Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Rinvoq

Active ingredient: Upadacitinib

Sponsor: AbbVie Pty Ltd

March 2023

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ABT-494	Drug development name for upadacitinib
ACM	Advisory Committee on Medicines
ADerm-IS	Atopic Dermatitis Impact Scale
ADerm-SS	Atopic Dermatitis Symptom Scale
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AST	Aspartate transaminase
AUC	Area under the curve
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
C_{max}	Maximum concentration
CrCL	Creatinine clearance
CYP	Cytochrome P450
DLP	Data lock point
DLQI	Dermatology Life Quality Index
EAIR	Exposure-adjusted incidence rate
EASI	Eczema Area and Severity Index
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency (European Union)

Abbreviation	Meaning
ePRO	Electronic patient-reported outcome
EU	European Union
FDA	Food and Drug Administration (United States of America)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HADS	Hospital Anxiety and Depression Scale
HCP	Healthcare Professional
HECSI	Hand Eczema Severity Index
IGA	Investigator's Global Assessment
IL	Interleukin
ITT	Intent-to-treat
JAK	Janus kinase
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Affairs
MMRM	Mixed Models for Repeated Measures
NB-UV	Narrowband ultraviolet
NRI-C	Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19
NRS	Numerical rating scale
PAC	Patient Alert Card
PIP	Paediatric Investigation Plan (European Union)
PIP	Paediatric Investigation Plan (European Medicines Agency)
PK	Pharmacokinetic(s)
PMDA	Pharmaceutical and Medical Devices Agency (Japan)
POEM	Patient Oriented Eczema Measure
PopPK	Population pharmacokinetic(s)

Abbreviation	Meaning
PREA	Pediatric Research Equity Act (Food and Drug Administration, United States of America)
PSUR	Periodic safety update reports
QD	Once daily
RMP	Risk management plan
SCORAD	Scoring Atopic Dermatitis index
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
UK	United Kingdom
US(A)	United States (of America)
UVA	Ultraviolet A
UVB	Ultraviolet B
vIGA-AD	Validated Investigator Global Assessment scale for Atopic Dermatitis

Product submission

Submission details

Type of submission:	Extension of indications and major variation (new strength)
Product name:	Rinvoq
Active ingredient:	Upadacitinib
Decision:	Approved
Date of decision:	17 September 2021
Date of entry onto ARTG:	20 September 2021
ARTG numbers:	312687, 346215
▼ *Black Triangle Scheme:*	Yes This product will remain in the scheme for 5 years, starting on the date the new indication was approved
Sponsor's name and address:	AbbVie Pty Ltd 241 O'Riordan Street Mascot, NSW 2020
Dose form:	Modified release tablet
Strengths:	15 mg and 30 mg
Container:	Blister pack
Pack sizes:	7 tablets (starter pack), and pack of 28 tablets
Approved therapeutic use:	*Atopic Dermatitis* *Rinvoq 30 mg and 15 mg (modified release tablet blister pack) is now also indicated for use in adults and adolescents aged 12 years and above who weigh at least 40 kg, for the treatment of moderate to severe atopic dermatitis which is inadequately controlled with active topical pharmacotherapies and for whom systemic therapy is indicated.*
Route of administration:	Oral
Dosage:	Therapy with Rinvoq should be initiated and monitored by a specialist physician well versed in the use of immunomodulatory therapeutic agents like Rinvoq with expertise in the management of the indicated conditions. Rinvoq should not be initiated in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm^3, an

absolute neutrophil count (ANC) less than 1000 cells/mm^3 or who have haemoglobin levels less than 8 g/dL (see section 4.4 *Special warnings and Precautions for use* and section 4.8 *Adverse effects of the Product Information* for further information).

Rinvoq tablets should be taken orally with or without food. Rinvoq tablets should be swallowed whole. Rinvoq should not be split, crushed, or chewed.

Atopic dermatitis (adults)

The recommended starting dose of Rinvoq is 15 mg once daily for adults. In adults aged less than 65 years, the dose may be increased to 30 mg once daily from 4 weeks after initiation of treatment, if clinically warranted and based on benefit-risk assessment. The lowest effective dose for maintenance should be considered.

Atopic dermatitis (adolescents 12 to 17 years of age)

The recommended dose of Rinvoq is 15 mg once daily for adolescents weighing at least 40 kg. Rinvoq has not been studied in adolescents weighing less than 40 kg. Rinvoq should be ceased if a satisfactory clinical response is not achieved after 16 weeks.

The safety and efficacy of Rinvoq in adolescents weighing less than 40 kg and in children aged zero to less than 12 years have not yet been established. No data are available.

Dose interruption

Rinvoq treatment should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.4 *Special warnings and Precautions for use* in the Product Information). Interruption of dosing may be needed for management of laboratory abnormalities (specifically absolute neutrophil count, absolute lymphocyte count, haemoglobin and hepatic transaminases) as described in the Product Information.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More

information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by AbbVie Pty Ltd (the sponsor) to register Rinvoq (upadacitinib) 15 mg and 30 mg modified release tablets for the following extended indication:

> *Rinvoq is indicated for use in adults and adolescents 12 years and above who weigh at least 40 kg, for the treatment of moderate to severe atopic dermatitis which is inadequately controlled with active topical pharmacotherapies and for whom systemic therapy in indicated.*

Atopic dermatitis, also called eczema, is a chronic, relapsing, pruritic, inflammatory skin disease that occurs more frequently in children than adults. The diagnosis of atopic dermatitis is made clinically and is based on history, morphology and distribution of skin lesions, and associated clinical signs and symptoms. Due to the broad differential diagnosis, it is important to exclude other conditions when diagnosing atopic dermatitis, such as other forms of eczema, psoriasis, and scabies; biopsy may be necessary in these cases. Various criteria have been developed to aid in classification.

Some of the most widely used diagnostic criteria are those developed by Hanifin and Rajka (1980);[1] which require that 3 of 4 major criteria and 3 of 23 minor criteria be met (as shown in Table 1 below); and the United Kingdom (UK) Working Party criteria (shown in Table 2).[2]

[1] Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl* (Stockh)1980; 92:44-7
[2] The UK working party's diagnostic criteria for atopic dermatitis III: Independent hospital validation. Williams HC, Burney PGJ, Pembroke AC, Hay RJ. *Br J Dermatol* 1994;131:406-416

Table 1: Hanifin and Rajka (1980) Criteria for Atopic Dermatitis

Hanifin and Rajka Criteria for Atopic Dermatitis	
Major criteria (must have 3 of 4)	• Itchy skin (pruritus) • Skin inflammation (dermatitis) affecting flexural surfaces in adults or face and extensor surfaces in infants • Chronic or relapsing dermatitis • Personal or family history of cutaneous or respiratory allergy
Minor criteria (must have 3 of 32)	*Facial features* • Facial pallor, erythema, hypopigmented patches, infraorbital darkening, cheilitis, infraorbital folds, recurrent conjunctivitis, anterior neck folds *Triggers* • Emotional factors, environmental factors, food, skin irritants *Complications* • Susceptibility to skin infections, impaired cell-mediated immunity, predisposition to keratoconus and anterior subcapsular cataracts, immediate skin reactivity *Other* • Early age of onset, dry skin, ichthyosis, hyperlinear palms, keratosis pilaris, hand and foot dermatitis, nipple eczema, white dermographism, perifollicular accentuation

Adapted from: Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl* (Stockh) 1980; 92:44-7

Table 2: UK Working Party Diagnostic Criteria for Eczema (1994)

UK Working Party Diagnostic Criteria for Eczema
[A patient must have an] itchy skin condition, plus three (or more) of the following: – Visible flexural eczema, for example antecubital and popliteal fossae (or visible dermatitis of the cheeks and extensor surfaces if under 18 months) – Personal history of dermatitis as above – Personal history of dry skin in the last 12 months – Personal history of asthma or allergic rhinitis (or history of eczema in a first degree relative if under 4 years of age) – Onset of signs and symptoms under the age of 2 years (this criteria should not be used in children under 4 years of age)

Adapted from: The UK working party's diagnostic criteria for atopic dermatitis III: Independent hospital validation. Williams HC, Burney PGJ, Pembroke AC, Hay RJ. *Br J Dermatol* 1994;131:406-416

The severity of atopic dermatitis is usually determined based on clinician assessment, including estimation of the proportion of body surface area involved and subjective assessment of signs and symptoms. One-third of patients with atopic dermatitis have moderate to severe disease that is often accompanied by negative impact on health-related quality of life, including fatigue, work productivity, and everyday activities

as well as an increased incidence of attention deficit hyperactivity disorder (ADHD) in children, depression, suicidal ideation and sleep disturbance.[3,4,5]

Adolescent patients are estimated to count for between 8% and 14% of all patients with moderate to severe atopic dermatitis.[3,4]

Certain age-related variations in disease presentation are characteristic of atopic dermatitis. Infants generally experience highly pruritic erythematous lesions on the face and scalp, whereas older children exhibit more lichenified lesions typical of chronic disease involving the extremities.[6] In adolescents and adults, disease typically involves flexural folds, face, neck, upper arms and back, and dorsal surfaces of the hands and feet. Generally, severe lesions are more frequent in adults than in children.[7,8]

Atopic dermatitis generally begins in childhood as indicated by its higher prevalence rate among children (6% to 14%) relative to adults (3.2% to 10.2%).[9,10] The prevalence of eczema (or atopic dermatitis) varies widely between populations and countries and is said to have doubled or tripled in industrialised countries in recent decades.[11] The population prevalence of eczema in Australia was estimated to be 16% in 4-year olds and 20.3% in 1-year olds.[12]

Current treatment options

The goal of treatment is control of symptoms and reduction of disease flares, not cure of the disease.

Management of atopic dermatitis in adults and children primarily consists of trigger avoidance, careful attention to skin care, and both pharmacologic and non-pharmacologic treatment. In the majority of cases, disease flares will occur despite appropriate non-pharmacologic skin care and trigger avoidance.

In adults and adolescents, the most commonly used topical agents are corticosteroids, calcineurin inhibitors and moisturisers (emollients). When topical therapies are insufficient for treating atopic dermatitis, phototherapy or systemic therapy are generally added to topical agents.

The following is an extract of a consensus statement (2021) published by the Australasian College of Dermatologists on the management of atopic dermatitis.[13,14]

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[3] Silverberg JI. Public Health Burden and Epidemiology of Atopic Dermatitis. *Dermatol Clin.* 2017;35(3):283-289.
[4] Drucker AM, et al. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *J Invest Dermatol.* 2017;137(1):26-30.
[5] Reed B, Blaiss MS. The burden of atopic dermatitis. *Allergy Asthma Proc.* 2018;39(6):406-410.
[6] Akdis CA, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *Allergy*. 2006;61(8):969-987.
[7] Kunz B, et al. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1997;195(1):10-19.
[8] Ring, J, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part I. *Journal of the European Academy of Dermatology and Venereology* (2012);26: 1045-1060.
[9] Garg N, Silverberg JI. Epidemiology of childhood atopic dermatitis. *Clin Dermatol.* 2015;33(3):281-288.
[10] Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet.* 2020;396(10247):345-360.
[11] Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab.* 2015;66 Suppl 1:8-16.
[12] Martin PE, Koplin JJ, Eckert JK, et al. The prevalence and socio-demographic risk factors of clinical eczema in infancy: a population-based observational study. *Clin Exp Allergy.* 2013;43(6):642-651.
[13] Smith S et al. (2020), Atopic dermatitis in adults: An Australian management consensus. *Australas J Dermatol*, 61: 23-32
[14] Australasian College of Dermatologists (ACD): Consensus statement Management of atopic dermatitis in adults. First endorsed by ACD: 9 March 2021. Current: 9 March 2021. Review due: 2 years from publication. Available at: ACD-Consensus-Statement-Management-of-Atopic-dermatitis-in-adults-March-2021.pdf (dermcoll.edu.au)

Table 3: Management of atopic dermatitis (Australasian College of Dermatologists consensus statement, 2021)

Australasian College of Dermatologists: Management of atopic dermatitis (consensus statement)	
General measures	All general skin measures (soap-free wash, moisturiser, short, lukewarm showers, bath oils) should be maintained as a constant background therapy in all patients. Moisturisers are a cornerstone of therapy and should be included in the daily management plan. Clinicians should optimise general measures and topical therapy before considering systemic medications for atopic dermatitis, unless the impact on quality of life is substantial at the initial consultation.
Topical therapy	The aim is always to optimise topical therapies which include topical microbiome measures (for example bleach baths), wet wrap therapy, emollients and appropriate use of topical corticosteroids and topical calcineurin inhibitors.

Table 3 (continued): Management of atopic dermatitis (Australasian College of Dermatologists consensus statement, 2021)

Management of atopic dermatitis (Australasian College of Dermatologists consensus statement, 2021)	
Systemic therapies	
Phototherapy	Phototherapy (narrowband ultraviolet B (NB-UVB) or ultraviolet A1 (UVA1)) should be considered before the use of other systemic therapy if accessible and practical. Phototherapy is usually safe and well tolerated, but adverse events due to sensitive skin in atopic dermatitis patients may impact compliance.
Systemic corticosteroids	Systemic corticosteroids are effective, but associated with short-term and long-term adverse events; use should be limited to bridging, rescue of flares, anticipation of a major life event or in patients with severe atopic dermatitis.
Systemic antimicrobial agents	Systemic antimicrobials should be reserved for short-term use only in the majority of patients with infected atopic dermatitis, excluding those with hyper-IgE syndromes and immunosuppression.
Other systemic therapies	Considering currently available data and the safety profiles of systemic therapies that are approved by the Australian Therapeutic Goods Administration (TGA) to treat atopic dermatitis, it is recommended that dupilumab could be considered as a first-line systemic treatment option in adults with severe atopic dermatitis who are uncontrolled with topical therapies.

This consensus statement has been adapted from Smith S et al. (2020), Atopic dermatitis in adults: An Australian management consensus. *Australas J Dermatol*, 61: 23-32. by The Australasian College of Dermatologists with permission from the authors.

From the same consensus statement,[13,14] the optimal duration of trial to establish treatment response to different therapeutic approaches are as set out below.

Table 4: Optimal duration of trialled therapy (Australasian College of Dermatologists consensus statement, 2021)

Therapy	Optimal trial duration[1]
Topical therapies	
Wet dressings	Several (5 to 7) days
Topical corticosteroids	2 to 4 weeks
Topical calcineurin inhibitors	2 to 4 weeks
Phototherapy	
Narrowband ultraviolet B (NB-UVB) or ultraviolet A1 (UVA1))	8 to 12 weeks
Systemic therapies	
Ciclosporin	6 weeks
Azathioprine[2]	12 weeks
Methotrexate[2]	12 to 16 weeks
Mycophenolate mofetil[2]	12 weeks
Dupilumab	16 weeks

1: Timeframes to response times may differ according to disease severity, disease location and patient factors.

2: Not approved by the Australian Therapeutic Goods Administration (TGA) to treat atopic dermatitis.

This consensus statement has been adapted from Smith S et al. (2020), Atopic dermatitis in adults: An Australian management consensus. *Australas J Dermatol*, 61: 23-32. by The Australasian College of Dermatologists with permission from the authors.

Systemic immunomodulatory agents that have and may be used to treat atopic dermatitis include the older medications including oral glucocorticoids, cyclosporine, methotrexate, azathioprine, and mycophenolyate; however, most of the above drugs cannot be used long term either due to cumulative toxicity (for example, with long term oral corticosteroids or cyclosporin) or are not approved for use in atopic dermatitis.

The following table (Table 5) gives an overview of systemic treatments used in the treatment of atopic dermatitis, their general regulatory status, and the safety issues associated with use, adapted from a European consensus-led guideline on treatment options for atopic dermatitis (Wollenberg et al. 2018).[15,16]

[15] Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children: Part I. *JEADV.* 2018;32(5):657-82.
[16] Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children: Part II. *JEADV.* 2018;32(6):850-78.

Table 5: Systemic treatments used in the treatment of atopic dermatitis

Therapeutic agent	Safety issues	Comments
Mainly used in short-term therapy		
Oral glucocorticoids	Cushing's (glucocorticoid excess); diabetes mellitus; osteoporosis	Limited data showing lower efficacy compared with cyclosporine. Approved for atopic dermatitis in the USA under a broad indication. Long term use is not recommended due to toxicity.
Cyclosporin	Nephrotoxicity; hypertension	Approved for severe atopic dermatitis in the EU. Typically used for short-term control (3 to 6 months) due to cumulative toxicity.
May be used in long-term therapy		
Methotrexate	Known human teratogen; liver enzyme elevations; gastrointestinal side effects	Not approved for atopic dermatitis. Lack of well-controlled efficacy data supporting use in moderate-to-severe atopic dermatitis
Azathioprine	Bone marrow suppression; liver enzyme elevations; gastrointestinal side effects	
Mycophenolate mofetil	Known human teratogen; leukopenia and thrombocytopenia; gastrointestinal side effects	

Recently, dupilumab, a monoclonal antibody that inhibits cytokines, specifically the interleukins (IL)-4 and IL-13 signalling pathway has been approved in the United States of America (USA), European Union (EU), Japan, Canada and Australia for the treatment of moderate to severe atopic dermatitis in adults and paediatric patients older than 6 years of age. Dupilumab is administered subcutaneously (300 mg every 2 weeks) and therefore, possibly a need for an oral treatment development.

Upadacitinib

Upadacitinib is an oral selective and reversible Janus kinase (JAK)-1 inhibitor. At the time this submission was considered, Rinvoq (upadacitinib) has been approved for use in the

treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis (see section: *Regulatory status,* below).

Clinical rationale

The following is an excerpt of the sponsor's rationale for the use of Rinvoq (upadacitinib) for the intending indication:

> Atopic dermatitis is a common, chronic, relapsing, inflammatory skin disease characterised by highly pruritic, erythematous, excoriated, and oozing papules and plaques that may become lichenified over time. Atopic dermatitis is driven by pro-inflammatory cytokines (including IL-4, IL-13, IL- 22, TSLP, IL-31 and IFN gamma via the JAK1 pathway;[17,18,19] and, inhibiting JAK1 with upadacitinib reduces the signaling of many mediators which drive the signs and symptoms of atopic dermatitis.
>
> The use of systemic immunomodulatory drugs is recommended for patients in whom optimised topical regimens or phototherapy do not provide effective control of signs and symptoms of atopic dermatitis;[20,21]
>
> There is lack of adequate data to enable definite recommendations regarding optimal dosing and monitoring for systemic immunomodulatory treatments and risk of cumulative toxicity limits duration of treatment. Hence, there is a need for oral treatments which provide rapid itch relief, clearance of skin lesions and have a safety profile suitable for long-term use.
>
> Upadacitinib (Rinvoq; ABT-494);[22] is a selective and reversible Janus kinase (JAK) inhibitor that was approved for rheumatoid arthritis (RA) in the United States (US) and in the European Union (EU) in 2019; it was also approved in Australia (in Jan 2020).

Regarding the mechanism of action, the following is an extract from the draft Product Information (PI):

> Upadacitinib is a selective and reversible inhibitor of JAK1. upadacitinib more potently inhibits JAK1 compared to JAK2 and JAK3. In cellular potency assays that correlated with the *in vivo* pharmacodynamic responses, upadacitinib demonstrated 33- to 197-fold greater selectivity for JAK1-associated signalling over JAK2-JAK2 signalling. In enzyme assays, upadacitinib had > 50-fold selectivity for JAK1 over JAK3. Atopic dermatitis pathogenesis is driven by pro-inflammatory cytokines (including [interleukins] IL-4, IL-13, IL-22, TSLP, IL-31 and IFN-γ

[17] Renert-Yuval Y, Guttman-Yassky E. New treatments for atopic dermatitis targeting beyond IL-4/IL-13 cytokines. *Ann Allergy Asthma Immunol.* 2020;124(1):28-35.
[18] O'Shea JJ, Schwartz DM, Villarino AV, et al. The JAK-STAT pathway: impact on human disease and therapeutic intervention. *Annu Rev Med.* 2015;66: 311-28.
[19] He H, Guttman-Yassky E. JAK Inhibitors for Atopic Dermatitis: An Update. *Am J Clin Dermatol.* 2019;20(2):181-92.
[20] Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children: Part I. *JEADV.* 2018;32(5):657-82.
[21] Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children: Part II. *JEADV.* 2018;32(6):850-78.
[22] ABT-494 is the sponsors drug development code for upadacitinib.

[interferon gamma]);[23,24] that transduce signals via the JAK1 pathway.[25,26] Inhibiting JAK1 with upadacitinib reduces the signaling of many mediators which drive the signs and symptoms of atopic dermatitis such as eczematous skin lesions and pruritus.

To further justify the inclusion of the above statement on the pathogenesis of atopic dermatitis, the sponsor added that results from a Phase III study for dupilumab showed that inhibition of signalling of IL-4 and IL-13 improved the signs and symptoms of atopic dermatitis.[27]

Current and proposed new strength

At the time that this submission was considered, Rinvoq (upadacitinib) 15 mg modified release tablets had already received approval and were registered on the Australian Register of Therapeutic Goods (ARTG) (see section: *Regulatory status,* below).

The dosing regimen for atopic dermatitis proposes to include both the 15 mg (as currently approved) and a new 30 mg strength modified release tablet.

Regulatory status

Rinvoq (upadacitinib) as 15 mg modified release tablets received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 17 January 2020;[28][29] for the following indication:

> *Rinvoq is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to, one or more disease-modifying anti-rheumatic drugs (DMARDs).*
>
> *Rinvoq may be used as monotherapy or in combination with methotrexate or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).*

Subsequently, Rinvoq (upadacitinib) was approved for an extension of indications on 7 May 2021;[30] for the following additional indications:

> *Psoriatic arthritis*
>
> *Rinvoq is indicated for the treatment of moderate to severe active psoriatic arthritis in adult patients who have responded inadequately to, or are intolerant to one or more DMARDs. Rinvoq may be used as monotherapy or in combination with a non-biological DMARD.*
>
> *Ankylosing spondylitis*

[23] Guttman-Yassky E, Krueger JG, Lebwohl MG. Systemic immune mechanisms in atopic dermatitis and psoriasis with implications for treatment. *Exp Dermatol*. 2018;27(4):409-17.
[24] Klonowska J, Gleń J, Nowicki RJ, et al. New Cytokines in the Pathogenesis of Atopic Dermatitis-New Therapeutic Targets. *Int J Mol Sci.* 2018;19(10).
[25] Virtanen AT, Haikarainen T, Raivola J, et al. Selective JAKinibs: Prospects in Inflammatory and Autoimmune Diseases. *BioDrugs.* 2019;33(1):15-32.
[26] Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. *Nat Rev Rheumatol.* 2017;13(4):234-43.
[27] Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med.* 2016;375(24):2335-48.
[28] Rinvoq (upadacitinib) 15 mg modified release tablet blister pack (ARTG number 312687) was first registered on the ARTG on 17 January 2020.
[29] AusPAR for Rinvoq (upadacitinib) AbbVie Pty Ltd, submission PM-2018-05603-1-3. Published May 2020. Available at: AusPAR: upadacitinib | Therapeutic Goods Administration (TGA)
[30] AusPAR for Rinvoq (upadacitinib) AbbVie Pty Ltd, submission PM-2020-02479-1-3. Published August 2021. Available at: AusPAR: upadacitinib | Therapeutic Goods Administration (TGA)

Rinvoq is now also indicated for the treatment of adults with active ankylosing spondylitis.

The following table summarises these submissions and provides the indications where approved.

Table 6: International regulatory status

Region	Submission date	Status	Approved indications
European Union (Centralised procedure)	8 October 2020	Approved 23 August 2021	*Rinvoq is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.*
United States of America	15 October 2020	Approved 14 January 2022	*Rinvoq is indicated for the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable.*
Great Britain	29 June 2021	Approved 25 August 2021	*Rinvoq is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.*
Canada	23 October 2020	Approved 6 October 2021	*Rinvoq is indicated for the treatment of adults and adolescents 12 years of age and older with refractory moderate to severe atopic dermatitis (AD) who are not adequately controlled with a systemic treatment (e.g., steroid or biologic) or when use of those therapies is inadvisable.*
New Zealand	25 November 2020	Approved 5 August 2021 (15 mg); 20 January 2022 (30 mg)	*Rinvoq is indicated for the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy.*
Singapore	31 August 2021	Approved 21 June 2022	*Rinvoq is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy and whose disease is not adequately controlled with topical medications or for whom topical treatments are otherwise medically inadvisable.*

Region	Submission date	Status	Approved indications
Switzerland	16 October 2020	Approved 26 November 2021	*Rinvoq is indicated for the treatment of moderate to severe atopic dermatitis in adults when conventional topical drug therapy does not provide adequate disease control or cannot be used.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 7: Timeline for Submission PM-2020-04791-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	2 November 2020
First round evaluation completed	30 March 2021
Sponsor provides responses on questions raised in first round evaluation	28 April 2021
Second round evaluation completed	24 May 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	6 July 2021
Sponsor's pre-Advisory Committee response	19 July 2021
Advisory Committee meeting	6 August 2021
Registration decision (Outcome)	17 September 2021
Completion of administrative activities and registration on the ARTG	20 September 2021
Number of working days from submission dossier acceptance to registration decision*	197

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

There are no standardised guidelines for evaluation of systemic therapies for management of atopic dermatitis. However, the upadacitinib Phase III atopic dermatitis clinical development program was designed in close collaboration with regulatory authorities, incorporating guidance and scientific advice from the US Food and Drug Administration (FDA), the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP), and the Japanese Pharmaceutical and Medical Devices Agency (PMDA).

The clinical evaluation has also considered the Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children (Parts I and II);[20,21] during evaluation of this submission.

Quality

Rinvoq (upadacitinib) 15 mg modified release tablets in blisters were approved by the TGA in January 2020. A full quality evaluation was conducted at the time this product received initial registration (see the related AusPAR for submission PM-2018-05603-1-3 for further details).[29]

With this submission to extend the registered indications for the upadacitinib 15 mg modified release tablets, the sponsor also proposed to register a new strength, that is, Rinvoq (upadacitinib) 30 mg modified release tablets, to facilitate once-daily dosing for atopic dermatitis.

The currently registered 15 mg upadacitinib modified release drug product appears as a purple, biconvex, oblong, film coated tablet with dimensions of 14 x 8 mm, and is debossed with 'a15' on one side.

The proposed 30 mg upadacitinib modified release drug product appears as a red, biconvex, oblong, film coated tablet with dimensions of 14 x 8 mm, and is debossed with 'a30' on one side.

The tablets are not scored. The tablets are to be taken with or without food, swallowed whole and not split, crushed or chewed

The proposed packaging are blister packs containing 7 tablets as a 'starter pack', or containing 28 tablets as a 'monthly pack'.

New strength formulation

An additional strength (30 mg) of the Rinvoq upadacitinib modified release tablets is proposed for registration. The 30 mg tablets contains 30.7 mg upadacitinib (hemihydrate) equivalent to 30.0 mg upadacitinib (anhydrous). The tablet strengths (15 mg versus 30 mg) are easily distinguishable from one another in terms of the colour and debossing used.

The tablets are manufactured using a conventional wet granulation followed by milling, blending, tableting and coating manufacturing process which is identical to that registered for the 15 mg strength tablet. The drug substance is highly soluble, and whilst particle size is controlled to a two tier limit it does not impact on the release rate of the drug substance from the dosage form.

Good Manufacturing Practice (GMP) clearances for the drug substance and drug product manufacturing sites are considered acceptable.

The quality of the drug products are controlled by specifications that include tests and limits for description, identification (by UV and HPLC), assay (by HPLC), degradation products (by HPLC), water content, dissolution and uniformity of dosage. Granulation, average and individual tablet weight and hardness are controlled during the manufacturing process.

The new 30 mg strength demonstrated stability under long-term conditions and there was no evidence of any significant physical or chemical change after 36 months in the batches tested.

The release and expiry limits are the same as those specified for the 15 mg Rinvoq upadacitinib modified release tablet.

The *in vitro* dissolution test method is identical to that used for the currently registered 15 mg Rinvoq upadacitinib modified release tablet, is discriminatory, and consistent with a 'modified release' drug product, a three tier dissolution limit is applied. The proposed dissolution limits are supported by dissolution data for the clinical study batches.

All test parameters and limits proposed for the drug product specifications are considered acceptable.

The analytical methods used to analyse the drug products were adequately described and validated.

The proposed commercial container closure system for the Rinvoq 30 mg drug product is PVC/PE/PCTFE (Aclar) film and aluminium push-through foil blister cards and is identical to that used for the Rinvoq 15 mg drug product. Each blister card contains seven tablets, equivalent to a weekly dose. One blister card is packaged in a weekly carton and four blister cards are packaged in a monthly carton (that is, 28 tablets).

The Product Information (PI) document is finalised from a pharmaceutical chemistry and quality control perspective.

The Product Labelling has been finalised from a pharmaceutical chemistry perspective and complies with the requirements of Therapeutic Goods Order No. 91 - Standard for labels of prescription and related medicines (TGO 91).

Biopharmaceutics

The Rinvoq 30 mg market-image upadacitinib formulation was found to be bioequivalent to the 30 mg strength Phase III formulation under fasting conditions and after a high-fat/high-calorie meal.

Conclusion

Approval is recommended from a pharmaceutical chemistry and quality control perspective.

Nonclinical

The sponsor has submitted an application to extend the indications for Rinvoq (upadacitinib) to include treatment of atopic dermatitis in adults and adolescents (12 years and older), and a new higher strength of 30 mg. The proposed dosing regimen involves oral administration of one single 30 mg tablet daily in adults and one single 15 mg tablet daily in adolescents. Rinvoq is currently registered for the treatment of adults with rheumatoid arthritis at a dose of 15 mg/day.

No nonclinical data was submitted by the sponsor. In terms of safety assessment, this is acceptable given the previous nonclinical evaluation of currently registered upadacitinib 15 mg tablet for adults with rheumatoid arthritis.

Based on studies previously submitted and evaluated at the initial registration of Rinvoq (see the related AusPAR for submission PM-2018-05603-1-3);[29] data from juvenile rats showed exposure ratios were higher in younger rats (post-natal Day 15) than in adult rats (post-natal Day 63) at equivalent doses (see Table 8 below).

Table 8: Summary of upadacitinib exposure ratio in nonclinical studies

Species	Study duration Study ID	Dose (mg/kg/day)	Day	$AUC_{0-24\,h}$^ (ng·h/mL)	Exposure ratio#
Juvenile Rat (SD)	48 days (PND 15 to 63) Study R&D/17/0588	5	PND 15	8255	23
		20		28450	81
		50		76850	218
		5	PND 63	542	2
		20		3715	11
		50		8730	25
Adolescent subjects (12 to 18 years)	Steady state PopPK analysis R&D/20/0641	15 mg/day	–	352	–

Abbreviations: $AUC_{0-24\,h}$ = area under the curve from time zero to 24 hours; PND =post-natal day; PopPK = population pharmacokinetics; SD = standard deviation.

animal: human plasma $AUC_{0-24\,h}$; ^ = data are from the last sampling occasion for the sexes combined.

Studies in juvenile rats (evaluated in the initial submission (see the related AusPAR for details);[29] revealed similar findings to those seen in treated adults: lymphopaenia and lymphoid depletion in the spleen, thymus and other lymphoid tissues (JAK1 inhibition) and, at higher doses, reduced red blood cell parameters and reticulocytes with decreased bone marrow haematopoiesis (JAK2 inhibition). Immune responses were compromised as demonstrated by the T cell dependent antibody response assay. Reversibility of effects was not examined. A no observable adverse effect level of 20 mg/kg/day was established in juvenile animals (relative exposure of 81 based on an area under the curve (AUC) of 28450 ng x h/mL in juvenile rats and 352 ng x h/mL in adolescent patients). Overall, juvenile animals do not appear to be more prone to upadacitinib toxicity compared to adults.

Population pharmacokinetic studies conducted in adults with atopic dermatitis following a dose of 30 mg/day demonstrated a roughly 2-fold increase in exposure compared to the 15 mg/day dose that is currently registered. Exposure margins calculated in the nonclinical evaluation of upadacitinib in the initial submission for registration;[29] that were calculated using exposure from a 15 mg/day dose are therefore lower by approximately 2-fold compared with the higher 30 mg/day dose, however this does not affect the safety assessment and potential risks identified in the original nonclinical evaluation. It is appropriate that the lower margins with the 30 mg/day dose are included in the PI.

The sponsor provided three literature references to support nonclinical statements proposed for the PI document regarding the mechanism of action of upadacitinib in the pathogenesis of atopic dermatitis. These and other published studies describe the pathogenesis of atopic dermatitis. Atopic dermatitis is driven by barrier dysfunction and abnormal immune activation of T helper cells (T_h)-2 (T_h2), and T_h22, with varying degrees of T_h1 and T_h17 also involved. The JAK–signal transducer and activator of transcription (STAT) and spleen tyrosine kinase (SYK) pathways are involved in signalling of several atopic dermatitis-related cytokines, such as interferon gamma (IFN-γ), the interleukins

(IL): IL-4, IL-13, IL-31, IL-33, IL-23, IL-22, IL-17; and thymic stromal lymphopoietin (TSLP), mediating downstream inflammation and barrier alterations.[31,32,33,34] The gamma chain (γc) family of cytokines, including IL-4, and a number of other key cytokines including interferons alpha (IFN-α) and beta (IFN-β; JAK1/TYK2 dependent), IFN-γ (JAK1/JAK2 dependent), IL-6 (JAK1/JAK2/TYK2 dependent), and IL-21 (JAK1/JAK3 dependent) require JAK1 for signal transduction.[31] In the Phase II clinical trials in adults with moderate to severe atopic dermatitis, upadacitinib resulted in a dose-dependent reduction in symptoms.[31]

Conclusions and recommendations

No new major target organs of toxicity have been identified in juvenile animals and overall, juvenile animals do not appear to be more prone to upadacitinib toxicity compared to adults.

In adults, a dose of 30 mg/day resulted in a 2-fold increase in exposure compared to the 15 mg/day dose. The increase in exposure does not change the overall safety assessment from the original nonclinical evaluation for the initial submission to approve Rinvoq (upadacitinib) for rheumatoid arthritis.[29]

There are no nonclinical objections to the proposed extension of indications for the treatment of atopic dermatitis in adults at a dose of 30 mg/day and adolescents at a dose of 15 mg/day.

Clinical

Summary of clinical studies

The clinical dossier consisted of the following:

- One Phase I study:
  - Study M20-017, a Phase I study to evaluate the bioavailability after a high-fat/ high-calorie meal and under fasting conditions of upadacitinib market-image formulation relative to the wet granulated formulation used in upadacitinib Phase III trials.
- Two population pharmacokinetic (popPK) analyses:
  - Analysis R&D/18/1079, the population pharmacokinetics of upadacitinib in healthy subjects and subjects with rheumatoid arthritis, Crohn's disease, ulcerative colitis or atopic dermatitis: analyses of Phase I and II studies.
  - Analysis R&D/20/0641, a population pharmacokinetic analysis of upadacitinib in healthy volunteers and adult and adolescent subjects with atopic dermatitis: analyses of Phase I, II and III studies.
- Three Phase III, pivotal, efficacy/safety studies:

[31] He H & Guttman-Yassky E (2019) JAK inhibitors for atopic dermatitis: an update. *Am. J. Clin. Dermatol.* 20:181–192.
[32] Guttman-Yassky E *et al.* (2018) Systemic immune mechanisms in atopic dermatitis and psoriasis with implications for treatment. *Experimental Dermatology.* 27:409–417.
[33] Klonowska J, *et al.* (2018) New cytokines in the pathogenesis of atopic dermatitis—new therapeutic targets. *Int. J. Mol. Sci*. 19: 3086.
[34] Virtanen AT *et al.* (2019) Selective JAKinibs: prospects in inflammatory and autoimmune diseases. *BioDrugs*. 33:15–32.

  - Study M16-045 and Study M18-891, two pivotal Phase III randomised, placebo-controlled, double-blind studies evaluated upadacitinib (30 mg and 15 mg) as monotherapy in adolescent and adult subjects with moderate to severe atopic dermatitis.
  - Study M16-047, one pivotal Phase III, randomised, placebo-controlled, double-blind study evaluated upadacitinib (30 mg and 15 mg) in combination with topical corticosteroids in adolescent and adult subjects with moderate to severe atopic dermatitis.
- Two supportive efficacy/safety studies:
  - Study M16-048, a Phase IIb multicentre, randomised, placebo controlled, double-blind dose-ranging study to evaluate ABT-494 (upadacitinib) in adult subjects with moderate to severe atopic dermatitis.
  - Study M17-377, a Phase III study for evaluation of upadacitinib in combination with topical corticosteroids in adolescent and adult subjects in Japan.
- Multiple other reports including an integrated summary of efficacy and safety, and cardiovascular adjudication, atopic dermatitis data monitoring charters and minutes, a clinical overview, summaries of clinical pharmacology, clinical efficacy and clinical safety, and literature references.
- Two exposure-response analyses:
  - Analysis R&D180643: Exposure-response analyses of upadacitinib efficacy and effects on laboratory parameters in subjects with moderate-to-severe atopic dermatitis: results of Period 1 of the Phase II Study M16-048.
  - Analysis R&D/20/0642: Exposure-response analyses for upadacitinib efficacy and safety in adult and adolescent subjects with atopic dermatitis: analyses of Phases II and III studies

Paediatric data

Upadacitinib has been evaluated in adolescents aged 12 to 17 years (and weighing more than 40 kg). There is no data in children aged 2 to 11 years.

There is an agreed Paediatric Investigation Plan (PIP) in Europe (the first study report was the non-clinical Study TA16-134, a dose range finding juvenile toxicity study, which was submitted in April 2018). Whilst a PIP has been agreed to by the EMA and is in place, a waiver for a subset of the paediatric population was also granted in accordance with Article 13 of Regulation (EC) No. 1901/2006. The waiver applies to: the paediatric population from birth to less than 2 years of age; prolonged-released tablet, prolonged-release capsule, age-appropriate oral solid dosage form, age-appropriate oral liquid dosage form, oral use. This waiver has been granted by the EMA on the grounds that the specific medicinal product is likely to be unsafe in these instances.

There is an agreed Pediatric Plan under the Pediatric Research Equity Act (PREA) in the USA. Clinical development of upadacitinib in subjects 6 months to 11 years old with atopic dermatitis is proposed to start in November 2018. This will reduce the risk of administering ineffective or poorly tolerated doses of upadacitinib to children in a Phase I pharmacokinetic study, which would not be appropriate both for ethical reasons and in view of other available treatment options in atopic dermatitis. JAK inhibition and selectivity is dose dependent, and certain adverse effects are related to the underlying pharmacology of JAK inhibition. It will therefore be important to adequately assess safety in the Phase I PK study prior to performing additional upadacitinib studies in the paediatric population below 12 years of age.

Good Clinical Practice

All clinical studies were conducted in compliance with current Good Clinical Practice (GCP) guidelines and were closely monitored by the sponsor or designated contract research organisation for compliance to the protocol, relevant standard operating procedures and adherence to applicable regulatory guidelines.

Pharmacokinetics

As per the clinical evaluation, the pharmacokinetic (PK) characteristics, in terms of absorption, distribution, metabolism, excretion (ADME), of upadacitinib after single and multiple doses, its drug-drug interaction (DDI) potential and PK in special populations were submitted and evaluated, in the regulatory submission dossier for its use in the treatment of rheumatoid arthritis [see the relevant AusPAR for further details].[29] No new PK studies were submitted in the current atopic dermatitis dossier.

The exception was Study M20-017, which assessed and compared the bioavailability of both the 15 mg and 30 mg upadacitinib formulation used in the Phase III atopic dermatitis clinical trial with the same strengths of the proposed upadacitinib market formulation, under fasting and fed (that is, after a high fat/ high calorie meal) conditions.

Table 9: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in healthy adults	Bioequivalence† (single dose)	Study M20-017
	Food effect	Study M20-017
Population PK analyses	Target population: pharmacokinetics of upadacitinib in healthy volunteers and adult and adolescent subjects with atopic dermatitis: analyses of Phase I, II and III studies	Analysis RD200641
	Other population: pharmacokinetics of upadacitinib in healthy subjects and subjects with rheumatoid arthritis, Crohn's disease, ulcerative colitis or atopic dermatitis: analyses of Phase I and II studies	Analysis RD181079

† Bioequivalence of different formulations.

Study M20-017 was a Phase I single-dose, open-label, randomised, four-period, four-sequence, two-part crossover study.

Bioequivalence between the Phase III atopic dermatitis clinical trial formulation and the proposed market formulation of both the 15 mg and 30 mg strengths upadacitinib modified-release tablets was established under fasting conditions, as well as after a high fat/ high calorie meal. The estimates of relative bioavailability and their 90% confidence intervals (CIs) were within the accepted bioequivalence limits of 0.80 to 1.25.

Additional analysis showed that the 15 mg strength modified-release upadacitinib market-image formulation provided equivalent dose-normalised plasma exposures to the 30 mg strength upadacitinib Phase III formulation under fasting conditions and after a high-fat/ high-calorie meal

The clinical evaluation noted that the 30 mg once daily dose is not approved for the treatment of rheumatoid arthritis, but is proposed for use in atopic dermatitis. The sponsors have proposed that only the lower dose of 15 mg once daily be used for proposed indication of atopic dermatitis in adolescents at this time as more safety data accrue on the 30 mg dose.

Studies submitted earlier for the rheumatoid arthritis indication;[29] showed higher upadacitinib exposure in subjects with severe renal impairment (44% higher upadacitinib area under the concentration versus time curve (AUC) compared to those with normal renal function) and when administered with strong cytochrome P450;[35] (CYP) 3A4 inhibitors (a 75% higher upadacitinib exposure following concomitant administration of ketoconazole, a potent CYP3A4 inhibitor).

Population pharmacokinetics

Population pharmacokinetics (popPK) was extracted from popPK Analysis R&D/20/0641, which included data from the Phase IIb Study M16-048; three global Phase III studies (Studies M16-045, M16-047 and M18-891; and a supportive Japanese Phase III study (Study M17-377).

Analysis R&D/20/0641

The objective of popPK Analysis R&D/20/0641 was to characterise the population pharmacokinetics of upadacitinib in adult and adolescent subjects, with moderate to severe atopic dermatitis and, to provide data to support dose justification for upadacitinib in adult and adolescent subjects with moderate to severe atopic dermatitis.
4,161 upadacitinib plasma concentrations were collected from 911 subjects following administration of upadacitinib doses of 7.5 mg, 15 mg and 30 mg.

A non-linear mixed-effects modelling approach was assumed to analyse the observed upadacitinib plasma concentration-time profiles. It yielded upadacitinib pharmacokinetics as being a two-compartment model with mixed zero and first order absorption, with lag time for the upadacitinib extended release formulation. Model evaluations assessed the predictive performance of the developed models and examined the usefulness of the models for describing observed data. Model parameters based on the original dataset were compared against the bootstrap results.

Demographics and baseline characteristics for subjects included in the PK analysis were similar to those of the overall study populations, indicating generalisability of the analysis results to the overall patient population enrolled in the Phase III studies.

Analysis R&D/20/0641 indicated that:

- Patient population (atopic dermatitis versus healthy volunteers), sex and creatinine clearance were statistically significant covariates on upadacitinib oral clearance.
- Compared to subjects with normal renal function, those with mild (creatinine clearance (CrCL) of 60 to < 90 mL/min) or moderate (CrCL of 30 to < 60 mL/min) renal impairment were predicted to have approximately 12% and 25% higher area

[35] **Cytochrome P450 (CYP) enzymes** are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds. Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

under the concentration versus time curve from time zero to 24 hours (AUC_{0-24h}) and 9% and 17% higher maximum concentration (C_{max}), respectively.

- Female subjects were predicted to have 20% higher AUC_{0-24h} and 14% higher C_{max}, respectively, compared to male subjects.
- Subjects with atopic dermatitis were predicted to have 18% higher AUC_{0-24h} and 12% higher C_{max} compared to healthy volunteers. However, the influence of the statistically significant covariates in the final model led to < 25% changes on model-predicted upadacitinib steady state exposures (AUC_{0-24h} and C_{max}) and, are unlikely to be clinically relevant in subjects with atopic dermatitis;

Other covariates, such as age, body weight, and geographic region (for example, Japan or China) did not show any impact on upadacitinib pharmacokinetics.

Comparison of the model predicted upadacitinib exposures between adolescent and adult subjects with atopic dermatitis showed that upadacitinib exposures were similar between the two age groups.

The observed upadacitinib concentrations in both subjects with atopic dermatitis and subjects with rheumatoid arthritis indicated that upadacitinib exposures were comparable between the two patient populations.

Upadacitinib plasma exposures were comparable between Japanese and non-Japanese subjects with atopic dermatitis for both the 15 mg and 30 mg once daily regimens. Results from previous Phase I studies (Studies M13-543 and M15-558) have demonstrated similar upadacitinib pharmacokinetics between Japanese, Chinese, and Western subjects. Hence, subjects with atopic dermatitis from other Asian countries (for example, China) are also expected to have similar upadacitinib plasma exposures to non-Asian subjects. Although the small sample size for subjects from other Asian countries (for example, China) did not allow for covariate testing, *post-hoc* exposures stratified by geographic regions showed similar upadacitinib pharmacokinetics across the different study regions, including Asian countries (for example Japan, and China).

Analysis R&D/18/1079

PopPK analysis R&D/18/1079 included data from the Phase I and II studies.

The objective of this analysis was to characterise the PopPK of upadacitinib in healthy subjects and subjects with rheumatoid arthritis, Crohn's disease, atopic dermatitis, or ulcerative colitis.

The R&D/18/1079 analysis indicated that:

- Compared to males, females had 21% higher steady state AUC.
- Compared to healthy subjects, subjects with atopic dermatitis, ulcerative colitis or Crohn’s disease had 21% higher steady state AUC, while subjects with rheumatoid arthritis had 35% higher steady state AUC.
- Subjects with mild or moderate renal impairment were estimated to have 8% or 18% higher AUC, respectively, compared to subjects with normal renal function.

Overall, the results from the population pharmacokinetic analysis indicated no clinically relevant covariate effects and suggest that upadacitinib pharmacokinetics are comparable between healthy subjects and subjects with rheumatoid arthritis, Crohn's disease, atopic dermatitis, or ulcerative colitis.

Conclusions

Bioequivalence between the Phase III atopic dermatitis clinical trial formulation and proposed market formulation of both the 15 mg and 30 mg extended release modified-release tablets was established, under both fasting conditions as well as after a high fat/

high calorie meal, as the estimates of relative bioavailability and their 90% confidence intervals (CIs) were within the accepted bioequivalence limits of 0.80 to 1.25.

Additional analysis showed that the 15 mg strength modified-release upadacitinib market-image formulation provides equivalent dose-normalised plasma exposures to the 30 mg strength upadacitinib Phase III formulation, under fasting conditions and after a high-fat/ high-calorie meal.

Overall, PopPK analyses demonstrated similar upadacitinib exposure in the atopic dermatitis and rheumatoid arthritis patients as well as across different ethnic groups with no dose adjustments warranted in any of these groups. PopPK modelling analyses also indicated similar upadacitinib exposures in adult and adolescent subjects with atopic dermatitis. However, it is noted that the sponsors do not propose use of the higher 30 mg dose in adolescents (reason stated was that they await more safety data on the 30 mg dose for adolescents).

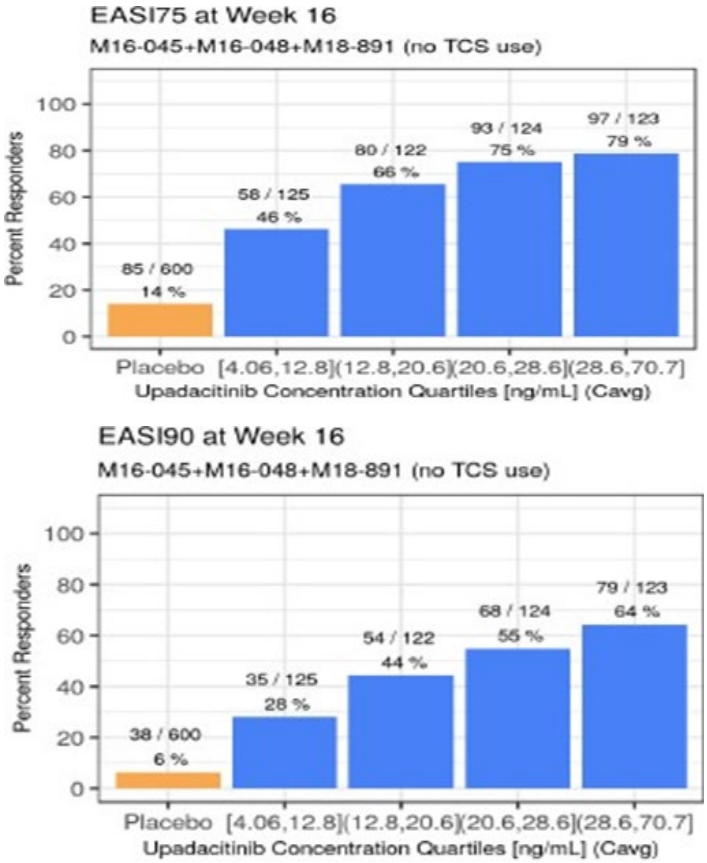
Pharmacodynamics

Through exposure response analyses, the relationships between upadacitinib plasma exposures and clinical efficacy and safety in adolescent and adult subjects with atopic dermatitis was analysed using data from one Phase IIb and three Phase III studies across subjects receiving upadacitinib alone or in combination with topical corticosteroids. upadacitinib individual average concentration values in subjects with atopic dermatitis were estimated using empirical Bayesian individual estimates from the population pharmacokinetics analysis.

Exposure-response analyses

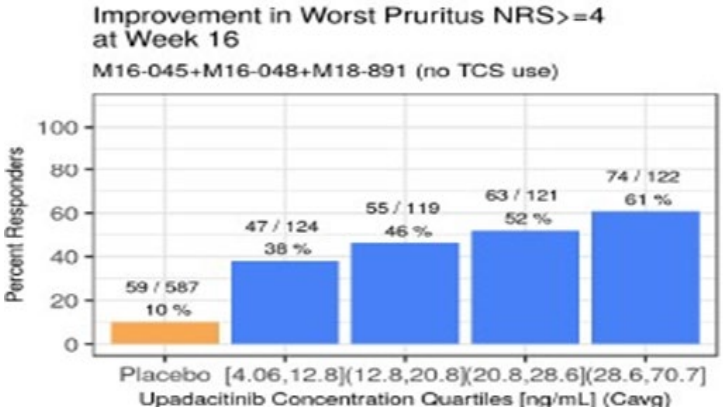
With regard to the outcome, in subjects receiving upadacitinib monotherapy, statistically significant exposure-dependent increases in upadacitinib efficacy were observed for Eczema Area and Severity Index (EASI) 75, EASI 90, Investigators Global Assessment (IGA) 0/1, IGA 0, and improvement in Worst Pruritus numerical rating scale (NRS) ≥ 4 from Baseline at Week 16 (see section: *Scoring systems used in the clinical studies* for more information on these outcome measures).

Figure 1: Exposure-response analyses, observed EASI75 and EASI90 responses rates (NRI-C) versus upadacitinib average concentration quartiles at Week 16 for upadacitinib monotherapy (Studies M16-048, M16-045, and M18-891)



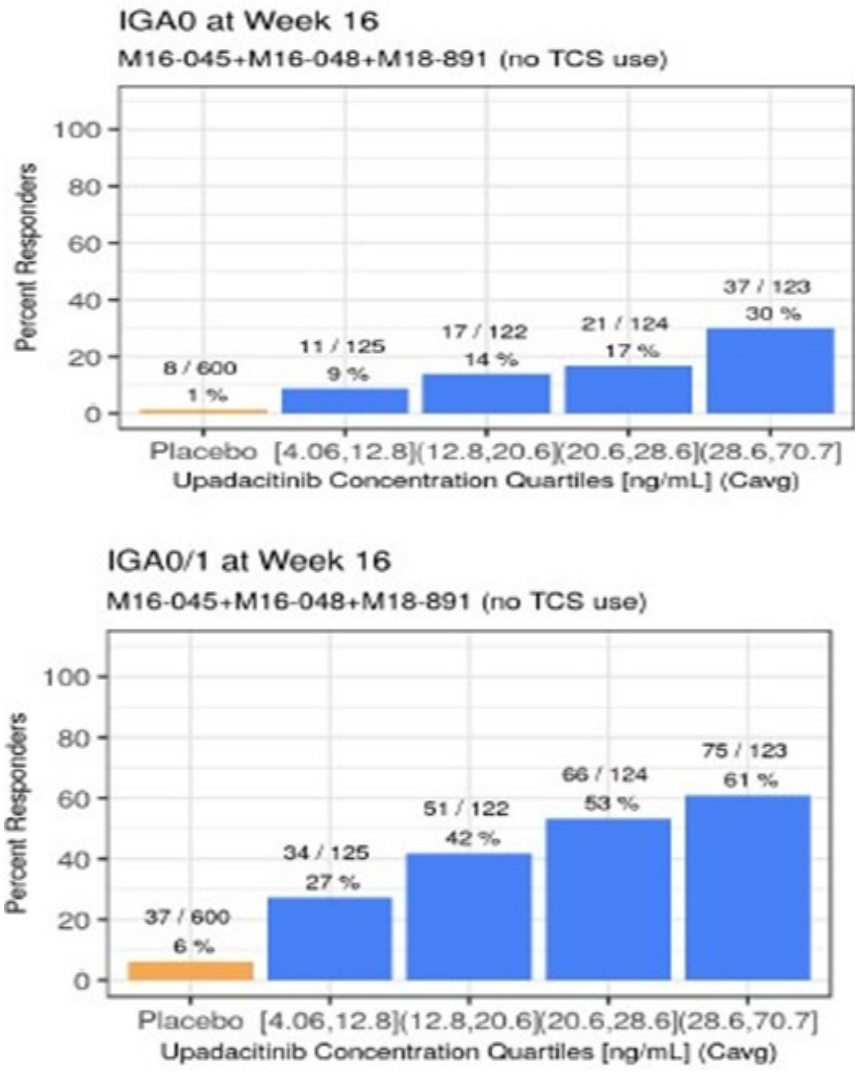
Abbreviations: Cavg = average concentration; EASI = Eczema Area Severity Index; EASI75 = Eczema Area Severity Index 75% improvement response; EASI90 = Eczema Area Severity Index 90% improvement response; NRI = non-responder imputation due to COVID-19 disease; TCS = topical corticosteroids.

