25 June 2026
EMADOC-1700519818-2969402
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rinvoq

International non-proprietary name: upadacitinib

Procedure No. EMA/VR/0000312506

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AA	alopecia areata
AASIS	Alopecia Areata Symptom Impact Scale
AD	atopic dermatitis
ADR	Adverse Drug Reaction
AE	adverse event
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
AUC24,ss	Area under the curve over a 24-hour period at steady state
BLQ	Below the Limit of Quantification
BMI	body mass index
C_{avg}	average concentration
CD	Crohn's Disease
CI	confidence interval
ClinRO	Clinician-Reported Outcome
CMH	Cochran–Mantel–Haenszel
Cmax	Maximum concentration
Ctrough	Minimum concentration
CV	Cardiovascular
CSE	clinical summary of efficacy
CSR	clinical study report
EMA	European Medicines Agency
E-R	Exposure-Response
ERA	Environmental Risk Assessment
EU	European Union
FDA	Food and Drug Administration
Fpen	Fraction of Population Entering Treatment
GCA	Giant Cell Arteritis
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GOF	Goodness-of-fit
HBV	Hepatitis B virus
HS	hidradenitis suppurativa
I-ALFA	global investigator assessment for beard hair loss
IBD	Inflammatory Bowel Disease
IIV	Inter-Individual Variability
IL	interleukin
ISE	Integrated Summary of Efficacy
JAK	Janus kinase
LC-MS/MS	Liquid Chromatography Method with Tandem Mass Spectrometric Detection
LLOQ	Lower Limit of Quantification

LS	least square
Max	maximum
MCID	minimal clinical important difference
Min	minimum
NONMEM	Non-linear Mixed-Effects modelling
nr-axSpA	non-radiographic axial spondyloarthritis
NRI	Non-Responder Imputation
OC	observed case
PBO	placebo
pcJIA	polyarticular juvenile idiopathic arthritis
pcVPC	prediction-corrected VPCs
PDCO	Paediatric Committee
PEC_{SW}	Predicted Environmental Concentration in Surface Water
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PRO	patient-reported outcome
PsA	psoriatic arthritis
PT	preferred term
QD	once daily
QoL	Quality of Life
RA	rheumatoid arthritis
R&D	research and development
RMP	Risk Management Plan
RTB	Return-to-Baseline
SALT	Severity of Alopecia Tool
SAP	statistical analysis plan
SD	standard deviation
SLE	systemic lupus erythematosus
SOC	system organ class
TSLD	Time-Since Last Dose
TYK2	Tyrosine kinase 2
UC	ulcerative colitis
US	United States
VPC	visual-predictive-checks
vs.	versus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Abbvie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 11 November an application for a variation

The following changes were proposed:

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

Extension of indication to include the treatment of severe alopecia areata (AA) in adult and adolescents 12 years and older for Rinvoq, based on interim results from 2 pivotal, Phase 3 studies (M23-716 Study 1 and Study 2); those are randomized, double blind, placebo-controlled, multi-center studies of upadacitinib evaluating the efficacy and safety of upadacitinib 15 mg QD and 30 mg QD versus placebo for the treatment of severe AA in subjects who are at least 12 years of age. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Annex II are updated in accordance. Version 18.0 of the RMP has also been submitted. As part of the application, the MAH is requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics (SmPC), Annex II, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0062/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0062/2024 was not yet completed as some measures were deferred.

The Phase 3 studies M23-716 Study 1 and Study 2 are not part of the agreed PIP, even though they included adolescent participants. This is because the MAH previously informed PDCO that the adolescent indication would not be based on data from the adult/adolescent studies.

A copy of the latest PIP Decision P/0062/2024 for upadacitinib for the condition 'treatment of alopecia areata' was provided. The PIP Opinion includes 4 measures, of which one is a randomised, double-blind, placebo-controlled paediatric PK efficacy study in participants aged from 6 to 18 years of age (PIP Study 2; M24-725) which has not yet started.

A positive outcome for the partial PIP compliance check (EMA/PE/0000269040) was received on 17 October 2025, which confirms compliance with the agreed PIP for upadacitinib for the condition 'treatment of alopecia areata' (PIP P/0062/2024).

The compliance status with regard to the agreed PIP is as follows:

Study No., identifier	Compliance status / conclusion	Description
Studies checked during this compliance check		
Study 3	Compliance of initiation confirmed	Population PK Modelling of adult / adolescent subjects with alopecia areata to describe upadacitinib pharmacokinetics in adult / adolescent subjects with alopecia areata, to assess the impact of covariates on PK parameters and to inform the recommended dosing regimen in PIP
Study 4	Compliance of initiation confirmed	Exposure-response model to characterise the relationship between upadacitinib plasma exposure and efficacy / safety parameters in children from 6 years to less than 18 years of age with alopecia areata

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.

Information relating to orphan market exclusivity

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. During the assessment of the procedure, the MAH withdrew their request for one additional year of market protection.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Dunder

Timetable	Actual dates
Submission date	11 November 2025
Start of procedure:	29 November 2025
CHMP Rapporteur's preliminary assessment report circulated on:	26 January 2026
PRAC Rapporteur's preliminary assessment report circulated on:	30 January 2026
PRAC comments	n/a
PRAC Rapporteur's updated assessment report circulated on:	n/a
PRAC Outcome	12 February 2026
CHMP comments	16 February 2026
CHMP Rapporteur's updated assessment report circulated on:	19 February 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 February 2026
MAH's responses submitted to the CHMP on:	20 March 2026
CHMP Rapporteur's preliminary response assessment report on the MAH's responses circulated on:	22 April 2026
PRAC Rapporteur's preliminary response assessment report on the MAH's responses circulated on:	23 April 2026
PRAC comments	n/a
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on:	30 April 2026
PRAC Outcome	07 May 2026
CHMP comments	11 May 2026
CHMP Rapporteur's updated response assessment report on the MAH's responses circulated on:	13 May 2026
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	21 May 2026
MAH's responses submitted to the CHMP on:	29 May 2026
CHMP Rapporteur's preliminary response assessment report on the MAH's responses circulated on:	15 June 2026
CHMP comments	n/a
CHMP Rapporteur's updated response assessment report on the MAH's responses circulated on:	18 June 2026
An Oral explanation took place on:	23 June 2026
CHMP opinion:	25 June 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

This is an application for the extension of indication of Rinvoq (upadacitinib).

Disease or condition

Alopecia Areata (AA) is a chronic immune-mediated inflammatory disease characterised by patches of hair loss that can affect any hair-bearing site of the body. The disease targets anagen (active, growing) hair follicles and causes nonscarring hair loss. It most commonly presents with discrete and smooth patches of hair loss on the scalp, but may also affect other hair-bearing areas including eyebrows, eyelashes, beard, torso, and extremities. The extent of hair loss can vary from isolated patches to complete hair loss.

State the claimed the therapeutic indication

The proposed indication is:

"Rinvoq is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years and older."

The posology is:

"For adults and adolescent patients 12 years of age and older weighing at least 30 kg, 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 or patients with an inadequate response to 15 mg once daily.
- The lowest effective dose to maintain response should be used.

For patients 65 years of age and older, the recommended dose is 15 mg once daily (see section 4.4)."

Epidemiology

The incidence and prevalence of AA varies across the world. The overall incidence in the UK and the USA has been estimated at 0.21 – 0.26 per 1000 patient-years; the cumulative lifetime incidence is appr. 2 percent (i.e. 1 in 50 persons will develop alopecia areata at some time during life). The disorder occurs at similar rates in males and females.[1] The disease can manifest at any age; most patients are relatively young, with 40% of AA patients experiencing their first onset by the age of 20 years and 83% to 88% of AA patients experiencing their first onset by 40 years of age.[2] Median onset in children is between 5 and 10 years of age. [2,3] In a review of 392 children with AA, extensive disease

[1] Strazzulla LC, Wang EHC, Avila L, et al. Alopecia areata: Disease characteristics, clinical evaluation, and new perspectives on pathogenesis. J Am Acad Dermatol. 2018;78(1):1-12.
[2] Villasante Fricke AC, Miteva M. Epidemiology and burden of alopecia areata: a systematic review. Clin Cosmet Investig Dermatol. 2015;8:397-403
[3] Kakourou T, Karachristou K, Chrousos G. A case series of alopecia areata in children: impact of personal and family history of stress and autoimmunity. J Eur Acad Dermatol Venereol. 2007;21(3):356–360.

(>50% hair loss) was reported in 12% of children aged 11 to 15 years, 5% of children aged 6 to 10 years, and 0% of children aged 1 to 5 years.[4]

Aetiology and pathogenesis

The mechanisms leading to alopecia areata are not fully understood. Insights into the immunopathogenesis of AA began with the recognition of the hair follicle as being an immune-privileged site like the eye and testes.[5] Disruption of this immune privilege occurs upon follicular influx by auto-reactive CD8+ T cells, leading to increases in major histocompatibility complex (MHC) Class I and II antigens and inflammation disrupting hair follicle biology.[6] Activation of the pathogenic T cells leads to Interferon-gamma (IFNγ) production which contributes both to enhanced MHC class I and II antigens and interleukin-15 (IL 15) [6] accompanied by additional cytokines including IL 2, IL-13, IL-23, and thymic stromal lymphopoietin.[7] All these inflammatory-related cytokines are dependent on JAK/STAT signalling, and of note IFNγ utilizes JAK1 and JAK2.

Clinical presentation, diagnosis

AA is an autoimmune disease characterized by patches of nonscarring hair loss. The diagnosis of AA is based upon the appearance of the hair loss. A health care provider will look for the characteristic patterns of hair loss, such as smooth patches with short, broken-off hairs around the borders. Biopsy is usually not necessary. AA is associated with atopic diseases such as atopic dermatitis and asthma. Up to 50% of patients who present with patchy alopecia areata experience spontaneous hair regrowth within one year, most will relapse months or years after remission.[6]

Severe AA is recognized as a significant autoimmune condition with emotional and psychosocial distress, including high prevalence of depression and anxiety. Health related QoL is also consistently diminished in participants with AA. [8]

Management

Baricitinib (Olumiant, inhibitor of JAK 1 and 2) and ritlecitinib (Litfulo, JAK3, TEC inhibitor) are both centrally approved in the EU for the treatment of severe AA in adolescents (from age of 12 years) and adults. Some authorized medicines (e.g. methylprednisolone and triamcinolone intra-lesion injections) are available in individual member states.

Topical treatments (e.g. corticosteroids and minoxidil) are frequently used in AA. However, according to European expert consensus statement on the systemic treatment of AA, a Severity of Alopecia Tool (SALT) score equal to or greater than 20 constitutes a commonly accepted indication for systemic therapy in AA.[9] Systemic medicines used off-label in alopecia areata include glucocorticosteroids,

[4] Tan et al. (2002), A Clinical Study of Childhood Alopecia Areata in Singapore. Pediatric Dermatology, 19: 298-301.
[5] Paus, R., Nickoloff, B.J. and Ito, T. (2005), A 'hairy' privilege. Trends in Immunology, 26: 32–40
[6] Islam et al. (2015), The autoimmune basis of alopecia areata: a comprehensive review. Autoimmunity Reviews, 14: 81–89.
[7] Suárez-Fariñas et al. (2015), Alopecia areata profiling shows TH1, TH2, and IL-23 cytokine activation without parallel TH17/TH22 skewing. Journal of Allergy and Clinical Immunology, 136: 1277–1287
[8] Janković et al. (2016), Quality of life in patients with alopecia areata: A hospital-based cross-sectional study. Journal of the European Academy of Dermatology and Venereology, 30: 840–846
[9] Rudnicka et al. (2024), European expert consensus statement on the systemic treatment of alopecia areata. Journal of the European Academy of Dermatology and Venereology, 38: 687–694.

cyclosporine, methotrexate and azathioprine. Oral minoxidil is considered an adjuvant therapy with limited data confirming its possible efficacy. [9]

Off-label treatments for AA in adults are used empirically for adolescent patients. Current treatments for children <10 years of age include topical corticosteroid (Class I–III) monotherapy or in combination with topical retinoids, topical anthralin, and rarely systemic steroids (pulse therapy).[10,11] Treatment in children >10 years of age may also include topical sensitisers and intralesional corticosteroids if tolerated (the latter treatment is locally approved in several European countries). [10,11] Methotrexate, hydroxychloroquine, azathioprine and other immunomodulators are used, despite limited efficacy data in this population.[9] Use of minoxidil is controversial both due to lack of efficacy [9] and tolerability concerns (light-headedness, adherence issues) in children.[11]

The limited authorized treatment options that exist for patients with AA, and the large psychosocial burden, present a high unmet need, especially in the adolescent population.

2.1.2. About the product

Rinvoq (upadacitinib) is a selective and reversible Janus kinase (JAK) inhibitor. 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. The relative affinity of JAK inhibitors for different members of the JAK kinase family allows for differentiation of JAK inhibitors in relation to their enzymatic inhibitory profile.

Rinvoq (upadacitinib) was first authorized in the EU in December 2019 for rheumatoid arthritis and has since been authorized for the treatment of adults with psoriatic arthritis, axial spondyloarthritis, giant cell arteritis, ulcerative colitis, and Crohn's disease. Rinvoq (upadacitinib) is also approved for the treatment of adolescents 12 years and older with atopic dermatitis.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific advice from regulatory agencies, including the US FDA, Swedish MPA, and Japan PMDA, was sought on the upadacitinib AA Phase 3 clinical development program. The MAH received advice from the MPA in March 2023. Key scientific advice feedback from the MPA for M23-716 studies and resulting changes to the study designs are summarized in Table 1.

[10] Alkhalifah et al. (2010), Alopecia areata update: Part II. Treatment. Journal of the American Academy of Dermatology, 62: 191–202
[11] Goldberg, L.J. and Castelo-Soccio, L. (2015), Alopecia areata in children: a review of treatment options. *Pediatric Dermatology*, 32: 453–461.

Table 1. Key Feedback Incorporated in M23-716 After Scientific Advice (modified)

Scientific Advice	Key Changes Following Scientific Advice
Endpoints:	
• Not fully agreed that itch is considered a major symptom in AA and a justification of measuring scalp itch would be needed. The proposed method for measuring scalp itch is acceptable and the preference is for validation and confirmation to be used separately (not the full sample for validation only).	• Changed scalp itch from multiplicity-controlled secondary endpoint to additional efficacy endpoints.
Study Design:	
• Treatment termination at Week 52 requires justification for late termination of non-responders.	• Revised study drug discontinuation criteria for Week 40 visit: non-responders to be discontinued and partial responders (defined as change in SALT < 30% from Baseline) to be continued in UPA 30 mg open-label arm and to be discontinued if change in SALT is still < 30% from Baseline at a subsequent visit.
Study Population:	
• Exclude cardiovascular disease from the studies based on the JAK inhibitor safety profile.	• Excluded subjects with recent major cardiovascular events or surgery. Included subjects with a history of atherosclerotic cardiovascular disease, long-time smoking, or known venous thromboembolism risk factors provided they had a favorable benefit-risk profile in the opinion of the investigator.
Statistical Methods:	
• Consider a consistent approach or provide scientific justifications for handling the intercurrent events of the continuous endpoints differently to the handling approach for binary endpoints.	• Revised the approach for handling intercurrent events for continuous endpoints from MMRM based on the MAR assumption to a more conservative RTB approach.
• Consider performing more sensitivity analyses if there are more imputed non-responders in 1 group, or if there is a different missing pattern between treatment groups.	• Tipping point analysis was added as an additional sensitivity analysis, which considered all possible non-responder imputation cases including the most conservative case, to confirm the primary missing data handling approach is robust.

Please refer to`Background information on the procedure´ for further information on the PIP.

2.1.4. General comments on compliance with GCP

The MAH states that M23-716 Study 1 and Study 2 are being conducted in accordance with the ICH and Good Clinical Practice (GCP) guidelines and relevant regulatory requirements.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH has provided an Environmental Risk Assessment (ERA) to include the new indication of AA, however no new data for the environmental risk assessment were included with this application. The submitted ERA was updated from the original ERA submitted for the MAA for RA approval, and the updates of the indications of Psoriatic Arthritis (PsA), Ankylosing Spondylitis(AS), Atopic Dermatitis (AD), Ulcerative Colitis (UC), Non-radiographic Axial Spondyloarthritis (nr-axSpA), Crohn's Disease (CD), Giant Cell Arteritis (GCA) and Polyarticular-course Juvenile Idiopathic Arthritis (pcJIA).

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.

Regarding the original ERA, the MAH submitted a final report an OECD TG107 study post-approval. The overall log Kow of the test substance was determined to be 1.81 (pH4), 2.50 (pH7), and 2.48 (pH9) at 25°C. The conclusion of the assessment was that the study report provided had an acceptable experimental design and fulfilled the quality/validation criteria and that the data was also included in the updated ERA in a satisfactory manner.

Phase I

The maximum daily dose for the indication AA is 30 mg/day, resulting in PEC_{SW} value of 0.15 µg/L, for each of the indications of RA, PsA, AS, nr-axSpA, GCA and pcJIA with the maximum daily dose of 15 mg/day, the PEC_{SW} values was 0.075 µg/L, for the indication AD with the maximum daily dose of 15 mg/day, the PEC_{SW} values was 0.15µg/L and for the indications UC and UC with the maximum daily dose of 45 mg/day, the $PEC_{SURFACEWATER}$ values was 0.225 µg/L, when using the default Fraction of Population Entering Treatment (Fpen) value of 0.01.

A $PEC_{SW\text{-}TOTAL}$ was calculated (1.20 µg/L) and was used to re-calculate the Phase II Tier A and Tier B PEC/PNEC ratios.

The Log Pow and Log D were 2.50 (pH 7) using the shake flask method (OECD 107). Since the values were below the criteria of 3 no PBT assessment was needed.

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 nine 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	0.0012 mg/L	0.63 mg/L	0.019 (<1)
Groundwater	0.0003 mg/L	0.16 mg/L	0.0019 (<1)
Microorganism	0.0012 mg/L	100 mg/L	0.000012 (<0.1)

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	1.33 mg/kg	15.6 mg/kg	0.085 (<1)

2.2.2. Discussion on non-clinical aspects

The non-clinical aspects of upadacitinib were thoroughly evaluated during the original approval procedure for Rinvoq. No new non-clinical studies were submitted in support of the present application. This is acceptable.

The original procedure for the approval concerned 15 mg daily dose. This is an extension application for Rinvoq (upadacitinib) to include a new indication; severe alopecia areata in adults and adolescents 12 years and older administrated up to 30 mg/day. The safety marginals at 30 mg/day has been reflected in section 5.3 of the SmPC.

The use of JAK inhibitors in alopecia areata can be regarded as established.

2.2.3. Conclusion on the non-clinical aspects

There are no objections from a non-clinical point of view concerning the application for Rinvoq (upadacitinib) to include a new indication; alopecia areata in adults and adolescents 12 years and older.

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

2.3.2. Pharmacokinetics

Exposure data on upadacitinib in patients with Alopecia Areata (AA) from the clinical studies M23-716 1 and 2, submitted in this Type II variation, were analysed with population pharmacokinetics (popPK) modelling. The analyses were performed to characterize the pharmacokinetics of upadacitinib in adult and adolescent subjects with AA, quantify covariate effects in the population, and to generate individual exposure metrics for use in the exposure-response (ER) analyses.

Methods

Bioanalytical methods

Plasma concentrations of upadacitinib were determined using a validated liquid chromatography method with tandem mass spectrometric detection (LC-MS/MS). Bioanalytical reports from the studies

included in this submission have been submitted and show acceptable method performance. The methods have been described and used in previous regulatory applications for the use of upadacitinib in other indications and assessed as adequately validated.

Evaluation and qualification of models

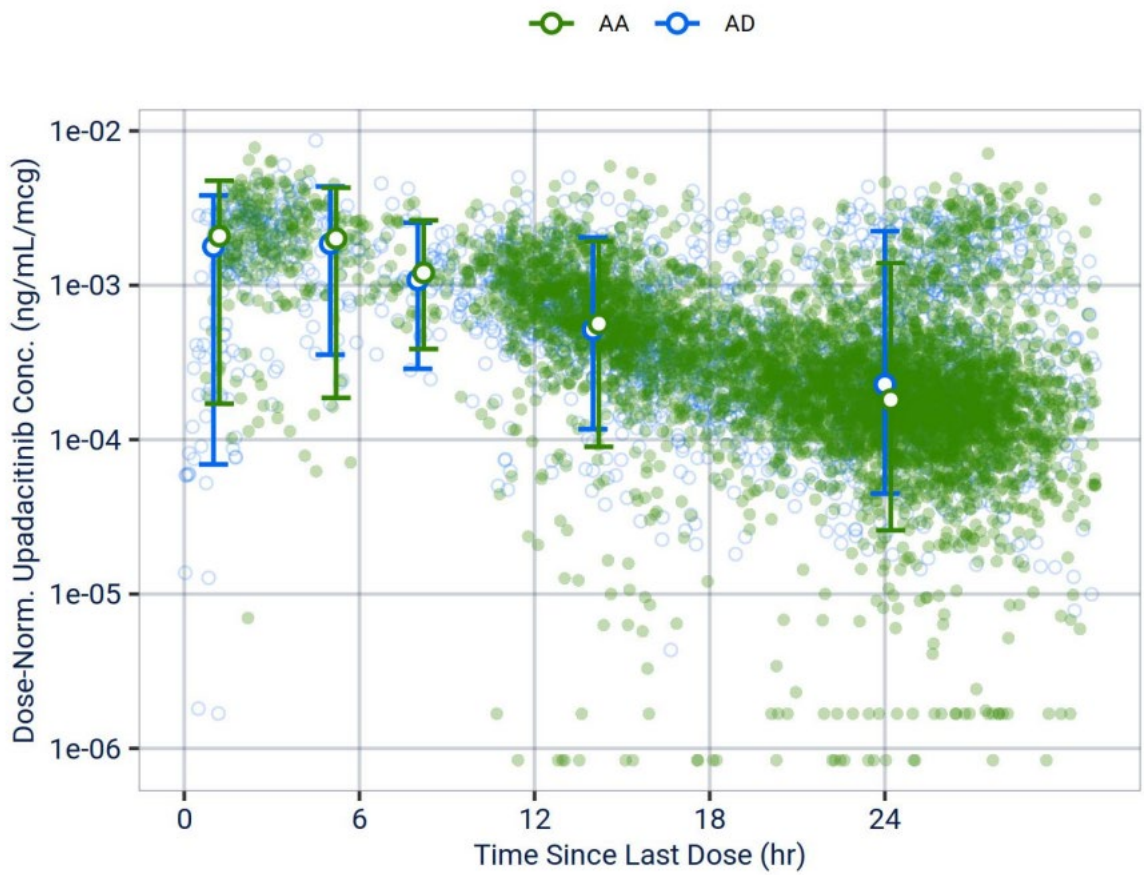
Population PK analysis

A previously developed population PK model that described upadacitinib PK across multiple indications was evaluated to describe observed upadacitinib concentrations in adult and adolescent subjects with AA, using a *post hoc* approach.

Data

Comparable dose-normalized upadacitinib concentration versus time-since last dose (TSLD) was observed between AA and AD, justifying the use of this previously developed model to characterize the PK of upadacitinib in AA Figure 1.

Figure 1. Dose-Normalized Observed Upadacitinib Concentrations in Subjects with AA Compared to Subjects with AD



The population PK model, describing upadacitinib across indications, age groups and formulations, was developed based on a pooled dataset including data from multiple clinical studies, as outlined in Table 2.

Table 2. Summary of Studies and Data Included in the Population Pharmacokinetic Analyses

Immunology Therapeutic Area	Population	Modeling Report	Study Phase	Age Group	Formulation Used in Study
Rheumatic	Healthy RA	R&D/18/0165	1 2 3	Adults	IR Capsule ER Tablet
Rheumatic	PsA	R&D/19/1199	3	Adults	ER Tablet
Rheumatic	GCA	R&D/24/0051	3	Adults	ER Tablet
Rheumatic	AS	R&D/20/0181	2/3	Adults	ER Tablet
Rheumatic	nr-axSpA	R&D/21/1212	3	Adults	ER Tablet
Rheumatic	SLE	R&D/23/1897	2	Adults	ER Tablet
Rheumatic	pcJIA	R&D/25/0393	1	Pediatrics	ER Tablet IR Oral Solution
Dermatologic	AD	R&D/20/0641	2 3	Adults Pediatrics	ER Tablet
Dermatologic	AD	R&D/22/1451	1	Pediatrics	ER Tablet IR Oral Solution
Dermatologic	NSV	R&D/24/0315	2	Adults	ER Tablet
Dermatologic	HS	R&D/23/1896	2	Adults	ER Tablet
IBD	UC	R&D/20/1629	2b/3	Adults Pediatrics	ER Tablet
IBD	UC	R&D/20/1628	2b/3 3	Adults Pediatrics	ER Tablet
IBD	CD	R&D/21/1457	3	Adults	ER Tablet
IBD	CD	R&D/21/1458	3	Adults	ER Tablet

The dataset to characterize the PK of upadacitinib in AA, included all subjects enrolled in Study M23-716 (Study 1 and 2) who received at least one dose of upadacitinib and had at least one measurable upadacitinib concentration (n=1242 subjects). PK sample collections before first dose or sampled > 168 hours after last dose were excluded from the analysis. A total of 5151 concentration records were included in the PK analysis. A total of 87 of these records (1.69%) were below the Lower Limit of Quantification (LLOQ) of 0.0503 ng/mL.

All observed plasma concentrations below LLOQ were set to LLOQ/2 and flagged. The first Below the Limit of Quantification (BLQ) concentration after each dose was flagged with BLQ = 1 and included in the population PK analysis. Subsequent BLQ concentrations before the next dosing record were flagged with BLQ = 2 and excluded from the population PK analysis (M6 method).

To account for the analytical difference between AbbVie bioanalysis and the bioanalytical lab in China (described in the Bioanalytical Methods section), all upadacitinib plasma concentrations for samples analysed at WuXiAppTec Co. in China were decreased by 11% in the population PK analysis dataset. This was consistent with prior population PK analyses of upadacitinib.

A summary of demographics and other baseline characteristics for subjects with AA from Study M23-716 who were included in the population PK analyse are presented in Table 3. Two dose levels of 15 mg and 30 mg QD were studied. PK sampling was conducted at Week 4, Week 8, Week 12, Week 24, Week 28, and Week 40.

Table 3. Demographic and Baseline Characteristics of Subjects with AA from Study M23-716 Included in the Population Pharmacokinetic Analysis

Characteristic	15 mg QD (N = 546)	30 mg QD (N = 544)	Placebo/15 mg QD (N = 76)	Placebo/30 mg QD (N = 76)	All Subjects (N = 1242)
Replicate Independent Study, n (%)					
M23-716 Study 1	267 (49%)	267 (49%)	37 (49%)	37 (49%)	608 (49%)
M23-716 Study 2	279 (51%)	277 (51%)	39 (51%)	39 (51%)	634 (51%)
Age (year)					
Mean (SD)	36 (14)	35 (13)	35 (14)	36 (13)	36 (13)
Median	36	34	32	34	35
Min, Max	12, 64	12, 64	12, 63	12, 64	12, 64
Body Weight (kg)					
Mean (SD)	74.4 (18.2)	73.6 (18.0)	71.8 (17.3)	72.3 (16.2)	73.8 (18.0)
Median	72.5	70.7	68.2	71.6	71.7
Min, Max	34.2, 166	32.5, 153	32.1, 116	37.2, 137	32.1, 166
Creatinine Clearance (mL/min)					
Mean (SD)	129 (37.1)	128 (35.5)	125 (33.5)	121 (33.9)	128 (36.0)
Median	123	121	118	114	121
Min, Max	56.4, 329	64.8, 267	67.3, 225	78.1, 255	56.4, 329
eGFR (mL/(min · 1.73 m^2))					
Mean (SD)	107 (16.3)	107 (14.7)	108 (15.3)	106 (17.9)	107 (15.7)
Median	108	108	108	108	108
Min, Max	45.3, 145	71.2, 150	64.6, 136	39.1, 159	39.1, 159
Bilirubin (mg/dL)					
Mean (SD)	0.523 (0.275)	0.526 (0.282)	0.570 (0.290)	0.557 (0.283)	0.529 (0.280)
Median	0.468	0.468	0.484	0.468	0.468
Min, Max	0.175, 1.87	0.175, 3.10	0.200, 1.40	0.200, 1.87	0.175, 3.10

Characteristic	15 mg QD (N = 546)	30 mg QD (N = 544)	Placebo/15 mg QD (N = 76)	Placebo/30 mg QD (N = 76)	All Subjects (N = 1242)
AST (IU/L)					
Mean (SD)	21.3 (11.5)	20.8 (9.08)	21.1 (6.55)	20.3 (7.50)	21.0 (10.0)
Median	19.0	19.0	20.0	18.0	19.0
Min, Max	7.00, 155	9.00, 103	11.0, 51.0	11.0, 47.0	7.00, 155
ALT (IU/L)					
Mean (SD)	20.3 (13.9)	20.3 (15.7)	21.1 (12.2)	19.8 (11.3)	20.3 (14.5)
Median	16.0	16.0	18.0	16.0	16.0
Min, Max	4.00, 125	4.00, 216	6.00, 83.0	6.00, 59.0	4.00, 216
hsCRP (mg/L)					
Mean (SD)	2.70 (5.22)	1.87 (2.66)	1.75 (2.55)	2.18 (3.26)	2.25 (4.03)
Median	1.00	1.00	1.00	1.00	1.00
Min, Max	0.200, 50.2	0.200, 35.5	0.200, 19.4	0.200, 20.5	0.200, 50.2
Albumin (g/dL)					
Mean (SD)	4.56 (0.249)	4.56 (0.248)	4.58 (0.262)	4.60 (0.259)	4.56 (0.250)
Median	4.60	4.60	4.60	4.60	4.60
Min, Max	3.80, 5.40	3.90, 5.50	3.90, 5.10	3.80, 5.20	3.80, 5.50
Sex, n (%)					
Male	227 (42%)	221 (41%)	35 (46%)	35 (46%)	518 (42%)
Female	319 (58%)	323 (59%)	41 (54%)	41 (54%)	724 (58%)
Race, n (%)					
White	343 (63%)	333 (61%)	38 (50%)	40 (53%)	754 (61%)
Black	36 (7%)	24 (4%)	3 (4%)	3 (4%)	66 (5%)
Asian	151 (28%)	167 (31%)	32 (42%)	33 (43%)	383 (31%)
American Indian or Alaska Native	3 (1%)	3 (1%)	1 (1%)	0 (0%)	7 (1%)
Native Hawaiian or Other Pacific Islander	0 (0%)	2 (0%)	0 (0%)	0 (0%)	2 (0%)
Multiple	13 (2%)	15 (3%)	2 (3%)	0 (0%)	30 (2%)

Characteristic	15 mg QD (N = 546)	30 mg QD (N = 544)	Placebo/15 mg QD (N = 76)	Placebo/30 mg QD (N = 76)	All Subjects (N = 1242)
Region, n (%)					
North America	134 (25%)	130 (24%)	15 (20%)	14 (18%)	293 (24%)
Asia	126 (23%)	144 (26%)	29 (38%)	29 (38%)	328 (26%)
Europe	205 (38%)	195 (36%)	22 (29%)	20 (26%)	442 (36%)
South or Central America	30 (5%)	29 (5%)	1 (1%)	3 (4%)	63 (5%)
Other	51 (9%)	46 (8%)	9 (12%)	10 (13%)	116 (9%)
Baseline Disease Severity, n (%)					
Severe [SALT score < 95]	265 (49%)	263 (48%)	36 (47%)	32 (42%)	596 (48%)
Very Severe [SALT score ≥ 95]	281 (51%)	281 (52%)	40 (53%)	44 (58%)	646 (52%)
AA Episode Duration at Baseline, n (%)					
< 3 years	310 (57%)	311 (57%)	36 (47%)	44 (58%)	701 (56%)
≥ 3 years	236 (43%)	233 (43%)	40 (53%)	32 (42%)	541 (44%)
Age Group, n (%)					
Adolescent	48 (9%)	47 (9%)	7 (9%)	6 (8%)	108 (9%)
Adult	498 (91%)	497 (91%)	69 (91%)	70 (92%)	1,134 (91%)

Some percentages may not add up to 100 due to rounding.

Model

PK Meta-Analysis model

The development of the PK Meta-analysis model, developed to describe upadacitinib across indications, was developed using an iterative *post hoc* approach. An initial model, including covariate analysis, was developed using data from healthy subjects and subjects with RA. This model was leveraged as an initial prior for subsequent models, where in a stepwise manner, priors were updated successively with data from all indications.

Once the final model was established, a *post hoc* approach was used to evaluate that the model captured the data from each indication. The structural, statistical (inter- and intra-individual variability) and covariate components of the model were retained, and the same model parameter values used by setting MAXEVALS=0 in the $ESTIMATION option in Non-linear Mixed-Effects modelling (NONMEM).

The final model was a two-compartment, mixed zero- and first-order absorption with lag time for the extended-release tablet, and linear elimination. The model included the following covariates: estimated glomerular filtration rate (eGFR) and body weight on apparent clearance (CL/F), as well as body weight and sex on apparent volume of distribution of central compartment (Vc/F). In addition, patient population (patient versus healthy) was included on CL/F and IR oral solution formulation was included on IR absorption lag time.

PopPK analysis for subjects with AA

The PK Meta-Analysis model, as depicted above, was utilized to describe observed upadacitinib concentrations in AA from upadacitinib using a *post hoc* approach. The population parameter estimates of the fixed effects and estimates for Inter-Individual Variability (IIV) of the Meta-Analysis model were used to generate individual *post hoc* estimates ($ESTIMATION MAXEVAL=0 in NONMEM) for subjects in Study M23-716. Statistically significant covariates identified in the previous model were eGFR (capped at 90 mL/(min · 1.73 m2) and body weight on CL/F, as well as body weight and sex on Vc/F. These were retained in the model for the current analysis. None of the model parameters were re-estimated.

The model results were evaluated using GOF and prediction-corrected VPCs (pcVPCs) in order to determine the model predictive performance and examine the usefulness of the model for describing the observed upadacitinib concentrations.

Estimates of the PK parameters and their associated variability for the final model used to describe upadacitinib in patients with AA are shown in Table 4.

Table 4. Parameter Estimates and Variability of Upadacitinib Pharmacokinetics in Subjects with AA

Parameter	Population Estimate	%RSE	95% Confidence Interval
CL/F (L/h)	43.0	--	--
Vc/F (L)	166	--	--
Q/F (L/h)	3.09	--	--
Vp/F (L)	65.0	--	--
IR KA (1/h)	2.69	--	--
IR Absorption Lag Time (h)	0.200	--	--
Bioavailability of the IR Oral Solution Formulation Relative to the IR Capsule Formulation (%)	117	--	--
Bioavailability of the ER Tablet Formulation Relative to the IR Capsule Formulation (%)	73.9	--	--
ER KA (1/h)	0.0822	--	--
ER Absorption Lag Time (h)	0.140	--	--
Fraction of ER Dose Absorbed through Zero-Order Process (%)	65.9	--	--
Zero-Order Absorption Duration (h)	3.27	--	--
Ratio of CL/F in Rheumatic Subjects Compared to Healthy Subjects	0.732	--	--
Ratio of CL/F in Dermatologic Subjects Compared to Healthy Subjects	0.716	--	--
Ratio of CL/F in IBD Subjects Compared to Healthy Subjects	0.955	--	--
Ratio of IR Absorption Lag Time in Oral Solution Formulation Compared to Capsule Formulation	0.641	--	--
Covariate Exponent of eGFR (Capped at 90 mL/(min · 1.73 m^2)) on CL/F[a]	0.525	--	--
Covariate Exponent of Weight on Vc/F	0.666	--	--
Covariate Exponent of Weight on CL/F	0.291	--	--
Ratio of Vc/F in Female Compared to Male Subjects	0.881	--	--
Proportional Error in Phase 2/3	0.314	--	--
Additive Error (ng/mL)	0.00544	--	--

Parameter	Population Estimate	%CV	%Shrinkage
IIV on CL/F in Phase 2/3	0.144	39.3	12.6
IIV on Vc/F in Phase 2/3	0.335	63.1	42.9
IIV on ER KA	0.336	63.2	47.2

%RSE was calculated as the standard error of the estimator divided by the absolute value of the mean of the estimator multiplied by 100. %CV was calculated as SQRT(exp(ω^2)-1)*100).

a. For eGFR a piecewise, normalized power model was used: min(eGFR$_i$, 90 mL/(min · 1.73 m^2)) / 90 mL/(min · 1.73 m^2)$^{\theta eGFR}$, where eGFR$_i$ is the individual eGFR and θ_{eGFR} the estimated exponent.

