19	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR

Data on DLQI, CDLQI, and SCORAD stratified by age were not available in JADE COMPARE, ECZTRA 1, ECZTRA 2, ECZTRA 3, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, and LIBERTY AD PEDS. ABRO: abrocitinib, AIC: academic-in-confidence, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NA: not applicable, NR: not reported, PBO: placebo, SD: standard deviation. *percent change.

Table D3.40. Outcomes by subgroup: SCORAD Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)[39,45,67]

Table D3.41. Outcomes by subgroup: CDLQI Stratified by Age[64]

Study Name	Arms	Category	CDLQI				
			n	N	Change from baseline	SD	p value
Dupilumab							
LIBERTY AD PED-OLE (Children subgroup 2)	**Week 52**						
	Overall*	6-11 years	7	NR	-10.1	5.9†	NR

Data on CDLQI stratified by age were available only in a children subgroup of LIBERTY AD PED-OLE. There were no data on Difference vs. placebo or 95% confidence intervals for this outcome. n: number, N: total number, NR: not reported, SD: standard deviation. *sample size here is from initial pediatric trial, †digitized estimate.

Table D3.42. Outcomes by subgroup: DLQI and CDLQI Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)[39,45,67]

Table D3.43. Outcomes by subgroup: POEM Stratified by Age (All available data were submitted by the manufacturer(s) as academic-in-confidence)[39]

Table D3.44. Outcomes by subgroup: POEM Stratified by Disease Severity (All available data were submitted by the manufacturer(s) as academic-in-confidence)[39,45,67]

Table D3.45. 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)[45]

Table D3.46. Short-Term Safety I[34-36,39,42-47,49,51,53-58,60-62,65-69,71,72,74-77,79]

Study Name	Arms	Sample Size (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-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 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 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
JADE TEEN	PBO	NR	12 weeks	NR	NR	NR	52.1	NR	NR	NR	2.1	NR	NR	[redacted]	
	ABRO 100 mg	NR		NR	NR	NR	56.8	NR	NR	NR	1.1	NR	NR		
	ABRO 200 mg	NR		NR	NR	NR	62.8	NR	NR	NR	2.1	NR	NR		
Phase 2 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		
Tralokinumab															
ECZTRA 1	PBO	196	16 weeks	151	77	[redacted]		NR	NR	8	4.1	8	4.1	[redacted]	
	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		
	Placebo	91	16 weeks	57	62.6	26	28.6	NR	NR	0	0	0	0	NR	NR

ECZTRA 2 sub-analysis	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															
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
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
	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
Heads Up	DUP 300 mg	344	16 weeks	NR	NR	NR	NR	NR	NR	NR	NR	4	1.2	NR	NR
	UPA 30 mg	348		NR	NR	NR	NR	NR	NR	NR	NR	10	2.9	NR	NR
Phase 2b 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
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
BREEZE-AD2	PBO	244	16 weeks	NR	NR	137	56.1	NR	NR	2	0.8	9	3.7	9[†]	3.7
	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 2 Guttman-Yasky 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
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
LIBERTY AD ADOL	PBO	85	16 weeks	NR	NR	59	69.4	NR	NR	1	1.2	NR	NR	1	1.2
	DUP 300 mg Q4W	83		NR	NR	53	63.9	NR	NR	0	0	NR	NR	0	0
	DUP 200/300 mg Q2W	82		NR	NR	59	72	NR	NR	0	0	NR	NR	0	0
Phase 2b AD-1021 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
LIBERTY AD PEDS	**Overall**														
	PBO + TCS	120	16 weeks	NR	NR	88	73.3	NR	NR	2[‡]	1.7	NR	NR	2	1.7
	DUP 300 mg Q4W + TCS	120		NR	NR	78	65	NR	NR	0[‡]	0	NR	NR	2	1.7
	DUP 100/200 mg Q2W + TCS	122		NR	NR	82	67.2	NR	NR	2[‡]	1.6	NR	NR	0	0
	Baseline weight <30 kg														

	PBO + TCS	60	16 weeks	NR	NR	43	71.7	NR	NR	2‡	3.3	NR	NR	0	0
	DUP 300 mg Q4W + TCS	60		NR	NR	39	65	NR	NR	0‡	0	NR	NR	2	3.3
	DUP 100 mg Q2W + TCS	63		NR	NR	46	73	NR	NR	1‡	1.6	NR	NR	0	0
	Baseline weight ≥30 kg														
	PBO + TCS	60	16 weeks	NR	NR	45	75	NR	NR	0‡	0	NR	NR	2	3.3
	DUP 300 mg Q4W + TCS	60		NR	NR	39	65	NR	NR	0‡	0	NR	NR	0	0
	DUP 200 mg Q2W + TCS	59		NR	NR	36	61	NR	NR	1‡	1.7	NR	NR	0	0

None of these short-term safety outcomes were available in LIBERTY AD CHRONOS. ABRO: abrocitinib, AE: adverse event, AIC: academic-in-confidence, 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.

Table D3.47. Short-Term Safety II[34-36,42-44,46,47,49,53,58,65,66,68,69,71,72,74-76,78,79]

Study Name	Arms	Sample Size (N)	Timepoint	Fatal TEAE		All-cause Mortality		Major Adverse Cardiovascular Event		Venous Thromboembolism	
				n	%	n	%	n	%	n	%
Abrocitinib											
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 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 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
	PBO	56	16 weeks	0	0	0	0	NR	NR	0*	0

Phase 2 Gooderham 2019	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
Upadacitinib											
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
	UPA 30 mg + TCS	297		NR	NR	0	0	0	0	0	0
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		
Heads Up	DUP 300 mg	344	16 weeks	NR	NR	0	0	0	0	0	0
	UPA 30 mg	348		NR	NR	1	0.3	0	0	0	0
Phase 2b 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
MEASURE UP 1, MEASURE UP 2, and Phase 2b POOLED	PBO	902	16 weeks	NR	NR	NR	NR	0	0	1	0.1
	UPA 15 mg	899		NR	NR	NR	NR	0	0	0	0
	UPA 30 mg	906		NR	NR	NR	NR	0	0	0	0
Baricitinib											
BREEZE-AD1	PBO	249	16 weeks	0	0	0	0	0	0	0	0
	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 2 Guttman-Yasky 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
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
LIBERTY AD ADOL	PBO	85	16 weeks	0	0	0	0	NR	NR	NR	NR
	DUP 300 mg Q4W	83		0	0	0	0	NR	NR	NR	NR
	DUP 200/300 mg Q2W	82		0	0	0	0	NR	NR	NR	NR
	Overall										
	PBO + TCS	120	16 weeks	NR	NR	0	0	NR	NR	NR	NR

LIBERTY AD PEDS	DUP 300 mg Q4W + TCS	120		NR	NR	0	0	NR	NR	NR	NR
	DUP 100/200 mg Q2W + TCS	122		NR	NR	0	0	NR	NR	NR	NR
	Baseline weight <30 kg										
	PBO + TCS	60	16 weeks	NR	NR	0	0	NR	NR	NR	NR
	DUP 300 mg Q4W + TCS	60		NR	NR	0	0	NR	NR	NR	NR
	DUP 100 mg Q2W + TCS	63		NR	NR	0	0	NR	NR	NR	NR
	Baseline weight ≥30 kg										
	PBO + TCS	60	16 weeks	NR	NR	0	0	NR	NR	NR	NR
	DUP 300 mg Q4W + TCS	60		NR	NR	0	0	NR	NR	NR	NR
	DUP 200 mg Q2W + TCS	59		NR	NR	0	0	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 2b AD-1021 Thaci 2016. ABRO: abrocitinib, AIC: academic-in-confidence, 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 D3.48. Short-Term Safety III[34-36,42-44,46,47,49,53,55,58,65-68,71,72,74-77,132]

