EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2021
EMA/396759/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rinvoq

International non-proprietary name: upadacitinib

Procedure No. EMEA/H/C/004760/X/0006/G

Note

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

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List of abbreviations

AD	atopic dermatitis
ADerm-IS	Atopic Dermatitis Impact Scale
ADerm-SS	Atopic Dermatitis Symptoms Scale
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransaminase
AS	ankylosing spondylitis
AS	active substance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BE	Blinded Extension
BMI	body mass index
BSA	body surface area
CAC	Cardiovascular Adjudication Committee
Cavg	average concentration
CDLQI	Children's Dermatology Life Quality Index
CHMP	Committee for Human Medicinal Products
CI	confidence interval
CK	creatine kinase
Cmax	maximum observed concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CSE	Clinical Summary of Efficacy
CSS	clinical summary of safety
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T cell lymphoma
CYP3A	cytochrome P450 3A isoform subfamily
DB	double-blind
DLQI	Dermatology Life Quality Index
DVT	deep vein thrombosis
E	event
EAER	exposure-adjusted event rate
EAIR	exposure-adjusted incidence rate
EASI 50/75/90/100	50%/75%/90% improvement (reduction) in Eczema Area and Severity Index
EMA	European Medicines Agency
ER	extended-release
EU	European Union
FDA	Food and Drug Administration
FP	finished product
HADS	Hospital Anxiety and Depression Scale
HDL-C	high-density lipoprotein cholesterol
HDPE	high-density polyethylene
HPLC	high performance liquid chromatography
HPMC	hypromellose

HR	hazard ratio
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigators Global Assessment
ISE	Integrated Summary of Efficacy
ISE SAP	ISE Statistical Analysis Plan
ISS	Integrated Summary of Safety
ITT	intent-to-treat
ITT_M	ITT Population for the main study
JAK	Janus kinase
KVE	Kaposi's varicelliform eruption
LRT	likelihood ratio test
LS	least square
MACE	major adverse cardiovascular event
MCC	microcrystalline cellulose
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model with repeated measures
MTX	methotrexate
NMSC	non-melanoma skin cancer
NRI	Non-Responder Imputation
NRI-C	non-responder imputation due to coronavirus 2019 pandemic
NRS	numerical rating scale
OC	Observed Cases
PASI	Psoriasis Area Severity Index
PBO	placebo
PE	pulmonary embolism
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
Ph. Eur.	European Pharmacopoeia
POEM	Patient Oriented Eczema Measure
PRO	patient-reported outcome
PsA	psoriatic arthritis
PT	preferred term
PY	patient-year
QbD	Quality by Design
QD	once a day
RA	rheumatoid arthritis
R&D	research and development
RH	relative humidity
RMP	risk management plan
SAE	serious adverse event
SAP	statistical analysis plan
SCORAD	Scoring Atopic Dermatitis
SCORAD 50/75/90/100	50%/75%/90%/100% improvement (reduction) in Scoring Atopic Dermatitis
SD	standard deviation
SIB	suicidal ideation and behaviours
SIR	standardised incidence ratio
SOC	system organ class

TB	tuberculosis
TC	total cholesterol
TCS	topic corticosteroids
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UPA	upadacitinib
US	United States
USP	United States Pharmacopoeia
UV	ultra violet spectrometry
vIGA-AD	validated Investigator Global Assessment for Atopic Dermatitis
vs.	versus
VTE	venous thromboembolic event
Wk	week

1. Background information on the procedure

1.1. Submission of the dossier

AbbVie Deutschland GmbH & Co. KG submitted on 9 October 2020 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new strength (30 mg prolonged-release tablet), grouped with a type II variation (C.I.6.a) to add a new indication (treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy for Rinvoq).
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 5.3 of the SmPC as well as the Package Leaflet are updated. The RMP (version 4.0) is updated in accordance.
In addition, the marketing authorisation holder (MAH) took the opportunity to include a minor update in the Annex II.

The MAH applied for a change or addition of a new strength.

In addition, the MAH proposed a new indication (treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy for Rinvoq) for the existing 15mg strength and the new 30mg strength.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0214/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0214/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH received Scientific advice from the CHMP on 22 March 2018 (EMEA/H/SA/3190/7/2018/II). The Scientific advice pertained to clinical aspects. See Type of Application and aspects on development.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Dunder

The application was received by the EMA on	9 October 2020
The procedure started on	29 October 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 January 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	25 January 2021
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	04 February 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 February 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 February 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	19 March 2021
The Rapporteur circulated the Assessment Report on the responses to the List of Questions to all CHMP members on	20 April 2021
The PRAC Rapporteur circulated the Assessment Report on the responses to the List of Questions to all CHMP members on	28 April 2021
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	29 April 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 May 2021
The Rapporteur circulated the updated Assessment Report on the responses to the List of Questions to all CHMP members on	12 May 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	20 May 2021
The MAH submitted the responses to the CHMP List of Outstanding Issues on	26 May 2021
The Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	09 June 2021
The PRAC Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	08 June 2021
The Rapporteur circulated the updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	17 June 2021

The PRAC Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 June 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rinvoq on	24 June 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Atopic dermatitis (AD) is a common, chronic, relapsing, inflammatory skin disease characterized by highly pruritic, erythematous, excoriated, and oozing papules and plaques that may become lichenified over time. The diagnosis of AD is made clinically and is based on history, morphology and distribution of skin lesions, and associated clinical signs and symptoms.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Atopic dermatitis generally begins in childhood as indicated by its higher prevalence rate among children (6% – 14%) relative to adults (3.2% – 10.2%). Evidence has suggested that the prevalence of AD has increased worldwide, and studies from the US and Norway have indicated a rising prevalence of AD in children over time. However, the majority of AD patients in the US are adults; 16.5 million individuals with AD are ≥ 18 years and 9.6 million individuals with AD are < 18 years. Further, recent estimates for adult AD prevalence rates in the US tend to be higher (6% – 10.2%) than rates reported from other countries. There could be several reasons for this increase in the estimated prevalence rate: an increase in persistence of the disease into adulthood, a higher prevalence of adult onset AD than initially understood, and potentially the same increased prevalence trend that has been observed for children. Approximately 8% – 14% of patients with moderate to severe AD are estimated to be adolescents.

2.1.3. Biologic features Aetiology and pathogenesis

Chronic eczematous rash and debilitating itch (pruritus) are the hallmark of the disease and are associated with significant negative impact on health-related quality of life, including depression, suicidal ideation, sleep disturbance, consequent fatigue, work productivity, and everyday activities. Atopic dermatitis pathogenesis is multifactorial and is driven by a complex combination of immune deviation, barrier dysfunction, and environmental risk factors. The AD immune map is comprehensive and contributes to the heterogenous phenotype of AD. The Janus kinase-signal transducer and activator of transcription (JAK-STAT) proteins are involved in several AD related cytokine pathways, including not only Th 2 signaling with IL-4 and IL-13 but also Th 22 and Th 1 signaling, which collectively mediate the inflammation underlying the clinical features of AD. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known. JAK1 inhibition with upadacitinib modulates the signaling of JAK dependent cytokines via more than one immune axis, and their blockade may provide therapeutic benefit across different AD phenotypes, including those not sufficiently responding to various Th2 centered treatment approaches.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Treatment of AD in adolescent and adult patients depends on the extent and severity of disease. One-third of AD patients have moderate to severe disease, which manifests as an itchy skin eruption, that is often accompanied by significant physical, psychological, and economic burden. The most commonly used topical agents are corticosteroids, calcineurin inhibitors, and moisturizers (emollients). When topical therapies are insufficient for treating AD, phototherapy or systemic therapy are generally added to topical agents.

2.1.5. Management

Mid-potency topical corticosteroids (TCS) are typically the first-line treatment for AD when non-pharmacologic interventions have failed (and low potency TCS or Topical Calcineurin Inhibitors (TCI) for sensitive areas such as the face, neck, and genital or intertriginous areas); however, AD disease activity may continue despite use of TCS, or patients may lose response over time.

Treatment guidelines developed by the American Academy of Dermatology (AAD), as well as the latest European and Japanese guidelines, recommend the use of systemic immunomodulatory agents for patients in whom optimized topical regimens or phototherapy do not adequately control the signs and symptoms of disease.

Dupilumab, a monoclonal antibody that inhibits IL-4 and IL-13 signalling, has been approved for the treatment of moderate to severe AD in adults and paediatric patients > 6 years of age. Olumiant (baricitinib), a JAK inhibitor, is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy. Tralokinumab (Adtralza) is a fully human IgG4 monoclonal antibody that specifically binds to the type 2 cytokine interleukin-13 (IL-13) and inhibits its interaction with the IL-13 receptors. It is indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy.

About the product

Upadacitinib is a JAK inhibitor that preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2, in human cellular assays. Janus Kinases (JAKs) are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, hematopoiesis and immune surveillance.

Rinvoq is currently approved in Rheumatoid arthritis, Psoriatic arthritis and Ankylosing spondylitis with a recommended dose of 15 mg QD.

The MAH proposed the following SmPC dosing recommendation for the atopic dermatitis (AD) indication:

> *Adults*
>
> *The recommended dose of upadacitinib is 15 mg or 30 mg once daily for adults. Consider dose selection based on individual patient presentation.*
>
> *Adolescents (from 12 to 17 years of age)*
>
> *The recommended dose of upadacitinib is 15 mg once daily for adolescents weighing at least 40 kg.*
>
> *Upadacitinib has not been studied in adolescents weighing less than 40 kg.*

> *Concomitant topical therapies*
>
> *Upadacitinib can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used for sensitive areas such as the face, neck, and intertriginous and genital areas.*

Type of Application and aspects on development

A full clinical development program, including a dose finding study as well as three pivotal, randomized, double-blind placebo-controlled studies, has been performed to support the AD application. In these studies, two dose levels of upadacitinib (15 mg QD and 30 mg QD) have been studied in mono-therapy or in combination with topical corticosteroids (TCS).

Scientific Advice has been provided by the CHMP in 2018 (EMEA/H/SA/3190/7/2018/II). Questions were raised on the proposed doses of upadacitinib to be studied in the Phase 3, study design for mono-therapy and combination treatment studies, PROs for pruritus (Worst Pruritus numeric rating scale, NRS) and symptoms and impact of AD using the new scales Atopic Dermatitis Symptoms Scale (ADerm-SS) and the Atopic Dermatitis Impact Scale (ADerm-IS), use of actigraphy, acceptance of the co-primary and key secondary endpoints, adequacy of the safety database and labelling. Overall, the advice has been followed, with some comments provided in some sections of this report.

There is no CHMP guidance available for the development of products for the treatment of AD.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as prolonged-release film-coated tablet containing upadacitinib hemihydrate as active substance, equivalent to 30 mg upadacitinib.

Other ingredients are:

-hypromellose, microcrystalline cellulose, mannitol, tartaric acid, silica colloidal anhydrous and magnesium stearate in the tablet core, and

-poly(vinyl alcohol), macrogol, talc, titanium dioxide (E171) and iron oxide red (E172) in the film-coating.

The product is available in HDPE bottles with desiccant and propylene cap or in polyvinyl chloride/ polyethylene/ polychlorotrifluoroethene-aluminium calendar blisters.

The 30 mg prolonged-release film-coated tablets were co-developed with the 7.5 mg and 15 mg tablets. Development information was provided in Module 3 about all three strengths of upadacitinib prolonged-release tablets in the original market application EMEA/H/C/004760, in which the 15 mg tablet strength was approved.

2.2.2. Active Substance

The active substance (AS) used to manufacture the new strength is the same as that of the already authorised 15 mg film-coated tablets (RINVOQ, EMEA/H/C/004760). The information on the AS had been assessed and found acceptable in the initial MAA application. No new information on the AS has been provided for the current application for the 30 mg strength. This is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as an oblong, biconvex film-coated prolonged-release tablet containing 30 mg of upadacitinib as the hemihydrate. The tablet has a red colour and the dimensions are 14.0 mm x 8.0 mm. The tablet is plain on one side and has "a30" debossed on the other side. The development of the FP in the initial application concerned three strengths (7.5, 15 and 30 mg), all described in the dossier but at the time of the initial application only the 15 mg strength was actually applied for and authorised. The finished product quality information, which are shared between the approved 15 mg strength and the proposed 30 mg strength tablets provided in original market application EMEA/H/C/004760, including pharmaceutical development, manufacturing process and control, analytical procedures and validation, reference standard, and container closure, has not been resubmitted for the 30 mg tablets.

The finished product (FP) is a prolonged release film coated tablet for once daily dosing. It is introduced to support a new indication that includes paediatric patients from the age of 12 years. The acceptability of the pharmaceutical form in the suggested age group years was adequately confirmed by the clinical programme and literature references. The FP contains standard excipients. The quality and function of each excipient used has been discussed. The daily exposure of the excipients in the intended age group (12-18 years) is considered acceptable and thus the use of the selected excipients is considered acceptably justified in relation to the proposed age group.

Upadacitinib is highly soluble according to the biopharmaceutics classification system. The crystalline form of the AS is chemically and physically stable and is controlled in the AS specification. It has been shown that different manufacturing methods (direct compression, wet granulation) generate product with similar dissolution profiles and confirmed bioequivalence. Stability studies further showed that during storage, neither changes to the AS diffraction pattern occur, nor changes in dissolution behaviour are observed. Based on this, the control of polymorphic form in the FP is not considered necessary. The AS particle size is also adequately controlled in the AS specification.

The basis of the design for development of the new strength was a common quality target product profile (QTPP) with that of the authorised strength, shown in Table 1.

Table 1. Quality Target Product Profile for Upadacitinib prolonged-release tablets.

Product Profile	Design Requirement
Route of administration	Oral solid (film-coated tablet)
Potential global dosage strength and frequency	(7.5), 15, and 30 mg dosed once daily.
Size	No more than 900 mg total tablet weight.
Appearance	Pharmaceutically elegant, globally acceptable, meets quality standards.
Container Closure system/Package configuration	Meets commercial needs for bottles and blisters. Must be capable of maintaining key product quality attributes under global climatic zone conditions, considers standard commodities with appropriate safety features.
Pharmacokinetic characteristic	Prolonged release.
Excipients	Globally acceptable, provides acceptable product stability, safety, and performance.
Drug Product Quality	Acceptance Criteria throughout Shelf Life
Dissolution	Meets pharmacopeia requirements for prolonged release for upadacitinib
Assay	Meets commercial limits for release and shelf-life.
Degradation Products	No more than toxicologically qualified.
Uniformity of Dosage Units	Meets USP <905>/Ph. Eur. 2.9.40
Microbiological Quality	Meets USP <1111>/Ph. Eur. 5.1.4-1
Stability	No special storage requirements under global climatic zone conditions for acceptable shelf life (≥24 months).

The FP is manufactured from a common milled granulate, in proportional amounts for the different strengths, and an extragranular portion where only the amount of filler (MCC) differs between strengths while the extragranular amount of hypromellose is adjusted so that the total amount of release control polymer (hypromellose) in the tablet is the same for all three strengths; the weight, size and shape of the tablets are identical. The formulation development has been assessed in the initial application. The formulation history has been described and changes explained. The choice of excipients, their quality and quantity has been sufficiently discussed, including the release controlling polymer, Hypromellose (HPMC).

The same release controlling polymer HPMC K4M (hypromellose 2208, 3550 mPa•s) is used for the new strength as in the already authorised strength, at the same amount level, enabling comparable exposure to the formulation used in PhI/PhII clinical studies. HPMC forms a gel layer around the tablet upon exposure to water through which upadacitinib molecules diffuse thus controlling the AS dissolution rate. The release rates are unchanged across tablet strengths as the level and grade of HPMC and tablet dimensions are kept constant.

The development of the proposed QC dissolution method has been sufficiently described. The proposed method has been developed simultaneously for all three strengths and is the same for the authorised 15mg and the proposed 30 mg strength. It employs a basket apparatus, 100rpm, 900 ml 0.05M sodium phosphate, pH 6.8; the proposed method is acceptable. The sensitivity of dissolution test to changes in the properties of HPMC was evaluated by using multiple lots of HPMC in the extragranular portion of the tablet (corresponding to 95% of the total HPMC content). Particle size, viscosity and substitution percentage of hydroxypropoxy groups (HP%) and methoxy groups (Methoxy%) were investigated. Based on dissolution data, it was concluded that viscosity and particle size have little impact on dissolution within the studied range. The percentage of HP substitution did influence release rate – low % HP substitution resulted in slow release. Based on these results, %HP, % methoxy and

particle size are controlled in the excipient used in the FP. All the above information already assessed during the initial application is applicable to the new strength.

The discriminating power of the proposed dissolution method was confirmed through the successful establishment of the level A IVIVC (*in vitro-in vivo* correlation). The establishment of a successful level A IVIVC and the evaluation of the IVIVC model were discussed in the initial procedure covering the 15 mg prolonged-release film-coated tablets, RINVOQ, EMEA/H/C/004760. The *in vitro-in vivo* correlation (IVIVC) presented in the initial application was developed for the 30 mg strength and has been assessed already and found acceptable.

Effect of alcohol on product performance
The risk of dose dumping due to the presence of alcohol was investigated. Drug release was slightly slowed down by the presence of alcohol and based on this, dose dumping due to consumption of alcohol by the patient is not expected.

A bioequivalence study (study M15-878) was conducted establishing the link between the PhIII and the proposed commercial formulation. Both the 15 mg and 30 mg tablet strengths were included in the study. Comparative dissolution profiles obtained at pH 1.1, 4.5 and 6.8, were provided for the biobatches and similarity was demonstrated by means of f2. Bioequivalence has been demonstrated between the 15 mg and 30 mg prolonged release tablet formulations used in the pivotal PhIII studies and the proposed commercial formulations.

The manufacturing process development has been adequately described and changes to the process after manufacture of stability batches has been discussed. Based on the information provided, the primary stability batches (PSBs) and site qualification batches (SQBs) are assessed as representative of commercial batches. The process is operated with PARs for milling, blending and tableting unit operations and with design spaces for granulation and film-coating. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces. This section was also assessed and found acceptable in the initial procedure covering the 15 mg prolonged-release film-coated tablets (RINVOQ, EMEA/H/C/004760).

The new strength is packaged either in HDPE bottles with desiccant, induction sealed with child resistant propylene cap, or in polyvinyl chloride/ polyethylene/ polychlorotrifluoroethene polymer blisters with push through aluminium foil. This is the same packaging material used for the authorised strength. Specifications were provided for all packaging materials and compliance with relevant EU legislation has been confirmed for the blister packaging materials and the bottle pack. At the time of initial approval, it has also been confirmed that the bottle with child resistant closure complies with ISO8317.

Manufacture of the product and process controls

The manufacturing process consists of six unit operations: wet granulation, milling, blending, tableting, coating and packaging.

A summary of the full finished product control strategy has been presented. The in-process controls (IPCs) and their applied limits have been justified and acceptable ranges have been set. The blending unit operation was identified as the only critical step in the process and is controlled by an appropriate IPC. Design spaces have been proposed for the granulation and coating steps of the manufacturing process of the medicinal product; these steps of the process are common for all the strengths as they are produced from a common blend. The design spaces have been developed at commercial scale. The overall control strategy for Rinvoq tablets is considered satisfactory and ensures adequate control of the process which is expected to produce tablets with consistent quality.

Process hold times were already established at the time of initial approval for the milled granulate, final blend, uncoated and coated tablets based on relevant stability studies.

The process is considered a non-standard process as per the process validation guideline because it concerns a modified release formulation. However, as with the authorised strength, it has been claimed that the manufacturing site has previous experience with similar types of products and in the meantime with the authorised RINVOQ tablets as well. In addition, to gain knowledge of the upadacitinib tablets specifically, commercial site-specific stability batches have been manufactured at the site on representative scale. It is considered that the applicant has sufficiently justified that the product process can be considered standard for the proposed particular manufacturer in line with the relevant guideline. Therefore, process validation will be conducted on three consecutive production-scale batches of the 30 mg tablets, following a traditional approach, before commercialization of the new strength. An acceptable validation plan including the additional sampling proposed is provided in the dossier.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), identification (UV, HPLC), assay (HPLC), degradation products (HPLC), water content (Ph. Eur.), dissolution (Ph. Eur.) and uniformity of dosage units (Ph. Eur.).

The proposed specifications for the upadacitinib tablets are acceptable. The specifications for release and shelf life are outlined in accordance with ICH Q6A. The acceptance criteria are set based on a combination of batch data, clinical exposure, manufacturing aspects, analytical aspects, knowledge gained during development and regulatory guidelines. The justifications provided are acceptable. Limits for degradation products are in line with ICH Q3B. For dissolution, a three-point specification is proposed which is relevant for a prolonged-release tablet. The selection of time points and proposed limit ranges are sufficiently justified based on the predicted effect a variation in this range will have on exposure; this is acceptable.

The exclusion of tests for microbiological quality, residual solvents, elemental impurities and mutagenic impurities have been acceptably justified based on the previously assessed information on the already approved strength.

A nitrosamine risk assessment in line with the requirements stated in EMA/409815/2020 has been performed. The summary provided covers currently known risk elements associated to the AS and the FP. The part of the risk assessment regarding the FP focused on the potential formation of Stage 5 nitrosamine, which may potentially form in the FP. Due to insufficient toxicological data, a risk based approach in line with ICH M7 was applied for this impurity and an acceptable daily intake (AI) was extrapolated based on lifetime exposure and typical patient weight (AI: 0.679 µg/day). Since the risk assessment did not identify any risk of nitrosamine introduction or formation above 10% of the 0.679 µg/day AI, no confirmatory testing of upadacitinib drug substance or FP was considered necessary.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data for a total of 22 batches of the 30 mg tablet strengths was provided, as well as supporting data for the 7.5 mg and 15 mg product strengths. The batch size of the 30 mg tablets varies from commercial scale to pilot; these batches have been used in clinical trials, primary stability

studies and site-specific stability studies. All results were within the proposed specification and therefore indicate consistent manufacture of the finished product.

Stability of the product

Stability data on three commercial scale batches of Rinvoq tablets 30 mg stored in the proposed blisters and bottles packaging for up to 36 months under long-term conditions at 25 ± 2 °C / 60% ± 5% RH and at 30 ± 2 °C / 75% ± 5% RH, and under accelerated conditions 40 ± 2 °C / 75% ± 5% RH for six months has been presented according to ICH guideline.

Supportive stability data from three batches of each strength (7.5 mg, 15 mg and 30 mg) manufactured at least at one-fourth the commercial scale at the development manufacturing facility were also presented and these are regarded representative of the commercial process. These batches were stored both in blisters and bottles for up to 36 months under long-term conditions at 30 ± 2 °C / 75% ± 5% RH and at 25 ± 2 °C / 60% ± 5% RH and for six months under accelerated conditions 40 ± 2 °C / 75% ± 5% RH according to ICH guideline.

Storage at 30 °C/75% RH is considered as a worst case scenario compared to ICH 25 °C / 60% RH or 30 °C / 65% RH.

Samples have been tested for description, assay, degradation products, water content, and dissolution. At selected intervals, the tablets are also tested for water activity, total aerobic microbial count (TAMC) and total combined yeasts and moulds count (TYMC) as per the respective Ph. Eur. methods. Crystal form was also evaluated on some stability batches.

No significant changes in any of the quality attributes monitored were seen after storage under either long term or accelerated conditions. However, for tablets packed in blister at 30 °C / 75% RH, a trend of decreasing dissolution was detected after 24 months of storage. In addition, a few out of specification (OOS) assay results were recorded (for one batch of the 30 mg strength, two of the 7.5 and one of 15 mg tablets). The root causes have been identified as process-related causes (water content misestimation) and an inappropriate sample preparation. Appropriate corrective/preventive actions were implemented. No conversion of the AS crystal form was observed.

Photostability
A photostability study as per ICH Q1B for 3 batches of each tablet strength was performed. The samples were tested for description, degradation products, assay, water content, and dissolution. No meaningful change was observed for tablets exposed without the primary packaging.

Temperature cycling
One batch per strength per package type was exposed to temperature cycling experiments comprising 5 cycles shifting between -20 °C and 50 °C followed by storage for 6 months at 30 °C / 75% RH. Testing included description, degradation products, assay, water content and dissolution. No meaningful changes were observed during the temperature cycling period. After the additional 6 months storage, the 7.5 mg strength product packaged in blisters showed some degradation. The degradation product was not observed in the other product strengths. The presented data support temperature excursions for upadacitinib tablets of -20 °C for 15 days, 50 °C for 1 month and up to 40 °C for 6 months.

In-use stability
Two in-use stability studies were performed on one commercial scale batch per strength and on two pilot scale batches per strength. The studies were designed to investigate (1) longer cycle time, equal to twice the expected in-use period, and (2) the effect on the stability of keeping the desiccant in the bottle during use or removing the desiccant at first opening. The samples were tested for description,

degradation products, assay, water content, and dissolution. Water content increased up to 6.7% in the study where the desiccant had been removed. The corresponding value when desiccant remained in the bottle throughout the study was 3.2%. With no desiccant present, a degradation product (A-1691599.0) formed, but remained within acceptance criteria. The increase in water content did not impact stability, quality or performance of the tablets as measured by the other tested attributes. Considering the overall in-use data generated at the end of the product shelf life as well as the presented (initial application) water activity data, there is no need to specify an in-use shelf life.

Bulk stability
Bulk stability was evaluated at -20 °C for 2 weeks, 30 °C/75% RH for up to 12 months, 40 °C/75% RH for up to 1 month and 50 °C/75% RH for 1 month. The film coated tablets were packaged in a single PE bag inside a heat-sealed laminate foil bag. No change in description, assay, or dissolution data were seen compared to initial values. Further, no change was observed for total aerobic microbial count (TAMC), total combined yeasts and moulds count (TYMC), or water activity at 30 °C/75% RH for up to 12 months.

Forced degradation studies
Forced degradation studies were performed on the 7.5 mg and 30 mg tablets. Samples were exposed to heat, heat/humidity, light, hydrolysis (exposure to acid and base in conjunction with heat) and oxidation (exposure to hydrogen peroxide and Iron (III)). Assay, total impurities, individual degradants at above the quantitation limit, mass balance (sum of assay and total impurities) and peak purity were determined. Mass balance was calculated relative to the mass balance of the control (unstressed samples). At each stress condition, no additional peaks were observed for the controls and the degradation products were separated from impurity A 1293543.0 peak. No significant degradation was observed under light and iron (III) stress conditions. Upon exposure to hydrogen peroxide, the total impurities were within the specification limits. An increase in the level of total impurities was seen after exposure to acid and base and was more prominent after treatment with heat and heat/humidity stress conditions. The major degradants were identified. As a result, the analytical methods were shown to be stability indicating.

Based on the data presented, the proposed shelf-life of 36 months for tablets stored in HDPE bottles with desiccant and the proposed shelf life of 24 months for tablets stored in blisters, as well as the storage conditions "Store in the original blister or bottle in order to protect from moisture. Keep the bottle tightly closed", (SmPC sections 6.3 and 6.4) are acceptable.

Adventitious agents

No excipient or materials of animal or human origin are used. Magnesium stearate are derived from vegetable source.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The new strength of 30 mg prolonged-release film-coated tablets is introduced to support a new indication that includes paediatric patients. The acceptability of the pharmaceutical form and the choice of excipients used in the suggested age group has been adequately justified. The new strength was co-developed with the already approved 15 mg tablets (and the lower not marketed strength of 7.5 mg). Extensive development information was provided about all three strengths of upadacitinib prolonged-release tablets in the initial application, in which the 15 mg tablets strength was approved. The information specific for the 30 mg tablets has been assessed in the current procedure and found satisfactory. The results of tests carried out indicate consistency and uniformity of

important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant has applied QbD principles in the development of the finished product and their manufacturing process. Design spaces have been proposed for two steps in the manufacture of the finished product concerning the manufacture of the common blend. The design spaces have been adequately verified.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

No new non-clinical studies were submitted which was considered acceptable to the CHMP. A brief summary from the EPAR for Rinvoq is given below.

2.3.2. Pharmacology

The primary pharmacodynamics program of upadacitinib included *in vitro* cell free (biochemical) and cellular assays and *in vivo* studies in two rodent models of arthritis to determine potency and selectivity of upadacitinib. Specificity has been determined by evaluating upadacitinib against a panel of other kinases, ion channels, transporters and cell surface receptors.

Janus Kinases (JAKs) are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, hematopoiesis and immune surveillance. The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and TYK2 which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation, in turn, modulates gene expression and cellular function. JAK1 is important in inflammatory cytokine signals while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function. Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.

Binding selectivity of upadacitinib against a panel of over 70 human protein kinases was investigated in a broad kinome selectivity screen. Of the kinases in the panel, six non-JAK kinases showed an IC50 below 5 µM, and two non-JAK kinases had IC50s equal to or below 1 µM (Rock1 at 1 µM and Rock2 at 0.42 µM). Thus, upadacitinib appears to be selective against a number of different non-JAK kinases and upadacitinib seems unlikely to interact with the tested kinases at clinically relevant exposures (Cmax = 71.5 ng/mL = 184 nM).

Upadacitinib was assessed in a series of GLP compliant safety pharmacology studies *in vitro* and *in vivo*. Decrease in locomotor activity was observed in rats at highest dose of 100 mg/kg (Cmax = 13.5 µg/mL).

No respiratory effects were observed in rats at an exposure margin of 54-fold above clinical Cmax (72 ng/mL)

A thorough QT study has not been conducted in clinical trials. However, an exposure-response analysis stated that no QT interval prolongation at therapeutic or supratherapeutic plasma exposures was observed in healthy subjects. From a non-clinical perspective, no further action is considered necessary with respect to safety pharmacology.

2.3.3. Pharmacokinetics

Upadacitinib displays rapid absorption after a single oral dose, with Tmax in plasma ranging from 1 to 2 h in rats, dogs and monkeys. The pharmacokinetics was further characterized by high to moderate plasma clearance in rat and dog, respectively, and high volume of distribution across all species. There was evidence of only limited decrease or accumulation (<2-fold) following multiple daily oral dosing in mice, rats, rabbits and dogs, which is in line with human data.

The *in vivo* tissue distribution in rat showed that upadacitinib related radioactivity was distributed rapidly into most tissues through 4 hr post-dose, with the liver, uveal tract and adrenal gland having the highest exposure. Lowest exposure was found in the CNS, spinal cord and eye lens. Radioactivity was present in the uveal tract through 192 hours post-dose and a slower clearance in pigmented skin indicating an apparent affinity for melanin. Placental transfer and subsequent foetal exposure to [14C]-upadacitinib-related radioactivity occurred at moderate to low levels. Exposure of [14C]-upadacitinib related radioactivity was approximately 31-fold greater in milk than in plasma.

Plasma protein binding of upadacitinib was low in all species (ranged from 0.41 in rat to 0.69 in dog) and independent of test concentration.

Biotransformation of upadacitinib in non-clinical species (mouse, rat, rabbit, dog) and human was, in general, low and unchanged parent was the primary drug-related component in dog (~88%) and in human (~79%) plasma, whereas unchanged parent represented about 56% of drug-related material in rats. In human plasma, the M4 metabolite was found to be a major metabolite, which was detected as a minor metabolite in rats and dogs. M4 is a Phase II conjugate, a normally non-reactive acyl glucuronide.

All human metabolites, including the major metabolite M4, were observed in one or more animal species.

Majority of upadacitinib is excreted as intact in all species (61% in rats, 56% in dogs). Mass balance data were obtained from rats, dogs and humans. Overall, the results indicate that elimination pathways for upadacitinib in non-clinical species and humans are similar; the majority of absorbed drug-related radioactivity being eliminated by excretion into biliary/fecal or renal routes whereas hepatic metabolism plays a secondary role.

2.3.4. Toxicology

Upadacitinib was evaluated in repeat-dose toxicity studies in mice (4 weeks with no recovery), rats (4 weeks with 4 weeks recovery, and 26 weeks with no recovery), and dogs (4 weeks with 4 weeks

recovery, and 39 weeks with no recovery). The main organs affected in the repeat-dose toxicity studies were primarily those related to JAK inhibition, that is the haematopoietic and immune system.

Upadacitinib was not tolerated in mice and rats at high doses, with large exposure margins to patients. The mortalities can be considered of limited clinical relevance although the observed microscopic findings were also observed in lower dose groups, but of a lesser magnitude.

In all the repeat-dose toxicity studies effects consistent with the inhibition of JAK1/3 were observed. The findings included decreases in circulating lymphocytes and lymphoid depletion in spleen, thymus, and lymph nodes.

Effects consistent with JAK2 inhibition such as decreases in red blood cell parameters [red blood cells, haemoglobin, and haematocrit] and reticulocytes were observed in rats and dogs.

Due to the potent pharmacological effect of upadacitinib on lymphoid tissue and subsequent secondary effects, it is not unexpected that the margin of exposure for these effects is relatively low in relation to the therapeutic doses of upadacitinib to be used in patients. However, reversible changes in hematological parameters associated with JAK inhibition generally occur earlier and at lower doses than the kidney and/or liver effects observed in the toxicological studies.

Upadacitinib was not mutagenic or genotoxic based on the results of *in vitro* and *in vivo* tests for gene mutations and chromosomal aberration.

The exposure in the *in vivo* chromosomal aberration study was considered sufficient (up to 72 times the clinical based on Cmax, and approximately 23 times on AUC for the highest dose tested).

Upadacitinib, at exposures (based on AUC) approximately 4 and 10 times the clinical dose of 15 mg and 2 and 5 times the clinical dose of 30 mg in male and female Sprague-Dawley rats, respectively, was not carcinogenic in a 2-year carcinogenicity study in Sprague-Dawley rats. Upadacitinib was not carcinogenic in a 26-week carcinogenicity study in CByB6F1-Tg(HRAS)2Jic transgenic mice.

There was no test article related unscheduled deaths or differences in mortality in any of the studies. No neoplastic findings were identified following upadacitinib treatment.

Studies were conducted to evaluate the standard reproductive and developmental toxicity profile of upadacitinib: one segment I 'fertility' study (Sprague-Dawley rats), three pivotal segment II 'EFD' studies (Sprague-Dawley rat and New Zealand white rabbits), and one segment III 'prenatal/postnatal study (Sprague Dawley rats). Additionally, one pivotal juvenile toxicity study was conducted in Sprague Dawley rats.

Upadacitinib had no effect on fertility in male or female rats at doses up to 50 mg/kg/day in males and 75 mg/kg/day in females in a fertility and early embryonic development study.

Two embryo-foetal development studies were conducted in rats. In the first study the animals were administered 0, 5, 25, and 75 mg/kg/day and since it was not possible to determine a NOAEL for the observed teratogenicity another study with lower doses (0, 1.5, and 4 mg/kg) was conducted.

There were no observed treatment related effects on implantation sites, viable foetuses, resorption sites or litter size. The foetal body weight was slightly reduced in both male and female foetuses from dams administered 75 mg/kg/day upadacitinib. An increased number of skeletal malformations was observed in all treatment groups, percent foetuses in the 0, 5, 25, and 75 mg/kg/day groups were 0, 1.4, 8, and 35. The skeletal malformations included misshapen humerus and bent scapula, bent, misshapen or shortened long bones of the fore- and hind limbs.

In the second EFD study in rat with lower doses of upadacitinib, skeletal malformations were observed in one fetus in the 4 mg/kg group. Since these malformations were similar as the ones observed in the

previous study, they were considered test-article-related. The NOAEL for developmental toxicity was the lowest dose, 1.5 mg/kg/day. The exposure in the dams at gestational day 16 was at this dose 115 ng*hr/mL, which represents 0.13 of the exposure observed in humans.

The embryo-foetal development study in rabbits was conducted at 0, 2.5, 10, and 25 mg/kg. In the rabbits an increase in post-implantation loss was observed (0%, 4.1%, 2.6%, 14.8% in the groups 0, 2.5, 10, and 25 mg/kg/day). There was no apparent increase of skeletal malformations, but an increased incidence of cardiac malformations was observed at 25 mg/kg/day. The NOAEL was considered 10 mg/kg/day and the exposure (AUC0-24) at gestational day 18 was 881 ng*hr/mL, which represents approximately the same exposure observed in humans.

The potential effects of upadacitinib on development, growth, behaviour, reproductive performance and fertility of F1 generation were evaluated in rats after administration of 0, 2.5, 5, and 10 mg/kg/day to F0 females from gestation day 6 through day 20 post-partum. In the study, only F0 dams were administered upadacitinib. The exposure in the pups was not measured in the study. In the previous EFD study it was however shown that the foetuses were exposed to upadacitinib (foetal/dam ratio at 10 mg/kg/day was 0.003). Furthermore, in a study with radiolabelled upadacitinib it was shown that upadacitinib readily transferred to milk in pregnant rats (presented in the section on pharmacokinetics). Thus, it is likely that also the pups were exposed to upadacitinib.

There were no treatment related effects on the F0 generation, including effects on parturition, lactation and maternal behaviour. There were no treatment related effects on the F1 generation in any of the investigated parameters, including viability, body weight, sexual maturation, behavioural testing (acoustic startle habituation, motor activity, and M-shaped water maze), or reproductive endpoints.

The NOAEL for maternal systemic toxicity and F1 development was considered to be 10 mg/kg/day. This corresponds to an exposure margin of 1.3 fold based on AUC and compared to AUC in patients with 30 mg/day.

In the non-GLP dose-finding study, doses ≥ 100 mg/kg/day resulted in mortality and clinical signs.

In a main GLP study with juvenile Sprague-Dawley rats, administered upadacitinib PND 15 to PND 63, accelerated pharmacologic effects on the lymphoid system and exposures similar to those observed in adult rats were evident. A T-cell Dependant Antibody Response (TDAR) assay within this study indicated that upadacitinib suppressed a Keyhole Limpet Hemocyanin (KLH)-specific primary IgM and IgG antibody concentrations when administered to juvenile rats from PND 15 through PND 59. This effect was comparable to that of the positive control cyclophosphamide A. Dose-dependent decrease in total T cells, T helper cells, T cytotoxic cells, B cells, NK cells and NKT cells at all doses was revealed by flow cytometric analysis.

2.3.5. Ecotoxicity/environmental risk assessment

The MAH submitted an environmental risk assessment (ERA) but no new data for the ERA were included with this application. The ERA was updated from the initial marketing authorisation application (MAA) for RA, and the updates to support the indications psoriatic arthritis and ankylosing spondylitis.

In the original ERA the results of the Phase I assessment triggered a Phase II Tier A assessment and the standard suite of fate and effect studies were completed.

Upadacitinib is very persistent in sediment according to the OECD 308 study. A Phase II Tier B extended effects on water sediment was thus triggered.

Phase 1

The maximum daily dose for the indication AD is 30 mg/day, resulting in $PEC_{SURFACEWATER}$ values of 0.15 µg/L for each of the indications when using the default Fpen value of 0.01.

A $PEC_{SW-TOTAL}$ was calculated (0.38 µg/L) and was used to re-calculate the Phase II Tier A and Tier B PEC/PNEC ratios.

The Log Pow were 1.81 (pH 4), 2.50 (pH 7), and 2.48 (pH 9).

Phase II

For this application, the same PNEC values were presented as for the original ERA submitted for the MAA. In the table below the updated PEC/PNEC ratios are presented, based on the PEC value obtained for all four indications. These ratios remain far below 0.1, and the conclusion remains: The clinical use of upadacitinib is not expected to be a risk for the environment.

The PEC values in relevant environmental compartments are compared to the PNEC values for these compartments by calculation of PEC/PNEC ratios.

Compartment	PEC	PNEC	PEC/PNEC (action limit)
Surface water	0.38 µg/L	63 µg/L	0.006 (<1)
Groundwater	0.095 µg/L	160 µg/L	0.0006 (<1)
Microorganism	0.38 µg/L	100000 µg/L	0.000004 (<0.1)

Phase II Tier B

The PEC value in sediment (dry) was recalculated with the updated $PEC_{SURFACEWATER}$ and compared to the PNEC values for this compartment.

Compartment	PEC	PNEC	PEC/PNEC (action limit)
Sediment	0.25 mg/kg	15.6 mg/kg	0.016 (<1)

Considering the above data, upadacitinib is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The non-clinical aspects of upadacitinib were thoroughly evaluated during the initial MAA. No new non-clinical studies were submitted in support of the present application which is acceptable to the CHMP.

The MAH applied for an indication in patients aged 12-18; hence, the results of the previously conducted reproductive and developmental toxicity studies, in particular the juvenile toxicity studies are of special interest. At the CHMP's request, the MAH provided a discussion on observed adverse effects in the juvenile rat toxicity studies with regards to the proposed indication in adolescents:

In the pivotal toxicity study in juvenile animals, rats were administered upadacitinib from postnatal day (PND) 15 to 63. The current application includes adolescents from 12 years old and it is agreed that in the presented study, the human equivalent age is significantly younger.

In the juvenile toxicity study, 1 male and 1 female animal administered upadacitinib 50 mg/kg were found dead on PND 22 and PND 18, respectively. The cause of death could not be established and a relation to exposure of upadacitinib could not be ruled out. There were treatment related effects on

immune and hematology parameters at all dose levels. The observed effects appeared to be consistent with those observed in adult rats.

Upon request from the CHMP, the MAH has also discussed possible effects on bone development. The CHMP agreed that the observed skeletal malformation that occurred during exposure in utero are not relevant for paediatric patients. Furthermore, no other signs of effects on bone development were observed in the non-clinical program. Exposure of juvenile animals started at PND15, which would then cover the period of long bone growth plate structure (PND 14-21). The MAH will continue assessing potential effects on height in growing children in the long-term extension studies and in a PASS (see safety section and RMP below).

The following SmPC updates were made in line with the data previously submitted as part the initial MAA and in relation to the 30mg dose and the use in adolescents:

Section 4.6 of the SmPC has been updated as the new indication includes paediatric patients aged 12 years and older:

"Female paediatric patients and/or their parents/caregivers should be informed about the need to contact the treating physician once the patient experiences menarche while taking upadacitinib."

Section 5.3 of the SmPC has been updated to include the following information:

- *"Upadacitinib had no effect on fertility in male or female rats at exposures up to approximately 21 and 43 times the maximum recommended human dose (MRHD) of 30 mg in males and females, respectively, on an AUC basis in a fertility and early embryonic development study."*

- *"Dose related increases in foetal resorptions associated with post-implantation losses in this fertility study in rats were attributed to the developmental/teratogenic effects of upadacitinib. No adverse effects were observed at exposures below clinical exposure (based on AUC). Post implantation losses were observed at exposures 11 times the clinical exposure at the MRHD of 30 mg (based on AUC)."*

- *"In animal embryo-foetal development studies, upadacitinib was teratogenic in both rats and rabbits. Upadacitinib resulted in increases in skeletal malformations in rats at 1.6 and 0.8 times the clinical exposure (AUC-based) at the 15 and 30 mg (MHRD) doses, respectively. In rabbits an increased incidence of cardiovascular malformations was observed at 15 and 7.6 times the clinical exposure at the 15 and 30 mg doses (AUC-based), respectively. No developmental toxicity was observed at approximately 0.15 times (rat) and at similar exposure in rabbits as the exposures at the MHRD of 30 mg."*

- *"In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 1.4 times the MRHD of 30 mg resulted in no maternal effects, no effects on parturition, lactation or maternal behaviour and no effects on the offspring."*

- *"Administration of upadacitinib to juvenile Sprague-Dawley rats (from postnatal day 15 to 63) resulted in exposures and pharmacologic effects on the lymphoid system similar to those observed in adult rats. No adverse findings were observed in juvenile rats at exposures (AUC) approximately 9.4 and 4.8 times the exposures at the clinical doses of 15 mg and 30 mg, respectively (based on exposures in adult RA patients)."*

Upadacitinib is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, the new strength (30 mg prolonged release tablets) and the new indication (treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy) are acceptable. The SmPC has been updated accordingly.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2 Atopic Dermatitis Studies

	Study M16-045	Study M16-047	Study M18-891	M16-048	M17-377
Type of Study	Pivotal Phase 3	Pivotal Phase 3	Pivotal Phase 3	Phase 2b	Phase 3 Regional Study in Japan
Type of Therapy	Monotherapy	Combination therapy with TCS	Monotherapy	Monotherapy	Combination therapy with TCS
Treatment Groups (N)	Upadacitinib 15 mg QD (281, including 42 adolescent patients) Upadacitinib 30 mg QD (285, including 42 adolescent patients) Placebo (281, including 40 adolescent patients)	Upadacitinib 15 mg QD + TCS (300, including 39 adolescent patients) Upadacitinib 30 mg QD + TCS (297, including 37 adolescent patients) Placebo + TCS (304, including 40 adolescent patients)	Upadacitinib 15 mg QD (276, including 33 adolescent patients) Upadacitinib 30 mg QD (282, including 35 adolescent patients) Placebo (278, including 36 adolescent patients)	Upadacitinib 7.5 mg QD (42)[a] Upadacitinib 15 mg QD (42) Upadacitinib 30 mg QD (42) Placebo (41)	Upadacitinib 15 mg QD + TCS (91, including 10 adolescent patients) Upadacitinib 30 mg QD + TCS (91, including 10 adolescent patients) Placebo + TCS (90, including 9 adolescent patients)
Placebo Duration	16 weeks	16 weeks	16 weeks	88 weeks[b]	16 weeks
Timepoint For Primary Endpoint	Week 16	Week 16	Week 16	Week 16	NA[d]
Data Cutoff Date Supporting CSS	04 June 2020[c]	04 June 2020[c]	04 June 2020[c]	31 January 2019[e]	02 December 2019[f]
Data Cutoff Date Supporting individual CSRs	13 April 2020[g,h]	10 April 2020[g]	08 May 2020[g, h]	31 January 2019[e]	02 December 2019[f]

QD = once daily; TCS = topical corticosteroids

a. This is not included as part of the PBO-controlled AD Analysis Set in the integrated summary of safety.
b. After the initial 16-week placebo-controlled period, subjects were rerandomized to upadacitinib or placebo groups.
c. Integrated safety data cutoff.
d. There were no primary or secondary efficacy variables. The efficacy variables in this study was exploratory.
e. Last subject last visit in the Final CSR.
f. Last subject last visit in the interim CSR (Week 24).
g. The data cutoff date is defined as the latter of the specified date or a subject's Week 16 visit date (provided the Week 16 visit date does not exceed Study Day 140).
h. Studies M16-045 and M18-891 were pooled for integrated efficacy analyses.

2.4.2. Pharmacokinetics

The characterization of upadacitinib pharmacokinetics (PK) after single and multiple doses, absorption, distribution, metabolism, excretion (ADME) characteristics, drug-drug interaction potential, and PK in special populations were assessed in the initial MAA. No new Phase 1 clinical pharmacology studies were included within this application which is acceptable to CHMP.

Bioequivalence

In the Phase 3 AD studies, upadacitinib regimens of 15 mg QD and 30 mg QD were administered using an extended release (ER) formulation which has the same core composition as the commercial formulation but a different color (yellow). The bioequivalence of the ER formulation used in AD Phase 3 studies and the commercial formulation was demonstrated in the Phase 1 Study M20-017 under fasting conditions and after a high-fat/high-calorie meal for both the 15 mg and 30 mg tablet strengths.

Population pharmacokinetic analysis

Subjects from one Phase 1 study (M14-680), one Phase 2 study (M16-048), and four Phase 3 studies (M16-045, M16-047, M17-377, and M18-891) were included in the population pharmacokinetic analysis. In total, 4161 upadacitinib plasma concentrations collected from 911 (103 adolescents) subjects following administration of upadacitinib doses of 7.5, 15 and 30 mg were included in the population pharmacokinetic analysis. Upadacitinib PK were described by a two-compartment model with mixed zero and first order absorption with lag time for the upadacitinib extended release formulation. Included covariates were patient population (HV versus AD/UC/CD), creatinine clearance, and sex on apparent clearance (CL/F). The estimated CL/F for AD patients were similar to the CL/F estimated for the RA population; 44.1 L/h and 40.1 L/h, respectively.

Upadacitinib observed and model-estimated plasma exposures were comparable between subjects with AD and subjects with RA who received the 15 mg QD and 30 mg QD regimens in Phase 3 trials (Figure and Tables below).
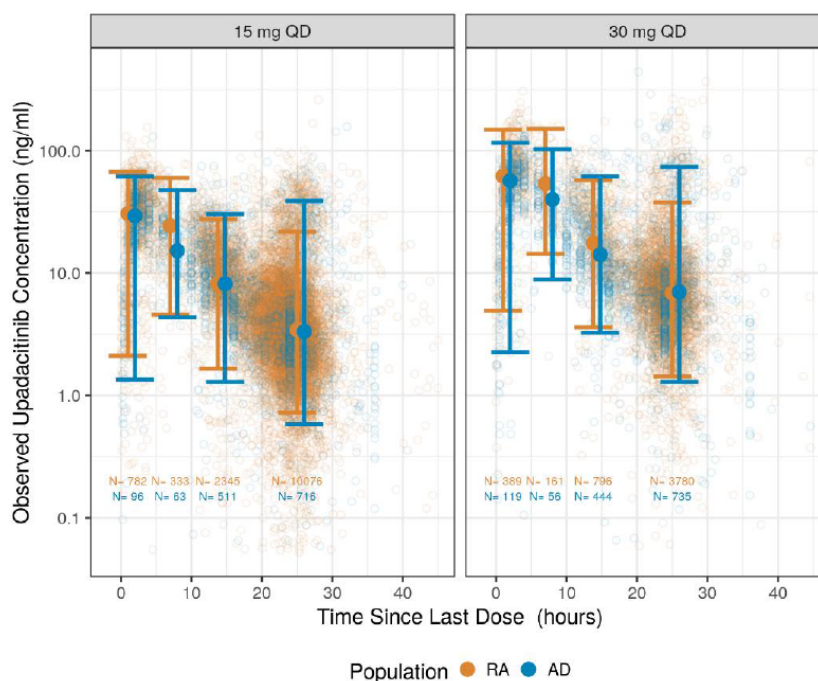
Orange circles represent observed upadacitinib concentrations from subjects with RA with extended-release formulation (Studies M13-542, M13-545, M13-549, M14-465, M14-663, M15-555). Blue circles represent observed upadacitinib concentrations from subjects with AD (Studies M16-045, M16-047, M16-048, M17-377, M18-891). Closed circles and error bars represent median and 5th and 95th percentiles for binned observed data.

Figure 1   Observed Upadacitinib Plasma Concentration-Time Profiles in Subjects with AD Compared to Subjects with RA Orange

Table 3 Summary of Model-Estimated Steady State Upadacitinib Plasma Exposures (C_{avg}, C_{min}, and C_{max}) for 15 mg and 30 mg QD Dosing Regimens in Subjects with AD or RA

Population	Treatment	C_{avg} (ng/mL) Median (90% CI)	C_{max} (ng/mL) Median (90% CI)	C_{min} (ng/mL) Median (90% CI)
AD	15 mg QD	14.7 (9.55 – 28.2)	35.5 (25.6 – 43.7)	3.76 (1.57 – 23.5)
	30 mg QD	29.0 (19.6 – 53.4)	71.5 (55.0 – 87.8)	7.46 (3.13 – 43.4)
RA	15 mg QD	15.1 (9.0 – 32.7)	41.1 (28.2 – 56.0)	3.82 (1.28 – 21.3)
	30 mg QD	30.0 (18.1 – 63.8)	82.0 (57.7 – 117)	7.74 (2.49 – 40.5)

In addition, the upadacitinib concentration-time profiles of 15 mg and 30 mg QD regimens in adolescent subjects with AD largely overlapped with the profiles in adult subjects with AD (Figure below), which indicates that the observed upadacitinib concentrations were comparable between adolescent and adult subjects with AD.
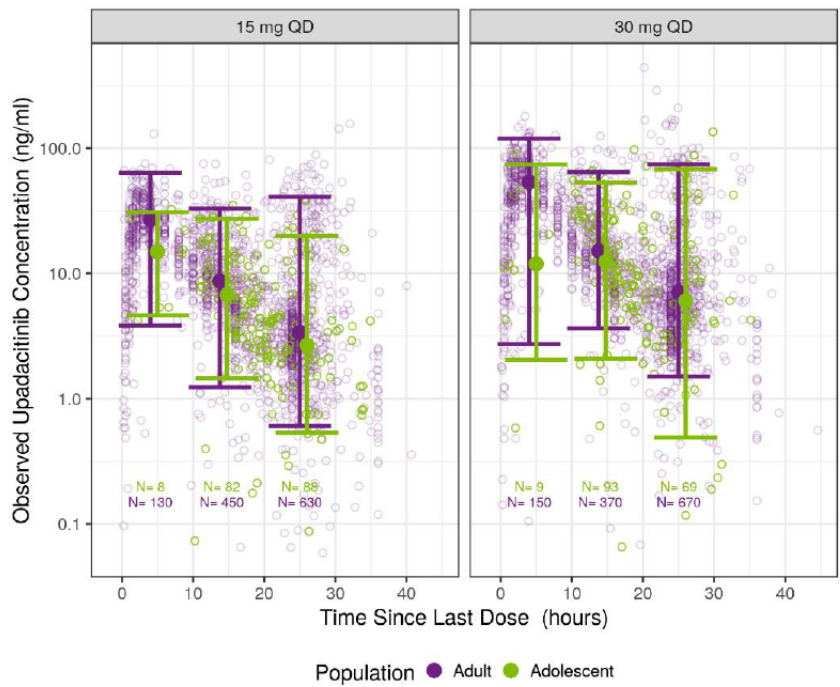
Purple circles represent observed upadacitinib concentrations from adult subjects (Studies M16-045, M16-047, M16-048, M17-377, M18-891). Green circles represent observed upadacitinib concentrations from adolescent subjects (Studies M16-045, M16-047, M17-377, M18-891). Closed circles and error bars represent median and 5th and 95th percentiles for the binned observed data.

Figure 2   Observed Upadacitinib Plasma Concentration-Time Profiles in Adolescent and Adult Subjects with AD

Table 4 Summary of Model-Estimated Upadacitinib Plasma Exposures (C_{avg}, C_{min}, and C_{max}) for 15 mg and 30 mg QD Dosing Regimens at Steady State in Adolescent and Adult Subjects with AD

Treatment	Population	C_{avg} (ng/mL) Median (90% CI)	C_{max} (ng/mL) Median (90% CI)	C_{min} (ng/mL) Median (90% CI)
15 mg QD	Adolescent	14.7 (9.63 – 22.3)	37.7 (27.3 – 43.6)	3.52 (1.62 – 13.7)
15 mg QD	Adult	14.6 (9.54 – 29.2)	35.3 (25.5 – 44.0)	3.90 (1.56 – 23.9)
30 mg QD	Adolescent	29.2 (20.1 – 53.5)	73.4 (56.0 – 81.9)	7.85 (3.61 – 40.4)
30 mg QD	Adult	29.0 (19.6 – 52.8)	70.8 (54.4 – 88.7)	7.38 (3.09 – 43.5)

Special populations

The effect of renal impairment on upadacitinib PK was evaluated in the Phase 1 Study M13-551, which was included in the original regulatory application for the use of upadacitinib in the treatment of RA. Results from Study M13-551 demonstrated that upadacitinib AUC central values were 18%, 33%, and 44% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. The predicted changes in upadacitinib AUC with varying degrees of renal impairment based on the final population pharmacokinetic model were in close agreement with previous results from the Phase 1 renal impairment study. Based on the results of Study M13-551, which demonstrated that subjects with severe renal impairment had 44% higher upadacitinib AUC compared to subjects with normal renal function, the MAH proposed upadacitinib 15 mg QD in patients with AD who have severe renal impairment.

Age was evaluated as a continuous covariate as well as a discrete covariate (adolescents [weighing ≥ 40 kg] versus adults) on upadacitinib clearance (CL/F) and volume of distribution (Vc/F) in the population pharmacokinetic analyses and was not found to be statistically significant.

The effects of race, sex, and body weight were previously described in the initial MAA. These intrinsic factors do not have clinically relevant effects on upadacitinib PK. No new effects of race, sex, or body weight were identified in the population pharmacokinetics analyses in subjects with AD.

Interactions

Based on results of Study M13-401 (included in the original regulatory application for the use of upadacitinib in the treatment of RA), which demonstrated 75% higher upadacitinib exposures when administered with the strong CYP3A inhibitor ketoconazole, the MAH proposed upadacitinib 15 mg QD for patients on chronic treatment with strong CYP3A inhibitors.

2.4.3. Pharmacodynamics

Exposure-Response

Exposure-response analyses were performed to describe the relationships between upadacitinib plasma exposures and clinical efficacy and safety in adolescent and adult subjects with AD using data from one Phase 2b and three Phase 3 studies across subjects receiving upadacitinib alone or in combination with topical corticosteroids (TCS). In total, 1746 subjects were included in the exposure-response analyses. Upadacitinib individual average plasma concentrations over a dosing interval at steady state (Cavg) and maximum plasma concentration (Cmax) based on the empirical Bayesian pharmacokinetic parameters from the population pharmacokinetic model were used as the exposure metrics for exposure-response analyses.

Exposure-Response for Efficacy

Exposure-response analyses for all efficacy endpoints were performed separately for monotherapy studies (Studies M16-048, M16-045, M18-891) and the combination therapy Study M16-047.

The efficacy endpoints evaluated for relationships with upadacitinib exposures included improvement (reduction) in Eczema Area and Severity Index (EASI) 75, EASI 90, Investigator's Global Assessment (IGA) response of 0/1, IGA 0, and improvement in Worst Pruritus Numerical Rating Scale (NRS) ≥ 4 from baseline at Week 16.

The observed and model-predicted percentage of subjects achieving the efficacy endpoints, for the identified E-R relationships, with monotherapy or combination therapy with TCS are presented in the Figures below. There were no significant differences in exposure-response relationships between adolescent and adult subjects with AD for both upadacitinib monotherapy and combination therapy with TCS.
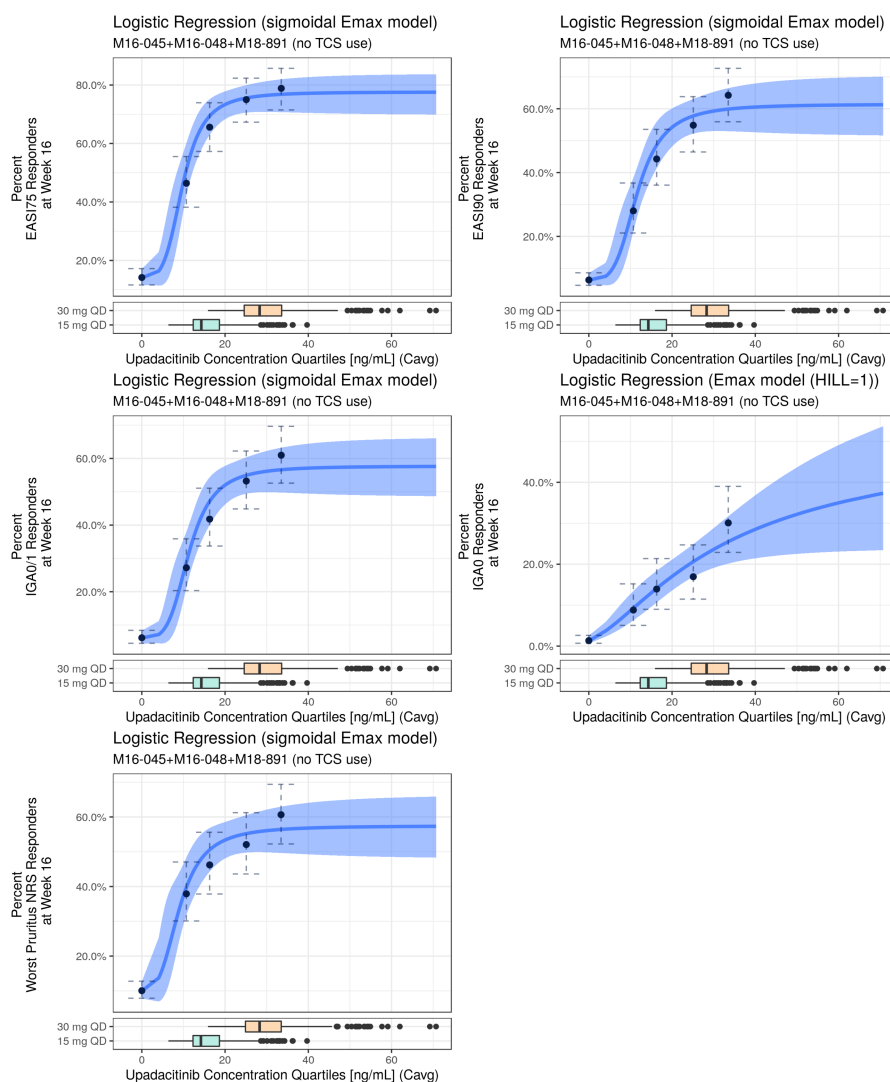
Note: The blue solid line represents median predicted response and the blue shaded area represent 95% confidence intervals of the predicted response. The dots and error bars represent median and 95% binomial CIs of binned observed rates. For the horizontal box plots, the band inside the box is the median of the upadacitinib average concentration C_{avg} per 15 mg QD and 30 mg QD dosing. The lower and upper hinges correspond to the 25th and 75th percentiles. Whiskers represent 1.5 IQR. The data beyond the end of the whiskers are plotted individually.