Figure 2: Exposure-response analyses, observed improvement in worst pruritus NRS of 4 or more responses rates (NRI) versus upadacitinib average concentration quartiles at Week 16 for upadacitinib monotherapy (Studies M16-048, M16-045, M18-891)



Abbreviations: Cavg = average concentration; NRS = numerical rating scale; NRI = non-responder imputation; TCS = topical corticosteroids.

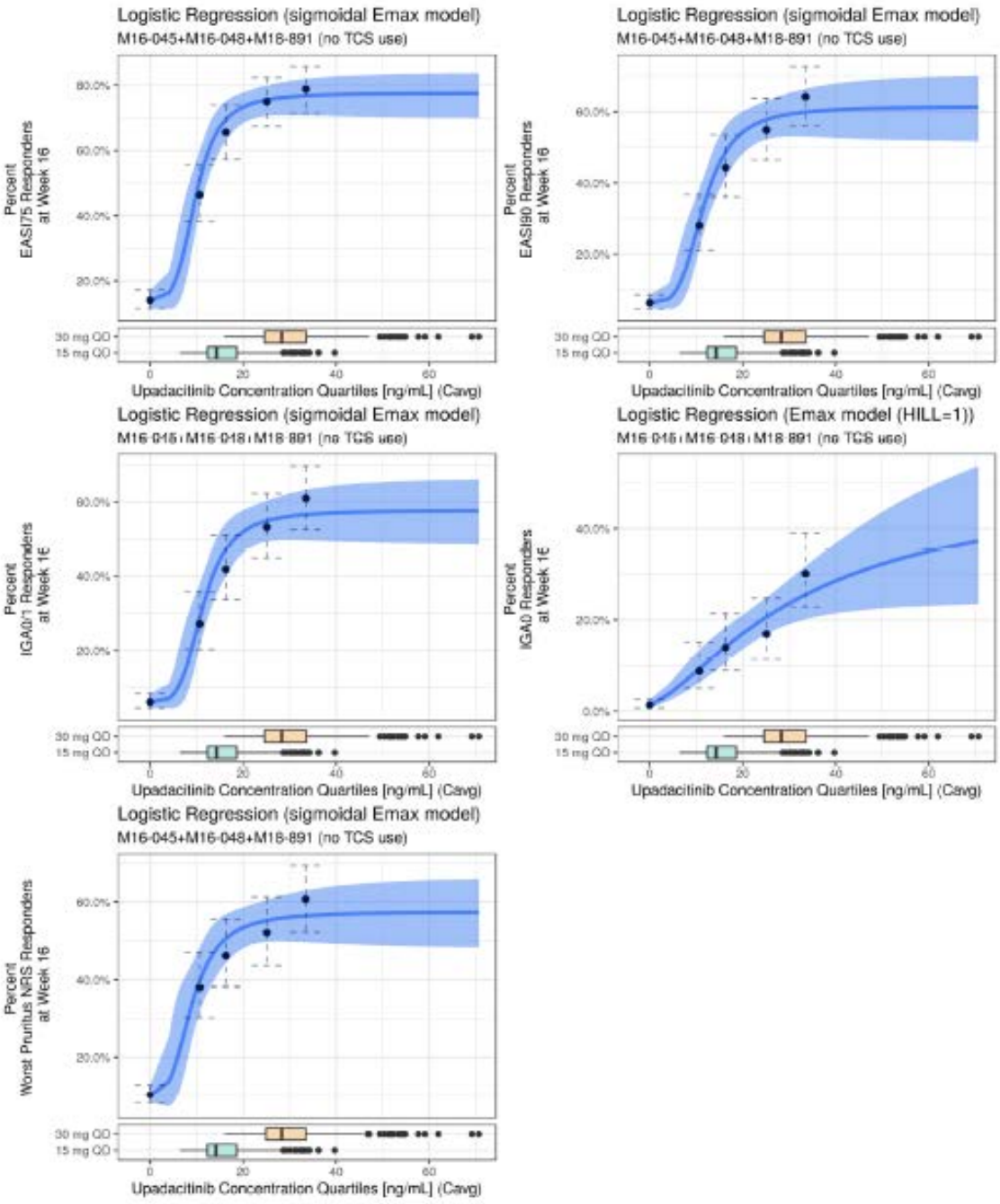
Figure 3: Exposure-response analyses, observed IGA0 and IGA0/1 responses rates (NRI) versus upadacitinib average concentration quartiles at Week 16 for upadacitinib monotherapy (Studies M16-048, M16-045, M18-891)



Abbreviations: Cavg = average concentration; IGA0/1 = Investigators Global Assessment score of 0 or 1; NRI = non-responder imputation; TCS = topical corticosteroids.

Similar statistically significant exposure-response relationships for all these endpoints were also demonstrated following logistic regression analyses as shown in Figure 4, below.

Figure 4: Exposure-response analyses, observed (NRI) and model-predicted efficacy responses at Week 16 versus upadacitinib average concentration for upadacitinib monotherapy (base models); (Studies M16-048, M16-045, M18-891)



Abbreviations: Cavg = average concentration; EASI = Eczema Area Severity Index; EASI75 = Eczema Area Severity Index 75% improvement response; EASI90 = Eczema Area Severity Index 90% improvement response; IGA0/1 = Investigators Global Assessment score of 0 or 1; NRS = numerical rating scale; NRI = non-responder imputation; TCS = topical corticosteroids.

Note the blue solid line represents median predicted response and the blue shaded area represent 95% confidence intervals of the predicted response. The dots and error bars represent median and 95% binomial CIs of binned observed rates. For the horizontal box plots, the band inside the box is the median of the upadacitinib average concentration per 15 mg once daily, and 30 mg once daily dosing. The lower and upper hinges correspond to the 25th and 75th percentiles. Whiskers represent 1.5 interquartile range. The data beyond the end of the whiskers are plotted individually.

No statistically significant effects of age group (adolescent versus adult subjects), weight, or race were identified in any of the exposure-response models.

In simulations using the final exposure-response models demonstrated clinically significant improvement in responses with both 15 mg and 30 mg doses.

Table 10: Exposure-response analyses, model simulated clinical efficacy responses at Week 16 (median and 90% confidence intervals) following placebo and upadacitinib 15 mg and 30 mg once daily regimens

Clinical Efficacy Response Variable	Placebo	15 mg QD	30 mg QD
EASI 75	14% (11% – 18%)	63% (56% – 69%)	75% (67% – 81%)
EASI 90	6% (4% – 10%)	43% (34% – 50%)	57% (50% – 63%)
IGA 0/1	6% (4% – 9%)	41% (34% – 47%)	55% (46% – 62%)
IGA 0	1% (0% – 3%)	14% (10% – 18%)	23% (17% – 29%)
Improvement in Worst Pruritus NRS ≥ 4	10% (7% – 13%)	46% (35% – 53%)	54% (40% – 60%)

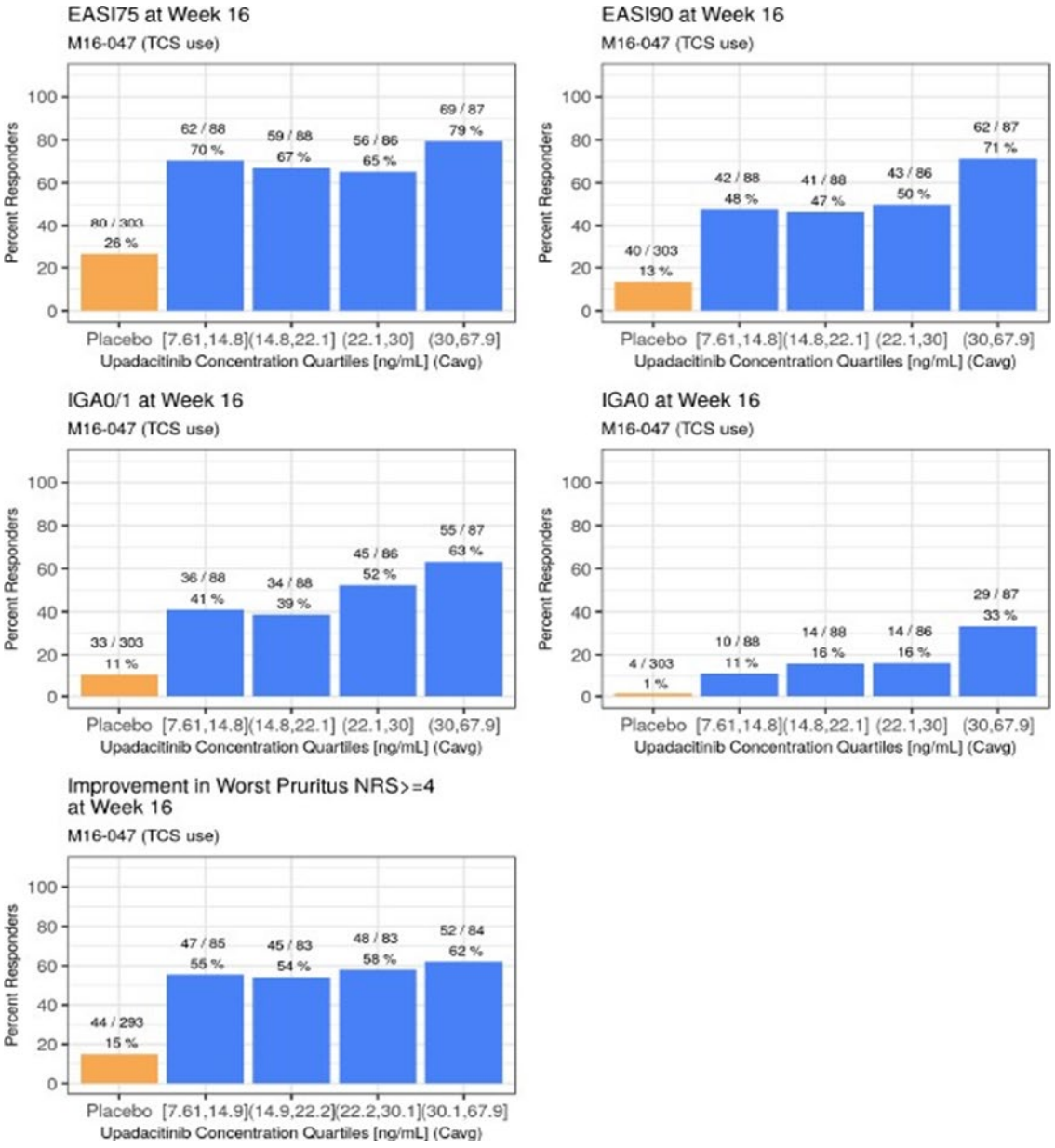
Note: Results presented as median percentage of subjects achieving response (and the 5th and 95th percentile) from 300 replicates with 300 subjects/dose group in each replicate.

Abbreviations: EASI = Eczema Area Severity Index; EASI75 = Eczema Area Severity Index 75% improvement response; EASI90 = Eczema Area Severity Index 90% improvement response; IGA0/1 = Investigators Global Assessment score of 0 or 1; NRS = numerical rating scale; QD = once daily; TCS = topical corticosteroids.

The 30 mg once daily dose showed greater benefits compared to the 15 mg once daily dose in terms of 12% to 14% greater response for EASI 75, EASI 90, and IGA 0/1 as well as 9% for IGA 0 (reflecting complete skin clearance).

In subjects receiving upadacitinib in combination with topical corticosteroids, statistically significant exposure- dependent increases in upadacitinib efficacy were observed for EASI 90, IGA 0/1, and IGA 0 at Week 16 (see Figure 5, below).

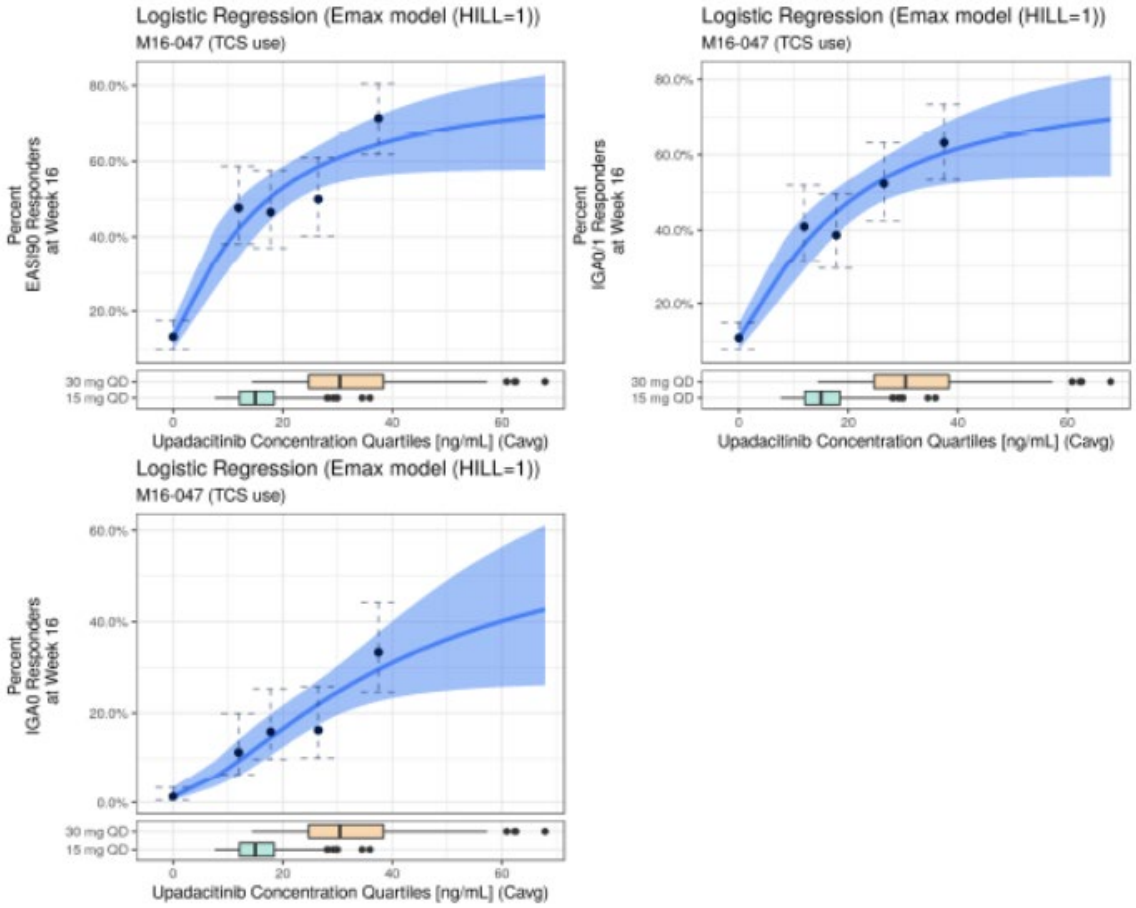
Figure 5: Exposure-response analyses, observed efficacy responses (NRI) versus upadacitinib average concentration quartiles at Week 16 for upadacitinib in combination with topical corticosteroids (Study M16-047)



Abbreviations: Cavg = average concentration; EASI = Eczema Area Severity Index; EASI75 = Eczema Area Severity Index 75% improvement response; EASI90 = Eczema Area Severity Index 90% improvement response; IGA0/1 = Investigators Global Assessment score of 0 or 1; NRS = numerical rating scale; QD = once daily; TCS = topical corticosteroids.

Similar statistically significant exposure-response relationships for all these endpoints were also demonstrated following logistic regression (see Figure 6, below). No statistically significant effects of age group (adult versus adolescent subjects), weight, or subject race were identified in any of the exposure-response models.

Figure 6: Exposure-response analyses, observed (NRI) and model-predicted efficacy responses at Week 16 versus upadacitinib average concentration for upadacitinib in combination with topical corticosteroids (base models; Study M16-047)



Abbreviations: Cavg = average concentration; EASI = Eczema Area Severity Index; EASI75 = Eczema Area Severity Index 75% improvement response; EASI90 = Eczema Area Severity Index 90% improvement response; IGA0/1 = Investigators Global Assessment score of 0 or 1; NRS = numerical rating scale; QD = once daily; TCS = topical corticosteroids.

Note the blue solid line represents median predicted response and the blue shaded area represent 95% confidence intervals of the predicted response. The dots and error bars represent median and 95% binomial CIs of binned observed rates. For the horizontal box plots, the band inside the box is the median of the upadacitinib average concentration per 15 mg once daily, and 30 mg once daily dosing. The lower and upper hinges correspond to the 25th and 75th percentiles. Whiskers represent 1.5 interquartile range. The data beyond the end of the whiskers are plotted individually.

Simulations using the final exposure-response models demonstrate clinically significant improvement in responses with both 15 mg and 30 mg doses in combination with topical corticosteroids, as shown in Table 11 below. The 30 mg once daily dose showed greater benefits compared to 15 mg once daily in terms of 12% to 14% greater response for EASI 90, IGA 0/1, and IGA 0 outcomes.

Table 11: Exposure-response analyses, model simulated clinical efficacy responses at Week 16 (median and 90% confidence interval) following placebo and upadacitinib 15 mg and 30 mg once weekly regimens in combination with topical corticosteroids

Clinical Efficacy Response Variable	Placebo	15 mg QD	30 mg QD
EASI 90	13% (9% – 18%)	47% (40% – 53%)	59% (50% – 66%)
IGA 0/1	11% (7% – 16%)	41% (33% – 47%)	55% (47% – 62%)
IGA 0	1% (0% – 4%)	13% (9% – 18%)	25% (18% – 32%)

Note: Results represents median percentage of subjects (5^{th} and 95^{th} percentile) from 300 replicates with 300 subjects/dose group in each replicate.

Abbreviations: Cavg = average concentration; EASI = Eczema Area Severity Index; EASI75 = Eczema Area Severity Index 75% improvement response; EASI90 = Eczema Area Severity Index 90% improvement response; IGA0/1 = Investigators Global Assessment score of 0 or 1; NRS = numerical rating scale; QD = once daily; TCS = topical corticosteroids.

Overall, response rates and exposure-response trends were similar between adolescent and adult subjects with atopic dermatitis as well as across the different weight and race groups for both subjects receiving upadacitinib as monotherapy and in combination with topical corticosteroids.

No clear or marked trends for exposure-dependent relationships were observed between upadacitinib average concentrations (average concentration) and probability of occurrence of any infection or acne at Week 16. There was a trend indicating increase in percentage of subjects experiencing a decrease in haemoglobin > 2 g/dL from Baseline at Week 16 with higher upadacitinib exposures, similar to that previously observed in subjects with rheumatoid arthritis or atopic dermatitis.

Conclusions

No new pharmacodynamic studies were provided in this submission.

The exposure-response analyses demonstrated that upadacitinib 15 mg and 30 mg once daily alone or in combination with topical corticosteroids provided significant clinical benefit for treatment of adult and adolescent subjects with atopic dermatitis.

The 30 mg once daily dose provided added clinical benefit over the 15 mg once daily dose dose across several endpoints of skin clearance or itch and regardless of topical steroid co-administration. These improvements were observed without clinically relevant higher exposure-dependent increases in the incidence of the tested adverse events or changes in laboratory parameters at Week 16 (with the exception of trend of the higher upadacitinib exposures, being associated with more subjects experiencing a decrease in haemoglobin > 2 g/dL from Baseline at Week 16).

Dose-finding data

Study M16-048

The Phase IIb double-blind, placebo-controlled Study M16-048 showed that upadacitinib at doses of 7.5 mg, 15 mg and 30 mg once daily for 16 weeks was effective in the treatment of adult subjects with moderate to severe atopic dermatitis.

In Period 1 of this study, upadacitinib met the primary (percent improvement in EASI) and key secondary endpoints (including EASI 75 and IGA 0/1) across all dose groups (see section: *Scoring systems used in the clinical studies* for more information on these outcome measures). Clear dose-response relationships were demonstrated for all key endpoints. Pair-wise comparison of treatment differences in EASI 75 and IGA 0/1 at Week 16 were

statistically significant for each upadacitinib dose versus placebo (p-value < 0.05 for the 7.5 mg group, and < 0.001 for both 15 mg and 30 mg groups).

Both the proposed doses of 15 mg and 30 mg once daily were evaluated in the pivotal Phase III studies.

The overall conclusions on dose finding for the pivotal studies from the clinical evaluation was that the selection of the 15 mg and 30 mg once daily doses for the pivotal Phase III atopic dermatitis studies was supported by results of the Phase IIb Study M16-048 and the exposure response analyses.

Efficacy

Scoring systems used in the clinical studies

Eczema Area and Severity Index (EASI)

The Eczema Area and Severity Index (EASI) is a validated scoring system;[36,37,38] that measures the physical signs of atopic dermatitis (eczema) by a composite score, that measures the extent (area) and severity of erythema, oedema/papulation scratches and lichenification across 4 different body sites.

Calculating the EASI score

Table 12 provides a summary of how the EASI score is assessed and calculated.

Table 12: Eczema Area and Severity Index (EASI) score calculation

Eczema Area and Severity Index (EASI) score calculation							
Body regions The body is divided into 4 regions as described below.							
Region	**Description**						
Head and neck	Face occupies 33% (17% each side), neck 33% (17% front and back). Scalp 33% of the head and neck region						
Trunk	Trunk includes chest, abdomen, pelvis, and back, and the genital area. Front surface of trunk 55%, back surface of trunk 45%						
Upper limbs	Each arm occupies 50% of the upper limbs region (front or back of one arm is 25%)						
Lower limbs	Each leg occupies 45% (front or back of one leg is 22.5%) Buttocks 10% of the lower limbs region						
Area score Area score is recorded for each of the four regions of the body. The area score is the percentage of skin affected by eczema for each body region.							
% involvement	0%	1 - 9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90-100%

[36] Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol.* 2001;10(1):11-18.
[37] Schram M, Spuls P, Leeflang M, Lindeboom R, Bos J, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference *Allergy*. 2012;67(1):99–106.
[38] Schmitt J, Langan S, Deckert S, et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation *J Allergy Clin Immunol*. 2013;132(6):1337–1347.

Eczema Area and Severity Index (EASI) score calculation

Area score	0	1	2	3	4	5	6

Severity score

A severity score is calculated by scoring each body region according to the severity of 4 signs:

- **Erythema** (redness, inflammation)
- **Oedema** (induration, papulation, swelling)
- **Excoriation** (scratches)
- **Lichenification** (lined skin, furrowing, prurigo nodules (chronic eczema)).

Average intensity for each of the four signs above is assessed for each body region on a scale of zero = none; 1 = mild; 2 = moderate and 3 = severe.

This results in 16 raw severity scores; 4 for each sign, scored once in each body region.

The raw severity scores for all 4 signs for each individual region is added up, giving a minimum and maximum possible severity score for each region of 0 to 16 points.

Severity score = intensity of redness + thickness + scratching + lichenification

EASI region total score calculation

The regional severity score and area score for each body region is multiplied by a factor of 0.1 for head and neck; 0.2 for upper limbs; 0.3 for trunk and 0.4 for lower limbs.

Body region	Total region scoring calculation
Head and neck	severity score x area score x 0.1 = head and neck total score (in children 0–7 years, x 0.2)
Trunk	severity score x area score x 0.3 = trunk total score
Upper limbs	severity score x area score x 0.2 = upper limb total score
Lower limbs	severity score x area score x 0.4 = lower limb total score (in children 0–7 years, x 0.3)

Total EASI score (composite score)

The final EASI score is the sum of all 4 regional total scores.

The minimum EASI score is 0 and the maximum EASI score is 72.

EASI total score interpretation

The total EASI score is a composite score and measure of overall severity and extent of atopic dermatitis disease in a patient. The total score ranges from a minimum of zero (clear, no signs of active atopic dermatitis to a maximum of 72 (very/most severe atopic dermatitis). Table 13 gives a clinical interpretation of total EASI scores.[39]

Table 13: EASI total (composite) score interpretation

Total EASI score	Interpretation
0	Clear
0.1 to 1	Almost clear
1.1 to 7	Mild atopic dermatitis
7 to 21	Moderate atopic dermatitis
21.1 to 50	Severe atopic dermatitis
50.1 to 72	Very severe atopic dermatitis

EASI response score interpretation

An EASI 75 response represents a 75% improvement in EASI total score (as a measure of atopic dermatitis extent and severity) compared with the EASI total score at Baseline.

Similarly an EASI 50, EASI 90 and EASI 100 response represents a 50%, 90%, and 100% improvement respectively.

An improvement of at least 75% in lesion extent and severity (an EASI-75 response) from Baseline is a clinically meaningful change.[37]

Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)

The Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD);[40] is a five-point scale that describes the appearance of atopic dermatitis skin lesions at a point in time. The skin is specifically examined for signs of erythema (redness), induration/papulation (thickness or swelling), lichenification, oozing and crusting), and overall impression on examination is given a score of between zero and 4. Zero is clear, 1 is almost clear, 2 is mild, 3 is moderate and 4 is severe atopic dermatitis.

A decrease in score relates to an improvement in signs and symptoms.

Table 14 (shown below) provides a copy of the assessment scale with scores and morphological descriptions.

[39] Leshem Y, Hajar T, Hanifin J, Simpson E. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *Br J Dermatol*. 2015;172(5):1353–1357
[40] Simpson E, Bissonnette R, Eichenfield LF. The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD): The development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis. *J Am Acad Dermatol*. 2020 Sep;83(3):839-846

Table 14: Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)

Score	Morphological description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Moderate Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Severe marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.
Instructions for use: The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under 'Morphological description' be present.	

Notes: In indeterminate cases, please use extent to differentiate between scores.

For example: Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered '3 – Moderate'.

2. Excoriations should not be considered when assessing disease severity.

Worst Pruritus numerical rating scale (NRS)

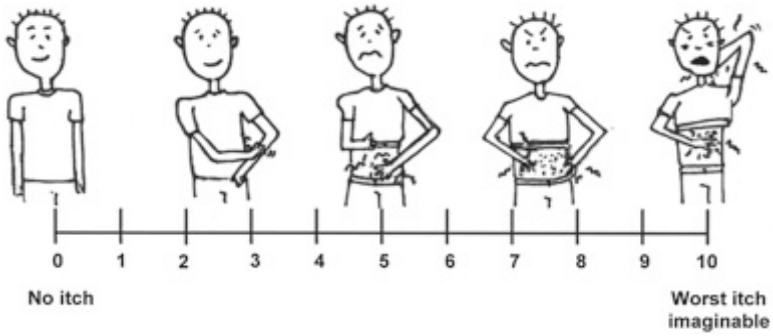
The Worst Pruritus numerical rating scale (NRS) is a validated, single-item questionnaire that assesses the intensity of pruritus (itching) over a 24-hour recall period using an 11-point NRS ranging from 0 for 'no itch' to 10 for 'worst imaginable itch.'[41,42] An improvement (reduction) in Worst Pruritus NRS ≥ 4 points is considered a clinically meaningful improvement.[43] Copies of the scale are shown in Table 15 and in mixed NRS/visual analog scale format in Table 16, below.

[41] Phan NQ, Blome C, Fritz F, Gerss J, Reich A, Ebata T, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol* 2012; 92: 502–507
[42] Storck M, et al. *J Eur Acad Dermatol Venereol.* 2021 May;35(5):1176-1185..
[43] Verweyen E at al. *Acta Derm Venereol.* 2019;99:657-66

Table 15: Worst Pruritus numerical rating scale (NRS)

1.) On scale from 0 (no itch) to 10 (worst imaginable itch)…
…how was your itch, on average, within the past 24 hours? Please select one number.
0 1 2 3 4 5 6 7 8 9 10
…how was your worst itch in the past 24 hours? Please select one number.
0 1 2 3 4 5 6 7 8 9 10

Table 16: Worst Pruritus numerical rating scale (NRS)



Patient Oriented Eczema Measure (POEM)

Patient Oriented Eczema Measure (POEM) is a validated questionnaire that assesses the frequency of atopic dermatitis symptoms in adolescents and adults.[44,45] Dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping are scored on a 5-point scale based on how frequent these symptoms were experienced in the past week, ranging from 0 for 'no days' to 4 for 'all days.' Item scores are added to yield a score ranging from 0 to 28.

An improvement (reduction) in POEM total score of 4 or more points is considered a clinically meaningful improvement.[46]

A copy of the POEM questionnaire is shown in Table 17, below.

[44] Charman CR, et al. 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.
[45] Charman CR, et al. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol.* Dec 2013; 169(6): 1326–1332.
[46] Howells L, Ratib S, Chalmers JR, Bradshaw L, Thomas KS; CLOTHES trial team. How should minimally important change scores for the Patient-Oriented Eczema Measure be interpreted? A validation using varied methods. *Br J Dermatol.* 2018;178(5):1135-1142.

Table 17: Patient Oriented Eczema Measure (POEM) questionnaire (for use in adults and children)

Please circle one response for each of the seven questions below about your/your child's eczema. If your child is old enough to understand the questions then please fill in the questionnaire together. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your/your child's skin been itchy because of the eczema?

No days | 1 to 2 days | 3 to 4 days | 5 to 6 days | Everyday

2. Over the last week, on how many nights has your/your child's sleep been disturbed because of the eczema?

No days | 1 to 2 days | 3 to 4 days | 5 to 6 days | Everyday

3. Over the last week, on how many days has your/your child's skin been bleeding because of the eczema?

No days | 1 to 2 days | 3 to 4 days | 5 to 6 days | Everyday

4. Over the last week, on how many days has your/your child's skin been weeping or oozing clear fluid because of the eczema?

No days | 1 to 2 days | 3 to 4 days | 5 to 6 days | Everyday

5. Over the last week, on how many days has your/your child's skin been cracked because of the eczema?

No days | 1 to 2 days | 3 to 4 days | 5 to 6 days | Everyday

6. Over the last week, on how many days has your /your child's skin been flaking off because of the eczema?

No days | 1 to 2 days | 3 to 4 days | 5 to 6 days | Everyday

7. Over the last week, on how many days has your/your child's skin felt dry or rough because of the eczema?

No days | 1 to 2 days | 3 to 4 days | 5 to 6 days | Everyday

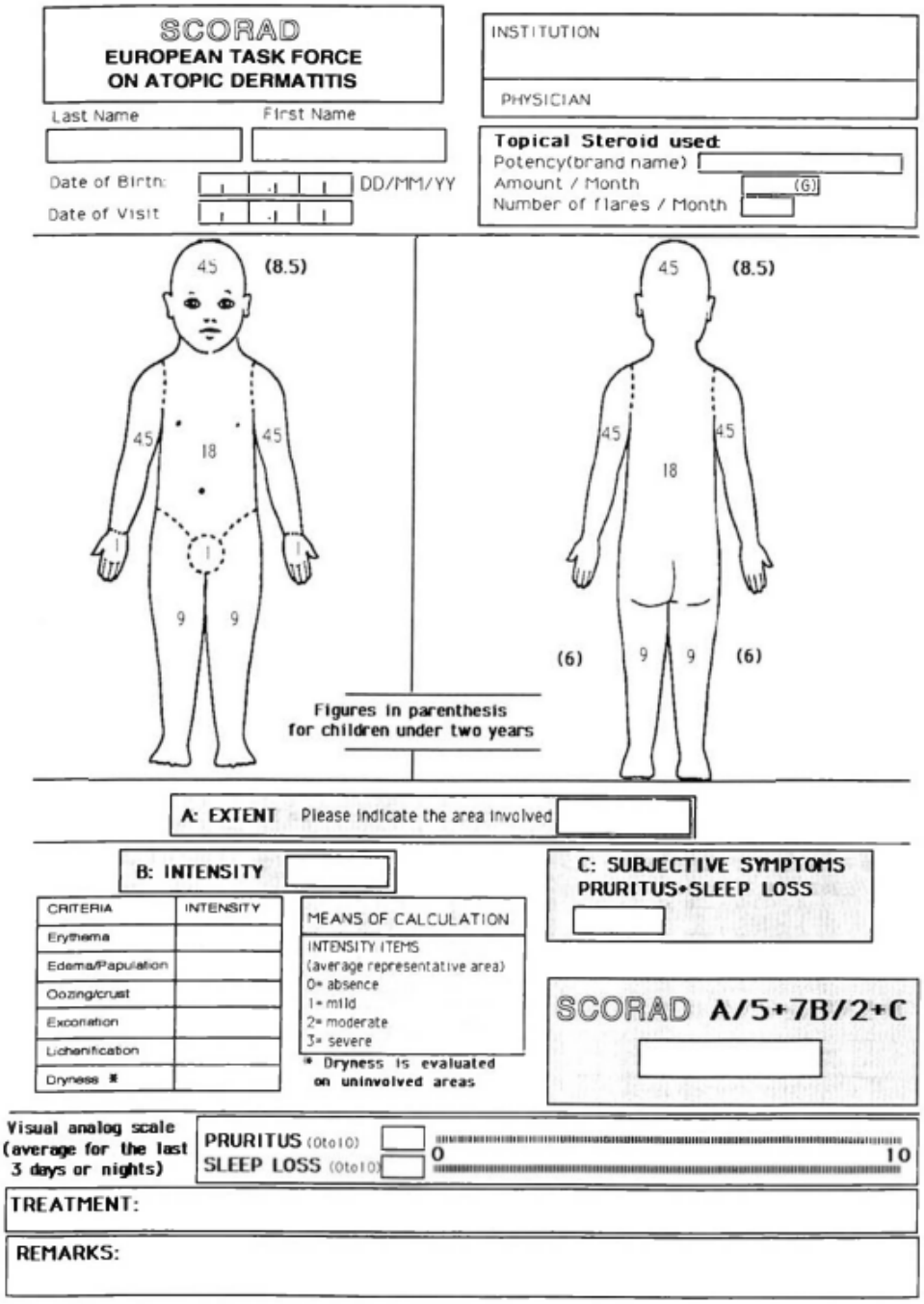
Total POEM Score (Maximum 28): _____

How is the scoring done?	**What does a POEM score mean?**
Each of the seven questions carries equal weight and is scored from 0 to 4 as follows: No days = 0, 1-2 days = 1, 3-4 days = 2, 5-6 days = 3, every day = 4. Note: If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 28. If two or more questions are left unanswered the questionnaire is not scored. If two or more response options are selected, the response option with the highest score should be recorded.	0 to 2 = Clear or almost clear 3 to 7 = Mild eczema 8 to 16 = Moderate eczema 17 to 24 = Severe eczema 25 to 28 = Very severe eczema

Scoring Atopic Dermatitis (SCORAD)

Scoring Atopic Dermatitis (SCORAD);[47] is a validated tool,[48] that measures the extent, severity and subjective symptoms of atopic dermatitis using three different components (parts A = extent, B = extensity, and C = subjective symptoms) which are then integrated in a formula to calculated a score for a patient. Figure 7 shows a SCORAD evaluation sheet that may be used to calculate a SCORAD score.

Figure 7: Scoring Atopic Dermatitis (SCORAD) Evaluation sheet



[47] Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology.* 1993;186(1):23-31.
[48] Silverberg JI, Lei D, Yousaf M, et al. Comparison of Patient-Oriented Eczema Measure and Patient-Oriented Scoring Atopic Dermatitis vs Eczema Area and Severity Index and other measures of atopic dermatitis: A validation study. *Ann Allergy Asthma Immunol.* 2020;125(1):78-83.

The eczema affected area section (part A) refers to the extent of body surface area affected:

- Head and neck (up to 9%);
- Upper extremities (up to 18% each);
- Anterior trunk (up to 18%);
- Back (up to 18%);
- Lower extremities (up to 18% each);
- Genitals (up to 1%).

The possible maximum score for this section is 100%.

The intensity section (part B) consists in six clinical signs that assess the intensity of the condition:

- Redness;
- Swelling;
- Oozing / Crusting;
- Scratch marks;
- Skin thickening (excoriations, lichenification);
- Dryness (independent of any inflammation present).

Each of the 6 clinical signs are awarded a number of points (from 0 to 3), dependent on their perceived severity, on the following scale:

- None (0);
- Mild (1);
- Moderate (2);
- Severe (3).

The minimum score for the intensity section is 0 and the maximum score is 18.

The subjective symptoms section (part C) consists in 2 items:

- Pruritis (or itchiness);
- Insomnia (sleeplessness).

The subjective symptoms may be evaluated by based on quality of life in three days preceding the evaluation. A visual analogue scale is used, with 0 for no symptoms and 10, most severe symptoms. The minimum score for the subjective symptoms section is 0 and the maximum score is 20.

To calculate the SCORAD score, the following formula is used:

SCORAD = Affected area score / 5 + 7 x Intensity score / 2 + Subjective symptoms score.

SCORAD results range from 0 to a maximum of 103. The extent of the lesions and subjective symptoms account for around 20% of the total score each, while the intensity items account for the rest of 60%.

The interpretation of SCORAD scores are shown below in Table 18.[47]

Table 18: SCORAD Index for classification of severity of eczema

Severity	SCORAD Index
Mild	Less than 25
Moderate	25 to 50
Severe	More than 50

Abbreviation: SCORAD = Scoring Atopic Dermatitis

In addition, SCORAD can also be described according to its separate components of Objective SCORAD, SCORAD Itch and SCORAD Sleep.

Atopic Dermatitis Symptom Scale (ADerm-SS)

The Atopic Dermatitis Symptom Scale (ADerm-SS) is an 11-item questionnaire used to assess the signs and symptoms that subjects experience due to atopic dermatitis using a 24-hour recall period.[49] The ADerm-SS includes 3 items that subjects complete daily and 8 items that subjects complete each week. An overview of the ADerm-SS is shown below in Table 19.

The ADerm-SS Total Symptom Score (TSS-7) assesses itch while asleep, itch while awake, skin pain, skin cracking, pain caused by skin cracking, dry skin, and flaking due to atopic dermatitis.

Note that both the ADerm-SS and ADerm-IS (see Atopic Dermatitis Impact Scale (ADerm-IS) are novel patient reported outcomes developed and validated by the sponsor. The sponsor validity, measurement properties, and evidence supporting the minimal clinical important difference thresholds were provided with this submission.[48,49]

The sponsor has stated that these been developed in alignment with patient-reported outcome guidance from both the US FDA;[50] and the EMA.[51]

Table 19: Atopic Dermatitis Symptom Scale (ADerm-SS)

Section	Concepts	Overall concepts	Recall period	Response options
Daily diary (Completed every night)	Itch during sleep hours	Signs/symptoms of atopic dermatitis at their worst	Past 24 hours	0 = 'No [sign/symptom]' 10 = 'Worst imaginable [sign/symptom]'
	Itch during awake hours			
	Skin pain			
	Skin cracking			

[49] Foley C, et al. Development and content validity of new patient-reported outcome questionnaires to assess the signs and symptoms and impact of atopic dermatitis: the Atopic Dermatitis Symptom Scale (ADerm-SS) and the Atopic Dermatitis Impact Scale (ADerm-IS). *Curr Med Res Opin.* 2019 Jul;35(7):1139-1148
[50] United States Food and Drug Administration: Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes. 2006;4:79.
[51] European Medicines Agency: Reflection paper on the regulatory guidance for the use of healthrelated quality of life (HRQL) measures in the evaluation of medicinal products. EMEA/CHMP/EWP/139391/2004. London, UK. 2005.

Section	Concepts	Overall concepts	Recall period	Response options
Weekly diary (Completed once per week)	Pain caused by skin cracking			
	Dry skin			
	Skin flaking			
	Rash (redness, blisters, bumpy skin)			
	Skin thickening			
	Bleeding			
	Skin oozing			

All items of the ADerm-SS are scored on an 11-point numerical rating scale (NRS) ranging from 0 (no sign/symptom) to 10 (worst possible sign/symptom). The ADerm-SS is scored as a 7-item total symptom score (TSS-7), defined as the algebraic sum of the responses to items 1 to 7 above, and an 11-item total symptom score (TSS-11), defined as the algebraic sum of all 11 items. An improvement (reduction) in TSS-7 and TSS-11 that is ≥ 28 points and ≥ 44 points, respectively, is considered a clinically meaningful improvement. In addition to the total symptom scores, the ADerm-SS Skin Pain score (ADerm-SS item 3) is individually evaluated to specifically characterize skin pain. An improvement (reduction) in ADerm-SS Skin Pain ≥ 4 is considered a clinically meaningful improvement.

Atopic Dermatitis Impact Scale (ADerm-IS)

Atopic Dermatitis Impact Scale (ADerm-IS) is a 10-item questionnaire designed to assess a variety of impacts that subjects experience due to their atopic dermatitis across both a 24-hour recall period (the daily items 1 to 3) and 7-day recall period (the weekly items 4 to 10).[49]

The ADerm-IS Sleep assesses difficulty falling asleep, sleep impact, and waking up at night due to atopic dermatitis. The ADerm-IS Daily Activities assesses atopic dermatitis effect on household activities, physical activities, social activities, and concentration.

ADerm-IS Emotional State assesses self-consciousness, embarrassment, and sadness due to atopic dermatitis.

Table 20: Atopic Dermatitis Impact Scale (ADerm-IS)

Section	Concepts	Overall concepts	Recall period	Response options
Daily diary (Completed every night)	Difficulty falling asleep	Sleep impacts of atopic dermatitis	Past 24 hours	0 = 'Not difficult' 10 = 'Extremely difficult'
	Level of impact on sleep			0 = 'Not at all' 10 = 'Extremely'
	Bothersomeness of waking up at night			0 = 'Not bothersome' 10 = 'Extremely bothersome

Section	Concepts	Overall concepts	Recall period	Response options
Weekly diary (Completed once per week)	Limitation in household activities	Impacts of atopic dermatitis	Past 7 days	0 = 'Not limited' 10 = 'Extremely limited'
	Limitation in physical activities			
	Limitation in social activities			
	Difficulty concentrating			0 = 'Not difficult' 10 = 'Extremely difficult'
	Feeling self-conscious			0 = 'Not self-conscious' 10 = 'Extremely self-conscious'
	Feeling embarrassed			0 = 'Not embarrassed' 10 = 'Extremely embarrassed'
	Feeling sad			0 = 'Not sad' 10 = 'Extremely sad'

All items of the ADerm-IS are scored on an 11-point NRS from 0 (no impact) to 10 (extreme impact).

The ADerm-IS yields 3 domain scores: sleep (Items 1 to 3; minimal clinically important difference (MCID) = 12)), daily activities (Items 4 to 7; MCID = 14), and emotional state (Items 8 to 10; MCID = 11).

Dermatology Life Quality Index

Dermatology Life Quality Index (DLQI) and Children's DLQI (CDLQI) are 10-item, validated questionnaires used to assess the impact of dermatologic disease symptoms and treatment on health-related quality of life.[52,53]

Each consists of 10 questions assessing the impact of skin diseases on different aspects of subject's quality of life over the prior week;

The DLQI items include symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the side effects of treatment;

Each item is scored from 0 (not at all/not relevant) to 3 (very much). Item scores are added to provide a total score range of 0 to 30; higher scores indicate greater quality of life impairment.

For general inflammatory skin conditions, an improvement (reduction) in DLQI ≥ 4 is considered a clinically meaningful improvement;[54] a DLQI score of 0/1 indicates that the skin condition has no effect on a patient's quality of life;

[52] Finlay, A. Y. and Khan, G. K. 1994. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clinical and Experimental Dermatology* 19 (3), pp.210-216.
[53] Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): Initial validation and practical use. *British Journal of Dermatology,* 1995; 132: 942-949.
[54] Basra, M. et al., 2015. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology* 230 (1), pp.27-33.

Subjects less than 16 years old at the time of the screening visit were administered the CDLQI for the duration of the study. A CDLQI score of 0/1 indicates that the skin condition has no effect on the child's quality of life.[55]

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a validated and frequently used measure of anxiety and depression.[56] The 14-item questionnaire is shown below in Table 21, with seven items related to anxiety (HADS-A) and seven items related to depression (HADS-D).[57] Each item is scored from 0 to 3; scores for each subscale range from 0 to 21 and scores for the entire scale (emotional distress) range from 0 to 42, with higher scores indicating more distress. For each subscale, scores ≤ 8 are considered normal, 8 to 10 are borderline, and 11 or higher indicate clinical anxiety or depression.

Table 21: Hospital Anxiety and Depression Scale (HADS)

A	**I feel tense or wound up**		D	**I still enjoy the things I used to enjoy**	
	Most of the time	3		Definitely as much	0
	A lot of the time	2		Not quite so much	1
	From time to time, occasionally	1		Only a little	2
	Not at all	0		Hardly at all	3
A	**I get a sort of frightened feeling as if something awful is about to happen**		D	**I can laugh and see the funny side of things**	
	Very definitely and quite badly	3		As much as I always could	0
	Yes, but not too badly	2		Not quite so much now	1
	A little, but it doesn't worry me	1		Definitely not so much now	2
	Not at all	0		Not at all	3
A	**Worrying thoughts go through my mind**		D	**I feel cheerful**	
	A great deal of the time	3		Not at all	3
	A lot of the time	2		Not often	2
	From time to time, but not too often	1		Sometimes	1
	Not at all	0		Most of the time	0
A	**I can sit at ease and feel relaxed**		D	**I feel as if I am slowed down**	
	Definitely	0		Nearly all the time	3
	Usually	1		Very often	2
	Not often	2		Sometime	1
	Not at all	3		Not at all	0
A	**I get a sort of frightened feeling like butterflies in the stomach**		D	**I have lost interest in my appearance**	
	Not at all	0		Definitely	3
	Occasionally	1		I don't take as much care as I should	2
	Quite often	2		I may not take quite as much care	1
	Very often	3		I take just as much care as ever	0
A	**I feel restless as if I have to be on the move**		D	**I look forward with enjoyment to things**	
	Very much indeed	3		As much as I ever did	0
	Quite a lot	2		Rather less than I used to	1
	Not very much	1		Definitely less than I used to	2
	Not at all	0		Hardly at all	3
A	**I get sudden feelings of panic**		D	**I can enjoy a good book, radio or television programme**	
	Very often indeed	3		Often	0
	Quite often	2		Sometimes	1
	Not very often	1		Not often	2
	Not at all	0		Very seldom	3

The HADS contains 14 items and consists of two subscales: anxiety and depression. Each item is rated on a 4-point scale, giving maximum scores of 21 for anxiety and depression. Scores of 11 or more on either subscale are considered to be a significant 'case' of psychological morbidity, while scores of 8 to 10 represent 'borderline case', and scores of 0–7 represent 'normal case'.

Questions relating to anxiety are indicated by an 'A' while those relating to depression are shown by a 'D'. Scores of 07 in respective subscales are considered normal, with 810 borderline and 11 or over indicating clinical 'caseness'.

[55] Olsen JR, Gallacher J, Finlay AY, Piguet V, Francis NA. Quality of life impact of childhood skin conditions measured using the Children's Dermatology Life Quality Index (CDLQI): a meta-analysis. *British Journal of Dermatology*. 2016 Apr;174(4):853-861.
[56] Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res.* 2002;52(2):69-77.
[57] Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983;67:361-370

Study M16-045 (monotherapy)

Study M16-045 was a Phase III, randomised, double-blind, placebo-controlled multicentre study that evaluated the efficacy and safety of upadacitinib in adolescents (12 to 17 years) and adults (18 to 75 years), with moderate to severe atopic dermatitis who were candidates for systemic therapy.

The study design included a 35-day screening period, a 16-week double-blind period, a blinded extension period of up to Week 136, and a 30-day follow-up visit.

After the target enrolment (810 subjects) was achieved in the main study, a supplemental study was opened (adolescent sub-study) [in an attempt] to ensure enrolment in total of 180 adolescent subjects in the overall study (comprising of the main part of Study M16-045 plus the adolescent sub-study).

The submitted clinical study report only provided interim results through Week 16 of the main study while the adolescent sub-study continues to enrol participants.

Primary objective

To assess the efficacy and safety of upadacitinib for the treatment of adolescent and adult subjects with moderate to severe atopic dermatitis who are candidates for systemic therapy.

The objective of the double blind period (through Week 16) was to compare the safety and efficacy of upadacitinib (15 mg and 30 mg once daily) with placebo.

The objective of the 136-week blinded extension period was to evaluate the long-term safety, tolerability, and efficacy of upadacitinib (15 mg and 30 mg) once daily in adolescents and adults, with moderate to severe atopic dermatitis who had completed the double-blind period.

Inclusion and exclusion criteria

Inability to meet any of these criteria led to exclusion from study participation:

- Subject must be at least ≥ 12 years old and ≤ 75 years old at screening visit;
- Adult subjects ≥ 18 years of age at screening visit, must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures and comply, with the requirements of this study protocol. For subjects aged < 18 years, consent form is to be signed by parent or legal guardian;
- Body weight ≥ 40 kg at the baseline visit for subjects between ≥ 12 and < 18 years of age.
- Subject is judged to be in general good health (other than atopic dermatitis) as determined by the Principal Investigator, based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG) performed during Screening.
- Chronic atopic dermatitis with onset of symptoms at least 3 years prior to Baseline and,
- Subject meets Hanifin and Rajka criteria for atopic dermatitis;[1] (shown in Table 1, above).
- Subject meets all of the following disease activity criteria:
  - Eczema Area and Severity Index (EASI) composite score ≥ 16 at the screening and baseline visits (see Section: *Eczema Area and Severity Index (EASI)*);

  - Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score ≥ 3 at the screening and baseline visits;
  - ≥ 10% body surface area (BSA) of atopic dermatitis involvement at the screening and baseline visits;
  - Baseline weekly average of daily Worst Pruritus Numerical Rating Scale (NRS) ≥ 4.
- Subject has applied a topical emollient (moisturiser) twice daily for at least 7 days before thebaseline visit.
- Documented history (within 6 months of the baseline visit) of inadequate response to topical corticosteroids or topical calcineurin inhibitors *or* documented systemic treatment for atopic dermatitis within 6 months prior to the baseline visit, *or* for whom topical treatments are otherwise medically inadvisable (for example, because of important side effects or safety risks).
- Negative urine pregnancy test at baseline visit, postmenopausal or practicing specified method of birth control.
- No prior exposure to any JAK inhibitor (including but not limited to ruxolitinib, tofacitinib,baricitinib, upadacitinib, abrocitinib and filgotinib).
- No prior exposure to dupilumab;
- Subjects must not have used the following atopic dermatitis treatments within the specified timeframe prior to baseline visit:
  - Systemic therapy for atopic dermatitis, including but not limited, to corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE4)-inhibitors, IFN-gamma and mycophenolate mofetil within 4 weeks;
  - Targeted biologic treatments (refer to within 5 half-lives [if known]) or within 12 weeks, whichever is longer;
  - Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks;
  - Oral or parenteral traditional Chinese medicine within 4 weeks;
  - Marijuana use within 2 weeks;
  - Topical treatments (with the exception of topical emollient treatments), including but not limited to topical corticosteroids, topical calcineurin inhibitors, or topical PDE-4 inhibitors within 7 days.
- Subjects must not have received any live vaccine within 4 weeks (or longer if required locally) prior to the first dose of study drug, or expected need of live vaccination during study participation, including at least 4 weeks (or longer if required locally) after the last dose of study drug.
- No systemic use of known strong CYP3A inhibitors or strong CYP3A induced from Screening through to the end of the study.
- No treatment with any investigational drug of chemical or biologic nature within 4 weeks or five half-lives of the drug (whichever is longer) prior to baseline visit or is currently enrolled in another clinical study.
- No current or past history of active skin diseases or infections, history of recurrent herpeszoster, active HIV, TB infections, hepatitis B or C (HBV or HCV).
- No clinically relevant medical conditions (including cardiovascular, malignancies or conditions that interfere with drug absorption).

- No clinically relevant laboratory abnormalities.
- No history of allergic reactions, sensitivity to constituents of study treatments, clinically significant drug or alcohol abuse.

Study treatments

Subjects who met eligibility criteria were randomised in a 1:1:1 ratio to receive a daily oral dose of either upadacitinib 15 mg or 30 mg or matching placebo once daily in the double blind period (beginning on Day 1 (Baseline), at approximately the same time each day with or without food).

At Week 16, subjects in the placebo group were re-randomised in a 1:1 ratio to receive daily oral doses of upadacitinib 15 mg or 30 mg in the blinded extension period. During the blinded extension period, subjects originally randomised to upadacitinib were to continue upadacitinib in the extension period at the same dose.

Required concomitant medications

- Beginning at the screening visit, twice daily use of an additive-free, bland emollient was required for at least 7 days prior to baseline and during the study until Week 16.
- Until Week 16, the subjects may use *prescription moisturisers or moisturisers containing ceramide, urea, filaggrin degradation products or hyaluronic acid* if such moisturisers were initiated before the screening visit.
- Starting at Week 16 Visit or after premature discontinuation of study drug, the use of emollients can be administered at the investigator's discretion.

Rescue therapy

This was permitted:

- starting at Week 4 through Week 24, if:
  - medically necessary; and
  - a response less than an EASI 50 response (that is, a less than 50% improvement in EASI total score compared to baseline EASI score) was reported at 2 consecutive visits compared to the baseline EASI score;
- after Week 24, if:
  - < EASI 50 response was reported at any visit (scheduled or unscheduled) compared to the baseline EASI score.

See Section: *Eczema Area and Severity Index (EASI)* for details.

The first step of rescue therapy should be limited to topical medications, and escalated to systemic medications only for those subjects who do not respond adequately after at least 7 days of topical treatment.

Starting at the Week 16 Visit, the use of any concomitant topical medication for atopic dermatitis was allowed per investigator discretion and was no longer considered as rescue therapy; only systemic treatments for atopic dermatitis were considered as rescue therapy for the purposes of statistical analyses of efficacy.

Subjects who received topical rescue treatment or oral corticosteroids during the study treatment period could continue study drug. However, oral corticosteroids are not allowed for routine treatment of atopic dermatitis. If oral corticosteroids must be used, rescue treatment will be limited to prednisone or prednisolone for up to 1 mg/kg for no more than 2 consecutive weeks. Any subject who receives oral corticosteroid formore than 2 consecutive weeks regardless of the dosage of corticosteroid should permanently discontinue study drug.