Study Name	Arms	Sample Size (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-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 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*	0.0	NR	NR	0	0	NR	NR	1	1
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 2 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
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		[redacted]		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 sub-analysis	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																	
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
MEASURE UP 1	PBO	281	16 weeks	NR	NR	NR	NR		0	0				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	16 weeks	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
Heads Up	DUP 300 mg	344	16 weeks	NR	NR	NR	NR	NR	NR	2	0.6	NR	NR	1	0.3	NR	NR
	UPA 30 mg	348		NR	NR	NR	NR	NR	NR	4	1.1	0	0	0	0	NR	NR
Phase 2b 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

MEASURE UP 1, MEASURE UP 2, and Phase 2b POOLED	PBO	902	16 weeks	NR	NR	NR	NR	18§§§	2	5	0.6	0§§	0	0	0	NR	NR
	UPA 15 mg	899		NR	NR	NR	NR	43§§§	4.8	7	0.8	0§§	0	3	0.3	NR	NR
	UPA 30 mg	906		NR	NR	NR	NR	68§§§	7.5	4	0.4	4§§	0.4	1	0.1	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
	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 2 Guttman-Yasky 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
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
LIBERTY AD ADOL	PBO	85	16 weeks	3	3.5	17	20	3[†††]	3.5	NR	NR	NR	NR	NR	NR	4	4.7
	DUP 300 mg Q4W	83		5	6	11	13.3	4[†††]	4.8	NR	NR	NR	NR	NR	NR	9	10.8
	DUP 200/300 mg Q2W	82		7	8.5	9	11	1[†††]	1.2	NR	NR	NR	NR	NR	NR	8	9.8
Phase 2b AD-1021 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
LIBERTY AD PEDS	**Overall**																
	PBO + TCS	120	16 weeks	7	5.8	16	13.3	6[†††]	5	NR	NR	NR	NR	NR	NR	5[¥¥¥]	4.2
	DUP 300 mg Q4W + TCS	120		12	10	7	5.8	2[†††]	1.7	NR	NR	NR	NR	NR	NR	8[¥¥¥]	6.7
	DUP 100/200 mg Q2W + TCS	122		13	10.7	10	8.2	4[†††]	3.3	NR	NR	NR	NR	NR	NR	18[¥¥¥]	14.8
	Baseline weight <30 kg																
	PBO + TCS	60	16 weeks	4	6.7	8	13.3	3[†††]	5	NR	NR	NR	NR	NR	NR	2[¥¥¥]	3.3
	DUP 300 mg Q4W + TCS	60		6	10	4	6.7	0[†††]	0	NR	NR	NR	NR	NR	NR	4[¥¥¥]	6.7
	DUP 100 mg Q2W + TCS	63		5	7.9	5	7.9	3[†††]	4.8	NR	NR	NR	NR	NR	NR	13[¥¥¥]	20.6

	Baseline weight ≥30 kg																
	PBO + TCS	60	16 weeks	3	5	8	13.3	3[†††]	5	NR	NR	NR	NR	NR	NR	3[¥¥¥]	5
	DUP 300 mg Q4W + TCS	60		6	10	3	5	2[†††]	3.3	NR	NR	NR	NR	NR	NR	4[¥¥¥]	6.7
	DUP 200 mg Q2W + TCS	59		8	13.6	5	8.5	1[†††]	1.7	NR	NR	NR	NR	NR	NR	5[¥¥¥]	8.5

None of these short-term safety outcomes were available in LIBERTY AD CHRONOS. ABRO: abrocitinib, AIC: academic-in-confidence, 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, [‡‡‡]herpes viral infections include oral herpes, herpes simplex, eczema herpeticum, herpes virus infection, and herpes zoster, [¶¶¶]conjunctival infections, irritations, and inflammation, [¥¥¥]conjunctivitis cluster, [###]eczema herpeticum, [§§§]oral herpes, herpes zoster, and eczema herpeticum.

Table D3.49. Long-Term Safety I[51,55,56,62-66,69,78]

Study Name	Arms	Sample Size (N)	Timepoint	Any AE		TEAE		Study Drug-Related AEs		D/C due to AE		Serious AE		Serious TEAE	
				n	%	n	%	n	%	n	%	n	%	n	%
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 1 and 2 pooled LTE	TRA Q2W→PBO	81	Weeks 16-32	57	70.4	NR	NR	NR	NR	0	0	0	0	NR	NR
	TRA Q2W→TRA Q2W	159		116	73	NR	NR	NR	NR	3	1.9	1	0.6	NR	NR
	TRA Q2W →TRA Q4W	165		109	66.1	NR	NR	NR	NR	2	1.2	6	3.6	NR	NR
ECZTRA 3	TRA 300 mg Q2W + TCS (PBO nonresponders)	79	Weeks 16-32	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	Sample Size (N)	Timepoint	Any AE		TEAE		Study Drug-Related AEs		D/C due to AE		Serious AE		Serious TEAE	
				n	%	n	%	n	%	n	%	n	%	n	%
Upadacitinib															
Phase 2b 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
	DUP 300 mg QW/Q2W	167		NR	NR	118	70.7	6†	3.6	0	0	NR	NR	NR	NR
LIBERTY AD PED-OLE	DUP 2 mg/kg	17	52 weeks	NR	NR	16	94	4‡	24	0¶	0	NR	NR	2	12
	DUP 4 mg/kg	16		NR	NR	16	100	2‡	13	0¶	0	NR	NR	3	19

Study Name	Arms	Sample Size (N)	Timepoint	Any AE		TEAE		Study Drug-Related AEs		D/C due to AE		Serious AE		Serious TEAE	
				n	%	n	%	n	%	n	%	n	%	n	%
(Children subgroup 1)															
LIBERTY AD PED-OLE (Children subgroup 2)	Overall	362[¥]	52 weeks	NR	NR	213	58.8	51[‡]	14.1	2[¶]	0.6	NR	NR	9	2.5
LIBERTY AD PED-OLE (Adolescent subgroup)	DUP 300 mg Q4W	79	52 weeks	NR	NR	57	72.2	9[‡]	11.4	0[¶]	0	NR	NR	3	3.8
	DUP 200/300 mg Q2W	215		NR	NR	160	74.4	44[‡]	20.5	2[¶]	0.9	NR	NR	2	0.9
Phase 2a AD-1412 Pediatric OL	DUP 2 mg/kg (Adolescents)	20	20 weeks	NR	NR	NR	NR	NR	NR	NR	NR	1	5	NR	NR
	DUP 2 mg/kg (Children)	18		NR	NR	NR	NR	NR	NR	NR	NR	0	0	NR	NR
	DUP 4 mg/kg (Adolescents)	20		NR	NR	NR	NR	NR	NR	NR	NR	1	5	NR	NR
	DUP 4 mg/kg (Children)	19		NR	NR	NR	NR	NR	NR	NR	NR	2	10.53	NR	NR

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 possible related to drug, [†]treatment-emergent SAE, [‡]any TEAE related to treatment, [¶]discontinuation due to TEAE, [¥]sample size here is from initial pediatric trial.