Simulations

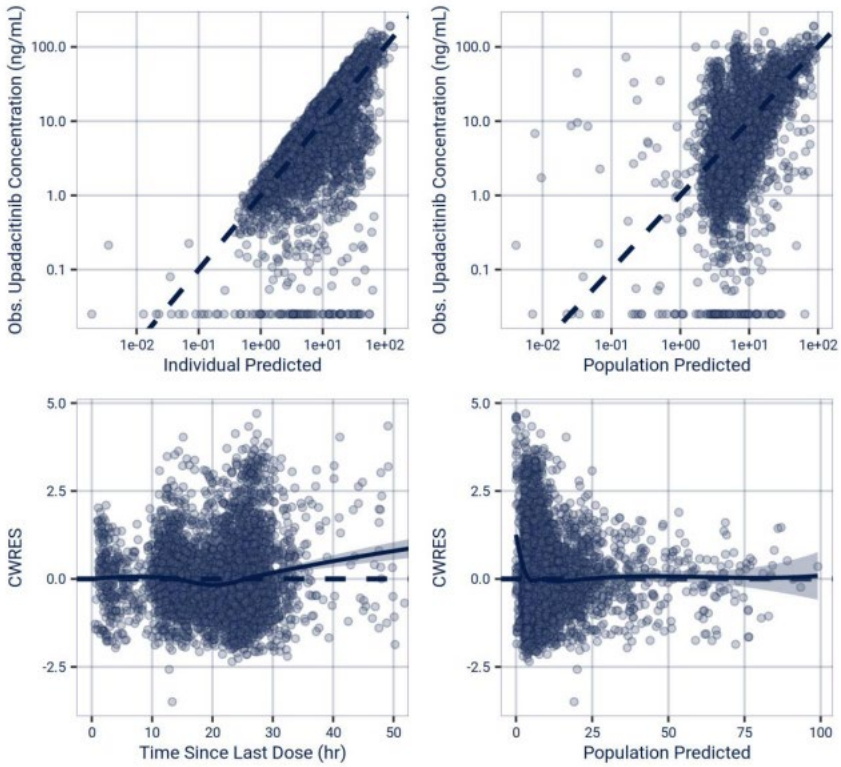
Simulations were performed to explore the impact of relevant covariate effects on upadacitinib exposure. Model-predicted steady-state upadacitinib Cavg was derived using empirical Bayesian estimates of all subjects included in the population PK analysis. Cavg based on the covariate of interest (test group) were compared to the corresponding reference group by calculating the geometric mean ratio and its 95% CI and summarized graphically using a forest plot.

Summaries were generated for upadacitinib exposures in adolescents and adults with AA versus AD. Additional summaries were generated for upadacitinib plasma exposures in Chinese versus non-Chinese and Japanese versus non-Japanese subjects.

Results

GOF plots and pcVPCs to evaluate the ability of the model to describe the observed upadacitinib concentrations in the AA population are displayed in Figure 2, Figure 3, and Figure 4 respectively.

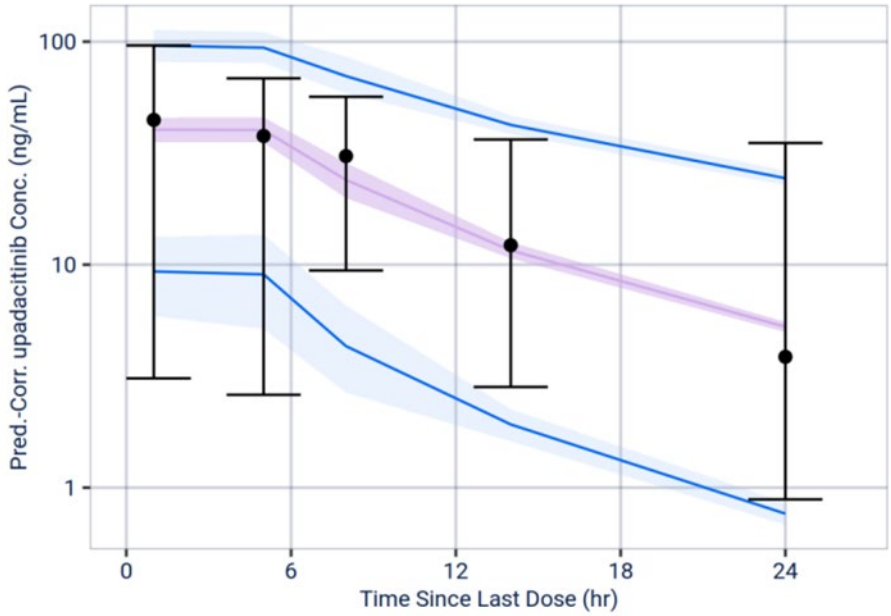
Figure 2. Goodness-of-Fit Plots of Upadacitinib Pharmacokinetic Final Model for Subjects Included in the Population Pharmacokinetic Analysis



Goodness-of-fit plots for the individual predicted and population predicted versus observed concentrations (top left and right, respectively) and CWRES versus TSLD and population prediction (bottom left and right, respectively) with loess smooth (95% CI).

Note: CWRES versus TSLD was cut at time since last dose of 50 hr.

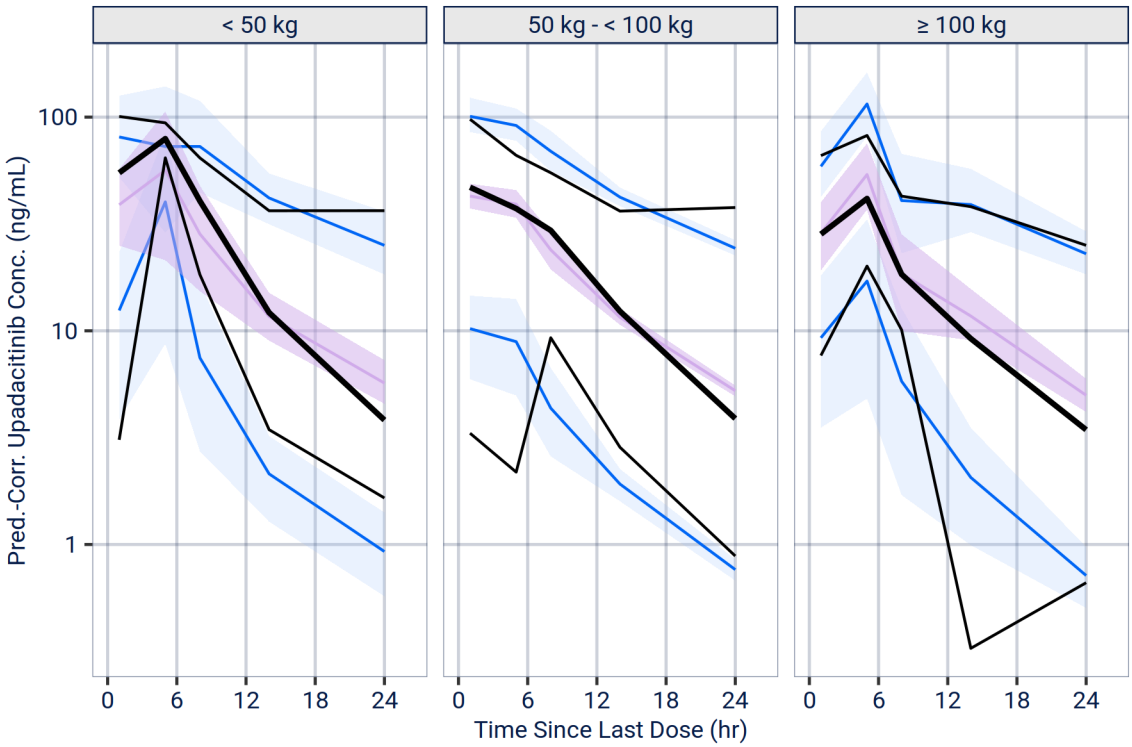
Figure 3. Prediction-Corrected Visual Predictive Checks of Upadacitinib Concentration in Subjects with AA in Study M23-716



The blue lines represent the 90% PI of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. The black dots and error bars represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively.

Note: Time bins were chosen at 1, 5, 8, 14, and 24 hours since last dose.

Figure 4. Prediction-Corrected Visual Predictive Checks of Upadacitinib Concentration in All Subjects with AA in Study M23-716



The blue lines represent the 90% PI of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. The black lines represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively.

Note: Time bins were chosen at 1, 5, 8, 14, and 24 hours since last dose.

Dose proportionality and time dependencies

Model-predicted upadacitinib exposures at steady-state (AUC24,ss, Cavg, Cmax and Ctrough) indicates a proportional increase in concentrations with dose in the Study M23-716 study (Table 5).

Table 5. Summary Statistics of Model-Predicted Steady-State Exposures for Upadacitinib, Using the Final Population Pharmacokinetic Model

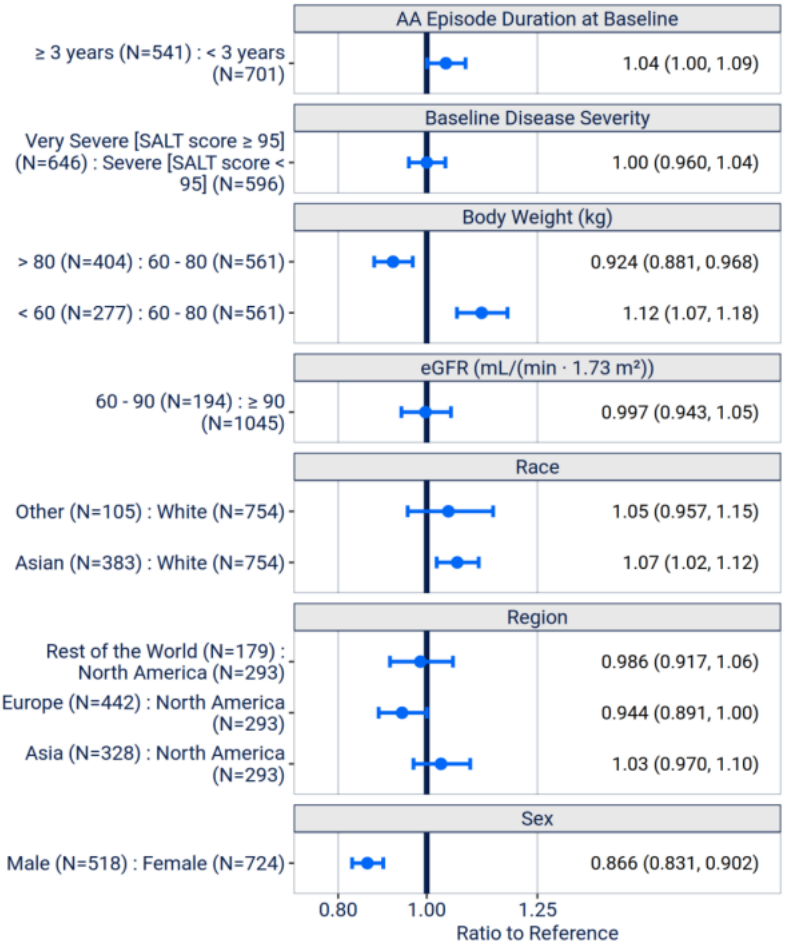
Regimen	Number of Subjects	$AUC_{24,ss}$ (ng·hr/mL) Median (5th to 95th Percentile)	C_{avg} (ng/mL) Median (5th to 95th Percentile)	C_{max} (ng/mL) Median (5th to 95th Percentile)	C_{trough} (ng/mL) Median (5th to 95th Percentile)
15 mg QD	546	355 (234, 738)	14.8 (9.74, 30.8)	45.2 (34.0, 72.5)	3.62 (1.32, 21.5)
30 mg QD	544	685 (469, 1352)	28.5 (19.6, 56.3)	88.7 (68.1, 114)	6.57 (2.39, 37.7)

Special populations

The dose-normalized, model-predicted steady-state exposure (C_{avg}) of upadacitinib was compared across specific demographic and disease-related subgroups (Figure 5). This comparison was illustrated using forest plots, where the estimated geometric mean ratio (GMR) and its 95% CI for each covariate stratum were presented relative to the reference stratum. The prediction was done using the individual *post hoc* PK parameters for the PK population of Study M23-716.

Overall, the impact of these covariates on the dose-normalized steady-state Cavg of upadacitinib was ≤13.4% relative to their reference groups. No relevant covariate effects were identified in the population pharmacokinetics analyses in subjects with AA, in accordance with original regulatory application for the use of upadacitinib in the treatment of RA.

Figure 5. Model-Predicted Covariate Effects on Dose-Normalized Upadacitinib Cavg



Dots and error bars represent geometric mean ratio and its 95% CI of model-predicted dose-normalized C_{avg} relative to reference groups. The vertical black line shows the exposure ratio of 1 relative to the reference group. AA episode duration at baseline < 3 years, severe [SALT score < 95] baseline disease severity, body weight 60 - 80 kg, eGFR ≥ 90 mL/(min· 1.73 m^2), white race, North America region, and female subjects were chosen as reference covariate categories.

In addition to the results shown in the figure above, model-estimated steady-state exposures of upadacitinib were comparable in Japanese and non-Japanese subjects as well as in Chinese and non-Chinese subjects (Table 6 and Table 7).

Table 6. Summary of Model-Predicted Upadacitinib Exposures Stratified by Japanese versus Non-Japanese Subjects

Regimen	Population	Number of Subjects	$AUC_{24,ss}$ (ng•hr/mL) Median (5^{th} to 95^{th} Percentile)	C_{avg} (ng/mL) Median (5^{th} to 95^{th} Percentile)	C_{max} (ng/mL) Median (5^{th} to 95^{th} Percentile)	C_{trough} (ng/mL) Median (5^{th} to 95^{th} Percentile)
15 mg QD	Japanese	18	411 (268, 647)	17.1 (11.2, 27.0)	52.9 (39.9, 82.8)	4.08 (2.18, 14.6)
	Non-Japanese	528	352 (233, 738)	14.7 (9.70, 30.7)	45.0 (34.0, 67.3)	3.58 (1.30, 21.7)
30 mg QD	Japanese	18	809 (530, 1480)	33.7 (22.1, 61.7)	97.6 (79.7, 125)	9.67 (2.40, 42.8)
	Non-Japanese	526	682 (469, 1346)	28.4 (19.6, 56.1)	88.6 (68.0, 113)	6.41 (2.39, 37.0)

Table 7. Summary of Model-Predicted Upadacitinib Exposures Stratified by Chinese versus Non-Chinese Subjects

Regimen	Population	Number of Subjects	$AUC_{24,ss}$ (ng•hr/mL) Median (5^{th} to 95^{th} Percentile)	C_{avg} (ng/mL) Median (5^{th} to 95^{th} Percentile)	C_{max} (ng/mL) Median (5^{th} to 95^{th} Percentile)	C_{trough} (ng/mL) Median (5^{th} to 95^{th} Percentile)
15 mg QD	Chinese	66	362 (276, 546)	15.1 (11.5, 22.7)	48.6 (38.6, 73.5)	3.48 (1.70, 11.1)
	Non-Chinese	480	352 (232, 775)	14.7 (9.65, 32.3)	44.4 (33.9, 70.4)	3.67 (1.25, 21.9)
30 mg QD	Chinese	80	721 (521, 1102)	30.1 (21.7, 45.9)	93.2 (74.7, 119)	7.06 (2.76, 22.2)
	Non-Chinese	464	678 (467, 1434)	28.3 (19.5, 59.8)	87.4 (65.8, 113)	6.45 (2.37, 39.8)

Adolescent Population

The number of adolescents subjects included in the PK analysis from the M23-716 1 & 2 studies was 48 and 47 in the 15 and 30 mg QD groups, respectively, with a balanced representation of subjects at each age from 12 - 17. The PK dataset covered subjects from 32.1 kg, with 3 subjects between 30-40 kg and >25 subjects between 40–50 kg.

Upadacitinib popPK model-predicted steady-state plasma exposure (Cavg, Cmin, and Cmax) in adolescent and adult subjects with AA are compared in Table 8. Based on the model predictions, the exposure in adolescents was comparable to adults. Model predicted exposures in adolescent subjects with AA were compared to adolescent subjects with atopic dermatitis (AD) in Table 9.

Table 8. Summary Statistics of Model-Predicted Steady-State Exposures for Upadacitinib, Stratified by Age Group, Using the Final Population Pharmacokinetic Model

Regimen	Age Group	Number of Subjects	$AUC_{24,ss}$ (ng·hr/mL) Median (5^{th} to 95^{th} Percentile)	C_{avg} (ng/mL) Median (5^{th} to 95^{th} Percentile)	C_{max} (ng/mL) Median (5^{th} to 95^{th} Percentile)	C_{trough} (ng/mL) Median (5^{th} to 95^{th} Percentile)
15 mg QD	Adolescent	48	351 (234, 566)	14.6 (9.73, 23.6)	47.5 (35.7, 71.7)	3.18 (1.30, 11.0)
	Adult	498	356 (234, 784)	14.8 (9.75, 32.7)	44.5 (34.0, 70.7)	3.69 (1.33, 21.9)
30 mg QD	Adolescent	47	687 (519, 1263)	28.6 (21.6, 52.6)	94.0 (70.4, 137)	6.00 (3.25, 34.7)
	Adult	497	684 (469, 1355)	28.5 (19.5, 56.5)	88.1 (67.7, 113)	6.66 (2.38, 38.1)

Table 9. Summary of Model-Predicted Upadacitinib Exposures in Adolescent Subjects with AA or AD

Regimen	Indication	Number of Subjects	C_{avg} (ng/mL) Median (5^{th} to 95^{th} Percentile)	C_{max} (ng/mL) Median (5^{th} to 95^{th} Percentile)	C_{min} (ng/mL) Median (5^{th} to 95^{th} Percentile)
15 mg QD	AA	48	14.6 (9.73, 23.6)	47.5 (35.7, 71.7)	3.18 (1.30, 11.0)
	AD	53	14.7 (9.63, 22.3)	37.7 (27.3, 43.6)	3.52 (1.62, 13.7)
30 mg QD	AA	47	28.6 (21.6, 52.6)	94.0 (70.4, 137)	6.00 (3.25, 34.7)
	AD	50	29.2 (20.1, 53.5)	73.4 (56.0, 81.9)	7.85 (3.61, 40.4)

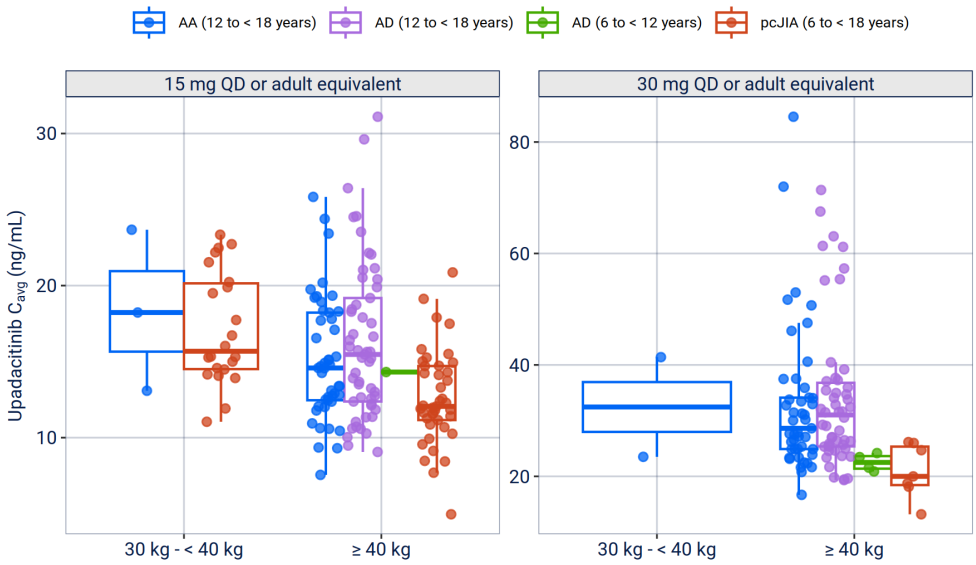
A summary available model predicted exposures of upadacitinib in adolescent subjects in the weight group 30-40 kg compared to paediatric subjects weighing ≥ 40 kg, including the indications AA, AD, and pcJIA, is provided in Table 10, Figure 6. Steady-state exposures were derived based on a previously developed population PK model that described upadacitinib PK using a *post hoc* approach. The upadacitinib plasma exposures in subjects in the 30 to < 40 kg body weight group are generally similar to those in the ≥ 40 kg body weight group.

Table 10. Summary Statistics of Model-Predicted Steady-State Exposures for Upadacitinib in Paediatric Age Groups, Stratified by Body Weight

					Median (5th to 95th Percentile)		
Indication	Regimen	Age Group	Body Weight Group	Number of Subjects	$AUC_{24,ss}$ (ng·hr/mL)	C_{avg} (ng/mL)	C_{max} (ng/mL)
AA	15 mg QD	12 to < 18 years	30 kg - < 40 kg	3	437 (326, 555)	18.2 (13.6, 23.1)	61.2 (54.0, 63.1)
		12 to < 18 years	≥ 40 kg	45	350 (230, 547)	14.6 (9.57, 22.8)	47.4 (35.7, 73.4)
	30 mg QD	12 to < 18 years	30 kg - < 40 kg	2	779 (586, 972)	32.5 (24.4, 40.5)	125 (107, 143)
		12 to < 18 years	≥ 40 kg	45	687 (519, 1266)	28.6 (21.6, 52.7)	93.8 (70.1, 122)
AD	15 mg QD	12 to < 18 years	≥ 40 kg	53	371 (244, 607)	15.5 (10.2, 25.3)	47.4 (39.4, 57.9)
	30 mg QD	12 to < 18 years	≥ 40 kg	50	744 (473, 1495)	31.0 (19.7, 62.3)	95.8 (67.6, 115)
	7.5 mg QD	6 to < 12 years	30 kg - < 40 kg	1	193 (--)	8.04 (--)	30.5 (--)
	15 mg QD	6 to < 12 years	≥ 40 kg	1	344 (--)	14.3 (--)	57.2 (--)
	30 mg QD	6 to < 12 years	≥ 40 kg	4	540 (504, 578)	22.5 (21.0, 24.1)	93.4 (87.5, 104)
pcJIA	7.5 mg QD adult equivalent	6 to < 18 years	30 kg - < 40 kg	2	147 (111, 183)	6.13 (4.62, 7.64)	25.1 (20.4, 29.9)
	15 mg QD adult equivalent	6 to < 18 years	30 kg - < 40 kg	22	376 (288, 545)	15.7 (12.0, 22.7)	60.1 (42.4, 80.4)
		6 to < 18 years	≥ 40 kg	41	289 (202, 430)	12.1 (8.44, 17.9)	44.3 (24.9, 65.1)
	30 mg QD adult equivalent	6 to < 18 years	≥ 40 kg	7	480 (352, 626)	20.0 (14.7, 26.1)	73.6 (51.5, 83.1)

Note: 7.5 mg QD, 15 mg QD, and 30 mg QD adult equivalent can be administered as the extended-release tablet or oral solution. In the 30 to < 40 kg body weight group, only 3 out of 24 subjects and in the ≥ 40 kg body weight group only 1 out of 48 subjects received the oral solution. The data was included for completeness.

Figure 6. Upadacitinib Average Concentration in the 30 kg to < 40 kg and ≥ 40 kg Body Weight Groups



Boxes show the median, 25th to 75th percentiles (IQR) and whiskers represent the 1.5-fold IQR of upadacitinib average concentration per body weight group.

2.3.3. Pharmacodynamics

Mechanism of action

Upadacitinib is a selective and reversible Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including

inflammatory responses, haematopoiesis, and immune surveillance. The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and TYK2. The relative affinity of JAK inhibitors for different members of the JAK kinase family allows for differentiation of JAK inhibitors in relation to their enzymatic inhibitory profile.

Primary and secondary pharmacology

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. Pro-inflammatory cytokines (e.g. IFNγ) transduce signals via the JAK1 pathway and are involved in the pathology of alopecia areata. Inhibition of JAK1 by upadacitinib may interrupt inflammatory pathways that contribute to the immunopathogenesis of AA. There is clinical evidence with other JAK inhibitors that also supports the investigation of baricitinib in the treatment of AA.

2.3.4. PK/PD modelling

Exposure-Response Analysis

Exposure-Response (E-R) model analyses was conducted to characterize the relationships between upadacitinib plasma exposures and clinical efficacy and safety in adolescent and adult subjects with AA using data from the M23-716 study (Safety_A population). In total, 1397 subjects were included in the exposure-response analyses Table 11. Upadacitinib individual average plasma concentrations over a dosing interval at steady state (Cavg), derived using empirical Bayesian estimates from the population pharmacokinetic model, were used as the exposure metrics for exposure-response analyses.

Non-linear and linear logistic regression models for efficacy and safety were evaluated to characterize the relationship between upadacitinib Cavg as a predictor variable and the different binary endpoints and Gaussian a regression models was constructed relating average upadacitinib concentration to percent change from Baseline in SALT score at Week 24.

The study stratification variables were included as pre-specified variables in the efficacy exposure-response models, as recommended by the International Council for Harmonisation (ICH) E9 guidance: baseline disease severity and AA episode duration at baseline. The following pre-specified variables were included in the safety exposure-response models: baseline haemoglobin, baseline lymphocyte count, and baseline neutrophil count.

The effect of significant covariates (including demographics, geographic region and baseline hsCRP) on exposure-response relationships was assessed. Standard methods for model evaluation including Bayesian information criterion (BIC), model stability, predictive performance, and adequate precision of parameter estimates were used.

Simulations, using the exposure-response models to generate the model-predicted efficacy of upadacitinib at Week 24 at 15 mg QD and 30 mg QD, were performed.

Table 11. Summary of Efficacy and Safety Endpoint Data Included in the Exposure-Response Modeling by Treatment Group Period A

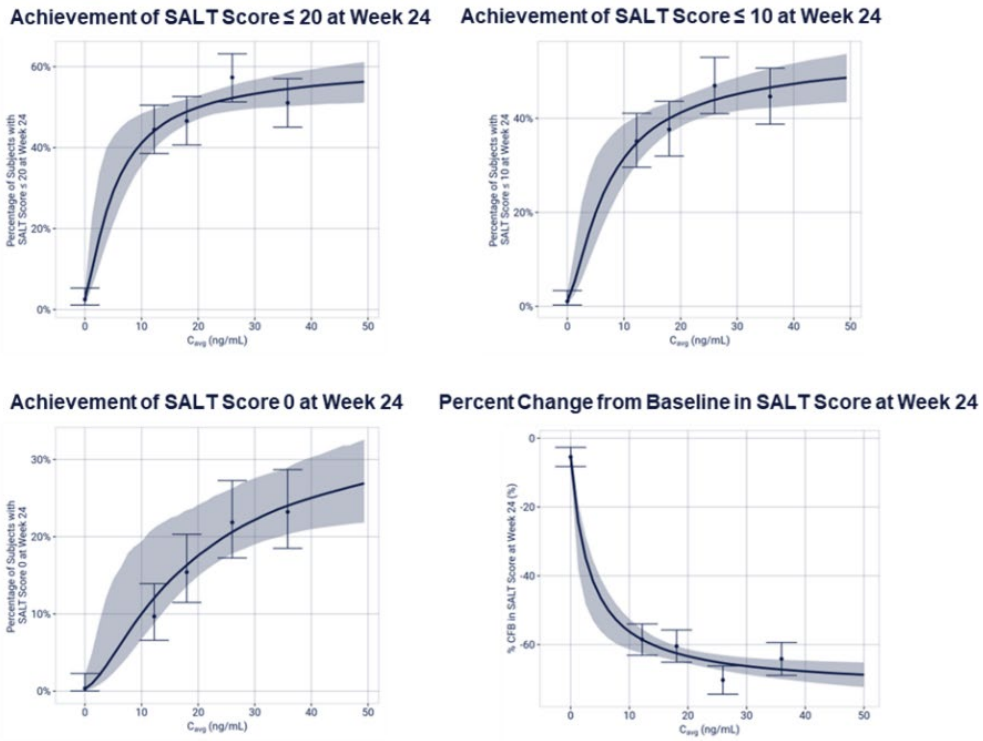
Endpoint	Placebo (N = 280)	15 mg QD (N = 557)	30 mg QD (N = 560)	All Subjects (N = 1397)
SALT Score ≤ 20 at Week 24, n (%)				
Non-Missing	280 (100%)	557 (100%)	560 (100%)	1,397 (100%)
SALT Score ≤ 10 at Week 24, n (%)				
Non-Missing	280 (100%)	557 (100%)	560 (100%)	1,397 (100%)
SALT Score 0 at Week 24, n (%)				
Non-Missing	280 (100%)	557 (100%)	560 (100%)	1,397 (100%)
% CFB in SALT Score at Week 24 (%), n (%)				
Missing	14 (5%)	26 (5%)	36 (6%)	76 (5%)
Non-Missing	266 (95%)	531 (95%)	524 (94%)	1,321 (95%)
Herpes Zoster, n (%)				
Non-Missing	280 (100%)	557 (100%)	560 (100%)	1,397 (100%)
Pneumonia, n (%)				
Non-Missing	280 (100%)	557 (100%)	560 (100%)	1,397 (100%)
Serious Infections, n (%)				
Non-Missing	280 (100%)	557 (100%)	560 (100%)	1,397 (100%)
Lymphopenia ≥ Grade 3, n (%)				
Missing	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Non-Missing	280 (100%)	556 (100%)	560 (100%)	1,396 (100%)
Neutropenia ≥ Grade 3, n (%)				
Missing	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Non-Missing	280 (100%)	556 (100%)	560 (100%)	1,396 (100%)
Anemia ≥ Grade 3, n (%)				
Missing	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Non-Missing	280 (100%)	556 (100%)	560 (100%)	1,396 (100%)
>2 g/dL Decrease in Hemoglobin, n (%)				
Missing	3 (1%)	7 (1%)	4 (1%)	14 (1%)
Non-Missing	277 (99%)	550 (99%)	556 (99%)	1,383 (99%)

Exposure-efficacy analysis

The efficacy endpoints evaluated for relationships with upadacitinib exposures included Severity of Alopecia Tool SALT score ≤ 20 at Week 24 (primary endpoint), achievement of SALT score ≤ 10 at Week 24, achievement of SALT score 0 at Week 24 and percent change from Baseline in SALT score at Week 24 (Figure 7).

For all efficacy endpoints a clear exposure-response relationships, with an increase in response with increasing exposures of upadacitinib, was shown. A maximum effect (Emax) model best described the exposure-response relationship for all efficacy endpoints (Figure 7).

Figure 7. Observed and Model-Predicted Percentage of Subjects who Achieved a SALT Score ≤ 20 at Week 24, a SALT Score ≤ 10 at Week 24, a SALT Score 0 at Week 24, and the Percent Change from Baseline in SALT Score at Week 24



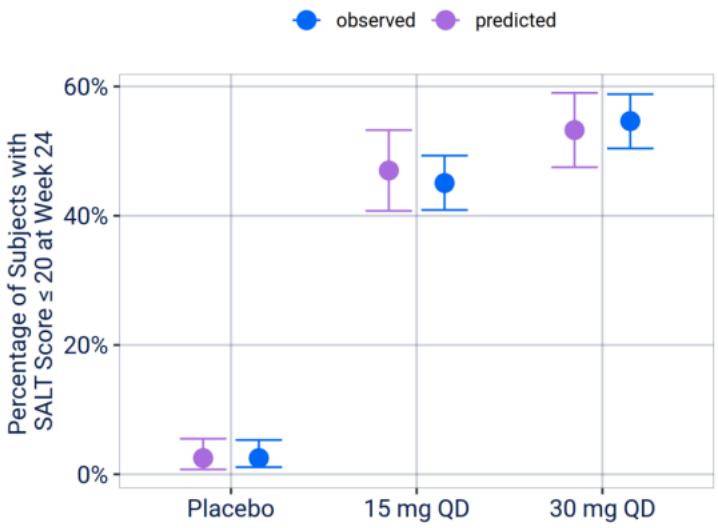
Both stratification factors, baseline disease severity and AA episode duration, were significant across all evaluated efficacy endpoints.

The exposure-response relationships stratified by baseline disease severity indicated that the exposure-response relationship reached a plateau for subjects with severe disease (50 ≤ SALT score < 95) at exposures associated with 15 mg QD, whereas the relationship approached a plateau for subjects with very severe disease (SALT score ≥ 95) at exposures associated with 30 mg QD.

Exploratory covariate evaluation was performed, identifying body weight and age group as significant predictor for the three categorical endpoints.

Simulations based on the exposure-response models showed that upadacitinib 30 mg is predicted to provide 6.2% to 7.4% higher absolute response rates for the categorical endpoints compared to upadacitinib 15 mg QD in the overall population (Figure 8, Table 12).

Figure 8. Efficacy Simulations of SALT Score ≤ 20 at Week 24



Predicted: Dots and error bars represent the median and 95% PIs of the response. Observed: Dots and error bars represent the proportion and 95% binomial CIs of the response.

Table 12. Summary of Efficacy Simulations of SALT Score ≤ 20 at Week 24 by Baseline Disease Severity

Regimen	Baseline Disease Severity	Observed (%) (95% CI)	Predicted (%) (95% PI)
Placebo	Severe [SALT score < 95]	5.00 (2.21, 10.4)	3.25 (1.00, 7.00)
	Very Severe [SALT score ≥ 95]	0 (0, 3.33)	1.75 (0.494, 4.25)
15 mg QD	Severe [SALT score < 95]	56.2 (50.1, 62.2)	54.2 (47.8, 60.8)
	Very Severe [SALT score ≥ 95]	34.4 (28.9, 40.3)	39.8 (33.7, 46.5)
30 mg QD	Severe [SALT score < 95]	56.9 (50.7, 62.8)	59.8 (53.5, 66.0)
	Very Severe [SALT score ≥ 95]	52.6 (46.7, 58.4)	46.8 (40.5, 53.0)

Exposure-safety analyses

There were not sufficient number of the safety variables of interest (anaemia (Grade ≥ 3), neutropenia (Grade ≥ 3), lymphopenia (Grade ≥ 3), a > 2 g/dL decrease in haemoglobin from baseline, serious infections, pneumonia, and herpes zoster at or through Week 24 were conducted) to enable adequate assessment of exposure-response relationships (Table 11).

2.3.5. Discussion on clinical pharmacology

The MAH has submitted PK data from the phase III-studies M23-716 1 & 2 in adult and adolescent patients with AA. A popPK model analysis approach was used to describe upadacitinib exposure in the AA population and to compare it to the exposure for previously characterised populations, such as AD and RA patients. The model was subsequently used to derive individual exposure metrics to evaluate if the exposures are comparable between adolescent and adult AA patients.

Moreover, individual average steady state upadacitinib concentrations were derived from the popPK model to evaluate the relationships between upadacitinib plasma exposures and efficacy as well as safety, using data from M23-716 Study 1 and Study 2.

Bioanalytical methods

The analytical methods have been validated and accepted previously (see initial RA application). Satisfactory method performance during study sample analysis was demonstrated.

For sample analyses at WuXiAppTec Co. (952 of 6305 according to the two bioanalytical reports), upadacitinib concentrations were decreased by 11% in the population PK analysis dataset to account for the differences in the methods identified at cross-validation. This approach has been applied in previous Rinvoq regulatory submissions (e.g. EMEA/H/C/004760/II/0015/G) and is acceptable in view of the limited number of affected samples and the relatively small adjustment.

Evaluation and qualification of models

The MAH developed a cross-indication popPK model, based on a previous population PK model on healthy subjects and subjects with RA, to describe upadacitinib PK across indications (including rheumatic, dermatologic, and Inflammatory Bowel Disease (IBD) indications), formulations and age-groups. The base model was leveraged as an initial prior for subsequent models, where in a stepwise manner, priors were updated successively with data from all indications. The structural, statistical (inter- and intra-individual variability) and covariate components of the model were maintained. Patient population (dermatologic patient vs healthy and IBD patient vs healthy) was added as covariate on CL/F. The parameter estimates are similar to the base model in RA and healthy and the uncertainty is low. Overall, the model development and evaluation were sensible, and the model could serve as a reasonable base for evaluation the PK of upadacitinib in the AA population.

The developed cross-indication PK model, as described above, was utilized to describe observed upadacitinib concentrations in AA. This was justified by showing comparable observed dose-normalized upadacitinib concentration versus time-since last dose (TSLD) in the AA population compared to the AD population. None of the model parameters were re-estimated and individual *post hoc* estimates were used to generate exposures for subjects in Study M23-716.

In the PK dataset <2% of the samples were BLQ. The M6 method was applied, setting the first BLQ concentration to LLOQ/2 and excluding subsequent BLQ samples before next dosing. Samples with TSLD > 168 hours, or sampled before dosing, were excluded from the analysis. The handling of BLQ samples and the exclusion criteria are acceptable and the potential effect on the analysis is negligible.

Included covariates were eGFR and body weight on CL/F, as well as body weight and sex on Vc/F. A factor/ratio of 0.716 to describe the difference in CL/F in dermatological subjects compared to healthy subjects was applied. The shrinkages for upadacitinib CL/F, Vc/F and KA were 12.6%, 42.9%, and 47.2%, respectively. The GOF plots indicate tendencies towards over prediction of exposure in a similar pattern as observed for other indications in the development of the model. PcVPCs on upadacitinib concentration vs TSLD showed an acceptable performance of the cross-indication model to generally describe the PK of the subjects with AA in the M23-716 1 and 2 studies. The variability at early time points after last dose was however underpredicted.

Based on the provided results, the model gives overall acceptable description of the observed PK data for general AA population. PcVPCs stratified on weight were submitted to evaluate the model's ability to describe the exposure in adolescents. The pcVPC displaying model predictions for subjects with BWT< 50 kg included data from only 77 subjects. The larger variability in this body weight group could thus be expected. A slight underprediction at Cmax and an overprediction at late time points are observed.

Nevertheless, the model appears to give a sufficiently acceptable description of the observed PK data for subjects with body weight <50 kg. Given the importance of body weight rather than age for PK in

subjects >12 years, the model is accordingly considered to be adequate for deriving individual predictions for the adolescent subgroup in the M23-716 study.

Special Populations

To assess differences in PK between special populations, a *post hoc* assessment of exposure differences between subgroups was made. The investigated covariates included body weight, sex, eGFR, race, region, baseline disease severity and episode duration. The results indicated ≤13.4% impact of these covariates on the dose-normalized steady-state Cavg of upadacitinib relative to their reference groups. No relevant covariate effects were identified in the population pharmacokinetics analyses in subjects with AA, in accordance with original application for the use of upadacitinib in the treatment of RA. It should be noted, however, that CL/F and V/F were allometrically scaled in the population PK model and hence an effect of body weight is incorporated in the model which is acceptable.