If a subject needed rescue treatment with a non-corticosteroid systemic agent (including but not limited to cyclosporin, methotrexate, mycophenolate mofetil, azathioprine, dupilumab) or with an injectable or parenteral corticosteroid, study drug was permanently discontinued prior to the initiation of rescue systemic agent. If such rescue treatment is medically necessary outside of the parameters described above (that is, to control intolerable atopic dermatitis symptoms), study drug should be permanently discontinued.

Subjects could request to be discontinued from participating in the study at any time for any reason including, but not limited to, disease progression or lack of response to treatment. The investigator may discontinue any subject's participation at any time for any reason, including but not limited, to disease progression, lack of response to treatment, an adverse event, safety concerns, or failure to comply with the protocol.

Randomisation and blinding methods

Randomisation for the main study was stratified by:

- baseline disease severity (moderate (vIGA-AD score of 3) versus severe (vIGA-AD score of 4));
- geographic region (USA/Puerto Rico/Canada, Japan, China (mainland), and other);
- age (adolescent (*ages 12 to 17*) versus adult (*ages 18 to 75*)).

Re-randomisation was stratified by Week 16 EASI 50 responder (yes/no plus the above stated stratification parameters).

Regarding the blinding of the extension:

- Study sites and subjects were to remain blinded for the duration of the study;
- The study team only had access to the unblinded subject level data for adverse events of special interests and serious adverse events for regulatory submissions;

In order to maintain the blind, the upadacitinib tablets and placebo tablets provided for the study were identical in appearance.

Efficacy parameters/endpoints

See section: *Scoring systems used in the clinical studies* for further information on these outcome measures.

Primary endpoint: The primary endpoint was to demonstrate superiority of each upadacitinib dose versus placebo.

Co-primary endpoints:

- Proportion of subjects achieving at least a 75% reduction in EASI score (achieving an EASI-75 response), from baseline EASI scores at Week 16; (see Section: *Eczema Area and Severity Index (EASI)*)
- Proportion of subjects achieving validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) of 0 or 1 with at least two grades of reduction from Baseline at Week16.

Key secondary endpoints: Separate sets of key secondary endpoints were analysed for EU/EMA and for US/FDA regulatory purposes:

- For EU/EMA regulatory purposes:
  - Proportion of subjects achieving an improvement (reduction) in Worst Pruritus Numerical Rating Scale (NRS) ≥ 4 from Baseline at Week 16 (and at Week 1) for subjects with Worst Pruritus NRS ≥ 4 at Baseline;

  - Proportion of subjects achieving EASI 90 at Week 16;
  - Percent change from Baseline of Worst Pruritus NRS at Week 16;
  - Percent change in EASI from Baseline at Week 16;
  - Proportion of subjects achieving EASI 75 at Week 2;
  - Proportion of subjects achieving an improvement (reduction) in Patient Oriented Eczema Measure (POEM) ≥ 4 from Baseline at Week 16 for subjects with POEM ≥ 4 at Baseline;
  - Proportion of subjects age ≥ 16 years old at screening achieving an improvement (reduction) in Dermatology Life Quality Index (DLQI) ≥ 4 from Baseline at Week 16 for subjects with DLQI ≥ 4 at Baseline;
  - Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 2 and Day 3 for subjects with Worst Pruritus NRS ≥ 4 at Baseline (upadacitinib 30 mg vs. placebo);
  - Proportion of subjects experiencing a flare, characterised as a clinically meaningful worsening in EASI, defined as an increase of EASI by ≥ 6.6 from Baseline for subjects with EASI ≤ 65.4 at Baseline, during double-blind treatment period (double-blind Period);
  - Percent change in Scoring Atopic Dermatitis (SCORAD) from Baseline at Week 16;
  - Proportion of subjects achieving an improvement (reduction) in Atopic Dermatitis Impact Scale (ADerm-IS) sleep domain score ≥ 12 (minimal clinically important difference (MCID)) from Baseline at Week 16 for subjects with ADerm-IS sleep domain score ≥ 12 at Baseline;
  - Proportion of subjects achieving an improvement (reduction) in Atopic Dermatitis Symptom Scale (ADerm-SS) skin pain score ≥ 4 (MCID) from Baseline at Week 16 for subjects with ADerm-SS skin pain score ≥ 4 at Baseline;
  - Proportion of subjects achieving an improvement (reduction) in ADerm-SS 7-item total symptom score (TSS-7) ≥ 28 (MCID) from Baseline at Week 16 for subjects with ADerm-SS TSS- 7 ≥ 28 at Baseline;
  - ADerm-SS TSS-7 is defined as the algebraic sum of the responses to items 1 – 7 of the ADerm-SS;
  - Proportion of subjects achieving an improvement (reduction) in ADerm-IS emotional state domain score ≥ 11 (MCID) from Baseline at Week 16 for subjects with ADerm-IS emotional state domain score ≥ 11 at Baseline;
  - Proportion of subjects achieving an improvement (reduction) in ADerm-IS daily activities domain score ≥ 14 (MCID) from Baseline at Week 16 for subjects with ADerm-IS daily activities domain score ≥ 14 at Baseline;
  - Proportion of subjects achieving EASI 100 at Week 16;
  - Proportion of subjects age ≥ 16 years old at screening achieving DLQI score of 0 or 1 at Week 16 for subjects with DLQI > 1 at Baseline.

- For US/FDA regulatory purposes:
  - Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 fromBaseline at Week 16 (and at Week 4 and Week 1) for subjects with Worst Pruritus NRS ≥ 4 at Baseline;
  - Proportion of subjects achieving EASI 90 at Week 16;
  - Percent change from Baseline of Worst Pruritus NRS at Week 16;

- Proportion of subjects achieving EASI 75 at Week 2;
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 2 for subjects with Worst Pruritus NRS ≥ 4 at Baseline (upadacitinib 30 mg versus placebo).
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 3 for subjects with Worst Pruritus NRS ≥ 4 at Baseline (upadacitinib 15 mg versus placebo).
- Proportion of subjects experiencing a flare, characterised as a clinically meaningful worsening in EASI, defined as an increase of EASI by ≥ 6.6 from Baseline for subjects with EASI ≤ 65.4 at Baseline, during double blind Period.
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS sleep domain score≥ 12 (MCID) from Baseline at Week 16 for subjects with ADerm-IS sleep domain score ≥ 12 at Baseline.
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS skin pain score ≥4 (MCID) from Baseline at Week 16 for subjects with ADerm-SS skin pain score ≥ 4 at Baseline.
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS TSS-7 ≥ 28 (MCID) from Baseline at Week 16 for subjects with ADerm-SS TSS-7 ≥ 28 at Baseline.
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS emotional state domain score ≥ 11 (MCID) from Baseline at Week 16 for subjects with ADerm-IS emotional state domain score ≥ 11 at Baseline.
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS daily activities domain score ≥ 14 (MCID) from Baseline at Week 16 for subjects with ADerm-IS daily activities domain score ≥ 14 at Baseline.
- Proportion of subjects achieving EASI 100 at Week 16.

Additional endpoints analysed at all visits are as listed below:

In addition to the previously stated primary and secondary endpoints, the following endpoints were also evaluated at all visits to demonstrate superiority of each upadacitinib dose versus placebo:

- Change from Baseline in EASI;
- Change from Baseline in Worst Pruritus NRS;
- Proportion of subjects achieving EASI 50 at Week 1;
- Proportion of subjects achieving Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline;
- Proportion of subjects achieving at least a 50%/75%/90% reduction in SCORAD (SCORAD 50/75/90) from Baseline;
- Proportion of subjects experiencing flare, characterised as a clinically meaningful worsening in EASI, defined as an increase of EASI by ≥ 6.6 from Baseline for subjects with EASI ≤ 65.4 at Baseline, by visit after Week 16;
- Among responders at Week 16, proportion of subjects experiencing loss of response after Week 16 until Week 52, by visit and overall; loss of response is defined as a loss of at least 50% of the EASI response at Week 16 and a vIGA-AD score of 2 or higher; for this analysis only, responders will be defined as subjects achieving vIGA-AD of 0 or 1 with at least two grades of reduction from Baseline and EASI 75 at Week 16;

- Change from Baseline in body surface area (BSA);
- Change and percent change from Baseline in HADS-A;
- Change and percent change from Baseline in HADS-D;
- Change and percent change from Baseline in HADS total score;
- Percent Change from Baseline in Hand eczema severity index (HECSI);
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS 11-item total symptom score (TSS- 11) ≥ 44 (MCID) from Baseline for subjects with ADerm-SS TSS-11 ≥ 44 at Baseline; ADerm-SS TSS-11 is defined as the algebraic sum of the responses of items 1 – 11 of the ADerm-SS;
- Change and percent change from Baseline in ADerm-SS TSS-7, ADerm-SS TSS-11, and skin pain score;
- Proportion of subjects achieving ADerm-SS skin pain score of 0 for subjects with ADerm-SS skin pain score > 0 at Baseline;
- Change and percent change from Baseline in ADerm-IS sleep domain score, emotional state domain score, and daily activities domain score;
- Change and percent change from Baseline in POEM;
- Proportion of subjects achieving POEM sleep item score of 0 for subjects with POEM sleep item score > 0 at Baseline;
- Change and percent change from Baseline in DLQI among subjects age ≥ 16 years old at screening;
- Proportion of subjects age < 16 years old at screening achieving Children's Dermatology Life Quality Index (CDLQI) score of 0 or 1 for subjects with CDLQI score > 1 at Baseline;
- Change and percent change from Baseline in CDLQI among subjects age < 16 years old at screening;
- Change and percent change from Baseline in Work Productivity and Activity Impairment Index: Atopic Dermatitis (WPAI:AD) domain scores (absenteeism, presenteeism, activity impairment, overall work productivity);
- Change and percent change from Baseline in EuroQoL Dimensions 5 Levels (EQ-5D-5L);
- Change and percent change from Baseline in Short Form-36 Health Survey (SF-36) summary scores (physical component summary, mental component summary) and scale scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, social role functioning, mental health);
- Change and percent change from Baseline in Patient Global Impression of Severity (PGIS);
- Proportion of subjects who report symptoms to be 'Minimal' or 'Absent' on the PGIS for subjects who did not report symptoms to be 'Minimal' or 'Absent' at Baseline;
- Proportion of subjects who are 'Very much improved' or 'Much improved' on the Patient Global Impression of Change (PGIC);
- Proportion of subjects who are 'Extremely satisfied' or 'Very satisfied' on the Patient Global Impression of Treatment (PGIT) for subjects who are not 'Extremely satisfied' or 'Very satisfied' on the PGIT at Baseline.

- Proportion of subjects achieving EASI 50;
- Proportion of subjects achieving a vIGA-AD of 0 with a reduction from Baseline of ≥ 2 points.

In the clinical evaluation it was noted that most of the secondary endpoints were similar for EU (EMA) and USA (FDA) regulatory purposes. However, it is noted that the US FDA secondary endpoints did not include quality of life (quality of life) measures (such as DLQI and HADS) and frequency of atopic dermatitis symptoms (POEM);

Participant flow

Overall, 1093 subjects were screened and a total of 847 subjects were randomised to study treatments: 281, 285 and 281 were randomised to upadacitinib 15 mg, upadacitinib 30 mg and placebo, respectively.

All the 847 subjects (100%) received study drug. 778 subjects (91.9%) completed study drug treatment through the double blinded period (Week 16), and 782 subjects (92.3%) completed study participation through Week 16.

Fifty-two (52) subjects discontinued the study drug treatment during the double blinded period. The most frequent primary reason for study discontinuation was withdrawal of consent by the subject; 184 of the 847 subjects (21.7%) received rescue medication in the double blinded period. No subject discontinued study drug due to COVID-19.

Of the 847 subjects randomised, 124 subjects (14.6%) were adolescents.

Regarding the adolescent subjects:

- all received study drug treatment (100%);
- 119 adolescent subjects (96.0%) completed study drug through the double blind period (Week 16) and completed study participation through Week 16;
- four (4) adolescent subjects discontinued study drug and the study participation during the double blind Period. The most frequent reason for study discontinuation was withdrawal of consent.

Of the adolescent subjects dosed in the double blind period, 25 subjects (20.2%) received rescue medication.

Of the 782 subjects that entered the blinded extension period, 777 subjects (96.5%) were dosed.

As of the cut-off date:

- 17 subjects (2.1%) received rescue medication;
- no subjects completed study drug treatment in the blinded extension Period (Week 136);
- 53 subjects (6.6%) discontinued study drug treatment in the blinded extension Period. Adverse event (2.1%) was the most frequent primary reason for study drug discontinuation in the blinded extension Period.

Of the 782 subjects that entered the blinded extension Period, 119 were adolescent subjects.

Regarding the adolescent subjects:

- all were dosed (100%);
- 2 adolescents (1.7%) received rescue medication;
- no subjects completed study drug in the blinded extension period (Week 136);

- 8 adolescent subjects (6.7%) discontinued study drug in the blinded extension period.
- The most frequent primary reason for study drug discontinuation for adolescent subjects in the blinded extension period was due to an adverse event (2.5%).

Analysis of populations

- The intent-to-treat (ITT) population consisted of all subjects, which included some adolescent subjects, who were randomised in the main study (ITT_M population) plus those adolescent subjects who were randomised in the adolescent sub-study (ITT_A population).
- Subjects randomised to placebo in the double blind Period and did not continue into the blinded extension Period were not included in the analysis of the blinded extension period.
- Additional sensitivity analyses were performed on a per-protocol population for the main study (PP_M), which did not include subjects with major protocol deviations that potentially affect the primary efficacy endpoints. The PP_M population included subjects who satisfy all the following criteria:
  - Receive at least 80% of planned study drug, per randomisation, before Week 16;
  - Have EASI and vIGA-AD assessment post-baseline on or before Week 16;
  - Meet all the following disease activity criteria at Baseline: EASI score ≥ 16; vIGA-AD score ≥ 10% body surface area of atopic dermatitis involvement;
  - Must not have used atopic dermatitis treatments previously stated under the inclusion criteria within the stated periods, prior to the Baseline.
- For the safety populations, subjects are stratified as per 'as treated' treatment group, regardless of the treatment randomised. The 'as treated' is determined by the treatment the subject received during the majority of the subject's drug exposure time, in the analysis period.

Sample size

For the main study, N= approximately 810, comprising of adults and some adolescents were to be randomised in a ratio of 1:1:1 into:

- n = 270 to upadacitinib 15 mg;
- n = 270 to upadacitinib 30 mg;
- n = 270 to placebo.

It is stated that the sample size was determined by the regulatory requirement to adequately characterise the safety profile.

From the participants' flow chart, a total of 847 subjects were actually randomised as follows:

- 281 subjects randomised to receive upadacitinib 15 mg ;
- 285 subjects randomised to receive upadacitinib 30 mg ;
- 281 subjects randomised to receive placebo.

Assumptions for the sample size:

- an EASI 75 response rate of 15%,
- vIGA-AD clear or almost clear, with at least a 2-point reduction response rate of 10% in the placebo group.

The above sample size provided more than 90% power to detect the treatment differences of 32% and 21%, respectively, for the above 2 endpoints simultaneously using two-sided test at a 0.05 significant level.

The assumptions of placebo response rates for EASI 75 and IGA-AD 0/1 were based on the maximum placebo rate in the upadacitinib atopic dermatitis Phase IIb study (Study M16-048; see section: Study M16-048 (supportive study); and the dupilumab Phase III monotherapy studies (SOLO 1 and SOLO 2 clinical trials).[58,59]

This sample size provided more than 90% power to detect the treatment differences of 38% and 20%, respectively, for the above 2 endpoints simultaneously using two-sided test at a 0.05 significant level.

For the adolescent sub-study, the determination to recruit further adolescents so as to make up the sum total sample size of 180 adolescent subjects in the overall study (main study + adolescent sub-study), was to ensure a total of 225 adolescent subjects with at least one year of exposure per dose across 3 pivotal studies.

Statistical methods

For the main ITT population (ITT_M), which includes some adolescents, comparisons between each upadacitinib group and the placebo group was conducted using the Cochran-Mantel-Haenszel test, adjusting for vIGA-AD categories and age (adolescent versus adult in the main study).

The primary approach for handling missing data in the analysis of categorical endpoints (including the co-primary endpoints) used non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C).

The clinical evaluation noted that the NRI-C categorised any subject who did not have an evaluation during a pre-specified visit window (either due to missing assessment or due to early withdrawal from the study) as a non-responder for the visit. The only exceptions were:

1. When the subject is a responder both before and after the visit window, the subject will be categorised as a responder for the visit.
2. Missing data due to COVID-19 infection or logistical restriction will be handled by Multiple Imputation. In addition, all assessments after the start of rescue medications were not included in the analyses; as a result, subjects were to be counted as non-responders thereafter and not be imputed by multiple imputation.

The NRI-C, multiple imputation and tipping point approaches were used as sensitivity analyses.

Per-protocol analysis was also based on the NRI-C approach.

For continuous endpoints, missing data was handled using a mixed models for repeated measures (MMRM) approach.

The clinical evaluation also noted that the MMRM approach was conducted using mixed model including observed measurements at all visits, except that measurements after any rescue medication were excluded. The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, main stratification factors at randomisation (vIGA-AD categories and age (adolescent versus adult) if applicable), and

[58] SOLO 1 trial: A Phase III confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate-to-severe atopic dermatitis. ClinicalTrials.gov Identifier: NCT02277743.
[59] SOLO 2 trial: A Phase III confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate-to-severe atopic dermatitis. ClinicalTrials.gov Identifier: NCT02277769.

the continuous fixed covariates of Baseline measurement. The parameter estimations are based on the method of restrictive maximum likelihood. The fixed effects will be used to report model-based means at corresponding visits.

Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C) was the primary approach to handle missing values.

For each ITT population, secondary efficacy endpoints in double blind period were analysed by comparing each upadacitinib treatment group and placebo. The categorical endpoints and continuous endpoints will be analysed by Cochran-Mantel-Haenszel test and MMRM, respectively. Pruritus NRS were analysed based on weekly rolling averages of daily scores with the following exceptions, which were analysed, based on daily scores:

- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 2 for subjects randomised to upadacitinib 30 mg with Worst Pruritus NRS ≥ 4 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 3 for subjects randomised to upadacitinib 15 mg with Worst Pruritus NRS ≥ 4 at Baseline.

The clinical evaluation noted these two variables will be analysed by day from Day 2 to Day 28. The baseline of the above two endpoints is defined as last non-missing daily Worst Pruritus NRS score before the first dose of the study drug.

Long-term efficacy in the blinded extension period was summarised using the observed case approach.

The clinical evaluation noted that for observed case while on study drug: The observed case analysis will be used for the summaries of long-term efficacy, which will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will not be included in the observed case analysis for that visit. The observed case analysis will be performed for all variables, and will not include values after more than 1 day after discontinuation of study drug.

Subgroup analyses were performed for the co-primary endpoints by demographics:

- Age Group 1 (< 18 years, and ≥ 18 years),
- Age Group 2 (< 18 years, ≥ 18 to ≤ 40 years, ≥ 40 to ≤ 65 years, and ≥ 65 years).

Regarding subgroup analyses:

- Age ≥ 65 years or BMI ≥ 30 subgroups will be combined with their adjacent subgroup when having fewer than 10% subjects.
- Sex (male, female);
- BMI (normal: < 25, overweight: ≥ 25 – < 30, obese: ≥ 30);
- Race (White, Asian, Black, and Other).
- Any race subgroups with fewer than 10% subjects will be combined with other for analyses.
- Weight (< median, ≥ median);
- Geographic regions (USA/Puerto Rico/Canada, Japan, China (mainland), and Other))
- Baseline characteristics (Baseline vIGA-AD (< 4, 4); Baseline EASI (< median, ≥ median); high-sensitivity C-reactive protein (hsCRP) (< median, ≥ median);
- Previous systemic therapy (with and without);

- Subjects who reported an intolerance to at least one prior topical corticosteroid or calcineurin therapy;
- Subjects that reported an inadequate response to at least one prior topical treatment.

For any subgroup, if there were zero subjects within a stratum in any treatment group, the Cochran-Mantel-Haenszel model was not adjusted by the stratification factors.

Baseline data

The overall demographic characteristics were generally balanced across the upadacitinib (30 mg and 15 mg) and placebo groups overall and, in adolescents (see Table 22, below).

Table 22: Study M16-045 Demographic characteristics and baseline data

	Overall					Adolescents				
	PBO (N = 281)	UPA 15 mg (N = 281)	UPA 30 mg (N = 285)	UPA Total (N = 566)	Total (N = 847)	PBO (N = 40)	UPA 15 mg (N = 42)	UPA 30 mg (N = 42)	UPA Total (N = 84)	Total (N = 124)
Sex - n (%)										
Male	144 (51.2)	157 (55.9)	155 (54.4)	312 (55.1)	456 (53.8)	17 (42.5)	21 (50.0)	22 (52.4)	43 (51.2)	60 (48.4)
Female	137 (48.8)	124 (44.1)	130 (45.6)	254 (44.9)	391 (46.2)	23 (57.5)	21 (50.0)	20 (47.6)	41 (48.8)	64 (51.6)
Age (years)										
Mean (SD)	34.4 (15.50)	34.1 (15.72)	33.6 (15.84)	33.8 (15.77)	34.0 (15.67)	15.3 (1.68)	15.6 (1.95)	15.7 (1.55)	15.6 (1.75)	15.5 (1.73)
Median	31.0	30.0	29.0	29.0	30.0	15.0	16.0	16.0	16.0	16.0
Min, Max	12, 75	12, 74	12, 75	12, 75	12, 75	12, 18	12, 18	12, 18	12, 18	12, 18
Age group (years) - n (%)										
< 18	40 (14.2)	42 (14.9)	42 (14.7)	84 (14.8)	124 (14.6)	40 (100)	42 (100)	42 (100)	84 (100)	124 (100)
≥ 18	241 (85.8)	239 (85.1)	243 (85.3)	482 (85.2)	723 (85.4)	0	0	0	0	0
18 - < 40	145 (51.6)	143 (50.9)	154 (54.0)	297 (52.5)	442 (52.2)	0	0	0	0	0
40 - < 65	85 (30.2)	83 (29.5)	74 (26.0)	157 (27.7)	242 (28.6)	0	0	0	0	0
≥ 65	11 (3.9)	13 (4.6)	15 (5.3)	28 (4.9)	39 (4.6)	0	0	0	0	0
Race - n (%)										
White	182 (64.8)	182 (64.8)	191 (67.0)	373 (65.9)	555 (65.5)	25 (62.5)	29 (69.0)	28 (66.7)	57 (67.9)	82 (66.1)
Black or African American	21 (7.5)	26 (9.3)	8 (2.8)	34 (6.0)	55 (6.5)	5 (12.5)	6 (14.3)	1 (2.4)	7 (8.3)	12 (9.7)
Asian	69 (24.6)	63 (22.4)	71 (24.9)	134 (23.7)	203 (24.0)	7 (17.5)	6 (14.3)	10 (23.8)	16 (19.0)	23 (18.5)
American Indian/Alaska Native	3 (1.1)	0	0	0	3 (0.4)	2 (5.0)	0	0	0	2 (1.6)
Native Hawaiian or Other Pacific Islander	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.4)	3 (0.4)	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0	0
Multiple	5 (1.8)	9 (3.2)	14 (4.9)	23 (4.1)	28 (3.3)	1 (2.5)	1 (2.4)	3 (7.1)	4 (4.8)	5 (4.0)
Ethnicity - n (%)										
Hispanic or Latino	33 (11.7)	35 (12.5)	41 (14.4)	76 (13.4)	109 (12.9)	3 (7.5)	8 (19.0)	7 (16.7)	15 (17.9)	18 (14.5)
Not Hispanic or Latino	248 (88.3)	246 (87.5)	244 (85.6)	490 (86.6)	738 (87.1)	37 (92.5)	34 (81.0)	35 (83.3)	69 (82.1)	106 (85.5)
Weight (kg)										
Mean (SD)	75.53 (19.935)	74.22 (19.361)	73.09 (18.325)	73.65 (18.838)	74.28 (19.218)	65.52 (17.442)	60.56 (11.942)	62.53 (17.664)	61.54 (15.019)	62.83 (15.879)
Median	73.00	70.30	70.80	70.30	71.00	65.75	57.10	56.75	57.10	58.00
Min, Max	38.3, 170.1	40.0, 160.6	36.3, 151.0	36.3, 160.6	36.3, 170.1	40.3, 106.1	40.0, 85.3	42.1, 135.6	40.0, 135.6	40.0, 135.6
BMI (kg/m^2) - n (%)										
< 25	121 (44.0)	148 (52.9)	150 (53.2)	298 (53.0)	419 (50.1)	23 (59.0)	32 (78.0)	32 (76.2)	64 (77.1)	87 (71.3)
25 - < 30	89 (32.4)	80 (28.6)	76 (27.0)	156 (27.8)	245 (29.3)	8 (20.5)	5 (12.2)	6 (14.3)	11 (13.3)	19 (15.6)
≥ 30	65 (23.6)	52 (18.6)	56 (19.9)	108 (19.2)	173 (20.7)	8 (20.5)	4 (9.8)	4 (9.5)	8 (9.6)	16 (13.1)
Missing	6	1	3	4	10	1	1	0	1	2
Tobacco use[a] - n (%)										
Current	56 (20.0)	48 (17.1)	54 (18.9)	102 (18.0)	158 (18.7)	1 (2.5)	2 (4.8)	2 (4.8)	4 (4.8)	5 (4.0)
Former	41 (14.6)	40 (14.2)	32 (11.2)	72 (12.7)	113 (13.4)	2 (5.0)	3 (7.1)	0	3 (3.6)	5 (4.0)
Never	183 (65.4)	193 (68.7)	199 (69.8)	392 (69.3)	575 (68.0)	37 (92.5)	37 (88.1)	40 (95.2)	77 (91.7)	114 (91.9)
Unknown	1	0	0	0	1	0	0	0	0	0
Alcohol use[b] - n (%)										
Current	148 (53.2)	134 (47.9)	147 (51.8)	281 (49.8)	429 (51.0)	0	4 (9.5)	1 (2.4)	5 (6.0)	5 (4.1)
Former	13 (4.7)	14 (5.0)	14 (4.9)	28 (5.0)	41 (4.9)	1 (2.6)	3 (7.1)	1 (2.4)	4 (4.8)	5 (4.1)
Never	117 (42.1)	132 (47.1)	123 (43.3)	255 (45.2)	372 (44.2)	38 (97.4)	35 (83.3)	40 (95.2)	75 (89.3)	113 (91.9)
Unknown	3	1	1	2	5	1	0	0	0	1

BMI = body mass index; ITT_M Population = Intent-to-Treat Population for Main Study; Min = minimum; Max = maximum; PBO = placebo; SD = standard deviation; UPA = upadacitinib

a. A subject may be a current user of one type of tobacco, a former user of another type of tobacco, and never used another type of tobacco.

b. A subject was counted in the category closest to user.

Note: Percentages calculated on non-missing values.

Overall, the majority of subjects were male (56.3%), aged 18 to 39 years (52.2%) compared to the adolescent group with majority of females (53.8%).

Baseline disease characteristics were generally balanced across the upadacitinib and placebo groups overall and, in adolescents. Overall, the most common medical/surgical history by body system was respiratory, thoracic and mediastinal disorders (60.6% of which asthma (39.9%) and allergic rhinitis (34.0%) most common),followed by immune system disorders (52.7%) with similar incidence across treatment groups.

Subjects had been diagnosed with atopic dermatitis for a mean of approximately 20.2 years overall and, 12.5 years for adolescents. Disease activity consistently reflected moderate (45%) to severe (55%) atopic dermatitis across the treatment groups. EASI, SCORAD (overall, objective, itch and sleep scores), DLQI, CDLQI, HAD scores were similar across all 3 treatment groups.

Overall, 845 (99.8%) of subjects had received prior atopic dermatitis therapy with majority using topical corticosteroids [66.7%, 50.1% and 27.4% used high potency, medium potency and low potency topical corticosteroids, topical calcinuerin inhibitor (35%), other topical therapy (23%) and phototherapy.

Topical betamethasone was the most frequently reported prior medication (38.6% of subjects).

385 subjects (45.5%) received prior non-biologic immunomodulating systemic therapies (29.4 to 100% of subjects per agent had lack of initial response).

Twenty-four subjects(2.8%) received prior biologic systemic therapies (50.0% to 100% of subjects per agent had a lack of initial response).

Concomitant medication usage was similar across all treatment groups; emollients and protectives were the most frequently reported concomitant medications (27.5% and 27.4% of subjects in the double blind period and blinded extension period).

Treatment compliance rates were high in the double blind period with mean compliance greater than 96% and median compliance greater than 99% in all three groups.

Regarding baseline data, the clinical evaluation noted that:

- Compliance was calculated as the number of tablets actually taken by the subject divided by the number of tablets planned to be taken by the subject during the double blinded and blinded extension period of the study, respectively.
- Overall, the study population was representative of the target patient population for upadacitinib with moderate to severe severity of atopic dermatitis who were candidates for systemic therapy (not responsive to local treatment and many had also not responded to prior systemic therapies);
- The use of previous systemic therapy was slightly higher in the placebo compared to the upadacitinib groups (42.7%, 45.3% and 51.2% in the 15 mg, 30 mg and placebo groups, respectively).
- The use of concomitant medications by 'category' was not provided in the clinical study report and was requested – the clinical study report had only provided listing of concomitant medications by generic names).

Major protocol violations and deviations

The incidence of at least one protocol deviation was 12.5% (35/281), 15.4% (44/285) and 14.9% (42/281) in the upadacitinib 15 mg, 30 mg and placebo groups, respectively. Total number of subjects excluded from the per protocol population was 5.3% (15/281), 4.9% (14/285) and 3.6% (10/281), respectively.

The most common protocol deviation was subject being entered into the study even though he/she did not fully satisfy the entry criteria. The most common eligibility criterion (criterion 7) not being met related to the atopic disease activity parameters. Subjects should meet all disease activity parameters, that is, an EASI score ≥ 16, vIGA score ≥ 3, ≥10% body surface area (BSA) of atopic dermatitis involvement and an average of daily worst pruritus NRS ≥ 4. This eligibility criterion was a requirement specified in the Paediatric Investigation Plan (PIP) for the EMA.

Almost all the deviations related to eligibility criterion 7 were due to missing a minimum of 4 daily Worst Pruritus NRS assessments out of the 7 consecutive days immediately preceding the baseline visit to calculate the baseline weekly average of daily Worst Pruritus NRS ≥ 4, while all other disease activity criteria were met. Subjects with missing data included 8 adolescent subjects with a baseline NRS < 4 or a missing baseline NRS.

The clinical evaluation noted that subjects on an ePRO device;[60] completed the Worst Pruritus NRS score daily. Data documented outside the ePRO device were not accepted in the study. Due to technical issues with the ePRO devices and lack of appropriate understanding by subjects and site personnel regarding the collection and calculation of the Worst Pruritus NRS score, the data were missed from some subjects, and eligibility as per the Worst Pruritus NRS score could not be confirmed at the time of the Baseline visit. The issue was resolved by trainingthe site personnel, close monitoring of subjects in screening and re-education of subjects in completing ePROs.

Results for the efficacy outcomes

Co-primary endpoints

The clinical evaluation of this study noted that the stated co-primary endpoints were met. The endpoints achieved were as follows:

- a statistically significantly larger proportion of subjects in the upadacitinib groups achieved an EASI 75 response compared with baseline scores (69.6%, 79.7% and 16.3% in the upadacitinib 15 mg, 30 mg and placebo groups, respectively; p < 0.001 for both upadacitinib groups versus placebo) (see Section: *Eczema Area and Severity Index (EASI))*
- patients with moderate and severe eczema treated with upadacitinib, demonstrated significant improvements over placebo, as per Table 23 below.

Table 23: Study M16-045 Proportion of subjects achieving a EASI 75 response by visit in double blind period (NRI-C) (main ITT population)

Time Point Strata Treatment	N	---- Responder ---- n (%) [95% CI]&	Missing Due to COVID-19 n	Response Rate Diff ---------- Compared to Placebo ---------- Diff(%)	Adjusted Diff(%)	[95% CI]#	P-value@	Breslow-Day P-value
Week 16								
All								
Placebo	281	46 (16.3) [12.0, 20.7]	4					
UPA 15 mg QD	281	196 (69.6) [64.2, 75.0]	1	53.3	53.3	[46.4, 60.2]	<0.001***	0.126
UPA 30 mg QD	285	227 (79.7) [75.0, 84.4]	2	63.4	63.4	[57.1, 69.8]	<0.001***	0.065
vIGA-AD 3 (Moderate)								
Placebo	156	32 (20.8) [14.3, 27.2]	3					
UPA 15 mg QD	154	109 (70.8) [63.6, 78.0]	0	50.0		[40.3, 59.7]	<0.001***	
UPA 30 mg QD	154	123 (80.1) [73.8, 86.5]	1	59.4		[50.3, 68.4]	<0.001***	
vIGA-AD 4 (Severe)								
Placebo	125	14 (10.8) [5.3, 16.3]	1					
UPA 15 mg QD	127	87 (68.2) [60.1, 76.3]	1	57.4		[47.5, 67.2]	<0.001***	
UPA 30 mg QD	131	104 (79.2) [72.2, 86.2]	1	68.4		[59.5, 77.3]	<0.001***	

Note: EASI = Eczema Area and Severity Index; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis.
NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
& 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.
# @ Across the strata, 95% CI for adjusted difference and P-value are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (Baseline vIGA-AD categories and age [adolescent vs. adult]) for the comparison of two treatment groups. Within each stratum, 95% CI for difference and P-value are calculated using Cochran-Mantel-Haenszel test without adjustment of strata. The calculations at each visit are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.
***, **, * Statistically significant at the 0.001, 0.01, 0.05 level, respectively.

Abbreviations: CI = confidence intervals; EASI 75 = Eczema Area and Severity Index 75 response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

[60] An **electronic patient-reported outcome** (**ePRO**) is a wearable or hand-held device that can be used to collect or record events from a patient, such as drug administration, patient satisfaction or wellbeing ratings, various self-rated scores or questionnaires, side effects or adverse events, with the information being uploaded electronically.

- A statistically significantly larger proportion of subjects in the upadacitinib groups, achieved a vIGA-AD score of 0 or 1 (clear or almost clear), with a clinically meaningful reduction (at least 2 grade reductions from baseline) at Week 16, compared with the placebo group based on the primary approach of NRI-C (48.1%, 62% and 8.4% in the upadacitinib 15 mg, 30 mg and placebo groups, respectively; $p < 0.001$ for both upadacitinib groups versus placebo) (see section: *Validated Investigator Global Assessment scale for Atopic Dermatitis* (vIGA-AD) for details on this measure);
- Patients with moderate and severe atopic dermatitis treated with udapacitinib, demonstrated significant improvements over placebo, as per Table 24 below.

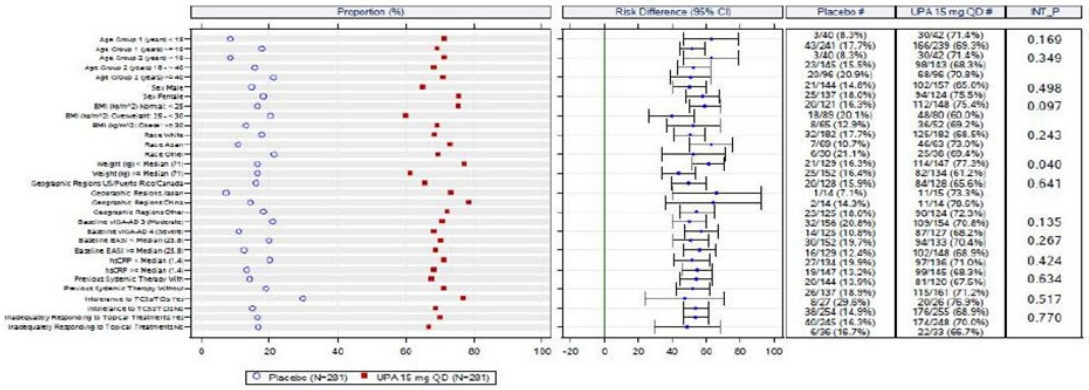
Table 24: Study M16-045 Proportion of subjects achieving vIGA-AD of 0 or 1 with at least 2 grades of reduction (main ITT population, NRI-C)

Time Point Strata Treatment	N	---- Responder ---- n (%) [95% CI]&	Missing Due to COVID-19 n	Response Rate Diff ---------- Compared to Placebo ---------- Diff(%)	Adjusted Diff(%)	[95% CI]#	P-value@
Week 16							
All							
Placebo	281	24 (8.4) [5.2, 11.7]	4				
UPA 15 mg QD	281	135 (48.1) [42.3, 54.0]	1	39.7	39.8	[33.2, 46.4]	<0.001***
UPA 30 mg QD	285	177 (62.0) [56.4, 67.7]	2	53.6	53.6	[47.2, 60.0]	<0.001***
vIGA-AD 3 (Moderate)							
Placebo	156	15 (9.4) [4.8, 14.0]	3				
UPA 15 mg QD	154	86 (55.8) [48.0, 63.7]	0	46.4		[37.3, 55.5]	<0.001***
UPA 30 mg QD	154	107 (69.3) [62.0, 76.6]	1	59.8		[51.2, 68.5]	<0.001***
vIGA-AD 4 (Severe)							
Placebo	125	9 (7.2) [2.7, 11.8]	1				
UPA 15 mg QD	127	49 (38.8) [30.3, 47.3]	1	31.6		[21.9, 41.2]	<0.001***
UPA 30 mg QD	131	70 (53.5) [44.9, 62.0]	1	46.3		[36.6, 55.9]	<0.001***

Abbreviations: CI = confidence intervals; vIGA-AD = validated investigator's global assessment; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

- The robustness of the co-primary endpoint results was supported by consistent results favouring both upadacitinib groups compared to placebo in all sensitivity analyses, including NRI-C, multiple imputation, tipping point analysis, and per protocol analysis.
- Treatment effects in all pre-specified sub-groups (across demographic and baseline characteristics), including adolescents consistently favoured both upadacitinib doses compared to placebo in EASI 75 and vIGA-AD with all 95% confidence intervals (CIs) excluding zero, as per Figure 8Figure 9Figure 10Figure 11Figure 12Figure 13 below.

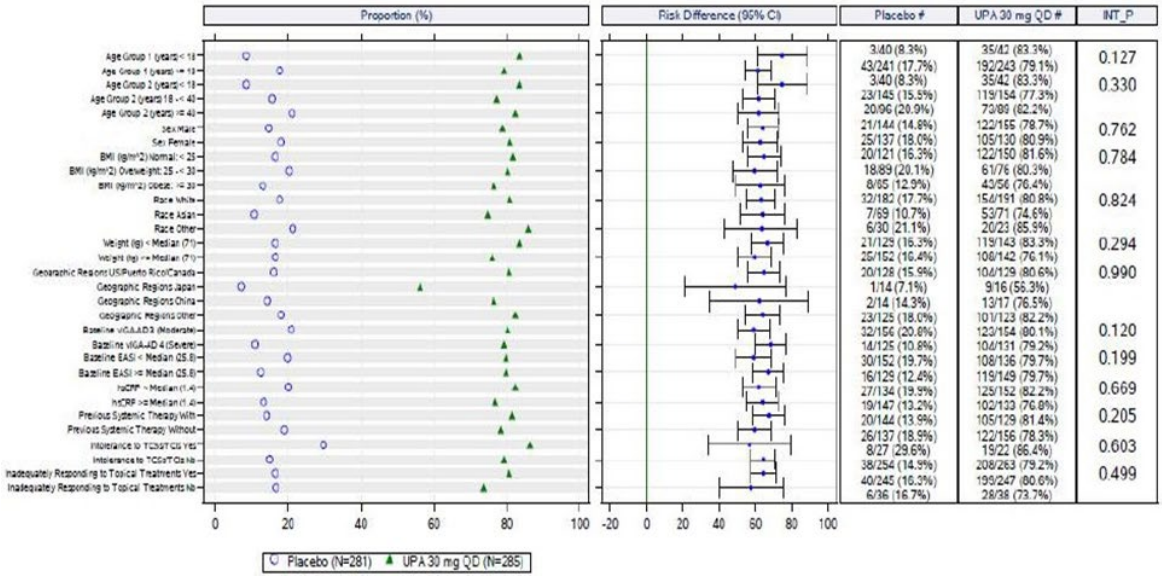
Figure 8: Study M16-015 Proportion of subjects achieving EASI 75 at Week 16 by subgroup in the upadacitinib proportion of subjects achieving EASI 75 at Week 16 by subgroup in the upadacitinib 15 mg group (NRI-C, main ITT population)



BMI = body mass index; CI = confidence interval for adjusted difference, calculated according to the Cochran-Mantel-Haenszel test adjusted for strata; EASI = Eczema Area and Severity Index; hsCRP = high-sensitivity C-reactive protein; INT_P = P-value for interaction between subgroup and treatment was calculated using a logistic regression with visit measurement at Week 16 as response variable, treatment, subgroup, strata, and treatment by subgroup interaction as factors; ITT_M = Intent-to-Treat Population for the Main Study; NRI-C = non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids; QD = once daily; UPA = upadacitinib; vIGA-AD = validated Investigator Global assessment for Atopic Dermatitis

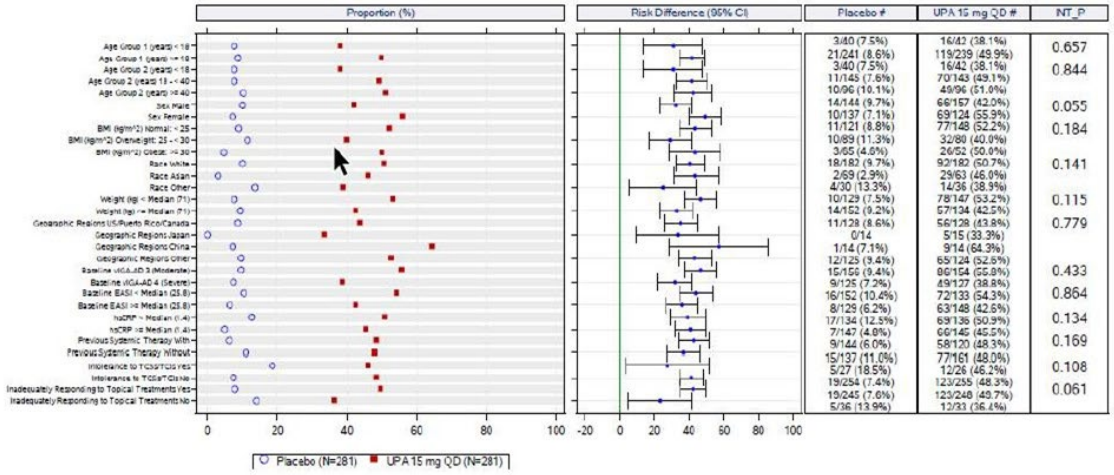
\# Placebo and UPA 15 mg QD represents n/N (xx.x%).

Figure 9: Study M16-045 Proportion of subjects achieving EASI 75 at Week 16 by subgroup in the upadacitinib 30 mg group (NRI-C, main ITT population)



Abbreviations: CI = confidence intervals; EASI 75 = Eczema Area and Severity Index 75 response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

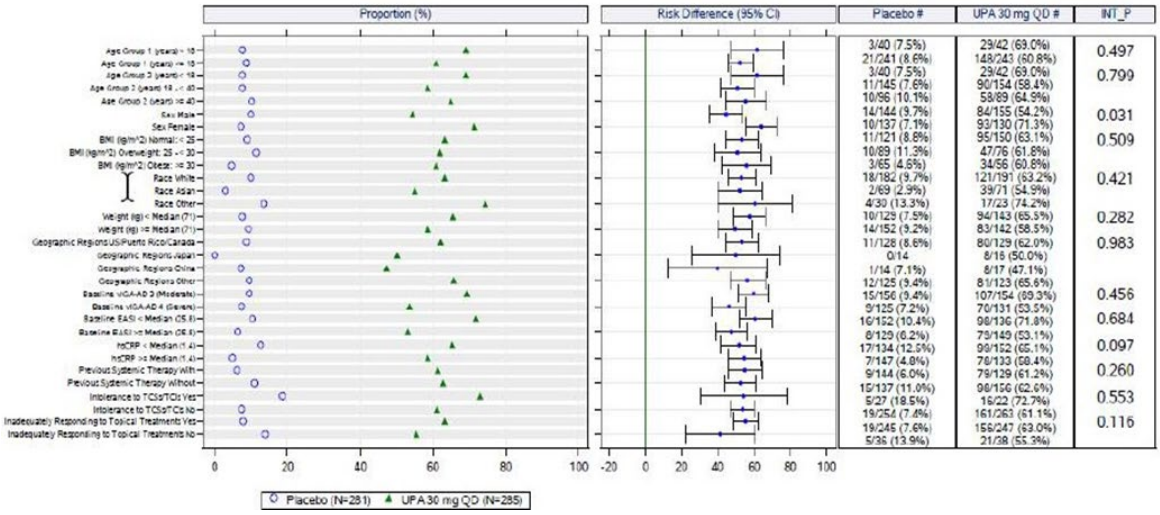
Figure 10: Proportion of subjects achieving vIGA-AD of 0 or 1 with at least 2 grades of reduction from baseline at week 16 by subgroup in the upadacitinib 15 mg group (NRI-C, main ITT population)



BMI = body mass index; CI = confidence interval for adjusted difference, calculated according to the Cochran-Mantel-Haenszel test adjusted for strata; EASI = Eczema Area and Severity Index; hsCRP = high-sensitivity C-reactive protein; INT_P = P-value for interaction between subgroup and treatment was calculated using a logistic regression with visit measurement at Week 16 as response variable, treatment, subgroup, strata, and treatment by subgroup interaction as factors; ITT_M = Intent-to-Treat Population for the Main Study; NRI-C = non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids; QD = once daily; UPA = upadacitinib; vIGA-AD = validated Investigator Global assessment for Atopic Dermatitis

\# Placebo and UPA 15 mg QD represents n/N (xx.x%).

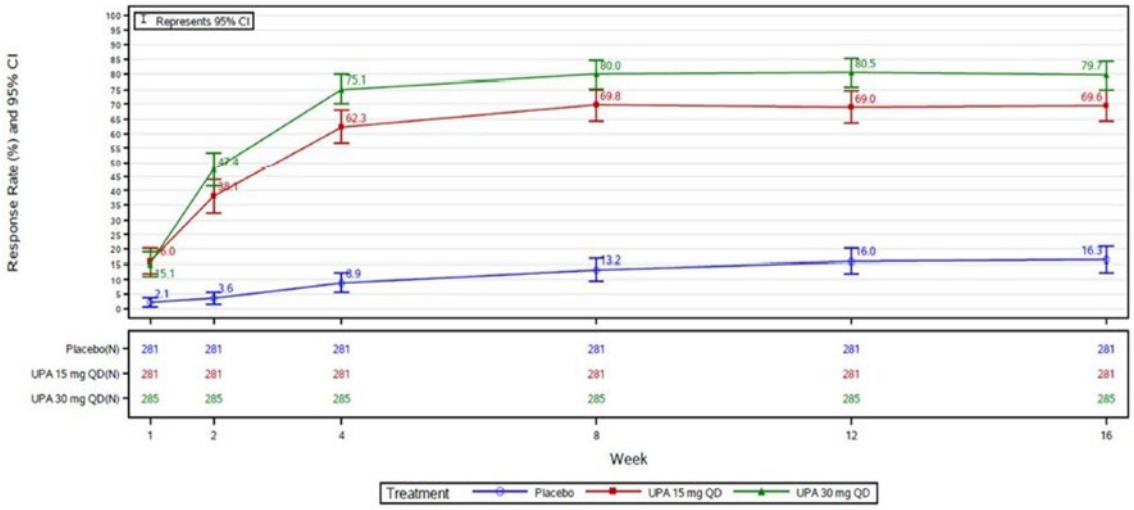
Figure 11: Proportion of subjects achieving vIGA-AD of 0 or 1 with at least 2 grades of reduction from baseline at week 16 by subgroup in the upadacitinib 30 mg group (NRI-C, main ITT population)



Abbreviations: CI = confidence intervals; EASI 75 = Eczema Area and Severity Index 75 response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

The onset of action was rapid with statistically significant improvement in EASI 75 observed from Week 2 onwards and, was maintained until Week 16, as per the figure below.

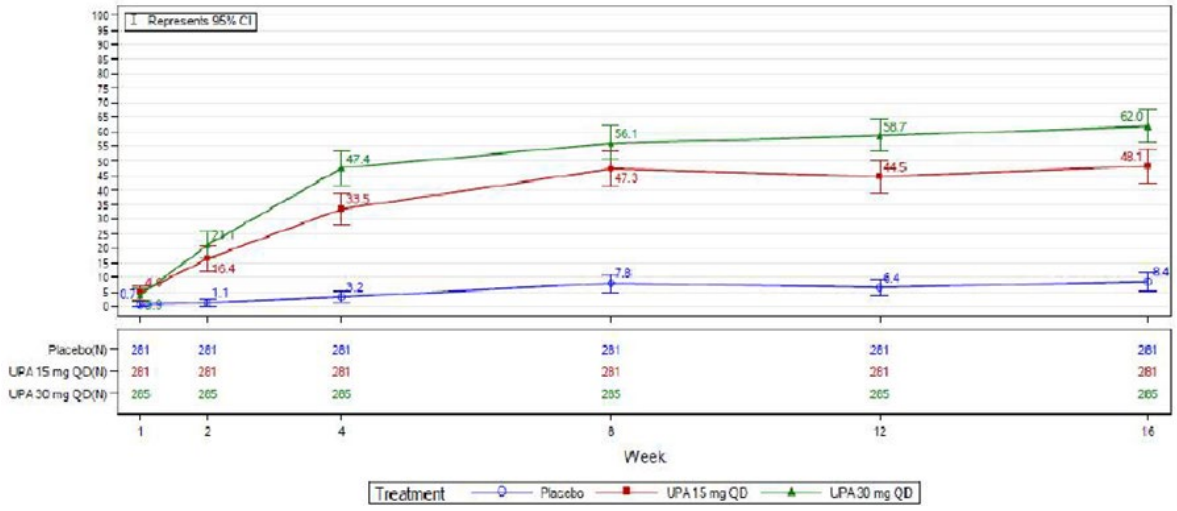
Figure 12: Study M16-045 EASI 75 response rates from Baseline to Week 16 (main ITT population, NRI-C)



Abbreviations: CI = confidence intervals; vIGA-AD = validated investigator's global assessment; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

Similar results were observed for vIGA-AD of 0 or 1 with at least 2 grades of reduction from Baseline, as per Figure 13, below.

Figure 13: Study M16-045 vIGA 0/1 score response rates from Baseline to Week 16 (main ITT population, NRI-C)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib; vIGA-AD = validated investigator's global assessment.

Key secondary endpoints

The key secondary endpoints demonstrated the superiority of each upadacitinib dose versus placebo with statistically significant and clinically relevant improvements in atopic dermatitis activity related to the skin, pruritus, health-related quality of life, impact of topic dermatitis on sleep and daily activities.

Most of these efficacy endpoints demonstrated numerically better improvements with the 30 mg upadacitinib dose compared to the 15 mg dose.

