25 June 2026
EMADOC-1700519818-3086714
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Opzelura

International non-proprietary name: Ruxolitinib

Procedure No. EMA/VR/0000313318

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AUC_{0-12h}	area under the steady-state concentration-time curve from Hour 0 to 12
BID	twice daily
BSA	body surface area
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
C_{ss}	mean steady-state concentrations
$C_{ss,vc}$	mean steady-state concentrations during vehicle-controlled period
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI50	≥ 50% improvement in EASI score
EASI75	≥ 75% improvement in EASI score
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment
IGA-TS	Investigator's Global Assessment – Treatment Success (defined as an IGA score of 0 or 1 with a ≥ 2-grade improvement from baseline)
IL	interleukin
IR	incidence rate
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITCH4	≥ 4-point improvement from baseline in Itch NRS score
ITT	intent-to-treat
JAK	Janus kinase
LFT	liver function test
LSM	least squares mean
LTS	long-term safety (period)
MAA	Marketing Authorisation Application
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
NE	not estimable
NRS	Numerical Rating Scale
PK	pharmacokinetic(s)
POEM	Patient-Oriented Eczema Measure

Abbreviation	Definition
PROMIS®	Patient-Reported Outcomes Measurement Information System
PT	preferred term
PY	person years
QD	once daily
ROW	rest of world
SE	standard error
SOC	system organ class
STD	standard deviation
TEAE	treatment-emergent adverse event
Th2	T helper 2
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Incyte Biosciences Distribution B.V. submitted to the European Medicines Agency on 14 November 2025 an application for a variation.

The following variation was requested:

Variation requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of moderate atopic dermatitis in adult patients who are inadequately controlled with, have a contraindication to, or are intolerant to topical corticosteroids and topical calcineurin inhibitors for OPZELURA, based on the results of the pivotal Phase III study INCB 18424-326 and the two supportive Phase III studies INCB 18424-303 and INCB 18424-304. INCB 18424-326 is a Phase 3b, double-blind, multicenter, randomized, vehicle-controlled, efficacy, and safety study of ruxolitinib cream in adults with moderate atopic dermatitis. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.0 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0486/2022 on the agreement of a paediatric investigation plan (PIP) for the treatment of atopic dermatitis.

At the time of submission of the application, PIP P/0486/2022 had not yet been completed as some measures had been deferred.

The PDCO issued on 12 September 2025 a positive partial compliance check for PIP P/0486/2022, in relation to:

Agreed studies/measures **(study identifier)**	**Description**
Study 2 (INCB 18424-303)	Double-blind, randomised, placebo-controlled trial to evaluate efficacy and safety of ruxolitinib cream in paediatric patients from 12 years to less than 18 years of age (and adults) with atopic dermatitis
Study 3 (INCB 18424-304)	Double-blind, randomised, placebo-controlled trial to evaluate efficacy and safety of ruxolitinib cream in paediatric patients from 12 years to less than 18 years of age (and adults) with atopic dermatitis
Study 4 (INCB 18424-316) [only study initiation checked for compliance]	Double-blind, randomised, placebo-controlled trial to evaluate efficacy and safety of ruxolitinib

Agreed studies/measures (study identifier)	Description
	cream in paediatric patients from 6 years to less than 18 years of age with atopic dermatitis
Study 7 (INCB 18424-102)	Open-label, non-comparative trial to evaluate safety and pharmacokinetics of ruxolitinib cream in paediatric patients from 2 years to less than 18 years of age with atopic dermatitis
Study 8 (INCB 18424-103)	Open-label, maximum use trial to evaluate pharmacokinetics, safety and efficacy of ruxolitinib cream in paediatric patients from 12 years to less than 18 years of age (and adults) with atopic dermatitis

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 29/01/2021 (EMA/SA/0000046303) and on 20/07/2023 (EMA/SA/0000138950). The Scientific Advice pertained to the following clinical aspects of the dossier:

- Adequacy of the performed clinical pharmacology studies to support a marketing authorisation application; adequacy of the clinical development program to support the intended indication, in particular the design of two vehicle-controlled Phase 3 studies (INCB 18424-303 and INCB 18424-304) including the primary efficacy assessment EASI75, key secondary endpoints, and the patient population.
- The design of a double-blind, vehicle-controlled Phase 3 study (INCB 18424-326), including primary/secondary endpoints, population, sample size, and statistical analysis; adequacy of the overall clinical development programme to support the intended indication.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: Alexandre Moreau

Timetable	Actual dates
Submission date	14 November 2025

Timetable	Actual dates
Start of procedure:	27 December 2025
CHMP Rapporteur's preliminary assessment report circulated on:	20 February 2026
PRAC Rapporteur's preliminary assessment report circulated on:	26 February 2026
CHMP Co-Rapporteur's preliminary assessment report circulated on:	3 March 2026
PRAC members comments	n/a
PRAC Rapporteur's updated assessment report circulated on:	n/a
PRAC Outcome	12 March 2026
CHMP members comments	13 March 2026
CHMP Rapporteur's updated joint assessment report circulated on:	20 March 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 March 2026
MAH's responses submitted to the CHMP on:	21 April 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	29 May 2026
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	29 May 2026
PRAC members comments	n/a
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on:	n/a
PRAC Outcome	11 June 2026
CHMP comments	n/a
CHMP Rapporteur's updated joint assessment report on the MAH's responses circulated on:	19 June 2026
CHMP opinion:	25 June 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Since 2023, Opzelura (ruxolitinib cream) is approved for the treatment of non-segmental vitiligo in adults and adolescents from 12 years of age. With this application, the MAH proposes to extend the currently approved indication to include adult patients with moderate atopic dermatitis, who would otherwise be candidates for systemic therapy.

Disease or condition

The new proposed indication is: *'Opzelura is indicated for the treatment of moderate atopic dermatitis in adult patients for whom topical corticosteroids and topical calcineurin inhibitors are inadequate or inappropriate.'*

Epidemiology

Atopic dermatitis (AD) is a chronic, recurring, inflammatory, and highly pruritic skin condition, with an estimated prevalence among adults of 5.5% across 27 European countries (Richard et al 2022, Rönmark et al 2012, Vinding et al 2014).

Comparative estimates of the prevalence of AD among adults in industrialised countries suggest that moderate AD is the most common disease presentation (Barbarot et al 2018). Depending on the scale used and study design, the proportion of patients with moderate to severe disease within the EU varies from 20% to 66% (Augustin et al 2022, Kleyn et al 2022), moderate AD may comprise roughly half of reported cases (Ameen et al 2020, Barbarot et al 2018).

Pathogenesis

Multiple isogenic factors and inflammatory cytokines are involved in the pathogenesis of AD. T helper 2 cytokines (IL-4, IL-5, IL-13, IL-22, and IL-31) and epithelial cytokine thymic stromal lymphopoietin play a central role in the pathogenesis of AD by activating inflammatory pathways in multiple cell types, impairing epidermal barrier structure and function, and inducing allergen sensitisation (Moreno et al 2016). Activation of JAK/STAT signaling is required for potentiating the proinflammatory actions downstream of these cytokines, underscoring the importance of JAK inhibition as a therapeutic target for inflammatory diseases including AD. In mouse models of dermatitis, topical administration of ruxolitinib cream significantly decreased expression of inflammatory cytokines in the skin, reduced dermatitis symptoms, and alleviated pruritic behaviors.

Clinical presentation

AD in adults typically presents as a chronic, relapsing inflammatory skin disease characterised by intense pruritus and eczematous lesions. Lesions are often ill-defined, erythematous, and scaly, with lichenification commonly seen in long-standing disease due to repeated scratching. In adults, involvement frequently affects flexural areas, the hands, face, neck, and upper trunk, although the distribution may be more localised or atypical compared with childhood AD.

Patients with AD report significantly diminished quality of life, owing in large part to chronic itch and associated sleep disturbances (Fasseeh et al 2022, Zuberbier et al 2006).

Moderate AD is characterised by more widespread or persistent eczematous lesions than mild disease, with noticeable erythema, excoriations, and early lichenification, but without the extensive skin involvement or marked thickening seen in severe disease. Pruritus is typically frequent and intense, leading to regular scratching and sleep disturbance. In both clinical practice and research, validated scoring systems are used to define moderate severity. These include the Eczema Area and Severity Index (for example, EASI 7–21), and the Investigator's Global Assessment (for example, IGA score of 3).

Management

European guidelines recommend a stepped-care approach in the treatment of AD in adults (Boguniewicz et al 2018, Wollenberg et al 2025). Initial management involves basic treatment strategies (ie, education of patients about skin hydration, the use of emollients, and avoidance of factors that worsen the disease) used in patients with mild disease.

When these non-pharmacologic interventions are insufficient to control inflammation and itching, topical anti-inflammatory medications are added, notably topical corticosteroids for the treatment of mild to moderate AD (Wollenberg et al 2025). For patients whose AD is not adequately controlled with or who are intolerant to or have contraindication to topical corticosteroids or when prolonged intermittent treatment with topical corticosteroids may be inappropriate (such as treating sensitive skin areas on the face and neck), topical calcineurin inhibitors (e.g. ProTopic) are recommended.

For patients with moderate/severe AD that is not adequately controlled with currently available topical therapies, or for whom those topical agents are not medically advisable, systemic treatments such as the Th2-blocking biologics tralokinumab, dupilumab, lebrikizumab and nemolizumab (Adtralza, Dupixent, Ebglyss, Nemluvio) and the oral JAK inhibitors baricitinib, upadacitinib and abrocitinib (Olumiant, Rinvoq, Cibingo) are approved.

2.1.2. About the product

Opzelura (ruxolitinib cream) is a topical formulation of ruxolitinib phosphate, a potent and selective inhibitor of JAK1 and JAK2 with modest to marked selectivity against tyrosine kinase 2 and JAK3. Many inflammatory and pruritic cytokines involved in the pathogenesis of AD, such as IL-4, IL-5, IL-13, IL-22, IL-31, and TSLP (thymic stromal lymphopoietin), require JAK/STAT pathway activation for downstream biological activity.

2.1.3. Literature references

Ameen M, Rabe A, Blanthorn-Hazell S, Millward R. The prevalence and clinical profile of atopic dermatitis (AD) in England: a population based linked cohort study using clinical practice research datalink (CPRD) and hospital episode statistics (HES). Value in Health 2020;23:S745 [abstr PSY17]

Augustin M, Misery L, von Kobyletzski L, et al. Systematic literature review assessing the overall costs and societal impacts of moderate-to-severe atopic dermatitis in Europe. J Eur Acad Dermatol Venereol 2022;36:2316-2324.

Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. Allergy 2018;73:1284-1293.

Fasseeh AN, Elezbawy B, Korra N, et al. Burden of atopic dermatitis in adults and adolescents: a systematic literature review. Dermatol Ther (Heidelb) 2022;12:2653-2668.

Kleyn CE, Barbarot S, Reed C, et al. Burden of moderate to severe atopic dermatitis in adults from France, Italy, and the UK: patient-reported outcomes and treatment patterns. Dermatol Ther (Heidelb) 2022;12:1947-1965.

Richard MA, Paul C, Nijsten T, et al. Prevalence of most common skin diseases in Europe: a population-based study. J Eur Acad Dermatol Venereol 2022;36:1088-1096.

Rönmark EP, Ekerljung L, Lötvall J, et al. Eczema among adults: prevalence, risk factors and relation to airway diseases. Results from a large-scale population survey in Sweden. Br J Dermatol 2012;166:1301-1308.

Vinding GR, Zarchi K, Ibler KS, Miller IM, Ellervik C, Jemec GB. Is adult atopic eczema more common than we think? – A population-based study in Danish adults. Acta Derm Venereol 2014;94;480-482.

Zuberbier T, Orlow SJ, Paller AS, et al. Patient perspectives on the management of atopic dermatitis. J Allergy Clin Immunol 2006;118:226-232.

2.2. Non-clinical aspects

2.2.1. Introduction

No new non-clinical studies have been submitted. However, an update of the safety margins and an updated Environmental Risk Assessment have been submitted in this application.

2.2.2. Toxicology

The MAH provided the safety margins associated with NOAELs for findings in toxicology studies relative to steady state plasma concentrations of ruxolitinib (AUC) observed in patients with moderate AD with new safety margins based on the added posology with the AD indication.

Safety Pharmacology

Based on single dose toxicokinetics in the rat (DMB-06.174), the projected Cmax in females at the NOAEL dose of 50 mg/kg in the respiratory study was 2.85 µM (0.51 µM unbound), which is 67-fold (total drug) and 362-fold (unbound drug) the geometric mean steady state plasma ruxolitinib concentration of 42.7 nM (1.41 nM unbound) in patients with moderate AD administered 1.5% ruxolitinib cream BID (Phase 3 study INCB 18424-326). In the dog cardiovascular study (T06-10-01), lower arterial blood pressure with compensatory increase in heart rate were observed following oral administration of ruxolitinib at 30 mg/kg, which peaked at approximately 2 to 3 hours post-dose (Tmax). Based on single dose toxicokinetics in the dog (T07-10-07), the projected Cmax at the NOAEL of 10 mg/kg in the cardiovascular study is approximately 7.99 µM (0.77 µM unbound), which is approximately 187-fold (total drug) and 546-fold (unbound drug) the steady state plasma ruxolitinib concentration in patients with moderate AD administered 1.5% ruxolitinib cream BID (Phase 3 study INCB 18424-326). Collectively, the MAH considered that these results indicate that the potential for unintended adverse pharmacological effects of ruxolitinib cream is low.

Toxicology

Safety margins associated with NOAELs for findings in toxicology studies relative to steady state plasma concentrations of ruxolitinib (AUC) observed in patients with vitiligo (INCB 18424-306 and INCB 18424-307) and in patients with moderate AD (INCB 18424-326) administered ruxolitinib 1.5% cream twice daily are summarised in Table 1. Exposures associated with toxicities resulting from oral administration of ruxolitinib in nonclinical studies are generally well above those observed following topical application of ruxolitinib cream.

Table 1. Safety Margins Based on NOAELs from Ruxolitinib Toxicity Studies

Study	Sex	NOAEL (mg/kg per day)	AUC_{0-24} (µM·h)		Safety Margin vs. INCB 18424-306/307[a]		Safety Margin vs. INCB 18424-326[b]	
			Total	Unbound[c]	Total	Unbound	Total	Unbound
3-month mouse - topical	M	1.0% QD	7.24	0.195	11	9.3	7.1	5.7
	F	1.0% BID	18.7	0.505	29	24	18	15
9-month minipig - topical	M	1.5% BID[d]	0.167	0.055	0.3	2.6	0.2	1.6
	F	1.5% BID[d]	0.219	0.072	0.3	3.4	0.2	2.1
6-month oral rat	M	30	0.662	0.119	1.0[e]	5.7[e]	0.6[e]	3.5[e]
	F	60[d]	25.8	4.64	40	221	25	136
52-week oral dog	M	1.5	2.36	0.229	3.7	11	2.3	6.7
	F	1.5	2.57	0.249	4.0	12	2.5	7.3
Fertility and Early Embryo Development - rat	M	60[d]	1.32[f]	0.238	2.1[e]	11[e]	1.3[e]	7.0[e]
	F	60[dg]	25.8[f]	4.64	40	221	25	136
		10[g]	1.56[h]	0.281	2.5	13	1.5	8.3
Embryofetal Development - rat	NA	30	2.98	0.536	4.7	26	2.9	16
Embryofetal Development - rabbit	NA	30	0.068	0.009	0.1[e]	0.4[e]	0.1[e]	0.3[e]
Pre/Postnatal Development - rat	NA	30[d]	3.34	0.60	5.2	29	3.3	18
Juvenile Rat (Day 7 pp initiation)	M	5	2.66	0.48	4.2	23	2.6	14
	F	5	2.57	0.46	4.0	22	2.5	14
Juvenile Rat (Day 21 pp initiation)	M	15	4.38	0.788	6.9	38	4.3	23
	F	15	3.73	0.671	5.9	32	3.6	20

Study	Sex	NOAEL (mg/kg per day)	AUC_{0-24} (µM·h)		Safety Margin vs. INCB 18424-306/307[a]		Safety Margin vs. INCB 18424-326[b]	
			Total	Unbound[c]	Total	Unbound	Total	Unbound
Carcinogenicity								
104-week mouse - topical	M	1.5% QD[d]	2.37	0.064	3.7	3.1	2.3	1.9
	F	1.5% QD[d]	2.70	0.073	4.2	3.5	2.6	2.2
104-week rat - oral	M	60[d]	2.99	0.538	4.7[e]	26[e]	2.9[e]	16[e]
	F	60[d]	23.7	4.27	37	203	23	126
6-month Tg.rasH2 mouse	M	125[d]	67.8	3.32	106	158	66	98
	F	125[d]	78.0	3.82	122	182	76	112

a Safety margins were calculated as the multiple of AUC0-24h at the NOAEL relative to steady state AUC0-24h in vitiligo patients that applied 1.5% ruxolitinib cream BID to up to 10% BSA in INCB 18424-306 and INCB 18424-307, calculated as Css (geometric mean; 26.6 nM) × 24. (638 nM·h total; 21 nM·h unbound). (DMB-21.53; Module 2.7.2. Section 2.3.2.2 of the original MAA).

b Safety margins were calculated as the multiple of AUC0-24h at the NOAEL relative to steady state AUC0-24h observed in patients with moderate atopic dermatitis that applied 1.5% ruxolitinib cream BID to up to 20% BSA in INCB 18424-326, calculated as Css (geometric mean; 42.7 nM) × 24. (1025 nM·h total; 34 nM·h unbound). (Module 2.7.2 Section 2.2.2.4.1 of the current application.).

c The ex vivo fraction unbound in plasma is 4.9% in Tg.rasH2 mice, 2.7% in CD-1 mice, 18% in rats, 13% in rabbits, 9.7% in beagle dogs, and 33% in Gottingen minipigs. In vitro fraction unbound in human plasma is 3.3%.

d Highest dose tested.

e Ruxolitinib exposure in male rats and rabbits is not reflective of total pharmacologic activity because of extensive metabolism to active metabolites. Thus, safety margins for pharmacology-driven effects are likely underestimated.

f Toxicokinetics were not included in the fertility study. AUC from 60 mg/kg per day in 6-month study in rats.

g NOAEL was 60 mg/kg per day for female reproductive function and 10 mg/kg per day for early embryonic toxicity.

h Toxicokinetics were not included in the fertility study. AUC estimated from exposure at 15 mg/kg per day in the 6-month study in rats.

M=male; F=female

2.2.3. Ecotoxicity/environmental risk assessment

The updated PEC, PNEC and RQ of ruxolitinib are summarised in Table 2.

Table 2. PEC, PNEC and RQ for the environmental risk assessment of ruxolitinib

Compartment	PEC	PNEC	RQ	Outcome
Water	1.54 µg/L	30.4 µg/L	0.051	The RQ<1, thus ruxolitinib does not pose a risk of adverse effects to surface water species and further evaluation is not necessary
Groundwater	0.38 µg/L	3.04 µg/L	0.127	The RQ<1, thus ruxolitinib does not present a risk to the groundwater compartment
Sewage treatment plant	15.4 µg/L	1139 µg/L	0.014	The RQ<1, thus ruxolitinib does not present a risk to microorganisms in sewage treatment plants
Sediment	0.455 mg/kgdw	3.63 mg/kgdw	0.125	The RQ<1, thus ruxolitinib does not present a risk to the sediment compartment

The revised Predicted Environmental Concentration in surface water (PECSURFACEWATER) was calculated to include all indications for ruxolitinib cream and resulted in a PECSURFACEWATER of 1.54 µg/L. The risk quotient (RQ) for water, groundwater, microorganisms in sewage treatment plants and sediment were calculated based on the revised PECSURFACEWATER and all RQ values remained < 1. Therefore, no adverse environmental effects to the aquatic environment are anticipated following the therapeutic use of ruxolitinib phosphate cream (1.5%) for the topical treatment of both indications (vitiligo and AD).

2.2.4. Discussion on non-clinical aspects

No non-clinical studies were submitted by the MAH within this application, which is considered acceptable by the CHMP.

No *in vivo* proof-of-concept was added. Nevertheless, in the previous indication (vitiligo), while the mouse models used were not "vitiligo mice model", ruxolitinib was topically applied in mouse models that could be considered to be relevant to vitiligo pathogenesis as all these models were characterised by increased inflammatory mediators that signal through the JAK-STAT pathway, T-helper and/or T-cytotoxic cells. This conclusion is also considered applicable to the AD indication. Therefore, the absence of the *in vivo* POC is acceptable.

Regarding the absence of additional PK/toxicity studies in animals, this new indication in AD is also covered by oral administration in rat study (6-month and 104-week studies) and 52-week dog study, as well as reprotoxicity package in rats and as it is also a dermal application, the 9-month minipig and the 104-week in mice by dermal administration are also supportive for this indication. Opzelura was previously authorised in adults and in adolescents from 12-year-old with vitiligo, in this new indication (moderate AD), targeted patient population are limited to adults; therefore, it is not warrented to discuss the age of the target population from a non-clinical perspective.

Finally, since the proposed posology in this new indication will be twice the previous authorised (up to 20% of BSA), the MAH has updated the multiple of exposures in the SmPC section 5.3 and presented rationale to justify these updates. The calculation of these new margins of exposure is based on the AD

patients in the pivotal clinical study 326; the results are accepted and adequately reported in the SmPC section 5.3.

In addition, the MAH has provided an updated ERA upon CHMP's request, considering the added indication. New calculations were provided for the Risk Quotients (RQ) of the different environmental compartments. The RQs remained below 1 for each compartment, indicating that there is no anticipated risk for the environment due to the use of Opzelura (ruxolitinib cream) when used as indicated.

2.2.5. Conclusion on the non-clinical aspects

Overall, ruxolitinib cream is considered approvable from a non-clinical point. Considering the above data, ruxolitinib phosphate is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Number/Title	Participants	Status
INCB 18424-103: A Maximum Use Trial of Ruxolitinib Cream in Adolescent and Adult Participants With AD	41 Enrolled	Completed
INCB 18424-206: A Phase 2, Randomised, Dose-Ranging, Vehicle-Controlled and Triamcinolone 0.1% Cream–Controlled Study to Evaluate the Safety and Efficacy of INCB018424 Phosphate Cream Applied Topically to Adults With AD	307 Enrolled	Completed
INCB 18424-215: A Phase 2, Efficacy and Safety Study of Ruxolitinib Cream in Participants With Facial and/or Neck AD Involvement	77 Enrolled	Completed
INCB 18424-303: Topical Ruxolitinib Evaluation in AD Study 1 (TRuE-AD1). A Phase 3, Double-Blind, Randomised, 8-Week, Vehicle-Controlled Efficacy and Safety Study of Ruxolitinib Cream Followed by a Long-Term Safety Extension Period in Adolescents and Adults With AD	631 Enrolled	Completed
INCB 18424-304: Topical Ruxolitinib Evaluation in AD Study 2 (TRuE-AD2). A Phase 3, Double-Blind, Randomised, 8-Week, Vehicle-Controlled Efficacy and Safety Study of Ruxolitinib Cream Followed by a Long-Term Safety Extension Period in Adolescents and Adults With AD	618 Enrolled	Completed
INCB 18424-326: Topical Ruxolitinib Evaluation in AD Study (TRuE-AD4): A Phase 3b, Double-Blind, Multicenter, Randomised, Vehicle-Controlled, Efficacy, and Safety Study of Ruxolitinib Cream in Adults With Moderate AD	241 Enrolled	Completed
INCB 18424-901: An Open-Label, Single-Arm Study to Evaluate the Effect of Ruxolitinib 1.5% Cream on Itch in Adult Participants With AD (SCRATCH-AD)	84 Enrolled	Completed
INCB 18424-902: An Open-Label, Single-Arm, Phase 4 Study of Ruxolitinib Cream in Adults With AD Experiencing Sleep Disturbance in the United States (Morpheus)	47 Enrolled	Terminated

2.3.2. Pharmacokinetics

Methods

Bioanalytical methods

No new bioanalytical method development or assay validation in human plasma was performed. The determination of ruxolitinib concentrations in human plasma samples from study 326 is described below.

Plasma ruxolitinib concentrations in study 326 were measured using a validated LC-MS/MS assay (1–1000 nM) across seven runs, with acceptable QC and calibration results. Maximum sample storage was 403 days, well within the verified plasma stability of 1560 days.

Six analytical runs were accepted, and one was rejected (Run 6); across accepted runs, QC samples at 3, 50, and 800 nM showed inter-day CVs of 1.9–4.8% and mean bias of −3.8 to 2.7%, while Run 6 failed acceptance criteria and was rejected.

In this bioanalysis, 36 samples were re-assayed: 27 due to carryover, 1 due to concentrations above the ULOQ, and 8 in duplicate due to unexpected quantifiable concentrations. Incurred sample

reanalysis met SOP requirements, with 59 reportable ISR samples representing 11% of 546 analysed plasma samples, and all ISR results were within 20% of the original values.

No deviations from the protocol, SOPs, validated method, or sample analysis plan occurred; 8 duplicate re-assay samples from Run 6 were reanalysed in Run 7 after Run 6 was rejected due to an instrument issue.

Pharmacokinetic data analysis

A pharmacometrics analysis plan for plasma concentrations of ruxolitinib from topical application of ruxolitinib cream in adult participants with AD was submitted by the MAH.

The data included only adult participants with AD from one Phase 2 (study 206) and three Phase 3 (studies 303, 304, and 326) studies. Analysis datasets were prepared using SAS v9.4 (SAS Institute Inc, Cary, NC) in compliance with the Analysis Data Model basic data structure. Descriptive summary statistics were calculated using SAS. Statistical graphs were created using SAS and/or R v3.6.1 or later (R Foundation for Statistical Computing, Vienna, Austria). Statistical analysis such as linear regression were performed using SAS.

Descriptive summaries and plots of plasma PK concentrations and parameters (e.g., C_{ss} or F) were generated by visit, treatment, and timepoint, with stratification by age, baseline disease severity, and region. Disease severity and geographic region were key covariates, but their effects could not be quantified without accounting for ruxolitinib dose and treated lesion area, so mixed-effects modelling was performed.

Evaluation and quantification of models

Mixed-Effect Modelling Analysis: Model development

The relationship between average ruxolitinib dose per application and plasma concentrations was best described as an E_{max} relationship with IIV on EMAX, fixed allometric scaling on EMAX, and an exponential residual error model. The EMAX model addressed biases identified between individual EBEs for SLP and average dose per application resulting from a linear model, suggesting a nonlinear relationship between ruxolitinib concentrations and dose.

The final model's parameter estimates are presented in Table 3.

Table 3. Final Model Parameter Estimates

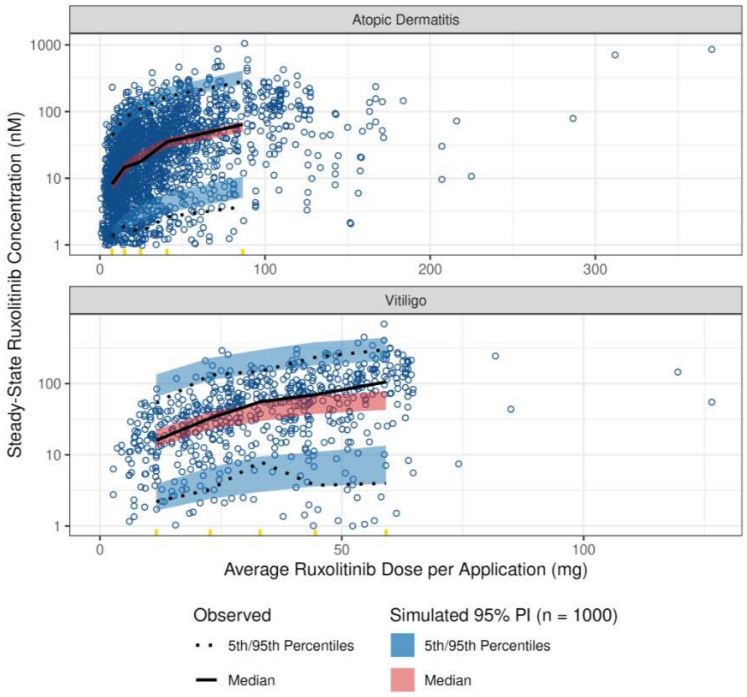
Parameter	Estimate	95% CI	Shrinkage (%)
Objective function value	20400.24	NA	NA
Condition number	197.82	NA	NA
Population parameters			
Maximum concentration (θ_{EMAX}; nM)	90.5	(63.5, 117)	NA
Half-maximal dose (θ_{ED50}; mg)	96.6	(65.2, 128)	NA
Box-Cox transformation parameter on EMAX (θ_{BXCXE})	−0.223	(−0.266, −0.180)	NA
Effect of vitiligo on EMAX ($\theta_{INDICATNEMAX3}$)	0.718	(0.457, 0.978)	NA
Effect of Europe region on EMAX ($\theta_{REGIONNEMAX1}$)	0.401	(0.255, 0.547)	NA
Effect of IGA ≥ 3 on EMAX for participants with AD ($\theta_{IGABEMAXHI}$)	0.250	(0.0919, 0.408)	NA
Interindividual variability			
ω^2_{EMAX}	0.972	(0.900, 1.04)	4.19
Random unexplained variability			
σ^2_{pro}	0.255	(0.237, 0.274)	12.9

Mixed-Effect Modelling Analysis: Model evaluation

An E_{max} model described the relationship between pre-dose steady-state ruxolitinib plasma concentrations and API dose in participants with AD and participants with vitiligo (see Figure 1). The effect of body weight was included a priori on the $EMAX$ parameter via allometric scaling (referenced to a 70 kg individual) with a fixed exponent of −0.75. The model parameter, E_{max}, is related to the inverse of apparent clearance based on PK first principles. The model included indication, geographic region, and AD disease severity on E_{max}; no residual trends were observed for age, sex, race, or vitiligo severity, and affected BSA was excluded due to high correlation with dose and AD severity.

It is noted that there is some discrepancy between observed and simulated summaries (lower percentiles) this is associated with highly variable and skewed data not remedied by the incorporation of a Box-Cox transformation on $EMAX$.

Figure 1. Final Model Visual Predictive Check Stratified by Indication



Note: The observed data against dose are represented by blue circles and dashed dotted lines (median: 5th and 95th percentiles). The simulated observations are based on the index population (n = 1000 simulations) and are represented by the red shaded regions (95% PI of the median) and blue shaded regions (95% PI of the 5th and 95th percentiles). Yellow indicators on the x-axis represent the dose bins for summarizing the data.

Pharmacokinetics

The key clinical pharmacology studies that describe the distribution, metabolism, and excretion characteristics of ruxolitinib were conducted after oral administration of ruxolitinib. These studies were described in the original application for the indication of vitiligo (EMEA/H/C/005843). No new dedicated clinical pharmacology studies were conducted that require updates.

The clinical PK of ruxolitinib after topical application in patients with AD were characterised in a comprehensive manner in the maximum-use Phase 1 study (study 103). Pooled analysis was performed with sparse PK (C_{trough}) data collected in studies 206, 303, 304 and 326 that enrolled adults with AD. An E_{max} model was developed to quantify the relationship between pre-dose steady-state ruxolitinib concentrations and API dose.

Study 103

Study 103 was an open-label, maximum-use study of ruxolitinib 1.5% cream applied BID to ≥ 25% body surface area (BSA) in adult and adolescent participants (aged ≥ 12 years to 65 years, inclusive) with AD. Blood samples were collected on days 1 and 28, and pre-application and 1-hour post-application samples were collected on day 15. A total of 41 participants enrolled and 39 completed the 28-day treatment period.

Application of ruxolitinib 1.5% cream BID resulted in the achievement of steady state by Day 15. The mean ± STD (median) plasma concentrations at preapplication were 124 ± 427 nM (21.2 nM) and 118 ± 379 nM (21.1 nM) on Day 15 and Day 28, respectively. The mean (STD) steady-state plasma concentration of ruxolitinib was 104 (309) nM (geometric mean: 26.5 nM; with mean (STD)) bioavailability of topical ruxolitinib cream was 2.54% (3.56%). After repeated BID topical applications of ruxolitinib cream, the mean ± SD (median; geometric mean) steady-state C_{max} was 137 ± 377 nM (38.6 nM; 43.9 nM).

Examination of the C_{max} and 12-hour post-dose concentration (C_{12}) ratios on Day 28 revealed mean (median) C_{max}/C_{12} ratios of 1.67 (1.07) in the overall population and 1.52 (1.09) in the adult population, indicating that the post-dose PK profiles are relatively flat and suggests that the trough concentration sufficiently represents the average plasma concentration. Based on the ratios of $AUC_{0\text{-}12h}$ between Day 28 and Day 1, the median (geometric mean) accumulation factor for ruxolitinib was 0.825 (0.954) in the overall population, indicating negligible accumulation of ruxolitinib following multiple dose administrations.

Study 206

Study 206 was a randomised, double-blind, vehicle- and active- (triamcinolone 0.1% cream) controlled study in adult participants with mild to moderate AD (affected BSA 3%-20%). A total of 307 participants were enrolled and randomised into equally sized treatment groups.

Application of ruxolitinib 0.15%, 0.5%, and 1.5% cream QD and ruxolitinib 1.5% cream BID resulted in mean trough plasma concentrations of ruxolitinib of 4.11 ± 9.06 nM, 9.35 ± 15.5 nM, 30.6 ± 44.2 nM, and 47.7 ± 79.6 nM, respectively. The means of estimated bioavailability of topical ruxolitinib cream in participants with AD were between 5% and 9% for all 4 treatment groups of ruxolitinib cream.

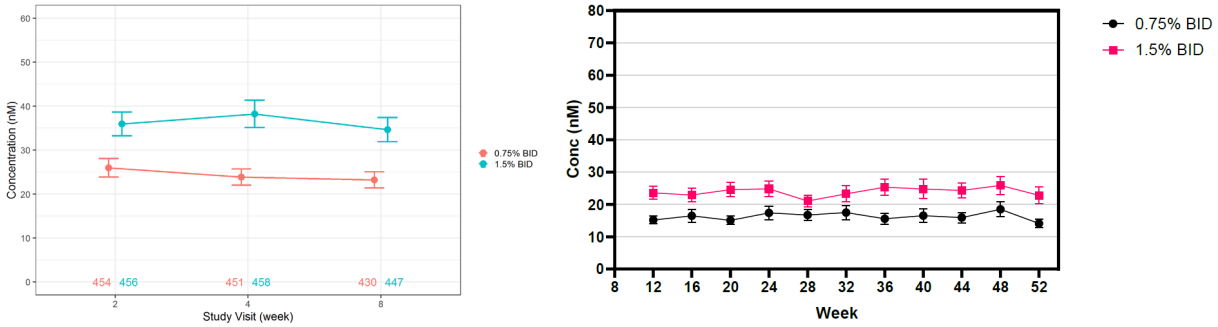
Both the BSA and percentage treated BSA (%BSA), and its interaction were statistically significant covariates predictors of C_{trough}. The impact of BSA on ruxolitinib $C_{through}$ after topical application of ruxolitinib cream is larger for participants with AD (≥ 10% BSA) than in those with < 10% BSA; this is not clinically significant in either %BSA category.

Study 303 and 304

Studies 303 and 304 are identical double-blind, randomised studies of adult and adolescent participants with 3% to 20% BSA affected by AD and an Investigator's Global Assessment (IGA) score of 2 or 3 at baseline composed of vehicle controlled (VC) (Day 1 through Week 8) and long-term safety (LTS) periods (Week 8 through Week 52). A total of 1249 participants were randomised 2:2:1 to ruxolitinib 1.5% cream BID, ruxolitinib 0.75% cream BID or vehicle cream. After 8 weeks, participants were randomised again from the vehicle cream to one of the two ruxolitinib creams. The PK population included 951 participants in the VC period and 1028 participants in the LTS period.

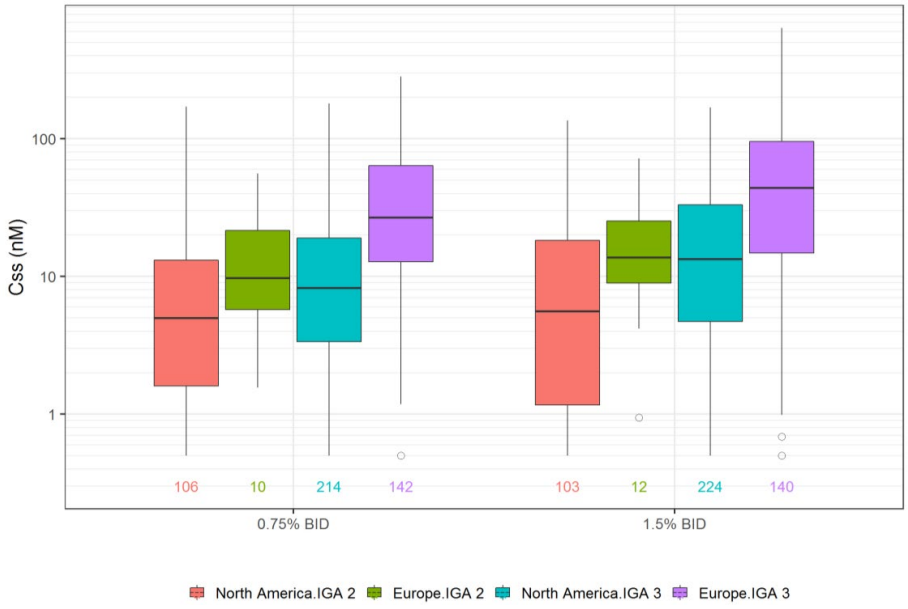
The mean values of trough concentration of ruxolitinib in plasma were stable within a narrow range of 23 to 26 nM and 34 to 39 nM for the treatment groups of ruxolitinib 0.75% cream BID and 1.5% BID, respectively, across Weeks 2, 4, and 8 visits during the VC period (Figure 2).

Figure 2. Ruxolitinib Plasma Trough Concentration (Mean ± SE) by Visit of studies 303 and 304 (Linear Scale) in Pooled Phase 3 Data. Left: Vehicle-Controlled Period. Right: Long-Term Safety Period.



Higher C_{ss} was observed in participants with a baseline IGA score of 3 versus an IGA score of 2 and in participants in Europe versus participants in North America; this difference was most pronounced for participants in Europe with a baseline IGA score of 3 (see Figure 3). Such differences were observed for both treatment groups in each Phase 3 study.

Figure 3. Boxplots of Ruxolitinib Steady-State Concentrations in Pooled Phase 3 Data Stratified by Geographic Region and Baseline IGA (Log_{10} Scale)



The difference in plasma concentrations between the 2 IGA groups is not unexpected since participants with a higher IGA score had more extensive, and probably more severe, lesion areas causing greater skin barrier disruptions leading to higher %BSA. The regional differences shown in Figure 3, are explained by the fact that a higher proportion of participants with greater than 15% BSA were enrolled in the baseline IGA 3 Europe stratum than in the corresponding North America stratum, suggesting that the higher ruxolitinib C_{ss} observed in European participants, particularly those with more severe disease, may be attributable to greater %BSA rather than true regional differences.

The mean (SD) bioavailability of topical ruxolitinib cream was 7.68% (8.88%) and 6.22% (7.66%) for the treatment groups of 0.75% cream BID and 1.5% cream BID, respectively. Bioavailability was not dependent on the formulation strength, baseline IGA score, or %BSA treated.

During the LTS period the mean profiles of trough concentrations were stable, yet the individual trough concentration profiles were not necessarily flat. This is expected considering the intermittent treatment practices during the LTS period treating persistent AD or new episodes of AD.

Study 326

Study 326 is a Phase 3b, multicentre, randomised, double-blind, vehicle-controlled study with an extension period in adult (aged ≥ 18 years) participants with moderate AD who had either an inadequate response to, were intolerant to, or contraindicated to topical calcineurin inhibitors and topical corticosteroids. Participants (n=241) had a mean ± STD BSA involvement at baseline of 15.2 ± 2.99% (range: 10.0% to 20.0%). The median amount of ruxolitinib 1.5% cream applied by each participant was approximately 3.84 g (the dose range was approximately 0.12 to 8.5 g of ruxolitinib 1.5% cream per application) to the same areas of skin BID for 8 weeks.

Ruxolitinib plasma concentrations were variable with a geometric CV% of ≥ 199%, which at least in part can be attributed to a broad range of %BSA treated (10%-20%) and associated range of ruxolitinib 1.5% cream per application. Although numerical measures of central tendency (median and geometric means) were higher for participants aged > 65 years versus participants aged ≤ 65 years and for Europe versus rest of world (ROW; e.g. US, Canada, Australia) region, these differences are not considered clinically meaningful on account of the large observed variabilities.