Table D3.50. Long-Term Safety II[51,55,56,62,65,66,71]

Study Name	Arms	Sample Size (N)	Timepoint	Fatal TEAE		All-cause Mortality		Major Adverse Cardiovascular Event		Venous Thromboembolism		Nausea	
				n	%	n	%	n	%	n	%	n	%
Tralokinumab													
ECZTRA 1	PBO	35	Week 36	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	TRA 300 mg Q2W	68		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	TRA 300 mg Q4W	76		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ECZTRA 2	PBO	46	Week 36	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	TRA 300 mg Q2W	91		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	TRA 300 mg Q4W	89		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ECZTRA 3	TRA 300 mg Q2W + TCS (PBO nonresponders)	79	Weeks 16-32	NR	NR	NR	NR	NR	NR	NR	NR	1	1.3
	PBO 300 mg Q2W + TCS (PBO responders)	41		NR	NR	NR	NR	NR	NR	NR	NR	0	0
	TRA 300 mg Q2W + TCS (TRA responders)	69		NR	NR	NR	NR	NR	NR	NR	NR	3	4.3
	TRA 300 mg Q4W + TCS (TRA responders)	69		NR	NR	NR	NR	NR	NR	NR	NR	4	5.8
	TRA 300 mg Q2W + TCS (TRA nonresponders)	95		NR	NR	NR	NR	NR	NR	NR	NR	3	3.2
Upadacitinib													
Phase 2b Guttman-Yassky 2020	PBO→PBO	10	32 weeks	NR	NR	NR	NR	0	0	0	0	NR	NR
	PBO→UPA 30 mg	10		NR	NR	NR	NR	0	0	0	0	NR	NR

Study Name	Arms	Sample Size (N)	Timepoint	Fatal TEAE		All-cause Mortality		Major Adverse Cardiovascular Event		Venous Thromboembolism		Nausea	
				n	%	n	%	n	%	n	%	n	%
	UPA 7.5 mg →PBO	15		NR	NR	NR	NR	0	0	0	0	NR	NR
	UPA 7.5 mg →UPA 7.5 mg	16		NR	NR	NR	NR	0	0	0	0	NR	NR
	UPA 15 mg→ PBO	19		NR	NR	NR	NR	0	0	0	0	NR	NR
	UPA 15 mg→ UPA 15 mg	18		NR	NR	NR	NR	0	0	0	0	NR	NR
	UPA 30 mg→ PBO	19		NR	NR	NR	NR	0	0	0	0	NR	NR
	UPA 30 mg→ UPA 30 mg	19		NR	NR	NR	NR	0	0	0	0	NR	NR
Dupilumab													
LIBERTY AD CHRONOS	PBO + TCS	315	52 weeks	NR	NR	0	0	NR	NR	NR	NR	NR	NR
	DUP 300 mg + TCS Q2W	110		NR	NR	0	0	NR	NR	NR	NR	NR	NR
	DUP 300 mg + TCS QW	315		NR	NR	1	<1	NR	NR	NR	NR	NR	NR
AD SOLO-CONTINUE	PBO	82	36 weeks	NR	NR	0	0	NR	NR	NR	NR	NR	NR
	DUP 300 mg Q8W	84		NR	NR	0	0	NR	NR	NR	NR	NR	NR
	DUP 300 mg Q4W	87		NR	NR	1	1.1	NR	NR	NR	NR	NR	NR
	DUP 300 mg QW/Q2W	167		NR	NR	0	0	NR	NR	NR	NR	NR	NR
LIBERTY AD PED-OLE (Children subgroup 1)	DUP 2 mg/kg	17	52 weeks	0*	0	NR	NR	NR	NR	NR	NR	NR	NR
	DUP 4 mg/kg	16		0*	0	NR	NR	NR	NR	NR	NR	NR	NR
Phase 2a AD-1412 Pediatric OL	DUP 2 mg/kg (Adolescents)	20	20 weeks	NR	NR	0	0	NR	NR	NR	NR	0	0
	DUP 2 mg/kg (Children)	18		NR	NR	0	0	NR	NR	NR	NR	0	0

Study Name	Arms	Sample Size (N)	Timepoint	Fatal TEAE		All-cause Mortality		Major Adverse Cardiovascular Event		Venous Thromboembolism		Nausea	
				n	%	n	%	n	%	n	%	n	%
	DUP 4 mg/kg (Adolescents)	20		NR	NR	0	0	NR	NR	NR	NR	0	0
	DUP 4 mg/kg (Children)	19		NR	NR	0	0	NR	NR	NR	NR	2	10.5

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. *TEAE resulting in death.

Table D3.51. Long-Term Safety III[51,55-57,62-66,69,78]

Study Name	Arms	Sample Size (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	Week 36	1	2.9	0*	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[†]	0.0	NR	NR	0[‡]	0	NR	NR	6[¶]	8.8
	TRA 300 mg Q4W	76		7	9.2	2*	2.6	0[†]	0.0	NR	NR	0[‡]	0	NR	NR	5[¶]	6.6
ECZTRA 2	PBO	46	Week 36	0	0	1*	2.2	0[†]	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[†]	0.0	NR	NR	1[‡]	1.1	NR	NR	5[¶]	5.6
ECZTRA 3	TRA 300 mg Q2W + TCS (PBO non-responders)	79	Weeks 16-32	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

Study Name	Arms	Sample Size (N)	Timepoint	Injection Site RXN		Skin Infection		Herpetic Infection		Serious Infection		Malignancy		Non-Melanocytic Skin Cancer		Conjunctivitis	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%
Upadacitinib																	
Phase 2b Guttman-Yassky 2020	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
	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
LIBERTY AD PED-OLE	Total		52 weeks			NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		

Study Name	Arms	Sample Size (N)	Timepoint	Injection Site RXN		Skin Infection		Herpetic Infection		Serious Infection		Malignancy		Non-Melanocytic Skin Cancer		Conjunctivitis	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%
LIBERTY AD PED-OLE (Children subgroup 1)	DUP 2 mg/kg	17	52 weeks	2	12	5	29	2	12	NR	NR	NR	NR	NR	NR	2	12
	DUP 4 mg/kg	16		1	6	6	38	8	50	NR	NR	NR	NR	NR	NR	5	31
LIBERTY AD PED-OLE (Children subgroup 2)	Overall	362¶¶¶	52 weeks	17	4.7	36	9.9	18††††	5	NR	NR	NR	NR	NR	NR	41	11.3
LIBERTY AD PED-OLE (Adolescent subgroup)	Dupilumab 300 mg Q4W	79	52 weeks	20	6.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	26‡‡‡	8.7
	Dupilumab 200/300 mg Q2W	215				NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		
Phase 2a AD-1412 Pediatric OL	DUP 2 mg/kg (Adolescents)	20	20 weeks	1##	5	0¥¥	0	0§§	0	NR	NR	NR	NR	NR	NR	0***	0
	DUP 2 mg/kg (Children)	18		0##	0	0¥¥	0	1§§	5.6	NR	NR	NR	NR	NR	NR	0***	0
	DUP 4 mg/kg (Adolescents)	20		1##	5	1¥¥	5	1§§	5	NR	NR	NR	NR	NR	NR	0***	0
	DUP 4 mg/kg (Children)	19		2##	10.5	0¥¥	0	1§§	5.3	NR	NR	NR	NR	NR	NR	1***	5.3

AIC: academic-in-confidence, 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, ##injection site urticaria, injection site swelling, injection site irritation, injection site erythema, §§herpes simplex + herpes virus infection + oral herpes, staphylococcal skin infection, ***allergic conjunctivitis and infectious conjunctivitis, †††herpes viral infection, ‡‡‡treatment-emergent narrow conjunctivitis, ¶¶¶sample size here is from initial pediatric trial.