Figure 3   Observed (NRI) and Model-Predicted Efficacy Responses at Week 16 Versus Upadacitinib Cavg for Upadacitinib Monotherapy [Base models]
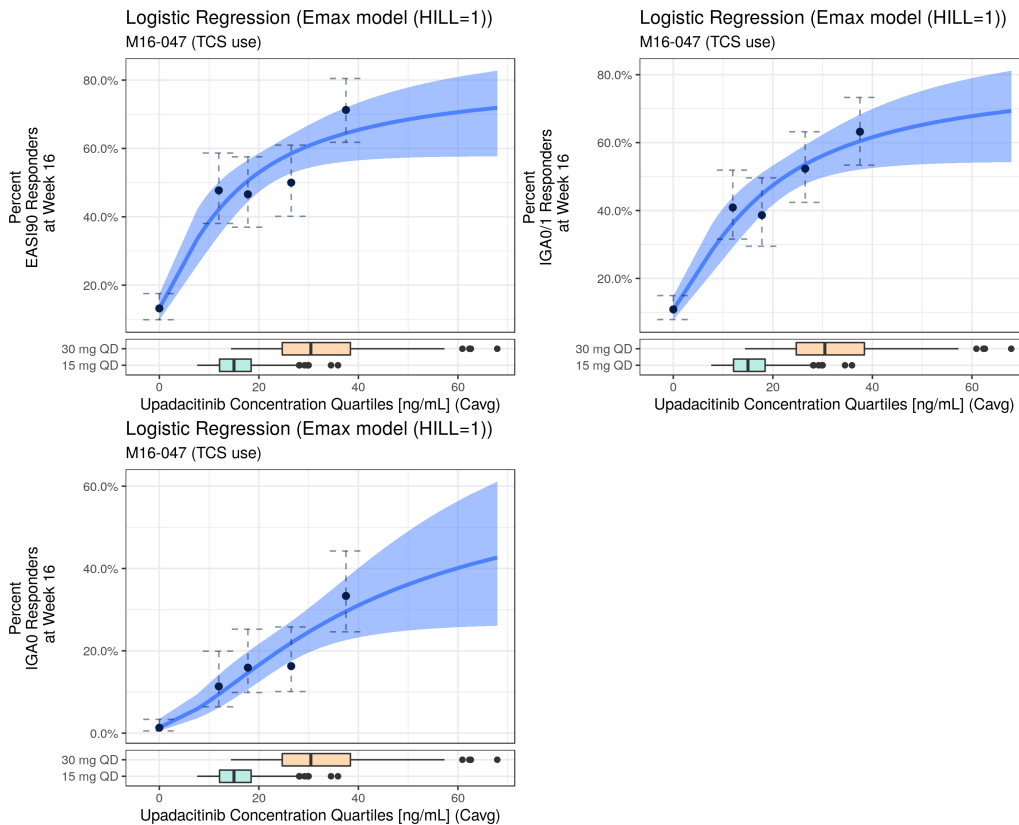
Note: The blue solid line represents median predicted response and the blue shaded area represent 95% confidence intervals of the predicted response. The dots and error bars represent median and 95% binomial CIs of binned observed rates. For the horizontal box plots, the band inside the box is the median of the upadacitinib average concentration C_{avg} per 15 mg QD and 30 mg QD dosing. The lower and upper hinges correspond to the 25th and 75th percentiles. Whiskers represent 1.5 IQR. The data beyond the end of the whiskers are plotted individually.

Figure 4   Observed (NRI) and Model-Predicted Efficacy Responses at Week 16 Versus Upadacitinib Cavg for Upadacitinib in Combination with TCS [Base models]

In subjects receiving upadacitinib monotherapy, simulations using the final exposure-response models demonstrate clinical benefit for the 30 mg QD regimen above that of 15 mg QD with predicted differences of 12%, 14%, 14%, 9%, and 8% for EASI 75, EASI 90, IGA 0/1, IGA 0, and improvement in Worst Pruritus NRS ≥ 4 responses at Week 16, respectively.

In subjects receiving upadacitinib in combination with TCS, simulations using the final exposure-response models demonstrate clinical benefit for the 30 mg QD regimen above that of 15 mg QD with predicted differences of 12%, 14%, and 12% for EASI 90, IGA 0/1, and IGA 0, respectively.

Exposure-safety analyses

There were sufficient number of events for only three of the safety variables of interest (decrease in hemoglobin > 2 g/dL from baseline, any infection, and acne) to enable adequate assessment of exposure-response relationships. The incidence of other safety endpoints of interest was too low to enable a meaningful exposure-response evaluation. Exposure-response quartile plots for decrease in hemoglobin > 2 g/dL from baseline, any infection, and acne are shown in the Figure below.

>2 g/dL Decrease in Hemoglobin at Week 16
M16-045+M16-047+M16-048+M18-891 (phase 2+3)

Acne
M16-045+M16-047+M16-048+M18-891 (phase 2+3)

Any Infection
M16-045+M16-047+M16-048+M18-891 (phase 2+3)
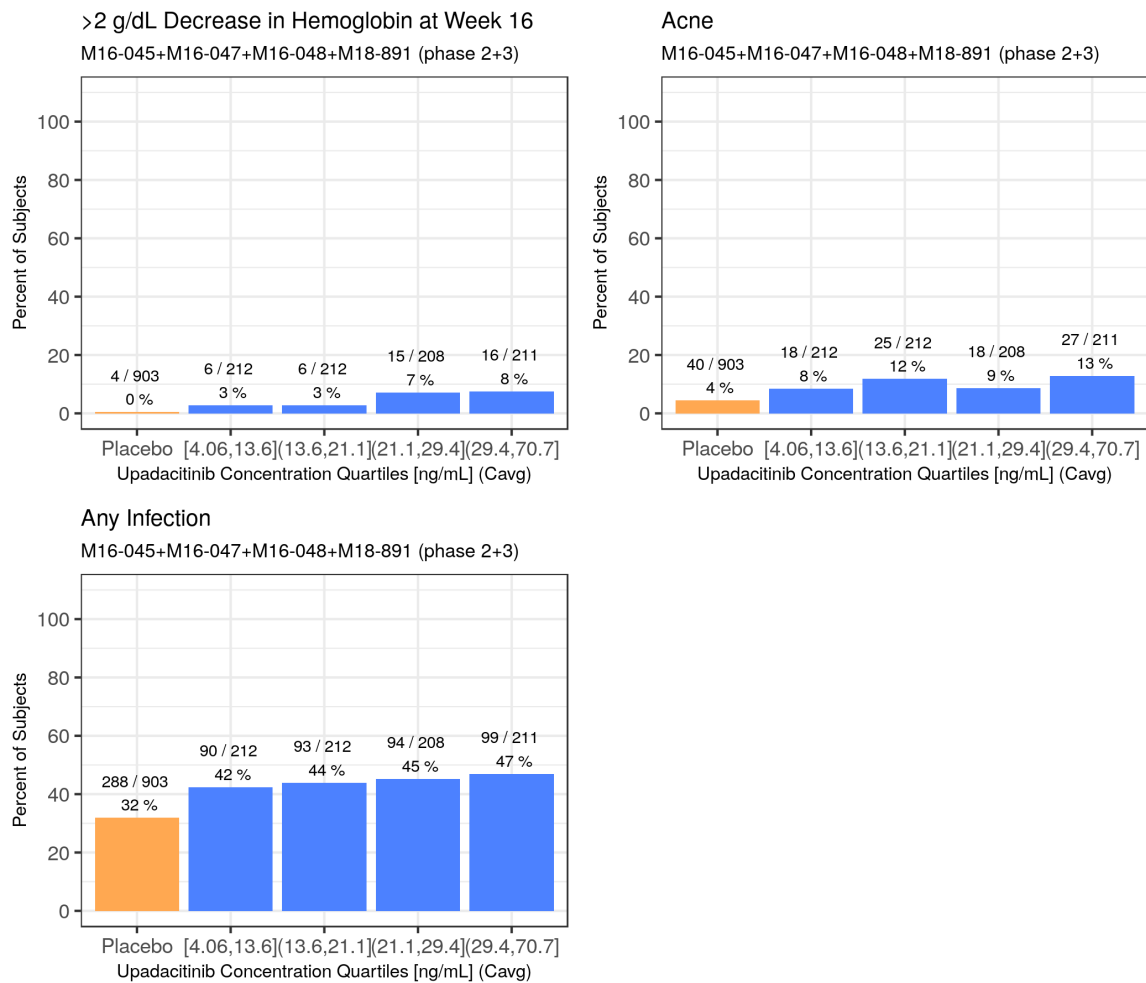
Figure 5   Exploratory Quartile Plots for Select Safety Endpoints at Week 16 Versus Upadacitinib Cavg

The percentages of subjects experiencing acne, or any infection did not show clear or marked trends with upadacitinib exposures based on the quartile plots and hence no logistic regression modelling was performed for these safety endpoints. Percentage of subjects experiencing a decrease in hemoglobin > 2 g/dL from baseline showed a trend of higher incidence with increasing upadacitinib exposures; similar to that observed in previous upadacitinib exposure-response analyses in subjects with RA and AS.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The PK of upadacatinib in the AD patient population have been characterised through population PK analysis. A pooled analysis was performed across studies M14-680, M16-048, M16-045, M16-047, M17-377, and M18-891 which included in total 911 patients. The model development methodology is considered adequate by the CHMP.

Similar PK characteristics were identified for the AD patient populations as previously identified for the RA patient population. The analysis results display that 30 mg QD result in a two-fold increase in plasma exposure compared to the 15 mg QD dosing regimen, as expected.

The MAH initially applied for a recommended dose of upadacitinib is 15 mg once daily for adolescents weighing at least 40 kg since upadacitinib has not been studied in adolescents weighing less than 40 kg. This proposal was questioned by the CHMP during the evaluation since body weight was not identified as a covariate in the PK model. As a sensitivity analysis, the MAH was therefore asked to re-estimate the model parameters with a fixed allometric scaling on CL/F and V/F and subsequently provide simulated exposures for body weights down to 25 kg (lower end of the weight distribution for 12-year olds). Furthermore, the MAH was encouraged to provide a justification for a body weight restriction that would be applicable to both adults and adolescents. In the response to questions, the MAH has provided modelling results that indicate that there is no apparent influence of body weight on PK in the adolescent and adult AD population. The results clearly show that allometric scaling do not describe the PK data well. In addition, the MAH provided exposure predictions used for supporting the dose selection to be used in AD patients 2-12 years, where a 30 kg weight limit is used for the 15 mg dose. The simulated exposures for AD patients 30-40 kg with a 15mg dose display a similar exposure range as established for adult AD patients. In conclusion, due to the low influence of body weight on upadacatinib PK in adolescent and adults AD patients, the weight limit was lowered to 30 kg weight for adolescents. This was supported by the CHMP. Of note, the inclusion of body weight is recommended in future applications of the population PK model in which younger age groups are targeted.

Creatinine clearance was identified as a covariate on CL/F, in line with initial MAA assessment. In the present analysis no patients with severe renal impairment were available. However, in accordance with the results of the renal impairment study, patients with severe renal impairment are expected to have an 44% increase of AUC. Hence, the MAH proposal to recommend a 15 mg QD dose to severe renal impairment patients was endorsed by the CHMP.

Study M13-401 was reviewed as part of the initial MAA. This study include 30 mg QD dosing regimen and demonstrated 75% higher upadacitinib exposures when administered with the strong CYP3A inhibitor ketoconazole. Thus, the CHMP agrees with the MAH's proposal that upadacitinib 15 mg QD should be the recommended dose for patients on chronic treatment with strong CYP3A inhibitors.

Overall, upadacitinib plasma exposures were similar between adults and adolescent subjects with AD, as well as between subjects with AD and subjects with RA.

Exposure-response

Response rates versus observed quartiles of upadacatinib as well as logistic regression analyses were presented for efficacy endpoints (EASI75/90, IGA0/1, IGA0, and Worst Pruritus NRS ≥4)**.** The modelling methodology was endorsed by the CHMP; however, the graphical presentation of the final E-R models was requested during the assessment. Since the basic and final models display a similar fit to data, the results from the exposure-response analyses were supported by the CHMP.

The logistic regression models for exposure-response relationships show that increasing exposure (C_{avg}) lead to increasing response rate with for all efficacy endpoints. Disease duration was identified as covariate on EC50 for the IGA0/1 model, where longer disease duration resulted in a slightly lower response. For the Improvement in Worst Pruritus NRS ≥4 model, age was found to influence the intercept. However, no difference in the age groups adolescents and adults could be detected. For the combination therapy, the response rate was higher at low exposure as well as an overall higher maximum effect, which is likely due to the additional effect of TCS.

Overall, there is a clear indication that the exposures given a 30 mg dose leads to a higher response rate for the full AD population. However, the recommendation of a 15 mg dose in adolescents is supported by the CHMP and discussed further in the Clinical section.

Exposure-safety evaluations were based on graphical presentation of response rates versus observed concentrations for safety endpoints; decrease in haemoglobin > 2 g/dL, any infection and acne. The

MAH claims that the incidence was too low for other safety endpoints. In line with previous findings of upadacatinib exposure-safety relationships, albeit low in incidence, a decrease in haemoglobin with increasing exposure was apparent. Very shallow trends of increasing incidence with increasing exposure were apparent for any infection and acne. Overall, no new findings in exposure-safety profile of upadacatinib were apparent in the AD population.

2.4.5. Conclusions on clinical pharmacology

The CHMP concluded that the PK and exposure-response relationships of upadacatinib in the AD patient population have been adequately characterised.

The influence of body weight on upadacatinib PK is low in adolescent and adult AD patients. A weight limit of 30 kg in adolescent AD patients is not expected to exceed the adult reference exposure range. Hence, the weight limit was lowered from 40kg to 30 kg for adolescent AD patients. This is supported by the CHMP.

The MAH proposal to recommend a 15 mg QD dose to severe renal impairment patients and patients on chronic treatment with strong CYP3A inhibitors was endorsed by the CHMP.

Overall, the following dosing recommendations were considered acceptable to the CHMP (see also discussions in the efficacy and safety sections):

Adults

The recommended dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation.

A dose of 30 mg once daily may be appropriate for patients with high disease burden.

A dose of 30 mg once daily may be appropriate for patients with an inadequate response to 15 mg once daily.

The lowest effective dose for maintenance should be considered.

For patients ≥ 65 years of age, the recommended dose is 15 mg once daily.

Adolescents (from 12 to 17 years of age)

The recommended dose of upadacitinib is 15 mg once daily for adolescents weighing at least 30 kg.

Concomitant topical therapies

Upadacitinib can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used for sensitive areas such as the face, neck, and intertriginous and genital areas.

Consideration should be given to discontinuing upadacitinib treatment in any patient who shows no evidence of therapeutic benefit after 12 weeks of treatment.

2.5. Clinical efficacy

The application for a new indication for Rinvoq in atopic dermatitis is primarily supported by three pivotal phase 3 studies; two mono-therapy studies (M16-045 and M18-891) and one study with upadacitinib used in combination with topical corticosteroids (M16-047). A Phase 2 dose-ranging study (Study M16-048) is also included as supportive data for the dosing recommendation. A tabular overview of the pivotal clinical studies is shown in the table below.

Table 5 Description of Clinical Efficacy and Safety Studies – Pivotal

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M16-045/ 151/ARG, AUS, BIH, BGR, CAN, CHN, COL, HRV, DNK, EST, FIN, FRA, DEU, ITA, JPN, MYS, NZL, ROU, RUS, CHE, TUR, UK, UKR, US (+PR) DB: 16 weeks BE: up to 136 weeks	13 Aug 2018 (First Subject, First Visit) Enrollment complete, Study ongoing 16 April 2020 (Last Subject Last Visit Week 16) 847/810	Multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a blinded long-term (136 weeks) extension	DB Period: 15 mg, 30 mg UPA or placebo QD, PO BE Period: 15 mg or 30 mg UPA QD, PO	To assess the efficacy and safety of upadacitinib for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy.	DB: PBO: 281/239 UPA 15 mg: 281/272 UPA 30 mg: 285/271 BE: UPA 15 mg: 272/0 UPA 30 mg: 271/0 PBO/UPA 15 mg: 118/0 PBO/UPA 30 mg: 121/0	M/F: 456/391 Median age: 30.0 (12 – 75)	Female and male subjects ≥ 12 yrs. old and ≤ 75 yrs. old with a diagnosis of chronic AD according to Hanifin and Rajka criteria, onset of symptoms at least 3 years prior to Baseline, and moderate or severe disease defined by an EASI ≥ 16, vIGA-AD ≥ 3, and ≥ 10% BSA, in addition to a baseline weekly average of daily Worst Pruritus NRS ≥ 4. Subjects were required to have had an inadequate response to treatment with TCS, TCI, or were permitted to enroll if topical treatments were medically inadvisable or if systemic treatment was previously used. Subjects were also required to use an emollient BID for ≥ 7 days prior to Baseline.	EASI 75 at Week 16 and vIGA-AD 0/1 with at least 2 grades of reduction at Week 16
M18-891 154/ AUS, AUT, BEL, BGR, CAN, HRV, CZE, DNK, FRA, DEU, GRC, HUN, IRL, ITA, NLD, NZL, PRT, SGP, South Korea, ESP, Taiwan, UK, US DB: 16 weeks BE: up to 136 weeks	27 July 2018 (First Subject, First Visit) Enrollment complete, Study ongoing 14 May 2020 (Last Subject Last Visit Week 16) 836/810	Multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a blinded long-term extension (up to Week 136)	DB Period: 15 mg, 30 mg UPA or placebo QD, PO BE Period: 15 mg or 30 mg UPA QD, PO	To assess the efficacy and safety of upadacitinib for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy.	DB: PBO: 278/237 UPA 15 mg: 276/264 UPA 30 mg: 282/267 BE: UPA 15 mg: 264/0 UPA 30 mg: 267/0 PBO/UPA 15 mg: 118/0 PBO/UPA 30 mg: 119/0	M/F: 471/365 Median age: 29.0 (12 – 75)	Female and male subjects ≥ 12 years old and ≤ 75 years old with a diagnosis of chronic AD according to Hanifin and Rajka criteria, onset of symptoms at least 3 years prior to Baseline, and moderate or severe disease defined by an EASI ≥ 16, vIGA-AD ≥ 3, and ≥ 10% BSA, in addition to a baseline weekly average of daily Worst Pruritus NRS ≥ 4. Subjects were required to have had an inadequate response to treatment with TCS, TCI, or were permitted to enroll if topical treatments were medically inadvisable or if systemic treatment was previously used. Subjects were also required to use an emollient BID for ≥ 7 days prior to Baseline.	EASI 75 at Week 16 and vIGA-AD 0/1 with at least 2 grades of reduction at Week 16
M16-047 171/AUS, AUT, BEL, CAN, CHN (+HKG), CZE, FRA, DEU, GRC, HUN, IRL, ISR, ITA, JPN, NLD, NZL, NOR, SVK, ESP, SWE, UK, US (+PR) DB 16 weeks BE: up to 136 weeks	09 Aug 2018 (First Subject, First Visit) Enrollment complete, Study ongoing 13 May 2020 (Last Subject Last Visit Week 16) 901/810	Multicenter 2-period: 16-week randomize, DB, placebo-controlled treatment period followed by a blinded long-term extension (136 weeks)	DB Period: 15 mg, 30 mg UPA or placebo QD, PO with TCS or TCI BE Period: 15 mg or 30 mg UPA QD, PO with TCS or TCI	To assess the efficacy and safety of upadacitinib combined with TCS for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy.	DB: PBO + TCS: 304/280 UPA 15 mg + TCS: 300/287 UPA 30 mg + TCS: 297/287 BE: UPA 15 mg + TCS: 287/0 UPA 30 mg + TCS: 287/0 PBO/UPA + TCS 15 mg: 143/0 PBO/UPA + TCS 30 mg: 137/0	M/F: 547/354 Median age: 30.0 (12 – 75)	Female and male subjects ≥ 12 years old and ≤ 75 years old with a diagnosis of chronic AD according to Hanifin and Rajka criteria, had onset of symptoms at least 3 years prior to Baseline, and moderate or severe disease defined by an EASI ≥ 16, vIGA-AD ≥ 3, and ≥ 10% BSA, in addition to a baseline weekly average of daily Worst Pruritus NRS ≥ 4. Subjects were required to have had an inadequate response to treatment with TCS, TCI, or if systemic treatment was previously used. Subjects were also required to use an emollient BID for ≥ 7 days prior to Baseline.	EASI 75 at Week 16 and vIGA-AD 0/1 with at least 2 grades of reduction at Week 16

AD = Atopic Dermatitis; ARG = Argentina; AUS = Australia; AUT = Austria; BE = blinded-extension; BEL = Belgium, BID = twice daily; BGR = Bulgaria; BIH = Bosnia and Herzegovina; CAN = Canada; CHE = Switzerland; CHN = China; COL = Columbia; CZE = Czech Republic; DB = double-blind; DEU = Germany; DNK= Denmark; EASI = Eczema Area and Severity Index; EST = Estonia; ESP = Spain; FIN = Finland; FRA = France; GRC = Greece; HKG = Hong Kong; HRV = Croatia; HUN = Hungry; IRL = Ireland; ISR = Israel; ITA = Italy; JPN = Japan; MYS = Malaysia; NLD = Netherlands; NZL = New Zealand; NOR = Norway; OL = open-label; PBO = placebo; PO = orally; PR = Puerto Rico; PRT = Portugal; SGP = Singapore; QD = once daily; RA = rheumatoid arthritis; ROU = Romania; RUS = Russian Federation; SVK = Slovakia; SWE = Sweden; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; TUR = Turkey; UK = United Kingdom; UKR = Ukraine; UPA = upadacitinib; US = United States; v-IGA-AD = validated Investigator Global Assessment of Atopic Dermatitis

2.5.1. Dose response study

Dose response study M16-048

Methods

This was an 88-week Phase 2b, randomized, double-blind, parallel-group, placebo-controlled multi-center study to evaluate the safety and efficacy of ABT-494 (upadacitinib) in adult subjects with moderate to severe AD.

Subjects enrolled in this study were between 18 and 75 years old with a diagnosis of AD confirmed by a dermatologist (according to the Hanifin and Rajka criteria), 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 (TCS), topical calcineurin inhibitors (TCI), or were permitted to enroll if topical treatments were medically inadvisable (e.g., 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.

The inclusion criteria are relevant to include a population with moderate to severe AD. The requirement to use a bland emollient is adequate since this is basic AD standard of care.

The exclusion criteria are also endorsed and are relevant for a JAK inhibitor, including the screening laboratory values, based on the known effects of upadacitinib and the similar requirements for initiation of therapy in the RA indication.

The study duration included a 35-day maximum screening period; a 16-week double-blind treatment period (Period 1); a 72-week double-blind treatment period (Period 2) for a total of 88 weeks of treatment. In addition, a 30-day follow-up period (call or visit) to determine the status of any ongoing or new adverse events (AEs)/serious adverse events (SAEs) was done.

A schematic of the overall study design is shown in the figure below.
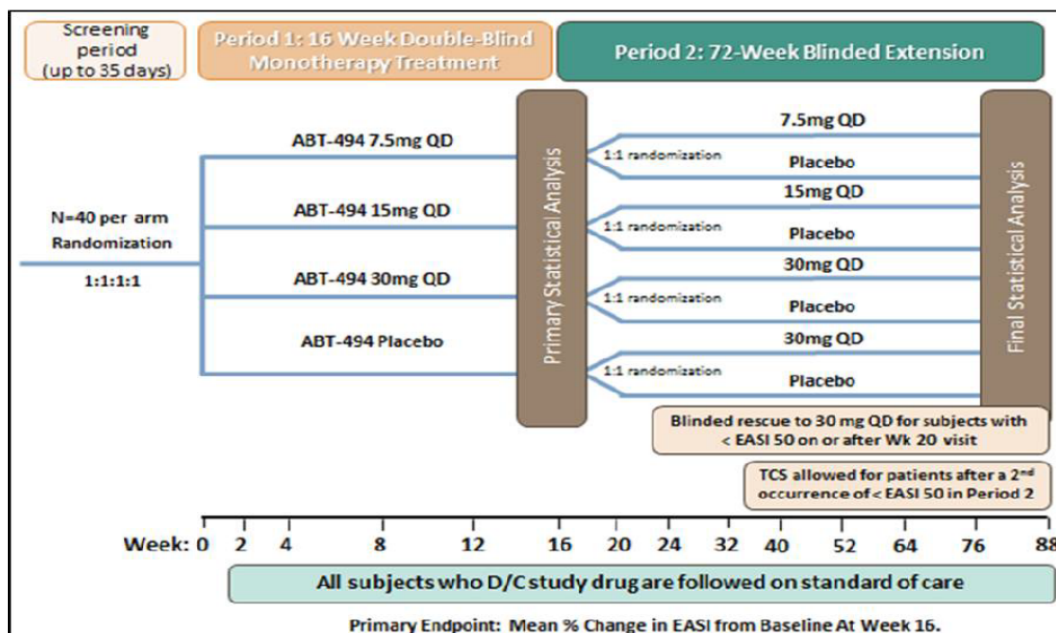
D/C = discontinue; EASI = Eczema Area and Severity Index; QD = once daily; TCS = topical corticosteroids

Figure 6   Study Design, study M16-048

Subjects who met eligibility criteria were randomized in a 1:1:1:1 ratio to one of the four treatment groups. Subjects who completed Period 1 were re-randomized at Week 16 into a 72-week double-blind, placebo-controlled treatment period (Period 2) in a 1:1 ratio:

- Group 1: upadacitinib 7.5 mg once daily (QD) (Day 1 to Week 16) → upadacitinib 7.5 mg QD or placebo (Week 16 - and thereafter)

- Group 2: upadacitinib 15 mg QD (Day 1 to Week 16) → upadacitinib 15 mg QD or placebo (Week 16 and thereafter)

- Group 3: upadacitinib 30 mg QD (Day 1 to Week 16) → upadacitinib 30 mg QD or placebo (Week 16 - and thereafter)

- Group 4: matching placebo for (Day 1 to Week 16) → upadacitinib 30 mg QD or placebo (Week 16 - and thereafter)

Study drug was to be taken orally QD, beginning on Day 1 (Baseline), and was to be taken at approximately the same time each day. The study drug could have been taken with or without food.

In Period 1, discontinuation from study drug was mandatory for any subject with an Eczema Area and Severity Index (EASI) score worsening of 25% or more compared with their Baseline EASI score at any 2 consecutive scheduled study visits from Week 4 to Week 12.

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

During Period 2, concomitant class III – 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 corticosteroid 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.

Subjects who prematurely discontinued study drug treatment continued to be followed for all regularly scheduled visits, unless they have decided to discontinue the study participation (withdrawal of informed consent).

The study had an adequate design and evaluated three dose levels of upadacitinib vs. placebo. The dose levels included 15 mg and 30 mg, doses that were studied in the rheumatoid arthritis indication, and also a lower dose of 7.5 mg.

The objective of this study was to evaluate the safety and efficacy of multiple doses of upadacitinib monotherapy versus placebo in the treatment of adults with moderate to severe AD.

The primary endpoint was the mean percent (%) change from Baseline (Day 1) in EASI score at Week 16. The EASI score is a well-known score for assessment of AD; corresponding largely to "PASI" in plaque psoriasis.

The secondary endpoints (e.g. the proportion of subjects achieving an EASI 75 response at Week 16, the 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 and proportion of subjects achieving EASI 50/75/90 response at Weeks 8 and 16) are also well known from other AD studies.

Approximately 160 subjects were planned to be randomized to three upadacitinib treatment groups and 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. The approach provided 99% average power to detect a dose effect at 5% level of significance (one-sided) with the linear, Emax, exponential, logistic and sigEmax models pre-specified as likely candidates to characterize 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 QD and placebo, and 78% power to detect a significant difference between 15 mg QD and placebo at two-sided level of significance of 5.0%.

Period 1 randomization was stratified by geographic region (US/Puerto Rico/Canada, European Union/Australia, and Japan). Period 2 re-randomization was stratified by geographic region (US/Puerto Rico/Canada, European Union/Australia, and Japan) and EASI 75 response at Week 16.

The study was double-blinded, and the ABT-494 (upadacitinib) tablets and placebo tablets provided for the study were stated to be identical in appearance.

Efficacy analyses were carried out in ITT_1 and ITT_2, respectively for Periods 1 and 2. Pairwise comparisons of each upadacitinib treatment group versus placebo were performed in Period 1.

For binary variables, frequencies and percentages were reported for each treatment group. Pairwise comparison of each upadacitinib group and placebo were performed using the Cochran Mantel-Haenszel test adjusting for stratification factors. For continuous variables, the model based mean and standard error were provided. The Baseline and visit means were presented for each treatment group. The 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.

Results

A total of 167 subjects were randomized at 36 study sites located in 8 countries. Enrollment in Japan was capped at 10% of subjects. Of the 167 subjects randomized, 166 subjects received study drug (1 subject in the placebo group was randomized but did not receive drug). A total of 126 subjects (75.4%) completed study drug through Week 16 (Period 1), and 130 subjects (77.8%) completed study participation through Period 1. Through Week 16, the most frequent primary reason for study drug discontinuation in Period 1 was lack of efficacy which was more frequent in placebo group. Premature discontinuation was more common with placebo (primarily because of lack of efficacy) than with upadacitinib.

A total of 126 subjects (75.4%) were re-randomized into Period 2. All 126 re-randomized subjects (100%) were dosed in Period 2. Eighty-one subjects (64.3%) received rescue with upadacitinib 30 mg treatment, 85 subjects (67.5%) completed study drug, and 41 subjects (32.5%) subjects discontinued study drug in Period 2. The most frequent primary reason for study drug discontinuation in Period 2 was lack of efficacy (11.1%).

The First Subject First Visit was 25 October 2016 and the Last Subject Last Visit was 31 January 2019.

No concerns are raised with respect to protocol deviations or amendments. The compliance was high (mean ≥96% across the upadacitinib dose groups).

The baseline demographic and disease characteristics were generally balanced across arms.

The majority of subjects in Period 1 and Period 2 were male, white, non-users of nicotine, and were <40 years of age with a body mass index (BMI) of 25 or greater (mean 27.2). The majority were from the US/Puerto Rico/Canada region (around 70%), around 25% from EU/Australia and 6% from Japan.

Subjects had been diagnosed with AD for a mean of approximately 26.0 years, the mean EASI score at baseline was 30.9, the mean Pruritus NRS score was 6.46 and the mean BSA was 46%. The overall proportions of subjects with IGA moderate and severe, respectively, were 58% and 42%.

At Week 16, subjects treated with upadacitinib (7.5 mg, 15 mg, and 30 mg) achieved significantly higher mean percentage improvement from Baseline in EASI versus placebo and a clear dose response was observed across upadacitinib groups:

Table 6 Summary of Primary Endpoint Results at Week 16 (LOCF;_ITT_1 Population)

Dose	Mean Percentage Improvement in EASI Score
Upadacitinib 30 mg QD (n = 42)	74%***
Upadacitinib 15 mg QD (n = 42)	62%***
Upadacitinib 7.5 mg QD (n = 42)	39%*
Placebo (n = 39)	23%

EASI = Eczema Area and Severity Index; QD = once daily

$*p < 0.05$, $***p < 0.001$

Table 7 Summary of Key Secondary Endpoint Results (ITT_1 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

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

The time to loss of EASI 50 response among those who were re-randomized as EASI 75 responders at Week 16 (time of entry into Period 2) is presented in the figure below.
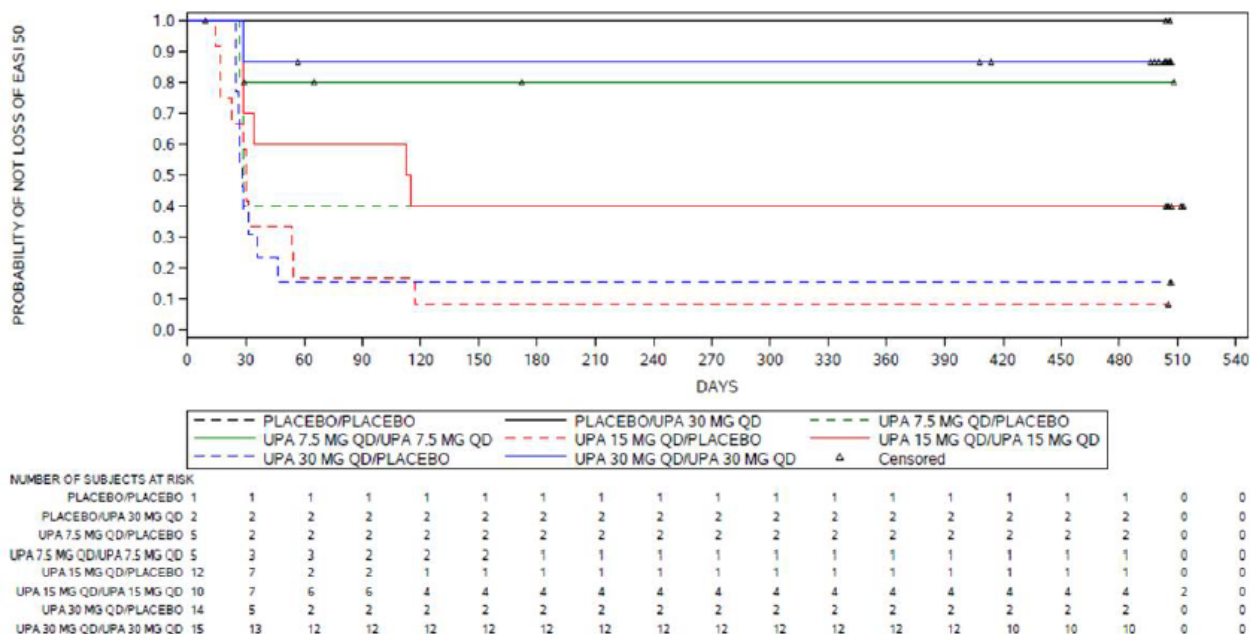
THE OUTCOME IS CENSORED AT THE END OF TREATMENT OR AT THE START OF RESCUE TREATMENT, WHICHEVER HAPPENS FIRST.

Figure 7   Time to Loss of EASI 50 Response During Period 2 Among Those who were Re-randomized as EASI 75 Responders at the Entry of Period 2 (OC; ITT_2 Population)

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

It can be concluded that a clear dose response was observed across the three doses levels, both for the primary as well as most secondary endpoints. Based on efficacy and safety data from this study, including exposure-response analyses, the 15 mg and 30 mg daily doses were chosen to be further studied in the Phase 3 program.

2.5.1. Main studies

Methods

The two monotherapy studies had replicate protocol designs and are therefore described together.

Study M16-045 and M18-891 (monotherapy studies)

Both studies were Phase 3, randomized, double-blind (DB), placebo-controlled multi-center studies. The study outline is shown below.
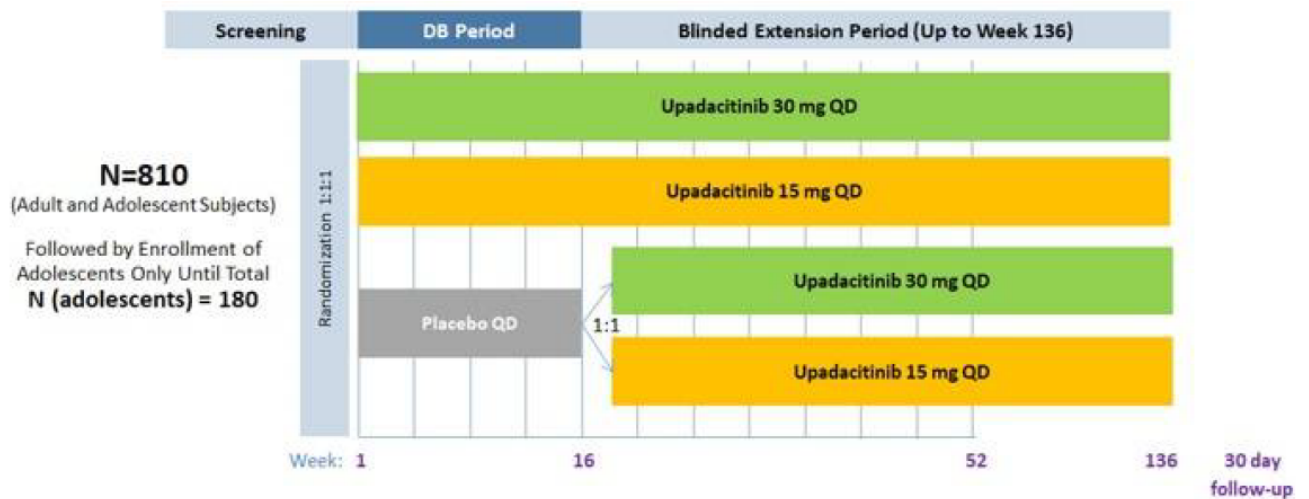
DB = double-blind; QD = once daily

Note: This schematic applies to both the Main Study and Adolescent Sub-study.

Figure 8   Study Design Schematic

Study Participants

Main inclusion/exclusion criteria

- Subject must be ≥ 12 years old and ≤ 75 years old at Screening Visit (adolescents below the age of 18 years old enrolled if approved by the country or regulatory/health authority)

- 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 AD) 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 AD with onset of symptoms at least 3 years prior to baseline and subject meets Hanifin and Rajka criteria.

- Subject meets all of the following disease activity criteria:

  o   EASI score ≥ 16 at the Screening and Baseline Visits;

  o   vIGA-AD score ≥ 3 at the Screening and Baseline Visits;

  o   ≥ 10% BSA of AD involvement at the Screening and Baseline Visits;

  o   Baseline weekly average of daily Worst Pruritus NRS ≥ 4. The baseline weekly average of daily Worst Pruritus NRS was calculated from the 7 consecutive days immediately preceding the Baseline Visit. A minimum of 4 daily scores out of the 7 days is needed.

- Subject has applied a topical emollient (moisturizer) twice daily for at least 7 days before the Baseline Visit.

- Documented history (within 6 months of the Baseline Visit) of inadequate response to TCS or TCI OR documented systemic treatment for atopic dermatitis within 6 months prior to the Baseline Visit, OR for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).

- Females of childbearing potential must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Baseline Visit prior to dosing.

- If female, subject must be postmenopausal OR permanently surgically sterile OR for females of childbearing potential practicing at least one protocol specified method of birth control, that is effective from the Baseline Visit through at least 30 days after the last dose of study drug.

- Female subject must not be pregnant, breastfeeding or considering becoming pregnant during the study or for approximately 30 days after the last dose of the study drug.

- No prior exposure to any JAK inhibitor.

- No prior exposure to dupilumab.

- Subjects must not have used the following AD treatments within the specified timeframe prior to Baseline Visit:

    o Systemic therapy for AD, including but not limited to corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE4)-inhibitors, IFN-γ and mycophenolate mofetil within 4 weeks;

    o Targeted biologic treatments (within 5 half-lives or within 12 weeks, whichever is longer;

    o Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks;

    o Oral or parenteral traditional Chinese medicine within 4 weeks;

    o Marijuana use within 2 weeks;

    o Topical treatments (with the exception of topical emollient treatments), including but not limited to TCS, TCIs, 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 inducers from Screening through the end of the study.

- Subjects must not have laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug:

    o Serum aspartate transaminase (AST) > 2 × upper limit of normal (ULN);

    o Serum alanine transaminase (ALT) > 2 × ULN;

    o Estimated glomerular filtration rate (GFR) of < 40 mL/min/1.73 m² by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula for adult subjects or by Schwartz equation for adolescent subjects;

    o Total white blood cell count (WBC) < 2,500/μL;

    o Absolute neutrophil count (ANC) < 1,500/μL;

    o Platelet count < 100,000/μL;

- o Absolute lymphocyte count < 800/µL;

- o Hemoglobin < 10 g/dL

- No current or past history of the following:

  - o Other active skin diseases or skin infections (bacterial, fungal, or viral) requiring systemic treatment within 4 weeks of the Baseline Visit or would interfere with the appropriate assessment of AD lesions;

  - o History of recurrent herpes zoster, or one or more episodes of disseminated herpes zoster;

  - o History of one or more episodes of disseminated herpes simplex (including eczema herpeticum);

  - o History of known invasive infection (e.g., listeriosis and histoplasmosis);

  - o Active human immunodeficiency virus (HIV) or immunodeficiency syndrome. Active HIV is defined as confirmed positive anti-HIV antibody test;

  - o Subject has active Tuberculosis (TB) or meets TB exclusionary parameters (specific requirements for TB testing were applied);

  - o Non-skin related active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the Baseline Visit;

  - o Chronic recurring infection and/or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study;

  - o Active hepatitis B virus (HBV) or hepatitis C virus (HCV)

- Subject must not have any of the following medical conditions:

  - o Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;

  - o Uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg;

  - o Any other unstable clinical condition

  - o Subject has been a previous recipient of an organ transplant which requires continued immunosuppression;

  - o History of gastrointestinal (GI) perforation (other than due to appendicitis or mechanical injury), diverticulitis or significantly increased risk for GI perforation per investigator judgment;

  - o Conditions that could interfere with drug absorption e.g. short bowel syndrome;

  - o History of any malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix;

  - o History of clinically significant medical conditions or any other reason, which would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug or would put the subject at risk by participating in the study.

The CHMP was of the view that the inclusion and exclusion criteria are adequate to define a population with moderate to severe AD in need of a systemic treatment. Disease severity criteria stipulated that patients should have an EASI score ≥ 16, a vIGA-AD score ≥ 3, ≥ 10% BSA of AD involvement at the Screening and Baseline Visits and a baseline weekly average of daily Worst Pruritus NRS ≥ 4. Patients should also have a documented history of inadequate response to TCS or TCI or documented systemic treatment for atopic dermatitis within 6 months prior to the Baseline Visit, or for whom topical treatments are otherwise medically inadvisable.

The main reason for eligibility to take part in the study with respect to prior treatments was prior inadequate response to TCS/TCI within 6 months prior to baseline. This was the reason in around 80% of the subjects. The second most common reason was Prior systemic treatment within 6 months prior to baseline, experienced by 40-50% of subjects. Topical treatment being inadvisable was a reason for inclusion (in the monotherapy studies) in <10% overall. The pattern was fairly consistent across studies and treatment groups.

The exclusion criteria are also deemed adequate and reflect the contraindications and warnings already in place for Rinvoq in the SmPC for the already approved RA indication. This relates e.g. to laboratory tests, previous or concomitant treatments, and pregnancy. See section 2.5.3.

Treatments

The study includes a 35-day screening period, a 16-week DB Period, and a BE Period of up to Week 136, and a 30-day Follow-up Visit.

Subjects who met eligibility criteria were randomized in a 1:1:1 ratio to receive a daily oral dose of upadacitinib 30 mg or upadacitinib 15 mg or matching placebo QD. The study drug could be taken with or without food.

After the target enrollment (810 subjects) was achieved in the Main Study, a supplemental study opened to continue to enroll adolescent subjects (Adolescent Sub-study) to ensure enrolment of a total of 180 adolescent subjects in the overall study (Main Study + Adolescent Sub-study). Interim results through Week 16 of the Main Study were summarized in the submitted reports. The Adolescent Sub-studies continue to enrol participants.

Randomization for the Main Study was stratified by baseline disease severity (moderate [vIGA-AD score of 3] vs. severe [vIGA-AD score of 4]), by geographic region (US/Puerto Rico/Canada, Japan, China [Mainland], and other; different regions for the two studies), and by age (adolescent [ages 12 to 17] versus adult [ages 18 to 75]).

At Week 16, subjects in the placebo group were re-randomized in a 1:1 ratio (stratified by Week 16 EASI 50 responder status [yes/no], geographic region [US/Puerto Rico/Canada, China [Mainland], Japan, and other], and age group [adolescent/adult]) to receive daily oral doses of upadacitinib 30 mg or upadacitinib 15 mg in the BE period.

Subjects originally randomized to upadacitinib were to continue upadacitinib in the extension period at the same dose. Starting at the Week 4 visit, rescue treatment for AD was permitted at the discretion of the investigator if medically necessary and specified parameters were met. This concerned subjects with < 50% reduction in EASI (EASI 50) response at 2 consecutive visits compared to the Baseline EASI score, or after Week 24 for subjects with < EASI 50 response at any visit compared to the Baseline EASI score.

A separate randomization for the Adolescent Sub-study was stratified by Baseline disease severity (moderate vs. severe AD) and by geographic region. Similarly, the re-randomization was stratified by EASI 50 responder (Yes/No) and by geographic region.

Rescue medication

Starting at the Week 4 visit, rescue treatment for AD could be provided, if medically necessary and the following parameters were met:

- At Week 4 through Week 24: subjects with < 50% reduction in EASI (EASI 50) response at any two consecutive scheduled visits (e.g., at Week 2 and Week 4 with rescue at Week 4; or at Week 20 and Week 24 with rescue at Week 24), compared to the Baseline EASI score.

- After Week 24: subjects with < EASI 50 response at any scheduled or unscheduled visit, compared to the Baseline EASI score.

Investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for those subjects who did 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 could be administered per investigator discretion and will no longer be considered as rescue therapy. Only systemic treatments for AD will be considered as rescue therapy for the purposes of statistical analyses of efficacy.

Subjects who receive topical rescue treatment or oral corticosteroids during the study treatment period could continue study drug. Any subject who receives oral corticosteroid for more than 2 consecutive weeks regardless of the dosage of corticosteroid should permanently discontinue study drug.

If a subject needs rescue treatment with a non-corticosteroid systemic agent (including but not limited to cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, dupilumab) or with an injectable or parenteral corticosteroid, study drug should be permanently discontinued prior to the initiation of rescue systemic agent.

If rescue treatment is medically necessary outside of the parameters described above (i.e., to control intolerable AD symptoms), study drug should be permanently discontinued.

Subjects who permanently discontinue study drug were encouraged to continue to participate in the study (no study drug given) and complete the schedule of study visits and assessments.

Rescue medication could be initiated from Week 4 based on certain criteria for the EASI response, which seem adequate. The rescue medication was reasonably defined in terms of type and duration (e.g. for oral corticosteroids) and when to stop upadacitinib treatment or not in case of their initiation. It is appreciated that subjects who permanently discontinued study drug were encouraged to continue participation in the study and complete the schedule of study visits and assessments.

Objectives

The objective was to assess the efficacy and safety of upadacitinib for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy. The aim was to demonstrate superiority of each upadacitinib dose vs. placebo.

Outcomes/endpoints

<u>Co-Primary Endpoints</u>

1. Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index (EASI 75) from Baseline at Week 16.

2. 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 Week 16.

The EASI score is the equivalent of PASI in psoriasis and measures the extent and severity of several signs (erythema, inflammation, induration, papulation, excoriations and lichenification) of the AD condition. The vIGA-AD score is a global score assessed by the investigator.

<u>Key Secondary Endpoints</u>

1. 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;

2. Proportion of subjects achieving EASI 90 at Week 16;

3. Percent change from Baseline of Worst Pruritus NRS at Week 16;

4. Percent change in EASI from Baseline at Week 16;

5. Proportion of subjects achieving EASI 75 at Week 2;

6. 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;

7. 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;

8. 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;

9. 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 vs. placebo);

10. 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 vs. placebo);

11. Proportion of subjects experiencing a flare, characterized 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 (DB Period);

12. Percent change in Scoring Atopic Dermatitis (SCORAD) from Baseline at Week 16;

13. Proportion of subjects achieving a Hospital Anxiety and Depression Scale anxiety (HADS-A) < 8 and Hospital Anxiety and Depression Scale-depression (HADS-D) < 8 at Week 16 among subjects with HADS-A ≥ 8 or HADS-D ≥ 8 at Baseline;

14. 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;

15. 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;

16. 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;

17. 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;

18. 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;

19. Proportion of subjects achieving EASI 100 at Week 16;

20. 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.

A very large number of multiplicity-controlled secondary endpoints were also evaluated. Among the highest ranked of these, there were endpoints assessing itch (proportion of subjects achieving an improvement in Worst Pruritus NRS ≥ 4 points and the percent change from Baseline of Worst Pruritus NRS at Week 16), one of the most prominent symptoms of AD. Another highly ranked endpoint was the proportion of subjects achieving EASI 90 at Week 16, which is a high hurdle endpoint reflecting almost total clearance of AD. EASI 100 (reflecting total clearance) at Week 16 was also assessed.

Some endpoints assessed the onset of effect, e.g. the proportion of subjects achieving EASI 75 by week 2 and the proportions achieving a reduction in Worst Pruritus NRS ≥ 4 at Week 1, or even at Day 2 or Day 3.

Occurrence of flares were also evaluated with a flare being defined as an increase of EASI by ≥ 6.6 from Baseline for subjects with EASI ≤ 65.4 at Baseline. The cut-off to define a flare was based on the established MCID of 6.6 for the EASI (Schram 2012).

Some established PROs used in several dermatological conditions (DLQI) and more specifically in AD (POEM, SCORAD) were also evaluated. In addition, the MAH has developed new PROs for AD; the Atopic Dermatitis Impact Scale (ADerm-IS) and the Atopic Dermatitis Symptom Scale (ADerm-SS). The CHMP noted that the development and validation of the ADerm scales have been performed by the MAH. This is acknowledged, but as mentioned in the CHMP scientific advice letter, it is not foreseen that all (key) secondary endpoints will be reported in Section 5.1. Other relevant information related to the pivotal studies can be found in the EPAR. See 2.5.2.

Sample size

Approximately 810 adolescent and adult subjects were planned to be randomized to upadacitinib 30 mg, upadacitinib 15 mg, or placebo in a ratio of 1:1:1 in the main study (270 subjects per treatment group). The sample size was determined by the regulatory requirement to adequately characterize the safety profile. Assuming an EASI 75 response rate of 15%, and vIGA-AD 0 or 1 with at least a 2-point reduction response rate of 10% in the placebo arm, this sample size would also provide more than 90% power to detect the treatment differences of 32% and 21%, respectively, for the above two endpoints simultaneously using two-sided test at a 0.05 significant level. Additional adolescent

subjects were enrolled in the adolescent sub-study and randomized to upadacitinib 15 mg, upadacitinib 30 mg, or placebo in a ratio of 1:1:1 for a total of 180 adolescent subjects in the overall study (main study + adolescent sub-study). This sample size was determined to ensure a total of 225 adolescent subjects with at least one year of exposure per dose across 3 pivotal studies.

The sample size was planned with adequate power to test 2 primary endpoints at 5% significance level (2-sided). The placebo response rates for EASI 75 and vIGA-AD 0/1 observed in the monotherapy studies were in line with the assumed 15% and 10%, respectively, except for the lower placebo response for vIGA-AD 0/1 in the M18-891 study. The assumed treatment differences of 32% for EASI 75 and 21% for vIGA-AD 0/1 were not described in terms of clinical relevance; however, the observed efficacy in both primary endpoints surpassed the expectations numerically and statistically. For the sub-study in adolescent subjects, the sample size was not determined based on power calculation but was instead judged by the Applicant to provide a sufficient amount of the data.

Randomisation and blinding (masking)

All subjects were assigned a unique identification number by the IRT at the screening visit. The IRT assigned a randomization number that would encode the subject's treatment group assignment according to the randomization schedule. Subjects in the main study were randomized in a 1:1:1 ratio to one of the three treatment groups:

- Group 1: Upadacitinib 15 mg (N = 270)
- Group 2: Upadacitinib 30 mg (N = 270)
- Group 3: Placebo (N = 270)

Upon completion of enrollment of 810 subjects in the main study, the adolescent sub-study was to continue to enroll adolescent subjects until a total of 180 adolescent subjects were enrolled in the overall study (main study + adolescent sub-study). Subjects in the adolescent sub-study are randomized in a 1:1:1 ratio to one of three treatment groups, similar to those for the main study.

For the main study, randomization was stratified by baseline disease severity (moderate, vIGA-AD = 3, versus severe, vIGA-AD = 4, AD), by geographic region (US/Puerto Rico/Canada, Other, China, and Japan; the latter only in study M16-045), and age (adolescent ages 12 - 17 versus adult ages 18 – 75 years). For the adolescent sub-study, randomization was stratified by baseline disease severity (moderate vs. severe) and by geographic region (US/Puerto Rico/Canada and Other).

At Week 16 of the main study and of the adolescent sub-study, the subjects remaining in Group 3 were re-randomized in a 1:1 ratio to one of two treatment groups:

- Group 4: Upadacitinib 15 mg
- Group 5: Upadacitinib 30 mg

For the main study, the re-randomization was stratified by EASI 50 responder (Yes/No), by geographic region (US/Puerto Rico/Canada, China, Japan, and Other; categories China and Japan only in study M16-045), and by age (adolescent [ages 12 to 17] versus adult [ages 18 to 75]). For the adolescent sub-study, the re-randomization was stratified by EASI 50 responder (Yes/No) and by geographic region (US/Puerto Rico/Canada and Other).

In study M16-045, enrollment in Japan and China was capped at 45 subjects (15 subjects per group) each, with a target enrolment number of approximately 30 to 45 subjects (10-15 subjects per group).

For the main study, the initial stratification factors used (vIGA-AD severity, geographic region, age) as well as the Week 16 Group 3 (placebo) re-randomisation stratifications factors (EASI 50 responder status, region and age) are endorsed.

Study sites and subjects were to remain blinded for the duration of the study. To maintain integrity of the trial and avoid introduction of bias, the study team will only have access to unblinded subject level data for AEs of special interests and SAEs for regulatory submissions. In order to maintain the blind, the upadacitinib tablets and placebo tablets provided for the study were identical in appearance.

Statistical methods

The planned analyses include:

- the primary analysis of the main study conducted after all ongoing subjects in the main study have completed the study activities up to Week 16 and all data pertaining to the DB Period are cleaned,

- an additional analysis of the main study when the required safety exposure target is reached,

- Week 52 analysis of the main study after all ongoing subjects complete Week 52 visit,

- an additional analysis for the adolescent subjects (including the adolescent subjects from the main study and the adolescent sub-study) after all ongoing adolescent subjects have completed Week 16,

- an additional analysis of the adolescent subjects after all ongoing adolescent subjects have provided at least 1 year of upadacitinib exposure.

Analysis populations

The Intent-to-treat (ITT) Population	all subjects who are randomized in the main study or the adolescent sub-study
The ITT Population for the main study (ITT_M)	all subjects who are randomized in the main study
The ITT Population for adolescents (ITT_A)	all adolescent subjects who are randomized in the main study or the adolescent sub-study
Per-protocol Population for the main study (PP_M)	excluded subjects with major protocol deviations that potentially affect the co-primary efficacy endpoints
The Safety Population in the DB Period (Safety_DB)	all randomized subjects who received at least one dose of study drug in the main study or the adolescent sub-study during the DB Period *(the corresponding population was defined for the BE period)*
The Safety Population in the DB Period for the main study (Safety_DB_M)	all randomized subjects in the main study who received at least one dose of study drug during the DB Period *(the corresponding population was defined for the BE period)*
The Safety Population for adolescents in the DB Period (Safety_DB_A)	all randomized adolescent subjects in the main study or the adolescent sub-study who received at least one dose of study drug during the DB Period

	(the corresponding population was defined for the BE period)

The efficacy analysis of the main study was conducted in the ITT_M Population. The efficacy analysis of the adolescent subjects in the main study or the adolescent sub-study was conducted in the ITT_A Population. In addition, a per-protocol analysis for co-primary endpoints in the main study was performed in the PP_M Population.

The co-primary endpoints for the primary analysis of efficacy are:

- Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index from baseline (EASI 75) at Week 16;

- Proportion of subjects achieving validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD) of 0 or 1 with at least two grades of reduction from baseline at Week 16.

Handling of intercurrent events and missing data

The probability of having missed visits and missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic could be reasonably assumed to be unrelated to the unobserved values. Therefore, for the purpose of statistical analysis, it was assumed that these missing data were missing at random (MAR) and the statistical models that require MAR assumption were deemed appropriate by the MAH. Sensitivity analyses were performed to assess the impact of missing data and the robustness of the conclusion.

For categorical endpoints (including the co-primary endpoints), the primary approach for handling of missing data used Non-Responder Imputation (NRI) while incorporating Multiple Imputation (MI) to handle missing data due to the COVID-19 pandemic (NRI-C) in which any subject who did not have an evaluation during a pre-specified visit window (either due to a missing assessment or due to an early withdrawal from the study) was categorized as a non-responder for the visit except:

- When the subject was a responder both before and after the visit window, the subject was categorized as a responder for the visit.

- Missing data due to COVID-19 infection or logistical restriction was handled by MI.

In addition, all assessments after the start of rescue medications were not included in the analyses; as a result, subjects were counted as non-responders thereafter and were not imputed by MI.

A sensitivity analysis for categorical endpoints used NRI with no special data handling for missing due to COVID-19 (NRI-NC). NRI-NC was similar to the NRI-C but with no special data handling for missing due to COVID-19 infection or logistical restriction, i.e. those missing values were to be counted as non-responders.

The co-primary endpoints were also analyzed using MI and tipping point analysis as the sensitivity approach. The MI model included variables: treatment group, major stratum (vIGA-AD categories, age [adolescent vs. adult] if applicable, and regions), gender, baseline, and measurements at each visit up to the end of the analysis period. For vIGA-AD related endpoints, the stratum vIGA-AD was not included in the imputation model. The tipping point analysis was to be performed based on the NRI-NC approach, which is more conservative and more likely to find a tipping point if it exists. Of note, an extreme case analysis was checked first, where all missing data in placebo arms are considered as responders and all missing data in the upadacitinib arms are considered as non-responders. If the extreme case analysis did not reverse the conclusion based on the primary approach (NRI-C), complete tipping point analysis was not performed.

For continuous endpoints, missing data were handled using Mixed-Effect Model Repeat Measurement (MMRM). The mixed model included observed measurements at all visits, except for measurements after any rescue medication were excluded.

Long-term efficacy analysis through the cutoff date was to be summarized using the observed case (OC) approach. This analysis does not impute values for missing evaluations. The OC analysis does not include values > 1 day after discontinuation of study drug.

Analysis of categorical endpoints, including co-primary endpoints:

Pairwise comparisons of each upadacitinib group vs. placebo were made using Cochran-Mantel-Haenszel (CMH) test adjusting for the main stratification factors (e.g., baseline vIGA-AD categories, and age [adolescent vs. adult]) for the ITT and the ITT_M population. Frequencies, percentages, 95% confidence intervals (CI) for response rates and p-values for pairwise comparison of each upadacitinib group vs. placebo were provided.

NRI-C was the primary approach to handle missing values for all categorical endpoints. The co-primary endpoints were analyzed using NRI-NC, MI and tipping point analysis as the sensitivity analyses. The key secondary categorical endpoints were analyzed using NRI-NC as the sensitivity analyses. Per-protocol analysis was based on the NRI-C approach.