The mean (STD) steady state trough plasma concentration was 82.3 (98.4 nM), with a median (geometric mean) value of 49.6 nM (42.7 nM). The projected AUC0-12h was 987.6 ± 1181 h·nM, which is approximately 36% of the observed mean AUC0-12h at steady state (2716 h·nM) following 15 mg BID oral administration in healthy participants. The mean (geometric mean) topical bioavailability for ruxolitinib 1.5% cream in participants with atopic dermatitis was 8.87% (4.97%).

Pooled analysis studies 206, 303, 304, 326

The PK analysis dataset contained 10123 samples from 1236 participants who applied ruxolitinib cream in four Phase 2 or Phase 3 AD studies. Taken together, the demographic and baseline disease characteristics were well-balanced across treatment groups (Table 4), minimising the potential for confounding in the interpretation of PK results.

Table 4. Baseline Demographic and Disease Characteristics of Participants with D by Treatment Group

Treatment Group (N)	IGA Score at Baseline Mean ± STD, Median, Min-Max	Age (years) Mean ± STD, Median, Min-Max	Total Affected BSA (%) Mean ± STD, Median, Min-Max	BSA at Baseline (m^2) Mean ± STD, Median, Min-Max	Lesion Area at Baseline (cm^2) Mean ± STD, Median, Min-Max
0.15% QD (N = 46)	2.67 ± 0.47, 3.00, 2.00-3.00	38.9 ± 13.1, 38.0, 19-69	8.91 ± 5.34, 7.75, 3.00-21.00	2.03 ± 0.26, 2.02, 1.48-2.83	1800 ± 1080, 1590, 465-4250
0.5% QD (N = 46)	2.67 ± 0.47, 3.00, 2.00-3.00	38.4 ± 13.9, 36.5, 18-70	8.87 ± 5.03, 7.00, 3.00-20.60	1.99 ± 0.30, 1.95, 1.47-2.81	1780 ± 1110, 1270, 585-5200
0.75% BID (N = 374)	2.75 ± 0.44, 3.00, 2.00-3.00	42.6 ± 16.8, 40.5, 18-85	9.66 ± 5.23, 8.00, 3.00-20.00	1.93 ± 0.29, 1.89, 1.37-3.07	1860 ± 1050, 1600, 436-5380
1.5% QD (N = 49)	2.71 ± 0.46, 3.00, 2.00-3.00	39.3 ± 14.3, 37.0, 18-65	9.89 ± 6.18, 8.00, 2.80-22.00	1.97 ± 0.30, 1.95, 1.18-2.65	1990 ± 1300, 1430, 501-4720
1.5% BID (N = 551)	2.81 ± 0.40, 3.00, 2.00-4.00	39.6 ± 16.5, 36.0, 18-88	10.7 ± 5.29, 10.0, 3.00-22.00	1.94 ± 0.29, 1.91, 1.38-2.98	2060 ± 1050, 1950, 429-4890

Following application of ruxolitinib 1.5% cream BID, plasma concentrations were quantifiable in the majority of participants beginning at Week 2 (median: 20.2 nM, mean ± STD: 43.4 ± 63.3 nM, N = 455) and remained measurable through Week 52 (median: 4.21 nM). Decline in plasma concentrations

of ruxolitinib during extension periods was observed consistently in studies 303, 304, and 326 relative to the VC periods, which reflects the reduction in % affected BSA. No meaningful accumulation of ruxolitinib concentrations was observed over time.

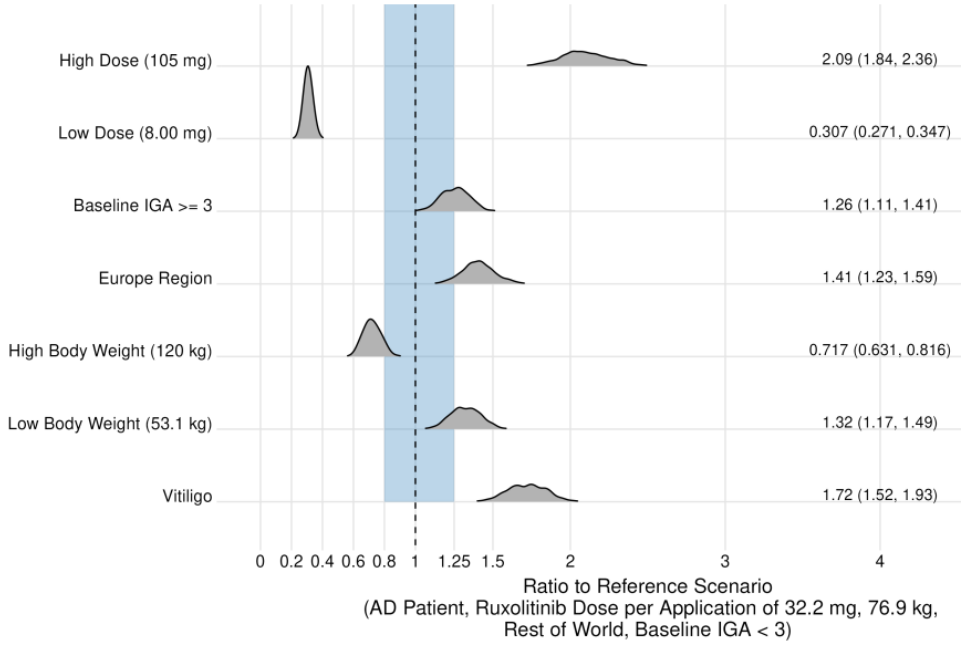
In the pooled adult PK (n=551), steady-state plasma concentrations during the VC period were quantifiable in nearly all participants. The mean daily ruxolitinib application dose was 41.7 ± 32.2 mg (median: 33.0 mg) with a range of 1.43-207 mg. Mean baseline total affected BSA was 10.7 ± 5.3%, and mean baseline lesion area was 2060 ± 1050 cm². These variables were the key drivers of plasma ruxolitinib concentration due to their influence on the extent of topical application. The median steady-state plasma concentration ($C_{ss,vc}$) was 22.4 nM (range: 0.00-646 nM) with mean (±STD) of 46.5 ± 71.5 nM. These concentrations reflect low plasma ruxolitinib concentrations relative to the 281 nM threshold associated with JAK2-mediated myelosuppression and are unlikely to produce any clinically relevant pharmacological effects, including the hematologic side effects associated with ruxolitinib.

Mixed-effect modelling analysis

A total of 1241 participants and 2819 observations across the VC periods of 6 ruxolitinib cream studies in adult participants with AD and participants with vitiligo were included in a mixed-effect modelling analysis. Most individuals had at least 2 steady-state ruxolitinib concentrations. The relationship between concentrations and dose appears to be approximately linear for the populations with AD and populations with vitiligo (see Figure 1).

The impact of covariates on steady-state ruxolitinib concentrations based on geometric mean ratios compared with the reference scenario are presented in Figure 4. The effects are quantified relative to the steady-state exposure of a participant with AD weighing 76.9 kg in the ROW region with baseline IGA<3. The ratios depicted are independent of other intrinsic and extrinsic factors that may modify ruxolitinib exposure. Vitiligo indication, lower body weight, residing within the European region, and baseline IGA≥3 resulted in higher ruxolitinib exposure.

Figure 4. Ratios of Steady-State Ruxolitinib Concentrations for Covariate Scenarios



Note: For each covariate scenario on the left y-axis, steady-state concentrations for 1000 trials of 350 randomly drawn individuals using topical ruxolitinib 1.5% cream BID were simulated and summarized. The geometric mean ratio of steady-state concentrations compared to the reference scenario (participant with AD, ruxolitinib 32.2 mg per application, 76.9 kg, ROW, and baseline IGA < 3) was calculated for each study. The gray density distributions represent the geometric mean ratios across all trials. Black numbers on the right y-axis are the median (5th and

95th percentiles) of geometric mean ratios for the covariate scenario. The blue shaded region is the range of geometric mean ratios from 0.8 to 1.25, and the black vertical dashed line is a geometric mean ratio of 1. Reference low and high body weights and doses are the 5th and 95th percentiles of the analysis population.

The effect of participants with vitiligo on E_{max} demonstrated the largest magnitude of effect on predicted steady-state ruxolitinib plasma concentrations. On average, participants with vitiligo reported a median (5th and 95th percentiles) of geometric mean ratio of 1.72 (1.52-1.93) systemic exposure compared to participants with AD (Figure 4). The effect is independent of other factors that may modify ruxolitinib exposure, including dose application patterns. Participants with AD in the Europe region or with baseline IGA ≥ 3 reported 41% and 26% higher exposure, respectively, compared to the reference participant with AD scenario.

Absorption

In summary, the application of ruxolitinib 0.15%-1.5% cream QD or BID resulted in a mean systemic relative bioavailability that was approximately 1.5%-15% and appeared independent of the strength of the cream formulation. Descriptive statistics for participants with AD revealed that plasma ruxolitinib concentrations were at steady state by the time of the first on-treatment assessment (Week 2), and remained consistent during the remainder of the 8-week VC periods in study 303 and 304 wherein BID cream application continued.

In study 326 with AD patients, the mean ± SD (median; geometric mean) steady-state trough plasma concentration was 82.3 ± 98.4 nM (49.6 nM; 42.7 nM) with a projected $AUC_{0\text{-}12h}$ at 987.6 ± 1181 h·nM; this is approximately 36% of the observed mean $AUC_{0\text{-}12h}$ at steady state (2716 h·nM) following 15 mg BID oral ruxolitinib administration in healthy participants. The mean (geometric mean) topical bioavailability for ruxolitinib cream in atopic dermatitis patients in the Phase 3 study was 8.87% (4.97%).

For vitiligo patients, The mean ± STD steady_state trough plasma concentration was 56.9 ± 62.6 nM with a projected $AUC_{0\text{-}12h}$ at 683 ± 751 h*nM, which is approximately 25% of the observed mean $AUC_{0\text{-}12h}$ at steady state (2716 h*nM) following 15 mg twice daily oral administration in healthy participants. The mean (geometric mean) topical bioavailability for ruxolitinib cream vitiligo patients in the pooled data of the two Phase 3 studies was 9.72% (5.78%).

Distribution

Based on the results from study 103, the arithmetic mean for the apparent volume of distribution during the terminal phase after extravascular administration (Vz/F) on Day 28 (n=9) is 115,000 L (CV = 168%). The mean percentage bound in plasma is 96.7% (CV = 18%).

Elimination

Based on the results from study 103, the application of ruxolitinib 1.5% cream resulted in a geometric mean apparent elimination $t_{½}$ of 32.5 hours (267% geometric CV) with a range of 10.0-777 hours (n=9) and an arithmetic mean apparent clearance at steady state (CL_{ss}/F) on Day 28 (n=38) of 2580 L/h (CV = 146%).

Dose proportionality and time dependencies

Based on the ruxolitinib $C_{through}$ plasma concentrations collected in studies 206, 303, and 304 an increased dose leads to a sub-proportional increase in plasma concentration.

In study 206, the increase was sub-proportional with respect to the application dose of API with the exponent of the power regression being estimated as 0.650. In studies 303 and 304 the application of ruxolitinib 0.75% BID and 1.5% BID resulted in mean ± SD (geometric mean) values of ruxolitinib C_{ss} of 23.8 ± 35.0 (9.86) nM and 35.7 ± 55.0 (13.4) nM for the 0.75% cream BID and 1.5% cream BID, respectively which indicates a sub-proportional increase in plasma concentration as the formulation strength doubled.

Special populations

Effect of age and weight

Plasma ruxolitinib concentration was not meaningfully affected by age. Among participants aged < 65 years (N = 498), the median $C_{ss,vc}$ was 22.1 nM (mean [±SD] of 43.1 ± 60.1 nM), while in participants aged ≥ 65 years (N = 53), the median $C_{ss,vc}$ was 29.2 nM (mean [±SD] of 79.1 ± 136 nM). The median application dose and affected BSA were comparable between age groups (33.5 mg vs 29.2 mg; 10.3% vs 9.00%, respectively).

These results indicate that age did not substantially influence plasma ruxolitinib concentration following topical administration of the 1.5% BID formulation. However, IIV was high, as reflected by the wide range of values observed in both age groups. Moreover, the sample size was small for the subgroup aged ≥ 65 years. A similar trend was observed during the extension period.

Body weight was included as a covariate on the E_{max} parameter in the mixed-effects model represents the reciprocal of clearance. The identified differences in ruxolitinib plasma concentrations are not considered clinically meaningful and are within the range of plasma concentrations expected for the ruxolitinib 1.5% cream BID.

Regional differences

Geographic region contributed to variability in plasma ruxolitinib concentration. Participants enrolled at European sites (N = 204) exhibited higher median plasma concentrations $C_{ss,vc}$ of 46.3 nM (mean [±SD]: 73.8 ± 88.6 nM) compared with participants from ROW (N = 347), who had a median $C_{ss,vc}$ of 13.7 nM (mean [±SD]: 30.5 ± 53.2 nM) (Figure 3).

The difference in exposure is probably due to regional differences in lesion area (Europe mean [±SD]: 2480 ± 995 cm² versus ROW: 1820 ± 1010 cm²) and API application dose (Europe median, mean [±SD]: 48.8, 56.1 ± 34.2 mg versus ROW: 25.8, 33.3 ± 27.7 mg). These results suggest that regional variability in plasma ruxolitinib concentration is more likely attributable to differences in disease extent and application practices than due to intrinsic differences in PK.

Other factors

No information regarding renal and hepatic function, was provided by the MAH. From the current SmPC, it is known that for renal impairment the estimated AUC which is adjusted for the pharmacological activity of ruxolitinib plus the metabolites increases approximately two-fold in case of end stage renal disease (ESRD). As a precautionary measure, Opzelura should not be used by patients with ESRD, due to lack of safety data. For hepatic impairment it is stated that although the AUC was increased following oral administration of ruxolitinib to patients with hepatic impairment, there was no clear relationship between the severity of hepatic impairment and the increase in AUC. A dosing advice for patients with hepatic impairment is therefore not necessary.

From the mixed-effect modelling analysis gender did not appear to explain variability in the data.

Pharmacokinetic interaction studies

No interaction studies have been performed with topically administered ruxolitinib.

The potential for interactions with ruxolitinib is considered to be low because of the limited systemic exposure following topical administration.

2.3.3. Pharmacodynamics

Mechanism of action

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate, a potent and selective inhibitor of JAK1 and JAK2 with modest to marked selectivity against tyrosine kinase 2 (TYK2) and JAK3.

Multiple isogenic and inflammatory cytokines are involved in the pathogenesis of AD. T helper 2 cytokines (IL-4, IL-5, IL-13, IL-22, and IL-31) and epithelial cytokine thymic stromal lymphopoietin play a central role in the pathogenesis of AD by activating inflammatory pathways in multiple cell types, impairing epidermal barrier structure and function, and inducing allergen sensitisation (Moreno et al 2016). Activation of JAK/STAT signalling is required for potentiating the proinflammatory actions downstream of these cytokines, underscoring the importance of JAK inhibition as a therapeutic target for inflammatory diseases including AD. In mouse models of dermatitis, topical administration of ruxolitinib cream significantly decreased expression of inflammatory cytokines in the skin, reduced dermatitis symptoms, and alleviated pruritic behaviors.

Primary and secondary pharmacology

The evaluation of hematologic parameters (Hgb, neutrophil count, and platelet count) by systemic ruxolitinib exposure ($C_{ss,vc}$) provides insight into the hematologic safety profile of topical ruxolitinib treatment in adult participants with AD.

Overall, across all 3 hematologic parameters evaluated, the absence of exposure-dependent effects across $C_{ss,vc}$ quartiles, and the maintenance of values within reference ranges throughout the double-blind, VC period demonstrates that ruxolitinib cream does not exert clinically meaningful effects on key hematologic parameters.

2.3.4. Discussion on clinical pharmacology

The key clinical pharmacology studies describing the distribution, metabolism, and excretion of the active substance after oral administration were conducted and adequately described in the original application for the indication of vitiligo (EMEA/H/C/005843).

No new bioanalytical method development or assay validation in human plasma was performed for this application. Overall, the bioanalysis was conducted in compliance with current ICH M10 guidance on bioanalytical method validation and study sample analysis.

The PK dataset used to characterise the PK of ruxolitinib following topical administration in adult participants with AD comprised one Phase 2 study (206) and three Phase 3 studies (303, 304, and 326). Disease severity and geographic region were identified as key covariates; however, their effects could not be fully quantified without accounting for dose and treated lesion area. To address this, mixed-effects modelling was applied.

The average ruxolitinib dose per application and plasma concentration relationship was adequately described by an E_{max} model. Covariate selection was systematic, and all relevant covariates were

appropriately retained where justified. The modelling development strategy was sufficiently described. Low shrinkage for inter-individual variability and residual error (4.19% and 12.9%, respectively) supports reliable parameter estimation. Model evaluation indicated that the E_{max} model adequately captures the average ruxolitinib dose per application and plasma relationship in participants with AD and vitiligo. Minor discrepancies observed in the lower percentiles are noted but are not expected to impact the overall adequacy or regulatory interpretation of the model.

The median amount of ruxolitinib 1.5% cream applied by each participant in study 326 was approximately 3.97 g (the dose range was approximately 0.12 to 8.5 g of ruxolitinib 1.5% cream per application) to the same areas of skin BID for 8 weeks. In the pooled analysis of PK from all AD studies, the mean baseline total affected body surface area (BSA) was 10.7 ± 5.3%, and the mean baseline lesion area was 2060 ± 1050 cm². The mean (geometric mean) topical bioavailability for ruxolitinib 1.5% cream in participants with AD in study 326 was 8.87% (4.97%). The mean ± STD (median; geometric mean) steady state trough plasma concentration was 82.3 ± 98.4 nM (49.6 nM; 42.7 nM) with a projected $AUC_{0\text{-}12h}$ at 987.6 ± 1181 h*nM, which is approximately 36% of the observed mean $AUC_{0\text{-}12h}$ at steady state (2716 h*nM) following 15 mg twice daily oral administration in healthy participants. Analysis of trough concentrations ($C_{through}$) from studies 206, 303, and 304 showed that an increase in dose from 0.75 to 1.5% led to a sub-proportional increase in ruxolitinib plasma concentration. Given that there is only one dose-formulation strength (1.5%) and the amount applied is dependent on disease severity, this is not considered to have clinical relevance. Overall, the concentrations across all subgroups maintained at least a 6-fold margin relative to the whole blood ruxolitinib IC50 for JAK2 inhibition (281 nM).

Comparison of ruxolitinib PK during the VC period and follow-up demonstrated a decrease in $C_{through}$ relative to the VC period, consistent with reductions in %BSA and systemic exposure as AD lesions improved. However, recurrence following treatment discontinuation and subsequent re-initiation may lead to renewed increases in exposure. In the context of the proposed "as-needed" regimen, clarification was requested on the impact of intermittent treatment on the exposure–response relationship. The MAH has submitted the PK data from the extension period of study 326, as requested by CHMP. Based on the available data, the proposed 'as-needed' dosing strategy was adequately justified by the MAH which allows for effective maintenance and control of disease signs and symptoms while keeping the systemic concentrations low.

According to the SmPC section 5.2, following topical ruxolitinib administration, the mean systemic exposures in patients with vitiligo and AD are reported to be approximately 25% and 36%, respectively, of those observed after 15 mg BID oral administration in healthy volunteers. However, the mean topical bioavailability (relative bioavailability in the reports for Studies 306, 307, and 326) is stated to be approximately 9% for both indications after comparable dosing (±0.1–8.5 g cream per application). This is explained by bioavailability estimate being derived from steady-state concentrations (C_{ss}) and average ruxolitinib dose using an estimated clearance that does not account for disease-related differences. Furthermore, because the calculation is based on C_{ss} divided by dose within each participant, the dose effect cancels out, resulting in generally similar bioavailability estimates across individuals.

The mixed-effects modelling analysis indicates that participants with vitiligo had a median (5th and 95th percentiles) of geometric mean ratio of 1.72 (1.52-1.93) systemic exposure compared to participants with AD, independent of other evaluated covariates. This finding appears inconsistent with the previously presented data indicating approximately 10% lower exposure in vitiligo patients relative to AD. The basis for this discrepancy is unclear. Considering that the applied amount of cream was similar across indications and that the treated %BSA was ≤10% for vitiligo and 10‑20% for AD, these factors would not be expected to result in lower exposure in vitiligo patients. Furthermore, age, body

weight, and geographical region were not identified as clinically relevant covariates. Upon CHMP's request, the MAH clarified that the clearance term applied in the model represents the apparent clearance (CL/F), and that the E_{max} model therefore reflects the reciprocal of apparent clearance. Consequently, larger covariate effects on E_{max} translate into lower CL/F and thus higher predicted concentrations. Vitiligo showed the largest covariate effect within the E_{max} model, leading to lower CL/F and correspondingly higher exposure. The MAH noted that the underlying reason for lower CL/F in these patients is not fully understood but may relate to disease characteristics such as lesion severity or systemic inflammation. The SmPC has been updated in section 5.2 to include median and geometric mean values for both patient populations. The applicant has adequately addressed the issue, and the SmPC update is considered acceptable. In addition, SmPC section 4.5 has also been updated to highlight that the use of ruxolitinib cream in combination with other topical medicinal products used to treat AD has not been evaluated and thus co-application on the same skin areas is not recommended.

The relatively flat PK profiles suggest that trough concentrations are comparable to the average plasma concentrations. The flat PK profiles along with the long terminal half-life indicate that systemic absorption following ruxolitinib 1.5% cream application is absorption rate-limited. After the first application of ruxolitinib 1.5% cream, detectable concentrations were observed within approximately 1 to 2 hours. Following the absorption phase, concentrations remained steady with no significant fluctuations up to 12 hours. Following multiple applications of ruxolitinib cream, concentrations reached steady state on Day 15 and beyond. No significant accumulation in plasma concentrations of ruxolitinib after multiple applications was observed.

Observed differences in plasma exposure by age, body weight, and geographical region were not considered clinically relevant and thus do not necessitate dose adjustments.

2.3.5. Conclusions on clinical pharmacology

Ruxolitinib cream exhibits low systemic bioavailability following topical administration of a 15 mg/g cream to patients with moderate AD. Overall, the PK of topically applied ruxolitinib cream was adequately characterised. The data submitted within this application have been adequately reflected in the SmPC.

2.4. Clinical efficacy

2.4.1. Dose response study

A Phase 2, randomised, dose-ranging, vehicle-controlled and triamcinolone 0.1% cream–controlled study to evaluate the safety and efficacy of INCB018424 phosphate cream qpplied topically to adults with AD (INCB 18424-206).

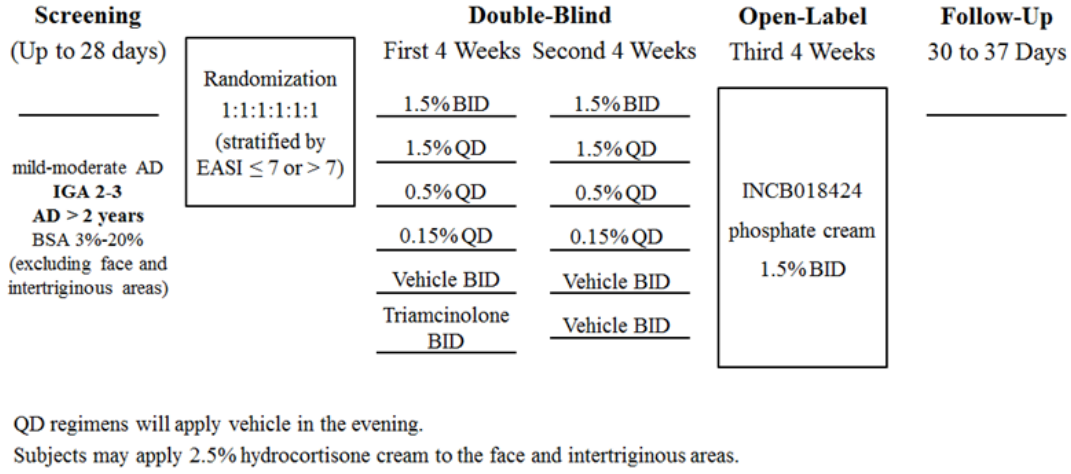
Objectives

The objectives were to establish the efficacy of a dose range (0.15% to 1.5%) of ruxolitinib cream once daily (QD) or twice daily (BID) in participants with AD compared with vehicle cream BID (primary objective) and as compared with triamcinolone 0.1% cream (secondary objective).

Design

Study INCB 18424-206 was a Phase 2, randomised, double-blind, vehicle- and active (triamcinolone acetonide cream) controlled, dose range–finding study in participants with mild to moderate AD (Figure 5).

Figure 5. Design of dose-response study INCB 18424 206



QD regimens will apply vehicle in the evening.
Subjects may apply 2.5% hydrocortisone cream to the face and intertriginous areas.

Approximately 300 participants were planned to be randomised 1:1:1:1:1:1:1 to ruxolitinib 1.5% cream BID, ruxolitinib 1.5% cream QD, ruxolitinib 0.5% cream QD, ruxolitinib 0.15% cream QD, vehicle cream BID, and active control (triamcinolone 0.1% cream BID) and stratified by EASI score (≤ 7 and > 7).

Participants applied blinded study drug for 8 weeks. Participants randomized to QD regimens applied vehicle for the evening application. Areas identified for treatment at baseline were treated through week 8 even if the areas began to improve. New or expanded AD lesions could be treated as long as the total treated BSA did not exceed 20%. At Week 8, participants who met criteria (compliant with the Protocol and no safety concerns) were offered open-label treatment with ruxolitinib 1.5% cream BID for 4 weeks.

The ITT population included all participants who were randomised to the study (treatment groups defined according to the treatment assignment at the time of randomisation). The primary alternative hypothesis (superiority of ruxolitinib 1.5% cream BID compared with vehicle cream) was tested at a 2-sided α = 0.05 level, using a mixed-model repeated measures (MMRM) on percentage change from baseline in EASI scores to Week 2 and Week 4. The test on the primary endpoint was used as a gatekeeper for 6 statistical tests on the secondary endpoints.

Results

A total of 306 participants (99.7%) were treated in the double-blind period. Overall, 92% of participants completed the study through week 4, and 85% of participants completed the study through week 8. In the double-blind period, 15% were discontinued from study drug, the most common reason was withdrawal by participant (6.5%).

Participants had a mean (range) age of 38 years (18-70), most participants (96%) were ≤ 65 years of age and 55% were female. The majority of participants were Caucasian (56%) or Black/African-American (28%). The mean time since onset of current AD was ~8 years, and the mean total BSA involvement at baseline was 9.6%. The mean EASI score at baseline ranged from 8.2 to 8.6 across treatment groups.

The most common (> 5%) prior AD medications were hydrocortisone (13%), triamcinolone (12%), betamethasone (8.1%), prednisone (6.5%), clobetasol (6.2%), emollients and protectives (5.9%), and tacrolimus (5.9%).

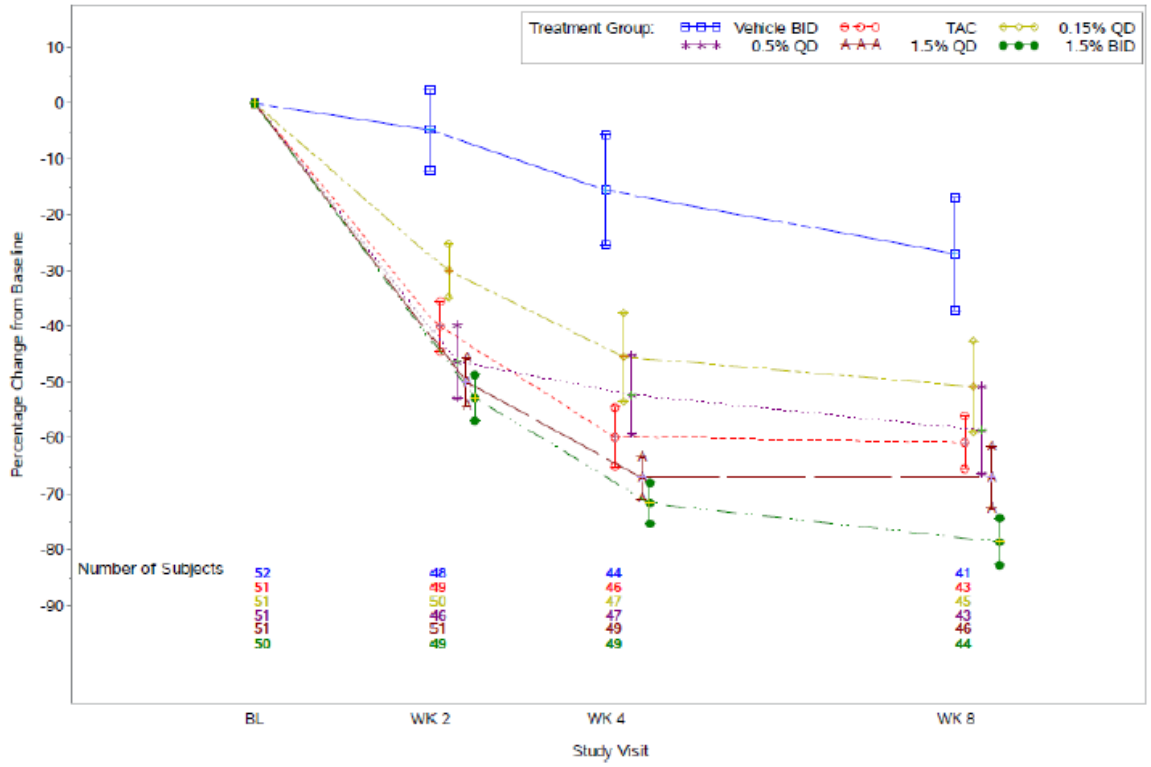
Fifty-three participants had important protocol deviations and were excluded from the PP population, mostly (n=47) due to important noncompliance (defined as < 60% compliant with either application or dose compliance) with the study treatment. There were 307 participants randomised and analysed for efficacy (ITT population); 254 participants were analysed for efficacy in the per-protocol population.

Outcomes and estimation

For the primary efficacy endpoint, the ruxolitinib 1.5% cream BID treatment group showed a statistically significantly larger mean percentage change from baseline in **EASI** score at week 4 (-72%) compared with the vehicle treatment group (-12%; $p < 0.0001$). Also, the ruxolitinib 1.5% cream QD and 0.5% cream QD treatment groups also had statistically significant larger mean percentage changes from baseline in EASI score at week 4 (-67% and -53%, respectively) compared with the vehicle treatment group (-12%; $p < 0.0001$). Also, at weeks 2 and 8, all 4 ruxolitinib treatment groups had larger percentage improvements (decreases) from baseline in **EASI** score than the vehicle treatment group (Figure 6).

At Weeks 2, 4, and 8, all ruxolitinib treatment groups had higher percentages of **IGA responders** than the vehicle treatment group. At Weeks 2, 4, and 8, all ruxolitinib treatment groups had greater mean improvements from baseline in the **itch** numerical rating scale (NRS) score than the vehicle treatment group.

Figure 6. Mean Percentage Change From Baseline in EASI Score by Visit and Treatment Group – Double-Blind Period (ITT Population).

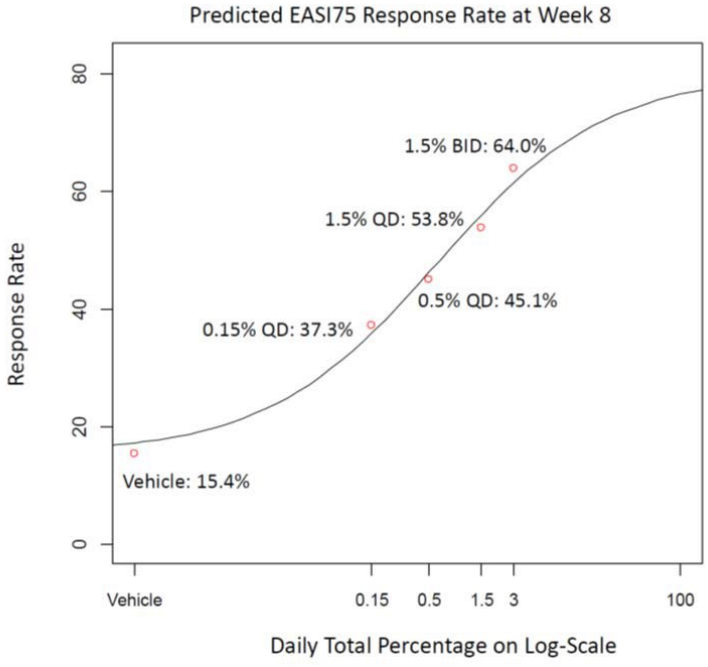


TAC = triamcinolone 0.1% cream.
Note: TAC was administered BID for 4 weeks followed by vehicle cream BID for 4 weeks.

Ancillary analyses

An E_{max} model was used to explore the dose-response relationship, see Figure 7 below.

Figure 7. Predicted EASI-75 Response Rate at Week 8 (ITT Population)



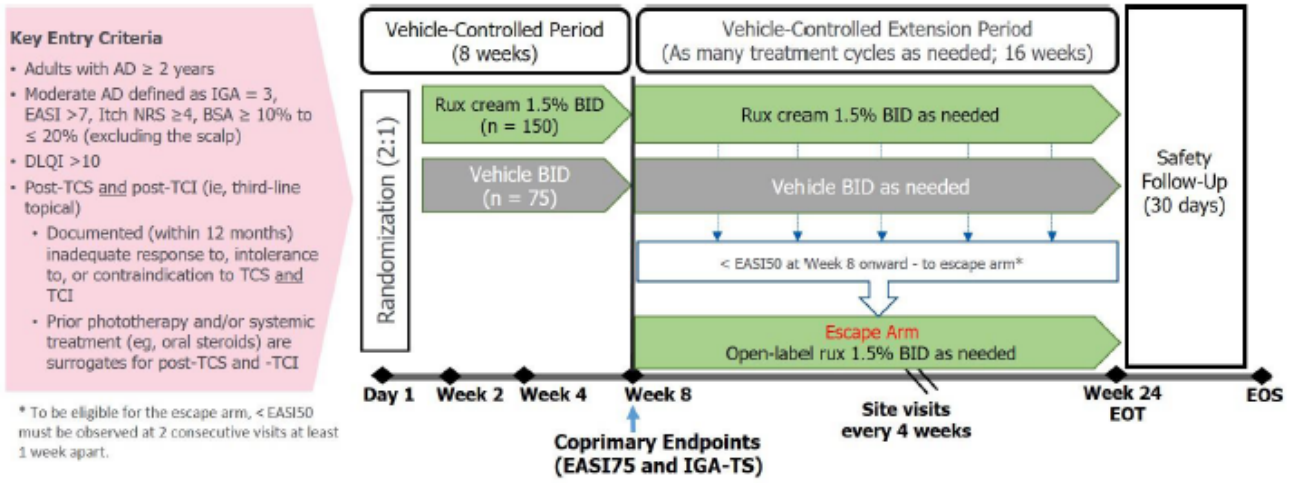
2.4.2. Main study

TRuE-AD4. A phase 3b, double-blind, multicenter, randomised, vehicle-controlled, efficacy, and safety study of ruxolitinib cream in adults with moderate AD (INCB 18424-326).

Methods

Design

Figure 8. Design of study 326.



TCI = topical calcineurin inhibitors; TCS = topical corticosteroids.

During the 8-week vehicle-controlled period, participants applied study cream BID to all areas identified for treatment at baseline even if the AD improved and lesions decreased in size. New areas could also be treated after consultation with the investigator up to a maximum of 20% BSA.

After completing 8 weeks of continuous treatment, eligible participants with an adequate response (at least EASI50 from baseline) continued blinded treatment and continued for an additional 16-week period. Participants who did not have an adequate response at Week 8 or had lost EASI50 response (< EASI50 at 2 consecutive visits at least 1 week apart) were eligible to enter the ruxolitinib 1.5% cream open-label escape arm. Efficacy was evaluated during the vehicle-controlled period, using the proportion of participants with EASI75 and IGA-TS (coprimary) and ITCH4 at Week 8 as well as ITCH4 at Day 7, Day 3, and Day 2 (key secondary) as endpoints.

Study visits during the vehicle-controlled extension, double-blind period and for the escape arm occurred every 4 weeks for up to 24 weeks. Participants' AD lesions were evaluated at each visit to determine if treatment should be continued (IGA score ≥ 1) or if the participant could (re)enter an observation/no treatment period (IGA score 0 [clear]). Between study visits, participants self-evaluated for recurrence of AD and treated skin areas with active lesions (not to exceed 20% BSA). Participants were to stop treatment application 3 days after lesions had cleared.

A safety follow-up visit was conducted 30 days after the Week 24/End of Treatment visit.

Study participants

Men and women aged 18 years or older, with moderate AD with a documented inadequate response, intolerance, or contraindication to TCSs and TCIs were enrolled in this study.

Main inclusion criteria

- Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria, with an AD duration of at least 2 years.
- Moderate AD severity according to: IGA score of 3, EASI score > 7, average daily Itch NRS score ≥4, AD involvement of 10 to 20% of BSA (excluding the scalp), DLQI score > 10.
- Documented history of inadequate response, intolerance, or contraindication to TCSs and TCIs, within 12 months before the screening visit. More specifically:
    - Inability of a given TCS or TCI to induce and maintain remission or to contain the AD severity at an acceptable level (comparable to IGA score of 0 or 1 of 'clear' or 'almost clear') despite treatment for 28 days or for the maximum duration recommended by the product information (PI), whichever is shorter (for TCSs) or despite treatment according to the PI (for TCIs). Documented systemic treatment for AD (eg, oral corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil) or phototherapy or photo(chemo)therapy within 12 months before the screening visit, could be considered as a surrogate for inadequate response to TCSs and TCIs.
    - Clinically relevant side effects, safety risks, or skin tolerability issues that outweigh the potential treatment benefits and are the reason why a topical treatment could not be restarted or continued. Documented history more than 12 months prior to the screening visit of clinically significant adverse reactions with use of TCSs and/or TCIs that in the opinion of the investigator outweigh the benefits of restarting treatment would also be considered as evidence of intolerance.
    - Contraindication: As defined in the PI.

Main exclusion criteria

- Atypical disease presentation: Unstable course of AD (spontaneously improving or rapidly deteriorating) as determined by the investigator in the 4 weeks prior to Day 1; Presence of AD lesions only on the hands or feet without prior history of involvement of other classic areas of involvement; other types of eczema within the 6 months prior to screening (except Seborrheic dermatitis on the scalp);
- Relevant comorbidities: Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome); chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before Day 1; active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chickenpox) within 1 week before Day 1; any concomitant skin disorder that may interfere with the evaluation of AD lesions or compromise participant safety; current or history of hepatitis B or C virus infection.
- Serious illness or conditions, such as: clinically significant or uncontrolled cardiovascular disease, including unstable angina, acute myocardial infarction, or stroke within 6 months before Day 1; New York Heart Association Class III or IV congestive heart failure; or arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mmHg); history of malignancy in the 5 years preceding Day 1, except for adequately treated, nonmetastatic, nonmelanoma skin cancer; current and/or history of arterial or venous thrombosis, including deep venous thrombosis and pulmonary embolism; current and/or

history of active tuberculosis or current and/or history of latent tuberculosis unless adequately treated; history of severe anemia, severe thrombocytopenia, or severe neutropenia.

- Any of the following clinical laboratory test results at screening:

  a. Hemoglobin < 10 g/dL.

  b. Liver function tests:

  – AST or ALT ≥ 2 × ULN.

  – Alkaline phosphatase > 1.5 × ULN.

  – Bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%) with the exception of Gilbert's disease.

  c. Estimated glomerular filtration rate < 30 mL/min/1.73 m2.

  d. Positive serology test results for HIV antibody.

  e. Any other clinically significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant.

- Previous treatment with biologics and other systemic treatments, topical AD treatments, artificial UV exposure, within predefined washout periods.
- History of treatment failure with any systemic or topical JAK inhibitor for AD or any other inflammatory condition.

Treatments

Experimental treatment

Ruxolitinib 1.5% cream or matching vehicle cream was applied as a thin film BID, with applications at least 8 hours apart in the morning and evening. Study cream was applied to all affected areas identified at baseline during the vehicle-controlled period and to active lesions only during the vehicle-controlled extension, double-blind period and the open-label escape arm.

If there were new areas to be treated, including expansion of existing areas or development of new areas, study cream was applied to these additional areas, up to a maximum total of 20% BSA. Once the lesions were clear (IGA score of 0), participants should continue to apply study cream for an additional 3 days to the areas of the body where lesions were last present before discontinuing treatment. Following clearance, if a lesion recurs, treatment should be resumed at the first sign of recurrence.