Table 25: Study M16-045 Key secondary endpoint results (US FDA- and EMA-agreed efficacy outcomes; main ITT population)

EMA Testing[a]	FDA Testing[a]	Secondary Endpoint	PBO (N = 281) n (%) or LS Mean (SE)	UPA 15 mg (N = 281) n (%) or LS Mean (SE); Adj Diff (P-value)	UPA 30 mg (N = 285) n (%) or LS Mean (SE); Adj Diff (P-value)
V3	V3	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Week 16	N = 272 32 (11.8)	N = 274 143 (52.2); 40.5 (< 0.001***)	N = 280 168 (60.0); 48.2 (< 0.001***)
V4	V4	EASI 90 at Week 16	N = 281 23 (8.1)	N = 281 149 (53.1); 45.1 (< 0.001***)	N = 285 187 (65.8); 57.8 (< 0.001***)
V5	NA	Percent change in Worst Pruritus NRS at Week 16	N = 123 –26.06 (5.407)	N = 225 –62.79 (4.490); –36.74 (< 0.001***)	N = 236 –72.04 (4.412); –45.98 (< 0.001***)
NA	V5	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Week 4	N = 272 12 (4.4)	N = 274 141 (51.5); 47.1 (< 0.001***)	N = 280 187 (66.8); 62.3 (< 0.001***)
V6	NA	Percent change in EASI at Week 16	N = 128 –40.71, (2.280)	N = 244 –80.24, (1.910); –39.53 (< 0.001***)	N = 259 –87.74 (1.875); –47.03 (< 0.001***)
V7	V6	EASI 75 at Week 2	N = 281 10 (3.6)	N = 281 107 (38.1); 34.5 (< 0.001***)	N = 285 135 (47.4); 43.9 (< 0.001***)
V8	V7	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Week 1	N = 272 1 (0.4)	N = 274 41 (15.0); 14.6 (< 0.001***)	N = 280 55 (19.6); 19.2 (< 0.001***)
V9	NA	Improvement in POEM ≥ 4 at Week 16	N = 276 63 (22.8)	N = 278 209 (75.0); 52.3 (< 0.001***)	N = 280 228 (81.4); 58.6 (< 0.001***)
V10	NA	Improvement in DLQI ≥ 4 at Week 16	N = 250 73 (29.0)	N = 254 192 (75.4); 46.7 (< 0.001***)	N = 256 210 (82.0); 53.2 (< 0.001***)
V11	V8	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Day 2	N = 270 10 (3.7)	NA	N = 279 33 (11.8); 8.1 (< 0.001***)
V12	V9	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Day 3	N = 270 9 (3.3)	N = 275 45 (16.4); 13.0 (< 0.001***)	NA
V13	V10	Flare during DB Period	N = 274 69 (25.2)	N = 279 3 (1.1); –24.1 (< 0.001***)	N = 285 0; –25.2 (< 0.001***)
V14	NA	Percent change in SCORAD at Week 16	N = 125 –32.68 (2.329)	N = 239 –65.71 (1.777); –33.03 (< 0.001***)	N = 253 –73.07 (1.729); –40.39 (< 0.001***)
V15	NA	HADS-A < 8 and HADS-D < 8 at Week 16	N = 126 18 (14.3)	N = 145 66 (45.5); 31.5 (< 0.001***)	N = 144 71 (49.2); 34.9 (< 0.001***)
V16-H a.	V11-H a.	Improvement in ADerm-IS Sleep Domain Score ≥ 12 at Week 16	N = 220 29 (13.2)	N = 218 120 (55.0); 41.8 (< 0.001***)	N = 218 144 (66.1); 52.9 (< 0.001***)
V16-H b.	V11-H b.	Improvement in ADerm-SS Skin Pain Score ≥ 4 at Week 16	N = 233 35 (15.0)	N = 237 127 (53.6); 38.7 (< 0.001***)	N = 249 158 (63.5); 48.6 (< 0.001***)
V16-H c.	V11-H c.	Improvement in ADerm-SS TSS-7 ≥ 28 at Week 16	N = 226 34 (15.0)	N = 233 125 (53.6); 38.3 (< 0.001***)	N = 246 167 (67.9); 52.9 (< 0.001***)
V16-H d.	V11-H d.	Improvement in ADerm-IS Emotional State Domain Score ≥ 11 at Week 16	N = 212 42 (19.8)	N = 227 142 (62.6); 42.7 (< 0.001***)	N = 226 164 (72.6); 52.5 (< 0.001***)
V16-H e.	V11-H e.	Improvement in ADerm-IS Daily Activities Domain Score ≥ 14 at Week 16	N = 197 40 (20.3)	N = 203 132 (65.0); 44.7 (< 0.001***)	N = 205 150 (73.2); 53.1 (< 0.001***)
V17	V12	EASI 100 at Week 16	N = 281 5 (1.8)	N = 281 47 (16.7); 15.0 (< 0.001***)	N = 285 77 (27.0) 25.3; (< 0.001)
V18	NA	DLQI 0 or 1 at Week 16	N = 252 11 (4.4)	N = 258 78 (30.3); 25.9 (< 0.001***)	N = 261 108 (41.5); 37.3 (< 0.001***)

ADerm-IS = Atopic Dermatitis Impact Scale; ADerm-SS = Atopic Dermatitis Symptom Scale; Adj diff = adjusted difference; DB = double blind; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EMA = European Medicines Agency; EASI 75 = 75% improvement in Eczema Area and Severity Index; FDA = Food and Drug Administration; HADS-A = Hospital Anxiety and Depression Scale-anxiety; HADS-D = Hospital Anxiety and Depression Scale-depression; ITT_M = Intent-to-Treat Population for the Main Study; LS = Least Square; MMRM = mixed-effect model with repeated measures; NA = endpoint not included under multiplicity control for overall type I error; NRI-C = non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; NRS = numerical rating scale; PBO = placebo; POEM = Patient orientated Eczema Measure; SAP = statistical analysis plan; SCORAD = Scoring Atopic Dermatitis; SE = standard error; TSS-7 = 7-item total symptom score; UPA = upadacitinib; V = variable; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis

*** p-value ≤ 0.001; UPA vs PBO.

a. Variables in the EMA and FDA graphical approach for overall type-I error control details in SAP Section 4.6. V1 and V2, not listed, are the co-primary endpoints (EASI 75 and vIGA-AD 0/1 at Week 16).

Note: Results for the binary endpoints are based on NRI-C and results for the continuous endpoints are based on MMRM, except for the endpoint on flare which was analyzed as observed prior to the initiation of rescue medication.

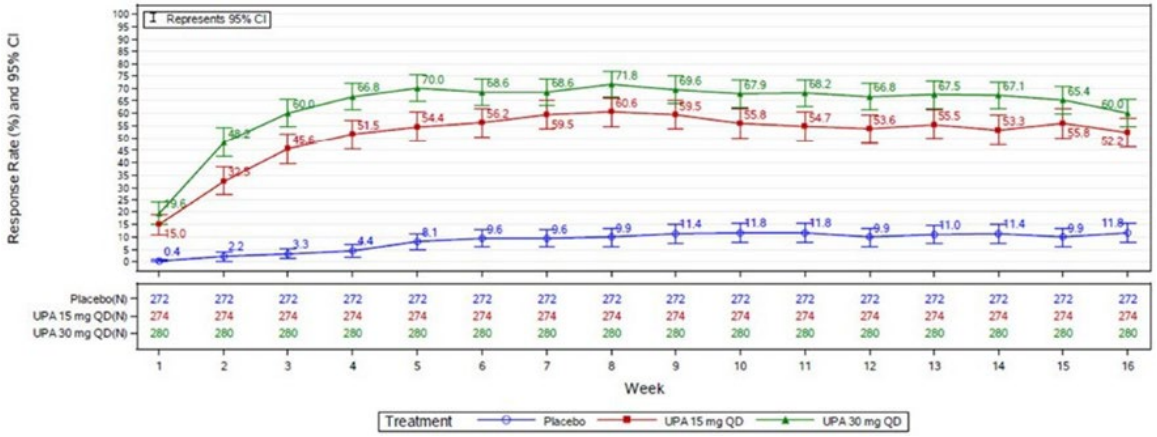
Upadacitinib 30 mg and 15 mg showed statistically significant improvements over placebo for all secondary endpoints of skin clearance and disease activity including vIGA score of 0/1, EASI 50/75/90/100 at Week 16.

The proportion of subjects who achieved SCORAD 50/75/90 continued to increase from Week 2 to Week 16 in subjects on upadacitinib 30 mg and 15 mg compared to placebo. This pattern was consistent with the percent change improvements in SCORAD and its individual components (Objective SCORAD, SCORAD Itch, and SCORAD Sleep). See section: *Scoring Atopic Dermatitis (SCORAD)* for details on this measure.

The body surface area affected by atopic dermatitis showed significantly greater reduction in the upadacitinib groups compared with placebo.

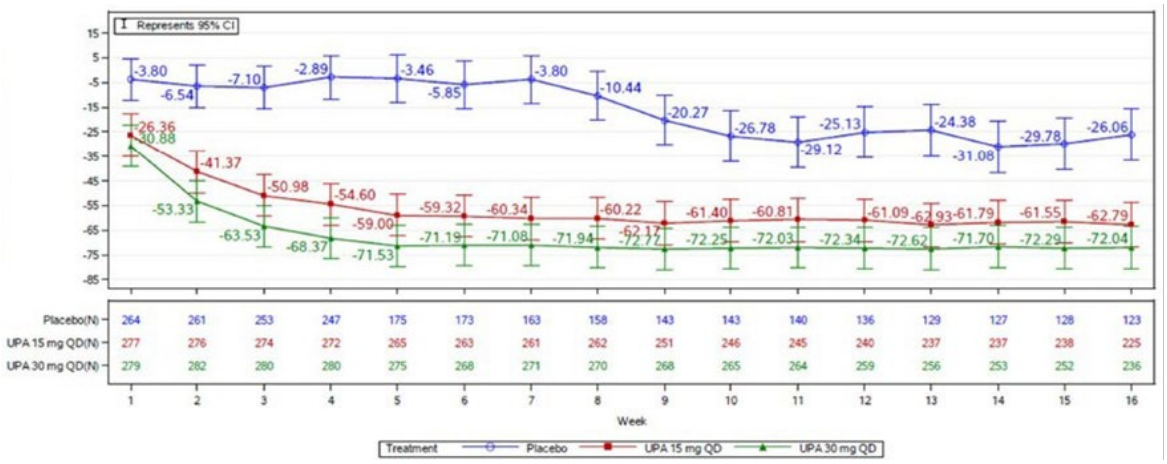
Upadacitinib 30 mg and 15 mg demonstrated superiority in all secondary endpoints of itch reduction, including improvement (reduction) in Worst Pruritus NRS ≥ 4 at Day 2, Day 3, Week 1, Week 4 and Week 16 (see Figure 14), and percent change in Worst Pruritus at Week 16 (see Figure 15). See section: *Worst Pruritus numerical rating scale (NRS)* for details on this measure.

Figure 14: Study M16-045 Improvement (reduction) in proportion of subjects recording a Worst Pruiritis NRS score of ≥ 4 from Baseline to Week 16 (main ITT population, NRI-C)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; NRS = numerical rating scale; QD = once daily; UPA = upadacitinib.

Figure 15: Study M16-045 Percentage change in Worst Pruiritis NRS scores from Baseline to Week 16 (main ITT population, NRI-C)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; NRS = numerical rating scale; QD = once daily; UPA = upadacitinib.

A greater proportion of subjects reported a Worst Pruritus NRS score of 0 or 1 compared with placebo, as early as Week 1 through to Week 16 with consistent results observed in adolescents.

Subjects on upadacitinib 30 mg and 15 mg achieved greater itch reduction as measured by the SCORAD itch assessment over placebo at Week 2 and Week 16.

A significantly greater proportion of subjects on upadacitinib 30 mg and 15 mg achieved clinically meaningful reductions in symptoms of atopic dermatitis, demonstrated as improvement in POEM ≥ 4 at Week 16 (EMA only), improvement in ADerm-SS skin pain score ≥ 4 at Week 16, and improvement in ADerm-SS TSS-7 ≥ 28 at Week 16.

See sections: *Patient Oriented Eczema Measure (POEM); Atopic Dermatitis Symptom Scale (ADerm-SS)Atopic Dermatitis Impact Scale (ADerm-IS); Dermatology Life Quality Index;* and *Hospital Anxiety and Depression Scale (HADS)* for details of these measures.

Subjects on upadacitinib 30 mg and 15 mg achieved a greater improvement (reduction) in skin pain compared to placebo subjects;

Subjects on upadacitinib 30 mg and 15 mg achieved a greater improvement (reduction) in ADerm-IS sleep domain score compared to placebo subjects. Additionally, a greater proportion of upadacitinib 30 mg and 15 mg subjects reported no sleep disturbance in the past 7 days (defined as POEM Sleep score = 0) compared to placebo and also showed greater improvement in the percent change from Baseline in SCORAD sleep.

Subjects on upadacitinib 30 and 15 mg achieved a greater improvement (reduction) in ADerm-IS emotional state domain score and ADerm-IS daily activities domain score compared to placebo subjects. A greater improvement (reduction) was also observed in HADS and in Work Productivity and Activity Impairment Questionnaire (WPAI): atopic dermatitis domain scores (specifically, work productivity loss, presenteeism, and activity impairment).

Upadacitinib 30 and 15 mg also demonstrated reductions in the health-related quality of life parameters, including improvement in DLQI ≥ 4 at Week 16, DLQI 0 or 1 at Week 16 CDLQI 0 or 1.

Similar improvements were observed in EQ-5D-5L scores, SF-36 assessments and patient global impression of severity (PGIS), patient global impression of change (PGIC) and patient global impression of treatment.

Study M18-891 (monotherapy)

Study M18-891 was a Phase III, randomised, double-blind, placebo-controlled multicentre study that evaluated the efficacy and safety of upadacitinib in adolescents (12 to 17 years) and adults (18 to 75 years), with moderate to severe atopic dermatitis who were candidates for systemic therapy.

Study design

The study design and primary objective of Study M18-891 were identical to that described for Study M16-045. See section: *Study M16-045 (monotherapy)* for further information.

The inclusion / exclusion criteria, study treatments, efficacy parameters and randomisation /blinding methods were identical to those described for Study M16-045.

The analysis of populations, sample size and statistical methods were identical to those described for Study M16-045.

Participant flow

Overall, 1143 subjects were screened and 836 were randomised to study treatment: 276, 282 and 278 were randomised to upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively.

Out of the 836 patients, a total of 764 (91.4%) completed study drug treatment (with or without rescue therapy), through the double blind period (Week 16). 768 subjects (91.9%) completed study participation through Week 16.

67 subjects discontinued study drug treatment in the double blind period. The most frequent reasons for discontinuation of study drug treatment were withdrawal of consent by the subject for the upadacitinib 30 mg group, adverse events for the upadacitinib 15 mg group, and mainly lack of efficacy for the placebo group.

Overall, 161 subjects (19.3%) received rescue medication, the majority of whom were from the placebo group (120 subjects). No subject discontinued from the study due to COVID-19

Regarding adolescents:

- Of the 836 subjects randomised, 104 subjects (12.4%) were adolescents;
- Study disposition observed in the adolescent subjects was similar to that observed overall, with 92.3% completing study drug (with or without rescue therapy) through the double blind Period (Week 16) and, only 7 discontinuations during double blind period (mainly due to lack of efficacy);
- 24 adolescent subjects (23.1%) received rescue medication, the majority of whom were from the placebo group (19 subjects).

Overall, 768 subjects entered the blinded extension period and 759 were dosed. As of the cut-off date:

- 10 subjects (1.3%) received rescue medication;
- no subject completed study drug (Week 136);
- 34 subjects (4.3%) discontinued study drug in the blinded extension period (most frequently due to adverse events (1.3%)).

Of the 768 subjects that entered the blinded extension period:

- 96 were adolescent subjects and all were dosed;
- one (1%) of the 96 adolescent subjects received rescue medication; and
- 4 (4%) discontinued study drug in the blinded extension period (mostly due to lack of efficacy (2.0%)).

Baseline data

Overall, the demographic characteristics were generally balanced across the upadacitinib (15 mg and 30 mg) and placebo groups and, in adolescents, as per Table 26, below.

Table 26: Study M18-891 Baseline data and demographic characteristics

	Overall					Adolescents				
	PBO (N = 278)	UPA 15 mg QD (N = 276)	UPA 30 mg QD (N = 282)	UPA Total (N = 558)	Total (N = 836)	PBO (N = 36)	UPA 15 mg QD (N = 33)	UPA 30 mg QD (N = 35)	UPA Total (N = 68)	Total (N = 104)
Sex, n (%)										
Male	154 (55.4)	155 (56.2)	162 (57.4)	317 (56.8)	471 (56.3)	16 (44.4)	14 (42.4)	18 (51.4)	32 (47.1)	48 (46.2)
Female	124 (44.6)	121 (43.8)	120 (42.6)	241 (43.2)	365 (43.7)	20 (55.6)	19 (57.6)	17 (48.6)	36 (52.9)	56 (53.8)
Age (years)										
Mean (SD)	33.4 (14.79)	33.3 (15.70)	34.1 (15.95)	33.7 (15.82)	33.6 (15.48)	15.8 (1.46)	15.3 (1.92)	15.8 (1.77)	15.6 (1.86)	15.7 (1.73)
Median	29.0	28.0	30.0	29.0	29.0	16.0	16.0	16.0	16.0	16.0
Min, Max	13, 71	12, 74	12, 75	12, 75	12, 75	13, 18	12, 18	12, 18	12, 18	12, 18
Age group (years), n (%)										
< 18	36 (12.9)	33 (12.0)	35 (12.4)	68 (12.2)	104 (12.4)	36 (100)	33 (100)	35 (100)	68 (100)	104 (100)
≥ 18	242 (87.1)	243 (88.0)	247 (87.6)	490 (87.8)	732 (87.6)	0	0	0	0	0
18 to < 40	161 (57.9)	165 (59.8)	161 (57.1)	326 (58.4)	487 (58.3)	0	0	0	0	0
40 to < 65	70 (25.2)	63 (22.8)	67 (23.8)	130 (23.3)	200 (23.9)	0	0	0	0	0
≥ 65	11 (4.0)	15 (5.4)	19 (6.7)	34 (6.1)	45 (5.4)	0	0	0	0	0
Race, n (%)										
White	195 (70.1)	184 (66.7)	198 (70.2)	382 (68.5)	577 (69.0)	30 (83.3)	24 (72.7)	26 (74.3)	50 (73.5)	80 (76.9)
Black or African American	16 (5.8)	17 (6.2)	18 (6.4)	35 (6.3)	51 (6.1)	1 (2.8)	1 (3.0)	1 (2.9)	2 (2.9)	3 (2.9)
Asian	56 (20.1)	65 (23.6)	62 (22.0)	127 (22.8)	183 (21.9)	4 (11.1)	3 (9.1)	7 (20.0)	10 (14.7)	14 (13.5)
American Indian/Alaska Native	5 (1.8)	5 (1.8)	2 (0.7)	7 (1.3)	12 (1.4)	0	1 (3.0)	1 (2.9)	2 (2.9)	2 (1.9)
Native Hawaiian or Other Pacific Islander	1 (0.4)	2 (0.7)	0	2 (0.4)	3 (0.4)	0	2 (6.1)	0	2 (2.9)	2 (1.9)
Other	0	0	0	0	0	0	0	0	0	0
Multiple	5 (1.8)	3 (1.1)	2 (0.7)	5 (0.9)	10 (1.2)	1 (2.8)	2 (6.1)	0	2 (2.9)	3 (2.9)
Ethnicity, n (%)										
Hispanic or Latino	31 (11.2)	24 (8.7)	23 (8.2)	47 (8.4)	78 (9.3)	6 (16.7)	5 (15.2)	5 (14.3)	10 (14.7)	16 (15.4)
Not Hispanic or Latino	247 (88.8)	252 (91.3)	259 (91.8)	511 (91.6)	758 (90.7)	30 (83.3)	28 (84.8)	30 (85.7)	58 (85.3)	88 (84.6)
Weight (kg)										
n	277	276	282	558	835	36	33	35	68	104
Mean (SD)	76.66 (19.560)	73.98 (18.521)	75.31 (18.355)	74.65 (18.432)	75.32 (18.826)	64.10 (14.679)	61.97 (15.172)	61.00 (12.454)	61.47 (13.744)	62.38 (14.060)
Median	74.10	71.15	72.70	71.80	72.90	60.45	57.60	61.70	61.00	60.95
Min, Max	41.0, 175.0	37.0, 136.1	37.4, 142.0	37.0, 142.0	37.0, 175.0	45.4, 105.3	40.0, 110.4	37.4, 97.0	37.4, 110.4	37.4, 110.4
BMI group (kg/m^2), n (%)										
< 25	129 (46.6)	147 (53.3)	141 (50.0)	288 (51.6)	417 (49.9)	27 (75.0)	26 (78.8)	29 (82.9)	55 (80.9)	82 (78.8)
25 to < 30	80 (28.9)	76 (27.5)	89 (31.6)	165 (29.6)	245 (29.3)	4 (11.1)	3 (9.1)	5 (14.3)	8 (11.8)	12 (11.5)
≥ 30	68 (24.5)	53 (19.2)	52 (18.4)	105 (18.8)	173 (20.7)	5 (13.9)	4 (12.1)	1 (2.9)	5 (7.4)	10 (9.6)
Missing	1	0	0	0	1					
Tobacco use, n (%)[a,b]										
Current	64 (23.0)	62 (22.7)	57 (20.3)	119 (21.5)	183 (22.0)	3 (8.3)	1 (3.1)	2 (5.7)	3 (4.5)	6 (5.8)
Former	32 (11.5)	36 (13.2)	32 (11.4)	68 (12.3)	100 (12.0)	1 (2.8)	0	0	0	1 (1.0)
Never	182 (65.5)	175 (64.1)	192 (68.3)	367 (66.2)	549 (66.0)	32 (88.9)	31 (96.9)	33 (94.3)	64 (95.5)	96 (93.2)
Unknown	0	3	1	4	4	0	1	0	1	1
Alcohol use, n (%)[a]										
Current	138 (49.8)	141 (51.3)	142 (50.9)	283 (51.1)	421 (50.7)	1 (2.8)	3 (9.4)	2 (5.7)	5 (7.5)	6 (5.8)
Former	12 (4.3)	15 (5.5)	16 (5.7)	31 (5.6)	43 (5.2)	2 (5.6)	1 (3.1)	0	1 (1.5)	3 (2.9)
Never	127 (45.8)	119 (43.3)	121 (43.4)	240 (43.3)	367 (44.2)	33 (91.7)	28 (87.5)	33 (94.3)	61 (91.0)	94 (91.3)
Unknown	1	1	3	4	5	0	1	0	1	1

BMI = body mass index; ITT_M = Intent-to-Treat Population for the Main Study; Max = maximum; Min = minimum; PBO = placebo; QD = once daily; SD = standard deviation; UPA = upadacitinib

a. Percentages calculated on non-missing/non-unknown values. A subject was counted in the category closest to user.

b. A subject may be a current user of 1 type of tobacco, a former user of another type of tobacco, and never used another type of tobacco.

Note: Percentages were calculated on non-missing values.

The majority of subjects were male (56.3%) and aged 18 to 39 years (58.3%). In the adolescent group, the majority of subjects were female (53.8%).

Baseline disease characteristics were generally balanced across the upadacitinib and placebo groups overall and, in adolescents. Subjects had been diagnosed with atopic dermatitis for a mean of approximately 20.2 years overall and 12.5 years for adolescents and disease activity consistently reflected moderate (45%) to severe (55%) atopic dermatitis across the treatment groups. EASI, SCORAD (overall, objective, itch and sleep scores), DLQI, CDLQI, HAD scores were similar across all 3 treatment groups. Overall, the most common medical/surgical history by body system was respiratory, thoracic and mediastinal disorders (59.4%; asthma (39.8%) and rhinitis allergic (34.0%) most

common), followed by immune system disorders (46.5%) with similar incidence across treatment groups.

Overall, all 836 (100%) of subjects had received prior atopic dermatitis therapy with majority using topical corticosteroids [81.5%, 31.3% and 26.6% used high potency, medium potency and low potency topical corticosteroids, topical calcinuerin inhibitor (34.4%), other topical therapy (17%) and phototherapy (19.3%).

There were 448 subjects (53.6%) who received prior non-biologic immunomodulating systemic therapies (0 to 100% of subjects per agent had lack of initial response).

Twenty-six subjects (3.1%) received prior biologic systemic therapies (0% to 87.5% of subjects per agent had a lack of initial response).

Concomitant medication usage was similar across all treatment groups; emollients and protectives were the most frequently reported prior medications (39.2% of subjects) and concomitant medications (38.9% and 37.9% of subjects in the double blind period and blinded extension period, respectively).

Treatment compliance rates were high in double blind Period with mean compliance greater than 95% and median compliance greater than 98%, in all three groups.

The clinical evaluation noted that:

- Compared to Study M16-045, this study included slightly greater number of severe patients (based on vIGA-AD score: 45% versus 55%) with greater use of prior non-biologic immunomodulating systemic therapy (45.5% versus 53.6%).

Major protocol violations/deviations

The incidence of protocol deviations was slightly higher in the placebo group (15.8%; 44/278) compared with the upadacitinib 15 mg (12.0%; 33/276) and 30 mg (11.7%; 33/282) groups. Total number of subjects excluded from the per protocol population was also slightly higher in the placebo group (5.4%; 15/278) compared with the upadacitinib 15 mg (2.5%; 7/276) and 30 mg (3.2%; 9/282) groups.

The most common protocol deviation was subject being entered into the study even though he/she did not satisfy the entry criteria. The most common eligibility criterion (criterion 7) not being met related to the atopic disease activity parameters.

The majority of the deviations related to eligibility criterion 7 were due to missing a minimum of 4 daily Worst Pruritus NRS assessments out of the 7 consecutive days, immediately preceding the baseline visit to calculate the baseline weekly average of daily Worst Pruritus NRS ≥ 4, while all other disease activity criteria were met. This included 5 adolescent subjects with a baseline NRS < 4 or a missing baseline NRS.

Results for the efficacy outcomes

Co-primary endpoints

The co-primary endpoints for stated for Study M18-891 were considered to have been achieved.

A statistically significantly larger proportion of subjects in the upadacitinib groups achieved EASI 75 (60.1%, 72.9% and 13.3% in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively; $p < 0.001$ for both upadacitinib versus placebo groups. See Section: *Eczema Area and Severity Index (EASI)* for details of this score.

Patients with moderate and severe eczema demonstrated significant improvements over placebo, as per Table 27, below.

Table 27: Study M18-891 Proportion of subjects achieving an EASI 75 response by visit in double blind period (NRI-C; main ITT population)

Time Point / Strata / Treatment	N	---- Responder ---- n (%) [95% CI]&	Missing Due to COVID-19 n	Response Rate Diff Compared to Placebo: Diff(%)	Adjusted Diff(%)	[95% CI]#	P-value@	Breslow-Day P-value
Week 16								
All								
Placebo	278	37 (13.3) [9.3, 17.3]	1					
UPA 15 mg QD	276	166 (60.1) [54.4, 65.9]	0	46.8	46.9	[39.9, 53.9]	<0.001***	0.401
UPA 30 mg QD	282	206 (72.9) [67.7, 78.2]	4	59.6	59.6	[53.1, 66.2]	<0.001***	0.197
vIGA-AD 3 (Moderate)								
Placebo	125	21 (16.8) [10.2, 23.4]	0					
UPA 15 mg QD	126	74 (58.7) [50.1, 67.3]	0	41.9		[31.1, 52.7]	<0.001***	
UPA 30 mg QD	126	89 (70.5) [62.4, 78.6]	3	53.7		[43.3, 64.1]	<0.001***	
vIGA-AD 4 (Severe)								
Placebo	153	16 (10.5) [5.6, 15.3]	1					
UPA 15 mg QD	150	92 (61.3) [53.5, 69.1]	0	50.9		[41.7, 60.1]	<0.001***	
UPA 30 mg QD	156	117 (74.9) [68.1, 81.7]	1	64.5		[56.1, 72.8]	<0.001***	

Abbreviations: CI = confidence intervals; EASI 75 = Eczema Area and Severity Index 75 response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

A statistically significantly larger proportion of subjects in the upadacitinib groups achieved a vIGA-AD score of 0 or 1 (clear or almost clear) with a clinically meaningful reduction (at least 2 grade reductions from Baseline) at Week 16 compared with the placebo group, based on the primary approach of NRI-C (48.1%, 62% and 8.4% in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively; $p < 0.001$ for both upadacitinib groups versus placebo); see Section: *Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)* for details on this score.

Patients with moderate and severe eczema demonstrated significant improvements over placebo, as per Table 28 below.

Table 28: Study M18-891 Proportion of subjects achieving vIGA-AD of 0 or 1 with at least 2 grades of reduction from Baseline by visit (observed cases) (NRI-C; main ITT population)

Time Point / Strata / Treatment	N	------ Responder ------ n (%) [95% CI]
Week 16		
All		
Placebo	238	16 (6.7) [3.5, 9.9]
UPA 15 mg QD	260	108 (41.5) [35.5, 47.5]
UPA 30 mg QD	262	146 (55.7) [49.7, 61.7]
vIGA-AD 3 (Moderate)		
Placebo	114	9 (7.9) [2.9, 12.8]
UPA 15 mg QD	120	53 (44.2) [35.3, 53.1]
UPA 30 mg QD	120	68 (56.7) [47.8, 65.5]
vIGA-AD 4 (Severe)		
Placebo	124	7 (5.6) [1.6, 9.7]
UPA 15 mg QD	140	55 (39.3) [31.2, 47.4]
UPA 30 mg QD	142	78 (54.9) [46.7, 63.1]
US/Puerto Rico/Canada		
Placebo	97	9 (9.3) [3.5, 15.1]
UPA 15 mg QD	98	43 (43.9) [34.1, 53.7]
UPA 30 mg QD	106	55 (51.9) [42.4, 61.4]

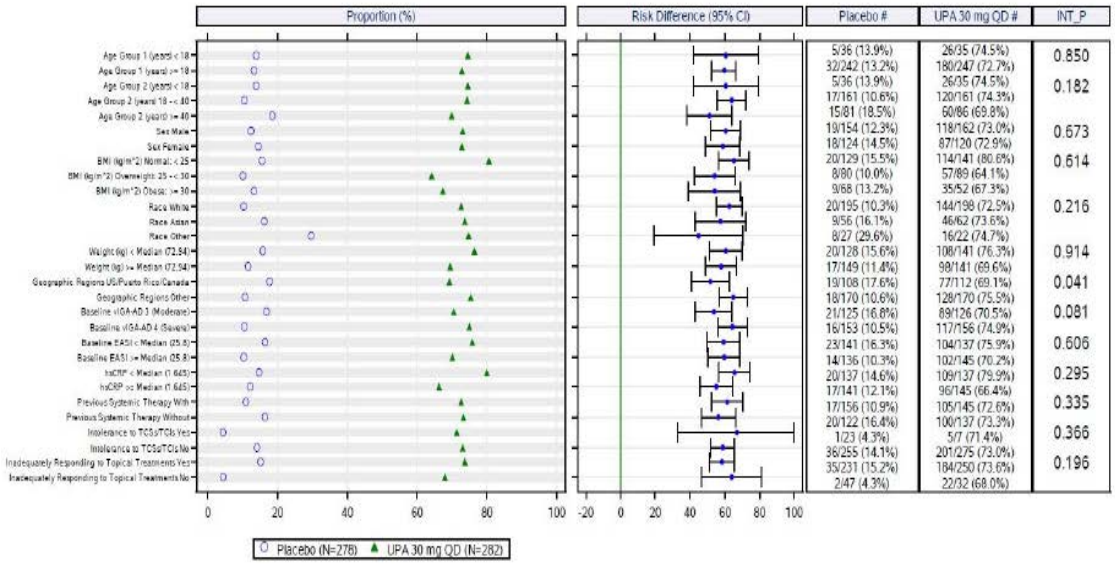
Note: vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis; EASI = Eczema Area and Severity Index.
OC is observed case. Measurements are used while subjects are on study drug.
95% CI for response rate is based on the normal approximation to the binomial distribution.

Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib; vIGA-AD = validated investigator's global assessment.

The robustness of the co-primary endpoints results was supported by consistent results favouring both upadacitinib groups compared to placebo in all sensitivity analyses, including NRI-C, multiple imputation, tipping point analysis, and per protocol analysis.

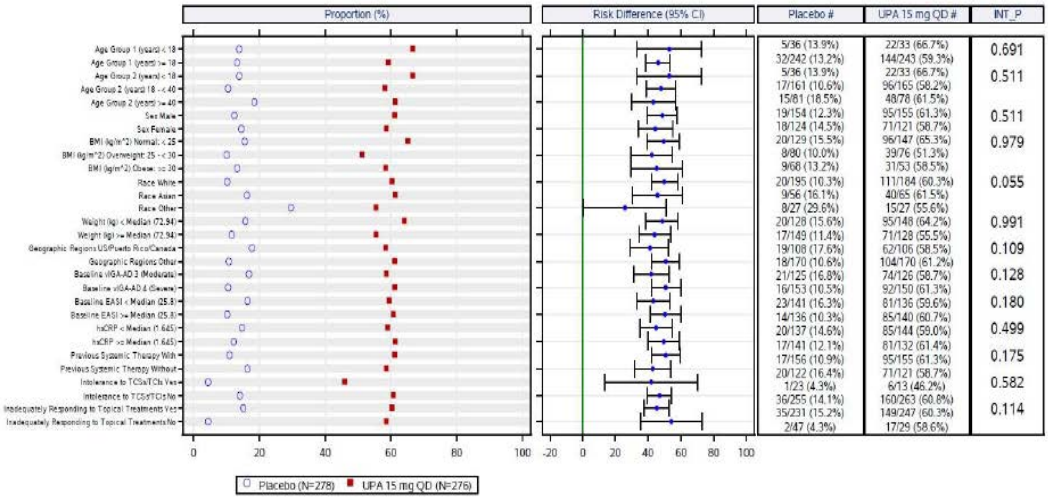
Treatment effects in all pre-specified sub-groups (across demographic and baseline characteristics), including adolescents consistently favoured both upadacitinib doses compared to placebo in EASI 75, and vIGA-AD with all 95% confidence intervals (CIs) excluding zero, as shown across the following figures.

Figure 16: Study M18-891 Proportion of subjects achieving an EASI 75 response at Week 16 by subgroup in the upadacitinib 30 mg group (NRI-C, main ITT population)



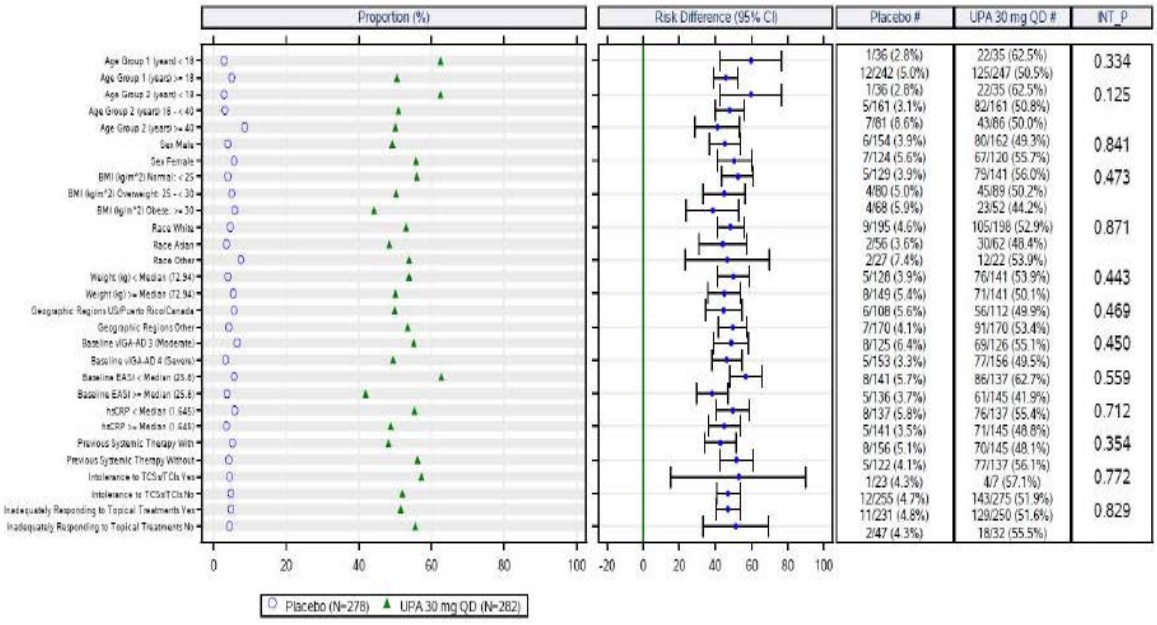
Abbreviations: CI = confidence intervals; EASI 75 = Eczema Area and Severity Index 75 response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

Figure 17: Study M18-891 Proportion of subjects achieving an EASI 75 response at Week 16 by subgroup in the upadacitinib 15 mg group (NRI-C, main ITT population)



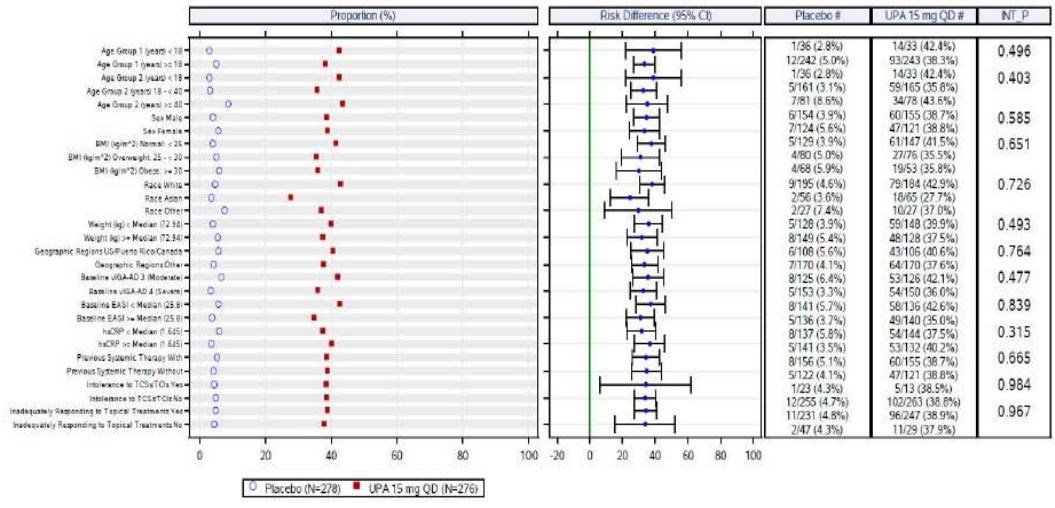
Abbreviations: CI = confidence intervals; EASI 75 = Eczema Area and Severity Index 75 response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

Figure 18: Study M18-891 Proportion of subjects achieving VIGA-AD of 0 or 1 with at least 2 grades of reduction from Baseline in upadacitinib 30 mg group (NRI-C, main ITT population population)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib; vIGA-AD = validated investigator's global assessment.

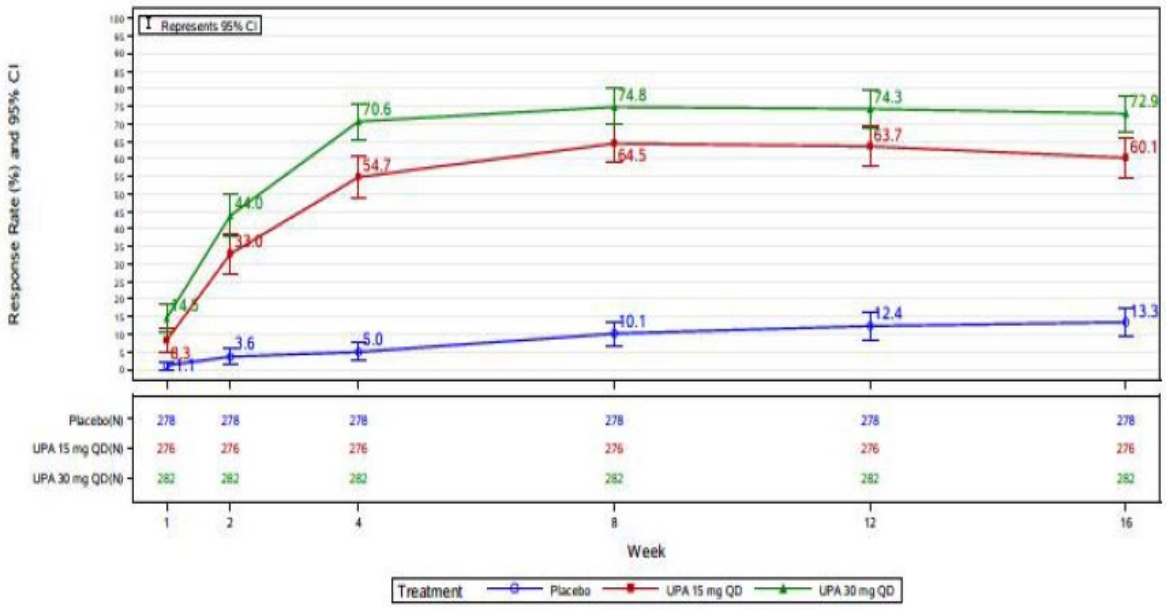
Figure 19: Study M18-891 Proportion of subjects achieving VIGA-AD of 0 or 1 with at least 2 grades of reduction from Baseline in upadacitinib 15 mg group (NRI-C, main ITT population)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib; vIGA-AD = validated investigator's global assessment.

The onset of action was rapid with statistically significant improvement in EASI 75 observed from Week 2 onwards and was maintained until Week 16, as shown in Figure 20, below.

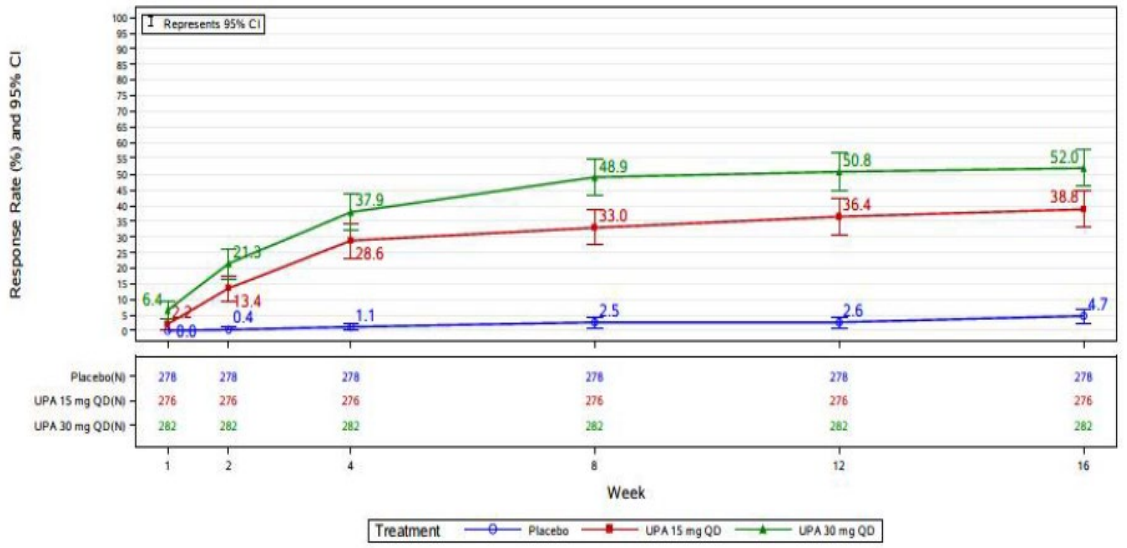
Figure 20: Study M18-891 Proportion of subjects reporting an EASI 75 response from Baseline to Week 16 (NRI-C; main ITT population)



Abbreviations: CI = confidence intervals; EASI 75 = Eczema Area and Severity Index 75 response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

Similar results were observed for vIGA-AD of 0 or 1 with at least 2 Grades of reduction from Baseline, as shown in Figure 21, below.

Figure 21: Study M18-891 Proportion of subjects with vIGA-AD scores of 0 or 1 with at least 2 Grades of reduction from Baseline by Week 16 (NRI-C, main ITT population)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib; vIGA-AD = validated investigator's global assessment.

Key secondary endpoints

Study M18-891 demonstrated superiority of each upadacitinib dose versus placebo, with statistically significant and clinically relevant improvements in atopic dermatitis activity in the skin, pruritus, and health-related quality of life.

Upadacitinib 30 mg showed numerically better results for the improvement for most of the secondary/other efficacy endpoints than upadacitinib 15 mg, as shown in the table below.

Table 29: Study M18-891 Key secondary endpoint results (US FDA- and EMA-agreed efficacy outcomes; main ITT population)

EMA Testing[a]	FDA Testing[a]	Secondary Endpoints	PBO (N = 278) n (%) or LS Mean (SE)	UPA 15 mg (N = 276) n (%) or LS Mean (SE); Adj Diff (P-value)	UPA 30 mg (N = 282) n (%) or LS Mean (SE); Adj Diff (P-value)
V3	V3	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Week 16	N = 274 25 (9.1)	N = 270 113 (41.9); 32.6 (< 0.001***)	N = 280 167 (59.6); 50.4 (< 0.001***)
V4	V4	EASI 90 at Week 16	N = 278 15 (5.4)	N = 276 117 (42.4); 36.9 (< 0.001***)	N = 282 165 (58.5); 53.1 (< 0.001***)
V5	NA	Percent change in Worst Pruritus NRS at Week 16	N = 119 –17.04 (2.727)	N = 224 –51.20 (2.341); –34.16 (< 0.001***)	N = 235 –66.49 (2.309); –49.45 (< 0.001***)
NA	V5	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Week 4	N = 274 10 (3.6)	N = 270 132 (48.9); 45.2 (< 0.001***)	N = 280 170 (60.7); 57.0 (< 0.001***)
V6	NA	Percent change in EASI at Week 16	N = 142 –34.51 (2.593)	N = 246 –74.13 (2.197); –39.62 (< 0.001***)	N = 250 –84.65 (2.180); –50.14 (< 0.001***)
V7	V6	EASI 75 at Week 2	N = 278 10 (3.6)	N = 276 91 (33.0); 29.4 (< 0.001***)	N = 282 124 (44.0); 40.4 (< 0.001***)
V8	V7	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Week 1	N = 274 2 (0.7)	N = 270 20 (7.4); 6.7 (< 0.001***)	N = 280 44 (15.7); 14.9 (< 0.001***)
V9	NA	Improvement in POEM ≥ 4 at Week 16	N = 268 77 (28.7)	N = 268 190 (70.9); 42.1 (< 0.001***)	N = 269 225 (83.5); 54.7 (< 0.001***)
V10	NA	Improvement in DLQI ≥ 4 at Week 16	N = 250 71 (28.4)	N = 251 180 (71.7); 42.8 (< 0.001***)	N = 251 195 (77.6); 49.0 (< 0.001***)
V11	V8	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Day 2	N = 267 2 (0.7)	N = 269 20 (7.4); 6.7 (< 0.001***)	N = 278 22 (7.9); 7.2 (< 0.001***)
V12	V9	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Day 3	N = 267 8 (3.0)	N = 269 31 (11.5); 8.6 (< 0.001***)	N = 278 48 (17.3); 14.3 (< 0.001***)
V13	V10	Flare during DB Period	N = 269 66 (24.5)	N = 274 6 (2.2); –22.4 (< 0.001***)	N = 277 4 (1.4); –23.1 (< 0.001***)
V14	NA	Percent change in SCORAD at Week 16	N = 136 –28.43 (2.501)	N = 245 –57.90 (2.005); –29.47 (< 0.001***)	N = 241 –68.44 (2.039); –40.01 (< 0.001***
V15	NA	HADS-A < 8 and HADS-D < 8 at Week 16	N = 140 16 (11.4)	N = 137 63 (46.0); 34.4 (< 0.001***)	N = 146 82 (56.1); 44.5 (< 0.001***)
V16-H a.	V11-H a.	Improvement in ADerm-IS Sleep Domain Score ≥ 12 at Week 16	N = 233 29 (12.4)	N = 219 110 (50.2); 37.9 (< 0.001***)	N = 228 142 (62.3); 49.8 (< 0.001***)
V16-H b.	V11-H b.	Improvement in ADerm-SS Skin Pain Score ≥ 4 at Week 16	N = 247 33 (13.4)	N = 237 117 (49.4); 35.9 (< 0.001***)	N = 238 155 (65.1); 51.8 (< 0.001***)
V16-H c.	V11-H c.	Improvement in ADerm-SS TSS-7 ≥ 28 at Week 16	N = 244 31 (12.7)	N = 230 122 (53.0); 40.3 (< 0.001***)	N = 234 155 (66.2); 53.3 (< 0.001***)
V16-H d.	V11-H d.	Improvement in ADerm-IS Emotional State Domain Score ≥ 11 at Week 16	N = 234 39 (16.7)	N = 228 130 (57.0); 40.3 (< 0.001***)	N = 228 163 (71.5); 54.8 (< 0.001***)
V16-H e.	V11-H e.	Improvement in ADerm-IS Daily Activities Domain Score ≥ 14 at Week 16	N = 227 43 (18.9)	N = 207 118 (57.0); 37.9 (< 0.001***)	N = 223 155 (69.5); 50.6 (< 0.001***)
V17	V12	EASI 100 at Week 16	N = 278 2 (0.7)	N = 276 39 (14.1); 13.4 (< 0.001***)	N = 282 53 (18.8); 18.1 (< 0.001***)
V18	NA	DLQI 0 or 1 at Week 16	N = 257 12 (4.7)	N = 252 60 (23.8); 19.1 (< 0.001***)	N = 256 97 (37.9); 33.3 (< 0.001***)

ADerm-IS = Atopic Dermatitis Impact Scale; ADerm-SS = Atopic Dermatitis Symptom Scale; Adj Diff = adjusted difference; DB = double-blind; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EMA = European Medicines Agency; EASI 75 = 75% improvement in Eczema Area and Severity Index from Baseline; FDA = Food and Drug Administration; HADS-A = Hospital Anxiety and Depression Scale-anxiety; HADS-D = Hospital Anxiety and Depression Scale-depression; ITT_M = Intent-to-Treat Population for the Main Study; LS = least square; MMRM = Mixed Effect Model Repeat Measurement; NA = not applicable (endpoint not included under multiplicity control for overall type I error); NRI-C = Non-Responder Imputation incorporating Multiple Imputation to handle missing data due to coronavirus disease 2019; NRS = Numerical Rating Scale; PBO = placebo; POEM = Patient Orientated Eczema Measure; SAP = Statistical Analysis Plan; SCORAD = Scoring Atopic Dermatitis; SE = standard error; TSS-7 = 7-item total symptom score; UPA = upadacitinib; V = variable; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis

a. Variables in the EMA and FDA graphical approach for overall type I error control details in SAP Section 4.6. V1 and V2, not listed, are the co-primary endpoints (EASI 75 and vIGA-AD 0/1 at Week 16).

*** p-value ≤ 0.001; UPA vs. PBO.

Note: Results for the binary endpoints are based on NRI-C and results for the continuous endpoints are based on MMRM, except for the endpoint on flare which was analyzed as observed prior to the initiation of rescue medication.

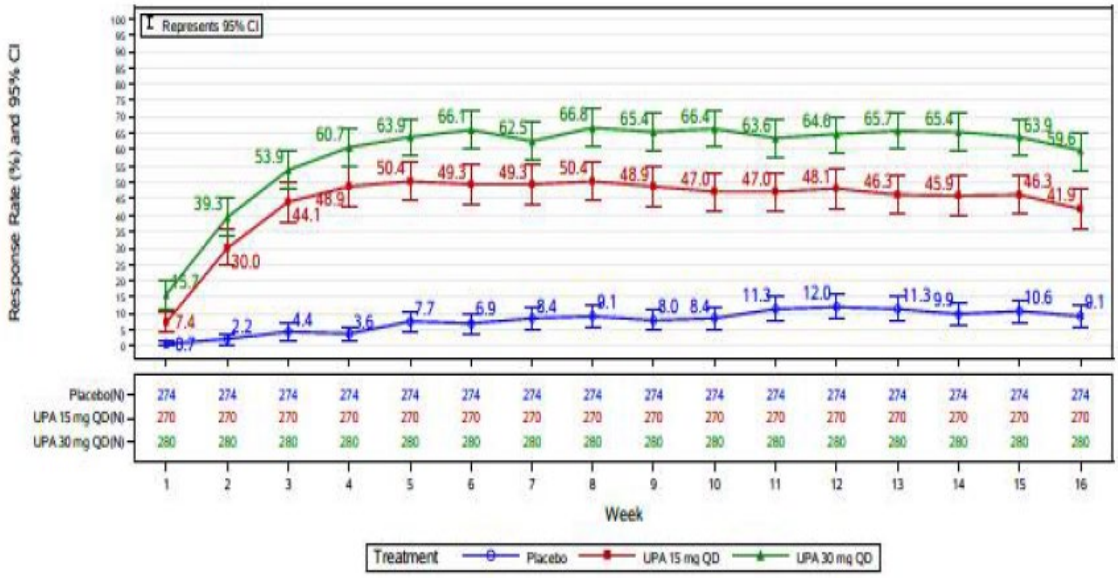
Upadacitinib 30 mg and 15 mg showed statistically significant improvements over placebo for all secondary endpoints of skin clearance and disease activity.

The proportion of subjects who achieved SCORAD 50/75/90 continued to increase from Week 2 to Week 16 in subjects on upadacitinib 30 mg and 15 mg compared to placebo. This pattern was consistent with the percent change improvements in SCORAD and its individual components (Objective SCORAD, SCORAD Itch, and SCORAD Sleep). See Section: *Scoring Atopic Dermatitis (SCORAD)* for further details on this score.

The body surface area affected by atopic dermatitis showed significantly greater reduction in the upadacitinib groups compared with placebo.

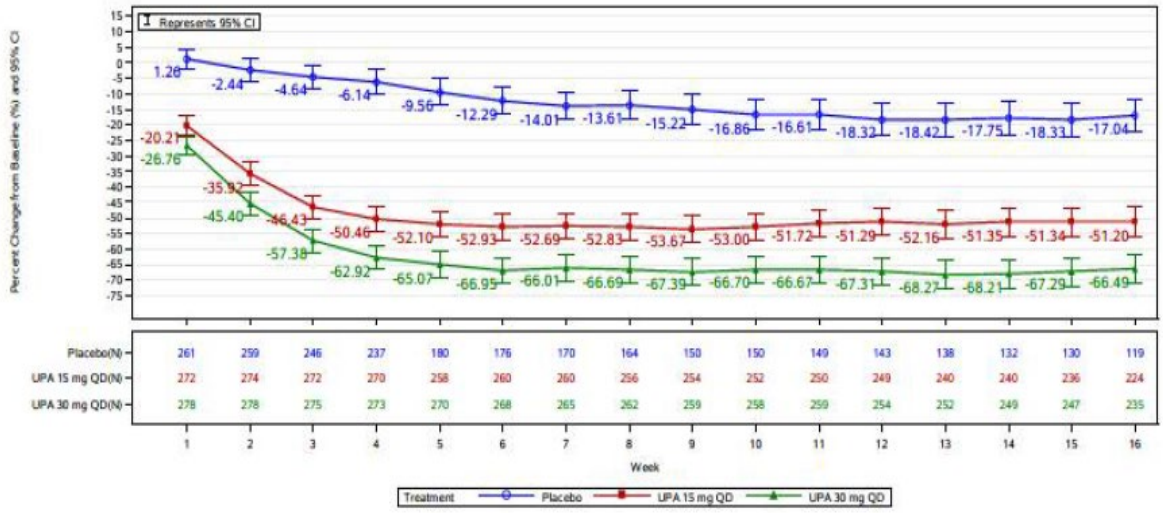
Upadacitinib 30 mg and 15 mg demonstrated superiority in all secondary endpoints of itch reduction, including improvement (reduction) in Worst Pruritus NRS ≥ 4 at Day 2, Day 3, Week 1, Week 4, and Week 16 and percent change in Worst Pruritus at Week 16.

Figure 22: Study M18-891 Proportion of subjects reporting an improvement (reduction) in Worst Pruritus NRS score of 4 or more from Baseline to Week 16 (NRI-C, main ITT population)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; NRS = numerical rating scale; QD = once daily; UPA = upadacitinib.

Figure 23: Study M18-891 Improvement (reduction) in Worst Pruritus NRS scores from Baseline to Week 16 (ITT population, NRI-C)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; NRS = numerical rating scale; QD = once daily; UPA = upadacitinib.

A greater proportion of subjects reported a Worst Pruritus NRS score of 0 or 1 compared with placebo, as early as Week 1 through to Week 16 with consistent results observed in adolescents.

Subjects on upadacitinib 30 mg and 15 mg achieved greater itch reduction as measured by the SCORAD itch assessment over placebo at Week 2 and Week 16.