Model predicted upadacitinib exposures were used to compare the PK in adolescents with AA to adults with AA, in the M23-716 1 and 2 studies. No significant differences could be detected when comparing the model-predicted upadacitinib exposures between adolescents and adults at steady-state (AUC24,ss, Cavg, Cmax and Ctrough). In addition, simulated exposure summaries were generated for virtual adolescents using the CDC growth charts to inform the consistency in exposures of upadacitinib in the adolescent patient population. The dataset from M23-716 covered subjects from 32.1 kg, with only 3 subjects between 30-40 kg and >25 subjects between 40–50 kg. An acceptable exposure for upadacitinib from 30 kg could however be confirmed by additional data for subjects <40 kg with pcJIA.

Upadacitinib is previously approved from 12 years in patients with AD, with the max dose of 30 mg QD. Model predicted upadacitinib exposures in adolescents with AA from the M23-716 1 and 2 studies are compared to predicted exposures for adolescents in AD. This is shown for both 15 and 30 mg QD dosing. Additional data, comparing model predicted upadacitinib exposures in all studied paediatric subjects weighing 30 to < 40 kg to paediatric subjects weighing ≥ 40 kg, showed comparable exposure for adolescents with AA as for adolescents with other indications. Safety data from adolescents with AD can thus be used as supportive information for the sought posology in adolescents from 30 kg with AA.

In the SmPC section 5.2, a statement of similar pharmacokinetics and steady-state concentrations for adults and adolescents 12 to 17 years of age with atopic dermatitis and alopecia areata are suggested. This statement is justified and accepted.

Exposure-Response analysis

Response rates versus observed quartiles of upadacitinib (Cavg), as well as logistic and Gaussian regression analyses, were presented for efficacy endpoints (achievement of SALT score ≤ 20, achievement of SALT score ≤ 10, achievement of SALT score 0 at Week 24 and percent change from Baseline in SALT score, all at week 24).

An exposure-response relationships was identified, with an increase in response for all endpoints with increasing exposures of upadacitinib. An Emax model best described the exposure-response relationship for all efficacy endpoints. The available data indicated that the response for the majority of endpoints approached a plateau at exposures associated with 30 mg QD. Due to the limited concentration range in the available dataset, with overlapping exposure range for the two studied dose groups, there are however uncertainties in the estimated exposure-response functions.

Simulations based on the exposure-response models showed that the 30 mg regimen is predicted to provide approximately 6% to 7% higher absolute response rates for the categorical endpoints

(compared to the 15 mg QD regimen in the overall population**.** Stratification of the population by disease severity and AA episode duration at baseline did not indicate that any subgroup would derive significantly greater benefit from the higher dose compared to the overall population. For subjects with very severe disease, the upadacitinib 30 mg QD regimen is predicted to provide approximately 7% to 8% higher absolute response rates for the categorical endpoints compared to the 15 mg QD regimen.

Overall, the modelling methodology is endorsed and an association with higher exposure with higher response rate for all efficacy endpoints were identified. Given the availability of efficacy and safety data in the AA population, the influence of the exposure-response information is only supportive in this application.

2.3.6. Conclusions on clinical pharmacology

PK-data were presented from in total 1090 patients with alopecia areata (AA), in two dose levels (15 and 30 mg QD), aged 12-64 years in Studies M23-716 Study 1 and Study 2. The PK-data were analysed using PopPK modelling. The exposure of upadacitinib in the general AA patient population was adequately described, showing similar PK in AA as in the populations of previously accepted indications.

Additionally, comparable exposure (Cavg) of upadacitinib is for adolescents with AA and adolescents with AD is shown both 15 and 30 mg QD dosing. Safety data from adolescents with AD can thus be used as supportive information for the sought posology in adolescents from 30 kg with AA.

2.4. Clinical efficacy

2.4.1. Dose response study

The Phase 3 program evaluated upadacitinib 15 mg QD and upadacitinib 30 mg QD for the treatment of severe AA in adults and adolescents. Upadacitinib 15 mg QD is approved for the treatment of RA, PsA, axial spondyloarthritis, ulcerative colitis (maintenance treatment), and Crohn's disease (maintenance treatment) in adults and for AD in adults and adolescents, while upadacitinib 30 mg is approved for the treatment of AD, ulcerative colitis (maintenance treatment), and Crohn's disease (maintenance treatment) in adults and for AD in adolescents if an adequate response is not achieved.

Baricitinib, another JAK inhibitor, is efficacious in RA, AD, and AA at doses of 2 mg QD and 4 mg QD. Based on the proof-of-concept of the mechanism of action (JAK inhibition with baricitinib) in the treatment of severe AA, upadacitinib 15 mg QD and 30 mg QD were expected to be efficacious in AA.

A dose lower than 15 mg QD (e.g., 7.5 mg QD) was sub-efficacious across different indications (e.g., AD and RA) and was not expected to be adequately efficacious in AA. Administration of upadacitinib at doses higher than 30 mg has not been studied for durations of use longer than 16 weeks.

Upadacitinib PK have been demonstrated to be comparable across multiple indications including RA and AD. Population PK analyses showed that the PK of upadacitinib were similar in adult and adolescent subjects with AD, and that neither age nor body weight had a relevant effect on the PK of upadacitinib (not statistically significant covariates). Based on the similarity of upadacitinib PK across indications as well as across age groups (adolescents and adults as demonstrated with AD), the plasma exposures of upadacitinib in adolescent subjects with AA were expected to be similar to those in adult subjects with AA. Hence, the same dosing regimens (15 mg QD and 30 mg QD) that were evaluated in adult subjects with AA were also evaluated in adolescent subjects with AA.

Therefore, based on the expected efficacy of upadacitinib in AA and the well-characterized safety profile, upadacitinib 15 mg QD and 30 mg QD were evaluated in the treatment of severe AA.

2.4.2. Main study

A Phase 3 Randomized, Placebo-Controlled, Double-Blind Program to Evaluate Efficacy and Safety of upadacitinib in Adult and Adolescent Subjects with Severe Alopecia Areata

The AA clinical development program includes four Phase 3 studies (Study 1, Study 2, Study 3, and Study 4), all under a single protocol (M23-716), and 1 additional Phase 3 study (Study M24-600). Study 1 and Study 2 are replicate, pivotal, global, randomized, double-blind, placebo-controlled, multi-center studies in adults and adolescents. Study 4 is a US-only, randomized, double-blind, placebo controlled, multi-center study in adolescents. Study 3 is a blinded, long-term extension study for subjects who completed Study 1, Study 2, and Study 4. Study M24 600 is a randomized, double-blind, placebo-controlled, multi-center study in adults and adolescents conducted in Japan. The schematic of Study 1, Study 2, Study 3, and Study 4 is shown in Figure 9, section `Design´.

This submission includes efficacy data from the primary analysis (i.e., Week 24 database locks) for the 2 replicate, pivotal Phase 3 studies (M23 716 Study 1 and Study 2).

Methods

Design

Study 1 and Study 2 are replicate, pivotal, global, randomized, double-blind, placebo-controlled, multi-center studies in adults and adolescents subjects who are at least 12 years old at Screening with severe AA (SALT score ⩾ 50 scalp hair loss). For Study 1 and Study 2, the study consists of 3 periods:

1. The 35-day Screening Period

Please refer to section `Study participants

The 24 week placebo-controlled, double-blind treatment period (Period A). Period A has completed.

Subjects were randomized 2:2:1 to one of 3 double-blinded treatment groups, stratified by Baseline age groups (adults ≥ 18 years vs. adolescents ≥ 12 to < 18 years, respectively), Baseline SALT score of severe AA vs. very severe AA (SALT score 50 to 94 vs. SALT score 95 to 100, respectively) and AA episode duration at Baseline (< 3 years vs. ≥ 3 years, respectively):

- Group 1A: upadacitinib 15 mg QD
- Group 2A: upadacitinib 30 mg QD
- Group 3A: matching placebo QD

2. The 28 week blinded extension treatment period (Period B). Period B is ongoing.

   Subjects initially randomized to placebo (Period A) who achieved a SALT score ≤ 20 at Week 24 were to remain on placebo until they meet the prespecified rescue criterion.

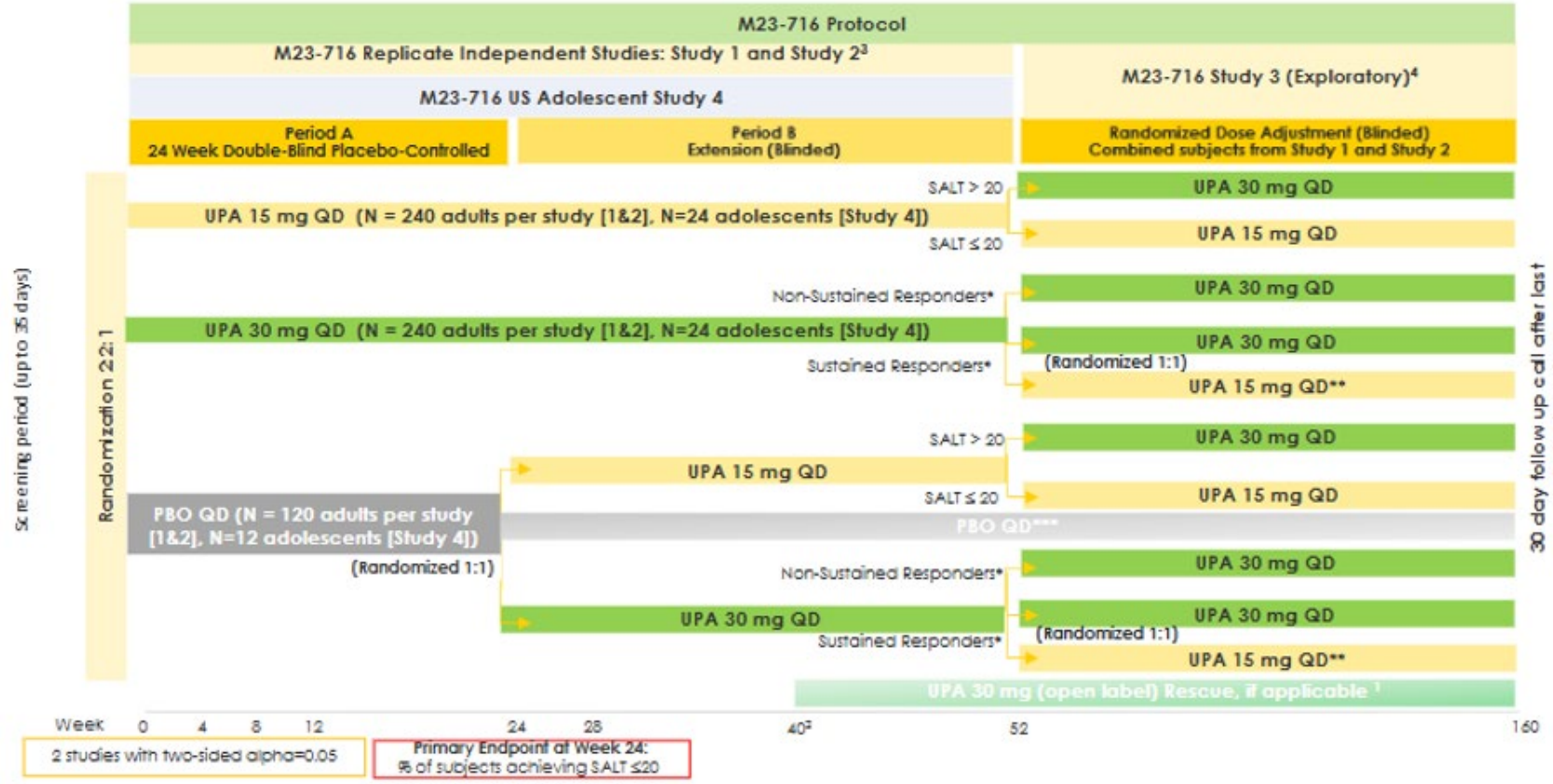
   Subjects initially randomized to placebo (Period A) with a SALT score > 20 at Week 24 were re randomized 1:1 after completion of the Week 24 assessments (Period A) to 1 of 2 double-blind treatment groups:

- Group 1B: upadacitinib 15 mg QD
- Group 2B: upadacitinib 30 mg QD

Subjects originally randomized to a upadacitinib dose group in Period A were to continue their same treatment in Period B.

Subjects with less than a 30% improvement from Baseline in their SALT score at the Week 40 visit or any scheduled visit thereafter will receive open-label upadacitinib 30 mg QD.

Figure 9. Upadacitinib Protocol M23-716 Schematic



* Sustained responders are defined as subjects with a SALT score ≤ 20 at Week 40 and Week 52. Non-sustained responders are defined as subjects with a SALT score > 20 at Week 40 or Week 52 of Study 1, Study 2 or Study 4.

** Subjects who lose response when re-randomized to 15 mg will have dose escalated back to 30 mg. Loss of response is defined as loss of 10 or more points in absolute SALT score after Week 52 re-randomization.

*** Only for placebo subjects with SALT score ≤ 20 at Week 24 who will remain on placebo until they meet rescue criteria.

1. Subjects who achieve less than a 30% improvement from Baseline in their SALT score at Week 40 or any scheduled visit thereafter will receive open-label upadacitinib 30 mg QD. If a subject on open-label upadacitinib 30 mg has less than 30% improvement from Baseline in SALT score at any subsequent scheduled visit (in Studies 1, 2, 3 or 4), the subject will be discontinued from study drug.
2. Subjects with no change or a worsening from Baseline in their SALT score at Week 40 will be discontinued.
3. Where permitted outside US/EU, an additional ~ 100 adolescent subjects may be enrolled per Studies 1 & 2.

4. Subjects who are 65 years of age or older and still on study drug, the Investigator may choose one time to administer open-label upadacitinib 15 mg QD. If subjects lose response (based on Investigator's discretion) after the dose change, the Investigator may choose one time that the subject be re-escalated to open-label upadacitinib 30 mg QD and remain on the 30 mg dose.

Study participants

In- and exclusion criteria

The in/exclusion criteria were similar for the phase 3 M23-716 Study 1 and Study 2. Subjects who met the following criteria were **included**:

- Female and male adult subjects < 64 years old at Baseline, adolescent subjects ≥ 12 years
- Diagnosis of severe AA with
    - SALT score ≥ 50 scalp hair loss at Screening and Baseline
    - no spontaneous scalp hair regrowth over the past 6 months, and
    - a current episode of AA < 8 years.
- Body weight must be ≥ 30 kg at the Baseline Visit for subjects who are ≥ 12 and < 18 years of age.

Subjects were **excluded** from participation, if they:

- Had a current diagnosis of primarily diffuse type of AA
- Had a current diagnosis of other types of alopecia that would interfere with evaluation of AA, including but not limited to female pattern hair loss, male pattern hair loss (androgenetic alopecia) Stage III or greater based on Hamilton-Norwood classification, and telogen effluvium, or
- Had a diagnosis of other types of inflammatory scalp, eyebrow, or eyelash disorders that would interfere with evaluation of AA, including but not limited to seborrheic dermatitis, scalp psoriasis, atopic dermatitis, and tinea capitis.
- Had used the following treatments, including but not limited to (specified time refers to timeframe prior to the Baseline Visit):
    - Oral JAK inhibitors (within 8 weeks)
        - Subjects who had an inadequate response in AA after at least 12 weeks of an oral JAK inhibitor treatment were not eligible for the study
    - Topical JAK inhibitor (within 4 weeks)
    - Systemic therapy with a potential effect on AA (within 4 weeks)
    - Targeted biologic therapies with immunosuppressive potential (within 5 half-lives [if known] or within 12 weeks, whichever is longer)
    - Phototherapy (within 4 weeks)
    - Intralesional corticosteroid injections used for AA (within 4 weeks)

Discontinuation

Subjects had the study drug discontinued if any of the following criteria were fulfilled, including but not limited to:

- The subject requested withdrawal from study drug or the study.

- Abnormal laboratory results or AEs that either met the criteria for discontinuation of study drug or precluded safe continuation of the study drug.
- The subject developed a major cardiovascular event (MACE: acute myocardial infarction, stroke)
- Serious infection (e.g., sepsis) which cannot be adequately controlled by anti-infective treatment or would put the subject at risk with continuation in the study drug.
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolus, or non-cardiac, non-neurologic arterial thrombosis.
- Malignancy except for a localized NMSC, or a carcinoma in situ of the cervix which can successfully be treated at its localization.
- Pregnancy.

Treatments

Upadacitinib and matching placebo was supplied as shown in Table 13.

Table 13. Description of Study drug.

Investigational Product	Mode of Administration	Dosage Form	Strength	Masking	Frequency
Upadacitinib (ABT-494)	Oral	Extended-release tablets	15 mg	Blinded, Open	QD
Upadacitinib (ABT-494)	Oral	Extended-release tablets	30 mg	Blinded, Open	QD
Placebo for Upadacitinib (ABT-494)	Oral	Film-coated tablets	Not applicable	Blinded	QD

Concomitant Therapy

The following were allowed concomitant medications/therapies:

- Oral nonprescription supplements (e.g., vitamin A, vitamin C) that may be used for hair growth.
- Topical corticosteroids or topical calcineurin inhibitors for conditions other than AA.
- HMG-CoA reductase inhibitors (statins) for conditions other than AA.
- Inhaled, ophthalmic drops and nasal corticosteroid formulations are allowed throughout the study. Subjects may be treated with systemic corticosteroids for non-AA reasons if medically necessary. Any subject who receives systemic corticosteroid for more than 2 consecutive weeks, regardless of the dosage of corticosteroid, should permanently discontinue study drug.
- Laser therapy (e.g., excimer laser) after Week 112 per Investigator discretion.
- Intralesional triamcinolone (maximum dose of 10 mg per month) after Week 112 per Investigator discretion.

- Systemic non-biologic therapy for AA, with the exception of cyclosporine, azathioprine, and mycophenolate mofetil, is allowed after the Week 112 Visit assessments at Investigator discretion. Oral minoxidil, finasteride, or dutasteride after Week 112 (maximum minoxidil dose of 2.5 mg per day, maximum finasteride dose 1 mg per day, and maximum dutasteride dose of 0.5 mg per day) per Investigator discretion.
- Topical AA therapy (e.g., topical corticosteroids, immunotherapy) after Week 112 per Investigator discretion.

Rescue treatment

No rescue medications were foreseen in the protocol. However, the following study drug rescue and discontinuation criteria, based on efficacy response, were listed:

- Subjects with no change or a worsening (i.e., increase) from Baseline in their SALT score at the Week 40 visit will be discontinued from study drug.
- Subjects with less than a 30% improvement from Baseline in their SALT score at the Week 40 visit or any scheduled visit thereafter will receive open-label upadacitinib 30 mg QD.
- Subjects on open-label upadacitinib 30 mg with less than 30% improvement from Baseline in SALT score at any subsequent scheduled visit (in Studies 1, 2, or 3) will be discontinued from study drug.

Objectives

Both Phase 3 studies (M23-716 Study 1 and Study 2) had the same objectives, which are as follows:

Double-blind Period, Baseline to Week 24 (Period A):

• To assess the efficacy, safety, and tolerability of upadacitinib 15 mg QD and 30 mg QD compared with placebo for the treatment of signs and symptoms of severe AA in adult and adolescent subjects.

Blinded Extension Period, Week 24 to Week 52 (Period B):

• To evaluate the efficacy, safety, and tolerability of upadacitinib 15 mg QD and 30 mg QD in extended treatment in adult and adolescent subjects with severe AA.

Outcomes/endpoints

For Study 1 and Study 2, the primary endpoint, the multiplicity-controlled secondary endpoints, and the additional endpoints were the same for both studies.

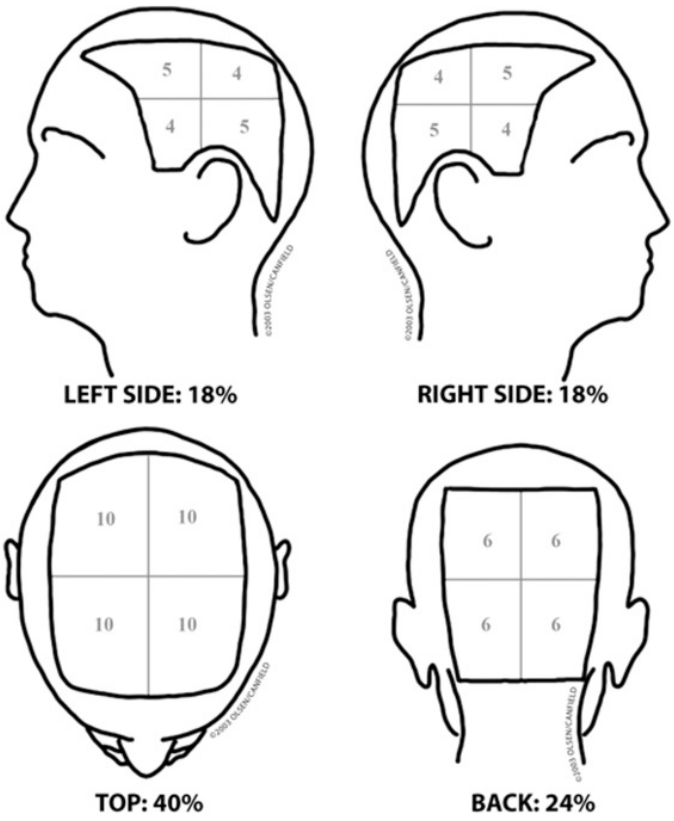
Primary Endpoint - Severity of Alopecia Tool (SALT)

The primary endpoint was the achievement of SALT score ≤ 20 at Week 24, defined as less than or equal to 20% scalp hair loss.

The SALT score is a tool developed by the National Alopecia Areata Foundation Working Committee to assess the extent of scalp hair loss in patients with AA.[12,13]

The score is determined by visually defining the amount of terminal hair loss in each of the 4 views of the scalp (left and right side each accounting for 18% of scalp area, the top for 40%, and the back for 24%) and adding these together with a maximum score of 100%.

Figure 10. SALT aid for determining scalp surface area [13]



The percentage of hair loss in any one of the 4 areas of the scalp = the percentage hair loss x percent surface area of the scalp in that area. The SALT score then equals the sum of the scalp hair loss in each of the 4 areas.[13]

Secondary endpoints (multiplicity-controlled)

The following secondary endpoints have been included in the SmPC. Other secondary endpoints were measured and are noted in the study protocol.

- Achievement of SALT score ≤ 20 at Week 24 for the comparison of upadacitinib 15 mg QD vs. placebo
- Achievement of SALT score ≤ 10 at Week 24

[12] Olsen EA, Hordinsky M, McDonald-Hull S, et al. Alopecia areata investigational assessment guidelines. *J Am Acad Dermatol.* 1999;40(2):242–246.
[13] Olsen EA, Hordinsky MK, Price VH, et al. Alopecia areata investigational assessment guidelines--Part II. National Alopecia Areata Foundation. J Am Acad Dermatol. 2004;51(3):440-7.

- Achievement of Clinician-Reported Outcome (ClinRO) measure for eyebrow hair loss of 0 or 1 at Week 24 with a ≥ 2-point improvement (reduction) from Baseline among subjects with Baseline score ≥ 2
- Achievement of ClinRO measure for eyelash hair loss of 0 or 1 at Week 24 with a ≥ 2-point improvement (reduction) from Baseline among subjects with Baseline score ≥ 2
- Percent change from Baseline in SALT score at Week 24
- Change from Baseline in Skindex-16 AA emotions domain score at Week 24
- Change from Baseline in Skindex-16 AA functioning domain score at Week 24
- Achievement of SALT score of 0 at Week 24
- Achievement of SALT score ≤ 20 at Week 8

Additional secondary efficacy endpoints

Additional efficacy endpoints were measured and are noted in the study protocol. The following was sufficiently justified to be included within the SmPC (see section 2.4.3.

- Achievement of ClinRO measure for Beard Hair Loss (I-ALFA) Grade of 2 or 3 with ≥ 2-point improvement from Baseline among subjects with Baseline Grade < 2

The following additional endpoint will only be evaluated at the Week 52 visit:

- Achievement of maintenance of response (SALT score ≤ 20) at Week 52 in subjects with a SALT score ≤ 20 at Week 24, among those randomized at Baseline to a upadacitinib treatment and continued with the same treatment in Period B.

Description of ClinRO Assessments

Eyebrow Hair Loss™

This ClinRO is comprised of the following response options: 0 = The eyebrows have full coverage and no areas of hair loss; 1 = There are minimal gaps in eyebrow hair and distribution is even; 2 = There are significant gaps in eyebrow hair or distribution is not even; 3 = No notable eyebrows.

Eyelash Hair Loss™

This ClinRO is comprised of the following response options: 0 = The eyelashes form a continuous line along the eyelids on both eyes; 1 = There are minimal gaps and the eyelashes are evenly spaced along the eyelids on both eyes; 2 = There are significant gaps along the eyelids or the eyelashes are not evenly spaced along the eyelids; 3 = No notable eyelashes.

Beard Hair Loss, Global Investigator Assessment, I-ALFA

This global investigator assessment for beard hair loss (I-ALFA) is comprised of the following response options: 0 = No hair growth; 1 = Mostly areas with hair loss, some areas of hair growth; 2 = Mostly normal hair growth, some areas of hair loss; 3 = Normal hair growth. Subjects evaluated for beard hair loss should be instructed by the Investigator to not shave their beard for at least 3 days prior to those assessments.

This ClinRO has not been implemented in previous clinical studies.

Description of selected PROs

Skindex-16-AA

The Skindex-16 for AA measures the effects of AA on a subject's health-related quality of life, with 3 domains including Emotions (7 items), Symptoms (4 items), and Functioning (5 items). The respondent rates how much each symptom or impact has bothered them in the past week, ranging from never bothered, with a score of 0, to always bothered, with a score of 6. Total scores range from 0 to 100, with higher scores indicating greater impact on health-related quality of life.

The Skindex-16 for AA Emotions and Functioning domains have been included as additional secondary efficacy endpoints for another AA treatment.

Sample size

In studies 1 and 2, approximately 600 adults per study were to be randomised. Assuming a Week 24 SALT score ≤20 response rate of 7.2% in the placebo group, this planned sample size (240 adults per upadacitinib dose and 120 adults for placebo) was expected to provide more than 90% power to detect a treatment difference of 19.5% in either upadacitinib doses vs. placebo using a 2-sided significance level of 0.05.

Randomisation

In Part A of studies 1 and 2, subjects were randomised 2:2:1 to upadacitinib 30 mg, upadacitinib 15 mg, or placebo. Randomisation was stratified by age group (adults ≥ 18 years vs. adolescents ≥ 12 to < 18 years, respectively), baseline SALT score of severe AA vs. very severe AA (SALT score 50 to 94 vs. SALT score 95 to 100, respectively), and AA episode duration at Baseline (< 3 years vs. ≥ 3 years, respectively).

Subjects who had been randomised to placebo in Period A and had a SALT score <20 at Week 24 remained on placebo in Part B until they met prespecified rescue criterion. Those who had a SALT score >20 at Week 24 were re-randomized 1:1 to double-blinded upadacitinib 15 mg or upadacitinib 30 mg in Part B. Subjects initially randomised to an upadacitinib dose group in Period A continued the same treatment in Period B.

Blinding (masking)

Studies 1 and 2 were double blinded. The upadacitinib and placebo tablets were identical in appearance.

Statistical methods

The statistical methods described below were used in both Study 1 and Study 2.

Analysis populations

The ITT Populations (used for efficacy):

- ITT_A: All subjects who were randomized at Baseline.
- ITT_B: All subjects who were randomized in Period A and continue into Period B.

The Safety Populations:

- Safety_A: All randomized subjects who received at least 1 dose of study drug during Period A.

- Safety_B: All randomized subjects who received at least 1 dose of study drug during Period B.
- ALL_UPA: All randomized subjects who received at least 1 dose of upadacitinib in the study.

Hypothesis testing

The primary endpoint was a Cochran–Mantel–Haenszel test adjusted for 2 stratification factors: baseline disease severity (severe [SALT score < 95] vs. very severe [SALT score ≥ 95]) and AA episode duration at Baseline (< 3 years vs. ≥ 3 years).

For the binary endpoints, similar analyses as the primary endpoint were conducted on the ITT_A Populations.

For the continuous endpoints, comparisons between each upadacitinib group and placebo were conducted using an analysis of covariance (ANCOVA) analysis with fixed effects of treatment group and 2 stratification factors (baseline disease severity and AA episode duration at Baseline) and the baseline value as covariate.

Interim analysis and primary analysis

No interim analyses were planned or performed. The primary efficacy analysis was conducted after all subjects had completed the Week 24 Visit (period A).

Intercurrent events

Two intercurrent events were defined:

- The use of confounding medication for AA that could impact the evaluation of the endpoint.
- Premature discontinuation of study drug

These events were handled using non-response imputation for binary endpoints. For continuous endpoints, return-to-baseline multiple imputation was used.

Missing data

For the binary endpoints in Period A, missing data were imputed as non-response. However, if a subject was a responder both before and after the visit window in the particular study period, the subject was categorised as a responder for the visit. Furthermore, missing data that could be reasonably assumed to be missing at random, in cases such as due to a pandemic, significant natural disaster, or a geopolitical conflict, were handled by multiple imputation.

For the continuous endpoints in Period A, missing data were imputed via multiple imputation (assuming missing at random).

In period B, the primary approach to handling missing data was observed case (OC). Thus, a subject who did not have an evaluation at a scheduled visit was not included for that visit.

Type-1-error control

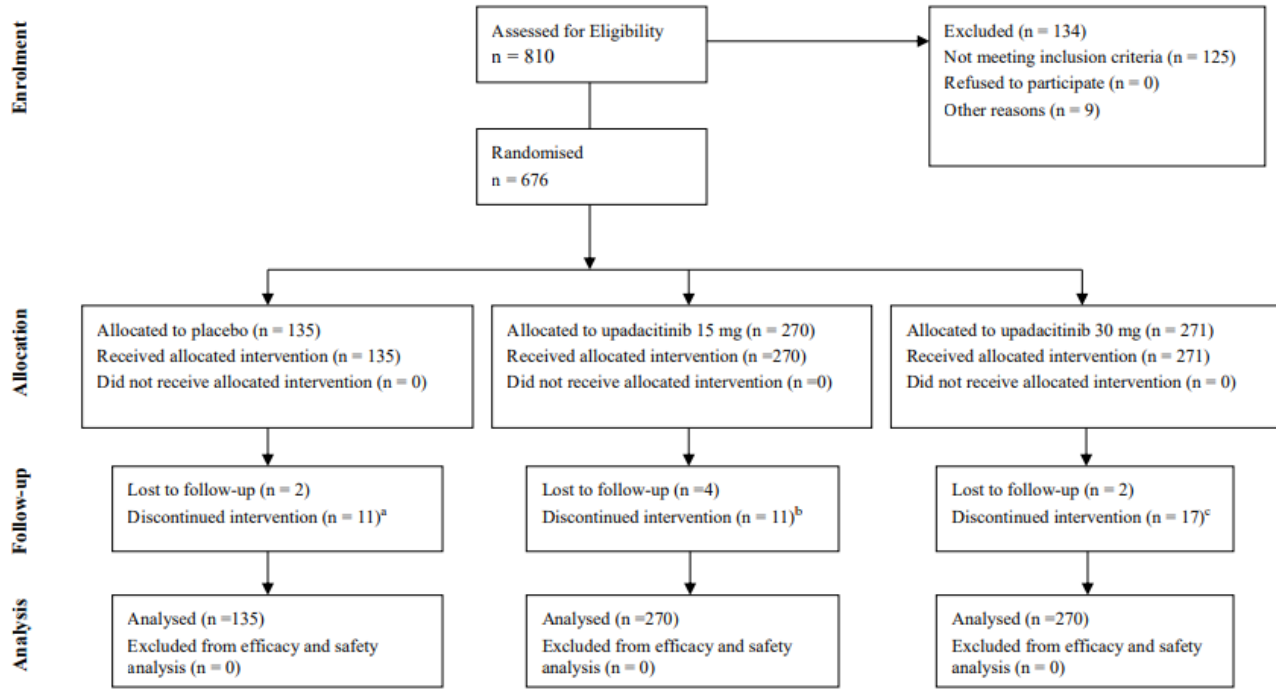
A graphical testing approach was employed to control the 2-sided familywise error rate at 0.05.

Results

Participant flow and numbers analysed

In studies 1 and 2, a total of 1654 subjects were assessed for eligibility and a total of 1399 subjects with severe AA were enrolled in Period A (Figure 11 and Figure 12). In total, 77 subjects (5.5%) discontinued study drug in Period A. Across treatment groups in Period A, the most frequent reason for study drug discontinuation was withdrawal from treatment by subject (Table 14: Subject Disposition in the Phase 3 Studies (ITT_A Population). Subjects who discontinued study drug were encouraged to remain in the study to complete all scheduled visits through the end of Period A for all safety and efficacy assessments as per protocol.

Figure 11. M23-716 Study 1 Subject Disposition – Period A

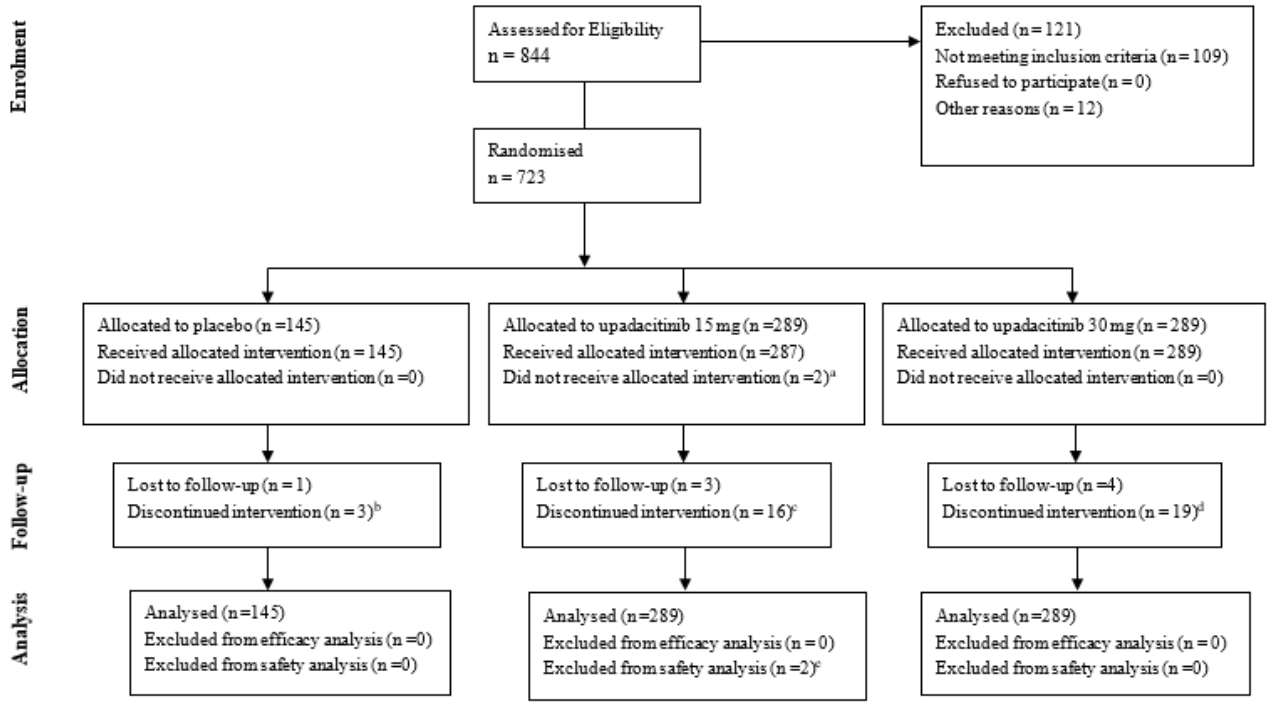


A Reasons: 2 subjects discontinued intervention due to Lost to follow-up, 8 subjects discontinued intervention due to Withdrawal from treatment by subject, 1 subject discontinued intervention due to Other reason (investigator decision).

B Reasons: 4 subjects discontinued intervention due to Lost to follow-up, 5 subjects discontinued intervention due to Withdrawal from treatment by subject, 2 subjects discontinued intervention due to Adverse event.

C Reasons: 2 subjects discontinued intervention due to Lost to follow-up, 9 subjects discontinued intervention due to Withdrawal from treatment by subject, 2 subjects discontinued intervention due to Adverse event, 4 subjects discontinued intervention due to Other reason (per endocrinologist and PI decision; pregnancy; in consideration of subject safety and treatment issues; and investigator judgement).

Figure 12. M23-716 Study 2 Subject Disposition – Period A



D Reasons: Subjects withdrew consent.

E Reasons: 1 subject discontinued intervention due to Lost to follow-up, 2 subjects discontinued intervention due to Withdrawal from treatment by subject.

F Reasons: 3 subjects discontinued intervention due to Lost to follow-up, 8 subjects discontinued intervention due to Withdrawal from treatment by subject, 2 subjects discontinued intervention due to Adverse event, 3 subjects discontinued intervention due to Other reason (investigator decision; investigator decision; and unable to contact subject).

G Reasons: 4 subjects discontinued intervention due to Lost to follow-up, 11 subjects discontinued intervention due to Withdrawal from treatment by subject, 2 subjects discontinued intervention due to Adverse event, 2 subjects discontinued intervention due to Other reason (PI decision; and investigator determines the subject is significant non-compliant with study procedures).

H Reasons: Subjects should receive at least 1 dose of study drug to be included in safety analysis.