Study cream was provided in 60-gram tubes.

Treatment compliance

Participants were considered compliant with the treatment regimen if they applied at least 80% but no more than 120% of the prescribed number of applications. Drug accountability was assessed by documenting the quantities of study cream used between study visits (tube counts and weighing).

Concomitant treatments

Bland emollients were allowed. Emollients should not be used within 4 hours before and 2 hours after application of study cream. Short-term use of systemic corticosteroids was permitted to treat acute AEs (eg, asthma) during the extension period. Sedating antihistaminic drugs were allowed as a pre-

existing stable regimen. Nonsedating antihistamines were allowed without restriction. Topical anti-infectives or other topical treatments applied to active AD lesions should not have been used for at least 4 hours before and 2 hours after application of study cream.

Rescue treatment

Open-label treatment with ruxolitinib 1.5% BID was offered as rescue treatment. If prohibited treatments were needed for rescue, this was considered a protocol violation.

Objectives

To evaluate the efficacy, safety, and tolerability of ruxolitinib cream in adults with moderate AD who had an inadequate response to, were intolerant to, or were contraindicated to topical corticosteroids and topical calcineurin inhibitors.

Outcomes/endpoints

Objectives	Endpoints
Primary	
To establish the efficacy of ruxolitinib cream in participants with moderate atopic dermatitis who had an inadequate response to, or were intolerant to, or contraindicated to topical corticosteroids and topical calcineurin inhibitors.	• Proportion of participants with EASI75 from baseline at Week 8. (EASI75 is defined as achieving ≥ 75% improvement in EASI score.) • Proportion of participants with IGA-TS at Week 8. (IGA-TS is defined as achieving an IGA score of 0 or 1 with ≥ 2-grade improvement from baseline.)
Key Secondary	
To further assess the treatment effects of ruxolitinib cream in participants with moderate atopic dermatitis who had an inadequate response to, or were intolerant to, or contraindicated to topical corticosteroids and topical calcineurin inhibitors.	• Proportion of participants with ITCH4 from baseline to Week 8. (ITCH4 is defined as achieving ≥ 4-point improvement in Itch NRS score.) • Proportion of participants with ITCH4 from baseline to Day 7. • Proportion of participants with ITCH4 from baseline to Day 3. • Proportion of participants with ITCH4 from baseline to Day 2.
Secondary	
To evaluate the safety and tolerability of ruxolitinib cream in participants with moderate atopic dermatitis who had an inadequate response to, or were intolerant to, or contraindicated to topical corticosteroids and topical calcineurin inhibitors.	• The type, frequency, and severity of AEs as well as changes from baseline in vital signs and laboratory data for hematology and serum chemistry.
To further evaluate the efficacy of ruxolitinib cream in participants with moderate atopic dermatitis who had an inadequate response to, or were intolerant to, or contraindicated to topical corticosteroids and topical calcineurin inhibitors.	• Proportion of participants with EASI75 from baseline at each postbaseline visit except Week 8. • Proportion of participants with IGA-TS from baseline at each postbaseline visit except Week 8. • Proportion of participants with ITCH4 from baseline at each postbaseline visit except Week 8. • Time to achieve ITCH4 during the vehicle-controlled period. • Time to achieve ITCH2 during the vehicle-controlled period. (ITCH2 is defined as achieving ≥ 2-point improvement from baseline in Itch NRS score.) • Change from baseline (pre–study cream application) in current Itch NRS score at 5, 15, 30, 45, and 60 minutes and 2, 4, and 6 hours post-initial dose on Day 1. • Proportion of participants achieving at least a 2-point decrease from baseline in current Itch NRS score at 5, 15, 30, 45, and 60 minutes and 2, 4, and 6 hours post–initial dose on Day 1.

Objectives	Endpoints
Secondary (continued)	
To further evaluate the efficacy of ruxolitinib cream in participants with moderate atopic dermatitis who had an inadequate response to, or were intolerant to, or contraindicated to topical corticosteroids and topical calcineurin inhibitors (continued).	• Proportion of participants achieving at least a 4-point decrease from baseline in current Itch NRS score at 5, 15, 30, 45, and 60 minutes and 2, 4, and 6 hours post–initial dose on Day 1. • Proportion of participants with EASI50 from baseline at each postbaseline visit. (EASI50 is defined as achieving ≥ 50% improvement in EASI score.) • Proportion of participants with EASI90 from baseline at each postbaseline visit. (EASI90 is defined as achieving ≥ 90% improvement in EASI score.) • Proportion of participants achieving both EASI75 from baseline and IGA-TS at each postbaseline visit. • Change from baseline at each postbaseline visit for the following: – atopic dermatitis-affected %BSA – EASI score – SCORAD score – Itch NRS score – Skin Pain NRS score • Time to open-label escape arm (defined as not achieving 50% improvement in EASI score from baseline at 2 consecutive visits at least 1 week apart) • Proportion of participants concurrently meeting all of the following criteria at each postbaseline visit: IGA score ≥ 3, EASI score ≥ 16, Itch NRS score ≥ 4, BSA ≥ 10%, and DLQI score > 10. • Time to concurrently meeting all of the following criteria: IGA score ≥ 3, EASI score ≥ 16, Itch NRS score ≥ 4, BSA ≥ 10%, and DLQI score > 10. • Proportion of participants who experience a relapse after study treatment discontinuation. (proportion of participants among EASI75 responders who are on study treatment at Week 24 who meet relapse criteria [loss of EASI50 from baseline] at the safety follow-up visit) • Time to first retreatment during the vehicle-controlled extension period. • Proportion of time off study treatment due to lesion clearance during the vehicle-controlled extension period by visit. • Proportion of time on study treatment during the vehicle-controlled extension period by visit.

Objectives	Endpoints
Secondary (continued)	
To evaluate quality of life and other PROs in participants with moderate atopic dermatitis who had an inadequate response to, or were intolerant to, or contraindicated to topical corticosteroids and topical calcineurin inhibitors.	• Proportion of participants who achieve ≥ 4-point improvement in DLQI from baseline at each postbaseline visit. • Change from baseline in the following scores at each postbaseline visit: – DLQI – POEM – EQ-5D-5L – HADS – PROMIS Short Form – Sleep-Related Impairment (8a – 7-day recall) – PROMIS Short Form – Sleep Disturbance (8b – 7-day recall) • Change from baseline score at Weeks 8 and 24 in WPAI-AD.
Exploratory	
To characterize the PK of ruxolitinib cream in participants with moderate atopic dermatitis who had an inadequate response to, or were intolerant to, or contraindicated to topical corticosteroids and topical calcineurin inhibitors.	• Trough and/or preapplication plasma concentrations of ruxolitinib at Weeks 2, 8, and 24.
To evaluate biomarkers in the blood of participants with moderate atopic dermatitis who had an inadequate response to, or were intolerant to, or contraindicated to topical corticosteroids and topical calcineurin inhibitors.	• Expression of select biomarkers in peripheral blood at baseline and Weeks 2 and 8.
To characterize the efficacy of ruxolitinib cream in participants with moderate atopic dermatitis and intertriginous region involvement who had an inadequate response to, or were intolerant to, or contraindicated to topical corticosteroids and topical calcineurin inhibitors	• Change from baseline in number of intertriginous regions with active atopic dermatitis involvement at each postbaseline visit

Primary Estimand

The proportion of participants within each treatment group who achieve the coprimary endpoints, assuming participants with missing Week 8 assessments due to any reasons are nonresponders, was the primary estimand, also see Table 5 below.

Table 5. Primary Estimand

Estimand Attribute	**Definition**		
Treatment effect	Ruxolitinib 1.5% cream BID vs vehicle cream BID		
Population	Participants with moderate AD who had an inadequate response to, or are intolerant to, or contraindicated to TCSs and TCIs (as defined by study inclusion/exclusion criteria)		
Variable	Coprimary endpoints: - The binary response status of EASI75 from baseline at Week 8. - The binary response status of IGA-TS at Week 8.		
Intercurrent events	**Events**	**Strategy**	**Rationale (if needed)**

	Treatment discontinuation due to any reason	Composite Strategy	Participants who discontinue treatment due to any reason prior to Week 8 will be considered as treatment failures (ie, nonresponders) after the intercurrent event. Therefore, composite strategy is used for this type of intercurrent event.
Population-level summary	Stratum-adjusted response proportions difference between–treatment groups		

Outcomes

Eczema Area and Severity Index (EASI)

AD signs were assessed using the valid EASI scoring system, that grades the physical signs of AD ranging from 0 to 72 (Hanifin et al 2022). The EASI scoring system examines 4 regions of the body (head/neck, upper limbs, trunk, and lower limbs) and weights them. Each of the 4 body regions is assessed separately for erythema (E), induration/papulation/edema (I), excoriations (Ex), and lichenification (L) for an average degree of severity of each sign in each region.

The severity strata for the EASI are as follows: 0 = clear; 0.1 to 1.0 = almost clear; 1.1 to 7.0 = mild; 7.1 to 21.0 = moderate; 21.1 to 50.0 = severe; and 50.1 to 72.0 = very severe.

EASI75 is defined as reaching a ≥75% improvement in EASI score. EASI50 and EASI90 are calculated analogously.

Investigator's Global Assessment (IGA)

IGA is an overall eczema severity rating on a 0 to 4 scale (Table 6). The IGA-TS is defined as an IGA score of 0 or 1 with a ≥ 2-grade improvement from baseline (participants must have an IGA score of 3 at the screening and baseline visits to enrol in the study).

Table 6. Investigator's Global Assessment of AD severity.

Grade	Severity	Status
0	Clear	No erythema or induration/papulation, no oozing/crusting; there may be minor residual discoloration
1	Almost clear	There may be trace faint pink erythema, with almost no induration/papulation, and no oozing/crusting
2	Mild	There may be faint pink erythema, with mild induration/papulation and no oozing/crusting
3	Moderate	There may be pink-red erythema with moderate induration/papulation and there may be some oozing/crusting
4	Severe	There may be deep or bright red erythema with severe induration/papulation and with oozing/crusting

Body Surface Area (BSA)

Total %BSA affected by AD was estimated at each visit, approximated to the nearest 0.1% using the handprint (Palmar) method as a guide.

Itch Numeric Rating Scale (NRS)

The Itch NRS is a daily participant-reported measure of the worst level of itch intensity (Silverberg et al 2021). Participants were asked to rate the itch severity of their AD by selecting a number from 0 (no itch) to 10 (worst itch imaginable) that best describes their worst level of itching in the past 24 hours (vehicle-controlled period) or past 7 days (extension period). On the morning of Day 1, randomised participants were asked to evaluate the current intensity of their itch directly before initial study cream application and 5, 15, 30, 45, and 60 minutes as well as 2, 4, and 6 hours post–study cream application.

Skin Pain Numeric Rating Scale

The Skin Pain NRS is a daily participant-reported measure (24-hour or 7-day recall) of the worst level of pain intensity from 0 (no pain) to 10 (worst pain imaginable); (Silverberg et al 2021).

SCORing AD

The SCORAD is a tool to assess the extent and severity (i.e., intensity) of eczema. To determine extent, the rule of 9 or handprint method is used to calculate the eczema affected area (A) as a percentage of the whole body. Scores are added up to give a possible maximum of 100%. To determine intensity, a representative area of eczema is selected. The intensity of redness, swelling, oozing/crusting, scratch marks, skin thickening (lichenification), dryness (this is assessed in an area where there is no inflammation) is assessed individually as: none (0); mild (1); moderate (2); severe (3). Intensity scores are added together to give "B" (maximum score of 18). Subjective symptoms of itch and sleeplessness are scored by the participant using a visual analog scale where "0" is no itch (or no sleeplessness) and "10" is the worst imaginable itch (or sleeplessness). These scores are added to give "C" (maximum score of 20).

Total score gives approximate weights of 60% to intensity and 20% each to extent and subjective signs for the participant and were calculated as: A/5 + 7B/2 + C.

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-question validated questionnaire to assess how much the skin problem has affected the participant over the previous 7 days (Finlay and Khan 1994). The questionnaire has 6 headings as follows: Symptoms and feelings (Questions 1 and 2); Daily activities (Questions 3 and 4); Leisure (Questions 5 and 6); Work and school (Question 7); Personal relations (Questions 8 and 9); Treatment (Question 10).

Patient-Oriented Eczema Measure (POEM)

The POEM is a 7-question quality-of-life assessment used for monitoring atopic eczema severity, focusing on the illness as experienced by the participant. The questionnaire asks how many days the participant has been bothered by various aspects of their skin condition during the past week. The response options and corresponding scoring questionnaires are no days (0), 1 to 2 days (1), 3 to 4 days (2), 5 to 6 days (3), and every day (4), with a range in score of 0 to 28 (Charman et al 2004).

PROMIS Sleep Questionnaires

The PROMIS Short Form – Sleep-Related Impairment (8a) questionnaire focuses on self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness (Buysse et al 2010). The questionnaire has 8 questions with a 5-point scale with a range in score from

8 to 40, with higher scores indicating greater severity of sleep-related impairment. Each item asks the participant to rate the severity of their sleep impairment, with a recall period of the past 7 days.

The PROMIS Short Form – Sleep Disturbance (8b) questionnaire is self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. The questionnaire is a 5-point scale with a range in score from 8 to 40, with higher scores indicating greater severity of sleep disturbance. Each item asks the participant to rate the severity of the participant's sleep disturbance. The recall period was the past 7 days.

Sample size

Approximately 225 participants were planned to be randomised 2:1 to ruxolitinib 1.5% cream or vehicle cream, stratified by baseline EASI score (< 16 or ≥ 16) and geographic region (ROW or Europe).

The sample size was calculated to provide sufficient power to detect a difference between the treatment groups in the coprimary and key secondary endpoints. The assumptions and powers for different endpoints are provided in Table 7. The assumed response rates were derived from the overall and subgroup analyses (population: baseline scores of Itch NRS ≥ 4, EASI > 7, post-TCS and -TCI, and IGA = 3) in 2 Phase 3 AD studies, INCB 18424-303 and INCB 18424-304. Fisher exact test was used to provide a conservative evaluation of statistical power. Using a 2-sided α of 0.05, the sample size would have > 95% power to detect a difference in the coprimary endpoints, EASI75 and IGA-TS response rates between the treatment groups, and > 95% power for all key secondary endpoints.

In addition to providing sufficient power for efficacy variables, the sample size provided an adequate database for safety evaluations.

Table 7. Powering for Coprimary and Key Secondary Endpoints

Variable	Response Rates in Ruxolitinib 1.5% BID	Response Rates in Vehicle	Power: Ruxolitinib vs Vehicle
EASI75	70%	15%	> 95%
IGA-TS	60%	10%	> 95%
ITCH4 at Week 8	50%	15%	> 95%
ITCH4 on Day 7	40%	12%	> 95%
ITCH4 on Day 3	35%	10%	> 95%
ITCH4 on Day 2	20%	3%	> 95%

Randomisation

All participants were centrally assigned to study treatment using an IRT system. The system assigned study treatment in a 2:1 ratio, stratified by baseline EASI score (< 16 or ≥ 16) and geographic region (ROW vs Europe). All eligible participants with an adequate response, defined as achieving at least EASI50 from baseline, continued into the 16-week VCE period with the same treatment regimen. Participants who did not achieve EASI50 at Week 8 or for whom an EASI50 response from baseline is lost during the VCE period were eligible to enter the ruxolitinib 1.5% cream open-label escape arm.

Blinding (masking)

Participants and investigators and the sponsor were blinded to each participant's initial treatment assignment throughout the study; however, participants who were eligible for the escape arm received open-label ruxolitinib 1.5% cream and the sponsor was unblinded after the primary database lock.

Matching vehicle cream contains the same excipients as the active drug product; the only difference is the replacement of the active component. Hence, the use of vehicle cream the blind for participants.

Statistical methods

Analysis Populations

The populations for analysis are provided in Table 8.

Table 8. Populations for Analysis

Population	Description
ITT	The ITT population included all randomised participants. Treatment groups for this population were defined according to the treatment assigned at randomisation.
PP	The PP population included randomised participants who were considered to be sufficiently compliant with the Protocol; participants with important Protocol deviations, were excluded from the PP Population.
VCE primary	The VCE primary population included all participants who entered the VCE period and applied study cream at least once during the VCE period. Participants were analysed according to the treatment assigned at randomisation. For participants who entered the escape arm, only information prior to entry to the escape arm was to be presented.
VCE escape	The VCE escape population included all participants in the VCE primary population who moved to the ruxolitinib 1.5% cream BID open-label escape arm.
Safety	The safety population included all participants who applied study cream at least once. Treatment groups for this population was determined according to the actual treatment the participant applied on Day 1.
PK-evaluable	The PK-evaluable population included participants who applied ruxolitinib 1.5% cream at least once and provided at least 1 postbaseline blood sample for PK analysis.

Multiplicity

An overall 2-sided type 1 error of 0.05 was used for the primary and key secondary efficacy analyses. The coprimary null hypotheses H1 and H2 were tested:

- Null hypothesis H1: $p1 = p2$, where $p1$ and $p2$ are the proportion of participants achieving EASI75 at Week 8 in the ruxolitinib 1.5% cream and vehicle cream group.
- Null hypothesis H2: $p3 = p4$, where $p3$ and $p4$ are the proportion of participants achieving IGA-TS at W8 in the ruxolitinib 1.5% cream and vehicle cream group.

The key secondary endpoints were tested in a fixed sequence as follows if the null hypotheses H1 and H2 for the coprimary endpoints were both rejected:

- Proportion of participants with ITCH4 from baseline at Week 8
- Proportion of participants with ITCH4 from baseline on Day 7
- Proportion of participants with ITCH4 from baseline on Day 3
- Proportion of participants with ITCH4 from baseline on Day 2

Coprimary analysis

The primary analysis was based on the ITT population. The primary alternative hypothesis (superiority of ruxolitinib 1.5% cream BID compared with vehicle cream BID) was tested using a CMH test stratified by baseline EASI score and geographic region. The p-values and overall odds ratio with 95% CI between the ruxolitinib 1.5% cream BID and vehicle cream BID treatment groups were provided. The p-values were compared with the 2-sided α level of 0.05. A summary of EASI75 and IGA-TS rates was reported for each treatment group. Stratum-adjusted rate differences (ruxolitinib 1.5% cream BID vs vehicle cream BID) on EASI75 and IGA-TS and the 95% CI were computed using Mantel-Haenszel weights.

All nonresponders during the VC period, as well as all participants missing the Week 8 assessment and who discontinued study treatment at any time before Week 8, or discontinued from the study for any reason, were defined as nonresponders for the nonresponder imputation analysis in both coprimary endpoints.

The coprimary endpoints were also examined for the PP population using the same model as the primary analysis.

Sensitivity analysis was performed using a longitudinal logistic regression with repeated measures and using multiple imputations.

A longitudinal logistic regression with repeated measures was applied in both of the coprimary endpoints. To adjust for the dependence underlying the hierarchical multilevel data structure (visit, participant, and site), visits were nested within participants, which were further nested within sites. The binary response (IGA-TS or EASI75) of each participant at Week 2, Week 4, and Week 8 was included as the dependent variable. Treatment, the randomisation stratification factors, visit, and treatment-by-visit interaction were included as fixed effects. Site level intercept and participant nested in site level intercept were included as random effects. The within-participant and within-site errors were modeled by an unstructured variance-covariance matrix. The Kenward-Roger approximation was used to estimate denominator degrees of freedom for this model.

Multiple imputation was used as an alternative method to handle missing data. A full conditional specification method (van Buuren 2007) that assumed the existence of a joint distribution for all variables was used to impute the IGA or EASI score. A regression model including treatment group, stratification factors and baseline and scheduled postbaseline scores up to Week 8 were specified for the fully conditional specification method. The imputation was repeated a number of times to generate corresponding complete datasets in order to reflect the uncertainty around the true values. The coprimary endpoints binary response were derived for each of the imputed datasets. Regardless of MI imputed values, subjects with a missing Week 8 IGA and EASI assessments after discontinuation from treatment due to lack of efficacy or adverse event were counted as nonresponders. The CMH test was applied to each of the imputed datasets. The results were then combined for the inference using Rubin's rule for each of the coprimary endpoints.

Secondary endpoint analysis

Secondary efficacy analyses were conducted in the ITT population.

The baseline Itch NRS score for by-visit summaries was determined by averaging the 7 daily NRS scores directly before Day 1 (Day –7 to Day –1). The by-visit Itch NRS score for postbaseline visits was determined by averaging the 7 daily NRS scores directly before the visit day. If 4 or more daily scores were missing (out of the 7), the Itch NRS score at the visit was set to missing. The key secondary endpoint of Itch NRS score responses at Week 8 was analysed the same way as the primary estimand.

For the key secondary endpoints of Itch NRS score responses on Day 7, Day 3, and Day 2, all participants who were missing Day 7, Day 3, and/or Day 2 daily Itch NRS scores were imputed using multiple imputations by fully conditional specification method. The variables to be included in the imputation regression model were treatment group, stratification factors, baseline itch score, and postbaseline daily itch score on Day 1 to Day 7. After the missing values were imputed, the binary variable for the ≥ 4-point improvement in Itch NRS score on Day 7, Day 3, and Day 2 was derived. Each imputed dataset was analysed the same way as the primary estimand, and then the results were combined for the inference.

Table 9 summarizes the analytical strategies that were conducted in the key secondary endpoints.

Table 9. Analytical Strategies for the Key Secondary Endpoints

Key Secondary Endpoints	Analysis Strategy for Missing Data	Missing Data Imputation Method
ITCH4 at Week 8	Composite: Set to nonresponder	Nonresponder imputation
ITCH4 on Day 7, Day 3, and Day 2	Hypothetical: Set to missing	Multiple imputation

For the time to achieve ITCH2 and ITCH4 from baseline, a log-rank test stratified by baseline EASI score and geographic region was used for between–treatment group comparisons. The hazard ratio and its 95% CI was estimated based on the stratified Cox regression model using Efron's method accounting for ties.

All other secondary efficacy variables were summarised using descriptive statistics.

Subgroup Analyses for the Coprimary Endpoints

Subgroup analysis were performed for the coprimary endpoints based on the following participant demographics and baseline disease characteristics variables for those participants whose data were available: baseline EASI score (≥ 16, < 16), age (18 to < 65 years, >= 65 years), sex (male, female), race, geographic region (Europe vs ROW), prior systemic or phototherapy (yes or no), and season the participant was enrolled.

Results

Participant flow

The participant disposition during the double-blind, vehicle-controlled period is summarised in the below table (Table 10).

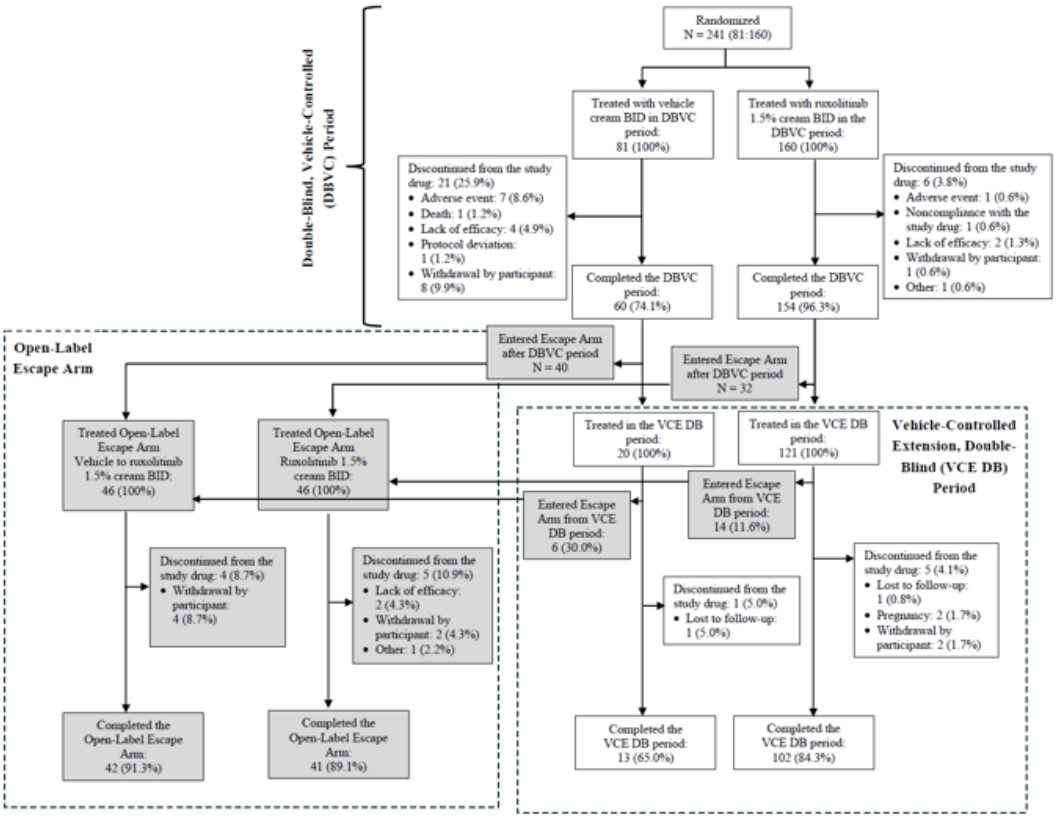
Table 10. Participant Disposition During the Double-Blind, Vehicle-Controlled Period (ITT Population)

Number (%) of Participants	Vehicle Cream BID (N = 81)	Ruxolitinib 1.5% Cream BID (N = 160)	Total (N = 241)
Randomized	81 (100.0)	160 (100.0)	241 (100.0)
Treated during the vehicle-controlled period	81 (100.0)	160 (100.0)	241 (100.0)
Completed treatment during the vehicle-controlled period	60 (74.1)	154 (96.3)	214 (88.8)
Discontinued treatment during the vehicle-controlled period	21 (25.9)	6 (3.8)	27 (11.2)
AE	7 (8.6)	1 (0.6)	8 (3.3)
Death	1 (1.2)	0 (0.0)	1 (0.4)
Lack of efficacy	4 (4.9)	2 (1.3)	6 (2.5)
Protocol deviation	1 (1.2)	0 (0.0)	1 (0.4)
Noncompliance with study drug	0 (0.0)	1 (0.6)	1 (0.4)
Withdrawal by participant	8 (9.9)	1 (0.6)	9 (3.7)
Other	0 (0.0)	1 (0.6)	1 (0.4)
Withdrew from the study during the vehicle-controlled period	21 (25.9)	6 (3.8)	27 (11.2)
AE	7 (8.6)	1 (0.6)	8 (3.3)
Death	1 (1.2)	0 (0.0)	1 (0.4)
Lack of efficacy	4 (4.9)	2 (1.3)	6 (2.5)
Protocol deviation	1 (1.2)	0 (0.0)	1 (0.4)
Withdrawal by participant	8 (9.9)	1 (0.6)	9 (3.7)
Other	0 (0.0)	2 (1.3)	2 (0.8)

Of the 214 participants who completed treatment in the double-blind, vehicle-controlled period, 72 participants entered the open-label ruxolitinib 1.5% escape arm and 142 participants entered the vehicle-controlled extension, double-blind period (Figure 9). Because 1 patient did not apply study cream at all, due to lesion clearance, the vehicle-controlled **extension period** is considered to include 141 patients, 121 on ruxolitinib cream (Figure 9). Of these patients, 14 (12%) had entered the escape arm and 5 (4.1%) had discontinued from study treatment during the vehicle-controlled extension, double-blind period. The most common reason for discontinuation was pregnancy, which occurred in 2 participants in the ruxolitinib group.

At time of study completion (17/10/2025), 92 participants have been treated in the open-label ruxolitinib 1.5% cream **escape arm**, n=46 were from the vehicle cream treatment group and n=46 were from the ruxolitinib cream group with n=32 entering at week 8. The majority of participants who switched to the open-label ruxolitinib 1.5% escape arm did so at Week 8. Of the participants who entered the open-label ruxolitinib 1.5% cream escape arm, 83 (90%) completed treatment and 9 (9.8%) discontinued from study treatment. The most common reasons for discontinuation were lack of efficacy (n=2) and withdrawal by participant (n=6).

Figure 9. Participant Flow in Study 326



Note 1: One participant in the ruxolitinib 1.5% cream BID treatment group entered the VCE DB period and was not treated through Week 24 due to lesion clearance.
Note 2: Eight participants (3 at Week 8 and 5 after Week 8) in the vehicle cream BID treatment group and 18 participants (12 at Week 8 and 6 after Week 8) in the ruxolitinib 1.5% cream BID treatment group were moved to the escape arm without meeting the criterion for entry (ie, participants had ≥ EASI50 at Week 8 and/or maintained ≥ EASI50 during the VCE DB period; refer to INCB 18424-326 CSR Listing 2.6.15).

Recruitment

A total of 241 participants were enrolled at 75 study sites: 6 in Australia, 45 in Europe, and 24 in North America.

Conduct of the study

There were no changes in the planned analyses for the study. However, the endpoints in the SAP were rephrased from the Protocol to align with estimand guidance and the definitions of the VCE Primary Population and the VCE Extension Population were modified to more accurately reflect the analysis populations.

The majority of participants (93%) had at least 1 Protocol deviation. Protocol deviations were most frequently minor deviations (88%) related to efficacy, subject IP compliance, visit schedule, and study procedures. Critical deviations and major deviations occurred in 12% and 47% of participants.

A total of 47 participants (26 and 21 participants in the vehicle cream and ruxolitinib 1.5% cream treatment groups) had deviations that affected the primary endpoint and were excluded from the PP Population. Reasons for exclusion were as follows (some participants were excluded for more than 1 reason): Missing data for the coprimary endpoints at Week 8 (27 participants); Overall application compliance < 80% during the double-blind, vehicle-controlled period (5 participants); IGA assessment outside the 14-day window for the Week 8 (11 participants); Deviation in eligibility criteria (11 participants) with 8 participants with deviations in Inclusion Criterion 9 (prior topical corticosteroid/ topical calcineurin inhibitor use), 1 participant with a deviation in Inclusion Criterion 4 (requirement of

IGA score of 3), 1 participant with a deviation in Exclusion Criterion 4d (positive HIV serology), 1 participant with a deviation in Exclusion Criterion 6 (history of treatment failure with JAK inhibitorsDuring the vehicle-controlled extension, double-blind period, critical and major protocol deviations occurred in 7.8% and 24% of participants, respectively. Critical protocol deviations were most commonly related to efficacy (7.8%), and major protocol deviations were most commonly related to PK/PD (12%). The most common minor Protocol deviations were visit schedule and study procedures.

Baseline data

Demographics

The mean (SD) age of participants in the study was 39 (16) years, and the majority (92%) of participants were between 18 to 65 years of age. Most participants were female (54%) and Caucasian (81%). Asian and Black/African American participants comprised 10% and 5.8% of the study population. Most (68%) patients were included in Europe. The mean (SD) BMI was 27 (6.4).

Disease characteristics

Participants on average had longstanding AD with a mean (SD) time since diagnosis of 20 (15) years before study baseline. Baseline disease characteristics reflected the main inclusion criteria (Table 11). All (but one) participants had IGA scores of 3, with AD affecting 10% to 20% BSA with a mean (SD) of 15% (3.0%). EASI scores were ranging from 7.1 to 40 with a mean (SD) of 13 (4.1), the majority of participants (80%) had baseline EASI scores <16. Itch NRS scores were ranging from 4 to 10 with a mean (SD) of 7.4 (1.5).

Previous treatment

In line with the inclusion criteria, all (see protocol deviations for exceptions) participants had a documented history of inadequate response, intolerance, or contraindication to TCSs and TCIs within 12 months of screening, or met the surrogate criteria of use of systemic drugs or phototherapy for AD within 12 months (Table 12). If more than 1 treatment was used in the previous 12 months, the most recent treatment prior to screening was considered.

The most frequently reported treatments in the previous 12 months were TCSs (96%) and TCIs (81%). Systemic treatments had been used in the previous 12 months by 30% and phototherapy had been used by 8.7% in the last 12 months.

Concomitant AD medications

The only concomitant medications for AD that were allowed in the study were bland emollients, nonsedating, over-the-counter antihistaminic drugs, and sedating antihistaminic drugs; rescue medications were not allowed (also see Exclusion criteria). During the double-blind, vehicle-controlled period, concomitant medications for AD were taken by 23.5% in the vehicle group and by 29% in the ruxolitinib cream group. This included: Emollients (14% *versus* 14%), antihistaminic drugs (11% *versus* 9.4%), corticosteroids of several strengths (6.2% *versus* 1.2%), and glucocorticoids (1.2% *versus* 0) in the vehicle versus ruxolitinib cream groups.

In the vehicle-controlled extension, double-blind period, concomitant medications for AD were taken by 20% of participants in the vehicle group and by 35.5% of the ruxolitinib cream group. This included:

Emollients (20%), antihistaminic drugs (10%), and corticosteroids (1.6%). In the open-label ruxolitinib 1.5% cream escape arm, concomitant medications for AD were taken by 23 of participants, including emollients (8.7%), antihistaminic drugs (7.6%), potent corticosteroids (2.2%), and tacrolimus (3.3%).

Table 11. Baseline Disease Characteristics (ITT Population)

Variable	Vehicle Cream BID (N = 81)	Ruxolitinib 1.5% Cream BID (N = 160)	Total (N = 241)
Years since initial diagnosis of atopic dermatitis			
n	81	160	241
Mean (STD)	20.08 (14.182)	20.39 (14.776)	20.29 (14.550)
Median (min, max)	18.54 (2.5, 60.7)	19.08 (2.2, 58.1)	18.97 (2.2, 60.7)
Total %BSA involvement in current atopic dermatitis episode			
n	81	160	241
Mean (STD)	15.43 (2.947)	14.98 (3.068)	15.13 (3.029)
Median (min, max)	15.90 (10.0, 20.0)	15.00 (10.0, 20.0)	15.00 (10.0, 20.0)
EASI score, n (%)			
n	81	160	241
Mean (STD)	12.84 (3.634)	12.50 (4.280)	12.62 (4.070)
Median (min, max)	12.20 (7.1, 26.8)	11.80 (7.1, 40.0)	11.90 (7.1, 40.0)
EASI score category, n (%)			
< 16	64 (79.0)	130 (81.3)	194 (80.5)
≥ 16	17 (21.0)	30 (18.8)	47 (19.5)
Facial and/or neck involvement during past episodes, n (%)			
Yes	58 (71.6)	117 (73.1)	175 (72.6)
No	23 (28.4)	43 (26.9)	66 (27.4)
Intertriginous involvement, n (%)			
Yes	12 (14.8)	22 (13.8)	34 (14.1)
No	69 (85.2)	138 (86.3)	207 (85.9)
Itch NRS score for by-visit summaries[a]			
n	81	160	241
Mean (STD)	7.39 (1.548)	7.45 (1.535)	7.43 (1.537)
Median (min, max)	7.57 (4.0, 10.0)	7.57 (4.0, 10.0)	7.57 (4.0, 10.0)
Itch NRS score for daily Itch summaries[b]			
n	81	160	241
Mean (STD)	7.3 (1.68)	7.6 (1.60)	7.5 (1.63)
Median (min, max)	7.0 (4, 10)	8.0 (4, 10)	7.0 (4, 10)
History of asthma, n (%)			
Yes	23 (28.4)	44 (27.5)	67 (27.8)
No	58 (71.6)	115 (71.9)	173 (71.8)
Missing	0 (0.0)	1 (0.6)	1 (0.4)
History of allergies (food, environmental), n (%)			
Yes	43 (53.1)	87 (54.4)	130 (53.9)
No	38 (46.9)	73 (45.6)	111 (46.1)
History of contact dermatitis, n (%)			
Yes	7 (8.6)	11 (6.9)	18 (7.5)
No	74 (91.4)	148 (92.5)	222 (92.1)
Missing	0	1 (0.6)	1 (0.4)
Common complications of atopic dermatitis, n (%)			
Skin infections requiring antibiotic treatment	6 (7.4)	7 (4.4)	13 (5.4)
Eczema herpeticum	3 (3.7)	1 (0.6)	4 (1.7)
None/NA	73 (90.1)	147 (91.9)	220 (91.3)

Note 1: EASI score was derived from the EASI eCRF data.

[a] Itch and Pain NRS baseline score was calculated for those participants who entered scores for at least 4 days during Day −7 to Day −1.

[b] Baseline for daily itch/Skin Pain NRS score was defined as the last available itch/Skin Pain NRS score during the week prior to Day 1 (Day −7 to Day −1).

Table 12. Recent History With TCS and TCI for the Treatment of AD (ITT Population)

Variable	Vehicle Cream BID (N = 81)	Ruxolitinib 1.5% Cream BID (N = 160)	Total (N = 241)
Recent history with topical corticosteroids			
Inadequate response to topical corticosteroids, n (%)			
Yes	73 (90.1)	141 (88.1)	214 (88.8)
No[a]	8 (9.9)	19 (11.9)	27 (11.2)
Prior systemic therapy over the last 12 months, n (%)			
Yes	4 (4.9)	16 (10.0)	20 (8.3)
No	4 (4.9)	3 (1.9)	7 (2.9)
Prior phototherapy over the last 12 months, n (%)			
Yes	1 (1.2)	6 (3.8)	7 (2.9)
No	7 (8.6)	13 (8.1)	20 (8.3)
Intolerance to topical corticosteroids, n (%)			
Yes	3 (3.7)	4 (2.5)	7 (2.9)
No	78 (96.3)	156 (97.5)	234 (97.1)
Contraindication to topical corticosteroids, n (%)			
Yes	1 (1.2)	0 (0.0)	1 (0.4)
No	80 (98.8)	160 (100.0)	240 (99.6)
Recent history with topical calcineurin inhibitors			
Inadequate response to topical calcineurin inhibitors, n (%)			
Yes	61 (75.3)	98 (61.3)	159 (66.0)
No[b]	19 (23.5)	57 (35.6)	76 (31.5)
Prior systemic therapy over the last 12 months, n (%)			
Yes	10 (12.3)	36 (22.5)	46 (19.1)
No	9 (11.1)	21 (13.1)	30 (12.4)
Prior phototherapy over the last 12 months, n (%)			
Yes	4 (4.9)	12 (7.5)	16 (6.6)
No	15 (18.5)	45 (28.1)	60 (24.9)
Missing	1 (1.2)	5 (3.1)	6 (2.5)
Intolerance to topical calcineurin inhibitors, n (%)			
Yes	7 (8.6)	23 (14.4)	30 (12.4)
No	73 (90.1)	131 (81.9)	204 (84.6)
Missing	1 (1.2)	6 (3.8)	7 (2.9)
Contraindication to topical calcineurin inhibitors, n (%)			
Yes	0 (0.0)	0 (0.0)	0 (0.0)
No	80 (98.8)	155 (96.9)	235 (97.5)
Missing	1 (1.2)	5 (3.1)	6 (2.5)

Note: The prior atopic dermatitis therapy status presented in this table represents the treatment used most recently for atopic dermatitis prior to enrollment and in accordance with INCB 18424-326 study Inclusion Criterion 9.

[a] Participants who did not have a recent documented history of inadequate response to topical corticosteroids but who had recent prior history of systemic therapy and/or phototherapy were considered to have inadequate response to topical corticosteroids.

[b] Participants who did not have a recent documented history of inadequate response to topical calcineurin inhibitors but who had recent prior history of systemic therapy and/or phototherapy were considered to have inadequate response to topical calcineurin inhibitors.

Numbers analysed

The analysis populations are summarised in the below table (Table 13).

Table 13. Analysis populations

Analysis Population, n (%)	Vehicle Cream BID (N = 81)	Ruxolitinib 1.5% Cream BID (N = 160)	Total (N = 241)
ITT Population	81 (100.0)	160 (100.0)	241 (100.0)
PP Population	55 (67.9)	139 (86.9)	194 (80.5)
VCE Primary Population	20 (24.7)	121 (75.6)	141 (58.5)
VCE Escape Population	46 (56.8)	46 (28.8)	92 (38.2)
VCE Re-Treatment Evaluable Population	20 (24.7)	122 (76.3)	142 (58.9)
Safety Population	81 (100.0)	160 (100.0)	241 (100.0)

Outcomes and estimation

Primary endpoints

The coprimary endpoints were the binary response status of EASI75 from baseline and the binary response status of IGA-TS at Week 8. Both endpoints were met.