Mild to Moderate Population

Table D3.52. Study Quality[89,92]

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
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

NA: not applicable

Table D3.53. Key Features

Trial	Patient Population	Interventions	Inclusion Criteria	Key Outcomes
Ruxolitinib Cream				
Phase III TRuE-AD1 (poster)[82,85,86] 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 0.75% • ruxolitinib cream 1.5% • 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)[82,85,86] 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 0.75% • ruxolitinib cream 1.5% • 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

Trial	Patient Population	Interventions	Inclusion Criteria	Key Outcomes
				•SCORAD, mean change from baseline
Phase II[83,84] 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[92] AD 301	N=763 RCT, MC, DB, vehicle-controlled phase III studies Patients 2 and older with mild to moderate AD	Crisborole 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	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

Trial	Patient Population	Interventions	Inclusion Criteria	Key Outcomes
Phase III[92] AD 302	N= 764 RCT, MC, DB, vehicle-controlled phase III studies Patients 2 and older with mild to moderate AD		acceptable bland emollients to manage dry skin areas around, but not overlapping, the treatable AD-involved areas.	score, pruritus severity, signs of AD
Phase III AD 303 Long-term safety study[87] 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
Post Hoc Analyses of AD 301/302[88,90,91,93]	*Same as AD 301/302*	*Same as AD 301/302*	*Same as AD 301/302*	QoL
Phase IV CrisADe CARE 1[89] 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 D3.54. Baseline Characteristics I[70,79,83-93,132]

Study Name	Arms	Sample Size (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
Pooled Analysis	Vehicle cream	244*	Median: 34.0	Range: 12 to 82	91	36.4	170	68	Median: 16.5	Range: 0.8 to 79.1
	RUX 0.75%	483†	Median: 33.0	Range: 12 to 85	196	39.2	345	69	Median: 15.1	Range: 0.1 to 68.8
	RUX 1.5%	481‡	Median: 31.0	Range: 12 to 85	191	38.3	355	71.1	Median: 16.1	Range: 0 to 69.2
	Total	1249	Median: 32.0	Range: 12 to 85	478	38.3	870	69.7	Median: 15.8	Range 0 to 79.1
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

Study Name	Arms	Sample Size (N)	Age (years)		Male		White		Disease duration (years)	
			mean	SD	n	%	n	%	mean	SD
	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	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
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 D3.55. Baseline Characteristics II[83-86,88-93,95-97,99]

Study Name	Arms	Sample Size (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
Pooled Analysis	Vehicle cream	244*	64	25.6	186	74.4	NA	NA	7.8	4.8	9.6	5.5
	RUX 0.75%	483†	125	250	375	75	NA	NA	8.1	4.9	10	5.3
	RUX 1.5%	481‡	123	24.6	376	75.4	NA	NA	7.8	4.8	9.6	5.3
	Total	1249	312	25	937	75	NA	NA	8	4.8	9.8	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	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

Study Name	Arms	Sample Size (N)	Disease Severity, n (%)						EASI score		% BSA affected	
			Mild		Moderate (3)		Severe (4)		mean	SD	mean	SD
			n	%	n	%	n	%				
	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
	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 D3.56. Baseline Characteristics III[83-93,95-97,99]

Study Name	Arms	Sample Size (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	%
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

Study Name	Arms	Sample Size (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	%
	RUX 1.5%	246	4.9	2.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pooled analysis	Vehicle cream	244[††]	5.1	2.4	9.4	6.4	15	6.6	8	5.8	5.1	2.4	9.4	6.4	15	6.6
	RUX 0.75%	483[‡‡]	5.2	2.4	9.9	6.5	15.5	6.3	7	6.2	5.2	2.4	9.9	6.5	15.5	6.3
	RUX 1.5%	481[¥¥]	5.1	2.5	9.5	6.3	15.5	6.3	9	6.3	5.1	2.5	9.5	6.3	15.5	6.3
	Total	1249	5.1	2.4	NR	NR	NR	NR	NR	NR	5.1	2.4	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
Weeks 4/8/12																
Phase II	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
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 D3.57. Efficacy Outcomes: IGA Response Rates[83-94]

Study Name	Arm	Sample Size (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	NR	REF	REF
	RUX 0.75%	252	252	126	50.0	NR	34.9	26.1 to 43.7
	RUX 1.5%	253	253	137	53.8	NR	38.7	29.9 to 47.4
TRuE AD 2	Vehicle cream	124	124	10	7.6	NR	REF	REF
	RUX 0.75%	248	248	97	39.0	NR	31.3	23.4 to 39.2
	RUX 1.5%	246	246	127	51.3	NR	43.7	35.6 to 51.8
Pooled Analysis	Vehicle cream	NR	244	28	11.5	NR	NR	REF
	RUX 0.75%	NR	483	216	44.7	NR	NR	<0.0001
	RUX 1.5%	NR	281	148	52.6	NR	NR	<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
Phase II	**Week 4**							
	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

Study Name	Arm	Sample Size (N)	IGA response					
			N	n	%	Diff from PBO	95% CI	p value
	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								
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 D3.58. Efficacy Outcomes: EASI Response Rates[83-87,94,95,97,99]

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	NR	31/126	24.6	REF	REF	REF	12/126	9.5
	RUX 0.75%	NR/NR	NR	142/252	56.0	31.4	21.7 to 41.1	<0.0001	96/252	38.1
	RUX 1.5%	NR/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	NR	18/124	14.4	REF	REF	REF	5/118	4.2
	RUX 0.75%	NR/NR	NR	128/248	51.5	37.1	28.1 to 46.2	<0.0001	81/231	35.1
	RUX 1.5%	NR/NR	NR	153/246	61.8	47.4	38.5 to 56.4	<0.0001	99/228	43.4
Pooled Analysis	Vehicle cream	NR/NR	NR	48/244	19.7	NR	NR	REF	NR/NR	NR
	RUX 0.75%	NR/NR	NR	260/483	53.8	NR	NR	<0.0001	NR/NR	NR
	RUX 1.5%	NR/NR	NR	298/481	62.0	NR	NR	<0.0001	NR/NR	NR
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	**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 8									
	Vehicle cream	NR/NR	NR	NR/NR	NR	NR	NR	NR	NR/NR	NR
	TRI 0.1% BID	NR/NR	NR	NR/NR	NR	NR	NR	NR	NR/NR	NR
	RUX 1.5% BID	NR/NR	NR	NR/NR	NR	NR	NR	NR	NR/NR	NR

Study Name	Arms	EASI 50		EASI 75					EASI 90	
		n/N	%	n/N	%	Diff from PBO	95% CI	p value	n/N	%
	Week 12									
	Vehicle cream	NR/NR	NR	NR/NR	NR	NR	NR	NR	NR/	NR
	TRI 0.1% BID	NR/NR	NR	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 crisaborole trials AD 301, AD 302, Post-Hoc AD 301/302, and CrisADe CARE 1. No trials reported on difference vs. placebo, 95% confidence intervals, or p-values 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 D3.59. Efficacy Outcomes: PP-NRS Response Rates[83-86,94,97,99]

Study Name	Arms	Sample Size (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
Pooled Analysis	Vehicle cream	NR	25/158	15.8	NR	NR	NR	REF
	RUX 0.75%	NR	130/313	41.5	NR	NR	NR	<0.0001
	RUX 1.5%	NR	158/307	51.5	NR	NR	NR	<0.0001
Subgroup analysis – partial response	Vehicle cream	174	NR	NR	NR	NR	NR	NR
	RUX 0.75%	213	NR	NR	NR	NR	NR	NR

Study Name	Arms	Sample Size (N)	Itch or PP-NRS (≥4-point improvement from baseline)					
			n/N	%	SD	Diff from PBO	95% CI	p value
	RUX 1.5%	197	NR	NR	NR	NR	NR	NR
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	**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
	Week 12							
	Vehicle cream	52	NR/NR	NR	NR	NR	NR	NR
	TAC 0.1% BID	39	NR/NR	NR	NR	NR	NR	NR
	RUX 1.5% BID	50	NR/NR	NR	NR	NR	NR	NR

Data on PP-NRS were not available in 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 improvement.

Table D3.60. SCORAD[85,86]

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 D3.61. DLQI, CLDQI, POEM[88,89,91,93,95]

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 D3.62. Safety[82-93,95,99]

Trial	Arms	Sample Size (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
Pooled analysis	Vehicle cream	250	83	33.2	28	11.2	8†	3.2	2	0.8	NR	NR	11	4.4	6	2.4	NR	NR
	RUX 0.75%	500	145	29	23	4.6	4†	0.8	4	0.8	NR	NR	3	0.6	4	0.8	NR	NR
	RUX 1.5%	499	132	26.5	24	4.8	4†	0.8	3	0.6	NR	NR	4	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	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

Trial	Arms	Sample Size (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	%
	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**																	
	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 D3.63. Efficacy Outcomes by Subgroup: IGA[98,100]

Study	Arm	Category	Sample Size (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 < 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 D3.64. Efficacy Outcomes by Subgroup: EASI 50[98,100]

Study	Arm	Category	Sample Size (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 crisaborole trials. CI: confidence interval, Diff: difference, n: number, N: total number, NR: not reported, PBO: placebo, RUX: ruxolitinib, %: percent.