Table 14. Subject Disposition in the Phase 3 Studies (ITT_A Population)

	Period A							
	Overall				Adolescents			
	PBO (N = 280) n (%)	UPA 15 mg (N = 559) n (%)	UPA 30 mg (N = 560) n (%)	Total (N = 1399) n (%)	PBO (N = 23) n (%)	UPA 15 mg (N = 48) n (%)	UPA 30 mg (N = 47) n (%)	Total (N = 118) n (%)
Enrolled (randomized)	280 (100)	559 (100)	560 (100)	1399 (100)	23 (100)	48 (100)	47 (100)	118 (100)
Study 1	135 (48.2)	270 (48.3)	271 (48.4)	676 (48.3)	13 (56.5)	25 (52.1)	26 (55.3)	64 (54.2)
Study 2	145 (51.8)	289 (51.7)	289 (51.6)	723 (51.7)	10 (43.5)	23 (47.9)	21 (44.7)	54 (45.8)
Took at least 1 dose of study drug	280 (100)	557 (99.6)	560 (100)	1397 (99.9)	23 (100)	48 (100)	47 (100)	118 (100)
Completed study drug in Period A	266 (95.0)	530 (94.8)	524 (93.6)	1320 (94.4)	23 (100)	47 (97.9)	47 (100)	117 (99.2)
Completed Period A	266 (95.0)	530 (94.8)	525 (93.8)	1321 (94.4)	23 (100)	47 (97.9)	47 (100)	117 (99.2)
Prematurely discontinued study drug in Period A	14 (5.0)	27 (4.8)	36 (6.4)	77 (5.5)	0	1 (2.1)	0	1 (0.8)
Primary reason for discontinuations								
AE	0	4 (0.7)	4 (0.7)	8 (0.6)	0	1 (2.1)	0	1 (0.8)
Lost to follow-up	3 (1.1)	7 (1.3)	6 (1.1)	16 (1.1)	0	0	0	0
Lack of efficacy	0	0	0	0	0	0	0	0
Withdrawal from treatment by subject	10 (3.6)	13 (2.3)	20 (3.6)	43 (3.1)	0	0	0	0
Other	1 (0.4)	3 (0.5)	6 (1.1)	10 (0.7)	0	0	0	0

Recruitment

The first subject's first visit was on 14 November 2023 for Study 1 and on 11 October 2023 for Study 2. The last subject's last visit (Week 24, corresponding to the data cutoff date) was on 8 July 2025 for Study 1 and on 13 June 2025 for Study 2.

Conduct of the study

Protocol amendments

The original protocol (Version 1.0, 01 June 2023) had 4 amendments and 1 administrative change:

- Version 1.1.1 (EU Only) (21 March 2024).

  Main changes: Clarified that adolescent subjects will not be enrolled in the US or EU.

- Version 2.0 (07 May 2024)

  Main changes:

  - Removed requirement of no significant scalp hair loss over the past 3 months prior to baseline for better alignment with clinical practice.
  - Removed allowed concomitant use of oral minoxidil, finasteride, or dutasteride, and topical minoxidil due to concerns regarding confounding of efficacy and safety assessments.
  - Removed cannabidiol (CBD)-containing products (including marijuana) from the eligibility criteria due to lack of scientific evidence for efficacy in AA.
  - Updated the exclusion criterion related to investigators opinion on subjects' unsuitability to participate in the study to include information related to atherosclerotic cardiovascular disease and VTE risk factors.
  - Added the intercurrent event of 'premature discontinuation of study drug due to lack of efficacy.'
  - Re-arranged multiplicity-controlled secondary endpoints for Skindex-16 and AASIS based on updated statistical power calculations.

- Version 3.0 (03 March 2025)

  Main changes:

  - Added Study 4.
  - Removed 'due to lack of efficacy' from the intercurrent event of 'premature discontinuation of study drug due to lack of efficacy.

Protocol deviations

Table 15. Protocol Deviations in Study 1 (ITT_A Population)

Category	Placebo (N=135) n (%)	Active	
		UPA 15 mg QD (N=270) n (%)	UPA 30 mg QD (N=271) n (%)
Subjects with at least one protocol deviation	16 (11.9)	27 (10.0)	30 (11.1)
Subjects who entered the study even though they did not satisfy the entry criteria	4 (3.0)	12 (4.4)	10 (3.7)
Inclusion criteria not met	3 (2.2)	5 (1.9)	3 (1.1)
Criterion number 1	1 (0.7)	1 (0.4)	0
Criterion number 4	0	1 (0.4)	0
Criterion number 8	1 (0.7)	0	0
Criterion number 17	1 (0.7)	2 (0.7)	1 (0.4)
Criterion number 18	0	0	1 (0.4)
Criterion number 20	0	1 (0.4)	1 (0.4)
Exclusion criteria met	1 (0.7)	7 (2.6)	7 (2.6)
Criterion number 4	0	1 (0.4)	0
Criterion number 9	0	3 (1.1)	3 (1.1)
Criterion number 11	1 (0.7)	0	1 (0.4)
Criterion number 13	0	2 (0.7)	2 (0.7)
Criterion number 17	0	1 (0.4)	0
Criterion number 20	0	1 (0.4)	1 (0.4)
Subjects who developed withdrawal criteria during the study but were not withdrawn	0	0	1 (0.4)
Subjects who received the wrong treatment or incorrect dose	1 (0.7)	1 (0.4)	4 (1.5)
Subjects who received an excluded concomitant treatment	12 (8.9)	15 (5.6)	18 (6.6)

Note: Includes important protocol deviation categories as suggested in the ICH E3 Guideline.

Subjects are counted only once in each category for which they had a deviation.

Table 16. Protocol Deviations in Study 2 (ITT_A Population)

Category	Placebo (N=145) n (%)	Active	
		UPA 15 mg QD (N=289) n (%)	UPA 30 mg QD (N=289) n (%)
Subjects with at least one protocol deviation	8 (5.5)	27 (9.3)	15 (5.2)
Subjects who entered the study even though they did not satisfy the entry criteria	3 (2.1)	11 (3.8)	5 (1.7)
Inclusion criteria not met	2 (1.4)	4 (1.4)	3 (1.0)
Criterion number 2	1 (0.7)	1 (0.3)	0
Criterion number 4	1 (0.7)	0	0
Criterion number 9	0	2 (0.7)	0
Criterion number 17	0	1 (0.3)	3 (1.0)
Exclusion criteria met	1 (0.7)	7 (2.4)	2 (0.7)
Criterion number 4	0	3 (1.0)	1 (0.3)
Criterion number 9	1 (0.7)	2 (0.7)	1 (0.3)
Criterion number 11	0	1 (0.3)	0
Criterion number 13	0	1 (0.3)	0
Subjects who developed withdrawal criteria during the study but were not withdrawn	0	0	0

Subjects who received the wrong treatment or incorrect dose	1 (0.7)	2 (0.7)	0
Subjects who received an excluded concomitant treatment	5 (3.4)	15 (5.2)	10 (3.5)

Note: Includes important protocol deviation categories as suggested in the ICH E3 Guideline. Subjects are counted only once in each category for which they had a deviation.

Baseline data

Patient Demographics

Baseline demographics from M23-716 Study 1 and Study 2 are presented in Table 17. Overall, the majority of subjects were female, white and in the age group ≥ 18 to < 40 years of age. The clinical program enrolled subjects across various geographic regions worldwide.

Table 17. Demographic Characteristics in the Phase 3 Studies (ITT_A Population) (modified)

	Overall				Adolescents			
Variable	PBO (N = 280)	UPA 15 mg (N = 559)	UPA 30 mg (N = 560)	Total (N = 1399)	PBO (N = 23)	UPA 15 mg (N = 48)	UPA 30 mg (N = 47)	Total (N = 118)
Sex - n (%)								
Female	160 (57.1)	330 (59.0)	336 (60.0)	826 (59.0)	9 (39.1)	15 (31.3)	22 (46.8)	46 (39.0)
Male	120 (42.9)	229 (41.0)	224 (40.0)	573 (41.0)	14 (60.9)	33 (68.8)	25 (53.2)	72 (61.0)
Age group - n (%)								
< 18 years	23 (8.2)	48 (8.6)	47 (8.4)	118 (8.4)	23 (100)	48 (100)	47 (100)	118 (100)
≥ 18 to < 40 years	146 (52.1)	278 (49.7)	294 (52.5)	718 (51.3)	0	0	0	0
≥ 40 years	111 (39.6)	233 (41.7)	219 (39.1)	563 (40.2)	0	0	0	0
Age (min, max) (years)	12, 64	12, 64	12, 64	12, 64	12, 17	12, 17	12, 17	12, 17
Race - n (%)								
White	166 (59.3)	354 (63.3)	345 (61.6)	865 (61.8)	7 (30.4)	22 (45.8)	15 (31.9)	44 (37.3)
Asian	94 (33.6)	151 (27.0)	168 (30.0)	413 (29.5)	16 (69.6)	22 (45.8)	29 (61.7)	67 (56.8)
Black	16 (5.7)	38 (6.8)	27 (4.8)	81 (5.8)	0	1 (2.1)	1 (2.1)	2 (1.7)
Other	4 (1.4)	16 (2.9)	20 (3.6)	40 (2.9)	0	3 (6.3)	2 (4.3)	5 (4.2)
Ethnicity - n (%)								
Hispanic or Latino	25 (8.9)	65 (11.6)	64 (11.4)	154 (11.0)	1 (4.3)	8 (16.7)	5 (10.6)	14 (11.9)
Not Hispanic or Latino	255 (91.1)	494 (88.4)	496 (88.6)	1245 (89.0)	22 (95.7)	40 (83.3)	42 (89.4)	104 (88.1)
Weight (kg)								
Mean (SD)	73.324 (16.7779)	74.383 (18.1179)	73.377 (18.0928)	73.769 (17.8422)	60.15 (15.316)	59.69 (16.897)	61.69 (15.035)	60.58 (15.765)
Median	72.000	72.500	70.403	71.900	60.80	58.25	59.00	58.45
Min, Max	32.10, 138.34	34.20, 166.00	32.50, 153.30	32.10, 166.00	32.1, 92.9	34.2, 113.6	32.5, 101.1	32.1, 113.6
BMI category (kg/m^2) - n (%)								
Normal: < 25	138 (49.3)	274 (49.1)	296 (52.9)	708 (50.6)	19 (82.6)	38 (79.2)	38 (80.9)	95 (80.5)
Overweight: ≥ 25 to < 30	88 (31.4)	167 (29.9)	156 (27.9)	411 (29.4)	3 (13.0)	7 (14.6)	6 (12.8)	16 (13.6)
Obese: ≥ 30	54 (19.3)	117 (21.0)	108 (19.3)	279 (20.0)	1 (4.3)	3 (6.3)	3 (6.4)	7 (5.9)
BMI Missing	0	1	0	1	0	0	0	0
BMI (min, max) (kg/m^2)	13.50, 43.76	15.83, 53.59	14.88, 52.98	13.50, 53.59	13.50, 33.71	15.83, 35.45	15.25, 33.23	13.50, 35.45
Geographic Region – n (%)								
Asia	82 (29.3)	126 (22.5)	145 (25.9)	353 (25.2)	14 (60.9)	22 (45.8)	26 (55.3)	62 (52.5)
Europe	102 (36.4)	209 (37.4)	200 (35.7)	511 (36.5)	0	4 (8.3)	5 (10.6)	9 (7.6)
North America	61 (21.8)	142 (25.4)	140 (25.0)	343 (24.5)	4 (17.4)	8 (16.7)	7 (14.9)	19 (16.1)

Variable	Overall				Adolescents			
	PBO (N = 280)	UPA 15 mg (N = 559)	UPA 30 mg (N = 560)	Total (N = 1399)	PBO (N = 23)	UPA 15 mg (N = 48)	UPA 30 mg (N = 47)	Total (N = 118)
South/Central America	9 (3.2)	31 (5.5)	29 (5.2)	69 (4.9)	1 (4.3)	7 (14.6)	4 (8.5)	12 (10.2)
Other	26 (9.3)	51 (9.1)	46 (8.2)	123 (8.8)	4 (17.4)	7 (14.6)	5 (10.6)	16 (13.6)

Baseline Disease Characteristics and Prior AA Therapy

In accordance with the inclusion criteria, subjects enrolled had a diagnosis of severe AA with SALT score ≥ 50 scalp hair loss at Screening and Baseline, no spontaneous scalp hair regrowth over the past 6 months and a current episode of AA of less than 8 years. There were 683 (48.8%) subjects with severe AA (SALT score < 95) and 716 (51.2%) subjects with very severe AA (SALT score ≥ 95) at Baseline. Subjects had a mean (SD) AA disease duration since diagnosis of 10.301 (10.8904) years (4.747 [3.6111] years, for adolescents). Subjects had a mean (SD) AA current episode duration of 3.076 (2.2179) years (2.478 [2.1056] years for adolescents).

In the Summary of Clinical Efficacy, no table showing baseline disease characteristics is presented.

Concomitant therapy

There were 392 subjects (72.5%) in Study 2 and 459 subjects (79.7%) in Study 2 that reported use of concomitant medications for any reason in Period A. The MAH states that concomitant medication usage was generally comparable across treatment groups.

Outcomes and estimation

Primary endpoint

The primary endpoint, achievement of SALT score ≤ 20 at Week 24, defined as less than or equal to 20% scalp hair loss, was met for each individual study. A greater proportion of subjects achieved the primary endpoint of SALT ≤ 20 at Week 24 in both the upadacitinib 15 mg (44.9 %) and 30 mg (54.6%) groups vs. the placebo group (2.5%), resulting in a placebo-adjusted difference of 42.3% for the upadacitinib 15 mg group (nominal P ≤ 0.001) and 52.0% for the upadacitinib 30 mg group (nominal P ≤0.001) using non-responder imputation. Sensitivity analyses of the primary endpoint, including multiple imputation and tipping point analysis, showed consistent results with the primary approach with nominal p-values ≤ 0.001 for the two upadacitinib dose groups vs placebo. Supplementary analysis of the primary endpoint based on OC showed consistent results with the primary approach, with a numerically higher response rate of the two upadacitinib dose groups vs placebo.

Table 18. Summary of Primary Endpoint Results for Study 1 (modified)

Analysis Description	**Primary Analysis**			
Analysis Population and Time Point Description	The ITT populations (ITT_A: all subjects who were randomized at Baseline were used for efficacy analyses in Period A. Subjects were analyzed according to treatment as randomized in Period A.			
Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	**Treatment group**	**Placebo QD**	**Upadacitinib 15 mg QD**	**Upadacitinib 30 mg QD**
	SALT score ≤ 20 at Week 24	135 subjects 1.5 (0.0, 3.5)	270 subjects 45.2 (39.2, 51.1)	271 subjects 55.0 (49.1, 60.9)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	43.8	53.5
		95% CI	(37.6, 49.9)	(47.4, 59.5)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant
Notes	Point estimates for binary endpoints are percentages.			

Table 19. Summary of Primary Endpoint Results for Study 2 (modified)

Analysis Description	**Primary Analysis**			
Analysis Population and Time Point Description	The ITT populations (ITT_A: all subjects who were randomized at Baseline were used for efficacy analyses in Period A. Subjects were analyzed according to treatment as randomized in Period A.			
Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	**Treatment group**	**Placebo QD**	**Upadacitinib 15 mg QD**	**Upadacitinib 30 mg QD**
	SALT score ≤ 20 at Week 24	145 subjects 3.4 (0.5, 6.4)	289 subjects 44.6 (38.9, 50.4)	289 subjects 54.3 (48.6, 60.1)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	41.0	50.7
		95% CI	(34.9, 47.1)	(44.3, 57.0)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant
Notes	Point estimates for binary endpoints are percentages.			

Table 20. Summary of Subjects Achieving SALT Score ≤ 20 at Week 24 by imputations for Study 1 and Study 2 (Non-Responder Imputation (NRI)) (ITT_A Population)

Intercurrent Event	Placebo	UPA 15 mg	UPA 30 mg
M23-716 Study 1	N=135	N=270	N=271
	n (%)	n (%)	n (%)
Subjects with observed data without ICE	124 (91.9)	260 (96.3)	255 (94.1)
Responder	2 (1.5)	122 (45.2)	149 (55.0)
Non-responder	122 (90.4)	138 (51.1)	106 (39.1)
Subjects with missing data without ICE (Imputed as Non-responder)	0	1 (0.4)	1 (0.4)
Subjects with ICE (Considered as Non-responder after ICE)	11 (8.1)	9 (3.3)	15 (5.5)
Discontinuation of study drug	11 (8.1)	9 (3.3)	15 (5.5)
Confounding medications	0	0	0
M23-716 Study 2	N=145	N=289	N=289
	n (%)	n (%)	n (%)
Subjects with observed data without ICE	142 (97.9)	271 (93.8)	269 (93.1)
Responder	5 (3.4)	129 (44.6)	157 (54.3)
Non-responder	137 (94.5)	142 (49.1)	112 (38.8)
Subjects with missing data without ICE (Imputed as Non-responder)	0	2 (0.7)	1 (0.3)

Subjects with ICE (Considered as Non-responder after ICE)	3 (2.1)	16 (5.5)	19 (6.6)
Discontinuation of study drug	3 (2.1)	16 (5.5)	19 (6.6)
Confounding medications	0	0	0

ICE: Intercurrent events

Secondary endpoints (multiplicity-controlled)

The results of some of the multiplicity-controlled secondary endpoints are provided in Table 21 and Table 22.

Table 21. Summary of Secondary Endpoint Results (modified)

Study	AA-1			AA-2		
	PBO N= 135	UPA 15 mg N= 270	UPA 30 mg N= 271	PBO N= 145	UPA 15 mg N= 289	UPA 30 mg N=289
Week 24 Endpoints						
SALT score ≤ 20	1%	45%[d]	55%[d]	3%	45%[d]	54%[d]
SALT score ≤ 10	1%	35%[d]	46%[d]	1%	36%[d]	47%[d]
SALT score of 0	0	14%[d]	20%[d]	1%	13%[d]	22%[d]
ClinRO Eyebrow Hair Loss score of 0 or 1[a]	1% N=87	41%[d] N=170	62%[d] N=178	3% N=93	42%[d] N=192	59%[d] N=197
ClinRO Eyelash Hair Loss score of 0 or 1[b]	6% N=72	44% [d] N=151	59 % [d] N=145	4% N=82	43%[d] N=166	61%[d] N=158
ClinRO for Beard Hair Loss (I-ALFA)[c]	0 N=34	27%[f] N=67	42%[f] N=73	2% N=44	37%[f] N=76	42%[f] N=72
Week 8 Endpoint						
SALT score of ≤ 20	1%	7%[e]	11%[d]	2%	9%[e]	12%[d]

[a] ClinRO assessment for eyebrow hair loss uses a 4-point response scale, ranging from 0 to 3 where 0 = The eyebrows have full coverage and no areas of hair loss; 1 = There are minimal gaps in eyebrow hair and distribution is even; 2 = There are significant gaps in eyebrow hair or distribution is not even; 3 = No notable eyebrows. The endpoint measured the proportion of subjects achieving a score of 0 or 1 with a ≥ 2-point improvement from baseline among subjects with baseline score ≥ 2

[b] ClinRO assessment for eyelash hair loss uses a 4-point response scale, ranging from 0 to 3 where 0 = The eyelashes form a continuous line along the eyelids on both eyes; 1 = There are minimal gaps and the eyelashes are evenly spaced along the eyelids on both eyes; 2 = There are significant gaps along the eyelids or the eyelashes are not evenly spaced along the eyelids; 3 = No notable eyelashes**.** The endpoint measured the proportion of subjects achieving a score of 0 or 1 with a ≥ 2-point improvement from baseline among subjects with baseline score ≥ 2

[c] ClinRO for beard hair loss (I-ALFA) uses a 4-point scale ranging from 0 = no hair growth, 1 = mostly areas with hair loss, some areas of hair growth; 2 = mostly normal hair growth, some areas of hair loss to 3 = normal hair growth. This measured the proportion of patients who achieved a grade of 2 or 3 with ≥ 2-point improvement from Baseline among subjects with Baseline grade < 2.

[d] multiplicity-controlled $p < 0.001$ upadacitinib vs placebo comparison

[e] multiplicity-controlled $p < 0.01$ upadacitinib vs placebo comparison

[f] nominal $p < 0.001$ upadacitinib vs placebo comparison

Table 22. Summary of Patient-reported Outcomes Results at Week 24 (modified)

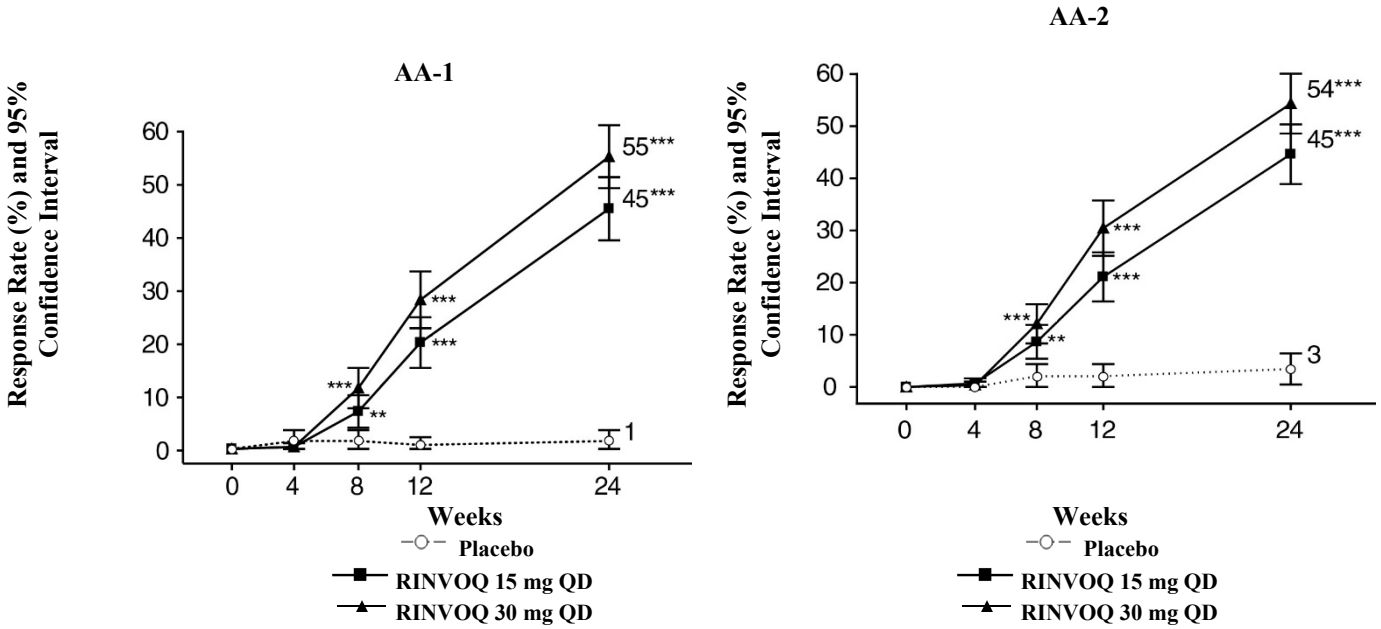
Study	AA-1			AA-2		
	PBO N=135	UPA 15 mg N=270	UPA 30 mg N=271	PBO N=145	UPA 15 mg N=289	UPA 30 mg N=289
CFB in Skindex-16 AA Emotions Domain scores[a]	-15	-30[b]	-36[b]	-10	-31[b]	-34[b]
CFB in Skindex-16 AA Functioning Domain scores[a]	-9	-22[b]	-25[b]	-7	-23[b]	-23[b]
The threshold values specified correspond to the clinically meaningful changes and was used to determine response. CFB = Change from Baseline [a] Skindex-16 for AA measures the effects of AA on a subject's health-related quality of life, with 3 domains including Emotions, Symptoms, and Functioning. Total scores range from 0 to 100, with higher scores indicating worse health-related quality of life. [b] multiplicity-controlled $p < 0.001$ upadacitinib vs placebo comparison						

More stringent SALT assessments and SALT assessments at earlier timepoints

In Period A, upadacitinib 15 mg and 30 mg showed a greater proportion of subjects achieving SALT ≤ 10 (less than or equal to 10% scalp hair loss) and SALT score of 0 (complete scalp hair recovery) vs placebo at Week 24. For SALT score of 0, responses to upadacitinib 15 mg and 30 mg were observed as early as Week 12 and 8, respectively, where a numerically greater proportion of subjects achieved SALT score of 0 compared to placebo.

Statistically significant differences in SALT score ≤ 20 were seen at week 8 with upadacitinib 15 mg and 30 mg compared to placebo. Data on SALT ≤ 20 response through week 24 are provided in Figure 13.

Figure 13. SALT ≤ 20 Response through week 24



** statistically significant vs. placebo with p ≤ 0.01
*** statistically significant vs. placebo with p ≤ 0.001

ClinRO Measure for Eyebrow and Eyelash Hair Loss

In Period A, a greater proportion of subjects among subjects with Baseline score ≥ 2 achieved ClinRO measure for eyebrow and eyelash hair loss of 0 or 1 with a ≥ 2-point improvement from Baseline at Week 24 in both the upadacitinib 15 mg and 30 mg groups vs. the placebo group.

In the overall study population, responses to upadacitinib 15 mg and 30 mg were observed as early as week 8, where numerically greater proportions of subjects with Baseline score ≥ 2 achieved the ClinRO measure for improvement in eyelash hair loss compared to placebo; for eyebrow hair loss, responses to upadacitinib 30 mg were seen as early as week 4 while responses to upadacitinib 15 mg were seen as early as week 8 (nominal P ≤ 0.05). Upadacitinib 30 mg showed numerically better results than upadacitinib 15 mg.

Skindex-16 for AA

In Period A, greater improvement from Baseline at Week 24 in Skindex-16 AA emotion and functioning domain scores were achieved in both the upadacitinib 15 mg and 30 mg treatment groups vs. the placebo group in the overall study population.

Additional Efficacy Endpoints

In Period A, a numerically greater proportion of male subjects (adult subjects and adolescent subjects with Baseline Tanner stage > 3) achieved a ClinRO measure for beard hair loss (I-ALFA) Grade of 2 or 3 with a ≥ 2-point improvement from Baseline at Week 24 among subjects with Baseline Grade < 2 in both the upadacitinib 15 mg and 30 mg groups compared to the placebo group in the overall study population (nominal P ≤ 0.05). Limited sample size in the adolescent subgroup complicates the interpretation of data for adolescents.

Ancillary analyses

Subgroup analyses

Subgroup analysis for efficacy aimed for in the protocol for Study 1 and Study 2, Period A were as follows:

· Age (≥ 12 to < 18, and ≥ 18)

· Age (≥ 12 to < 18, ≥ 18 to < 40, and ≥ 40)

· Gender (Male, Female)

· BMI (normal (< 25), overweight (≥ 25 to < 30), obese (≥ 30))

· Race (White, Asian, Black, Other)

· Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

· Geographic region (Asia, Europe, North America, Rest of the World)

· Weight (< median weight, ≥ median weight)

· CRP (< median CRP, ≥ median CRP)

· AA severity (Severe (SALT score < 95), Very Severe (SALT score ≥ 95))

· AA episode duration (< 3 years, and ≥ 3 years)

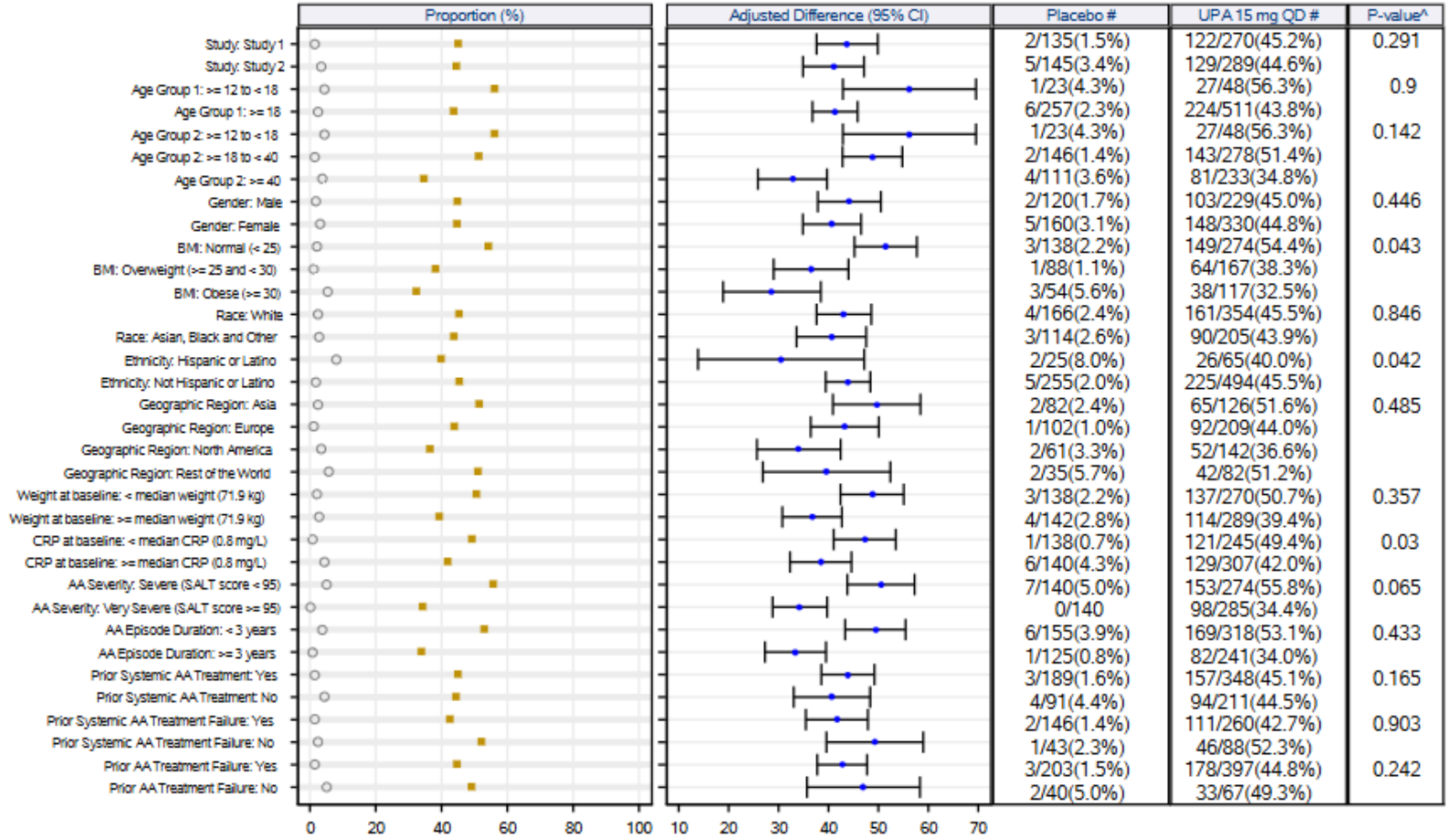
· Prior systemic AA treatment (Yes, No)

· Prior systemic AA treatment failure (Yes, No)

· Prior AA treatment failure (Yes, No)

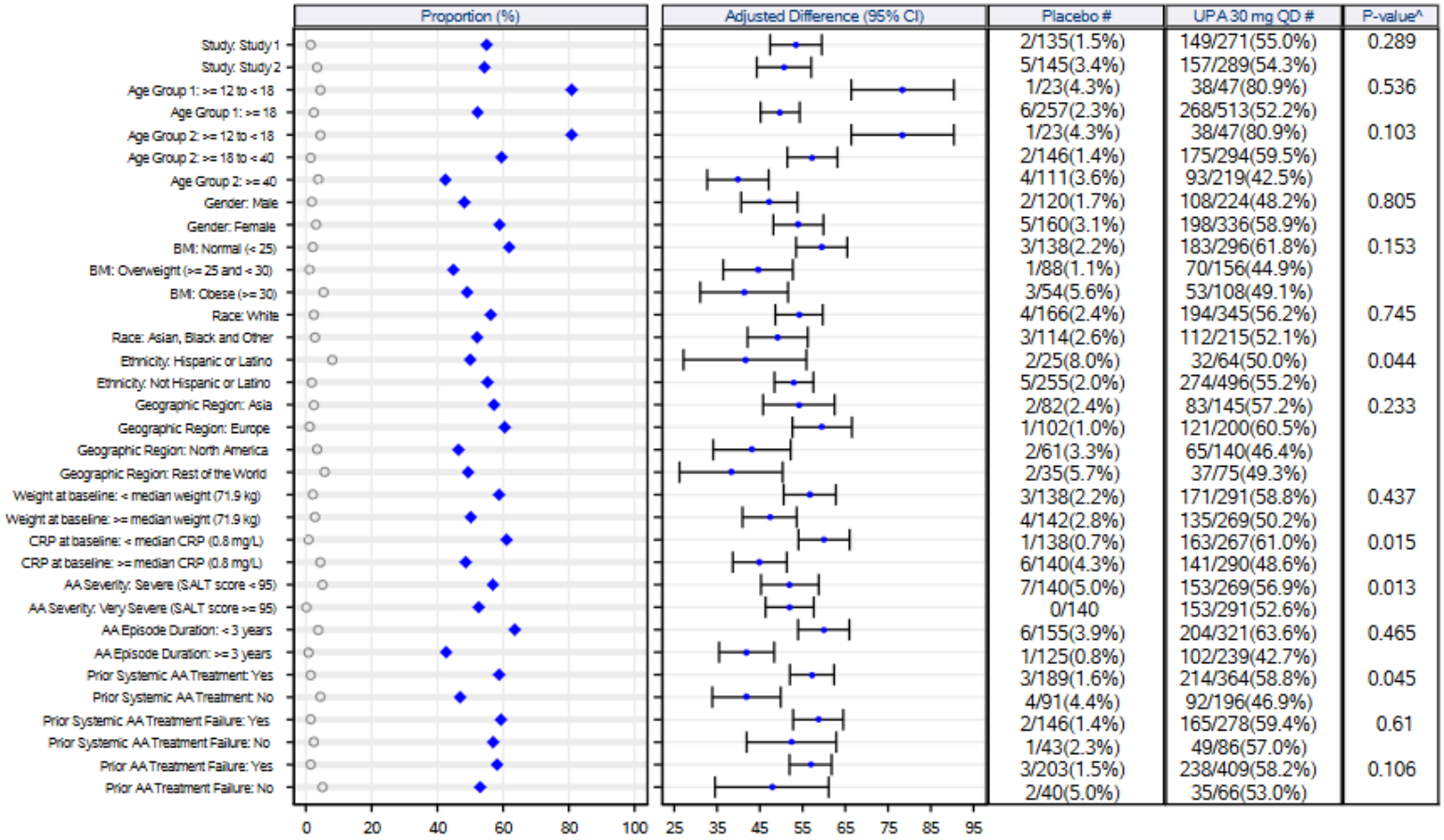
Treatment effects in all pre-specified subgroups consistently favoured both upadacitinib doses compared to placebo in the proportion of subjects achieving SALT score ≤ 20 at Week 24 with all 95% CI excluding zero Figure 14, Figure 15).

Figure 14. Proportion of Subjects Achieving SALT Score <= 20 at Week 24 by Subgroup – 15mg UPA (NRI). (ITT_A Population)



Note: NRI is non-responder imputation.
95% CI for adjusted difference is calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (Baseline SALT categories [<95 vs. ≥ 95], AA Episode Duration categories [< 3 years vs. >= 3 years]) and study (Study 1, Study 2) for the comparison of two treatment groups. The CMH model will not adjust for AA severity for the AA severity subgroups, and will not adjust for AA Episode Duration for the AA Episode Duration subgroups, and will not adjust for study for the study subgroups.
Placebo and UPA 15 mg QD represents n/N(xx.x%).
^ P-value is based on Breslow-Day test performed across subgroups.

Figure 15. Proportion of Subjects Achieving SALT Score <= 20 at Week 24 by Subgroup – 30mg UPA (NRI). (ITT_A Population)



Note: NRI is non-responder imputation.

95% CI for adjusted difference is calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (Baseline SALT categories [<95 vs. ≥ 95], AA Episode Duration categories [< 3 years vs. >= 3 years]) and study (Study 1, Study 2) for the comparison of two treatment groups. The CMH model will not adjust for AA severity for the AA severity subgroups, and will not adjust for AA Episode Duration for the AA Episode Duration subgroups, and will not adjust for study for the study subgroup

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

^ P-value is based on Breslow-Day test performed across subgroups.