The proportion of participants with **EASI75 at Week 8** was statistically significantly higher ($p < 0.0001$) in the ruxolitinib 1.5% cream treatment group (70%) compared with the vehicle cream (19%) group (Table 14). The proportion of participants with **IGA-TS at Week 8** was also statistically significantly higher ($p < 0.0001$) in the ruxolitinib 1.5% cream treatment group (61%) compared with the vehicle cream (13%) group (Table 15). For both co-primary endpoints, sensitivity analyses to evaluate the impact of missing data (longitudinal logistic regression and multiple imputation) as well as the analysis in the PP population confirmed these results.

Table 14. Proportions of Participants Achieving EASI75 at Week 8 (ITT Population)

	Vehicle Cream BID (N = 81)	Ruxolitinib 1.5% Cream BID (N = 160)
Nonresponder imputation		
Yes, n (%)	15 (18.5)	112 (70.0)
SE	4.32	3.62
(95% CI)	(10.8, 28.7)	(62.3, 77.0)
No, n (%)	66 (81.5)	48 (30.0)
Nonresponse	45 (55.6)	42 (26.3)
Missing at the visit	21 (25.9)	6 (3.8)
Active treatment vs vehicle		
Stratum-adjusted difference in response rate (95% CI)	—	51.4 (40.48, 62.24)
Overall odds ratio (95% CI)	—	11.26 (5.692, 22.260)
p-value	—	< 0.0001
Longitudinal logistic		
Estimated EASI75 response rate (SE), %	24.5 (8.53)	82.8 (4.80)
Active treatment vs vehicle		
Difference in response rate	—	58.3
Odds ratio (95% CI)	—	14.80 (5.545, 39.504)
p-value	—	< 0.0001
Multiple imputation		
Estimated EASI75 response rate (SE), %	22.5 (4.86)	71.6 (3.58)
Active treatment vs vehicle		
Pooled stratum-adjusted difference in response rate (95% CI)	—	48.9 (37.30, 60.58)
Pooled overall odds ratio (95% CI)	—	9.88 (4.972, 19.647)
p-value	—	< 0.0001

Note 1: Binomial CI was calculated using normal approximation method.
Note 2: Nonresponder imputation: missing postbaseline values were imputed as nonresponders at Week 8.
Note 3: Overall odds ratio and p-values were calculated by CMH test stratified by baseline EASI score and geographic region.
Note 4: Stratum-adjusted rate differences and 95% CI were computed using Mantel Haenszel weights.

Table 15. Proportions of Participants Achieving IGA-TS at Week 8 (ITT Population)

	Vehicle Cream BID (N = 81)	Ruxolitinib 1.5% Cream BID (N = 160)
Nonresponder imputation		
Yes, n (%)	11 (13.6)	98 (61.3)
SE	3.81	3.85
(95% CI)	(7.0, 23.0)	(53.2, 68.8)
No, n (%)	70 (86.4)	62 (38.8)
Nonresponse	49 (60.5)	56 (35.0)
Missing at the visit	21 (25.9)	6 (3.8)
Active treatment vs vehicle		
Stratum-adjusted difference in response rate (95% CI)	—	47.6 (36.98, 58.20)
Overall odds ratio (95% CI)	—	10.14 (4.904, 20.975)
p-value	—	< 0.0001
Longitudinal logistic		
Estimated IGA-TS response rate (SE), %	12.7 (5.52)	66.7 (7.17)
Active treatment vs vehicle		
Difference in response rate	—	53.9
Odds ratio (95% CI)	—	13.71 (5.007, 37.562)
p-value	—	< 0.0001
Multiple imputation		
Estimated IGA-TS response rate (SE), %	16.0 (4.30)	62.2 (3.85)
Active treatment vs vehicle		
Pooled stratum-adjusted difference in response rate (95% CI)	—	46.1 (34.84, 57.32)
Pooled overall odds ratio (95% CI)	—	8.93 (4.359, 18.296)
p-value	—	< 0.0001

Note 1: Binomial CI was calculated using normal approximation method.
Note 2: Nonresponder imputation: missing postbaseline values were imputed as nonresponders at Week 8.
Note 3: Overall odds ratio and p-values were calculated by CMH test stratified by baseline EASI score and geographic region.
Note 4: Stratum-adjusted rate differences and 95% CI were computed using Mantel Haenszel weights.
Note 5: Longitudinal logistic regression: (response = treatment + stratification factors + visit + treatment × visit + random participant-level intercept + random site-level intercept).
Note 6: Multiple imputation: missing IGA score was imputed by fully conditional specification multiple imputation method with treatment and stratification factors, baseline and scheduled postbaseline scores as predicators.
Note 7: Pooled overall odds ratio and p-value were computed by applying Rubin's rule.

Key secondary endpoints

Each key secondary endpoint was formally tested only if the preceding one was significant at the 2-sided 0.05 significance level. The 4 key-secondary endpoints all regarded itch and were met.

For the proportions of participants reaching **ITCH4**, the effects in the ruxolitinib 1.5% cream treatment group at Week 8, Day 7, Day 3, and Day 2 were statistically significantly larger than those in the vehicle cream treatment group (Table 16).

Table 16. Proportion of Participants With ITCH4 From Baseline to Week 8 and Days 7, 3, and 2 (ITT Population)

Endpoint	Vehicle Cream BID (N = 81)	Ruxolitinib 1.5% Cream BID (N = 160)
Proportion of participants with ITCH4 from baseline to Week 8, n/N (%)[a]	16/81 (19.8)	100/160 (62.5)
Active treatment vs vehicle		
Overall odds ratio (95% CI)	—	6.99 (3.675, 13.314)
p-value	—	< 0.0001
Proportion of participants with ITCH4 from baseline to Day 7, n/N (%)[b]	11/78 (14.1)	76/146 (52.1)
Active treatment vs vehicle		
Pooled overall odds ratio (95% CI)	—	6.8 (3.31, 14.02)
p-value	—	< 0.0001
Proportion of participants with ITCH4 from baseline to Day 3, n/N (%)[b]	8/77 (10.4)	51/147 (34.7)
Active treatment vs vehicle		
Pooled overall odds ratio (95% CI)	—	5.4 (2.37, 12.35)
p-value	—	< 0.0001
Proportion of participants with ITCH4 from baseline to Day 2, n/N (%)[b]	11/77 (14.3)	44/151 (29.1)
Active treatment vs vehicle		
Pooled overall odds ratio (95% CI)	—	2.7 (1.31, 5.51)
p-value	—	0.0072

Note 1: Overall odds ratio and p-values were calculated by CMH test stratified by baseline EASI score and geographic region.
Note 2: Pooled overall odds ratio and p-value were computed by applying Rubin's rule.
[a] Nonresponder imputation: Missing postbaseline values were imputed as nonresponders at Week 8.
[b] Multiple imputation: Missing Itch NRS score was imputed by fully conditional specification multiple imputation method with treatment and observed stratification factors, baseline and scheduled postbaseline itch scores on Days 1 to 7 as predicators.

The between-group response rate differences with 95% CI of the proportion of participants with ITCH4 from baseline to week 8 and days 7, 3, and 2 are provided in Table 17.

Table 17. Between-group response rate differences with 95% CI of the proportion of participants with ITCH4 from baseline to week 8 and days 7, 3, and 2 (ITT population)

Endpoint Variable	**Vehicle Cream BID (N = 81)**	**Ruxolitinib 1.5% Cream BID (N = 160)**
Proportion of participants with ITCH4 from baseline to Week 8[a], % (SE)	19.8 (4.42)	62.5 (3.83)
Active treatment vs vehicle		
Stratum-adjusted response rate difference (95% CI)	—	42.8 (31.44, 54.21)
Proportion of participants with ITCH4 from baseline to Day 7[b], % (SE)	13.86 (3.875)	51.20 (4.004)
Active treatment vs vehicle		
Pooled stratum-adjusted response rate difference (95% CI)	—	37.5 (26.71, 48.33)
Proportion of participants with ITCH4 from baseline to Day 3[b], % (SE)	9.88 (3.315)	35.09 (3.818)
Active treatment vs vehicle		
Pooled stratum-adjusted response rate difference (95% CI)	—	25.5 (15.81, 35.20)
Proportion of participants with ITCH4 from baseline to Day 2[b], % (SE)	13.67 (3.832)	29.75 (3.636)
Pooled stratum-adjusted response rate difference (95% CI)	—	16.2 (5.82, 26.57)

[a] Nonresponder imputation: Missing postbaseline values were imputed as nonresponders at Week 8.

[b] Multiple imputation: Missing Itch NRS scores were imputed by the fully conditional specification multiple imputation method with treatment and observed stratification factors, baseline and scheduled postbaseline itch scores on Days 1 to 7 as predicators.

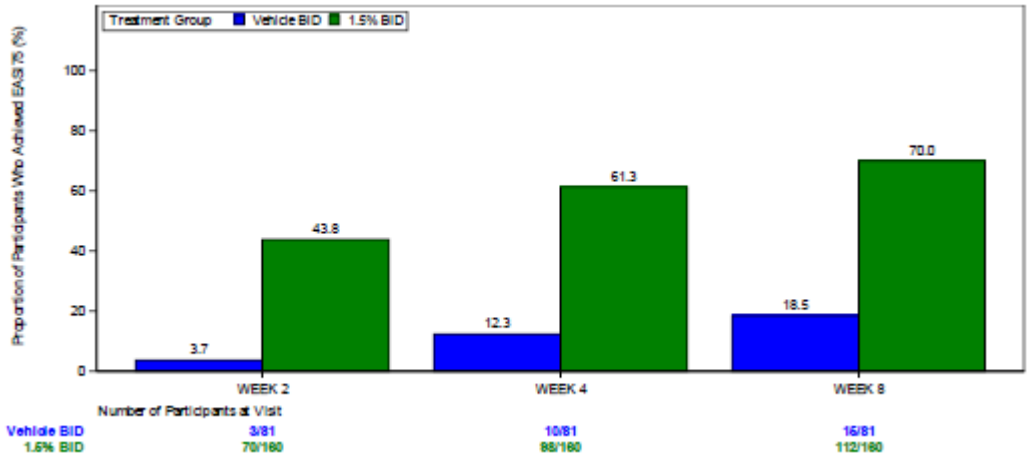
Other secondary endpoints

Secondary endpoints outside the key secondary endpoints were not corrected for multiplicity in statistical testing; statistical test results are thus nominal.

EASI75 response over time

The proportion of participants reaching EASI75 increased during the double-blind, vehicle-controlled period, with a numerical separation for the ruxolitinib 1.5% cream treatment group from the vehicle cream treatment group by the first postbaseline visit at Week 2 (Figure 10).

Figure 10. Proportion of Participants with EASI75 at Each Visit During the Double-Blind, Vehicle-Controlled Period (ITT Population)



Participants with an adequate response (≥ EASI50) at week 8 could enter the vehicle-controlled **extension period**. The proportion of participants with EASI75 on ruxolitinib cream ranged between 82% and 86% from week 12 through week 24 (Table 18). In the **escape arm** over that same period, the proportions of patients with EASI75 increased from 45% at week 12 (was 0 at week 8) to about 66% at week 24, in patients from both sources.

Table 18. Proportion of Participants Achieving EASI75 at Each Visit During the Vehicle-Controlled Extension, Double-Blind Period and for the Escape Arm

	Vehicle-Controlled Extension, Double-Blind Period (ITT Population)[a]		Open-Label Escape Arm (VCE Escape Population Who Entered the Escape Arm at Week 8)[b]		
Visit, n/N (%)	Vehicle Cream BID (N = 81)	Ruxolitinib 1.5% Cream (N = 160)	Vehicle Cream BID to Ruxolitinib 1.5% Cream BID (N = 40)	Ruxolitinib 1.5% Cream BID to Ruxolitinib 1.5% Cream BID (N = 32)	Total (N = 72)
Week 12	16/18 (88.9)	97/119 (81.5)	19/38 (50.0)	11/29 (37.9)	30/67 (44.8)
Week 16	11/14 (78.6)	95/111 (85.6)	24/37 (64.9)	13/29 (44.8)	37/66 (56.1)
Week 20	10/14 (71.4)	90/105 (85.7)	26/37 (70.3)	16/28 (57.1)	42/65 (64.6)
Week 24	11/13 (84.6)	87/103 (84.5)	26/37 (70.3)	17/28 (60.7)	43/65 (66.2)

[a] Participants (20 and 121 participants in the vehicle cream BID and ruxolitinib 1.5% cream BID groups, respectively) with an adequate response, defined as achieving EASI50 at Week 8, continued blinded treatment during the vehicle-controlled extension, double-blind period.

[b] Participants with inadequate response at Week 8 and participants (6 and 14 participants in the vehicle cream BID and ruxolitinib 1.5% cream BID, respectively) who lost EASI50 response (ie, < EASI50 observed at 2 consecutive visits at least 1 week apart) during the vehicle-controlled extension, double-blind period were eligible to enter the open-label escape arm. Data from participants who lost response after Week 8 were excluded from the results for the open-label escape arm.

IGA-TS over time

The proportion of participants reaching IGA-TS increased through week 8, with separation between the ruxolitinib 1.5% cream treatment group and the vehicle cream treatment group by the first postbaseline visit at week 2 (Figure 11). For participants with an adequate response (≥ EASI50) at week 8 who entered the **extension period**, the proportion of participants reaching IGA-TS on ruxolitinib cream was between 66% and 71% through week 24 (Table 19). In the **escape arm**, the proportion of IGA-TS responders increased from 37% at week 12, to 55% at week 24.

Figure 11. Proportion of Participants Achieving IGA-TS at Each Visit During the Double-Blind Vehicle-Controlled Period (ITT Population)

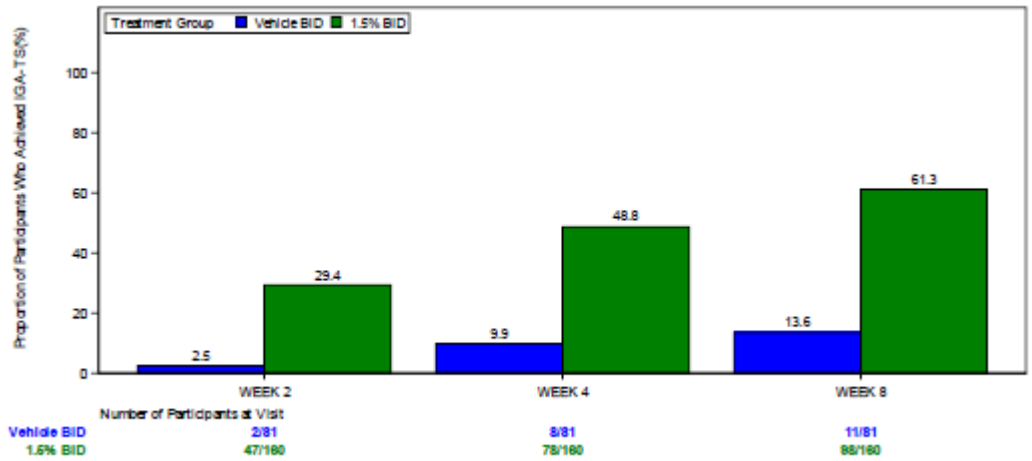


Table 19. Proportion of Participants Achieving IGA-TS at Each Visit During the Vehicle-Controlled Extension, Double-Blind Period and for the Escape Arm

	Vehicle-Controlled Extension, Double-Blind Period (ITT Population)[a]		Open-Label Escape Arm (VCE Escape Population Who Entered the Escape Arm at Week 8)[b]		
Visit, n/N (%)	Vehicle Cream BID (N = 81)	Ruxolitinib 1.5% Cream (N = 160)	Vehicle Cream BID to Ruxolitinib 1.5% Cream BID (N = 40)	Ruxolitinib 1.5% Cream BID to Ruxolitinib 1.5% Cream BID (N = 32)	Total (N = 72)
Week 12	11/18 (61.1)	78/119 (65.5)	15/38 (39.5)	10/29 (34.5)	25/67 (37.3)
Week 16	10/14 (71.4)	72/111 (64.9)	19/37 (51.4)	11/29 (37.9)	30/66 (45.5)
Week 20	9/14 (64.3)	72/105 (68.6)	22/37 (59.5)	13/28 (46.4)	35/65 (53.8)
Week 24	9/13 (69.2)	73/103 (70.9)	23/37 (62.2)	13/28 (46.4)	36/65 (55.4)

[a] Participants (20 and 121 participants in the vehicle cream BID and ruxolitinib 1.5% cream BID groups, respectively) with an adequate response, defined as achieving EASI50 at Week 8, continued blinded treatment during the vehicle-controlled extension, double-blind period.

[b] Participants with inadequate response at Week 8 and participants (6 and 14 participants in the vehicle cream BID and ruxolitinib 1.5% cream BID, respectively) who lost EASI50 response (ie, < EASI50 observed at 2 consecutive visits at least 1 week apart) during the vehicle-controlled extension, double-blind period were eligible to enter the open-label escape arm. Data from participants who lost response after Week 8 were excluded from the results for the open-label escape arm.

Itch response over time

The proportion of participants reaching ITCH4 was larger in the ruxolitinib cream group, as compared to the vehicle cream groups, also at week 2 (48% *versus* 9.9%) and week 4 (56% *versus* 17%).

The proportion of participants reaching daily ITCH4 (the worst level of itch intensity in the prior 24 hours) increased during the first week of ruxolitinib 1.5% cream BID application, with a numerical separation at day 1 (Figure 12).

Mean Itch NRS scores (7-day recall of the worst level of itch intensity) were also evaluated during the vehicle-controlled **extension period**. Itch NRS scores (7-day recall) remained low, with lower scores among participants in the ruxolitinib 1.5% cream treatment group than participants in the vehicle cream treatment group up to week 24 (Table 20).

Figure 12. Proportion of Participants Achieving ITCH4 From Day 1 to Day 7 in Study INCB 18424-326 (ITT Population)

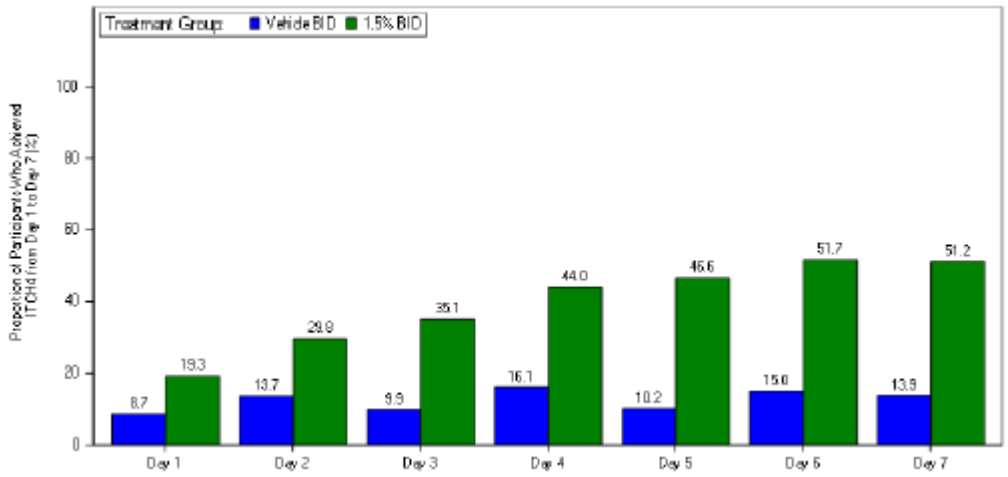


Table 20. Itch NRS Scores (7-Day Recall) During the Vehicle-Controlled Extension, Double-Blind Period (ITT Population)

Visit Variable	Vehicle-Controlled Extension, Double-Blind Period[a]	
	Vehicle Cream BID (N = 20)	Ruxolitinib 1.5% Cream BID (N = 121)
Week 12	n = 18	n = 115
Mean (STD)	3.67 (2.744)	2.79 (2.422)
Week 16	n = 14	n = 109
Mean (STD)	2.43 (2.563)	2.63 (2.231)
Week 20	n = 14	n = 104
Mean (STD)	3.14 (2.627)	2.39 (1.903)
Week 24	n = 13	n = 102
Mean (STD)	3.15 (2.512)	2.35 (2.109)

[a] The VCE Primary Population includes all participants who entered the vehicle-controlled extension, double-blind period and applied study drug at least once. For participants who entered the escape arm after Week 8 (6 and 14 participants in the vehicle cream BID and ruxolitinib 1.5% cream BID, respectively), only data prior to entry to the escape arm are included.

The proportion of participants achieving ITCH4 at each visit in the VCE, double-blind period (ITT Population) is presented in the below Table 21.

Table 21. Proportion of Participants Achieving ITCH4 at Each Visit in the Vehicle-Controlled Extension, Double-Blind Period (ITT Population)

Visit, n/N (%)	Vehicle Cream BID (N = 81)	Ruxolitinib 1.5% Cream BID (N = 160)
Week 12	6/18 (33.3)	72/115 (62.6)
Week 16	8/14 (57.1)	72/109 (66.1)
Week 20	7/14 (50.0)	72/104 (69.2)
Week 24	6/13 (46.2)	66/102 (64.7)

Percent BSA affected over time

At baseline, the mean (SD) by-visit total %BSA affected by AD was 15% (2.9%) and 15% (3.1%) for the vehicle cream and ruxolitinib 1.5% cream treatment groups. The mean %BSA affected by AD

decreased throughout the double-blind, vehicle-controlled period for the ruxolitinib 1.5% cream treatment group, with separation from the vehicle cream BID group evident at Week 2. The mean (SD) %BSA affected by AD at Week 8 was 11% (6.5%) and 4.2% (5.4%) for the vehicle cream and ruxolitinib 1.5% cream treatment groups. In the vehicle-controlled **extension period**, decreases (improvements) from baseline in %BSA affected by AD were maintained in both treatment groups and the **escape** ruxolitinib arm up to week 24 and ranged between -5% and -12%.

Table 22. Summary of Percent BSA Affected by Atopic Dermatitis During the Vehicle-Controlled Extension, Double-Blind Period and for the Escape Arm

	Vehicle-Controlled Extension, Double-Blind Period (ITT Population)[a]		Open-Label Escape Arm (VCE Escape Population Who Entered the Escape Arm at Week 8)[b]	
Visit Variable	Vehicle Cream BID (N = 81)	Ruxolitinib 1.5% Cream BID (N = 160)	Vehicle Cream BID to Ruxolitinib 1.5% Cream BID (N = 40)	Ruxolitinib 1.5% Cream BID to Ruxolitinib 1.5% Cream BID (N = 32)
Week 12	n = 18	n = 119	n = 38	n = 29
Mean (STD)	2.79 (3.198)	3.30 (4.265)	7.11 (5.397)	8.82 (6.538)
Mean change from baseline (STD)	−11.28 (3.230)	−11.79 (4.725)	−8.78 (5.804)	−5.29 (5.589)
Week 16	n = 14	n = 111	n = 37	n = 29
Mean (STD)	1.93 (2.898)	2.90 (3.960)	5.30 (4.931)	7.86 (5.677)
Mean change from baseline (STD)	−11.74 (4.010)	−12.22 (4.109)	−10.61 (5.288)	−6.24 (4.415)
Week 20	n = 14	n = 105	n = 37	n = 28
Mean (STD)	2.41 (4.069)	3.02 (3.941)	4.92 (4.287)	6.73 (5.193)
Mean change from baseline (STD)	−11.26 (4.309)	−12.04 (4.559)	−11.26 (4.410)	−7.42 (4.335)
Week 24	n = 13	n = 103	n = 37	n = 28
Mean (STD)	1.75 (2.402)	2.48 (3.638)	4.60 (5.393)	5.79 (4.764)
Mean change from baseline (STD)	−11.83 (3.255)	−12.50 (4.691)	−11.58 (4.829)	−8.32 (3.620)

[a] Participants (20 and 121 participants in the vehicle cream BID and ruxolitinib 1.5% cream BID groups, respectively) with an adequate response, defined as achieving EASI50 at Week 8, continued blinded treatment during the vehicle-controlled extension, double-blind period.

[b] Participants (6 and 14 participants in the vehicle cream BID and ruxolitinib 1.5% cream BID, respectively) who lost EASI50 response (ie, < EASI50 observed at 2 consecutive visits at least 1 week apart) during the vehicle-controlled extension, double-blind period were eligible to enter the open-label escape arm. Data from participants who lost response after Week 8 were excluded from the results for the open-label escape arm.

Skin pain

At baseline, the mean (SD) Skin Pain NRS scores were 6.5 (2.3) and 7.0 (1.9) for the vehicle cream and ruxolitinib 1.5% cream treatment groups. Skin Pain NRS scores decreased from baseline during the double-blind, vehicle-controlled period, with separation between the ruxolitinib 1.5% cream and vehicle cream treatment groups by the first postbaseline visit (week 2). At week 8, Skin Pain NRS had decreased from baseline with mean (SD) of −2.6 (3.0) and −5.2 (2.7) for the vehicle cream and ruxolitinib 1.5% cream treatment groups.

SCORing Atopic Dermatitis

At baseline, the mean (SD) total SCORAD score was 53 (10) and 54 (11) for the vehicle cream and ruxolitinib 1.5% cream treatment groups. Total SCORAD scores decreased (improved) from baseline during the double-blind, vehicle-controlled period, with separation between the ruxolitinib 1.5% cream and vehicle cream treatment groups by the first postbaseline visit at Week 2. At week 8, the SCORAD scores had decreased from baseline with a mean (SD) of −15 (15) and −36 (18) in the vehicle cream and ruxolitinib 1.5% cream treatment groups. In the vehicle-controlled **extension period**, decreases from baseline in SCORAD scores were maintained in both treatment groups up to week 24.

Dermatology Life Quality Index

Larger proportions of participants in the ruxolitinib 1.5% cream BID group achieved DLQI4 compared with participants in the vehicle cream BID group. At week 8, the proportion of participants achieving DLQI4 was 78% and 97% for the vehicle cream and ruxolitinib 1.5% cream treatment groups.

Patient-Oriented Eczema Measure

At baseline, the mean (SD) POEM scores were 19 (5.3) and 20 (4.9) for the vehicle cream and ruxolitinib 1.5% cream treatment groups. At week 8, POEM scores had decreased with a mean (SD)

from baseline of −6 (7.4) and −15 (8.0) for the vehicle cream and ruxolitinib 1.5% cream treatment groups. At week 8, the proportion of participants achieving POEM 0 to 2 was 8.6% and 40% for the vehicle cream and ruxolitinib 1.5% cream treatment groups.

PROMIS Sleep Questionnaires

At baseline, the mean (SD) PROMIS Sleep-Related Impairment scores were 21 (7.6) and 22 (7.5) for the vehicle cream and ruxolitinib 1.5% cream treatment groups. At week 8, PROMIS Sleep-Related Impairment scores had decreased with mean (SD) from baseline with −2.9 (7.1) and −6.5 (8.0) for the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups.

At baseline, the mean (SD) PROMIS Sleep Disturbance scores were 24 (7.1) and 25 (7.3) for the vehicle cream and ruxolitinib 1.5% cream treatment groups. At week 8, PROMIS Sleep Disturbance scores had decreased by mean (SD) of −3.0 (6.2) and −7.3 (8.9) for the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups.

Ancillary analyses

Off treatment

During the vehicle-controlled extension, double-blind period, participants in the ruxolitinib 1.5% cream treatment group reported a higher proportion of time off study treatment due to lesion clearance and a lower proportion of time on study treatment for weeks 8 – 12, thereafter proportions were similar (Table 23).

Table 23. Proportion of Time On and Off Study Treatment During the Vehicle-Controlled Extension, Double-Blind Period (VCE Primary Population)

	% Time On Treatment[a]		% Time Off Treatment	
Timepoint Variable	Vehicle Cream BID (N = 20)	Ruxolitinib 1.5% Cream (N = 121)	Vehicle Cream BID (N = 20)	Ruxolitinib 1.5% Cream (N = 121)
Weeks 8 to 12	n = 20	n = 121	n = 20	n = 121
Mean (STD)	90.97 (18.729)	79.28 (26.663)	4.10 (14.041)	15.83 (23.644)
Median (min, max)	100.00 (38.8, 100.0)	94.44 (1.4, 100.0)	0.00 (0.0, 60.0)	0.00 (0.0, 98.6)
Weeks 12 to 16	n = 14	n = 113	n = 14	n = 113
Mean (STD)	79.83 (37.797)	76.43 (29.169)	19.16 (38.275)	17.86 (27.221)
Median (min, max)	100.00 (0.0, 100.0)	92.86 (0.0, 100.0)	0.00 (0.0, 100.0)	0.00 (0.0, 100.0)
Weeks 16 to 20	n = 14	n = 106	n = 14	n = 106
Mean (STD)	76.63 (41.362)	72.46 (31.409)	21.86 (41.707)	22.72 (30.994)
Median (min, max)	100.00 (0.0, 100.0)	85.36 (0.0, 100.0)	0.00 (0.0, 100.0)	0.00 (0.0, 100.0)
Weeks 20 to 24	n = 13	n = 102	n = 13	n = 102
Mean (STD)	72.70 (38.905)	71.25 (33.319)	26.12 (38.323)	24.29 (32.962)
Median (min, max)	100.00 (0.0, 100.0)	85.83 (0.0, 100.0)	0.00 (0.0, 100.0)	0.00 (0.0, 100.0)

[a] Proportion of time on study treatment = (total intended days on treatment − missed dose days between visits) / total days between visits per participant.

Retreatment

In the vehicle-controlled extension period, retreatment upon clearance occurred in 64/68 (94%) of patients who stopped due to total clearance. The median number of days to retreatment was 5 days.

Rebound

Relapse was assessed during the 30-day Safety Follow-up Period for participants who had an EASI75 response from baseline at the end of the vehicle-controlled extension, double-blind period at week 24. Relapse was defined as loss of EASI50 response from baseline during the Safety Follow-up Period. Among participants who had EASI75 at week 24, 0/9 participants (0%) in the vehicle cream treatment group and 15/81 participants (19%) in the ruxolitinib cream treatment group relapsed at the safety

follow-up visit after study treatment discontinuation. Two of the 15 participants who relapsed had an EASI score above their baseline score (rebound definition).

Increased severity

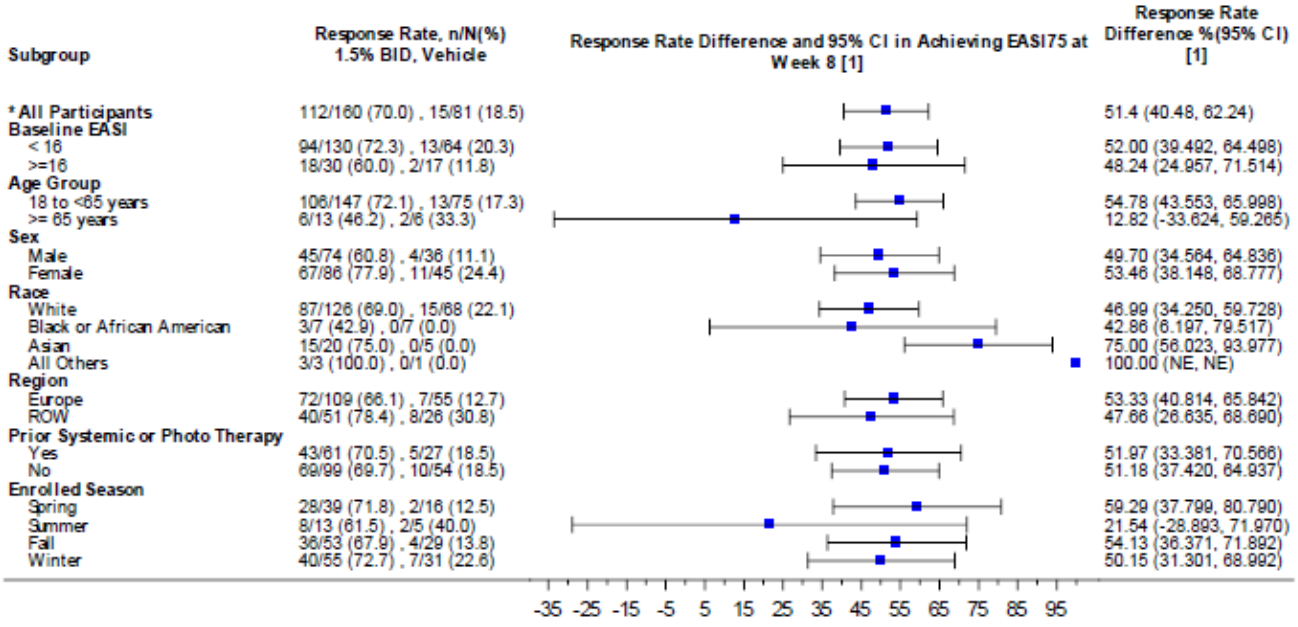
Among the participants evaluated in the vehicle-controlled extension, double-blind period, the proportion who met criteria typical criteria for escalation to systemic therapy (IGA score ≥ 3, EASI score ≥ 16, Itch NRS score ≥ 4, BSA ≥ 10%, and DLQI score >10), was lower for the ruxolitinib 1.5% cream group (3.8%) compared with the vehicle cream group (15%).

Subgroup analyses

Subgroup analyses were performed for each of the coprimary endpoints. The proportions of participants achieving EASI75 and IGA-TS at Week 8 were consistently higher among participants on active treatment compared with vehicle for all subgroups: Baseline EASI score (≥ 16, < 16), age (< 65 years, ≥ 65 years), sex (female, male), race, geographic region (Europe, ROW), prior systemic or phototherapy (yes/no), and the season in which the participant was enrolled (**Figure *13***). Lower estimates and wider confidence intervals were present for the smallest subgroups (>65 years of age, Black or African American, enrolled in Summer).

The results of the forest plot with IGA-TS as outcome were similar as the forest plot with EASI75.

Figure 13. Forest Plot of Response Rate Difference in Achieving EASI75 at Week 8 (ITT Population)



Supportive studies

TRuE-AD1 and TRuE-AD2, phase 3, double-blind, Randomised, 8-week, vehicle-controlled efficacy and safety studies of ruxolitinib cream followed by a long-term safety extension period in adolescents and adults with AD (INCB 18424-303 and INCB 18424-304).

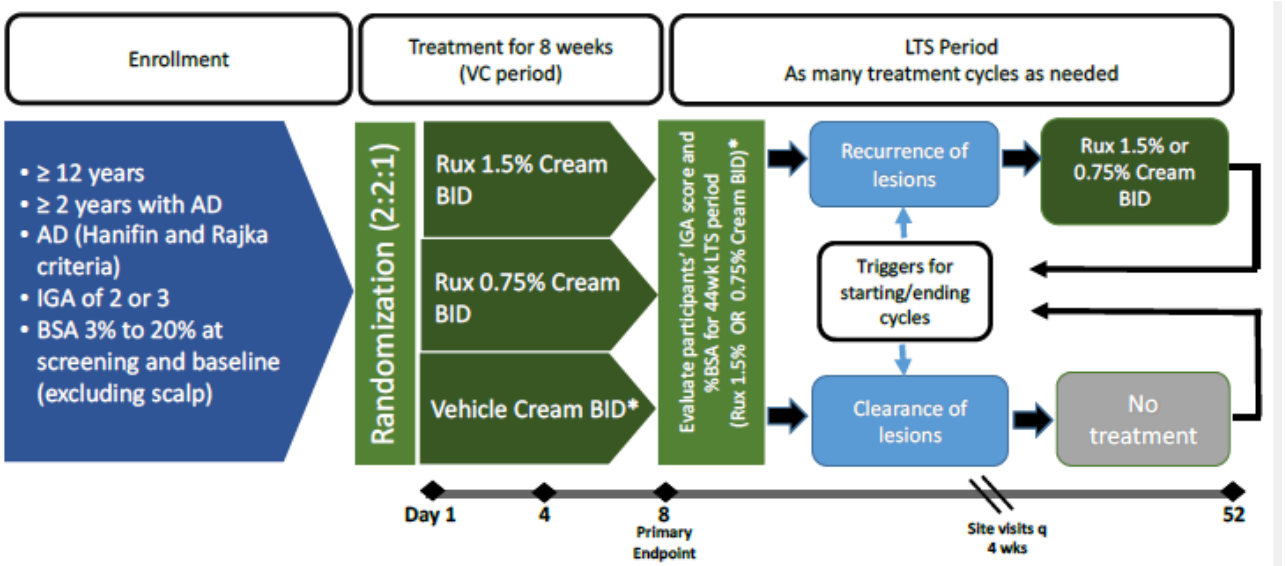
Objectives

The main objectives were to assess the efficacy and safety of ruxolitinib cream, versus vehicle cream, in adolescent (≥ 12 years old) and adult participants with mild to moderate (IGA 2 or 3) AD eligible for topical therapy.

Design

Studies 303 and 304 were Phase 3 randomised, double blind, vehicle-controlled studies and were identical in objectives and design (Figure 14). Per study, approximately 600 participants (≈20% of whom were adolescents) with AD involvement of 3% to 20% BSA (excluding the scalp) and a baseline IGA score of 2 or 3 were planned to be randomised 2:2:1 to receive ruxolitinib 0.75% cream BID, ruxolitinib 1.5% cream BID, or vehicle cream BID during the 8 week, double blind, vehicle controlled period. Participants were stratified by baseline IGA score (2 or 3) and geographic region (North America or Europe). Areas identified for treatment at baseline were treated through Week 8 even if the areas began to improve.

Figure 14. Design of studies 303 and 304



**At Week 8 (LTS baseline), participants initially on vehicle were randomized to either ruxolitinib 1.5% or 0.75% cream BID. Additionally, to qualify for the LTS period, the IGA score of 0 to 4 and %BSA of 0% to 20% was required.*

The primary endpoint was the proportion of participants achieving EASI75 at Week 8. Key secondary endpoints included the proportion of participants achieving IGA-TS at Week 8 and the proportion of participants with ITCH4 at Week 8.

Participants who completed the Week 8 assessments with no safety concerns continued into the 44-week, double blind, long-term treatment period. Participants initially randomised to vehicle cream were rerandomised 1:1 to 1 of the 2-ruxolitinib cream BID treatment groups, and those on active treatment continued on the same treatment regimen. At each study visit (every 4 weeks) during the LTS period, the investigator evaluated the AD lesions to confirm whether the participant required continuation of therapy (IGA score ≥ 1) or could (re)enter the observation/no treatment cycle (IGA score of 0). Between study visits, participants self-evaluated for recurrence of AD and treated skin areas with active lesions (not to exceed 20% BSA). Participants stopped treatment of a lesion 3 days after it cleared and restarted treatment at the first sign of recurrence.

During the vehicle-controlled and long-term treatment periods, if new AD lesions developed outside of and/or were more widespread than the treatment area assigned at baseline, participants could treat these additional areas with the investigator's approval as long as the total treated BSA did not exceed 20% and there were no safety concerns regarding the additional application of study drug.

Efficacy and safety assessments (AE monitoring, vital signs, clinical laboratory tests, and physical examinations) were performed at scheduled timepoints throughout the study.

The ITT population included all participants who were randomised to the study (treatment groups defined according to the treatment assignment at the time of randomisation); this population was used for all efficacy analyses in the double-blind treatment period. *Post hoc* analyses of efficacy data (EASI75, IGA-TS, and ITCH4 during the vehicle-controlled period and IGA score of 0 or 1 and %BSA with AD throughout the study) for the subset of adult participants with moderate AD (defined as participants with a baseline EASI score > 7 and IGA score of 3) were performed to support this application.

The alternative hypothesis (superiority of ruxolitinib 1.5% or 0.75% cream compared with vehicle cream) was tested using exact logistic regression. This model included the treatment group and stratification factors (baseline IGA score and geographic region). The unadjusted p-values between each treatment group and vehicle were calculated based on Wald test. Odds ratio and 95% confidence (CI) interval in response rates (ruxolitinib cream vs vehicle) at Week 8 were also computed. All nonresponders during the VC period, as well as all participants who were missing postbaseline values, were defined as non-responders for the non-responder imputation analysis.

Results

Participant flow

All 1249 participants randomised in Studies 303 (N = 631) and 304 (N = 618) applied study drug at least once, 1119 participants (90%) completed treatment through Week 8 (the end of the double-blind, vehicle-controlled period), and 130 participants (10.4%) discontinued treatment before Week 8 (Table 24).

Table 24. Disposition in the vehicle-controlled period of supportive studies 303 and 304.