A significantly greater proportion of subjects on upadacitinib 30 mg and 15 mg achieved clinically meaningful reductions in symptoms of AD, demonstrated as improvement in POEM ≥ 4 at Week 16 (EMA only), improvement in ADerm-SS skin pain score ≥ 4 at Week 16, and improvement in ADerm-SS TSS-7 ≥ 28 at Week 16.

The proportion of subjects on upadacitinib 30 mg and 15 mg who achieved improvement (reduction) in ADerm-SS TSS-11 was greater than subjects on placebo and was consistent, with an improvement (reduction) in ADerm-SS TSS-7 in subjects on upadacitinib 30 mg and 15 mg compared to placebo subjects.

Subjects on upadacitinib 30 mg and 15 mg achieved a greater improvement (reduction) in skin pain compared to placebo subjects. In addition, subjects on upadacitinib 30 mg and 15 mg achieved a greater improvement (reduction) in POEM compared to placebo subjects.

Subjects on upadacitinib 30 mg and 15 mg achieved a greater improvement (reduction) in ADerm-IS sleep domain score compared to placebo subjects. Additionally, a greater proportion of upadacitinib 30 mg and 15 mg subjects reported no sleep disturbance in the past 7 days (defined as POEM Sleep score = 0) compared to placebo. A greater improvement in the percent change from baseline in SCORAD sleep was observed in subjects on upadacitinib 30 mg and 15 mg compared to placebo subjects.

Subjects on upadacitinib 30 and 15 mg achieved a greater improvement (reduction) in ADerm-IS emotional state domain score and ADerm-IS daily activities domain score compared to placebo subjects. A greater improvement (reduction) was also observed in HADS and in Work Productivity and Activity Impairment Questionnaire (WPAI) atopic dermatitis domain scores (work productivity loss, presenteeism, and activity impairment).

Upadacitinib 30 and 15 mg also demonstrated reductions in the health-related quality of life parameters, including improvement in DLQI ≥ 4 at Week 16, DLQI 0 or 1 at Week 16 CDLQI 0 or 1. Similar improvements were observed in EQ-5D-5L scores, SF-36 and patient global impression of severity (PGIS), patient global impression of change (PGIC) and patient global impression of treatment (PGIT).

See sections: *Patient Oriented Eczema Measure (POEM); Atopic Dermatitis Symptom Scale (ADerm-SS)Atopic Dermatitis Impact Scale (ADerm-IS); Dermatology Life Quality Index;* and *Hospital Anxiety and Depression Scale (HADS)* for details of these measures.

Study M16-047 (combination therapy)

Study M16-047 is a Phase III, randomised, double blind, placebo-controlled multicentre study that evaluated the efficacy and safety of upadacitinib combined with topical corticosteroids in adolescents (12 to 17 years of age at the time of the screening visit) and adults (18 to 75 years of age), with moderate to severe atopic dermatitis who were candidates for systemic therapy. Those subjects less than 18 years of age were required to have a body weight ≥ 40 kg at Baseline.

The study design included a 35-day screening period; 16-week double blind period; blinded extension (blinded extension) period of up to Week 136; and a 30-day follow-up visit.

After the target enrolment (810 subjects) was achieved in the main portion of Study M16-047, a supplemental study was opened to continue enrolling adolescent subjects (adolescent sub-study) to ensure enrolment in total of 180 adolescent subjects in the overall study.

Primary objective

The primary objective was:

- To assess the efficacy and safety of upadacitinib combined with topical corticosteroids for the treatment of adolescent and adult subjects with moderate to severe atopic dermatitis, who are candidates for systemic therapy.

The objective of the double blind period (through Week 16) was to compare the safety and efficacy of upadacitinib (15 mg and 30 mg once daily plus topical corticosteroids; versus placebo plus topical corticosteroids.

The objective of the 136 week blinded extension period was to evaluate the long-term safety, tolerability, and efficacy of upadacitinib (15 mg and 30 mg) once daily in adolescents and adults, with moderate to severe atopic dermatitis who had completed the double blind period.

Inclusion criteria

These are similar to those in the monotherapy trials except that:

- eligible subjects must have had a documented history of inadequate response to treatment with topical corticosteroids or topical calcineurin inhibitors or use of systemic treatment for atopic dermatitis within 6 months prior to Baseline; and
- subjects must not have ≥ 30% of atopic dermatitis lesional surface involvement at Baseline that cannot be safely treated with medium or higher potency topical corticosteroids (for example, areas of skin atrophy, face, groin, intertriginous areas).

Study treatments

Subjects who met eligibility criteria were randomised in a 1:1:1 ratio to receive concomitant topical corticosteroids with a daily oral dose of upadacitinib 15 mg or 30 mg

(or matching placebo) once daily (beginning on Day 1 (Baseline), at approximately the same time each day with or without food.

Concomitant topical corticosteroids therapy was started at Baseline and, continued through Week 52 using a step-down regimen:

- A medium potency topical corticosteroids (for example triamcinolone acetonide 0.1% cream, fluocinolone acetonide 0.025% ointment) was applied daily to active lesions for a maximum of 3 consecutive weeks;
- Low potency topical corticosteroids or topical calcineurin inhibitors could be applied to sensitive skin areas or areas where medium potency topical corticosteroids would be considered unsafe;

After lesions were clear or almost clear, or after 3 consecutive weeks of medium or low (sensitive areas) potency topical corticosteroids, a low potency topical corticosteroids (for example, hydrocortisone 1% cream) was to be used daily for 7 days and then stopped;

The step-down regimen starting with medium potency topical corticosteroids was to be resumed if atopic dermatitis lesions returned or persisted (until Week 52).

The Delegate for this submission commented that:

> If topical corticosteroids therapy only continued until Week 52, then only part of the Week 136 long term period was covered by combination therapy of upadacitinib and topical corticosteroids.

Rescue therapy

Rescue therapy was permitted:

- from Week 4 through Week 24, if:
  - medically necessary; and
  - there was a less than an EASI 50 response (that is, less than a 50% reduction in EASI scores compared to Baseline) at any two consecutive scheduled visits compared to Baseline.
- after Week 24, rescue therapy was permitted if:
  - medically necessary; and
  - there was a < EASI 50 response at any visit compared to Baseline.

Randomisation and blinding methods

Randomisation for the main part of Study M16-047 was stratified by:

- baseline disease severity (moderate (vIGA-AD score of 3) versus severe (vIGA-score of 4);
- age (adolescent aged 12 to 17 versus adult aged 18 to 75);
- geographic region (USA/Puerto-Rico/Canada, Japan, China (mainland), and other).

At the end of the double blind period (that is, Week 16), subjects in the placebo group were randomised in a 1:1 ratio (stratified by Week 16 EASI 50 responders (yes/no) plus, the above stated stratification parameters) to receive daily oral doses of either upadacitinib 15 mg or 30 mg in the blinded extension period (up to Week 136).

Subjects originally randomised to upadacitinib continued upadacitinib in the blinded extension period at the same dose.

Regarding blinded extension blinding:

- study sites and subjects were to remain blinded for the duration of the study; and
- the study team only had access to unblinded subject level data for adverse events of special interests and adverse events for regulatory submissions;

In order to maintain the blind, the upadacitinib tablets and placebo tablets provided for the study were identical in appearance.

Efficacy parameters and endpoints

See Section: *Scoring systems used in the clinical studies* for further details on scoring systems and measures.

Co-primary and key secondary endpoints:

- to demonstrate superiority of each upadacitinib dose versus placebo.

Co-primary endpoints:

- the proportion of subjects achieving at least a 75% reduction in EASI (EASI 75) from Baseline at Week 16; and
- the proportion of subjects achieving vIGA-AD of 0 or 1 (clear or almost clear) with at least two grades of reduction from Baseline at Week 16.

Key secondary endpoints

Note that these key secondary endpoints were negotiated with the EMA for the EU, and the US FDA for the USA. Key secondary endpoints for EU/EMA regulatory purposes were identical to those described for US/FDA regulatory purposes. EMA/EU regulatory purposes, with the exception of 2 secondary endpoints which were not included in the US/FDA list (percent change in EASI score and of Worst Pruritus NRS at Week 16).

The following key multiplicity-adjusted secondary endpoints were analysed to demonstrate superiority of each upadacitinib dose versus placebo, unless otherwise specified:

- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus Numerical Rating
- Scale (NRS) ≥ 4 from Baseline at Week 16 for subjects with Worst Pruritus NRS ≥ 4 at Baseline;
- Proportion of subjects achieving a 90% reduction in EASI (EASI 90) at Week 16;
- Percent change from Baseline of Worst Pruritus NRS at Week 16;
- Percent change in EASI score from Baseline at Week 16;
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from
- Baseline at Week 4 for subjects with Worst Pruritus NRS ≥ 4 at Baseline;
- Proportion of subjects achieving EASI 75 at Week 4;
- Proportion of subjects achieving EASI 75 at Week 2;
- Proportion of subjects achieving EASI 90 at Week 4;
- Proportion of subjects achieving EASI 100 at Week 16 for 30 mg;
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Week 1 for subjects with Worst Pruritus NRS ≥ 4 at Baseline.

Participant flow

Overall, 1160 subjects were screened and 901 subjects were randomised to the study treatments:

- n = 300 to upadacitinib 15 mg + topical corticosteroids
- n = 297 to upadacitinib 30 mg + topical corticosteroids
- n = 304 to placebo + topical corticosteroids.

Almost all subjects completed study treatment in the double blind period (94.8%):

- adverse events (< 5 subjects in any treatment groups) were the most common reasons for study drug discontinuation for all subjects, including adolescents);
- more subjects on placebo (25.7%) received rescue therapy than subjects on upadacitinib (5.3 to 5.4%);
- most adolescents (95.7%) completed study drug in the double blind period (4 adolescents discontinued the study drug due (2 subjects were lost to follow-up, one subject for a treatment-emergent adverse event, and one subject withdrew consent)).

Six subjects who discontinued study drug in the double blind period, continued to be followed in the study as permitted by the protocol while off study drug treatment.

A total of 854 subjects (97.4%) including 111 adolescents, continued into the blinded extension period:

- at the cut-off date, 50 subjects (5.7 %) including 7 adolescents discontinued study treatment;
- the most frequent reason for treatment discontinuation in the blinded extension period was lack of efficacy, which was more frequently reported in the placebo + topical corticosteroids/upadacitinib 15 mg once daily +topical corticosteroids and upadacitinib 15 mg once daily + topical corticosteroids. For the later, the respective (percentage %) values were:
  - Overall subjects, 2.8 and 5;
  - Adolescent subjects, 10.5 and 5.1.
- For the other treatment ratio (placebo + topical corticosteroids/upadacitinib 30 mg once daily + topical corticosteroids) or combination (upadacitinib 30 mg once daily + topical corticosteroids):
  - Overall subjects, 0 and 0.7;
  - Adolescent subjects, 0 and 0.

No subjects discontinued study drug due to protocol mandated systemic rescue therapy, as a primary reason for discontinuation.

One subject in the upadacitinib 30 mg group who withdrew consent from the study, also indicated COVID-19 logistical restrictions as a secondary reason for discontinuation.

At the time of the cut-off date:

- none of the subjects completed the blinded extension period;
- 10 subjects who discontinued study drug continued to be followed in the off study treatment period.

Analysis of populations

The main ITT population (ITT_M) was used for the efficacy analyses. Subjects in this population were analysed according to randomisation in the main part of Study M16-047.

Subjects who were randomised to placebo in the double blind period and who did not continue into the blinded extension period were not included in the analysis in the blinded extension period.

The per protocol population (PP_M) of the main part of Study M16-047 was a subset of the ITT_M population, that excluded subjects with major protocol deviations that could potentially affect the co-primary efficacy endpoints.

The safety population in the double blind period for the main part of Study M16-047 (Safety DB_M), included all randomised subjects who received at least 1 dose of study drug in the main part of the study during the double blind period,

The all upadacitinib-treated population for the main part of Study M16-047 (ALL_upadacitinib_M) included subjects who received at least one dose of upadacitinib;

For the safety populations, subjects were assigned to a treatment group based on the 'as treated' treatment group, regardless of the treatment randomised. The 'as treated' was determined by the treatment the subject received during the majority of the subject's drug exposure time in the analysis period.

Sample size

For the main study, approximately 810 persons, comprising of adults and some adolescents were to be randomised in a ratio of 1:1:1 into:

- n = 270 to upadacitinib 15 mg with concomitant use of topical corticosteroids;
- n = 270 to upadacitinib 30 mg with concomitant use of topical corticosteroids;
- n = 270 to placebo with concomitant use of topical corticosteroids.

A total of 901 subjects were actually randomised into:

- n = 300 to upadacitinib 15 mg with concomitant use of topical corticosteroids;
- n = 297 to upadacitinib 30 mg with concomitant use of topical corticosteroids;
- n = 304 to placebo with concomitant use of topical corticosteroids.

It is stated that the sample size was determined by the regulatory requirement to adequately characterise the safety profile.

Assumptions for the sample size:

- an EASI 75 response rate of 24%, a vIGA-AD clear or almost clear,
- with at least a 2-point reduction response rate of 13% in the placebo/topical corticosteroids group.

The above sample size provided more than 90% power to detect the treatment differences of 38% and 20%, respectively, for the above 2 endpoints simultaneously using two-sided test at a 0.05 significant level.

The assumptions of placebo response rates for EASI 75 and IGA-AD 0/1 were based on the maximum placebo rate in Study M16-048 (the upadacitinib in atopic dermatitis Phase IIb study) and the Phase III monotherapy studies using dupilumab in atopic dermatitis (SOLO 1 and SOLO 2 clinical trials);[58,59] adding the estimation of topical treatment effect which is

also based on the difference between the mono- and combo-therapy (CHRONOS trials) in dupilumab.[61]

The total sample size of 180 adolescents in the overall study (main study + adolescent sub-study) was determined to ensure 1 year of data for a total of 225 subjects per dose across 3 pivotal studies.

Statistical methods

The efficacy analysis of the main study was conducted in the ITT_M population, which includes some adolescents, while that for adolescents was conducted in the ITT_A population. In addition, the primary efficacy endpoints were also analysed in the PP_M population.

In the double blind period, categorical variables were analysed using Cochran-Mantel-Haenszel test, stratified by vIGA-AD categories and age (adolescent versus adult) for the ITT_M Population, and stratified by vIGA-AD categories and study portion (main study vs. adolescent sub-study) for the ITT_A Population.

Continuous variables were analysed using mixed effect model with repeated measures (MMRM).

In the double blind period, missing values and visits after the rescue were handled by non-responder imputation (NRI) for categorical variables, or MMRM for the continuous variables. This handling also will be applied to selective additional endpoints (that is, primary and key secondary variables evaluated at visits from Week 16 to Week 52) in the blinded extension period.

Assessments of long-term efficacy (across the double blind and blinded extension Periods) for subjects who stayed on treatment will also be summarised by Observed Case approach at each visit. No missing data imputation will be applied, and all assessments prior to premature discontinuation from study drug will be used.

There were no changes after the finalisation of version 3 of the statistical analysis plan. Additional (*post-hoc*) analyses were requested by the Swedish Medical Products Agency, including sensitivity analysis of the co-primary endpoints and long-term efficacy outcomes for EASI 75, vIGA-AD 0/1 and improvement in Worst Pruritus NRS ≥ 4.

Missing efficacy data/missed visits due to COVID-19 infection or logistical restrictions were recorded in the database. The primary approach for handling missing data in the analysis of categorical endpoints (including the co-primary endpoints) used Non-Responder Imputation. while incorporating multiple imputation was incorporated to handle missing data due to COVID-19 (NRI-C) in which, any subject who does not have an evaluation during a pre-specified visit window (either due to missing assessment or due to early withdrawal from the study), was categorised as a non-responder for the visit except when:

- the subject was a responder both before and after the visit window. In that case, the subject was categorised as a responder for the visit; or
- there is missing data due to COVID-19 infection or logistical restriction and in that case, it was handled by multiple imputation.

A sensitivity analysis for the co-primary endpoints and the key secondary categorical endpoints used NRI with no special data handling for missing data due to COVID-19 (Non-Responder Imputation with no special data handling for missing data, due to COVID-19

[61] CHRONOS studies: A randomized, double-blind, placebo-controlled study to demonstrate the efficacy and long-term safety of dupilumab in adult patients with moderate-to-severe atopic dermatitis; ClinicalTrials.gov Identifier: NCT02260986.

(NRI-C)), in which subjects with missing data due to COVID-19 infection or logistical restriction were counted as non-responders.

Baseline data

Demographic characteristics were generally balanced between the treatment groups (see Table 30 below).

Table 30: Study M16-048 Demographic characteristics and baseline data

	Overall			Adolescents		
	PBO + TCS (N=304)	UPA 15 mg QD + TCS (N=300)	UPA 30 mg QD + TCS (N=297)	PBO + TCS (N=40)	UPA 15 mg QD + TCS (N=39)	UPA 30 mg QD + TCS (N=37)
Male	178 (58.6)	179 (59.7)	190 (64.0)	16 (40.0)	22 (56.4)	25 (67.6)
Age Group (years), n (%)						
< 18	40 (13.2)	39 (13.0)	37 (12.5)	40 (100)	39 (100)	37 (100)
18 - 39	156 (51.3)	176 (58.7)	158 (53.2)	0	0	0
40 - 64	94 (30.9)	80 (26.7)	85 (28.6)	0	0	0
≥ 65	14 (4.6)	5 (1.7)	17 (5.7)	0	0	0
Age (years)						
Mean ± SD	34.3 (15.12)	32.5 (14.02)	35.5 (15.79)	15.1 (1.85)	15.7 (1.34)	15.6 (1.98)
Median (min, max)	31.0 (12, 75)	28.0 (13, 74)	31.0 (12, 72)	15.0 (12, 18)	16.0 (13, 18)	16.0 (12, 18)
Weight (kg), n	303	300	297	40	39	37
Mean ± SD	75.99 (20.471)	75.06 (20.421)	75.46 (17.800)	62.48 (18.421)	63.39 (18.830)	66.04 (17.415)
Median (min, max)	74.40 (40.1, 159.7)	73.00 (33.0, 169.0)	72.80 (40.1, 146.2)	59.20 (40.1, 105.4)	59.00 (40.1, 125.5)	66.00 (40.1, 106.5
Height (cm), n	303	299	296	40	39	37
Mean ± SD	170.40 (10.232)	170.12 (10.044)	170.89 (9.769)	162.56 (9.224)	165.20 (9.296)	167.78 (12.685)
BMI (kg/m^2), n	303	299	296	40	39	37
Mean ± SD	25.92 (5.667)	25.81 (6.159)	25.74 (5.420)	23.35 (5.625)	23.01 (5.604)	23.29 (4.913)
Geographic Region, n (%)						
US/PR/Canada	108 (35.5)	108 (36.0)	106 (35.7)	18 (45.0)	18 (46.2)	17 (45.9)
Japan	18 (5.9)	16 (5.3)	17 (5.7)	0	0	0
Mainland China	18 (5.9)	17 (5.7)	16 (5.4)	2 (5.0)	2 (5.1)	1 (2.7)
Other[a]	160 (52.6)	159 (53.0)	158 (53.2)	20 (50.0)	19 (48.7)	19 (51.4)
Race, n (%)						
White	225 (74.0)	204 (68.0)	218 (73.4)	29 (72.5)	27 (69.2)	30 (81.1)
Black/African American	18 (5.9)	19 (6.3)	13 (4.4)	3 (7.5)	4 (10.3)	4 (10.8)
Asian	60 (19.7)	64 (21.3)	61 (20.5)	8 (20.0)	7 (17.9)	3 (8.1)
Multiple	0	8 (2.7)	1 (0.3)	0	1 (2.6)	0
Ethnicity, n (%)						
Hispanic or Latino	26 (8.6)	32 (10.7)	20 (6.7)	6 (15.0)	7 (17.9)	2 (5.4)

Overall, most subjects were male (60.7%) with a mean age of 34.1 years. Adolescents had a mean age of 15.5 years (standard deviation (SD) of 1.75 years), with more female adolescents initially randomised to placebo compared to the upadacitinib groups.

Baseline disease characteristics were also generally balanced across the treatment groups for all subjects, including adolescents. The most common medical/surgical history by body system was respiratory, thoracic and mediastinal disorders (63.8%, of which asthma

(45.3%) and allergic rhinitis (34.2%) were the most common), followed by immune system disorders (56.0% of which food allergies were most common (33.5%)) with similar incidence across treatment groups.

Subjects had a mean atopic dermatitis disease duration since diagnosis of 23.44 years (12.38 years for adolescents). Moderate (46 to 47%) to severe (52 to 54%) atopic dermatitis was consistently observed across all treatment groups.

Prior use of high potency topical corticosteroids was similar across treatment groups, with 629 (69.8%) having received high, medium (40 (45.4%)) and low (277 (30.7%)) potency topical corticosteroids. The most common topical corticosteroids used prior to start of study were:

- high potency topical corticosteroids:
  - betamethasone (n = 358, with 80.2% showing inadequate response/ loss of response);
- medium potency topical corticosteroids:
  - triamcinolone (n = 186 with 86% showing inadequate response/ loss of response) and
  - mometasone (n = 256 with 81.6% showing inadequate response/ loss of response);
- low potency topical corticosteroids:
  - hydrocortisone (n = 222 with 82% showing inadequate response/ loss of response).

It is noted, that prior use of these topical corticosteroids was similar across all treatment groups.

More than half of the subjects (n = 492 (54.6. %)) received prior non-biologic immunomodulating systemic therapies and only 30 subjects (3.3%) received prior biologic systemic therapies.

The clinical evaluation noted that prior use of non-biologic immunomodulating systemic therapy was slightly higher in the upadacitinib treatment groups compared to the placebo group at 56.0%, 56.9% and 51.0% in the upadacitinib 15 mg + topical corticosteroids, upadacitinib 30 mg + topical corticosteroids and placebo + topical corticosteroids groups, respectively).

Concomitant topical corticosteroid use

The most common concomitant medications during the double blind treatment period were:

- Hydrocortisone (n = 522 (58%));
  - 57.3%, 55.6% and 61.1% in the upadacitinib 15 mg + topical corticosteroids, upadacitinib 30 mg + topical corticosteroids and placebo + topical corticosteroids groups, respectively);
- Mometasone (n = 252 (28%));
  - 27.3%, 23.9% and 32.7%, respectively; and
- Betamethasone (n = 187 (20.8%));
  - 16.3%, 18.9% and 27.1%, respectively.

Use of other concomitant treatments

Emollients and protectives (n = 205 (22.8%)); were used in 23.7%, 26.3% and 18.5%, respectively. The clinical evaluation noted that use of emollients and protectives was slightly higher in the upadacitinib treatment groups compared to the placebo group.

Other commonly used medications were salbutamol (17%); ibuprofen (10.2%); and paracetamol (9.9%).

Commonly used antihistamines included:

- Cetirizine (n = 120 (13.3%); 13.7%, 11.8% and 14.5%, respectively);
- Others antihistamines with similar incidence of use across treatment groups included fexofenadine, diphenhydramine, and loratidine.

The clinical evaluation noted that the concomitant use of topical calcinuerin inhibitors was not clarified in this study.

Use of rescue therapy

The proportion of subjects receiving one or more rescue medications was much higher in the placebo + topical corticosteroids (78 (25.7%)) compared to the upadacitinib 15 mg + topical corticosteroids (16 (5.3%)) and upadacitinib 30 mg + topical corticosteroids (16 (5.4%)) groups.

The most commonly used rescue medications were high potency topical corticosteroids (4.7%, 4.4% and 23.4% in the upadacitinib 15 mg + topical corticosteroids, upadacitinib 30 mg + topical corticosteroids and placebo + topical corticosteroids groups, respectively) and, non-biologic immunomodulating systemic therapy (1.0%, 0.7% and 4.9%, respectively).

Treatment compliance rates were high in double blind Period with mean compliance greater than 94% and median compliance greater than 97% in all three groups. Mean compliance during the blinded extension period was greater than 91% in all treatment groups and median compliance was greater than 95% in all groups.

Major protocol violations and deviations

The proportion of subjects who had at least one protocol deviation was similar across treatment groups: 16%, 15.8% and 15.8% in the upadacitinib 15 mg + topical corticosteroids, upadacitinib 30 mg + topical corticosteroids and placebo + topical corticosteroids groups, respectively.

The majority of deviations relating to eligibility criterion 7 not being met were due to missing a minimum of 4 daily Worst Pruritus NRS assessments out of the 7 consecutive days, immediately preceding the Baseline Visit to calculate the baseline weekly average of daily Worst Pruritus NRS ≥ 4, while all other disease activity criteria were met. This included 11 adolescent subjects with a Baseline Worst Pruritus NRS < 4 or a missing Baseline Worst Pruritus NRS. None of the deviations was considered to have affected the study outcome or interpretation of the study results or conclusions.

Results for the efficacy endpoints

Co-primary endpoints

A statistically significantly larger proportion of subjects in the upadacitinib groups achieved EASI 75 (60.1%, 72.9% and 13.3% in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively; $p < 0.001$ for both upadacitinib groups versus placebo). Both patients with moderate and severe eczema demonstrated significant improvements over placebo as shown in Table 31 below.

See Section: *Eczema Area and Severity Index (EASI)* for details of this scoring measure.

Table 31: Study M16-047 Proportion of subjects achieving EASI 75 by visit in the double blind period (NRI-C, main ITT population)

Time Point Strata Treatment	N	---- Responder ---- n (%) [95% CI]&	Missing Due to COVID-19 n	Response Rate Diff ---------- Compared to Placebo ---------- Diff(%)	Adjusted Diff(%)	[95% CI]#	P-value@	Breslow-Day P-value
Week 16								
All								
Placebo	278	37 (13.3) [9.3, 17.3]	1					
UPA 15 mg QD	276	166 (60.1) [54.4, 65.9]	0	46.8	46.9	[39.9, 53.9]	<0.001***	0.401
UPA 30 mg QD	282	206 (72.9) [67.7, 78.2]	4	59.6	59.6	[53.1, 66.2]	<0.001***	0.197
vIGA-AD 3 (Moderate)								
Placebo	125	21 (16.8) [10.2, 23.4]	0					
UPA 15 mg QD	126	74 (58.7) [50.1, 67.3]	0	41.9		[31.1, 52.7]	<0.001***	
UPA 30 mg QD	126	89 (70.5) [62.4, 78.6]	3	53.7		[43.3, 64.1]	<0.001***	
vIGA-AD 4 (Severe)								
Placebo	153	16 (10.5) [5.6, 15.3]	1					
UPA 15 mg QD	150	92 (61.3) [53.5, 69.1]	0	50.9		[41.7, 60.1]	<0.001***	
UPA 30 mg QD	156	117 (74.9) [68.1, 81.7]	1	64.5		[56.1, 72.8]	<0.001***	

Note: EASI = Eczema Area and Severity Index; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis.
NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
& 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.
# @ Across the strata, 95% CI for adjusted difference and P-value are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (Baseline vIGA-AD categories and age [adolescent vs. adult]) for the comparison of two treatment groups. Within each stratum, 95% CI for difference and P-value are calculated using Cochran-Mantel-Haenszel test without adjustment of strata. The calculations at each visit are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.
***, **, * Statistically significant at the 0.001, 0.01, 0.05 level, respectively.

A statistically significant larger proportion of subjects in the upadacitinib groups achieved EASI 75 and achieved a vIGA-AD score of 0 or 1 (clear or almost clear) with a clinically meaningful reduction (at least 2 grade reduction from Baseline) at Week 16 compared with the placebo group , as per Table 32 below based on the primary approach of NRI-C.

See Section: *Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)* for details on this score.

Table 32: Study M16-047 Comparison in the proportion of subjects achieving EASI 75, and vIGA-AD score of 0 or 1 at Week 16 in the double blind period (NRI-C) (main ITT population)

EMA Testing[a]	FDA Testing[a]	Primary Endpoint	PBO + TCS (N = 304) n (%)	UPA 15 mg + TCS (N = 300) n (%); Adjusted Diff (P-value)	UPA 30 mg + TCS (N = 297) n (%); Adjusted Diff (P-value)
V1	V1	EASI 75 at Week 16	80 (26.4)	194 (64.6); 38.1 (<0.001***)	229 (77.1); 50.6 (<0.001***)
V2	V2	vIGA-AD Score 0/1 (clear or almost clear)[b] at Week 16	33 (10.9)	119 (39.6); 28.5 (<0.001***)	174 (58.6); 47.6 (<0.001***)

Adj Diff = adjusted difference; EASI = Eczema Area and Severity Index; EMA = European Medicines Agency; FDA = Food and Drug Administration; NRI-C = Non-Responder Imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO = placebo; TCS = topical corticosteroids; UPA = upadacitinib; V = variable; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis

*** p-value ≤ 0.001: UPA + TCS vs PBO. + TCS.

a. Variables in the EMA and FDA graphical approach for overall type-I error control details in SAP Section 4.6.

b. vIGA-AD of clear or almost clear included reduction ≥ 2 grades at Week 16 from Baseline.

The co-primary endpoint results were supported by all sensitivity analyses, including NRI-C, multiple imputation, tipping point analysis, and per protocol analysis.

The robustness of these results were confirmed by significant improvements in the upadacitinib + topical corticosteroids groups compared with placebo + topical corticosteroids groups in all pre-specified sub-groups across demographic and baseline in EASI 75 and vIGA-AD, as per the figures below.

Figure 24: Study M16-048 Proportion of subjects achieving EASI 75 at Week 16 by subgroup in the upadacitinib 15 mg group (NRI-C, ITT_M population)

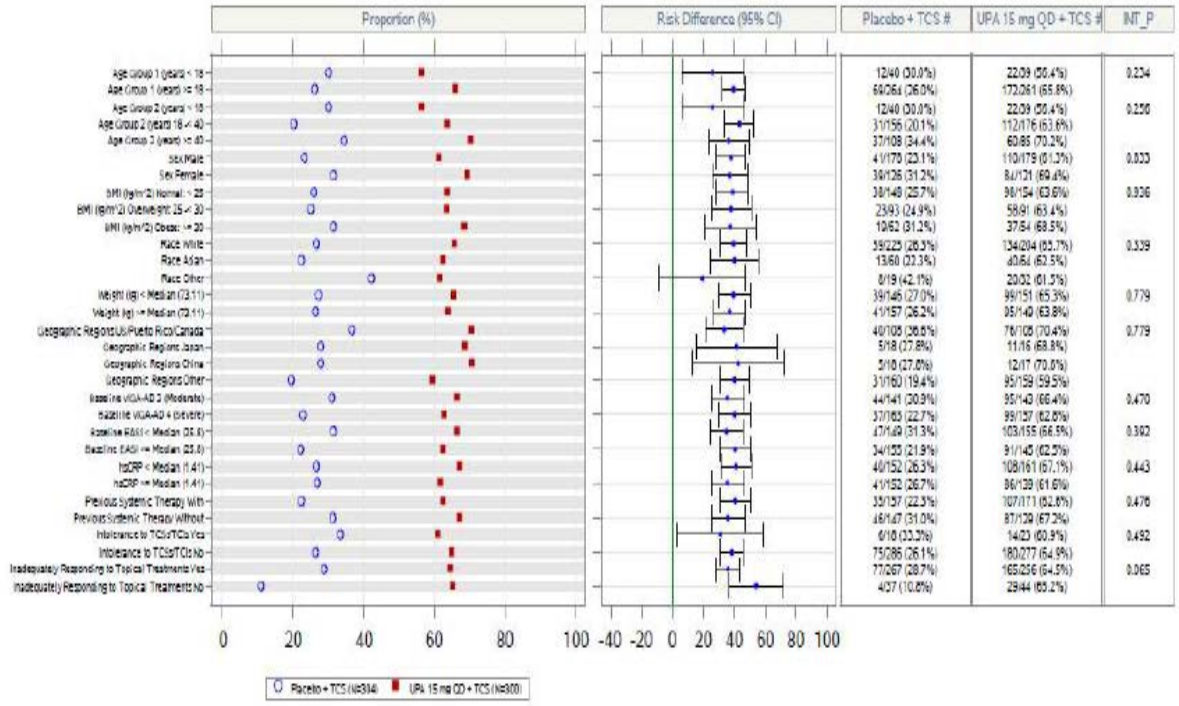


Figure 25: Study M16-048 Proportion of subjects achieving EASI 75 at Week 16 by subgroup in the upadacitinib 30 mg group (NRI-C, ITT_M population)

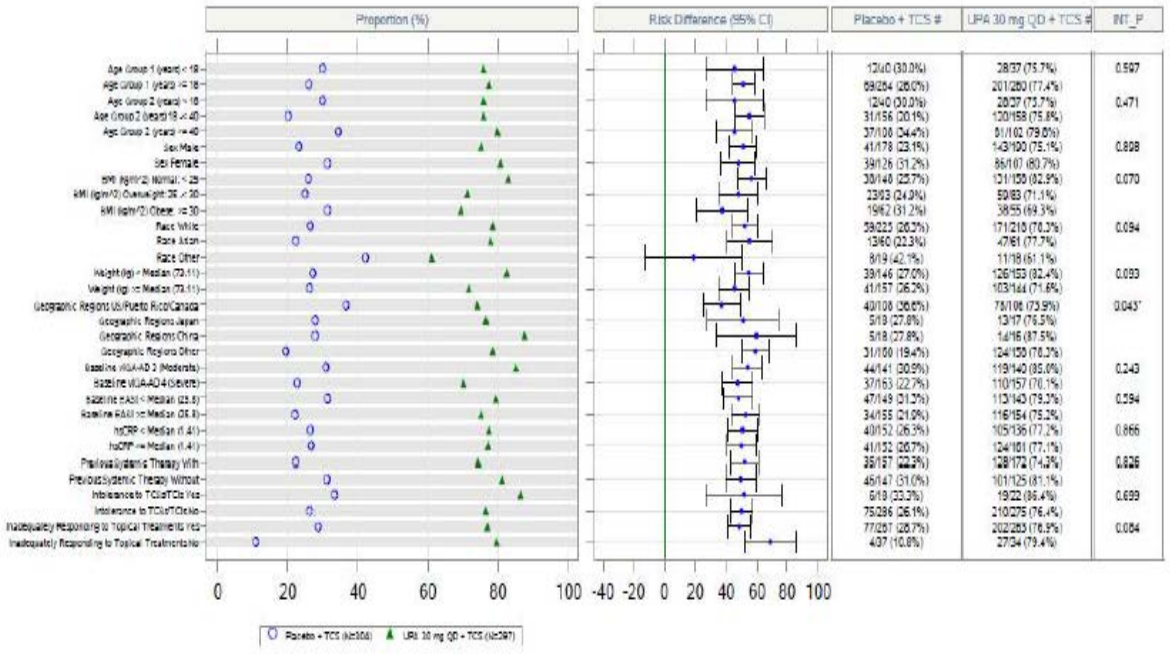


Figure 26: Study M16-047 Proportion of subjects achieving vIGA-AD of 0 or 1 with at least 2 Grades of Reduction from Baseline at Week 16 by Subgroup in the upadacitinib 15 mg Group (NRI-C, ITT_M Population)

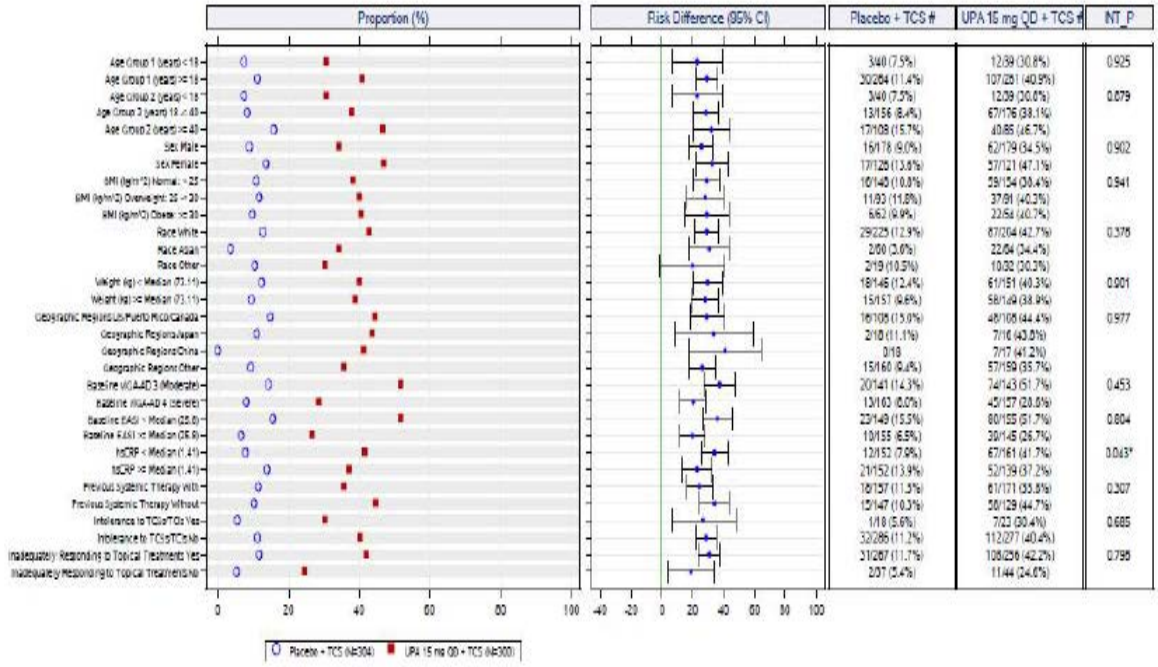
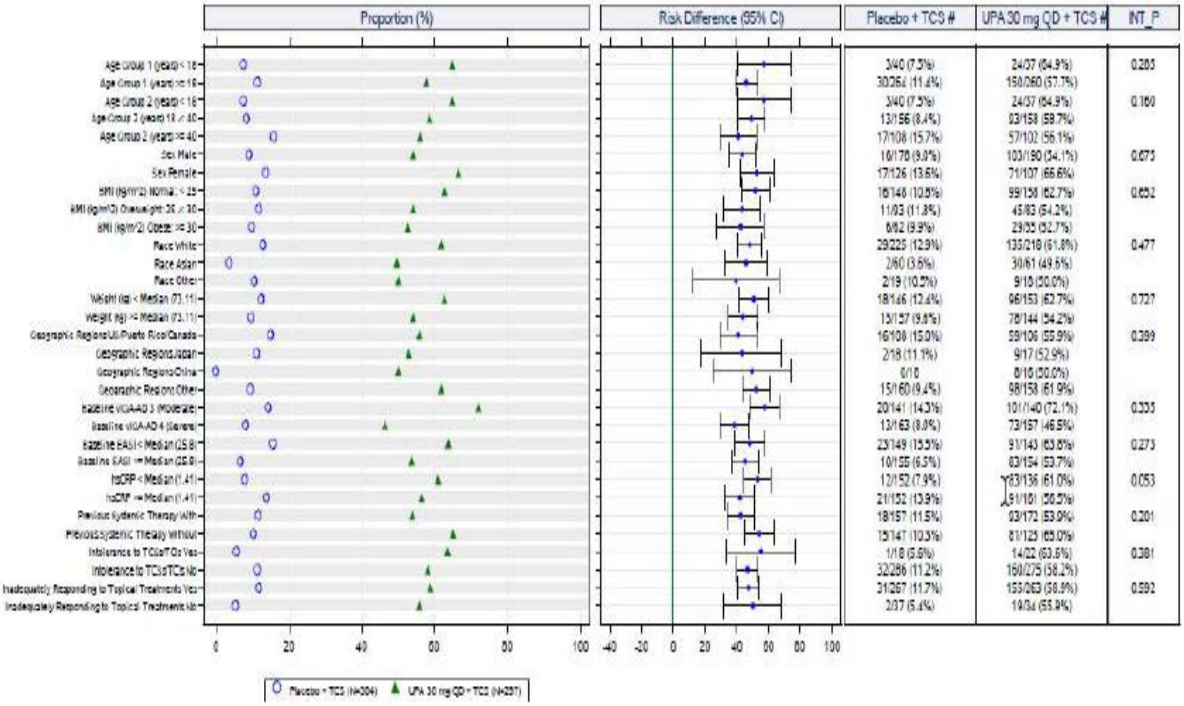


Figure 27: Study M16-048 Proportion of subjects achieving vIGA-AD of 0 or 1 with at least 2 Grades of Reduction from Baseline at Week 16 by Subgroup in the upadacitinib 30 mg Group (NRI-C, ITT_M Population)



The clinical evaluation did not however that subgroup efficacy analysis based on concomitant use of topical calcinuerin inhibitors, emollients and oral antihistamines was not provided when this study was evaluated.

Key secondary endpoints

The superiority of each upadacitinib dose versus placebo was demonstrated in all pre-specified key secondary endpoints, as shown by the clinically meaningful and statistically significant treatment differences in terms of improvements for skin clearance, disease activity as well as pruritus as shown in Table 33, below.

Table 33: Study M16-048 Key secondary endpoint results (US FDA- and EMA-agreed efficacy outcomes; main ITT population)

EMA Testing[a]	FDA Testing[a]	Secondary Endpoints	PBO + TCS (N = 304) n (%) or LS Mean (SE)	UPA 15 mg+ TCS (N = 300) n (%) or LS Mean (SE); Adjusted Diff (P-value)	UPA 30 mg+ TCS (N = 297) n (%) or LS Mean (SE); Adjusted Diff (P-value)
V3	V3	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Week 16	N = 294 44 (15.0)	N = 288 149 (51.7); 36.8 (<0.001***)	N = 291 186 (63.9); 48.8 (<0.001***)
V4	V4	EASI 90 at Week 16	N = 304 40 (13.2)	N = 300 128 (42.8); 29.5 (<0.001***)	N = 297 187 (63.1); 49.9 (<0.001***)
V5	NA	Percent change in Worst Pruritus NRS at Week 16	N = 184 -25.07 (3.351)	N = 260 -58.14 (3.105); -33.08 (<0.001***)	N = 247 -66.85 (3.125); -41.79 (<0.001***
V6	NA	Percent change in EASI at Week 16	N = 206 -45.86 (2.156)	N = 275 -77.99 (1.981); -32.13 (<0.001***)	N = 276 -87.31 (1.984); -41.45 (<0.001***
V7	V7	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Week 4	N = 294 44 (15.0)	N = 288 151 (52.4); 37.4 (<0.001***)	N = 291 191 (65.6); 50.6 (<0.001***)
V8	V8	EASI 75 at Week 4	N = 304 45 (14.8)	N = 300 176 (58.7); 43.8 (<0.001***)	N = 297 215 (72.4); 57.6 (<0.001***)
V9	V9	EASI 75 at Week 2	N = 304 21 (6.9)	N = 300 93 (31.0); 24.0 (<0.001***)	N = 297 131 (44.1); 37.2 (<0.001***)
V10	V10	EASI 90 at Week 4	N = 304 15 (4.9)	N = 300 85 (28.3); 23.3 (<0.001***)	N = 297 130 (43.8); 38.8 (<0.001***)
V11	V11	EASI 100 at Week 16 (30 mg only)	N = 304 4 (1.3)	NA	N = 297 67 (22.6); 21.2 (<0.001***)
V12-H	V12-H	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Week 1	N = 294 9 (3.1)	N = 288 35 (12.2); 9.2 (<0.001***)	N = 291 56 (19.2); 16.2 (<0.001***)

Diff = difference; EASI = Eczema Area and Severity Index; EMA = European Medicines Agency; FDA = Food and Drug Administration; H = Hochberg Method; LS = Least Square; NA = endpoint not included under multiplicity control for overall type I error; NRS = numerical rating scale; PBO = placebo; SE = standard error; TCS = topical corticosteroids; UPA = upadacitinib; V = variable

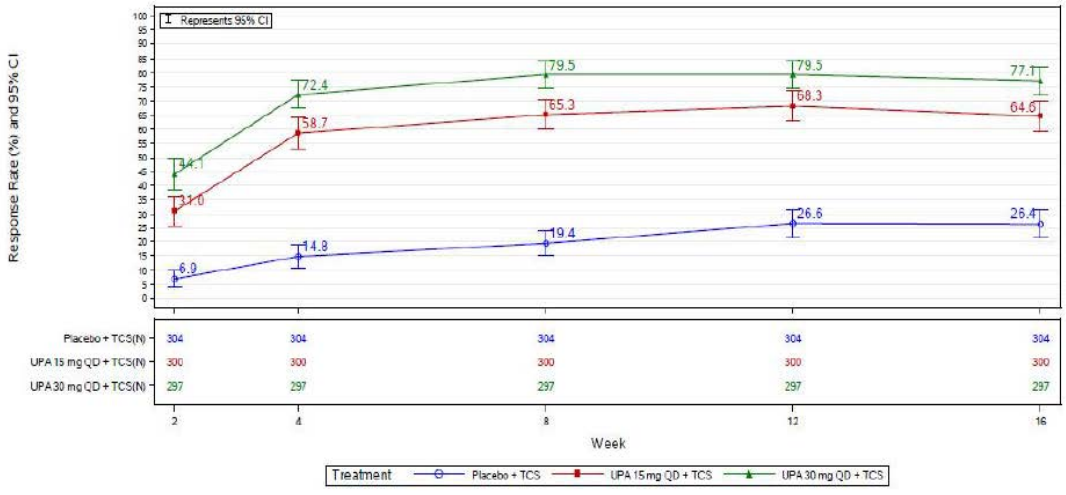
*** p-value ≤ 0.001; UPA + TCS vs PBO. + TCS.

a. Variables in the EMA and FDA graphical approach for overall type-I error control details in SAP Section 4.6. V1 and V2, not listed, are the co-primary endpoints (EASI 75 and vIGA-AD 0/1 at Week 16).

Note: Results for the binary endpoints are based on NRI-C and results for the continuous endpoints are based on MMRM.

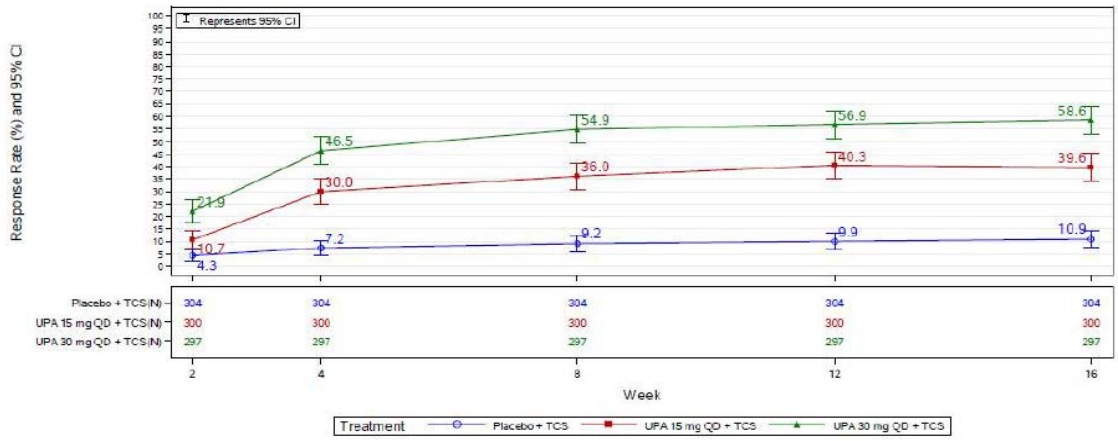
The significant improvements following upadacitinib treatment compared to placebo in EASI 75/90/100, as shown in the following figures.

Figure 28: Study M16-048 EASI 75 results by visit through to Week 16 (NRI-C, main ITT population)



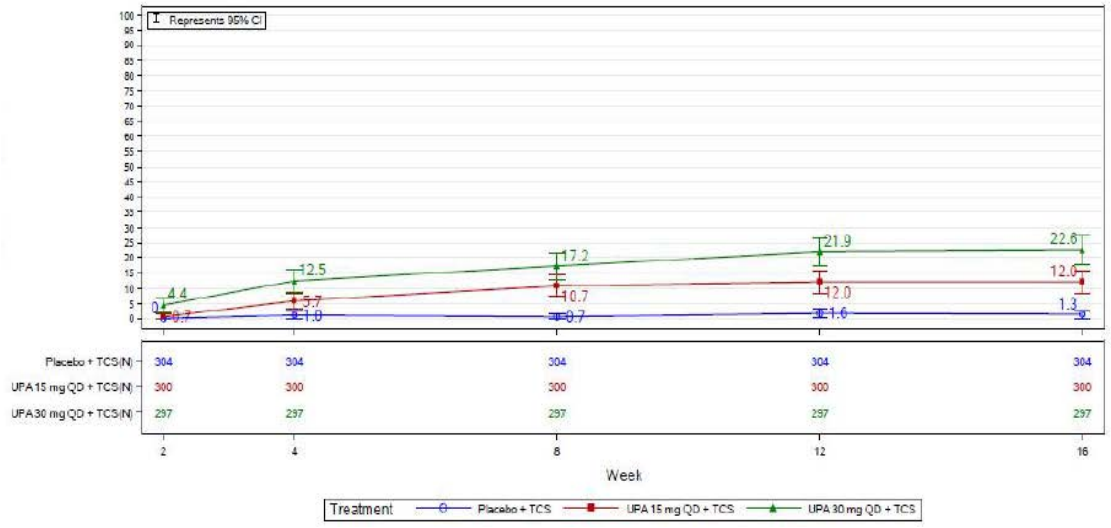
Abbreviations: CI = confidence intervals; EASI 75 = Eczema Area and Severity Index 75 response; ITT = intention to treat; NRI C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

Figure 29: Study M16-048 EASI 90 results by visit through to Week 16 (NRI-C, main ITT population)



Abbreviations: CI = confidence intervals; EASI 90 = Eczema Area and Severity Index 90 response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

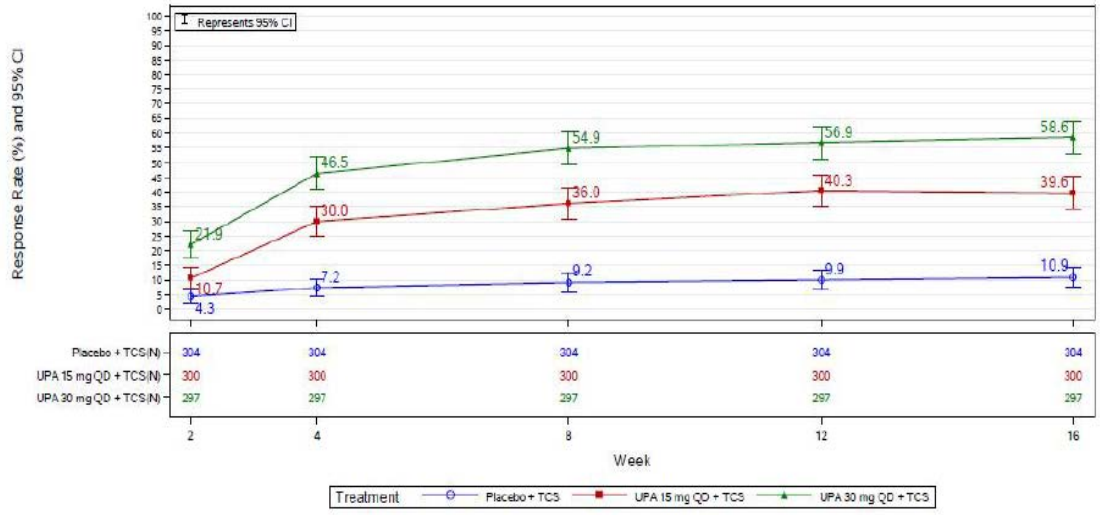
Figure 30: Study M16-048 EASI 100 results by visit through to Week 16 (NRI-C, main ITT population)



Abbreviations: CI = confidence intervals; EASI 100 = Eczema Area and Severity Index 100 response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

vIGA-AD score 0/1 (clear or almost clear) were observed from Week 2 and were maintained through to Week 16 as per the figure below.

Figure 31: Study M16-048 vIGA-AD 0/1 score results by visit through to Week 16 (NRI-C, main ITT population)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; NRS = numerical rating scale; QD = once daily; UPA = upadacitinib; vIGA-AD = validated investigator's global assessment.

Upadacitinib 30 mg showed numerically better results on skin clearance and disease activity measures compared to upadacitinib 15 mg.

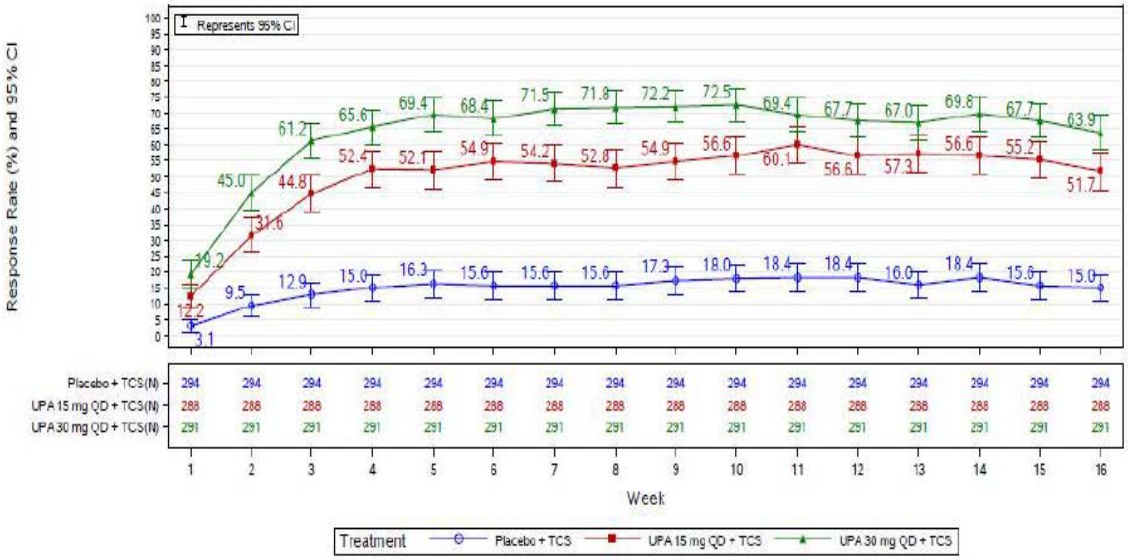
The proportion of subjects achieving an improvement (reduction) in SCORAD 50/75/90 at Week 16 was also significantly greater in the upadacitinib treatment groups compared with placebo. This was consistent with improvements SCORAD and its individual components (Objective SCORAD, SCORAD Itch, and SCORAD Sleep) as well as reduction in body surface area affected (see section: *Scoring Atopic Dermatitis (SCORAD)* for further details).