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 23. Summary of Efficacy for M23-716 Study 1 – Interim Week 24 (modified)

Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Program to Evaluate Efficacy and Safety of Upadacitinib in Adult and Adolescent Subjects with Severe Alopecia Areata	
Study Identifier	M23-716 (Study 1)
Design	The study consists of a 35-day Screening Period, a 24-week placebo controlled, double-blinded treatment period (Period A); and a 28 week blinded extension treatment period (Period B). Subjects who complete Study 1 may enter into Study 3 which consists of a 108-week long-term, blinded, re-randomization period and a 30-day follow-up period. **Period A:** Subjects were randomized in a 2:2:1 to 1 of 3 double-blinded treatment groups, stratified by Baseline age groups (adults ≥ 18 years vs. adolescents ≥ 12 to < 18 years, respectively), Baseline SALT score of severe alopecia areata vs. very severe alopecia areata (SALT score 50 to < 95 vs. SALT score 95 to 100, respectively) and alopecia areata episode duration at Baseline (< 3 years vs. ≥ 3 years, respectively): • Group 1A: upadacitinib 15 mg QD • Group 2A: upadacitinib 30 mg QD • Group 3A: matching placebo QD Enrollment was closed when the adult sample size was reached. **Period B:** Subjects initially randomized to placebo (Period A) who achieved a SALT score ≤ 20 at Week 24 were to remain on placebo in Period B until they met the prespecified rescue criterion outlined in the protocol. Subjects initially randomized to placebo (Period A) with a SALT score of > 20 at Week 24 were re-randomized 1:1 after completion of the Week 24 assessments (Period A) to 1 of 2 double blinded treatment groups: • Group 1B: upadacitinib 15 mg QD • Group 2B: upadacitinib 30 mg QD Subjects originally randomized to the upadacitinib dose group in Period A continued their same treatment in Period B.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Period A: 24 weeks; Period B: 28 weeks Screening Period: 35 days Not applicable
Hypothesis	Superiority of upadacitinib vs. placebo at Week 24		
Treatments groups	Group 1A: upadacitinib 15 mg QD		Upadacitinib 15 mg QD for 24 weeks, N = 270 randomized
	Group 2A: upadacitinib 30 mg QD		Upadacitinib 30 mg QD for 24 weeks, N = 271 randomized
	Group 3A: matching placebo QD		Placebo QD for 24 weeks, N = 135 randomized
	Group 1B: upadacitinib 15 mg QD		Upadacitinib 15 mg QD for 28 weeks, N = 61 randomized
	Group 2B: upadacitinib 30 mg QD		Upadacitinib 30 mg QD for 28 weeks, N = 59 randomized
Multiplicity-Controlled Endpoints and Definitions	Primary endpoint	SALT score ≤ 20 at Week 24	Achievement of SALT score ≤ 20 at Week 24, defined as less than or equal to 20% scalp hair loss.
	Secondary	SALT score ≤ 10 at Week 24	Achievement of SALT score ≤ 10 at Week 24
	Secondary	SALT score ≤ 20 at Week 12	Achievement of SALT score ≤ 20 at Week 12
	Secondary	Eyebrow Hair Loss of 0 or 1 at Week 24; ≥ 2-point improvement	Achievement of ClinRO measure for Eyebrow Hair Loss of 0 or 1 at Week 24 with a ≥ 2-point improvement (reduction) from Baseline among subjects with Baseline score ≥ 2
	Secondary	Eyelash Hair Loss of 0 or 1 at Week 24; ≥ 2-point improvement	Achievement of ClinRO measure for Eyelash Hair Loss of 0 or 1 at Week 24 with a ≥ 2-point improvement (reduction) from Baseline among subjects with Baseline score ≥ 2
	Secondary	Scalp Hair 0 or 1; ≥ 2-point improvement (reduction) from Baseline at Week 24 among subjects with Baseline score ≥ 3	Achievement of PRO for Scalp Hair Assessment 0 or 1 with ≥ 2-point improvement (reduction) from Baseline at Week 24 among subjects with Baseline score ≥ 3
	Secondary	Baseline Change in Skindex-16 AA Emotions Domain at Week 24	Change from Baseline in Skindex-16 AA Emotions Domain scores at Week 24

	Secondary	Baseline Change in Skindex-16 AA Functioning Domain at Week 24	Change from Baseline in Skindex-16 AA Functioning Domain scores at Week 24
	Secondary	SALT score 0 at Week 24	Achievement of SALT score 0 at Week 24
	Secondary	SALT score ≤ 20 at Week 8	Achievement of SALT score ≤ 20 at Week 8

Database Lock	12 August 2025			
Results and Analysis				
Analysis Description	**Primary Analysis**			
Analysis Population and Time Point Description	The ITT populations (ITT_A: all subjects who were randomized at Baseline were used for efficacy analyses in Period A. Subjects were analyzed according to treatment as randomized in Period A.			
Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	**Treatment group**	**Placebo QD**	**Upadacitinib 15 mg QD**	**Upadacitinib 30 mg QD**
	SALT score ≤ 20 at Week 24	135 subjects 1.5 (0.0, 3.5)	270 subjects 45.2 (39.2, 51.1)	271 subjects 55.0 (49.1, 60.9)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	43.8	53.5
		95% CI	(37.6, 49.9)	(47.4, 59.5)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant
Notes	Point estimates for binary endpoints are percentages.			

Analysis Description	**Secondary Analyses**			
Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	**Treatment group**	**Placebo QD**	**Upadacitinib 15 mg QD**	**Upadacitinib 30 mg QD**
	SALT score ≤ 10 at Week 24	135 subjects 0.7 (0.0, 2.2)	270 subjects 35.2 (29.5, 40.9)	271 subjects 45.8 (39.8, 51.7)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	34.5	45.0
		95% CI	(28.8, 40.2)	(38.9, 51.0)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant
Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	SALT score ≤ 20 at Week 12	135 subjects 0.7 (0.0, 2.2)	270 subjects 20.0 (15.2, 24.8)	271 subjects 28.0 (22.7, 33.4)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	19.3	27.6
		95% CI	(14.4, 24.2)	(22.1, 33.1)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant

Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	Eyebrow Hair Loss of 0 or 1 at Week 24; ≥ 2-point improvement	87 subjects 1.1 (0.0, 3.4)	170 subjects 40.6 (33.2, 48.0)	178 subjects 61.8 (54.7, 68.9)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	39.7	60.9
		95% CI	(32.0, 47.4)	(53.6, 68.2)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant
Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	Eyelash Hair Loss of 0 or 1 at Week 24; ≥ 2-point improvement	72 subjects 5.6 (0.3, 10.8)	151 subjects 43.7 (35.8, 51.6)	145 subjects 58.6 (50.6, 66.6)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	37.9	52.7
		95% CI	(28.3, 47.5)	(43.2, 62.2)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant

Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	Scalp Hair 0 or 1 with ≥ 2-point improvement (reduction) from Baseline at Week 24 among subjects with Baseline score ≥ 3	124 subjects 2.4 (0.0, 5.1)	250 subjects 42.4 (36.3, 48.5)	251 subjects 52.6 (46.4, 58.8)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	39.8	50.3
		95% CI	(33.2, 46.4)	(43.7, 56.9)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant

Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	Baseline Change in Skindex-16 AA Emotions Domain at Week 24	135 subjects -14.564 (-19.222, -9.906)	270 subjects -30.095 (-33.357, -26.832)	271 subjects -36.209 (-39.531, -32.887)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	-15.530	-21.645
		95% CI	(-21.219, -9.842)	(-27.296, -15.994)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant

Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	Baseline Change in Skindex-16 AA Functioning Domain at Week 24	135 subjects -9.291 (-13.586, -4.997)	270 subjects -21.543 (-24.506, -18.580)	271 subjects -24.595 (-27.619, -21.570)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	-12.252	-15.303
		95% CI	(-17.429, -7.076)	(-20.485, -10.122)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant

Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	SALT score 0 at Week 24	135 subjects 0	270 subjects 14.1 (9.9, 18.2)	271 subjects 20.3 (15.5, 25.1)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	14.1	20.4
		95% CI	(10.0, 18.2)	(15.6, 25.2)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant
Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	SALT score ≤ 20 at Week 8	135 subjects 1.5 (0.0, 3.5)	270 subjects 7.0 (4.0, 10.1)	271 subjects 11.4 (7.6, 15.2)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	5.6	10.3
		95% CI	(2.0, 9.2)	(6.0, 14.6)
		P-value	0.002	< 0.001
		Statistical Significance	Significant	Significant

Table 24. Summary of Efficacy for M23-716 Study 2 – Interim Week 24 (modified)

Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Program to Evaluate Efficacy and Safety of Upadacitinib in Adult and Adolescent Subjects with Severe Alopecia Areata		
Study Identifier	M23-716 (Study 2)	
Design	The study consists of a 35-day Screening Period, a 24-week placebo controlled, double-blinded treatment period (Period A); and a 28 week blinded extension treatment period (Period B). Subjects who complete Study 2 may enter into Study 3 which consists of a 108-week long-term, blinded, re-randomization period and a 30-day follow-up period. **Period A:** Subjects were randomized in a 2:2:1 to 1 of 3 double-blinded treatment groups, stratified by Baseline age groups (adults ≥ 18 years vs. adolescents ≥ 12 to < 18 years, respectively), Baseline SALT score of severe alopecia areata vs. very severe alopecia areata (SALT score 50 to < 95 vs. SALT score 95 to 100, respectively) and alopecia areata episode duration at Baseline (< 3 years vs. ≥ 3 years, respectively): • Group 1A: upadacitinib 15 mg QD • Group 2A: upadacitinib 30 mg QD • Group 3A: matching placebo QD Enrollment was closed when the adult sample size was reached. **Period B:** Subjects initially randomized to placebo (Period A) who achieved a SALT score ≤ 20 at Week 24 were to remain on placebo in Period B until they met the prespecified rescue criterion outlined in the protocol. Subjects initially randomized to placebo (Period A) with a SALT score of > 20 at Week 24 were re-randomized 1:1 after completion of the Week 24 assessments (Period A) to 1 of 2 double blinded treatment groups: • Group 1B: upadacitinib 15 mg QD • Group 2B: upadacitinib 30 mg QD Subjects originally randomized to the upadacitinib dose group in Period A continued their same treatment in Period B.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Period A: 24 weeks; Period B: 28 weeks Screening Period: 35 days Not applicable

Hypothesis	Superiority of upadacitinib vs. placebo at Week 24		
Treatments groups	Group 1A: upadacitinib 15 mg QD		Upadacitinib 15 mg QD for 24 weeks, N = 289 randomized
	Group 2A: upadacitinib 30 mg QD		Upadacitinib 30 mg QD for 24 weeks, N = 289 randomized
	Group 3A: matching placebo QD		Placebo QD for 24 weeks, N = 145 randomized
	Group 1B: upadacitinib 15 mg QD		Upadacitinib 15 mg QD for 28 weeks, N = 68 randomized
	Group 2B: upadacitinib 30 mg QD		Upadacitinib 30 mg QD for 28 weeks, N = 67 randomized
Multiplicity-Controlled Endpoints and Definitions	Primary endpoint	SALT score ≤ 20 at Week 24	Achievement of SALT score ≤ 20 at Week 24, defined as less than or equal to 20% scalp hair loss
	Secondary	SALT score ≤ 10 at Week 24	Achievement of SALT score ≤ 10 at Week 24
	Secondary	SALT score ≤ 20 at Week 12	Achievement of SALT score ≤ 20 at Week 12
	Secondary	Eyebrow Hair Loss of 0 or 1 at Week 24; ≥ 2-point improvement	Achievement of ClinRO measure for Eyebrow Hair Loss of 0 or 1 at Week 24 with a ≥ 2-point improvement (reduction) from Baseline among subjects with Baseline score ≥ 2
	Secondary	Eyelash Hair Loss of 0 or 1 at Week 24; ≥ 2-point improvement	Achievement of ClinRO measure for Eyelash Hair Loss of 0 or 1 at Week 24 with a ≥ 2-point improvement (reduction) from Baseline among subjects with Baseline score ≥ 2
	Secondary	Scalp Hair 0 or 1; ≥ 2-point improvement (reduction) from Baseline at Week 24 among subjects with Baseline score ≥ 3	Achievement of PRO for Scalp Hair Assessment 0 or 1 with ≥ 2-point improvement (reduction) from Baseline at Week 24 among subjects with Baseline score ≥ 3
	Secondary	Baseline Change in Skindex-16 AA Emotions Domain at Week 24	Change from Baseline in Skindex-16 AA Emotions Domain scores at Week 24
	Secondary	Baseline Change in Skindex-16 AA Functioning Domain at Week 24	Change from Baseline in Skindex-16 AA Functioning Domain scores at Week 24
	Secondary	SALT score 0 at Week 24	Achievement of SALT score 0 at Week 24
	Secondary	SALT score ≤ 20 at Week 8	Achievement of SALT score ≤ 20 at Week 8

Database Lock	18 July 2025			
Results and Analysis				
Analysis Description	**Primary Analysis**			
Analysis Population and Time Point Description	The ITT populations (ITT_A: all subjects who were randomized at Baseline were used for efficacy analyses in Period A. Subjects were analyzed according to treatment as randomized in Period A.			
Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	**Treatment group**	**Placebo QD**	**Upadacitinib 15 mg QD**	**Upadacitinib 30 mg QD**
	SALT score ≤ 20 at Week 24	145 subjects 3.4 (0.5, 6.4)	289 subjects 44.6 (38.9, 50.4)	289 subjects 54.3 (48.6, 60.1)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	41.0	50.7
		95% CI	(34.9, 47.1)	(44.3, 57.0)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant
Notes	Point estimates for binary endpoints are percentages.			

Analysis Description	**Secondary Analyses**			
	Treatment group	**Placebo QD**	**Upadacitinib 15 mg QD**	**Upadacitinib 30 mg QD**
Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	SALT score ≤ 10 at Week 24	145 subjects 1.4 (0.0, 3.3)	289 subjects 36.0 (30.5, 41.5)	289 subjects 47.1 (41.3, 52.8)

Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	34.3	45.4
		95% CI	(28.9, 39.8)	(39.4, 51.4)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant
Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	SALT score ≤ 20 at Week 12	145 subjects 2.1 (0.0, 4.4)	289 subjects 21.1 (16.4, 25.8)	289 subjects 30.4 (25.1, 35.8)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	18.9	28.5
		95% CI	(13.9, 23.9)	(22.8, 34.2)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant

Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	Eyebrow Hair Loss of 0 or 1 at Week 24; ≥ 2-point improvement	93 subjects 3.2 (0.0, 6.8)	192 subjects 41.7 (34.7, 48.6)	197 subjects 58.9 (52.0, 65.8)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	38.1	55.7
		95% CI	(30.4, 45.9)	(48.0, 63.4)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant
Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	Eyelash Hair Loss of 0 or 1 at Week 24; ≥ 2-point improvement	82 subjects 3.7 (0.0, 7.7)	166 subjects 42.8 (35.2, 50.3)	158 subjects 61.4 (53.8, 69.0)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	38.9	57.7
		95% CI	(30.5, 47.4)	(49.1, 66.3)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant

Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	Scalp Hair 0 or 1 with ≥ 2-point improvement (reduction) from Baseline at Week 24 among subjects with Baseline score ≥ 3	132 subjects 4.5 (1.0, 8.1)	263 subjects 39.5 (33.6, 45.5)	260 subjects 53.1 (47.0, 59.1)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	34.4	48.3
		95% CI	(27.8, 41.0)	(41.3, 55.2)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant

Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	Baseline Change in Skindex-16 AA Emotions Domain at Week 24	145 subjects -10.353 (-14.781, -5.925)	289 subjects -31.300 (-34.505, -28.095)	289 subjects -34.372 (-37.551, -31.192)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	-20.947	-24.019
		95% CI	(-26.439, -15.455)	(-29.476, -18.561)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant

Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	Baseline Change in Skindex-16 AA Functioning Domain at Week 24	145 subjects -7.039 (-10.916, -3.163)	289 subjects -22.511 (-25.266, -19.755)	289 subjects -23.380 (-26.180, -20.579)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	-15.471	-16.340
		95% CI	(-20.223, -10.720)	(-21.094, -11.586)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant

Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	SALT score 0 at Week 24	145 subjects 0.7 (0.0, 2.0)	289 subjects 13.1 (9.3, 17.0)	289 subjects 22.5 (17.7, 27.3)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	12.2	21.8
		95% CI	(8.4, 16.1)	(16.8, 26.7)
		P-value	< 0.001	< 0.001
		Statistical Significance	Significant	Significant
Descriptive statistics and estimate variability (all numbers in parentheses indicate 95% CI)	SALT score ≤ 20 at Week 8	145 subjects 2.1 (0.0, 4.4)	289 subjects 8.7 (5.4, 11.9)	289 subjects 12.1 (8.3, 15.9)
Effect estimate per comparison		Comparison groups	Upadacitinib 15 mg QD Vs Placebo	Upadacitinib 30 mg QD Vs Placebo
		Difference	6.4	10.1
		95% CI	(2.6, 10.3)	(5.8, 14.4)
		P-value	0.001	< 0.001
		Statistical Significance	Significant	Significant

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Clinical program and study design

The AA clinical development program includes four Phase 3 studies (Study 1, Study 2, Study 3, and Study 4), all under a single protocol (M23-716), and 1 additional Phase 3 study (Study M24-600). This application provides efficacy data from the Primary Analysis of M23-716 Study 1 and Study 2. Study 1 and Study 2 are considered the main studies and described in further detail below. These are replicate, pivotal, randomized, double-blind, placebo-controlled studies in adults and adolescents. Overall, the design of Study 1 and Study 2 is acceptable.

No separate dose-response study was performed in the AA population. However, based on the experience of upadacitinib in other indications, combined with its well-characterized safety profile, the 15 and 30 mg doses seem appropriate to be studied in the Phase 3 AA program. As PK seems comparable across different indications and age groups, suggesting that adolescent and adult subjects with AA would have similar plasma exposures, the MAH's approach to study the same doses in adolescents and adults is considered acceptable.

This application provides a primary analysis of M23-716 Study 1 and Study 2 and includes efficacy data through Week 24 (Period A) and cumulative data through Period B (up to 52 weeks) using a data cutoff date of 08 July 2025 (Study 1) and 13 June 2025 (Study 2). Data on treatment extension until 52 weeks is important in assessment of the overall long-term efficacy. The MAH has agreed to submit the CSRs for Study 1 and Study 2 Period B, Study 3, and Study 4 in Q1 2029.

The MAH did not address how long it is recommended to continue treatment once a stable response has been achieved. However, this information could be added to the Product Information once long-term data are finalized and assessed.

Sufficient efficacy data has been submitted for Study 1 and 2, Period A, which corresponds to 24 weeks of treatment. The SmPC, section 4.2, was revised to reflect this: *"Efficacy data are available for 24 weeks of treatment. The benefit-risk of treatment should be re-assessed at regular intervals on an individual basis."*

Patient population

Eligible adult or adolescent subjects who were at least 12 years and less than 64 years old with severe AA were randomized in a 2:2:1 ratio to 1 of 3 treatment groups: upadacitinib 15 mg QD (N = 559), upadacitinib 30 mg QD (N = 560), or matching placebo QD (N=280). Overall, the inclusion/exclusion criteria are representative of the targeted population (patients with severe AA defined as SALT score $\geq$ 50). In the indication of the SmPC, it is referred to section 5.1 to make the definition of severe AA clearer. In the SmPC, section 5.1 it is clarified that the definition of severe AA is at least 50% scalp hair loss as measured by the Severity of Alopecia Tool (SALT).

The Phase 3 studies M23-716 Study 1 and Study 2 are not part of the agreed PIP, even though adolescent participants are included. This is because the MAH previously informed PDCO that the adolescent indication would not be based on data from these studies. One of the concerns regarding PIP Study 2 (a clinical study in children from 6-18 years of age), raised by the PDCO, was that as AA is a benign disease, other treatments (including topical) with a better safety profile should be used before initiating systemic treatment with upadacitinib. In Study 1 and Study 2, prior AA treatment was not an inclusion criterion. In the clinical setting, it is generally assumed that the majority of adults and adolescents will have undergone an alternative treatment prior to the initiation of JAK-inhibitors. The

Rapporteur considers that the baseline demographic in Study 1 and 2 reflects this matter, i.e., the majority of patients included in the studies had prior AA treatment.

Another recommendation from the PDCO regarding PIP Study 2, was that only adolescents with documented psychological impact from AA should be enrolled. The program was also recommended to be designed to show a positive effect with this regard. In Study 1 and Study 2, psychological impact from AA was not an inclusion criterion. Although the Rapporteur considers the concern raised by the PDCO valid, the lack of this inclusion criterion is accepted. In clinical practice, it is presumed that only adolescents impacted by their AA will receive treatment.

Treatments

Concomitant systemic corticosteroids for non-AA reasons if medically necessary was allowed for up to 2 consecutive weeks. Additionally, topical corticosteroids or topical calcineurin inhibitors for conditions other than AA were also permitted. This is further discussed in the section `Concomitant therapy´ below.

Endpoints and outcomes

The primary endpoint of Study 1 and Study 2 was the achievement of SALT score ≤ 20 at Week 24, defined as less than or equal to 20% scalp hair loss. The SALT score is often used in clinical practice and scientific research to measure the severity of AA disease.[13] It has been used for previous AA programs. The primary endpoint is accepted in adults and adolescents.

The AA studies included several multiplicity-controlled secondary endpoints, e.g. more stringent SALT assessments and SALT assessments at earlier timepoints. Other key secondary endpoints included ClinRO Measure for Eyebrow Hair Loss, ClinRO Measure for Eyelash Hair Loss, and Skindex-16 for AA. These endpoints have been used in other AA programs. The validation data in adults have been considered scarce for some of these endpoints, but acceptable. Some of the secondary endpoints have not been validated in adolescents and are therefore considered supportive.

A greater improvement from Baseline at week 24 in Skindex-16 AA emotion and functioning domain scores was achieved in both upadacitinib groups compared to the placebo group in the overall study population.

The 'ClinRo for Beard Hair Loss' was included as a non-type-1-error-controlled secondary endpoint, but it has not been used in previous clinical studies. To validate 'ClinRo for Beard Hair Loss', the MAH interviewed 9 dermatologists with experience in treating AA. The dermatologists all agreed that 'ClinRo for Beard Hair Loss' was interpretable. They were also of the opinion that an improvement of 1 or 2 points on the 4-point scale would be clinically meaningful. The psychometric properties of the scale (that is, test-retest validation, inter-rater reliability, construct validity, and responsiveness to change) were evaluated in a pooled analysis of their two pivotal trials. These results suggested adequate validity and reliability (data not shown in this report).

Ideally, the MAH would have validated the scale prior to its inclusion as a secondary endpoint. However, requiring pre-validation does not seem reasonable, since 'ClinRo for Beard Hair Loss' is the addition of one item to the previously established ClinRo scale, which contains similar items for other parts of the body (eye lashes, for example). Therefore, this scale was accepted as sufficiently validated.

Sample size

Both studies randomised substantially more than the target number of 600 patients: 676 patients in study 1 and 723 in study 2. However, the efficacy results were highly statistically significant, so there was no concern that the studies had overrecruited to obtain smaller p-values.

Statistical considerations

The two trials were identical in design but conducted at different sites, so they can be considered independent.

The protocol amendments were minor and do not affect the interpretation of the efficacy results.

The trials were stratified for 3 factors. Only 2 of these factors were adjusted for in the primary analysis. Although adjusting for all randomisation factors is typically recommended, adjusting for only some of the factors is acceptable if it is pre-specified.

The type-1-error was adequately controlled across several secondary endpoints and the two upadacitinib dose groups.

Intercurrent events

In both studies, no patients were reported to have used a confounding medication, so this intercurrent event had no impact on the efficacy analyses.

Premature treatment discontinuations were handled using a composite strategy (non-response imputation). This strategy is typically discouraged because treatment discontinuations do not necessarily reflect a treatment failure. Furthermore, a composite strategy is only conservative if treatment discontinuations are more common in the active-treatment arms than in the placebo arms, which was the case in study 2 but not in study 1. A treatment policy strategy is typically preferable. In the current trials, however, a treatment-policy strategy would have yielded similar results because all patients in Study 1 and nearly all patients in Study 2 who discontinued treatment also discontinued follow up, so they would have been imputed as non-responders anyway due to missing data.

Missing data

Missing data were handled using non-response imputation for binary endpoints (including the primary endpoint) and multiple imputation (assuming missing at random) for continuous endpoints. These methods are appropriate, and sensitivity analyses are needed due to the small amount of missing data.

Efficacy data and additional analyses

Participant flow and numbers analysed

A total of 1399 subjects (including 118 adolescents) with severe AA were enrolled, and 1397 subjects (including 118 adolescents) received at least 1 dose of study drug in Period A. A total of 1320 subjects (117 adolescents) completed the study drug in Period A.

In total, 77 subjects (5.5%) discontinued the study drug in Period A. Across treatment groups in Period A, the most frequent reason for study drug discontinuation was withdrawal from treatment by subject. The overall rate of discontinuations in Period A is considered low.

Patient Demographics and Baseline Disease Characteristics

Overall, subject demographics and baseline disease characteristics are considered representative of the target population with severe AA. Additionally, subject demographics and baseline disease characteristics were comparable between the different treatment groups in the Phase 3 studies.

Most patients were of white race, female, and with a normal BMI. The mean age was 36 years (approximately 14 years in the adolescent population). Mean weight in the adolescent population was approximately 60 kg. The number of adolescents with lower weight is assumed to be small. PK data are considered crucial for enabling the extrapolation of efficacy data to this group of adolescents.

In the subgroup of adolescents, the spread of some baseline disease characteristics was slightly greater (e.g., for Skindex-16 AA Functioning Domain scores). Given that the adolescents represent a smaller subgroup, this is expected and it is not possible to draw any major conclusions from this.

Prior AA Therapy

83.8% of the total population (95.8% for adolescents) in Study 1 and Study 2 had prior AA medication and 64.4% (79.7% for adolescents) had prior AA systemic medication. This is considered to reflect the target population, where it is generally assumed that the majority of patients will have undergone an alternative treatment prior to the initiation of JAK-inhibitors.

Concomitant therapy

Concomitant therapies for the treatment of alopecia areata were not allowed. This is reflected in the SmPC, section 5.1.

The overall use of concomitant medications assessed to have a possible impact on efficacy during Study 1 and Study 2, Period A is considered comparable across different treatment groups. The use of concomitant medications does not suggest a significant impact on the efficacy results.

Outcomes and estimation

The **primary endpoint**, achievement of SALT score ≤ 20 at Week 24, defined as less than or equal to 20% scalp hair loss, was met ($p<0.001$) in both upadacitinib treatment groups (15 mg and 30 mg) in both Study 1 and Study 2. The results in primary outcome of both studies were quite similar. Adolescents showed a numerically better treatment effect than the overall study population. Please refer to the section `Ancillary analyses´ below for further discussion on the adolescent subgroup.

A greater proportion of subjects achieved the primary endpoint of SALT ≤ 20 at week 24 in both the upadacitinib 15 mg (45.2 % in Study 1, 44.6 % in Study 2) and 30 mg (55.0% in Study 1, 54.3% in Study 2) groups vs. the placebo group (1.5% in Study 1, 3.4% in Study 2).

As explained above, patients were not followed up after premature treatment discontinuation, and this intercurrent event was handled using a composite strategy (non-response imputation). Only a few other patients had missing data in the primary analysis (2 patients in Study 1, 3 patients in Study 2). Sensitivity analyses, including the use of multiple imputation and a tipping-point analysis, showed consistent results with the primary approach with nominal p-values ≤ 0.001 for the two upadacitinib dose groups vs placebo.

Overall, the key multiplicity-controlled **secondary endpoints** are supporting the effectiveness of upadacitinib in treatment of AA. Generally, the proportions of patients achieving the secondary endpoints measured at week 24 were larger for the high-dose upadacitinib compared to the low-dose upadacitinib and placebo.

In Period A, upadacitinib showed a greater proportion of subjects achieving SALT ≤ 10 at week 24 for both the 15 mg and 30 mg doses vs placebo. Proportions of patients achieving SALT 0 at week 24 were also larger for the upadacitinib groups compared to placebo groups in Study 1 and Study 2.

The proportion of patients achieving a SALT score ≤ 20 from week 8 onwards showed a gradual increase over time, with a notable differentiation between the low-dose and high-dose groups, up to week 24. The SALT assessments at earlier timepoints overall suggest a relatively early onset of treatment benefit.

A greater proportion of subjects among subjects achieved the ClinRO measure for eyebrow and eyelash hair loss at week 24 in both the upadacitinib 15 mg and 30 mg groups vs. the placebo group.

In Period A, a greater proportion of subjects achieved a PRO for scalp hair assessment at week 24 in both the upadacitinib 15 mg and 30 mg groups vs. the placebo group in the overall study population (statistically significant results). Although the results are indicating recovery from a patient perspective, the endpoint is considered to be of limited added clinical value in the SmPC. To enhance clarity and readability of the SmPC, the PRO for scalp hair assessment was removed.

A greater improvement from Baseline at week 24 in Skindex-16 AA emotion and functioning domain scores was achieved in both upadacitinib groups compared to the placebo group in the overall study population.

Additional efficacy results beyond week 24 were submitted. The proportion of subjects achieving a SALT score of ≤ 20 appears to be sustained or improved. However, the efficacy results in Period B should be interpreted with caution as < 25% of subjects have either completed Period B or discontinued the study in Period B as of the data cutoff. Results beyond week 40 should also be interpreted with caution due to protocol-mandated subject discontinuation and rescue treatment starting at Week 40.

Achievement of ClinRO measure for Beard Hair Loss (I-ALFA) Grade of 2 or 3 with ≥ 2-point improvement from Baseline to Week 24 among subjects with Baseline Grade < 2 was a secondary endpoint, but it was not type-1-error controlled. Such an improvement was achieved by 26.9% and 36.8% of subjects with the upadacitinib 15 mg dose and by 42.5% and 41.7% of subjects with the upadacitinib 30 mg dose compared to 0% and 2.3% of subjects on placebo in Study 1 and Study 2, respectively. Despite the lack of Type 1 error control, the results were considered sufficiently convincing and clinically relevant for inclusion in the SmPC.

Ancillary analyses (with a particular emphasis on adolescents)

A subgroup analysis was conducted to assess the proportion of subjects achieving a SALT score of ≤20 at Week 24. The analysis included various subgroups based on age, gender, BMI, and other factors. Results consistently favored both upadacitinib doses over placebo, with all 95% confidence intervals excluding zero, indicating consistency in efficacy across subgroups. Notably, the 30 mg dose appeared to show higher efficacy than the 15 mg dose, particularly in patients with very severe AA, but these results are only descriptive.

Adolescents showed a numerically better treatment effect (SALT score of ≤20 at week 24) than the overall study population, which is reassuring. Generally, the same tendency was noted in the proportion of adolescents achieving the secondary endpoints SALT score of ≤10 at week 24, SALT score of ≤20 at week 8 and SALT score of ≤20 at week 12. Overall, it is considered that treatment effects at Week 24 in the subgroup of adolescents 12 to less than 18 years of age were consistent with the results observed in the overall study population.

For PIP Study 2, the PDCO recommended that mean change in the Children's Dermatology Life Quality Index at 24 weeks should be assessed as a secondary endpoint. The MAH agreed with this. In Study 1 and Study 2, this endpoint was not included. However, Skindex-16 AA scores improved significantly in both upadacitinib groups vs. placebo in the overall study population. Generally, adolescents receiving upadacitinib 30 mg showed numerically slightly better responses on Skindex-16 AA emotion domain scores than the overall study population, whereas adolescents receiving upadacitinib 15 mg had scores consistent with the overall study population. This is reassuring, but as previously stated, these results are only considered supportive.

The disease mechanism of alopecia areata is considered to be similar between adults and adolescents, with no substantial evidence to support significant differences. There are some differences in baseline characteristics between adults and adolescents in Study 1 and Study 2. However, the baseline characteristics are considered to be reasonably similar. In the context of the overall assessment of efficacy in the adolescent population, it is therefore considered that efficacy data, including data on psychological impact from AA, can be extrapolated from the adult AA population.

2.4.4. Conclusions on the clinical efficacy

The study population is considered to be largely representative of the target population with severe AA.

The primary endpoint, achievement of SALT score ≤20 at week 24, was met ($p<0.001$) in both upadacitinib treatment groups (15 mg and 30 mg) in Study 1 and Study 2. The results in primary outcome of both studies were quite similar.

Overall, the key multiplicity-controlled secondary endpoints support the effectiveness of upadacitinib in the treatment of severe alopecia areata in adults and adolescents 12 years and older.

Adolescents showed a numerically better treatment effect (SALT score of ≤20 at week 24) than the overall study population. However, as subgroup results were not type-1-error controlled, they are not statistically compelling and therefore considered supportive. The disease mechanism of alopecia areata is regarded to be similar between adults and adolescents, with no substantial evidence to support significant differences. Furthermore, the baseline characteristics in Study 1 and Study 2 are viewed as being reasonably similar between adults and adolescents. In the context of the overall assessment of efficacy in the adolescent population, it is therefore considered that efficacy data, including data on psychological impact from AA, can be extrapolated from the adult AA population.

Data on treatment extension up to 52 weeks is important in assessment of the overall long-term efficacy. The MAH has agreed to submit the CSRs for Study 1 and Study 2 Period B, Study 3, and Study 4 in Q1 2029. These Category 3 studies are expected to further characterise efficacy beyond 24 weeks.

2.5. Clinical safety

Introduction

The safety data submitted in support of the current variation is derived from 2 ongoing phase 3 studies, M23-716 Study 1 and Study 2. Study 1 and Study 2 are replicate, pivotal, global, randomized, double blind, placebo-controlled, multi-centre studies in adults and adolescents. Refer to the efficacy part for a detailed description of the study design.

An independent, external DMC was established for periodic review of unblinded safety data and to alert AbbVie to possible safety concerns related to the conduct of the study to ensure subject safety.

An independent external committee of physician experts in cardiovascular (CV) adjudication was utilized to assess potential CV, cerebrovascular, embolic, and thrombotic AEs. Additionally, an independent committee of physician experts in gastroenterology was utilized to assess and adjudicate potential gastrointestinal (GI) perforation events.

Analysis sets

Data is presented as integrated safety data from M23-716 Study 1 and Study 2 (Table 25). Longer-term integrated safety data (up to 52 weeks) are presented through the data cutoff dates of 08 July 2025 for M23-716 Study 1 and 13 June 2025 for M23-716 Study 2.

Additionally, a review of upadacitinib adolescent safety data from ongoing atopic dermatitis (AD) Phase 3 Studies M16-045, M16-047, and M18-891 (data cutoff 15 August 2024) is included as supportive data.

Table 25. Integrated Safety Analysis Sets

Analysis Set	Safety Objectives/Analyses	Pooled Studies	Summarized Treatment Group(s)
PBO-controlled 24-week Safety Analysis Set (ISS_24WK)	• Primary safety analysis set • Summary of safety of UPA vs. PBO during the 24-week PBO-controlled period (Period A of Study 1 and Study 2)	M23-716 Study 1 and Study 2	• PBO • UPA 15 mg QD • UPA 30 mg QD
All Treated 52-week Safety Analysis Set (ISS_52WK)	• Longer-term safety for Study 1 and Study 2 (up to 52 weeks) • Summary of safety of UPA during the 52-week treatment period (Period A and Period B) of Study 1 and Study 2	M23-716 Study 1 and Study 2	• PBO • UPA 15 mg QD • UPA 30 mg QD • Any UPA 15 mg QD • Any UPA 30 mg QD • Any UPA

Note: The PBO, UPA 15 mg QD, and UPA 30 mg QD groups include subjects who were initially randomized in Period A to the respective treatment. The "Any" UPA groups include subjects who received at least 1 dose of the respective UPA treatment.

All Treated 52-week Safety Analysis Set

The placebo, UPA 15 mg, and UPA 30 mg groups are based on subjects with continuous exposure on the respective treatment and dose. Open-label and rescue treatment exposure for UPA 15 mg and UPA 30 mg are included as long as there was no dose change. Exposure on UPA for subjects that first received placebo in Period A is not included in the continuous dose groups. For subjects that switched UPA doses from UPA 15 mg to UPA 30 mg, only the respective time on dose before the switch is included. Subjects with long-term exposure to placebo in Period B will be included in the continuous dose group for placebo. If a subject receiving placebo in Period A receives open-label (OL) rescue UPA in Period B, the exposure on placebo is counted until the switch to UPA.

The any upadacitinib 15 mg, any upadacitinib 30 mg, and any upadacitinib groups contain subjects who received any dose of UPA 15 mg, UPA 30 mg, or UPA overall respectively, during the 52-week

period (Period A and/or Period B) including rescue OL treatment with upadacitinib 30 mg. Subjects who received placebo in Period A and UPA in Period B are counted in the any upadacitinib groups.

Patient exposure

Table 26. Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (PBO-controlled 24-week Safety Analysis Set, Overall and Adolescents)

	Overall				Adolescents			
Duration	PBO (N = 280) n (%)	UPA 15 mg QD (N = 557) n (%)	UPA 30 mg QD (N = 560) n (%)	Total UPA (N = 1117) n (%)	PBO (N = 23) n (%)	UPA 15 mg QD (N = 48) n (%)	UPA 30 mg QD (N = 47) n (%)	Total UPA (N = 95) n (%)
≥ 1 dose	280 (100)	557 (100)	560 (100)	1117 (100)	23 (100)	48 (100)	47 (100)	95 (100)
≥ 4 weeks	278 (99.3)	554 (99.5)	554 (98.9)	1108 (99.2)	23 (100)	48 (100)	47 (100)	95 (100)
≥ 8 weeks	273 (97.5)	544 (97.7)	545 (97.3)	1089 (97.5)	23 (100)	47 (97.9)	47 (100)	94 (98.9)
≥ 12 weeks	272 (97.1)	538 (96.6)	538 (96.1)	1076 (96.3)	23 (100)	47 (97.9)	47 (100)	94 (98.9)
≥ 16 weeks	269 (96.1)	536 (96.2)	534 (95.4)	1070 (95.8)	23 (100)	47 (97.9)	47 (100)	94 (98.9)
≥ 20 weeks	269 (96.1)	533 (95.7)	530 (94.6)	1063 (95.2)	23 (100)	47 (97.9)	47 (100)	94 (98.9)
≥ 24 weeks	206 (73.6)	404 (72.5)	397 (70.9)	801 (71.7)	13 (56.5)	32 (66.7)	33 (70.2)	65 (68.4)
Mean duration (weeks)	23.5	23.4	23.3	23.4	23.9	23.6	24.1	23.8
Mean duration (patient-years)	0.5	0.4	0.4	0.4	0.5	0.5	0.5	0.5

Cross reference: ISS Table 2.3__1.1.1, Table 2.3__1.1.2

Table 27. Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (All Treated 52-week Safety Analysis Set, Overall)

	Overall					
Duration	PBO (N = 280) n (%)	UPA 15 mg QD (N = 557) n (%)	UPA 30 mg QD (N = 560) n (%)	Any UPA 15 mg QD (N = 686) n (%)	Any UPA 30 mg QD (N = 719) n (%)	Any UPA (N = 1372) n (%)
≥ 1 dose	280 (100)	557 (100)	560 (100)	686 (100)	719 (100)	1372 (100)
≥ 4 weeks	278 (99.3)	554 (99.5)	554 (98.9)	669 (97.5)	699 (97.2)	1338 (97.5)
≥ 8 weeks	273 (97.5)	544 (97.7)	545 (97.3)	635 (92.6)	661 (91.9)	1271 (92.6)
≥ 12 weeks	272 (97.1)	538 (96.6)	538 (96.1)	614 (89.5)	631 (87.8)	1230 (89.7)
≥ 16 weeks	269 (96.1)	536 (96.2)	534 (95.4)	591 (86.2)	599 (83.3)	1194 (87.0)
≥ 20 weeks	269 (96.1)	533 (95.7)	531 (94.8)	569 (82.9)	583 (81.1)	1164 (84.8)
≥ 24 weeks	208 (74.3)	530 (95.2)	527 (94.1)	554 (80.8)	566 (78.7)	1131 (82.4)
≥ 40 weeks	4 (1.4)	264 (47.4)	264 (47.1)	264 (38.5)	264 (36.7)	531 (38.7)
≥ 52 weeks	1 (0.4)	78 (14.0)	82 (14.6)	78 (11.4)	82 (11.4)	169 (12.3)
Mean duration (weeks)	24.0	38.4	38.3	33.9	33.1	34.3
Mean duration (patient-years)	0.5	0.7	0.7	0.6	0.6	0.7

Note: The PBO, UPA 15 mg QD, and UPA 30 mg QD groups include subjects who were initially randomized in Period A to the respective treatment. The "Any" UPA groups include subjects who received at least 1 dose of the respective UPA treatment.