	Study INCB 18424-303				Study INCB 18424-304			
Number (%) of Participants	Vehicle Cream BID (N = 126)	Ruxolitinib 0.75% Cream BID (N = 252)	Ruxolitinib 1.5% Cream BID (N = 253)	Total (N = 631)	Vehicle Cream BID (N = 124)	Ruxolitinib 0.75% Cream BID (N = 248)	Ruxolitinib 1.5% Cream BID (N = 246)	Total (N = 618)
Treated	126 (100.0)	252 (100.0)	253 (100.0)	631 (100.0)	124 (100.0)	248 (100.0)	246 (100.0)	618 (100.0)
Completed treatment	101 (80.2)	225 (89.3)	232 (91.7)	558 (88.4)	106 (85.5)	220 (88.7)	235 (95.5)	561 (90.8)
Discontinued from treatment	25 (19.8)	27 (10.7)	21 (8.3)	73 (11.6)	18 (14.5)	28 (11.3)	11 (4.5)	57 (9.2)
Primary reason:								
AE	5 (4.0)	3 (1.2)	2 (0.8)	10 (1.6)	3 (2.4)	1 (0.4)	1 (0.4)	5 (0.8)
Lack of efficacy	1 (0.8)	1 (0.4)	0 (0.0)	2 (0.3)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Lost to follow-up	5 (4.0)	12 (4.8)	7 (2.8)	24 (3.8)	3 (2.4)	13 (5.2)	4 (1.6)	20 (3.2)
Physician decision	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.8)	0 (0.0)	1 (0.4)	2 (0.3)
Pregnancy	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.3)
Noncompliance with study drug	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Withdrawal by participant	12 (9.5)	7 (2.8)	12 (4.7)	31 (4.9)	9 (7.3)	10 (4.0)	5 (2.0)	24 (3.9)
Other	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.8)	1 (0.4)	0 (0.0)	2 (0.3)
Withdrawn from study	31 (24.6)	30 (11.9)	28 (11.1)	89 (14.1)	19 (15.3)	39 (15.7)	22 (8.9)	80 (12.9)
Primary reason:								
AE	4 (3.2)	2 (0.8)	1 (0.4)	7 (1.1)	1 (0.8)	1 (0.4)	0 (0.0)	2 (0.3)
Lack of efficacy	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	5 (4.0)	12 (4.8)	8 (3.2)	25 (4.0)	3 (2.4)	13 (5.2)	4 (1.6)	20 (3.2)
Physician decision	1 (0.8)	1 (0.4)	0 (0.0)	2 (0.3)	3 (2.4)	0 (0.0)	1 (0.4)	4 (0.6)
Pregnancy	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	3 (1.2)	0 (0.0)	3 (0.5)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.3)
Withdrawal by participant	17 (13.5)	11 (4.4)	19 (7.5)	47 (7.4)	11 (8.9)	21 (8.5)	15 (6.1)	47 (7.6)
Other	2 (1.6)	1 (0.4)	0 (0.0)	3 (0.5)	1 (0.8)	2 (0.8)	2 (0.8)	5 (0.8)

Baseline data

In studies 303 and 304, 29% of patients were included in European countries. There were 481 (40%) patients on ruxolitinib 1.5% cream and 244 (20%) patients on vehicle cream (the other patients had been allocated to ruxolitinib 0.75% cream).

The majority of participants in studies 303 and 304 were Caucasian (69% and 69%, respectively) and female (62% and 60%, respectively). Black/African American participants comprised 22% and 26% of the study populations, and Asian participants comprised 5.1% and 2.4% of the study populations, respectively. Most (80%) of the participants were adults; the mean (SD) age was 35 (18) and 37 (19) years of age, respectively and overall, 9.4% were ≥65 years of age.

Most participants had long-standing AD: The mean time since diagnosis was 19 and 20 years before study entry for Studies 303 and 304, respectively. The majority of participants (76% and 72%, respectively) had a baseline IGA score of 3, and EASI scores were approximately evenly distributed between scores ≤ 7 and scores > 7.

Study drug exposure

In the 8-week vehicle-controlled period, patients allocated to ruxolitinib cream used an daily average (SD) of 7.7 (4.1) gram cream (range: 0.2 – 17). In the extension period up to week 24, patients with a good response (EASI50) who remained on ruxolitinib used an daily average (SD) of 2.3 (1.8) gram cream (range: 0 – 7). In the escape arm of patients who used ruxolitinib after having had insufficient response at week 8, used an daily average (SD) of 4.9 (4.0) gram cream (range: 0.3 – 14).

Table 25. Baseline disease characteristics in the supportive studies 303 and 304.

Variable	Study INCB 18424-303				Study INCB 18424-304			
	Vehicle Cream BID (N = 126)	Ruxolitinib 0.75% Cream BID (N = 252)	Ruxolitinib 1.5% Cream BID (N = 253)	Total (N = 631)	Vehicle Cream BID (N = 118)	Ruxolitinib 0.75% Cream BID (N = 231)	Ruxolitinib 1.5% Cream BID (N = 228)	Total (N = 577)
Years since initial diagnosis of atopic dermatitis								
Mean (STD)	20.39 (16.139)	19.66 (15.373)	18.76 (13.931)	19.45 (14.962)	21.69 (17.167)	20.09 (15.280)	19.57 (14.533)	20.21 (15.393)
Median	17.85	14.10	16.00	15.30	15.90	15.20	15.70	15.50
Min, max	1.9, 79.1	1.0, 68.8	0.0, 69.2	0.0, 79.1	0.8, 70.7	0.1, 68.6	0.0, 68.8	0.0, 70.7
Facial involvement of atopic dermatitis, n (%)								
Yes	52 (41.3)	112 (44.4)	118 (46.6)	282 (44.7)	41 (34.7)	78 (33.8)	75 (32.9)	194 (33.6)
No	74 (58.7)	140 (55.6)	135 (53.4)	349 (55.3)	77 (65.3)	153 (66.2)	153 (67.1)	383 (66.4)
Total %BSA involvement in current atopic dermatitis episode								
Mean (STD)	9.16 (5.141)	9.92 (5.357)	9.31 (5.234)	9.53 (5.267)	9.93 (5.711)	9.51 (4.998)	9.48 (5.104)	9.58 (5.186)
Median	7.75	8.00	8.00	8.00	8.00	8.10	8.35	8.00
Min, max	3.0, 20.0	3.0, 20.0	3.0, 20.0	3.0, 20.0	3.0, 20.0	3.0, 20.0	3.0, 22.0	3.0, 22.0
IGA score, n (%)								
Mild: 2	31 (24.6)	61 (24.2)	60 (23.7)	152 (24.1)	33 (28.0)	64 (27.7)	63 (27.6)	160 (27.7)
Moderate: 3	95 (75.4)	191 (75.8)	193 (76.3)	479 (75.9)	85 (72.0)	167 (72.3)	165 (72.4)	417 (72.3)
EASI score								
Mean (STD)	7.44 (4.296)	8.18 (4.813)	7.93 (4.648)	7.93 (4.648)	8.17 (5.282)	7.94 (5.074)	7.64 (4.981)	7.87 (5.076)
Median	6.40	7.10	7.60	7.00	7.30	6.90	6.70	7.00
Min, max	1.2, 23.6	0.6, 24.2	0.8, 24.8	0.6, 24.8	0.6, 26.0	1.0, 30.6	0.8, 27.4	0.6, 30.6
EASI score category, n (%)								
≤ 7	71 (56.3)	126 (50.0)	121 (47.8)	318 (50.4)	55 (46.6)	120 (51.9)	118 (51.8)	293 (50.8)
> 7	55 (43.7)	126 (50.0)	132 (52.2)	313 (49.6)	63 (53.4)	111 (48.1)	110 (48.2)	284 (49.2)
Itch NRS score for by-visit summaries								
n	118	233	245	596	111	217	215	543
Mean (STD)	5.06 (2.536)	5.13 (2.298)	5.15 (2.479)	5.13 (2.418)	5.25 (2.369)	5.15 (2.494)	5.02 (2.459)	5.12 (2.452)
Median	5.20	5.17	5.29	5.29	5.67	5.25	5.14	5.25
Min, max	0.0, 9.9	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0

Note: Data from participants enrolled at Site 461 in Study INCB 18424-304 were excluded.

Outcomes and estimation

The proportion of participants reaching **EASI75** at Week 8 and the proportion of participants reaching **IGA-TS** at Week 8 was statistically significantly superior for both ruxolitinib cream treatment regimens compared with the vehicle cream BID treatment group ($p < 0.0001$ for all comparisons) in the supportive Phase 3 studies (Table 26). Sensitivity analyses confirmed the primary analysis results. The analysis of the primary and first key secondary endpoint for the PP Population yielded similar results for both studies.

The proportion of participants achieving **ITCH4** at Week 8 was statistically significantly superior for both ruxolitinib cream treatment regimens compared with the vehicle cream BID treatment group ($p < 0.001$ for all comparisons (Table 27). Numerical larger itch responses in the ruxolitinib groups, as compared to vehicle, became apparent from day 2.

Table 26. Participants Achieving EASI75 and IGA-TS at Week 8 in the Supportive Phase 3 Studies (ITT Population)

Endpoint Analysis Variable	INCB 18424-303			INCB 18424-304		
	Vehicle Cream BID (N = 126)	Ruxolitinib 0.75% Cream BID (N = 252)	Ruxolitinib 1.5% Cream BID (N = 253)	Vehicle Cream BID (N = 118)	Ruxolitinib 0.75% Cream BID (N = 231)	Ruxolitinib 1.5% Cream BID (N = 228)
EASI75 response rate at Week 8						
Nonresponder imputation						
Response rate, % (SE)	24.6 (3.84)	56.0 (3.13)	62.1 (3.05)	14.4 (3.23)	51.5 (3.29)	61.8 (3.22)
Response rate difference (95% CI)	—	31.3 (21.6, 41.1)	37.5 (27.8, 47.1)	—	37.1 (28.1, 46.1)	47.4 (38.5, 56.4)
Odds ratio (95% CI)	—	4.04 (2.441, 6.808)	5.22 (3.145, 8.831)	—	6.84 (3.723, 13.184)	10.67 (5.775, 20.732)
p-value	—	< 0.0001	< 0.0001	—	< 0.0001	< 0.0001
Longitudinal logistic regression						
Estimated response rate, % (SE)	33.4 (7.49)	72.8 (5.25)	77.1 (4.69)	19.8 (5.87)	65.2 (5.73)	74.6 (4.78)
Response rate difference	—	39.3	43.7	—	45.5	54.9
Odds ratio (95% CI)	—	5.32 (2.736, 10.332)	6.71 (3.454, 13.053)	—	7.62 (3.587, 16.169)	11.94 (5.616, 25.366)
p-value	—	< 0.0001	< 0.0001	—	< 0.0001	< 0.0001
Multiple imputation						
Estimated response rate, % (SE)	27.5 (4.13)	59.6 (3.22)	66.4 (3.03)	15.4 (3.37)	55.9 (3.56)	64.3 (3.26)
Response rate difference	—	32.1	38.9	—	40.5	48.8
Odds ratio (95% CI)	—	3.99 (2.431, 6.554)	5.36 (3.281, 8.753)	—	7.44 (4.109, 13.468)	10.69 (5.936, 19.265)
p-value	—	< 0.0001	< 0.0001	—	< 0.0001	< 0.0001
Last observation carried forward						
Estimated response rate, % (SE)	28.4 (4.19)	59.0 (3.15)	67.3 (3.00)	16.1 (3.47)	54.7 (3.32)	64.9 (3.20)
Response rate difference (SE)	—	30.6 (5.24)	38.9 (5.15)	—	38.6 (4.80)	48.8 (4.72)
Odds ratio (95% CI)	—	3.69 (2.230, 6.210)	5.32 (3.192, 9.024)	—	6.58 (3.612, 12.526)	10.23 (5.575, 19.659)
p-value	—	< 0.0001	< 0.0001	—	< 0.0001	< 0.0001
IGA-TS response rate at Week 8						
Nonresponder imputation						
Response rate, % (SE)	15.1 (3.19)	50.0 (3.15)	53.8 (3.13)	7.6 (2.44)	39.0 (3.21)	51.3 (3.31)
Response rate difference (95% CI)	—	34.9 (26.1, 43.7)	38.7 (29.9, 47.4)	—	31.3 (23.4, 39.2)	43.7 (35.6, 51.8)
Odds ratio (95% CI)	—	6.38 (3.556, 11.923)	7.50 (4.178, 14.040)	—	8.84 (4.125, 21.202)	15.80 (7.354, 38.061)
p-value	—	< 0.0001	< 0.0001	—	< 0.0001	< 0.0001
Longitudinal logistic regression						
Estimated response rate, % (SE)	11.3 (3.89)	53.9 (6.58)	57.0 (6.42)	5.3 (2.40)	36.1 (6.37)	51.8 (6.74)
Response rate difference	—	42.6	45.7	—	30.9	46.5
Odds ratio (95% CI)	—	9.16 (4.284, 19.596)	10.39 (4.873, 22.153)	—	10.17 (3.952, 26.170)	19.28 (7.490, 49.645)
p-value	—	< 0.0001	< 0.0001	—	< 0.0001	< 0.0001
Multiple imputation						
Estimated response rate, % (SE)	16.4 (3.55)	52.2 (3.27)	56.3 (3.16)	8.4 (2.67)	40.4 (3.27)	51.9 (3.33)
Response rate difference	—	35.8	39.9	—	32.0	43.5
Odds ratio (95% CI)	—	6.39 (3.554, 11.488)	7.64 (4.244, 13.754)	—	8.58 (4.035, 18.227)	14.78 (7.009, 31.180)
p-value	—	< 0.0001	< 0.0001	—	< 0.0001	< 0.0001
Last observation carried forward						
Estimated response rate, % (SE)	17.2 (3.51)	53.7 (3.19)	58.0 (3.15)	8.9 (2.69)	41.3 (3.28)	53.2 (3.35)
Response rate difference (SE)	—	36.4 (4.74)	40.7 (4.72)	—	32.4 (4.25)	44.2 (4.30)
Odds ratio (95% CI)	—	6.19 (3.458, 11.509)	7.53 (4.194, 14.038)	—	7.90 (3.783, 18.190)	13.56 (6.469, 31.344)
p-value	—	< 0.0001	< 0.0001	—	< 0.0001	< 0.0001

Note 1: Data from participants enrolled at Site 461 in Study INCB 18424-304 were excluded.
Note 2: Refer to INCB 18424-303/304 Statistical Analysis Plan, Section 7 for details regarding the statistical methodology.

Table 27. Proportion of Participants Achieving ITCH4 at Week 8, Day 7, Day 3, and Day 2 in the Supportive Phase 3 Studies (ITT Population)

Endpoint Variable	INCB 18424-303			INCB 18424-304		
	Vehicle Cream BID (N = 78)	Ruxolitinib 0.75% Cream BID (N = 156)	Ruxolitinib 1.5% Cream BID (N = 161)	Vehicle Cream BID (N = 80)	Ruxolitinib 0.75% Cream BID (N = 157)	Ruxolitinib 1.5% Cream BID (N = 146)
ITCH4 at Week 8[a], n	78	156	161	80	157	146
Response rate, % (SE)	15.4 (4.09)	40.4 (3.93)	52.2 (3.94)	16.3 (4.12)	42.7 (3.95)	50.7 (4.14)
Response rate difference (95% CI)	—	25.0 (13.9, 36.1)	36.8 (25.7, 47.9)	—	26.4 (15.2, 37.6)	34.4 (23.0, 45.9)
Odds ratio (95% CI)[b]	—	3.66 (1.773, 8.083)	6.01 (2.931, 13.220)	—	4.17 (2.045, 9.036)	5.80 (2.833, 12.657)
p-value	—	0.0002	< 0.0001	—	< 0.0001	< 0.0001
ITCH4 at Day 7, n	68	141	150	74	140	133
Response rate, % (SE)	8.8 (3.44)	22.7 (3.53)	34.0 (3.87)	5.4 (2.63)	25.7 (3.69)	26.3 (3.82)
Odds ratio (95% CI)[b]	—	3.04 (1.166, 9.389)	5.34 (2.117, 16.130)	—	6.69 (2.227, 27.247)	7.05 (2.336, 28.783)
p-value	—	0.0190	< 0.0001	—	< 0.0001	< 0.0001
ITCH4 at Day 3, n	72	143	147	70	143	129
Response rate, % (SE)	4.2 (2.35)	11.9 (2.71)	18.4 (3.19)	0.0 (0)	14.7 (2.96)	13.2 (2.98)
Odds ratio (95% CI)[b]	—	3.03 (0.833, 16.669)	5.06 (1.475, 26.974)	—	18.79 (4.007, NE)	16.79 (3.534, NE)
p-value	—	0.1095	0.0049	—	< 0.0001	0.0002
ITCH4 at Day 2, n	70	143	147	75	150	130
Response rate, % (SE)	2.9 (1.99)	9.1 (2.40)	11.6 (2.64)	1.3 (1.32)	8.7 (2.30)	10.8 (2.72)
Odds ratio (95% CI)[b]	—	3.33 (0.722, 31.261)	4.44 (1.008, 40.745)	—	7.12 (1.030, 308.621)	9.12 (1.334, 393.798)
p-value	—	0.1626	0.0482	—	0.0446	0.0148

Note: Data from participants enrolled at Site 461 in Study INCB 18424-304 were excluded.
[a] Nonresponder imputation: Missing postbaseline values were imputed as nonresponders.
[b] Exact logistic regression: Response at Week 8 = treatment + stratification factors (baseline IGA 2/3, region North America/Europe).

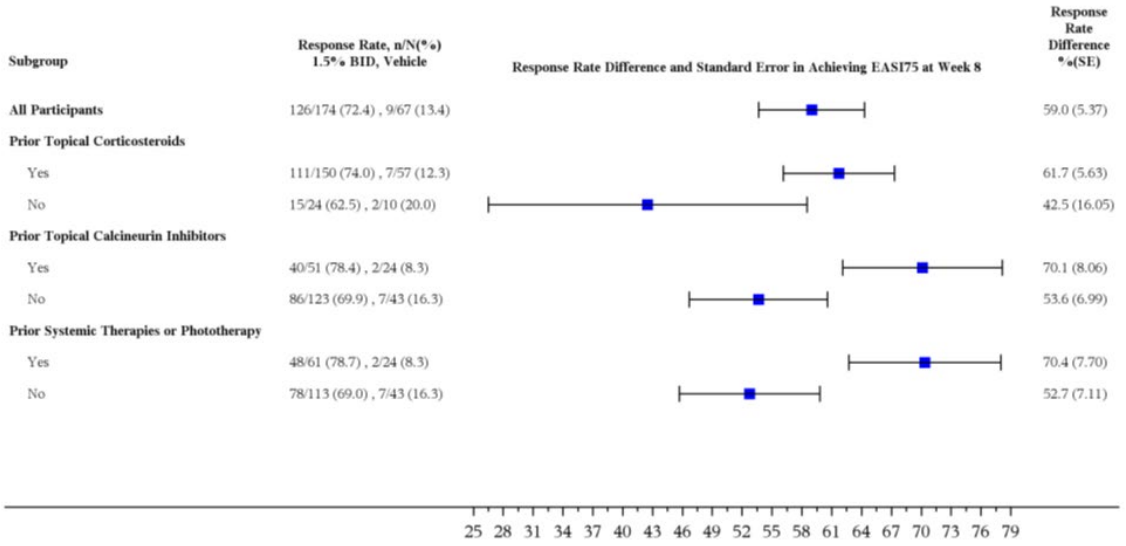
Ancillary analyses

Post hoc subgroup analyses were performed on the pooled ITT Population for Studies 303 and 304. A consistent treatment effect of ruxolitinib 0.75% and 1.5% cream BID was observed across subgroups for the proportion of participants achieving IGA-TS and EASI75.

The treatment effect of ruxolitinib 1.5% cream versus vehicle, tended to be larger in: adults, in females, in patients with moderate disease, as well as in patients included in European centres.

Subgroups were also based on prior TCS, TCI, or systemic therapy or phototherapy use. A consistent treatment effect of ruxolitinib 1.5% cream BID was observed across subgroups for the proportion of participants achieving EASI75 (Figure 15) or IGA-TS. In both studies 303 and 304, the treatment effects were larger in patients who had prior TCI or prior systemic therapies/phototherapy. For patients with prior TCS use (yes/no) the treatment effect was similar (study 303) and larger in patients with prior TCS use (study 304).

Figure 15. Forest Plot of Response Rate Differences in the Proportion of Participants Achieving EASI75 at Week 8 by Prior Medication Subgroup in the Supportive Phase 3 Studies (Pooled ITT Population)



Analysis performed across trials (pooled analyses)

Subset analysis of adult patients with moderate AD from the pooled data of studies 303 and 304

Design

As supportive data, a subset from the pooled study population of studies **303 and 304** was defined, to approximate the study population in the pivotal study 326. Accordingly, an **adult** population with **moderate AD** was selected (age ≥ 18 years, baseline EASI Score > 7, baseline IGA Score = 3); adolescents and patients with mild AD were thus excluded. The proportions of participants achieving EASI75 at Week 8 (the primary endpoint in the supportive Phase 3 studies 303 and 304) and IGA-TS at Week 8 (the first key secondary endpoint) and also Itch4 response at Week 8 (key secondary endpoint), were evaluated. For design and results of the complete study population of studies 303 and 304, it is referred to the section above.

Results

Participant flow

All 434 selected subset participants from Studies 303 (N = 228) and 304 (N = 206) applied study drug at least once, 388 participants (89%) completed treatment through Week 8 (the end of the double blind, vehicle-controlled period), and 46 participants (11%) discontinued treatment before Week 8. In both studies, a higher proportion of participants in the vehicle cream BID treatment group discontinued study drug and withdrew from the study during the vehicle-controlled period than in either of the ruxolitinib cream BID treatment groups. One participant in a vehicle cream BID treatment group discontinued study drug due to lack of efficacy during the vehicle-controlled period.

Baseline data

Of the subset, 46% of patients were included in European countries. There were 181 (42%) patients on ruxolitinib 1.5% cream and 88 (20%) patients on vehicle cream (the other patients had been allocated to ruxolitinib 0.75% cream).

Most participants had long-standing AD; the mean time since diagnosis was 23 and 24 years before study entry for Studies 303 and 304, respectively (Table 28). All participants in this subset had a baseline IGA score of 3 and EASI score > 7, the mean (SD) EASI score was 12 (3.6) and 12 (4.3), respectively. The mean (range) percent BSA affected at baseline for the study population was 12% (3.0%-20%) and 12% (3.5%-22%), respectively. The mean (range) Itch NRS score at baseline was 5.5 (0-10) and 5.9 (0.7-10), respectively.

A total of 88% of participants had used TCSs, 31% of participants had used TCIs, 30% of participants had used TCSs and TCIs, and 36% of participants had used systemic therapies or phototherapy to treat their AD.

Table 28. Baseline Disease Characteristics in the Supportive Phase 3 Studies (ITT Population With Age ≥ 18 Years, Baseline EASI Score > 7, and Baseline IGA Score = 3)

	Study INCB 18424-303				Study INCB 18424-304			
Variable	Vehicle Cream BID (N = 40)	Ruxolitinib 0.75% Cream BID (N = 87)	Ruxolitinib 1.5% Cream BID (N = 101)	Total (N = 228)	Vehicle Cream BID (N = 48)	Ruxolitinib 0.75% Cream BID (N = 78)	Ruxolitinib 1.5% Cream BID (N = 80)	Total (N = 206)
Years since initial diagnosis of atopic dermatitis								
Mean (STD)	24.40 (15.020)	23.53 (15.975)	21.36 (14.304)	22.72 (15.072)	27.36 (17.858)	24.76 (15.396)	20.67 (15.601)	23.78 (16.220)
Median	22.00	22.20	18.80	19.85	27.05	20.15	19.65	20.55
Min, max	1.9, 55.1	1.0, 60.2	1.9, 65.1	1.0, 65.1	2.1, 66.7	1.9, 60.1	0.2, 68.8	0.2, 68.8
Facial involvement of atopic dermatitis, n (%)								
Yes	25 (62.5)	54 (62.1)	61 (60.4)	140 (61.4)	24 (50.0)	38 (48.7)	37 (46.3)	99 (48.1)
No	15 (37.5)	33 (37.9)	40 (39.6)	88 (38.6)	24 (50.0)	40 (51.3)	43 (53.8)	107 (51.9)
Total %BSA involvement in current atopic dermatitis episode								
Mean (STD)	12.00 (4.972)	12.95 (4.975)	12.03 (4.817)	12.38 (4.904)	13.00 (5.393)	11.90 (4.930)	12.38 (4.786)	12.34 (4.980)
Median	12.00	13.00	11.00	12.00	12.50	12.00	12.70	12.00
Min, max	3.0, 20.0	3.5, 20.0	4.0, 20.0	3.0, 20.0	4.0, 20.0	3.5, 20.0	4.0, 22.0	3.5, 22.0
EASI score								
Mean (STD)	11.73 (3.773)	11.82 (3.658)	11.47 (3.585)	11.65 (3.634)	12.06 (4.056)	12.57 (4.811)	11.89 (4.015)	12.18 (4.332)
Median	10.75	11.40	10.40	10.80	11.50	11.40	11.00	11.40
Min, max	7.5, 23.6	7.2, 24.2	7.1, 24.8	7.1, 24.8	7.1, 22.5	7.2, 30.6	7.1, 27.4	7.1, 30.6
Itch NRS score for by-visit summaries								
n	39	81	98	218	47	75	74	196
Mean (STD)	5.41 (2.234)	5.46 (2.298)	5.68 (2.540)	5.55 (2.391)	6.51 (1.861)	5.73 (2.228)	5.75 (2.170)	5.92 (2.138)
Median	5.43	5.57	5.77	5.69	6.29	6.00	5.71	6.00
Min, max	1.0, 8.8	0.0, 9.3	0.0, 10.0	0.0, 10.0	2.7, 10.0	1.3, 10.0	0.7, 10.0	0.7, 10.0

Note: Data from participants enrolled at Site 461 in Study INCB 18424-304 were excluded.

Exposure

The duration of study cream exposure during the double-blind, vehicle-controlled period, in which study cream was applied twice daily for 8 weeks, was (median) 56 days in both treatment groups. Participants who completed treatment in the vehicle cream and ruxolitinib 1.5% cream treatment groups applied in mean (SD) 9.39 (3.495) and 7.75 (4.091) gram of study cream daily.

Study cream exposure during the vehicle-controlled extension, double-blind period, in which study cream twice daily was applied as needed, was similar between the treatment groups. The amount of cream used per day was lower as compared to the vehicle-controlled period with a mean (SD) of 1.84 (1.662) gram in the vehicle group and 2.00 (1.689) gram in the ruxolitinib treatment group.

Outcomes and estimation

Vehicle-controlled period

The treatment differences for the ruxolitinib 1.5% cream treatment group versus the vehicle cream treatment were positive and showed nominal p-values < 0.0001 for all comparisons between the active treatment groups and the vehicle cream group (Table 29**Error! Reference source not found.**).

The proportion of **EASI75** responders at week 8 was 10% in the vehicle group and 70% in the ruxolitinib 1.5% cream group (p<0.0001) and the proportion of **IGA-TS** was 8.0% in the vehicle group and 64% in the ruxolitinib 1.5% cream group (p<0.0001). Up to week 8, EASI75 response rates increased over time, with separation from the vehicle group by the first postbaseline visit at Week 2 (Figure 16).

At Week 8, the proportion of participants with an **ITCH4** response was 14% in the vehicle cream group and 61% in the ruxolitinib 1.5% cream group (p<0.0001); (Table 29). Numerical larger itch responses in the ruxolitinib groups, as compared to vehicle, became apparent from day 2 (Table 30; Figure 17).

Table 29. Proportion of Participants Achieving EASI75 and IGA-TS at Week 8 in the Supportive Phase 3 Studies (ITT Population With Age ≥ 18 Years, Baseline EASI Score > 7, and Baseline IGA Score = 3)

Endpoint Variable	INCB 18424-303			INCB 18424-304			Pooled Population		
	Vehicle Cream BID (N = 40)	Ruxolitinib 0.75% Cream BID (N = 87)	Ruxolitinib 1.5% Cream BID (N = 101)	Vehicle Cream BID (N = 48)	Ruxolitinib 0.75% Cream BID (N = 78)	Ruxolitinib 1.5% Cream BID (N = 80)	Vehicle Cream BID (N = 88)	Ruxolitinib 0.75% Cream BID (N = 165)	Ruxolitinib 1.5% Cream BID (N = 181)
EASI75 at Week 8[a]									
Response rate, % (SE)	12.5 (5.23)	55.2 (5.33)	66.3 (4.70)	8.3 (3.99)	61.5 (5.51)	73.8 (4.92)	10.2 (3.23)	58.2 (3.84)	69.6 (3.42)
Stratum-adjusted response rate difference (95% CI)[b]	—	43.1 (28.38, 57.77)	53.6 (39.79, 67.47)	—	53.1 (39.86, 66.34)	65.3 (53.00, 77.65)	—	48.3 (38.45, 58.06)	59.5 (50.29, 68.64)
Overall odds ratio (95% CI)[c]	—	8.76 (3.127, 24.523)	13.67 (4.873, 38.332)	—	18.74 (5.951, 59.011)	34.07 (10.443, 111.144)	—	12.73 (5.925, 27.334)	20.94 (9.646, 45.453)
p-value[c]	—	< 0.0001	< 0.0001	—	< 0.0001	< 0.0001	—	< 0.0001	< 0.0001
IGA-TS at Week 8[a]									
Response rate, % (SE)	12.5 (5.23)	54.0 (5.34)	62.4 (4.82)	4.2 (2.88)	48.7 (5.66)	65.0 (5.33)	8.0 (2.88)	51.5 (3.89)	63.5 (3.58)
Stratum-adjusted response rate difference (95% CI)[b]	—	41.9 (27.01, 56.88)	49.3 (35.10, 63.50)	—	44.4 (31.91, 56.88)	60.8 (48.90, 72.69)	—	43.8 (34.19, 53.45)	55.3 (46.21, 64.44)
Overall odds ratio (95% CI)[c]	—	7.77 (2.844, 21.247)	10.77 (3.930, 29.519)	—	21.30 (4.880, 92.961)	42.32 (9.571, 187.143)	—	11.51 (5.108, 25.938)	18.99 (8.353, 43.186)
p-value[c]	—	< 0.0001	< 0.0001	—	< 0.0001	< 0.0001	—	< 0.0001	< 0.0001

Note 1: Data from participants enrolled at Site 461 in Study INCB 18424-304 were excluded. Sensitivity analyses showed similar results with the inclusion of data from Site 461. Refer to the INCB 18424-304 CSR, Section 6.2.2, 9.1, and 9.2 for further details.
Note 2: EASI75 is defined as achieving ≥ 75% improvement from baseline in EASI score.
Note 3: IGA-TS is defined as achieving an IGA score of 0 or 1 with a ≥ 2-grade improvement from baseline.
[a] Missing postbaseline values were imputed as nonresponders.
[b] Stratum-adjusted rate difference and 95% CI were computed using Mantel-Haenszel weights.
[c] Overall odds ratio and p-values were calculated by the CMH test stratified by baseline IGA score and geographic region.

Figure 16. EASI75 at Each Visit During the Double-Blind, Vehicle-Controlled Period of the Supportive Phase 3 Studies (ITT Population With Age ≥ 18 Years, Baseline EASI Score > 7, and Baseline IGA Score = 3)

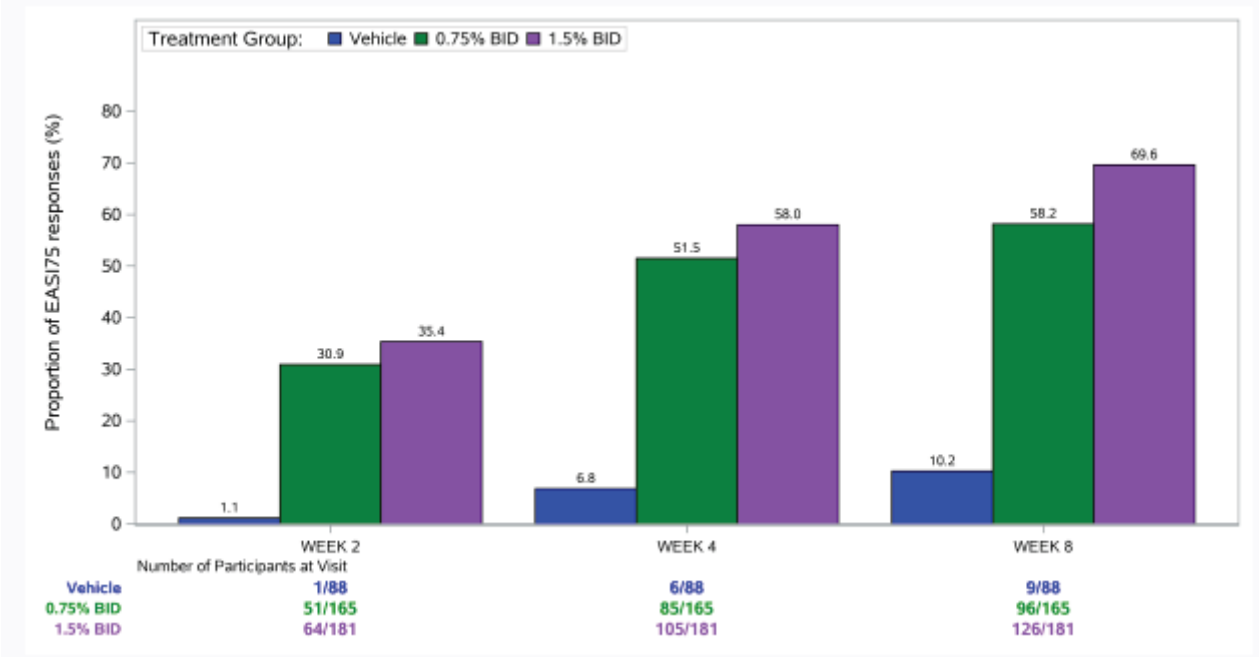
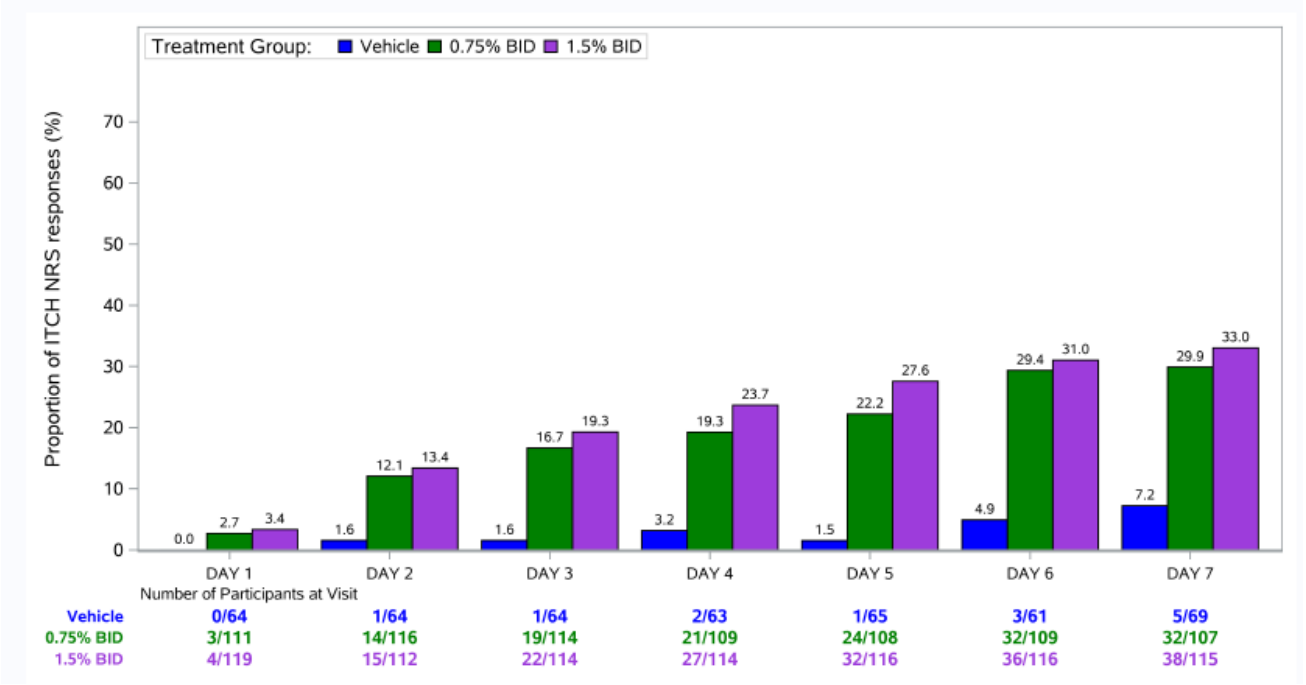


Table 30. Proportion of Participants Achieving ITCH4 at Week 8 and Days 7, 3, and 2 in the Supportive Phase 3 Studies (ITT Population With Age ≥ 18 Years, Baseline EASI Score > 7, Baseline IGA Score = 3, and Baseline Itch NRS Score ≥ 4)

Endpoint Variable	INCB 18424-303			INCB 18424-304			Pooled Population		
	Vehicle Cream BID (N = 28)	Ruxolitinib 0.75% Cream BID (N = 61)	Ruxolitinib 1.5% Cream BID (N = 67)	Vehicle Cream BID (N = 43)	Ruxolitinib 0.75% Cream BID (N = 59)	Ruxolitinib 1.5% Cream BID (N = 57)	Vehicle Cream BID (N = 71)	Ruxolitinib 0.75% Cream BID (N = 120)	Ruxolitinib 1.5% Cream BID (N = 124)
ITCH4 at Week 8									
% (SE)	14.3 (6.61)	52.5 (6.39)	58.2 (6.03)	14.0 (5.28)	47.5 (6.50)	63.2 (6.39)	14.1 (4.13)	50.0 (4.56)	60.5 (4.39)
Stratum-adjusted response rate difference (95% CI)[a]	—	38.6 (20.67, 56.44)	43.3 (25.24, 61.37)	—	34.3 (18.00, 50.53)	49.2 (32.93, 65.46)	—	36.0 (23.89, 48.09)	46.2 (34.29, 58.08)
Overall odds ratio (95% CI)[b,c]	—	6.86 (2.073, 22.707)	7.47 (2.394, 23.294)	—	5.95 (2.142, 16.500)	10.52 (3.806, 29.093)	—	6.05 (2.841, 12.891)	9.13 (4.276, 19.484)
p-value[b]	—	0.0007	0.0001	—	0.0003	< 0.0001	—	< 0.0001	< 0.0001
ITCH4 at Day 7									
% (SE)	11.5 (6.27)	27.3 (6.01)	33.9 (6.01)	4.7 (3.21)	32.7 (6.51)	32.1 (6.41)	7.2 (3.12)	29.9 (4.43)	33.0 (4.39)
95% CI[c]	2.4, 30.2	16.1, 41.0	22.3, 47.0	0.6, 15.8	20.3, 47.1	19.9, 46.3	2.4, 16.1	21.4, 39.5	24.6, 42.4
ITCH4 at Day 3									
% (SE)	3.8 (3.77)	17.5 (5.04)	23.3 (5.46)	0.0 (0)	15.8 (4.83)	14.8 (4.83)	1.6 (1.55)	16.7 (3.49)	19.3 (3.70)
95% CI[c]	0.1, 19.6	8.7, 29.9	13.4, 36.0	0, 9.3	7.5, 27.9	6.6, 27.1	0.0, 8.4	10.3, 24.8	12.5, 27.7
ITCH4 at Day 2									
% (SE)	0.0 (0)	13.8 (4.53)	16.9 (4.88)	2.5 (2.47)	10.3 (4.00)	9.4 (4.02)	1.6 (1.55)	12.1 (3.02)	13.4 (3.22)
95% CI[c]	0, 14.2	6.1, 25.4	8.4, 29.0	0.1, 13.2	3.9, 21.2	3.1, 20.7	0.0, 8.4	6.8, 19.4	7.7, 21.1

Note 1: Data from participants enrolled at Site 461 in Study INCB 18424-304 were excluded.
Note 2: ITCH4 is defined achieving a ≥ 4-point improvement from baseline in Itch NRS score.
[a] Stratum-adjusted rate difference and 95% CI were computed using Mantel Haenszel weights.
[b] Overall odds ratio and p-values were calculated by the CMH test stratified by baseline IGA score and geographic region.
[c] Confidence interval was calculated based on exact methods for binomial distribution.

Figure 17. Proportion of Participants Achieving ITCH4 From Day 1 to Day 7 in the Supportive Phase 3 Studies (ITT Population With Age ≥ 18 Years, Baseline EASI Score > 7, Baseline IGA Score = 3, and Baseline Itch NRS Score ≥ 4)



Long-term treatment period

Following the 8-week vehicle-controlled period there was a long-term treatment period of 44 weeks, in which participants treated AD flares on demand (Figure 14). EASI had not been assessed and assessment of IGA and of BSA affected by AD had been continued. The proportions of participants with no or minimal lesions (IGA scores of 0 or 1) remained between 70%-77% throughout the long-term treatment period, when participants applied study drug as needed (Figure 18). The IGA responses are also reflected in the low percentage of BSA during the long-term treatment period (Figure 19).