Table D3.65. Efficacy Outcomes by Subgroup: EASI 75/90[98,100]

Study name	Arm	Category	Sample Size (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 crisaborole trials. There were no Difference vs. placebo or 95% confidence intervals available for this outcome. n: number, N: total number, NR: not reported, RUX: ruxolitinib, %: percent.

Table D3.66. Efficacy Outcomes by Subgroup: PP-NRS ≥4[98,100]

Study	Arm	Category	Sample Size (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.

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	October 2, 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 six systematic literature reviews (SLRs) evaluating systemic treatments for patients with moderate-to-severe atopic dermatitis, two of which are summarized below. We did not identify any SLRs that assessed ruxolitinib in atopic dermatitis.

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	X	X	
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[133]

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[134-136 71 65,66,137-139]Weighted averages from drug trials[134-136 71 65,66,137-139]

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)
- Baricitnib (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

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. [140]

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.

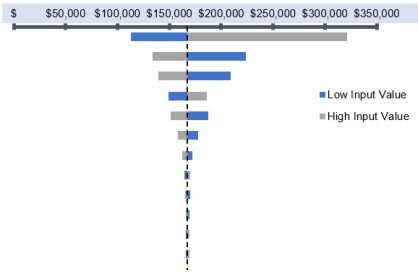
6. We use the same calculations in the comparator arm to derive its evLY.

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.

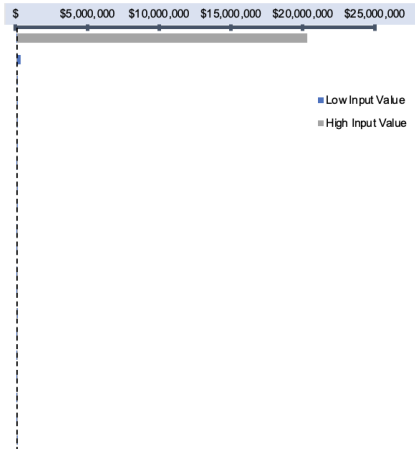
Figure E3.1 Tornado Diagram for Abrocitinib versus Standard of Care



Parameter	Low Input Value	High Input Value	Low Result	High Result
Utility of non-responder state (off treatment) - Soc/Placebo	0.54	0.66	113148.8	321314.5
Utility of non-responder state (off treatment) - Abrocitinib	0.54	0.66	223686.8	133697.0
Utility of achieving EASI 90 (on treatment) - Abrocitinib	0.8	0.97	209166.1	139484.6
Cost per dose - Net price - Abrocitinib	102.01	124.67	148812	185913
Utility of achieving EASI 75 (on treatment) - Abrocitinib	0.77	0.94	187511.1	151123.2
Utility of achieving EASI 50 (on treatment) - Abrocitinib	0.72	0.89	177478.0	158337.2
Annual Direct Cost - Non-Responder	11704.97	14306.07	172289.7	162434.5
Utility of achieving EASI 50 (on treatment) - Soc/Placebo	0.72	0.89	164811.2	169993.2
Probability of initial transition EASI 90 - Abrocitinib	0.33	0.4	170072.9	164979.1
Risk of discontinuation - SoC	0.23	0.28	169383.3	165691.6
Utility of achieving EASI 75 (on treatment) - Soc/Placebo	0.77	0.94	165551.5	169212.7
Utility of achieving EASI 90 (on treatment) - Soc/Placebo	0.8	0.97	165612.0	169149.6
Annual Direct Cost - EASI 90	5966.38	7292.24	165604.6	169119.6

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

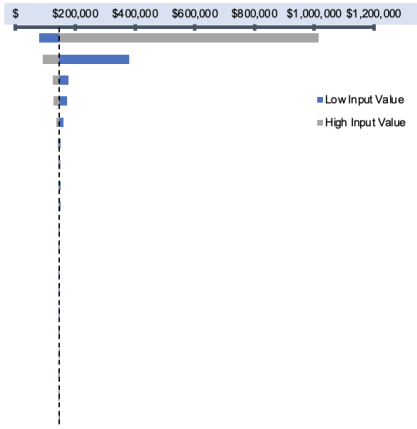
Figure E3.2 Tornado Diagram for Baricitinib versus Standard of Care



Parameter	Low Input Value	High Input Value	Low Result	High Result
Utility of non-responder state (off treatment) - Soc/Placebo	0.54	0.66	43055.84	20318418.59
Utility of non-responder state (off treatment) - Baricitinib	0.54	0.66	356013.49	48861.55
Utility of achieving EASI 90 (on treatment) - Baricitinib	0.8	0.97	104168.32	73126.01
Utility of achieving EASI 50 (on treatment) - Baricitinib	0.72	0.89	97775.72	76643.72
Utility of achieving EASI 75 (on treatment) - Baricitinib	0.77	0.94	97398.28	76877.25
Annual Direct Cost - Non-Responder	11704.97	14306.07	91070	80789
Utility of achieving EASI 50 (on treatment) - Soc/Placebo	0.72	0.89	83251.64	88785.53
Risk of discontinuation - SoC	0.23	0.28	88332	83986
Probability of initial transition EASI 90 - Baricitinib	0.18	0.22	88014.24	84067.46
Utility of achieving EASI 75 (on treatment) - Soc/Placebo	0.77	0.94	84020	87928
Utility of achieving EASI 90 (on treatment) - Soc/Placebo	0.8	0.97	84083	87859
Annual Direct Cost - EASI 90	5966.38	7292.24	84508	87351
Risk of discontinuation - Baricitinib	0.07	0.08	84803.03	87082.02
Probability of initial transition EASI 75 - Baricitinib	0.12	0.15	86936.06	84990.67
Annual Direct Cost - EASI 75	5966.38	7292.24	85012	86847
Annual Direct Cost - EASI 50	5966.38	7292.24	85021	86838
Probability of initial transition EASI 50 - Placebo/SoC	0.09	0.1	85042	86832
Probability of initial transition EASI 90 - Placebo/SoC	0.05	0.06	85208	86661
Probability of initial transition EASI 75 - Placebo/SoC	0.06	0.07	85230	86638
Probability of initial transition EASI 50 - Baricitinib	0.13	0.16	86406.12	85481.57
Risk of discontinuation - Baricitinib	0.07	0.08	85476	86395

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

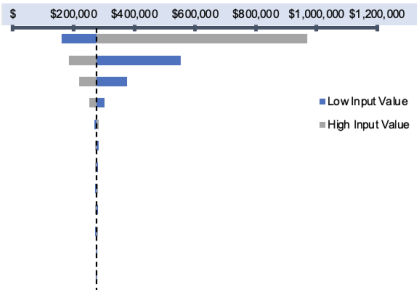
Figure E3.3 Tornado Diagram for Tralokinumab versus Standard of Care