Analysis of continuous endpoints:

The MMRM method was used and included categorical fixed effects of treatment, visit, treatment-by-visit interaction, main stratification factors at randomization (baseline vIGA-AD categories and age [adolescent vs. adult]), and the continuous fixed covariates of baseline measurement, for the ITT and the ITT_M population. Point estimates, standard error, 95% CI of least square mean change from baseline within treatment groups and the p-value between each upadacitinib treatment group and the placebo were provided. For the endpoints with only one post-baseline assessment in DB Period, e.g., WPAI:AD, an ANCOVA model including baseline and treatment was applied.

Multiplicity:

The overall type I error rate of the primary and secondary endpoints for upadacitinib 15 mg and 30 mg was strongly controlled using a graphical multiple testing procedure following a pre-specified alpha transfer path which included downstream transfer along the endpoints sequence within each dose as well as cross-dose transfer.

In the graph below, V1 to V18 denotes the endpoints in the pre-specified order. If more than one arrow originates from an endpoint, the significance level for this endpoint (once rejected) was split between multiple subsequent endpoints following the arrows. The numbers on the arrows denote the weights for transferring and (possibly) splitting significance levels.

In addition, within each dose, selected PROs were grouped into one block (denoted by V16-H) and tested together using Hochberg method. The significance level assigned to this group of endpoints continued to be transferred if all endpoints within the group were rejected by the Hochberg method at the given significance level.
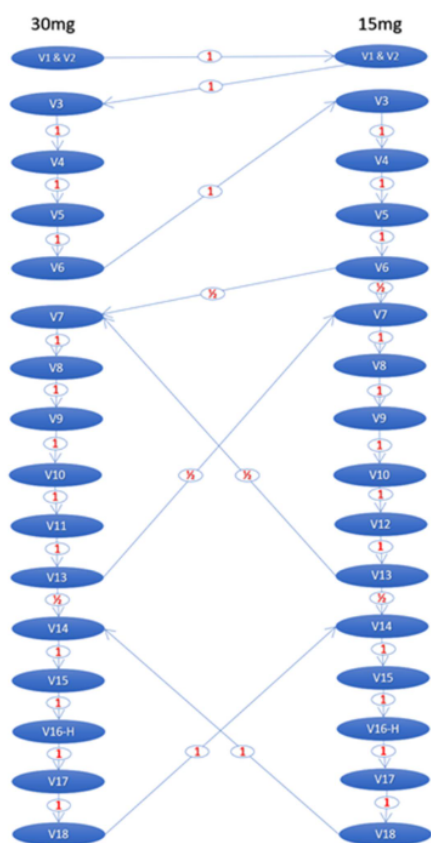
Figure 9   Graphical Approach for Multiplicity Adjustment

<u>Subgroup analyses</u> were performed for the co-primary endpoints by demographics and baseline characteristics. All efficacy endpoints were also analyzed within each stratum of the three stratification factors: vIGA-AD, age (adolescent vs. adult) and region. Analysis model within each stratum was not adjusted for stratification factors.

<u>Integrated Analysis of Efficacy</u>

The integrated efficacy analyses included two replicate monotherapy Studies M16-045 and M18-891 using the same statistical analysis methods in the individual studies with the addition of study as a covariate in the models.

<u>Post-hoc analyses of efficacy</u>

To evaluate the overall treatment effect of upadacitinib 30 mg QD vs 15 mg QD over the DB Period, a post-hoc analysis using likelihood ratio test (LRT) was performed in each of the pivotal Phase 3 studies (studies M16-045, M18-891, and M16-047) for the co-primary endpoints: EASI 75 and vIGA-AD 0/1. Generalized linear mixed models were used to compare the full model assuming additional upadacitinib 30 mg effect on top of the 15 mg dose versus the reduced model assuming no additional upadacitinib 30 mg effect over the 16-week placebo-controlled period.

<u>Safety analyses</u> included adverse events, laboratory, and vital sign measurements. Safety summaries were provided using the safety populations in both the DB period and the BE period, and across the DB period and the BE period for the main study, adolescent population, and overall study. Missing safety data were not imputed.

<u>Changes from the planned analyses</u>

There were no changes to the planned analyses after finalization of the Statistical analysis plan (SAP) version 3 (May 29, 2020 for study M16-045; Jun 4, 2020 for study M18-891). Both SAPs were finalized prior to the corresponding Week 16 database lock, and incorporated changes made in the amendment 5 of each study protocol concerning updates of the key secondary endpoints and the graphical multiple testing procedure, as well as timing of additional analyses and adolescent sub-study. Also, updates were made to the methods of handling intercurrent events and missing data due to COVID-19 and on the details on the tipping point analyses. In study M18-891, a non-compliance site (6 randomized subjects) was excluded from the analysis.

Additional post-hoc analyses were performed per request of the Swedish Medical Products Agency (MPA) related to sensitivity analyses of co-primary endpoints and analyses of long-term efficacy outcomes (EASI 75, vIGA-AD 0/1, and improvement in pruritus NRS ≥ 4) past the DB Period.

The CHMP noted that the statistical plans pre-specified for studies M16-045 and M18-891 are identical and in general acceptable. Statistical comparisons of treatment groups using CMH test and MMRM for the categorical and continuous endpoints, respectively, are appropriate. The approaches applied to handle intercurrent events and missing data are plausible to investigate robustness of the efficacy results. The amount of intercurrent events, missing and imputed values, including reasons for missingness, should be presented by treatment group. In the primary analysis and in the post-hoc analysis using treatment policy strategy, the presented data for the test treatment arms are not alarming in regards to the amount of missing data due to covid-19 or other reasons, and the numbers of responders by multiple imputation (MI). Not surprisingly, the summary for analysis at Week 52 shows somewhat higher numbers of missing data; however, with no obvious pattern. Considering the amount of non-responder imputations due to intercurrent events (rescue medication intake), there is a trend of treatment dependent frequency and a clear separation between upadacitinib treatment arms and placebo group. Of note, in the primary analysis, assessments after the start of rescue medications were counted as non-responders, where the estimated treatment differences are impacted by the substantially higher amount of intercurrent events observed in placebo. Sensitivity analyses using treatment policy approach did confirm the statistically significant results.

The definitions of ITT populations based on the randomised subjects are endorsed. A summary over all analysis populations defined should be presented and were provided for clarification as requested. The graphical multiple testing procedure for the co-primary and the key secondary endpoints combining hierarchical testing and alpha re-cycling controls the overall type-I error rate at the 0.05 (two-sided) level for each pivotal study. There were no interim analyses to add to multiplicity, as the first analysis in each of the studies was the primary analysis performed after the database lock for the Week 16 data. Post-hoc analyses were performed in terms of the co-primary endpoints analysed using treatment policy approach. This supplemental estimand was based on all observed data regardless of the use of other medications or treatment discontinuations, while missing data were handled by multiple imputation. These analyses fully supported the primary analysis.

Study M16-047 (TCS combination study)

Study M16-047 was a Phase 3, randomized, double-blind, placebo-controlled multi-center study that evaluated the efficacy and safety of upadacitinib combined with TCS 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 AD who were candidates for systemic therapy. The study outline is shown below.
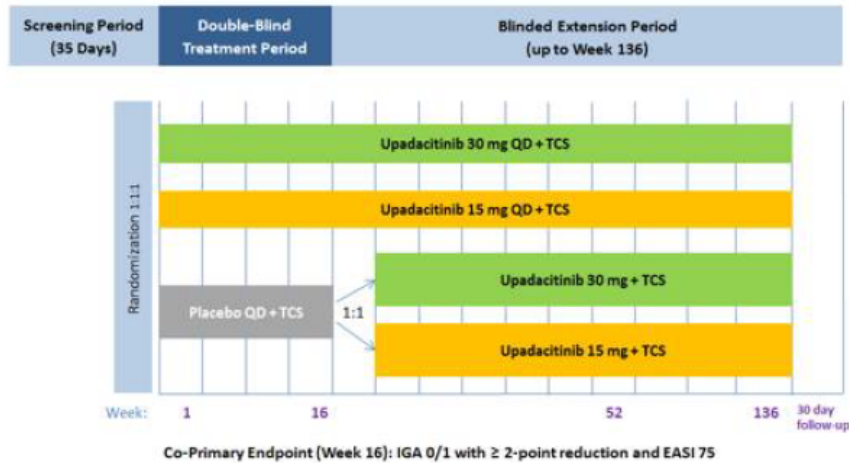
EASI 75 = 75% improvement (reduction) in Eczema Area and Severity Index; QD = once daily; TCS = topical corticosteroids; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis

Note: This schematic applies to both the Main study and Adolescent sub-study. Topical calcineurin inhibitors were permitted for use in areas where TCS is generally not advisable.

Figure 10   Study Design Schematic

Study participants

Main inclusion/exclusion criteria:

The inclusion/exclusion criteria were almost identical to those applied in the mono-therapy studies (M16-045 and M18-891) described above and are not displayed in full here. There were some differences due to the concomitant use of TCS/TCI in this study:

- The patients should have a documented history (within 6 months of the Baseline Visit) of inadequate response to TCS or TCI OR documented systemic treatment for atopic dermatitis within 6 months prior to the Baseline Visit, however, patients for whom topical treatments were medically inadvisable (e.g., because of important side effects or safety risks) were not included.

- Subjects must not have ≥ 30% of AD lesional surface involvement at Baseline that could not be safely treated with medium or higher potency TCS (e.g., areas of skin atrophy, face, groin, intertriginous areas).

- Subjects must not have used topical treatments (with the exception of topical emollient treatments), including but not limited to TCS, TCIs, or topical PDE-4 inhibitors within 7 days prior to Baseline Visit

- Patients should have no contraindication to topical corticosteroids or topical calcineurin inhibitors.

The inclusion and exclusion criteria in this study were broadly similar to those in the mono-therapy studies, and thus, adequate to define a population with moderate to severe AD. The disease severity criteria were the same (EASI ≥ 16, vIGA-AD ≥ 3, ≥ 10% BSA of AD involvement and a baseline weekly average of daily Worst Pruritus NRS ≥ 4). Similar to the mono-therapy studies, patients should have a documented history (within 6 months of the Baseline Visit) of inadequate response to TCS or TCI or documented systemic treatment for atopic dermatitis within 6 months prior to the Baseline Visit. However, patients for whom topical treatments are otherwise medically inadvisable or patients with contraindication to TCS/TCI were not included in this study, as TCS/TCI were applied concomitantly to

upadacitinib treatment. At the CHMP's request, the MAH clarified that the pattern of prior TCS/TCI inadequate response within 6 months prior to baseline was similar in this study as in the monotherapy studies, with around 80% fulfilling this criterion.

Subjects were not allowed to have used topical treatments (except emollients), including but not limited to TCS, TCIs, or topical PDE-4 inhibitors within 7 days prior to Baseline Visit.

Treatments

The study includes a 35-day screening period, a 16-week DB Period, and a BE Period of up to Week 136, and a 30-day Follow-up Visit.

Subjects who met eligibility criteria were randomized in a 1:1:1 ratio to receive concomitant TCS with a daily oral dose of upadacitinib 30 mg or upadacitinib 15 mg or matching placebo QD. The study drug could be taken with or without food.

After the target enrollment (810 subjects) was achieved in the Main Study, a supplemental study opened to continue to enroll adolescent subjects (Adolescent Sub-study) to ensure enrollment of a total of 180 adolescent subjects in the overall study (Main Study + Adolescent Sub-study). Interim results through Week 16 of the Main Study were summarized in the submitted study report. The Adolescent Sub-studies continue to enrol participants.

Randomization in the Main Study was stratified by baseline disease severity (moderate, vIGA-AD 3 vs. severe, vIGA 4; age [adolescent ages 12 to 17 vs. adult ages 18 – 75] and geographic region [US/Puerto-Rico/Canada, Japan, Mainland China, and other]). At the end of the DB Period, Week 16, subjects in the placebo group were re-randomized in a 1:1 ratio (stratified by Week 16 EASI 50 responders [yes/no], geographic region [US/Puerto-Rico, Canada, Japan, Mainland China, and other] and age group [adolescent vs. adult]) to receive oral upadacitinib 30 mg or upadacitinib 15 mg QD in a blinded fashion up to Week 136. Subjects originally randomized to upadacitinib will continue upadacitinib in the BE Period at the same dose.

Thus, this study investigated the same two doses of upadacitinib as the monotherapy studies; 15 mg QD and 30 mg QD vs. matching placebo QD. The placebo-controlled part continued up to Week 16 and thereafter patients in the placebo arm were re-randomized in a 1:1 ratio to 15 or 30 mg upadacitinib.

Concomitant TCS therapy

Concomitant TCS therapy was started at Baseline and continued through Week 52 using a step-down regimen. A medium potency TCS (e.g., 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 TCS or TCI could be applied to sensitive skin areas or areas where medium potency TCS would be considered unsafe. After lesions were clear or almost clear, or after 3 consecutive weeks of medium potency TCS, a low potency TCS (e.g., hydrocortisone 1% cream) was to be used daily for 7 days and then stopped. The step-down regimen starting with medium potency TCS was to be resumed if AD lesions returned or persisted, as long as there was no sign of local or systemic TCS toxicity.

Rescue therapy

Rescue therapy was permitted from Week 4 through Week 24, if medically necessary and with a <EASI 50 response at any two consecutive scheduled visits compared to baseline. After Week 24, rescue therapy was permitted if medically necessary with a <EASI 50 response at any visit compared to baseline.

Investigators should attempt to limit the first step of rescue therapy to high or super-high potency TCS (unless higher potency TCS are considered unsafe) or other alternative topical AD medications, and escalate to systemic medications only for those subjects who do not respond adequately after at least 7 days of topical treatment.

Starting at the Week 52 visit, the use of any concomitant topical medication for AD could be administered per investigator discretion and will no longer be considered as rescue therapy. Only systemic treatments for AD were considered as rescue therapy for the purposes of statistical analyses of efficacy.

Subjects who receive topical rescue treatment or oral corticosteroids during the study treatment period could continue study drug. Oral corticosteroids were not allowed for routine treatment of AD. 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 received oral corticosteroid for more 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 cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, dupilumab) or with an injectable or parenteral corticosteroid, study drug should be permanently discontinued prior to the initiation of rescue systemic agent.

If rescue treatment is medically necessary outside of the parameters described above (i.e., to control intolerable AD symptoms), study drug should be permanently discontinued.

Subjects who permanently discontinue study drug were encouraged to continue to participate in the study (no study drug given) and complete the schedule of study visits and assessments.

Investigators should conduct efficacy and safety assessments (e.g., disease severity scores, safety labs) before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

Thus, also in this study, similar to the monotherapy studies, rescue medication could be initiated from Week 4 based on certain criteria for the EASI response. In this study, however, the topical rescue therapy as a first step was proposed to be *high or super-high potency TCS* or other alternative topical AD medications. This is reasonable in view of the already allowed use of medium potency TCS as background therapy.

Objectives

The study objective was to assess the efficacy and safety of upadacitinib combined with TCS for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy. The aim was to demonstrate superiority of each upadacitinib dose plus TCS vs. placebo plus TCS, which is adequate.

Outcomes/endpoints

Co-Primary Endpoints

1. Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index (EASI 75) from Baseline at Week 16.

2. Proportion of subjects achieving vIGA-AD of 0 or 1 with at least two grades of reduction from Baseline at Week 16.

<u>Key Secondary Endpoints</u>

The following key multiplicity-adjusted secondary endpoints were analyzed to demonstrate superiority of each upadacitinib dose vs. placebo, unless otherwise specified. Separate sets of key secondary endpoints were analyzed for EU/EMA and for US/FDA regulatory purposes.

1. 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;

2. Proportion of subjects achieving a 90% reduction in EASI (EASI 90) at Week 16;

3. Percent change from Baseline of Worst Pruritus NRS at Week 16;

4. Percent change in EASI score from Baseline at Week 16;

5. 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;

6. Proportion of subjects achieving EASI 75 at Week 4;

7. Proportion of subjects achieving EASI 75 at Week 2;

8. Proportion of subjects achieving EASI 90 at Week 4;

9. Proportion of subjects achieving EASI 100 at Week 16 for 30 mg;

10. 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.

Furthermore, a number of additional endpoints were also evaluated, for instance:

- Number of TCS free days with EASI 75 response up to Week 16;

- Number of medium or higher potency TCS-free days with EASI 75 response up to Week 16;

- Time to first discontinuation of all TCS with EASI 75 response (discontinuation of all TCS is defined as the subject stops the TCS treatment > 7 consecutive days) up to Week 16; Note: endpoints related to TCS free-days, days from the start of systemic rescue was not considered as TCS-free days.

- Proportion of subjects achieving 50%/75%/90% reduction in Scoring Atopic Dermatitis (SCORAD) (SCORAD 50/75/90) from Baseline;

- Change from Baseline in body surface area (BSA);

- Proportion of subjects experiencing a flare, characterized 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 DB Period;

A number of multiplicity-controlled secondary endpoints were evaluated. Among the highest ranked of these, there were endpoints assessing itch, EASI 90 and EASI 100.

Some endpoints assessed the onset of effect also in this study, e.g. the proportion of subjects achieving EASI 75 by Week 2 and 4 and the proportions achieving a reduction in Worst Pruritus NRS ≥ 4 at Week 4 or Week 1.

A large number of 'Additional Endpoints' were also evaluated, and these were not multiplicity-controlled. Among these were endpoints related to TCS use (number of TCS-free days with EASI 75 response up to Week 16, number of medium or higher potency TCS-free days with EASI 75 response

up to Week 16 and time to first discontinuation of all TCS with EASI 75 response up to Week 16. In addition, several of the endpoints (e.g. PROs) assessed in the monotherapy studies were evaluated.

Sample size

Approximately 810 adolescent and adult subjects were planned to be randomized to upadacitinib 15 mg with concomitant use of topical corticosteroids, upadacitinib 30 mg with concomitant use of topical corticosteroids, or placebo with concomitant use of topical corticosteroids in a ratio of 1:1:1 in the main study (270 subjects per treatment group). The sample size was determined by the regulatory requirement to adequately characterize the safety profile. Assuming an EASI 75 response rate of 24%, and vIGA-AD 0 or 1 with at least a 2-point reduction response rate of 13% in the placebo arm, this sample size would also provide more than 90% power to detect the treatment differences of 38% and 20%, respectively, for the above two endpoints simultaneously using two-sided test at a 0.05 significant level. Additional adolescent subjects were enrolled in the adolescent sub-study and randomized to upadacitinib 15 mg, upadacitinib 30 mg, or placebo in a ratio of 1:1:1 for a total of 180 adolescent subjects in the overall study (main study + adolescent sub-study). This sample size was determined to ensure a total of 225 adolescent subjects with at least one year of exposure per dose across 3 pivotal studies.

The planned sample size was the same as in the monotherapy studies, but with assumptions on treatment effects altered for combination therapy. The placebo response rates for EASI 75 and vIGA-AD 0/1 observed in the combination study were not far from the assumed. The expected treatment differences of 38% for EASI 75 and 20% for vIGA-AD 0/1 were not described in terms of clinical relevance; however, the observed efficacy in both primary endpoints surpassed the expectations numerically and statistically. The number of randomized subjects was quite higher than planned (approximately 810 planned, 901 randomized). The MAH clarified that the higher number of randomized subjects was due to the robust patient interest in participating the studies and to ensure the appropriate numbers of subjects with the required upadacitinib exposures for at least 1 year.

Randomisation and blinding (masking)

Subjects in the main study were randomized in a 1:1:1 ratio to one of the three treatment groups, in addition to concomitant TCS:

- Group 1: Upadacitinib 15 mg with TCS (N = 270)

- Group 2: Upadacitinib 30 mg with TCS (N = 270)

- Group 3: Placebo with TCS (N = 270)

Upon completion of enrollment of 810 subjects in the main study, the adolescent sub-study will continue to enroll adolescent subjects until a total of 180 adolescent subjects are enrolled in the overall study (main study + adolescent sub-study). Subjects in the adolescent sub-study are randomized in a 1:1:1 ratio to one of three treatment groups, similar to those for the main study.

For the main study, randomization was stratified by baseline disease severity (moderate vs. severe), by geographic region and age (adolescents vs. adults). For the adolescent sub-study, randomization was stratified by baseline disease severity and by geographic region.

At Week 16 of the main study and of the adolescent sub-study, the subjects remaining in Group 3 were re-randomized in a 1:1 ratio to one of two treatment groups:

- Group 4: Upadacitinib 15 mg with TCS

- Group 5: Upadacitinib 30 mg with TCS

For the main study, the re-randomization was stratified by EASI 50 responder (Yes/No), by geographic region, and by age (adolescent vs. adult). For the adolescent sub-study, the re-randomization will be stratified by EASI 50 responder (Yes/No) and by geographic region.

Similar IRT procedures for dispensing study drug, etc., applied as in the monotherapy studies.

Enrollment in Japan and China was capped at 51 subjects (17 subjects per group) each, with a target enrolment number of approximately 30 to 51 subjects (10-17 subjects per group).

The initial stratification factors used (vIGA AD severity, geographic region, age) as well as the Week 16 Group 3 (placebo) re-randomisation stratifications factors (EASI 50 responder status, region and age) were similar to those used in the monotherapy studies and are endorsed.

For blinding, the same procedures were applied as in the monotherapy studies.

Statistical methods

The planned analyses were identical as described for studies M16-045 and M18-891 in respect to the definitions of analysis populations, analysis methods for categorical (including co-primary) and continuous endpoints, handling of intercurrent events and missing data, subgroups analyses, safety analyses, and the sequence of the planned additional analyses after performing the primary analysis in the main study.

Regarding analysis of continuous endpoints, the SAP includes an addition of analysis of BE period up to Week 52, using stratification factors EASI 50 response at Week 16 and age [adolescent vs. adult]).

Similar as in the monotherapy studies, the overall type I error rate was strongly controlled using a graphical multiple testing procedure including two doses and the primary and secondary endpoints in the pre-specified order denoted as V1 to V12 in the graph below. The endpoints of pruritus NRS improvement ≥ 4 for both doses are grouped into one block (V12-H in the graph) and tested together using Hochberg method.
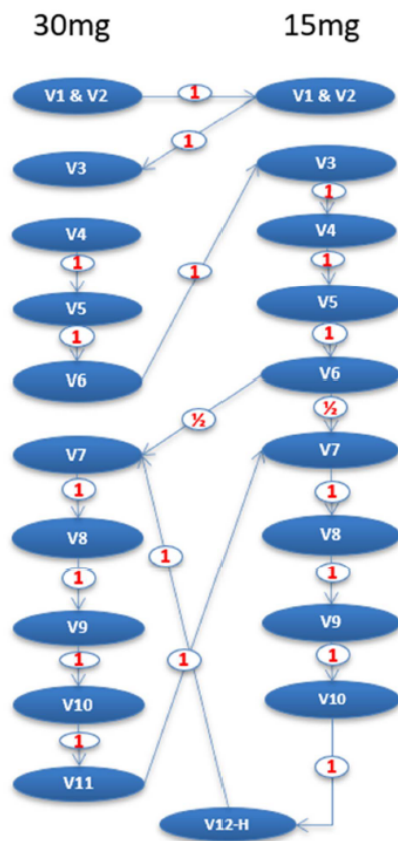
Figure 11   Graphical Approach for Multiplicity Control

Additional analyses of efficacy

The number of TCS free days or number of medium or higher potency TCS free days with EASI 75 response up to Week 16 was summarized until the subject was discontinued from study drug. For subjects who achieved EASI 75 response at any visit in the DB Period before taking any rescue medication, the number of TCS free days or number of medium or higher potency TCS free days was summarized up to Week 16, or up to discontinuation from study drug, whichever was earlier. Days from the start of systemic rescue or phototherapy were not considered as TCS-free days thereafter. For subjects who did not achieve EASI 75 response on and prior to rescue medication during the DB Period, their TCS free days or medium or higher potency TCS free days was counted as 0. The treatment comparison between groups was performed using a one-way ANOVA.

Time-to-event analysis was performed for all three arms until Week 16 for the time to first discontinuation of all TCS in any time intervals when a subject first achieves EASI 75 until the subject fails to achieve EASI 75 (discontinuation of all TCS was defined as the subject stops all TCS treatment > 7 consecutive days). If a subject never achieved this endpoint until Week 16, then that subject's time to first achievement was censored at the study drug discontinuation or the start of rescue therapy or up to Week 16. The event could be counted only before the start of the rescue therapy. Time to event was analyzed using Kaplan-Meier estimates for each treatment group. Treatment comparisons were performed using stratified Log-rank test.

Post-hoc analyses

To examine the TCS effect in addition to the treatment effect of upadacitinib, post-hoc analyses using logistic regression were performed for the co-primary endpoints EASI 75 and vIGA-AD 0/1 at Week 16

by integrating data from Studies M16-045, M18-891 and M16-047, to estimate the TCS impact on top of the efficacy achieved with the upadacitinib 30 mg and 15 mg doses as well as with placebo.

Changes from the planned analyses

The SAP (version 3) was finalized on Jun 3, 2020, prior to the Week 16 database lock, and incorporated the common changes described for studies M16-045 and M18-891. Specific for this study is addition of long-term efficacy analyses up to Week 24 and Week 52.

The same additional post-hoc analyses were performed as for the monotherapy studies.

The graphical multiple testing procedure follows the same principle as seen in the monotherapy studies and is acceptable.

Results

Study M16-045 & M18-891 (monotherapy studies) and M16-047 (TCS combination study)

In the following, results for all three studies will be presented both in combined tables for all three studies as well as in tables/figures per study, respectively.

Participant flow

Table 8 Subject Disposition in the Phase 3 Studies, ITT_M (Primary Analysis)

Study/ Treatment Group	Randomized n	Completed Study Drug to Week 16 n (%)	Randomized n	Completed Study Drug to Week 16 n (%)
M16-045 (Monotherapy)	**Overall**		**Adolescents**	
Placebo	281	**239 (85.1)**	40	35 (87.5)
UPA 15 mg	281	**272 (96.8)**	42	42 (100)
UPA 30 mg	285	**271 (95.1)**	42	42 (100)
M18-891 (Monotherapy)	**Overall**		**Adolescents**	
Placebo	278	**237 (85.3)**	36	33 (91.7)
UPA 15 mg	276	**264 (95.7)**	33	31 (93.9)
UPA 30 mg	282	**267 (94.7)**	35	32 (91.4)
M16-047 (Combination)	**Overall**		**Adolescents**	
Placebo + TCS	304	**280 (92.1)**	40	36 (90.0)
UPA 15 mg + TCS	300	287 (95.7)	39	38 (97.4)
UPA 30 mg + TCS	297	287 (96.6)	37	37 (100.0)

ITT_M = intent to treat for the Main Study; TCS = topic corticosteroids; UPA = upadacitinib

Study M16-045

Double-blind Period (Through Week 16)

A total of 847 subjects were randomized at 151 study sites located in 24 countries (Argentina, Australia, Bosnia and Herzegovina, Bulgaria, Canada, China, Colombia, Croatia, Denmark, Estonia, Finland, France, Germany, Italy, Japan, Malaysia, New Zealand, Romania, Russian Federation,

Switzerland, Turkey, Ukraine, United Kingdom, and United States [including Puerto Rico]). All 847 subjects (100%) received study drug.

A total of 778 subjects (91.9%) completed study drug through the DB Period (Week 16), and 782 subjects (92.3%) completed study participation through Week 16. Fifty-two subjects discontinued the study during the DB Period and the most frequent primary reason for study discontinuation was withdrawal of consent by the subject.

Sixty-one subjects discontinued study drug in the DB Period and the most frequent primary reason for discontinuation of study drug was withdrawal of consent. Subjects who discontinued study drug were allowed to remain in the study off study drug. Of the 847 subjects in the DB Period, 184 subjects (21.7%) received rescue medication. No subject discontinued study drug due to COVID-19.

Of the 847 subjects randomized, 124 subjects (14.6%) were adolescents and all received study drug. Of the 124 adolescent subjects, 119 adolescent subjects (96.0%) completed study drug through the DB Period (Week 16) and completed study participation through Week 16. Four adolescent subjects discontinued study drug and the study during the DB Period, and the most frequent reason for study discontinuation was withdrawal of consent. Of the adolescent subjects dosed in the DB Period, 25 subjects (20.2%) received rescue medication.

Blinded Extension phase - Through the cut-off date

A total of 782 subjects entered the BE Period and of these, 777 subjects (96.5%) were dosed. As of the cut-off date, 17 subjects (2.1%) received rescue medication, no subjects completed study drug in the BE Period (Week 136), and 53 subjects (6.6%) discontinued study drug in the BE Period. The most frequent primary reason for study drug discontinuation in the BE Period was AE (2.1%). Of the 782 subjects that entered the BE Period, 119 were adolescent subjects and all 119 were dosed.

Study M18-891

Double-blind Period (Through Week 16)

A total of 836 subjects were randomized at 154 study sites located in 23 countries (Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czechia, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Korea, Netherlands, New Zealand, Portugal, Singapore, Spain, Taiwan, United Kingdom, and US).

All 836 subjects (100%) received study drug. A total of 764 subjects (91.4%) completed study drug (with or without rescue therapy) through the DB Period (Week 16), and 768 subjects (91.9%) completed study participation through Week 16. Sixty-seven subjects discontinued study drug in the DB Period, and the most frequent primary reasons for discontinuation of study drug were withdrawal of consent by the subject for the upadacitinib 30 mg group, AE for the upadacitinib 15 mg group, and lack of efficacy for the placebo group. Subjects who discontinued study drug were allowed to remain in the study off study drug. Fifty-seven subjects discontinued the study during the DB Period, and the most frequent primary reasons for study discontinuation were withdrawal of consent by the subject for the upadacitinib 30 mg group, AE for the upadacitinib 15 mg group, and "other" for the placebo group; within the category of "other," lack of efficacy was the most frequent reason 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.

Of the 836 subjects randomized, 104 subjects (12.4%) were adolescents. Of the 104 adolescent subjects, 96 (92.3%) completed study drug (with or without rescue therapy) through the DB Period (Week 16) and completed study participation through the DB Period. Seven adolescent subjects discontinued study drug (all 7 subjects also discontinued from the study) during the DB Period.

<u>Blinded Extension phase - Through the cut-off date</u>

A total of 768 subjects (96.6%) entered the BE 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), and 34 subjects (4.3%) discontinued study drug in the BE Period. The most frequent primary reason for study drug discontinuation in the BE Period was AE (1.3%). Of the 768 subjects that entered the BE Period, 96 were adolescent subjects and all 96 were dosed.

The rate of completion up to Week 16 was high in both mono-therapy studies, >90% (85 % in the placebo arms, though). The main reasons for discontinuation were withdrawal of consent by the subject in study M16-045 and in M18-891 the reasons were withdrawal of consent by the subject for the upadacitinib 30 mg group, AE for the upadacitinib 15 mg group, and "other" for the placebo group (primarily 'lack of efficacy'). In both studies around 20% in total received rescue medication, the majority being in the placebo group (>40%), while less than 10% in the upadacitinib groups received rescue, fewest in the 30 mg group. No subject in either study discontinued from the study due to COVID-19.

The blinded extension phases are still ongoing with no subjects completed so far. In both studies, around 90% are 'Ongoing study drug in BE Period'. At the CHMP's request, the MAH presented updated results, see below.

M16-047

<u>Double-blind Period (Through Week 16)</u>

A total of 901 subjects were randomized and 900 subjects (including 115 adolescents) were treated with study drug (1 adolescent was randomized but not treated) at 171 sites located in 22 countries (Australia, Austria, Belgium, Canada, China [including Hong Kong], Czechia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Norway, Slovakia, Spain, Sweden, United Kingdom, United States [including Puerto Rico]).

Almost all subjects completed study treatment in the double-blind (DB) Period (94.8%). The primary reason for study drug discontinuation for all subjects including adolescents was adverse events, however, few subjects were in this category (≤5 subjects in any treatment group). More subjects on placebo received rescue therapy than subjects on upadacitinib. Six subjects who discontinued study drug in the DB Period, continued to be followed in the study as permitted by the protocol while off study drug treatment. Most adolescents (95.7%) completed study drug in the DB Period and 4 adolescents discontinued the study drug (2 subjects were lost to follow-up, 1 subject for a TEAE and 1 subject withdrew consent).

Thus, the rate of completion up to Week 16 was high, almost 95%. The main reason for discontinuation was adverse events in both adults and adolescents, although still at low rates.

In the placebo + TCS arm, around 25% received rescue medication, while around 5% in the upadacitinib + TCS did so. No subject discontinued from the study/study drug due to COVID-19 (one subject had COVID-19 logistical restrictions as a secondary reason for discontinuation in the BE part).

<u>Blinded Extension phase - Through the cut-off date</u>

A total of 854 subjects (97.4%) including 111 adolescents continued into the blinded extension BE Period. At the cut-off date, 50 subjects (5.7 %) including 7 adolescents discontinued study treatment, the most frequent reason being lack of efficacy, which was more frequently reported in the upadacitinib 15 mg or placebo/upadacitinib 15 mg groups than the other treatment groups. The BE phase is still ongoing with no subjects completed so far. In all study arms except UPA 15 mg + TCS,

more than 90% are 'Ongoing study drug in BE Period'. The MAH was asked to present updated results when available. This has been done in the response, see below.

Baseline data

Baseline demographics from the monotherapy studies (Study M16-045 and Study M18-891) and the combination study (Study M16-047) in subjects with moderate to severe AD are presented in the table below.

Table 9 Overall Demographic Characteristics in the Phase 3 Studies (ITT_M Population)

Demographic Characteristics	Overall			Adolescents		
	M16-045 N = 847	M18-891 N= 836	M16-047 N= 901	M16-045 N = 124	M18-891 N= 104	M16-047 N= 116
Sex, n (%)						
Male	456 (53.8)	471 (56.3)	547 (60.7)	60 (48.4)	48 (46.2)	63 (54.3)
Age group (years), n (%)						
< 18	124 (14.6)	104 (12.4)	116 (12.9)	124 (100)	104 (100)	116 (100)
18 – 39	442 (52.2)	487 (58.3)	490 (54.4)	0	0	0
40 – 64	242 (28.6)	200 (23.9)	259 (28.7)	0	0	0
≥ 65	39 (4.6)	45 (5.4)	36 (4.0)	0	0	0
Race, n (%)						
White	555 (65.5)	577 (69.0)	647 (71.8)	82 (66.1)	80 (76.9)	86 (74.1)
Asian	203 (24.0)	183 (21.9)	185 (20.5)	23 (18.5)	14 (13.5)	18 (15.5)
Black or African American	55 (6.5)	51 (6.1)	50 (5.5)	12 (9.7)	3 (2.9)	11 (9.5)
Weight (kg), n	847	835	900	124	104	116
mean (SD)	74.28 (19.218)	75.32 (18.826)	75.51 (19.594)	62.83 (15.879)	62.38 (14.060)	63.92 (18.151)
median	71.00	72.90	73.10	58.00	60.95	59.60
(min, max)	(36.3, 170.1)	(37.0, 175.0)	(33.0, 169.0)	(40.0, 135.6)	(37.4, 110.4)	(40.1, 125.5)
Height (cm), n	837	835	898	122	104	116
mean (SD)	168.62 (10.027)	169.88 (9.841)	170.47 (10.013)	164.34 (10.039)	165.90 (9.362)	165.11 (10.600)
BMI (kg/m^2), n	837	835	898	122	104	116
mean	26.03	25.99	25.83	23.16	22.58	23.22
(SD)	(6.114)	(5.684)	(5.752)	(5.074)	(4.349)	(5.356)
Region, n (%)						
US/Canada/PR	385 (45.5)	326 (39.0)	322 (35.7)	62 (50.0)	37 (35.6)	53 (45.7)
Japan	45 (5.3)	--	51 (5.7)	4 (3.2)	--	0
Mainland China	45 (5.3)	--	51 (5.7)	4 (3.2)	--	5 (4.3)
Other[a]	372 (43.9)	510 (61.0)	477 (52.9)	54 (43.5)	67 (64.4)	58 (50.0)

BMI = body mass index; ITT_M = intent to treat for the Main Study; max = maximum; min = minimum; PR = Puerto Rico; SD = standard deviation; US = United States

a. Other regions include Europe, South America, and Australia.

The overall demographic characteristics were generally balanced across the upadacitinib (30 mg and 15 mg) and placebo groups, in all studies. 50-60% of subjects were male, the majority (65-70%) were white, and more than 50% were 18 to 39 years of age; around 50% of subjects had a body mass

index (BMI) of < 25 kg/m^2 at screening. The clinical program enrolled subjects across various geographic regions worldwide.

Adolescents comprised 12-15% across studies. The adolescent group characteristics were also generally balanced across the upadacitinib (30 mg and 15 mg) and placebo groups. The weight of adolescents ranged from 37.4 kg to 135.6 kg. There were few patients aged > 65 years (about 5%) across all three studies.

Baseline disease characteristics across treatment groups were generally balanced within each study and were similar across the 3 studies (see table below).

Table 10   Overall Baseline Disease Characteristics in the Phase 3 Studies (ITT_M_Population)

Disease Characteristics	Overall			Adolescents		
	M16-045 **N = 847**	**M18-891** **N= 836**	**M16-047** **N= 901**	**M16-045** **N = 124**	**M18-891** **N= 104**	**M16-047** **N = 116**
AD Duration since symptoms						
(years), n	847	836	899	124	104	115
mean (SD)	23.851 (14.6902)	22.342 (13.4575)	25.621 (14.2787)	13.640 (3.7229)	13.439 (3.6487)	13.425 (3.3579)
vIGA-AD 3, n (%)	464 (54.8)	377 (45.1)	424 (47.1)	73 (58.9)	45 (43.3)	54 (46.6)
vIGA-AD 4, n (%)	383 (45.2)	459 (54.9)	477 (52.9)	51 (41.1)	59 (56.7)	62 (53.4)
EASI, n	847	835	901	124	104	116
mean (SD)	29.46 (12.190)	29.11 (12.002)	29.72 (12.207)	30.65 (13.122)	29.89 (13.147)	30.54 (11.824)
BSA, n	847	835	901	124	104	116
% mean (SD)	47.07 (21.940)	46.58 (22.746)	47.93 (22.618)	50.05 (22.724)	47.61 (22.940)	45.07 (23.961)
Worst Pruritus NRS, Weekly						
n	837	833	895	123	104	115
mean (SD)	7.260 (1.6068)	7.252 (1.5596)	7.185 (1.6815)	7.306 (1.7726)	6.920 (1.7193)	6.812 (1.9781)
Worst Pruritus NRS, Daily						
n	839	833	--	123	104	--
mean (SD)	7.5 (1.79)	7.4 (1.78)	--	7.5 (2.02)	7.2 (1.90)	--
POEM						
n	834	807	892	121	96	113
mean (SD)	21.4 (5.08)	21.6 (5.05)	21.2 (5.13)	20.6 (4.95)	20.1 (5.43)	19.1 (5.71)
SCORAD, Overall						
n	834	811	893	122	98	114
mean (SD)	67.207 (12.6981)	67.071 (12.5217)	67.220 (12.3847)	68.133 (12.4151)	65.177 (13.9378)	67.741 (12.1517)
ADerm-SS TSS-7						
n	784	784	860	118	99	112
mean (SD)	46.1 (13.92)	46.8 (13.51)	46.4 (14.02)	45.2 (15.86)	45.2 (13.85)	44.8 (14.52)

Disease Characteristics	Overall			Adolescents		
	M16-045 N = 847	M18-891 N= 836	M16-047 N= 901	M16-045 N = 124	M18-891 N= 104	M16-047 N = 116
ADerm-SS Skin Pain						
n	836	833	895	123	104	115
mean (SD)	6.403 (2.2723)	6.425 (2.1776)	6.389 (2.2938)	6.317 (2.6537)	6.236 (2.3060)	6.308 (2.4080)
ADerm-IS Sleep						
n	836	833	895	123	104	115
mean (SD)	18.291 (7.5499)	18.891 (7.4842)	18.376 (7.6234)	17.659 (8.5337)	16.040 (8.2987)	16.682 (8.2233)
ADerm-IS Daily Activities						
n	784	784	860	118	99	112
mean (SD)	22.6 (10.90)	23.6 (10.17)	23.4 (10.59)	21.6 (12.23)	21.1 (10.67)	20.5 (10.89)
ADerm-IS Emotional State						
n	784	784	860	118	99	112
mean (SD)	20.1 (8.21)	20.5 (8.01)	19.8 (8.02)	19.4 (9.17)	19.3 (8.97)	18.0 (8.72)
HADS Anxiety						
n	835	811	892	122	98	114
mean (SD)	7.3 (4.25)	7.4 (4.24)	7.5 (4.11)	7.5 (4.49)	7.1 (4.55)	7.3 (3.91)
HADS Depression						
n	835	811	892	122	98	114
mean (SD)	5.1 (4.03)	5.7 (4.14)	5.5 (3.98)	4.5 (4.02)	4.7 (4.10)	4.5 (3.25)
DLQI ($\geq$ 16 years old)						
n	772	766	825	57	53	46
mean (SD)	16.5 (6.94)	16.9 (7.04)	16.6 (7.07)	15.5 (7.14)	14.4 (6.97)	13.1 (5.76)
CDLQI (< 16 years old)						
n	--	--	--	65	45	68
mean (SD)	--	--	--	13.7 (6.24)	14.2 (5.72)	13.2 (5.99)

AD = Atopic Dermatitis; ADerm-IS = Atopic Dermatitis Impact Scale; ADerm-SS = Atopic Dermatitis Symptoms Scale; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; HADS = Hospital Anxiety and Depression Scale; NRS = numerical rating scale; POEM = Patient Oriented Eczema Measure; SCORAD = Scoring Atopic Dermatitis; SD = standard deviation; TTS-7 = total symptom score 7-items; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis

Baseline disease characteristics were generally balanced across the upadacitinib and placebo groups overall and in adolescents. Subjects had been diagnosed with AD for a mean of approximately 20 years overall (23-24 years in Study M16-047) and 12-13 years for adolescents. The mean EASI score was slightly below 30 (median around 25-26), the mean percent BSA affected was around 47%. In study M16-045, the proportion of subjects with moderate AD (vIGA-AD 3) was approximately 55% and the proportion with severe AD (vIGA-AD 4) 45% while the reverse proportions were seen in Study M18-891 (45% moderate, 55% severe) and M16-047 (proportion with moderate AD was 47% and the proportion with severe AD 53%). The mean Worst Pruritus NRS weekly average score was above 7 in all studies, reflecting rather substantial itch severity. Thus, the study population in all three studies reflected a population with moderate to severe AD. There was no obvious difference between the populations included in the mono-therapy studies vs. the TCS combination study.

Most subjects had prior TCS, TCI or systemic treatments with documentation of inadequate response –
see table below. Study M16-047 included a medium and low potency TCS as part of the study drug
regimen.

Table 11   Subjects with Prior Treatment for Atopic Dermatitis in Phase 3 Studies

Variable, n%	M16-045 Monotherapy N = 847	M18-891 Monotherapy N = 836	M16-047 Combination N = 901
All classes of TCS	812 (95.9)	775 (92.7)	848 (94.1)
High potency topical corticosteroids	565 (66.7)	681 (81.5)	629 (69.8)
Medium potency topical corticosteroids	424 (50.1)	262 (31.3)	409 (45.4)
Low potency topical corticosteroids	232 (27.4)	222 (26.6)	277 (30.7)
Topical calcineurin inhibitor	299 (35.3)	288 (34.4)	364 (40.4)
Biologic systemic therapy	24 (2.8)	26 (3.1)	30 (3.3)
Non-biologic immunomodulating systemic therapy	385 (45.5)	448 (53.6)	492 (54.6)
Phototherapy	137 (16.2)	161 (19.3)	204 (22.6)
Other topical therapies for AD	198 (23.4)	142 (17.0)	165 (18.3)

AD = Atopic Dermatitis; TCS = topic corticosteroids

The previous treatments were as expected in an AD population, i.e. mainly topical corticosteroids,
emollients and protectives. Around half of the subjects had received prior non-biologic
immunomodulating systemic therapies while only around 3% had received prior biologic systemic
therapies.

Atopic co-morbidities included asthma (39.8% – 45.3%), allergic rhinitis (34.0% – 34.2%), food
allergies (27.9% – 33.5%), nasal polyps (1.7% – 2.0%) and eosinophilic esophagitis (0.4% – 0.6%)
across all 3 Phase 3 studies.

Numbers analysed

In all three studies, the ITT_M Population, consisting of all randomized subjects of the Main Study, was
used for all efficacy analyses. Subjects who were randomized to placebo in the DB Period and did not
continue into the BE Period were not included in the analysis in the BE Period. The Per Protocol
Population of Main Study (PP_M) was a subset of the ITT_M Population that excluded subjects with
major protocol deviations that could potentially affect the co-primary efficacy endpoints. Sensitivity
analyses of the co-primary efficacy endpoints were conducted on the PP_M Population.

In study M18-891, data from 11 subjects screened (6 randomized) at one site were not included in any
descriptive summaries or statistical analyses for the report due to a significant site GCP non-
compliance and closure of the site.

The proportions of subjects excluded from the PP population were rather small (<5% in the mono-
therapy studies and 7% in study M16-047).

Outcomes and estimation

Results from Double-blind period

Co-primary endpoints

M16-045

The co-primary endpoints were met; a statistically significantly larger proportion of subjects in the upadacitinib groups achieved EASI 75 and a vIGA-AD score of 0 or 1 (clear or almost clear) with a reduction of at least 2 grade reductions from baseline at Week 16 compared with the placebo group based on the primary approach of NRI-C.

Table 12   Co-Primary Endpoints: EASI 75 and vIGA-AD 0 or 1 at Week 16 (ITT_M Population) M16-045

EMA Testing[a]	FDA Testing[a]	Primary Endpoint[b]	PBO (N = 281) n (%)	UPA 15 mg (N = 281) n (%); Adj Diff (P-value)	UPA 30 mg (N = 285) n (%); Adj Diff (P-value)
V1	V1	EASI 75 at Week 16	46 (16.3)	196 (69.6); 53.3 (< 0.001***)	227 (79.7); 63.4 (< 0.001***)
V2	V2	vIGA-AD clear or almost clear at Week 16	24 (8.4)	135 (48.1); 39.8 (< 0.001***)	177 (62.0); 53.6 (< 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; UPA = upadacitinib; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis

*** p-value ≤ 0.001 according to the Cochran-Mantel Haenzel test; UPA vs PBO.

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

b.   Results are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C).

Note: 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-NC, MI, Tipping Point Analysis, and Per Protocol Analysis.

M18-891

The co-primary endpoints were achieved also in this study.

Table 13   Co-Primary Endpoints: EASI 75 and vIGA-AD 0 or 1 at Week 16 (ITT_M Population) M18-891

EMA Testing[a]	FDA Testing[a]	Primary Endpoint[b]	PBO (N = 278) n (%)	UPA 15 mg (N = 276) n (%); Adj Diff (P-value)	UPA 30 mg (N = 282) n (%); Adj Diff (P-value)
V1	V1	EASI 75 at Week 16	37 (13.3)	166 (60.1); 46.9 (< 0.001***)	206 (72.9); 59.6 (< 0.001***)
V2	V2	vIGA-AD of 0 or 1 (clear or almost clear) at Week 16	13 (4.7)	107 (38.8); 34.0 (< 0.001***)	147 (52.0); 47.4 (< 0.001***)

Adj Diff = adjusted difference; EASI = Eczema Area and Severity Index; EMA = European Medicines Agency; FDA = Food and Drug Administration; ITT_M = Intent-to-Treat Population for the Main Study; NRI-C = Non-Responder Imputation incorporating Multiple Imputation to handle missing data due to coronavirus disease 2019; PBO = placebo; 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.

b.   Results are based on NRI incorporating MI to handle missing data due to COVID-19 (NRI-C).

*** p-value ≤ 0.001; UPA vs. PBO.

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

The co-primary endpoints, the proportions of patients achieving EASI 75 and a vIGA-AD score of 0 or 1 with a reduction of at least 2 grade reductions from baseline at Week 16 were clearly higher for both upadacitinib dose levels vs. placebo, in both mono-therapy studies. The results were highly statistically significant and are also considered clinically relevant.

A dose dependency was observed, with overall 10-14% difference in responder rates for EASI 75 and vIGA (0,1) between the 15 mg and the 30 mg doses.

Sensitivity and PP analyses supported the primary analysis.

M16-047

The co-primary endpoints were met; a statistically significantly larger proportion of subjects in the upadacitinib + TCS groups achieved EASI 75 and a vIGA-AD score of 0 or 1 (clear or almost clear) with a reduction of at least 2 grade reductions from baseline at Week 16 compared with the placebo + TCS group based on the primary approach of NRI-C.

Table 14   Co-Primary Endpoints: EASI 75 and vIGA-AD 0 or 1 at Week 16 (ITT_M Population) M16-047

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 results were highly statistically significant and are also considered clinically relevant.

A dose dependency was observed, with a 12.5% difference in responder rate for EASI 75 and a 19% difference for vIGA-AD 0,1, respectively, between the 15 mg and the 30 mg doses.

The co-primary endpoint results were supported by all sensitivity analyses, including NRI-NC, MI, Tipping Point Analysis, and Per Protocol Analysis.

Sensitivity and PP analyses supported the primary analysis.

Secondary endpoints

M16-045

The key secondary endpoints for the EU/EMA and the US/FDA respectively, are described in the table below. Superiority of each upadacitinib dose vs. placebo was demonstrated for all key secondary endpoints, based on showing statistical significance under the overall type I error control.

Table 15   Results of Key Secondary Endpoints – EMA and FDA (ITT_M Population) M16-045

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.

M18-891

Also in study M18-891, superiority of each upadacitinib dose vs. placebo was demonstrated for all key secondary endpoints, based on showing statistical significance under the overall type I error control.

Table 16   *Results of Key Secondary Endpoints – EMA and FDA (ITT_M Population) M18-891*

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.

A very large number of endpoints referred to as 'key secondary endpoints' were included in the mono-therapy studies. Superiority of each upadacitinib dose vs. placebo was demonstrated for all key secondary endpoints, based on showing statistical significance under the overall type I error control, in both studies. Similar to the co-primary endpoints, a dose-related difference generally in the range 10-18% was observed.

Effects on itch were evaluated by the reduction in Worst pruritus NRS by ≥ 4 points at Week 16. A separation from placebo was observed as early as Day 2, although the numbers of upadacitinib responders at these early times points (Day 2, Day 3 and Week 1) were rather few. Still, it can be observed that both effects on itch and on AD lesions assessed by EASI 75 at Week 2 show a rapid onset of effect.

The number of flares during the DB period were also much lower in the upadacitinib arms (0-2%) vs. the placebo arm (around 25%).

Also for the patient-reported outcomes (POEM, DLQI, HADS and the company-developed ADerm scores), both upadacitinib doses showed superior effects vs. placebo and a dose-dependent effect was observed.

M16-047

The key secondary endpoints for the EU/EMA and the US/FDA respectively, are described in the table below. Superiority of each upadacitinib dose vs. placebo was demonstrated for all key secondary endpoints, based on showing statistical significance under the overall type I error control.

Table 17   Results of Key Secondary Endpoints – EMA and FDA (ITT_M Population) M16-047

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.

There were fewer key (multiplicity-controlled) secondary endpoints in this study compared with the mono-therapy studies. For all of these, superiority of each upadacitinib dose vs. placebo was demonstrated, based on showing statistical significance under the overall type I error control.

Topical Corticosteroid Free Days

The number of Topical Corticosteroid Free Days was evaluated as an other endpoint and among all subjects through Week 16, the mean number of days off of all TCS and achieving an EASI 75 response was 47 days (median 57 days) in the upadacitinib 30 mg group, 34 days (median 26 days) in the upadacitinib 15 mg group and 8 days (median 0 days) in the placebo group.

Among all subjects, the mean number of days off all medium and high potency TCS and achieving an EASI 75 response was 56 days (median: 69 days) in the upadacitinib 30 mg group, 40 days (median: 31 days) in the upadacitinib 15 mg group and 10 days (median 0 days) in the placebo group through Week 16.

The time to first discontinuation of all TCS with an EASI 75 response through Week 16 is described in figure below. The median time to first discontinuation of TCS 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.
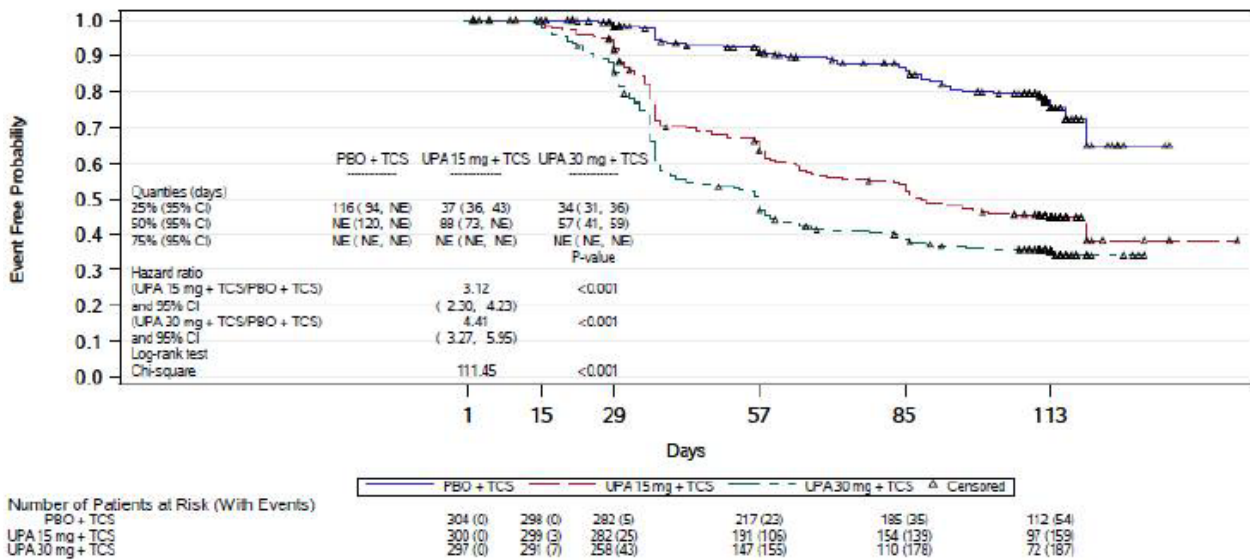
CI = confidence interval; EASI = Eczema Area and Severity Index; PBO = placebo; TCS = topical corticosteroids; UPA = upadacitinib
Note: Discontinuation of all TCS was defined as when the subject stops all TCS treatment for > 7 consecutive days. Days after the start of systemic rescue were not considered as TCS-free days.

Figure 12   The Time to First Discontinuation of All TCS with an EASI 75 Response Through Week 16, M16-047

Results from Blinded Extension period *(updated week-52 data)*

Since the date of submission, all subjects in the three upadacitinib Phase 3 Studies M16-045 (Measure Up 1, monotherapy), M18-891 (Measure Up 2, monotherapy), and M16-047 (AD Up, combination therapy with TCS) have reached Week 52 or were prematurely discontinued. Efficacy results through Week 52 were provided for all primary and secondary endpoint variables based on data cuts performed for each study after the last subject reached the Week 52 visit (21 December 2020, 15 January 2021, and 18 December 2020 for Studies M16-045, M18-891, and M16-047, respectively).

Below, tables and figures are shown for each study, for the groups who received UPA continuously from baseline (UPA 15 mg and UPA 30 mg) and for those initially randomised to placebo who were randomised to UPA 15 mg or 30 mg at Week 16 (PBO/UPA 15 mg and PBO/UPA 30 mg, respectively).

M16-045

Table 18   Selected Efficacy Endpoints at Week 52 in Study M16-045

Selected Efficacy Endpoints (Analysis Method)	PBO/ UPA 15 mg n (%) or LS Mean (SE)	PBO/ UPA 30 mg n (%) or LS Mean (SE)	UPA 15 mg n (%) or LS Mean (SE)	UPA 30 mg n (%) or LS Mean (SE)
EASI 75				
OC	N = 102	N = 111	N = 233	N = 232
	84 (82.4)	101 (91.0)	191 (82.0)	197 (84.9)
MI	N = 65	N = 67	N = 281	N = 285
	56 (85.5)	62 (92.3)	194 (69.0)	212 (74.5)
vIGA-AD 0/1				
OC	N = 102	N = 111	N = 233	N = 232
	63 (61.8)	83 (74.8)	138 (59.2)	145 (62.5)
MI	N = 65	N = 67	N = 281	N = 285
	47 (72.8)	56 (83.9)	148 (52.5)	163 (57.1)
Worst Pruritus Numerical Rating Scale (NRS) improvement ≥ 4				
OC	N = 100	N = 108	N = 226	N = 229
	60 (60.0)	78 (72.2)	152 (67.3)	155 (67.7)
MI	N = 62	N = 64	N = 274	N = 280
	40 (63.8)	44 (68.8)	156 (57.0)	167 (59.7)
EASI 90				
OC	N = 102	N = 111	N = 233	N = 232
	64 (62.7)	88 (79.3)	146 (62.7)	170 (73.3)
MI	N = 65	N = 67	N = 281	N = 285
	45 (69.0)	56 (83.9)	146 (51.9)	173 (60.7)
Percent change from Baseline of Worst Pruritus NRS				
OC	N = 102	N = 108	N = 230	N = 229
	-43.76 (9.339)	-72.99 (9.185)	-61.52 (7.133)	-64.23 (7.505)
MMRM	N = 55	N = 58	N = 212	N = 221
	-24.79 (12.474)	-69.79 (12.309)	-51.26 (6.600)	-54.87 (6.506)
Percent change in EASI from Baseline				
OC	N = 102	N = 111	N = 233	N = 232
	-89.59 (2.038)	-96.10 (1.990)	-82.29 (1.562)	-85.01 (1.642)
MMRM	N = 56	N = 61	N = 214	N = 224
	-88.04 (2.530)	-92.15 (2.433)	-76.24 (1.515)	-78.65 (1.533)
Percent change in SCORAD from Baseline				
OC	N = 101	N = 111	N = 235	N = 225
	-74.34 (2.676)	-83.69 (2.593)	-62.83 (2.003)	-67.84 (2.166)
MMRM	N = 55	N = 62	N = 219	N = 224
	-77.00 (3.710)	-82.86 (3.511)	-62.38 (2.405)	-67.05 (2.496)
EASI 100				
OC	N = 102	N = 111	N = 233	N = 232
	30 (29.4)	49 (44.1)	65 (27.9)	83 (35.8)
MI	N = 65	N = 67	N = 281	N = 285
	20 (30.8)	34 (50.8)	64 (22.9)	83 (29.2)
Worst Pruritus NRS of 0/1				
OC	N = 101	N = 108	N = 230	N = 229
	50 (49.5)	65 (60.2)	103 (44.8)	115 (50.2)
MI	N = 63	N = 64	N = 279	N = 282

| 29 (46.6) | 38 (59.1) | 104 (37.2) | 122 (43.1) |

Note: For the OC approach, N = the number of subjects (Main Study only) with observed clinical measurements (up to treatment discontinuation) at Week 52 in each treatment group. For the MI approach, N= the number of intent-to-treat subjects of the main study in each treatment group with one exception: Placebo subjects who were rescued in the DB Period and re-randomized at Week 16 were not included in the above summaries, because placebo subjects rescued during the DB Period may bring forward confounding effects of the prior rescue treatment.