Cross reference: ISS Table 2.3__2.1.1

Table 28. Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (All Treated 52-week Safety Analysis Set, Adolescents)

	Adolescents					
Duration	PBO (N = 23) n (%)	UPA 15 mg QD (N = 48) n (%)	UPA 30 mg QD (N = 47) n (%)	Any UPA 15 mg QD (N = 62) n (%)	Any UPA 30 mg QD (N = 57) n (%)	Any UPA (N = 117) n (%)
≥ 1 dose	23 (100)	48 (100)	47 (100)	62 (100)	57 (100)	117 (100)
≥ 4 weeks	23 (100)	48 (100)	47 (100)	61 (98.4)	55 (96.5)	115 (98.3)
≥ 8 weeks	23 (100)	47 (97.9)	47 (100)	58 (93.5)	54 (94.7)	112 (95.7)
≥ 12 weeks	23 (100)	47 (97.9)	47 (100)	56 (90.3)	54 (94.7)	110 (94.0)
≥ 16 weeks	23 (100)	47 (97.9)	47 (100)	53 (85.5)	52 (91.2)	105 (89.7)
≥ 20 weeks	23 (100)	47 (97.9)	47 (100)	52 (83.9)	51 (89.5)	103 (88.0)
≥ 24 weeks	14 (60.9)	47 (97.9)	47 (100)	52 (83.9)	51 (89.5)	103 (88.0)
≥ 40 weeks	1 (4.3)	25 (52.1)	28 (59.6)	25 (40.3)	28 (49.1)	54 (46.2)
≥ 52 weeks	0	9 (18.8)	8 (17.0)	9 (14.5)	8 (14.0)	17 (14.5)
Mean duration (weeks)	24.8	39.9	41.7	34.5	37.4	36.5
Mean duration (patient-years)	0.5	0.8	0.8	0.7	0.7	0.7

Note: The PBO, UPA 15 mg QD, and UPA 30 mg QD groups include subjects who were initially randomized in Period A to the respective treatment. The "Any" UPA groups include subjects who received at least 1 dose of the respective UPA treatment.

Cross reference: ISS Table 2.3 2.1.2

Adverse events

Table 29. Overview of Number and Percentage of Subjects with TEAEs and All Deaths (PBO-controlled 24-week Safety Analysis Set, Overall and Adolescents)

	Overall			Adolescents		
	PBO (N = 280) n (%)	UPA 15 mg QD (N = 557) n (%)	UPA 30 mg QD (N = 560) n (%)	PBO (N = 23) n (%)	UPA 15 mg QD (N = 48) n (%)	UPA 30 mg QD (N = 47) n (%)
Any TEAE	160 (57.1)	349 (62.7)	376 (67.1)	12 (52.2)	31 (64.6)	31 (66.0)
Any TEAE with reasonable possibility of being related to study drug according to the investigator	72 (25.7)	196 (35.2)	236 (42.1)	5 (21.7)	15 (31.3)	18 (38.3)
Any severe TEAE	7 (2.5)	33 (5.9)	29 (5.2)	1 (4.3)	1 (2.1)	1 (2.1)
Any serious TEAE	1 (0.4)	9 (1.6)	13 (2.3)	1 (4.3)	0	0
Any TEAE leading to discontinuation of study drug	0	5 (0.9)	8 (1.4)	0	1 (2.1)	0
All deaths	0	0	0	0	0	0

Cross reference: ISS Table 2.4 1.1.1, Table 2.4 1.7.1

Table 30. Overview of TEAEs and All Deaths Per 100 PY During Administration of Upadacitinib (All Treated 52-week Safety Analysis Set, Overall and Adolescents)

	Overall			Adolescents		
	Any UPA 15 mg QD (N = 686) (PY = 445.1)	Any UPA 30 mg QD (N = 719) (PY = 456.7)	Any UPA (N = 1372) (PY = 901.8)	Any UPA 15 mg QD (N = 62) (PY = 41.0)	Any UPA 30 mg QD (N = 57) (PY = 40.9)	Any UPA (N = 117) (PY = 81.9)
EAER	**E (E/100 PY)**			**E (E/100 PY)**		
Any TEAE	1422 (319.5)	1572 (344.2)	2994 (332.0)	136 (331.7)	165 (403.6)	301 (367.6)
Any TEAE with reasonable possibility of being related to study drug according to the investigator	658 (147.8)	806 (176.5)	1464 (162.3)	62 (151.2)	70 (171.2)	132 (161.2)
Any severe TEAE	59 (13.3)	69 (15.1)	128 (14.2)	4 (9.8)	5 (12.2)	9 (11.0)
Any serious TEAE	15 (3.4)	31 (6.8)	46 (5.1)	0	2 (4.9)	2 (2.4)
Any TEAE leading to discontinuation of study drug	9 (2.0)	17 (3.7)	26 (2.9)	1 (2.4)	0	1 (1.2)
EAIR	**n/PY (n/100 PY)**			**n/PY (n/100 PY)**		
All deaths	0/445.1	0/456.7	0/901.8	0/41.0	0/40.9	0/81.9

Cross reference: ISS Table 2.4 2.1.2.1, Table 2.4 2.7.2.1

Common TEAEs

Table 31. Summary of Most Frequent (≥2% Subjects in Any Treatment Group) TEAEs by Decreasing Frequency in the UPA 30 mg QD Group (PBO-controlled 24-week Safety Analysis Set, Overall)

MedDRA 27.1 Preferred Term	PBO (N = 280) n (%)	UPA 15 mg QD (N = 557) n (%)	UPA 30 mg QD (N = 560) n (%)
Any TEAE	160 (57.1)	349 (62.7)	376 (67.1)
Acne	10 (3.6)	65 (11.7)	91 (16.3)
Upper respiratory tract infection	33 (11.8)	53 (9.5)	74 (13.2)
Nasopharyngitis	26 (9.3)	67 (12.0)	67 (12.0)
Blood creatine phosphokinase increased	11 (3.9)	29 (5.2)	37 (6.6)
Folliculitis	5 (1.8)	17 (3.1)	23 (4.1)
Headache	12 (4.3)	27 (4.8)	23 (4.1)
Influenza	9 (3.2)	15 (2.7)	20 (3.6)
Oral herpes	4 (1.4)	13 (2.3)	17 (3.0)
Gastroenteritis	4 (1.4)	11 (2.0)	14 (2.5)
Neutrophil count decreased	1 (0.4)	5 (0.9)	13 (2.3)
Alanine aminotransferase increased	3 (1.1)	12 (2.2)	12 (2.1)
COVID-19	5 (1.8)	9 (1.6)	12 (2.1)
Cough	4 (1.4)	17 (3.1)	11 (2.0)
Diarrhoea	5 (1.8)	4 (0.7)	11 (2.0)
Oropharyngeal pain	8 (2.9)	12 (2.2)	11 (2.0)
Urinary tract infection	5 (1.8)	13 (2.3)	10 (1.8)
Pyrexia	5 (1.8)	13 (2.3)	8 (1.4)
Fatigue	5 (1.8)	13 (2.3)	7 (1.3)
Sinusitis	7 (2.5)	6 (1.1)	5 (0.9)

Cross reference: ISS Table 2.4 1.3.7

Table 32. Summary of Most Frequent (≥5% Adolescents in Any Treatment Group) TEAEs by Decreasing Frequency in the UPA 30 mg QD Group (PBO-controlled 24-week Safety Analysis Set, Adolescents)

MedDRA 27.1 Preferred Term	PBO (N = 23) n (%)	UPA 15 mg QD (N = 48) n (%)	UPA 30 mg QD (N = 47) n (%)
Any TEAE	12 (52.2)	31 (64.6)	31 (66.0)
Upper respiratory tract infection	2 (8.7)	8 (16.7)	13 (27.7)
Acne	0	10 (20.8)	12 (25.5)
Nasopharyngitis	3 (13.0)	9 (18.8)	5 (10.6)
Blood creatine phosphokinase increased	0	1 (2.1)	3 (6.4)
Cough	0	2 (4.2)	3 (6.4)
Folliculitis	0	1 (2.1)	3 (6.4)
Oropharyngeal pain	2 (8.7)	0	1 (2.1)

Cross reference: ISS Table 2.4__1.10.7

Table 33. Summary of Most Frequent (≥2 Events per 100 PY in the Any UPA 15 QD or Any UPA 30 mg QD Groups) TEAEs by Decreasing Frequency in the Any UPA Group (All Treated

52-week Safety Analysis Set, Overall)

MedDRA 27.1 Preferred Term	Any UPA 15 mg QD (N = 686) (PYs = 445.1) Events (E/100 PYs)	Any UPA 30 mg QD (N = 719) (PYs = 456.7) Events (E/100 PYs)	Any UPA (N = 1372) (PYs = 901.8) Events (E/100 PYs)
Any TEAE	1422 (319.5)	1572 (344.2)	2994 (332.0)
Nasopharyngitis	155 (34.8)	114 (25.0)	269 (29.8)
Upper respiratory tract infection	99 (22.2)	160 (35.0)	259 (28.7)
Acne	91 (20.4)	113 (24.7)	204 (22.6)
Blood creatine phosphokinase increased	59 (13.3)	71 (15.5)	130 (14.4)
Headache	42 (9.4)	39 (8.5)	81 (9.0)
Oral herpes	32 (7.2)	39 (8.5)	71 (7.9)
Folliculitis	29 (6.5)	38 (8.3)	67 (7.4)
Influenza	23 (5.2)	29 (6.3)	52 (5.8)
Urinary tract infection	29 (6.5)	18 (3.9)	47 (5.2)
Gastroenteritis	21 (4.7)	25 (5.5)	46 (5.1)
Alanine aminotransferase increased	17 (3.8)	21 (4.6)	38 (4.2)
Oropharyngeal pain	20 (4.5)	16 (3.5)	36 (4.0)
Neutrophil count decreased	9 (2.0)	26 (5.7)	35 (3.9)
Weight increased	13 (2.9)	19 (4.2)	32 (3.5)
Pyrexia	18 (4.0)	14 (3.1)	32 (3.5)
Cough	20 (4.5)	11 (2.4)	31 (3.4)
Diarrhoea	7 (1.6)	23 (5.0)	30 (3.3)
Fatigue	19 (4.3)	11 (2.4)	30 (3.3)
COVID-19	14 (3.1)	14 (3.1)	28 (3.1)
Aspartate aminotransferase increased	7 (1.6)	19 (4.2)	26 (2.9)
Herpes zoster	8 (1.8)	18 (3.9)	26 (2.9)
Bronchitis	13 (2.9)	9 (2.0)	22 (2.4)
Pruritus	6 (1.3)	15 (3.3)	21 (2.3)
Herpes simplex	9 (2.0)	12 (2.6)	21 (2.3)
Neutropenia	10 (2.2)	11 (2.4)	21 (2.3)
Viral upper respiratory tract infection	3 (0.7)	15 (3.3)	18 (2.0)
White blood cell count decreased	6 (1.3)	12 (2.6)	18 (2.0)
Pharyngitis	7 (1.6)	11 (2.4)	18 (2.0)
Nausea	9 (2.0)	9 (2.0)	18 (2.0)
Hypertension	10 (2.2)	8 (1.8)	18 (2.0)
Sinusitis	11 (2.5)	7 (1.5)	18 (2.0)
Vomiting	9 (2.0)	8 (1.8)	17 (1.9)
Hypercholesterolaemia	5 (1.1)	10 (2.2)	15 (1.7)
Arthralgia	9 (2.0)	4 (0.9)	13 (1.4)
Back Pain	11 (2.5)	2 (0.4)	13 (1.4)

Cross reference: ISS Table 2.4 2.3.14.1

Table 34. Summary of Most Frequent (≥5 Events per 100 PY in the Any UPA 15 QD or Any UPA 30 mg QD Groups) TEAEs in Adolescents by Decreasing Frequency in the Any UPA Group (All Treated 52-week Safety Analysis Set, Adolescents)

MedDRA 27.1 Preferred Term	Any UPA 15 mg QD (N = 62) (PYs = 41.0) Events (E/100 PYs)	Any UPA 30 mg QD (N = 57) (PYs = 40.9) Events (E/100 PYs)	Any UPA (N = 117) (PYs = 81.9) Events (E/100 PYs)
Any TEAE	136 (331.7)	165 (403.6)	301 (367.6)
Upper respiratory tract infection	16 (39.0)	31 (75.8)	47 (57.4)
Nasopharyngitis	27 (65.8)	9 (22.0)	36 (44.0)
Acne	17 (41.5)	12 (29.4)	29 (35.4)
Folliculitis	3 (7.3)	5 (12.2)	8 (9.8)
Gastroenteritis	5 (12.2)	3 (7.3)	8 (9.8)
Blood creatine phosphokinase increased	2 (4.9)	6 (14.7)	8 (9.8)
Headache	4 (9.8)	4 (9.8)	8 (9.8)
Diarrhoea	3 (7.3)	4 (9.8)	7 (8.5)
Abdominal pain	2 (4.9)	3 (7.3)	5 (6.1)
Cough	2 (4.9)	3 (7.3)	5 (6.1)
Pyrexia	0	4 (9.8)	4 (4.9)
Pharyngitis	1 (2.4)	3 (7.3)	4 (4.9)
Viral upper respiratory tract infection	1 (2.4)	3 (7.3)	4 (4.9)
Weight increased	0	4 (9.8)	4 (4.9)
Vomiting	0	3 (7.3)	3 (3.7)
Rash	3 (7.3)	0	3 (3.7)

Cross reference: ISS Table 2.4 2.10.14.1

Treatment-related TEAEs

Table 35. Summary of Most Frequent (≥2% Subjects in Any Treatment Group) TEAEs with a Reasonable Possibility of Relationship to Study Drug by Decreasing Frequency in the UPA 30 mg QD Group (PBO-controlled 24-week Safety Analysis Set, Overall)

MedDRA 27.1 Preferred Term	Placebo (N = 280) n (%)	UPA 15 mg QD (N = 557) n (%)	UPA 30 mg QD (N = 560) n (%)
Any TEAE	72 (25.7)	195 (35.0)	236 (42.1)
Acne	9 (3.2)	58 (10.4)	81 (14.5)
Upper respiratory tract infection	15 (5.4)	21 (3.8)	33 (5.9)
Nasopharyngitis	7 (2.5)	21 (3.8)	26 (4.6)
Blood creatine phosphokinase increased	6 (2.1)	20 (3.6)	25 (4.5)
Folliculitis	4 (1.4)	15 (2.7)	21 (3.8)
Neutrophil count decreased	1 (0.4)	5 (0.9)	13 (2.3)
Headache	5 (1.8)	18 (3.2)	13 (2.3)
Oral herpes	1 (0.4)	10 (1.8)	11 (2.0)

Cross reference: ISS Table 2.4__1.3.4

Table 36. Summary of Most Frequent (≥5% Adolescents in Any Treatment Group) TEAEs with a Reasonable Possibility of Relationship to Study Drug by Decreasing Frequency in the UPA 30 mg QD Group (PBO-controlled 24-week Safety Analysis Set, Adolescents)

MedDRA 27.1 Preferred Term	Placebo (N = 23) n (%)	UPA 15 mg QD (N = 48) n (%)	UPA 30 mg QD (N = 47) n (%)
Any TEAE	5 (21.7)	15 (31.3)	18 (38.3)
Acne	0	8 (16.7)	10 (21.3)
Upper respiratory tract infection	2 (8.7)	1 (2.1)	5 (10.6)
Folliculitis	0	0	3 (6.4)
Nasopharyngitis	1 (4.3)	3 (6.3)	1 (2.1)

Cross reference: ISS Table 2.4__1.10.4

Table 37. Summary of Most Frequent (≥2 Events per 100 PY in the Any UPA 15 QD or Any UPA 30 mg QD Groups) TEAEs with a Reasonable Possibility of Relationship to Study Drug by Decreasing Frequency in the Any UPA Group (All Treated 52-week Safety Analysis Set, Overall)

MedDRA 27.1 Preferred Term	Any UPA 15 mg QD (N = 686) (PYs = 445.1) Events (E/100 PYs)	Any UPA 30 mg QD (N = 719) (PYs = 456.7) Events (E/100 PYs)	Any UPA (N = 1372) (PYs = 901.8) Events (E/100 PYs)
Any TEAE	657 (147.6)	806 (176.5)	1463 (162.2)
Acne	82 (18.4)	101 (22.1)	183 (20.3)
Upper respiratory tract infection	41 (9.2)	72 (15.8)	113 (12.5)
Nasopharyngitis	58 (13.0)	47 (10.3)	105 (11.6)
Blood creatine phosphokinase increased	39 (8.8)	50 (10.9)	89 (9.9)
Folliculitis	25 (5.6)	34 (7.4)	59 (6.5)
Oral herpes	29 (6.5)	25 (5.5)	54 (6.0)
Headache	22 (4.9)	23 (5.0)	45 (5.0)
Neutrophil count decreased	8 (1.8)	25 (5.5)	33 (3.7)
Alanine aminotransferase increased	12 (2.7)	15 (3.3)	27 (3.0)
Urinary tract infection	15 (3.4)	10 (2.2)	25 (2.8)
Herpes zoster	8 (1.8)	16 (3.5)	24 (2.7)
Weight increased	9 (2.0)	14 (3.1)	23 (2.6)
Oropharyngeal pain	12 (2.7)	8 (1.8)	20 (2.2)
Neutropenia	8 (1.8)	11 (2.4)	19 (2.1)
Herpes simplex	6 (1.3)	11 (2.4)	17 (1.9)
Aspartate aminotransferase increased	4 (0.9)	13 (2.8)	17 (1.9)
White blood cell count decreased	5 (1.1)	12 (2.6)	17 (1.9)
Fatigue	10 (2.2)	5 (1.1)	15 (1.7)
Pruritus	3 (0.7)	12 (2.6)	15 (1.7)
Cough	9 (2.0)	3 (0.7)	12 (1.3)

Cross reference: ISS Table 2.4 2.3.11.1

Table 38. Summary of Most Frequent (≥5 Events per 100 PY in the Any UPA 15 QD or Any UPA 30 mg QD Groups) TEAE PTs with a Reasonable Possibility of Relationship to Study Drug by Decreasing Frequency in the Any UPA Group (All Treated 52-week Safety Analysis Set, Adolescents)

MedDRA 27.1 Preferred Term	Any UPA 15 mg QD (N = 62) (PYs = 41.0) Events (E/100 PYs)	Any UPA 30 mg QD (N = 57) (PYs = 40.9) Events (E/100 PYs)	Any UPA (N = 117) (PYs = 81.9) Events (E/100 PYs)
Any TEAE	62 (151.2)	70 (171.2)	132 (161.2)
Acne	14 (34.1)	10 (24.5)	24 (29.3)
Nasopharyngitis	18 (43.9)	4 (9.8)	22 (26.9)
Upper respiratory tract infection	4 (9.8)	12 (29.4)	16 (19.5)
Folliculitis	2 (4.9)	5 (12.2)	7 (8.5)
Blood creatine phosphokinase increased	1 (2.4)	4 (9.8)	5 (6.1)
Gastroenteritis	3 (7.3)	1 (2.4)	4 (4.9)
Pyrexia	0	3 (7.3)	3 (3.7)
Weight increased	0	3 (7.3)	3 (3.7)

Cross reference: ISS Table 2.4__2.10.11.1

TEAEs by severity

PBO-controlled 24-week Safety Analysis Set

Overall, the most frequent severe TEAEs by PT (occurring in ≥2 subjects in any treatment group) were blood CPK increased, upper respiratory tract infection, neutropenia, herpes zoster, alanine aminotransferase increase, aspartate aminotransferase increased, and neutrophil count decreased.

In the **adolescent** subgroup, by PT, no severe TEAE was reported in more than 1 subject in any treatment group.

All Treated 52-week Safety Analysis Set

Overall, the most frequent severe TEAE by PT among subjects receiving any upadacitinib (≥2 E/100 PY in the any upadacitinib group) was blood CPK increased.

In the **adolescent** subgroup, the most frequent severe TEAE by PT among adolescents receiving any upadacitinib (≥2 E/100 PY in the Any upadacitinib group) was blood CPK increased.

Adverse drug reactions

The decision to consider an AE as an ADR was based on the level of evidence taking into account the following considerations: dose dependence, disproportionate number of reports between placebo and upadacitinib, similar trend among medically related events, temporal relationship, dechallenge/rechallenge information for relevant event reports, and biological plausibility based on mechanism of action and/or class effect.

Data for the analysis of ADRs for upadacitinib in the treatment of adults and adolescents with severe AA were derived from the integrated placebo-controlled periods (Period A) of M23-716 Studies 1 and 2. All TEAEs were examined regardless of the investigator causality assessment. Statistical thresholds for

ADR determination were based on the sample sizes and study designs of M23-716 Studies 1 and 2. Pooled data for these 2 replicate studies were considered sufficiently large to be informative for ADR determination.

For the determination of ADRs, PTs were grouped into medical concepts (grouped terms) for acne, abdominal pain, anemia, bone fracture, herpes simplex, herpes zoster, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, lymphopenia, neutropenia, pneumonia, rash, upper respiratory tract infection (URTI), and gastrointestinal infection.

PTs and grouped terms were considered for ADR determination if they occurred in at least 2% of subjects in either the upadacitinib 15 mg group OR in the upadacitinib 30 mg group and if there was a delta of at least 1% to placebo. AEs observed at a frequency of <2% of subjects that were deemed events of medical importance (serious, fatal/life threatening) or AEs of special interest were also reviewed.

The rationale of this ADR strategy was the following:

The AD population is used as a reference given it represents a similar patient population in another dermatologic indication. In the original AD submission, ADRs were assessed using placebo-controlled data to identify AEs in ≥1% of subjects in the upadacitinib 15 mg OR upadacitinib 30 mg groups AND greater than placebo with a sample size of 899 subjects in the upadacitinib 15 mg group, 906 subjects in the upadacitinib 30 mg group, and 902 subjects in the placebo group (approximately 1:1:1 ratio). In the AA clinical program, the sample size includes 559 subjects in the upadacitinib 15 mg group, 560 subjects in the upadacitinib 30 mg group, and 280 subjects in the placebo group (approximately 2:2:1 ratio), representing almost half the sample size of the original AD submission. In order to achieve a similar threshold in number of subjects as AD, a rate of ≥2% (≥12 subjects) in the upadacitinib 15 mg group OR in the upadacitinib 30 mg group AND ≥1% delta to placebo was used in the ADR assessment for the AA clinical program.

The PTs and grouped terms that were identified as ADRs following the assessment process described above are shown in Table 39. All PTs and grouped terms that were identified as ADRs have been previously identified as ADRs for upadacitinib treatment, and the frequency of occurrence of these ADRs seen in the AA clinical program is consistent with frequency categories in the upadacitinib SmPC. No new ADRs for upadacitinib treatment were identified in the AA clinical program.

Table 39. Number and Percentage of Subjects with Treatment-Emergent Adverse Events with Adverse Drug Reaction Grouped Terms (Placebo-Controlled 24-Week Safety Analysis Set)

MedDRA 27.1 Preferred Term[a]	PBO (N = 280) n (%)	UPA 15 mg QD (N = 557) n (%)	UPA 30 mg QD (N = 560) n (%)
Alanine aminotransferase increased	3 (1.1)	12 (2.2)	12 (2.1)
Blood creatine phosphokinase increased	11 (3.9)	29 (5.2)	37 (6.6)
Cough	4 (1.4)	17 (3.1)	11 (2.0)
Folliculitis	5 (1.8)	17 (3.1)	23 (4.1)
Grouped Term: Neutropenia	1 (0.4)	12 (2.2)	22 (3.9)
Grouped Term: URTI	67 (23.9)	134 (24.1)	156 (27.9)
Grouped Term: Acne	10 (3.6)	69 (12.4)	94 (16.8)
Grouped Term: Herpes Simplex	5 (1.8)	21 (3.8)	22 (3.9)

a. Adverse Drug Reactions that are not designated grouped terms are individual preferred terms.

Cross reference: ISS Table 2.4 1.5.13

Serious adverse event/deaths/other significant events

Deaths

There were no deaths reported in the PBO-controlled 24-week Safety Analysis Set or All Treated 52-week Safety Analysis Set through the data cutoff dates.

SAEs

Table 40. Number and Percentage of Subjects with Treatment-Emergent Serious Adverse Events by Primary MedDRA SOC and PT (Placebo-Controlled 24-Week Safety Analysis Set, Overall and Adolescents)

	Overall			Adolescents		
MedDRA 27.1 System Organ Class Preferred Term	PBO (N = 280) n (%)	UPA 15 mg QD (N = 557) n (%)	UPA 30 mg QD (N = 560) n (%)	PBO (N = 23) n (%)	UPA 15 mg QD (N = 48) n (%)	UPA 30 mg QD (N = 47) n (%)
Any SAE	1 (0.4)	9 (1.6)	13 (2.3)	1 (4.3)	0	0
Blood and lymphatic system disorders	0	0	1 (0.2)	0	0	0
Sickle cell anaemia with crisis	0	0	1 (0.2)	0	0	0
Eye disorders	0	1 (0.2)	0	0	0	0
Retinal detachment	0	1 (0.2)	0	0	0	0
Gastrointestinal disorders	0	1 (0.2)	0	0	0	0
Large intestinal obstruction	0	1 (0.2)	0	0	0	0
Infections and infestations	1 (0.4)	2 (0.4)	4 (0.7)	1 (4.3)	0	0
Appendicitis	0	1 (0.2)	0	0	0	0
COVID-19 pneumonia	0	0	1 (0.2)	0	0	0
Cellulitis staphylococcal	0	1 (0.2)	0	0	0	0
Erysipelas	0	0	1 (0.2)	0	0	0
Pneumonia	1 (0.4)	0	0	1 (4.3)	0	0
Pneumonia streptococcal	0	0	1 (0.2)	0	0	0
Urinary tract infection	0	0	1 (0.2)	0	0	0
Injury, poisoning and procedural complications	0	2 (0.4)	3 (0.5)	0	0	0
Foot fracture	0	1 (0.2)	0	0	0	0
Hand fracture	0	1 (0.2)	0	0	0	0
Joint dislocation	0	0	1 (0.2)	0	0	0
Limb traumatic amputation	0	0	1 (0.2)	0	0	0
Tendon rupture	0	0	1 (0.2)	0	0	0
Investigations	0	0	1 (0.2)	0	0	0
Alanine aminotransferase increased	0	0	1 (0.2)	0	0	0
Aspartate aminotransferase increased	0	0	1 (0.2)	0	0	0
Blood creatine phosphokinase increased	0	0	1 (0.2)	0	0	0
Blood creatinine increased	0	0	1 (0.2)	0	0	0
Musculoskeletal and connective tissue disorders	0	1 (0.2)	1 (0.2)	0	0	0
Finger deformity	0	1 (0.2)	0	0	0	0
Rhabdomyolysis	0	0	1 (0.2)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (0.4)	0	0	0	0
Benign breast neoplasm	0	1 (0.2)	0	0	0	0
Breast cancer	0	1 (0.2)	0	0	0	0
Nervous system disorders	0	0	1 (0.2)	0	0	0
Vertebral artery stenosis	0	0	1 (0.2)	0	0	0
Psychiatric disorders	0	1 (0.2)	2 (0.4)	0	0	0
Delusional disorder, unspecified type	0	0	1 (0.2)	0	0	0
Depression	0	1 (0.2)	0	0	0	0
Drug abuse	0	0	1 (0.2)	0	0	0
Reproductive system and breast disorders	0	1 (0.2)	0	0	0	0
Ovarian mass	0	1 (0.2)	0	0	0	0
Surgical and medical procedures	0	0	1 (0.2)	0	0	0
Abortion induced	0	0	1 (0.2)	0	0	0

Cross reference: ISS Table 2.4__1.3.2, Table 2.4__1.10.2

Table 41. Treatment-Emergent Serious Adverse Events in EAER per 100 PYs by Primary MedDRA SOC and PT (All Treated 52-week Safety Analysis Set, Overall and Adolescents)

	Overall			Adolescents		
MedDRA 27.1 System Organ Class Preferred Term	Any UPA 15 mg QD (N = 686) (PYs = 445.1) Events (E/100 PYs)	Any UPA 30 mg QD (N = 719) (PYs = 456.7) Events (E/100 PYs)	Any UPA (N = 1372) (PYs = 901.8) Events (E/100 PYs)	Any UPA 15 mg QD (N = 62) (PYs = 41.0) Events (E/100 PYs)	Any UPA 30 mg QD (N = 57) (PYs = 40.9) Events (E/100 PYs)	Any UPA (N = 117) (PYs = 81.9) Events (E/100 PYs)
Any SAE	15 (3.4)	31 (6.8)	46 (5.1)	0	2 (4.9)	2 (2.4)
Blood and lymphatic system disorders	0	1 (0.2)	1 (0.1)	0	0	0
Sickle cell anaemia with crisis	0	1 (0.2)	1 (0.1)	0	0	0
Cardiac disorders	1 (0.2)	2 (0.4)	3 (0.3)	0	0	0
Acute myocardial infarction	0	1 (0.2)	1 (0.1)	0	0	0
Atrial fibrillation	1 (0.2)	0	1 (0.1)	0	0	0
Left ventricular failure	0	1 (0.2)	1 (0.1)	0	0	0
Eye disorders	1 (0.2)	1 (0.2)	2 (0.2)	0	0	0
Macular hole	0	1 (0.2)	1 (0.1)	0	0	0
Retinal detachment	1 (0.2)	0	1 (0.1)	0	0	0
Gastrointestinal disorders	2 (0.4)	0	2 (0.2)	0	0	0
Large intestinal obstruction	2 (0.4)	0	2 (0.2)	0	0	0
Hepatobiliary disorders	0	1 (0.2)	1 (0.1)	0	0	0
Hepatic function abnormal	0	1 (0.2)	1 (0.1)	0	0	0
Infections and infestations	3 (0.7)	6 (1.3)	9 (1.0)	0	0	0
Appendicitis	1 (0.2)	0	1 (0.1)	0	0	0
COVID-19 pneumonia	0	1 (0.2)	1 (0.1)	0	0	0
Cellulitis staphylococcal	1 (0.2)	0	1 (0.1)	0	0	0
Erysipelas	0	1 (0.2)	1 (0.1)	0	0	0
Herpes zoster	1 (0.2)	0	1 (0.1)	0	0	0
Pneumonia	0	1 (0.2)	1 (0.1)	0	0	0
Pneumonia streptococcal	0	2 (0.4)	2 (0.2)	0	0	0
Urinary tract infection	0	1 (0.2)	1 (0.1)	0	0	0
Injury, poisoning and procedural complications	2 (0.4)	4 (0.9)	6 (0.7)	0	0	0
Foot fracture	1 (0.2)	0	1 (0.1)	0	0	0
Hand fracture	1 (0.2)	0	1 (0.1)	0	0	0
Joint dislocation	0	1 (0.2)	1 (0.1)	0	0	0
Limb traumatic amputation	0	1 (0.2)	1 (0.1)	0	0	0
Spinal fracture	0	1 (0.2)	1 (0.1)	0	0	0
Tendon rupture	0	1 (0.2)	1 (0.1)	0	0	0

Investigations	0	5 (1.1)	5 (0.6)	0	0	0
Alanine aminotransferase increased	0	1 (0.2)	1 (0.1)	0	0	0
Aspartate aminotransferase increased	0	1 (0.2)	1 (0.1)	0	0	0
Blood creatine phosphokinase increased	0	2 (0.4)	2 (0.2)	0	0	0
Blood creatinine increased	0	1 (0.2)	1 (0.1)	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.2)	3 (0.7)	4 (0.4)	0	0	0
Finger deformity	1 (0.2)	0	1 (0.1)	0	0	0
Foot deformity	0	1 (0.2)	1 (0.1)	0	0	0
Rhabdomyolysis	0	2 (0.4)	2 (0.2)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.7)	0	3 (0.3)	0	0	0
Benign breast neoplasm	1 (0.2)	0	1 (0.1)	0	0	0
Breast cancer	1 (0.2)	0	1 (0.1)	0	0	0
Uterine leiomyoma	1 (0.2)	0	1 (0.1)	0	0	0
Nervous system disorders	0	1 (0.2)	1 (0.1)	0	0	0
Vertebral artery stenosis	0	1 (0.2)	1 (0.1)	0	0	0
Pregnancy, puerperium and perinatal conditions	0	1 (0.2)	1 (0.1)	0	0	0
Anembryonic gestation	0	1 (0.2)	1 (0.1)	0	0	0
Psychiatric disorders	1 (0.2)	4 (0.9)	5 (0.6)	0	2 (4.9)	2 (2.4)
Affective disorder	0	1 (0.2)	1 (0.1)	0	1 (2.4)	1 (1.2)
Behaviour disorder	0	1 (0.2)	1 (0.1)	0	1 (2.4)	1 (1.2)
Delusional disorder, unspecified type	0	1 (0.2)	1 (0.1)	0	0	0
Depression	1 (0.2)	0	1 (0.1)	0	0	0
Drug abuse	0	1 (0.2)	1 (0.1)	0	0	0
Reproductive system and breast disorders	1 (0.2)	0	1 (0.1)	0	0	0
Ovarian mass	1 (0.2)	0	1 (0.1)	0	0	0
Surgical and medical procedures	0	2 (0.4)	2 (0.2)	0	0	0
Abortion induced	0	1 (0.2)	1 (0.1)	0	0	0
Selective abortion	0	1 (0.2)	1 (0.1)	0	0	0

Cross reference: ISS Table 2.4 2.3.9.1, Table 2.4 2.10.9.1

PBO-controlled 24-week Safety Analysis Set

Overall, the percentages of subjects with SAEs were higher in the upadacitinib groups than the placebo group. By PT, all SAEs were reported in 1 subject each.

The SAE of vertebral artery stenosis was reported in an adult subject in the upadacitinib 30 mg group ; the SAE, which led to discontinuation of study drug, was considered by the investigator to have no reasonable possibility of being related to study drug.

The SAE of drug abuse was reported in an adult subject in the upadacitinib 30 mg group with medical history of alcohol abuse and smoking who was admitted to the hospital for drug abuse; study drug was interrupted, and ultimately withdrawn, and the event was considered by the investigator to have no reasonable possibility of being related to study drug.

In the **adolescent** subgroup, 1 SAE (PT of pneumonia) was reported in the placebo group; no SAEs were reported in the upadacitinib groups.

All Treated 52-week Safety Analysis Set

Overall, the EAER of SAEs was higher in the any upadacitinib 30 mg group than the any upadacitinib 15 mg group. By PT, all SAEs among subjects receiving any upadacitinib were reported in 1 subject each, with the exception of blood CPK increased and rhabdomyolysis, which were reported in 2 subjects each.

One adult subject with a medical history of hypothyroidism developed SAEs of acute myocardial infarction and left ventricular failure in the postoperative period of a pre-planned surgical procedure (removal of an anastomosis after surgical treatment of hallux valgus). Study drug was discontinued, and the events were considered by the investigator to have no reasonable possibility of being related to study drug. The external cardiac adjudication committee did not adjudicate these 2 events as MACE.

In the **adolescent** subgroup, a total of 2 SAEs were reported among adolescents receiving any upadacitinib (PTs of affective disorder and behaviour disorder, both reported at the same time in a adolescent subject with preexisting conditions of affective disorder and behaviour disorder.

Other significant events

Please refer to the section on discontinuation due to adverse events.