Parameter	Low Input Value	High Input Value	Low Result	High Result
Utility of non-responder state (off treatment) - Soc/Placebo	0.54	0.66	79067.52	1015877.31
Utility of non-responder state (off treatment) - Tralokinumab	0.54	0.66	380341	90888
Utility of achieving EASI 90 (on treatment) - Tralokinumab	0.8	0.97	177863	124852
Utility of achieving EASI 50 (on treatment) - Tralokinumab	0.72	0.89	172483	127647
Utility of achieving EASI 75 (on treatment) - Tralokinumab	0.77	0.94	159970	135490
Annual Direct Cost - Non-Responder	11704.97	14306.07	151947	141485
Utility of achieving EASI 50 (on treatment) - Soc/Placebo	0.72	0.89	142770.00	150886.09
Probability of initial transition EASI 90 - Tralokinumab	0.18	0.21	149983	143798
Risk of discontinuation - SoC	0.23	0.28	149955	144080
Utility of achieving EASI 75 (on treatment) - Soc/Placebo	0.77	0.94	143905	149638
Utility of achieving EASI 90 (on treatment) - Soc/Placebo	0.8	0.97	143999	149538
Annual Direct Cost - EASI 90	5966.38	7292.24	145265	148167
Annual Direct Cost - EASI 50	5966.38	7292.24	145473	147959
Probability of initial transition EASI 50 - Placebo/SoC	0.09	0.1	145527	147921
Risk of discontinuation - Tralokinumab	0.05	0.06	145532	147922
Probability of initial transition EASI 75 - Tralokinumab	0.09	0.11	147773	145709
Probability of initial transition EASI 90 - Placebo/SoC	0.05	0.06	145728	147716
Probability of initial transition EASI 75 - Placebo/SoC	0.06	0.07	145766	147676
Probability of initial transition EASI 50 - Tralokinumab	0.16	0.2	147457	146029
Annual Direct Cost - EASI 75	5966.38	7292.24	146104	147327

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

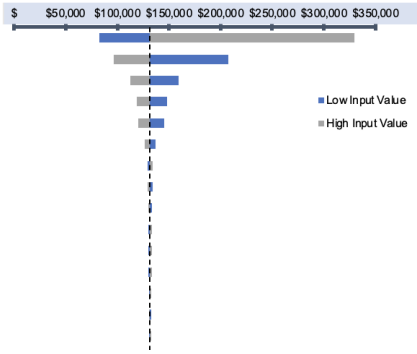
Figure E3.4 Tornado Diagram for Upadacitinib versus Standard of Care



Parameter	Low Input Value	High Input Value	Low Result	High Result
Utility of non-responder state (off treatment) - Soc/Placebo	0.54	0.66	160434.24	970134.42
Utility of non-responder state (off treatment) - Upadacitinib	0.54	0.66	552789	183323
Utility of achieving EASI 90 (on treatment) - Upadacitinib	0.8	0.97	375928	217212
Utility of achieving EASI 75 (on treatment) - Upadacitinib	0.77	0.94	302864	252394
Utility of achieving EASI 50 (on treatment) - Soc/Placebo	0.72	0.89	269109.45	281856.23
Probability of initial transition EASI 90 - Upadacitinib	0.42	0.51	281980	269745
Annual Direct Cost - Non-Responder	11704.97	14306.07	279980	270691
Utility of achieving EASI 75 (on treatment) - Soc/Placebo	0.77	0.94	270907	279911
Risk of discontinuation - SoC	0.23	0.28	280124	271416
Utility of achieving EASI 90 (on treatment) - Soc/Placebo	0.8	0.97	271054	279754
Utility of achieving EASI 50 (on treatment) - Upadacitinib	0.72	0.89	278418	272321
Risk of discontinuation - Upadacitinib	0.08	0.1	272589	278131
Annual Direct Cost - EASI 90	5966.38	7292.24	272998	277673

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

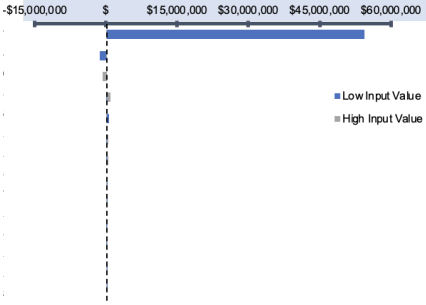
Figure E3.5 Tornado Diagram for Dupilumab versus Standard of Care



Parameter	Low Input Value	High Input Value	Low Result	High Result
Utility of non-responder state (off treatment) - Soc/Placebo	0.54	0.66	82212.08	329670.61
Utility of non-responder state (off treatment) - Dupilumab	0.54	0.66	207572	96345
Utility of achieving EASI 90 (on treatment) - Dupilumab	0.8	0.97	159230	112148
Utility of achieving EASI 75 (on treatment) - Dupilumab	0.77	0.94	148118	118404
Utility of achieving EASI 50 (on treatment) - Dupilumab	0.72	0.89	145615	120054
Annual Direct Cost - Non-Responder	11704.97	14306.07	136695	126515
Utility of achieving EASI 50 (on treatment) - Soc/Placebo	0.72	0.89	129099.43	134209.69
Probability of initial transition EASI 90 - Dupilumab	0.24	0.29	133945	129512
Risk of discontinuation - SoC	0.23	0.28	133661	129914
Utility of achieving EASI 75 (on treatment) - Soc/Placebo	0.77	0.94	129825	133435
Utility of achieving EASI 90 (on treatment) - Soc/Placebo	0.8	0.97	129884	133372
Annual Direct Cost - EASI 90	5966.38	7292.24	130117	133093
Annual Direct Cost - EASI 75	5966.38	7292.24	130661	132549
Probability of initial transition EASI 75 - Dupilumab	0.16	0.2	132526	130743
Annual Direct Cost - EASI 50	5966.38	7292.24	130821	132389
Risk of discontinuation - Dupilumab	0.04	0.05	130841	132381

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

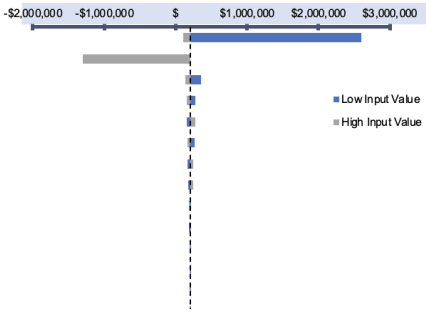
Figure E3.6. Tornado Diagram for Abrocitinib versus Dupilumab



Parameter	Low Input Value	High Input Value	Low Result	High Result
Utility of achieving EASI 90 (on treatment) - Abrocitinib	0.8	0.97	54385947	148730
Utility of non-responder state (off treatment) - Abrocitinib	0.54	0.66	-1185983	131836
Utility of non-responder state (off treatment) - Dupilumab	0.54	0.66	121014	-657251
Utility of achieving EASI 90 (on treatment) - Dupilumab	0.8	0.97	175739	950804
Utility of achieving EASI 75 (on treatment) - Abrocitinib	0.77	0.94	637566	193292
Utility of achieving EASI 75 (on treatment) - Dupilumab	0.77	0.94	205702	531746
Utility of achieving EASI 50 (on treatment) - Dupilumab	0.72	0.89	214721	479665
Utility of achieving EASI 50 (on treatment) - Abrocitinib	0.72	0.89	414102	231100
Probability of initial transition EASI 90 - Abrocitinib	0.33	0.4	376135	255726
Probability of initial transition EASI 90 - Dupilumab	0.24	0.29	259541	354879
Probability of initial transition EASI 75 - Dupilumab	0.16	0.2	274485	325458
Probability of initial transition EASI 75 - Abrocitinib	0.18	0.22	324990	276029
Risk of discontinuation - Dupilumab	0.04	0.05	320670	278081
Risk of discontinuation - Abrocitinib	0.03	0.04	281499	314785

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

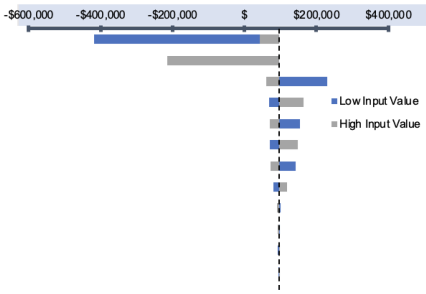
Figure E3.7 Tornado Diagram for Baricitinib versus Dupilumab