Figure 18. Proportion of Participants Achieving IGA Score of 0 or 1 at Each Visit in the Supportive Phase 3 Studies (ITT Population With Age ≥ 18 Years, Baseline EASI Score > 7, and Baseline IGA Score = 3)

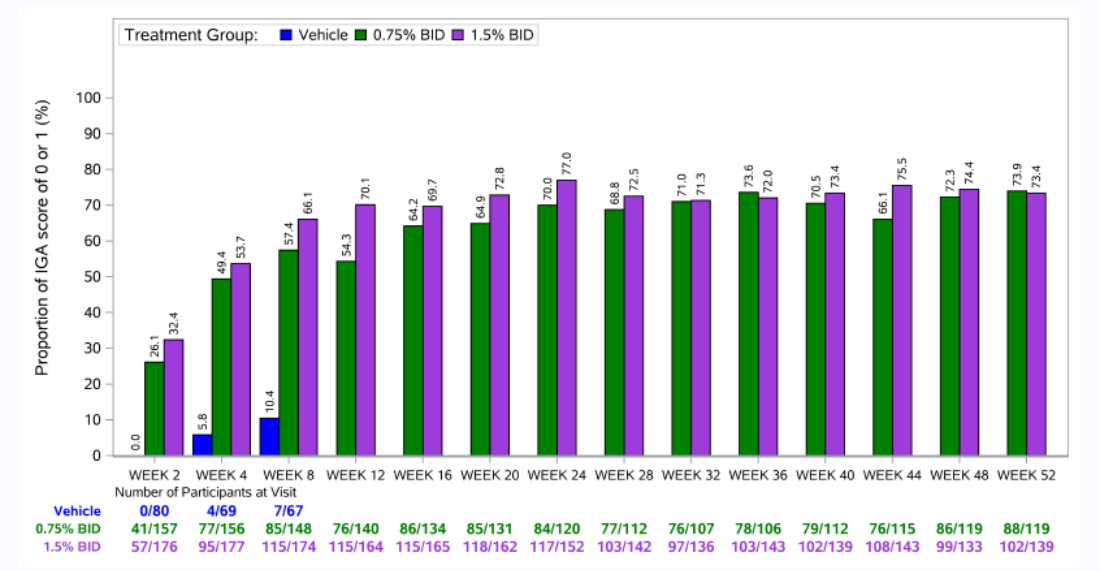
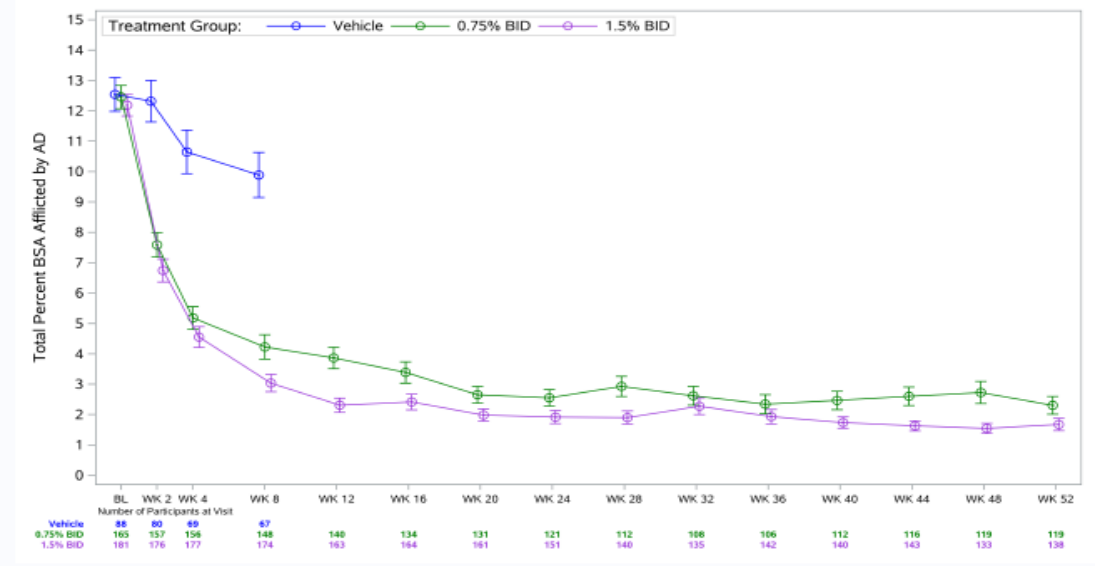


Figure 19. Mean and Standard Error Plot of Total Percent BSA Afflicted by AD in the Treatment Periods (Intent-To-Treat Population with Moderate AD)



Summary of main study(ies)

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial 326

Title: TRuE-AD4. A Phase 3b, Double-Blind, Multicenter, Randomised, Vehicle-Controlled, Efficacy, and Safety Study of Ruxolitinib Cream in Adults With Moderate AD.			
Study design			
Study identifier	(INCB 18424-326).		
Design	Randomised (2:1), double-blind, vehicle-controlled, parallel-group, multi-site, phase 3 trial.		
	Duration of main phase: Duration of Extension phase: Duration of safety follow-up		8 weeks 16 weeks 30 days
Hypothesis	Superiority		
Treatments groups	Ruxolitinib 1.5% cream BID		n=160
	Vehicle cream BID		n=81
Endpoints and definitions	Co-primary endpoints	Proportions EASI75 responders from baseline at Week 8	≥ 75% improvement in Eczema Area and Severity Index score
		Proportions with IGA-TS at Week 8	Investigator's Global Assessment – Treatment Success: score of 0 or 1
	Key secondary endpoint	ITCH4 response rate at Week 8	Improvement ≥4 points in Itch 0-10 NRS
	Key secondary endpoint	ITCH4 response rate at Day 7	
	Key secondary endpoint	ITCH4 response rate at Day 3	
	Key secondary endpoint	ITCH4 response rate at Day 2	
Database lock	17-October-2025		
Results and Analysis			

Between-group comparison				
	Vehicle cream BID	Ruxolitinib 1.5% cream BID	Treatment effect (95% CI)	P-value

Co-primary endpoints				
EASI75 at week 8	15/81 (18.5%)	112/160 (70.0%)	51.4% (40.5 – 62.2)	<0.0001
IGA-TS at week 8	11/81 (13.6%)	98/160 (61.3%)	47.6% (36.9 - 58.2)	<0.0001
Key secondary endpoints				
ITCH4 at week 8	16/81 (19.8%)	100/160 (62.5%)	42.8% (31.4 – 54.2)	<0.0001
ITCH4 at day 7	11/81 (13.9%)	82/160 (51.2%)	37.5% (26.7 – 48.3)	<0.0001
ITCH4 at day 3	8/81 (9.9%)	56/160 (35.1%)	25.5% (15.8 – 35.2)	<0.0001
ITCH4 at day 2	11/81 (13.7%)	48/160 (29.8%)	16.2% (5.8 – 26.6)	0.0072

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose response

The data of the 8-week dose-response study in patients with mild to moderate AD support the choice for ruxolitinib 1.5% cream as the most effective dose for the claimed indication. This dose was also more effective than triamcinolone 0.1% cream.

Design of the pivotal study

The overall design of the pivotal trial (326) is endorsed, in line with the CHMP Scientific Advice (EMA/SA/0000138950), including the inclusion of ruxolitinib 1.5% cream as the only strength, the 'as needed' regimen in the extension phase, and the in-/exclusion criteria.

The pivotal trial was a randomised double-blind vehicle-controlled study of 8 weeks duration, which is considered adequate by the CHMP. The 8-week period is followed by an extension period of 24 weeks with 'as needed' treatment in line with the intended use in practice. The patient population of adults with moderate AD with 10-20% BSA involvement was appropriately selected, notably also regarding a documented recent history of unresponsiveness to TCS/TCI, contra-indications or intolerance to TCS/TCI. The proposed wording of the indication adequately reflects the study population and is in line with centrally approved topical products in dermatology. The choice for EASI75 and IGA-TS as co-primary endpoints is in line with centrally approved products for AD, and inclusion of measures of itch as key-secondary outcomes is also agreed.

In addition, studies 303 and 304 were considered supportive, since they included subjects with moderate AD (75% of the study population) and included a significant number of subjects who had previously used TCS/TCI, though not with a strict requirement for having failed.

Statistical analyses

For the pivotal study 326, the MAH defined an estimand including treatment discontinuation due to any reason as the sole intercurrent event, which would be handled using a composite strategy. If treatment discontinuation is caused by lack of efficacy or adverse events, these reasons can indeed be regarded as treatment failure. Therefore, the proposed estimand, using composite strategy for discontinuation, is acceptable.

The sample size calculation, and assumptions for treatment effect, derived from two phase three studies (303 and 304) are considered acceptable. The randomisation and blinding procedures are considered adequate. The definition of the analysis populations is considered standard and acceptable.

The two co-primary endpoints both had to be statistically significant to claim study success. Key secondary endpoints were analysed in a fixed sequence. This protects the overall type I error rate and is an acceptable method for handling multiplicity.

The analysis of the co-primary endpoints used a Cochrane-Mantel-Haenszel test stratified for baseline EASI score and region, which is considered a standard method for dichotomous data and thus is acceptable. Data after treatment discontinuation and further missing data was handled by non-responder imputation, which follows the estimand strategy, this agreed. To test the missing data handling, sensitivity analysis was performed applying hypothetical strategies, , which is acceptable.

Key secondary endpoints were analysed using the same method as for the coprimary endpoints, which is acceptable.

For the subgroup analyses in the pooled data of supportive studies 303 and 304, the population for the efficacy analyses was the ITT population; *post-hoc*, supportive analyses for this application were performed in the subset of adult patients with moderate AD (baseline EASI score > 7 and IGA score of 3), which is agreed. The primary analysis was performed using an exact logistic regression model, which is suitable for the endpoints, and thus considered acceptable.

Participant flow

The completion rate of the 8-week vehicle-controlled period was 89% overall and 96% for the ruxolitinib group, which is high. Considerably more patients on vehicle (26%) as compared to patients on ruxolitinib 1.5% cream (3.8%) discontinued study treatment, most commonly due to AEs, lack of efficacy or patient withdrawal. While this was appropriately dealt with using the estimand strategy, it is also supportive of the tolerability to ruxolitinib 1.5% cream BID.

Upon CHMP's request, the MAH submitted the final results of study 326 where the efficacy up to week 24 has been confirmed, as already indicated by the long-term supportive data from studies 303 and 304.

Of the 154 patients who completed the 8 weeks of treatment with ruxolitinib 1.5% cream in the vehicle-controlled period, 32 (21%) did have an insufficient response (<EASI50) and were transferred to the escape arm where treatment with ruxolitinib was continued.

Upon CHMP's request, the MAH analysed the follow-up data in patients with insufficient response at week 8 in studies 326 (n=20) and 303/304 (n=22). However, the sample of patients with insufficient response were considered to be too small to draw any robust conclusions. Therefore, the included a discontinuation rule of 8 weeks in SmPC section 4.2, in line with the design of the pivotal study. This was agreed by the CHMP.

Study conduct

Critical protocol deviations and major protocol deviations, occurred in 11% and 48% of participants, respectively. While the critical deviations were more frequent in the ruxolitinib group, as compared to

the vehicle group; given the size of the treatment effect in the co-primary outcomes and the results of the sensitivity analyses as well as the analysis in the PP set, this is not considered to have an impact on the clinical efficacy of ruxolitinib cream in AA.

Baseline data

In the pivotal study, all participants were adult and the study population included approximately as many males as females. There only was a small proportion (8%) of elderly patients, which is in line with the patient population in practice; the availability of only limited data in the elderly is mentioned in the SmPC (section 4.2). Most (68%) patients included in the study were recruited in European countries, which is supportive for generalisability to the EU target population.

The demographic characteristics, as well as the disease characteristics and previous AD treatments, were overall evenly distributed across the two treatment groups.

The disease severity at baseline was reflective of patients with long standing AD (average of 20 years) and moderate disease activity. All participants (but one) had IGA scores of 3, with AD affecting 10% to 20% BSA with a mean (SD) of 15% (3.0%). EASI scores were ranging from 7.1 to 40 with a mean (SD) of 13 (4.1), the majority of participants (80%) had baseline EASI scores <16. Itch NRS scores were ranging from 4 to 10 with a mean (SD) of 7.4 (1.5). In line with the inclusion criteria, all participants had a documented history of inadequate response, intolerance, or contraindication to TCSs and TCIs within 12 months of screening. As expected, all patients had used TCSs (96%) and most had used TCIs (81%); systemic treatments had been used in the previous 12 months by 30% and phototherapy had been used by 8.7%. This is considered critical for supporting the proposed 2nd-line indication (post TCSs and TCIs treatment).

Efficacy data and additional analyses

Treatment effects

The **coprimary endpoints** in the pivotal study 326 were the binary response status of EASI75 from baseline and the binary response status of IGA-TS at Week 8; both endpoints were met. The 4 **key-secondary endpoints** all regarded itch and were met, while being corrected for multiplicity. The treatment effects in both primary endpoints and in the key secondary endpoints are considered as clinically relevant. Overall, the secondary endpoints, not corrected for multiplicity, were supportive of the findings in the co-primary and key secondary endpoints.

The proportion of participants with **EASI75** at week 8 was statistically significantly higher ($p < 0.0001$) in the ruxolitinib 1.5% cream treatment group compared with the vehicle cream group (70% *versus* 19%). The proportion of participants with **IGA-TS** at week 8 also was statistically significantly higher ($p < 0.0001$) in the ruxolitinib 1.5% cream treatment group compared with the vehicle cream group (61% *versus* 14%). For both co-primary endpoints, sensitivity analyses to evaluate the impact of missing data (longitudinal logistic regression and multiple imputation) as well as the analysis in the PP population confirmed these results. For the proportions of participants reaching **ITCH4**, the effects in the ruxolitinib 1.5% cream treatment group at week 8, day 7, day 3, and day 2 were statistically significantly larger than those in the vehicle cream treatment group. At week 8, the proportion of patients with a reduction in Itch NRS of ≥4 points was larger ($p<0.0001$) in the ruxolitinib group as compared to the vehicle group (63% *versus* 20%). The treatment effects (ruxolitinib *versus* placebo) were also statistically significant at day 7 (52% *versus* 14%), day 3 (35% *versus* 10%), and day 2 (29% *versus* 14%).

Clinical relevance

The treatment effect (ruxolitinib – vehicle) in EASI75 was 51% and in IGA-TS was 48%, which is of similar size. This is considered a clinically relevant treatment effect for 8 weeks treatment of moderate AD and translates in a NNT of 2 patients. This is especially relevant, as IGA-TS is an absolute measure reflecting the treatment target of clear/almost clear skin. A reduction in itch of 4 points is considered a clinically relevant outcome, and the treatment effects at Week 8 and earlier are considered as clinically relevant in size. For patients it is especially important that an early effect in itch reduction can be experienced, as itch is the cardinal patient symptom of AD.

Besides effects on itch as main patient symptom, there were also supportive effects on skin pain, in patients treated with ruxolitinib as compared to vehicle. There also were supportive treatment effects in PROs including SCORAD, DLQI, POEM and the PROMIS Sleep questionnaire. Sleep disturbance due to itch is a known phenomenon for patients with AD, therefore an effect on sleep is considered clinically relevant.

The following additional secondary endpoints were considered clinically relevant and thus their inclusions in SmPC section 5.1 were found acceptable: the proportion of patients achieving IGA-TS, EASI75, ITCH4, as well as DLQI, POEM, PROMIS sleep disturbance and sleep-related impairment, at each postbaseline visit.

Onset of effect

While there was a treatment effect in EASI75 at week 8 of 50%, already at week 2 the proportion of responders was much larger in the ruxolitinib group as compared to vehicle (44% *versus* 3.7%), and the treatment effect had approached 50% in week 4 (61% *versus* 12%).

Continued treatment on demand

In patients with a sufficient response (EASI50) at week 8, treatment was continued and of the patients treated with ruxolitinib, most (82% - 86%) patients could maintain EASI75 response in weeks 12 to 24. These trends in EASI75 are reflected by similar results in IGA-TS over time. In this follow-up period, itch scores remained low for patients with a sufficient response (EASI50) at week 8 who used ruxolitinib as needed.

Treatment with ruxolitinib cream is intended to be applied on active lesions until lesions are clear, as reflected in the SmPC (section 4.2). That also means that treatment will be intermittent when lesions recur, as also reflected in the posology section. It is thus supportive that, during the extension period in which study treatment was applied on demand, participants in the ruxolitinib 1.5% cream treatment group maintained the proportion of time off study treatment due to lesion clearance compared with the week 8 – 12 period. In the vehicle-controlled extension period, retreatment upon clearance occurred in 64/68 (94%) of patients who stopped due to total clearance. Time off treatment ranged between 24% - 33%, which also means that some treatment still is necessary. It is supportive for the treatment effect that in the ruxolitinib 1.5% cream group only few patients needed escalation to systemic treatment. Most patients who stopped due to total clearance needed retreatment, the median time to retreatment was 5 days. However, the reduction in % BSA over time and the high proportions of IGA-TS over time, show that the area to be treated was reduced as compared to baseline. Consequently, the amount of cream used in the on-demand period was considerably lower than in the first 8 weeks. Initially the patients used a daily average of nearly 8-gram cream (range: 0.2 – 17), which reduced to a daily average of about 2-gram cream (range: 0 – 7) in the extension period. This is relevant for long-term safety, given that not many patients could completely stop treatment without recurrence of AD (see safety discussion).

In addition, the proposed as-needed dosing strategy was adequately justified by the MAH which allows for effective maintenance and control of disease signs and symptoms while keeping the systemic concentrations low.

Treatment discontinuation

For patients with an *insufficient* response (<EASI50) at week 8 while being on ruxolitinib, treatment with ruxolitinib was continued in the open-label escape arm. Based on the available data, about 66% of patients eventually reached EASI75 and 55% eventually reached IGA-TS after 4 additional weeks of treatment (week 12). The MAH included a discontinuation rule of 8 weeks, in line with the design of the pivotal study. This is agreed. This information has been adequately reflected in SmPC section 4.2.

Rebound

No randomised withdrawal design to study rebound was performed, although recommended in the given CHMP SA. Instead, rebound/relapse was assessed during the 30-day Safety Follow-up Period for participants who had an EASI75 response from baseline at the end of the extension period at week 24. Among participants who had EASI75 at week 24, 15/81 participants (19%) in the ruxolitinib cream treatment group relapsed at the safety follow-up visit after study treatment discontinuation. Two of the participants who relapsed had an EASI score above their baseline score (rebound). However, the 2 instances of disease activity scores higher than baseline after treatment withdrawal are not interpreted as a causal sign of rebound. Indeed, the course of AD is fluctuating, and it cannot be excluded that some patients with relapse after treatment withdrawal will have higher disease activity than baseline. To date, there also is no clear mechanistic reason or suspect of rebound following treatment withdrawal with JAKi (in contrast to treatment with e.g. corticosteroids). In SmPC section 4.2, a clear recommendation has been introduced to re-initiate treatment as needed in case of recurrence of signs and symptoms, which is considered sufficient by the CHMP.

Subgroup analyses

Subgroup analyses were performed for each of the coprimary endpoints, EASI75 and IGA-TS. According to the results, the treatment effects were constant over the predefined subgroups of baseline EASI score (≥ 16, < 16), age (< 65 years, ≥ 65 years), sex (female, male), race, geographic region (Europe, ROW), prior systemic or phototherapy (yes/no), and season. Only for the small subgroups of patients >65 years of age and patients included in summer, the size of the treatment effect is uncertain and seemingly lower. Due to the small groups, this is however not considered relevant for the overall B/R assessment.

Supportive studies

The approach of subgroup analysis in adult patients with moderate AD to support the results of the single pivotal study is endorsed, in line with the CHMP SA.

The main differences in design between the pivotal study 326 and identical supportive studies 303 and 304 are, that in the supportive studies patients with mild and moderate AD and adolescents and adults were included. While basically most patients had experience with previous therapies, there was no strict requirement of failure to TCS/TCI. Further, only IGA-TS, not EASI75, was used in the follow-up period.

In the overall population of the supportive studies separately, all three main endpoints of EASI75, IGA-TS and Itch response at week 8, were met, and the results were supported by the sensitivity analyses. The treatment effects in EASI75 (ruxolitinib 1.5% cream - vehicle) were 37% and 47% in the two studies, the treatment effects in IGA-TS were of similar magnitude, and the treatment effects in ITCH4 were around 35%. This means that the treatment effects of the supportive studies overall are positive

and robust, as well as of relevant size. Consequently, the supportive studies are suitable for the subgroup analysis on adults with moderate AD, as performed by the MAH. The subgroup analyses concerning previous treatments in the pooled data of adult patients with moderate AD, although *post-hoc*, were similar as in the pivotal trial and thus supported the claimed indication in moderate AD.

In the subset of adults with moderate AD in the pooled supportive studies, the baseline demographic, disease, and previous treatment characteristics were overall evenly distributed over the treatment groups. The data were also reflective of a population of adult patients with moderate AD having had experience in first-line therapies and/or systemic therapies.

The treatment differences for the ruxolitinib 1.5% cream treatment group versus the vehicle cream treatment were positive and showed nominal p-values <0.0001 for all main endpoints. The treatment effects at week 8 were similar in size as the treatment effects found in the pivotal study, which is supportive for robustness of results. The proportion of EASI75 responders at week 8 was 10% in the vehicle group and 70% in the ruxolitinib 1.5% cream group (p<0.0001) and the proportion of IGA-TS was 8.0% in the vehicle group and 64% in the ruxolitinib 1.5% cream group (p<0.0001). At week 8, the proportion of participants with an ITCH4 response was 14% in the vehicle cream group and 61% in the ruxolitinib 1.5% cream group (p<0.0001). Like in the pivotal study, the treatment effect in EASI75 was apparent at week 2 and a treatment effect in itch was apparent at day 2. From week 12 to week 52, patients applied ruxolitinib cream on demand. Like in the pivotal study, the treatment effects remained constantly high over time, ranging between 70% - 77% in IGA-TS (EASI75 was not assessed) and low %BSA affected by AD.

Assessment of paediatric data on clinical efficacy

A total of 130 adolescents (12 to < 18 years; n = 87 ruxolitinib 1.5% cream; n = 43 vehicle) with mild-to-moderate atopic dermatitis were included in a pooled analysis of the two Phase 3 supportive studies (303 and 304). Ruxolitinib 1.5% cream had a higher response rate than vehicle at week 8 for the primary endpoint, EASI75 (61% versus 35%), and the key secondary endpoints, IGA-TS (51% versus 14%) and ITCH4 (52% versus 17%). Those paediatric results are included in SmPC section 5.1, including a cross-reference to and from SmPC section 4.2 highlighting that no recommendation on a posology can currently be made.

2.4.4. Conclusions on the clinical efficacy

In the pivotal study 326 in adult patients with moderate AD, ruxolitinib 1.5% cream BID was more effective than vehicle in reducing signs and symptoms of AD. The co-primary endpoints (EASI75 and IGA-TS at week 8) and the multiplicity-corrected key-secondary endpoints (Itch NRS response at week 8 and earlier) were all met. The treatment effects were considered clinically relevant. The data of on demand treatment of ruxolitinib 1.5% cream from week 8 up to week 24 show maintenance of response and reduction of the % BSA to be treated. The data are supported by comparable results in the subgroup of adult patients with moderate AD in the pooled data of the 2 identical randomised vehicle-controlled studies (303 and 304). The efficacy results support the indication of treatment of moderate atopic dermatitis in adult patients for whom topical corticosteroids and topical calcineurin inhibitors are inadequate or inappropriate.

2.4.5. Literature references

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16:219-242.

Buysse DJ, Yu L, Moul DE. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. Sleep 2010;33:781-792.

Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol 2004;140:1513-1519.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)-- a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-216.

Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1980;92:44-47.

Hanifin JM, Baghoomian W, Grinich E, et al. The Eczema Area and Severity Index—A Practical Guide. Dermatitis 2022;33(3):187-92.

Silverberg JI, DeLozier A, Sun L, et al. Psychometric properties of the itch numeric rating scale, skin pain numeric rating scale, and atopic dermatitis sleep scale in adult patients with moderate-to-severe atopic dermatitis. Health Qual Life Outcomes. 2021;19:247.

2.5. Clinical safety

Introduction

The safety findings from the pivotal Phase 3b study (INCB 18424-326) are supported by integrated analyses from three pooled safety populations derived from the overall clinical development program of ruxolitinib cream in adults with AD:

Pool 1a includes data from adult participants in the supportive Phase 3 studies INCB 18424-303 and INCB 18424-304 during the 8-week double-blind, vehicle-controlled period (n = 612).

Pool 1b comprises data from the same studies across the full 52-week duration, including both the vehicle-controlled period and the long-term safety (LTS) period (n = 484). This pool provides information on the long-term safety of ruxolitinib 1.5% cream following 8 weeks of continuous treatment and subsequent as-needed use.

The largest integrated dataset, designated as the All AD Population (Pool 2), includes 1113 adult patients treated with ruxolitinib 1.5% cream BID (486.77 patient-years) and incorporates data from the pivotal Phase 3b study (INCB 18424-326) as well as all supportive studies involving patients with AD affecting up to 20% body surface area (INCB 18424-206, INCB 18424-215, INCB 18424-303, INCB 18424-304, INCB 18424-901, and INCB 18424-902). Additionally, safety under conditions of exaggerated use was evaluated in a dedicated maximum-use study (INCB 18424-103).

Patient exposure

A total of 1113 adult participants with AD applied ruxolitinib 1.5% cream at least once in the pooled studies. Across the pooled studies included in this submission, 257 participants (23.1%) were treated with ruxolitinib 1.5% cream BID for ≥ 24 to < 52 weeks and 180 participants (16.2%) were treated

with ruxolitinib 1.5% cream BID for ≥ 52 weeks. Overall ruxolitinib 1.5% cream exposure was 486.77 PY for the 1113 participants in the All-AD Population.

Data on ruxolitinib 1.5% cream exposure under maximum-use conditions are available for 41 participants (21 adolescents and 20 adults) with extensive AD (ie, affecting ≥ 25% BSA and an IGA score of ≥ 2) in the maximum-use study INCB 18424-103.

As expected with the maximum-use study design, participants in Study INCB 18424-103 had a higher mean total %BSA involvement at baseline (38%, compared with 15% in the pivotal Phase 3b study) and applied higher amounts of study drug.

Adverse events

In study 326, during the 8-week double-blind, vehicle-controlled period, the overall incidences of treatment-emergent adverse events (TEAEs) were similar between the ruxolitinib 1.5% cream and vehicle groups (35.0% vs. 35.8%, respectively). Few participants experienced serious TEAEs (1.9% in ruxolitinib vs. 1.2% in vehicle), and one participant in the vehicle group had a TEAE with a fatal outcome (sudden death, unrelated to study drug).

In the ongoing vehicle-controlled extension double-blind period and open-label ruxolitinib 1.5% cream escape arm, the overall incidences of TEAEs were generally consistent with those observed in the initial vehicle-controlled period.

Similar patterns were noted for participants who received ruxolitinib 1.5% cream throughout the study (i.e., those initially randomised to ruxolitinib and continuing in the extension or entering the escape arm). Overall, rates of serious TEAEs (2.5%), TEAEs leading to discontinuation (0.6%) or interruption (1.3%), and Grade 3 or higher TEAEs (3.8%) remained low, with no fatal outcomes reported.

These findings are supported by analyses from the supportive Phase 3 studies (INCB 18424-303 and INCB 18424-304). In **Pool 1a** (supportive Phase 3 vehicle-controlled population, n=612), the overall TEAE incidence was comparable between ruxolitinib 1.5% cream and vehicle, aligning with observations from the vehicle-controlled period of Study INCB 18424-326.

In **Pool 1b** (supportive Phase 3 52-week population, n=484), the TEAE incidence was higher in the ruxolitinib 1.5% cream group compared to vehicle, as expected given the longer period of observation (44-52 weeks compared with 8 weeks) for participants on active treatment. This difference was not apparent after adjusting for exposure.

The incidences of Grade 3 or higher TEAEs, serious TEAEs, and TEAEs leading to study drug discontinuation or interruption remained low, and no participant had a TEAE with a fatal outcome. With the inclusion of participants from additional studies in the All-AD Population (Pool 2), the safety findings were consistent with those observed in the pivotal Phase 3b study 326 and the supportive Phase 3 studies (303 and 304). The overall incidences of Grade 3 or higher TEAEs, serious TEAEs, and TEAEs leading to study drug discontinuation or interruption for the All-AD Population were low (< 4% for all categories). There were no TEAEs with a fatal outcome among participants on ruxolitinib cream.

All AD Population (Pool 2): A total of 483 participants (43.4%) had at least 1 TEAE; the exposure-adjusted IR of TEAEs was 99.2 per 100 PY. Of these, 63 participants (5.7%) had treatment-related TEAEs. The overall incidences of Grade 3 or higher severity TEAEs, serious TEAEs, and TEAEs leading to study drug discontinuation or interruption were low (< 4% for all categories). There were no TEAEs with a fatal outcome. With the additional participants from other studies included in the All AD Population, the overall incidences of TEAEs across all categories and the exposure-adjusted IRs of TEAEs remained generally consistent with those observed in participants who applied ruxolitinib 1.5%

cream BID in the pivotal Phase 3b Study326 and the Supportive Phase 3, 52-Week Population, suggesting that treatment with ruxolitinib 1.5% cream BID was safe and well tolerated among participants with AD.

Serious adverse event/deaths/other significant events

Adverse Events of Grade 3 or Higher Severity

The overall incidence of Grade 3 or higher severity TEAEs in the Supportive Phase 3, Vehicle-Controlled Population was low and similar between the treatment groups (1.5% and 2.0% of participants in the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups, respectively).

Except for AD in 2 participants in the vehicle cream BID treatment group, all other Grade 3 or higher severity TEAEs were reported in 1 participant each in either treatment group. The majority of Grade 3 or higher severity TEAEs resolved with no action taken with the study drug. Grade 3 or higher severity TEAEs of interest included cerebrovascular accident (MACE and other thromboembolic events), hypopharyngeal cancer (malignancies excluding nonmelanoma skin neoplasms), and herpes zoster (herpes zoster and other viral skin infections). Two participants each in both treatment groups had Grade 3 or higher severity TEAEs considered related to the study drug by the investigator, including AD in 2 participants in the vehicle cream BID treatment group and herpes zoster and papule in 1 participant each in the ruxolitinib 1.5% cream BID treatment group. No meaningful trends were observed in the incidence of Grade 3 or higher severity TEAEs between the Supportive Phase 3, Vehicle-Controlled Population and the pivotal Phase 3b Study INCB 18424-326.

The overall incidence of Grade 3 or higher severity TEAEs in the vehicle cream BID and ruxolitinib 1.5% cream BID (total) treatment groups remained low (1.5% and 5.8%, respectively) in the Supportive Phase 3, 52-Week Population (pool 1b). The higher incidence of Grade 3 or higher severity TEAEs in the ruxolitinib 1.5% cream BID (total) treatment group was reflective of the longer period of observation (44-52 weeks compared with 8 weeks) for participants on active treatment. The most frequently reported Grade 3 or higher severity TEAEs in the ruxolitinib 1.5% cream BID (total) treatment group were bronchitis and herpes ophthalmic (2 participants [0.4%] each); all other Grade 3 or higher severity TEAEs were reported in 1 participant each. Five participants (1.0%) in the ruxolitinib 1.5% cream BID (total) treatment group had Grade 3 or higher severity TEAEs considered related to the study drug by the investigator, including hypertriglyceridemia in 1 participant in the vehicle to ruxolitinib 1.5% cream BID treatment group, and herpes ophthalmic in 2 participants and herpes zoster, hordeolum, and papule in 1 participant each in the ruxolitinib 1.5% cream BID treatment group. All of these events were Grade 3, nonserious, and resolved after dose reduction (herpes ophthalmic), study drug interruption (hypertriglyceridemia, herpes ophthalmic, and hordeolum), or study drug discontinuation (papule); no action was taken with study drug for the event of herpes zoster. No meaningful differences were observed in the incidence of Grade 3 or higher severity TEAEs during the 8-week, double-blind, vehicle-controlled period and with an additional 44 weeks of as-needed treatment with ruxolitinib 1.5% cream.

All AD Population (Pool 2): The incidence of Grade 3 or higher severity TEAEs remained low (3.5%) and consistent with that observed in participants who applied ruxolitinib 1.5% cream BID in the pivotal Phase 3b Study 326 and the Supportive Phase 3, 52-Week Population. The majority of events resolved and did not result in a change in study drug application. The majority of Grade 3 or higher severity TEAEs were considered not related to ruxolitinib 1.5% cream by the investigator. Five participants (0.4%), all of whom were in the Supportive Phase 3, 52-Week Population, had Grade 3 or higher severity TEAEs considered related to the study drug by the investigator.

Deaths

Pivotal Phase 3b Study 326: One participant (1.2%) in the vehicle cream BID treatment group (79-year-old male with a history of hypertension) had a TEAE of sudden death (cause unknown) during the double-blind, vehicle-controlled period. The event was considered not related to the study drug by the investigator. There were no TEAEs with a fatal outcome during the vehicle-controlled extension, double-blind period and open-label escape arm of the study as well as in participants who applied ruxolitinib 1.5% cream BID from baseline to Week 24.

Supportive Phase 3 Studies 303 and 304 (Pool 1a and Pool 1b): There were no TEAEs with a fatal outcome in the Supportive Phase 3, Vehicle-Controlled Population and Supportive Phase 3, 52-Week Population.

All AD Population (Pool 2): There were no TEAEs with a fatal outcome.

Serious Adverse Events

Pivotal Phase 3b Study 326: The incidence of SAEs during the double-blind, vehicle-controlled period was similar between the treatment groups (1.2% and 1.9% in the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups, respectively). All serious TEAEs were reported in 1 participant each, namely, sudden death in the vehicle cream BID treatment group and radius fracture, suicide attempt, and hypertension in the ruxolitinib 1.5% cream BID treatment group. All serious TEAEs were Grade 3 or higher in severity. Serious TEAE of interest included sudden death (all-cause mortality); all other serious TEAEs resolved without action taken with study drug except for suicide attempt that led to discontinuation of study drug. One participant (0.8%) in the ruxolitinib 1.5% cream BID treatment group had a serious TEAE of spontaneous abortion on Day 144 during the vehicle-controlled extension, double-blind period. The action taken with the study drug was not applicable as the participant had already discontinued treatment on Day 130. No participant in the escape arm had serious TEAEs. Overall, 4 participants (2.5%) who applied ruxolitinib 1.5% cream from baseline to Week 24 had serious TEAEs; all events were reported in 1 participant each. None of the serious TEAEs were considered related to the study drug by the investigator.

The overall incidence of serious TEAEs for the vehicle cream BID (1.0%) and ruxolitinib 1.5% cream BID (0.7%) treatment groups was low, and no serious TEAEs (by PT) were reported in more than 1 participant. AD in 1 participant in the vehicle cream BID treatment group was the only serious TEAE considered related to the study drug by the investigator. Serious TEAEs of interest included cerebrovascular accident (MACE and other thromboembolic events) and hypopharyngeal cancer.

In the Supportive Phase 3, 52-Week Population, the overall incidence of serious TEAEs in the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups remained low (1.0% and 2.1%, respectively). No serious TEAEs (by PT) were reported in more than 1 participant, and the event of AD in 1 participant in the vehicle cream BID treatment group was the only serious TEAE considered related to the study drug by the investigator. No action was taken with the study drug in the majority of serious TEAEs except for hypopharyngeal cancer and AD in the vehicle cream BID treatment group and cerebrovascular accident in the ruxolitinib 1.5% cream BID treatment group, which led to discontinuation of study drug, and cholangitis, jaundice cholestatic, and pneumonia in the ruxolitinib 1.5% cream BID treatment group, which led to interruption of study drug. Serious TEAEs of interest among participants in the supportive Phase 3 studies included hypopharyngeal cancer in 1 participant in the vehicle cream BID treatment group (malignancies excluding nonmelanoma skin neoplasms); cerebrovascular accident in 1 participant in the ruxolitinib 1.5% cream BID treatment group and deep vein thrombosis and pulmonary embolism in 1 participant in the ruxolitinib 1.5% cream BID treatment group (MACE and other thromboembolic events); and bronchitis, chronic tonsillitis, and pneumonia in 1 participant each in the ruxolitinib 1.5% cream BID treatment group.

All AD Population (Pool 2): No safety concerns were identified with 8 weeks of continuous use of ruxolitinib 1.5% cream followed by as-needed use for up to additional 44 weeks in adult participants with AD.

A total of 14 participants (1.3%) had ≥ 1 serious TEAE; all serious TEAEs were reported in 1 participant each, and none of the events were considered related to the study drug by the investigator. The majority of events resolved and did not result in a change in the study drug application.

Other Significant Adverse Events

Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation

Pivotal Phase 3b Study INCB 18424-326

The incidence of TEAEs leading to discontinuation of study drug during the double-blind, vehicle-controlled period of Study 326 was higher in the vehicle cream BID treatment group (7 participants [8.6%]) compared with the ruxolitinib 1.5% cream BID treatment group (1 participant [0.6%]). Suicide attempt was the only TEAE leading to discontinuation of study drug in the ruxolitinib 1.5% cream BID treatment group; the event was Grade 4, serious, considered not related to the study drug by the investigator, and resolved.

In the vehicle cream BID treatment group, TEAEs leading to discontinuation of study drug were predominantly the result of exacerbations of the underlying condition (PT: AD in 4 participants [4.9%]); all other TEAEs leading to discontinuation of study drug (application site dermatitis, dermatitis infected, and eczema) were reported in 1 participant each. All events were Grade 1 or 2 and nonserious; the events of AD in 2 participants and application site dermatitis in 1 participant were considered related to the study drug by the investigator. The events of AD in 2 participants and dermatitis infected and eczema in 1 participant each were not resolved.

There were no TEAEs leading to discontinuation of study drug during the vehicle-controlled extension, double-blind period and open-label escape arm of the study.

Overall, 1 participant (0.6%) who applied ruxolitinib 1.5% cream from baseline to Week 24 had a TEAE of suicide attempt leading to discontinuation of study drug, consistent with that reported during the double-blind, vehicle-controlled period.

Supportive Phase 3 Studies INCB 18424-303 and INCB 18424-304 (Pool 1a and Pool 1b)

The overall incidence of TEAEs leading to study drug discontinuation was low, with a higher incidence for participants in the vehicle cream BID treatment group (3.9%) compared with the ruxolitinib 1.5% cream BID treatment group (1.0%). Similar to those in the pivotal Phase 3b study, TEAEs leading to discontinuation of study drug in the vehicle cream BID treatment group in the Supportive Phase 3, Vehicle-Controlled Population were predominantly the result of exacerbations of the underlying condition (PT: AD in 5 participants [2.4%]). In the ruxolitinib 1.5% cream BID treatment group, the majority of events were Grade 1 or 2, with the exception of Grade 4 serious event of cerebrovascular accident and Grade 3 nonserious event of papule. The events of papule, pruritus, and urticaria in the ruxolitinib 1.5% cream BID treatment group were considered related to the study drug by the investigator and resolved after study drug discontinuation.

Of note, the participant in the ruxolitinib 1.5% cream BID treatment group who discontinued study drug due to a TEAE of urticaria had completed the double-blind, vehicle-controlled treatment period prior to discontinuation; hence, this event was not reflected in the disposition as the primary reason for study drug discontinuation of AE.

The overall incidence of TEAEs leading to study drug discontinuation in the vehicle cream BID and ruxolitinib 1.5% cream BID (total) treatment groups remained low (3.9% and 0.8%, respectively) in the Supportive Phase 3, 52-Week Population. There were no additional TEAEs leading to study drug discontinuation reported during the 44-week LTS period of the supportive Phase 3 studies.

All Atopic Dermatitis Population (Pool 2)

No safety concerns were identified.

A total of 5 participants (0.4%) had ≥ 1 TEAE leading to study drug discontinuation.

Treatment-Emergent Adverse Events Leading to Study Drug Interruption

Pivotal Phase 3b Study INCB 18424-326

The incidence of TEAEs leading to study drug interruption during the double-blind, vehicle-controlled period of Study INCB 18424-326 was low in both treatment groups (2 participants each [2.5% and 1.3% in the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups, respectively]. All TEAEs leading to interruption of study drug were related to exacerbations of the underlying condition, application site reactions, or other skin-related events. In the ruxolitinib 1.5% cream BID treatment group, the events included application site acne and AD in 1 participant each. In the vehicle cream BID treatment group, the events included application site erythema, application site pain, and application site pruritus in 1 participant and application site infection in another participant. All events were Grade 1 or 2, nonserious, considered related to the study drug by the investigator except for application site infection, and resolved.