Adverse events of special interest

Table 42. Overview of Number and Percentage of Subjects with Treatment-Emergent AESI (PBO-controlled 24-week Safety Analysis Set, Overall and Adolescents)

	Overall			Adolescents		
	PBO (N = 280) n (%)	UPA 15 mg QD (N = 557) n (%)	UPA 30 mg QD (N = 560) n (%)	PBO (N = 23) n (%)	UPA 15 mg QD (N = 48) n (%)	UPA 30 mg QD (N = 47) n (%)
Serious infections	1 (0.4)	2 (0.4)	4 (0.7)	1 (4.3)	0	0
Herpes zoster	1 (0.4)	4 (0.7)	6 (1.1)	0	0	0
Malignancy	0	1 (0.2)	0	0	0	0
Malignancy excluding NMSC	0	1 (0.2)	0	0	0	0
Hepatic disorder	5 (1.8)	15 (2.7)	18 (3.2)	0	1 (2.1)	1 (2.1)
Anemia	1 (0.4)	4 (0.7)	4 (0.7)	0	0	0
Neutropenia	1 (0.4)	12 (2.2)	22 (3.9)	0	0	2 (4.3)
Lymphopenia	1 (0.4)	1 (0.2)	5 (0.9)	0	0	0
CPK elevation	11 (3.9)	29 (5.2)	37 (6.6)	0	1 (2.1)	3 (6.4)
Adjudicated VTE	0	1 (0.2)	0	0	0	0
Bone fractures	1 (0.4)	3 (0.5)	3 (0.5)	0	0	0
Retinal detachment	1 (0.4)	1 (0.2)	0	0	0	0

Cross reference: ISS Table 2.4 1.2.1, Table 2.4 1.8.1

Table 43. Overview of Treatment-Emergent AESI Per 100 PY (All Treated 52-week Safety Analysis Set, Overall and Adolescents)

	Overall			Adolescents		
	Any UPA 15 mg QD (N = 686) (PY = 445.1)	Any UPA 30 mg QD (N = 719) (PY = 456.7)	Any UPA (N = 1372) (PY = 901.8)	Any UPA 15 mg QD (N = 62) (PY = 41.0)	Any UPA 30 mg QD (N = 57) (PY = 40.9)	Any UPA (N = 117) (PY = 81.9)
EAER	**Events (E/100PY)**			**Events (E/100PY)**		
Serious infections	3 (0.7)	6 (1.3)	9 (1.0)	0	0	0
Herpes zoster	9 (2.0)	20 (4.4)	29 (3.2)	0	0	0
Hepatic disorder	31 (7.0)	55 (12.0)	86 (9.5)	1 (2.4)	2 (4.9)	3 (3.7)
Anemia	8 (1.8)	10 (2.2)	18 (2.0)	0	0	0
Neutropenia	19 (4.3)	38 (8.3)	57 (6.3)	1 (2.4)	3 (7.3)	4 (4.9)
Lymphopenia	4 (0.9)	12 (2.6)	16 (1.8)	0	1 (2.4)	1 (1.2)
CPK elevation	59 (13.3)	71 (15.5)	130 (14.4)	2 (4.9)	6 (14.7)	8 (9.8)
EAIR	**n/PY (n/100PY)**			**n/PY (n/100PY)**		
Malignancy	1/445.0 (0.2)	0/456.7	1/901.8 (0.1)	0/41.0	0/40.9	0/81.9
Malignancy excluding NMSC	1/445.0 (0.2)	0/456.7	1/901.8 (0.1)	0/41.0	0/40.9	0/81.9
Adjudicated VTE	1/445.1 (0.2)	0/456.7	1/901.8 (0.1)	0/41.0	0/40.9	0/81.9
Bone fractures	6/443.3 (1.4)	5/454.7 (1.1)	11/898.0 (1.2)	1/40.7 (2.5)	0/40.9	1/81.6 (1.2)
Retinal detachment	1/444.8 (0.2)	0/456.7	1/901.5 (0.1)	0/41.0	0/40.9	0/81.9

Cross reference: ISS Table 2.4__2.2.2.1, Table 2.4__2.2.2.2, Table 2.4__2.9.2.1, Table 2.4__2.9.2.2

No treatment-emergent AESIs of opportunistic infections (excluding TB and herpes zoster), NMSC, lymphoma, adjudicated GI perforations, renal dysfunction, active TB, adjudicated MACE, or serious hypersensitivity reactions were reported in M23-716 Study 1 or Study 2 (up to 52 weeks) through the data cutoff dates.

Serious infections

PBO-controlled 24-week Safety Analysis Set

Overall, the percentage of subjects with serious infections was higher in the upadacitinib 30 mg group than the upadacitinib 15 mg and placebo groups. By PT, all serious infections were reported in 1 subject each. One subject in the upadacitinib 30 mg group discontinued study drug due to a serious infection (PT of pneumonia streptococcal).

The SAE of erysipelas (infragluteal region) was reported in an adult subject with no relevant medical history and no report of preceding injury, trauma, or arthropod bite. Study drug was interrupted, and the event resolved with antibiotic treatment; the event was considered by the investigator to have a reasonable possibility of being related to study drug.

In the **adolescent** subgroup, 1 serious infection (pneumonia) was reported in the placebo group, with no serious infections reported in the upadacitinib groups.

All Treated 52-week Safety Analysis Set

Overall, the EAER of serious infections was higher in the any upadacitinib 30 mg group than the any upadacitinib 15 group. By PT, all serious infections among subjects receiving any upadacitinib were reported in 1 subject each. Among subjects receiving any upadacitinib, a total of 1 subject discontinued study drug due to a serious infection (PT of pneumonia streptococcal).

In the **adolescent** subgroup, no serious infections were reported among adolescents receiving any upadacitinib.

Herpes zoster

PBO-controlled 24-week Safety Analysis Set

Overall, the percentages of subjects with treatment-emergent events of herpes zoster were higher in the upadacitinib groups than the placebo group.

Most events of herpes zoster involved 1 or 2 dermatomes. There were no events reported of disseminated or ophthalmic herpes zoster or herpes zoster with liver or CNS involvement. All treatment emergent events of herpes zoster were nonserious; most of the events were moderate in severity, and none led to discontinuation of study drug.

One adult subject with a medical history of varicella zoster and no herpes zoster vaccination had herpes zoster affecting 4 dermatomes on the left side and experienced post-herpetic neuralgia; the events were moderate in severity and considered by the investigator to have a reasonable possibility of being related to study drug. Study drug was interrupted, and the event of herpes zoster resolved with pain medication and antiviral treatment.

One adult subject with a medical history of varicella zoster and unknown vaccination status experienced an event of herpes zoster affecting multiple dermatomes bilaterally that resolved with antiviral treatment; study drug was interrupted, and the event was considered by the investigator to have a reasonable possibility of being related to study drug.

In the **adolescent** subgroup, no treatment-emergent events of herpes zoster were reported.

All Treated 52-week Safety Analysis Set

Overall, the EAER of herpes zoster was higher in the any upadacitinib 30 mg group than the any upadacitinib 15 group.

Among subjects receiving any upadacitinib, most events of herpes zoster involved 1 or 2 dermatomes, and there were no events reported of disseminated or ophthalmic herpes zoster or herpes zoster with liver or CNS involvement. All events were nonserious, with the exception of 1 serious event of herpes zoster affecting multiple dermatomes bilaterally that occurred in an adult subject with a medical history of varicella zoster and no herpes zoster vaccination and resolved with pain medication and anti-viral treatment; study drug was interrupted, and the event was considered by the investigator to have a reasonable possibility of being related to study drug. Most events were moderate in severity and were considered by the investigator to have a reasonable possibility of being related to study drug. No events of herpes zoster led to discontinuation of study drug.

No treatment-emergent events of herpes zoster were reported among **adolescents** receiving any upadacitinib.

Most subjects had no prior history of herpes zoster or herpes zoster vaccination. In subjects with no history of herpes zoster vaccination, the EAER of herpes zoster was higher in the any upadacitinib 30 mg group than the any upadacitinib 15 mg group; no subject with a prior history of herpes zoster vaccination reported an AE of herpes zoster. In subjects with no prior history of herpes zoster, the EAER of herpes zoster was higher in the any upadacitinib 30 mg group than in the any upadacitinib 15 mg group. In subjects with a prior history of herpes zoster infection, 2 events of herpes zoster were reported in the any upadacitinib 30 mg group, with no events reported in the any upadacitinib 15 mg group.

Malignancy

In the *PBO-controlled 24-week Safety Analysis Set*, 1 treatment-emergent event of malignancy excluding NMSC (PT of breast cancer) was reported in the upadacitinib 15 mg group; no events were reported in the upadacitinib 30 mg or placebo groups. The event occurred in an adult subject with pre-existing nodules on a mammogram. The subject was diagnosed approximately 4 months after initiating study drug. The event was serious, led to study drug discontinuation, and was considered by the investigator to have a reasonable possibility of being related to study drug. A temporal association does not seem plausible given the relatively short time to onset after start of upadacitinib and long latency for induction of solid tumors such as breast cancer, noted to be approximately 16 years from onset to diagnosis (Nadler 2014).

In the *All Treated 52-week Safety Analysis Set*, a total of 1 treatment-emergent event of malignancy excluding NMSC (PT of breast cancer) was reported among subjects receiving any upadacitinib (previously described for the PBO-controlled 24 week Safety Analysis Set).

No treatment-emergent events of NMSC or lymphoma were reported in the PBO controlled 24-week Safety Analysis Set or All Treated 52-week Safety Analysis Set.

No treatment-emergent events of malignancy (including NMSC, malignancy excluding NMSC, lymphoma) were reported in **adolescents** in the PBO-controlled 24-week Safety Analysis Set or All Treated 52-week Safety Analysis Set.

Hepatic disorder

PBO-controlled 24-week Safety Analysis Set

Overall, the percentages of subjects with treatment-emergent events of hepatic disorder were higher in the upadacitinib groups than the placebo group. Transaminase elevations accounted for most of the events of hepatic disorder. Most treatment-emergent events of hepatic disorder were nonserious and did not lead to discontinuation of study drug.

In the **adolescent** subgroup, treatment-emergent events of hepatic disorder were infrequent and included 1 nonserious event of ALT increased in the upadacitinib 15 mg group and 1 nonserious event of hepatic steatosis in the upadacitinib 30 mg group:

- The event of ALT increased was reported in an adolescent subject with a medical history of anxiety and food allergy. The event of ALT increased was severe and considered by the investigator to have a reasonable possibility of being related to study drug. Study drug was discontinued, and the event resolved. Other labs remained within normal ranges. No other relevant TEAEs were reported at the time of event.
- The event of hepatic steatosis was reported in an adolescent subject with a medical history of bipolar disorder and extrapyramidal syndrome on multiple concomitant medications who also experienced TEAEs of weight increased, acne, CPK increased, AST increased, headache, peripheral oedema, hyperuricemia, and extrapyramidal disorder. The event of hepatic steatosis was mild in severity and was considered by the investigator to have no reasonable possibility of being related to study drug. The event hepatic steatosis did not result in interruption of study drug and was ongoing at the time of last observation.

All Treated 52-week Safety Analysis Set

Overall, the EAER of treatment-emergent events of hepatic disorder was higher in the any upadacitinib 30 mg group than the any upadacitinib 15 group. Transaminase elevations accounted for most of the events of hepatic disorder among subjects receiving any upadacitinib. Most events of hepatic disorder were nonserious and did not lead to discontinuation of study drug.

In the **adolescent** subgroup, treatment-emergent events of hepatic disorder among adolescent subjects receiving any upadacitinib were infrequent (2 nonserious events [hepatic steatosis, AST increased] in the any upadacitinib 30 mg group and 1 nonserious event of ALT increased in the any upadacitinib 15 mg group). The events of hepatic steatosis and ALT increased are described for the PBO-controlled 24-week Safety Analysis Set. The event of AST increased was mild in severity, considered by the investigator to have a reasonable possibility of being related to study drug, and did not result in interruption of study drug.

Anaemia

PBO-controlled 24-week Safety Analysis Set

Overall, the percentages of subjects with treatment-emergent events of anemia were the same in the upadacitinib 15 mg and 30 mg groups, which were slightly higher than the placebo group. All events of anemia were mild or moderate in severity. No events of anemia were serious, and none led to discontinuation of study drug.

In the **adolescent** subgroup, no treatment-emergent events of anemia were reported.

All Treated 52-week Safety Analysis Set

Overall, the EAERs of treatment-emergent events of anemia were similar between the any upadacitinib 30 mg group and the any upadacitinib 15 group. All events of anemia were mild or moderate in severity; no event was serious, and none led to discontinuation of study drug.

No treatment-emergent events of anemia were reported among **adolescents** receiving any upadacitinib.

Neutropenia

PBO-controlled 24-week Safety Analysis Set

Overall, the percentages of subjects with treatment-emergent events of neutropenia were higher in the upadacitinib groups than the placebo group, exhibiting a dose dependence. Most events of neutropenia were mild or moderate in severity. No event of neutropenia was serious, and 1 event of neutropenia led to discontinuation of study drug.

In the **adolescent** subgroup, treatment-emergent events of neutropenia were only reported in the upadacitinib 30 mg group; a total of 2 adolescent subjects experienced nonserious, moderate events of neutropenia that resolved without interruption of study drug.

All Treated 52-week Safety Analysis Set

Overall, the EAER of treatment-emergent events of neutropenia was higher in the any upadacitinib 30 mg group than the any upadacitinib 15 group. Among subjects receiving any upadacitinib, most events of neutropenia were mild or moderate in severity, and no event of neutropenia was serious; a total of 2 events of neutropenia led to discontinuation of study drug.

In the **adolescent** subgroup, the EAER of treatment-emergent events of neutropenia was higher in the any upadacitinib 30 mg group than the any upadacitinib 15 mg group; all 4 events of neutropenia on upadacitinib treatment were mild or moderate and did not result in interruption of study drug.

Lymphopenia

PBO-controlled 24-week Safety Analysis Set

Overall, the percentage of subjects with treatment-emergent events of lymphopenia was higher in the upadacitinib 30 mg group than the upadacitinib 15 mg and placebo groups. Most events of lymphopenia were mild or moderate in severity. No event of lymphopenia was serious and none led to discontinuation of study drug.

In the **adolescent** subgroup, no treatment-emergent events of lymphopenia were reported.

All Treated 52-week Safety Analysis Set

Overall, the EAER of treatment-emergent events of lymphopenia was higher in the any upadacitinib 30 mg group than the any upadacitinib 15 mg group. Among subjects receiving any upadacitinib, most events of lymphopenia were mild or moderate in severity, no event was serious, and none led to discontinuation of study drug.

In the **adolescent** subgroup, a total of 1 treatment-emergent event of lymphopenia was reported among adolescents receiving any upadacitinib. The event of lymphopenia was nonserious, severe, and associated with a Grade 3 decrease in lymphocyte count; the event resolved following interruption of study drug and was considered by the investigator as having a reasonable possibility of being related to study drug.

CPK elevation

PBO-controlled 24-week Safety Analysis Set

Overall, the percentages of subjects with treatment-emergent events of CPK elevation were higher in the upadacitinib groups than the placebo group. Most events of CPK elevation were mild or moderate in severity. One event of CPK elevation was serious, and none led to discontinuation of study drug.

A total of 1 TEAE of rhabdomyolysis was reported:

- An adult subject in the upadacitinib 30 mg group experienced concurrent SAEs of rhabdomyolysis, blood CPK increased, AST increased, ALT increased, and blood creatinine increased. The subject had a relevant medical history of alcohol use (>4 drinks/week) and IV methamphetamine use prior to the event, had engaged in "severe and excessive" exercise, and was dehydrated at the time of event. Study drug was discontinued due to the SAE of rhabdomyolysis. With rehydration, the subject recovered from the above events. The investigator considered the events to have no reasonable possibility of being related to study drug and secondary to exercise, dehydration, and methamphetamine use.

In the **adolescent** subgroup, the percentage of subjects with treatment-emergent events of CPK elevation was higher in the upadacitinib 30 mg group (3 subjects [6.4%]) than the upadacitinib 15 mg group (1 subject [2.1%]), and no events were reported in the placebo group. No event of CPK elevation in adolescents was serious.

All Treated 52-week Safety Analysis Set

Overall, the EAER of treatment-emergent events of CPK elevation was higher in the any upadacitinib 30 mg group than the any upadacitinib 15 group. Among subjects receiving any upadacitinib, most treatment-emergent events of CPK elevation were mild or moderate in severity; 2 events of CPK elevation were serious, and none led to discontinuation of study drug.

A total of 2 TEAEs of rhabdomyolysis were reported among subjects receiving any upadacitinib:

- An adult subject in the upadacitinib 30 mg group experienced concurrent SAEs of rhabdomyolysis, blood CPK increased, AST increased, ALT increased, and blood creatinine increased (previously described for the PBO controlled 24-week Safety Analysis Set).
- An adult subject in the any upadacitinib 30 mg group experienced concurrent SAEs of rhabdomyolysis and hepatic function abnormal and nonserious AEs of ALT increased and blood CPK increased after exercising. The subject had a relevant medical history of alcohol use and previous nonserious TEAEs of blood CPK increased (Period A on placebo) and proteinuria (Period B). The subject was hospitalized, received IV hydration, and recovered without interruption of study drug. The investigator considered these events to have a reasonable possibility of being related to study drug; based on medical review, exercise was identified as an alternative etiology for these events.

In the **adolescent** subgroup, the EAER of treatment-emergent events of CPK elevation was higher in the any upadacitinib 30 mg group than the any upadacitinib 15 group. No event of CPK elevation in adolescents receiving any upadacitinib was serious, and no TEAE of rhabdomyolysis was reported in adolescents.

Adjudicated thrombotic events

In the *PBO-controlled 24-week Safety Analysis Set*, 1 adjudicated VTE was reported in the upadacitinib 15 mg group; no adjudicated VTE was reported in the upadacitinib 30 mg or placebo groups. The adjudicated VTE (concurrent nonserious TEAEs of venous thrombosis and pulmonary embolism) was reported in an adult subject with several risk factors. Study drug was discontinued; the TEAEs of venous thrombosis and pulmonary embolism were considered by the investigator to have no reasonable possibility of being related to study drug.

In the *All Treated 52-week Safety Analysis Set*, 1 adjudicated VTE was reported among subjects receiving any upadacitinib (previously described for the PBO controlled 24-week Safety Analysis Set).

No adjudicated VTE was reported in **adolescents** in the PBO-controlled 24-week Safety Analysis Set or All Treated 52-week Safety Analysis Set.

Bone fractures

PBO-controlled 24-week Safety Analysis Set

Overall, the percentages of subjects with treatment-emergent bone fractures were similar across treatment groups. All treatment-emergent bone fractures were due to trauma; no TEAEs of bone fracture were considered by the investigator to have a reasonable possibility of being related to study drug. All bone fractures were moderate or severe, and 2 serious bone fractures (PTs of foot fracture and hand fracture) were reported; none led to discontinuation of study drug.

In the **adolescent** subgroup, no treatment-emergent bone fractures were reported.

All Treated 52-week Safety Analysis Set

Overall, the EAIR of bone fractures was similar between the any upadacitinib 30 mg group and the any upadacitinib 15 group. All treatment-emergent bone fractures were due to trauma; no TEAEs of bone fracture were considered by the investigator to have a reasonable possibility of being related to study drug. Most bone fractures were moderate or severe, and 3 serious bone fractures (PTs of foot fracture, hand fracture, and spinal fracture) were reported; none led to discontinuation of study drug.

In the **adolescent** subgroup, a total of 1 treatment-emergent bone fracture (PT of shoulder fracture) was reported among subjects receiving any upadacitinib; the event was nonserious.

Retinal detachment

In the *PBO-controlled 24-week Safety Analysis Set*, 3 treatment-emergent events of retinal detachment were reported in the upadacitinib 15 mg (1 subject with 2 events [0.2%]) and placebo (1 subject [0.4%]) groups; no events were reported in the upadacitinib 30 mg group:

- An adult subject in the upadacitinib 15 mg group with no relevant medical history experienced an SAE of retinal detachment with a concurrent nonserious TEAE of retinal tear approximately 5 months after starting study drug. The events resolved without drug interruption. The events were considered by the investigator to have no reasonable possibility of being related to study drug.
- An adult subject in the placebo group with a medical history of myopia and presbyopia experienced a nonserious event of retinal tear, which was treated with laser treatment and resolved without drug interruption.

In the **adolescent** subgroup, no treatment-emergent events of retinal detachment were reported.

In the, a total of 2 treatment-emergent events of retinal detachment were reported among subjects receiving any upadacitinib (both events occurred in 1 (adult) subject receiving upadacitinib 15 mg, as described for the PBO-controlled 24-week Safety Analysis Set).

No treatment-emergent events of retinal detachment were reported among **adolescents** receiving any upadacitinib.

Updated data on adverse events of special interest in adolescent patients

As part of the procedure, the MAH has submitted updated safety data for adolescent patients in terms of AESIs. Data is derived from study 1 (data cut-off 14 January 2026), study 2 (data cut-off 22 December 2025) and study 3 (All Treated Long-term Safety analysis set). Exposure in the Any UPA 15 mg and Any UPA 30 mg groups was 72.0 PYs and 70.9 PYs, respectively; 79 patients in the Any UPA 15 mg group and 73 patients in the Any UPA 30 mg group had been exposed to upadacitinib for ≥18 months.

Table 44. Treatment-Emergent Adverse Events of Special Interest in Exposure-Adjusted Event Rate per 100 Patient Years by Adolescent (All Treated Long-Term Safety Analysis Set)

	Placebo (N=23) (PYs=11.5) Events (E/100 PYs)	UPA 15 mg QD (N=48) (PYs=57.7) Events (E/100 PYs)	UPA 30 mg QD (N=47) (PYs=58.5) Events (E/100 PYs)	Any UPA 15 mg QD (N=80) (PYs=72.0) Events (E/100 PYs)	Any UPA 30 mg QD (N=69) (PYs=70.9) Events (E/100 PYs)	Any UPA (N=117) (PYs=142.9) Events (E/100 PYs)
Serious infections	1 (8.7)	0	2 (3.4)	0	2 (2.8)	2 (1.4)
Opportunistic infection excluding tuberculosis and herpes zoster	0	0	0	0	0	0
Malignancy	0	0	0	0	0	0
Non-Melanoma skin cancer (NMSC)	0	0	0	0	0	0
Malignancy excluding NMSC	0	0	0	0	0	0
Lymphoma	0	0	0	0	0	0
Hepatic disorder	0	1 (1.7)	4 (6.8)	1 (1.4)	4 (5.6)	5 (3.5)
Adjudicated gastrointestinal perforations	0	0	0	0	0	0
Anemia	0	0	0	0	0	0
Neutropenia	1 (8.7)	1 (1.7)	3 (5.1)	1 (1.4)	3 (4.2)	4 (2.8)
Lymphopenia	0	0	2 (3.4)	0	2 (2.8)	2 (1.4)
Herpes zoster	0	0	0	0	0	0
Renal dysfunction	0	0	0	0	0	0
Active tuberculosis	0	0	0	0	0	0
Adjudicated MACE*	0	0	0	0	0	0
Adjudicated VTE**	0	0	0	0	0	0
Bone fractures	0	1 (1.7)	0	1 (1.4)	0	1 (0.7)
Retinal detachment	0	0	0	0	0	0
Serious hypersensitivity Reactions	0	0	0	0	0	0
Elevated CPK	0	3 (5.2)	7 (12.0)	3 (4.2)	7 (9.9)	10 (7.0)

Note: Treatment-Emergent Adverse Events for the long-term analysis set for the continuous dose and treatment groups are defined as any Adverse Events that begin or worsen on or after the first dose of study treatment in Period A, and through the minimum of 1 day prior to the date of dose or treatment switch, or 30 days after the last dose date in the last study in which the subject participated.

Treatment-Emergent Adverse Events for the long-term analysis set for the Any UPA 15 mg, Any UPA 30 mg, and Any UPA groups are defined as any Adverse Events that begin or worsen on or after initiation of UPA 15 mg, UPA 30 mg, or Any UPA overall respectively in Period A and/or Period B (whichever is earlier) including rescue or open-label Upadacitinib, and through 30 days after the last dose date in the last study in which the subject participated.

Retinal detachment includes the additional preferred term of "Proliferative vitreoretinopathy" for adolescents.

E/100 PYs = Number of events per 100 patient-years.

* Major Adverse Cardiovascular Event (MACE) defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

** Venous Thromboembolism (VTE) include deep vein thrombosis (DVT) and pulmonary embolism (PE)(fatal and non-fatal).

Summary of MAH's rationale for the proposed warnings & precautions language (Section 4.4 of the SmPC):

Class warnings, including a boxed warning, were introduced during the Article 20 procedure for JAK inhibitors used in the treatment of chronic inflammatory disorders (EMEA/H-A20/1517/C/004760/0017), state that upadacitinib should only be used if no suitable treatment alternatives are available in patients over 65 years of age, patients with cardiovascular risk factors or patients with malignancy risk factors. The MAH proposed to indicate that these limitations, regarding suitable alternatives, do not apply to patients treated for severe alopecia areata.

The MAH considered that a specific language for the AA indication should be introduced in view of the low incidence of patients with risk factors in the patient population with severe AA:

The MAH noted that large cohort studies show that patients with AA tend to be younger, with similar or lower prevalence of obesity, cardiovascular diseases, tobacco use, hypertension, dyslipidemia, diabetes, COPD, and other major risk factors, as well as similar medication use compared to those without chronic inflammatory skin conditions[14] [15]. The MAH stated that current evidence indicates that

[14] Lee H, Kim YC, Choi JW. Alopecia areata is not a risk factor for heart diseases: A 10 year retrospective cohort study. PLoS One. 2021;16(5):e0250216.
[15] Schneeweiss MC, Kim SC, Wyss R, et al. Incidence of venous thromboembolism in patients with dermatologist-diagnosed chronic inflammatory skin diseases. JAMA Dermatol. 2021;157(7):805-16.

patients with AA have a risk profile for major adverse events such as MACE and VTE that is comparable to individuals without AA [14] [15] Furthermore, the MAH noted that the overall incidence of malignancy in patients with AA is low[16] [17] [18] and possibly even lower than that in the general population[16] [19] [20] [21].

In response to the request for supplementary information, the MAH maintained its position that the current wording in SmPC section 4.4 for Rinvoq introduced after the Article 20 procedure should be modified considering the differential labelling between upadacitinib and ritlecitinib.

The MAH proposed to add the following text in section 4.4 of the SmPC: *"In the statement within the box above, suitable treatment alternatives do not include other systemic JAK inhibitors."*

To support their proposal, the MAH argued that upadacitinib data do not suggest any increased risk in comparison to ritlecitinib safety data, as summarised hereafter. Further, the MAH provided real world evidence for ritlecitinib in AA.

The following was provided to support the MAH's position that upadacitinib data do not suggest any increased risk in comparison to ritlecitinib safety data:

- indirect comparative safety data (including rates of MACE, VTE, malignancy excluding NMSC, and NMSC) of upadacitinib and ritlecitinib development programmes for alopecia areata

The MAH presented a detailed review of the available safety data for ritlecitinib and upadacitinib, including rates of MACE, VTE, malignancy excluding NMSC, and NMSC, in the ritlecitinib and upadacitinib development programmes for AA.

The MAH considered that long-term incidence rates of malignancy excluding NMSC, NMSC, MACE and VTE between ritlecitinib and upadacitinib in AA overall were low and generally similar in both development programmes with no evidence of increased risk when compared to background rates. It was noted that there were no deaths in the upadacitinib AA studies and 2 deaths on ritlecitinib in AA studies (1 occurring after study drug discontinuation secondary to an event of breast cancer on study drug).

Table 45. AEs observed in OS in the Ritlecitinib and Upadacitinib AA Development Programs

Event	Ritlecitinib All 50 mg N=1521		Any UPA 15 mg QD N=686		Any UPA 30 mg QD N=814		Any UPA QD N=1373	
	n	IR	n	IR	n	IR	n	IR
MACE	3	0.15	0	0	1	0.1	1	0.06
VTE	1	0.06	1	0.1	0	0	1	0.06
Malignancy (excluding NMSC)	7	0.37	1	0.1	1	0.1	2	0.1
NMSC	5	0.26	0	0	2	0.3	2	0.1

Ref: R-Litfulo - EPAR (EMA/357337/2023), Table 29; Upadacitinib Week 52 ISS Table 2.4_3.2.2.2

[16] George P, Jagun O, Liu Q, et al. Incidence Rates of Infections, Malignancies, Thromboembolism, and Cardiovascular Events in an Alopecia Areata Cohort from a US Claims Database. Dermatol Ther (Heidelb). 2023;13(8):1733-46.
[17] Chen CC, Chang YT, Liu HN, et al. Cancer risk in patients with alopecia areata: a nationwide population-based matched cohort study. Cancer Med. 2018;7(5):2153-9.
[18] Kridin K, Laufer-Britva R, Jimenez F, et al. Alopecia Areata and malignancies: uncertainties clarified by a large-scale population-based study. Arch Dermatol Res. 2024;316(10):678.
[19] Mostaghimi A, Qureshi S, Joyce C, et al. Reduced incidence of skin cancer in patients with alopecia areata: A retrospective cohort study. Cancer Epidemiol. 2016;41:129-31.
[20] Teulings HE, Overkamp M, Ceylan E, et al. Decreased risk of melanoma and nonmelanoma skin cancer in patients with vitiligo: a survey among 1307 patients and their partners. Br J Dermatol. 2013;168(1):162-71.
[21] Seo HM, Han SS, Kim JS. Cancer risks among patients with alopecia areata: A population-based case-control study in Korea. J Am Acad Dermatol. 2018;78(1):209-11.

- discussion on the role of the JAK isoforms:

The MAH noted the followings:

Upadacitinib is a selective JAK1 inhibitor. It preferentially inhibits signalling by JAK1 or JAK1/3, with functional selectivity over cytokine receptors that signal via JAK2 pairs. This selectivity distinguishes upadacitinib from other JAK inhibitors with different selectivity (and often broader isoform) profiles, such as baricitinib (Olumiant) (JAK1/JAK2) ritlecitinib (Litfulo) (JAK3), and tofacitinib (JAK1, JAK2, JAK3, and TYK2).

The scientific literature does not establish that any particular JAK isoform is responsible for the AEs observed in OS. On the contrary, the precise mechanism by which JAK inhibition may contribute to these events remains unknown. Multiple experts, including leading investigators for the ritlecitinib pivotal trials,[22] agree that it is not known whether JAK specificity alters the safety profile, and additional long-term data are needed to assess the risk of selective JAK3/TEC inhibition and JAKi more broadly. Literature provides, for instance, that "The exact mechanism for the reported adverse events is not understood and it is currently not known whether JAK specificity alters the safety profile."[23]

Laboratory findings

Hemoglobin

PBO-controlled 24-week Safety Analysis Set

Overall, mean hemoglobin values decreased from baseline over the first 12 weeks of upadacitinib treatment, exhibiting a dose dependence, and then trended upward at Week 24.

No Grade 3 laboratory value decreases in hemoglobin were reported in any treatment group.

All Treated 52-week Safety Analysis Set

No Grade 3 laboratory value decreases in hemoglobin were reported among subjects receiving any upadacitinib.

Neutrophils

PBO-controlled 24-week Safety Analysis Set

Overall, administration of upadacitinib was associated with small decreases in mean neutrophil count versus placebo during the treatment period.

The percentage of subjects with Grade 3 laboratory value decreases in neutrophil count was higher in the upadacitinib 30 mg group (2.0%) than the upadacitinib 15 mg group (0.9%), with none in the placebo group. No Grade 4 laboratory value decreases in neutrophil count were reported in any treatment group.

In the **adolescent** subgroup, Grade 3 laboratory value decreases in neutrophil count were only reported in the upadacitinib 30 mg group (2 subjects [4.3%]).

[22] King, B. *et al.* Integrated Safety Analysis of Ritlecitinib, an Oral JAK3/TEC Family Kinase Inhibitor, for the Treatment of Alopecia Areata from the ALLEGRO Clinical Trial Program. *Am. J. Clin. Dermatol.* **25**, 299–314 (2024).
[23] Kragstrup, T. W. *et al.* Waiting for JAK inhibitor safety data. *RMD Open* **8**, e002236 (2022).

All Treated 52-week Safety Analysis Set

Overall, the percentage of subjects with Grade 3 laboratory value decreases in neutrophil count was higher in the any upadacitinib 30 mg group (2.3%) than the any upadacitinib 15 mg group (1.1%); no Grade 4 laboratory value decreases in neutrophil count were reported.

Among subjects receiving any upadacitinib, 4 (adult) subjects experienced concurrent nonserious infections (PTs of bronchitis, nasopharyngitis, oral herpes, and upper respiratory infection, and viral upper respiratory tract infection) immediately preceding Grade 3 laboratory value decreases in neutrophil count.

In the **adolescent** subgroup, Grade 3 laboratory value decreases in neutrophil count were reported in a total of 2 adolescent subjects (1.8%) receiving any upadacitinib; none were associated with an infection.

Lymphocytes

PBO-controlled 24-week Safety Analysis Set

Overall, administration of upadacitinib was associated with initial small increases in mean lymphocyte count from baseline followed by small decreases in mean lymphocyte count to around the baseline levels with continued treatment.

Overall, the percentage of subjects with Grade 3 laboratory value decreases in lymphocyte count was similar between the upadacitinib 30 mg group (0.2%) and the upadacitinib 15 mg group (0.5%); no Grade 3 laboratory value decreases in lymphocyte count were reported in the placebo group. No Grade 4 laboratory value decreases in lymphocyte count were reported in any treatment group.

No Grade 3 or 4 laboratory value decreases in lymphocyte count were reported in **adolescents**.

All Treated 52-week Safety Analysis Set

Overall, the percentage of subjects with Grade 3 laboratory value decreases in lymphocyte count was similar between the any upadacitinib 30 mg group (0.4%) and the any upadacitinib 15 mg group (0.5%); no Grade 4 laboratory value decreases in lymphocyte count were reported.

In the **adolescent** subgroup, a total of 1 adolescent subject (0.9%) receiving any upadacitinib experienced a Grade 3 laboratory value decrease in lymphocyte count; no Grade 4 laboratory value decreases in lymphocyte count were reported in adolescent subjects.

Among subjects receiving any upadacitinib:

- 1 (adult) subject experienced a serious infection (PT of pneumonia) within 1 week prior to a Grade 3 laboratory value decrease in lymphocyte count;
- 2 (adult) subjects experienced concurrent nonserious infections (PTs of nasopharyngitis and upper respiratory tract infection) immediately preceding Grade 3 laboratory value decreases in lymphocyte count; and
- 1 (adolescent) subject experienced a nonserious infection (PT of upper respiratory tract infection) on the same day as a Grade 3 laboratory value decrease in lymphocyte count.

CPK

Table 46. Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Important Values for CPK (PBO-controlled 24-week Safety Analysis Set)

	Overall			Adolescents		
Creatine Kinase (U/L)	PBO (N = 280) n/N_OBS (%)	UPA 15 mg QD (N = 557) n/N_OBS (%)	UPA 30 mg QD (N = 560) n/N_OBS (%)	PBO (N = 23) n/N_OBS (%)	UPA 15 mg QD (N = 48) n/N_OBS (%)	UPA 30 mg QD (N = 47) n/N_OBS (%)
Grade 3	3/278 (1.1)	9/551 (1.6)	7/555 (1.3)	0/23	1/48 (2.1)	0/47
Grade 4	3/278 (1.1)	10/551 (1.8)	12/555 (2.2)	0/23	1/48 (2.1)	1/47 (2.1)
At least Grade 3	6/278 (2.2)	19/551 (3.4)	19/555 (3.4)	0/23	2/48 (4.2)	1/47 (2.1)

Cross reference: ISS Table 2.5__1.4.1, Table 2.5__1.4.2

Table 47. Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Important Values for CPK (All Treated 52-Week Safety Analysis Set)

	Overall			Adolescents		
Creatine Kinase (U/L)	Any UPA 15 mg QD (N = 686) n/N_OBS (%)	Any UPA 30 mg QD (N = 719) n/N_OBS (%)	Any UPA (N = 1372) n/N_OBS (%)	Any UPA 15 mg QD (N = 62) n/N_OBS (%)	Any UPA 30 mg QD (N = 57) n/N_OBS (%)	Any UPA (N = 117) n/N_OBS (%)
Grade 3	11/666 (1.7)	13/687 (1.9)	24/1335 (1.8)	1/60 (1.7)	0/54	1/114 (0.9)
Grade 4	14/666 (2.1)	17/687 (2.5)	31/1335 (2.3)	1/60 (1.7)	1/54 (1.9)	2/114 (1.8)
At least Grade 3	25/666 (3.8)	30/687 (4.4)	55/1335 (4.1)	2/60 (3.3)	1/54 (1.9)	3/114 (2.6)

Cross reference: ISS Table 2.5__2.4.1, Table 2.5__2.4.2

PBO-controlled 24-week Safety Analysis Set

Overall, administration of upadacitinib was associated with mean increases from baseline in CPK values during the treatment period.

Overall, Grade 3 and 4 laboratory value increases in CPK occurred across all treatment groups, including placebo.

In the **adolescent** subgroup, Grade 3 and 4 laboratory value increases in CPK were reported in the upadacitinib groups; none were reported in the placebo group.

All Treated 52-week Safety Analysis Set

Overall, the percentages of subjects with Grade 3 and 4 laboratory value increases in CPK were similar between the any upadacitinib 30 mg and the any upadacitinib 15 mg groups.

In the **adolescent** subgroup, Grade 3 and 4 laboratory value increases in CPK were reported in 3 adolescent subjects receiving any upadacitinib:

- A Grade 4 laboratory value increase in CPK was reported in an adolescent subject receiving upadacitinib 15 mg. The subject had no relevant medical history. No concurrent TEAEs and no other laboratory abnormalities were reported with occurrence of CPK >10×ULN. Study drug was not interrupted and CPK values returned to normal range with continued study drug administration.
- A Grade 4 laboratory value increase in CPK was reported in an adolescent subject receiving upadacitinib 30 mg, with no relevant medical history and no concurrent TEAEs except for the nonserious TEAE of blood CPK increased. ALT, AST, and ALP were elevated during the same visit. ALT, AST, and CPK values returned to the normal range with no interruption of study drug; ALP remained elevated through the last observation. The subject experienced associated

muscle pain, with exercise or other vigorous physical activity reported as underlying etiology by the investigator.