Figure 13   Achievement of EASI 75 at Each Visit in Study M16-045; OC (upper) and MI (lower)

Proportion of Subjects Achieving vIGA-AD of 0 or 1 with at Least 2 Grades of Reduction from Baseline by Visit up to Week 52 (OC) (ITT_M Population)
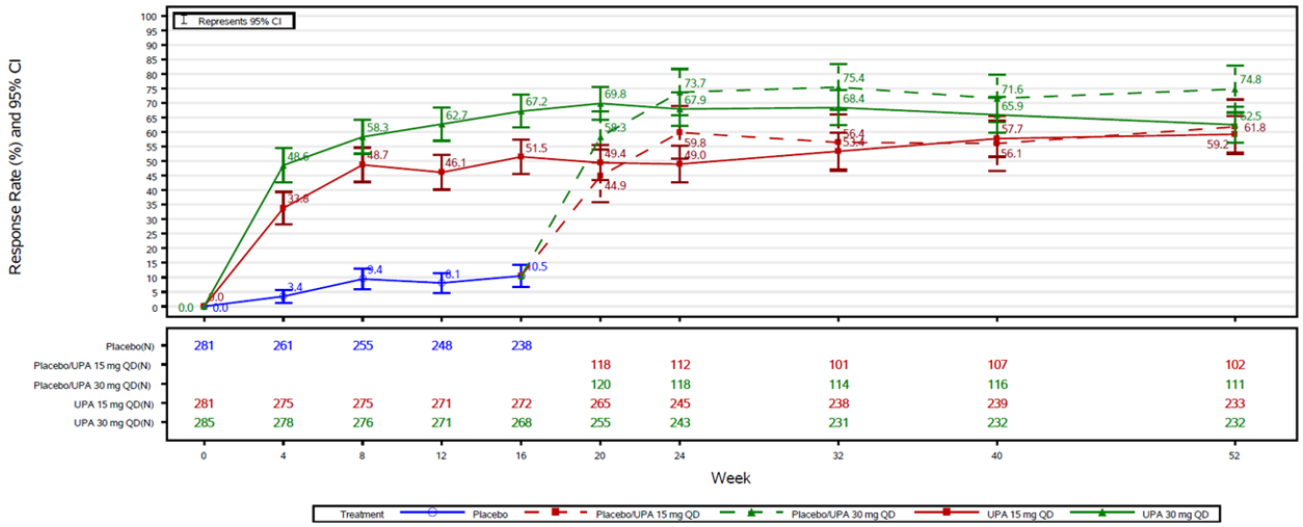
Proportion of Subjects Achieving vIGA-AD of 0 or 1 with at Least 2 Grades of Reduction from Baseline by Visit up to Week 52 (MI) (ITT_M Population)
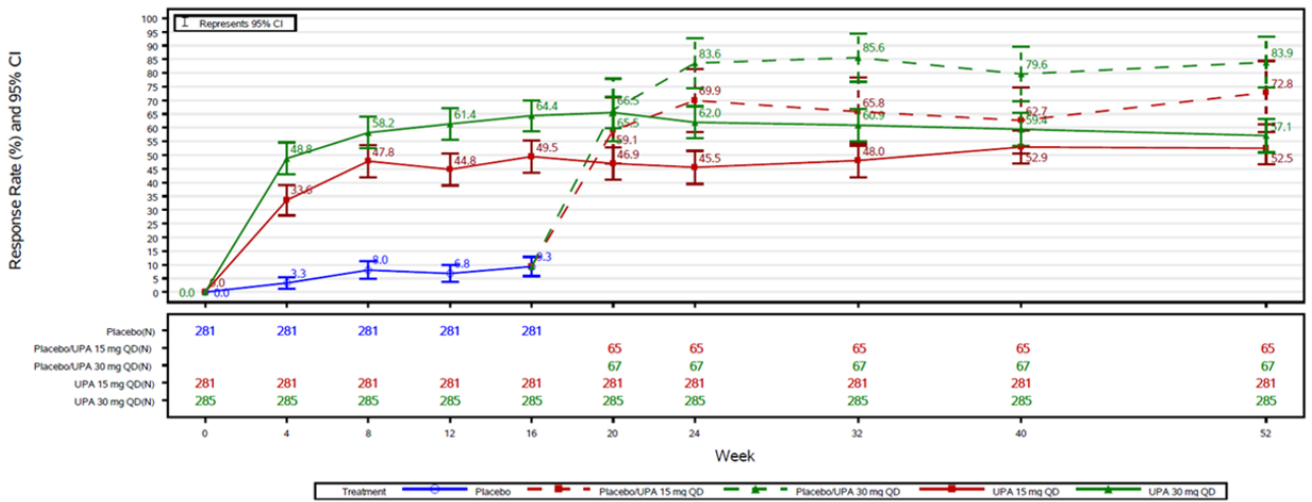
Figure 14   Achievement of vIGA-AD 0/1 at Each Visit in Study M16-045; OC (upper) and MI (lower)

M18-891

Table 19   Selected Efficacy Endpoints at Week 52 in Study M18-891

Selected Efficacy Endpoints	PBO/UPA 15 mg n (%) or LS Mean (SE)	PBO/UPA 30 mg n (%) or LS Mean (SE)	UPA 15 mg n (%) or LS Mean (SE)	UPA 30 mg n (%) or LS Mean (SE)
EASI 75				
OC	N = 103	N = 108	N = 230	N = 229
	84 (81.6)	99 (91.7)	182 (79.1)	193 (84.3)
MI	N = 62	N = 74	N = 276	N = 282
	45 (72.7)	65 (87.9)	184 (66.8)	202 (71.5)
vIGA-AD 0/1				
OC	N = 103	N = 108	N = 230	N = 229
	56 (54.4)	70 (64.8)	121 (52.6)	149 (65.1)
MI	N = 62	N = 74	N = 276	N = 282
	36 (57.4)	50 (67.3)	127 (46.0)	163 (57.7)
Worst Pruritus Numerical Rating Scale (NRS) improvement ≥ 4				
OC	N = 102	N = 103	N = 226	N = 225
	63 (61.8)	75 (72.8)	141 (62.4)	164 (72.9)
MI	N = 62	N = 70	N = 270	N = 280
	36 (58.7)	50 (71.2)	143 (53.1)	173 (61.9)
EASI 90				
OC	N = 103	N = 108	N = 230	N = 229
	62 (60.2)	78 (72.2)	141 (61.3)	161 (70.3)
MI	N = 62	N = 74	N = 276	N = 282
	33 (53.9)	52 (70.7)	139 (50.3)	161 (57.2)
Percent change from Baseline of Worst Pruritus NRS				
OC	N = 102	N = 106	N = 229	N = 226
	-61.01 (3.867)	-71.19 (3.789)	-56.25 (3.063)	-63.69 (3.154)
MMRM	N = 48	N = 67	N = 209	N = 214
	-57.39 (5.309)	-69.80 (4.616)	-50.49 (3.035)	-55.66 (3.099)
Percent change in EASI from Baseline				
OC	N = 103	N = 108	N = 230	N = 229
	-87.53 (2.140)	-92.31 (2.095)	-81.63 (1.698)	-83.11 (1.754)
MMRM	N = 49	N = 68	N = 209	N = 217
	-81.88 (3.410)	-89.76 (2.982)	-73.82 (1.936)	-73.65 (1.971)
Percent change in SCORAD from Baseline				
OC	N = 98	N = 108	N = 229	N = 227
	-72.72 (2.898)	-78.28 (2.773)	-63.06 (2.247)	-67.77 (2.318)
ANCOVA	N = 47	N = 68	N = 216	N = 219
	-73.76 (4.104)	-77.31 (3.455)	-59.99 (2.506)	-64.58 (2.620)
EASI 100				
OC	N = 103	N = 108	N = 230	N = 229
	25 (24.3)	35 (32.4)	64 (27.8)	82 (35.8)
MI	N = 62	N = 74	N = 276	N = 282
	17 (27.6)	27 (36.5)	60 (21.8)	81 (28.9)
Worst Pruritus NRS of 0/1				
OC	N = 102	N = 106	N = 229	N = 226
	43 (42.2)	56 (52.8)	96 (41.9)	118 (52.2)
MI	N = 62	N = 73	N = 275	N = 281

Selected Efficacy Endpoints	PBO/UPA 15 mg n (%) or LS Mean (SE)	PBO/UPA 30 mg n (%) or LS Mean (SE)	UPA 15 mg n (%) or LS Mean (SE)	UPA 30 mg n (%) or LS Mean (SE)
	25 (40.9)	39 (53.4)	93 (33.6)	121 (43.0)

Note: For the OC approach, N = the number of subjects (Main Study only) with observed clinical measurements (up to treatment discontinuation) at Week 52 in each treatment group. For the MI approach, N= the number of intent-to-treat subjects of the main study in each treatment group with one exception: Placebo subjects who have been rescued in the DB Period and re-randomized at Week 16 were not included in the above summaries, because placebo subjects rescued during the DB Period may bring forward confounding effects of the prior rescue treatment.

Proportion of Subjects Achieving EASI 75 by Visit up to Week 52 (OC) (ITT_M Population)
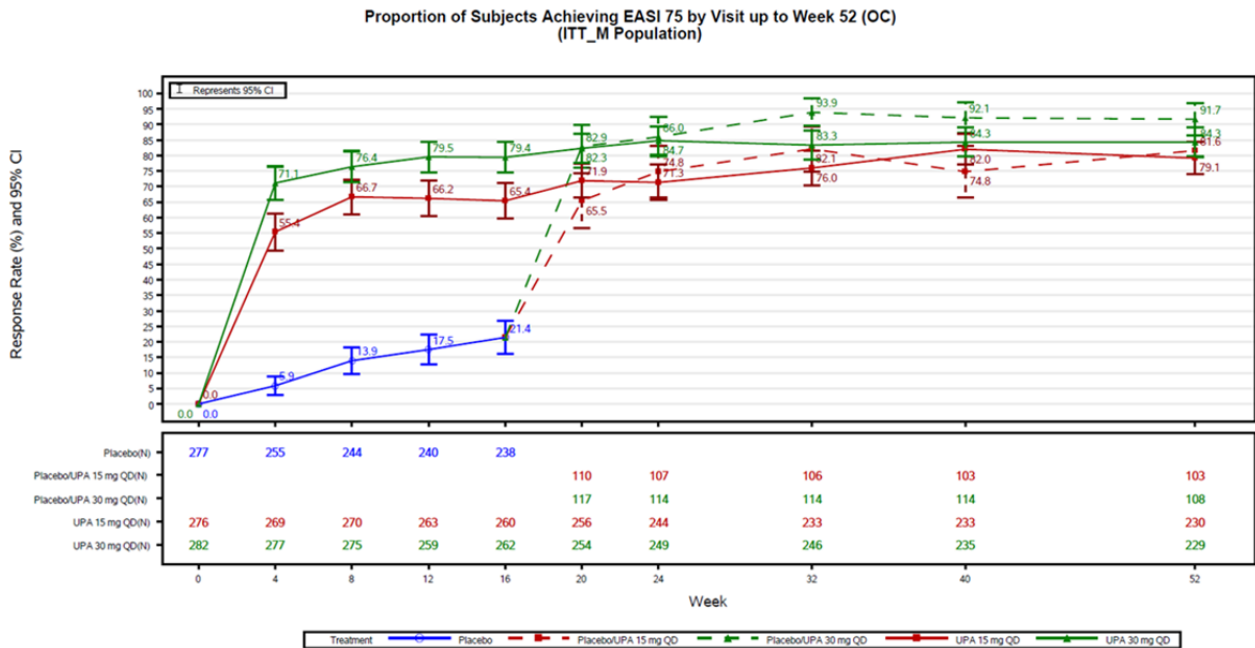
Proportion of Subjects Achieving EASI 75 by Visit up to Week 52 (MI, ITT_M Population)
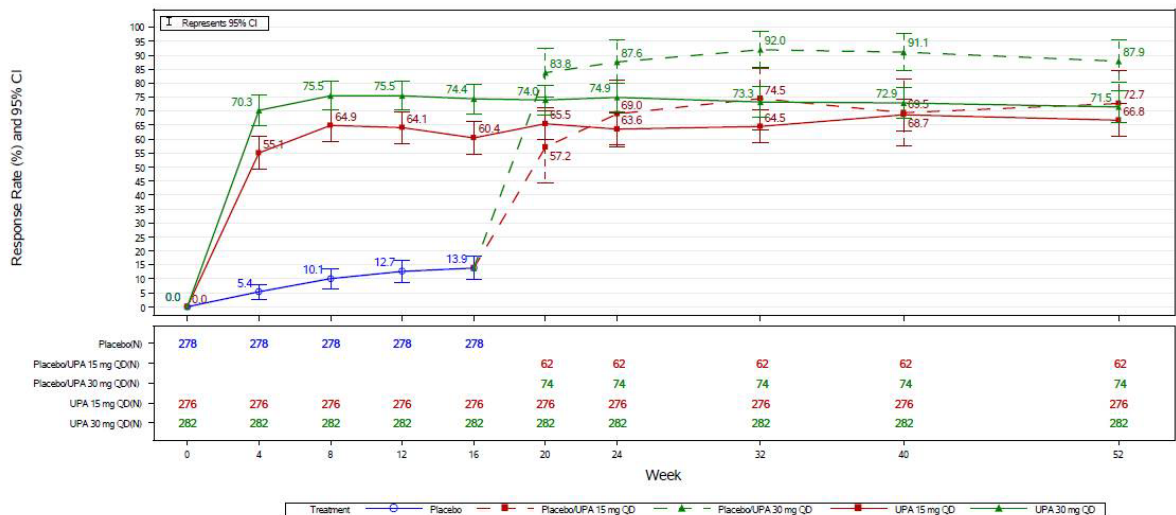
Figure 15   Achievement of EASI 75 Each Visit in Study M18-891; OC (upper) and MI (lower)
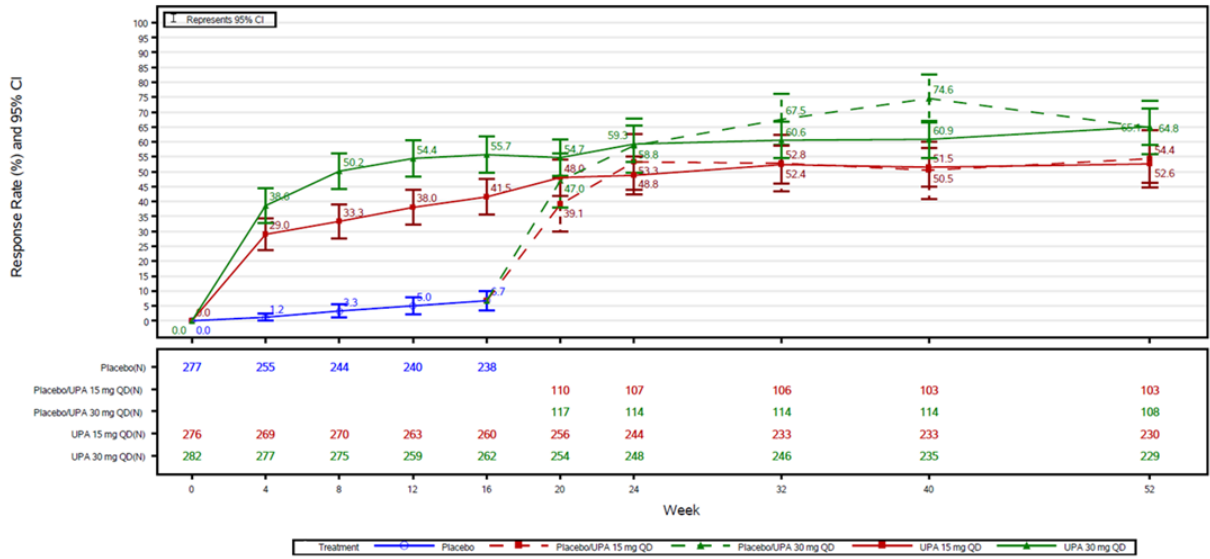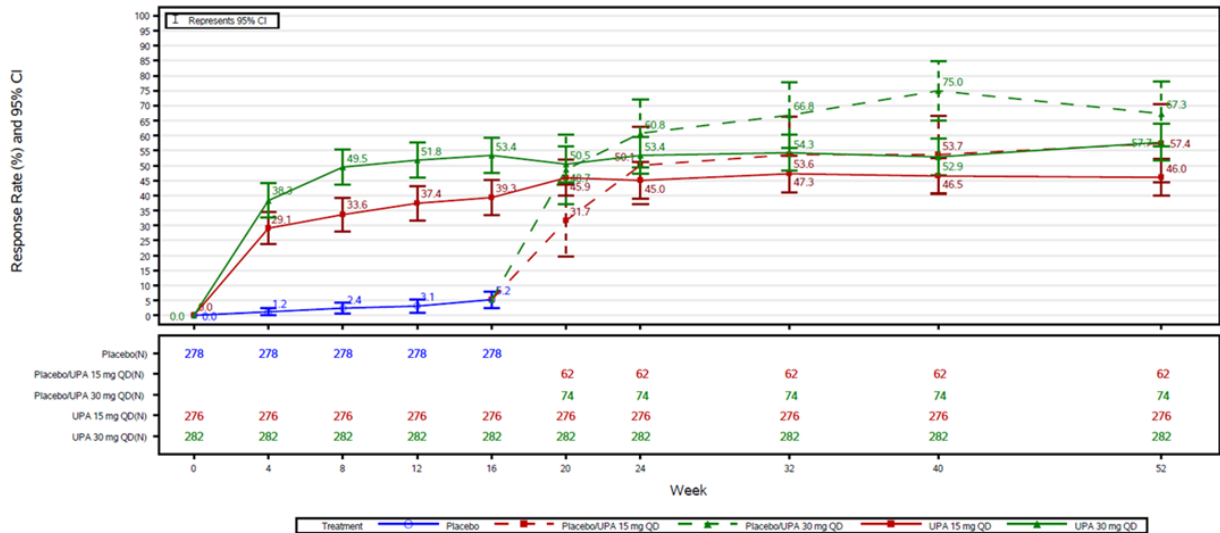
Figure 16   Achievement of vIGA-AD 0/1 Each Visit in Study M18-891; OC (upper) and MI (lower)

Table 20   Selected Efficacy Endpoints at Week 52 in Study M16-047

Selected Efficacy Endpoints	PBO+TCS / UPA 15 mg+TCS n (%) or LS Mean (SE)	PBO+TCS / UPA 30 mg+TCS n (%) or LS Mean (SE)	UPA 15 mg+TCS n (%) or LS Mean (SE)	UPA 30 mg+TCS n (%) or LS Mean (SE)
EASI 75				
NRI-C	N = 115	N = 92	N = 300	N = 297
	91 (79.1)	78 (84.7)	152 (50.8)	205 (69.0)
OC	N = 127	N = 126	N = 243	N = 255
	107 (84.3)	116 (92.1)	172 (70.8)	213 (83.5)
MI	N = 115	N = 92	N = 300	N = 297
	92 (80.0)	82 (88.7)	160 (53.5)	215 (72.5)
vIGA-AD 0/1				
NRI-C	N = 115	N = 92	N = 300	N = 297
	65 (56.9)	60 (65.5)	101 (33.5)	134 (45.2)
OC	N = 127	N = 126	N = 242	N = 255
	69 (54.3)	89 (70.6)	112 (46.3)	142 (55.7)
MI	N = 115	N = 92	N = 300	N = 297
	66 (57.3)	64 (69.1)	108 (36.0)	146 (49.1)
Worst Pruritus Numerical Rating Scale (NRS) improvement ≥ 4				
NRI-C	N = 111	N = 90	N = 288	N = 291
	68 (61.3)	64 (70.7)	130 (45.3)	167 (57.5)
OC	N = 125	N = 118	N = 232	N = 244
	78 (62.4)	94 (79.7)	144 (62.1)	174 (71.3)
MI	N= 111	N = 90	N = 288	N = 291
	70 (63.0)	70 (77.2)	142 (49.4)	183 (62.8)
EASI 90				
OC	N = 127	N = 126	N = 243	N = 255
	79 (62.2)	95 (75.4)	128 (52.7)	167 (65.5)
MI	N = 115	N = 92	N = 300	N = 297
	70 (60.8)	66 (71.8)	113 (37.7)	165 (55.4)
Percent change from Baseline of Worst Pruritus NRS				
OC	N = 128	N = 120	N = 240	N = 248
	-57.30 (3.547)	-73.86 (3.670)	-46.99 (3.078)	-57.58 (3.101)
MMRM	N = 102	N = 74	N = 208	N = 227
	-55.20 (4.141)	-69.77 (4.672)	-39.02 (3.328)	-54.55 (3.358)
Percent change in EASI from Baseline				
OC	N = 127	N = 126	N = 243	N = 255
	-84.21 (2.159)	-93.32 (2.184)	-75.37 (1.858)	-82.75 (1.869)
MMRM	N = 101	N = 77	N = 209	N = 234
	-82.24 (2.260)	-89.41 (2.532)	-67.65 (1.727)	-77.38 (1.720)
Percent change in SCORAD from Baseline				
OC	N = 129	N = 122	N = 256	N = 247
	-65.66 (2.537)	-77.87 (2.616)	-52.84 (2.141)	-63.86 (2.207)
MMRM	N = 102	N = 76	N = 226	N = 231

Selected Efficacy Endpoints	PBO+TCS / UPA 15 mg+TCS n (%) or LS Mean (SE)	PBO+TCS / UPA 30 mg+TCS n (%) or LS Mean (SE)	UPA 15 mg+TCS n (%) or LS Mean (SE)	UPA 30 mg+TCS n (%) or LS Mean (SE)
	-68.02 (2.805)	-75.86 (3.144)	-52.14 (2.356))	-63.38 (2.438)
EASI 100				
OC	N = 127	N = 126	N = 243	N = 255
	32 (25.2)	41 (32.5)	41 (16.9)	74 (29.0)
MI	N = 115	N = 92	N = 300	N = 297
	31 (27.0)	24 (26.3)	39 (13.1)	70 (23.6)
Worst Pruritus NRS of 0/1				
OC	N = 128	N = 119	N = 239	N = 246
	46 (35.9)	74 (62.2)	85 (35.6)	120 (48.8)
MI	N = 114	N = 90	N = 296	N = 293
	42 (36.9)	51 (56.5)	84 (28.2)	119 (40.5)

Note: For the OC approach, N = the number of subjects (Main Study only) with observed clinical measurements (up to treatment discontinuation) at Week 52 in each treatment group. For the NRI-C and MI approach, N= the number of intent-to-treat subjects of the main study in each treatment group with one exception: Placebo subjects who were rescued in the DB Period and re-randomized at Week 16 were not included in the above summaries, because placebo subjects rescued during the DB Period may bring forward confounding effects of the prior rescue treatment

Proportion of Subjects Achieving EASI 75 by Visit up to Week 52 (NRI-C) (ITT_M Population)

Proportion of Subjects Achieving EASI 75 by VISIT up to Week 52 (OC)
(ITT_M Population)
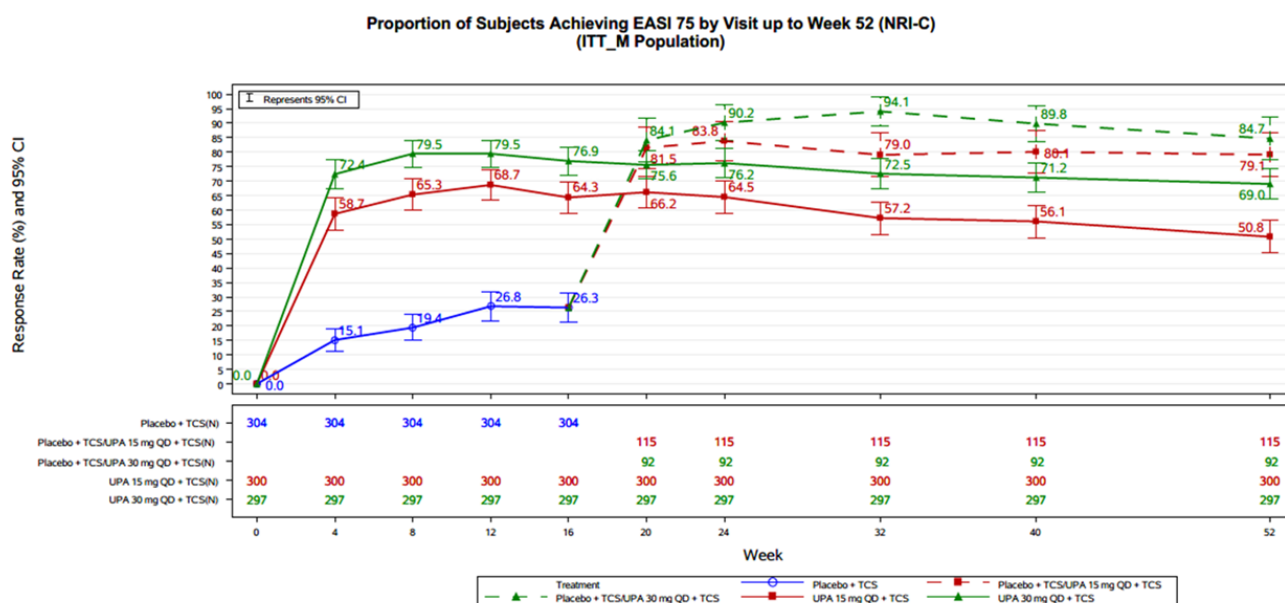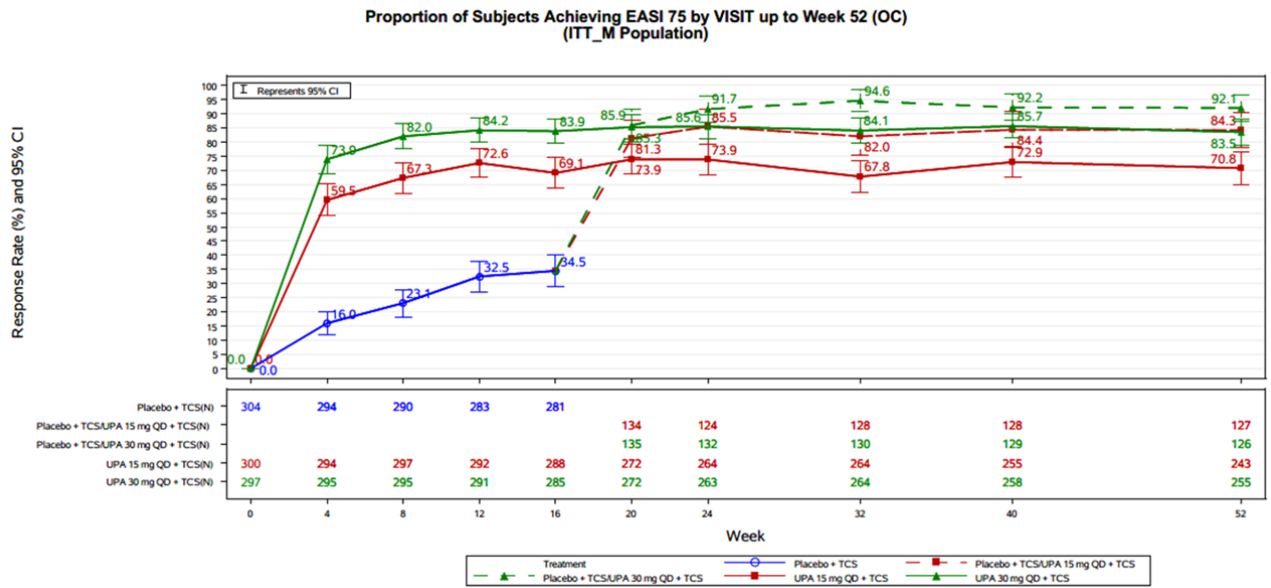
Figure 17   Achievement of EASI 75 at Each Visit Up to Week 52 in Study M16-047 (NRI-C, OC)

Proportion of Subjects Achieving vIGA-AD of 0 or 1 with at Least 2 Grades of Reduction from Baseline
by Visit up to Week 52 (NRI-C)
(ITT_M Population)

Proportion of Subjects Achieving vIGA-AD of 0 or 1 with at Least 2 Grades of Reduction from Baseline by Visit up to Week 52 (OC)
**(ITT_M Population)**
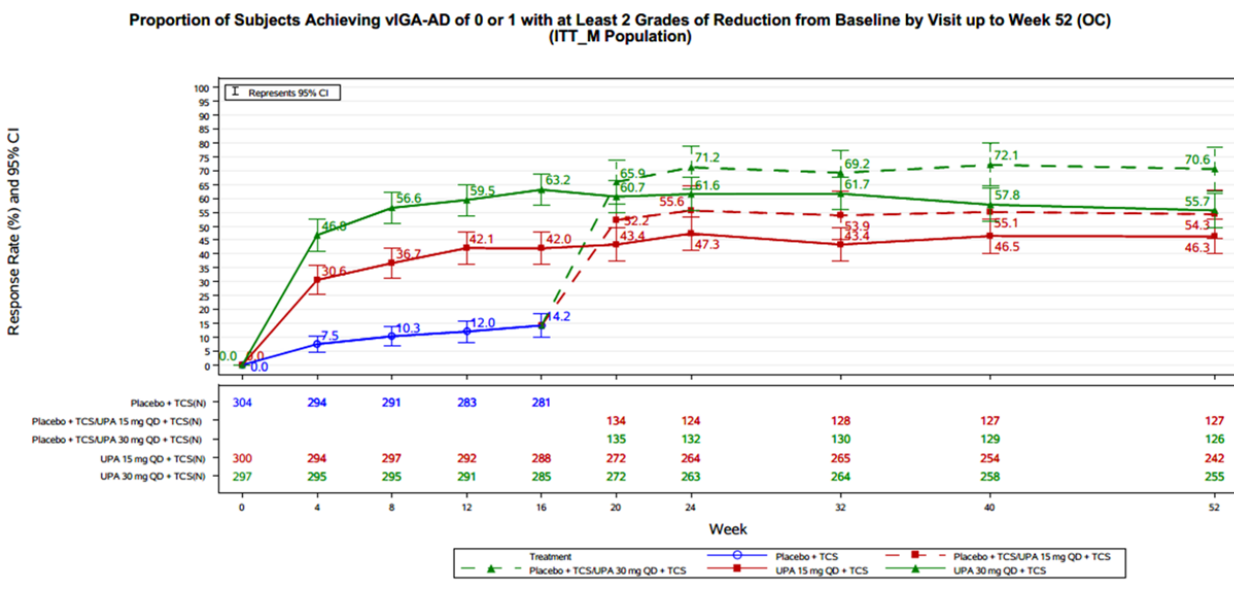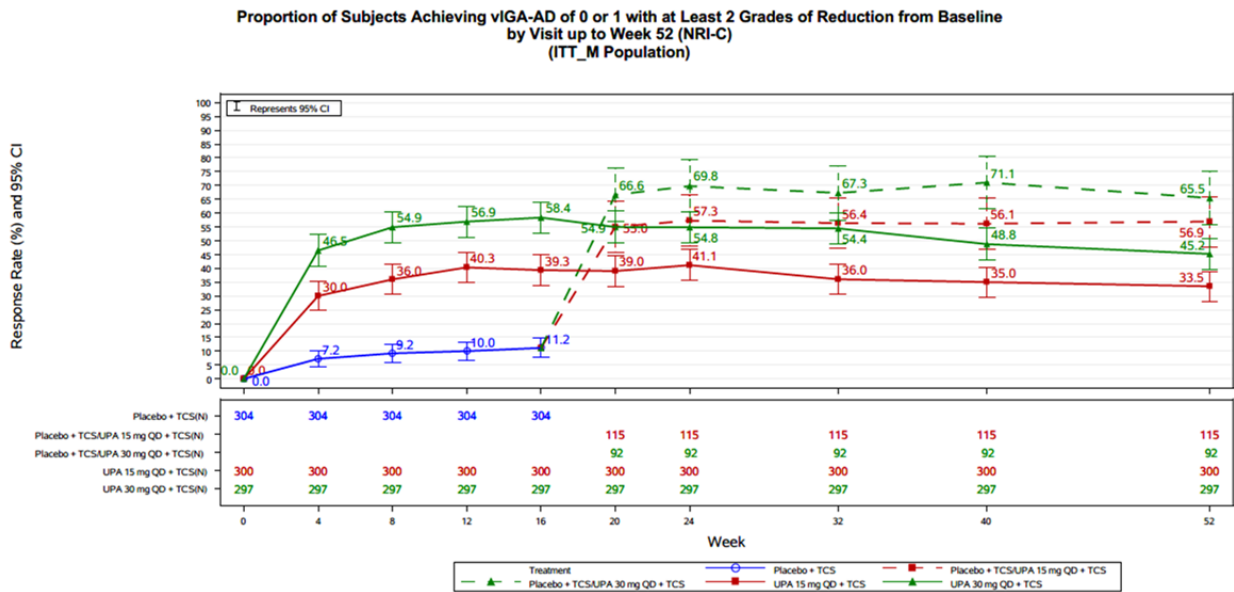
Figure 18   Achievement of vIGA-AD 0/1 at Each Visit Up to Week 52 in Study M16-047 (NRI-C, OC)

It can be concluded that among subjects who continued upadacitinib in the BE Period, treatment responses were generally maintained in the BE Period up to Week 52 and were numerically greater in the upadacitinib 30 mg groups compared with upadacitinib 15 mg, based on EASI 75, vIGA-AD 0/1 and other endpoints.

The proportions of subjects who achieved EASI 75 and a vIGA-AD Score of 0/1, among subjects who started on placebo and switched to upadacitinib at Week 16, were similar to those observed after upadacitinib initiation in subjects who started upadacitinib on Day 1. Similar trends were seen for EASI 90, EASI 100, and Worst Pruritus NRS improvement (reduction) ≥4.

Results showed overall similar patterns for the two monotherapy studies and the TCS combination study M16-047.

Summary of main studies

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

Table 21   Summary of efficacy for trial M16-045

Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis – MEASURE UP 1		
Study identifier	Study M16-045 (EudraCT Number: 2017-005125-20)	
Design	This is a Phase 3, randomized, double-blind, placebo-controlled multi-center study that will evaluate upadacitinib in adolescents (12 – 17 years of age) and adults (18 – 75 years of age) with moderate to severe AD who are candidates for systemic therapy. The study has a main portion (Main Study) with both adults and adolescents and an Adolescent Substudy, each comprising a 35-day Screening Period, a 16-week Double-Blind period, a 120-week Blinded Extension period, and a 30-day Follow-up Visit. Subjects who meet eligibility criteria were randomized in a 1:1:1 ratio to receive daily oral doses of upadacitinib 15 mg or of upadacitinib 30 mg or matching placebo. At Week 16, subjects in the placebo group were re-randomized in a 1:1 ratio to receive daily oral doses of upadacitinib 15 mg or upadacitinib 30 mg during the Blinded Extension period. Subjects originally in the upadacitinib 15 mg QD and upadacitinib 30 mg QD group can continue their treatment into the Blinded Extension period up to the Week 136 visit.	
	Duration of double-blind, placebo-controlled period: Duration of blinded extension period:	16 weeks Up to 120 weeks
Hypothesis	Superiority	
Treatments groups	Upadacitinib 15 mg QD	Upadacitinib 15 mg QD for up to 136 weeks, n=281
	Upadacitinib 30 mg QD	Upadacitinib 30 mg QD for up to 136 weeks, n=285
	Placebo	Placebo for 16 weeks; n = 281 After Week 16: Placebo / Upadacitinib 15 mg QD; n=118 Placebo / Upadacitinib 30 mg QD; n=121
Endpoints and definitions	Co-primary endpoint (Upadacitinib 15 mg and 30 mg vs placebo)	1. Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index from Baseline (EASI 75) at Week 16 2. 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 Week 16
	Key secondary endpoints (at Week 16 unless otherwise specified)	The key multiplicity adjusted secondary efficacy endpoints (each dose of upadacitinib versus placebo unless otherwise specified) are: 1. 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 2. Proportion of subjects achieving a 90% reduction in EASI (EASI 90) at Week 16 3. Percent change from Baseline of Worst Pruritus NRS at Week 16 4. Percent change in EASI from Baseline at Week 16

		5. Proportion of subjects achieving EASI 75 at Week 2
		6. 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
		7. 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
		8. Proportion of subjects age ≥ 16 years old at screening achiving an improvement (reduction) in Dermatology Life Quality Index (DLQI) ≥ 4 from Baseline at Week 16 for subjects with DLQI ≥ 4 at Baseline.
		9. 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 vs. placebo);
		10. 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 vs. placebo);
		11. Proportion of subjects experiencing a flare, characterized 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 DB Period;
		12. Percent change in Scoring Atopic Dermatitis (SCORAD) from Baseline at Week 16;
		13. Proportion of subjects achieving a Hospital Anxiety and Depression Scale anxiety (HADS-A) < 8 and Hospital Anxiety and Depression Scale-depression (HADS-D) < 8 at Week 16 among subjects with HADS-A ≥ 8 or HADS-D ≥ 8 at Baseline;
		14. 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;
		15. 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;
		16. 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;
		17. 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; 18. 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; 19. Proportion of subjects achieving EASI 100 at Week 16; 20. 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.			
Database lock	Week 16 database lock: Jun 11, 2020				
Results and Analysis					
Analysis description	Primary Analysis				
Analysis population and time point description	Intent to treat (includes all subjects who are randomized in the main study); Week 16 unless otherwise specified				
Effect Estimate per Comparison	Treatment Group	Placebo	Upadacitinib 15 mg QD	Upadacitinib 30 mg QD	
	Number of randomized subjects	281	281	285	
	Co-Primary endpoints:				
	EASI 75 at Week 16 % responders vs placebo: Diff. (95% CI) p-value	16.3	69.6 53.3 (46.4, 60.2) <0.001***	79.7 63.4 (57.1, 69.8) <0.001***	
	vIGA-AD 0/1 at Week 16 % responders vs placebo: Diff. (95% CI) p-value	8.4	48.1 39.8 (33.2, 46.4) <0.001***	62.0 53.6 (47.2, 60.0) <0.001***	

	Key Secondary Endpoints:			
Effect Estimate per Comparison	Worst Pruritus NRS improvement ≥ 4 at Week 16[a]			
	% responders vs placebo: Diff. (95% CI) p-value	11.8	52.2 40.5 (33.5, 47.5) <0.001***	60.0 48.2 (41.3, 55.0) <0.001***
	EASI 90 at Week 16 % responders vs placebo: Diff. (95% CI) p-value	8.1	53.1 45.1 (38.6, 51.7) <0.001***	65.8 57.8 (51.5, 64.1) <0.001***
	Percent change from Baseline in Worst Pruritus NRS at Week 16 LS Mean vs placebo: Diff. (95% CI) p-value	-26.06	-62.79 -36.74 (-49.66, -23.81) <0.001***	-72.04 -45.98 (-58.82, -33.15) <0.001***
	Percent change from Baseline in EASI at Week 16 LS Mean vs placebo: Diff. (95% CI) p-value	-40.71	-80.24 -39.53 (-44.91, -34.15) <0.001***	-87.74 -47.03 (-52.37, -41.70) <0.001***
	EASI 75 at Week 2 % responders vs placebo: Diff. (95% CI) p-value	3.6	38.1 34.5 (28.6, 40.5) <0.001***	47.4 43.9 (37.7, 50.0) <0.001***
	Worst Pruritus NRS Improvement ≥ 4 at Week 1[a] % responders vs placebo: Diff. (95% CI) p-value	0.4	15.0 14.6 (10.3, 18.8) <0.001***	19.6 19.2 (14.6, 23.9) <0.001***
	POEM Improvement ≥ 4 at Week 4[b] % responders vs placebo:	22.8	75.0 52.3	81.4 58.6
	Diff. (95% CI) p-value		(45.2, 59.4) <0.001	(51.9, 65.3) <0.001
	DLQI improvement ≥ 4 at Week 16[c] % responders vs placebo: Diff. (95% CI) p-value	29.0	75.4 46.7 (39.0, 54.4) <0.001***	82.0 53.2 (45.9, 60.5) <0.001***

Worst Pruritus NRS Improvement ≥ 4 at Day 2[d]			
% responders vs placebo: Diff. (95% CI) p-value	3.7	NA NA NA NA	11.8 8.1 (3.8, 12.5) <0.001***
Worst Pruritus NRS Improvement ≥ 4 at Day 3 [d]			
% responders vs placebo: Diff. (95% CI) p-value	3.3	16.4 13.0 (8.1, 17.8) <0.001***	NA NA NA NA
EASI increase ≥ 6.6 (Flare) during DB Period[e]			
% responders vs placebo: Diff. (95% CI) p-value	25.2	1.1 -24.1 (-29.3, -18.9) <0.001***	0.0 -25.2 (-30.3, -20.1) <0.001***
Percent change in SCORAD from Baseline at Week 16			
LS Mean vs placebo: Diff. (95% CI) p-value	-32.68	-65.71 -33.03 (-38.44, -27.61) <0.001***	-73.07 -40.39 (-45.75, -35.03) <0.001***
HADS-A < 8 and HADS-D < 8 at Week 16[f]			
% responders vs placebo: Diff. (95% CI) p-value	14.3	45.5 31.5 (21.4, 41.6) <0.001***	49.2 34.9 (24.8, 45.1) <0.001***
ADerm-IS Sleep improvement ≥ 12 at Week 16[g]			
% responders vs placebo: Diff. (95% CI) p-value	13.2	55.0 41.8 (33.9, 49.7) <0.001***	66.1 52.9 (45.2, 60.6) <0.001***
ADerm-SS Skin Pain improvement ≥ 4 at Week 16[h]			
% responders vs placebo: Diff. (95% CI) p-value	15.0	53.6 38.7 (30.9, 46.5) <0.001***	63.5 48.6 (41.0, 56.1) <0.001***
ADerm-SS TSS-7 improvement ≥ 28 at Week 16[i]			
% responders vs placebo: Diff. (95% CI)	15.0	53.6 38.3 (30.4, 46.2)	67.9 52.9 (45.4, 60.3)

p-value		<0.001***	<0.001***
ADerm-IS Emotional State improvement ≥ 11 at Week 16[j]			
% responders	19.8	62.6	72.6
vs placebo:		42.7	52.5
Diff. (95% CI)		(34.4, 50.9)	(44.7, 60.4)
p-value		<0.001***	<0.001***
ADerm-IS Daily Activities improvement ≥ 14 at Week 16[k]			
% responders	20.3	65.0	73.2
vs placebo:		44.7	53.1
Diff. (95% CI)		(36.2, 53.2)	(44.9, 61.3)
p-value		<0.001***	<0.001***
EASI 100 at Week 16			
% responders	1.8	16.7	27.0
vs placebo:		15.0	25.3
Diff. (95% CI)		(10.4, 19.6)	(20.0, 30.6)
p-value		<0.001***	<0.001***
DLQI 0/1 at Week 16 (Age ≥16)[l]			
% responders	4.4	30.3	41.5
vs placebo:		25.9	37.3
Diff. (95% CI)		(19.7, 32.1)	(30.8, 43.8)
p-value		<0.001***	<0.001***

Notes	
	***: Statistically significant at 0.001. The overall type I error rate of the primary and secondary endpoints for upadacitinib 15 mg and 30 mg was strongly controlled at the 2-sided significance level of 0.05 using a graphical multiple testing procedure
	NA: Not Available
	a. For subjects with Worst Pruritus NRS (Weekly Average) ≥ 4 at Baseline (N=272, 274 and 280 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)
	b. For subjects with POEM ≥ 4 at Baseline (N=276, 278 and 280 for placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)
	c. For subjects with DLQI ≥ 4 at Baseline (N=250, 254 and 256 for placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)
	d. For subjects with Worst Pruritus NRS (Daily) ≥ 4 at Baseline for daily endpoints (N=270, 275 and 279 for placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)
	e. For subjects with EASI ≤ 65.4 at Baseline (N=274, 279 and 285 for placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)
	f. For subjects with HADS-A ≥ 8 or HADS-D ≥ 8 at Baseline (N=126, 145 and 144 for placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)
	g. For subjects with ADerm-IS sleep domain score ≥ 12 at Baseline (N=220, 218 and 218 for placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)
	h. For subjects with ADerm-SS skin pain score ≥ 4 at Baseline (N=233, 237 and 249 for placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)
	i. For subjects with ADerm-SS TSS-7 ≥ 28 at Baseline (N=226, 233 and 246 for placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)
	j. For subjects with ADerm-IS emotional state domain score ≥ 11 at Baseline (N=212, 227 and 226 for placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)
	k. For subjects with ADerm-IS daily activities domain score ≥ 14 at Baseline (N=197, 203 and 205 for placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)
	l. For subjects with DLQI > 1 at Baseline (N=252, 258 and 261 for placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

Table 22   Summary of efficacy for trial M18-891

Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis – MEASURE UP 2	

Study identifier	Study M18-891 (EudraCT Number: 2018-001383-28)	
Design	This is a Phase 3, randomized, double-blind, placebo-controlled multi-center study that will evaluate upadacitinib in adolescents (12 – 17 years of age) and adults (18 – 75 years of age) with moderate to severe AD who are candidates for systemic therapy. The study has a main portion (Main Study) with both adults and adolescents and an Adolescent Substudy, each comprising a 35-day Screening Period, a 16-week Double-Blind period, a 120-week Blinded Extension period, and a 30-day Follow-up Visit. Subjects who meet eligibility criteria were randomized in a 1:1:1 ratio to receive daily oral doses of upadacitinib 15 mg or of upadacitinib 30 mg or matching placebo. At Week 16, subjects in the placebo group were re-randomized in a 1:1 ratio to receive daily oral doses of upadacitinib 15 mg or upadacitinib 30 mg during the Blinded Extension period. Subjects originally in the upadacitinib 15 mg QD and upadacitinib 30 mg QD group can continue their treatment into the Blinded Extension period up to the Week 136 visit.	
	Duration of Double-Blind, placebo-controlled period:	16 weeks
	Duration of Blinded Extension period:	Up to 120 weeks
Hypothesis	Superiority	
Treatments groups	Upadacitinib 15 mg QD	Upadacitinib 15 mg QD for up to 136 weeks, n = 276
	Upadacitinib 30 mg QD	Upadacitinib 30 mg QD for up to 136 weeks, n = 282
	Placebo	Placebo for 16 weeks, n=278 After week 16, Placebo / Upadacitinib 15 mg QD, N=118 Placebo / Upadacitinib 30 mg QD, N=119
Endpoints and definitions	Co-Primary endpoints (Upadacitinib 15 mg and 30 mg vs placebo)	1. Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index from Baseline (EASI 75) at Week 16 2. 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 Week 16
	Key secondary endpoints (at Week 16 unless otherwise specified)	The key multiplicity adjusted secondary efficacy endpoints (each dose of upadacitinib versus placebo unless otherwise specified) are: 1. 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 2. Proportion of subjects achieving EASI 90 at Week 16 3. Percent change from Baseline of Worst Pruritus NRS at Week 16 4. Percent change in EASI from Baseline at Week 16 5. Proportion of subjects achieving EASI 75 at Week 2

		6. 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
		7. 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
		8. 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
		9. 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 vs. placebo)
		10. 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 vs. placebo)
		11. Proportion of subjects experiencing a flare, characterized 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 DB Period
		12. Percent change in Scoring Atopic Dermatitis (SCORAD) from Baseline at Week 16
		13. Proportion of subjects achieving a Hospital Anxiety and Depression Scale-anxiety (HADS-A) < 8 and Hospital Anxiety and Depression Scale-depression (HADS-D) < 8 at Week 16 among subjects with HADS-A ≥ 8 or HADS-D ≥ 8 at Baseline
		14. 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
		15. 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
		16. 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
		17. 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
		18. 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 19. Proportion of subjects achieving EASI 100 at Week 16 20. 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		

Database lock	Week 16 database lock: July 11, 2020
RESULTS AND ANALYSIS	
Analysis description	Primary Analysis
Analysis population and time point description	INTENT TO TREAT (consists of all subjects who are randomized in the Main Study) WEEK 16 (unless otherwise specified)

Effect estimate per comparison	Treatment group	Placebo	Upadacitinib 15 mg QD	Upadacitinib 30 mg QD
	Number of randomized subjects	278	276	282
	Co-Primary endpoints:			
	EASI 75 at Week 16 % responder vs placebo: Diff. (95% CI) p-value	13.3	60.1 46.9 (39.9, 53.9) <0.001***	72.9 59.6 (53.1, 66.2) <0.001***
	vIGA-AD 0/1 at Week 16 % responder vs placebo: Diff. (95% CI) p-value	4.7	38.8 34.0 (27.8, 40.2) <0.001***	52.0 47.4 (41.0, 53.7) <0.001***
	Key secondary endpoints:			
	WORST PRURITUS NRS IMPROVEMENT ≥ 4 AT WEEK 16[a] % responder vs placebo: Diff. (95% CI) p-value	9.1	41.9 32.6 (25.8, 39.4) <0.001***	59.6 50.4 (43.8, 57.1) <0.001***
	EASI 90 at Week 16	5.4	42.4	58.5

	% responder		36.9	53.1
	vs placebo:			
	Diff. (95% CI)		(30.6, 43.3)	(46.7, 59.4)
	p-value		<0.001***	<0.001***
	Percent change from Baseline of Worst Pruritus NRS at Week 16			
	LS Mean	-17.04	-51.20	-66.49
	vs placebo:		-34.16	-49.45
	Diff. (95% CI)		(-40.81, -27.51)	(-56.05, -42.84)
	p-value		<0.001***	<0.001***
	Percent change in EASI from Baseline at Week 16			
	LS Mean	-34.51	-74.13	-84.65
	vs placebo:		-39.62	-50.14
	Diff. (95% CI)		(-45.79, -33.46)	(-56.28, -44.00)
	p-value		<0.001***	<0.001***
	EASI 75 at Week 2			
	% responder	3.6	33.0	44.0
	vs placebo:		29.4	40.4
	Diff. (95% CI)		(23.5, 35.3)	(34.2, 46.5)
	p-value		<0.001***	<0.001***
	WORST PRURITUS NRS IMPROVEMENT ≥ 4 AT WEEK 1[a]			
	% responder	0.7	7.4	15.7
	vs placebo:		6.7	14.9
	Diff. (95% CI)		(3.4, 10.0)	(10.6, 19.3)
	p-value		<0.001***	<0.001***
	POEM IMPROVEMENT ≥ 4 AT WEEK 16[b]			
	% responder	28.7	70.9	83.5
	vs placebo:		42.1	54.7
	Diff. (95% CI)		(34.5, 49.8)	(47.7, 61.7)
	p-value		<0.001***	<0.001***
	DLQI IMPROVEMENT ≥ 4 AT WEEK 16[c]			
	% responder	28.4	71.7	77.6
	vs placebo:		42.8	49.0
	Diff. (95% CI)		(35.0, 50.6)	(41.4, 56.5)
	p-value		<0.001***	<0.001***

Worst Pruritus NRS improvement ≥ 4 at Day 2[d]			
% responder	0.7	NA	7.9
vs placebo:		NA	7.2
Diff. (95% CI)		NA	(3.8, 10.5)
p-value		NA	<0.001***
Worst Pruritus NRS improvement ≥ 4 at Day 3[d]			
% responder	3.0	11.5	NA
vs placebo:		8.6	NA
Diff. (95% CI)		(4.3, 12.9)	NA
p-value		<0.001***	NA
EASI increase ≥ 6.6 (Flare) during DB Period[e]			
% responder	24.5	2.2	1.4
vs placebo:		-22.4	-23.1
Diff. (95% CI)		(-27.8, -16.9)	(-28.4, -17.8)
p-value		<0.001***	<0.001***
Percent change in SCORAD from Baseline at Week 16			
LS Mean	-28.43	-57.90	-68.44
vs placebo:		-29.47	-40.01
Diff. (95% CI)		(-35.24, -23.69)	(-45.80, -34.22)
p-value		<0.001***	<0.001***
HADS-A < 8 and HADS-D < 8 at Week 16[f]			
% responder	11.4	46.0	56.1
vs placebo:		34.4	44.5
Diff. (95% CI)		(24.7, 44.2)	(35.0, 54.1)
p-value		<0.001***	<0.001***
ADerm-IS Sleep improvement ≥ 12 at Week 16[g]			
% responder	12.4	50.2	62.3
vs placebo:		37.9	49.8
Diff. (95% CI)		(30.1, 45.8)	(42.2, 57.3)
p-value		<0.001***	<0.001***
ADerm-SS Skin Pain improvement ≥ 4 at Week 16[h]	13.4	49.4	65.1

% responder vs placebo: Diff. (95% CI)		35.9 (28.2, 43.5)	51.8 (44.4, 59.1)
p-value		<0.001***	<0.001***
ADERM-SS TSS-7 IMPROVEMENT ≥ 28 AT WEEK 16[i]			
% responder vs placebo: Diff. (95% CI)	12.7	53.0 40.3 (32.7, 48.0)	66.2 53.3 (46.0, 60.6)
p-value		<0.001***	<0.001***
ADERM-IS EMOTIONAL STATE IMPROVEMENT ≥ 11 AT WEEK 16[j]			
% responder vs placebo: Diff. (95% CI)	16.7	57.0 40.3 (32.3, 48.3)	71.5 54.8 (47.2, 62.3)
p-value		<0.001***	<0.001***
ADERM-IS DAILY ACTIVITIES IMPROVEMENT ≥ 14 AT WEEK 16[k]			
% responder vs placebo: Diff. (95% CI)	18.9	57.0 37.9 (29.5, 46.3)	69.5 50.6 (42.8, 58.5)
p-value		<0.001***	<0.001***
EASI 100 at Week 16			
% responder vs placebo: Diff. (95% CI)	0.7	14.1 13.4 (9.2, 17.6)	18.8 18.1 (13.5, 22.7)
p-value		<0.001***	<0.001***
DLQI 0/1 AT WEEK 16 (AGE ≥16)[l]			
% responder vs placebo: Diff. (95% CI)	4.7	23.8 19.1 (13.3, 24.9)	37.9 33.3 (26.9, 39.8)
p-value		<0.001***	<0.001***

***: Statistically significant at 0.001. The overall type I error rate of the primary and secondary endpoints for upadacitinib 15 mg and 30 mg was strongly controlled at the 2-sided significance level of 0.05 using a graphical multiple testing procedure

NA: Not Available

a. For subjects with Worst Pruritus NRS (Weekly Average) >= 4 at Baseline (N=274, 270, and 280 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

b. For subjects with Worst Pruritus POEM >= 4 at Baseline (N=268, 268, and 269 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

c. For subjects with DLQI >= 4 at Baseline (N=250, 251, and 251 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

d. For subjects with Worst Pruritus NRS (Daily) >= 4 at Baseline (N=267, 269, and 278 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

e. For subjects with EASI <=65.4 at Baseline (N=269, 274, and 277 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

f. For subjects with HADS-A >= 8 or HADS-D >= 8 at Baseline (N=140, 137, and 146 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

g. For subjects with ADerm-IS Sleep Domain Score >= 12 at Baseline (N=233, 219, and 228 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

h. For subjects with ADerm-SS Skin Pain Score >= 4 at Baseline (N=247, 237, and 238 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

i. For subjects with ADerm-SS TSS-7 >= 28 at Baseline (N=244, 230, and 234 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

j. For subjects with ADerm-IS Emotional State Domain Score >= 11 at Baseline (N=234, 228, and 228 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

k. For subjects with ADerm-IS Daily Activities Domain Score >= 14 at Baseline (N=227, 207, and 223 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

l. For subjects with DLQI > 1 at Baseline (N=257, 252, and 256 for Placebo, Upadacitinib 15 mg, and Upadacitinib 30 mg, respectively)

Table 23   Summary of efficacy for trial M16-047

Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Combination with Topical Corticosteroids in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis – AD UP		
Study identifier	Study M16-047 (EudraCT Number: 2017-005126-37)	
Design	This is a Phase 3, randomized, double-blind, placebo-controlled multi-center study that will evaluate upadacitinib combined with TCS in adolescents (12 – 17 years of age) and adults (18 – 75 years of age) with moderate to severe AD who are candidates for systemic therapy. The study has a main portion (Main Study) with both adults and adolescents and an Adolescent Substudy, each comprising a 35-day Screening Period, a 16-week Double-Blind period, a 120-week Blinded Extension period, and a 30-day Follow-up Visit. Subjects who meet eligibility criteria were randomized in a 1:1:1 ratio to receive concomitant topical corticosteroid with daily oral doses of upadacitinib 15 or 30 mg or matching placebo. At Week 16, subjects in the placebo group were re-randomized in a 1:1 ratio to receive concomitant topical corticosteroid with daily oral doses of upadacitinib 15 mg or 30 mg during the Blinded Extension period. Subjects originally in the upadacitinib 15 mg QD and 30 mg QD group can continue their treatment into the Blinded Extension period up to the Week 136 visit.	
	Duration of double-blind, placebo-controlled period:	16 weeks
	Duration of blinded extension period:	Up to 120 weeks
Hypothesis	Superiority	
Treatments groups	Upadacitinib 15 mg QD + TCS	Concomitant topical corticosteroid with upadacitinib 15 mg QD for up to 136 weeks, n=300
	Upadacitinib 30 mg QD + TCS	Concomitant topical corticosteroid with upadacitinib 30 mg QD for up to 136 weeks, n=297
	Placebo QD + TCS	Placebo for 16 weeks; n=304

		After Week 16:
		Placebo + TCS / Upadacitinib 15 mg QD + TCS; n=143
		Placebo + TCS / Upadacitinib 30 mg QD + TCS; n=137
Endpoints and definitions	Co-primary endpoint (Upadacitinib 15 mg and 30 mg vs placebo)	3. Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index from Baseline (EASI 75) at Week 16 4. 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 Week 16
	Key secondary endpoints (at Week 16 unless otherwise specified)	The key multiplicity adjusted secondary efficacy endpoints (each dose of upadacitinib versus placebo unless otherwise specified) are: 21. 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 22. Proportion of subjects achieving a 90% reduction in EASI (EASI 90) at Week 16 23. Percent change from Baseline of Worst Pruritus NRS at Week 16 24. Percent change in EASI from Baseline at Week 16 25. Proportion of subjects achieving an improvement (reduction) in Worst Pruritus Numerical Rating Scale (NRS) ≥ 4 from Baseline at Week 4 for subjects with Worst Pruritus NRS ≥ 4 at Baseline 26. Proportion of subjects achieving EASI 75 at Week 4 27. Proportion of subjects achieving EASI 75 at Week 2 28. Proportion of subjects achieving EASI 90 at Week 4 29. Proportion of subjects achieving EASI 100 at Week 16 for 30 mg 30. Proportion of subjects achieving an improvement (reduction) in Worst Pruritus Numerical Rating Scale (NRS) ≥ 4 from Baseline at Week 1 for subjects with Worst Pruritus NRS ≥ 4 at Baseline

Database lock	Week 16 database lock: Jul 14, 2020		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat (includes all subjects who are randomized in the main study); Week 16 unless otherwise specified		

Effect Estimate per Comparison	Treatment Group	Placebo	Upadacitinib 15 mg QD + TCS	Upadacitinib 30 mg QD + TCS
	Number of randomized subjects	304	300	297
	Co-Primary endpoints:			
	EASI 75 at Week 16 % responders vs placebo: Diff. (95% CI) p-value	26.4	64.6 38.1 (30.8, 45.4) <0.001***	77.1 50.6 (43.8, 57.4) <0.001***
	vIGA-AD 0/1 at Week 16 % responders vs placebo: Diff. (95% CI) p-value	10.9	39.6 28.5 (22.1, 34.9) <0.001***	58.6 47.6 (41.1, 54.0) <0.001***
	Key Secondary Endpoints:			
	Worst Pruritus NRS improvement ≥ 4 at Week 16[a] % responders vs placebo: Diff. (95% CI) p-value	15.0	51.7 36.8 (29.7, 43.8) <0.001***	63.9 48.8 (41.9, 55.7) <0.001***
	EASI 90 at Week 16 % responders vs placebo: Diff. (95% CI) p-value	13.2	42.8 29.5 (22.8, 36.3) <0.001***	63.1 49.9 (43.3, 56.4) <0.001***
	Percent change from Baseline of Worst Pruritus NRS at Week 16 LS Mean vs placebo: Diff. (95% CI) p-value	-25.07	-58.14 -33.08 (-41.72, -24.44) <0.001***	-66.85 -41.79 (-50.46, -33.11) <0.001***

Percent change from Baseline in EASI at Week 16 LS Mean vs placebo: Diff. (95% CI) p-value	-45.86	-77.99 -32.13 (-37.35, -26.91) <0.001***	-87.31 -41.45 (-46.68, -36.22) <0.001***
Worst Pruritus NRS improvement ≥ 4 at Week 4[a] % responders vs placebo: Diff. (95% CI) p-value	15.0	52.4 37.4 (30.4, 44.3) <0.001***	65.6 50.6 (43.8, 57.3) <0.001***
EASI 75 at Week 4 % responders vs placebo: Diff. (95% CI) p-value	14.8	58.7 43.8 (37.0, 50.5) <0.001***	72.4 57.6 (51.2, 63.9) <0.001***
EASI 75 at Week 2 % responders vs placebo: Diff. (95% CI) p-value	6.9	31.0 24.0 (18.1, 29.9) <0.001***	44.1 37.2 (31.0, 43.3) <0.001***
EASI 90 at Week 4 % responders vs placebo: Diff. (95% CI) p-value	4.9	28.3 23.3 (17.7, 28.9) <0.001***	43.8 38.8 (32.8, 44.8) <0.001***
EASI 100 at Week 16 % responders vs placebo: Diff. (95% CI) p-value	1.3	NA NA NA NA	22.6 21.2 (16.3, 26.1) <0.001***
Worst Pruritus NRS improvement ≥ 4 at Week 1[a] % responders vs placebo: Diff. (95% CI) p-value	3.1	12.2 9.2 (4.9, 13.4) <0.001***	19.2 16.2 (11.3, 21.1) <0.001***
Notes	***: Statistically significant at 0.001. The overall type I error rate of the primary and secondary endpoints for upadacitinib 15 mg and 30 mg was strongly controlled at the 2-sided significance level of 0.05 using a graphical multiple testing procedure NA: Not Available a. For subjects with Worst Pruritus NRS (Weekly Average) ≥ 4 at Baseline (N=294, 288, 291 for Placebo + TCS, Upadacitinib 15 mg + TCS, and Upadacitinib 30 mg + TCS, respectively)		

Analysis performed across trials (pooled analyses and meta-analysis)

Double-blind period – pooled monotherapy study results

Integrated efficacy analyses of the two monotherapy studies (Study M16-045 and Study M18-891) were conducted on all common endpoints in those studies for the Placebo-Controlled Population.