Rapid response and consistent improvement in skin clearance and disease activity was observed in adolescents too.

During the double blind period, fewer subjects on upadacitinib experienced a flare (increase in EASI by ≥ 6.6 from Baseline) than on placebo (4, 2 and 38 subjects in the upadacitinib 15 mg plus topical corticosteroids, upadacitinib 30 mg plus topical corticosteroids and placebo plus topical corticosteroids groups, respectively). Among adolescents, only one subject on upadacitinib 15 mg + topical corticosteroids and 5 subjects on placebo + topical corticosteroids experienced a flare during the double blind period.

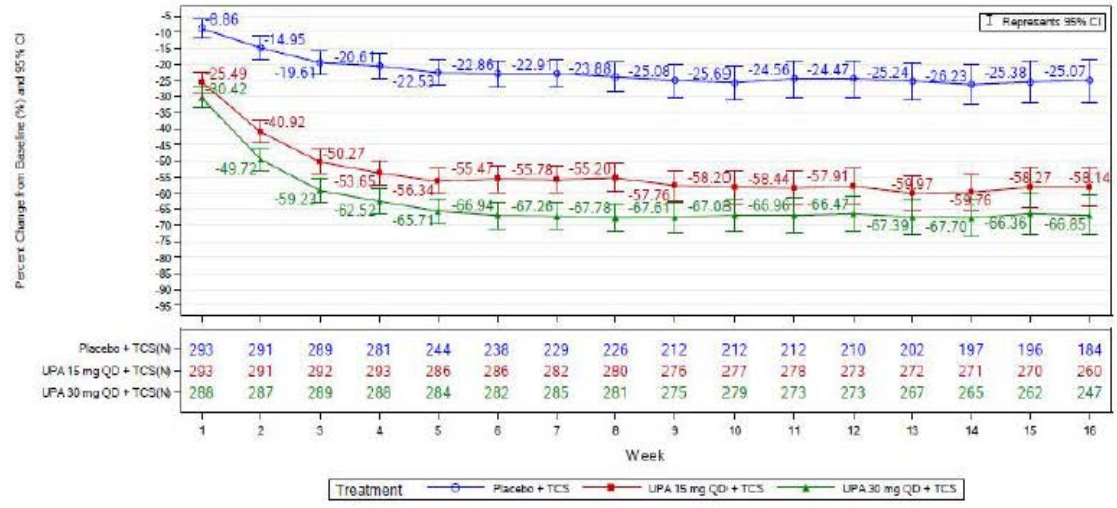
Upadacitinib (30 mg and 15 mg) demonstrated superiority in all secondary endpoints of itch reduction in Worst Pruritus NRS ≥ 4 at Week 1, Week 4, and Week 16 and percent change from Baseline in Worst Pruritus at Week 16. The onset of action for reduction in Worst Pruritus NRS ≥ 4 and the percent change from Baseline in Worst Pruritus NRS was rapid (from Week 1) and continued to improve through Week 16.

Figure 32: Study M16-048 Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline in the double blind period (NRI-C, main ITT population)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; NRS = numerical rating scale; QD = once daily; UPA = upadacitinib.

Figure 33: Study M16-048 Percent change from Baseline in Worst Pruritus NRS (weekly average) by visit in the double blind period (main ITT population)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; NRS = numerical rating scale; QD = once daily; UPA = upadacitinib.

A significantly greater proportion of subjects on upadacitinib (30 mg or 15 mg) achieved improvement in the additional endpoints related to skin pain (ADerm-SS Skin Pain) and overall symptoms (ADerm-SS TSS-7, POEM) at Week 16 compared with placebo.

Upadacitinib-related improvements in skin symptoms, such as itching, were associated with significant improvements in additional endpoints of atopic dermatitis-related sleep disturbances compared to placebo. The latter was as measured by: ADerm-IS sleep domain score ≥ 12, POEM Sleep score of 0 and the percent change from baseline in SCORAD sleep

at Week 16. upadacitinib 30 mg showed numerically better results than upadacitinib 15 mg.

Treatment with upadacitinib (30 mg and 15 mg) led to significant improvements (reduction) in the patient-reported impact of atopic dermatitis compared to placebo. The latter was as measured by: improvement in ADerm-IS emotional state domain score ≥ 11, improvement in ADerm-IS daily activities domain score ≥ 14, reduction in anxiety and depression symptoms (HADS) and in select WPAI questionnaire: atopic dermatitis domain scores (work productivity loss, presenteeism, and activity impairment) at Week 16.

The proportion of subjects showing improvements in impact of atopic dermatitis was numerically greater in the upadacitinib 30 mg + topical corticosteroids group compared to the upadacitinib 15 mg +topical corticosteroids group.

Compared with placebo, treatment with upadacitinib (30 mg and 15 mg) in combination with topical corticosteroids also led to greater improvement in endpoints, reflecting health-related quality of life. The latter includes the additional endpoints of: improvement (reduction) in DLQI ≥ 4, DLQI 0 or 1, CDLQI 0 or 1, and improvement in EQ-5D-5L, as well as in PGIS, PGIC and PGIT.

Improvements in skin clearance, disease activity, itch reduction, sleep disturbances, impact of atopic dermatitis and health-related quality of life measures observed in adolescents were consistent with those observed in all subjects.

See sections: *Patient Oriented Eczema Measure (POEM); Atopic Dermatitis Symptom Scale (ADerm-SS)Atopic Dermatitis Impact Scale (ADerm-IS); Dermatology Life Quality Index;* and *Hospital Anxiety and Depression Scale (HADS)* for details of these measures.

Long-term efficacy results

Regarding long term efficacy results from the blinded extension period:

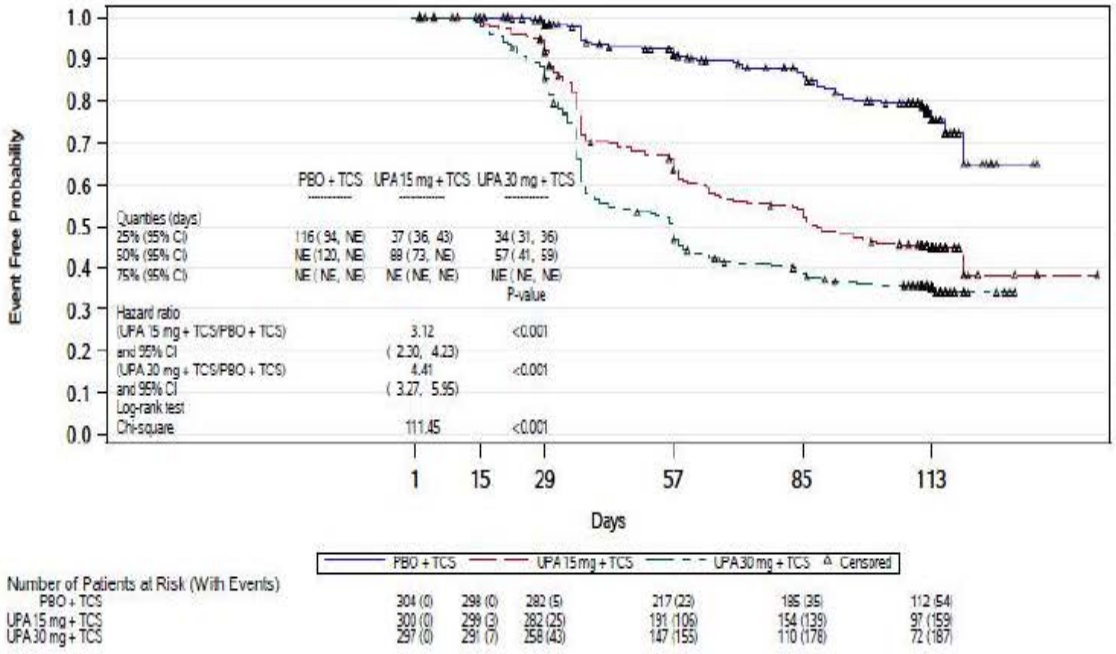
- The long-term blinded extension period was described with observed case analysis that did not impute values for missing evaluations.
- Additional long-term summaries were provided for EASI 75, vIGA-AD 0/1, and Worst Pruritus NRS improvement ≥ 4 from Baseline using missing imputation approach:
  - EASI response rate was maintained up to Week 52 in those subjects who continued with their double blind treatments; placebo subjects who started treatment with upadacitinib after 16 weeks also showed good EASI 75 response rates which were maintained through to Week 52.
  - Similar results were observed for vIGA-AD scores of 0/1.
  - Reduction in pruritus was observed for placebo subjects who started treatment with upadacitinib after 16 weeks and was maintained through to Week 52 as well as for those patients who continued with their upadacitinib treatment from their double blind phase.
  - Response rates were higher in EASI 50 responders compared to the EASI 50 non-responders.

Another issue relates to topical corticosteroids-free days:

- The mean number of days off all topical corticosteroids and achieving EASI 75 response (through week 16) was 33.53 days (median 26 days), 47.47 days (median: 57 days) and 7.88 days (median: 0 days) in the upadacitinib 15 mg, 30 mg and placebo groups, respectively.
- The mean number of days off all medium and high potency topical corticosteroids and achieving an EASI 75 response was 39.50 days (median: 31 days), 55.86 days (median: 69 days) and 10.14 days (median 0 days), respectively.

- The median time to first discontinuation of topical corticosteroids with an EASI 75 response was 57 days for the upadacitinib 30 mg group, 88 days for the upadacitinib 15 mg group, and not observed for the placebo group.

Figure 34: Study M16-048 Event free probability of discontinuation of topical steroids with an EASI 75 response (observed case/missing imputation analysis)



Abbreviations: CI = confidence interval; EASI = Eczema Area and Severity Index; PBO = placebo; TCS = topical corticosteroids; UPA = upadacitinib/

Discontinuation of all topical corticosteroids was defined as when the subject stops all topical corticosteroids treatment for more than 7 consecutive days. Days after the start of systemic rescue were not considered as topical corticosteroid-free days.

The clinical evaluation noted that although improvement in pruritus was maintained till 52 weeks for patients with worst pruritus (NRS weekly average > 4) at Baseline, there was a trend indicating reduced efficacy over time:

- For placebo subjects who started treatment with upadacitinib after 16 weeks, response rate for upadacitinib 15 mg and 30 mg groups was 71.5% and 82.4%, respectively at Week 20 while it was 50.6% and 70.5%, respectively at Week 52.
- For patients who continued with their upadacitinib treatment from double blind phase, response rates were 53.5% and 66.5% for upadacitinib 15 mg and 30 mg groups, respectively at Week 20, while it was 39.2% and 56.3% at Week 52.

Study M16-048 (supportive study)

Study M16-048 was a Phase IIb, randomised, double-blind, parallel-group, placebo-controlled multicentre study of 88 weeks, to evaluate the safety and efficacy of upadacitinib in adult subjects with moderate to severe atopic dermatitis.

The study design included a 35-day maximum screening period; 16-week double blind treatment period (Period 1); 72-week double blind treatment period (Period 2) (that is, a blinded extension period.

A 30-day follow-up period (call or visit) to determine the status of any ongoing or new adverse events (AEs) or serious adverse events (SAEs) were to be done.

Primary objective

The primary objective was to evaluate the safety and efficacy of multiple doses of upadacitinib monotherapy versus placebo, in the treatment of adults with moderate to severe atopic dermatitis.

Inclusion criteria

Inclusion criteria included:

- Age between 18 and 75 years old;
- A diagnosis of atopic dermatitis confirmed by a dermatologist (according to the Hanifin and Rajka criteria),[1] (see Table 1);
- Had onset of symptoms of at least 1 year prior to Baseline, and moderate or severe disease defined by an EASI ≥ 16, body surface area (BSA) ≥ 10% and an Investigator's Global Assessment (IGA) score ≥ 3;
- Subjects were required to have had an inadequate response to treatment with topical corticosteroids, topical calcineurin inhibitors, or were permitted to enroll if topical treatments were medically inadvisable (for example, because of important side effects or safety risks);
- Subjects were also required to use an additive-free, bland emollient twice daily for at least 7 days prior to Baseline.

Exclusion criteria

Exclusion criteria were:

- Prior exposure to any Janus kinase (JAK) inhibitor;
- Treatment with topical corticosteroids, topical calcineurin inhibitors, prescription moisturisers or moisturisers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin within 10 days prior to Baseline;
- Any prior exposure to dupilumab or exposure to systemic therapies for atopic dermatitis including corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE4)-inhibitors and mycophenolate mofetil within 4 weeks prior to Baseline;
- Abnormal laboratory values that met the following criteria at screening:
  - serum aspartate transaminase (AST) > 2 × upper limit of normal (ULN);
  - serum alanine transaminase (ALT) > 2 × ULN;
  - estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula < 40 mL/min/1.73 m^2;
  - total white blood cell count < 2,500/µL;
  - absolute neutrophil count < 1,500/µL;
  - platelet count < 100,000/µL;
  - absolute lymphocyte count < 800/µL;
  - haemoglobin < 10 g/dL.

Study treatments

Subjects who met eligibility criteria were to be randomised in a 1:1:1:1 ratio to one of the four treatment groups from Day 1 to Week 16 (Period 1):

- Group 1 = upadacitinib 7.5 mg once daily;

- Group 2 = upadacitinib 15 mg once daily;
- Group 3 = upadacitinib 30 mg once daily;
- Group 4 = placebo once daily.

Subjects who completed Period 1 per group were re-randomised at Week 16 in a 1:1 ratio to either continue the active treatment for that group or enter placebo (Period 2, Week 16; thereafter; a 72 –week double blind, placebo controlled treatment period):

- Group 1 = upadacitinib 7.5 mg or placebo once daily;
- Group 2 = upadacitinib 15 mg or placebo once daily;
- Group 3 = upadacitinib 30 mg or placebo once daily;
- Group 4 = placebo once daily or placebo.

For Period 1, the randomisation was stratified by geographic region (USA/Puerto Rico/Canada, EU/Australia, and Japan).

For Period 2, the re-randomisation was stratified by geographic region as above and, EASI 75 response at Week 1.

Study drug was to be taken orally once daily (with or without food), beginning on Day 1 (Baseline), and was to be taken at approximately the same time each day.

In Period 1, discontinuation from study drug was mandatory for any subject with an EASI score worsening of ≥25% compared with their baseline EASI score at any 2 consecutive scheduled study visits from Week 4 to Week 1.

In Period 2, blinded rescue therapy with upadacitinib 30 mg once daily was provided after the first instance of a < EASI 50 response starting at the Week 20 visit (4 weeks after re-randomisation into Period 2).Subjects receiving rescue therapy were continued on upadacitinib 30 mg once daily for the remainder of the study.

During Period 2, concomitant class III to IV, medium potency topical corticosteroid treatment was permitted starting at Week 24 after a second instance of < EASI 50 response beginning from Week 20. For subjects who receive topical corticosteroids rescue therapy, an additional visit was required 4 weeks later. Discontinuation from study drug was mandatory for subjects with < EASI 50 response compared with their baseline EASI score 4 weeks following rescue with topical corticosteroids or at any visit thereafter.

Efficacy parameters/endpoints

See Section: *Scoring systems used in the clinical studies* for details of these scoring systems/outcome measures.

Primary: The mean (%) change from Baseline (Day 1) in EASI score at Week 16.

Secondary:

- The proportion of subjects achieving an EASI 75 response, defined as at least a 75% reduction in EASI score, at Week 16 relative to the Baseline (Day 1);
- Proportion of subjects achieving an Investigator Global Assessment (IGA) of 0 or 1 at Week 16;
- Percent change from Baseline to Weeks 2, 8 and 16 in Pruritus Numerical Rating Scale (NRS);
- Percent change in EASI score from Baseline at Week 8;
- Percent change in Scoring Atopic Dermatitis (SCORAD) score from Baseline at Weeks 8 and 16;

- Proportion of subjects achieving EASI 50/75/90 response at Weeks 8 and 16;
- Proportion of subjects achieving SCORAD 50/75/90 response at Weeks 8 and 16;
- Proportion of subjects with Dermatology Life Quality Index (DLQI) = "0" or "1" at Weeks 8 and 16;
- Change from Baseline in DLQI at Weeks 8 and 16;
- Change and percent change from Week 16 (re-randomisation) in EASI score at all Period 2 visits;
- Time to loss of EASI 50 response relative to Baseline among those who were re-randomised as EASI 75 responders at Week 16;
- Summary of EASI 75 at all visits in Period 2 among those who were re-randomised as EASI 75 non-responders at Week 16.

Exploratory:

- Time to EASI 50/75/90 and IGA "0" or "1" response in Period 1;
- Proportion of subjects achieving EASI 50/75/90/100 response at all visits;
- Proportion of subjects achieving SCORAD 50/75/90 response at all visits;
- Change from Baseline to Week 16 in Patient Oriented Eczema Measure (POEM);
- Change from Baseline to Week 16 in Medical Outcomes Study (MOS) Sleep Scale;
- Change from Baseline to Week 16 in Asthma Symptoms Questionnaire;
- Change from Baseline to Week 16 in Daytime Nasal Symptoms Questionnaire;
- Change from Baseline in total sleep time (TST) per night (TST min), sleep efficiency percentage (%), wake after sleep onset (WASO), number of scratching events per hour, mean activity during rest (sleep) periods as measured by actigraphy.

The primary and secondary endpoints were also evaluated at all scheduled visits through Week 88 (Period 1 = 16 Weeks and Period 2 = 72 Weeks).

Participant flow and protocol deviations

A total of 167 subjects were randomised. Of the 167 randomised subjects, 166 subjects received study drug (one subject in the placebo group was randomised but did not receive drug).

A total of 126 subjects (75.4%) completed study drug treatment through Week 16 (Period 1).130 subjects (77.8%) completed study participation through Period 1, with lack of efficacy being most common reason for study drug discontinuation in Period 1, especially in placebo group**.**

Overall, 126 subjects (75.4%) were re-randomised into Period 2 and all received study treatment.

Eighty-one (81) subjects (64.3%) received rescue with upadacitinib 30 mg treatment. 85 subjects (67.5%) completed study drug. 41 subjects (32.5%) subjects discontinued study drug in Period 2 (mainly due to lack of efficacy)**.**

Overall, 18.6% (31/167) of the subjects reported protocol violations with slightly higher incidence in upadacitinib groups (19%, 19% and 23.8% in 7.5 mg, 15 mg and 30 mg groups, respectively) compared with placebo (12.2%). The most common protocol deviations were related to subjects receiving excluded or prohibited concomitant treatments**.**

Statistical methods and sample size

Approximately 160 subjects were planned to be randomised to one of three upadacitinib treatment groups or to receive placebo in a ratio of 1:1:1:1.

The sample size for this study was based on the percent change in EASI from Baseline at Week 16.

Assumptions for the sample size:

- a percent change in EASI from Baseline at Week 16 of 35, 45, 60, and 70 in the placebo, 7.5 mg, 15 mg, and 30 mg arms, respectively;
- standard deviation of 40 and a maximum efficacy of 80.

Given the above, it was assessed that a sample size of 40 subjects per treatment group was sufficient to:

- test for the presence of a dose response signal;
- select the best dose response model for the observed data out of a pre-specified set of candidate models and, estimate target doses of interest (for example, the minimum effective dose) using Multiple comparison procedure and modeling approach.

The above approach provided 99% average power to detect a dose effect at 5% level of significance (one-sided) with the linear, Emax;[62] exponential, logistic and sigEmax models pre-specified, as likely candidates to characterise the dose-response for upadacitinib for the percent change in EASI.

A sample of size 40 per group provided 97% power to detect a significant difference between 30 mg once daily and placebo, and 78% power to detect a significant difference between 15 mg once daily and placebo at two-sided level of significance of 5.0%.

Efficacy analyses were performed on the intention-to-treat (ITT) populations (ITT_1 and ITT_2 populations) for Periods 1 and 2, respectively. Pairwise comparisons of each upadacitinib treatment group versus placebo was performed in Period 1 and descriptive summaries provided for all treatment groups in Period 2.

For binary variables, frequencies and percentages were reported for each treatment group. Pairwise comparison of each upadacitinib group and placebo was performed using the Cochran Mantel-Haenszel test, adjusting for stratification factors.

For continuous variables, the model based mean and standard error were provided (baseline and visit means were also to be presented for each treatment group); treatment groups were compared using the analysis of covariance (ANCOVA) model with treatment group and stratification factors as fixed effects, and the corresponding baseline value as covariates.

Time to EASI 50/75/90 response and IGA 0 or 1 response were evaluated for Period 1. Time to loss of EASI 50 response among those who were re-randomised as EASI 75 responders at Week 16 (or to placebo) were evaluated for Period 2. Time to event variables were analysed by stratified log-rank test adjusting for stratification factors.

The dose-response relationship among the 3 upadacitinib dose groups and, the placebo were characterised for the primary efficacy endpoint percent change from Baseline in EASI score at Week 16 and two secondary endpoints of EASI 75 and IGA 0/1 at Week 16. Characterisation used the multiple comparison procedure modeling method (response based on the last observation carried forward imputation was used).[63]

[62] The Emax model is a nonlinear model frequently used in dose–response analyses.
[63] Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics.* 2005;61(3):738-748.

The clinical evaluation noted that for efficacy related analyses, if there were multiple measurements for a particular parameter collected on the same day for the same subject, the most conservative measurement indicating the worst disease status was used in the analyses. Imputation of missing data for the efficacy analyses was also clearly specified. The latter enabled a conservative evaluation of results.

Baseline data

The majority of subjects in Period 1 and Period 2 were male, and were < 40 years of age with a body mass index ≥ 25 kg/m^2.

The demographic characteristics were generally balanced across the treatment groups in Period 1, as per Table 34, below.

Table 34: Study M16-048 Demographic characteristics and baseline data (Period 1)

	PBO (N = 41)	UPA 7.5 mg QD (N = 42)	UPA 15 mg QD (N = 42)	UPA 30 mg QD (N = 42)	UPA Total (N = 126)	Overall Total (N = 167)
Sex, n (%)						
Female	17 (41.5)	14 (33.3)	12 (28.6)	20 (47.6)	46 (36.5)	63 (37.7)
Male	24 (58.5)	28 (66.7)	30 (71.4)	22 (52.4)	80 (63.5)	104 (62.3)
Age group (years), n (%)						
< 40	25 (61.0)	22 (52.4)	25 (59.5)	22 (52.4)	69 (54.8)	94 (56.3)
40 - 64	11 (26.8)	16 (38.1)	14 (33.3)	17 (40.5)	47 (37.3)	58 (34.7)
≥ 65	5 (12.2)	4 (9.5)	3 (7.1)	3 (7.1)	10 (7.9)	15 (9.0)
Age (years)						
Mean ± SD	39.9 ± 17.52	41.5 ± 15.36	38.5 ± 15.24	39.9 ± 15.30	39.9 ± 15.23	39.9 ± 15.77
Median (min, max)	34.0 (18, 72)	38.5 (20, 70)	37.0 (19, 75)	38.0 (19, 69)	37.0 (19, 75)	37.0 (18, 75)
Race, n (%)						
White	28 (68.3)	24 (57.1)	21 (50.0)	23 (54.8)	68 (54.0)	96 (57.5)
Black or African American	6 (14.6)	7 (16.7)	10 (23.8)	6 (14.3)	23 (18.3)	29 (17.4)
Asian	7 (17.1)	9 (21.4)	9 (21.4)	13 (31.0)	31 (24.6)	38 (22.8)
American Indian/Alaska Native	0	0	1 (2.4)	0	1 (0.8)	1 (0.6)
Native Hawaiian or Other Pacific Islander	0	2 (4.8)	1 (2.4)	0	3 (2.4)	3 (1.8)
Ethnicity, n (%)						
Hispanic or Latino	0	2 (4.8)	2 (4.8)	1 (2.4)	5 (4.0)	5 (3.0)
Not Hispanic or Latino	41 (100)	40 (95.2)	40 (95.2)	41 (97.6)	121 (96.0)	162 (97.0)
Weight overall (kg)						
Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Median (min, max)	71.50 (45.0, 150.1)	80.45 (46.2, 115.2)	79.75 (49.0, 136.5)	76.95 (50.0, 115.5)	78.90 (46.2, 136.5)	76.50 (45.0, 150.1)
Body mass index (kg/m^2), n (%)						
< 25	22 (53.7)	16 (38.1)	18 (42.9)	20 (47.6)	54 (42.9)	76 (45.5)
≥ 25 - < 30	11 (26.8)	13 (31.0)	11 (26.2)	11 (26.2)	35 (27.8)	46 (27.5)
≥ 30 - < 40	6 (14.6)	11 (26.2)	12 (28.6)	9 (21.4)	32 (25.4)	38 (22.8)
≥ 40	2 (4.9)	2 (4.8)	1 (2.4)	2 (4.8)	5 (4.0)	7 (4.2)
Body mass index (kg/m^2), n (%)						
Mean ± SD	26.17 ± 6.81	27.85 ± 6.26	27.35 ± 6.73	27.36 ± 6.04	27.52 ± 6.30	27.19 ± 6.44
Median (min, max)	24.20 (16.9, 51.8)	27.85 (16.8, 44.8)	25.80 (18.1, 41.9)	26.05 (19.8, 45.2)	26.50 (16.8, 45.2)	25.70 (16.8, 51.8)
Geographic Region, n (%)						
US/PR/Canada	29 (70.7)	29 (69.0)	29 (69.0)	29 (69.0)	87 (69.0)	116 (69.5)
EU/AUS	10 (24.4)	11 (26.2)	10 (23.8)	10 (23.8)	31 (24.6)	41 (24.6)
Japan	2 (4.9)	2 (4.8)	3 (7.1)	3 (7.1)	8 (6.3)	10 (6.0)
Nicotine use,[a,b] n (%)						
Current	6 (14.6)	9 (21.4)	9 (21.4)	9 (21.4)	27 (21.4)	33 (19.8)
Former	8 (19.5)	9 (21.4)	5 (11.9)	8 (19.0)	22 (17.5)	30 (18.0)
Never	27 (65.9)	24 (57.1)	28 (66.7)	25 (59.5)	77 (61.1)	104 (62.3)
Unknown	0	0	0	0	0	0
Alcohol use,[b] n (%)						
Current	Current	Current	Current	Current	Current	Current
Former	3 (7.3)	2 (4.8)	5 (11.9)	3 (7.1)	10 (7.9)	13 (7.8)
Never	4 (9.8)	10 (23.8)	9 (21.4)	7 (16.7)	26 (20.6)	30 (18.0)
Unknown	0	0	0	0	0	0

AUS = Australia; EU = European Union; PBO = placebo; PR = Puerto Rico; QD = once daily; SD = standard deviation; UPA = upadacitinib; US = United States

a. A subject may be a current user of one type of tobacco, a former user of another type of tobacco, and never used another type of tobacco.

b. A subject was counted in the category closest to user. Percentages were calculated on non-unknown values.

There were some numerical imbalances observed in Period 2 (likely due to small sample size in each treatment group), as per Table 35 below.

Table 35: Study M16-048 Demographic characteristics and baseline data (Period 2)

Period 1 Treatment	PBO/		UPA 7.5 mg QD/		UPA 15 mg QD/		UPA 30 mg QD/		
Period 2 Treatment	PBO	UPA 30 mg QD	PBO	UPA 7.5 mg QD	PBO	UPA 15 mg QD	PBO	UPA 30 mg QD	Overall Total
	(N = 10)	(N = 10)	(N = 15)	(N = 16)	(N = 19)	(N = 18)	(N = 19)	(N = 19)	(N = 126)
Sex, n (%)									
Female	4 (40.0)	4 (40.0)	5 (33.3)	4 (25.0)	7 (36.8)	2 (11.1)	11 (57.9)	8 (42.1)	45 (35.7)
Male	6 (60.0)	6 (60.0)	10 (66.7)	12 (75.0)	12 (63.2)	16 (88.9)	8 (42.1)	11 (57.9)	81 (64.3)
Age group (years), n (%)									
< 40	7 (70.0)	5 (50.0)	7 (46.7)	9 (56.3)	14 (73.7)	8 (44.4)	8 (42.1)	11 (57.9)	69 (54.8)
40 - 64	2 (20.0)	4 (40.0)	6 (40.0)	5 (31.3)	3 (15.8)	9 (50.0)	8 (42.1)	8 (42.1)	45 (35.7)
≥ 65	1 (10.0)	1 (10.0)	2 (13.3)	2 (12.5)	2 (10.5)	1 (5.6)	3 (15.8)	0	12 (9.5)
Age (years)									
Mean ± SD	38.3 ± 18.66	45.1 ± 18.65	43.3 ± 15.24	40.8 ± 17.32	35.4 ± 14.45	42.3 ± 16.97	45.1 ± 16.17	35.7 ± 13.09	40.5 ± 16.06
Median (min, max)	28.5 (23, 68)	44.5 (18, 71)	45.0 (24, 70)	37.5 (20, 69)	30.0 (20, 66)	44.0 (19, 75)	46.0 (19, 69)	31.0 (20, 63)	37.0 (18, 75)
Race, n (%)									
White	7 (70.0)	5 (50.0)	10 (66.7)	6 (37.5)	10 (52.6)	8 (44.4)	9 (47.4)	11 (57.9)	66 (52.4)
Black or African American	0	4 (40.0)	2 (13.3)	3 (18.8)	4 (21.1)	5 (27.8)	4 (21.1)	2 (10.5)	24 (19.0)
Asian	3 (30.0)	1 (10.0)	2 (13.3)	7 (3.8)	4 (21.1)	4 (22.2)	6 (31.6)	6 (31.6)	33 (26.2)
American Indian/Alaska Native	0	0	0	0	1 (5.3)	0	0	0	1 (0.8)
Native Hawaiian or Other Pacific Islander	0	0	1 (6.7)	0	0	1 (5.6)	0	0	2 (1.6)
Ethnicity, n (%)									
Hispanic or Latino	0	0	0	0	0	2 (11.1)	0	1 (5.3)	3 (2.4)
Not Hispanic or Latino	10 (100)	10 (100)	15 (100)	16 (100)	19 (100)	16 (88.9)	19 (100)	18 (94.7)	123 (97.6)
Weight overall (kg)									
Mean ± SD	72.26 ± 17.92	91.24 ± 26.25	86.17 ± 16.99	76.88 ± 17.90	83.47 ± 26.90	81.55 ± 16.41	75.88 ± 16.93	80.34 ± 17.10	80.79 ± 19.81
Median (min, max)	71.35 (47.1, 110.0)	87.60 (63.4, 150.1)	92.90 (50.9, 104.4)	74.10 (46.2, 114.6)	79.00 (49.0, 136.5)	80.55 (53.2, 112.5)	71.00 (50.0, 112.5)	77.50 (52.4, 115.5)	78.90 (46.2, 150.1)
Body mass index (kg/m^2), n (%)									
< 25	5 (50.0)	4 (40.0)	3 (20.0)	8 (50.0)	8 (42.1)	7 (38.9)	10 (52.6)	8 (42.1)	53 (42.1)
≥ 25 - < 30	4 (40.0)	2 (20.0)	6 (40.0)	3 (18.8)	5 (26.3)	6 (33.3)	6 (31.6)	4 (21.1)	36 (28.6)
≥ 30 - < 40	0	3 (30.0)	6 (40.0)	4 (25.0)	5 (26.3)	5 (27.8)	3 (15.8)	5 (26.3)	31 (24.6)
≥ 40	1 (10.0)	1 (10.0)	0	1 (6.3)	1 (5.3)	0	0	2 (10.5)	6 (4.8)
Body mass index (kg/m^2), n (%)									
Mean ± SD	25.79 ± 6.77	30.09 ± 9.23	28.86 ± 5.75	26.83 ± 6.89	27.57 ± 7.30	27.03 ± 5.87	26.59 ± 5.04	28.39 ± 7.23	27.59 ± 6.61
Median (min, max)	24.85 (16.9, 43.0)	28.05 (21.9,	29.10 (17.5, 36.3)	26.10 (16.8, 44.8)	25.40 (18.1, 41.9)	26.80 (19.0, 37.2)	24.80 (20.8, 37.1)	26.50 (19.8, 45.2)	26.35 (16.8, 51.8)
Geographic Region, n (%)									
US/PR/Canada	9 (90.0)	10 (100)	12 (80.0)	11 (68.8)	14 (73.7)	13 (72.2)	14 (73.7)	15 (78.9)	98 (77.8)
EU/AUS	1 (10.0)	0	2 (13.3)	4 (25.0)	3 (15.8)	4 (22.2)	4 (21.1)	3 (15.8)	21 (16.7)
Japan	0	0	1 (6.7)	1 (6.3)	2 (10.5)	1 (5.6)	1 (5.3)	1 (5.3)	7 (5.6)
Nicotine use,[a,b] n (%)									
Current	0	0	1 (6.7)	4 (25.0)	4 (21.1)	4 (22.2)	4 (21.1)	5 (26.3)	22 (17.5)
Former	3 (30.0)	2 (20.0)	4 (26.7)	3 (18.8)	1 (5.3)	2 (11.1)	3 (15.8)	4 (21.1)	22 (17.5)
Never	7 (70.0)	8 (80.0)	10 (66.7)	9 (56.3)	14 (73.7)	12 (66.7)	12 (63.2)	10 (52.6)	82 (65.1)
Alcohol use,[b] n (%)									
Current	9 (90.0)	7 (70.0)	11 (73.3)	10 (62.5)	11 (57.9)	14 (77.8)	12 (63.2)	16 (84.2)	90 (71.4)
Former	0	2 (20.0)	1 (6.7)	1 (6.3)	3 (15.8)	1 (5.6)	2 (10.5)	1 (5.3)	11 (8.7)
Never	1 (10.0)	1 (10.0)	3 (20.0)	5 (31.3)	5 (26.3)	3 (16.7)	5 (26.3)	2 (10.5)	25 (19.8)
Unknown	0	0	0	0	0	0	0	0	0

The baseline disease characteristics were generally balanced across the upadacitinib and placebo groups in Period 1 and between those subjects who were re-randomised to the upadacitinib and placebo groups in Period 2. Overall, the most common medical/surgical history by body system was immune system disorders (58.1%; of which seasonal allergy, 20.4%; and multiple allergies, 16.8%), followed by respiratory, thoracic and mediastinal disorders (44.9%) with similar incidences across all treatment groups. There were few subjects with latent TB at screening or prior to entering the study across the treatment groups (2.4%, 4.8%, 0%, and 0% in upadacitinib 30 mg, upadacitinib 15 mg, upadacitinib 7.5 mg, and placebo groups, respectively). All subjects with latent TB received prophylaxis prior to or during the study.

Subjects had been diagnosed with atopic dermatitis for a mean of approximately 26.0 years.

The clinical evaluation noted that in Period 1, there were more subjects with severe eczema in terms of IGA in the placebo and upadacitinib 15 mg groups (55 to 56%) compared to the upadacitinib 7.5 mg and upadacitinib 30 mg groups (26 to 31%).

Topical corticosteroids were the most frequently reported prior medication; Eucerin (46%) (an emollient) and betamethasone (32%) were used most frequently across treatment groups, with some imbalances in terms of prior use in upadacitinib and placebo groups.

The clinical evaluation noted that the following statement in the clinical study report is incorrect:

> Eucerin was the most frequently reported prior medication for subjects in the upadacitinib 15 mg, 30 mg, and placebo groups. Betamethasone was the most frequently reported prior medication for subjects in the upadacitinib 7.5 mg group';

It is noted, that prior use of Eucerin (a lanolin, water and oil (petrolatum) based emollient) was more frequent in the upadacitinib 15 mg and upadacitinib 30 mg groups (52 to 55%) compared to the placebo and upadacitinib 7.5 mg groups (38 to 39%). Prior use of betamethasone was slightly lower in the placebo (24.4%) compared to the upadacitinib groups (31%, 35.7% and 38.1% in upadacitinib 7.5 mg, 15 mg and 30 mg groups, respectively).

Approximately 94% of the subjects in the study reported use of concomitant medications during the study. The use of the most frequent concomitant medication (Eucerin) was higher in the upadacitinib 15 mg and 30 mg groups (36.6%, 35.7%, 47.6% and 52.4% in placebo, upadacitinib 7.5 mg, 15 mg and 30 mg groups, respectively).

There were some numerical imbalances in terms of concomitant use of other commonly used drugs such as antihistamines (cetirizine, diphenhydramine, hydroxyzine) as well.

The clinical evaluation noted that the clinical study report mentions that 43% of concomitant medications were 'not coded'. As part of the submission evaluation, the sponsor was requested to clarify what 'not coded' means and also to provide table of concomitant medications by therapeutic class of drugs used.

Mean treatment compliance in Period 1 was 162.95% 96.01%, 96.56%, and 98.27% in placebo, upadacitinib 7.5 mg, 15 mg and 30 mg groups, respectively. Mean compliance rate greater than 100% was due to subjects in the placebo group who were prematurely discontinued from study drug and did not return any pills back from the last dispensed drug kit. The median treatment compliance in Period 1 was 98.34%, 100%, 98.2%, and 99.55%, respectively.

Among re-randomised subjects in Period 2, mean treatment compliance ranged from 96.62% to 106.25% while the median treatment compliance ranged from 96.81% to 100.00%.

The clinical evaluation noted that compliance in Period 1 was calculated as the number of tablets taken divided by the number of tablets planned to be taken by the subject during the double-blind treatment period of the study. Compliance in Period 2 was calculated up to the date prior to the first dose of rescue. Based on a daily dose of one tablet for the study drug, treatment compliance was calculated as: number of tablets taken divided by the duration of treatment, multiplied by 100%.

Results for the efficacy outcomes

Primary endpoint

The primary endpoint (percent change from Baseline in EASI score at Week 16) showed statistically significantly higher and dose-dependent mean percentage improvement from Baseline in EASI with upadacitinib (7.5 mg, 15 mg, and 30 mg) compared to placebo (23%, 39%, 62% and 74% in placebo, upadacitinib 7.5 mg, 15 mg and 30 mg groups, respectively).

Table 36: Study M16-048 Results for the primary endpoint, percent change from Baseline in EASI score at Week 16 (last observation carried forward, ITT population, Period 1)

IMPUTATION VISIT	STRATA	TREATMENT	N	BASELINE MEAN	VISIT MEAN	WITHIN GROUP -PERCENT CHANGE FROM BASELINE- LSMEAN	SE	BETWEEN GROUP COMPARISON COMPARED TO PLACEBO LSMEAN DIFF	95% CI	SE	P-VALUE [A]
LOCF WEEK 16	ALL	UPA 30 MG QD	42	28.2	5.8	-74.4	6.13	-51.4	(-66.5, -36.3)	7.65	<0.001***
		UPA 15 MG QD	42	31.4	11.7	-61.7	6.12	-38.7	(-53.7, -23.6)	7.61	<0.001***
		UPA 7.5 MG QD	42	31.4	18.8	-39.4	6.24	-16.4	(-31.4, -1.4)	7.61	0.032*
		PLACEBO	39	32.1	23.9	-23.0	6.42				

Abbreviations: CI = confidence intervals; EASI = Eczema Area and Severity Index response; ITT = intention to treat; LOCF = last observation carried forward; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

Table 37: Study M16-048 Results for the primary endpoint, percent change from Baseline in EASI score at Week 16 (observed case analysis, ITT population, Period 1)

PERCENT CHANGE FROM BASELINE IN EASI SCORE BY VISIT DURING PERIOD 1 (LOCF, OC)
(ITT_1 POPULATION)

IMPUTATION VISIT	STRATA	TREATMENT	N	BASELINE MEAN	VISIT MEAN	WITHIN GROUP -PERCENT CHANGE FROM BASELINE- LSMEAN	SE	BETWEEN GROUP COMPARISON COMPARED TO PLACEBO LSMEAN DIFF	95% CI	SE	P-VALUE [A]
OBSERVED CASE WEEK 16	ALL	UPA 30 MG QD	40	27.2	5.0	-74.6	5.49	-38.8	(-54.0, -23.6)	7.69	<0.001***
		UPA 15 MG QD	38	32.2	10.9	-67.1	5.56	-31.3	(-46.4, -16.1)	7.65	<0.001***
		UPA 7.5 MG QD	34	32.0	17.6	-47.3	5.90	-11.5	(-27.0, 4.0)	7.82	0.144
		PLACEBO	25	34.6	22.9	-35.8	6.74				

Abbreviations: CI = confidence intervals; EASI = Eczema Area and Severity Index response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

The clinical evaluation noted that although the last observation carried forward (LOCF) analysis showed statistically significant improvement for all upadacitinib doses, the observed case analysis did not show statistical significant improvement for the upadacitinib 7.5 mg dose.

Secondary and exploratory endpoints

Clinically meaningful and highly statistically significant dose-dependent improvements were observed for all key secondary endpoints in all upadacitinib dose groups (7.5 mg, 15 mg and 30 mg) compared with the placebo group, as per the table below.

Table 38: Study M16-048 Summary of key secondary endpoint results (ITT population)

	Week 16 (unless otherwise specified)			
	PBO (N = 41)	UPA 7.5 mg QD (N = 42)	UPA 15 mg QD (N = 42)	UPA 30 mg QD (N = 42)
EASI score				
% change in EASI at Wk 8, LS mean	18%	44%***	65%***	83%***
EASI 50 at Wk 16, %	22%	50%**	71%***	83%***
EASI 50 at Wk 8, %	22%	55%***	71%***	93%***
EASI 75 at Wk 16, %	10%	29%*	52%***	69%***
EASI 75 at Wk 8, %	7%	31%**	52%***	81%***
EASI 90 at Wk 16, %	2%	14%*	26%**	50%***
EASI 90 at Wk 8, %	0%	10%	26%***	45%***
IGA score				
0/1 Score at Wk 16, %	2%	14%*	31%***	50%***
Pruritus NRS				
% change in pruritus NRS at Wk 16, LS mean	10%	40%**	48%***	69%***
pruritus NRS score improvement ≥ 4-point from Baseline of ≥ 4 at Wk 16	6%	24%*	59%***	53%***
SCORAD score				
% change in SCORAD score at Wk 16, LS mean	12%	33% **	47%***	60%***
% change in SCORAD score at Wk 8, LS mean	7%	35%***	44%***	65%***
SCORAD 50 at Wk 16, %	7%	29%**	43%***	62%***
SCORAD 50 at Wk 8, %	7%	33%**	43%***	76%***
SCORAD 75 at Wk 16, %	2%	5%	21%**	41%***
SCORAD 75 at Wk 8, %	0%	10%*	10%	31%***
SCORAD 90 at Wk 16, %	0%	2%	10%*	24%***
SCORAD 90 at Wk 8, %	0%	5%	2%	14%*
BSA				
% BSA affected at Wk 16, LS mean	4%	12%	27%***	31%***

BSA = body surface area; CI = confidence interval; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; LS = least square; NRS = Numerical Rating Scale; PBO = placebo; QD = once daily; SCORAD = Scoring Atopic Dermatitis; UPA = upadacitinib; Wk = Week

*p < 0.05, **p < 0.01, ***p < 0.001

The clinical evaluation noted that the majority of the endpoints showed numerically greater improvements with the 30 mg dose compared to the 15 mg dose with exception of improvement in pruritus score (6%, 24%, 59% and 53% in placebo, upadacitinib 7.5 mg, 15 mg and 30 mg groups, respectively).

In Period 2 a statistically significant difference was observed following upadacitinib treatment in the percent change from Week 16 (re-randomisation) of EASI score at all visits except Week 40 for upadacitinib 30 mg/upadacitinib 30 mg compared to upadacitinib 30 mg/placebo.

In Period 2, for the upadacitinib 30 mg and 15 mg doses, point estimates indicated better response rates for continued treatment versus withdrawal of treatment, with statistically significant differences observed at Week 32 in the achievement of EASI 75 response, and a 4-point reduction in pruritus NRS. Loss of EASI 50 occurred sooner and more frequently in the withdrawal groups. Switching from placebo to upadacitinib 30 mg confirmed efficacy results that was observed with upadacitinib 30 mg in Period 1. For subjects who were on upadacitinib 7.5 mg, 15 mg, or 30 mg from Baseline through Week 88, efficacy response was either maintained or further improved.

The clinical evaluation noted that upadacitinib 30 mg demonstrated the best efficacy over time in all key efficacy variables across Period 1 and Period 2. However, interpretation

may have been confounded by imbalance in distribution of patients with severe eczema at baseline (there were more subjects with severe eczema in terms of IGA in the placebo and upadacitinib 15 mg groups (55 to 56%) compared to the upadacitinib 7.5 mg and 30 mg groups (26 to 31%)).

The number of subjects who were re-randomised as EASI 75 non-responders at Week 16 (time of entry into Period 2) and (later) achieved an EASI 75 response was small among the treatment groups.

Lack of EASI-75 response in subjects who were non-responders at Week 16 suggests that continuing treatment beyond 16 weeks in non-responders is unlikely to provide any benefit.

A general reduction of scratching events per hour was observed following upadacitinib treatment (30 mg, 15 mg, and 7.5 mg) compared to placebo in Period 1. Significant improvement was observed following all upadacitinib groups (30 mg, 15 mg, and 7.5 mg) compared to placebo during Weeks 1 through 4 and through Week 16, following upadacitinib 30 mg compared to placebo.

No significant improvement was observed following any upadacitinib treatment compared to placebo for total sleep time per night (TST; minimum value) or wake after sleep onset (WASO), with the exception of upadacitinib 30 mg at Weeks 5, 6, and 11 for TST and Weeks 2 to 4 and Week 9 for WASO.

No deterioration or improvement in asthma or nasal symptoms were observed as reflected in the Asthma Symptoms Questionnaire and the Nasal Symptoms Questionnaire at Weeks 16 and 40 compared to Baseline.

Study M17-377 (supportive study)

Study M17-377 was a Phase III, randomised, double-blind, multicentre study that evaluated upadacitinib combined with topical corticosteroids in adolescent and adult subjects in Japan, with moderate to severe atopic dermatitis who were candidates for systemic therapy.

The study design included a 35-day screening period; a 16-week double blind treatment period; a 36-week blinded expansion period (Week 16 to 52); an open-label long-term extension (Week 52 to Week 136) or permanent withdrawal of the marketing application; a 30-day follow-up Visit.

Primary objective

The primary objective was:

- To assess the safety of upadacitinib combined with topical corticosteroids in adolescent and adult subjects in Japan with moderate to severe atopic dermatitis who are candidates for systemic therapy.

Inclusion criteria

- Eligible subjects must have had a documented history of inadequate response to treatment with topical atopic dermatitis treatments or documented systemic treatment for atopic dermatitis within 6 months prior to the baseline visit;

Study treatments

Subjects who met eligibility criteria were randomised in a 1:1:1 ratio to receive, in combination with topical corticosteroids, daily oral doses of upadacitinib 15 mg, upadacitinib 30 mg, or placebo until Week 16.

At the end of Week 16, subjects in the placebo group were re-randomised in a 1:1 ratio to receive daily oral doses either of upadacitinib 15 mg or of upadacitinib 30 mg

Subjects originally in the upadacitinib 15 mg once daily and upadacitinib 30 mg once daily groups continued their treatment into the long-term extension period up to Week 136.

Required concomitant medications

A topical corticosteroid regimen in combination with study drug was mandatory until Week 16. After Week 16, the use of any concomitant topical medication for atopic dermatitis could be administered per investigator's discretion and was no longer required.

Rescue therapy

High potency topical corticosteroids were not considered as rescue treatment after Week 16. At Week 4 through Week 24, rescue treatment for atopic dermatitis may be provided at the discretion of the investigator if medically necessary (that is, to control intolerable atopic dermatitis symptoms). The latter refers to subjects with < 50% reduction in EASI 50 response at any 2 consecutive scheduled visits. After Week 24, systemic rescue treatment may be provided for subjects with < EASI 50 response at any scheduled or unscheduled visit.

Randomisation

Randomisation was stratified by baseline disease severity (moderate validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD 3) versus severe vIGA-AD 4); and age (< 18 years versus 18 to 40 years versus > 40 years old).

Re-randomisation was stratified by 50% reduction in Eczema Area and Severity Index (EASI 50) responder (Yes/No) plus the above stated parameters.

Efficacy parameters and endpoints

See Section: *Scoring systems used in the clinical studies* for information on the scoring systems and measures used.

Exploratory endpoints were:

- Proportion of subjects achieving vIGA-AD 0 or 1 with at least 2 grades of reduction from Baseline;
- Proportion of subjects achieving EASI 50/75/90) from Baseline;
- Change and percent change from Baseline in EASI;
- Proportion of subjects achieving an improvement (reduction) in worst pruritus Numerical
- Rating Scale (NRS) ≥ 4 from Baseline;
- Change and percent change from Baseline in worst pruritus NRS.

Participants flow and sample size

Overall, 272 subjects were randomised and received study drug:

- n = 90 for placebo + topical corticosteroids;
- n = 91 for upadacitinib 15 mg + topical corticosteroids;
- n = 91 for upadacitinib 30 mg + topical corticosteroids;

264 subjects (97.1%) completed the study through Week 16 (double blinded period) and continued to the blinded extension/open-label periods.

Six (6) and five (5) subjects discontinued the study during the double blinded and blinded extension/open-label periods, respectively. The most frequent primary reason for study discontinuation was withdrawal by subjects in both study periods.

Analysis of populations

The sample size was determined to meet regulatory requirements for safety exposure in Japan. The Intent-to-Treat (ITT) population, which includes all randomised subjects, was used for all efficacy analyses.

The clinical evaluation noted that subjects were analysed according to treatment as randomised, regardless of which treatment the subjects actually received. Subjects who were randomised to placebo in double blind Period and did not continue into blinded extension/open-label periods were automatically excluded from the analysis in blinded extension/open-label periods.

Baseline data

Demographic characteristics were generally balanced across the treatment groups as shown below.

Table 39: Study M17-377 Demographic characteristics and baseline data

	PBO (N = 90)	UPA 15 mg QD (N = 91)	UPA 30 mg QD (N = 91)	UPA Total (N = 182)	Total (N = 272)
Sex - n (%)					
Female	16 (17.8)	23 (25.3)	22 (24.2)	45 (24.7)	61 (22.4)
Male	74 (82.2)	68 (74.7)	69 (75.8)	137 (75.3)	211 (77.6)
Age (years)					
Mean (SD)	36.3 (12.64)	35.9 (13.22)	34.7 (12.74)	35.3 (12.96)	35.6 (12.84)
Median (Min, Max)	37.0 (13, 59)	37.0 (13, 66)	34.0 (13, 66)	35.0 (13, 66)	36.0 (13, 66)
Age group (years) - n (%)					
< 18	9 (10.0)	8 (8.8)	8 (8.8)	16 (8.8)	25 (9.2)
≥ 18	81 (90.0)	83 (91.2)	83 (91.2)	166 (91.2)	247 (90.8)
18 - < 40	44 (48.9)	45 (49.5)	47 (51.6)	92 (50.5)	136 (50.0)
40 - < 65	37 (41.1)	37 (40.7)	35 (38.5)	72 (39.6)	109 (40.1)
≥ 65	0	1 (1.1)	1 (1.1)	2 (1.1)	2 (0.7)
Race - n (%)					
Asian[a]	90 (100)	91 (100)	91 (100)	182 (100)	272 (100)
Ethnicity - n (%)					
Not Hispanic or Latino	90 (100)	91 (100)	91 (100)	182 (100)	272 (100)
Weight (kg)					
Mean (SD)	67.64 (12.755)	65.05 (14.164)	66.22 (14.398)	65.63 (14.254)	66.30 (13.785)
Median (Min, Max)	65.80 (43.7, 98.0)	64.00 (36.1, 105.0)	65.60 (40.6, 101.6)	64.20 (36.1, 105.0)	64.70 (36.1, 105.0)
BMI (kg/m^2) - n (%)					
< 25	55 (61.1)	63 (69.2)	60 (65.9)	123 (67.6)	178 (65.4)
25 - < 30	26 (28.9)	19 (20.9)	21 (23.1)	40 (22.0)	66 (24.3)
≥ 30	9 (10.0)	9 (9.9)	10 (11.0)	19 (10.4)	28 (10.3)
Tobacco use[b] – n (%)					
Current	27 (30.0)	19 (20.9)	18 (19.8)	37 (20.3)	64 (23.5)
Former	11 (12.2)	11 (12.1)	12 (13.2)	23 (12.6)	34 (12.5)
Never	52 (57.8)	61 (67.0)	61 (67.0)	122 (67.0)	174 (64.0)
Alcohol[b] - n (%)					
Current	53 (58.9)	54 (60.0)	60 (65.9)	114 (63.0)	167 (61.6)
Former	7 (7.8)	5 (5.6)	8 (8.8)	13 (7.2)	20 (7.4)
Never	30 (33.3)	31 (34.4)	23 (25.3)	54 (29.8)	84 (31.0)
Unknown	0	1	0	1	1

a. All subjects in this study were Japanese.

b. A subject may be current user of one type of tobacco, a former user of another type of tobacco and never used another type of tobacco.

Note: Percentages calculated on non-missing/unknown values.

The majority of subjects were male and with a body mass index of less than 25 kg/m^2. The median age of subjects was 36 years (50% aged 18 to < 40 years and 40% were aged 40 to ≤ 65 years); 9.2% of overall ITT population were adolescents (median age 16 years).

Baseline disease characteristics were generally balanced across the upadacitinib and placebo groups. Baseline disease characteristics in adolescents were generally similar to the overall ITT population.

Subjects had been diagnosed with atopic dermatitis for a mean of approximately 23.0 years, had a mean baseline EASI score of 34.91, a mean baseline vIGA-AD score of 3.5, and a mean worst pruritus NRS score (weekly rolling average) of 6.8. The mean duration of time since atopic dermatitis diagnosis in adolescents was 10.65 years for adolescents.

All enrolled subjects had inadequate response to previous treatment with topical atopic dermatitis treatments.

White/soft paraffin (85.7%) followed by betamethasone (79.8%) were the most frequently reported prior medication for subjects in the ITT population.

All subjects in the study reported use of concomitant medications during the study in both the double blinded and blinded extension/open-label periods; topical corticosteroids (prednisolone, mometasone) was used most commonly followed by antihistamines and moisturisers). Almost 50% of subjects overall were using products containing heparinoid in this Japanese study.