One participant (0.8%) in the ruxolitinib 1.5% cream BID treatment group had a TEAE of application site folliculitis (2 events) leading to study drug interruption during the vehicle-controlled extension, double-blind period. This participant also had a TEAE of application site acne leading to study drug interruption during the double-blind, vehicle-controlled period. The events of application site folliculitis and application site acne were Grade 1, nonserious, and considered related to the study drug by the investigator. The second event of application site folliculitis was not resolved at the time of data cutoff.

No participant in the escape arm had TEAEs leading to study drug interruption.

Overall, 2 participants (1.3%) who applied ruxolitinib 1.5% cream from baseline to Week 24 had TEAEs leading to study drug interruption: application site acne and application site folliculitis in 1 participant and AD in 1 participant.

Supportive Phase 3 Studies INCB 18424-303 and INCB 18424-304 (Pool 1a and Pool 1b)

In the Supportive Phase 3, Vehicle-Controlled Population, the incidence of TEAEs leading to study drug interruption was low in both treatment groups (5 participants [2.4%] in the vehicle cream BID and 7 participants [1.7%] in the ruxolitinib 1.5% cream BID treatment groups;). No TEAEs leading to study drug interruption were reported in more than 1 participant. In the ruxolitinib 1.5% cream BID treatment group, the majority of events were Grade 1 or 2, with the exception of Grade 3 serious events of cholangitis and cholestatic jaundice. The investigator assessed the events of skin irritation, application site irritation, neutropenia, herpes simplex, and differential white blood cell count abnormal as related to the study drug. All events resolved.

The overall incidence of TEAEs leading to study drug interruption in the vehicle cream BID and ruxolitinib 1.5% cream BID (total) treatment groups remained low (2.4% and 3.5%, respectively). Neutropenia (2 participants [0.4%] in the ruxolitinib 1.5% cream BID [total] treatment group) was the only TEAE leading to study drug interruption reported in more than 1 participant; all other events were reported in 1 participant each in either treatment group. The majority of events were Grade 1 or 2 in

severity; additional Grade 3 or higher severity TEAEs included Grade 4 serious pneumonia and Grade 3 nonserious treatment-related events of hypertriglyceridemia, herpes ophthalmic, and hordeolum. All events resolved.

No meaningful differences were observed in the incidence of TEAEs leading to study drug interruption during the 8-week, double-blind, vehicle-controlled period and with an additional 44 weeks of as-needed treatment with ruxolitinib 1.5% cream.

All Atopic Dermatitis Population (Pool 2)

The incidence of TEAE leading to study drug interruption in the All-AD Population remained low (21 participants [1.9%]) and consistent with that observed in participants who applied ruxolitinib 1.5% cream BID in the pivotal Phase 3b Study INCB 18424-326 and the Supportive Phase 3, 52-Week Population. Neutropenia, application site irritation, and AD (2 participants [0.2%] each) were the only TEAEs occurring in > 1 participant in the ruxolitinib 1.5% cream BID treatment group. The majority of events were Grade 1 or 2 in severity and resolved; no additional participants in the All-AD Population had Grade 3 TEAEs leading to study drug interruption other than those reported in the supportive Phase 3 studies.

Application Site Reactions

Pivotal Phase 3b Study INCB 18424-326

The overall incidence of application site reactions was low and similar between the treatment groups (7.4% and 5.6% of participants in the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups, respectively). Among these, application site pain was more commonly reported in the vehicle cream BID treatment group (6.2% vs 1.3% in the ruxolitinib 1.5% cream BID treatment group), which could be attributed to worsening of the underlying disease in the absence of an active treatment, and application site acne was reported in the ruxolitinib 1.5% cream BID treatment group only (4.4% vs 0 in the vehicle cream BID treatment group).

Application site reaction events were Grade 1 or 2 in severity and nonserious, and most events were considered related to the study drug by the investigator except for application site infection in 1 participant in the vehicle cream BID treatment group. A single event, application site dermatitis in a participant in the vehicle cream BID treatment group, led to permanent discontinuation of study drug and was treated with topical methylprednisolone aceponate. In addition, 2 participants with application site reaction events (application site infection in 1 participant in the vehicle cream BID treatment group and application site acne in 1 participant in the ruxolitinib 1.5% cream BID treatment group) were treated with a concomitant medication.

There were no application site reaction events reported in the vehicle cream BID treatment group during the 16-week, vehicle-controlled extension, double-blind period. The incidences of application site reaction events in the ruxolitinib 1.5% cream BID treatment group during the vehicle-controlled extension, double-blind period (2.5%) and for the escape arm (1.2%) remained low. All 3 participants in the ruxolitinib 1.5% cream BID treatment group with application site reaction events (application site acne, application site folliculitis, and application site infection in 1 participant each) during the 16-week, vehicle-controlled extension, double-blind period were treated with a concomitant medication.

The cumulative incidence of application site reaction events in participants who applied ruxolitinib 1.5% cream from baseline to Week 24 included application site acne (5.0%); application site pain (1.3%); and application site folliculitis, application site infection, and application site edema in 1 participant (0.6%) each.

Across the whole study (baseline to Week 24), the incidence of application site reaction events was similar between the treatment groups (7.4% and 5.9% in the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups, respectively); however, the exposure-adjusted IR was higher in the vehicle cream BID treatment group compared with the ruxolitinib 1.5% cream BID treatment group.

Supportive Phase 3 Studies INCB 18424-303 and INCB 18424-304 (Pool 1a and Pool 1b)

In the Supportive Phase 3, Vehicle-Controlled Population, the incidence of application site reaction events was higher in the vehicle cream BID treatment group compared with the ruxolitinib 1.5% cream BID treatment group (6.8% vs 1.5%). The most frequently reported application site reactions were application site pain (LLTs were primarily application site burning or application site stinging; 4.9% in the vehicle cream BID treatment group and 0.7% in the ruxolitinib 1.5% cream BID treatment group) followed by application site pruritus (2.4% and 0.2%, respectively). The higher frequency of application site pain (similar to Study INCB 18424-326) and application site pruritus in the vehicle cream BID treatment group could be attributed to worsening of the underlying disease in the absence of active treatment.

No application site reaction events in the ruxolitinib 1.5% cream BID treatment group led to study drug discontinuation, and 2 participants (1.0%) in the vehicle cream BID treatment group had application site reactions that led to discontinuation of study drug (application site burn and application site swelling in 1 participant and application site pain in 1 participant). All application site reaction events were nonserious, Grade 1 or 2 in severity, and resolved.

The incidence of application site reaction events with inclusion of data from the LTS periods of the Phase 3 studies remained low overall. Application site reaction events in the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups in the Supportive Phase 3, 52-Week Population were similar to those in the Supportive Phase 3, Vehicle-Controlled Population.

Application site reactions were more common in participants who applied vehicle cream BID compared with participants who applied ruxolitinib 1.5% cream BID (6.8% vs 1.2%). Similarly, the exposure-adjusted IR of application site reactions was higher in the vehicle cream BID treatment group compared with the ruxolitinib 1.5% cream BID treatment group (49.3 vs 1.6 per 100 PY).

The most frequently reported application site reactions were application site pain (LLTs included application site burning, application site stinging, and application site pain; 4.9% in the vehicle cream BID treatment group and 0.6% in the ruxolitinib 1.5% cream BID [total] treatment group) and application site pruritus (2.4% in the vehicle cream BID treatment group and 0.2% in the ruxolitinib 1.5% cream BID [total] treatment group). No application site reactions led to study drug discontinuation aside from those described in the Supportive Phase 3, Vehicle-Controlled Population.

All Atopic Dermatitis Population (Pool 2)

Overall, the incidence of application site reaction events in the All-AD Population remained low (2.1%) and consistent with that observed in participants who applied ruxolitinib 1.5% cream BID in the pivotal Phase 3b Study INCB 18424-326 and the Supportive Phase 3, 52-Week Population. Events were most frequently application site acne (0.7%) and application site pain (0.6%), which resolved or were resolving with no change to study drug application in most instances.

Adverse Events of Interest for JAK Inhibitors for the Treatment of Inflammatory Diseases

A critical safety consideration for topical drugs is whether application to the skin results in significant systemic exposure to the active ingredient following dermal penetration. Plasma ruxolitinib concentrations following topical application of ruxolitinib cream were evaluated in the pivotal Phase 3b

study (326) and in a pooled analysis of PK data from adult participants with AD (Studies 206, 303, and 304).

Plasma ruxolitinib concentrations and the bioavailability of ruxolitinib cream in the pivotal Phase 3b study were low and generally consistent with the results of the supportive Phase 2 and 3 studies.

- Application of ruxolitinib 1.5% cream BID in Study 326 resulted in median and geometric mean ruxolitinib C_{ss} values of 49.6 and 42.7 nM, respectively, during the double-blind, vehicle-controlled period when each participant treated a constant %BSA (10% to 20% BSA affected by AD at baseline;). The mean (STD) bioavailability of ruxolitinib cream during the double-blind, vehicle-controlled period was 8.85% (9.41%).
- The pooled PK analysis in adult participants with AD yielded similar results, with median and geometric mean ruxolitinib C_{ss} values of 22.4 and 21.1 nM, respectively, following topical applications of ruxolitinib 1.5% cream BID to 3% to 22% BSA affected by AD at baseline during the double-blind, vehicle-controlled period.

Importantly, these low ruxolitinib C_{ss} values maintained at least a 6-fold margin to the threshold concentration of 281 nM, which is the IC_{50} for JAK2 inhibition in whole blood assays and considered a clinically relevant threshold value for encountering hematologic side effects associated with ruxolitinib (Quintás-Cardama et al 2010).

Taken together, these PK results suggest that the likelihood of AEs caused by systemic exposure following topical application of ruxolitinib 1.5% cream is low. Nevertheless, a number of queries were performed on the integrated clinical database to evaluate the potential for systemic AEs following topical application of ruxolitinib cream. Adverse events of interest were selected due to their relevance for safety monitoring in chronic inflammatory diseases across the JAK inhibitor class and included all-cause mortality, MACE and other thromboembolic events, nonmelanoma skin neoplasms, other malignancies, serious infections, cytopenias, herpes zoster and other viral skin infections, LFT elevations, and thrombocytosis.

Across the 8 studies in AD, AEs of interest for JAK inhibitors for the treatment of inflammatory diseases either were not observed or were infrequent. Based on review of all available evidence, including plasma ruxolitinib concentration data and results from clinical laboratory tests, a causal relationship between ruxolitinib cream and events of interest for JAK inhibitors for the treatment of inflammatory diseases could not be established, consistent with the findings presented in the initial marketing application for patients 12 years of age and older with nonsegmental vitiligo.

All-Cause Mortality

One participant (79-year-old male with a history of hypertension) in the vehicle cream BID treatment group had a TEAE of sudden death during the double-blind, vehicle-controlled period of Study INCB 18424-326. The cause of death was unknown, and the event was considered not related to the study drug. No other fatal TEAEs occurred in any of the other 7 studies in participants with AD.

Major Adverse Cardiovascular and Other Thromboembolic Events and Thrombocytosis Events

Concerns have been raised regarding a class effect of venous and arterial thromboembolism and MACE with oral JAK inhibitors; however, there is no established mechanism that would link JAK1 or JAK2 inhibition with thromboembolic events. In order to assess these risks for ruxolitinib cream, multiple approaches were used, including the following:

- Querying the integrated clinical database for MACE, arterial and venous thromboembolic events (embolic and thrombotic events SMQ), and thrombocytosis events. Treatment-emergent AEs reported

in the maximum-use study (INCB 18424-103) were also reviewed for the occurrence of MACE and other thromboembolic and thrombocytosis events.

- Assessing the risks of these events as measured by clinical laboratory data in the integrated ruxolitinib cream clinical database, specifically increases in platelet counts, as well as assessing the relationship between the trough plasma concentrations of ruxolitinib after topical application and platelet counts.

MACE and Other Thromboembolic Events

No MACE or other thromboembolic events were reported in the pivotal Phase 3b Study 326 as of the data cutoff date.

In the Supportive Phase 3, Vehicle-Controlled Population, the incidence of MACE and other thromboembolic events was low. No participant in the vehicle cream BID treatment group had a MACE or other thromboembolic event, and 1 participant (0.2%) in the ruxolitinib 1.5% cream BID treatment group experienced an event of cerebrovascular accident.

In the Supportive Phase 3, 52-Week Population, 2 participants (0.4%) in the ruxolitinib 1.5% cream BID (total) treatment group had thromboembolic events. In addition to the participant with cerebrovascular accident, 1 participant (0.2%) reported events of deep vein thrombosis and pulmonary embolism during the 44-week LTS period. The overall IR of thromboembolic events after adjusting for exposure was low (0.5 per 100 PY).

No additional participants had MACE or other thromboembolic events in the All-AD Population other than those reported in the supportive Phase 3 studies. The overall incidence and exposure-adjusted IR of thromboembolic events were 0.2% and 0.4 per 100 PY, respectively (0.1% and 0.2 per 100 PY, respectively, for each of cerebrovascular accident, deep vein thrombosis, and pulmonary embolism). These exposure-adjusted IRs were low and similar to background rates (when available). The IR of stroke in the general US population is 0.12 per 100 PY (GBD 2021). An increased incidence of venous thrombotic events exists among participants aged 50 years and older with skin diseases (0.23 per 100 PY; Schneeweiss et al 2021). Both participants who experienced a thromboembolic event were aged 50 years or older.

A total of 2 participants in the ruxolitinib 1.5% cream BID treatment group had thromboembolic events across the 8 studies. Neither of these events was considered related to the study drug by the investigator, and medical review by the sponsor to assess a causal relationship supported the investigators' assessments. In both cases, the participant was > 60 years of age and had predisposing conditions (eg, hypertension, hyperlipidemia, type 2 diabetes mellitus, and history of deep vein thrombosis). In both cases, plasma ruxolitinib concentrations were substantially lower than the IC_{50} (281 nM; Quintás-Cardama et al 2010) for JAK2 inhibition in whole blood assays at all timepoints evaluated.

No MACE or other thromboembolic events were reported in the maximum-use study.

Thrombocytosis Events

No thrombocytosis events were reported in the pivotal Phase 3b Study 326 as of the data cutoff date.

In the Supportive Phase 3, Vehicle-Controlled Population, 2 participants (0.5%) in the ruxolitinib 1.5% cream BID treatment group had thrombocytosis events: platelet count increased and thrombocytosis in 1 participant (0.2%) each. Both events were Grade 1 in severity, nonserious, considered not related to the study drug by the investigator, and ongoing at the time of study completion, with no action taken with study drug as a result of the event.

No additional participants had thrombocytosis events in the Supportive Phase 3, 52-Week Population or in the All-AD Population. Exposure-adjusted IRs of thrombocytosis events were low (0.5 and 0.4 per 100 PY for Pools 1b and 2, respectively).

A total of 2 participants in the ruxolitinib 1.5% cream BID treatment group had thrombocytosis and platelet count increased events across the 8 studies. Both participants with events had baseline platelet counts above the ULN. Of note, onset of the event for 1 participant was on Day 1; as blood samples for laboratory testing were to be collected before study drug application, it is unlikely this event was treatment emergent. Neither participant had an associated MACE or thromboembolic event, and, in both cases, plasma ruxolitinib concentrations were lower than the IC_{50} (281 nM; Quintás-Cardama et al 2010) for JAK2 inhibition in whole blood assays at all timepoints evaluated except for a transient increase at Week 2 for the participant with an event of platelet count increased.

No thrombocytosis events were reported in the maximum-use study.

Nonmelanoma Skin Neoplasms

To evaluate the risk of nonmelanoma skin neoplasms, the integrated clinical database was queried for AEs using the high-level term skin neoplasms malignant and unspecified (excluding melanoma). Treatment-emergent AEs reported in the maximum-use study (INCB 18424-103) were also reviewed for the occurrence of nonmelanoma skin neoplasms.

No TEAEs of nonmelanoma skin neoplasms were reported in the pivotal Phase 3b Study 326 as of the data cutoff date.

In the Supportive Phase 3, Vehicle-Controlled Population, the incidence of TEAEs of nonmelanoma skin neoplasms was low. No participant in the vehicle cream BID treatment group had a TEAE of nonmelanoma skin neoplasms, and 1 participant (0.2%) in the ruxolitinib 1.5% cream BID treatment group experienced an event of squamous cell carcinoma of skin.

In the Supportive Phase 3, 52-Week Population, 3 participants (0.6%) in the ruxolitinib 1.5% cream BID (total) treatment group had TEAEs of nonmelanoma skin neoplasms: 2 participants (0.4%) with squamous cell carcinoma of skin and 1 participant (0.2%) with basal cell carcinoma. The overall IR of nonmelanoma skin neoplasms after adjusting for exposure was low (0.8 per 100 PY, with IRs of 0.5 per 100 PY for squamous cell carcinoma of skin and 0.3 per 100 PY for basal cell carcinoma).

No additional participants had TEAEs of nonmelanoma skin neoplasms in the All-AD Population. The overall incidence and exposure-adjusted IR of nonmelanoma skin neoplasms were 0.3% and 0.6 per 100 PY, respectively (0.2% and 0.4 per 100 PY, respectively, for squamous cell carcinoma of skin and 0.1% and 0.2 per 100 PY, respectively, for basal cell carcinoma). These exposure-adjusted IRs were low and higher than background age-standardized IRs in the US general population (≈0.0633 per 100 PY; Ferlay et al 2024) but lower than the IRs among older adults based on Medicare data (4.5 per 100 PY; Rogers et al 2021). Of note, non-melanoma skin neoplasm is often excluded from reporting of cancer statistics because it is very common, underdiagnosed, and often treated in a primary care setting.

A total of 3 participants, all of whom were on ruxolitinib 1.5% cream at the time of event onset, had TEAEs of nonmelanoma skin neoplasm across the 8 studies. Of note, the participant who experienced an event of squamous cell carcinoma of skin during the vehicle-controlled period had a recurrent event at the same location during the extension period. None of the events were serious or considered related to the study drug by the investigator, and medical review by the sponsor to assess a possible causal relationship supported the investigators' assessments. In all 3 cases, the participants were > 65 years of age. In 2 participants, the events had an onset during the LTS period when ruxolitinib cream application was as needed. Plasma ruxolitinib concentrations for all 3 participants with nonmelanoma

skin neoplasm events were substantially lower than the IC_{50} (281 nM; Quintás-Cardama et al 2010) for JAK2 inhibition in whole blood assays at all timepoints evaluated, indicating that there is no evidence of association between nonmelanoma skin neoplasms and systemic exposure to ruxolitinib following application of ruxolitinib cream.

No TEAEs of nonmelanoma skin neoplasms were reported in the maximum-use study.

It should be noted that these epithelial cancers develop over the years and are asymptomatic in their early stages. The scrutiny in the examination of the participants' skin in the framework of the clinical studies most likely led to the detection of these neoplasms. No neoplastic changes were observed from ruxolitinib cream application in a 2-year dermal carcinogenicity study in mice.

Based on these observations, it is unlikely that ruxolitinib 1.5% cream contributed to the induction of nonmelanoma skin neoplasms.

Malignancies Excluding Nonmelanoma Skin Neoplasms

To evaluate TEAEs of malignancies, events under the SOC of neoplasms benign, malignant, and unspecified (including cysts and polyps) were reviewed for the integrated clinical database as well as for Study 103.

No TEAEs of malignancies excluding nonmelanoma skin neoplasms were reported in the pivotal Phase 3b Study 326 as of the data cutoff date.

A single event of malignancy excluding nonmelanoma skin neoplasms was reported in adults with AD who applied vehicle cream BID and/or ruxolitinib 1.5% cream BID across the 8 studies. One participant in the vehicle cream BID treatment group had a TEAE of hypopharyngeal cancer (onset on Day 1).

Serious Infections

To evaluate serious infections, serious TEAEs under the SOC of infections and infestations were reviewed for the integrated clinical database as well as for Study 103.

No serious TEAEs in the infections and infestations SOC were reported in the pivotal Phase 3b Study 326 as of the data cutoff date and in the Supportive Phase 3, Vehicle-Controlled Population.

In the Supportive Phase 3, 52-Week Population, 3 participants (0.6%) in the ruxolitinib 1.5% cream BID (total) treatment group had a serious TEAE in the infections and infestations SOC; the events were bronchitis, chronic tonsillitis, and pneumonia.

No additional participants had serious TEAEs in the infections and infestations SOC in the All-AD Population.

The IRs of each of the serious infections after adjusting for exposure (0.2 per 100 PY) were low and similar to or lower than the IRs in the general population when available: community-acquired pneumonia (1.6-2.3 cases per 100 PY with higher rates as age increases) and hospitalisations for community-acquired pneumonia (0.5-0.7 cases per 100 PY).

Across the 8 studies, a total of 4 participants, all of whom were on ruxolitinib 1.5% cream at the time of event onset, had a serious TEAE in the infections and infestations SOC: bronchitis, chronic tonsillitis, pneumonia, and abscess limb in 1 participant each. All events resolved; the events of pneumonia and abscess limb led to study drug interruption. None of the events were considered related to the study drug by the investigator, and medical review by the sponsor to assess a possible causal relationship supported the investigators' assessments. All participants had risk factors for the events (ie, predisposing medical conditions, such as asthma and allergies, and/or demographic characteristics).

Plasma ruxolitinib concentrations for participants in the Phase 3 studies with serious infections were substantially lower than the IC_{50} (281 nM; Quintás-Cardama et al 2010) for JAK2 inhibition in whole blood assays at all timepoints evaluated. Plasma concentrations for the participant in the maximum-use study with a serious TEAE of abscess limb (reported term: left leg abscess) were higher than the IC_{50} for JAK2 inhibition in whole blood assays at a number of timepoints. However, the participant's medical history of ruptured Achilles tendon and Achilles tendon surgery provides a plausible alternative cause for the event.

Cytopenias (Anemia, Neutropenia, Thrombocytopenia)

The dependence of erythropoietin and thrombopoietin signaling on JAK2 and the dependence of granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor signaling on JAK2 and JAK1, respectively, result in a potential for cytopenias as consequences of prolonged JAK1 and JAK2 inhibition (Parganas et al 1998, Schindler et al 2007, Shimoda et al 1997). However, such hematologic events were not anticipated with ruxolitinib cream, owing to the low bioavailability and plasma ruxolitinib concentrations.

To evaluate specific hematologic TEAEs, the hematopoietic anemia, hematopoietic thrombocytopenia, and hematopoietic leukopenia SMQs were reviewed, and clinically relevant terms were identified for anemia, thrombocytopenia, and neutropenia. These focused MedDRA queries were run against the integrated clinical database for this submission. Treatment-emergent AEs reported in the maximum-use study (103) were also reviewed for the occurrence of cytopenia events.

No cytopenia (anemia, neutropenia, and thrombocytopenia) events were reported in the pivotal Phase 3b Study 326 as of the data cutoff date.

In the Supportive Phase 3, Vehicle-Controlled Population, the incidences of anemia and neutropenia events were low, and there were no thrombocytopenia events.

In the Supportive Phase 3, 52-Week Population, the incidence of cytopenia events remained low. The incidence of anemia events was similar between the treatment groups. The incidence of neutropenia events, which were reported in the ruxolitinib 1.5% cream BID treatment group only, was higher compared with that in the vehicle-controlled period, which may be reflective of the longer period of observation (44-52 weeks compared with 8 weeks for the vehicle-controlled period).

In addition to the events reported in the supportive Phase 3 Studies 303 and 304, an event of anemia was reported in 1 participant in Study 206. There were no treatment-emergent thrombocytopenia events across the studies.

A total of 16 participants had cytopenia events. Of these, 8 participants had events considered related to the study drug by the investigator: neutropenia in 7 participants (including 1 participant in the maximum-use study) and idiopathic neutropenia in 1 participant. None of the events were serious, and all were Grade 1 or 2 in severity. The majority of cytopenia events resolved with no concomitant medications given and no action taken with study drug.

Other data that inform the analysis of cytopenia events include laboratory data and exposure-safety analyses conducted across the range of concentrations for populations with AD. These data demonstrate no meaningful trends (decreases) in the corresponding laboratory parameters and no concentration-response relationship for key hematologic indices, including hemoglobin, absolute neutrophil count, or platelet count, when stratified by C_{ss} during the double-blind, vehicle-controlled period. Based on the totality of data, a causal relationship with ruxolitinib cream has not been demonstrated.

Herpes Zoster and Other Viral Skin Infections

The herpes simplex and varicella-zoster viruses, following primary infection, reside for life in the sensory nerves of specific dermatomes (herpes simplex virus) or in the dorsal ganglia of the spinal cord (varicella-zoster virus) of their hosts. Alterations of local (herpes simplex virus) or generalized (varicella-zoster virus and perhaps herpes simplex virus) immune surveillance can lead to reactivation of such dormant viruses. Consistent with these data, patients with AD are at increased risk of developing cutaneous infections, including herpes simplex and varicella (Langan et al 2017, Narla and Silverberg 2018, Silverberg and Silverberg 2014, Wan et al 2022).

Herpes zoster, the incidence of which appears to be increasing in recent decades, is not infrequent in the general population (0.72 per 100 PY in adults aged ≥ 35 years in 2016; Hales et al 2013, Harpaz and Leung 2019, Kawai et al 2016), and the probability of herpes zoster recurrence is correlated with increasing age (Harpaz and Leung 2019). The estimated global prevalence of herpes simplex Type 2 is 13.3%, with a global incidence in the general population of approximately 0.7% (Harfouche et al 2025). The global burden of herpes simplex Type 1 is much more substantial, with an estimated prevalence of 64.2% and a global incidence in the general population of approximately 2.1% (Harfouche et al 2025).

The integrated clinical database for this submission was queried to identify TEAEs in the category of viral skin infection events. Treatment-emergent AEs reported in the maximum-use study (INCB 18424-103) were also reviewed for the occurrence of viral skin infection events.

In the pivotal Phase 3b Study INCB 18424-326, no participants in the vehicle cream BID treatment group had a herpes zoster or other viral skin infection event and 1 participant (0.6%) in the ruxolitinib 1.5% cream BID treatment group had a nonserious TEAE of oral herpes zoster (Grade 2) during the double-blind, vehicle-controlled period. The event did not occur at an application site, was considered not related to the study drug by the investigator and resolved with no action taken with the study drug.

There were no herpes zoster or other viral skin infection events during the 16-week, vehicle-controlled extension, double-blind period of Study INCB 18424-326. Of note, 1 participant in the ruxolitinib 1.5% cream BID treatment group had a nonserious TEAE of application site infection (Grade 2; reported term: herpes simplex infection on application site [chin]) in the SOC of infections and infestations during the 16-week, vehicle-controlled extension, double-blind period; hence, this event was reported under application site reactions. The event was considered related to the study drug by the investigator and resolved 6 days after treatment with oral valaciclovir and with no action taken with the study drug. One participant (1.2%; vehicle cream BID to ruxolitinib 1.5% cream BID treatment group) in the escape arm had a nonserious TEAE of herpes simplex (Grade 2) that was considered not related to the study drug by the investigator, treated with topical acyclovir, and resolved with no action taken with the study drug.

In the Supportive Phase 3, Vehicle-Controlled Population, the incidences of herpes zoster events (2 participants [0.5%]) and other viral skin infection events (3 participants [0.7%]) were low. By PT, herpes zoster was reported in 2 participants (0.5%) in the ruxolitinib 1.5% cream BID treatment group and herpes simplex and post herpetic neuralgia were reported in 1 participant (0.2%) each in the ruxolitinib 1.5% cream BID treatment group.

In the Supportive Phase 3, 52-Week Population, incidences and exposure-adjusted IRs of herpes zoster events (0.8% and 1.1 per 100 PY) and other viral skin infection events (2.1% and 2.7 per 100 PY) remained low. Incidences and exposure-adjusted IRs for each of the events by PT are summarised in Table 31.

Table 31. Herpes Zoster and Other Viral Skin Infection Events in the Supportive Phase 3, 52-Week Population (Pool 1b)

MedDRA PT, n (%)/ Exposure-Adjusted IR per 100 PY	Vehicle Cream BID[a] (N = 205)	Vehicle Cream BID to Ruxolitinib 1.5% Cream BID[b] (N = 77)	Ruxolitinib 1.5% Cream BID[c] (N = 407)	Ruxolitinib 1.5% Cream BID Total[d] (N = 484)
Herpes simplex	0	0	6 (1.5)/1.9	6 (1.2)/1.6
Herpes zoster	0	0	4 (1.0)/1.2	4 (0.8)/1.1
Post herpetic neuralgia	0	0	1 (0.2)/0.3	1 (0.2)/0.3

[a] Participants applied vehicle cream BID for up to 8 weeks.

[b] Participants applied ruxolitinib 1.5% cream as needed for up to 44 weeks.

[c] Participants applied ruxolitinib 1.5% cream BID for 8 weeks followed by ruxolitinib 1.5% cream BID as needed for up to 44 weeks.

[d] Participants applied ruxolitinib 1.5% cream BID or vehicle cream BID for 8 weeks followed by ruxolitinib 1.5% cream BID as needed for up to 44 weeks.

The incidence and exposure-adjusted IRs of herpes zoster events (0.5% and 1.2 per 100 PY) and other viral skin infection events (1.2% and 2.7 per 100 PY) in the All-AD Population remained low. Incidences and exposure-adjusted IRs for each of the events by PT are summarised in Table 32. Additional events other than those reported in the pivotal Phase 3b Study INCB 18424-326 and supportive Phase 3 Studies INCB 18424-303 and INCB 18424-304 were reported in 1 participant each only (herpes simplex and molluscum contagiosum).

Table 32. Herpes Zoster and Other Viral Skin Infection Events in the All Atopic Dermatitis Population (Pool 2)

MedDRA PT, n (%)/Exposure-Adjusted IR per 100 PY	Ruxolitinib 1.5% Cream BID (N = 1113)
Herpes simplex	7 (0.6)/1.4
Herpes zoster	5 (0.4)/1.0
Molluscum contagiosum	1 (0.1)/0.2
Oral herpes zoster	1 (0.1)/0.2
Post herpetic neuralgia	1 (0.1)/0.2

Across the 8 studies, a total of 14 participants, all of whom were on ruxolitinib 1.5% cream at the time of event onset, had herpes zoster or other viral skin infection events. None of the events were serious; all events were Grade 1 or 2 in severity except for a Grade 3 event of herpes zoster that was considered related to the study drug by the investigator. The Grade 3 event of herpes zoster was treated with oral acyclovir and resolved after 26 days with no action taken with the study drug. The event was not at the application site and resolved during continued application of ruxolitinib 1.5% cream BID. The participant subsequently interrupted ruxolitinib 1.5% cream due to a TEAE of skin irritation and elected not to resume treatment thereafter. The participant did not report a history of herpes zoster. All herpes zoster and other viral skin infection events resolved or were resolving without discontinuation of study drug. Two participants had herpes zoster and other viral skin infection events that led to study drug interruption: 1 participant had a Grade 1 herpes simplex on the left lateral torso

and 1 participant had a Grade 2 herpes zoster that led to study drug interruption and subsequently developed Grade 2 post herpetic neuralgia. All participants, with the exception of the aforementioned participant who interrupted study drug due to skin irritation, were able to continue ruxolitinib 1.5% cream application without complications.

No herpes zoster or other viral skin infection events were reported in the maximum-use study.

The herpes zoster and other viral skin infection events observed in these studies are unlikely attributed to ruxolitinib 1.5% cream application.

Liver Function Test Elevations

The clinical database was queried to identify TEAEs of LFT elevations.

In the pivotal Phase 3b Study INCB 18424-326, 1 participant (0.6%) in the ruxolitinib 1.5% cream BID treatment group had a nonserious TEAE of transaminases increased (Grade 1) during the double-blind, vehicle-controlled period that was considered not related to the study drug by the investigator. The event was resolving with no action taken with the study drug.

One participant (0.8%) in the ruxolitinib 1.5% cream BID treatment group had a nonserious TEAE of hepatic function abnormal (Grade 2) during the vehicle-controlled extension, double-blind period that was considered not related to the study drug by the investigator. The event was resolving with no action taken with the study drug.

There were no LFT elevation events in the escape arm of Study INCB 18424-326 as of the data cutoff date.

In the Supportive Phase 3, Vehicle-Controlled Population, the incidence of LFT elevation events was low and not meaningfully different between the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups. No action was taken with the study drug for the majority of LFT elevation events, except for the TEAE of hepatic enzyme increased (Grade 2) in the vehicle cream BID treatment group that led to study drug discontinuation.

In the Supportive Phase 3, 52-Week Population, incidences and exposure-adjusted IRs of LFT elevation events remained low. The incidence of LFT elevation events was higher in the ruxolitinib 1.5% cream BID (total) treatment group compared with the vehicle cream BID treatment group (2.5% vs 1.0%), which may be reflective of the longer period of observation (44-52 weeks compared with 8 weeks for the vehicle cream BID). However, this difference was not apparent after adjusting for exposure (3.2 per 100 PY vs 7.0 per 100 PY).

No additional participants had LFT elevation events other than those previously reported in the pivotal Phase 3b Study INCB 18424-326 and the supportive Phase 3 Studies INCB 18424-303 and INCB 18424-304, resulting in an overall frequency of 1.3% and an exposure-adjusted IR of 2.9 per 100 PY.

A total of 14 participants in the ruxolitinib 1.5% cream BID treatment group (1.3%) had LFT elevation events. None of the events were serious, and all were Grade 1 or 2 in severity. Alanine aminotransferase increased in 1 participant was the only event considered related to the study drug by the investigator. All LFT elevation events in the ruxolitinib 1.5% cream BID treatment group resolved or were resolving with no action taken with the study drug, with the exception of a Grade 2 event of transaminases increased that resolved after study drug interruption and did not recur.

In the maximum-use study (INCB 18424-103), 3 participants had LFT elevation events (ALT increased and AST increased in 1 adolescent participant, AST increased in 1 adult participant, and LFT increased in 1 adult participant). None of the events were serious, and all were Grade 1 in severity and resolved. All events of ALT increased and AST increased were considered related to the study drug by the

investigator. The event of LFT increased led to study drug discontinuation on Day 4 and was considered not related to the study drug by the investigator.

Clinical chemistry laboratory test results also informed these analyses. These data demonstrate no meaningful trends (increases) in ALT, AST, or bilirubin.

Laboratory findings

Clinical Hematology

Hemoglobin Levels

Mean Changes Over Time

Pivotal Phase 3b Study INCB 18424-326

At all visits through Week 8 of the pivotal Phase 3b study, mean hemoglobin levels were similar between the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups, and observed fluctuations were minor and not clinically significant. The median change from baseline in hemoglobin levels at Week 8 was −0.5 g/L in the vehicle cream BID treatment group and −2.0 g/L in the ruxolitinib 1.5% cream BID treatment group. There were no apparent trends over time for mean changes from baseline in hemoglobin levels.

During the vehicle-controlled extension, double-blind period of the Phase 3b study, mean hemoglobin levels remained consistent with those at baseline and throughout the double-blind, vehicle-controlled period. There were no notable differences in mean changes from baseline in hemoglobin levels between the treatment groups. Similar observations in mean changes from baseline in hemoglobin levels were noted in the escape arm.

Supportive Phase 3 Studies INCB 18424-303 and INCB 18424-304 (Pool 1b)

Results for the Supportive Phase 3, 52-Week Population were consistent with the results for the pivotal Phase 3b Study INCB 18424-326. At all visits through Week 8, the mean hemoglobin levels were similar between the vehicle cream BID and the ruxolitinib 1.5% cream BID (total) treatment groups, and observed fluctuations were minor and not clinically significant. The median change from baseline in hemoglobin levels at Week 8 was 0 g/L in the vehicle cream BID treatment group and −1.0 g/L in the ruxolitinib 1.5% cream BID (total) treatment group. There were no apparent trends over time for mean changes from baseline in hemoglobin levels up to Week 8 and through Week 52.

Individual Changes in Hemoglobin Levels

Pivotal Phase 3b Study INCB 18424-326

In both treatment groups, no participants had a postbaseline shift to CTCAE Grade 2 or 3 low hemoglobin concentration values. Overall, the proportion of postbaseline shifts in low hemoglobin concentration CTCAE grade values was small. Most participants with baseline Grade 0 hemoglobin concentrations remained at Grade 0, with 2.6% of participants in the vehicle cream BID treatment group and 3.2% of participants in the ruxolitinib 1.5% cream BID treatment group having a postbaseline shift to Grade 1. Most participants with abnormal low hemoglobin levels at baseline remained at the same grade postbaseline.

Low hemoglobin abnormalities by CTCAE grade during the vehicle-controlled extension, double-blind period and for the escape arm of the Phase 3b study were consistent with those reported during the vehicle-controlled period. No participant had a postbaseline shift to CTCAE Grade 2 or 3 low hemoglobin concentration values.

Supportive Phase 3 Studies INCB 18424-303 and INCB 18424-304 (Pool 1b)

Overall, the proportion of postbaseline shifts in low hemoglobin concentration CTCAE grade values was small. Most participants with baseline Grade 0 hemoglobin concentrations remained at Grade 0, with 1.0% of participants in the vehicle cream BID treatment group and 6.3% of participants in the ruxolitinib 1.5% cream BID (total) treatment group having a postbaseline shift to Grade 1 and 1.5% of participants in the vehicle cream BID treatment group and 0.2% of participants in the ruxolitinib 1.5% cream BID (total) treatment group having a postbaseline shift to Grade 2. Most participants with abnormal low hemoglobin levels at baseline remained at the same grade postbaseline. The majority of shifts in low hemoglobin concentration values were to Grade 1 or 2 and were not clinically significant; 1 participant (5.3%) in the ruxolitinib 1.5% cream BID (total) treatment group had a Grade 1 to Grade 3 postbaseline shift in hemoglobin concentration values. The shift occurred during the follow-up period (Day 400; the day of study completion) and was reported as a Grade 2 event of iron deficiency anemia. Of note, the participant had a medical history of anemia and was receiving ferrous sulfate and folic acid. The participant also had a concurrent Grade 3 event of thrombocytopenia associated with a shift in platelet count from Grade 0 to Grade 3. The participant had low hemoglobin since baseline (Grade 1) and normal platelet count at baseline. Both events were not treatment emergent.

All Atopic Dermatitis Population (Pool 2)

In the largest dataset, the All-AD Population, shifts in low hemoglobin values were consistent with those observed in participants who applied ruxolitinib 1.5% cream BID in the pivotal Phase 3b Study INCB 18424-326 and the Supportive Phase 3, 52-Week Population. There were no trends in shifts from baseline in CTCAE grade, and no clinically meaningful impact on hemoglobin levels was seen with ruxolitinib 1.5% cream treatment. No additional participants had a shift in worst postbaseline low hemoglobin to Grade 3.

Platelet Counts

Mean Changes Over Time

Pivotal Phase 3b Study INCB 18424-326

Small, transient increases in mean platelet counts (within the normal range) were seen at Week 2 in the ruxolitinib 1.5% cream BID treatment group; these changes were not clinically relevant in magnitude. There were no meaningful differences between the treatment groups in changes from baseline in platelet counts.

During the vehicle-controlled extension, double-blind period of the Phase 3b study, mean platelet counts remained consistent with those at baseline and throughout the double-blind, vehicle-controlled period. There were no notable differences in mean changes from baseline in platelet counts between the treatment groups. Similar observations in mean changes from baseline in platelet counts were noted in the escape arm.

Supportive Phase 3 Studies INCB 18424-303 and INCB 18424-304 (Pool 1b)

Results for the Supportive Phase 3, 52-Week Population were consistent with the results for the pivotal Phase 3b Study INCB 18424-326. Small, transient increases in mean platelet counts (within the normal range) were seen at Week 2 in the ruxolitinib 1.5% cream BID treatment group; these changes were not clinically relevant in magnitude. There were no other trends over time for mean changes from baseline in platelet counts up to Week 8 and through Week 52.

Individual Changes in Platelet Counts

Pivotal Phase 3b Study INCB 18424-326

In both treatment groups, no participants had a postbaseline shift to CTCAE Grade 2 or 3 in platelet count. Overall, the proportion of postbaseline shifts in low platelet count CTCAE grade values was small. All participants with baseline Grade 0 platelet count remained at Grade 0. Most participants with abnormal low platelet count at baseline remained at the same grade postbaseline.