Parameter	Low Input Value	High Input Value	Low Result	High Result
Utility of non-responder state (off treatment) - Dupilumab	0.54	0.66	2600504	104585
Utility of non-responder state (off treatment) - Baricitinib	0.54	0.66	93354.38	-1305984.48
Utility of achieving EASI 90 (on treatment) - Dupilumab	0.8	0.97	357409	139894
Utility of achieving EASI 75 (on treatment) - Dupilumab	0.77	0.94	279699	156964
Utility of achieving EASI 90 (on treatment) - Baricitinib	0.8	0.97	158791.47	274077.96
Utility of achieving EASI 50 (on treatment) - Dupilumab	0.72	0.89	265479	161828
Utility of achieving EASI 50 (on treatment) - Baricitinib	0.72	0.89	169791.24	246513.11
Utility of achieving EASI 75 (on treatment) - Baricitinib	0.77	0.94	170537.24	244957.38
Probability of initial transition EASI 90 - Dupilumab	0.24	0.29	218957	187622
Probability of initial transition EASI 90 - Baricitinib	0.18	0.22	189230.46	215158.39
Risk of discontinuation - Baricitinib	0.07	0.08	210871.05	192937.94
Probability of initial transition EASI 75 - Dupilumab	0.16	0.2	209811	193691
Probability of initial transition EASI 75 - Baricitinib	0.12	0.15	193900.77	209065.43
Risk of discontinuation - Dupilumab	0.04	0.05	194669	208160

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

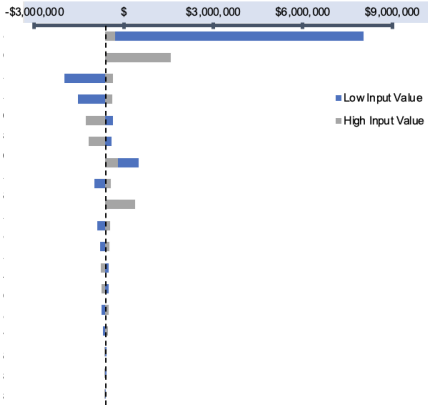
Figure E3.8 Tornado Diagram for Tralokinumab versus Dupilumab



Parameter	Low Input Value	High Input Value	Low Result	High Result
Utility of non-responder state (off treatment) - Dupilumab	0.54	0.66	-419087	43056
Utility of non-responder state (off treatment) - Tralokinumab	0.54	0.66	39196	-213993
Utility of achieving EASI 90 (on treatment) - Dupilumab	0.8	0.97	229928	60642
Utility of achieving EASI 90 (on treatment) - Tralokinumab	0.8	0.97	67923	163482
Utility of achieving EASI 75 (on treatment) - Dupilumab	0.77	0.94	153405	69828
Utility of achieving EASI 50 (on treatment) - Tralokinumab	0.72	0.89	70970	148168
Utility of achieving EASI 50 (on treatment) - Dupilumab	0.72	0.89	141781	72536
Utility of achieving EASI 75 (on treatment) - Tralokinumab	0.77	0.94	80285	119276
Annual Direct Cost - Non-Responder	11704.97	14306.07	100729	91214
Probability of initial transition EASI 50 - Tralokinumab	0.16	0.2	98607	92817
Probability of initial transition EASI 50 - Dupilumab	0.15	0.18	93102	98405
Annual Direct Cost - EASI 75	5966.38	7292.24	94243	97700
Annual Direct Cost - EASI 90	5966.38	7292.24	94396	97547

*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 Value	Low Result	High Result
Utility of achieving EASI 90 (on treatment) - Dupilumab	0.8	0.97	8030736	-296973
Utility of achieving EASI 90 (on treatment) - Upadacitinib	0.8	0.97	-257707	1568417
Utility of achieving EASI 75 (on treatment) - Dupilumab	0.77	0.94	-2002270	-364518
Utility of achieving EASI 50 (on treatment) - Dupilumab	0.72	0.89	-1531052	-386154
Probability of initial transition EASI 90 - Upadacitinib	0.42	0.51	-362289	-1285382
Utility of achieving EASI 75 (on treatment) - Upadacitinib	0.77	0.94	-418631	-1170900
Utility of non-responder state (off treatment) - Dupilumab	0.54	0.66	485054	-188522
Probability of initial transition EASI 90 - Dupilumab	0.24	0.29	-993023	-434249
Utility of non-responder state (off treatment) - Upadacitinib	0.54	0.66	-170689	382289
Risk of discontinuation - Upadacitinib	0.08	0.1	-880200	-464701
Probability of initial transition EASI 75 - Dupilumab	0.16	0.2	-801714	-494496
Risk of discontinuation - Dupilumab	0.04	0.05	-510493	-760528
Probability of initial transition EASI 75 - Upadacitinib	0.15	0.18	-512715	-754551
Probability of initial transition EASI 50 - Dupilumab	0.15	0.18	-750322	-518449
Risk of discontinuation - Upadacitinib	0.08	0.1	-709444	-541631
Utility of achieving EASI 50 (on treatment) - Upadacitinib	0.72	0.89	-583141	-654479
Risk of discontinuation - Dupilumab	0.03	0.04	-583898	-652769
Probability of initial transition EASI 50 - Upadacitinib	0.02	0.02	-603712	-630185
Annual Direct Cost - Non-Responder	11704.97	14306.07	-609345	-624163

*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

	Intervention		Comparator		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Abrocitinib vs SoC						
Total Costs	$171,000	($157,000 - $186,000)	$61,500	($55,000 - $68,000)	$110,000	($102,000 - $118,000)
Total QALYs	3.63	(3.41 - 3.82)	2.98	(2.69 - 3.25)	0.65	(0.72 - 0.57)
ICER					$169,000	($140,000 - $207,000)
Baricitnib vs SoC						
Total Costs	$80,300	($74,000 - $87,100)	$61,534.45	($55,400 - $67,600)	$18,800	($18,600 - $19,500)
Total QALYs	3.17	(2.90 - 3.42)	2.98	(2.69 - 3.25)	0.19	(0.21 - 0.16)
ICER					$96,800	($86,500 - $119,000)
Tralokinumab vs SoC						
Total Costs	$98,000	($91,000 - $105,000)	$61,500	($55,000 - $67,600)	$36,600	($35,600 - $37,300)
Total QALYs	3.22	(2.98 - 3.44)	2.98	(2.69 - 3.25)	0.24	(0.30 - 0.19)
ICER					$154,000	($120,000 - $195,000)
Upadacitinib vs SoC						
Total Costs	$197,000	($182,000 - $213,000)	$61,500	($55,000 - $68,000)	$135,000	($126,000 - $146,000)
Total QALYs	3.48	(3.26 - 3.70)	2.98	(2.69 - 3.25)	0.50	(0.58 - 0.45)
ICER					$269,000	($219,000 - $326,000)
Dupilumab vs SoC						
Total Costs	$129,000	($120,000 - $138,000)	$61,5	($55,400 - $67,600)	$67,500	($65,000 - $71,000)
Total QALYs	3.50	(3.30 - 3.69)	2.98	(2.69 - 3.25)	0.52	(0.62 - 0.43)
ICER					$129,000	($106,000 - $163,000)
Abrocitinib vs Dupilumab						
Total Costs	$171,000	($157,000 - $186,000)	$129,000	($120,000 - $138,000)	$42,000	($36,600 - $47,300)
Total QALYs	3.63	(3.41 - 3.82)	3.50	(3.30 - 3.69)	0.13	(0.11 - 0.14)
ICER					$324,000	($339,000 - $348,000)