Results for the co-primary endpoints are shown in the table and figures below.

Table 24   Primary Efficacy Results from the Integrated Phase 3 Monotherapy Studies 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

CI = confidence interval; EASI = Eczema Area and Severity Index; UPA = upadacitinib; vs. = versus

Notes: 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.

95% CI for adjusted difference and p-value are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (study, Baseline vIGA-AD categories, and age [adolescent vs. adult]) for the comparison of two treatment groups. 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.
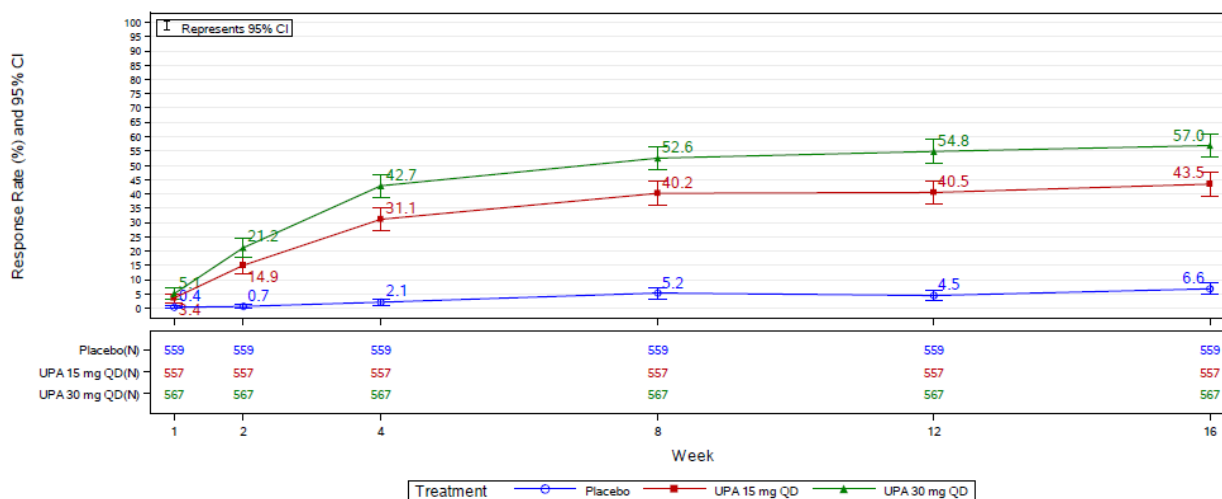
CI = confidence interval; NRI-C = non-responder imputation due to COVID-19; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis

Note: 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.

Figure 19   Subjects Who Achieved vIGA-AD 0/1 Through Week 16 (ISE of Monotherapy Studies, Placebo-Controlled Population, NRI-C)
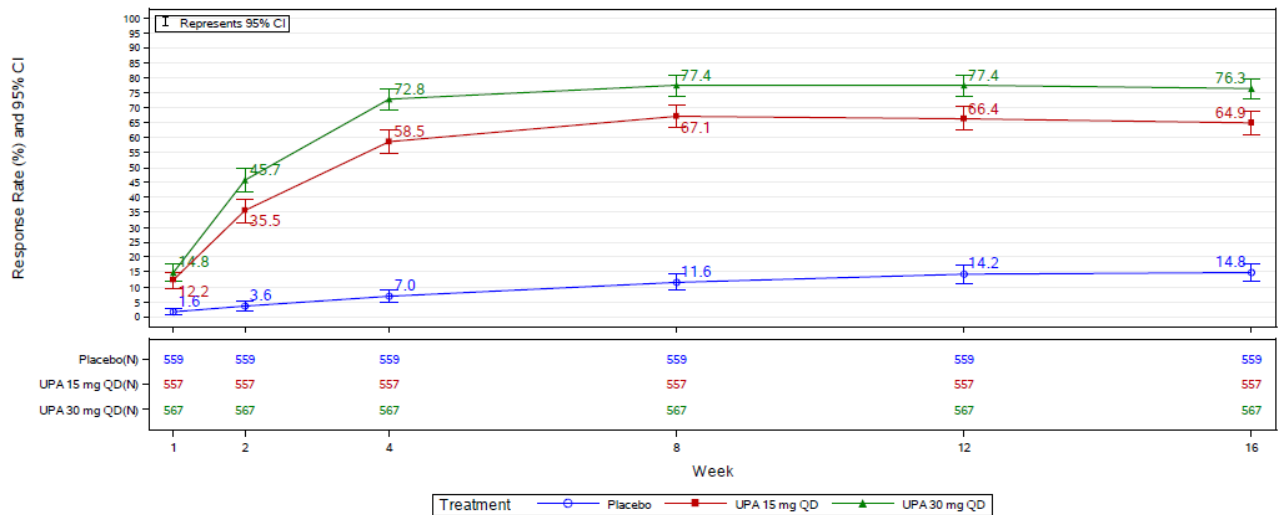
CI = confidence interval; EASI = Eczema Area and Severity Index; NRI-C = non-responder imputation due to COVID-19

Note: 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.

Figure 20   Subjects Achieving EASI 75 Through Week 16 (ISE of Monotherapy Studies, Placebo-Controlled Population, NRI-C)

The results of the two pivotal mono-therapy results were very similar. Hence, pooling the results of these studies is deemed adequate.

Post-hoc analyses to evaluate the efficacy benefit with Upadacitinib 30 mg

The MAH presented post-hoc analyses performed to evaluate the efficacy benefit with the upadacitinib 30 mg dose compared with the 15 mg dose. This was based on integrated data from the Phase 3 monotherapy studies (Studies M16-045 and M18-891). For all point estimates depicted, those for 30 mg were higher compared to those for 15 mg. The CIs were non-overlapping for all skin clearance and itch reduction endpoints as well as for most health-related quality of life endpoints.
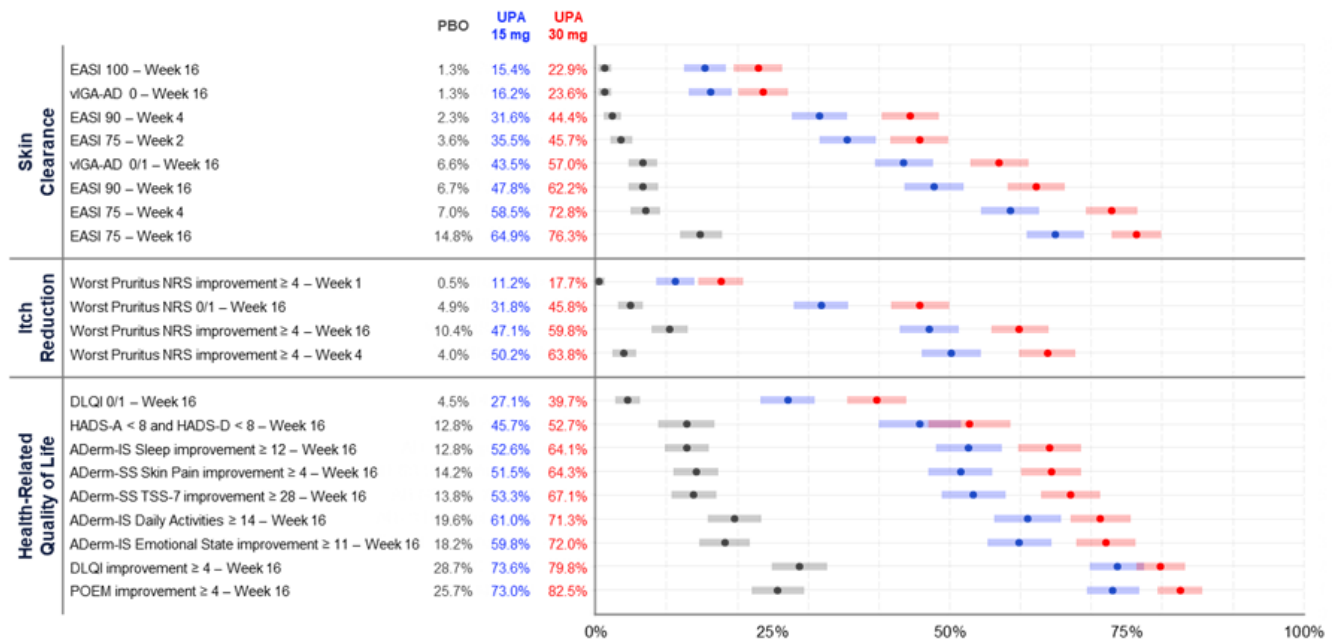
Figure 21   Efficacy of Upadacitinib 30 mg and 15 mg Across AD Domains in the PBO-controlled Period (Integrated Phase 3 Monotherapy Studies, NRI-C)

Summary of results for all three studies, Double-Blind period

Summary figures were provided, showing the results for the co-primary endpoints for all three studies.
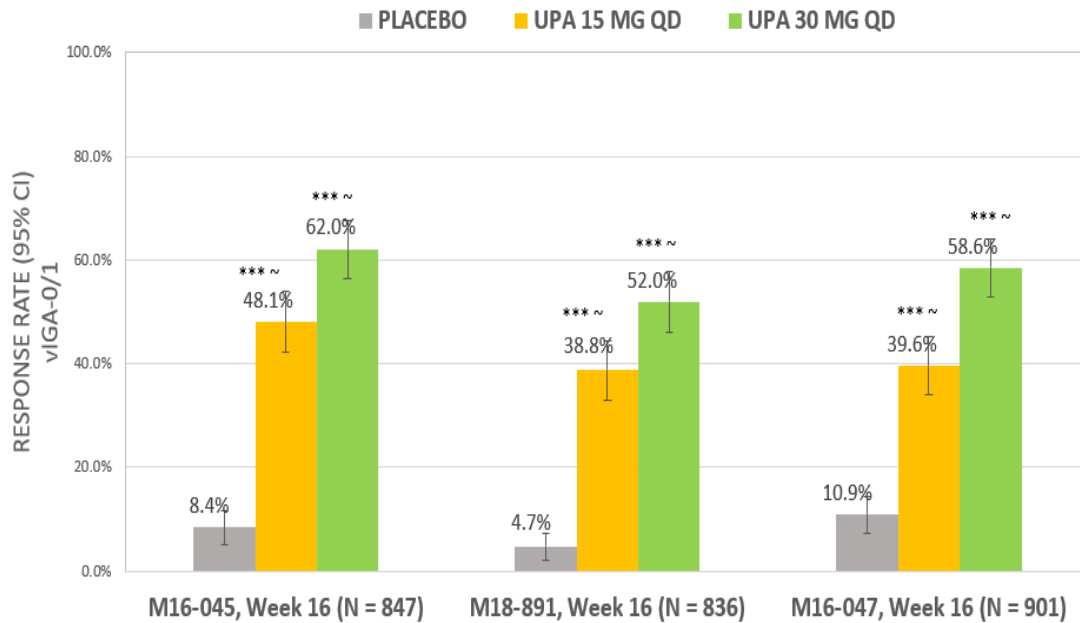
*** p < 0.001 for upadacitinib vs. placebo.

~ Statistically significant in the multiplicity-controlled analysis.

Figure 22   vIGA-AD 0/1 at Week 16 for Pivotal Phase 3 Studies (NRI-C, ITT_M Population)
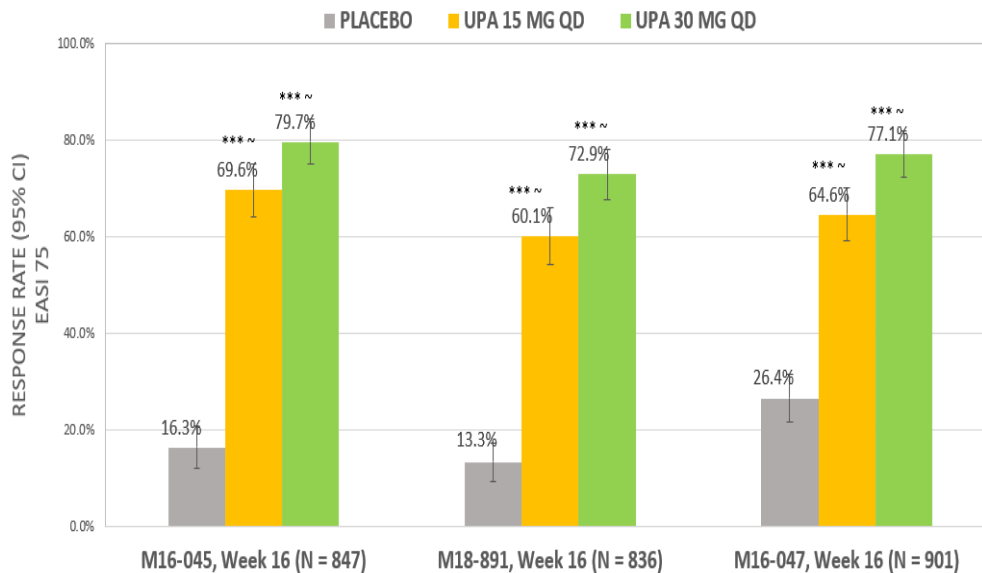
*** p < 0.001 for upadacitinib vs. placebo.

~ Statistically significant in the multiplicity-controlled analysis.

Figure 23   Improvement in EASI 75 at Week 16 for the Pivotal Phase 3 Studies (NRI-C, ITT_M Population)
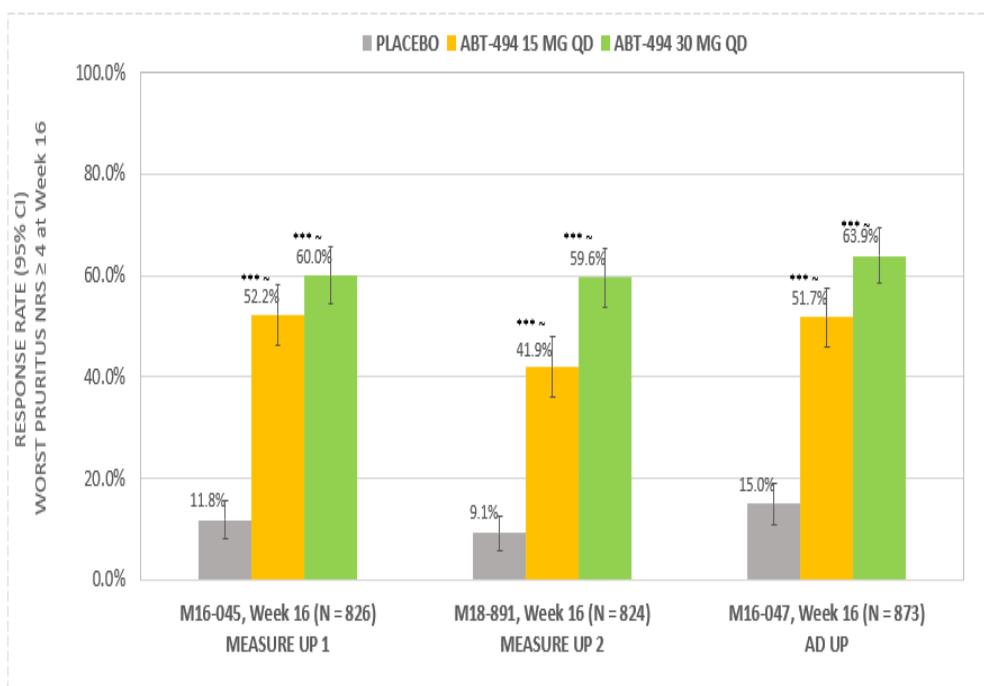
*** p <0.001 for upadacitinib vs. placebo.

~ Statistically significant in the multiplicity-controlled analysis.

Figure 24 Worst Pruritus NRS Improvement (Reduction) ⩾ 4 at Week 16 for Pivotal Phase 3 Studies (NRI-C; ITT_M Population)

Blinded extension period

No pooled Week 52 results for EASI 75 and vIGA-AD for the mono-therapy studies based on the updated data were included in the response. Blinded extension data per study are presented above.

Clinical studies in special populations

Efficacy results in adolescents

Double-Blind period

There were 124 adolescents included in Study M16-045 and 104 in Study M18-891. Pooled results for adolescents included in the two mono-therapy studies are presented below.

Table 25   Skin Clearance and Disease Activity – Adolescents (ISE of Monotherapy Studies, Placebo-Controlled Population, NRI-C)

Endpoint, NRI-C Treatment	N	Response % (95% CI)	Response Rate Difference Compared to Placebo	
			Adjusted Difference % (95% CI)	p-value
vIGA-AD of 0/1 clear at Week 16				
Placebo	76	5.3 (0.2, 10.3)		
UPA 15 mg	75	40.0 (28.9, 51.1)	34.5 (22.6, 46.3)	< 0.001
UPA 30 mg	77	66.3 (55.6, 77.0)	61.0 (49.8, 72.1)	< 0.001
EASI 75 at Week 16				
Placebo	76	10.8 (3.7, 17.8)		
UPA 15 mg	75	69.3 (58.9, 79.8)	58.5 (46.1, 70.9)	< 0.001
UPA 30 mg	77	79.6 (70.4, 88.7)	68.8 (57.5, 80.0)	< 0.001
EASI 75 at Week 2				
Placebo	76	2.6 (0.0, 6.2)		
UPA 15 mg	75	34.7 (23.9, 45.4)	32.0 (20.9, 43.1)	< 0.001
UPA 30 mg	77	50.6 (39.5, 61.8)	48.0 (36.4, 59.5)	< 0.001
EASI 90 at Week 16				
Placebo	76	1.5 (0.0, 4.5)		
UPA 15 mg	75	44.0 (32.8, 55.2)	42.4 (30.9, 54.0)	< 0.001
UPA 30 mg	77	69.7 (59.3, 80.2)	68.2 (57.8, 78.5)	< 0.001
EASI 100 at Week 16				
Placebo	76	0		
UPA 15 mg	75	10.7 (3.7, 17.7)	10.6 (3.8, 17.5)	0.002
UPA 30 mg	77	26.1 (16.2, 35.9)	25.9 (16.7, 35.0)	< 0.001
EASI, % change from Baseline to Week 16				
Placebo	34	–41.94 (–50.46, –33.43)		
UPA 15 mg	68	–77.73 (–84.44, –71.03)	–35.79 (–46.62, –24.97) 5.483	< 0.001
UPA 30 mg	67	–87.77 (–94.49, –81.05)	–45.83 (–56.67, –34.99) 5.492	< 0.001
SCORAD, % change at Week 16				
Placebo	32	–28.42 (–36.75, –20.09)		
UPA 15 mg	68	–61.21 (–67.17, –55.25)	–32.79 (–43.03, –22.55) 5.188	< 0.001
UPA 30 mg	63	–76.63 (–82.82, –70.44)	–48.22 (–58.57, –37.86) 5.247	< 0.001

CI = confidence interval; EASI = Eczema Area and Severity Index; MMRM = Mixed-Effect Model Repeated Measures; NRI = non-responder imputation due to COVID-19; SCORAD = Scoring Atopic Dermatitis; SE = standard error; vIGA-AD = Validated Investigator Global Assessment of AD

Note: 95% CI for response rate was the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there were missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there were no missing data due to COVID-19. The between group difference 95% CI and p-value were based on Cochran- Mantel-Haenszel test.

As in adults, both upadacitinib doses showed a clearly statistically significant difference vs. placebo for the co-primary endpoints and most secondary endpoints. A dose-related difference was observed also in this group. The same pattern was observed in the TCS combination study (see below). In adolescents, only the 15 mg QD dose is recommended in the proposed SmPC, which did not seem justified from an efficacy point of view (please refer to benefit-risk discussion).

Blinded extension period

Updated week 52 results for adolescents are presented below for each study.

Table 26   Long-Term Efficacy Summary for Adolescents at Week 52 for Study M16-045 (12 to <18 Years Old)

Selected Efficacy Endpoints	PBO/UPA 15 mg n (%) or LS Mean (SE)	PBO/UPA 30 mg n (%) or LS Mean (SE)	UPA 15 mg n (%) or LS Mean (SE)	UPA 30 mg n (%) or LS Mean (SE)
EASI 75				
OC	N = 14 10 (71.4)	N = 13 11 (84.6)	N = 33 29 (87.9)	N = 37 33 (89.2)
MI	N = 8 7 (83.8)	N = 11 9 (78.5)	N = 42 30 (72.3)	N = 42 36 (85.6)
vIGA-AD 0/1				
OC	N = 14 8 (57.1)	N = 13 9 (69.2)	N = 33 20 (60.6)	N = 37 28 (75.7)
MI	N = 8 7 (85.8)	N = 11 8 (74.8)	N = 42 22 (52.9)	N = 42 31 (72.7)
Worst Pruritus NRS improvement ≥ 4				
OC	N = 14 9 (64.3)	N = 13 8 (61.5)	N = 32 19 (59.4)	N = 38 28 (73.7)
MI	N = 8 5 (64.6)	N = 11 6 (54.8)	N = 40 21 (51.6)	N = 42 30 (70.6)
EASI 90				
OC	N = 14 9 (64.3)	N = 13 11 (84.6)	N = 33 23 (69.7)	N = 37 29 (78.4)
MI	N = 8 6 (79.2)	N = 11 7 (67.6)	N = 42 24 (56.5)	N = 42 31 (72.7)
Percent change from Baseline of Worst Pruritus NRS				
OC	N = 14 -65.89 (11.879)	N = 13 -68.57 (12.355)	N = 33 -50.84 (7.757)	N = 38 -71.55 (7.209)
MMRM	N = 7 -65.22 (16.757)	N = 7 -69.29 (15.308)	N = 31 -52.85 (7.942)	N = 38 - 70.26 (7.297)
Percent change in EASI from Baseline				
OC	N = 14 -87.66 (4.488)	N = 13 -87.95 (4.590)	N = 33 -89.29 (2.892)	N = 37 -91.93 (2.761)
MMRM	N = 7 -93.88 (6.040)	N = 7 -88.83 (5.555)	N = 31 -88.26 (2.806)	N = 37 -91.79 (2.589)
Percent change in SCORAD from Baseline				
OC	N = 14 -68.76 (6.553)	N = 14 - 75.25 (6.627)	N = 35 - 70.81 (4.161)	N = 37 - 80.30 (4.031)
MMRM	N = 7 -77.99 (9.219)	N = 8 -75.00 (8.995)	N = 33 -69.70 (4.278)	N = 37 -79.99 (4.010)
EASI 100				
OC	N = 14 3 (21.4)	N = 13 6 (46.2)	N = 33 11 (33.3)	N = 37 17 (45.9)
MI	N = 8 2 (25.0)	N = 11 3 (27.6)	N = 42 10 (24.2)	N = 42 17 (40.6)
Worst Pruritus NRS of 0/1				
OC	N = 14 7 (50.0)	N = 13 7 (53.8)	N = 33 11 (33.3)	N = 38 22 (57.9)
MI	N = 8 3 (39.2)	N = 11 5 (48.8)	N = 41 12 (29.8)	N = 42 23 (54.1)

Note: For the OC approach, N = the number of subjects (Main Study only) with observed clinical measurements (up to treatment discontinuation) at Week 52 in each treatment group. For the MI approach, N= the number of intent-to-treat subjects of the main study in each treatment group with one exception: Placebo subjects who have been rescued in the DB Period and re-randomized at Week 16 were not included in the above summaries, because placebo subjects rescued during the DB Period may bring forward confounding effects of the prior rescue treatment.

Table 27   Long-Term Efficacy Summary for Adolescents at Week 52 for Study M18-891 (12 to <18 Years Old)

Selected Efficacy Endpoints	PBO/UPA 15 mg n (%) or LS Mean (SE)	PBO/UPA 30 mg n (%) or LS Mean (SE)	UPA 15 mg n (%) or LS Mean (SE)	UPA 30 mg n (%) or LS Mean (SE)
EASI 75				
OC	N = 16	N = 15	N = 27	N = 29
	14 (87.5)	14 (93.3)	22 (81.5)	26 (89.7)
MI	N = 7	N = 10	N = 33	N = 35
	4 (57.1)	9 (90.0)	23 (68.6)	28 (78.6)
vIGA-AD 0/1				
OC	N = 16	N = 15	N = 27	N = 29
	5 (31.3)	8 (53.3)	15 (55.6)	25 (86.2)
MI	N = 7	N = 10	N = 33	N = 35
	3 (42.9)	7 (70.0)	17 (51.3)	27 (76.4)
Worst Pruritus NRS improvement ≥ 4				
OC	N = 16	N = 15	N = 24	N = 28
	6 (37.5)	10 (66.7)	13 (54.2)	18 (64.3)
MI	N = 7	N = 10	N = 30	N = 34
	3 (42.9)	7 (70.0)	15 (49.7)	19 (56.2)
EASI 90				
OC	N = 16	N = 15	N = 27	N = 29
	6 (37.5)	10 (66.7)	18 (66.7)	24 (82.8)
MI	N = 7	N = 10	N = 33	N = 35
	2 (28.6)	8 (80.0)	18 (53.8)	25 (72.0)
Percent change from Baseline of Worst Pruritus NRS				
OC	N = 16	N = 15	N = 26	N = 29
	-46.12 (10.512)	-67.08 (10.919)	-49.37 (8.233)	-75.23 (7.854)
MMRM	N = 6	N = 9	N = 25	N = 27
	-51.61 (19.168)	-75.57 (15.395)	-45.70 (9.172)	-69.47 (8.855)
Percent change in EASI from Baseline				
OC	N = 16	N = 15	N = 27	N = 29
	-77.84 (6.392)	-91.15 (6.798)	-87.71 (4.889)	-89.89 (4.735)
MMRM	N = 6	N = 9	N = 26	N = 27
	-57.92 (23.519)	-96.06 (19.197)	-76.60 (10.975)	-78.61 (10.645)
Percent change in SCORAD from Baseline				
OC	N = 14	N = 15	N = 26	N = 27
	-63.29 (6.364)	-74.32 (6.220)	-72.81 (4.671)	-80.31 (4.648)
ANCOVA	N = 5	N = 9	N = 27	N = 26
	-67.97 (13.067)	-85.66 (9.709)	-65.99 (5.601)	-82.43 (5.742)
EASI 100				
OC	N = 16	N = 15	N = 27	N = 29
	1 (6.3)	5 (33.3)	12 (44.4)	15 (51.7)
MI	N = 7	N = 10	N = 33	N = 35
	1 (14.3)	5 (50.0)	12 (36.4)	15 (43.0)
Worst Pruritus NRS of 0/1				
OC	N = 16	N = 15	N = 26	N = 29
	3 (18.8)	7 (46.7)	11 (42.3)	17 (58.6)

Selected Efficacy Endpoints	PBO/UPA 15 mg n (%) or LS Mean (SE)	PBO/UPA 30 mg n (%) or LS Mean (SE)	UPA 15 mg n (%) or LS Mean (SE)	UPA 30 mg n (%) or LS Mean (SE)
MI	N = 7	N = 10	N = 33	N = 35
	2 (28.6)	6 (60.0)	12 (36.2)	17 (47.9)

Note: For the OC approach, N = the number of subjects (Main Study only) with observed clinical measurements (up to treatment discontinuation) at Week 52 in each treatment group. For the MI approach, N= the number of intent-to-treat subjects of the main study in each treatment group with one exception: Placebo subjects who have been rescued in the DB Period and re-randomized at Week 16 were not included in the above summaries, because placebo subjects rescued during the DB Period may bring forward confounding effects of the prior rescue treatment.

Table 28   Long-Term Efficacy Summary for Adolescents at Week 52 for Study M16-047 (12 to <18 Years Old)

Selected Efficacy Endpoints	PBO+TCS / UPA 15 MG+TCS n (%) or LS Mean (SE)	PBO+TCS / UPA 30 MG+TCS n (%) or LSMEAN (SE)	UPA 15 MG+TCS n (%) or LSMEAN (SE)	UPA 30 MG+TCS n (%) or LSMEAN (SE)
EASI 75				
OC	N=16	N=15	N=34	N=35
	14 (87.5)	14 (93.3)	25 (73.5)	30 (85.7)
MI	N=16	N=14	N=39	N=37
	13 (79.6)	13 (90.7)	22 (57.3)	28 (76.3)
vIGA-AD 0/1				
OC	N=16	N=15	N=34	N=35
	10 (62.5)	9 (60.0)	13 (38.2)	19 (54.3)
MI	N=16	N=14	N=39	N=37
	9 (58.1)	8 (57.4)	12 (31.9)	17 (46.1)
Worst Pruritus NRS improvement ≥ 4				
OC	N=16	N=15	N=33	N=31
	11 (68.8)	13 (86.7)	18 (54.5)	19 (61.3)
MI	N=15	N=14	N=36	N=33
	9 (60.9)	11 (77.9)	17 (47.2)	18 (55.9)
EASI 90				
OC	N=16	N=15	N=34	N=35
	12 (75.0)	13 (86.7)	17 (50.0)	24 (68.6)
MI	N=16	N=14	N=39	N=37
	10 (64.0)	11 (76.0)	14 (36.0)	22 (59.7)
Percent change from Baseline of Worst Pruritus NRS				
OC	N=17	N=15	N=34	N=34
	-59.13 (11.398)	-72.44 (12.104)	-43.12 (8.053)	-60.20 (8.085)
MMRM	N=13	N=12	N=29	N=31
	-58.12 (16.566)	-71.09 (17.350)	-27.98 (11.165)	-61.94 (10.894)
Percent change in EASI from Baseline				
OC	N=16	N=15	N=34	N=35
	-85.80 (5.657)	-92.04 (5.844)	-79.27 (3.884)	-87.68 (3.830)
MMRM	N=12	N=12	N=29	N=32
	-87.01 (5.707)	-90.57 (5.880)	-76.73 (3.797)	-88.33 (3.657)
EASI 100				
OC	N=16	N=15	N=34	N=35
	4 (25.0)	3 (20.0)	2 (5.9)	10 (28.6)
MI	N=16	N=14	N=39	N=37
	3 (18.8)	2 (14.5)	2 (5.1)	9 (24.4)
Worst Pruritus NRS 0/1				
OC	N=17	N=15	N=34	N=32
	4 (23.5)	10 (66.7)	7 (20.6)	13 (40.6)
MI	N=16	N=14	N=37	N=34
	4 (25.0)	9 (61.0)	6 (16.7)	12 (35.6)
Percent change in SCORAD from Baseline				
OC	N=17	N=15	N=35	N=34

Selected Efficacy Endpoints	PBO+TCS / UPA 15 MG+TCS n (%) or LS Mean (SE)	PBO+TCS / UPA 30 MG+TCS n (%) or LSMEAN (SE)	UPA 15 MG+TCS n (%) or LSMEAN (SE)	UPA 30 MG+TCS n (%) or LSMEAN (SE)
	-64.04 (6.601)	-73.10 (6.976)	-56.59 (4.585)	-72.63 (4.633)
MMRM	N=14	N=12	N=31	N=32
	-76.51 (6.696)	-67.84 (7.242)	-54.77 (4.518)	-72.78 (4.456)

Note: For the OC approach, N = the number of subjects (Main Study only) with observed clinical measurements (up to treatment discontinuation) at Week 52 in each treatment group.

Sub-group analyses based on pooled data for the mono-therapy studies

Subgroup analyses were conducted for the co-primary endpoints vIGA-AD 0/1 and EASI 75 at Week 16 by the baseline subgroups listed below for the Placebo-Controlled Population in the integrated analysis sets:

- Age Group 1 (< 18 years, ≥ 18)

- Age Group 2 (< 18 years, ≥ 18 – < 40 years, ≥ 40 – < 65 years, ≥ 65 years)

- Sex (male, female)

- Body mass index (BMI) (normal: < 25, overweight: ≥ 25 – < 30, obese: ≥ 30)

- Race (White, Asian, Black, and Other)

- Weight (< 60 kg, 60 – 100 kg, > 100 kg)

- Geographic regions ([US/PR/Canada], Japan, China [Mainland], and Other)

- Baseline vIGA-AD (< 4, 4)

- Baseline EASI (< median, ≥ median)

- hsCRP (< median, ≥ median)

- Previous systemic therapy (with and without)

- Subjects who reported an intolerance to at least one prior TCS or TCI therapy

- Subjects who reported an inadequate response to at least one prior topical treatment.

If fewer than 10% of subjects were in age category ≥ 65 years or BMI category ≥ 30, they were combined with the adjacent subgroup. If the race category had fewer than 10% of subjects, it was combined in the "other" category. For any subgroup, if there were zero subjects within a stratum in any treatment group within a study, the CMH model was not adjusted for study and stratification factors. Results are shown in the figures below.

	Placebo #	UPA 15 mg QD #	INT_P
Age Group 1 (years) < 18	4/76 (5.3%)	30/75 (40.0%)	0.845
Age Group 1 (years) >= 18	33/483 (6.9%)	212/482 (44.0%)	
Age Group 2 (years) < 18	4/76 (5.3%)	30/75 (40.0%)	0.633
Age Group 2 (years) 18 - < 40	16/306 (5.3%)	129/308 (42.0%)	
Age Group 2 (years) >= 40	17/177 (9.5%)	83/174 (47.7%)	
Sex Male	20/298 (6.8%)	126/312 (40.4%)	0.280
Sex Female	17/261 (6.4%)	116/245 (47.5%)	
BMI (kg/m^2) Normal: < 25	16/250 (6.3%)	138/295 (46.9%)	0.244
BMI (kg/m^2) Overweight: 25 - < 30	14/169 (8.5%)	59/156 (37.8%)	
BMI (kg/m^2) Obese: >= 30	7/133 (5.3%)	45/105 (42.9%)	
Race White	27/377 (7.2%)	171/366 (46.8%)	0.258
Race Asian	4/125 (3.2%)	47/128 (36.7%)	
Race Other	6/57 (10.6%)	24/63 (38.1%)	
Weight (kg) < 60 Kg	9/115 (7.7%)	63/128 (49.2%)	0.599
Weight (kg) 60 - 100 Kg	26/380 (6.9%)	156/375 (41.7%)	
Weight (kg) > 100 Kg	2/63 (3.2%)	23/54 (42.6%)	
Geographic Regions US/Puerto Rico/Canada	17/236 (7.2%)	99/234 (42.3%)	0.842
Geographic Regions Japan	0/14	5/15 (33.3%)	
Geographic Regions China	1/14 (7.1%)	9/14 (64.3%)	
Geographic Regions Other	19/295 (6.5%)	129/294 (44.0%)	
Baseline vIGA-AD 3 (Moderate)	23/281 (8.1%)	139/280 (49.6%)	0.901
Baseline vIGA-AD 4 (Severe)	14/278 (5.1%)	103/277 (37.3%)	
Baseline EASI < Median (25.8)	24/293 (8.2%)	130/269 (48.4%)	0.746
Baseline EASI >= Median (25.8)	13/265 (4.9%)	112/288 (38.9%)	
hsCRP < Median (1.51)	25/270 (9.3%)	126/280 (45.1%)	0.057
hsCRP >= Median (1.51)	12/289 (4.2%)	116/277 (41.9%)	
Previous Systemic Therapy With	17/300 (5.6%)	118/275 (42.9%)	0.402
Previous Systemic Therapy Without	20/259 (7.8%)	124/282 (44.1%)	
Intolerance to TCSs/TCIs Yes	6/50 (12.0%)	17/39 (43.6%)	0.172
Intolerance to TCSs/TCIs No	31/509 (6.1%)	225/518 (43.5%)	
Inadequately Responding to Topical Treatments Yes	30/476 (6.3%)	219/495 (44.3%)	0.172
Inadequately Responding to Topical Treatments No	7/83 (8.4%)	23/62 (37.1%)	

CI = confidence interval for adjusted difference, DB = double blind; NRI-C = non-responder imputation incorporating MI to handle missing data due to COVID-19; QD = once daily; TCS = topical corticosteroids; UPA = upadacitinib; vIGA-AD = validated investigator global assessment of atopic dermatitis

\#   Placebo plus TCS and UPA 30 mg QD plus TCS represents n/N (xx.x%)/

Notes: CI calculated according to the Cochran-Mantel-Haenszel Test adjusted for strata.

INT_P is the P-value for the interaction between subgroup and treatment. It was calculated using a logistic regression with visit measurement at Week 16 as response variable and treatment, subgroup, strata, and treatment by subgroup interaction as factors.

Figure 25   Proportion of Subjects on Upadacitinib 15 mg Who Achieved a vIGA-AD 0/1 at Week 16, by Subgroup (ISE of Monotherapy Studies, Placebo-Controlled Population NRI-C)

	Proportion (%)	Risk Difference (95% CI)	Placebo #	UPA 30 mg QD #	INT_P
Age Group 1 (years) < 18			4/76 (5.3%)	51/77 (66.0%)	0.239
Age Group 1 (years) >= 18			33/483 (6.9%)	272/490 (55.6%)	
Age Group 2 (years) < 18			4/76 (5.3%)	51/77 (66.0%)	0.238
Age Group 2 (years) 18 - < 40			16/306 (5.3%)	172/315 (54.5%)	
Age Group 2 (years) >= 40			17/177 (9.5%)	100/175 (57.4%)	
Sex Male			20/298 (6.8%)	164/317 (51.6%)	0.130
Sex Female			17/261 (6.4%)	159/250 (63.7%)	
BMI (kg/m^2) Normal: < 25			16/250 (6.3%)	173/291 (59.5%)	0.616
BMI (kg/m^2) Overweight: 25 - < 30			14/169 (8.5%)	92/165 (55.6%)	
BMI (kg/m^2) Obese: >= 30			7/133 (5.3%)	57/108 (52.8%)	
Race White			27/377 (7.2%)	225/389 (57.9%)	0.492
Race Asian			4/125 (3.2%)	69/133 (51.8%)	
Race Other			6/57 (10.6%)	29/45 (64.4%)	
Weight (kg) < 60 Kg			9/115 (7.7%)	82/134 (61.1%)	0.837
Weight (kg) 60 - 100 Kg			26/380 (6.9%)	219/388 (56.5%)	
Weight (kg) > 100 Kg			2/63 (3.2%)	22/45 (48.9%)	
Geographic Regions US/Puerto Rico/Canada			17/236 (7.2%)	136/241 (56.4%)	0.930
Geographic Regions Japan			0/14	8/16 (50.0%)	
Geographic Regions China			1/14 (7.1%)	8/17 (47.1%)	
Geographic Regions Other			19/295 (6.5%)	171/293 (58.4%)	
Baseline vIGA-AD 3 (Moderate)			23/281 (8.1%)	176/280 (62.7%)	0.867
Baseline vIGA-AD 4 (Severe)			14/278 (5.1%)	147/287 (51.4%)	
Baseline EASI < Median (25.8)			24/293 (8.2%)	183/273 (67.2%)	0.507
Baseline EASI >= Median (25.8)			13/265 (4.9%)	140/294 (47.5%)	
hsCRP < Median (1.51)			25/270 (9.3%)	176/289 (60.9%)	0.123
hsCRP >= Median (1.51)			12/289 (4.2%)	147/278 (52.9%)	
Previous Systemic Therapy With			17/300 (5.6%)	149/274 (54.3%)	0.762
Previous Systemic Therapy Without			20/259 (7.8%)	174/293 (59.5%)	
Intolerance to TCSs/TCIs Yes			6/50 (12.0%)	20/29 (69.0%)	0.725
Intolerance to TCSs/TCIs No			31/509 (6.1%)	303/538 (56.3%)	
Inadequately Responding to Topical Treatments Yes			30/476 (6.3%)	285/497 (57.2%)	0.308
Inadequately Responding to Topical Treatments No			7/83 (8.4%)	39/70 (55.1%)	

○ Placebo (N=559)   ▲ UPA 30 mg QD (N=567)

CI = confidence interval for adjusted difference, DB = double blind; NRI-C = non-responder imputation incorporating MI to handle missing data due to COVID-19; QD = once daily; TCS = topical corticosteroids; UPA = upadacitinib; vIGA-AD = validated investigator global assessment of atopic dermatitis

Placebo plus TCS and UPA 30 mg QD plus TCS represents n/N (xx.x%). Notes: CI calculated according to the Cochran-Mantel-Haenszel Test adjusted for strata.

   INT_P is the P-value for the interaction between subgroup and treatment. It was calculated using a logistic regression with visit measurement at Week 16 as response variable and treatment, subgroup, strata, and treatment by subgroup interaction as factors.

Figure 26   Proportion of Subjects on Upadacitinib 30 mg Who Achieved a vIGA-AD 0/1 at Week 16, by Subgroup (ISE of Monotherapy Studies, Placebo-Controlled Population NRI-C)

Figure 27 — proizvод column headers:

	Proportion (%)	Risk Difference (95% CI)	Placebo #	UPA 15 mg QD #	INT_P
Age Group 1 (years) < 18			8/76 (11.0%)	52/75 (69.3%)	0.197
Age Group 1 (years) >= 18			75/483 (15.4%)	310/482 (64.2%)	
Age Group 2 (years) < 18			8/76 (11.0%)	52/75 (69.3%)	0.255
Age Group 2 (years) 18 - < 40			40/306 (12.9%)	194/308 (62.8%)	
Age Group 2 (years) >= 40			35/177 (19.8%)	116/174 (66.7%)	
Sex Male			40/298 (13.5%)	197/312 (63.1%)	0.898
Sex Female			43/261 (16.4%)	165/245 (67.2%)	
BMI (kg/m^2) Normal: < 25			40/250 (15.9%)	208/295 (70.4%)	0.219
BMI (kg/m^2) Overweight: 25 - < 30			26/169 (15.3%)	87/156 (55.8%)	
BMI (kg/m^2) Obese: >= 30			17/133 (12.9%)	67/105 (63.8%)	
Race White			52/377 (13.9%)	236/366 (64.4%)	0.150
Race Asian			16/125 (13.0%)	86/128 (67.2%)	
Race Other			14/57 (25.2%)	40/63 (63.5%)	
Weight (kg) < 60 Kg			21/115 (18.4%)	101/128 (78.9%)	0.126
Weight (kg) 60 - 100 Kg			56/380 (14.7%)	226/375 (60.2%)	
Weight (kg) > 100 Kg			6/63 (9.5%)	35/54 (64.8%)	
Geographic Regions US/Puerto Rico/Canada			39/236 (16.6%)	146/234 (62.4%)	0.357
Geographic Regions Japan			1/14 (7.1%)	11/15 (73.3%)	
Geographic Regions China			2/14 (14.3%)	11/14 (78.6%)	
Geographic Regions Other			41/295 (13.8%)	194/294 (65.8%)	
Baseline vIGA-AD 3 (Moderate)			53/281 (19.0%)	183/280 (65.4%)	0.036
Baseline vIGA-AD 4 (Severe)			30/278 (10.6%)	179/277 (64.5%)	
Baseline EASI < Median (25.8)			53/293 (18.1%)	175/269 (64.9%)	0.078
Baseline EASI >= Median (25.8)			30/265 (11.3%)	187/288 (64.9%)	
hsCRP < Median (1.51)			47/270 (17.2%)	183/280 (65.2%)	0.223
hsCRP >= Median (1.51)			36/289 (12.6%)	179/277 (64.6%)	
Previous Systemic Therapy With			37/300 (12.3%)	176/275 (64.0%)	0.215
Previous Systemic Therapy Without			46/259 (17.7%)	186/282 (65.8%)	
Intolerance to TCSs/TCIs Yes			9/50 (18.0%)	26/39 (66.7%)	0.680
Intolerance to TCSs/TCIs No			74/509 (14.5%)	336/518 (64.8%)	
Inadequately Responding to Topical Treatments Yes			75/476 (15.7%)	323/495 (65.2%)	0.394
Inadequately Responding to Topical Treatments No			8/83 (9.6%)	39/62 (62.9%)	

○ Placebo (N=559)   ■ UPA 15 mg QD (N=557)

CI = confidence interval for adjusted difference, DB = double blind; EASI = Eczema Area and Severity Index; NRI-C = non-responder imputation incorporating MI to handle missing data due to COVID-19; QD = once daily; TCS = topical corticosteroids; UPA = upadacitinib

\#   Placebo plus TCS and UPA 30 mg QD plus TCS represents n/N (xx.x%).

Notes: CI calculated according to the Cochran-Mantel-Haenszel Test adjusted for strata.

INT_P is the P-value for the interaction between subgroup and treatment. It was calculated using a logistic regression with visit measurement at Week 16 as response variable and treatment, subgroup, strata, and treatment by subgroup interaction as factors.

Figure 27 Proportion of Subjects on Upadacitinib 15 mg Who Achieved EASI 75 at Week 16, by Subgroup (ISE of Monotherapy Studies, Placebo-Controlled Population NRI-C)

CI = confidence interval for adjusted difference, DB = double blind; EASI = Eczema Area and Severity Index; NRI-C = non-responder imputation incorporating MI to handle missing data due to COVID-19; QD = once daily; TCS = topical corticosteroids; UPA = upadacitinib; vIGA-AD = validated investigator global assessment of atopic dermatitis

\#   Placebo plus TCS and UPA 30 mg QD plus TCS represents n/N (xx.x%).

Notes: CI calculated according to the Cochran-Mantel-Haenszel Test adjusted for strata

INT_P is the P-value for the interaction between subgroup and treatment. It was calculated using a logistic regression with visit measurement at Week 16 as response variable and treatment, subgroup, strata, and treatment by subgroup interaction as factors.

Figure 28   Proportion of Subjects on Upadacitinib 30 mg Who Achieved EASI 75 at Week 16, by Subgroup (ISE of Monotherapy Studies, Placebo-Controlled Population NRI-C)

Study M16-047

Corresponding sub-group analyses were performed for the TCS combination study as for the mono-therapy studies.

In the TCS combination study there were 116 adolescents included. A similar pattern for the efficacy results as in the mono-therapy studies was observed (refer to figures below).

Proportion (%) | Risk Difference (95% CI) | Placebo + TCS # | UPA 15 mg QD + TCS # | INT_P

Subgroup	Placebo + TCS #	UPA 15 mg QD + TCS #	INT_P
Age Group 1 (years) < 18	3/40 (7.5%)	12/39 (30.8%)	0.925
Age Group 1 (years) >= 18	30/264 (11.4%)	107/261 (40.9%)	
Age Group 2 (years) < 18	3/40 (7.5%)	12/39 (30.8%)	0.879
Age Group 2 (years) 18 -< 40	13/156 (8.4%)	67/176 (38.1%)	
Age Group 2 (years) >= 40	17/108 (15.7%)	40/85 (46.7%)	
Sex Male	16/178 (9.0%)	62/179 (34.5%)	0.902
Sex Female	17/126 (13.6%)	57/121 (47.1%)	
BMI (kg/m^2) Normal: < 25	16/148 (10.8%)	59/154 (38.4%)	0.941
BMI (kg/m^2) Overweight: 25 -< 30	11/93 (11.8%)	37/91 (40.3%)	
BMI (kg/m^2) Obese: >= 30	6/62 (9.9%)	22/54 (40.7%)	
Race White	29/225 (12.9%)	87/204 (42.7%)	0.378
Race Asian	2/60 (3.6%)	22/64 (34.4%)	
Race Other	2/19 (10.5%)	10/32 (30.3%)	
Weight (kg) < Median (73.11)	18/146 (12.4%)	61/151 (40.3%)	0.901
Weight (kg) >= Median (73.11)	15/157 (9.6%)	58/149 (38.9%)	
Geographic Regions US/Puerto Rico/Canada	16/108 (15.0%)	48/108 (44.4%)	0.977
Geographic Regions Japan	2/18 (11.1%)	7/16 (43.8%)	
Geographic Regions China	0/18	7/17 (41.2%)	
Geographic Regions Other	15/160 (9.4%)	57/159 (35.7%)	
Baseline vIGA-AD 3 (Moderate)	20/141 (14.3%)	74/143 (51.7%)	0.453
Baseline vIGA-AD 4 (Severe)	13/163 (8.0%)	45/157 (28.6%)	
Baseline EASI < Median (25.8)	23/149 (15.5%)	80/155 (51.7%)	0.804
Baseline EASI >= Median (25.8)	10/155 (6.5%)	39/145 (26.7%)	
hsCRP < Median (1.41)	12/152 (7.9%)	67/161 (41.7%)	0.043*
hsCRP >= Median (1.41)	21/152 (13.9%)	52/139 (37.2%)	
Previous Systemic Therapy With	18/157 (11.5%)	61/171 (35.8%)	0.307
Previous Systemic Therapy Without	15/147 (10.3%)	58/129 (44.7%)	
Intolerance to TCSs/TCIs Yes	1/18 (5.6%)	7/23 (30.4%)	0.685
Intolerance to TCSs/TCIs No	32/286 (11.2%)	112/277 (40.4%)	
Inadequately Responding to Topical Treatments Yes	31/267 (11.7%)	108/256 (42.2%)	0.798
Inadequately Responding to Topical Treatments No	2/37 (5.4%)	11/44 (24.6%)	

○ Placebo + TCS (N=304)   ■ UPA 15 mg QD + TCS (N=300)

Note: vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis; EASI = Eczema Area and Severity Index.

NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.

95% CI for adjusted difference is 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 with exceptions: 1) Age subgroup analyses are stratified by Baseline vIGA-AD categories; 2) Baseline vIGA-AD subgroup analysis is stratified by age [adolescent vs. adult]. The calculation is 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. For any subgroup, if there are zero subjects within a stratum in any treatment 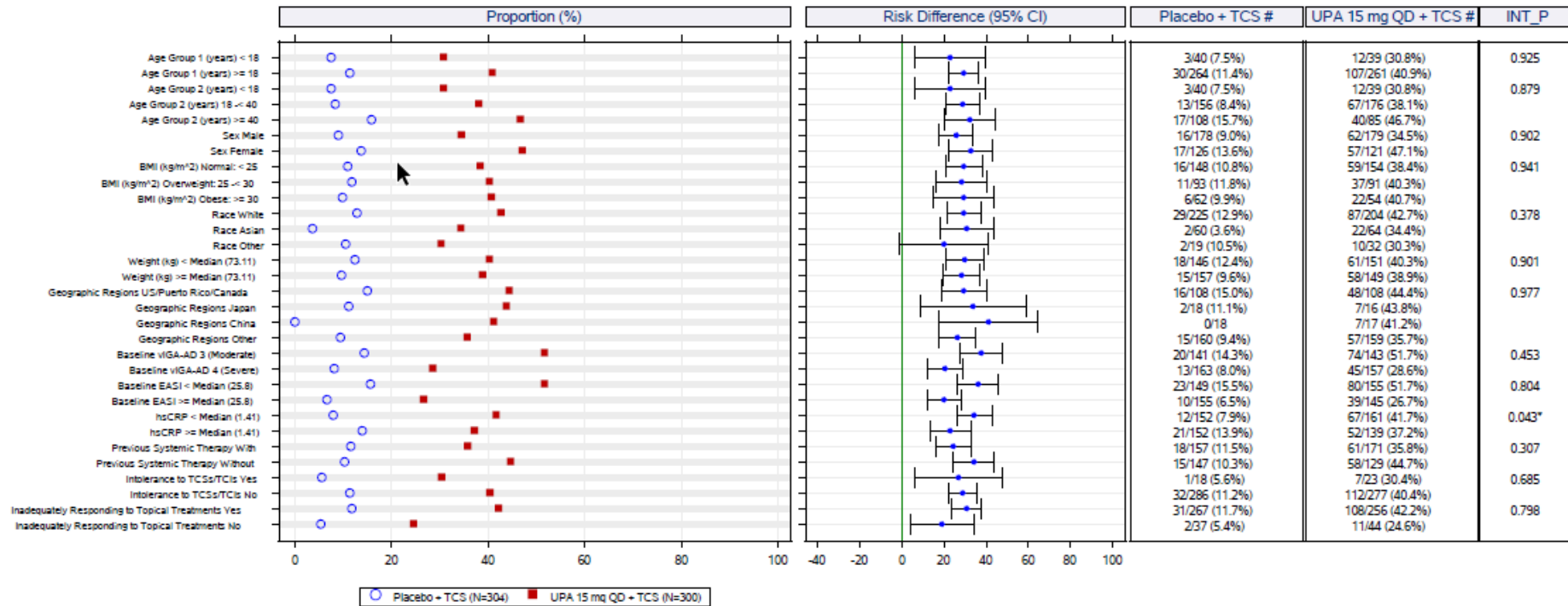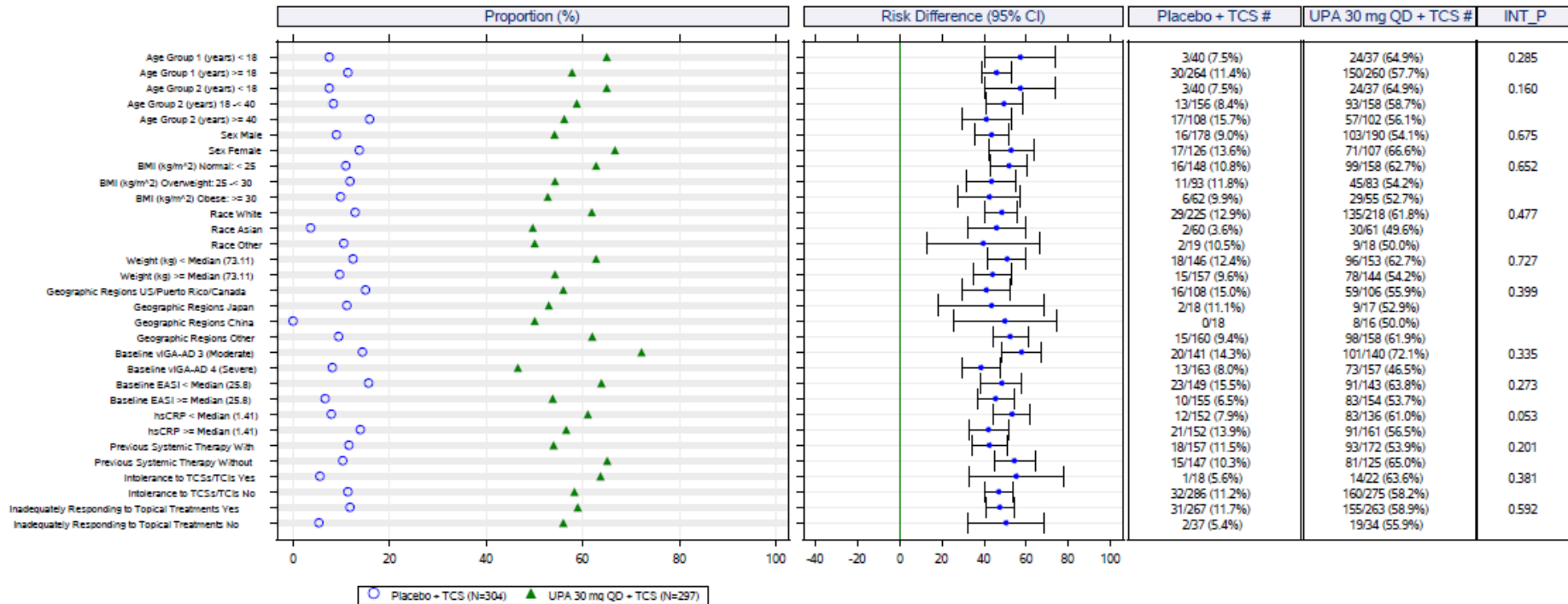group, the CMH model will not be adjusted for the stratification factors. INT_P is P-value for interaction between subgroup and treatment is calculated using a logistic regression with visit measurement at Week 16 as response variable, treatment, subgroup, Baseline vIGA-AD categories, age [adolescent vs. adult], and treatment by subgroup interaction as factors with exceptions: 1) Age subgroup analyses are stratified by Baseline vIGA-AD categories; 2) Baseline vIGA-AD subgroup analysis is stratified by age [adolescent vs. adult]. Logistic regression is 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. For multiple imputation data, one-sided P-value is calculated based on Student's t-distribution from PROC MIANALYZE procedure according to the Chi-square test using the Wilson-Hilferty transformation.