In the double blind period, mean treatment compliance was 97.76%, and 98.04%, and 97.16% in the placebo, upadacitinib 15 mg and 30 mg groups, respectively and median treatment compliance was > 99% in all treatment groups. In the blinded extension/open-label period, mean treatment compliance ranged from 77.41% (placebo/upadacitinib 15 mg once daily group) to 81.16% (upadacitinib 15 mg once daily/ upadacitinib 15 mg once daily group); median treatment compliance ranged from 76.62% to 83.50%.

Major protocol violations and deviations

The overall incidence of protocol deviations was 16.2% (44/272) and similar across treatment groups (16.7%, 17.6% and 14.3% in the placebo, upadacitinib 15 mg and 30 mg groups, respectively). The most frequently reported protocol deviations were related to compliance issues and subject receiving excluded concomitant medications.

Results for the efficacy endpoints

The efficacy endpoints in Study M17-377 were all exploratory endpoints.

At Week 16, a statistically significantly higher percentage of subjects in both of the upadacitinib groups had clear or almost clear skin with at least 2 grades of reduction compared to the placebo group, and these improvements were maintained through Week 24. Similar results were observed for EASI 50/ 75 /90 response rates and improvement (reduction) in Worst Pruritus NRS > 4 from baseline for subjects with worst Pruritus NRS > 4 at Baseline, as per Table 40, below.

Table 40: Study M17-377 Summary of Exploratory Efficacy Variables at Week 16 (ITT population)

Efficacy Variable	PBO (N = 90)	UPA 15 mg QD (N = 91)	UPA 30 mg QD (N = 91)
vIGA-AD Score of 0/1 (NRI), n (%) [95% CI][a]	6 (6.7) [1.5, 11.8]	37 (40.7) [30.6, 50.8]	43 (47.3) [37.0, 57.5]
vIGA-AD Score of 0 (NRI), n (%) [95% CI]	1 (1.1) [0.0, 3.3]	0 [0.0, 0.0]	4 (4.4) [0.2, 8.6]
% change in EASI (MMRM) LS Mean (SE) [95% CI]	−36.85 (3.885) [−44.49, −29.21]	−75.40 (3.479) [−82.25, −68.55]	−82.34 (3.493) [−89.22, −75.46]
EASI 100 (NRI), n (%) [95% CI]	1 (1.1) [0.0, 3.3]	0 [0.0, 0.0]	4 (4.4) [0.2, 8.6]
EASI 90 (NRI), n (%) [95% CI]	6 (6.7) [1.5, 11.8]	38 (41.8) [31.6, 51.9]	44 (48.4) [38.1, 58.6]
EASI 75 (NRI), n (%) [95% CI]	17 (18.9) [10.8, 27.0]	59 (64.8) [55.0, 74.6]	68 (74.7) [65.8, 83.7]
EASI 50 (NRI), n (%) [95% CI]	26 (28.9) [19.5, 38.3]	77 (84.6) [77.2, 92.0]	79 (86.8) [79.9, 93.8]
Reduction in worst pruritus NRS ≥ 4 from Baseline[b] (NRI), n (%) [95% CI]	11 (12.2) [5.5, 19.0]	37 (41.1)[c] [30.9, 51.3]	43 (47.3) [37.0, 57.5]
Percent change from Baseline in worst pruritus NRS (MMRM), LS Mean (SE) [95% CI]	−28.323 (3.9658) [−36.124, −20.523]	−47.095 (3.6933) [−54.363, −39.826]	−53.654 (3.6840) [−60.904, −46.403]

CI = confidence interval; DB = double blind; LS Mean = least squares mean; MMRM = Mixed-Effect Model Repeat Measurement; NRI = non-responder imputation; NRS = numerical rating score; PBO = placebo; QD = once daily; SE = standard error; UPA = upadacitinib; vIGA-AD = validated Investigator Global Assessment for atopic dermatitis

a. With at least 2 grades of reduction.

b. Among subjects with baseline pruritus NRS ≥ 4.

c. N = 90.

The efficacy results in the upadacitinib 30 mg group were numerically higher than in the upadacitinib 15 mg group. Improvements in efficacy measures were observed from Week 4 and, maintained throughout the double blind period (up to Week 16);

In adolescents, both upadacitinib 15 mg and 30 mg showed numerically higher efficacy than placebo for all exploratory efficacy variables.

The clinical evaluation noted that exploratory efficacy analyses during the placebo-controlled period showed that upadacitinib 15 mg and 30 mg had higher response rates than placebo including EASI 75, achievement of vIGA-AD score 0 or 1, and reduction of worst pruritus NRS ≥ 4, which were maintained up to the cutoff date (Week 24).

Analyses performed across trials: pooled efficacy and meta-analyses

An integrated analysis of efficacy was conducted for the 2 monotherapy studies (Studies M16-045 and M18-891, discussed individually under Sections: *Study M16-045* (monotherapy) and *Study M18-891* (monotherapy), above), given their design similarities. The integration relates to the efficacy outcome from the randomised double blind period in the two studies at Week 16.

From the Integrated Summary of Efficacy (ISE), the clinical evaluation noted that there was:

- a statistically and clinically significant improvements with upadacitinib 30 mg and upadacitinib 15 mg as monotherapy compared to placebo in the co-primary endpoints of vIGA-AD 0/1 and EASI 75 at Week 16, as per the table below. This was supported by the sensitivity analyses (NRI-C, multiple imputation, and tipping point), see Table 41 (below).

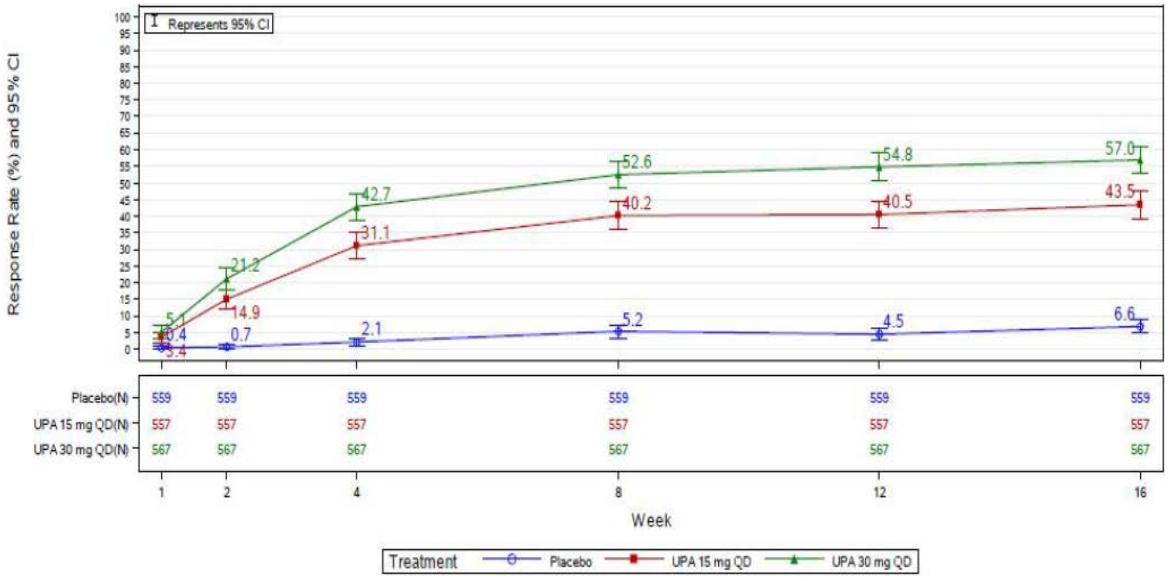
Table 41: Integrated monotherapy Studies M16-045 and M18-891; Primary efficacy results at Week 16 (NRI-C, all subjects)

Assessment/ Treatment	N	Within Group Point Estimate (95% CI)	Point Estimate vs. Placebo (95% CI)	Nominal p-value	Multiplicity Adjusted Result
EASI 75 at Week 16					
Placebo	559	14.8 (11.9, 17.8)			
UPA 15 mg	557	64.9 (60.9, 68.9)	50.1 (45.2, 55.0)	< 0.001	Significant
UPA 30 mg	567	76.3 (72.8, 79.9)	61.5 (57.0, 66.1)	< 0.001	Significant
vIGA-AD Score 0/1 at Week 16					
Placebo	559	6.6 (4.6, 8.7)			
UPA 15 mg	557	43.5 (39.4, 47.6)	36.8 (32.3, 41.4)	< 0.001	Significant
UPA 30 mg	567	57.0 (52.9, 61.1)	50.4 (45.9, 54.9)	< 0.001	Significant

Abbreviations: CI = confidence intervals; EASI 75 = Eczema Area and Severity Index 75 response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib; vIGA-AD = validated investigator's global assessment.

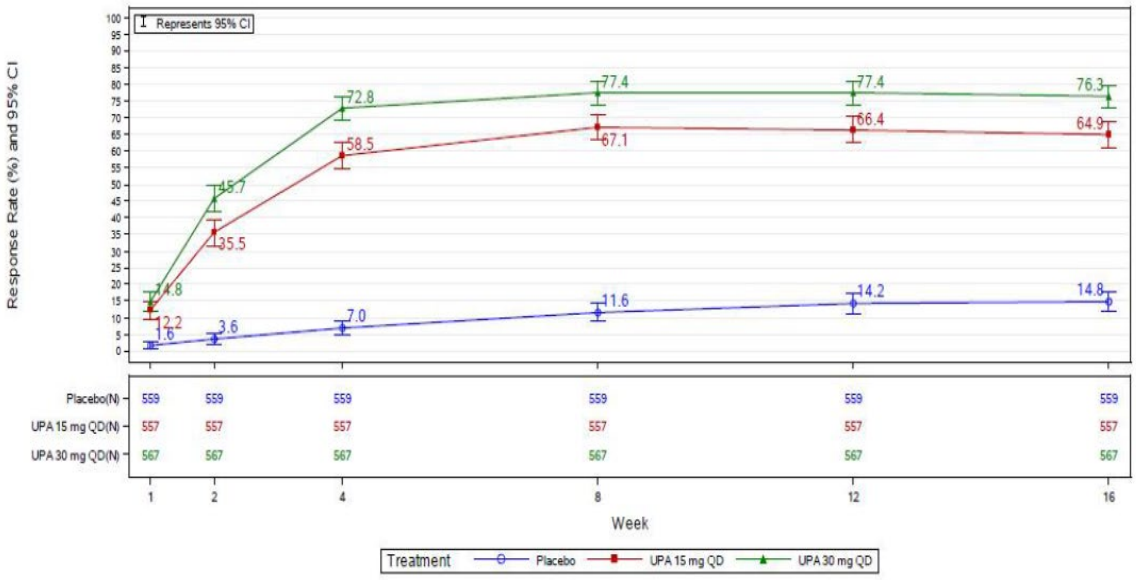
Skin clearance and disease activity based on vIGA-AD 0/1 and EASI 75, showed significantly greater improvements with both upadacitinib 30 mg and 15 mg compared with placebo at Week 16. The upadacitinib 30 mg group showed consistently higher response rates (> 10%) compared to the upadacitinib 15 mg group with non-overlapping 95% confidence intervals between the two upadacitinib doses. Furthermore, upadacitinib-treated patients demonstrated rapid onset of action with significant improvements over placebo from Week 2, which were then maintained until Week 16, as shown in the figures below.

Figure 35: Integrated monotherapy Studies M16-045 and M18-891; Subjects who achieved vIGA-AD 0/1 through Week 16 (placebo-controlled population, NRI-C)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib; vIGA-AD = validated investigator's global assessment.

Figure 36: Integrated monotherapy Studies M16-045 and M18-891; Subjects who achieved EASI 75 through Week 16 (placebo-controlled population, NRI-C)



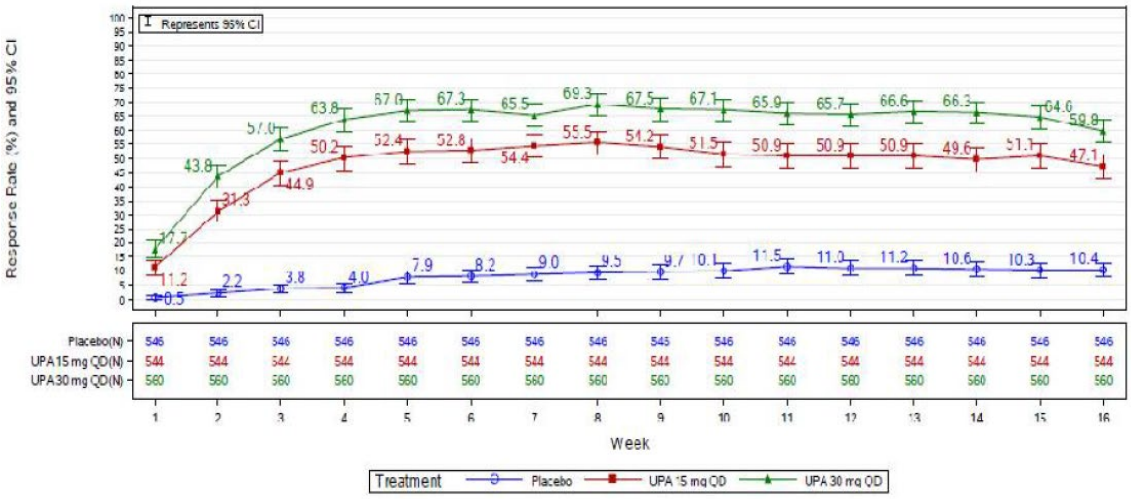
Abbreviations: CI = confidence intervals; EASI = Eczema Area and Severity Index response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

Similar favourable results were observed in adolescents following treatment with upadacitinib 30 mg and 15 mg compared with placebo.

Fewer subjects experienced a flare on upadacitinib 30 mg once daily (0.7%) and upadacitinib 15 mg once daily (1.6%) than placebo (24.9%) in the overall subject population with a similar trend seen in adolescents.

Compared with placebo, both upadacitinib 30 mg and 15 mg demonstrated significantly greater itch reduction (based on improvement in Worst Pruritus NRS ≥ 4 at Week 16) with higher response rates in the 30 mg dose group (compared to the 15 mg dose), as per the figure below.

Figure 37: Integrated monotherapy Studies M16-045 and M18-891; Subjects who achieved worst pruritus NRS > 4 through Week 16 (placebo-controlled population, NRI-C)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; NRS = numerical rating scale; QD = once daily; UPA = upadacitinib.

Adolescents demonstrated similarly favorable results on itch reduction with upadacitinib 30 mg and 15 mg compared with placebo.

Subjects on upadacitinib (30 mg and 15 mg once daily) also achieved clinically meaningful improvement in patient reported outcomes in both adults and adolescents. Among subjects with a HADS-A ≥ 8 or HADS-D ≥ 8 at Baseline, a greater proportion of subjects on upadacitinib (30 mg and 15 mg once daily) achieved HADS scores within the normal range on both subscales at Week 12 and Week 16 compared to subjects on placebo (nominal $p < 0.001$) with similar results observed in adolescents. Greater proportions of subjects (both ≥ 16 years and < 16 years) showed improvement in DLQI outcome measures (reduction ≥ 4, DLQI 0/1) at each post-baseline visit in the double blind period (Week 8 and Week 16) compared to placebo (nominal $p < 0.001$).

An integrated analysis of efficacy was also conducted, based on observed cases for the two monotherapy studies (Studies M16-045 and M18-891) this time, on the efficacy outcome from the long-term randomised blinded extension period, up to Week 52. Additional (*post-hoc*) analyses were requested from the Swedish Medical Products Agency for long-term analysis in the integrated summary of efficacy for EASI 75, vIGA-AD 0/1 and improvement in Worst Pruritus NRS ≥ 4 using multiple imputation.

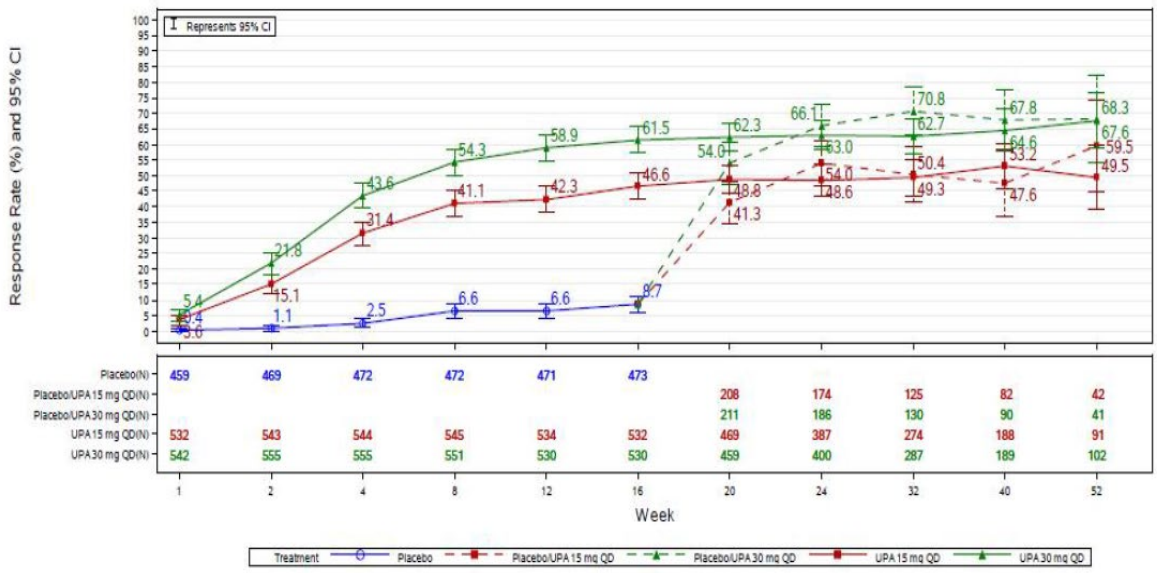
It is noted, that the blinded extension period was scheduled for 136 weeks.

From the above analyses, the clinical evaluation stated that:

- The mean duration of exposure at the cut-off date was 250.1 to 251.9 days (SD 109.52 to 113.10) for subjects originally randomised to upadacitinib and who remained on upadacitinib; and 153.4 to 155.5 days (SD 101.21 to 104.67) for subjects originally randomised to placebo and who switched to upadacitinib (30 mg or 15 mg) at Week 16. There were 223 subjects on upadacitinib including 17 subjects who began the study on placebo at Week 52. Similar long-term exposure was observed in adolescents with 36 adolescents on upadacitinib treatment at the Week 52 visit.
- In the observed case analysis, among subjects who were initially randomised to placebo and switched to upadacitinib at Week 16, the proportion of subjects who achieved vIGA-AD 0/1 by the next scheduled visit was similar to the response rates in

those subjects initially randomised to upadacitinib. Among subjects who were initially randomised to upadacitinib and continued on upadacitinib, the proportion of subjects who achieved vIGA-AD 0/1 was maintained at similar response rates beyond Week 16 with the upadacitinib 30 mg group achieving higher rates than upadacitinib 15 mg through Week 52, as per the figure below.

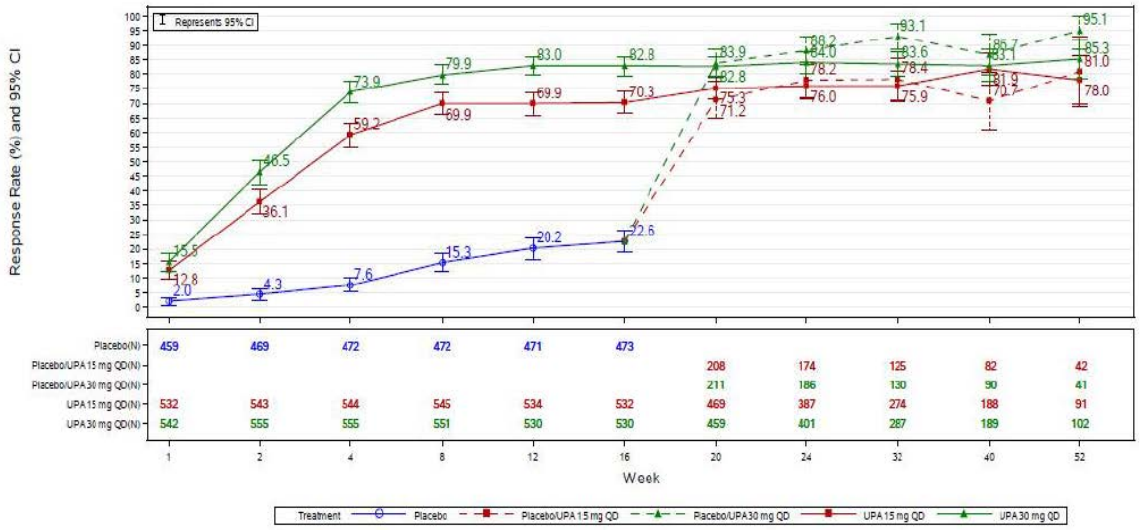
Figure 38: Integrated monotherapy Studies M16-045 and M18-891; Subjects achieving vIGA-AD 0/1 through Week 52 (long-term upadacitinib population, observed case analysis)



Abbreviations: CI = confidence intervals; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib; vIGA-AD = validated investigator's global assessment.

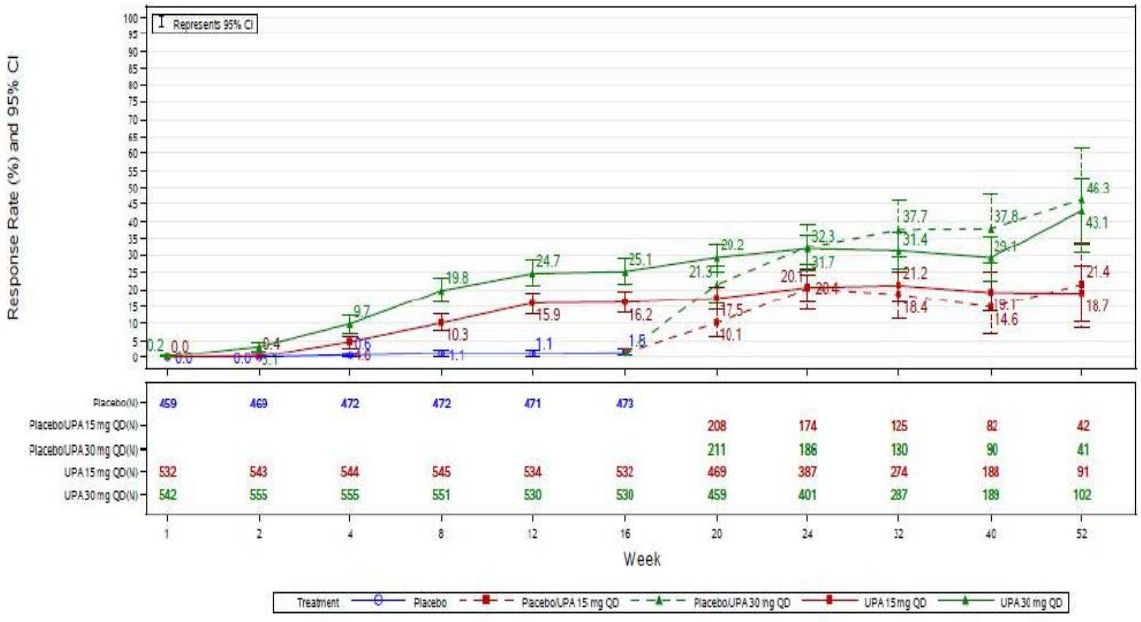
Similar patterns of improvements were observed following observed case analysis for EASI 75 and EASI 100 as per the figures below.

Figure 39: Integrated monotherapy Studies M16-045 and M18-891; Subjects achieving EASI 75 through Week 52 (long-term upadacitinib population, observed case analysis)



Abbreviations: CI = confidence intervals; EASI 75 = Eczema Area and Severity Index 75 response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

Figure 40: Integrated monotherapy Studies M16-045 and M18-891; Subjects achieving EASI 100 through Week 52 (long-term upadacitinib population, observed case analysis)



Abbreviations: CI = confidence intervals; EASI 100 = Eczema Area and Severity Index 100 response; ITT = intention to treat; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; QD = once daily; UPA = upadacitinib.

Similar results were observed in the multiple imputation analysis of vIGA-AD 0/1, EASI 75 and EASI 100.

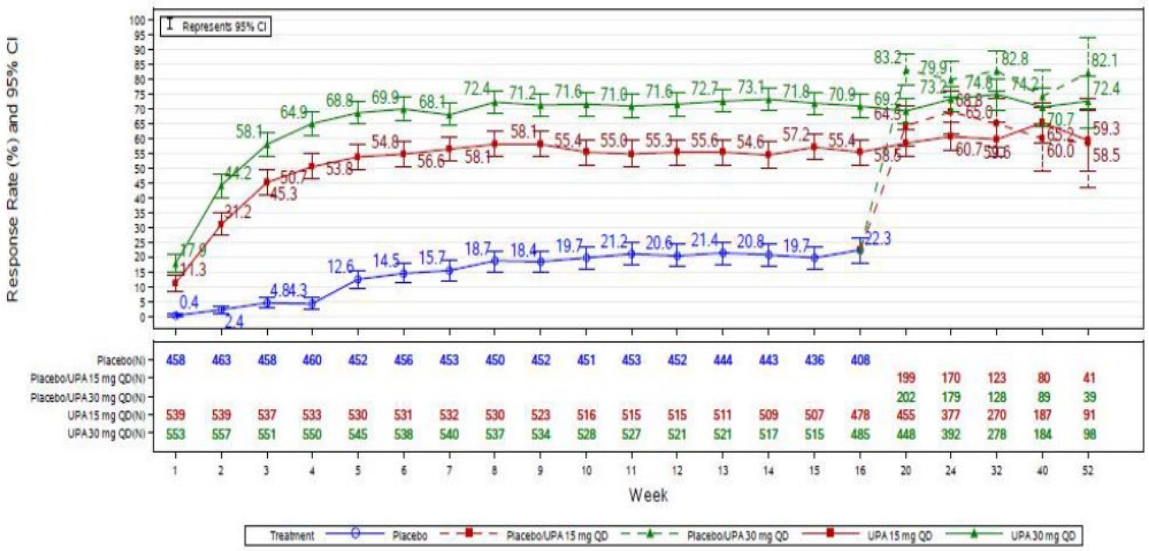
In the integrated summary of efficacy, flares (defined by an increase in EASI by ≥ 6.6 from Baseline for subjects with EASI ≤ 65.4 at Baseline) were reported for ≤ 3 subjects (1.1%)

per visit in each upadacitinib group (30 mg and 15 mg once daily) after Week 16 and through Week 52 among subjects who were originally randomised to upadacitinib and continued upadacitinib. Loss of response after Week 16 (defined as loss of at least 50% of the Week 16 EASI response and a vIGA-AD score of 2 or higher, among those who achieved vIGA-AD 0/1 and EASI 75 at Week 16) was experienced by 12 subjects (2.2% on 30 mg and 2.8% on 15 mg) at any visit after Week 16 and through Week 52, among subjects who were originally randomised to upadacitinib and continued on upadacitinib.

The proportions of subjects who achieved SCORAD 50/75/90 continued to be similar from the end of the double blind period to Week 52 with higher response rates observed in the 30 mg group compared to 15 mg;

In the observed case analysis, among subjects who were initially randomised to placebo and switched to upadacitinib at Week 16, the proportion who had an improvement (reduction) in Worst Pruritus ≥ 4 by the next scheduled visit was similar to the response rates in those subjects initially randomised to upadacitinib. Among subjects who were initially randomised to upadacitinib and continued on upadacitinib, the proportion of subjects who achieved improvement (reduction) in Worst Pruritus NRS maintained similar response rates beyond Week 16, with the upadacitinib 30 mg group achieving higher rates than upadacitinib 15 mg through Week 52, (see following figure).

Figure 41: Integrated monotherapy Studies M16-045 and M18-891; Subjects achieving Worst Pruritus NRS through Week 52 (long-term upadacitinib population, observed case analysis)



Abbreviations: CI = confidence intervals; ITT = intention to treat; LOCF = last observation carried forward; NRI-C = Nonresponder Imputation incorporating Multiple Imputation (MI) to handle missing data due to COVID-19; NRS = numerical rating scale; QD = once daily; UPA = upadacitinib.

Similar improvements were observed until Week 52 for ADerm-SS score and ADerm-IS scores. Among subjects, who were initially randomised to placebo, and switched to upadacitinib (30 mg once daily or 15 mg once daily) at Week 16, the proportion achieving HADS-A < 8 and HADS-D < 8 at their next evaluation (Week 32) exceeded 50% in both upadacitinib treatment groups. However, very few subjects reached the Week 52 visit with a HADS evaluation to determine durability of response. Among subjects who were initially randomised to upadacitinib, beyond Week 16 and through Week 52, the proportion of subjects who achieved HADS-A < 8 and HADS-D < 8 were maintained.

Among subjects who were initially randomised to placebo and switched to upadacitinib (30 mg or 15 mg once daily) at Week 16, the proportions achieving an improvement

(reduction) in DLQI ≥ 4 and DLQI score 0/1 at the next evaluation (8 weeks later) was similar to the response rates, in those subjects who were initially randomised to upadacitinib. Improvements were maintained through Week 52. Among subjects who were initially randomised to upadacitinib, beyond Week 16 and through Week 52, the proportions of subjects who achieved an improvement (reduction) in DLQI ≥ 4 and DLQI score 0/1 continued to improve or were maintained.

Conclusions on efficacy from the clinical evaluation

The main evidence to support efficacy of upadacitinib (15 mg and 30 mg once daily) for treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis, who are candidates for systemic therapy was provided by three well-conducted pivotal Phase III, multicentre, randomised, double-blind, placebo-controlled studies involving 2240 adults and 344 adolescents.

Two of these studies evaluated the proposed upadacitinib 30 mg and 15 mg doses as monotherapy (Studies M16-045 and M18-891) and one pivotal study (Study M16-047) evaluated upadacitinib 30 mg and 15 mg in combination with topical corticosteroids.

The proposed extended release tablet formulation of upadacitinib was evaluated in all three pivotal Phase III studies. Selection of the proposed marketing dose (and doses used in Phase III studies) was mainly based on results observed in the Phase IIb Study M16-048. The Phase III Study M17-377 was primarily conducted to evaluate safety of upadacitinib (30 mg and 15 mg once daily) in Japanese patients. It provided supportive evidence of efficacy, which was evaluated using exploratory endpoints.

Patients enrolled in the three pivotal Phase III studies were representative of the target patient population for upadacitinib and had active disease characterised by a vIGA-AD score of 3 or 4 (moderate or severe) and mean EASI and Worst Pruritus NRS consistent with moderate to severe atopic dermatitis. Adequate number of adolescents were evaluated with 344 adolescents included in the three pivotal studies. However, adolescents (12 to 17 years) weighing under 40 kg were excluded from the studies as were subjects aged over 75 years.

The efficacy endpoints used in the clinical studies are acceptable, validated and have been used for evaluation and approval of other systemic immunomodulatory drug (dupilumab) for treatment of atopic dermatitis; (see Section: *Scoring systems used in the clinical studies* for further information):

- Investigator's Global Assessment (IGA) reflects the physician's overall assessment. The Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD) gives a whole body average of atopic dermatitis skin lesions.
- Eczema Area and Severity Index (EASI) is a composite score (ranging from 0 to 72) based on the extent and severity of the atopic dermatitis lesions assessed systematically for erythema, induration/papulation/oedema, excoriation, and lichenification for each anatomical region.
- The pruritus numerical rating scale (NRS) is a patient-reported measure which assesses maximum itch intensity in the previous 24-hours using a 0-10-point scale (0 = no itch; 10 = worst itch imaginable).
- The SCORAD index (Severity scoring of atopic dermatitis) is used to assess extent and severity of atopic dermatitis signs and includes two visual analogue scales for symptoms (itch and sleep).
- The Patient Oriented Eczema Measure (POEM) evaluates frequency of topic dermatitis symptoms (including itch) and the impact of atopic dermatitis on sleep (score ranging from 0 to 28).

- The Dermatology Life Quality Index (DLQI) evaluates the health-related quality of life in dermatological patients (score ranging from 0 to 30).
- The Hospital Anxiety and Depression Scale (HADS) measures anxiety and depression symptoms (total score ranging from 0 to 42).
- The Atopic Dermatitis Symptom Scale (ADerm-ss) symptom scale and Impact Scale (Aderm-IS) were developed and validated by the sponsor and are not globally accepted endpoints.

  However, results observed for these sponsor-developed endpoints were consistent with more widely accepted endpoints such as SCORAD, POEM, DLQI and the pruritus/itch numeric rating scale (NRS).[64,65]

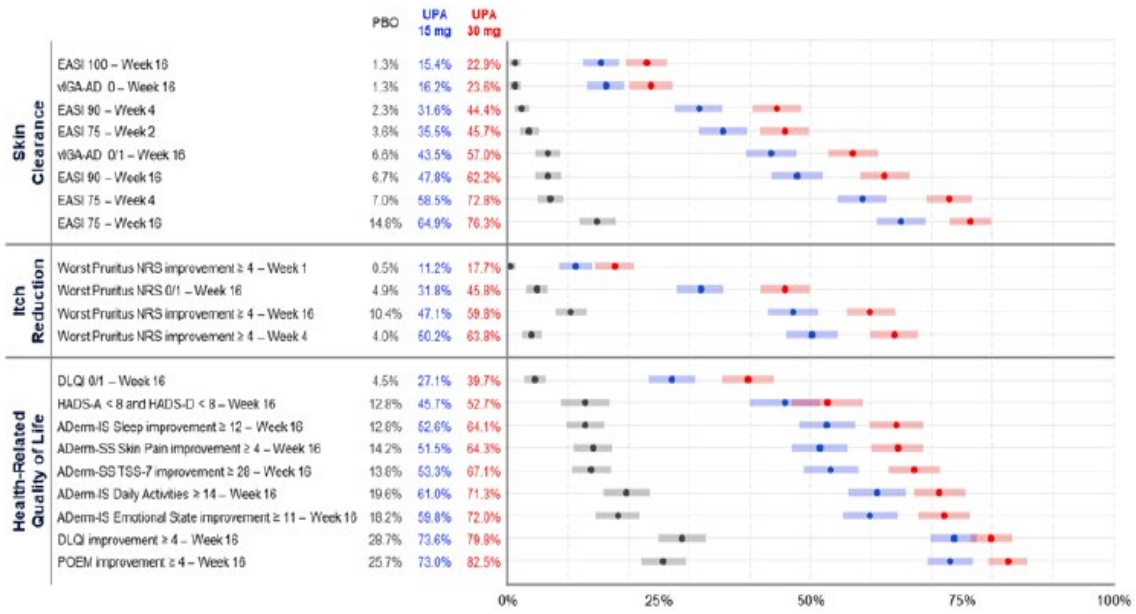
Statistical methods used for analysis of efficacy endpoints were acceptable. Handling of missing data was clearly stated and sensitivity analyses were performed to assess the impact of missing data and the robustness of the conclusion;

Robust evidence was provided showing statistically and clinically significant improvements with upadacitinib 30 mg and upadacitinib 15 mg as monotherapy compared to placebo in the co-primary endpoints of vIGA-AD 0/1 and EASI 75 at Week 16 in 1783 patients (including 228 adolescents) with moderate to severe AD. In addition, each of multiplicity-controlled secondary endpoints demonstrated superiority of upadacitinib 30 mg and 15 mg versus placebo with clinically relevant improvements (see Figure 42) in itch, atopic dermatitis symptoms, impact on all aspects of life (sleep, atopic dermatitis symptoms, quality of life, HADS, DLQI, patient perceptions of treatment,). Numerically better outcomes were observed for the upadacitinib 30 mg group than the upadacitinib 15 mg group across the co-primary and key secondary endpoints.

Figure 43, shown below, summarises the co-primary and key secondary endpoints from the Phase III monotherapy studies (Studies M18-891 and M16-045) for this submission.

[64] Leshem YA, Chalmers JR, Apfelbacher C, et al. Measuring atopic eczema symptoms in clinical practice: The first consensus statement from the Harmonising Outcome Measures for Eczema in clinical practice initiative. *J Am Acad Dermatol.* 2020;82(5):1181-1186.
[65] Barrett A, Hahn-Pedersen J, Kragh N, Evans E, Gnanasakthy A. Patient-Reported Outcome Measures in Atopic Dermatitis and Chronic Hand Eczema in Adults. Patient. 2019;12(5):445-459.

Figure 42: Integrated monotherapy Studies M16-045 and M18-891; efficacy of upadacitinib 30 mg and 15 mg across atopic dermatitis (NRI-C)



Abbreviations: ADerm-IS = Atopic Dermatitis Impact Scale; ADerm-SS = Atopic Dermatitis Symptom Scale; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; HADS = Hospital Anxiety and Depression Scale; PBO = placebo; POEM = Patient Oriented Eczema Measure; SCORAD = Severity scoring of atopic dermatitis; UPA = upadacitinib.

Study M16-047 was a pivotal Phase III, double-blind 16-week placebo-controlled study which evaluated the efficacy of combination therapy with topical corticosteroids and upadacitinib (15 mg and 30 mg) compared to placebo in 901 patients (including 116 adolescents) with moderate to severe atopic dermatitis.

Results showed:

- robust, consistent, clinically and statistically relevant improvements in the co-primary endpoints (proportion of subjects who achieved EASI 75 and the proportion of subjects who achieved vIGA-AD Score of 0/1 (clear or almost clear) with at least 2 grade reductions at Week 16) following treatment with upadacitinib 15 mg and 30 mg compared with placebo.
- these results were supported by significant improvements in key secondary endpoints of multiple skin clearance measures and response thresholds to pruritus.
- upadacitinib (30 and 15 mg) plus topical corticosteroids significantly reduced itch compared with placebo plus topical corticosteroids with a greater proportion of subjects on upadacitinib achieving a reduction in Worst Pruritus NRS ≥ 4 at Week 16.
- upadacitinib (30 and 15 mg) plus topical corticosteroids demonstrated rapid onset of action with significantly higher EASI 75 responses as early as Week 2 and a reduction in Worst Pruritus NRS ≥ 4 as early as Week 1 compared to placebo plus topical corticosteroids.
- upadacitinib (30 and 15 mg) plus topical corticosteroids had more topical corticosteroids free days with an EASI 75 response and an earlier discontinuation of all topical corticosteroids with an EASI 75 response than placebo plus topical corticosteroids at Week 16.

- furthermore, upadacitinib was also associated with significant improvements in sleep disturbance, impact of atopic dermatitis, health-related quality of life, self-assessment of disease parameters.
- while both doses of upadacitinib (30 mg and 15 mg) were efficacious, upadacitinib 30 mg plus topical corticosteroids provided numerically greater benefit to subjects than upadacitinib 15 mg plus topical corticosteroids across the endpoints tested. Consistent efficacy was demonstrated for adolescents across all endpoints.

Subgroup analyses were conducted for the co-primary endpoints vIGA-AD 0/1 and EASI 75 at Week 16 in each of the pivotal Phase III studies.

Overall, efficacy of both doses of upadacitinib 30 mg and 15 mg once daily compared with placebo was demonstrated across all subgroups by age, gender, BMI, race, weight, geographic region, Baseline vIGA-AD, Baseline EASI, high sensitivity-C-reactive protein, previous systemic therapy, intolerance to at least one prior topical corticosteroids/topical calcineurin inhibitors, inadequate response to at least one topical treatment.

A *post-hoc* analysis was performed to evaluate overall treatment effect of upadacitinib 30 mg once daily versus 15 mg once daily over the double blind period in each of the pivotal Phase III studies (Studies M16-045, M18-891, and M16-047), on the co-primary endpoints: EASI 75 and vIGA-AD 0/1. The following information was provided in the sponsor's clinical summary of efficacy:

> Superiority of upadacitinib 30 mg compared to upadacitinib 15 mg (nominal $p < 0.001$) for both EASI 75 and vIGA-AD 0/1 was demonstrated in all 3 pivotal studies. In addition, upadacitinib 30 mg independently contributed a beneficial treatment effect over that of upadacitinib 15 mg on EASI 75 starting from Week 2 for Study M16-045, and at all post baseline visits for Studies M18-891 and M16-047 (nominal $p < 0.05$). Similar results were also shown on vIGA-AD 0/1, with upadacitinib 30 mg independently contributing a beneficial treatment effect over that of upadacitinib 15 mg starting from Week 4 for Study M16-045, and at all post-baseline visits for Studies M18-891 and M16-047 (nominal $p < 0.05$).

Long-term efficacy was demonstrated in 1542 subjects (1319 adults and 223 adolescents) who received at least 24 weeks and 344 subjects (290 adults and 54 adolescents) who received at least 1 year of upadacitinib treatment (30 mg or 15 mg once daily):

- Significant improvements (in IGA-AD 0/1, EASI75 and Worst Pruritus NRS ≥ 4) were observed in those who were initially randomised to placebo and switched to upadacitinib at Week 16, as well as among those who were initially randomized to upadacitinib and continued on upadacitinib.
- upadacitinib 30 mg group demonstrated greater response rates than upadacitinib 15 mg through Week 52 in terms of vIGA-AD 0/1, EASI75, EASI 100 and reduction in Worst Pruritus NRS $\geq$ 4.

Overall, there is adequate evidence to support efficacy of upadacitinib 15 mg and 30 mg once daily in adults and adolescents (weighing > 40kg) when used as monotherapy or in combination with topical corticosteroids in patients with moderate to severe atopic dermatitis who are candidates for systemic therapy.

Topical calcineurin inhibitors were allowed for use in the monotherapy studies after Week 16 and at any time in the combination Study M16-047 for areas of thin skin (face, neck, intertriginous and genital areas) or for areas where medium potency topical corticosteroids were considered unsafe (for example, areas of skin atrophy). In all global Phase III studies, topical calcineurin inhibitors were allowed to be used as rescue medication. It is noted, that adolescents weighing < 40kg and subjects aged > 75 years were not evaluated in the submitted studies.

Safety

Exposure

Overall, 906, 899 and 902 subjects were treated with upadacitinib 30 mg, 15 mg and placebo respectively with similar mean exposure across treatment groups. These included 114, 114 and 115 adolescents treated with upadacitinib 30 mg, 15 mg and placebo, respectively. Overall, 263 (21.2%) and 246 (19.9%) subjects had at least 12 months exposure to upadacitinib 30 mg or upadacitinib 15 mg, respectively. In adolescents, the respective numbers were 46 (27.7%) and 37 (22.2%), respectively. Exposure to proposed doses of upadacitinib (15 mg and 30 mg once daily) was adequate to enable assessment of safety in the proposed indication.

Treatment-emergent adverse events

Overall incidence of treatment-emergent adverse events (TEAEs) was higher in the upadacitinib groups compared with placebo (58.5%, 63.8% and 69.5% in placebo upadacitinib 15 mg and upadacitinib 30 mg groups, respectively) with similar trend observed in adolescents (46.1%, 64.9% and 72.8%, respectively).

The most frequently reported TEAEs by Preferred Term (≥ 5% of subjects) in upadacitinib groups were acne, nasopharyngitis, upper respiratory tract infection, headache, blood blood creatine phosphokinase increased, and oral herpes all of which were reported more frequently in the upadacitinib groups compared with placebo; worsening of atopic dermatitis was the only adverse event reported more frequently in the placebo group.

The majority of the adverse events were mild to moderate in intensity. The incidence of severe adverse events was low and similar across treatment groups (4.8%, 4.8% and 4.6% in placebo upadacitinib 15 mg and upadacitinib 30 mg groups, respectively). No severe adverse event was reported in more than 2 subjects in any group in this analysis set. The exceptions were blood creatine phosphokinase increased (5 and 7 subjects in the upadacitinib 30 mg and upadacitinib 15 mg groups, respectively), neutropenia (3 subjects in the upadacitinib 30 mg group), appendicitis (3 subjects in the upadacitinib 15 mg group), dermatitis atopic (7 subjects in the upadacitinib 15 mg group and 14 subjects in the placebo group).

In the long-term upadacitinib Phase III atopic dermatitis analysis set, compared with the 15 mg upadacitinib group, the incidence of TEAEs was higher in the upadacitinib 30 mg group (333.3 versus 386.5 events/100 patient-years) compared with the 15 mg upadacitinib group. Similar trend was observed in adolescents. The common severe TEAEs (≥ 0.5 events/100 patient-years) which occurred at a higher exposure-adjusted event rate in upadacitinib 30 mg compared with upadacitinib 15 mg were herpes zoster, blood creatine phosphokinase increased and asthma.

The incidence of treatment-related TEAEs was higher in the upadacitinib groups compared with placebo (20.5%, 33.1% and 40.5% in placebo upadacitinib 15 mg and upadacitinib 30 mg groups, respectively) with similar trend observed in adolescents (12.2%, 30.7% and 35.1%, respectively).

Treatment-related adverse events

The most common (> 2% incidence) treatment-related adverse events in the upadacitinib groups were acne, blood creatine phosphokinase increased, headache, nasopharyngitis, neutropenia, oral herpes, and upper respiratory tract infection. In the long-term upadacitinib Phase III atopic dermatitis analysis set, acne, diarrhoea, herpes zoster, neutropenia, and oral herpes had higher rates in the upadacitinib 30 mg group than in the upadacitinib 15 mg group.

New adverse drug reactions identified in the atopic dermatitis clinical program were folliculitis, influenza, anaemia, abdominal pain, fatigue, urticaria and headache.

Furthermore, the frequency of a few existing adverse drug reactions was changed compared to what was observed in the rheumatoid arthritis clinical program: herpes simplex and herpes zoster were changed to common (≥ 1% to < 10%) rather than uncommon (< 1%). Acne was identified in the psoriatic arthritis clinical program at a common rate and meets the very common criteria (≥ 10%) in the atopic dermatitis clinical program.

Acne has been reported following administration of other JAK inhibitors although incidence of acne observed in the atopic dermatitis studies was much higher than that observed in the psoriasis or rheumatoid arthritis clinical studies. Overall, incidence of acne events was higher in upadacitinib groups compared with placebo (2.2%, 10% and 15.8% in placebo, upadacitinib 15 mg and upadacitinib 30 mg groups, respectively) with similar trend observed in adolescents (0.9%, 14% and 16.7%, respectively). No events of acne were serious in the upadacitinib treatment groups and one (1) event was severe in a subject on upadacitinib 30 mg. Two (2) subjects discontinued study drug due to an AE of acne (1 each in 15 mg and 30 mg upadacitinib).

Serious adverse events and deaths

No deaths were reported in the pivotal Phase III atopic dermatitis studies, but 2 deaths were reported in the upadacitinib 30 mg group in the Phase IIb dose-ranging Study M16-048.

The incidence of serious adverse events was similar in the upadacitinib and placebo groups (2.9%, 2.1% and 2.1% in placebo upadacitinib 15 mg and upadacitinib 30 mg groups, respectively). The majority of serious adverse events (by MedDRA Preferred Term)[66] were reported in one (1) subject per group, except for anaphylactic reaction (2 subjects in upadacitinib 30 mg), appendicitis (3 subjects in upadacitinib 15 mg), retinal detachment (2 subjects in upadacitinib 15 mg), dermatitis atopic (6 subjects in placebo), and dermatitis exfoliative, generalised; and eczema (2 subjects in placebo).

In the long-term upadacitinib atopic dermatitis analysis set, serious adverse events were slightly more frequently reported (8.4 events/100 patient-years and 7.1 events/100 patient-years) for the overall upadacitinib 30 mg and 15 mg groups, respectively.

The corresponding numbers for adolescents were 5.6 and 4.9 events/100 patient-years, respectively. Pneumonia (0.6 events/100 patient-years) and dermatitis atopic (worsening) (0.5 events/100 patient years) were reported most frequently in the upadacitinib 30 mg and 15 mg groups, respectively. Discontinuations due to AEs were reported more frequently in the placebo compared to the upadacitinib groups mainly due to worsening of atopic dermatitis.

Adverse events of special interest

Transient, asymptomatic transaminase elevations were observed in subjects treated with upadacitinib and was similar between upadacitinib 30 mg and 15 mg. In both the placebo-controlled atopic dermatitis analysis set and the long-term upadacitinib Phase III atopic dermatitis analysis set, the percentages of subjects with alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 5 × upper limit of normal were less than 1% in both upadacitinib treatment groups. Transaminase elevations usually resolved or were resolving with study drug ongoing or temporary interruption. No subjects treated with

[66] The **Medical Dictionary for Regulatory Activities (MedDRA)** is an internationally used set of terms relating to medical conditions, medicines and medical devices. It was created to assist regulators with sharing information. It is also used by industry, academics, health professionals and other organisations that communicate medical information.

upadacitinib in the atopic dermatitis clinical studies met criteria for Hy's Law;[67] and there were no reports of acute hepatic toxicity.

More subjects reported Grade 2 decrease in haemoglobin in the upadacitinib 30 mg group compared to one subject with a Grade 3 haemoglobin decrease. In the long term atopic dermatitis analysis set, mean haemoglobin decrease (from Baseline to Week 52) was greater in the upadacitinib 30 mg group compared with the 15 mg group (–4.9 g/L versus –3.0 g/L, respectively). In the placebo-controlled atopic dermatitis analysis set, the incidence of more than Grade 3 decreases in neutrophils was higher in the upadacitinib 30 mg compared to the upadacitinib 15 mg group (1.3% versus 0.4% and no reports in the placebo group). There were no reports of $\geq$ Grade 4 decreases in neutrophils in any treatment group in the placebo-controlled analysis set, but there were 2 reports of Grade 4 neutropenia in the long-term atopic dermatitis analysis set (both in the upadacitinib 30 mg group). There was a dose-related increase in the percentage of subjects with treatment-emergent adverse events (TEAEs) of neutropenia (1.1%, 2.9% and 0.3% in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively) and 2 events of neutropenia (both in upadacitinib 30 mg group) led to discontinuation of study drug although neither was associated with symptoms or infections. There were no clinically significant changes in lymphocyte or platelet counts. Similar changes in haematologic parameters were reported in the adolescents. There were no reports of agranulocytosis, aplastic anaemia or severe thrombocytopenia following upadacitinib treatment in the atopic dermatitis clinical studies.

Overall, there were 3 reports of major adverse cardiovascular events (MACE). One in the upadacitinib 30 mg (cerebrovascular accident) and 2 in the upadacitinib 15 mg group (ischaemic stroke and cerebellar haemorrhage) in the atopic dermatitis studies, but none of these were fatal and multiple cardiovascular risk factors were present in 2 of the 3 subjects. Although the demographics and proportion of subjects with cardiovascular risk factors at Baseline were balanced among groups across the placebo-controlled atopic dermatitis analysis set and long-term upadacitinib Phase III atopic dermatitis analysis set, the prevalence of cardiovascular risk factors such as hypertension and dyslipidemia was low. In the overall atopic dermatitis program, there was one (1) adjudicated venothrombotic events of pulmonary embolism reported in a subject receiving upadacitinib 30 mg in the Phase II Study M16-048. No adjudicated arterial thrombosis event occurred in subjects receiving upadacitinib through the data cutoff date;

In the placebo-controlled atopic dermatitis analysis set, the incidence of serious infections was low and similar across the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups (0.8%, 0.4% and 0.6%, respectively). However, in the long-term upadacitinib atopic dermatitis analysis set, the incidence of serious infections was higher in the upadacitinib 30 mg group compared to the upadacitinib 15 mg group (3.4 versus 2.4 events/100 patient-years) with more prominent dose-related incidence observed in adolescents (0.8 vs 5.6 events/100 patient-years). Pneumonia was reported most frequently.

In the placebo-controlled atopic dermatitis Analysis set, all the opportunistic infections excluding tuberculosis (TB) and herpes zoster were related to eczema herpeticum (disseminated viral infection in atopic dermatitis). The incidence of treatment-emergent eczema herpeticum was higher in the upadacitinib groups compared with placebo (0.7%, 0.8% and 0.4% in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively). There was one (1) report of a serious adverse event of eczema herpeticum

[67] **Hy's Law**: Evidence of hepatocellular injury with a rise in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3 x the upper limit of normal (ULN) and total bilirubin > 2 x ULN, and no other reason to explain rise in aminotransferases and total bilirubin. Hy's law is a rule of thumb that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury with jaundice.

(considered treatment-related), but there were no deaths or discontinuations of study drug due to these events. No events of treatment-emergent opportunistic infections, excluding TB and herpes zoster, were reported in adolescent subjects. In the long-term upadacitinib Phase III atopic dermatitis analysis set, the exposure-adjusted event rates of eczema herpeticum were similar in the upadacitinib 30 mg (2.2 events/100 patient-years) and 15 mg groups (2.1 events/100 patient-years).

In the placebo-controlled atopic dermatitis analysis set, the incidence of herpes zoster was higher in the upadacitinib groups compared with placebo but no dose-related increase was observed (1.6%, 1.5% and 0.6% in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively). Most AEs of herpes zoster were mild or moderate in severity with no reports of serious adverse events or discontinuations due to herpes zoster events. However, in the adolescents a higher incidence of herpes zoster was observed in the upadacitinib 30 mg compared to upadacitinib 15 mg (2.6% versus 0.9%) with no reports in the placebo group. in the long-term upadacitinib Phase III atopic dermatitis analysis set, the incidence of herpes zoster was higher in the upadacitinib 30 mg compared to upadacitinib 15 mg group with similar trends observed in the adolescents;

There was only one (1) active case of TB each in the upadacitinib 30 mg and 15 mg groups and no reports in adolescent subjects.

In the placebo-controlled analysis set, all malignancies excluding non-melanoma skin cancer were reported in the upadacitinib 30 mg group (4 subjects, 0.4%); non-melanoma skin cancer was reported in 9.3%, 0.2% and 0% in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively. In the long-term upadacitinib Phase III atopic dermatitis analysis set, the exposure-adjusted incidence rates (EAIRs) of malignancy, excluding non-melanoma skin cancer, was 0.7 events/100 patient years in the upadacitinib 30 mg group; and there were no events of malignancy, excluding non-melanoma skin cancer, in the upadacitinib 15 mg group. The incidence of non-melanoma skin cancer was similar in the upadacitinib 15 mg (0.5 events/100 patient-years) and upadacitinib 30 mg (0.3 events/100 patient-years) groups. There were no reports of malignancies in the adolescents.