Low platelet count abnormalities by CTCAE grade during the vehicle-controlled extension, double-blind period and for the escape arm of the Phase 3b study were consistent with those reported during the vehicle-controlled period. No participant had a postbaseline shift to CTCAE Grade 2 or 3 low platelet count.

Supportive Phase 3 Studies INCB 18424-303 and INCB 18424-304 (Pool 1b)

Overall, the proportion of postbaseline shifts in low platelet count CTCAE grade values was small. Most participants with baseline Grade 0 platelet count remained at Grade 0, with 3.0% of participants in the vehicle cream BID treatment group and 3.4% of participants in the ruxolitinib 1.5% cream BID (total) treatment group having a postbaseline shift to Grade 1. Most participants with abnormal low platelet count at baseline remained at the same grade postbaseline. The majority of shifts in low platelet count were to Grade 1 or 2 and were not clinically significant; 1 participant (0.2%) in the ruxolitinib 1.5% cream BID (total) treatment group had a Grade 0 to Grade 3 postbaseline shift in platelet count. This shift, which occurred during the follow-up period (Day 400; the day of study completion), was reported as a Grade 3 event of thrombocytopenia that was not treatment emergent. The participant also had a concurrent Grade 2 event of iron deficiency anemia associated with a shift in hemoglobin from Grade 1 to Grade 3.

All Atopic Dermatitis Population (Pool 2)

In the largest dataset, the All-AD Population, shifts in low platelet count were consistent with those observed in participants who applied ruxolitinib 1.5% cream BID in the pivotal Phase 3b Study INCB 18424-326 and the Supportive Phase 3, 52-Week Population. There were no trends in shifts from baseline in CTCAE grade, and no clinically meaningful impact on platelet count values was seen with ruxolitinib 1.5% cream treatment. No additional participants had a shift in worst postbaseline low platelet count to Grade 3.

Neutrophil Counts

Mean Changes Over Time

Pivotal Phase 3b Study INCB 18424-326

At all visits through Week 8 of the pivotal Phase 3b study, mean neutrophil counts were similar between the vehicle cream BID and ruxolitinib 1.5% cream BID treatment groups and observed fluctuations were minor and not clinically significant. There were no apparent trends over time for mean changes from baseline in neutrophil counts.

During the vehicle-controlled extension, double-blind period of the Phase 3b study, mean neutrophil counts remained consistent with those at baseline and throughout the double-blind, vehicle-controlled period. There were no notable differences in mean changes from baseline in neutrophil counts between the treatment groups. Similar observations in mean changes from baseline in neutrophil counts were noted in the escape arm.

Supportive Phase 3 Studies INCB 18424-303 and INCB 18424-304 (Pool 1b)

Results for the Supportive Phase 3, 52-Week Population were consistent with the results for the pivotal Phase 3b Study INCB 18424-326. At all visits through Week 8, the mean neutrophil counts were similar between the vehicle cream BID and ruxolitinib 1.5% cream BID (total) treatment groups and observed fluctuations were minor and not clinically significant. There were no apparent trends over time for mean changes from baseline in neutrophil counts up to Week 8 and through Week 52.

Individual Changes in Neutrophil Counts

Pivotal Phase 3b Study INCB 18424-326

In both treatment groups, no participants had a postbaseline shift to CTCAE Grade 2 or 3 in low neutrophil count. Overall, the proportion of postbaseline shifts in low neutrophil count CTCAE grade values was small. Most participants with baseline Grade 0 neutrophil count remained at Grade 0, with 6.3% of participants in the vehicle cream BID treatment group and 10.3% of participants in the ruxolitinib 1.5% cream BID treatment group having a postbaseline shift to Grade 1. Most participants with abnormal low neutrophil count at baseline remained at the same grade postbaseline.

Low neutrophil count abnormalities by CTCAE grade during the vehicle-controlled extension, double-blind period and for the escape arm of the Phase 3b study were generally consistent with those reported during the vehicle-controlled period, with the exception of 1 participant in the escape arm who had a shift from baseline Grade 0 low neutrophil count to Grade 4 postbaseline. The participant who applied ruxolitinib 1.5% cream BID throughout the study had a Grade 4 low neutrophil count at Week 12. The participant had neutrophils within the normal range at baseline and throughout the double-blind, vehicle-controlled period, and values returned to within normal range at the subsequent measurement (Week 24). The investigator considered this to be a laboratory error, and no TEAEs were reported in relation to this laboratory abnormality.

Supportive Phase 3 Studies INCB 18424-303 and INCB 18424-304 (Pool 1b)

Overall, the proportion of postbaseline shifts in low neutrophil count CTCAE grade values was small. Most participants with baseline Grade 0 low neutrophil count remained at Grade 0, with 3.5% of participants in the vehicle cream BID treatment group and 3.6% of participants in the ruxolitinib 1.5% cream BID (total) treatment group having a postbaseline shift to Grade 1 and 1.0% of participants in the vehicle cream BID treatment group and 3.6% of participants in the ruxolitinib 1.5% cream BID (total) treatment group having a postbaseline shift to Grade 2. Most participants with abnormal low neutrophil count at baseline remained at the same grade postbaseline. The majority of shifts in low neutrophil count were to Grade 1 or 2 and were not clinically significant; 3 participants (0.6%) in the ruxolitinib 1.5% cream BID (total) treatment group had a Grade 0 to Grade 3 postbaseline shift in neutrophil count and 1 participant (25.0%) in the ruxolitinib 1.5% cream BID (total) treatment group had a Grade 1 to Grade 3 postbaseline shift in neutrophil count. One participant reported TEAEs of neutrophil count decreased and neutropenia associated with the shift in neutrophil count and were considered as TEAEs of interest. The participant's neutrophil count was normal (Grade 0) at baseline, and a shift to Grade 2 occurred on Days 169 and 224, which were both reported as a nonserious TEAE of neutrophil count decreased (Grade 2) that was considered not related to the study drug by the investigator and resolved after study drug interruption. Subsequently, a shift in low neutrophil count to Grade 3 occurred on Day 281, which was reported as a nonserious TEAE of neutropenia (Grade 1) that was considered related to the study drug by the investigator and resolved with no action taken with the study drug.

All Atopic Dermatitis Population (Pool 2)

In the largest dataset, the All-AD Population, shifts in low neutrophil count were consistent with those observed in participants who applied ruxolitinib 1.5% cream BID in the pivotal Phase 3b Study INCB 18424-326 and the Supportive Phase 3, 52-Week Population. There were no trends in shifts from baseline in CTCAE grade, and no clinically meaningful impact on neutrophil count values was seen with ruxolitinib 1.5% cream treatment. No additional participants had a shift in worst postbaseline low neutrophil count to Grade 4.

Clinical Chemistry

In the pivotal Phase 3b Study INCB 18424-326, the majority of shifts in postbaseline chemistry abnormalities by CTCAE grade during the double-blind, vehicle-controlled period; vehicle-controlled extension, double-blind period; and escape arm were to Grade 1 or 2. During the double-blind, vehicle-controlled period, no participants in both treatment groups had a postbaseline shift to CTCAE Grade 3 in ALT, AST, or bilirubin. Of note, 1 participant in the vehicle cream BID treatment group had a shift to Grade 3 in decreased derived calcium corrected for albumin at Week 2. The participant had values for derived calcium corrected for albumin within the normal range at baseline and these values had recovered to within normal range by the subsequent measurement. In the escape arm, 1 participant in the ruxolitinib 1.5% cream BID treatment group had a shift in AST to Grade 3 postbaseline concurrent with a shift in ALT to Grade 1 postbaseline on Day 169. At an unscheduled visit on Day 176, the participant had Grade 1 high ALT value, Grade 3 high AST value, and Grade 4 high creatine kinase. The participant had normal LFT values at all other timepoints (note that creatine kinase was not measured at other timepoints). No TEAEs were reported in relation to these laboratory abnormalities.

In the Supportive Phase 3, 52-Week Population, the majority of shifts in postbaseline chemistry abnormalities by CTCAE grade were to Grade 1 or 2. Shifts to CTCAE Grade 3 or 4 in postbaseline chemistry abnormalities included the following:

- ALT: 1 participant in the ruxolitinib 1.5% cream BID (total) treatment group with a shift from not graded at baseline to Grade 3 postbaseline
- AST: 1 participant each in the ruxolitinib 1.5% cream BID (total) treatment group with a shift from not graded at baseline to Grade 3 and Grade 4 postbaseline
- Creatinine: 1 participant in the ruxolitinib 1.5% cream BID (total) treatment group with a shift from Grade 0 at baseline to Grade 3 postbaseline
- Glucose: 1 participant in the ruxolitinib 1.5% cream BID (total) treatment group with a shift from Grade 0 at baseline to Grade 3 (low) postbaseline
- Triglycerides: 1 participant in the vehicle cream BID treatment group with a shift from Grade 1 at baseline to Grade 3 postbaseline; 11 participants in the ruxolitinib 1.5% cream BID (total) treatment group with shifts from Grade 0, 1, or 2 at baseline to Grade 3 postbaseline; and 1 participant in the vehicle cream BID treatment group and 2 participants in the ruxolitinib 1.5% cream BID (total) treatment group with a shift from Grade 3 at baseline to Grade 4 postbaseline

In most cases of triglyceride elevations, participants had high values at baseline and/or a relevant medical history (eg, type 1 or 2 diabetes mellitus, hypertriglyceridemia, or hyperlipidemia). The abnormalities were not considered clinically significant for the majority of these participants. In cases where the investigator considered the abnormality to be clinically significant (ie, a TEAE), the event was considered not related to the study drug with the exception of a nonserious Grade 3 TEAE of

hypertriglyceridemia. The event was reported on Day 337, resolved 17 days after study drug interruption, and did not recur after restarting study drug. Plasma ruxolitinib levels were 149 nM on Day 280 (Week 40) and 330 nM on Day 336. This participant had Grade 1 elevated triglycerides at baseline and several timepoints during treatment, prior to the Grade 3 TEAE of hypertriglyceridemia.

The shifts in ALT and AST to Grade 3 or 4 postbaseline in the 2 participants in the ruxolitinib 1.5% cream BID treatment group were associated with TEAEs of LFT elevation. Both participants' ALT and AST levels were normal at baseline. For 1 participant, the shifts to Grade 3 high ALT and Grade 4 high AST on Day 246 were reported as a Grade 2 TEAE of hepatic enzyme increased. For the other participant, the shift to Grade 3 high AST occurred concurrently with a shift to Grade 2 high ALT on Day 337 and were reported as Grade 2 TEAEs of AST increased and ALT increased, respectively. All TEAEs were nonserious, considered not related to the study drug by the investigator, and resolved with no action taken with the study drug.

Shifts in abnormal chemistry values in the All-AD Population were consistent with those observed in participants who applied ruxolitinib 1.5% cream BID in the pivotal Phase 3b Study INCB 18424-326 and the Supportive Phase 3, 52-Week Population. One additional participant had a shift in AST to worst postbaseline Grade 3 aside from the 1 participant each in the escape arm of Study INCB 18424-326 and the Supportive Phase 3, 52-Week Population. For this participant, the shift to Grade 3 high AST on Day 69 occurred concurrently with a shift to Grade 2 high ALT. At baseline, the participant's AST level was elevated and ALT level was normal. No TEAEs were reported in relation to the LFT elevations.

Vital Signs and Electrocardiograms

In the pivotal Phase 3b Study INCB 18424-326, most participants had normal vital signs (systolic/diastolic blood pressure, pulse, respiratory rate, body temperature) at baseline and postdose timepoints during the double-blind vehicle-controlled period, extension, and escape arm; no meaningful trends in changes over time were observed. Vital sign alerts were infrequent, with transient pulse increases most common. In the supportive Phase 3 studies (INCB 18424-303 and -304), no notable differences in vital sign parameters were seen between vehicle cream BID and ruxolitinib 1.5% cream BID groups during the 8-week vehicle-controlled periods, and no trends suggestive of treatment-related increases in systolic or diastolic blood pressure were identified over up to 52 weeks. Electrocardiograms were not performed in the atopic dermatitis studies. A thorough QT study with oral ruxolitinib at a supratherapeutic dose (200 mg), producing plasma concentrations well above those observed with ruxolitinib 1.5% cream BID, was negative for QT prolongation per ICH E14 guidance (as reported in the initial marketing authorisation).

Safety in special populations

Intrinsic and Extrinsic Factors

The possible effect of intrinsic factors (age, sex, race, and ethnicity) and an extrinsic factor (geographic region) on the safety profile of ruxolitinib cream was evaluated for the pivotal Phase 3b study and each of the pooled populations.

Overall, there were no meaningful differences in the TEAE profile of ruxolitinib 1.5% cream BID based on age, sex, race, ethnicity, or geographic region.

Pivotal Phase 3b Study INCB 18424-326

The overall incidence of TEAEs for participants in the ruxolitinib 1.5% cream BID treatment group was similar between male and female participants (32.4% and 37.2%, respectively) and lower in younger participants (34.0% in the 18 to < 65 years subgroup vs 46.2% in the ≥ 65 years subgroup), Black or

African American participants (0% vs 35.7% and 45.0% for the White and Asian subgroups, respectively), not Hispanic or Latino participants (35.1% vs 42.9% for the Hispanic or Latino subgroup), and participants in Europe (33.0% vs 39.2% in Rest of World). However, results should be interpreted with caution due to the small sample size of ≥ 65 years, Black or African American, Asian and all other races, and Hispanic or Latino participants.

No meaningful differences were observed between the different age, sex, race, ethnicity, or geographic region subgroups for other TEAE categories.

Generally, the types and frequencies of TEAEs reported in participants in the ruxolitinib 1.5% cream BID treatment group were similar regardless of age, sex, race, ethnicity, or geographic region. Of note, nasopharyngitis in the ruxolitinib 1.5% cream BID treatment group was more frequently reported in the 18 to < 65 years subgroup (3.4% vs 0% in the ≥ 65 years subgroup), White subgroup (4.0% vs 0% in Black or African American and Asian subgroups), not Hispanic or Latino subgroup (3.4% vs 0% in the Hispanic or Latino subgroup), and Europe subgroup (4.6% vs 0% in the Rest of World subgroup). The overall incidences of TEAEs remained low, and there were no notable trends among subgroups based on age, sex, race, ethnicity, or region during the vehicle-controlled extension, double-blind period and for the escape arm.

There were no notable trends in the types and frequencies of TEAEs among subgroups based on age, sex, race, ethnicity, or region during the vehicle-controlled extension, double-blind period and for the escape arm.

Supportive Phase 3 Studies INCB 18424-303 and INCB 18424-304 (Pool 1a and Pool 1b)

The overall incidence of TEAEs for participants who applied ruxolitinib 1.5% cream BID was similar between male and female participants (25.9% and 30.1%, respectively) and lower in younger participants (28.0% in the 18 to < 65 years subgroup vs 33.3% in the ≥ 65 years subgroup), Black or African American participants (23.0% vs 30.4% and 29.2% for the White and Asian and other race subgroups, respectively), Hispanic or Latino participants (23.4% vs 28.9% for the not Hispanic or Latino subgroup), and participants in Rest of World (25.6% vs 34.6% in Europe. However, results should be interpreted with caution due to the small sample size of ≥ 65 years, Black or African American, Asian and other race, and Hispanic or Latino participants.

No meaningful differences were observed between the different age, sex, race, ethnicity, and geographic region subgroups for other TEAE categories.

Generally, the types and frequencies of TEAEs reported in participants who applied ruxolitinib 1.5% cream BID were similar regardless of age, sex, race, ethnicity, and geographic region. Consistent with Study INCB 18424-326, nasopharyngitis in the ruxolitinib 1.5% cream BID treatment group was more frequently reported in the 18 to < 65 years subgroup (3.0% vs 0% in the ≥ 65 years subgroup), White and Asian and other race subgroups (3.5% and 4.2%, respectively, vs 0% in Black or African American subgroup), and Europe subgroup (6.9% vs 0.7% in the Rest of World subgroup); no meaningful differences were observed based on sex (3.2% in the male subgroup and 2.4% in the female subgroup) and ethnicity (2.8% in the not Hispanic or Latino subgroup and 2.1% in the Hispanic or Latino subgroup).

The overall incidence of TEAEs for all participants who applied ruxolitinib 1.5% cream BID was similar between male and female participants (59.8% and 58.3%, respectively) and lower in 18 to < 65 years subgroup (56.9% vs 75.0% in the ≥ 65 years subgroup), Black or African American participants (49.2% vs 62.4% and 57.1% for the White and Asian and other race subgroups, respectively), Hispanic or Latino participants (31.1% vs 62.9% for the not Hispanic or Latino subgroup), and participants in Rest of World (51.7% vs 73.9% in Europe subgroup).

Nasopharyngitis in the ruxolitinib 1.5% cream BID treatment group was more frequently reported in the 18 to < 65 years subgroup (10.6% vs 5.8% in the ≥ 65 years subgroup), White and Asian and other race subgroups (12.7% and 10.7%, respectively, vs 2.5% in Black or African American subgroup), not Hispanic or Latino subgroup (11.4% vs 1.6% in the Hispanic or Latino subgroup), and Europe subgroup (24.8% vs 3.1% in the Rest of World subgroup); no meaningful difference was observed based on sex (7.9% in the male subgroup and 11.5% in the female subgroup).

All Atopic Dermatitis Population (Pool 2)

The overall incidence of TEAEs for all participants who applied ruxolitinib 1.5% cream BID was similar between male and female participants (42.6% and 43.9%, respectively) and lower in younger participants (42.1% in the 18 to < 65 years subgroup vs 57.8% in the ≥ 65 years subgroup), Black or African American participants (35.9% vs 46.1% and 41.0% for the White and Asian and other race subgroups, respectively), Hispanic or Latino participants (29.4% vs 44.6% for the not Hispanic or Latino subgroup), and participants in Rest of World (38.3% vs 57.4% in Europe). However, results should be interpreted with caution due to the small sample size of ≥ 65 years, Black or African American, Asian and other race, and Hispanic or Latino participants.

Nasopharyngitis was more frequently reported in the White and Asian and other race subgroups (8.5% and 6.6%, respectively, vs 2.8% in Black or African American subgroup), not Hispanic or Latino subgroup (7.6% vs 2.0% in the Hispanic or Latino subgroup), and Europe subgroup (16.8% vs 3.4% in the Rest of World subgroup); no differences were observed based on age (7.0% in the 18 to < 65 years subgroup and 6.7% in the ≥ 65 years subgroup) and sex (6.8% in the male subgroup and 7.1% in the female subgroup).

Use in Pregnancy and Lactation

When pregnant rats and rabbits were administered oral ruxolitinib during the period of organogenesis, adverse developmental outcomes occurred at doses associated with maternal toxicity.

No adequate and well-controlled studies of ruxolitinib cream have been conducted in pregnant women to inform drug-associated risks. Women who were pregnant or lactating were excluded from all clinical studies. Women of childbearing potential were required to use effective contraception, and men must have been willing to abide by protocol-specified methods throughout the study to avoid fathering a child.

A total of 4 pregnancies have been reported in the integrated clinical safety database for this submission (ie, adult participants with atopic dermatitis in the vehicle cream BID or ruxolitinib 1.5% cream BID treatment groups); no pregnancies of a partner were reported. Two pregnancies in the ruxolitinib 1.5% cream BID treatment group resulted in spontaneous abortion (both assessed as not related to the study drug by the investigator). For the other 2 pregnancies, the pregnancy was ongoing at the time of data cutoff in 1 participant in the ruxolitinib 1.5% cream BID treatment group, and the outcome of the pregnancy was not reported for the other participant in the vehicle cream BID treatment group who was lost to follow-up.

No data are available regarding the presence of ruxolitinib in human milk, the effects on the breast-fed child, or the effects on milk production. Ruxolitinib and/or its metabolites were present in the milk of lactating rats.

Overdose

No TEAEs of overdose have been reported in adult participants who applied ruxolitinib 1.5% cream across the 8 atopic dermatitis studies.

For a topical drug, potential overuse may be related to very high quantities of the drug being applied to the skin (e.g., when treating extensive BSA) or too frequent use of the drug. Exaggerated use of ruxolitinib cream, which best reflects the former, was evaluated in a maximum-use study. In this study, BID applications of ruxolitinib cream (mean daily cream use: 21.8 g; median: 22.3 g) onto extensive skin lesions (mean %BSA involved at baseline: 38.09%; range: 25.0%-90.0%) for 4 weeks followed by 4 weeks of as-needed applications did not result in clinically significant laboratory changes or previously unreported adverse safety findings.

Safety related to drug-drug interactions and other interactions

No specific drug-drug interaction studies of ruxolitinib cream have been conducted. There are no new data since the time of the initial marketing application.

Discontinuation due to adverse events

Discontinuations due to adverse events remained low across the clinical development programme. In the pooled safety database (Pool 2: 1,113 participants, 486.77 patient-years), the incidence of TEAEs leading to study drug discontinuation was 0.4%. Rates were consistent under maximum-use conditions (Study INCB 18424-103) and in the updated data from study 326 (VCE double-blind period and escape arm). No new safety signals were identified.

Supportive studies

The safety of ruxolitinib 1.5% cream BID under maximum-use conditions was evaluated in Study INCB 18424-103. This study was conducted in 41 adolescent and adult participants with AD.

Thirteen participants (31.7%) experienced ≥ 1 TEAE. Of these, 4 participants experienced 6 treatment-related TEAEs (dyspnoea, neutropenia, hemoglobin decreased, and ALT increased [1 participant each] and AST increased [2 participants]), all of which were Grade 1 or 2 and transitory. No deaths or application site reaction TEAEs were reported in the study, and no TEAEs occurring in ≥ 5% of participants were reported. The most common TEAEs were upper respiratory tract infection and AST increased in 2 participants (4.9%) each; no TEAEs of nasopharyngitis were reported. Treatment-emergent AEs were Grade 1 or 2 in severity with 1 exception: a participant (2.4%) with a medical history of ruptured Achilles tendon and Achilles tendon surgery had a serious Grade 3 TEAE of abscess limb (reported term: left leg abscess), which was not on a treated area, that led to study drug interruption and was considered not related to ruxolitinib cream. Also, a single participant (2.4%) with %BSA affected by atopic dermatitis of 60% had a TEAE that led to study drug discontinuation (LFT increased) with onset before the first application of ruxolitinib cream, and study drug was discontinued on Day 4. The event was Grade 1 in severity and considered not related to the study drug by the investigator. All TEAEs had resolved or were resolving at the end of the study.

The safety of ruxolitinib 1.5% cream was also evaluated in study INCB-18424-102. This study was conducted in 39 patients aged 2 to < 18 years with mild to severe AD. The safety profile was in line with the one reported in the pivotal phase 3 study 326.

2.5.1. Discussion on clinical safety

The safety profile of ruxolitinib 1.5% cream has been evaluated in adult patients with moderate AD inadequately controlled by TCSs or TCIs, in addition to the already authorised vitiligo indication. The integrated safety database comprises three main analysis pools, each serving a specific purpose:

- Pivotal Phase 3b study (INCB 18424-326): primary controlled efficacy/safety dataset (vehicle-controlled period 8 weeks + extension/escape); provides short-term comparative safety vs vehicle.
- Supportive Phase 3 pools:
    - Pool 1a (vehicle-controlled population; n=612): short-term safety vs vehicle across supportive studies (INCB 18424-303 and -304).
    - Pool 1b (52-week population; n=484 ruxolitinib total): long-term safety up to 52 weeks, including intermittent as-needed use after 8-week controlled periods.
    - Pool 2 (All AD Population): largest integrated dataset (n=1113 adults exposed to ruxolitinib 1.5% cream BID; 486.77 patient-years total exposure), combining all studies for overall safety characterisation.

The long-term safety data (Pool 1b and Pool 2) are considered sufficient and in line with ICH E1 requirements for chronic-use indications (≥1000 exposed patients, ≥300 for ≥6 months, ≥100 for ≥12 months): 257 participants exposed ≥24 to <52 weeks and 180 participants ≥52 weeks. After the initial 8-week BID controlled periods, patients transitioned to intermittent as-needed application (BID upon recurrence until resolution), reflecting real-world use.

Overall, the safety profile in adult AD patients is consistent with that observed in vitiligo, with no new safety signals identified. Treatment-emergent adverse events (TEAEs) were generally mild to moderate, with low incidences of Grade ≥3 TEAEs (3.5%), and TEAEs leading to discontinuation (1.1%) or interruption (3.2%). Application site acne is listed as a common ADR in SmPC section 4.8. In addition, within the last PSUSA of ruxolitinib cream (PSUSA/00011052/202509 - EMA/PSUR/0000317686), the PRAC recommended including 'herpes zoster' in SmPC sections 4.4 and 4.8, and to update the patient leaflet accordingly. The MAH has implemented the PI changes accordingly.

No new risks were identified in the adult AD population compared with the vitiligo indication. Important potential risks listed in the current RMP (also see section 2.7 below) remain unchanged.

Systemic exposure remains minimal (C_{ss} 22–50 nM; ≥6-fold margin below JAK2 IC50 of 281 nM, see PK assessment), supporting the minimal odds of oral JAK inhibitor class effects (MACE, VTE, serious infections, malignancies, cytopenias). Rare events (e.g., herpes zoster 0.4%/IR 1.0 per 100 PY, neutropenia 1.0%/IR 2.3 per 100 PY, NMSC 0.3%/IR 0.6 per 100 PY) were sporadic, background-appropriate, and not causally related to treatment. No Hy's law cases, fatalities attributable to ruxolitinib, or clinically meaningful laboratory trends were observed. Subgroup analyses (age, sex, race, ethnicity, region) were limited by small sample sizes in several categories (≥65 years n=13–39, Black/African American n=7–100, Asian n=20–24, Hispanic/Latino n=7–47). Numerically higher TEAE rates were seen in older patients, White participants, and European regions, but no consistent differences emerged for serious TEAEs, discontinuations, or interruptions, and differences were considered likely due to sample imbalance and background epidemiology rather than treatment effect. No subgroup-specific warnings are warranted.

Overall, considering both mean changes over time and individual changes, results suggest that long-term use of ruxolitinib 1.5% cream BID does not have a clinically meaningful effect on chemistry parameters.

Pregnancy and lactation data remain very limited (4 pregnancies reported, 2 spontaneous abortions assessed as unrelated; no new data on ruxolitinib in human milk). The current SmPC section 4.6 appropriately states that ruxolitinib cream should not be used during pregnancy and breastfeeding,

with precautionary language based on non-clinical findings and limited human data.

Upon CHMP's request, the MAH provided updated safety data from study 326. No new safety issues were observed with the additional safety data. Safety results for the VCE double-blind period and the escape arm were consistent with those for the double-blind, vehicle-controlled period. No participant died during Weeks 8 through 24, and the incidences of serious TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to study drug interruption, and Grade 3 or higher severity TEAEs remained low (< 2%). The most frequently reported TEAEs among participants on ruxolitinib 1.5% cream, upper respiratory tract infection and nasopharyngitis, were generally consistent with those during the double-blind, VC period.

The safety of ruxolitinib 1.5% cream BID under maximum-use conditions was evaluated in Study INCB 18424-103. This study was conducted in 41 adolescent and adult participants with AD. The limited dataset (N=41) under exaggerated use conditions (BSA >4× the proposed 20% maximum) is reassuring and does not reveal any new safety signals. Thirteen participants (31.7%) experienced ≥1 TEAE; only 4 participants had 6 treatment-related TEAEs (all Grade 1–2 and transient: Dyspnoea, neutropenia, haemoglobin decreased, ALT increased [1 each], AST increased [n=2]). One unrelated SAE was noted (abscess limb) leading to temporary interruption, and there was one unrelated discontinuation due to liver function test elevation (pre-existing). No new signals were observed for JAK class effects (serious infections, clinically relevant cytopenias, hepatic injury) despite higher systemic exposure in some participants (occasional C_{ss} > JAK2 IC50 of 281 nM). The safety profile remains consistent with the overall clinical database (Pool 2: 1,113 participants, 486.77 PY) and post-marketing experience. The safety of ruxolitinib 1.5% cream was also evaluated in study INCB-18424-102. This study was conducted in 39 patients aged 2 to < 18 years with mild to severe AD. The safety profile was in line with the one reported in the pivotal phase 3 study 326. SmPC section 5.1 was updated to reflect that the safety of ruxolitinib 1.5% cream in paediatric studies 102 and 103 was consistent with the profile reported in the pivotal study 326 in adults with moderate AD.

2.5.2. Conclusions on clinical safety

The safety profile was in line with the previously observed one for the vitiligo indication. Key findings are sufficiently reflected in the current SmPC (section 4.8: application site acne as common; section 4.4: warning for non-melanoma skin cancer and precautions for large area/excessive use).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.1 is acceptable.

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Non-melanoma skin cancer at long-term use Embryo-foetal toxicity
Missing information	Impaired bone growth and development in paediatric patients < 18 years of age

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Study INCB88888-037 (PASS) Ongoing	To evaluate the safety of long-term ruxolitinib cream use with respect to incidence of non-melanoma skin cancers	NMSC at long-term use	Protocol submission - within 6 months of EC decision First report to contain data on use of ruxolitinib cream from 2023-mid 2025 Interim reports to be provided yearly with updated available data for period of 5 years.	First report expected availability Dec 2025 Interim reports provided annually from 2026 to 2030
			Final report	2031

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study INCB 18424-309 Ongoing	To evaluate efficacy and safety of ruxolitinib cream in children from 6 years to less than 12 years of age with non-segmental vitiligo	Impaired bone growth and development in paediatric patients < 18 years of age	LPLV Milestones will be aligned with the Paediatric Investigation Plan.	December 2027

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Non-melanoma skin cancer at long-term use	Routine risk minimisation measures: • SmPC Section 4.4 Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study INCB88888-037 (PASS)
Embryo-foetal toxicity	Routine risk minimisation measures: • SmPC Sections 4.3 and 4.6 Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Standard Pregnancy Forms Additional pharmacovigilance activities: None
Impaired bone growth and development in paediatric patients < 18 years of age	Routine risk minimisation measures: • SmPC Section 4.2 Paediatric population • Section 5.3 Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study INCB 18424-308 Study INCB 18424-309

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Moderate AD is characterised by more widespread or persistent eczematous lesions than mild disease, with noticeable erythema, excoriations, and early lichenification, but without the extensive skin involvement or marked thickening seen in severe disease. Pruritus is typically frequent and intense, leading to regular scratching and sleep disturbance.

The therapeutic indication was amended to: *'Treatment of moderate atopic dermatitis in adult patients for whom topical corticosteroids and topical calcineurin inhibitors are inadequate or inappropriate.'* The indication is confined to moderate disease severity and adults, and a specifier is included to describe second-line (topical) treatment after standard first-line topical treatment.

3.1.2. Available therapies and unmet medical need

First-line pharmacological treatment of mild to moderate AD is with TCSs; TCIs are recommended when TCS are insufficiently effective or inappropriate (e.g. treatment of sensitive skin areas). For patients with moderate/severe AD that is not adequately controlled with currently available topical therapies, or for whom those topical agents are not medically advisable, systemic treatments such as the biologics targeting key pathways involved in Th2 mediated inflammation and oral JAK inhibitors are approved.

Ruxolitinib 1.5% cream is intended as a topical second-line product. As such, it is expected to fulfil a medical need in patients with moderate AD for whom standard first-line topical treatment is insufficiently effective or not (anymore) appropriate due to contra-indications or intolerance.

Main clinical studies

A single 24-week pivotal randomised vehicle-controlled trial (study 326) was performed in the target population of adults (N=214) with moderate AD for whom first-line treatment was insufficiently effective or inappropriate. The 8-week vehicle-controlled period is followed by an extension period with 'as needed' treatment in line with the intended intermittent use in practice.

This study is supported by a pooled subgroup analysis including subjects that mimic the intended target population from two identical 52-week clinical trials (studies 303 and 304) in adults and adolescents with mild to moderate AD having had first-line treatment.

3.1.3. Main clinical studies

3.2. Favourable effects

Versus vehicle

The coprimary endpoints in the pivotal study 326, EASI75 and IGA-TS at week 8, were both met. The 4 key-secondary endpoints all regarded itch and were also all met, while being corrected for multiplicity.

The proportion of participants with **EASI75** at week 8 was statistically significantly higher ($p < 0.0001$) in the ruxolitinib 1.5% cream treatment group compared with the vehicle cream group (70% *versus* 19%).

The proportion of participants with **IGA-TS** at week 8 also was statistically significantly higher ($p < 0.0001$) in the ruxolitinib 1.5% cream treatment group compared with the vehicle cream group (61% *versus* 14%).

The proportion of patients with a reduction in **Itch NRS of ≥4** points at week 8 was larger ($p<0.0001$) in the ruxolitinib group as compared to the vehicle group (63% versus 20%). The treatment effects (ruxolitinib *versus* placebo) were also statistically significant at day 7 (52% *versus* 14%), day 3 (35% *versus* 10%), and day 2 (29% *versus* 14%).

Treatment continuation

In patients with a sufficient response (EASI50) at week 8, treatment was continued and of the patients treated with ruxolitinib, most patients could maintain EASI75 response in weeks 12 to 24. The trends in EASI75 are reflected by similar results in IGA-TS over time. These responses are also reflected in the relatively low percentage of BSA affected.

Rebound

Rebound/relapse was assessed during the 30-day Safety Follow-up Period after week 24. Among participants who had an EASI75 response from baseline at week 24, 2/81 participants in the ruxolitinib cream treatment group had higher-than-baseline EASI scores at the safety follow-up visit after study treatment discontinuation.

Supportive data

In the subset of adults with moderate AD of the pooled supportive studies, the treatment effects for the ruxolitinib 1.5% cream treatment group versus the vehicle cream treatment showed nominal p-values < 0.0001 for **EASI75, IGA-TS, Itch4 response**, and were similar in size as the treatment effects found in the pivotal study. The proportions of participants with no or minimal lesions (IGA scores of 0 or 1) remained between 70%-77% throughout the 44-week long term treatment period when participants applied study drug as needed. The IGA responses are also reflected in the relatively low percentage of BSA affected.

3.3. Uncertainties and limitations about favourable effects

No uncertainties or limitations regarding favourable effects have been identified.

3.4. Unfavourable effects

The main unfavourable effect of ruxolitinib 1.5% cream in AD is application site reactions, reported in 2.1% of patients in the integrated All AD Population (Pool 2; exposure-adjusted incidence rate 4.7 per 100 patient-years). The most frequent event is application site acne (0.7%; incidence rate 1.6 per 100 patient-years), which is mild to moderate (Grade 1 or 2), non-serious, and consistent with a known class effect of topical JAK inhibitors. Application site acne is a listed ADRs in SmPC section 4.8 with a frequency 'common'. Other application site reactions (e.g. pain, folliculitis, irritation, dryness, erythema, infection, oedema, papules, pruritus) occur at ≤0.2%. These events are generally transient, resolve without study drug modification in most cases, and rarely lead to discontinuation or interruption.

Other unfavourable effects are infrequent and not considered treatment-related in the majority of cases. Serious TEAEs occurred in 1.3% of patients, Grade ≥3 TEAEs in 3.5%, TEAEs leading to discontinuation in 1.1%, and TEAEs leading to interruption in 3.2%. No treatment-related fatalities were reported. Rare events of special interest for JAK inhibitors (e.g. herpes zoster 0.4%/incidence rate 1.0 per 100 patient-years, neutropenia 1.0%/incidence rate 2.3 per 100 patient-years, non-

melanoma skin neoplasms 0.3%/incidence rate 0.6 per 100 patient-years) were sporadic, occurred in patients with predisposing factors or background risk consistent with atopic dermatitis, and showed no causal relationship to ruxolitinib cream. Liver function test elevations occurred in 1.3% (incidence rate 2.9 per 100 patient-years), all Grade 1 or 2, with no Hy's law cases or clinically meaningful trends in ALT, AST or bilirubin. No clinically relevant changes were observed in haemoglobin or platelet counts.

3.5. Uncertainties and limitations about unfavourable effects

No uncertainties or limitations regarding unfavourable effects have been identified.

3.6. Effects Table

Table 33. Effects Table for Opzelura for the treatment of moderate AD (data cut-off: 21 May)

Effect	Short description	Unit	Ruxolitinib	Vehicle	Uncertainties / Strength of evidence	References
Favourable Effects						
EASI75 at week 8	Responders	%	70	19	SoC: treatment effect (95%CI) of 51 (40 – 62)%, consistent in supportive studies Unc: not all 24-week data completed.	Study 326
IGA-TS at week 8	Responders	%	61	14	SoC: treatment effect (95%CI) of 48 (37 – 58)% Unc: see above	
Itch4 at week 8	Responders	%	63	20	SoC: treatment effect (95%CI) of 43 (31 – 54)% Unc: see above	
Unfavourable Effects						
Application site reactions	Predominantly acne; mild/moderate (Grade 1–2), non-serious, transient in most cases	%	2.1% (IR 4.7 / 100 PY)	Higher with vehicle in controlled periods	SoC: Expected topical JAKi effect; low discontinuation impact; Unc: Small subgroup sizes	Pool 2; Tables 11.11–11.15
Application site acne	Most frequent treatment-related local effect	%	0.7% (IR 1.6 / 100 PY)	0%	SoC: mild/transient; no severe/persistent cases	Pool 2; pivotal cumulative 5.0%

Abbreviations: IR = exposure-adjusted incidence rate per 100 patient-years

Notes: The most important unfavourable effects are selected based on frequency (application site reactions/acne) and potential clinical relevance.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The treatment effect (ruxolitinib – vehicle) in EASI75 was 51% and in IGA-TS was 48%, which is of comparable size. This is considered a clinically relevant treatment effect for 8 weeks treatment of moderate AD and translates in a NNT of 2 patients. This is relevant for patients, especially because IGA-TS is an absolute measure reflecting the treatment target of clear/almost clear skin. Further, itch is the major patient symptom of AD; thus, a clinically relevant effect on itch is also considered to be an important favourable effect for AD patients. Besides effects on itch, there were also supportive effects on skin pain and in PROs including DLQI, POEM and the PROMIS Sleep questionnaire. Sleep disturbance due to itch is a known phenomenon for patients with AD, therefore an effect on sleep is considered patient relevant.

In line with the reduction of %BSA affected, the amount of ruxolitinib cream used in the study reduced from a daily average of 8 gram to a daily average of about 2-gram cream (range: 0 – 7) in the extension period. This reduction is considered to be relevant from a long-term safety perspective, given that not all patients could completely stop treatment without recurrence of AD. There was no evidence of rebound, which supports safe treatment discontinuation.

The most important unfavourable effect is application site reactions, primarily site acne, a listed ADR for ruxolitinib cream, which is mild, transient, and consistent with approved topical JAK inhibitors.

3.7.2. Balance of benefits and risks

Ruxolitinib 1.5% cream is intended as a topical second-line product. It is considered to fulfil a medical need in patients with moderate AD for whom standard first-line topical treatment is insufficiently effective or not (anymore) appropriate.

Overall, the clinical development programme for ruxolitinib cream in moderate AD in adults is robust. Ruxolitinib cream has clinically relevant benefits in the treatment of moderate AD in adults for whom TCSs or TCIs are inadequate or inappropriate.

Ruxolitinib 1.5% cream BID was more effective than vehicle in reducing signs and symptoms of AD, with clinically relevant treatment effects on EASI75 and IGA-TS that translates in a NNT of 2, and a meaningful treatment effect on itch. Most patients were able to maintain treatment response and low %BSA affected using on-demand treatment. Favourable effects have also been demonstrated by patient-reported outcomes (subject rated AD severity, sleep impairment and disturbance; and AD-related quality of life).

Overall, the safety profile in adult AD patients is consistent with that observed in vitiligo. Application site reactions remained the most frequent treatment-related finding.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Opzelura is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of moderate atopic dermatitis in adult patients for whom topical corticosteroids and topical calcineurin inhibitors are inadequate or inappropriate for Opzelura, based on the results of the pivotal Phase 3 study INCB 18424-326 and the two supportive Phase 3 studies INCB 18424-303 and INCB 18424-304. INCB 18424-326 is a Phase 3b, double-blind, multicenter, randomised, vehicle-controlled, efficacy, and safety study of ruxolitinib cream in adults with moderate atopic dermatitis. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP is considered acceptable.

The variation leads to amendments to the annexes I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

In this procedure, the CHMP reviewed the available data from the studies conducted in accordance with the agreed PIP P/0486/2022, namely studies INCB 18424-303, INCB 18424-304, INCB 18424-102 and INCB 18424-103. The results of these studies are reflected in section 5.1 of the Summary of Product Characteristics (SmPC).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Opzelura-H-C-5843-II-EMAVR0000313318'

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 25 June 2026.