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

Figure 29 Proportion of Subjects on Upadacitinib 15 mg Achieving vIGA-AD of 0 or 1 with at Least 2 Grades of Reduction from Baseline at Week 16 by Subgroup (NRI-C) (ITT_M Population), M16-047

	Proportion (%)	Risk Difference (95% CI)	Placebo + TCS #	UPA 30 mg QD + TCS #	INT_P
Age Group 1 (years) < 18			3/40 (7.5%)	24/37 (64.9%)	0.285
Age Group 1 (years) >= 18			30/264 (11.4%)	150/260 (57.7%)	
Age Group 2 (years) < 18			3/40 (7.5%)	24/37 (64.9%)	0.160
Age Group 2 (years) 18 -< 40			13/156 (8.4%)	93/158 (58.7%)	
Age Group 2 (years) >= 40			17/108 (15.7%)	57/102 (56.1%)	
Sex Male			16/178 (9.0%)	103/190 (54.1%)	0.675
Sex Female			17/126 (13.6%)	71/107 (66.6%)	
BMI (kg/m^2) Normal: < 25			16/148 (10.8%)	99/158 (62.7%)	0.652
BMI (kg/m^2) Overweight: 25 -< 30			11/93 (11.8%)	45/83 (54.2%)	
BMI (kg/m^2) Obese: >= 30			6/62 (9.9%)	29/55 (52.7%)	
Race White			29/225 (12.9%)	135/218 (61.8%)	0.477
Race Asian			2/60 (3.6%)	30/61 (49.6%)	
Race Other			2/19 (10.5%)	9/18 (50.0%)	
Weight (kg) < Median (73.11)			18/146 (12.4%)	96/153 (62.7%)	0.727
Weight (kg) >= Median (73.11)			15/157 (9.6%)	78/144 (54.2%)	
Geographic Regions US/Puerto Rico/Canada			16/108 (15.0%)	59/106 (55.9%)	0.399
Geographic Regions Japan			2/18 (11.1%)	9/17 (52.9%)	
Geographic Regions China			0/18	8/16 (50.0%)	
Geographic Regions Other			15/160 (9.4%)	98/158 (61.9%)	
Baseline vIGA-AD 3 (Moderate)			20/141 (14.3%)	101/140 (72.1%)	0.335
Baseline vIGA-AD 4 (Severe)			13/163 (8.0%)	73/157 (46.5%)	
Baseline EASI < Median (25.8)			23/149 (15.5%)	91/143 (63.8%)	0.273
Baseline EASI >= Median (25.8)			10/155 (6.5%)	83/154 (53.7%)	
hsCRP < Median (1.41)			12/152 (7.9%)	83/136 (61.0%)	0.053
hsCRP >= Median (1.41)			21/152 (13.9%)	91/161 (56.5%)	
Previous Systemic Therapy With			18/157 (11.5%)	93/172 (53.9%)	0.201
Previous Systemic Therapy Without			15/147 (10.3%)	81/125 (65.0%)	
Intolerance to TCSs/TCIs Yes			1/18 (5.6%)	14/22 (63.6%)	0.381
Intolerance to TCSs/TCIs No			32/286 (11.2%)	160/275 (58.2%)	
Inadequately Responding to Topical Treatments Yes			31/267 (11.7%)	155/263 (58.9%)	0.592
Inadequately Responding to Topical Treatments No			2/37 (5.4%)	19/34 (55.9%)	

Placebo + TCS (N=304)   UPA 30 mg QD + TCS (N=297)

Note: vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis; EASI = Eczema Area and Severity Index.
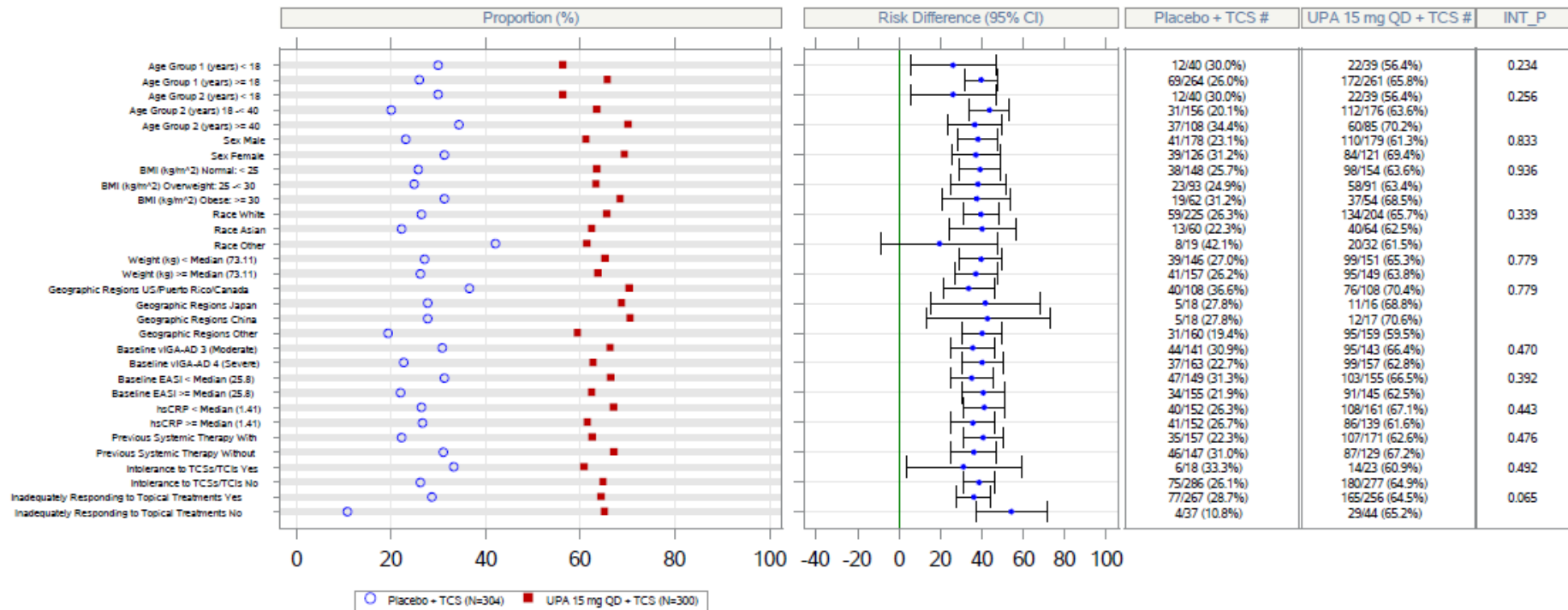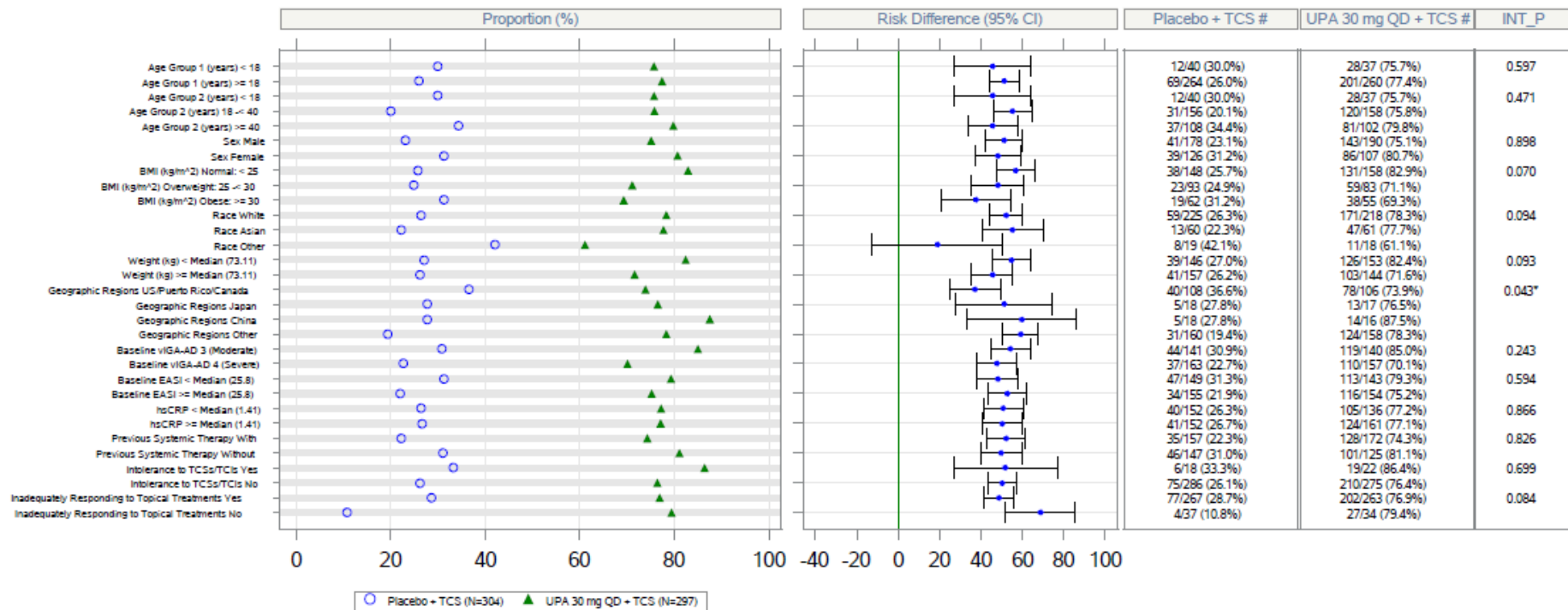
NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.

95% CI for adjusted difference is 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 with exceptions: 1) Age subgroup analyses are stratified by Baseline vIGA-AD categories; 2) Baseline vIGA-AD subgroup analysis is stratified by age [adolescent vs. adult]. The calculation is 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. For any subgroup, if there are zero subjects within a stratum in any treatment group, the CMH model will not be adjusted for the stratification factors.

INT_P is P-value for interaction between subgroup and treatment is calculated using a logistic regression with visit measurement at Week 16 as response variable, treatment, subgroup, Baseline vIGA-AD categories, age [adolescent vs. adult], and treatment by subgroup interaction as factors with exceptions: 1) Age subgroup analyses are stratified by Baseline vIGA-AD categories; 2) Baseline vIGA-AD subgroup analysis is stratified by age [adolescent vs. adult]. Logistic regression is 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. For multiple imputation data, one-sided P-value is calculated based on Student's t-distribution from PROC MIANALYZE procedure according to the Chi-square test using the Wilson-Hilferty transformation.

Placebo + TCS and UPA 30 mg QD + TCS represents n/N (xx.x%).

Figure 30   Proportion of Subjects on Upadacitinib 30 mg Achieving vIGA-AD of 0 or 1 with at Least 2 Grades of Reduction from Baseline at Week 16 by Subgroup (NRI-C) (ITT_M Population), M16-047

Forest plot with table:

	Proportion (%)	Risk Difference (95% CI)	Placebo + TCS #	UPA 15 mg QD + TCS #	INT_P
Age Group 1 (years) < 18			12/40 (30.0%)	22/39 (56.4%)	0.234
Age Group 1 (years) >= 18			69/264 (26.0%)	172/261 (65.8%)	
Age Group 2 (years) < 18			12/40 (30.0%)	22/39 (56.4%)	0.256
Age Group 2 (years) 18 -< 40			31/156 (20.1%)	112/176 (63.6%)	
Age Group 2 (years) >= 40			37/108 (34.4%)	60/85 (70.2%)	
Sex Male			41/178 (23.1%)	110/179 (61.3%)	0.833
Sex Female			39/126 (31.2%)	84/121 (69.4%)	
BMI (kg/m^2) Normal: < 25			38/148 (25.7%)	98/154 (63.6%)	0.936
BMI (kg/m^2) Overweight: 25 -< 30			23/93 (24.9%)	58/91 (63.4%)	
BMI (kg/m^2) Obese: >= 30			19/62 (31.2%)	37/54 (68.5%)	
Race White			59/225 (26.3%)	134/204 (65.7%)	0.339
Race Asian			13/60 (22.3%)	40/64 (62.5%)	
Race Other			8/19 (42.1%)	20/32 (61.5%)	
Weight (kg) < Median (73.11)			39/146 (27.0%)	99/151 (65.3%)	0.779
Weight (kg) >= Median (73.11)			41/157 (26.2%)	95/149 (63.8%)	
Geographic Regions US/Puerto Rico/Canada			40/108 (36.6%)	76/108 (70.4%)	0.779
Geographic Regions Japan			5/18 (27.8%)	11/16 (68.8%)	
Geographic Regions China			5/18 (27.8%)	12/17 (70.6%)	
Geographic Regions Other			31/160 (19.4%)	95/159 (59.5%)	
Baseline vIGA-AD 3 (Moderate)			44/141 (30.9%)	95/143 (66.4%)	0.470
Baseline vIGA-AD 4 (Severe)			37/163 (22.7%)	99/157 (62.8%)	
Baseline EASI < Median (25.8)			47/149 (31.3%)	103/155 (66.5%)	0.392
Baseline EASI >= Median (25.8)			34/155 (21.9%)	91/145 (62.5%)	
hsCRP < Median (1.41)			40/152 (26.3%)	108/161 (67.1%)	0.443
hsCRP >= Median (1.41)			41/152 (26.7%)	86/139 (61.6%)	
Previous Systemic Therapy With			35/157 (22.3%)	107/171 (62.6%)	0.476
Previous Systemic Therapy Without			46/147 (31.0%)	87/129 (67.2%)	
Intolerance to TCSs/TCIs Yes			6/18 (33.3%)	14/23 (60.9%)	0.492
Intolerance to TCSs/TCIs No			75/286 (26.1%)	180/277 (64.9%)	
Inadequately Responding to Topical Treatments Yes			77/267 (28.7%)	165/256 (64.5%)	0.065
Inadequately Responding to Topical Treatments No			4/37 (10.8%)	29/44 (65.2%)	

○ Placebo + TCS (N=304)   ■ UPA 15 mg QD + TCS (N=300)

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 adjusted difference is 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 with exceptions: 1) Age subgroup analyses are stratified by Baseline vIGA-AD categories; 2) Baseline vIGA-AD subgroup analysis is stratified by age [adolescent vs. adult]. The calculation is 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. For any subgroup, if there are zero subjects within a stratum in any treatment group, the CMH model will not be adjusted for the stratification factors.
INT_P is P-value for interaction between subgroup and treatment is calculated using a logistic regression with visit measurement at Week 16 as response variable, treatment, subgroup, Baseline vIGA-AD categories, age [adolescent vs. adult], and treatment by subgroup interaction as factors with exceptions: 1) Age subgroup analyses are stratified by Baseline vIGA-AD categories; 2) Baseline vIGA-AD subgroup analysis is stratified by age [adolescent vs. adult]. Logistic regression is 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. For multiple imputation data, one-sided P-value is calculated based on Student's t-distribution from PROC MIANALYZE procedure according to the Chi-square test using the Wilson-Hilferty transformation.
Placebo + TCS and UPA 15 mg QD + TCS represents n/N (xx.x%).

Figure 31   Proportion of Subjects on Upadacitinib 15 mg Achieving EASI 75 at Week 16 by Subgroup (NRI-C) (ITT_M Population), M16-047

Figure: Proportion (%) | Risk Difference (95% CI) | Placebo + TCS # | UPA 30 mg QD + TCS # | INT_P

Subgroup	Placebo + TCS #	UPA 30 mg QD + TCS #	INT_P
Age Group 1 (years) < 18	12/40 (30.0%)	28/37 (75.7%)	0.597
Age Group 1 (years) >= 18	69/264 (26.0%)	201/260 (77.4%)	
Age Group 2 (years) < 18	12/40 (30.0%)	28/37 (75.7%)	0.471
Age Group 2 (years) 18 -< 40	31/156 (20.1%)	120/158 (75.8%)	
Age Group 2 (years) >= 40	37/108 (34.4%)	81/102 (79.8%)	
Sex Male	41/178 (23.1%)	143/190 (75.1%)	0.898
Sex Female	39/126 (31.2%)	86/107 (80.7%)	
BMI (kg/m^2) Normal: < 25	38/148 (25.7%)	131/158 (82.9%)	0.070
BMI (kg/m^2) Overweight: 25 -< 30	23/93 (24.9%)	59/83 (71.1%)	
BMI (kg/m^2) Obese: >= 30	19/62 (31.2%)	38/55 (69.3%)	
Race White	59/225 (26.3%)	171/218 (78.3%)	0.094
Race Asian	13/60 (22.3%)	47/61 (77.7%)	
Race Other	8/19 (42.1%)	11/18 (61.1%)	
Weight (kg) < Median (73.11)	39/146 (27.0%)	126/153 (82.4%)	0.093
Weight (kg) >= Median (73.11)	41/157 (26.2%)	103/144 (71.6%)	
Geographic Regions US/Puerto Rico/Canada	40/108 (36.6%)	78/106 (73.9%)	0.043*
Geographic Regions Japan	5/18 (27.8%)	13/17 (76.5%)	
Geographic Regions China	5/18 (27.8%)	14/16 (87.5%)	
Geographic Regions Other	31/160 (19.4%)	124/158 (78.3%)	
Baseline vIGA-AD 3 (Moderate)	44/141 (30.9%)	119/140 (85.0%)	0.243
Baseline vIGA-AD 4 (Severe)	37/163 (22.7%)	110/157 (70.1%)	
Baseline EASI < Median (25.8)	47/149 (31.3%)	113/143 (79.3%)	0.594
Baseline EASI >= Median (25.8)	34/155 (21.9%)	116/154 (75.2%)	
hsCRP < Median (1.41)	40/152 (26.3%)	105/136 (77.2%)	0.866
hsCRP >= Median (1.41)	41/152 (26.7%)	124/161 (77.1%)	
Previous Systemic Therapy With	35/157 (22.3%)	128/172 (74.3%)	0.826
Previous Systemic Therapy Without	46/147 (31.0%)	101/125 (81.1%)	
Intolerance to TCSs/TCIs Yes	6/18 (33.3%)	19/22 (86.4%)	0.699
Intolerance to TCSs/TCIs No	75/286 (26.1%)	210/275 (76.4%)	
Inadequately Responding to Topical Treatments Yes	77/267 (28.7%)	202/263 (76.9%)	0.084
Inadequately Responding to Topical Treatments No	4/37 (10.8%)	27/34 (79.4%)	

○ Placebo + TCS (N=304)   ▲ UPA 30 mg QD + TCS (N=297)

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 adjusted difference is 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 with exceptions: 1) Age subgroup analyses are stratified by Baseline vIGA-AD categories; 2) Baseline vIGA-AD subgroup analysis is stratified by age [adolescent vs. adult]. The calculation is 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. For any subgroup, if there are zero subjects within a stratum in any treatment group, the CMH model will not be adjusted for the stratification factors.

INT_P is P-value for interaction between subgroup and treatment is calculated using a logistic regression with visit measurement at Week 16 as response variable, treatment, subgroup, Baseline vIGA-AD categories, age [adolescent vs. adult], and treatment by subgroup interaction as factors with exceptions: 1) Age subgroup analyses are stratified by Baseline vIGA-AD categories; 2) Baseline vIGA-AD subgroup analysis is stratified by age [adolescent vs. adult]. Logistic regression is 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. For multiple imputation data, one-sided P-value is calculated based on Student's t-distribution from PROC MIANALYZE procedure according to the Chi-square test using the Wilson-Hilferty transformation.

Placebo + TCS and UPA 30 mg QD + TCS represents n/N (xx.x%).

Figure 32   Proportion of Subjects on Upadacitinib 30 mg Achieving EASI 75 at Week 16 by Subgroup (NRI-C) (ITT_M Population), M16-047

The sub-group analyses performed were relevant, based on demographic (age, gender, BMI, race, weight) and disease-related factors (Baseline vIGA-AD, Baseline EASI, hsCRP, previous systemic therapy, intolerance to at least one prior TCS/TCI, inadequate response to at least one topical treatment) and geographic region. These analyses were performed within each study separately and in a combined analysis for the two mono-therapy studies.

Consistent treatment effects in all pre-specified subgroups in favour of upadacitinib 30 mg and upadacitinib 15 mg were observed when compared to placebo for the co-primary endpoints of vIGA-AD 0/1 and EASI 75. Some groups were small (e.g. the Chinese and Japanese groups), resulting in wide confidence intervals. In study M16-047 (TCS study), all 95% confidence intervals (CIs) excluded zero, except for the race sub-group category "other" (that consisted of Black or African American, Indian/Alaska Native and Native Hawaiian or other Pacific Islander or multiple) for most comparison. The number of subjects in this category was low (69 subjects).

In adolescents as in adults, both upadacitinib doses showed a clearly statistically significant difference vs. placebo for the co-primary endpoints and most secondary endpoints. A dose-related difference was observed also in this group. The same pattern was observed in the TCS combination study.

For the group of subjects aged ≥65 years, only few subjects were included and if fewer than 10% of subjects were in age category ≥ 65 years they were combined with the adjacent subgroup.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of upadacitinib in moderate to severe atopic dermatitis is supported by one Phase 2b dose finding study (M16-048) and three pivotal Phase studies; two studies with upadacitinib used as mono-therapy (M16-045 and M18-891) while the third one (M16-047) is a study with upadacitinib used together with topical corticosteroids (TCS).

All studies, including the dose-finding study, had a randomized, double-blind, parallel-group, placebo-controlled, multi-centre design, which was considered adequate by the CHMP. An active comparator was not included in any study. This could have been of interest but is not viewed by the CHMP as a requirement.

The objective of the dose response study was to evaluate the safety and efficacy of multiple doses of upadacitinib monotherapy versus placebo in the treatment of adults with moderate to severe AD. The primary endpoint was the mean percent (%) change from Baseline (Day 1) in EASI score at Week 16. The EASI score is a well-known score for assessment of AD; corresponding largely to "PASI" in plaque psoriasis. Evaluation of the mean percent change from baseline in EASI score at Week 16 is therefore agreed by the CHMP. Use of a continuous rather than a dichotomous endpoint in a dose-finding study is endorsed. The secondary endpoints (e.g. the proportion of subjects achieving an EASI 75 response at Week 16, the 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 and proportion of subjects achieving EASI 50/75/90 response at Weeks 8 and 16) are also well known from other AD studies and are endorsed by the CHMP.

Since the design was rather similar for all Phase 3 studies, they are described together in the following, with differences indicated when applicable.

The population included was fairly similar across all studies. The inclusion and exclusion criteria are adequate to define a population with moderate to severe AD in need of a systemic treatment. Disease severity criteria stipulated that patients should have an EASI score ≥ 16, a vIGA-AD score ≥ 3, ≥ 10% BSA of AD involvement at the Screening and Baseline Visits and a baseline weekly average of daily Worst Pruritus NRS ≥ 4. Patients should also have a documented history (within 6 months of the Baseline Visit) of inadequate response to TCS or TCI *or* documented systemic treatment for atopic dermatitis within 6 months prior to the Baseline Visit. The mono-therapy studies included also subjects for whom topical treatments were medically inadvisable. In the MAH's response it was clarified how these criteria were documented and which definitions were used for inadequate response. The procedures to establish inadequate response seem adequate. No formal, specific criterion, e.g. an IGA score above a certain level despite a defined course of TCS, was used to define inadequate response. However, the subjects anyway had to meet the inclusion criteria with respect to IGA and EASI above certain thresholds for inclusion.

In the study with upadacitinib used together with topical corticosteroids (TCS), patients should have had inadequate response to TCS/TCI and are then required to use TCS/TCI as basic standard of care treatment in the study. Patients in the placebo arm may thus be a priori expected to have a poor response. Nevertheless, the CHMP acknowledged that the design will to some extent reflect clinical practice, i.e. many patients are not being sufficiently treated with TCS/TCI and a systemic treatment is added, which will likely often be administered on top of topical therapy, at least initially.

The exclusion criteria are also deemed adequate and reflect the contraindications and warnings already in place for Rinvoq in the SmPC for the already approved RA indication. This relates e.g. to laboratory tests, previous or concomitant treatments, and pregnancy.

The phase 3 studies included a 35-day screening period, a 16-week double-blind Period, and a blinded extension Period of up to Week 136, and a 30-day Follow-up Visit. Subjects who met eligibility criteria were randomized in a 1:1:1 ratio to receive a daily oral dose of upadacitinib 30 mg or upadacitinib 15 mg or matching placebo QD. The study drug could be taken with or without food.

In Study M16-047 the same upadacitinib dose were administered but with concomitant use of topical treatment. Concomitant TCS therapy was started at Baseline and continued through Week 52 using a step-down regimen. A medium potency TCS was applied daily to active lesions for a maximum of 3 consecutive weeks. Low potency TCS or TCI could be applied to sensitive skin areas. After lesions were clear or almost clear, or after 3 consecutive weeks of medium potency TCS, a low potency TCS was used daily for 7 days and then stopped. The step-down regimen starting with medium potency TCS was to be resumed if AD lesions returned or persisted. This regimen reflects clinical practice, i.e. starting with a medium potency TCS and use it for some weeks and thereafter step-down to a low potency TCS. At the CHMP's request, the MAH clarified that another course of TCS could be re-initiated at any time in the case of recurring AD lesions. This means that in practise, several TCS courses close in time could be used. It was however also clarified that safeguards were in place for sensitive skin areas where low potency TCS or a topical calcineurin inhibitor was to be applied once daily to areas of thin skin or to areas where medium TCS were considered unsafe. The TCS was not weighed in this study to estimate the amount of TCS used, due to operational complexity. The cumulative TCS amount used was not included as an endpoint and thus, a potential 'steroid-sparing' effect of upadacitinib was not captured. The number of days off TCS with an EASI 75 response was evaluated, though. Since this was not among the multiplicity-controlled secondary endpoints, the MAH agreed to remove it from their proposed section 5.1 of the SmPC.

The choice of the upadacitinib doses 15 mg QD and 30 mg QD were based on results of the dose finding study that investigated three dose levels; 7.5 mg QD, 15 mg QD and 30 mg QD. A clear dose response was observed across the three doses levels, both for the primary as well as most secondary

endpoints. Based on efficacy and safety data from this study, including exposure-response analyses, the 15 mg and 30 mg daily doses were chosen to be further studied in the Phase 3 program. This is considered an adequate approach by the CHMP and are also the same doses as those studied in the RA program, although only the 15 mg is recommended in the RA indication.

The placebo-controlled part continued up to Week 16 and thereafter patients in the placebo arm were re-randomized in a 1:1 ratio to 15 or 30 mg upadacitinib. Subjects originally randomized to upadacitinib were to continue upadacitinib in the extension period at the same dose. This design was considered acceptable to the CHMP.

Rescue medication could be initiated from Week 4 based on certain criteria for the EASI response, which was considered adequate by the CHMP. The rescue medication was reasonably defined in terms of type and duration (e.g. for oral corticosteroids) and when to stop upadacitinib treatment or not in case of their initiation. It is appreciated that subjects who permanently discontinued study drug were encouraged to continue participation in the study and complete the schedule of study visits and assessments.

The objective was to assess the efficacy and safety of upadacitinib for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy. The aim was to demonstrate superiority of each upadacitinib dose vs. placebo, which was considered acceptable to the CHMP.

The co-primary endpoints in all three studies were the Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index (EASI 75) from Baseline at Week 16 and the 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 Week 16. These are relevant and endorsed by the CHMP. The EASI score is the equivalent of PASI in psoriasis and measures the extent and severity of several signs (erythema, inflammation, induration, papulation, excoriations and lichenification) of the AD condition. The vIGA-AD score is a global score assessed by the investigator.

A large number of multiplicity-controlled secondary endpoints were also evaluated. Among the highest ranked of these, there were endpoints assessing itch (proportion of subjects achieving an improvement in Worst Pruritus NRS) ≥ 4 points and the percent change from Baseline of Worst Pruritus NRS at Week 16), one of the most prominent symptoms of AD. Another highly ranked endpoint was the proportion of subjects achieving EASI 90 at Week 16, which is a high hurdle endpoint reflecting almost total clearance of AD. EASI 100 (reflecting total clearance) at Week 16 was also assessed.

Some endpoints assessed the onset of effect, e.g. the proportion of subjects achieving EASI 75 by week 2 and the proportions achieving a reduction in Worst Pruritus NRS ≥ 4 at Week 1, or even at Day 2 or Day 3.

Occurrence of flares were also evaluated with a flare being defined as an increase of EASI by ≥ 6.6 from Baseline for subjects with EASI ≤ 65.4 at Baseline. The cut-off to define a flare was based on the established MCID of 6.6 for the EASI (Schram 2012).

Some established PROs used in several dermatological conditions (DLQI) and more specifically in AD (POEM, SCORAD) were also evaluated, as well as some newly developed PROs for AD; the Atopic Dermatitis Impact Scale (ADerm-IS) and the Atopic Dermatitis Symptom Scale (ADerm-SS).

A 1:1:1 randomisation was applied for the two upadacitinib dose arms and the placebo arm. The initial stratification factors used (vIGA-AD severity, geographic region, age) as well as the Week 16 Group 3 (placebo) re-randomisation stratifications factors (EASI 50 responder status, region and age) are endorsed. Study sites and subjects were to remain blinded for the duration of the study. In order to

maintain the blind, the upadacitinib tablets and placebo tablets provided for the study were identical in appearance. Blinding was considered acceptable to the CHMP.

The statistical plans pre-specified for the pivotal studies M16-045, M18-891 and M16-047 were similar and in general acceptable to the CHMP. Statistical comparisons of treatment groups using CMH test and MMRM for the categorical and continuous endpoints, respectively, are appropriate. The approaches applied to handle intercurrent events and missing data are plausible to investigate robustness of the efficacy results. The amount of intercurrent events, missing and imputed values, including reasons for missingness, are presented on request. Considering the amount of non-responder imputations due to intercurrent events (rescue medication intake), there is a trend of treatment dependent frequency and a clear discrepancy between upadacitinib treatment arms and placebo group. Of note, in the primary analysis, subjects with assessments after the start of rescue medications were counted as non-responders, where the estimated treatment differences are impacted by the substantially higher amount of intercurrent events observed in placebo. Sensitivity analyses using treatment policy approach did confirm the statistically significant results, although with lower estimates of treatment differences. In the primary analysis, the imbalance between the treatment groups in non-responder imputations due to intercurrent events (rescue medication) may bias the efficacy estimates. Therefore, the CHMP requested the MAH to complement presentation of primary endpoints results in the SmPC with information on observed versus imputed non-response, and specifically non-responders due to rescue intake. The MAH agreed with this request and updated the SmPC accordingly.

The definitions of ITT populations based on the randomised subjects are endorsed. A summary over all analysis populations has been presented at the CHMP request. The graphical multiple testing procedure for the co-primary and the key secondary endpoints combining hierarchical testing and alpha re-cycling controls the overall type-I error rate at the 0.05 (two-sided) level for each pivotal study. There were no interim analyses to add to multiplicity, as the first analysis in each of the studies was the primary analysis performed after the database lock for the Week 16 data. Post-hoc analyses were performed in terms of the co-primary endpoints analysed using treatment policy approach. This supplemental estimand was based on all observed data regardless of the use of other medications or treatment discontinuations, while missing data were handled by multiple imputation. These analyses fully supported the primary analysis.

Overall, the design of the Phase 3 studies is adequate and broadly in line with the CHMP scientific advice provided and similar developments in the AD condition. After Week 16, subjects originally randomized to upadacitinib continued upadacitinib in the extension period at the same dose and patients in the placebo arm were re-randomized in a 1:1 ratio to 15 or 30 mg upadacitinib. Although this is a reasonable design, the CHMP advice also recommended that it could be of interest to study duration of remission/response, rebound, time to relapse, and efficacy of re-treatment. Such data were not available from the pivotal studies and a discussion on these topics was requested from the MAH (see below, *Long term efficacy*).

Efficacy data and additional analyses

In Study M16-045, a total of 847 subjects were randomized at 151 study sites located in 24 countries. All 847 subjects (100%) received study drug. A total of 778 subjects (91.9%) completed study drug through the DB Period (Week 16), and 782 subjects (92.3%) completed study participation through Week 16.

In Study M18-891, a total of 836 subjects were randomized at 154 study sites in 23 countries. All 836 subjects received study drug. A total of 764 subjects (91.4%) completed study drug through the DB Period (Week 16), and 768 subjects (91.9%) completed study participation through Week 16.

In Study M16-047 (TCS study), a total of 901 subjects were randomized and 900 subjects (including 115 adolescents) were treated with study drug (1 adolescent randomized but not treated) at 171 sites in 22 countries. Almost all subjects completed study treatment in the double-blind Period (94.8%).

Thus, the rate of completion up to Week 16 was high in all studies, >90% (around 85% in the placebo arms in the mono-therapy studies, though). Common reasons for discontinuation were withdrawal of consent by the subject, AEs and lack of efficacy (primarily for the placebo group). In both mono-therapy studies around 20% in total received rescue medication, the majority being in the placebo group (>40%), while less than 10% in the upadacitinib groups received rescue, fewest in the 30 mg group. No subject in either study discontinued from the study due to COVID-19.

In study M16-047, the main reason for discontinuation was adverse events in both adults and adolescents, although still at low rates. In the placebo + TCS arm, around 25% received rescue medication, while around 5% in the upadacitinib + TCS did so.

In the initial submission, the blinded extension phases were still ongoing and updated results were requested by the CHMP during the evaluation.

No major concerns were raised with respect to protocol deviations or amendments. Concerning protocol modifications and deviations related to COVID-19 were captured and included in appendices. At the CHMP request, summary figures on COVID-19-related deviations were provided for all three studies and showed that COVID -19-related deviations occurred to a low extent in the initial, Double-Blind periods of the studies. There were overall 1-3% of subjects who had at least one protocol deviation related to COVID-19 in this period, mainly due to Missed visits or Virtual or partially performed visits. The majority of COVID-19-related protocol deviations occurred in the Blinded Extension Period for all three studies, ranging from overall 16-22% across the three studies. Overall, the results do not indicate cause for concern and it is reassuring that the double-blind parts of all three studies were only minimally affected by COVID-19 related protocol deviations.

In Study M18-891, one site was closed due to significant GCP non-compliance. Data from the six subjects randomized at this site were excluded from any analyses provided in the study report. The MAH concludes that the closure of this site impacted the scientific value of clinical study (data integrity), but the impact is not deemed significant due to the small number of subjects as part of an overall large study (N = 842). The CHMP shared this view.

The compliance of study drug intake was high in all studies.

The overall demographic characteristics were generally balanced across the upadacitinib (30 mg and 15 mg) and placebo groups, in both mono-studies. Slightly above 50% of subjects were male, 65-69% were white, and 52-58% were 18 to 39 years of age; 50% of subjects had a body mass index (BMI) of < 25 kg/m2 at screening. There were few patients aged > 65 years (about 5%). If fewer than 10% of subjects were in age category ≥ 65 years they were combined with the adjacent subgroup, in sub-group analyses with respect to age. Adolescents comprised 14.6% in M16-045 and 12.4% in M18-891. The adolescent group characteristics were also generally balanced across the upadacitinib (30 mg and 15 mg) and placebo groups.

Baseline disease characteristics were generally balanced across the upadacitinib and placebo groups overall and in adolescents. Subjects had been diagnosed with AD for a mean of approximately 20 years overall and 12-13 years for adolescents. The mean EASI score was slightly below 30 (median around 25), the mean percent BSA affected was around 47%. In study M16-045, the proportion of subjects with moderate AD (vIGA-AD 3) was approximately 55% and the proportion with severe AD 45% while the reverse proportions were seen in Study M18-891 (45% moderate, 55% severe). The mean Worst Pruritus NRS weekly average score was above 7 in both studies, reflecting rather substantial itch severity. In Study M16-047, the study population was very similar to the population included in the

monotherapy studies. Thus, the study population in all three studies reflected a population with moderate to severe AD.

The previous treatments were as expected in an AD population, i.e. mainly topical corticosteroids, emollients and protectives. Around half of the subjects had received prior non-biologic immunomodulating systemic therapies while only around 3% had received prior biologic systemic therapies.

Short term efficacy

The co-primary endpoints, the proportions of patients achieving EASI 75 and a vIGA-AD score of 0 or 1 with a reduction of at least 2 grade reductions from baseline at Week 16 were clearly higher for both upadacitinib dose levels vs. placebo, in all three studies. The results were highly statistically significant and are also considered clinically relevant.

A dose dependency was observed in all studies, with overall 10-19% difference in Week 16 responder rates for EASI 75 and vIGA-AD (0,1) between the 15 mg and the 30 mg doses. In the mono-therapy studies, the EASI 75 response was 60-70% for the 15 mg upadacitinib dose and 73-80% for the 30 mg dose (13-16% for placebo). For the vIGA-AD (0,1) endpoint, corresponding figures were 39-48% for upadacitinib 15 mg, 52-62% for upadacitinib 30 mg and 5-8% for placebo, respectively.

In the TCS study (M16-047), the results were rather similar; EASI 75 for the upadacitinib 15 mg, 30 mg and placebo groups were 65%, 77% and 26%, respectively, and vIGA-AD (0,1) responses were 40%, 59% and 11%, respectively. Thus, the placebo responses were somewhat larger in the TCS study compared with the mono-therapy studies, which can be expected. This response was observed even though patients included were to be inadequate responders to TCS. The CHMP commented on that point that some degree of efficacy may still be expected also in such patients and may potentially be a result of better compliance to TCS use.

In the mono-therapy studies, a very large number of endpoints referred to as 'key secondary endpoints' were included. Superiority of each upadacitinib dose vs. placebo was demonstrated for all key secondary endpoints, based on showing statistical significance under the overall type I error control, in both studies. Similar to the co-primary endpoints, a dose-related difference generally in the range 10-18% was observed.

Effects on itch were observed evaluated by the reduction in Worst pruritus NRS by ≥ 4 points at Week 16. A separation from placebo was observed as early as Day 2, although the numbers of upadacitinib responders at these early times points (Day 2, Day 3 and Week 1) were rather few. Still, it can be observed that both effects on itch and on AD lesions assessed by EASI 75 at Week 2 show a rapid onset of effect.

The number of flares during the DB period were also much lower in the upadacitinib arms (0-2%) vs. the placebo arm (around 25%).

Also, for the patient-reported outcomes (POEM, DLQI, HADS), both upadacitinib doses showed superior effects vs. placebo and a dose-dependent effect was observed.

Even if the key secondary endpoints were included in the multiplicity-controlled statistical testing procedure and were all statistically significant, the inclusion of all of them in section 5.1 was not endorsed by the CHMP. The MAH agreed to reduce the information in the SmPC.

In Study M16-047, there were fewer key (multiplicity-controlled) secondary endpoints compared with the mono-therapy studies. For all of these, superiority of each upadacitinib dose vs. placebo was also demonstrated, based on showing statistical significance under the overall type I error control.

The number of Topical Corticosteroid Free Days was evaluated as an 'other' endpoint and among all subjects through Week 16, the mean number of days off of all TCS and achieving an EASI 75 response was 47 days (median 57 days) in the upadacitinib 30 mg group, 34 days (median 26 days) in the upadacitinib 15 mg group and 8 days (median 0 days) in the placebo group.

The data submitted supports the use of upadacitinib with or without topical corticosteroids. Topical calcineurin inhibitors may be used for sensitive areas such as the face, neck, and intertriginous and genital areas. This is adequately reflected in the SmPC.

Long term efficacy

At the CHMP's request, updated results have been submitted for review and confirmed that the effect of upadacitinib seems to be maintained over time with a numerically better response to 30 mg vs. 15 mg, as seen in the double-blind phases.

No randomised withdrawal study was performed to assess maintenance of response and/or the possibility of dose reduction (e.g. from the 30 mg dose to the 15 mg dose once a response is achieved). As mentioned above, results on rebound have not been presented or discussed, nor have data following cessation of treatment and re-treatment. The CHMP considered that these are drawbacks as in clinical practice, both dose reductions and dose interruptions may be realistic scenarios, e.g. due to safety concerns. At the CHMP's request, the MAH provided data from a small Phase 2b study which included a randomised withdrawal part. This was a small dose-finding study and each sub-group evaluated in Part 2 of the study consisted of less than 20 individuals. Nevertheless, the data showed that the proportion of subjects achieving EASI 75 or EASI 90 declined by Week 20 after withdrawal of either upadacitinib 15 mg QD or 30 mg QD at Week 16 and only very few subjects retained response to Week 88, after upadacitinib withdrawal.

Concerning time to relapse/flare (defined as loss of EASI 50 response), the median time to loss of response was 30 and 28 days, respectively, in subjects who had achieved an EASI 75 at the time of re-randomization to placebo in Period 2 from upadacitinib 15 mg or 30 mg QD in Period 1.

Although based on limited data, the results did not suggest a risk of rebound after stopping upadacitinib administration (defined as EASI ≥25% or ≥50% above baseline EASI score). For the 15 mg and 30 mg upadacitinib dose groups (re-randomised to placebo), almost 90% of subjects did not have a worsening of EASI at the time of start of rescue. The data also suggest that re-treatment with upadacitinib 30 mg could restore an EASI 75 response for at least half of the subjects by 8 weeks post-rescue.

There are situations when upadacitinib treatment may need to be stopped, continuously or temporarily. Although the Phase 2b data is not extensive, the data still suggest that withdrawal of treatment will result in return of AD symptoms within about a month and a half of the subjects. Data also indicate that upadacitinib treatment may be re-initiated successfully and there seem to be no obvious issues with rebound. At the CHMP's request, the Section 4.2 of the SmPC was modified to state that the lowest effective dose for maintenance should be considered. This is considered adequate in view of these data.

Sub-group results

In adolescents, both upadacitinib doses showed a clearly statistically significant difference vs. placebo for the co-primary endpoints and most secondary endpoints. A dose-related difference was observed also in this group. The MAH initially recommended only the 15 mg QD dose in adolescents in the proposed SmPC. This was not considered justified from an efficacy point of view by the CHMP and the MAH clarified that they have taken a conservative view until further safety data are available for the 30 mg dose. The CHMP did not object to this rationale (please refer also to benefit-risk discussion).

Concerning elderly patients, the sub-group ≥65 years was small and was not analysed separately for efficacy. At the CHMP's request, the dose in patients ≥ 65 years of age has been limited to 15 mg once daily (see safety section).

For other sub-groups, relevant sub-group analyses have been performed, based on demographic (age, gender, BMI, race, weight) and disease-related factors (Baseline vIGA-AD, Baseline EASI, hsCRP, previous systemic therapy, intolerance to at least one prior TCS/TCI, inadequate response to at least one topical treatment) and geographic region. These analyses have been performed within each study separately and in a combined analysis for the two mono-therapy studies.

Consistent treatment effects in all pre-specified subgroups in favour of upadacitinib 30 mg and upadacitinib 15 mg were observed when compared to placebo for the co-primary endpoints of vIGA-AD 0/1 and EASI 75. Some groups were small (e.g. the Chinese and Japanese groups), resulting in wide confidence intervals. In study M16-047 (TCS study), all 95% confidence intervals (CIs) excluded zero, except for the race sub-group category "other" (that consisted of Black or African American, Indian/Alaska Native and Native Hawaiian or other Pacific Islander or multiple) for most comparison. The number of subjects in this category was low (69 subjects).

In the SmPC initially proposed by the MAH, both the 15 mg dose and the not previously approved 30 mg dose was recommended for use in the treatment of AD, with the choice of dose proposed to be based on 'individual patient presentation'. While the inclusion of both dose levels in the posology was endorsed by the CHMP, the dosing recommendations were considered too unclear. The dosing recommendations were revised at the CHMP request as follows (see also Section 2.4.5):

- The recommended dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation.

- The CHMP agreed that the 30 mg dose overall showed higher response rates (differences of 10-20%) for all endpoints compared with the 15 mg dose. No subgroup analyses have been performed to more specifically look at responder rates for the two doses in patients with moderate vs. severe AD at baseline. However, starting with the high dose primarily in those with high AD disease burden is considered reasonable. Hence, a dose of 30 mg once daily may be appropriate for patients with high disease burden.

- A dose of 30 mg once daily may be appropriate for patients with an inadequate response to 15 mg once daily. This has not been formally studied. However, based on the observed responder rates in those randomised initially to 15 mg or 30 mg, respectively, the proposal was agreed by the CHMP.

- The lowest effective dose for maintenance should be considered. No randomised withdrawal part was included in the pivotal studies to evaluate maintenance of response with dose reduction or dose cessation or to evaluate dose escalation. See discussion above. For a JAK inhibitor with some known dose-related safety issues, use of the lowest effective dose for maintenance treatment is considered adequate by the CHMP.

- A recommendation to discontinue upadacitinib treatment in patients who show no evidence of therapeutic benefit after 12 weeks of treatment was also added. The time point of 12 weeks has been substantiated at the CHMP's request based on efficacy data at different time points and is endorsed.

2.5.3. Conclusions on the clinical efficacy

Three adequately designed and performed Phase 3 studies provide support for the efficacy of upadacitinib in atopic dermatitis. Efficacy has been clearly demonstrated. The co-primary endpoints, the proportions of patients achieving EASI 75 and a vIGA-AD score of 0 or 1 with a reduction of at least 2 grade reductions from baseline at Week 16 were clearly higher for both upadacitinib dose levels vs. placebo, in all three studies. The results were highly statistically significant and are also considered clinically relevant. The results were supported by a large number of multiplicity-controlled secondary endpoints in the mono-therapy studies and fewer, but also relevant, secondary endpoints in the TCS combination study.

A dose dependency was observed in all studies, with overall 10-19% difference in responder rates between the 15 mg and the 30 mg upadacitinib doses. In post-hoc analyses for the mono-therapy studies, the CIs for the efficacy results of the two doses were non-overlapping for almost all endpoints. The recommended dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation. For adolescents and elderly > 65, the 15 mg once daily dose is recommended.

In conclusion, the CHMP considered that the data supported the following indication from an efficacy perspective:

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.

2.6. Clinical safety

Patient exposure

The global Phase 3 development program for AD consisted of three pivotal trials that evaluated the efficacy and safety of upadacitinib in subjects 12 years of age and older for the treatment of moderate to severe AD who are candidates for systemic therapy. Two upadacitinib doses, 15 mg and 30 mg QD extended-release tablets, were evaluated in the AD studies. In two of the Phase 3 studies, upadacitinib was administered as monotherapy, and in one it was administered in combination with topical corticosteroids. The development program for AD also included a global Phase 2b Study M16-048 and the Japan regional Study M17-377, which were included in the integrated safety evaluation.

In order to evaluate the safety of upadacitinib compared with placebo as well as after long-term use, subject data were integrated into three different analysis sets:

- Placebo (PBO)-controlled AD Analysis Set (16 weeks treatment; includes Phase 2b and Phase 3 studies)

- Long-term Upadacitinib Phase 3 AD Analysis Set (includes data from the three pivotal Phase 3 studies)All Upadacitinib AD Analysis Set includes data from the Phase 2b study and the Japan regional study, in addition to the pivotal Phase 3 studies.

The data was analysed per dose (15 mg vs. 30 mg), for the overall study population and for adolescents only.

In the original submission, data up to the cut-off date 04 June, 2020 was presented. At the CHMP's request, a Safety Update Report (SUR) was submitted with additional data up to the cut-off date 24 November 2020. When applicable, tables below have been updated with data from the latter cut-off.

The number of patients (overall and adolescents only) and duration of treatment in the three datasets are summarised below.

The pivotal Phase 3 studies include an extension sub-study in adolescents, enrolment to this part of the studies was ongoing at the original submission. Additional data from the extension part was submitted at the CHMP's request.

Table 29   Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (PBO-controlled Analysis Set) 16-weeks treatment.

Duration	Overall			Adolescents		
	PBO (N = 902) n (%)	**UPA 15 mg QD (N = 899) n (%)**	**UPA 30 mg QD (N = 906) n (%)**	**PBO (N = 115) n (%)**	**UPA 15 mg QD (N = 114) n (%)**	**UPA 30 mg QD (N = 114) n (%)**
≥ 4 weeks	849 (94.1)	893 (99.3)	900 (99.3)	109 (94.8)	114 (100)	113 (99.1)
≥ 12 weeks	803 (89.0)	870 (96.8)	873 (96.4)	105 (91.3)	112 (98.2)	112 (98.2)
Mean duration (days)	103.3	110.2	110.2	105.3	110.9	111.6

PBO = placebo; QD = once daily; UPA = upadacitinib

Table 30   Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (Long-term Upadacitinib Phase 3 AD Analysis Set)

	CSS (Data Cutoff 04 June 2020)				SUR (Data Cutoff 24 November 2020)			
	Overall		Adolescents		Overall		Adolescents	
Days	UPA 15 mg QD (N = 1238) n (%)	UPA 30 mg QD (N = 1242) n (%)	UPA 15 mg QD (N = 167) n (%)	UPA 30 mg QD (N = 166) n (%)	UPA 15 mg QD (N = 1239) n (%)	UPA 30 mg QD (N = 1246) n (%)	UPA 15 mg QD (N = 167) n (%)	UPA 30 mg QD (N = 166) n (%)
≥ 4 weeks	1229 (99.3)	1235 (99.4)	167 (100)	164 (98.8)	1230 (99.3)	1240 (99.5)	167 (100)	165 (99.4)
≥ 12 weeks	1155 (93.3)	1161 (93.5)	159 (95.2)	157 (94.6)	1203 (97.1)	1215 (97.5)	164 (98.2)	164 (98.8)
≥ 24 weeks	968 (78.2)	976 (78.6)	137 (82.0)	135 (81.3)	1155 (93.2)	1171 (94.0)	158 (94.6)	160 (96.4)
≥ 36 weeks	589 (47.6)	616 (49.6)	85 (50.9)	92 (55.4)	1072 (86.5)	1098 (88.1)	147 (88.0)	148 (89.2)
≥ 48 weeks	312 (25.2)	333 (26.8)	51 (30.5)	55 (33.1)	897 (72.4)	938 (75.3)	128 (76.6)	130 (78.3)
≥ 52 weeks	246 (19.9)	263 (21.2)	37 (22.2)	46 (27.7)	791 (63.8)	826 (66.3)	110 (65.9)	113 (68.1)
≥ 72 weeks	41 (3.3)	42 (3.4)	3 (1.8)	4 (2.4)	298 (24.1)	326 (26.2)	49 (29.3)	53 (31.9)
≥ 104 weeks	0	0	0	0	18 (1.5)	14 (1.1)	2 (1.2)	2 (1.2)
Mean duration (days)	257.3	262.5	268.1	276.1	404.9	414.6	419.4	431.1

AD = atopic dermatitis; CSS = clinical summary of safety; QD = once daily; SUR = Safety Update Report; UPA = upadacitinib

Table 31   *Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (All Upadacitinib AD Analysis Set)*

	CSS				SUR			
Days	UPA 15 mg QD[a] (N = 1371) n (%)	UPA 30 mg QD[a] (N = 1378) n (%)	Phase 2 All Doses[b] (N = 144) n (%)	Total (N = 2893) n (%)	UPA 15 mg QD[a] (N = 1372) n (%)	UPA 30 mg QD[a] (N = 1382) n (%)	Phase 2 All Doses[b] (N = 144) n (%)	Total (N = 2898) n (%)
≥ 4 weeks	1361 (99.3)	1370 (99.4)	140 (97.2)	2871 (99.2)	1362 (99.3)	1375 (99.5)	140 (97.2)	2877 (99.3)
≥ 12 weeks	1279 (93.3)	1286 (93.3)	130 (90.3)	2695 (93.2)	1333 (97.2)	1348 (97.5)	130 (90.3)	2811 (97.0)
≥ 24 weeks	1076 (78.5)	1084 (78.7)	106 (73.6)	2266 (78.3)	1285 (93.7)	1299 (94.0)	106 (73.6)	2690 (92.8)
≥ 36 weeks	640 (46.7)	666 (48.3)	102 (70.8)	1408 (48.7)	1200 (87.5)	1226 (88.7)	102 (70.8)	2528 (87.2)
≥ 48 weeks	329 (24.0)	346 (25.1)	98 (68.1)	773 (26.7)	1011 (73.7)	1047 (75.8)	98 (68.1)	2156 (74.4)
≥ 52 weeks	253 (18.5)	267 (19.4)	94 (65.3)	614 (21.2)	895 (65.2)	931 (67.4)	94 (65.3)	1920 (66.3)
≥ 72 weeks	41 (3.0)	42 (3.0)	78 (54.2)	161 (5.6)	322 (23.5)	352 (25.5)	78 (54.2)	752 (25.9)
≥ 104 weeks	0	0	0	0	18 (1.3)	14 (1.0)	0	32 (1.1)
Mean duration (days)	254.4	258.2	422.0	264.6	405.9	413.3	422.0	410.2

AD = atopic dermatitis; CSS = clinical summary of safety; QD = once daily; SUR = Safety Update Report; UPA = upadacitinib

a.   Includes Phase 3 global and Japan only.

b.   All upadacitinib doses in the Phase 2 study will be combined and data are presented as one All Doses group.

Adverse events

Frequencies of treatment-emergent adverse events (TEAEs) were presented as percent in the Placebo-controlled dataset (16-weeks treatment) and as exposure-adjusted event rates (EAERs), i.e. events per 100 patient years (E/100 PY) for the long-term datasets.

During the 16-week placebo-controlled period, the overall rate of AEs and of AEs considered by the investigator to be related to treatment were higher in the upadacitinib groups than in the placebo group, and higher in the upadacitinib 30 mg group than in the 15 mg group. There were no apparent differences between the placebo-treated group and the upadacitinib-treated groups in terms of SAEs or severe AEs. The frequency of discontinuation due to AE was highest in the placebo-treated group and the most common reason was lack of efficacy. In general, similar trends were observed in the adolescent group as in the overall population (table below).

Table 32   Overview of Subjects with Treatment-Emergent Adverse Events (PBO-controlled AD Analysis Set)

	Overall			Adolescents		
Subject with any treatment-emergent	PBO (N = 902) n (%)	UPA 15 mg QD (N = 899) n (%)	UPA 30 mg QD (N = 906) n (%)	PBO (N = 115) n (%)	UPA 15 mg QD (N = 114) n (%)	UPA 30 mg QD (N = 114) n (%)
Adverse event (AE)	528 (58.5)	574 (63.8)	630 (69.5)	53 (46.1)	74 (64.9)	83 (72.8)
AE with reasonable possibility of being drug related[a]	185 (20.5)	298 (33.1)	367 (40.5)	14 (12.2)	35 (30.7)	40 (35.1)
Severe AE	43 (4.8)	43 (4.8)	42 (4.6)	3 (2.6)	9 (7.9)	0
Serious AE	26 (2.9)	19 (2.1)	19 (2.1)	3 (2.6)	3 (2.6)	0
AE leading to discontinuation of study drug	34 (3.8)	21 (2.3)	26 (2.9)	3 (2.6)	3 (2.6)	0
AE leading to death	0	0	0	0	0	0
Death[b]	0	0	0	0	0	0

AD = atopic dermatitis; AE = adverse event; PBO = placebo; QD = once a day; UPA = upadacitinib
a.   As assessed by investigator.
b.   Includes both treatment-emergent and non-treatment-emergent deaths.

In the Long-term Upadacitinib Phase 3 Analysis Set (Table below) and in the All upadacitinib AD analysis set (not shown), the EAERs of TEAEs, SAEs, TEAE leading to discontinuation of study drug, and severe TEAEs were higher in the upadacitinib 30 mg than in the 15 mg group. In the adolescent group, a similar trend was observed for the EAERs of TEAEs category as in the overall population at both cutoff dates.

Table 33   Overview of Treatment-Emergent Adverse Events Per 100 PY (Long-term Upadacitinib Phase 3 AD Analysis Set)

	CSS (Data Cutoff 04 Jun 2020)				SUR (Data Cutoff 24 Nov 2020)			
	Overall		Adolescents		Overall		Adolescents	
	UPA 15 mg QD (N = 1238) (PY = 872.2)	UPA 30 mg QD (N = 1242) (PY = 892.7)	UPA 15 mg QD (N = 167) (PY = 122.6)	UPA 30 mg QD (N = 166) (PY = 125.5)	UPA 15 mg QD (N = 1239) (PY = 1373.4)	UPA 30 mg QD (N =1246) (PY = 1414.2)	UPA 15 mg QD (N = 167) (PY = 191.7)	UPA 30 mg QD (N = 166) (PY = 195.9)
Exposure-adjusted event rate: E (E/100 PY)								
Any AE	2907 (333.3)	3450 (386.5)	421 (343.5)	447 (356.2)	3771 (274.6)	4411 (311.9)	532 (277.4)	562 (286.8)
Any SAE	62 (7.1)	75 (8.4)	6 (4.9)	7 (5.6)	98 (7.1)	109 (7.7)	15 (7.8)	7 (3.6)
Any AE leading to discontinuation of study drug	47 (5.4)	62 (6.9)	7 (5.7)	9[c] (7.2)	60 (4.4)	81 (5.7)	9 (4.7)	7 (3.6)[c]
Any severe AE	112 (12.8)	139 (15.6)	17 (13.9)	13 (10.4)	170 (12.4)	215 (15.2)	31 (16.2)	18 (9.2)
Any AE with reasonable possibility of being related to study drug[a]	1077 (123.5)	1354 (151.7)	170 (138.7)	174 (138.7)	1308 (95.2)	1663 (117.6)	205 (106.9)	206 (105.1)
Any AE leading to death	0	0	0	0	0	1 (<0.1)	0	0
Exposure-adjusted incidence rate: n/PY (n/100 PY)								
Deaths[b]	0/872.2	0/892.7	0/122.6	0/125.5	0/1373.4	1/1414.2 (<0.1)	0/191.7	0/195.9

AD = atopic dermatitis; AE = adverse event; CSS = clinical summary of safety; PY = patient-years; QD = once daily; SAE = serious adverse event; SUR = Safety Update Report; UPA = upadacitinib

a.   As assessed by investigator.

b.   Included both treatment-emergent and non-treatment emergent deaths.

c.   Two events of blood culture positive and culture urine positive reported in 1 subject that led to study drug discontinuation reported in the CSS were removed by the investigator prior to the cutoff for this SUR.

Common TEAEs: Placebo-controlled period

Overall, the common TEAEs in the AD studies were largely similar to what has been reported from RA, PsA and AS studies.

During the 16-week placebo-controlled period, the most frequent TEAEs by SOC in upadacitinib-treated patients (reported in ≥ 10% of subjects in either upadacitinib group) were infections and infestations, gastrointestinal (GI) disorders, investigations, and skin and subcutaneous tissue disorders. For adolescent subjects, the most frequent TEAEs in upadacitinib-treated groups were within the SOC infections and infestations; investigations; skin and subcutaneous tissue disorders; respiratory, thoracic, and mediastinal disorders; and gastrointestinal disorders.

In the placebo group, the most frequent TEAEs by SOC were infections and infestations and skin and subcutaneous tissue disorders in the overall population as well as in the adolescent population.

TEAEs by PT Reported in ≥ 2% of Subjects in Any Treatment Group are shown in the table below. The rates of TEAEs reported in ≥ 5% of adolescent subjects are shown in the table below.

Table 34   TEAEs Reported in ≥ 2% of Subjects in Any Treatment Group of <u>All Subjects</u> by Decreasing Frequency (PBO-controlled AD Analysis Set)

MedDRA 22.1 Preferred Term	PBO (N = 902) n (%)	UPA 15 mg QD (N = 899) n (%)	UPA 30 mg QD (N = 906) n (%)
Any adverse event	528 (58.5)	574 (63.8)	630 (69.5)
Acne	20 (2.2)	86 (9.6)	137 (15.1)
Nasopharyngitis	64 (7.1)	79 (8.8)	94 (10.4)
Upper respiratory tract infection	58 (6.4)	70 (7.8)	83 (9.2)
Headache	39 (4.3)	50 (5.6)	57 (6.3)
Blood creatine phosphokinase increased	21 (2.3)	41 (4.6)	50 (5.5)
Oral herpes	9 (1.0)	23 (2.6)	47 (5.2)
Diarrhoea	23 (2.5)	31 (3.4)	29 (3.2)
Cough	13 (1.4)	29 (3.2)	27 (3.0)
Folliculitis	10 (1.1)	19 (2.1)	29 (3.2)
Nausea	5 (0.6)	24 (2.7)	24 (2.6)
Dermatitis atopic	74 (8.2)	31 (3.4)	14 (1.5)
Oropharyngeal pain	9 (1.0)	19 (2.1)	20 (2.2)
Herpes simplex	5 (0.6)	15 (1.7)	21 (2.3)
Pyrexia	9 (1.0)	15 (1.7)	19 (2.1)
Urinary tract infection	18 (2.0)	12 (1.3)	22 (2.4)
Influenza	3 (0.3)	19 (2.1)	14 (1.5)
Neutropenia	2 (0.2)	7 (0.8)	21 (2.3)

MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; QD = once daily; TEAE = treatment-emergent adverse event; UPA = upadacitinib

Table 35   TEAEs Reported in ≥ 5% of Adolescent Subjects in Any Treatment Group by Decreasing Frequency (PBO-controlled AD Analysis Set)

MedDRA 22.1 Preferred Term	PBO (N = 115) n (%)	UPA 15 mg QD (N = 114) n (%)	UPA 30 mg QD (N = 114) n (%)
Any adverse event	53 (46.1)	74 (64.9)	83 (72.8)
Acne	1 (0.9)	15 (13.2)	17 (14.9)
Upper respiratory tract infection	5 (4.3)	12 (10.5)	14 (12.3)
Nasopharyngitis	6 (5.2)	11 (9.6)	8 (7.0)
Dermatitis atopic	11 (9.6)	5 (4.4)	2 (1.8)
Headache	6 (5.2)	7 (6.1)	10 (8.8)
Blood creatine phosphokinase increased	3 (2.6)	6 (5.3)	9 (7.9)
Vomiting	1 (0.9)	1 (0.9)	7 (6.1)
Diarrhoea	3 (2.6)	2 (1.8)	6 (5.3)
Pyrexia	0	3 (2.6)	6 (5.3)
Influenza	0	2 (1.8)	6 (5.3)
Oropharyngeal pain	0	6 (5.3)	2 (1.8)

MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; QD = once daily; TEAE = treatment-emergent adverse event; UPA = upadacitinib

The TEAEs that were most frequently (≥ 2% subjects in either group) assessed by the investigators as having a possible relationship to study drug in the upadacitinib groups were acne, blood CPK increased, headache, nasopharyngitis, neutropenia, oral herpes and upper respiratory tract infection.

Common TEAEs: Long-term Phase 3 data

The long-term safety profile in terms of common TEAEs in the Phase 3 population was largely similar to the safety profile during the 16-week placebo-controlled treatment period. The most common TEAEs (reported in ≥ 2% of subjects in any treatment group) are shown in the table below.