	Intervention		Comparator		Incremental	
	Mean	**Credible Range**	**Mean**	**Credible Range**	**Mean**	**Credible Range**
Baricitnib vs Dupilumab						
Total Costs	$80,300	($74,000 - $87,100)	$129,000	($120,000 - $138,000)	-$48,700	(-$46,500 - - $51,200)
Total QALYs	3.17	(2.90 - 3.42)	3.50	(3.30 - 3.69)	-0.33	(-0.40 - - 0.27)
ICER					$149,000 (Less costly, less effective)	($116,000 - $189,000)
Tralokinumab vs Dupilumab						
Total Costs	$98,000	($91,000 - $105,000)	$129,000	($120,000 - $138,000)	-$30,900	(-$29,000 - - $33,000)
Total QALYs	3.22	(2.98 - 3.44)	3.50	(3.30 - 3.69)	-0.28	(-0.32 - -0.24)
ICER					$109 (Less costly, less effective)	($92,000 - $137,000)
Upadacitinib vs Dupilumab						
Total Costs	$197,000	($182,000 - $213,000)	$129,000	($120,000 - $138,000)	$68,500	($61,300 - $75,200)
Total QALYs	3.48	(3.26 - 3.70)	3.50	(3.30 - 3.69)	-0.02	(-0.04 - 0.01)
ICER					-$3,400,000 (Dominated)	(-$1,500,000- $6,200,000)

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%	33%	10%	0%	0%
$100,000	1%	68%	34%	0%	19%
$150,000	34%	82%	58%	3%	67%
$200,000	72%	87%	71%	19%	86%
	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.[114]

Table E4.1. Scenario Analysis Inputs – Productivity Loss

Health State	Value	Source
Non-responder	$6,629.31	MEASURE UP 1 & 2
EASI 50	$4,041.48	
EASI 75	$3,130.95	
EASI 90	$1,598.39	

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 14 to 31% for the interventions and 51% 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*	$158,000	$180,000	3.54	4.85	3.54
Baricitinib	$85,600	$113,000	3.25	4.85	3.25
Tralokinumab*	$110,000	$135,000	3.29	4.85	3.29
Upadacitinib	$168,000	$192,000	3.35	4.85	3.35
Dupilumab	$123,000	$146,000	3.43	4.85	3.43
Standard of Care	$61,800	$93,000	2.97	4.85	2.97

*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 5% to 18% 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	$151,000	$-	$151,000
Baricitinib	SoC	$70,500	$-	$70,500
Tralokinumab*	SoC	$131,300	$-	$131,300
Upadacitinib	SoC	$258,000	$-	$258,000
Dupilumab	SoC	$116,000	$-	$116,000
Abrocitinib*	Dupilumab	$290,000	$-	$290,000
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

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*	$189,000	$484,000	15.74	24.31	15.74
Baricitinib	$37,150	$499,000	15.03	24.31	15.03
Tralokinumab*	$81,000	$537,000	15.19	24.31	15.19
Upadacitinib	$134,000	$593,000	15.13	24.31	15.13
Dupilumab	$107,000	$556,000	15.42	24.31	15.42
Standard of Care	$0	$475,000	14.65	24.31	14.65

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	$154,000	$ -	$154,000
Baricitinib	SoC	$62,900	$ -	$62,900
Tralokinumab	SoC	$115,100	$ -	$115,100
Upadacitinib	SoC	$246,000	$ -	$246,000
Dupilumab	SoC	$105,000	$ -	$105,000
Abrocitinib	Dupilumab	$234,000	$ -	$234,000
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 11% to 22% across the therapies evaluated.

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	$107,000	$105,000	-1.45%
Total Cost	$158,000	$157,000	-1.00%
ICER vs SoC	$167,000	$165,000	-1.51%
ICER vs Dupilumab	$308,000	$297,000	-3.74%

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

E5. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and Report Supplement materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

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.

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.[141,142] 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.[141] 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.[142] 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.[109] 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).[143] 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.[143] For adolescents (age 12-17), evidence suggests 389,000 US individuals have moderate-to-severe uncontrolled disease and are eligible for treatment.[143] 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.[144] 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.[145,146] 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.

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 ($37,500, $26,400, and $15,200 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 ($31,300, $22,000, and $12,800 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 ($31,700, $22,400, and $13,000 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 ($36,200, $25,400, and $14,500 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

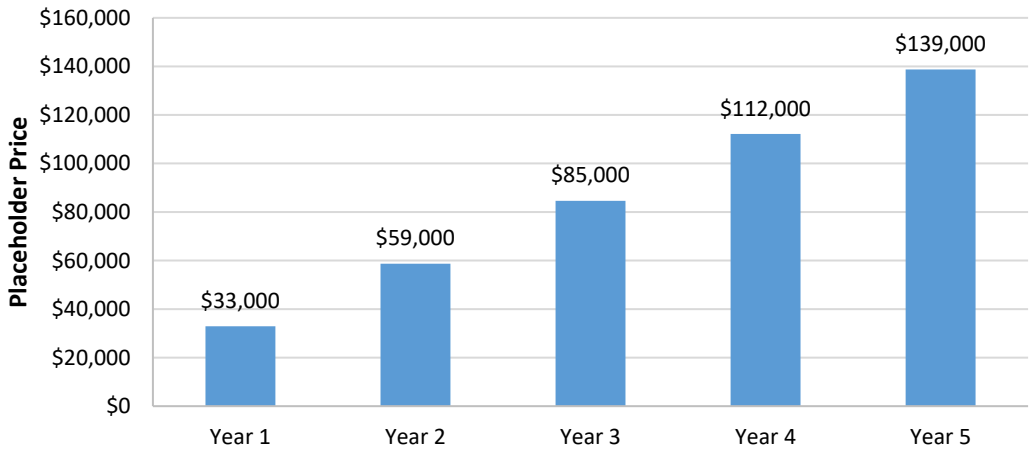
	Average Annual Per Patient Budget Impact				
	WAC*	**Discounted WAC***	**$150,000/QALY**	**$100,000/QALY**	**$50,000/QALY**
Abrocitinib vs. usual care	$31,100	$27,700	$24,500	$16,600	$8,700
Baricitinib vs. usual care	$10,8200	$6,300	$11,800	$8,000	$4,200
Tralokinumab vs. usual care	$18,100	$13,200	$13,300	$9,000	$4,800
Upadacitinib vs. usual care	$32,600	$32,800	$17,000	$11,500	$6,000

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.

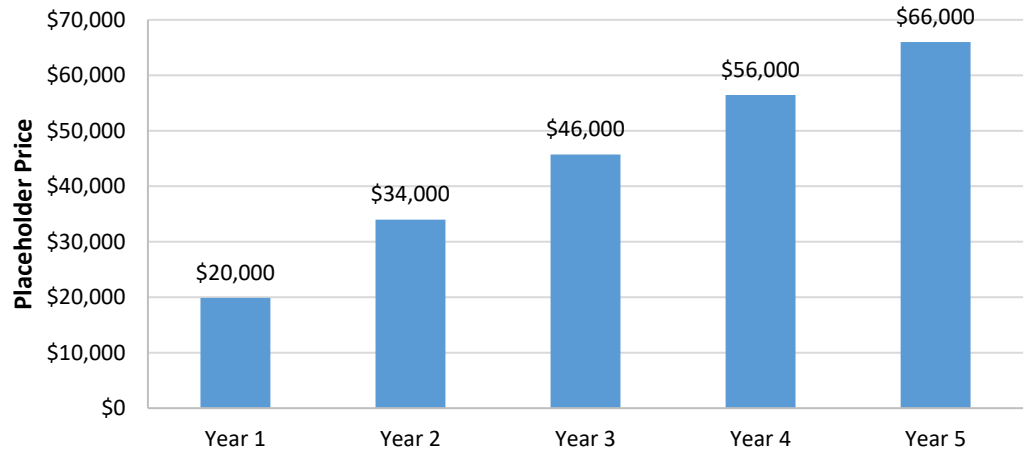
Figure F1. Cumulative Net Cost Per Patient Treated with Abrocitinib for Five Years at Placeholder $41,400 per Year Price*



* 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