No treatment-emergent adjudicated gastrointestinal perforations were reported in the upadacitinib atopic dermatitis clinical studies.

Other safety topics

Interpretation of effect of upadacitinib treatment on maturation and growth of adolescents was limited due to lack of adequate data on Tanner stage in majority of the adolescents in the placebo-controlled and the long-term Phase III atopic dermatitis analysis sets.

Overall, race, age, sex, BMI, weight, or screening estimated glomerular filtration rate (eGFR) did not have any significant impact on safety profile of upadacitinib in atopic dermatitis subjects, although interpretation was limited by smaller sample size in certain subgroups (non-White race populations, those aged < 18 years, or aged > 65 years, and those with a screening eGFR ≥ 40 and < 60 mL/min/1.73 m^2). Across the placebo-controlled atopic dermatitis analysis set and the long-term upadacitinib Phase III atopic dermatitis analysis set and across the upadacitinib treatment groups, the percentages of subjects with treatment-emergent adverse events (TEAEs), serious adverse events, severe TEAEs, and TEAEs leading to discontinuation were generally similar between the upadacitinib monotherapy and upadacitinib combination therapy subgroups.

Post-marketing data on currently approved 15 mg upadacitinib dose did not reveal new safety concerns. However, integrated data from ongoing global rheumatoid arthritis studies showed that event rate per 100 patient years for serious adverse events and

TEAEs leading to discontinuation continued to be higher in the upadacitinib 30 mg group compared to the 15 mg group. Hence, during the reporting interval of submitted periodic safety update report (for the period of February to August 2020), the decision was made to amend the rheumatoid arthritis studies to switch subjects from 30 mg once daily to 15 mg once daily due to the 15 mg dose demonstrating the optimal benefit risk profile in patients with rheumatoid arthritis and being an approved marketed dose for that indication.

Conclusions and recommendation of the clinical data from the clinical evaluation

Assessment of benefits

Table 42, shown below, summarises the benefits found through the TGA's clinical evaluation of the data submitted for the following proposed indication:

> *Rinvoq is indicated for the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy.*

Table 42: Assessment of benefits for the proposed indication

Benefits	Strengths and Uncertainties
Robust evidence for statistically and clinically significant improvements with upadacitinib 30 mg and upadacitinib 15 mg as monotherapy compared to placebo in the co-primary endpoints of vIGA-AD score of 0 or 1 and EASI 75 response at Week 16. These results were supported by significant improvements in key secondary endpoints of multiple skin clearance measures and response thresholds to pruritus.	Integrated monotherapy efficacy results: • EASI 75 response rate: 14.8%, 64.9% and 76.3% in placebo, upadacitinib 15 mg and 30 mg groups, respectively. • IGA-AD 0/1 response rate: 10.9%, 39.6% and 58.6%, respectively. • Worse pruritus NRS (> 4 point improvement): 15.0%, 51.7% and 63.9 %, respectively. • Few subjects experienced flare on upadacitinib 30 mg (0.7%) and upadacitinib 15 mg (1.6%) compared with placebo (24.9%).
Efficacy of combination therapy with topical corticosteroids and upadacitinib (15 mg and 30 mg) compared to placebo in 901 patients (including adolescent subjects) with moderate-to-severe atopic dermatitis. These results were supported by significant improvements in key secondary endpoints of multiple skin clearance measures and response thresholds to pruritus.	EASI 75 response rate: 26.4%, 64.6% and 77.1% in placebo, upadacitinib 15 mg and upadacitinib 30 mg groups, respectively. IGA-AD 0/1 response rate: 10.9%, 39.6% and 58.6%, respectively. Worse pruritus NRS (> 4 point improvement): 15%, 51.7% and 63.9%, respectively.
Upadacitinib was also associated with significant improvements in sleep disturbance, impacts, health-related quality of life, self-assessment of disease parameters.	

Benefits	Strengths and Uncertainties
Numerically better outcomes were observed for the upadacitinib 30 mg group than the upadacitinib 15 mg group across the co-primary and key secondary endpoints in both monotherapy and combination studies.	Advantage of better outcomes with the higher 30 mg dose would have to be balanced against the risk of certain adverse events which occur at a higher incidence in the 30 mg group (Refer Section 9.2, below).
Consistent efficacy was demonstrated for adolescents across all endpoints.	
Rapid onset of action and evidence of long-term maintenance of efficacy up to 52 weeks.	
Single oral daily dosing.	

Assessment of risks

Table 43, shown below, summarises the risks found through the TGA's clinical evaluation of the data submitted for the following proposed indication:

> *Rinvoq is indicated for the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy.*

Table 43: Assessment of risks for the proposed indication

Risks	Strengths and Uncertainties
Acne, nasopharyngitis, upper respiratory tract infection, headache, blood creatinine phosphokinase increased, and oral herpes all of which were reported more frequently in the upadacitinib groups compared with placebo. Compared to the upadacitinib 15 mg group, the incidence of acne, herpes zoster and oral herpes was higher in the upadacitinib 30 mg group.	The majority of the adverse events were mild to moderate in intensity. The incidence of severe adverse events was low and similar across treatment groups (4.8%, 4.8% and 4.6% in placebo upadacitinib 15 mg and upadacitinib 30 mg groups, respectively). No severe adverse events was reported in more than 2 subjects in any group in this analysis set, with the exception of blood creatine phosphokinase increased (5 and 7 subjects in the upadacitinib 30 mg and upadacitinib 15 mg groups, respectively), neutropenia (3 subjects in the upadacitinib 30 mg group), appendicitis (3 subjects in the upadacitinib 15 mg group), dermatitis atopic (7 subjects in the upadacitinib 15 mg group and 14 subjects in the placebo group).
Common severe treatment-emergent adverse events (≥ 0.5 events/100 patient-years) which occurred at a higher exposure adjusted event rate in upadacitinib 30 mg compared with upadacitinib 15 mg were herpes zoster, blood creatine phosphokinase increased and asthma.	

Risks	Strengths and Uncertainties
The incidence of treatment-related treatment-emergent adverse events was higher in the upadacitinib groups compared with placebo (20.5%, 33.1% and 40.5% in placebo upadacitinib 15 mg and upadacitinib 30 mg groups, respectively) with similar trend observed in adolescents (12.2%, 30.7% and 35.1%, respectively). The most common (> 2% incidence) treatment-emergent adverse events in the upadacitinib groups were acne, blood CPK increased, headache, nasopharyngitis, neutropenia, oral herpes, and upper respiratory tract infection.	In the long-term upadacitinib Phase III adverse events analysis set, acne, diarrhoea, herpes zoster, neutropenia, blood creatine phosphokinase and oral herpes had higher rates in the upadacitinib 30 mg group than in the upadacitinib 15 mg group.
Risk of serious infections	In the placebo-controlled atopic dermatitis analysis set, the incidence of serious infections was low and similar across the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups (0.8%, 0.4% and 0.6%, respectively). However, in the long-term upadacitinib atopic dermatitis analysis set, it was higher in the upadacitinib 30 mg group compared to the upadacitinib 15 mg group (3.4 versus 2.4 events/100 patient-years) with more prominent dose-related incidence observed in adolescents (0.8 versus 5.6 events/100 patient-years).
Risk of opportunistic infections.	All the opportunistic infections excluding TB and herpes zoster were eczema herpeticum. The incidence of treatment-emergent eczema herpeticum was higher in the upadacitinib groups compared with placebo (0.7%, 0.8% and 0.4% in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively
Risk of herpes zoster.	Incidence of herpes zoster: 0.6%, 1.6% and 1.5% in placebo-controlled safety dataset. The majority of cases were mild or moderate with no serious adverse events or discontinuations due to herpes zoster events. Adequate precautions included in PI.
Malignancies.	In the placebo-controlled analysis set, all malignancies excluding non-melanoma skin cancer were reported in the upadacitinib 30 mg group (4 subjects, 0.4%); non-melanoma skin cancer was reported in 9.3%, 0.2% and 0% in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively. In the long-term upadacitinib Phase III atopic dermatitis analysis set, the exposure-adjusted incidence rates (EAIRs) of malignancy, excluding non-melanoma skin cancer, was 0.7 events/100 patient years in the upadacitinib 30 mg group; and there were no events of malignancy, excluding non-melanoma

Risks	Strengths and Uncertainties
	skin cancer, in the upadacitinib 15 mg group. The incidence of non-melanoma skin cancer was similar in the upadacitinib 15 mg (0.5 events / 100 patient-years) and upadacitinib 30 mg (0.3 events / 100 patient-years) groups. There were no reports of malignancies in the adolescents.
Anaemia, neutropenia, and lymphopenia. Incidence of anaemia and neutropenia was higher in subjects treated with 30 mg upadacitinib compared to the 15 mg dose.	Two events of neutropenia led to discontinuation of study drug (both in upadacitinib 30 mg group) but neither was associated with symptoms or infections. Recommendation for dose interruption of upadacitinib if haemoglobin < 8g/dL or absolute neutrophil count < 1000 cells/mm^3 or ALC < 500cells/mm^3.) provided in the product labelling. In addition, anaemia is proposed as an adverse drug reaction for upadacitinib for the atopic dermatitis indication.
Elevated creatine phosphokinase	Creatine phosphokinase changes following upadacitinib treatment were mostly mild or moderate in severity and have generally not been associated with confirmed rhabdomyolysis, renal failure or other serious adverse events.
Acne: Incidence of acne adverse events was higher in upadacitinib groups compared with placebo (2.2%, 10% and 15.8% in placebo, upadacitinib 15 mg and upadacitinib 30 mg groups, respectively) with similar trend observed in adolescents (0.9%, 14% and 16.7%, respectively).	A higher incidence in subjects treated with upadacitinib 30 mg compared to 15 mg. Incidence of acne observed in the atopic dermatitis studies was much higher than that observed in the psoriatic arthritis or rheumatoid arthritis clinical studies. It has been added to adverse drug reactions in the draft PI.
Missing information in adolescents weighing < 40 kg, children aged < 12 years and elderly patients > 75 years.	

Assessment of benefit-risk balance

The following summarises the benefit-risk balance found through the TGA's clinical evaluation of the data submitted for the following proposed indication:

> *Rinvoq is indicated for the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy*

Upadacitinib (drug development name ABT-494, tradename Rinvoq) is a selective and reversible Janus kinase (JAK) inhibitor that was approved for rheumatoid arthritis in the USA and in the EU in 2019. It was also approved in Australia (in January 2020);[68,69] however, only the 15 mg dose is approved for the rheumatoid arthritis indication.

[68] AusPAR for Rinvoq (upadacitinib) AbbVie Australia Pty Ltd; submission PM-2018-05603-1-3. Published online April 2020; available at: AusPAR: upadacitinib | Therapeutic Goods Administration (TGA)
[69] AusPAR for Rinvoq (upadacitinib) AbbVie Australia Pty Ltd; submission PM-2020-02479-1-3. Published online August 2021; available at: AusPAR: upadacitinib | Therapeutic Goods Administration (TGA).

The main evidence for efficacy and safety of upadacitinib (15 mg and 30 mg once daily) was provided by three well-conducted pivotal Phase III studies (2 monotherapy and one study using a combination with topical corticosteroids). Overall, 906, 899 and 902 subjects were treated with upadacitinib 30 mg, 15 mg and placebo, respectively. Adolescent subjects were evaluated in all 3 studies (overall 114, 114 and 115 adolescent subjects treated with upadacitinib 30 mg, 15 mg and placebo, respectively). Overall, 263 (21.2%) and 246 (19.9%) subjects had at least 12 months exposure to upadacitinib 30 mg or 15 mg, respectively (in adolescent subjects, 46 (27.7%) and 37 (22.2%), respectively). Exposure to proposed doses of upadacitinib (15 mg and 30 mg once daily) was adequate to enable assessment of efficacy and safety in the proposed indication.

Treatment with upadacitinib 30 mg and upadacitinib 15 mg as monotherapy and in combination with topical corticosteroids demonstrated statistically and clinically significant improvements in the co-primary endpoints of vIGA-AD 0/1 and EASI 75 at Week 16 consistently in all 3 studies. In addition, each of multiplicity-controlled secondary endpoints demonstrated superiority of upadacitinib 30 mg and 15 mg vs. placebo demonstrating clinically relevant improvements in itch, atopic dermatitis symptoms, impact on all aspects of life (sleep, atopic dermatitis symptoms, quality of life, HADS, DLQI, patient perceptions of treatment,). Furthermore, upadacitinib was also associated with significant improvements in sleep disturbance, impact of atopic dermatitis, health-related quality of life, self-assessment of disease parameters.

Comparison of predicted efficacy responses for EASI 90, IGA 0/1, and IGA 0 between upadacitinib monotherapy and combination with topical corticosteroids show consistent efficacy for both doses regardless of topical corticosteroids use. Although, the predicted placebo response rates were higher by 5% to 7% when upadacitinib was administered with topical corticosteroids compared to monotherapy, this did not affect the predicted response rates for upadacitinib 15 mg and 30 mg doses. While both doses of upadacitinib (30 mg and 15 mg) were efficacious, upadacitinib 30 mg plus topical corticosteroids provided numerically greater benefit to subjects than upadacitinib 15 mg plus topical corticosteroids across the endpoints tested. Consistent efficacy was demonstrated for adolescents across all endpoints.

There was adequate evidence to support long-term maintenance of efficacy with significant improvements observed in those who were initially randomised to placebo and switched to upadacitinib at Week 16, as well as among subjects who were initially randomised to upadacitinib and continued on upadacitinib beyond Week 16.

The upadacitinib 30 mg group demonstrated greater response rates than upadacitinib 15 mg through Week 52 in terms of vIGA-AD 0/1, EASI75, EASI 100 and reduction in worst pruritus NRS > 4.

Efficacy and safety of both doses of upadacitinib 30 mg and 15 mg once daily compared with placebo was demonstrated across all subgroups by age, gender, BMI, race, weight, geographic region, baseline vIGA-AD, baseline EASI, high sensitivity C-reactive protein (hsCRP), previous systemic therapy, intolerance to at least one prior topical corticosteroids/topical calcineurin inhibitors, inadequate response to at least one topical treatment. However, there was lack of analysis of efficacy in subgroups based on concomitant use of topical calcineurin inhibitors, emollients and oral antihistamines. Subjects with prior exposure to dupilumab were excluded from the Phase III studies.

Treatment guidelines developed by the Japanese Dermatological Association;[70,71] similar to the American Academy of Dermatology (AAD); recommend the use of systemic immunomodulatory agents for subjects in whom optimised topical regimens and/or phototherapy do not adequately control the signs and symptoms of disease. These guidelines recognise that insufficient data exist to firmly recommend optimal dosing, duration of therapy, and precise monitoring protocols for most systemic immunomodulating medications. Currently very few systemic agents are approved for atopic dermatitis and, of those, cyclosporin A and oral prednisone are not suitable for long-term use. Recently, dupilumab, a monoclonal antibody that inhibits IL-4 and IL-13 signaling, has been approved in the USA, EU, Japan, Canada, and in Australia for the treatment of moderate to severe atopic dermatitis in adults and paediatric patients over 6 years of age.[72] However, dupilumab is associated with risks of ocular adverse events (including conjunctivitis), protracted onset of action and need for subcutaneous administration (300 mg every 2 weeks).

Rinvoq (upadacitinib 15 mg and 30 mg once daily) provides a once daily oral treatment option for patients with moderate to severe atopic dermatitis in whom optimised topical regimens and/or phototherapy do not adequately control the signs and symptoms of disease. It provides rapid itch relief, clearance of skin lesions and appears to have a safety profile suitable for long-term use.

Overall, there is adequate evidence to support efficacy and safety of upadacitinib in adults and adolescents (weighing more than 40kg) when used as monotherapy or in combination with topical corticosteroids in patients with moderate to severe atopic dermatitis who are candidates for systemic therapy. However, there are some caveats with regards to efficacy of upadacitinib in combination with topical calcineurin inhibitors as these were not allowed in the monotherapy studies and their use in the combination Study M16-047 was not specified. Furthermore, it is noted that adolescents weighing less than 40 kg and subjects aged over 75 years were not evaluated in the submitted studies.

The higher 30 mg dose of upadacitinib was associated with greater improvements in all primary and secondary efficacy outcomes compared to the 15 mg dose, but was also associated with an increased risk of acne, serious infections, herpes zoster, anaemia, neutropenia and creatine phosphokinase increased. Furthermore, recent post-marketing data showed that sponsors have discontinued 30 mg dose in ongoing rheumatoid arthritis studies due to 15 mg once daily being the approved dose for rheumatoid arthritis and the 30 mg dose not adding notable efficacy, whilst demonstrating increased incidence of adverse events, over the 15 mg once daily dose in rheumatoid arthritis. There is lack of data on effects on growth and development as majority of the adolescents had missing data on Tanner score. However, the sponsors have only proposed use of the lower 15 mg once daily dose in adolescents, which is acceptable. Hence, approval of the 30 mg dose in adults should be conditional to results from ongoing long-term studies and post-marketing surveillance of the 30 mg dose for proposed atopic dermatitis indication.

Overall, the benefit risk balance of Rinvoq (upadacitinib) in the proposed use is favourable.

[70] Committee for Clinical Practice Guidelines for the Management of Atopic Dermatitis 2018, The Japanese Society of Allergology, The Japanese Dermatology Association: Japanese guidelines for atopic dermatitis 2020, *Allergology International*, Volume 69, Issue 3, 2020.
[71] Committee for Clinical Practice Guidelines for the Management of Atopic Dermatitis 2018, The Japanese Society of Allergology, The Japanese Dermatology Association: Executive summary: Japanese guidelines for atopic dermatitis (ADGL) 2021, *Allergology International*, Volume 71, Issue 4, 2022.
[72] AusPAR for Dupixent (dupilumab) Sanofi-Aventis Australia Ltd; submission PM-2020-03043-1-5. Published online May 2022; available at: AusPAR: Dupilumab | Therapeutic Goods Administration (TGA)

Recommendation regarding authorisation

The clinical evaluation of this submission recommended that the application for marketing authorisation for Rinvoq be approved at for the following extension of indication:

> *Rinvoq is indicated for the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy.*

Risk management plan

The sponsor applied to extend the indications of upadacitinib (Rinvoq) which is currently approved for treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to, one or more disease-modifying anti-rheumatic drugs (DMARDs). The recommended dose for rheumatoid arthritis is one 15 mg tablet once daily. The current submission seeks to extend the indications to include treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy. The proposed dosing regimen involves oral administration of one tablet (15 mg or 30 mg) once daily for adults or 15 mg once daily for adolescents weighing at least 40 kg.

The submission also seeks to register an additional strength of upadacitinib tablets (30 mg) to facilitate once-daily dosing in adult patients with atopic dermatitis.

The most recently evaluated core risk management plan (RMP) was version 1.6 (date October 2019; data lock point (DLP) 13 September 2018) and Australian-specific annex (ASA) version 1.5 (dated January 2020). In support of the extended indications, the sponsor has submitted core RMP version 4.0 (date September 2020; DLP 23 July 2020) and ASA version 3.0 (date October 2020).

At the fourth round of RMP evaluation the sponsor submitted Core/EU-RMP version 4.3 (date June 2021; DLP 23 July 2020) and ASA version 5.0 (date July 2021).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 44. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 44: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Serious and opportunistic infections including TB	✓*	✓†	✓	✓§
	Herpes zoster	✓*	✓†	✓	✓§
Important potential risks	Malignancies	✓*	✓†	✓	-
	Major adverse cardiovascular event (MACE)	✓*	✓†	✓	✓§
	VTEs (deep venous thrombosis and pulmonary embolus)	✓*	✓†	✓	✓§
	Gastrointestinal perforation	✓	✓†	✓	-

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Drug-induced liver injury (DILI)	✓	✓†	✓	-
	Foetal malformation following exposure in utero	✓*	✓†	✓	✓§
Missing information	Use in very elderly (≥ 75 years of age)	✓	✓†	✓	-
	Effect on vaccination efficacy	✓	✓†	✓	-
	Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C	✓	✓†	✓	-
	Use in patients with moderate hepatic impairment	✓	✓†	✓	-
	Use in patients with severe renal impairment	✓	✓†	✓	-
	Long-term safety	✓*	✓†	✓	-
	Long-term safety in adolescents with atopic dermatitis	✓	✓†	✓	-

* Targeted follow-up forms

† Long-term extension, safety and cohort studies for Rheumatoid arthritis, atopic dermatitis, psoriatic arthritis and ankylosing spondylitis indications (see Appendix II)

§ Health Care Professional (HCP) educational brochure, Patient Alert Card (PAC)

The summary of safety concerns is the same as the safety summary evaluated during the previous submission (PM-2020-02479-1-3);[73] which was considered acceptable. The sponsor considers that the risk of eczema herpeticum/ Kaposi's varicelliform eruption, applicable to the atopic dermatitis indication, is adequately covered under the important identified risk 'serious and opportunistic infections'. The sponsor has acknowledged the RMP evaluator request to monitor the risk of eczema herpeticum/ Kaposi's varicelliform eruption specifically in the periodic safety update reports (PSURs). 'Long-term safety in adolescents with atopic dermatitis' has been included as missing information as this risk requires further characterisation.

Routine and additional pharmacovigilance activities have been proposed as shown in Table 44 above. Additional pharmacovigilance activities were included and extended at the fourth round of RMP evaluation, to further characterise the risk of 'long-term safety in adolescents with atopic dermatitis' The pharmacovigilance plan is acceptable from an RMP perspective.

Routine and additional risk minimisation activities have been proposed which are the same as proposed in the previous submission with alterations made to include the atopic dermatitis indication. The additional activities include education material for healthcare professionals (HCPs) as well as a Patient Alert Card. The sponsor has included specific

[73] AusPAR for Rinvoq (upadacitinib) AbbVie Australia Pty Ltd; submission PM-2020-02479-1-3. Published online August 2021; available at: AusPAR: upadacitinib | Therapeutic Goods Administration (TGA)

information about eczema herpeticum in the PI, Consumers Medicines Information (CMI), Healthcare professional educational brochure and patient alert card. The proposed risk minimisation plan is acceptable.

New and outstanding recommendations

At fourth round, the sponsor submitted updated additional risk minimisation materials (Healthcare Professional Educational Brochure and Patient Alert Card) for review. There are two new recommendations as a result, however from an RMP perspective these should not impede the decision on this submission.

1. Full guidance for determining the most appropriate Rinvoq dose for a patient, for all indications, is provided in the PI and is particularly important for the atopic dermatitis indication. It is recommended that the sponsor removes reference to specific doses for all from the 'Further Information' section of the Healthcare Professional Brochure.
2. The minutes of the 5 August 2021 Advisory Committee on Medicines meeting (the meeting discussing approvability of this submission) were not yet available. Any outcomes from ACM or recommendations by the Delegate that affect the content of the PI, CMI or additional risk minimisation materials should be addressed in updated routine and/or additional risk minimisation materials and updated ASA and provided to the TGA for review and acceptance prior to product launch.
3. Although there are no plans to submit Studies P20-390 and P21-824 to the TGA, the sponsor is requested to update the ASA with the relevant findings from the studies when they are available.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> The Rinvoq Core/EU RMP (version 4.3, dated June 2021; data lock point 23 July 2020), with Australian Specific Annex (version 5.0, dated July 2021), included with submission PM-2020-04791-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.

The following wording is recommended for the periodic safety update report (PSUR) requirement:

> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As the indications for Rinvoq are being extended into a significantly different population and condition it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> Rinvoq (upadacitinib) is to be included in the Black Triangle Scheme. The PI and CMI for Rinvoq must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.

Risk-benefit analysis

Delegate's considerations

Atopic dermatitis, also called eczema, is a chronic, relapsing, pruritic, inflammatory skin disease that occurs more frequently in children than adults. The diagnosis of atopic dermatitis is made clinically and is based on history, morphology and distribution of skin lesions, and associated clinical signs and symptoms. Because of the broad differential diagnosis, it is important to exclude other conditions when diagnosing atopic dermatitis, such as other forms of eczema, psoriasis, and scabies; biopsy may be necessary in these cases. The most widely used diagnostic criteria are those developed by Hanifin and Rajka;[1] (see Table 1 (above) for a summary of these criteria).

The severity of atopic dermatitis is usually determined based on clinician assessment, including estimation of the proportion of body surface area involved and subjective assessment of signs and symptoms. One third of atopic dermatitis patients have moderate-to-severe disease that is often accompanied by negative impact on health-related quality of life, including fatigue, work productivity, and everyday activities as well as suicidal ideation, and sleep disturbance;[3,4,5] and, an increased incidence of attention deficit hyperactivity disorder in children.

Certain age-related variations in disease presentation are characteristic of atopic dermatitis:

- infants generally experience highly pruritic erythematous lesions on the face and scalp;
- older children exhibit more lichenified lesions typical of chronic disease involving the extremities;[6] and
- in adolescents and adults, atopic dermatitis typically involves flexural folds, face, neck, upper arms and back, and dorsal surfaces of the hands and feet.

In general:

- atopic dermatitis begins in childhood as indicated by its higher prevalence rate among children (6% to 14%) relative to adults (3.2% to 10.2%);[9,10]
  - the population prevalence of eczema in Australia was estimated to be 16% in 4-year olds and 20.3% in 1-year olds;[12]
  - severe lesions are more frequent in adults than in children.[7,8]

The goal of atopic dermatitis treatment is control of symptoms and reduction of disease flares, not cure of the disease. The management of atopic dermatitis includes:

- trigger avoidance and careful attention to skin care;
- use of topical therapies, most commonly corticosteroids, calcineurin inhibitors and moisturisers (emollients);
- phototherapy or systemic therapy, when topical therapies are insufficient. Note, systemic immunomodulatory agents include these older medications such as oral glucocorticoids; cyclosporin; methotrexate; azathioprine and mycophenolate. However, most of those drugs cannot be used long term either due to cumulative toxicity (oral glucocorticoids, cyclosporine) or are not approved for use in atopic dermatitis.

Atopic dermatitis is driven by pro-inflammatory cytokines (including interleukins IL-4, IL-13, IL- 22, IL-31, thymic stromal lymphopoietin (TSLP), and interferon gamma via the JAK1 pathway;[17,18,19] and, inhibiting JAK1 with upadacitinib reduces the signalling of many mediators which drive the signs and symptoms of atopic dermatitis.

Recently, dupilumab, a monoclonal antibody that inhibits the interleukins IL-4 and IL-13 signaling pathway has been approved for the treatment of moderate to severe atopic dermatitis in adults and paediatric patients over 6 years of age.[74] Dupilumab is administered subcutaneously (300 mg every 2 weeks). There may therefore, possibly be a need for an oral treatment development.

Upadacitinib

Regulatory history

Upadacitinib (proposed tradename Rinvoq, also known by it's drug development code 'ABT-494') is a selective and reversible Janus kinase (JAK) inhibitor. It has previously been approved for use in rheumatoid arthritis in Australia (in January 2020) as well as the EU and USA;[75] and has had approved extensions of indications for use in psoriatic arthritis and ankylosing spondylitis (in May 2021).[76]

Mechanism of action

Upadacitinib more potently inhibits JAK1 compared to JAK2 and JAK3. In cellular potency assays that correlated with the *in vivo* pharmacodynamic responses, upadacitinib demonstrated 33- to 197-fold greater selectivity for JAK1-associated signalling over JAK2 signalling. In enzyme assays, upadacitinib had more than 50-fold selectivity for JAK1 over JAK3. Atopic dermatitis pathogenesis is driven by pro- inflammatory cytokines (including IL-4, IL-13, IL-22, TSLP, IL-31 and interferon-gamma) that transduce signals via the JAK1 pathway. Inhibiting JAK1 with upadacitinib reduces the signalling of many mediators which drive the signs and symptoms of atopic dermatitis such as eczematous skin lesions and pruritus.

Current submission

The submission by the sponsor is a dual application consisting of a submission to extend the current indications, and a submission for a major variation to the current approval (in the form of a new strength) of Rinvoq (upadacitinib).

[74] AusPAR for Dupixent (dupilumab) Sanofi-Aventis Australia Ltd; submission PM-2020-03043-1-5. Published online May 2022; available at: AusPAR: Dupilumab | Therapeutic Goods Administration (TGA)
[75] AusPAR for Rinvoq (upadacitinib) AbbVie Australia Pty Ltd; submission PM-2018-05603-1-3. Published online April 2020; available at: AusPAR: upadacitinib | Therapeutic Goods Administration (TGA)
[76] AusPAR for Rinvoq (upadacitinib) AbbVie Australia Pty Ltd; submission PM-2020-02479-1-3. Published online August 2021; available at: AusPAR: upadacitinib | Therapeutic Goods Administration (TGA)

Major variation (new medicine strength)

The submitted data for the major variation/new strength component was a Phase I study (Study M20-017) to evaluate the bioavailability after a high-fat/high-calorie meal and under fasting conditions of upadacitinib 30 mg *market-image formulation* relative to the *wet granulated formulation* used in the upadacitinib Phase III trials.

From both the perspectives of the TGA's quality evaluation and clinical evaluation:

- the Rinvoq 30 mg market-image upadacitinib formulation (ER18) is bioequivalent to the 30 mg strength Phase III formulation (ER18Y), under fasting conditions and after a high-fat/high-calorie meal.
- the clinical evaluation further stated that an additional analysis showed that the 15 mg strength upadacitinib market-image formulation (ER17) provided equivalent dose-normalised plasma exposures to the 30 mg strength upadacitinib Phase III formulation (ER18Y) under fasting conditions and after a high fat/high-calorie meal.

The clinical evaluation commented that:

> It is noted, that the 30 mg once daily dose is not approved for the treatment of rheumatoid arthritis, but is proposed for use in adults with atopic dermatitis. The sponsors have proposed that only the lower dose of 15 mg once daily be used for proposed indication of atopic dermatitis in adolescents at this time as more safety data accrue on the 30 mg dose.
>
> Studies submitted earlier for the rheumatoid arthritis dossier showed higher upadacitinib exposure in subjects with severe renal impairment (44% higher upadacitinib AUC [exposure] compared to those with normal renal function) and when administered with strong CYP3A4 inhibitors;[77] (up to 75% higher upadacitinib exposure) following concomitant administration of ketoconazole.

Given the above, the Delegate for this submission believes that it will not be in the interest of public safety to go beyond the 15 mg dose, either in adults or adolescents with atopic dermatitis, pending further safety data on the 30 mg dose, unless it is absolutely essential based on sound clinical judgement. The concomitant use of upadacitinib with strong CYP3A4 inhibitors is already listed as a contraindication in the draft PI .

In addition, the predictions from the PopPK analysis (Report RD 200641), *a lower dose might be required in those with severe renal impairment.*

The pharmacodynamic data revealed a trend towards:

> *an increase in percentage of subjects experiencing a decrease in haemoglobin > 2 g/dL from Baseline at Week 16 with higher 30 mg upadacitinib exposures, similar to that previously observed in subjects with rheumatoid arthritis or ankylosing spondylitis. The latter might give further cause to not using the 30 mg dose in the absence of cogent clinical judgement.*

[77] **Cytochrome P450 (CYP) enzymes** are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds. Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

New indication: use in atopic dermatitis

Submitted data

Regarding the extension of indication component of this submission, on the efficacy and safety of upadacitinib in adolescents and adults with moderate to severe atopic dermatitis, the sponsor submitted the following:

- Two pivotal Phase III randomised, placebo-controlled , double-blind studies (Studies M16-045 and M18-891) assessing upadacitinib (at doses of 30 mg and 15 mg) as monotherapy;
- One pivotal Phase III, randomised, placebo-controlled, double-blind study (Study M16-047) assessing upadacitinib (at doses of 30 mg and 15 mg) in combination with topical corticosteroids

Two other clinical trials were also provided to support the extension of indication:

- A Phase IIb multicentre, randomised, placebo controlled, double-blind, dose-ranging study (Study M16-048) to evaluate upadacitinib) in adult subjects with moderate to severe atopic dermatitis; and
- A Phase III study (Study M17-377) for evaluation of upadacitinib in combination with topical corticosteroids in adolescent and adult subjects in Japan.

Efficacy

The Delegate agrees with the TGA's current clinical evaluation that adequate evidence had been provided through Studies M16-045 and M18-891, showing statistically and clinically significant improvements with both the 15 mg and 30 mg upadacitinib doses as monotherapy over placebo in the co-primary endpoints of vIGA-AD 0/1 and EASI 75 at Week 16 in 1783 patients (including 228 adolescents) with moderate to severe atopic dermatitis.

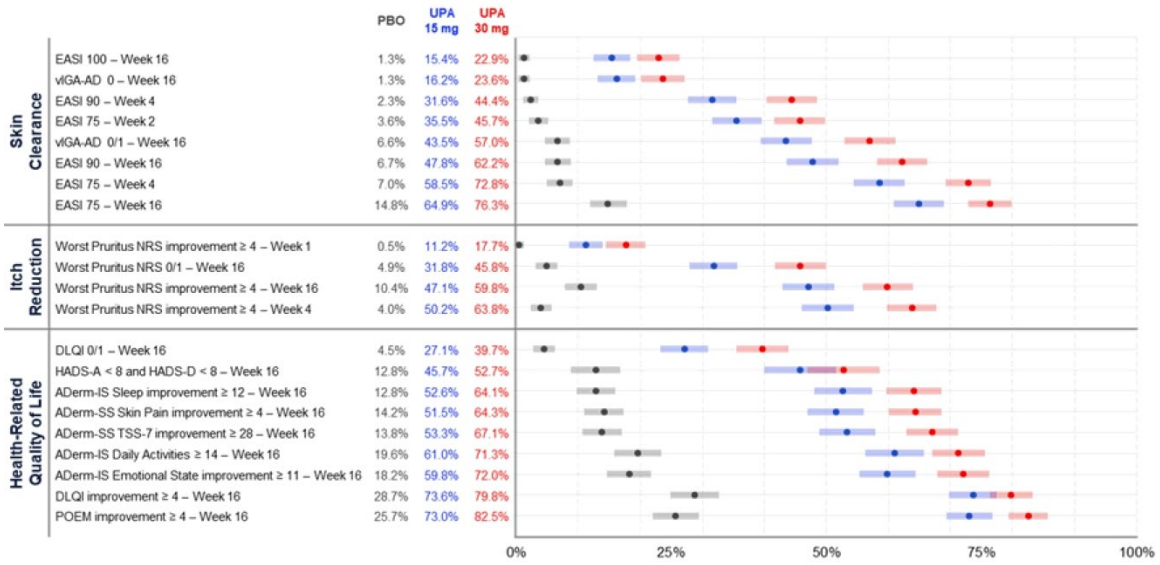
Precisely as per the clinical evaluation, for the primary EASI 75 end-point at Week 16 double blind period:

- In Study M16-045, a statistically significantly larger proportion of subjects in the upadacitinib groups achieved EASI 75 (69.6%, 79.7% and 16.3% in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively; $p < 0.001$ for both upadacitinib groups versus placebo;
- In Study MI8-891, a statistically significantly larger proportion of subjects in the upadacitinib groups achieved EASI 75 (60.1%, 72.9% and 13.3% in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively; $p < 0.001$ for both upadacitinib versus placebo groups).

Also, each of the multiplicity-controlled secondary endpoints demonstrated superiority of both the 15 mg and 30 mg upadacitinib doses as monotherapy against placebo with clinically relevant improvements in itch, atopic dermatitis symptoms, impact on all aspects of life, including sleep, atopic dermatitis symptoms, quality of life, HADS, DLQI, and patient perceptions of treatment.

Figure 43, shown below, summarises the efficacy outcomes across the integrated Phase III monotherapy studies.

Figure 43: Efficacy of upadacitinib 30 mg and 15 mg across atopic dermatitis domains in the placebo-controlled period (integrated Phase III monotherapy studies)



Abbreviations: AD = atopic dermatitis; ADerm-IS = Atopic Dermatitis Impact Scale; ADerm-SS = Atopic Dermatitis Symptoms Scale; DLQI =Dermatology Life Quality Index; EASI 50/75/90/100 = 50%/75%/90% improvement (reduction) in Eczema Area and Severity Index; HADS = Hospital Anxiety and Depression Scale; NRS = numerical rating scale; PBO = placebo; POEM = Patient Oriented Eczema Measure; upadacitinib = upadacitinib; vIGA-AD validated Investigator Global Assessment for Atopic Dermatitis.

Note: non-responder imputation due to Coronavirus 2019 pandemic.

There is also evidence via Study M16-048**,** showing statistically significantly higher and dose-dependent mean percentage improvement from Baseline in Eczema Area and Severity Index (EASI) score at Week 16 (primary endpoint) with upadacitinib (7.5 mg, 15 mg, and 30 mg) compared to placebo (23%, 39%, 62% and 74% in placebo, upadacitinib 7.5 mg, 15 mg and 30 mg groups, respectively. Clinically meaningful and highly statistically significant dose-dependent improvements were also observed for all key secondary endpoints in all upadacitinib dose groups (7.5 mg, 15 mg and 30 mg) compared with the placebo group.

It is accepted that numerically better outcomes were observed for the upadacitinib 30 mg dose than either the 7.5 mg or the 15 mg dose across the primary and key secondary endpoints in the monotherapy studies.

Safety

Given the above and the range of multiple potential serious adverse effects (pneumonia, TB (reactivation), herpes Zoster reactivation, herpes simplex reactivation, malignancies, non-melanoma skin cancer, eczema herpeticum with the associated opportunistic infections, haematological derangements (such as lowered haemoglobin, neutropenia, elevated transaminases and so on) associated with upadacitinib, most especially with the 30 mg dose, the Delegate for this submission was not inclined to approve the 30 mg dose at this point in time without further hindsight knowledge of extensive long term safety data. According to the clinical evaluation, 906, 899 and 902 subjects were treated overall with upadacitinib 30 mg, 15 mg and placebo, respectively with similar mean exposure across treatment groups. These included 114, 114 and 115 adolescents treated with upadacitinib 30 mg, 15 mg and placebo, respectively. Overall, 263 (21.2%) and 246 (19.9%) subjects had at *least 12 months* exposure to upadacitinib 30 mg or upadacitinib

15 mg, respectively. In adolescents, the respective numbers were 46 (27.7%) and 37 (22.2%), respectively.

The clinical evaluation further stated:

> 'Integrated data from ongoing global RA [rheumatoid arthritis] studies showed that event rate per 100 patient years for SAEs [serious adverse events] and TEAEs [treatment-emergent adverse events] leading to discontinuation continued to be higher in the upadacitinib 30 mg group compared to the 15 mg group. Hence, during the reporting interval of submitted PSUR [periodic safety update report] (Feb-Aug 2020), the decision was made to amend the RA studies to switch subjects from 30 mg QD [once daily] to 15 mg QD due to the 15 mg dose demonstrating the optimal benefit risk profile in patients with RA and being an approved marketed dose for RA.'

Considering all of the above, it is preferred that:

- The starting upadacitinib dose for atopic dermatitis is 7.5 mg daily, increasing to a maximum of 15 mg daily. The EASI 75 improvement between the 15 mg and the 30 mg dose is only about 10 points and does not safely justify a maximum dose of 30 mg, unless the treating physician thinks otherwise based on absolute benefit/risk balance;
- upadacitinib be initiated and managed by the treating dermatologist, paediatrician or specialist physician well versed in the use of immunomodulatory therapeutic agents, like upadacitinib.

In agreement with the clinical evaluation, Study M16-047 involving 901 subjects with atopic dermatitis (including 116 adolescent subjects) provided sufficient clinically and statistically relevant improvements in the co-primary endpoints (that is, the proportion of subjects who achieved EASI 75 and the proportion of subjects who achieved vIGA-AD Score of 0/1 (clear or almost clear) with at least a 2 grade reductions at Week 16) following treatment with upadacitinib 15 mg and 30 mg compared with placebo.

Precisely as reported in the clinical evaluation, for the primary EASI 75 end-point at Week 16 of the double blind period:

> 'In [Study] M16-047, a statistically significantly larger proportion of subjects in the upadacitinib groups achieved EASI 75 (60.1%, 72.9% and 13.3% in the upadacitinib [upadacitinib] 15 mg, upadacitinib 30 mg and PBO [placebo] groups, respectively; $p < 0.001$ for both upadacitinib groups vs [versus] placebo).'

These results were supported by significant improvements in key secondary endpoints of multiple skin clearance measures and response thresholds to pruritus:

- upadacitinib (30 and 15 mg) plus topical corticosteroids significantly reduced itch compared with placebo plus topical corticosteroids with a greater proportion of subjects on upadacitinib achieving a reduction in Worst Pruritus NRS ≥ 4 at Week 16;
- upadacitinib (30 and 15 mg) plus topical corticosteroids demonstrated rapid onset of action with significantly higher EASI 75 responses as early as Week 2 and a reduction in Worst Pruritus numerical rater scale (NRS score) ≥ 4 as early as Week 1 compared to placebo plus topical corticosteroids.
- upadacitinib (30 and 15 mg) plus topical corticosteroids had more topical corticosteroids free days with an EASI 75 response and an earlier discontinuation of all topical corticosteroids with an EASI 75 response than placebo plus topical corticosteroids at Week 16;

Furthermore, upadacitinib was also associated with significant improvements in sleep disturbance, impact of atopic dermatitis, health-related quality of life, self-assessment of disease parameters.

While both doses of upadacitinib (30 mg and 15 mg) were efficacious, upadacitinib 30 mg plus topical corticosteroids provided numerically greater benefit to subjects than upadacitinib 15 mg plus topical corticosteroids across the endpoints tested. Consistent efficacy was demonstrated for adolescents across all endpoints.

Study M17-377 provided support the combination therapy.

Following subgroup analyses of the co-primary endpoints validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of 0 or 1 and an EASI 75 response at Week 16 in each of the pivotal Phase III studies, efficacy of both doses of upadacitinib 30 mg and 15 mg once daily compared with placebo, was demonstrated overall across all subgroups by age, gender, body mass index, race, weight, geographic region, baseline vIGA-AD, baseline EASI, high specificity C-reactive protein (hsCRP), previous systemic therapy, intolerance to at least one prior topical corticosteroids/topical calcineurin inhibitors and inadequate response to at least one topical treatment.

As per the clinical evaluation, in the long term (that is, blinded extension) period:

- efficacy was demonstrated in 1542 subjects (1319 adult and 223 adolescent subjects who received at least 24 weeks of upadacitinib and 344 subjects (290 adult and 54 adolescent subjects) who received at least 1 year of upadacitinib treatment (30 mg or 15 mg once daily);
- significant improvements (in vIGA-AD 0/1, EASI 75 and Worst Pruritus NRS ≥ 4) were observed in those who were initially randomised to placebo and switched to upadacitinib at Week 16, as well as being maintained among those who were initially randomised to upadacitinib and continued on upadacitinib;
- upadacitinib 30 mg group demonstrated greater response rates than upadacitinib 15 mg through Week 52 in terms of vIGA-AD 0/1, EASI75, EASI 100 and reduction in worst pruritus NRS > 4;
- the number of subjects who were re-randomised as EASI 75 non-responders at Week 16 (time of entry into blinded extension Period 2 of Study M16-048) (and possibly later) achieved an EASI 75 response was small among the treatment groups.

The Delegate agrees with the findings of the clinical evaluation that lack of EASI 75 response in subjects who were non-responders at Week 16 suggests that continuing treatment beyond 16 weeks in non-responders is unlikely to provide any benefit.

The multitude of adverse effects associated with the use of upadacitinib, some of which are dose related, are as alluded to earlier on and, detailed in the clinical evaluation's overall conclusions on clinical safety in this overview.

Candidly, the sponsor discontinued the 30 mg dose in on-going rheumatoid arthritis studies due to 15 mg once daily being the approved dose for rheumatoid arthritis and the 30 mg dose not adding notable efficacy, whilst demonstrating increased incidence of adverse events, over the 15 mg once daily dose in rheumatoid arthritis.

The latter is following the sponsor, (via their responses to TGA evaluations and questions), submitting their integrated long term safety data from Phase III studies, conducted in subjects with rheumatoid arthritis, as of 30 June 2020.

Draft product information

While not proposing the 30 mg dose for use in adolescents, the sponsor's statement under *Dose and method of administration for Adults* of the Rinvoq PI reads:

> 'The recommended dose of Rinvoq is 15 mg or 30 mg once daily for adults. Consider dose selection based on individual patient presentation'.

The Delegate is mindful of the following:

- the proven efficacy of the 7.5 mg dose;
- dose related severe adverse effects of upadacitinib in both adolescents and adults; and
- the lack of extensive safety data on the 30 mg dose;
  - current data is limited to 52 weeks. According to the sponsor in its response to TGA evaluations and questions, data beyond 52 weeks for the global Phase III studies in atopic dermatitis are not available at present and are anticipated to be available in the third quarter of 2023 based on an interim data cut-off of approximately 3 years.

The Delegate's preferred statement under *Dose and method of administration section* of the PI is as follows:

> *'The recommended starting dose of Rinvoq is 7.5 mg daily, increasing to a maximum of 15 mg daily in both adolescents and adults. Dose reaching up to 30 mg daily in adults should be based on thorough benefit/risk assessment by the treating specialist physician'.*

The latter will equally serve as a safety net for those with renal impairment, especially severe, which is associated with higher upadacitinib exposure.

The sponsor's decision to add the following text to the *Dose and method of administration* section of the PI is acceptable:

> 'Rinvoq has not been studied in adolescents weighing less than 40 kg.'

Information on the duration of treatment in the clinical trial section of the draft product information should be highlighted.

Regarding recommendation for authorisation, the Delegate agreed with the TGA's clinical evaluation for approval of the submission with salient differences in the detail of what is to be approved.

Deficiencies of the data

The Delegate suggested that the lack of a direct head-to-head trial of upadacitinib alone versus upadacitinib plus topical corticosteroids, may possibly be considered a data deficiency.

Indication

Original indication

The indication as originally proposed by sponsor, and confirmed through the clinical evaluation is as follows:

> *Rinvoq is indicated for the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy.*

Delegate's modified indication

The Delegate has proposed changes to the original indication proposed by the sponsor (see above). The Delegate's preferred indication is as follows:

> *Rinvoq is indicated for the treatment of adults and adolescents >12 years old with moderate to severe atopic dermatitis, who have inadequate response to topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs) and, who are candidates for systemic therapy and in continuation with or without TCS/TCIs (for sensitive or unsafe areas).*

The Delegate's rationale for this modified indication are, as follows:

- better comprehension;

- the inclusion criteria listed failed prior use of both topical corticosteroids and topical calcineurin inhibitors; and documented systemic therapy;
- upadacitinib has proven efficacy by itself;
- Adjunctive use of upadacitinib and topical corticosteroids was better than placebo and topical corticosteroids;

Given that International treatment guidelines suggest that mid-potency topical corticosteroids are typically the first-line treatment for atopic dermatitis when non-pharmacological interventions have failed low potency topical corticosteroids or topical calcineurin inhibitors are used for sensitive areas such as the face, neck, and genital or intertriginous areas (as discussed via communication with the sponsor in their response to the TGA's evaluation), it is logical to include an aspect of this guidance in the indication, separate from the concomitant topical therapies section of the PI.

Conclusion

The efficacy and safety of upadacitinib both as monotherapy and combination therapy with topical corticosteroids, in the management of moderate to severe atopic dermatitis in adolescents have been documented in two pivotal trials, and documented in adults in one pivotal trial. In conjunction to these trials have been two supportive trials. More extensive long-term safety data (more than 52 weeks) will be required to assess the risk/benefit of the higher dose of 30 mg upadacitinib. The current lack of such data has led to the Delegate's recommended modifications to the statement under the *Dose and method of administration* section of the draft Rinvoq PI document.

Proposed action

The Delegate considered the present submission to be approvable.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Please can the ACM advise on the approvability of the submission

The ACM acknowledged that the efficacy of upadacitinib has been well demonstrated for atopic dermatitis and there is a place in therapy for this treatment as a management option, in line with the indication and dosage proposed below in response to Question 2, given below.

The ACM noted that no paediatric data (patients under 12 years of age) was included within this data package. Given the prevalence of atopic dermatitis within the paediatric population, the ACM welcomed the planned studies for this population.

2. Please can the ACM advise on the following:

a. Consideration of the Delegate's modified indication

Rinvoq is indicated for the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis, who have inadequate response to topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs) and, who are candidates for systemic therapy and in continuation with or without TCS/TCIs (for sensitive or unsafe areas).

The ACM agreed that the benefit/risk profile for upadacitinib in the treatment of atopic dermatitis is favourable for the following indication:

> *Rinvoq is indicated for use in adults and adolescents aged 12 years and above who weigh at least 40 kg, for the treatment of moderate to severe atopic dermatitis which is inadequately controlled with active topical pharmacotherapies and for whom systemic therapy is indicated.*

The ACM were of the view that clinical judgement should be used to determine whether concomitant topical corticosteroids or topical calcineurin inhibitors would be beneficial and advised that this does not need to be specified in the indication.

The ACM recommended the exclusion of topical corticosteroids combination therapy from the indication, citing that the efficacy outcomes appeared similar for upadacitinib with or without topical corticosteroid usage.

The ACM further advised that concomitant topical calcineurin inhibitor use was not included in the efficacy studies and therefore should not be included in the indication.

b. Consideration of the Delegate's modified dosing schedule

> *The recommended starting dose of Rinvoq is 7.5 mg daily, increasing to a maximum of 15 mg daily in both adolescents and adults.*
>
> *Dose reaching up to 30 mg daily in adults should be based on thorough benefit/risk assessment by the treating specialist physician.*

The ACM agreed that the benefit/risk profile for upadacitinib in the treatment of atopic dermatitis, is favourable for the following dose recommendations:

> Treatment should not be initiated with the 30 mg dose. The recommended starting dose of Rinvoq is 15 mg once daily for both adults and adolescents. In adults aged less than 65 years, the dose may be increased to 30 mg once daily if a clinically relevant response is not evident after review at 4 weeks, provided that the anticipated benefit of the higher dose outweighs any associated higher risk of adverse events.
>
> Rinvoq should be ceased if a satisfactory clinical response is not achieved after 16 weeks.

The ACM agreed that a clinical effect was established for the 7.5 mg, 15 mg and 30 mg doses. On balance, the ACM were of the view that 15 mg was an appropriate starting dose for both adults and adolescents.

The ACM noted that the 30 mg daily dose provided additional clinical benefit over the 15 mg daily dose across the endpoints of skin clearance or itch and regardless of topical corticosteroid, however due to increased toxicity with the 30 mg dose (dose response) they were inclined to recommend 15 mg as a starting dose. The ACM noted most people achieve a response within 4 weeks and if needed the dose can be increased at review after 4 weeks.

They noted that a 7.5 mg dose does not appear to be marketed and that splitting the extended release tablet is not recommended.

3. Does the ACM have any other advice applicable to this submission?

The ACM requested that renal impairment be classified according to the stages of kidney disease (CKD) rather than 'mild, moderate and severe' renal impairment and noted that moderate is stage 3 (glomerular filtration rate (GFR) 60-30 mL/min/1.73 m_2), severe is stage 4 (GFR 30-15 mL/min/1.73 m_2) and stage 5 (GFR less than 15 mL/min/1.73 m_2) and mild is normal.

Based on this the ACM recommended that the PI state:

> 'Patients with AD [atopic dermatitis] and stage 3 kidney disease have an increased pharmacokinetic exposure to UPA [upadacitinib] which may increase potential for adverse events. There are no evaluable data on use of UPA in stage 4-5 kidney disease. (see [section] 5.2 PHARMACOKINETIC PROPERTIES). While the majority of UPA elimination occurs through non-renal clearance, prudent dosing is recommended in these groups – 15mg is the maximum recommended daily dose.'

The ACM were of the view that combination therapy did not demonstrate any improvement over monotherapy and noted that there is no data on topical calcineurin inhibitors, as such they propose the removal of the following statement from the PI:

> 'Rinvoq can be used with or without topical corticosteroids. Topical calcineurin inhibitors maybe used for sensitive areas such as the face, neck, and intertriginous and genital areas.'

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the following indication:

> *Rinvoq is indicated for use in adults and in adolescents aged 12 years and above who weigh at least 40 kg, for the treatment of moderate to severe atopic dermatitis which is inadequately controlled with active topical pharmacotherapies and for whom systemic therapy is indicated.*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of a new strength of Rinvoq (upadacitinib): Rinvoq upadacitinib 30 mg modified release tablets (blister pack); and to extend the indications of the previously approved Rinvoq upadacitinib 15 mg modified release tablets for the following new extension of indications:

> ***Atopic Dermatitis***
>
> *Rinvoq is indicated for use in adults and adolescents aged 12 years and above who weigh at least 40 kg, for the treatment of moderate to severe atopic dermatitis which is inadequately controlled with active topical pharmacotherapies and for whom systemic therapy is indicated.*

Note, the Rinvoq 30 mg upadacitinib modified release tablet (AUST R 346215) is only approved for the submission above.

For the Rinvoq 15 mg upadacitib modified release tablet (AUST R 312687) is approved for the following full set of indications:

> ***Rheumatoid Arthritis***
>
> *Rinvoq is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to, one or more disease-modifying anti-rheumatic drugs (DMARDs).*
>
> *Rinvoq may be used as monotherapy or in combination with methotrexate or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).*
>
> ***Psoriatic Arthritis***
>
> *Rinvoq is indicated for the treatment of moderate to severe active psoriatic arthritis in adult patients who have responded inadequately to, or are intolerant to one or more DMARDs.*

Rinvoq may be used as monotherapy or in combination with a non-biological DMARD.

Ankylosing Spondylitis

Rinvoq is indicated for the treatment of adults with active ankylosing spondylitis.

Atopic Dermatitis

Rinvoq is indicated for use in adults and adolescents aged 12 years and above who weigh at least 40 kg, for the treatment of moderate to severe atopic dermatitis which is inadequately controlled with active topical pharmacotherapies and for whom systemic therapy is indicated.

The above extension of indications are inclusive of the previous approved indications.

Specific conditions of registration applying to these goods

- Rinvoq (upadacitinib) is to be included in the Black Triangle Scheme. The PI and CMI for Rinvoq must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.
- The Rinvoq Core/EU RMP (version 4.3, dated June 2021; data lock point 23 July 2020), with Australian Specific Annex (version 5.0, dated July 2021), included with submission PM-2020-04791-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Rinvoq approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

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