The most common TEAEs that were by the investigator considered related to treatment included acne, blood creatine phosphokinase increased, oral herpes, upper respiratory tract infection, nasopharyngitis, herpes simplex, and herpes zoster.

Table 36   TEAEs Reported in ≥ 2% of Subjects in Any Treatment Group of All Subjects by Decreasing Frequency (Long-term Upadacitinib Phase3 AD Analysis Set)

| | CSS (Data Cutoff 04 Jun 2020) | | SUR (Data Cutoff 24 Nov 2020) | |
| | UPA 15 mg QD (N = 1238) n (%) | UPA 30 mg QD (N = 1242) n (%) | UPA 15 mg QD (N = 1239) n (%) | UPA 30 mg QD (N = 1246) n (%) |
MedDRA 22.1 Preferred Term				
Any adverse event	833 (67.3)	914 (73.6)	912 (73.6)	1007 (80.8)
Acne	145 (11.7)	215 (17.3)	164 (13.2)	246 (19.7)
Nasopharyngitis	135 (10.9)	148 (11.9)	147 (11.9)	154 (12.4)
Upper respiratory tract infection	114 (9.2)	124 (10.0)	125 (10.1)	129 (10.4)
Blood creatine phosphokinase increased	65 (5.3)	86 (6.9)	74 (6.0)	123 (9.9)
Headache	68 (5.5)	67 (5.4)	79 (6.4)	77 (6.2)
Dermatitis atopic	70 (5.7)	46 (3.7)	108 (8.7)	67 (5.4)
Oral herpes	40 (3.2)	73 (5.9)	44 (3.6)	82 (6.6)
Cough	56 (4.5)	46 (3.7)	63 (5.1)	50 (4.0)
Folliculitis	32 (2.6)	46 (3.7)	43 (3.5)	55 (4.4)
Herpes simplex	32 (2.6)	46 (3.7)	39 (3.1)	56 (4.5)
Diarrhoea	38 (3.1)	39 (3.1)	43 (3.5)	45 (3.6)
Pyrexia	37 (3.0)	38 (3.1)	44 (3.6)	41 (3.3)
Herpes zoster	29 (2.3)	42 (3.4)	44 (3.6)	62 (5.0)
Nausea	31 (2.5)	38 (3.1)	35 (2.8)	40 (3.2)
Urinary tract infection	27 (2.2)	41 (3.3)	36 (2.9)	57 (4.6)
Weight increased	23 (1.9)	32 (2.6)	28 (2.3)	40 (3.2)
Oropharyngeal pain	25 (2.0)	30 (2.4)	28 (2.3)	31 (2.5)
Influenza like illness	23 (1.9)	30 (2.4)	23 (1.9)	33 (2.6)
Influenza	24 (1.9)	26 (2.1)	25 (2.0)	25 (2.0)
Gastroenteritis	20 (1.6)	29 (2.3)	25 (2.0)	31 (2.5)
Bronchitis	18 (1.5)	25 (2.0)	20 (1.6)	25 (2.0)
Abdominal pain upper	23 (1.9)	14 (1.1)	26 (2.1)	14 (1.1)
Impetigo	21 (1.7)	18 (1.4)	32 (2.6)	24 (1.9)
Alanine aminotransferase increased	20 (1.6)	18 (1.4)	28 (2.3)	32 (2.6)
Aspartate aminotransferase increased	12 (1.0)	16 (1.3)	19 (1.5)	28 (2.2)
Back pain	21 (1.7)	23 (1.9)	24 (1.9)	27 (2.2)
Abdominal pain	13 (1.1)	20 (1.6)	17 (1.4)	25 (2.0)
Urticaria	22 (1.8)	22 (1.8)	31 (2.5)	26 (2.1)
Eczema	16 (1.3)	12 (1.0)	25 (2.0)	20 (1.6)

AD = atopic dermatitis; CSS = clinical summary of safety; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; SUR = Safety Update Report; TEAE = treatment-emergent adverse event; UPA = upadacitinib

TEAES by severity

The EAER of severe TEAEs was lower in the upadacitinib 15 mg group compared with the upadacitinib 30 mg group. The most common severe TEAEs (≥ 0.5 E/100 PY) which occurred at a higher EAER in upadacitinib 30 mg compared with upadacitinib 15 mg were herpes zoster, blood creatine phosphokinase increased, and asthma.

New Adverse Drug Reactions for Labelling

Within the AD study program, seven new ADRs were identified that have previously not been identified in RA, PsA or AS studies (table below). For the purposes of representation in the ADR table in section 4.8, the frequencies in the upadacitinib 30 mg and 15 mg groups are presented based on the PBO-controlled AD Analysis Set. Of note, all existing ADRs included in the prescribing information for the indication of RA remain for the indication of AD based on the safety data available and/or considering the mechanism of action for JAK inhibitors.

In addition to the seven new ADRs, acne was identified in the AD studies. This ADR was previously identified within the PsA program but is not listed in the currently approved SmPC (for the RA indication). Within the PsA program, the ADR of acne was observed at a rate of ≥ 1% – < 10% in the placebo-controlled period that meets the frequency of common compared to a higher rate (≥ 10%) in the placebo-controlled period of the AD program that meets the very common category.

Table 37   New Adverse Drug Reactions Identified in the Atopic Dermatitis Program (PBO-controlled AD Analysis Set)

System Organ Class	Preferred Term	UPA 15 mg QD N = 899 n (%)	UPA 30 mg QD N = 906 n (%)	PBO N = 902 n (%)
Infections and Infestations	Folliculitis	2.1	3.2	1.1
	Influenza	2.1	1.5	0.3
Blood and lymphatic system disorders	Anaemia	0.2	1.0	0.2
Gastrointestinal disorders	Abdominal pain[a]	2.9	2.3	0.8
General disorders and administration site conditions	Fatigue	1.3	1.9	0.6
Skin and subcutaneous tissue disorders	Urticaria	0.9	1.5	0.3
Nervous system disorders	Headache	5.6	6.3	4.3

a.   Includes abdominal pain and abdominal pain upper.

Additionally, the frequency of a few existing ADRs was changed compared to what was observed in the RA clinical program.

Increased frequency: herpes simplex and herpes zoster occurred at rates which were common (≥ 1% – < 10%) rather than uncommon (< 1%).

Decreased frequency: hypercholesterolemia, ALT increased, and AST increased occurred at rates which were uncommon rather than common.

The updated data provided with the SUR (24 November 2020 cut-off) did not change the conclusions regarding ADRs as compared with the originally submitted data (04 June, 2020 cut-off).

Covid-19

As of the data cut-off for SUR (24 Nov, 2020), there were 21 subjects in the upadacitinib 30 mg group and 17 subjects in the upadacitinib 15 mg group who reported events of corona virus infection (PT). Additionally, 1 subject with a positive coronavirus test and no associated symptoms was reported in the upadacitinib 15 mg group. Most of these cases have been reported after the original CSS, consistent with the increasing numbers of COVID-19 cases being reported in the general population in several countries.

Cumulatively, the event rate of COVID-19 was 1.5 E/100 PY and 1.1 E/100 PY in the upadacitinib 30 mg and 15 mg groups, respectively. Of the new COVID-19 cases, 4 were reported as SAEs in the upadacitinib 30 mg group. In the initial submission, there were 2 SAEs of COVID-19 infection, 1 each in the upadacitinib 30 mg and 15 mg treatment groups. The event rate of serious COVID-19 infection was 0.3 E/100 PY in the upadacitinib 30 mg group and < 0.1 E/100 PY in the upadacitinib 15 mg group.

Adverse events of special interest

Adverse event of special interest (AESI) were identified for upadacitinib based on safety concerns reported for other JAK inhibitor products, as well as upadacitinib data from preclinical studies, and customary regulatory concerns for novel small molecule drugs.

The AESIs were, thus:

- serious infection;

- opportunistic infections (excluding TB and herpes zoster);

- herpes zoster;

- active TB;

- malignancy (including NMSC, malignant tumours excluding NMSC, and lymphoma);

- hepatic disorders;

- adjudicated GI perforation;

- adjudicated MACE (defined as CV death, non-fatal myocardial infarction [MI] and non-fatal stroke);

- adjudicated venous thromboembolic events (VTE), defined as PE and deep vein thrombosis (DVT) and other venous and arterial thromboembolic events (non-cardiac, non-neurologic);

- anaemia;

- neutropenia;

- lymphopenia;

- renal dysfunction, and

- CPK elevation.

Serious infection

During the 16-week placebo-controlled period, the percentages of subjects with serious infections were similar across the upadacitinib 30 mg, upadacitinib 15 mg, and placebo groups (0.4%, 0.8%, and 0.6%, respectively). The percentage of subjects with serious infection that led to discontinuation of study drug was 0.2% in the upadacitinib 30 mg, 0.1% in the placebo group; no subjects in the upadacitinib 15 mg group discontinued study drug due to a serious infection. No adolescent subject discontinued study drug due to a serious infection.

Original CSS (04 June 2020 cut-off)

In the Long-term Upadacitinib Phase 3 AD Analysis Set, the EAERs of serious infections were higher in the upadacitinib 30 mg group (3.4 E/100 PY) compared with the upadacitinib 15 group (2.4 E/100 PY). Pneumonia was the most commonly reported serious infection.

One subject (with a total of 2 serious events) in the upadacitinib 15 mg group and 8 subjects (with a total of 12 serious events) in the upadacitinib 30 mg group experienced serious infections that led to discontinuation of study drug, with an EAER of 0.2 E/100PY and 1.3 E/100 PY, respectively.

The risk of subjects experiencing a serious infection with upadacitinib therapy remained generally stable up to Month 12. After Month 12, the small sample size limits a meaningful interpretation of the data.

Based on analysis of the limited data for elderly (28.8 PY for upadacitinib 15 mg and 48.6 PY for upadacitinib 30 mg), no consistent pattern was observed regarding the risks of serious infection between subjects ≥ 65 years of age and those < 65 years of age.

SUR (24 Nov 2020 cut-off)

The EAER of serious infections with upadacitinib 30 mg and upadacitinib 15 mg was 2.8 E/100 PY and 2.3 E/100 PY, respectively, in this SUR compared to 3.4 E/100 PY and 2.4 E/100 PY, respectively, in the originally submitted CSS. The EAER of serious infections in adolescents was similar between the upadacitinib 30 mg and 15 mg groups. The types of serious infections reported continued to be consistent with those anticipated in a population of patients with AD known for upadacitinib, or reflective of the current COVID-19 pandemic outbreak. The risk of subjects experiencing a serious infection in the upadacitinib 30 mg or upadacitinib 15 mg groups did not appear to increase with longer duration of treatment.

Of note, in the CSS, 4 serious infectious events were reported at the same time in 1 subject in the upadacitinib 30 mg group. Two of the serious events (blood culture positive and culture urine positive) were diagnostic test results for the reported serious infections of staphylococcal sepsis and osteomyelitis. Thus, these 2 diagnostic test result events were deleted by the investigator after the database lock for the CSS. As a result, the number of serious infections in the upadacitinib 30 mg group for adolescents was fewer in the SUR compared to the CSS.

Opportunistic Infection excluding tuberculosis and herpes zoster

Original CSS (04 June, 2020 cut-off)

In the AD clinical trials, all but one of the 47 opportunistic infection (excluding TB and herpes zoster) were cases of eczema herpeticum or Kaposi's varicelliform eruption, which are known to be associated with AD. These events were reported in both the placebo and upadacitinib treatment groups. The rates of eczema herpeticum were similar in the upadacitinib 30 mg and 15 mg groups with long term treatment. Across the AD clinical program, 4 events of eczema herpeticum were serious and the numbers of serious cases were not higher on upadacitinib 30 mg.

Most opportunistic infections reported in the global Phase 3 studies continued to be eczema herpeticum or the synonymous Kaposi's varicelliform eruption. The EAERs of opportunistic infections with upadacitinib 30 mg and 15 mg treatment were similar in this SUR (1.9 E/100 PY and 1.6 E/100 PY, respectively) compared to the CSS (2.2 E/100 PY and 2.1 E/100 PY, respectively). No additional events of eczema herpeticum were reported in adolescents since the initial AD submission.

Herpes zoster

Original CSS (04 June, 2020 cut-off)

In the PBO-controlled AD Analysis Set, the rates of herpes zoster were similar between the upadacitinib 30 mg and 15 mg groups but higher compared to the placebo group. In the adolescent group, the rate of herpes zoster was higher in the upadacitinib 30 mg compared to the upadacitinib 15 mg group; no herpes zoster events were reported in the placebo group. Most events of herpes zoster were mild or moderate in severity and were considered by the investigator to have a reasonable possibility of being related to study drug.

In the Long-term Upadacitinib Phase 3 AD Analysis Set, EAERs for TEAEs of herpes zoster were higher in the upadacitinib 30 mg compared to the upadacitinib 15 mg group. No subject had ocular, CNS, lung, or liver involvement. One serious event of disseminated herpes zoster were reported in the upadacitinib 30 mg group and two in the upadacitinib 15 mg group; one led to discontinuation of study drug. The pattern was similar in adolescents (table below).

Table 38   Treatment-Emergent Herpes Zoster EAER Per 100 PY (Long-term Upadacitinib Phase 3 AD Analysis Set)

System Organ Class MedDRA 22.1 Preferred Term	Overall		Adolescents	
	UPA 15 mg QD (N = 1238) (PY = 872.2)	UPA 30 mg QD (N = 1242) (PY = 892.7)	UPA 15 mg QD (N = 167) (PY = 122.6)	UPA 30 mg QD (N = 166) (PY = 125.5)
	E (E/100 PY)			
Any adverse event	33 (3.8)	47 (5.3)	1 (0.8)	5 (4.0)
Infections and infestations	31 (3.6)	46 (5.2)	1 (0.8)	5 (4.0)
Herpes zoster	29 (3.3)	44 (4.9)	1 (0.8)	5 (4.0)
Herpes zoster cutaneous disseminated	1 (0.1)	0	0	0
Herpes zoster disseminated	1 (0.1)	0	0	0
Herpes zoster oticus	0	1 (0.1)	0	0
Varicella zoster virus infection	0	1 (0.1)	0	0
Nervous system disorders	2 (0.2)	1 (0.1)	0	0
Post herpetic neuralgia	2 (0.2)	1 (0.1)	0	0

Similar to what has been reported in the published literature, subjects living in Asian regions who received upadacitinib had a higher rate of herpes zoster infection. Data were too limited to draw conclusions for subgroups age ≥65 years or prior history of herpes zoster vaccination or prior history of herpes zoster.

The risk of subjects experiencing a herpes zoster event appeared to increase over the first 6 months and then tended to stabilize between 6 to 12 months with continued treatment with upadacitinib. However, the number of subjects at month 12 and after was small for a meaningful interpretation.

SUR (24 Nov, 2020 cut-off)

The EAER of herpes zoster with upadacitinib 30 mg was higher than 15 mg treatment in this SUR (5.2 E/100 PY and 3.5 E/100 PY, respectively), similar to what was observed in the CSS (5.3 E/100 PY and 3.8 E/100 PY, respectively). A similar trend was observed in adolescents. The majority of the herpes zoster cases continued to be nonserious and manifest as localized cutaneous involvement (1 dermatome or 2 dermatomes on the same side). No events of central nervous system (CNS), lung, or liver involvement have been reported in the AD clinical program.

Active tuberculosis

Subjects with latent TB were allowed to enrol in the AD studies after initiating appropriate prophylactic treatment at least 2 weeks prior to first administration of study drug (or per local guidelines, whichever was longer).

Original CSS (04 June, 2020 cut-off)

There were no cases of active TB during the 16-week placebo-controlled period.

In the Long-term Upadacitinib Phase 3 AD Analysis Set, EAERs for TEAEs of active TB were the same in both upadacitinib groups (1 case each, 0.1E/100PY). Both active TB events were considered by the investigator to have a reasonable possibility of being related to study drug.

No adolescent subjects reported an event of active TB in the upadacitinib AD program.

SUR (24 Nov, 2020 cut-off)

No additional events of active TB were reported since the initial submission. Cumulatively there remains 2 events of active TB reported (1 event each on upadacitinib 30 mg and upadacitinib 15 mg).

Malignancy

Patients with AD have been reported to have an increased incidence of cancer overall as well as of specific cancer subtypes including skin lymphoma and non-melanoma skin cancer (NMSC).

Original CSS (04 June, 2020 cut-off)

NMSC was the most common type of malignancy reported in the AD studies but the rates were within that observed in the general population. None of the NMSC were serious. All but one NMSC (keratoacanthoma) were considered by the investigator to have no reasonable possibility of being related to study drug.

In the pivotal Phase 3 studies, the EAIRs for NMSC were similar in the upadacitinib 30 mg and 15 mg groups (table below). One subject, in the upadacitinib 30 mg group, experienced a non-serious, moderate TEAE of cutaneous T-cell lymphoma (CTCL) considered by the investigator to have no reasonable possibility of being related to study drug. Medical review of this case indicates that the subject likely had CTCL at baseline based on the clinical history and histological findings. Furthermore, the weak temporal association with less than 7 months of study drug exposure makes the risk of CTCL due to upadacitinib unlikely. Another case of CTCL was entered in error.

A third case of CTCL was observed in the phase 2b study. The subject was initially on upadacitinib 15 mg until Study Day 146 followed by upadacitinib 30 mg until Study Day 574, when CTCL was diagnosed and treatment was discontinued. The event was assessed by the investigator as having no reasonable possibility of being related to study drug. Thus, altogether two confirmed events of

lymphoma (both in the upadacitinib 30 mg group) were reported in the AD clinical program (0.1 n/100 PY).

Of the 5 cases of malignancy excluding NMSC (see below), the time to onset ranged from 7 to 64 days after study start. The short time to event onset suggested an unlikely causation for upadacitinib in the occurrence of these malignant events. In addition, most of these malignancies were at an advanced stage (e.g., colon T4aN2b, anal T2N1MO, bilateral invasive ductal carcinoma) reinforcing the implausibility of the role of upadacitinib in the development of these malignancies. None of the malignancies were assessed by the investigator as having a reasonable possibility of being related to study drug.

No malignancy was reported in adolescents.

Table 39 Treatment-Emergent NMSC EAIR Per 100 PY by SOC and PT (Long-term Upadacitinib Phase 3 AD Analysis Set)

System Organ Class MedDRA 22.1 Preferred Term	Overall	
	UPA 15 mg QD (N = 1238) n/PY (n/100 PY)	UPA 30 mg QD (N = 1242) n/PY (n/100 PY)
Any adverse event	4/870.2 (0.5)	3/890.7 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4/870.2 (0.5)	3/890.7 (0.3)
Basal cell carcinoma	1/871.8 (0.1)	0/892.7
Bowen's disease	1/871.3 (0.1)	0/892.7
Cutaneous T-cell lymphoma*	0/872.2	2/891.9 (0.2)
Keratoacanthoma	0/872.2	1/891.5 (0.1)
Squamous cell carcinoma of skin	2/871.5 (0.2)	0/892.7

*One case was entered in error and the event was a fungal infection – mycosis inquinalis

Table 40 Treatment-Emergent Malignancy Excluding NMSC EAIR per 100 PY by SOC and PT (Long-term Upadacitinib Phase3 AD Analysis Set)

System Organ Class MedDRA 22.1 Preferred Term	Overall	
	UPA 15 mg QD (N = 1238) n/PY (n/ 100PY)	UPA 30 mg QD (N = 1242) n/PY (n/ 100PY)
Any adverse event	0/872.2	6/891.4 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0/872.2	6/891.4 (0.7)
Adenocarcinoma of colon	0/872.2	1/892.6 (0.1)
Anal squamous cell carcinoma	0/872.2	1/892.7 (0.1)
Gastric cancer	0/872.2	1/892.7 (0.1)
Invasive ductal breast carcinoma	0/872.2	1/892.7 (0.1)
Malignant melanoma in situ	0/872.2	1/892.4 (0.1)
Squamous cell carcinoma*	0/872.2	1/891.9 (0.1)

*Medical review confirmed event was a squamous cell carcinoma of the skin (a NMSC)

The exposure-adjusted incidence rates (EAIRs) for malignancies excluding NMSC with upadacitinib 30 mg and 15 mg were 0.5 n/100 PY and 0.1 n/100 PY, respectively, in this SUR compared to 0.7 n/100 PY with upadacitinib 30 mg and no events in the upadacitinib 15 mg group, respectively, in the CSS. The age-gender-adjusted standardized incidence ratio (SIR) for malignancies excluding NMSC in this SUR continues to indicate that the malignancy risk with upadacitinib treatment remained within what is expected for the general population. For NMSC, rates in the upadacitinib 30 mg and 15 mg groups were similar as of the data cut-off for the SUR (0.4 n/100 PY and 0.3 n/100 PY, respectively). No additional events of lymphoma were reported. No malignancy was reported in adolescents.

Hepatic disorders

Original CSS (04 June, 2020 cut-off)

Most events of hepatic disorder were transient, asymptomatic elevations in transaminases detected by laboratory testing. The transaminase elevations were similar between upadacitinib 30 mg and upadacitinib 15 mg. No hepatic events were serious, and few led to study drug discontinuation (table below). No subjects were identified as meeting biochemical criteria for Hy's Law.

The percentages of subjects with ALT or AST $\geq 5 \times$ ULN were less than 1% in both upadacitinib treatment groups. No subjects experienced ALT $\geq 10 \times$ ULN. The percentages of subjects with AST $\geq 10\times$ ULN were similar for both upadacitinib 30 mg and 15 mg groups (0.3% vs. 0.2%). After the placebo-controlled period, 1 subject in the upadacitinib 15 mg group experienced AST$\geq 20 \times$ ULN.

Transaminase elevations usually resolved or were resolving with study drug ongoing or temporary interruption. Most elevations in ALT and/or AST were confounded by use of concomitant medications including nonsteroidal anti-inflammatory drug (NSAID).

Five adolescent subjects, all in the upadacitinib 15 mg group reported a treatment-emergent hepatic disorder event. All these events were nonserious transaminase or bilirubin elevations.

Table 41   Treatment-Emergent Hepatic Disorder in EAER (Long-term Upadacitinib Phase 3 AD Analysis Set)

System Organ Class MedDRA 22.1 Preferred Term	Overall		Adolescents	
	UPA 15 mg QD (N = 1238) (PY = 872.2) E (E/100 PY)	UPA 30 mg QD (N = 1242) (PY = 892.7) E (E/100 PY)	UPA 15 mg QD (N = 167) (PY = 122.6) E (E/100 PY)	UPA 30 mg QD (N = 166) (PY = 125.5) E (E/100 PY)
Any Adverse Event	52 (6.0)	66 (7.4)	9 (7.3)	2 (1.6)
Hepatobiliary disorders	5 (0.6)	16 (1.8)	1 (0.8)	1 (0.8)
Hepatic function abnormal	4 (0.5)	1 (0.1)	1 (0.8)	0
Hepatic steatosis	1 (0.1)	9 (1.0)	0	0
Hepatocellular injury	0	1 (0.1)	0	0
Hepatomegaly	0	3 (0.3)	0	0
Hyperbilirubinaemia	0	1 (0.1)	0	1 (0.8)
Non-alcoholic steatohepatitis	0	1 (0.1)	0	0
Investigations	47 (5.4)	50 (5.6)	8 (6.5)	1 (0.8)
Alanine aminotransferase abnormal	0	1 (0.1)	0	0
Alanine aminotransferase increased	25 (2.9)	23 (2.6)	1 (0.8)	0
Aspartate aminotransferase abnormal	1 (0.1)	0	0	0
Aspartate aminotransferase increased	14 (1.6)	17 (1.9)	4 (3.3)	0
Blood bilirubin increased	3 (0.3)	0	1 (0.8)	0
Hepatic enzyme increased	2 (0.2)	2 (0.2)	1 (0.8)	1 (0.8)
Liver function test increased	1 (0.1)	0	0	0
Transaminases increased	1 (0.1)	7 (0.8)	1 (0.8)	0

<u>SUR (24 Nov, 2020 cut-off)</u>

The cumulative proportions of subjects on any upadacitinib dose with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 5 × upper limit of normal (ULN) on at least 1 occasion in this SUR was similar (< 2.0%) to that in the CSS. A similar trend was observed in adolescents. Most events of hepatic disorder continued to be transient elevations in transaminases. Cumulatively, through the data cut-off for this SUR, no reports were judged to be true Hy's law cases.

GI perforation

No treatment-emergent adjudicated GI perforation event was reported in the AD clinical program.

Anaemia

<u>Original CSS (04 June, 2020 cut-off)</u>

The mean haemoglobin values decreased dose-dependently over the first 16 weeks of upadacitinib 30 mg and 15 mg treatment and then improved towards baseline and stabilised with continued treatment (see figure below). TEAEs of anaemia were similar in the placebo and upadacitinib 15 mg groups, but higher in the upadacitinib 30 mg group. Grade 2 haemoglobin decreases were slightly

higher in the upadacitinib 30 mg group and similar between the upadacitinib 15 mg and placebo groups. One subject in the upadacitinib 30 mg group had a Grade 3 haemoglobin decrease. One event of anaemia was serious and led to discontinuation of study drug in subjects on upadacitinib 30 mg. A similar trend was observed in adolescents but with no events being severe, serious, or leading to discontinuation of study drug.

As discussed above, anaemia has been identified as an ADR in the AD population for listing in section 4.8 of the SmPC.
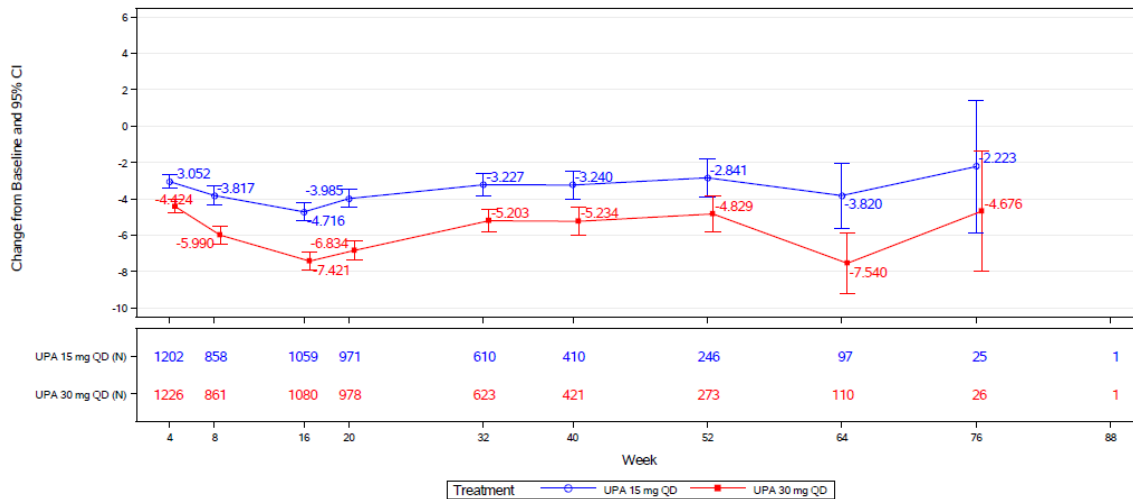
Figure 33   Plot of Mean Change from Baseline in Haemoglobin Values Over Time (Long-term Upadacitinib Phase 3 AD Analysis Set)

SUR (24 Nov, 2020 cut-off)

Mean haemoglobin decreases and TEAE rates of anaemia observed in this SUR were consistent with the initial submission. Grade 3 haemoglobin decreases were only seen in subjects in the upadacitinib 30 mg group. Similar to the CSS, TEAEs of anaemia were reported at a higher rate in the upadacitinib 30 mg group compared to the upadacitinib 15 mg group. Since the initial submission, there were no new SAEs of anaemia and treatment discontinuation due to events of anaemia was uncommon (≤0.2%). In adolescents, a lower rate of anaemia in the upadacitinib 30 mg group compared to the upadacitinib 15 mg group was observed.

Neutropenia

Original CSS (04 June, 2020 cut-off)

Administration of upadacitinib was associated with small decreases in mean neutrophil count during the treatment period. The event rate of TEAEs of neutropenia were greater for subjects in the upadacitinib 30 mg compared with subjects in the upadacitinib 15 mg group. The percentage of subjects with Grade 3 decreases in neutrophil count was higher but still low for subjects in the upadacitinib 30 mg group (1.3%) as compared to the upadacitinib 15 mg group. Two subjects, both in the upadacitinib 30 mg group, experienced Grade 4 decreases in neutrophils, which did not lead to discontinuation. No neutropenia events were serious, but two events led to discontinuation of study drug in the upadacitinib 30 mg group. There was no clear evidence of an association of overall infections, serious infections, opportunistic infections and herpes zoster with low neutrophil counts.

In the adolescent subgroup, similar dose dependent patterns were noted.

SUR (24 Nov, 2020 cut-off)

Mean decreases in neutrophil count observed in this SUR were consistent with the initial submission. Similar to the CSS, Grade 3 decreases in neutrophils remained lower with upadacitinib 15 mg than upadacitinib 30 mg. The EAER of TEAEs of neutropenia with upadacitinib 30 mg and 15 mg treatment did not increase in this SUR (3.2 E/100 PY and 1.8 E/100 PY, respectively) compared to the CSS (4.7 E/100 PY and 2.5 E/100 PY, respectively). No SAEs of neutropenia were reported, and treatment discontinuation due to neutropenia AEs remained uncommon (≤ 0.2%). A similar trend was observed in adolescents.

Lymphopenia

Original CSS (04 June, 2020 cut-off)

The rate of reported TEAEs of lymphopenia were similar with upadacitinib 30 mg and upadacitinib 15 mg (0.7 E/100 PY and 0.6 E/100 PY, respectively). However, Grade 3 decreases in lymphocytes appeared to be slightly more common at the 30 mg dose. In two subjects in the upadacitinib 30 mg group, grade 3 decreases in lymphocyte count were associated with herpes zoster infection and eczema herpeticum, respectively. The events were non-serious. In both cases, the lymphopenia normalised and did not reoccur despite continuing study drug. No subjects discontinued study drug due to a TEAE of lymphopenia.

SUR (24 Nov, 2020 cut-off)

Similar to the CSS, Grade ≥ 3 lymphopenia and TEAEs of lymphopenia were observed at a higher rate on upadacitinib 30 mg compared with upadacitinib 15 mg. No subject discontinued study drug due to a TEAE of lymphopenia in the upadacitinib AD program and no adolescent subjects had a TEAE of lymphopenia in the upadacitinib AD program.

Creatine Phosphokinase Elevation

Original CSS (04 June, 2020 cut-off)

Mean increases from baseline to Week 52 in CPK values, the percentage of subjects with ≥ Grade 3 CPK elevations, and the rates of TEAEs of CPK elevation were higher in the upadacitinib 30 mg group compared to the upadacitinib 15 mg group. Grade 4 CPK elevations were similar between the two groups. Most of these CPK elevations were transient. No reported TEAEs of blood CPK elevation were serious. TEAEs of blood CPK elevations leading to study drug discontinuation were infrequent.

In adolescent subjects, the EAER of TEAEs of CPK elevation were lower in the upadacitinib 30 mg group compared with the upadacitinib 15 mg group. There were no SAEs or TEAEs which led to study drug discontinuation in adolescent subjects.

One subject in the upadacitinib 15 mg group experienced blood CPK increase that was diagnosed and reported as rhabdomyolysis. This subject experienced a creatine phosphokinase (CPK) increase (27,814 – 47,012 U/L) with muscle pain after riding a jet ski, which was diagnosed as rhabdomyolysis on Study Day 85. There was no change of renal function. Study drug was discontinued. The patient was hospitalized, treated with intravenous hydration, and the event resolved on Study Day 113. This severe, serious event was considered by the investigator to have a reasonable possibility of being related to study drug with the alternative etiology of jet ski riding.

SUR (24 Nov, 2020 cut-off)

Similar to the CSS, rates of creatine phosphokinase (CPK) elevation in this SUR were higher in the upadacitinib 30 mg group compared to the 15 mg group. CPK elevations were generally nonserious and treatment discontinuation due to CPK elevation was infrequent (≤ 0.2%). A similar trend of CPK

elevations was observed in adolescents. A new case of asymptomatic Grade 4 blood CPK increased was reported as serious in a patient who was hospitalized for IV hydration.

Renal dysfunction

Original CSS (04 June, 2020 cut-off)

Administration of upadacitinib was generally associated with small increases in mean serum creatinine during the treatment period (see figure below). Through the data cutoff, a total of two nonserious renal dysfunction (both acute kidney injury) were reported, one case each in the upadacitinib 30 mg and 15 mg groups. Neither was considered to be study drug related. Neither event led to discontinuation of study drug. No adolescent subjects experienced TEAEs of renal dysfunction.
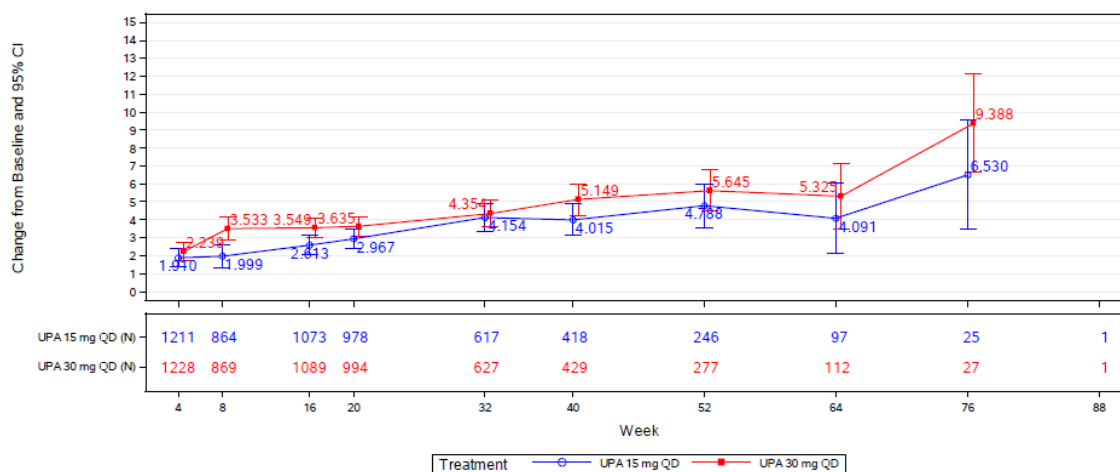
Figure 34   Plot of Mean Change from Baseline in Creatinine Values Over Time (Long-term Upadacitinib Phase 3 AD Analysis Set)

SUR (24 Nov, 2020 cut-off)

Serum creatinine levels and TEAE rates of renal dysfunction observed in this SUR were consistent with the initial submission. TEAEs of renal dysfunction continued to remain infrequent (0.1%) in subjects treated with upadacitinib 30 mg or 15 mg. No adolescent subjects experienced TEAEs of renal dysfunction.

Adjudicated major adverse cardiovascular event (MACE) and Other Cardiovascular Events

Original CSS (04 June, 2020 cut-off)

In the global phase 3 studies, the EAIRs of treatment-emergent MACE were the same for upadacitinib 30 mg group and the upadacitinib 15 mg group (0.1 n/100 PY) with one event each in both groups: cerebrovascular accident and ischemic stroke, respectively. One additional event (cerebellar haemorrhage) was observed in the upadacitinib 15 mg in the Japan Study M17-377. All three MACE were serious and led to discontinuation of study drug. No MACE was fatal. Multiple CV risk factors were present in two of the three subjects who had an event of MACE, including pre-existing CV conditions, hyperlipidemia, diabetes, smoking, and obesity. In the case from the Japan study, no specific risk factors were reported by the investigator. There were no other adjudicated CV events reported in the upadacitinib AD program.

SUR (24 Nov, 2020 cut-off)

Since the initial submission, 1 additional subject receiving upadacitinib 15 mg had a treatment-emergent adjudicated major adverse cardiovascular event (MACE) of non-fatal stroke. Cumulatively as of the data cut-off for this SUR, there was 1 event of MACE (< 0.1 n/100 PY) in the upadacitinib 30 mg

group and 2 events of MACE (0.1 n/100 PY) in the upadacitinib 15 mg group. No MACE was reported in adolescents.

Adjudicated Thrombotic Events

Original CSS (04 June, 2020 cut-off)

No adjudicated VTEs were reported in subjects receiving upadacitinib in the global Phase 3 studies. In the overall AD program, there was 1 adjudicated VTE event of PE reported in a subject receiving upadacitinib 30 mg in the Phase 2 Study M16-048. This subject was a 69-year-old female subject with a history of hypertension, hypercholesterolemia, ischemic heart disease, obesity, and current smoker who experienced pulmonary emboli on Study Day 463.

SUR (24 Nov, 2020 cut-off)

Since the initial submission, there was 1 new treatment-emergent adjudicated venous thromboembolic event each in a subject on upadacitinib 30 mg (PE, < 0.1 n/100 PY) and on upadacitinib 15 mg (DVT, < 0.1 n/100 PY) in the global Phase 3 studies. The overall exposure adjusted incidence rate (EAIR) of treatment-emergent adjudicated VTEs was < 0.1 n/100 PY in subjects receiving upadacitinib. No VTE was reported in adolescents.

Serious adverse event/deaths/other significant events

In the PBO-controlled AD Analysis Set, the percentages of subjects with SAEs was similar between the treatment groups (2.1% for both the upadacitinib 30 mg group and the upadacitinib 15 mg group, and 2.9% for the placebo group) (see table below).

Table 42   Treatment-Emergent Serious Adverse Events Reported in ≥ 0.2% in any Treatment Group by Decreasing Frequency Overall (PBO-controlled AD Analysis Set)

System Organ Class MedDRA 22.1 Preferred Term	Overall			Adolescent		
	Placebo (N = 902) n (%)	UPA 15 mg QD (N = 899) n (%)	UPA 30 mg QD (N = 906) n (%)	Placebo (N = 115) n (%)	UPA 15 mg QD (N = 114) n (%)	UPA 30 mg QD (N = 114) n (%)
Any TEAE	26 (2.9)	19 (2.1)	19 (2.1)	3 (2.6)	3 (2.6)	0
Dermatitis atopic	6 (0.7)	1 (0.1)	0	2 (1.7)	1 (0.9)	0
Appendicitis	0	3 (0.3)	0	0	0	0
Retinal detachment	0	2 (0.2)	0	0	0	0
Anaphylactic reaction	1 (0.1)	0	2 (0.2)	0	0	0
Dermatitis exfoliative generalized	2 (0.2)	0	0	0	0	0
Eczema	2 (0.2)	0	0	0	0	0
Cellulitis	1 (0.1)	0	0	1 (0.9)	0	0
Impetigo	1 (0.1)	1 (0.1)	0	0	1 (0.9)	0
Subcutaneous abscess	1 (0.1)	0	0	1 (0.9)	0	0
Suicide attempt	1 (0.1)	1 (0.1)	1 (0.1)	0	1 (0.9)	0
Pneumomediastinum	0	1 (0.1)	0	0	1 (0.9)	0

AD = atopic dermatitis; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; QD = once daily; TEAE = treatment-emergent serious adverse event; UPA = upadacitinib

In the Long-term Upadacitinib Phase 3 AD Analysis Set, the EAERs of SAEs were 7.7 E/100 PY and 7.1 E/100 PY in the upadacitinib 30 mg and 15 mg groups, respectively in the SUR, compared to 8.4 E/100 PY and 7.1 E/100 PY for the overall upadacitinib 30 mg and 15 mg groups, respectively, in the CSS.

The most frequently reported SAEs per PT (≥ 0.2 E/100 PY in any treatment group) are presented in the table below.

The majority of SAEs (by MedDRA PT) were reported in 1 subject each in the treatment groups. SAEs with the highest EAER in the upadacitinib 30 mg and 15 mg groups were pneumonia and coronavirus infection (upadacitinib 30 mg) and dermatitis atopic (upadacitinib 15 mg).

In the initial submission, a total of five serious hypersensitivity events, all in adult patients, were reported across the treatment groups (two in the placebo group, one in the upadacitinib 15 mg group, and two in the upadacitinib 30 mg group). None of these events were considered by the investigator to have a reasonable possibility of being related to study drug, all having likely alternative etiologies.

Since the initial submission, 1 additional SAE of drug hypersensitivity was reported in a subject on upadacitinib 30 mg. The event was considered by the investigator related to study drug and the subject was withdrawn from the study.

Table 43 Treatment-Emergent Serious Adverse Events Reported in ≥ 0.2 Events Per 100 PY in any Treatment Group by Decreasing Frequency Overall (Long-term Upadacitinib Phase 3 AD Analysis Set)

System Organ Class MedDRA 22.1 Preferred Term	CSS (Data Cutoff 04 Jun 2020)				SUR (Data Cutoff 24 Nov 2020)			
	Overall		Adolescents		Overall		Adolescents	
	UPA 15 mg QD (N = 1238) (PY = 872.2)	UPA 30 mg QD (N = 1242) (PY = 892.7)	UPA 15 mg QD (N = 167) (PY = 122.6)	UPA 30 mg QD (N = 166) (PY = 125.5)	UPA 15 mg QD (N = 1239) (PY = 1373.4)	UPA 30 mg QD (N = 1246) (PY = 1414.2)	UPA 15 mg QD (N = 167) (PY = 191.7)	UPA 30 mg QD (N = 166) (PY = 195.9)
	E (E/100 PY)							
Any Adverse Event	62 (7.1)	75 (8.4)	6 (4.9)	7 (5.6)	98 (7.1)	109 (7.7)	15 (7.8)	7 (3.6)
Pneumonia	2 (0.2)	5 (0.6)	0	1 (0.8)	2 (0.1)	5 (0.4)	0	1 (0.5)
Dermatitis atopic	4 (0.5)	0	1 (0.8)	0	7 (0.5)	2 (0.1)	3 (1.6)	1 (0.5)
Eczema herpeticum	3 (0.3)	1 (0.1)	0	0	4 (0.3)	1 (<0.1)	0	0
Coronavirus infection	1 (0.1)	1 (0.1)	0	0	1 (<0.1)	5 (0.4)	0	0
Appendicitis	3 (0.3)	0	0	0	3 (0.2)	0	0	0
Retinal detachment	3 (0.3)	0	0	0	3 (0.2)	0	0	0
Mania	2 (0.2)	0	0	0	2 (0.1)	0	0	0
Asthma	1 (0.1)	2 (0.2)	0	0	2 (0.1)	2 (0.1)	0	0
Abortion Induced	1 (0.1)	2 (0.2)	0	0	2 (0.1)	2 (0.1)	0	0
Rhegmatogenous retinal detachment	0	2 (0.2)	0	0	0	2 (0.1)	0	0
Palpitations	0	2 (0.2)	0	0	0	2 (0.1)	0	0
Pancreatitis	0	2 (0.2)	0	0	0	2 (0.1)	0	0
Anaphylactic reaction	0	2 (0.2)	0	0	0	2 (0.1)	0	0
Eczema infected	0	1 (0.1)	0	1 (0.8)	1 (<0.1)	1 (<0.1)	1 (0.5)	1 (0.5)
Impetigo	1 (0.1)	0	1 (0.8)	0	2 (0.1)	0	2 (1.0)	0
Osteomyelitis	0	1 (0.1)	0	1 (0.8)	0	1 (<0.1)	0	1 (0.5)
Pyelonephritis	0	1 (0.1)	0	1 (0.8)	0	2 (0.1)	0	1 (0.5)
Staphylococcal sepsis	0	1 (0.1)	0	1 (0.8)	0	1 (<0.1)	0	1 (0.5)
Blood culture positive*	0	1 (0.1)	0	1 (0.8)	0	0	0	0
Culture urine positive*	0	1 (0.1)	0	1 (0.8)	0	0	0	0
Major depression#	1 (0.1)	0	1 (0.8)	0	0	0	0	0
Suicidal ideation	1 (0.1)	0	1 (0.8)	0	1 (<0.1)	0	1 (0.5)	0
Suicide attempt	1 (0.1)	1 (0.1)	1 (0.8)	0	3 (0.2)	1 (<0.1)	2 (1.0)	0
Pneumomediastinum	1 (0.1)	0	1 (0.8)	0	1 (<0.1)	0	1 (0.5)	0
Herpes simplex	0	0	0	0	0	3 (0.2)	0	0
Periorbital cellulitis	0	0	0	0	1 (<0.1)	0	1 (0.5)	1 (0.5)
Ovarian cyst	0	0	0	0	1 (<0.1)	0	1 (0.5)	0
Cataract	0	0	0	0	0	1 (<0.1)	0	1 (0.5)
Bacterial infection	0	0	0	0	1 (<0.1)	0	1 (0.5)	0
Cat scratch disease	0	0	0	0	1 (<0.1)	0	1 (0.5)	0
Blood creatine phosphokinase increased	0	0	0	0	1 (<0.1)	0	1 (0.5)	0

AD = atopic dermatitis; CSS = clinical summary of safety; E/100PY = Events per 100 patient-years; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PY = patient-years; QD = once daily; SUR = Safety Update Report; UPA = upadacitinib

*   After database lock for the CSS, events of blood culture positive and culture urine positive were deleted by the investigator as distinctive PTs.

\#   Recoded as suicide attempt after database lock for the CSS.

Deaths

There were no treatment-emergent deaths reported in the PBO-controlled AD Analysis Set or the Long-term Upadacitinib Phase 3 AD Analysis Set at the original cut-off (04 June, 2020). However, in the All Upadacitinib AD Analysis set, there were 2 deaths reported in the Phase 2b study in adult subjects on upadacitinib 30 mg (one non-treatment emergent and one treatment emergent death). These events were considered unrelated to study treatment.

One treatment-emergent death in the upadacitinib 30 mg group was reported in the updated Safety report (cut-off 24 Nov, 2020). The cause of death was reported as myocardial infarction after COVID-19 in an adult subject.

Laboratory findings

Lipids

As observed previously in subjects with RA and PsA, dose dependent increases in total cholesterol (TC), HDL-C, LDL-C over placebo were seen with upadacitinib 15 mg and 30 mg in the AD studies. These increases were also observed in the long-term dataset. At 52 weeks of treatment with upadacitinib in the Phase 3 studies, the change from baseline in LDL-C in the subjects with AD was similar to that observed in subjects with RA.

Despite the increases in lipids with upadacitinib treatment, the ratios of TC/HDL-C and LDL-C/HDL-C (often used to assess the overall atherogenic potential) were maintained.
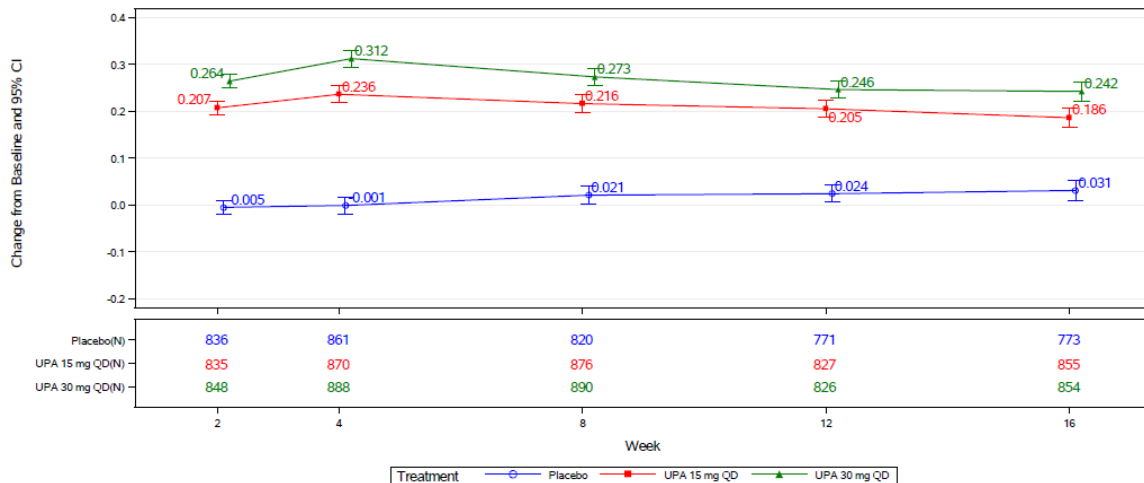
Figure 35   Mean Change from Baseline in HDL-C Over Time (PBO-controlled AD Analysis Set)
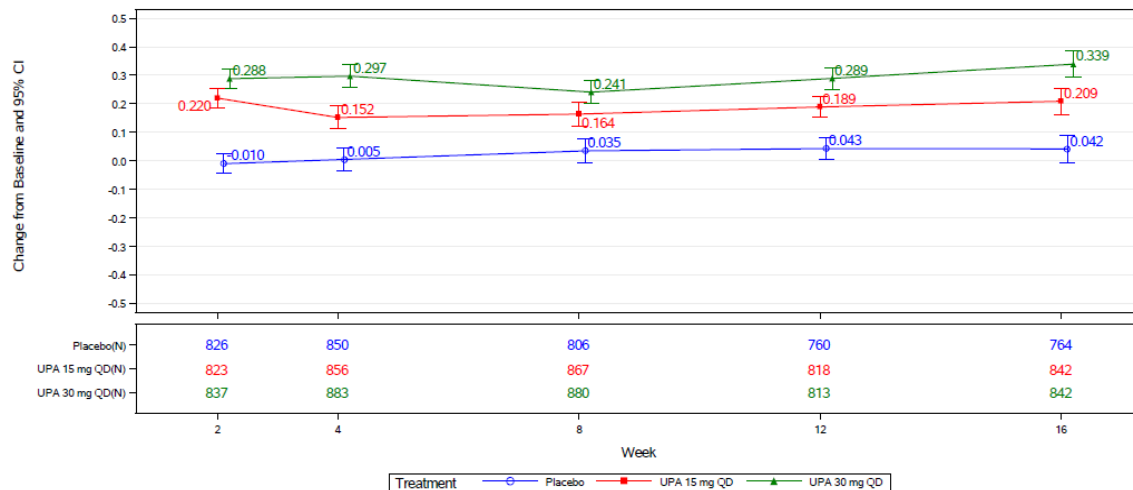
Figure 36   Mean Change from Baseline in LDL-C Over Time (PBO-controlled AD Analysis Set)

Weight and height

Weight increased is previously considered an ADR for upadacitinib and this was observed also in AD studies. In the PBO-controlled AD Analysis Set, the percentage of subjects who experienced weight increase (> 7%) was higher in the upadacitinib 30 mg (13.6%) and upadacitinib 15 mg (9.7%) groups than in the placebo group (4.4%).

In the Long-term Upadacitinib Phase 3 AD Analysis Set, the percentages of subjects with weight increase (> 7%) and weight decrease (> 7%) were 21.9% and 3.6%, respectively, in the upadacitinib 30 mg group, and 18.1% and 4.6%, respectively, in the upadacitinib 15 mg group.

The number of young adolescents in the different groups was small, however, it is noted that the mean change from baseline in height in adolescents increased similarly in the first 52 weeks for the upadacitinib 30 mg and 15 mg groups.

Additional safety topics

Suicidal Ideation and Behaviour

A medical review of the safety data from the AD clinical program was performed to identify events of suicidal ideation and behaviours (SIB), including events coded to the preferred terms of intentional overdose, intentional self-injury, suicidal ideation, suicidal behaviour, depression suicidal, suicide attempt and completed suicide.

Original CSS (04 June, 2020 cut-off)

A total of 11 events were reported among 10 subjects. Two of these were observed in placebo-treated subjects. Six events were observed in subjects treated with upadacitinib 15 mg and three at upadacitinib 30 mg. Six events were considered serious. Among the serious events, three were considered possibly related to study treatment by the investigator, including one with worsening of bipolar disorder, which however was ongoing after discontinuation of study treatment. Ages of the subjects ranged from 15 to 29 years old among the serious cases. No cases of completed suicide were reported in the upadacitinib AD program. All subjects experiencing an event of SIB had an underlying history of psychiatric disorder including depression, suicide attempt, bipolar disorder, personality disorder, and/or social stressors.

The rates of other depression-related events in the upadacitinib treatment groups were not higher than that in the placebo group.

SUR (24 Nov, 2020 cut-off)

There was 1 new event of suicidal ideation reported in the upadacitinib 30 mg group. The rates of suicidal ideation and behaviour in subjects on upadacitinib remain unchanged in the SUR compared to the CSS.

The MAH suggests that given the high background rate of suicidal ideation and behaviour including suicide attempt in the AD population, reports of these events were not unexpected in the clinical studies of AD patients.

Pancytopenia

Two cases of pancytopenia (one serious) were reported in the upadacitinib 30 mg group. One of the two events of pancytopenia had an alternative etiology of being related to influenza B infection and both events had negative rechallenge.

Retinal Detachment

During the placebo-controlled period, one subject in the placebo group and two subjects in the upadacitinib 15 mg group experienced events of retinal detachment. Beyond the placebo-controlled period, there was one additional serious event of retinal detachment in the upadacitinib 15 mg group and three events reported in one subject in the upadacitinib 30 mg group. Three subjects (one in placebo group, two in 15 mg upadacitinib group) had previous history of retinal detachment, and the

events were not considered related to treatment. The other two subjects (one receiving 15 mg group and one 30 mg) had no history of retinal detachment. Both had had a history of myopia. The events in these subjects were considered by the investigator to have a reasonable possibility of being drug related. The MAH suggests that as AD patients have an increased risk for retinal detachment and as all subjects experiencing such events had also other risk factors, data are not sufficient to suggest a causal relationship between these events and upadacitinib.

Since the initial submission, 1 SAE of "perforation of the right eye cornea due to corneal melting" (PT: corneal disorder) was reported in a subject on upadacitinib 30 mg. The event was considered by the investigator as related to study drug. The event was ongoing at the time of data cut-off for this SUR.

Safety in special populations

The majority of subjects were white (approximately 70%). Thus, the sample sizes for non-whites were smaller compared with whites and therefore results should be interpreted with caution. Across both analysis sets, the rates of AEs leading to discontinuation, SAEs, and severe TEAEs were higher for whites compared with non-whites in both upadacitinib treatment groups. The rates of malignancy, non-melanoma skin cancer and malignancy excluding NSMC were consistently higher for whites compared with non-whites in both upadacitinib groups. Conversely, the rates of neutropenia were dose dependent and higher for non-whites compared with whites.

The number of subjects < 18 years of age and ≥ 65 to <75 years was smaller compared to the group ≥ 18 years and < 65 of age and therefore results comparing age groups should be interpreted with caution. In the long-term dataset, there appeared to be an increased frequency of AEs, SAEs and AEs leading to discontinuation in the group ≥ 65 to < 75, especially at the 30 mg dose (see tables below for the original CSS and the SUR, respectively). However, this difference was not seen in AEs considered (by the investigator) to be possibly related to study treatment. Also the short-term data (placebo-controlled period), indicated no increased frequency of treatment-related AEs, or increased rate of serious or severe AEs, or AEs leading to discontinuation, with the 30 mg dose compared with placebo in this age group (table below).

The number of subjects ≥ 75 exposed to upadacitinib was markedly smaller (5 subjects) and comparisons of this group with other subgroups were not done.

Table 44   Original CSS: Overview of TEAEs in different age groups (long-term upadacitinib dataset).

	Age <65 number (E/100 PY)		Age 65-74 number (E/100 PY)	
	15 mg N=1190	30 mg N=1175	15 mg N=48	30 mg N=67
Total AEs	2803 (332,4)	3220 (381,5)	104 (360,8)	230 (473,3)
Serious AEs – Total	58 (6,9)	61 (7,2)	4 (13,9)	14 (28,8)
- Fatal	0	0	0	0
AE leading to discontinuation	44 (5,2)	52 (6,2)	3 (10,4)	10 (20,6)

Table 45   Safety Update report: Overview of TEAEs in different age groups (long-term upadacitinib dataset, 24 Nov, 2020 cut-off).

	Age <65 number (E/100 PY)		Age 65-75 number (E/100 PY)	
	15 mg N=1191	30 mg N=1179	15 mg N=48	30 mg N=67
Total AEs	3637 (274,2)	4133 (308,2)	134 (284,4)	278 (380,4)
AE with reasonable possibility of being drug-related	1275 (96,1)	1594 (118,9)	33 (70,0)	69 (94,4)
Serious AEs – Total	92 (6,9)	86 (6,4)	6 (12,7)	23 (31,5)
- Fatal	0	0	0	1 (1.4)
AE leading to discontinuation	55 (4,1)	65 (4,8)	5 (10,6)	16 (21,9)

Table 46   Number and Percentage of Subjects with Treatment-Emergent Adverse Events by Age Group (Short-term, Placebo-Controlled AD Analysis Set)

	< 65 years			>= 65 and <= 75 years		
		Active			Active	
	Placebo (N=861) n (%)	UPA 15 mg QD (N=863) n (%)	UPA 30 mg QD (N=852) n (%)	Placebo (N=41) n (%)	UPA 15 mg QD (N=36) n (%)	UPA 30 mg QD (N=54) n (%)
Subjects with any treatment-emergent						
Adverse event (AE)	503 (58.4)	550 (63.7)	588 (69.0)	25 (61.0)	24 (66.7)	42 (77.8)
AE with reasonable possibility of being drug related$	182 (21.1)	289 (33.5)	349 (41.0)	3 (7.3)	9 (25.0)	18 (33.3)
Severe AE	39 (4.5)	41 (4.8)	38 (4.5)	4 (9.8)	2 (5.6)	4 (7.4)
Serious AE	23 (2.7)	17 (2.0)	15 (1.8)	3 (7.3)	2 (5.6)	4 (7.4)
AE leading to discontinuation of study drug	30 (3.5)	20 (2.3)	21 (2.5)	4 (9.8)	1 (2.8)	5 (9.3)
AE leading to death	0	0	0	0	0	0
All deaths	0	0	0	0	0	0
occurring <= 30 days after last dose	0	0	0	0	0	0
occurring > 30 days after last dose	0	0	0	0	0	0

The rates of SAEs, TEAEs with a reasonable possibility of being related to study drug, and severe AEs were generally similar between males and females in both upadacitinib doses. The rates and EAER of CPK elevation and hepatic disorders were higher in males compared with females in both upadacitinib doses. Rates of nausea, acne, and herpes simplex tended to be higher in females in both upadacitinib doses.

There was no consistent pattern for the types of TEAEs and AESIs by BMI or weight groups across both analysis sets. However, the rates of SAEs and serious infections were noted to be higher in subjects with BMI ≥ 30 kg/m2 in the upadacitinib 30 mg group compared to the upadacitinib 15 mg group as well as other BMI subgroups in both upadacitinib groups.

Based on relatively limited number of AESIs reported, slightly lower event rates of serious infections, opportunistic infections (excluding TB and herpes zoster) and herpes zoster were reported in subjects with mild renal impairment compared to those with normal renal function in both treatment groups. However, the event rates of AEs of anaemia was higher in both treatment groups in subjects with mild renal impairment than those with normal renal function. Most of the malignancies were reported in

subjects with mild renal impairment. Patients with eGFR < 40 mL/min/1.73 m^2 were excluded from the studies.

Safety related to drug-drug interactions and other interactions

Across the PBO-controlled AD Analysis Set and the Long-term Upadacitinib Phase 3 AD Analysis Set and across the upadacitinib treatment groups, the percentages of subjects with TEAEs, SAEs, severe TEAEs, and TEAEs leading to discontinuation were generally similar between the upadacitinib monotherapy and upadacitinib combination therapy subgroups. There were also no clear differences for the ADRs acne, eczema herpeticum and the AESIs, however, for most of these the number of events were too small to draw definite conclusion.

Discontinuation due to AEs

During the 16-week placebo-controlled period, the percentage of subjects with TEAEs leading to discontinuation of study drug was 2.9% in the upadacitinib 30 mg group, 2.3% in the upadacitinib 15 mg group and 3.8% the placebo group. The most common SOCs where TEAEs leading to discontinuation of study drug were reported were Skin and subcutaneous tissue disorders (11, 7 and 20 subjects in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively) and Infections and infestation (3, 5 and 4 subjects, respectively). No single PT was reported in more than 2 subjects in any group, except for dermatitis atopic (3 subjects in upadacitinib 30 mg, 7 subjects in upadacitinib 15 mg, 15 subjects in placebo).

The most frequently reported TEAEs leading to discontinuation of study drug (≥ 0.2 E/100 PY in either treatment group) in the long-term Phase 3 dataset are presented in the table below.

Table 47 Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug Reported in ≥ 0.2 Events Per 100 PY in any Treatment Group by Decreasing Frequency Overall (Long-term Upadacitinib Phase 3 AD Analysis Set)

	CSS (Data Cutoff 04 Jun 2020)				SUR (Data Cutoff 24 Nov 2020)			
	Overall		Adolescent		Overall		Adolescent	
System Organ Class MedDRA 22.1 Preferred Term	UPA 15 mg QD (N = 1238) (PY = 872.2)	UPA 30 mg QD (N = 1242) (PY = 892.7)	UPA 15 mg QD (N = 167) (PY = 122.6)	UPA 30 mg QD (N = 166) (PY = 125.5)	UPA 15 mg QD (N = 1239) (PY = 1373.4)	UPA 30 mg QD (N = 1246) (PY = 1414.2)	UPA 15 mg QD (N = 167) (PY = 191.7)	UPA 30 mg QD (N = 166) (PY = 195.9)
	E (E/100 PY)							
Any Adverse Event	47 (5.4)	62 (6.9)	7 (5.7)	9 (7.2)	60 (4.4)	81 (5.7)	9 (4.7)	7 (3.6)
Dermatitis atopic	13 (1.5)	4 (0.4)	1 (0.8)	1 (0.8)	14 (1.0)	7 (0.5)	2 (1.0)	1 (0.5)
Herpes simplex	0	3 (0.3)	0	0	0	3 (0.2)	0	0
Pruritus	2 (0.2)	0	1 (0.8)	0	2 (0.1)	0	1 (0.5)	0
Asthma	2 (0.2)	0	1 (0.8)	0	2 (0.1)	0	1 (0.5)	0
Eczema	0	2 (0.2)	0	0	0	2 (0.1)	0	0
Neutropenia	0	2 (0.2)	0	0	0	3 (0.2)	0	0
ALT increased	0	2 (0.2)	0	0	1 (< 0.1)	2 (0.1)	0	0
AST increased	0	2 (0.2)	0	0	0	2 (0.1)	0	0
Haemoglobin decreased	0	2 (0.2)	0	0	0	2 (0.1)	0	0
Pyrexia	1 (0.1)	0	1 (0.8)	0	1 (< 0.1)	0	1 (0.5)	0
Hepatic function abnormal	1 (0.1)	0	1 (0.8)	0	1 (< 0.1)	0	1 (0.5)	0
Osteomyelitis	0	1 (0.1)	0	1 (0.8)	0	1 (< 0.1)	0	1 (0.5)
Pharyngotonsillitis	1 (0.1)	0	1 (0.8)	0	1 (< 0.1)	0	1 (0.5)	0
Pneumonia	1 (0.1)	1 (0.1)	0	1 (0.8)	1 (< 0.1)	1 (< 0.1)	0	1 (0.5)
Pyoderma	0	1 (0.1)	0	1 (0.8)	0	1 (< 0.1)	0	1 (0.5)
Sepsis	0	1 (0.1)	0	1 (0.8)	0	1 (< 0.1)	0	1 (0.5)
Staphylococcal sepsis	0	1 (0.1)	0	1 (0.8)	0	1 (< 0.1)	0	1 (0.5)
Blood culture positive*	0	1 (0.1)	0	1 (0.8)	0	0	0	0
Cardiac murmur	0	1 (0.1)	0	1 (0.8)	0	1 (< 0.1)	0	1 (0.5)
Culture urine positive*	0	1 (0.1)	0	1 (0.8)	0	0	0	0
Depression	1 (0.1)	0	1 (0.8)	0	1 (< 0.1)	0	1 (0.5)	0
ECG QT interval abnormal	0	0	0	0	2 (0.1)	0	1 (0.5)	0

AD = atopic dermatitis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CSS = clinical summary of safety; E/100PY = Events per 100 patient-years; ECG = electrocardiogram; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PY = patient-years; QD = once daily; SUR = Safety Update Report; UPA = upadacitinib
* After database lock for the CSS, events of blood culture positive and culture urine positive were deleted by the investigator as distinctive PTs.

Post marketing experience

Upadacitinib 15 mg daily dose was first approved for the treatment of RA on 16 August 2019 (international birth date) in the US. Through 31 July 2020, upadacitinib has been approved in 50 countries with estimated cumulative post-marketing exposure of 21,838 patient treatment years.

Review of the post-marketing safety data reported for upadacitinib up to date demonstrated a similar safety profile as observed in the clinical studies for RA. The most frequently reported AEs were in the SOC of General disorders and administration site conditions and Musculoskeletal and connective tissue disorders. Pneumonia was the most commonly reported serious infection.

2.6.1. Discussion on clinical safety

Upadacitinib at a dose of 15 mg daily is approved for treatment of adult RA patients and adult patients with PsA or AS.

For the current application concerning the AD indication, in addition to safety in an overall new patient population, the safety evaluation should consider also the following two new issues:

- Upadacitinib at a dose of 15 mg once daily is for the first time proposed for use in patients < 18 years of age, namely adolescents (12 to 17 years)

- In addition to the 15 mg dose a new, higher dose is proposed for adult AD patients (≥ 18 years); 30 mg dose once daily

The original submission included a Clinical Summary of Safety (CSS) with a Phase 3 study data cut-off at June 04, 2020. At the CHMP's request, a Safety Update report (SUR) was provided with longer-term follow-up (data cut-off at Nov. 24, 2020).

Overall, the SUR confirmed the findings reported in the original CSS and indicated no worsening of the safety profile at long-term exposure.

Extent of exposure

Safety of upadacitinib in the AD population has been evaluated within the three global, placebo-controlled Phase 3 studies evaluating the 15 mg and 30 mg doses in adults and adolescents, a global Phase 2, dose-ranging study (adults only) and a Japan regional Phase 3 study.

A total of 2898 subjects (adult and adolescents) were enrolled in the AD studies and received at least 1 dose of upadacitinib. At the Nov 24, 2020 cut-off, the mean duration of treatment was 413.3 days in the upadacitinib 30 mg group (N = 1382) and 405.9 days in the upadacitinib 15 mg group (N = 1372). Of these subjects, 931 and 895 had exposure to upadacitinib 30 mg or upadacitinib 15 mg, respectively, for at least 12 months.

The Phase 3 studies included 333 adolescents who received at least one dose of upadacitinib, with 166 and 167 in the 30 mg and 15 mg dose group, respectively. i. Among adolescents, 223 subjects received treatment for ≥ 52 weeks (113 and 110 for the 30 mg and the 15 mg dose, respectively) at the Nov 24, 2020 data cut-off.

The safety of the 15 mg dose has previously been established in other indications, and the overall safety database indicates that the safety profile of upadacitinib is largely similar across indications. The current data showed a qualitatively similar safety profile for the 30 mg dose and the previously established 15 mg dose, while there was a dose-dependent increase in frequency of most treatment-related ADRs, including serious infections (further described below). The extent of exposure to the 30 mg dose is considered sufficient for assessment of this dose.

Common adverse events/ADRs

During the 16-week placebo-controlled period, the overall rate of AEs and of AEs considered by the investigator to be related to treatment were higher in the upadacitinib groups than in the placebo group, and were higher in the upadacitinib 30 mg group than in the 15 mg group. Also, in the long-term treatment analysis sets, the 30 mg dose in general showed a higher rate of events per 100 PY (SAEs, severe AEs, AEs leading to discontinuation and AEs considered by the investigator to be related to study drug), than the 15 mg dose.

The common TEAEs observed in the AD population were largely the same as those observed in the previously approved RA indication. The rates of these TEAEs were generally higher in the upadacitinib

groups compared with the placebo group and were higher in the upadacitinib 30 mg group than in the 15 mg group, indicating dose/exposure dependency of the common AEs.

Eight new ADRs were identified for listing in the SmPC section 4.8, in addition to the ADRs listed for the previously approved RA indication. These were: Folliculitis (common), Influenza (common), Anaemia (common), Abdominal pain (common), Fatigue (common), Urticaria (common), Headache (common) and Acne (very common). The frequency estimation is based on the 16-week placebo-controlled period. During the placebo-controlled period, the frequency of these ADRs was higher at 30 mg upadacitinib than at 15 mg, except for influenza and abdominal pain. In the long-term treatment analysis set, the difference between doses were no longer present or were reversed for abdominal pain, headache, fatigue and urticaria, while folliculitis, anaemia, acne and influenza appeared to be dose dependent. The proposed updated to Section 4.8 of the SmPC were considered acceptable to the CHMP.

The rate of acne was around 16%, 10% and 2% at upadacitinib 30 mg, upadacitinib 15 mg and placebo, respectively. Acne has also been identified in PsA studies, albeit at a lower rate than in the AD population. The higher rate of acne reported in AD studies may reflect the younger patient population as well as the investigators being dermatologists.

The remaining seven new ADRs have not been identified in AS or PsA studies. Overall, these ADRs are not considered indicative of a relevantly different safety profile in AD patients as compared with other indications for upadacitinib. However, the higher frequency of anaemia, one of the Adverse Events of Special Interest (AESI) identified for upadacitinib, at the 30 mg dose (1% vs. 0.2% at the 15 mg dose) is of some concern, which is further discussed below.

Herpes simplex and herpes zoster are previously listed ADRs for upadacitinib. In the AD studies, the frequencies of these events were 'Common', while for RA they are listed as 'Uncommon'. These reactions were also observed at the frequency of 'Common' in the PsA program (15 mg dose). In the AD studies the rate of these events was dose dependent.

For the ADRs hypercholesterolemia, ALT increased, and AST increased a decreased frequency was observed in the AD population compared with the RA population ('Uncommon' rather than 'Common').

Adverse events of special interest

AESIs identified for upadacitinib included:

- serious infection;

- opportunistic infections (excluding TB and herpes zoster);

- herpes zoster;

- active TB;

- malignancy (including NMSC, malignant tumours excluding NMSC, and lymphoma);

- hepatic disorders;

- adjudicated GI perforation;

- adjudicated MACE (defined as CV death, non-fatal myocardial infarction [MI] and non-fatal stroke);

- adjudicated venous thromboembolic events (VTE), defined as PE and deep vein thrombosis (DVT) and other venous and arterial thromboembolic events (non-cardiac, non-neurologic);

- anaemia;

- neutropenia;

- lymphopenia;

- renal dysfunction, and

- CPK elevation

Serious infection is an identified risk of upadacitinib treatment and a warning regarding this risk is described in the current SmPC. During the 16-week placebo-controlled period, the rate of serious infections was not higher in the two upadacitinib-treated groups than in the placebo group. At long-term treatment, the risk for serious infections appeared to be somewhat higher with the 30 mg dose (2.8 E/100 PY) than with the 15 mg dose (2.3 E/100 PY). Pneumonia was the most common serious infection. Pneumonia is a previously labelled adverse reaction for upadacitinib. The occurrence of serious infections is, thus, not a new safety concern for upadacitinib, there is potentially higher risk of serious infection with the 30 mg dose.

Opportunistic infection is also an identified risk for upadacitinib, which is described in the SmPC. An overall increased frequency of herpes zoster was observed in AD patients compared to that previously reported in RA patients. Literature data indicate that AD patients might be more susceptible to herpes zoster, but the effect appears also to be driven by upadacitinib, as the effect was dose dependent. Altogether two cases of active TB were described, one in each dose group. These cases do not affect previous assessment of the risk. Except TB and herpes zoster, all reported opportunistic infections except one (oesophageal candidiasis) in the pivotal Phase 2 and 3 studies in AD (n=49) were events reported as eczema herpeticum or Kaposi's varicelliform eruption, which are known to be associated with AD. There was no apparent dose dependency in this effect.

Due to the immunomodulatory effects of upadacitinib, malignancies are considered a potential risk with upadacitinib treatment and are described in the current SmPC. However, the MAH presents data indicating that the age-gender adjusted SIR for malignancies, excluding NMSC, observed in the upadacitinib AD studies subjects were not higher than the expected range for the general population. It is agreed that the short time to onset for the malignancies excluding NMSC in the AD studies suggests lack of relationship between upadacitinib and these malignancies. The rate of NMSC reported in subjects receiving upadacitinib was also reportedly within the range observed in the general population. No malignancy was reported in adolescents within the AD clinical program. The data does therefore not give raise to any new or additional concern regarding the risk for malignancies at treatment of AD patients with upadacitinib 15 mg or 30 mg.

Treatment with upadacitinib is associated with an increased incidence of liver enzyme elevation and both 'ALT increased' and 'AST increased' are included in the previously approved SmPC as adverse drug reactions. The data for AD patients does not lead to new concerns about hepatic disorders.

The effect of upadacitinib was clearly dose-dependent on haemoglobin levels (anaemia), as well as on absolute neutrophil count (neutropenia). Anaemia has been proposed for addition as ADR in section 4.8 of the SmPC. The anaemia and neutropenia in AD patients were, however, in most cases manageable by dose interruption and did only in one and two cases, respectively, lead to treatment discontinuation. The increased risk at 30 mg may therefore not be of major concern.

The events of decreased absolute lymphocyte count (lymphopenia) were few in the AD studies and no clear dose dependency or overall relationship with infection could be seen.

CPK elevation is a known ADR for upadacitinib. As for other AESIs, the effect appeared to be dose-related with a higher rate reported with the 30 mg dose of upadacitinib, than with the 15 mg dose, but no TEAEs of CPK elevation were reported as serious. However, there was one event reported as rhabdomyolysis. The upadacitinib case was observed in the 15 mg dose group during the placebo-

controlled treatment period and an alternative etiology was injury during jet ski. This single case is not considered a cause for concern.

Increases in serum creatinine, not considered clinically meaningful, were observed in the upadacitinib-treated groups in AD studies. Asymptomatic increases in serum creatinine, without deterioration of renal function, were previously observed also in RA studies. The data from AD studies do not change the previous assessment of this risk.

Four events of MACE and no other cardiovascular events were reported in the AD studies, except one myocardial infarction following a Covid-19 infection, which was not adjudicated as a MACE. There were no events of MACE in adolescents. The data from the AD studies do, thus, not give raise to new concerns regarding cardiovascular safety of upadacitinib.

Altogether, three events of VTE was reported in the upadacitinib clinical program. The subjects had other risk factors. There were no events of VTE in adolescents. The data from AD studies do not change the previous assessment of this risk.

Serious adverse events and deaths

During the 16-week placebo-controlled period, the rate of SAEs was similar in the upadacitinib groups and the placebo group.

In the long-term dataset, the overall rate of SAEs was higher in the upadacitinib 30 mg group than in the 15 mg group (7.7 vs. 7.1 events/100 PY). In the adolescent subset, the rate of SAEs was higher in the 15 mg group (7.8 events/100 PY) than in the 30 mg group (3.6 events/100 PY), which was primarily driven by infectious events without a specific pattern. There was also a higher rate of serious dermatitis atopic, i.e. lack of efficacy, at the 15 mg dose in adolescents (1.6 events/100 PY) than in adults (0.5 events/100 PY).

The MAH did not use any specific instrument for measuring suicidal risk. A total of 11 events classified as suicidal ideation and behaviour (SIB) were reported within the AD studies. All subjects experiencing an event of SIB had an underlying history of psychiatric disorder including depression, suicide attempt, bipolar disorder, personality disorder, and/or social stressors. Given a reported high background rate of SIB in AD patients, the current data are not considered sufficient to suggest a causal relationship between upadacitinib treatment and SIB events. Of note, as part of the latest PSUR, the MAH was requested by the PRAC to continue close monitoring of cases of suicidal and self-injurious behaviour as well as anxiety, and to make every effort to provide more information about cases. Indeed, considering imbalance observed in clinical trials, and based on cumulative review of cases (including 2 positive dechallenge cases of suicidal ideation) psychiatric adverse reactions (suicidal ideation, anxiety) should be included as potential risk in the next PSUR of upadacitinib.

Two cases of pancytopenia were reported, one of which was serious. The serious case was considered by the investigator to be secondary to influenza B infection, and unlikely to be related to study treatment.

There were three deaths in the AD study population. All three were considered unlikely to be related to study treatment. One case was a myocardial infarction during serious Covid-19 infection.

Laboratory findings, vital signs and other observations

There were no relevant findings for platelets or blood pressure.

An effect on lipids has been previously observed in RA patients and was also seen in the AD studies. Indeed, treatment with upadacitinib is associated with dose-dependent increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL)

cholesterol. The risk is adequately described in the SmPC, the guide for healthcare professionals and in the patient alert card.

Weight increased is a previously identified ADR for upadacitinib and this was observed also in AD studies.

The mean change from baseline in height in adolescents increased similarly in the first 52 weeks for the upadacitinib 30 mg and 15 mg groups; thus, there were no dose-dependent effect on height in growing children. However, the number of young adolescents in the different groups was small. The MAH will continue assessing potential effects on height in growing children in the long-term extension studies and in a PASS (see non-clinical section and RMP below).

Special populations

The MAH initially proposed no dose adjustment in patients aged 65 years and older. However, the CHMP considered that the data for AD subjects ≥ 65 years is limited and should be interpreted with caution. No marked difference compared with the younger population was seen during the 16-week placebo-controlled period, but the long-term data indicates an overall higher frequency of AEs, SAEs and AEs leading to discontinuation in this group, in particular with the 30 mg dose. Therefore, the MAH accepted to revise the Section 4.2 of the SmPC to recommend the 15 mg dose in patients aged 65 or older.

There were only 5 subjects ≥ 75 years in the AD studies (all in the 15 mg group) and no analyses were made for this group. The lack of data for patients ≥ 75 years is adequately described in the SmPC.

The majority of subjects in the AD studies were white and subgroups analysis for other race should be interpreted with caution. Some differences were observed, but definite conclusion cannot be drawn.

The rates of SAEs, TEAEs with a reasonable possibility of being related to study drug and severe AEs were generally similar between males and females in both upadacitinib doses. There were also no clear patterns in terms of AEs due to weight, BMI or renal function.

The information on pregnancies occurring in the AD studies is very limited. The product is contraindicated in pregnancy and Section 4.6 has been updated as the new indication includes paediatric patients aged 12 years and older (see non-clinical discussions). This topic will be followed in PSURs.

Discontinuations due to AEs

The most common SOCs where TEAEs leading to discontinuation of study drug were reported were Skin and subcutaneous tissue disorders and Infections and infestations.

During the 16-week placebo-controlled part of the study, a slightly higher percentage of the patients discontinued the study due to a TEAE in the 30 mg dose group than in the 15 mg dose group. However, the highest percentage of discontinuation due to AE was observed in the placebo group, where the PT 'dermatitis atopic' was the most common reason (i.e. lack of efficacy).

Also, in the long-term dataset, the single PT with the highest discontinuation rate per 100 PY was dermatitis atopic, the highest rate observed in the 15 mg upadacitinib group. Overall, though, a higher discontinuation rate due to AEs was observed in the 30 mg group than in the 15 mg group (5.7 E/100 PY and 4.4 E/100 PY, respectively), mirroring the general pattern of a higher frequency of TEAEs at the 30 mg dose. Apart from dermatitis atopic, the single PTs for discontinuation reported in ≥ 2 subjects were herpes simplex, pruritus and asthma (3 subjects each); and eczema, neutropenia, ALT increased, AST increased and haemoglobin decreased (2 subjects each).

The discontinuation rate due to AEs is relatively low, indicating that AEs are generally manageable by dose modifications and, if relevant, treatment.

Adolescents – overall assessment

With the current application, upadacitinib is for the first time proposed for use in subjects < 18 years of age. Throughout the safety evaluation, specific analyses were therefore performed for the adolescent subgroup in the AD studies.

The safety profile appeared largely similar in adolescents as compared with the overall population. There was no consistent trend with regard to age and TEAEs, SAEs, AEs leading to discontinuation of study drug, or severe AEs. The 30 mg dose did not seem less well tolerated in adolescents than in the overall population, except for high frequencies of vomiting and diarrhoea (6.1 % and 5.3 %, respectively) that was observed in adolescents at the 30 mg dose during the placebo-controlled period. At the 15 mg dose, the frequency of these events did not differ markedly from placebo. This dose-dependency was not seen in the overall population, where diarrhoea was reported at about 3 % in both dose groups. The difference between the doses in the rate of vomiting and diarrhoea was maintained in adolescents in the long-term treatment. However, due to the small sample size in the adolescent subgroup, these results should be interpreted with caution. The time to onset of vomiting and diarrhoea varied considerably, from 8 to 283 days and from 2 to 349 days, respectively, and also duration of event varied. None of the events required study drug interruption, and the events did not recur with continued drug administration. The MAH considers it unlikely that higher rates of these events would only be observed in adolescents receiving upadacitinib 30 mg dose if there was a causal association of diarrhoea and vomiting with upadacitinib use. The CHMP agreed that from a clinical study point of view, the observation could be a chance finding. As indicated in the efficacy section, only the 15 mg dose is recommended for adolescents.

Pharmacokinetic and metabolism data may suggest that there are no pharmacokinetic reasons to expect a different safety profile in adolescents compared with adults. As indicated in the clinical pharmacology section, the weight limit was changed to >30 kg during the evaluation.

Long term safety data is included as missing information in the RMP. In order to evaluate potential effects on bone growth, height was monitored in adolescent subjects in the AD studies, but the number of young adolescents in the different groups was small. The mean change from baseline in height in adolescents increased similarly in the first 52 weeks for the upadacitinib 30 mg and 15 mg groups. Thus, there were no dose-dependent effect on height in growing children. Considering also that non-clinical juvenile toxicity data indicated no effects on bone development, there is currently no concern for use of upadacitinib in growing children. The MAH will continue assessing potential effects on height in growing children in the long-term extension studies and in a PASS (see non-clinical section and RMP below).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety database indicates a quantitatively similar safety profile in AD patients as compared with that in other patient populations, i.e. RA, PsA and AS. A few new ADRs for addition in section 4.8 of the SmPC have been identified: Folliculitis (common), Influenza (common), Anaemia (common), Abdominal pain (common), Fatigue (common), Urticaria (common), Headache (common) and Acne (very common). The CHMP was of the view that these are not considered indicative of a clinically relevantly different safety profile in AD patients. Based on data from two different cut-off dates in the Phase 3 studies, there was no worsening of the rate of AEs upon longer treatment and follow-up. Thus,

from a safety perspective, the data are considered sufficient for approval of the 15 mg and 30 mg doses to adult patients. Most of the common AEs as well as AESIs, including serious infections, were dose dependent, with a higher rate of events observed for the 30 mg dose. In most cases, the events appeared to be manageable with dose interruption and/or treatment, as discontinuation rates were relatively low. Adequate recommendations for monitoring of ANC, ALC, Hb, hepatic transaminases and hyperlipidaemia are included in the SmPC.

The MAH initially proposed no dose adjustment in patients aged 65 years and older. However, the CHMP considered that the data for AD subjects ≥ 65 years is limited and should be interpreted with caution. No marked difference compared with the younger population was seen during the 16-week placebo-controlled period, but the long-term data indicates an overall higher frequency of AEs, SAEs and AEs leading to discontinuation in this group, in particular with the 30 mg dose. Therefore, the MAH accepted to revise the Section 4.2 of the SmPC to recommend the 15 mg dose in patients aged 65 or older.

The safety database in adolescents is still relatively small. However, the available data indicates a similar safety profile and an overall similar upadacitinib tolerability in adolescents with AD as in the adult AD study population. Long term safety data is included as missing information in the RMP. The non-clinical juvenile toxicity study did not indicate a risk for effects on bone development. Thus, the currently presented safety data is considered sufficient for approval of use of upadacitinib in the adolescent population. The MAH will continue to assess long-term safety in adolescents post-marketing (see RMP).

Overall, the CHMP is of the view that the safety data support the new 30 mg strength and the new indication in the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

2.7. Risk Management Plan

Table 48   Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious and opportunistic infections including TB	Routine risk minimization measures: • SmPC Section 4.4 summarizes the risk and provides guidance on ways to reduce the risk. • The PL warns that patients who have an infection or who have a recurring infection should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL advises that patients do not take Rinvoq if they have active TB and warns that patients with a history of TB, or who have been in close contact with someone with TB should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.2 outlines lymphocyte and neutrophil counts	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for serious and opportunistic infections including TB Additional pharmacovigilance activities: • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • P20-390: Prospective Cohort Study of Long-term safety of Upadacitinib in the treatment of Atopic Dermatitis in Denmark and Sweden

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities

	and when not to initiate upadacitinib dosing.
	
	• SmPC Section 4.2 outlines interruption guidelines based on ALC and ANC.
	
	• SmPC Section 4.3 indicates that upadacitinib is contraindicated in patients with active TB or active serious infections.
	
	• SmPC Section 4.4 states that patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib and that upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection.
	
	• SmPC Section 4.4 advises to consider the risks and benefits of initiating upadacitinib in patients with active, chronic, or recurrent infections.
	
	   o A patient who develops a new infection during treatment with upadacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and upadacitinib should be interrupted if the patient is not responding to therapy.
	
	   o Screening for TB prior to initiation is advised, and upadacitinib should not be given if active TB is diagnosed. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with untreated latent TB or in patients with risk factors for TB infection.
	
	Additional risk minimization measures:
	
	• HCP educational brochure
	
	• PAC
	
	Other routine risk minimization measures:
	
	Prescription only medicine.
		• P21-825: Effectiveness Evaluation of Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Atopic Dermatitis
		
		• Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545)
		
		• Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)

Herpes zoster	Routine risk minimization measures:	Pharmacovigilance activities beyond adverse reaction reporting and signal detection:

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• SmPC Section 4.4 describes the risk of viral reactivation such as herpes zoster. • SmPC Section 4.8 describes findings from upadacitinib clinical trials. • The PL warns that patients who have an infection or who have a recurring infection should consult their doctor or pharmacist before and during treatment with Rinvoq and will describe the risk of viral reactivation. • The PL warns that patients who have had a herpes zoster infection (shingles) should tell their doctor if they get a painful skin rash with blisters as these can be signs of shingles. • SmPC Section 4.4 advises that if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. Additional risk minimization measures: • HCP educational brochure • PAC Other routine risk minimization measures: Prescription only medicine.	Routine pharmacovigilance activities including follow-up questionnaire for serious infections Additional pharmacovigilance activities: • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden • P21-825: Effectiveness Evaluation of Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Atopic Dermatitis • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)
Malignancies	Routine risk minimization measures: • SmPC Section 4.4 describes the risk in patients with RA and indicates that upadacitinib clinical data are currently limited and long-term studies are ongoing. • The PL warns that patients who have cancer, develop a new lesion or any change in the appearance of an area on the skin, or are at high risk of developing skin cancer should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 advises that periodic skin examination is recommended for patients who are at increased risk for skin cancer. Additional risk minimization measures: None Other routine risk minimization measures:	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities: • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Prescription only medicine.	• Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)
MACE	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on lipids and describes that impact on CV morbidity and mortality has not been determined. • SmPC Section 4.4 contains a section on CV risk including a statement on increased CV risk in RA patients and need for management of CV risk factors as part of usual standard care. • SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. • The PL warns that patients who have heart problems, high blood pressure, or high cholesterol should consult their doctor or pharmacist before and during treatment with Rinvoq. Additional risk minimization measures: • HCP educational brochure • PAC Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for MACE Additional pharmacovigilance activities: • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden • P21-825: Effectiveness Evaluation of Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Atopic Dermatitis • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)
VTEs (deep venous thrombosis and pulmonary embolus)	Routine risk minimization measures: • SmPC Section 4.4 indicates that events of deep vein thrombosis and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib. • The PL warns that patients who have had blood clots in the veins of the legs (deep vein thrombosis) or lungs (pulmonary embolism) should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get a painful swollen leg, chest pain, or shortness of breath. • SmPC Section 4.4 advises that upadacitinib should be used with caution in patients at high risk for	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including: • Follow-up questionnaire for VTEs • Monitoring of VTE risk and literature review provided within the PSUR Additional pharmacovigilance activities: • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	deep vein thrombosis/pulmonary embolism. Risk factors that should be considered in determining the patient's risk for deep venous thrombosis/pulmonary embolism include older age, obesity, a medical history of deep venous thrombosis/pulmonary embolism, patients undergoing major surgery, and prolonged immobilisation. • SmPC Section 4.4 advises that if clinical features of deep vein thrombosis/pulmonary embolism occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment. Additional risk minimization measures: • HCP educational brochure • PAC Other routine risk minimization measures: Prescription only medicine.	• P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden • P21-825: Effectiveness Evaluation of Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Atopic Dermatitis • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)
GI perforation	Routine risk minimization measures: None Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)
DILI	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on transaminases. • SmPC Section 4.4 recommends prompt investigation of the cause of	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities:

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	liver enzyme elevation to identify potential cases of DILI. • SmPC Section 4.4 advises that if increases in ALT or AST are observed during routine patient management and DILI is suspected, upadacitinib should be interrupted until this diagnosis is excluded. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	• P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)
Foetal malformation following exposure in utero	Routine risk minimization measures: • SmPC Section 4.6 describes the teratogenic effects observed in animals receiving upadacitinib and states that there are no or limited data from use of upadacitinib in pregnant women. • The PL advises that patients do not take Rinvoq if they are pregnant, that Rinvoq must not be used during pregnancy, and that patients who become pregnant while taking Rinvoq must consult their doctor straight away. • SmPC Section 4.3 and Section 4.6 indicate that upadacitinib is contraindicated during pregnancy. • SmPC Section 4.6 and PL advise on use of effective contraception. • SmPC Section 4.6 advises that female paediatric patients and or/their caregivers should be informed about the need to contact the treating physician once the patient experiences menarche. • The PL informs caregivers to let their doctor know if their child has their first menstrual period while using RINVOQ. Additional risk minimization measures: • HCP educational brochure • PAC Other routine risk minimization measures:	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaires for pregnancies Additional pharmacovigilance activities: • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • P21-825: Effectiveness Evaluation of Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Atopic Dermatitis • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Prescription only medicine.	
Use in very elderly (≥ 75 years of age)	Routine risk minimization measures: • SmPC Section 4.2 states that there are limited data in patients aged 75 years and older. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden
Effect on vaccination efficacy	Routine risk minimization measures: • SmPC Section 4.4 includes language that no data are available on the response to vaccination with live or inactivated vaccines in patients receiving upadacitinib. • SmPC Section 4.4 states that use with live, attenuated vaccines during, or immediately prior to, upadacitinib therapy is not recommended. • SmPC Section 4.4 includes language that prior to initiating upadacitinib, it is recommended that patients be brought up to date with all immunisations, including prophylactic zoster vaccinations, in agreement with current immunisation guidelines. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Vaccination substudy

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C	Routine risk minimization measures: • SmPC Section 4.4 describes the risk of viral reactivation. • The PL warns that patients who have ever had hepatitis B or hepatitis C should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 describes the need for screening and consultation with a hepatologist if HBV DNA is detected. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden
Use in patients with moderate hepatic impairment	Routine risk minimization measures: • SmPC Section 4.2 describes use in patients with hepatic impairment. • SmPC Section 4.2 states that upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment. • SmPC Section 4.3 indicates that upadacitinib is contraindicated for use in patients with severe hepatic impairment. • The PL advises that patients do not take Rinvoq if they have severe liver problems and warns that patients should consult their doctor or pharmacist before and during treatment with Rinvoq if their liver does not work as well as it should. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with severe renal impairment	Routine risk minimization measures: • SmPC Section 4.2 describes use in patients with renal impairment. • SmPC Section 4.2 that upadacitinib 15 mg QD should be used with caution in patients with severe renal impairment. Upadacitinib 30 mg QD is not recommended for patients with severe renal impairment. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden
Long-term safety	Routine risk minimization measures: SmPC Section 4.4 indicates that upadacitinib clinical data on malignancies are currently limited and long-term studies are ongoing. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities: • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)
Long-term safety in adolescents with AD	Routine risk minimization measures: None Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Additional pharmacovigilance activities: • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden • P21-824: A Study of Growth in Adolescents With Atopic Dermatitis Who Receive Upadacitinib

AD = atopic dermatitis; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; aRMMs = additional risk minimization measures; AST = aspartate transaminase; CV = cardiovascular; DILI = drug-induced liver injury; DNA = deoxyribonucleic acid; GI = gastrointestinal; HBV = hepatitis B virus; HCP = healthcare professional; JAK = Janus kinase; MACE = major adverse cardiovascular event; PAC = patient alert card; PL = package leaflet; PSUR = periodic safety update report; QD = once daily; RA = rheumatoid arthritis; SmPC = Summary of Product Characteristics; TB = tuberculosis; US = United States; VTE = venous thromboembolic event

Conclusion

The CHMP and PRAC considered that the risk management plan version 4.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Rinvoq 15 mg prolonged-release tablets. The bridging report submitted by the MAH has been found acceptable.

2.9.2. Quick Response (QR) code

A request to include a QR code in the package leaflet for the purpose of providing statutory information on the medicinal product has been submitted by the MAH and has been found acceptable.

The following elements (statutory information) have been agreed to be provided through a QR code: package leaflet, educational material for patients as outlined in the Risk Management Plan.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH applied for a new indication for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. A new strength 30mg was also proposed with this application.

Atopic dermatitis (AD) is a common, chronic, relapsing, inflammatory skin disease characterized by highly pruritic, erythematous, excoriated, and oozing papules and plaques that may become lichenified over time. The diagnosis of AD is made clinically and is based on history, morphology and distribution of skin lesions, and associated clinical signs and symptoms.

The aim of the treatment with Rinvoq is to provide relief of AD symptoms based on efficacy outcomes reflecting skin clearance, pruritus, and health-related quality of life.

3.1.2. Available therapies and unmet medical need

Treatment of AD in adolescent and adult patients depends on the extent and severity of disease. One-third of AD patients have moderate to severe disease, manifesting as itchy skin eruptions, often accompanied by physical, psychological, and economic burden. The most commonly used topical agents are corticosteroids, calcineurin inhibitors, and moisturizers (emollients). When topical therapies are insufficient, phototherapy or systemic therapy are generally added to topical agents.

Mid-potency topical corticosteroids (TCS) are typically the first-line treatment for AD when non-pharmacologic interventions have failed (and low potency TCS or TCIs for sensitive areas such as the face, neck, and genital or intertriginous areas); however, AD disease activity may continue despite use of TCS, or patients may lose response over time.

Several treatment guidelines recommend the use of systemic immunomodulatory agents for patients in whom optimized topical regimens or phototherapy do not adequately control the signs and symptoms of disease. However, there is limited well controlled efficacy data supporting their use in moderate to severe AD, and the duration of use of many traditional systemic immunomodulatory agents is limited due to cumulative toxicity. Only few systemic agents are currently approved for AD in most countries. Of those, cyclosporin A and oral prednisone are not suitable or recommended for long-term use.

Dupixent (dupilumab), a monoclonal antibody that inhibits IL-4 and IL-13 signalling, is approved in the EU and other regions/countries for the treatment of moderate to severe AD in adults and paediatric patients >6 years of age. Olumiant (baricitinib), a JAK inhibitor, is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy.

3.1.3. Main clinical studies

The efficacy of upadacitinib in moderate to severe atopic dermatitis is primarily supported by three pivotal Phase studies; two studies with upadacitinib used as mono-therapy (M16-045 and M18-891) and the third one (M16-047) is a study with upadacitinib used together with topical corticosteroids (TCS). All three studies had a randomized, double-blind, parallel-group, placebo-controlled, multi-center design.

The population included was similar across all studies and the inclusion and exclusion criteria are adequate to define a population with moderate to severe AD in need of a systemic treatment. Subjects who met eligibility criteria were randomized in a 1:1:1 ratio to receive a daily oral dose of upadacitinib 30 mg or upadacitinib 15 mg or matching placebo QD. In study M16-047, upadacitinib or placebo was given concomitantly with topical therapy, using medium and low potency TCS in a step-down regimen to reflect clinical use. In Study M16-045, 847 subjects were randomized, in study M18-891 836 subjects and in the TCS study M16-047, 901 subjects were randomized. Adolescents from the age of 12 years could be included and this group comprised 12-14% of the population across the studies.

The co-primary endpoints were evaluated at week 16 and were the Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index (EASI 75) from Baseline and the 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.

The placebo-controlled part continued up to Week 16 and thereafter patients in the placebo arm were re-randomized in a 1:1 ratio to 15 or 30 mg upadacitinib. Subjects originally randomized to upadacitinib were to continue upadacitinib in the extension period at the same dose.

3.2. Favourable effects

The co-primary endpoints, the proportions of patients achieving EASI 75 and a vIGA-AD score of 0 or 1 with a reduction of at least 2 grade reductions from baseline at Week 16, were clearly higher for both upadacitinib dose levels vs. placebo, in all three studies. The results were highly statistically significant (p<0.001).

A dose dependency was observed in all studies, with overall 10-19% difference in Week 16 responder rates for EASI 75 and vIGA (0,1) between the 15 mg and the 30 mg doses. In the mono-therapy studies, the EASI 75 response was 60-70% for the 15 mg upadacitinib dose and 73-80% for the 30 mg dose (13-16% for placebo). For the vIGA-AD (0,1) endpoint, corresponding figures were 39-48% for upadacitinib 15 mg, 52-62% for upadacitinib 30 mg and 5-8% for placebo, respectively.

In the TCS study (M16-047), the results were similar; EASI 75 for the upadacitinib 15 mg, 30 mg and placebo groups were 65%, 77% and 26%, respectively, and vIGA-AD (0,1) responses were 40%, 59% and 11%, respectively.

In the mono-therapy studies, superiority of each upadacitinib dose vs. placebo was demonstrated for all key secondary endpoints, based on showing statistical significance under the overall type I error control, in both studies. Similar to the co-primary endpoints, a dose-related difference generally in the range 10-18% was observed.

For instance, effects on itch were observed evaluated by the reduction in Worst pruritus NRS by ≥ 4 points at Week 16, with the number of responders for upadacitinib 15 mg, upadacitinib 30 mg and placebo being 47%, 60% and 10%, respectively, for the pooled monotherapy studies. A separation from placebo was observed as early as Day 2, although the numbers of upadacitinib responders at these early times points (Day 2, Day 3 and Week 1) were rather few. Still, it can be observed that both effects on itch and on AD lesions (assessed by EASI 75 at Week 2) show a rapid onset of effect.

The number of flares during the double-blind period were also lower in the upadacitinib arms (0-2%) vs. the placebo arm (around 25%).

Also, for patient-reported outcomes (POEM, DLQI, HADS), both upadacitinib doses showed superior effects vs. placebo and a dose-dependent effect was observed.

In the TCS study M16-047, there were fewer key (multiplicity-controlled) secondary endpoints compared with the mono-therapy studies. For all of these, superiority of each upadacitinib dose vs. placebo was demonstrated. In a post-hoc analysis to examine the contribution of TCS on the treatment effect of upadacitinib, there was no evidence that TCS contributes additional efficacy in the upadacitinib 30 mg or 15 mg groups. However, TCS did contribute to the efficacy achieved in the placebo group. The number of days off of all TCS and achieving an EASI 75 response was larger for the upadacitinib groups compared with the placebo group.

Consistent treatment effects in the pre-specified subgroups (age, gender, BMI, race, weight; baseline vIGA-AD and EASI, hsCRP, previous systemic therapy, intolerance to at least one prior TCS/TCI, inadequate response to at least one topical treatment and geographic region) in favour of upadacitinib 30 mg and upadacitinib 15 mg were observed when compared to placebo for the co-primary endpoints of vIGA-AD 0/1 and EASI 75.

In adolescents, both upadacitinib doses showed a clearly statistically significant difference vs. placebo for the co-primary endpoints and most secondary endpoints. A dose-related difference was observed also in this group.

All three pivotal studies showed very consistent results, in terms of magnitude of effect for the two dose levels and that both co-primary and key secondary were met across all studies.

In addition, the evaluated exposure-efficacy relationships (average plasma concentration vs EASI75/90, vIGA-AD 0/1, vIGA-AD 0, and Worst Pruritus NRS ≥4, respectively) indicate clear relationships between increased effect with increased exposure.

Updated results for the three pivotal studies up to 52 weeks have shown sustained efficacy over time.

3.3. Uncertainties and limitations about favourable effects

For the TCS study M16-047, the TCS use was not weighed; hence, information on the total TCS used in respective study arms has not been captured. The number of days off TCS with an EASI 75 response was evaluated, though. Since this was not among the not multiplicity-controlled secondary endpoints, the MAH agreed to remove it from their proposed section 5.1 of the SmPC.

Only limited data are available from a phase 2 study on maintenance of response and/or a possibility of dose reduction (e.g. from the 30 mg dose to the 15 mg dose once a response is achieved) since none of the large pivotal studies included a randomised withdrawal part. Although the Phase 2b data is not extensive, the data still suggest that withdrawal of treatment will result in return of AD symptoms within about a month in half of the subjects. At the CHMP's request, the Section 4.2 of the SmPC was modified to state that the lowest effective dose for maintenance should be considered.

Some of the analysed sub-groups were small (e.g. the Chinese and Japanese groups), resulting in wide confidence intervals and in some instances the 95% confidence interval did not exclude zero (e.g. for the race sub-group category "other" in the TCS study). However, consistent treatment effects in all pre-specified subgroups in favour of upadacitinib 30 mg and upadacitinib 15 mg were observed when compared to placebo for the co-primary endpoints of vIGA-AD 0/1 and EASI 75.

Concerning elderly patients, the sub-group ≥65 years was small and was not analysed separately for efficacy. At the CHMP's request, the dose in patients ≥ 65 years of age has been limited to 15 mg once daily.

None of the three studies included an active comparator. This could have been of interest but is not viewed by the CHMP as a requirement.

3.4. Unfavourable effects

The safety database consists of a total of 2898 subjects (adult and adolescents) who were enrolled in the AD studies and received at least 1 dose of upadacitinib. At the Nov 24, 2020 cut-off, the mean duration of treatment was 413.3 days in the upadacitinib 30 mg group (N = 1382) and 405.9 days in the upadacitinib 15 mg group (N = 1372). Of these subjects, 931 and 895 had exposure to upadacitinib 30 mg or upadacitinib 15 mg, respectively, for at least 12 months. The Phase 3 studies included 333 adolescents who received at least one dose of upadacitinib, with 166 and 167 in the 30 mg and 15 mg dose group, respectively. Among adolescents, 223 subjects received treatment for ≥ 52 weeks (113 and 110 for the 30 mg and the 15 mg dose, respectively) at the Nov 24, 2020 data cut-off.

The common TEAEs observed in the AD population were largely the same as those observed in the previously approved RA, PsA and AS indications. The rates of these TEAEs were generally higher in the upadacitinib 30 mg group than in the 15 mg group, indicating dose/exposure dependency of the common AEs. Based on data from two different cut-off dates in the Phase 3 studies (04 June, 2020 and 24 Nov., 2020, respectively), there was no worsening of the rate of AEs upon longer treatment and follow-up.

Eight new ADRs were added in the SmPC section 4.8: Folliculitis (common), Influenza (common), Anaemia (common), Abdominal pain (common), Fatigue (common), Urticaria (common), Headache (common) and Acne (very common). During the placebo-controlled period, the frequency of these ADRs was higher at 30 mg upadacitinib than at 15 mg, except for influenza and abdominal pain. In the long-term treatment analysis set, the difference between doses were no longer present or were reversed for abdominal pain, headache, fatigue and urticaria. However, folliculitis, anaemia, acne and influenza appeared to be dose dependent also in the long-term set. The rate of acne was 15.8%, 10.0% and 2.2% at upadacitinib 30 mg, upadacitinib 15 mg and placebo, respectively. Acne has also been identified in PsA studies, albeit at a lower rate than in the AD population. The remaining seven new ADRs have not been identified in AS or PsA studies. Overall, these ADRs are not considered to indicate that the safety profile in AD patients to a clinically relevant extent differs, at least not qualitatively, from that in other indications for upadacitinib. Decreased haemoglobin levels is a previously identified risk with upadacitinib, but anaemia has not been identified as ADR for other indications, which might mirror an increased frequency of decreased haemoglobin at the 30 mg dose.

During the 16-week placebo-controlled period, the rate of SAEs was relatively low and was similar in the upadacitinib groups and the placebo group. In the long-term dataset the overall rate of SAEs was higher in the upadacitinib 30 mg group than in the 15 mg group (7.7 vs. 7.1 events/100 PY).

Most SAEs were reported within the SOC Infections and infestations. The previously identified risks with upadacitinib treatment include serious infection. In the AD studies, at long-term treatment, the frequency of serious infections was 2.8 E/100 PY with the 30 mg dose and 2.3 E/100 PY with the 15 mg dose. Most serious infections were anticipated in a population of patients with AD, labelled for upadacitinib, or reflective of the current COVID-19 pandemic outbreak. Pneumonia was the most common serious infection.

Opportunistic infection is another identified risk with upadacitinib treatment. An overall increased frequency of herpes zoster was observed in AD patients compared to that previously reported in RA patients. AD patients might be more susceptible to herpes zoster, but the events appeared also to be driven by upadacitinib, as the effect was dose dependent. Altogether two cases of active TB were described, one in each dose group. These cases do not affect previous assessment of the risk in other indications. Except active TB and herpes zoster, all reported opportunistic infections in the pivotal Phase 2 and 3 studies in AD (n=49) were events reported as eczema herpeticum or Kaposi's

varicelliform eruption, which are known to be associated with AD. There was no apparent dose dependency in this effect.

During the placebo-controlled period, the discontinuation rate due to and AE was 3.8%, 2.3% and 2.9% in the placebo group, the 15 mg upadacitinib and the 30 mg upadacitinib groups, respectively. The most frequently reported reason was dermatitis atopic (lack of efficacy) at 1.7%, 0.9% and 0.4%, respectively, followed by SOC Infection at 0.5%, 0.4% and 0.6%, respectively. In the long-term upadacitinib analysis set, the overall discontinuation rate due to an AE was 4.4 E/100 PY and 5.7 E/100 PY in the 15 mg and 30 mg upadacitinib group, respectively. In the same set, the most common reason was dermatitis atopic (1.0 and 0.5 E/100 PY, respectively), followed by herpes simplex in 3 subjects or 0.2 E/100 PY in the 30 mg group.

There were no major differences between the safety profile in the overall population and that observed in adolescents, for either dose.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile for upadacitinib in the AD population was not qualitatively different from that observed in other indications. However, the rate of AEs was generally dose dependent. The increased risk for AEs with the 30mg dose seems to be manageable with relatively low discontinuation rates. Nevertheless, the increased risk for AEs with the 30 mg dose must be weighed against the possible gain in efficacy. In patients ≥65 years of age, the gain in efficacy might not be considered to outweigh the increased risk of AEs and SAEs. At the CHMP's request, the dose in patients ≥ 65 years of age has been limited to 15 mg once daily.

The safety database in adolescents is considered sufficiently large by the CHMP. The available data indicated no major differences in safety profile between adolescents and the overall study population. Long-term safety data in adolescents is added as Missing information in the RMP. The non-clinical juvenile toxicity study with upadacitinib did not indicate effects on bone development, and there was no difference between the two doses in terms of height in adolescents in the clinical studies. However, as clinical data on potential effects on bone growth are still limited, the MAH will continue assessing potential effects on height in growing children in the long-term extension studies and in a PASS (see RMP).

3.6. Effects Table

Table 49   Effects Table for Rinvoq (upadacitinib) in atopic dermatitis

(data cut offs: 13 April 2020 (M16-045), 10 April 2020 (M16-047), 08 May 2020 (M18-891))

Effect	Short Description	Unit	Treatment		Control	Uncertainties/ Strength of evidence	References
			15 mg	30 mg			
Favourable Effects							
vIGA-AD (0,1)	vIGA-AD score 0,1 response at Week 16	%	43.5	57.0	6.6	p <0.001 for both doses	Pooled mono-studies[1]
			39.6	58.6	10.9	p <0.001 for both doses	TCS study[2]
EASI 75	EASI 75 response at Week 16	%	64.9	76.3	14.8	p <0.001 for both doses	Pooled mono-studies[1]
			64.6	77.1	26.4	p <0.001 for both doses	TCS study[2]
NRS pruritus	Reduction in worst pruritus NRS ≥4 Week 16	%	52.2	60.0	11.8	p <0.001 for both doses	M16-045[1]
			41.9	59.6	9.1	p <0.001 for both doses	M18-891[1]
			51.7	63.9	15.0	p <0.001 for both doses	M16-047[2]
EASI 90	EASI 90 response at Week 16	%	53.1	65.8	8.1	p <0.001 for both doses	M16-045[1]
			42.4	58.5	5.4	p <0.001 for both doses	M18-891[1]
			42.8	63.1	13.2	p <0.001 for both doses	M16-047[2]

Effect	Short Description	Unit	Treatment		Control	Uncertainties/ Strength of evidence	References
			15 mg	30 mg			

Unfavourable Effects (data cut-off 04 June, 2020)							
Effect	Unit	Treatment 15 mg	Treatment 30 mg	Control	Uncertainties/ Strength of evidence	References	
Common adverse events							
Acne	N (%)	86 (9.6)	137 (15.1)	20 (2.2)	Data from 16-week placebo-controlled period	M16-048 M16-045 M16-047 M18-891	
Nasopharyngitis	N (%)	79 (8.8)	94 (10.4)	64 (7.1)	"	"	
Upper respiratory tract infection	N (%)	70 (7.8)	83 (9.2)	58 (6.4)	"	"	
Headache	N (%)	50 (5.6)	57 (6.3)	39 (4.3)	"	"	
Blood creatine phosphokinase increased	N (%)	41 (4.6)	50 (5.5)	21 (2.3)	"	"	
Oral herpes	N (%)	23 (2.6)	47 (5.2)	9 (1.0)	"	"	
Diarrhoea	N (%)	31 (3.4)	29 (3.2)	23 (2.5)	"	"	
Cough	N (%)	29 (3.2)	27 (3.0)	13 (1.4)	"	"	
Folliculitis	N (%)	19 (2.1)	29 (3.2)	10 (1.1)	"	"	
Nausea	N (%)	24 (2.7)	24 (2.6)	5 (0.6)	"	"	
Dermatitis atopic	N (%)	31 (3.4)	14 (1.5)	74 (8.2)	"	"	
Oropharyngeal pain	N (%)	19 (2.1)	20 (2.2)	9 (1.0)	"	"	
Adverse events of special interest (Long-term treatment)							
Serious infection	E (E/100 PY)	21 (2.4)	30 (3.4)	N/A	Phase 3 data	M16-045 M16-047 M18-891	
Opportunistic infection	E (E/100 PY)	18 (2.1)	20 (2.2)	N/A	"	"	
Herpes zoster	E (E/100 PY)	33 (3.8)	47 (5.3)	N/A	"	"	

Effect	Short Description	Unit	Treatment		Control	Uncertainties/ Strength of evidence		References
			15 mg	30 mg				
Hepatobiliary disorders	E (E/100 PY)	52 (6.0)		66 (7.4)	N/A	"	"	
Anaemia	E (E/100 PY)	10 (1.1)		28 (3.1)	N/A	"	"	
Neutropenia	E (E/100 PY)	22 (2.5)		42 (4.7)	N/A	"	"	
Lymphopenia	E (E/100 PY)	5 (0.6)		6 (0.7)	N/A	"	"	
Creatine phosphokinase elevation	E (E/100 PY)	82 (9.4)		101 (11.3)	N/A	"	"	

Abbreviations: N=Number of subjects, E=Number of events, PY=patient years, N/A= not applicable
[1] Monotherapy studies: M16-045 and M18-891 [2] TCS study: M16-047

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy results for upadacitinib in AD were highly statistically significant and clearly clinically relevant for both doses across all three pivotal studies. This relates to important efficacy outcomes reflecting skin clearance, pruritus, and health-related quality of life. The onset of effect was rapid.

Concomitant TCS treatment did not contribute much additional efficacy in the upadacitinib groups (but some in the placebo group) and support that upadacitinib may be used with or without TCS. No data vs. an active comparator are available; however, this is not viewed as a requirement by the CHMP.

Updated data on upadacitinib long term efficacy and safety in AD have been submitted from the extension phases of the studies. Only limited phase 2 data are available on rebound, possibility for dose reduction (in case response is achieved initially on the 30 mg dose) or data following cessation of treatment and re-treatment. In clinical practice, both dose reductions and dose interruptions may be realistic scenarios, e.g. due to safety concerns. The phase 2 data, albeit limited, together with the long-term phase 3 data are considered sufficient to support the currently proposed wording in the posology section of the SmPC related to these topics.

A dose dependency for efficacy was observed in all studies, with overall 10-19% differences in responder rates for both co-primary and key secondary endpoints. In post-hoc analyses presented by the MAH for the mono-therapy studies, it was clear that the CIs for the efficacy results of the two doses were non-overlapping for almost all endpoints. Thus, although the 30 mg upadacitinib dose has not previously been recommended in the other approved Rinvoq indications (RA, PsA, AS), the use of 30 mg in AD is considered justified in this indication. At the CHMP's request, the MAH has updated section 4.2 of the SmPC to further clarify when the respective doses are most appropriate to use. For instance, it is now stated that a dose of 30 mg once daily may be appropriate for patients with high disease burden and that a dose of 30 mg once daily may be appropriate for patients with an inadequate response to 15 mg once daily. It is also stated that the lowest effective dose for

maintenance should be considered. Clearer dose recommendations for when to use the 15 mg vs. the 30 mg dose are included in the SmPC. The CHMP agreed that either dose can be the starting dose (i.e. no need to start all patients on 15 mg).

The influence of body weight on upadacatinib PK is low in adolescent and adult AD patients. A weight limit of 30 kg in adolescent AD patients is not expected to exceed the adult reference exposure range. Hence, the weight limit was lowered from 40kg to 30 kg for adolescent AD patients. This is supported by the CHMP.

There were no new important safety findings in the AD population, including the adolescent subgroup, as compared with studies in other indications with upadacitinib. However, the known adverse events occurred at an overall higher frequency with the 30 mg dose compared with the 15 mg dose.

3.7.2. Balance of benefits and risks

A clearly clinically relevant effect of upadacitinib has been demonstrated in AD combined with an overall acceptable safety profile, which did not qualitatively differ from that observed in other indications. The observed gain in efficacy of the 30 mg dose over the 15 mg dose is, in patients < 65 years, considered to outweigh the increased risk of AEs at the 30 mg dose.

The benefit-risk of the 30 mg dose in patients ≥65 years of age was considered uncertain. At the CHMP's request, the dose in patients ≥ 65 years of age has been limited to 15 mg once daily.

In adolescents from 12 years > 30kg, the MAH's recommendation for the 15mg dose is endorsed by the CHMP. As clinical data on potential effects on bone growth are still limited, growth will be monitored in the long-term extension studies and in a PASS (see RMP).

3.8. Conclusions

The overall B/R of Rinvoq in the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Rinvoq new 30 mg strength is favourable in the following indication:

"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."

The CHMP therefore recommends the extension(s) of the marketing authorisation for Rinvoq subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

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

Additional risk minimisation measures

Prior to launch of RINVOQ in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The objective of the programme is to increase awareness of HCPs and patients on the risks of serious and opportunistic infections including TB, herpes zoster, foetal malformation (pregnancy risk), MACE, and VTEs and how to manage these risks.

The MAH shall ensure that in each Member State where RINVOQ is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use RINVOQ have access to/are provided with the following educational package:

The physician educational material should contain:

- The Summary of Product Characteristics

- Guide for healthcare professionals

- Patient Alert Card (PAC)

The Guide for healthcare professionals shall contain the following key elements:

- General introductory language that the HCP measure contains important information to assist the discussion with patients when prescribing upadacitinib. The brochure also informs on steps which can be taken to reduce a patient's risk for key safety aspects of upadacitinib.

- Language for HCPs to inform patients of the importance of the PAC

- Risk of serious and opportunistic infections including TB

  o Language on the risk of infections during treatment with upadacitinib

  o Language on increased risk of serious infections in patients ≥ 65 years of age

  o Details on how to reduce the risk of infection with specific clinical measures (what laboratory parameters should be used to initiate upadacitinib, screening for tuberculosis (TB), and getting patients immunised as per local guidelines, and interruption of upadacitinib if an infection develops)

  o Language on avoidance of live vaccines (i.e., Zostavax) prior to and during upadacitinib treatment

  o Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.

- Risk of herpes zoster

  o Language on the risk of herpes zoster during treatment with upadacitinib

  o Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.

- Risk of foetal malformation

  o Language on teratogenicity of upadacitinib in animals

  o Details on how to reduce the risk of exposure during pregnancy for women of childbearing potential based on the following: upadacitinib is contraindicated during pregnancy, women of childbearing potential should be advised to use effective contraception both during treatment and for 4 weeks after the final dose of upadacitinib treatment, and to advise patients to inform their HCP immediately if they think they could be pregnant or if pregnancy is confirmed.

- Risk of MACE

  o Language on the increased risk of major adverse cardiovascular event (MACE) in patients with immune-mediated inflammatory diseases and the need to consider typical CV risk factors (e.g., hypertension, hyperlipidaemia) when treating patients

  o Language on the risk of MACE during treatment with upadacitinib

  o Language on the risk of hyperlipidaemia during upadacitinib therapy

  o Details on monitoring of lipid levels and management of elevated lipid levels per clinical guidelines

- Risk of VTE

  o Examples of the risk factors which may put a patient at higher risk for venous thromboembolic events (VTE) and in whom caution is needed when using upadacitinib.

  o Language on the risk of VTE during treatment with upadacitinib

  o Language on need for discontinuation of upadacitinib, evaluation, and appropriate treatment for VTE if clinical features of deep venous thrombosis or pulmonary embolism develop

Information for upadacitinib use in moderate to severe AD

The 30 mg upadacitinib dose in atopic dermatitis

- Language on dose-dependent increase in serious infections and herpes zoster with upadacitinib.

- Language on dose-dependent increase in plasma lipids with upadacitinib.

- Language that eczema herpeticum occurred in both placebo and upadacitinib-treated subjects with similar rates in the 30 mg and 15 mg groups.

- Language that the 30 mg dose is not recommended in certain populations (patients with severe renal impairment and patients taking strong CYP3A4 inhibitors).

- Reminder that the 15 mg dose is the recommended dose in patients ≥ 65 years of age.

Upadacitinib use in adolescents 12 years and older

- Reminder that live, attenuated vaccines (ie. varicella, MMR, BCG) which depending on local guidelines may be considered in adolescents. Language not to administer these vaccines immediately prior to or during upadacitinib treatment.

- Language to remind adolescents of the potential pregnancy risks and on the appropriate use of effective contraception.

- Language if their adolescent patient has not experienced menarche, to inform their adolescent patient or caregiver to let them know when they do.

Instructions for how to access digital HCP information

Instructions on where to report AEs

The patient information pack should contain:

- Patient information leaflet

- A patient alert card

- The patient alert card shall contain the following key messages:
    - Contact details of the upadacitinib prescriber
    - Language that the PAC should be carried by the patient at any time and to share it with HCPs involved in their care (i.e., non-upadacitinib prescribers, emergency room HCPs, etc.)
    - Description of signs/symptoms of infections the patient needs to be aware of, so that they can seek attention from their HCP:
        - Language to advise patients and their HCPs about the risk of live vaccinations when given during upadacitinib therapy. Examples of live vaccines are provided.

- Description of targeted risks for awareness by the patient and for HCPs involved in their care including:

    - Elevations in plasma lipids and the need for monitoring and lipid lowering treatment

    - A reminder to use contraception, that upadacitinib is contraindicated during pregnancy, and to notify their HCPs if they become pregnant while taking upadacitinib

  - Description of signs/symptoms of deep venous thrombosis or pulmonary embolism which the patient needs to be aware of, so that they can seek attention from an HCP

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A

Extension application to introduce a new strength (30 mg prolonged-release tablet), grouped with a type II variation (C.I.6.a) to add a new indication (treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy for Rinvoq). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3 of the SmPC, Annex II as well as the Package Leaflet are updated. The RMP (version 4.3) is adopted.