- A Grade 3 laboratory value increase in CPK was reported in an adolescent male subject, with no relevant medical history, who had previously discontinued upadacitinib 15 mg due to the TEAE of ALT increased. ALT values returned to the normal range following discontinuation of study drug. The CPK elevation occurred on the subject's follow-up visit; no further information is available

Liver function tests

PBO-controlled 24-week Safety Analysis Set

Overall, few subjects had potentially clinically important laboratory abnormalities of increased ALT, AST, or total bilirubin values. There were no subjects with ALT or AST >20×ULN.

There were 4 (adult) subjects with ALT or AST >10×ULN:

- An adult subject in the upadacitinib 15 mg group with a relevant medical history of current alcohol use and no relevant concomitant medication use experienced ALT >3×ULN, AST >10×ULN, and CPK >10×ULN on the same visit. The laboratory abnormalities were reported as nonserious TEAEs and were considered by the investigator to have a reasonable possibility of being related to study drug. The subject had no signs or symptoms, and no other TEAEs were reported. Study drug was temporarily interrupted, and ALT, AST, and CPK values were close to normal ranges at the subsequent laboratory assessment. There was no recurrence with continued treatment.
- An adult subject in the upadacitinib 30 mg group experienced concurrent SAEs of rhabdomyolysis, blood CPK increased, AST increased (>10×ULN), ALT increased (>5×ULN), and blood creatinine increased (refer to the AESI of CPK elevation).
- An adult subject in the upadacitinib 30 mg group with a relevant medical history of e-cigarettes/vaping and alcohol use experienced nonserious TEAEs of ALT increased (>10×ULN) and AST increased (>10×ULN) on the same visit. The subject was asymptomatic and reported an increase in alcohol consumption at a social event prior to laboratory testing. Study drug was interrupted, and ALT and AST values returned to normal ranges.
- An adult subject in the placebo group experienced concurrent nonserious TEAEs of ALT increased (>10×ULN) and AST increased (>5×ULN). The subject had a relevant medical history of latent TB and received isoniazid treatment at the time of events. Study drug was interrupted and ALT and AST values returned to normal ranges.

One (adult) subject in the upadacitinib 15 mg group met the biochemical criteria within 30 days for Hy's Law during Period A:

- An adult subject with a medical history of a positive QuantiFERON test and initiation of isoniazid treatment at screening experienced AST >3×ULN, TBL >2×ULN, and CPK >10×ULN on the same visit. The subject had no signs or symptoms, and no TEAEs were reported. At the subsequent laboratory measurement, AST levels decreased to within normal range, and TBL and CPK were <2×ULN, without study drug interruption or isoniazid discontinuation. This case does not represent a true Hy’s law case given there was an alternate aetiology of isoniazid treatment (a common cause of idiosyncratic liver injury associated with transient and often asymptomatic serum aminotransferase elevations).

All Treated 52-week Safety Analysis Set

Few subjects had potentially clinically important laboratory abnormalities of increased ALT, AST, or total bilirubin values. No subjects receiving any upadacitinib experienced ALT or AST >20×ULN. Among subjects receiving any upadacitinib, a total of 3 (adult) subjects experienced AST or ALT >10×ULN, and 1 (adult) subject met the biochemical criteria for Hy's Law; however, this case does not represent a true Hy's law case given there was an alternate etiology (all subjects previously described for the PBO controlled 24-week Safety Analysis Set).

Lipids

Similar to observations in subjects from other upadacitinib clinical programs, upadacitinib treatment was associated with mean increases in lipid parameters (cholesterol, HDL-C, and LDL-C) from baseline in subjects with AA. The mean changes were generally small and likely due to natural variations that occur among the population analysed.

Overall, Grade 3 laboratory increases in triglycerides were reported in a total of 8 (adult) subjects (0.6%) receiving any upadacitinib; Grade 4 laboratory increases in triglycerides were reported in a total of 1 (adult) subject (<0.1%) receiving any upadacitinib. No Grade 3 or 4 triglyceride increases were observed in the **adolescent** subgroup.

Vital signs, physical findings, and other observations related to safety

Vital signs

Across M23 716 Study 1 and Study 2 (up to 52 weeks) through the data cutoff dates, mean changes from Baseline in vital signs over time were not considered clinically meaningful. No safety concerns from vital signs were identified.

Physical findings

Adults

At Week 24, the mean weight increase from baseline in adult subjects was 0.92 kg in the upadacitinib 30 mg group, 0.81kg in the upadacitinib 15 mg group, and 0.18 kg in the placebo group. During the placebo controlled period (Period A), the percentage of adult subjects who experienced weight increase (>7%) was higher in the upadacitinib 30 mg (11.2%) and upadacitinib 15 mg (7.7%) groups than in the placebo group (3.5%); and the percentage of adult subjects who experienced weight decrease (>7%) was higher in the upadacitinib 30 mg (5.1%) than the upadacitinib 15 mg (3.6%) and placebo (3.1%) groups.

Growth and Development Assessments for Adolescents

Weight

At Week 24, the mean weight increase from baseline in adolescents was 2.75 kg in the upadacitinib 30 mg group, 2.48 kg in the upadacitinib 15 mg group, and 1.31 kg in the placebo group. Adolescents, who are still growing in height, are expected to have corresponding weight gain. Weight gain in adolescents was similar among the upadacitinib groups and slightly lower in the placebo group.

During the placebo-controlled period (Period A), potentially clinically important weight decrease (>7%) was observed in 1 subject (2.1%) in the upadacitinib 30 mg, 1 subject (4.3%) in the placebo group, and no subjects in the upadacitinib 15 mg group. The adolescent subject with a potentially clinically

important weight decrease (>7%) in the upadacitinib 30 mg group had a relevant medical history of hypothyroidism and was started on levothyroxine prior to starting the study; weight returned to baseline during the study.

Height and BMI

The mean age of adolescents in this study was 14.4 years with a range of 12 to 17 years. Peak height velocity occurs at a mean age of 13.5 years in boys and 11.5 years in girls (Abbassi 1998). At Week 24, mean changes from baseline in height were generally similar across treatment groups for female and male adolescents: in female adolescents, mean changes from baseline in height were 0.89 cm in the upadacitinib 30 mg group, 0.75 cm in the upadacitinib 15 mg group, and 0.63 cm in the placebo group; and in male adolescents, mean changes from baseline in height were 1.79 cm in the upadacitinib 30 mg group, 2.09 cm in the upadacitinib 15 mg group, and 1.93 cm in the placebo group. Changes in height z-scores were minimal. These data were as expected, given the growth spurt during puberty occurs earlier and for a shorter duration of time in girls.

Overall, mean changes from baseline in BMI were minimal, indicating proportional increases in height and weight.

Normal growth was observed in adolescents during this study; however, data are limited by a relatively short timeframe (approximately 6 months) to measure growth in height. Height will continue to be monitored in adolescents continuing in the AA clinical program and results will be reported in future CSRs.

Tanner Staging

During the placebo-controlled period (Period A), almost all subjects achieved the appropriate Tanner stage at the applicable visits. Of the 3 subjects with inappropriate Tanner stage (2 adolescent subjects in the upadacitinib 15 mg group and 1 subject in the placebo group), all were noted to be Tanner Stage 3.

No TEAEs related to abnormal growth or growth deficiency (PTs of growth disorder, growth failure, growth retardation, body height below normal, body height abnormal, body height decreased) were reported in M23-716 Study 1 or Study 2.

Safety in special populations

Race, age, geographic region, sex

PBO-controlled 24-week Safety Analysis Set

The majority of subjects were White. The sample size for Black subjects was small, and results should be interpreted with caution. In the adolescent subgroup, most patients were Asian. Across treatment groups, the rates of treatment-emergent AEs, AEs with a reasonable possibility of being related to study drug, severe AEs, and SAEs were generally similar across race, age, geographic region, and sex. In male subjects, SAEs were reported only in the upadacitinib 30 mg group; in female subjects, SAEs were reported across treatment groups. No SAEs were reported in adolescents (<18 years of age) receiving upadacitinib treatment.

Rates across all treatment-emergent AESIs were generally similar across race, age, geographic region and sex, except for the following observed differences. Higher rates of hepatic disorders, neutropenia, and CPK elevations were reported in Asian subjects than White and Black subjects; similarly, rates of hepatic disorders and neutropenia were higher in the Asian geographic region than other geographic regions. Rates of neutropenia were higher in subjects ≥40 years than the other age groups; and rates of CPK elevations were higher in male subjects than female subjects.

All Treated 52-week Safety Analysis Set

The EAERs of treatment-emergent AEs, AEs with a reasonable possibility of being related to study drug, severe AEs, and SAEs were generally similar across race, age, geographic region, and sex among subjects receiving any upadacitinib. In male subjects, SAEs were reported only in the any upadacitinib 30 mg group; in female subjects, SAEs were reported across both any upadacitinib groups. A total of 2 SAEs were reported in 1 adolescent subject (<18 years of age) receiving any upadacitinib. The EAER of TEAEs leading to discontinuation of study drug in subjects receiving any upadacitinib was higher in North America than other geographic regions.

The EAERs across all treatment-emergent AESIs were generally similar across race, age, geographic region, and sex among subjects receiving any upadacitinib. Adverse event reporting patterns are expected to vary between countries and geographic regions due to differences in the underlying populations and clinical settings as well as differences in reporting cultures and regulation (Wakao 2019). These variations influence the rates and types of reported TEAEs. Consistent with this, the EAERs of hepatic disorders and neutropenia were higher in Asian subjects than other races, likely due to differences in reporting practices at clinical sites, with several Asian clinical sites reporting a high number of mild to moderate events with no action taken with study drug; similarly, the EAERs of hepatic disorders and neutropenia were higher in the Asian geographic region than other geographic regions. JAK inhibition has been associated with an increased risk of herpes zoster with the highest risk reported in the Asian region, and the results are consistent with what has been reported previously with upadacitinib in subjects with RA and other JAK inhibitors (Cohen 2020, Taylor 2022, Winthrop 2022). The EAERs of herpes zoster were higher in Asian subjects and in the Asian geographic region than in other races and geographic regions. Few AESIs were reported in adolescents (<18 years) receiving any upadacitinib treatment, and only in the hepatic disorders, neutropenia, lymphopenia, CPK elevation, and bone fractures categories. The EAER of herpes zoster was higher in subjects in the ≥40 years age category than other age categories; and the EAER of CPK elevations was higher in subjects in the 18 - <40 years age category than other age categories. The EAERs of hepatic disorders and CPK elevations were higher in male subjects than female subjects.

Baseline renal function

Most subjects had normal renal function or mild renal impairment; there were few subjects with moderate renal impairment or with missing information on renal function. As the number of subjects with moderate renal impairment was small, comparisons with other subgroups are not included; furthermore, the results for subjects with missing information on renal function should be interpreted with caution.

In the *PBO-controlled 24-week Safety Analysis Set*, the rates of treatment-emergent AEs, AEs with a reasonable possibility of being related to study drug, severe AEs, and SAEs across treatment groups were generally similar between subjects with normal renal function and subjects with mild renal impairment. In subjects with missing information on renal function, the rates of TEAEs across treatment groups were generally similar to those observed in subjects with normal renal function, with rates of treatment-emergent severe AEs and SAEs too low in these subjects to draw any meaningful conclusions. The rates of AESIs across treatment groups were generally similar between subjects with normal renal function and subjects with mild renal impairment; the rates of AESIs in subjects with missing information were too low to draw any meaningful conclusion.

Use during pregnancy

A total of 167 maternal pregnancies in 160 subjects have been reported in upadacitinib clinical studies. Of the 167 reported pregnancies:

- 4 pregnancies (4 subjects) remain blinded to treatment allocation, all in the HS indication.
- 41 pregnancies (36 subjects) have been unblinded to treatment assignment and the female subject was not exposed to upadacitinib at the time of pregnancy (on placebo or comparator; or conceived at least 1 month after discontinuation of upadacitinib)
- 122 pregnancies (122 subjects) have been unblinded to treatment assignment and the female subject was exposed to upadacitinib within 1 month prior to conception and during the first trimester.

The 122 maternal pregnancies (122 subjects) with upadacitinib exposure during preconception and the first trimester occurred in clinical studies of the following indications: AD (42), RA (39), UC (15), CD (9), PsA (7), AA (6), HS (2), AS (1) and SLE (1).

Pregnancies that occurred during the **AA clinical development program** through 08 July 2025 are summarized in Table 48. All pregnant subjects were adults and were exposed to upadacitinib during the first trimester. There were no live births or spontaneous abortions reported to date. There were 3 elective terminations without foetal defects reported. Two elective terminations were for family planning purposes, and 1 elective termination was a result of an anembryonic pregnancy. There were 3 ongoing pregnancies as of the data cutoff date (08 July 2025).

Table 48. Pregnancies Occurring in the Alopecia Areata Clinical Development Program

Study	Treatment	Pregnancy	Comment
M23-716	Upadacitinib 30 mg daily	Elective termination - no fetal defects or unknown	Elective termination was performed for family planning purposes
M23-716	Upadacitinib 30 mg daily	Elective termination - no fetal defects or unknown	Elective termination was performed for family planning purposes
M23-716	Upadacitinib 30 mg daily	Elective termination - no fetal defects or unknown	Anembryonic pregnancy
M23-716	Upadacitinib 15 mg daily	Ongoing	
M23-716	Upadacitinib 15 mg daily	Ongoing	
M23-716	Upadacitinib 15 mg daily	Ongoing	

Note: Based on cumulative exposure through 08 July 2025.

Use during lactation

AbbVie's global safety database was searched for all clinical trial reports received through 08 July 2025 using the route of administration as Transmammary, Neonatal exposures via breastmilk SMQ, MedDRA Version 28.0.

There are no clinical trial reports in lactation.

Long-term adolescent data from AD studies M16-045, M16-047 and M18-891 (supportive data)

Accumulated, integrated, long-term adolescent safety data from the global Phase 3 pivotal studies in AD (Studies M16-045, M16-047, and M18-891) using a data cutoff of 15 August 2024 are summarized in this section as supportive information for upadacitinib in paediatric AA patients. These studies enrolled adolescents 12 to <18 years of age and evaluated both the 15 and 30 mg QD tablet formulations of upadacitinib.

A total of 541 adolescents are summarized in the global Phase 3 AD studies, including 264 and 265 subjects who received at least 1 dose of upadacitinib 15 mg and 30 mg, respectively. Overall, subjects had a median duration of 1437.0 days and 1463.0 days exposure to upadacitinib 15 mg and 30 mg, respectively, through the data cutoff. Total exposure to upadacitinib 15 mg and 30 mg was 864.5 PY and 915.0 PY, respectively (Table 49).

The EAERs of TEAEs overall, TEAEs with a reasonable possibility of being related to study drug, and TEAEs leading to discontinuation of study drug were similar between the upadacitinib 15 mg and 30 mg groups (Table 49). The EAERs of severe TEAEs and treatment-emergent SAEs were higher in the upadacitinib 15 mg group than the upadacitinib 30 mg group. No deaths were reported.

Skin papilloma was observed to be a new ADR in the AD adolescent population.

Table 49. Overview of TEAEs in Exposure-Adjusted Rate per 100 PY (Long-Term Upadacitinib Phase 3 AD Adolescent Analysis Set)

	UPA 15 mg QD (N = 264) (PY = 864.5)	UPA 30 mg QD (N = 265) (PY = 915.0)
EAER (events [E/100 PY])		
TEAE	1626 (188.1)	1775 (194.0)
TEAE with reasonable possibility of being drug-related[a]	493 (57.0)	521 (56.9)
Severe TEAE	108 (12.5)	91 (9.9)
Treatment-emergent SAE	49 (5.7)	40 (4.4)
TEAE leading to discontinuation of study drug	25 (2.9)	27 (3.0)
TEAE leading to death	0	0
EAIR (n/PY)		
All deaths	0/864.5	0/915.0

a. As assessed by investigator.

Note: Data cutoff = 15 August 2024.

Cross reference: Safety Update Table 2.4 2.1.2

There were no TEAEs in the following AESI categories: active TB, adjudicated GI perforation, renal dysfunction, retinal detachment, NMSC, lymphoma, adjudicated MACE, and adjudicated VTE (Table 50).

Serious infections occurring more than once were eczema infected and impetigo. Other serious infections occurring only once were COVID-19, eczema herpeticum, herpes zoster cutaneous disseminated, and pneumonia. The EAER of treatment-emergent opportunistic infections excluding TB and herpes zoster was higher on upadacitinib 15 mg than 30 mg (Table 50). Most of the opportunistic infections excluding TB and herpes zoster were eczema herpeticum. The EAER of herpes zoster was higher in the upadacitinib 30 mg group than the upadacitinib 15 mg group. Two disseminated herpes zoster (1 in each treatment group) and 2 ophthalmic herpes zoster (both in the upadacitinib 30 mg group) cases occurred, with no cases involving the central nervous system.

One malignancy (SAE) was reported in an adolescent subject who developed headaches less than 1 month after the start of study drug and was diagnosed with medulloblastoma approximately 7.5 months after the start of upadacitinib. Study drug was discontinued, and the investigator assessed the event as having no reasonable possibility of being related to the study drug.

Hepatic disorders TEAEs were primarily transaminase elevations. Consistent with the overall safety profile for upadacitinib and JAK class effect, a dose-response was observed for neutropenia and CPK elevation (Table 50). No clear association between low neutrophil counts and the occurrence of serious or opportunistic infections has been observed.

The majority of serious hypersensitivity events in adolescents were anaphylactic reactions due to known or unknown food allergies (i.e., peanuts, tree nuts) or exposure to a triggering allergen and were assessed as having no reasonable possibility of being related to the study drug by the investigator.

Table 50. Overview of Treatment-Emergent AESIs per 100 PY (Long-Term Upadacitinib Phase 3 AD Adolescent Analysis Set)

	UPA 15 mg QD (N = 264) (PY = 864.5)	UPA 30 mg QD (N = 265) (PY = 915.0)
EAER (events [E/100 PY])		
Serious infection	17 (2.0)	11 (1.2)
Opportunistic infection excluding TB and herpes zoster	13 (1.5)	5 (0.5)
Herpes zoster	17 (2.0)	25 (2.7)
Hepatic disorder	40 (4.6)	25 (2.7)
Anemia	17 (2.0)	8 (0.9)
Neutropenia	16 (1.9)	25 (2.7)
Lymphopenia	3 (0.3)	0
CPK elevation	52 (6.0)	75 (8.2)
Bone fracture	10 (1.2)	18 (2.0)
Serious hypersensitivity reaction	0	5 (0.5)
EAIR (n/PY [n/100 PY])		
Malignancy	1/864.3 (0.1)	0/915.0
Malignancy excluding NMSC	1/864.3 (0.1)	0/915.0

Note: Data cutoff = 15 August 2024.

Cross reference: Safety Update Table 2.4 2.2.2

In conclusion, the safety profile of upadacitinib in adolescents with moderate to severe AD from the Phase 3 studies was consistent with the known safety profile of upadacitinib. Skin papilloma was observed to be a new ADR in the AD adolescent population.

Safety related to drug-drug interactions and other interactions

The potential for drug-drug interactions between upadacitinib and commonly used concomitant medications has been previously assessed.

Discontinuation due to adverse events

Table 51. Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by Primary MedDRA System Organ Class and Preferred Term by Adolescent/adult (Placebo-Controlled 24-Week Safety Analysis Set)

MedDRA 27.1 System Organ Class Preferred Term	Placebo (N=23) n (%) [SSA%]	UPA 15 mg QD (N=48) n (%) [SSA%]	UPA 30 mg QD (N=47) n (%) [SSA%]
Adolescent			
Any adverse event	0	1 (2.1) [2.2]	0
Investigations	0	1 (2.1) [2.2]	0
Alanine aminotransferase increased	0	1 (2.1) [2.2]	0
Adult			
Any adverse event	0	4 (0.8) [0.8]	8 (1.6) [1.6]
Congenital, familial and genetic disorders	0	0	1 (0.2) [0.2]
Atrial septal defect	0	0	1 (0.2) [0.2]
Gastrointestinal disorders	0	1 (0.2) [0.2]	0
Dyspepsia	0	1 (0.2) [0.2]	0
Infections and infestations	0	1 (0.2) [0.2]	1 (0.2) [0.2]
Pneumonia	0	1 (0.2) [0.2]	0
Pneumonia streptococcal	0	0	1 (0.2) [0.2]
Investigations	0	0	2 (0.4) [0.4]
Alanine aminotransferase increased	0	0	1 (0.2) [0.2]
Neutrophil count decreased	0	0	1 (0.2) [0.2]
Musculoskeletal and connective tissue disorders	0	0	1 (0.2) [0.2]
Rhabdomyolysis	0	0	1 (0.2) [0.2]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.2) [0.2]	0
Breast cancer	0	1 (0.2) [0.2]	0
Nervous system disorders	0	0	2 (0.4) [0.4]
Syncope	0	0	1 (0.2) [0.2]
Vertebral artery stenosis	0	0	1 (0.2) [0.2]
Respiratory, thoracic and mediastinal disorders	0	1 (0.2) [0.2]	0
Pulmonary embolism	0	1 (0.2) [0.2]	0
Skin and subcutaneous tissue disorders	0	0	2 (0.4) [0.4]
Acne	0	0	1 (0.2) [0.2]
Pruritus	0	0	1 (0.2) [0.2]
Surgical and medical procedures	0	0	1 (0.2) [0.2]
Abortion induced	0	0	1 (0.2) [0.2]
Vascular disorders	0	1 (0.2) [0.2]	0
Venous thrombosis	0	1 (0.2) [0.2]	0

Note: Treatment-Emergent Adverse Events for Week 24 are defined as any Adverse Events that begin or worsen on or after the first dose of study treatment in Period A, and through: (i) 30 days after the last dose date in Period A for subjects who do not continue into Period B, or (ii) the minimum of (30 days after the last dose date in Period A, the first dose date in Period B - 1) for subjects who continue into Period B.
SSA = Study-size adjusted.
Subjects are counted once in each row, regardless of the number of events they may have had.

Table 52. Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by Primary MedDRA System Organ Class and Preferred Term by Adolescent/adult (All Treated 52-Week Safety Analysis Set)

MedDRA 27.1 System Organ Class Preferred Term	Placebo (N=23) n (%)	UPA 15 mg QD (N=48) n (%)	UPA 30 mg QD (N=47) n (%)	Any UPA 15 mg QD (N=62) n (%)	Any UPA 30 mg QD (N=57) n (%)	Any UPA (N=117) n (%)
Adolescent						
Any adverse event	0	1 (2.1)	0	1 (1.6)	0	1 (0.9)
Investigations	0	1 (2.1)	0	1 (1.6)	0	1 (0.9)
Alanine aminotransferase increased	0	1 (2.1)	0	1 (1.6)	0	1 (0.9)
Adult						
Any adverse event	0	6 (1.2)	11 (2.1)	6 (1.0)	13 (2.0)	19 (1.5)
Cardiac disorders	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Acute myocardial infarction	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Left ventricular failure	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Congenital, familial and genetic disorders	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Atrial septal defect	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Gastrointestinal disorders	0	1 (0.2)	0	1 (0.2)	1 (0.2)	2 (0.2)
Dyspepsia	0	1 (0.2)	0	1 (0.2)	0	1 (<0.1)
Gastrooesophageal reflux disease	0	0	0	0	1 (0.2)	1 (<0.1)
Infections and infestations	0	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)
Pneumonia	0	1 (0.2)	0	1 (0.2)	0	1 (<0.1)
Infections and infestations (cont.)						
Pneumonia streptococcal	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Investigations	0	1 (0.2)	2 (0.4)	1 (0.2)	2 (0.3)	3 (0.2)
Alanine aminotransferase increased	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Neutrophil count decreased	0	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)
White blood cell count decreased	0	1 (0.2)	0	1 (0.2)	0	1 (<0.1)
Musculoskeletal and connective tissue disorders	0	0	2 (0.4)	0	2 (0.3)	2 (0.2)
Foot deformity	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Rhabdomyolysis	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.2)	0	1 (0.2)	0	1 (<0.1)
Breast cancer	0	1 (0.2)	0	1 (0.2)	0	1 (<0.1)
Nervous system disorders	0	0	2 (0.4)	0	3 (0.5)	3 (0.2)
Headache	0	0	0	0	1 (0.2)	1 (<0.1)
Syncope	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Vertebral artery stenosis	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Anembryonic gestation	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	0	1 (0.2)	0	1 (0.2)	0	1 (<0.1)
Pulmonary embolism	0	1 (0.2)	0	1 (0.2)	0	1 (<0.1)
Skin and subcutaneous tissue disorders	0	1 (0.2)	2 (0.4)	1 (0.2)	2 (0.3)	3 (0.2)
Acne	0	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)
Pruritus	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Surgical and medical procedures	0	0	2 (0.4)	0	2 (0.3)	2 (0.2)
Abortion induced	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Selective abortion	0	0	1 (0.2)	0	1 (0.2)	1 (<0.1)
Vascular disorders	0	1 (0.2)	0	1 (0.2)	0	1 (<0.1)
Venous thrombosis	0	1 (0.2)	0	1 (0.2)	0	1 (<0.1)

Note: Treatment-Emergent Adverse Events for Week 52 continuous dose and treatment groups are defined as any Adverse Events that begin or worsen on or after the first dose of study treatment in Period A, and through the minimum of 1 day prior to the date of dose or treatment switch, the first dose date in Study 3 -1 , or 30 days after the last dose date in Period B.
Treatment-Emergent Adverse Events for Week 52 Any UPA 15 mg, Any UPA 30 mg, and Any UPA groups are defined as any Adverse Events that begin or worsen on or after initiation of UPA 15 mg, UPA 30 mg, or UPA overall respectively in Period A and/or Period B (whichever is earlier) including rescue or open-label Upadacitinib, and through the minimum of the first dose date in Study 3 -1 or 30 days after the last dose date in Period B.
Subjects are counted once in each row, regardless of the number of events they may have had.

PBO-controlled 24-week Safety Analysis Set

Overall, the percentages of subjects with TEAEs leading to discontinuation of study drug were higher in the upadacitinib groups than the placebo group. By PT, all TEAEs leading to discontinuation of study drug were reported in 1 subject each.

The (serious) TEAE of vertebral artery stenosis, which led to discontinuation of study drug, is discussed in the section on SAEs.

The TEAE of syncope, which led to discontinuation of study drug, was nonserious and was reported in an adult subject with a medical history of anemia, dysmenorrhea, headaches, and hot flashes; the event was considered by the investigator to have a reasonable possibility of being related to study drug.

In the adolescent subgroup, 1 TEAE leading to discontinuation of study drug was reported in the upadacitinib 15 mg group (PT of alanine aminotransferase increased); no TEAEs leading to discontinuation of study drug were reported in the placebo or upadacitinib 30 mg groups.

All Treated 52-week Safety Analysis Set

Overall, the EAER of TEAEs leading to discontinuation of study drug was higher in the any upadacitinib 30 mg than the any upadacitinib 15 mg group. By PT, all TEAEs leading to discontinuation of study drug among subjects receiving any upadacitinib were reported in 1 subject each, with the exception of alanine aminotransferase increased, neutrophil count decreased, and acne.

In the adolescent subgroup, a total of 1 TEAE leading to discontinuation of study drug (PT of alanine aminotransferase increased) was reported among adolescents receiving any upadacitinib.

Post marketing experience

The overall safety of upadacitinib therapy was evaluated through review of postmarketing reports (spontaneous, solicited, literature) received from 16 August 2019 through 31 July 2025, using MedDRA Version 28.0. Search of the AbbVie global safety database retrieved 351,644 reports. Overall, 87.5% of the reports were considered nonserious and 91.7% were from solicited sources. The indications with the highest number of reported AEs are the following: RA (44.8.%), AD (12.5%), unknown (12.5%), UC (9.4%), CD (6.5%), PsA (6.0%), AS (3.1%), and psoriasis (1.7%). Less than 1% of all postmarketing reports were from other indications.

Among all the reports, the most common AEs reported included pain (3.5%), arthralgia (3.0%), and drug ineffective (2.9%). The most frequent SAEs were surgery and hospitalization, which accounted for 2.8% of all SAEs and less than 0.5% of all AEs. The remaining SAEs contributed to less than 0.2% of all AEs reported from postmarketing sources. Generally, the type and pattern of SAEs reported were similar to what has been observed in the clinical studies for upadacitinib.

Among the 219 reports of patients receiving upadacitinib for AA, the most common AEs reported were off-label use (65.5%), acne (4.3%), drug ineffective (3.0%), therapeutic response unexpected (2.7%), and drug ineffective for unapproved indication (2.3%). SAEs consisted of less than 2% of all AEs reported in this population. There was 1 report each of the following SAEs: malignant melanoma, ophthalmic herpes zoster, sickle cell anemia with crisis, and thrombocytopenic purpura.

Most of the postmarketing events were either expected for upadacitinib or commonly seen in the general population or patient populations indicated for upadacitinib. Review of the postmarketing reports did not identify any new safety risks for upadacitinib.

2.5.1. Discussion on clinical safety

The applied for indication concerns treatment of severe alopecia areata (AA) in adult and adolescent patients aged ≥12 years. The proposed recommended dose is 15 mg or 30 mg once daily.

The safety data in support of this variation is based on 2 phase 3 studies, M23-716 Study 1 and Study 2, with a similar study design, comprising a double-blind 24-week period (Period A) and a blinded 28-week extension period (Period B). In Period A, a total of 1397 patients were randomised in a 2:2:1 ratio to UPA 15 mg (n=557; adolescents n=48), UPA 30 mg (n=560; adolescents n=47) or placebo (n=280; adolescents n=23). At the end of Period A, patients on placebo were re-randomised to 15 or 30 mg in case of a SALT score of >20. Patients on UPA were to continue treatment at the same dose in Period B; patients with less than 30% improvement from baseline in SALT score received open-label UPA 30 mg.

For the assessment of safety, data from both studies have been pooled into 2 analysis sets, the placebo-controlled 24-week analysis set and the 52-week analysis set. The assessment of safety for Period B (up to 52 weeks) will focus on the Any upadacitinib 15 and 30 mg treatment groups.

For both studies, period A has been completed, whilst Period B is ongoing final CSRs are expected to be submitted by Q1 2029 as outlined in the RMP. Data cut-off dates for Period B are 08 July 2025 for M23-716 Study 1 and 13 June 2025 for M23-716 Study 2.

Extent of exposure

A total of 1372 patients, including 117 adolescents, received at least 1 dose of upadacitinib. At the data cut-off date for Period B, mean duration of exposure was 33.9 weeks for the any upadacitinib 15 mg group (n=686) and 33.1 weeks for the ny upadacitinib 30 mg group (n=719). A total of 169 patients (12.3%) was exposed to any dose of UPA for at least 52 weeks.

In **adolescent** patients, mean duration of exposure was 34.5 weeks for the Any UPA 15 mg group (n=62) and 37.4 weeks for the any upadacitinib 30 mg group (n=57). A total of 17 patients (14.5%) was exposed to any dose of upadacitinib for at least 52 weeks.

The size of the overall safety database for the indication of severe AA is considered adequate for the assessment of safety. Whilst long-term exposure for at least 1 year in the overall population is considered adequate, the number of adolescent patients exposed for at least 1 year is limited.

The safety of upadacitinib has been established previously in other indications, including the dermatologic indication of atopic dermatitis (AD). Given the similarities between the patient populations in the AD and AA indications as well as the identical posology in terms of recommended doses, comparison of the safety profile in the AA indication will primarily focus on the AD indication. For adolescent AA patients, safety will be compared with safety data in adults and with safety data in adolescent AD patients (submitted as supportive data).

Since the safety profile in adult patients is relatively well known, the discussion will primarily focus on the adolescent population.

<u>Overall safety profile</u>

During the 24-week placebo-controlled period, the overall rate of TEAEs and related TEAEs was higher in the UPA treatment groups compared with placebo, and was higher with UPA 30 mg compared with 15 mg. In the 52-week analysis set, a similar trend was observed between the any upadacitinib groups.

Common TEAEs in the adolescent population (reported in ≥5% of patients on UPA in the placebo-controlled 24-week period or ≥10 events per 100 PY during the 52-week period) were upper respiratory tract infections, acne, nasopharyngitis, blood CPK increased, cough, folliculitis and gastroenteritis. Most TEAEs were mild or moderate in severity. Common TEAEs in adolescents were generally consistent with those in the overall population.

No deaths were reported during either study.

The frequency of SAEs in the overall population was higher in the UPA treatment groups compared with placebo and was also higher in the any upadacitinib 30 mg group (6.8%) compared with any upadacitinib 15 mg (3.4%). SAEs reported in more than 1 patient were CPK increased and rhabdomyolysis, reported in 2 adult patients receiving upadacitinib 30 mg (0.4 E/100 PY, each). In the adolescent population, no SAE was reported in the upadacitinib groups in the 24-week analysis set. In the 52-week analysis set, the SAEs of affective disorder and behaviour disorder in the any upadacitinib 30 mg group were reported in a single adolescent patient with a relevant medical history of psychiatric disorders. No concern is raised. No other SAEs were reported in adolescents.

Treatment discontinuations due to TEAEs were reported at a low frequency: in 0.9% and 1.4% of patients with UPA 15 mg and UPA 30 mg vs. none with placebo in the placebo-controlled 24-week analysis set and in 1.0% and 1.8% in the any upadacitinib 15 mg and any upadacitinib 30 mg group in the 52-week analysis set. In the adolescent population, ALT increased led to treatment discontinuation in a single patient in either analysis set. Overall, the TEAEs leading to treatment discontinuation do not raise a concern. The low discontinuation rate indicates that AEs were generally manageable.

The criteria for identification of potential adverse reactions (ADRs) are acceptable. No new ADRs were identified based on the TEAEs reported in the 24-week placebo-controlled analysis set.

Special populations

No patients aged ≥65 years have been included in M23-716 Study 1 and 2, reflecting the inclusion criteria. No apparent differences in AE profile were reported across different patient populations in terms of race, geographic region or sex.

The small number of patients with moderate renal impairment at baseline (0.5%) precludes analysis of the safety profile in this patient population. No apparent differences in AE profile were reported across patients with normal or mild renal impairment at baseline.

During both studies in the AA indication, 6 pregnancies were reported in adult patients, with outcome reported as elective termination in 3 pregnancies and ongoing in the remaining 3 pregnancies. Upadacitinib is contraindicated in pregnancy. Section 4.6 of the SmPC includes relevant information, including information specifically addressing paediatric patients.

Adverse events of special interest (AESIs)

In the **overall population**, no treatment-emergent AESIs of opportunistic infections (excluding TB and herpes zoster), NMSC, lymphoma, adjudicated GI perforations, renal dysfunction, active TB, adjudicated MACE or serious hypersensitivity reactions were reported in the clinical studies. The AESIs of serious infections, herpes zoster, hepatic disorder, anaemia, neutropenia, lymphopenia and CPK elevation were reported at a higher rate in the any upadacitinib 30 mg group compared with any upadacitinib 15 mg. Hepatic disorder events concerned increases in transaminases and bilirubin; no events of DILI were reported. The events of rhabdomyolysis reported in 2 adult patients presented with alternative aetiology; causality is assessed as not related. No concerns are raised regarding malignancies, adjudicated VTE, bone fracture and retinal detachment.

Serious infections and herpes zoster are important identified risks in the context of the RMP; malignancies, VTE, DILI and fractures are important potential risks. The data on AESIs in the overall population is consistent with the known safety profile of upadacitinib. Information on AESIs is adequately reflected in the product information.

In the **adolescent population**, no AESIs of serious infections, herpes zoster, anaemia, adjudicated VTE or retinal detachment with upadacitinib were reported. In the 52-week analysis set, AESIs were generally reported at a higher rate with UPA 30 mg compared with the 15 mg dose.

Hepatic disorder events were reported at a higher rate in the any upadacitinib 30 mg group (4.9 E/100 PY) compared with any upadacitinib 15 mg (2.4 E/100 PY). Events of hepatic disorders were reported in 3 adolescent patients and concerned ALT increased, AST increased and hepatic steatosis. No cases of DILI have been reported.

Neutropenia events were reported in 2 adolescent patients in the 30 mg UPA group during the 24-week period. In the 52-week analysis set, neutropenia events were reported at a higher rate with any upadacitinib 30 mg (7.3 E/100 PY) compared with any upadacitinib 15 mg (2.4 E/100 PY). Neutropenia events were of mild or moderate severity and did not lead to treatment interruption.

Lymphopenia was reported in 1 adolescent patient on 30 mg upadacitinib in the 52-week analysis set. The event was severe, non-serious and resolved following treatment interruption.

CPK elevations (all non-serious events) were reported at a higher rate with Any UPA 30 mg (14.7 E/100 PY) compared with Any UPA 15 mg (4.9 E/100 PY). No events of rhabdomyolysis were reported in adolescent patients.

One event of bone fracture (PT shoulder fracture) was reported in an adolescent patient. The event was associated with trauma.

To contextualise the assessment of the safety profile in adolescents, long-term safety data for upadacitinib in adolescent patients, aged 12 years and older, in the AD indication has been submitted as supportive data. The safety data in AD comprised 541 patients, having received upadacitinib 15 mg (n=264) or upadacitinib 30 mg (n=265). Median duration of exposure was 1437 days (864 PY) with 15 mg and 1463 days (915 PY) with 30 mg.

Updated safety data for adolescent patients in terms of AESIs have been submitted as part of the procedure. Data is derived from study 1 (data cut-off 14 January 2026), study 2 (data cut-off 22 December 2025) and study 3 (All Treated Long-term Safety analysis set). Exposure in the Any UPA 15 mg and Any UPA 30 mg groups was 72.0 PYs and 70.9 PYs, respectively; 79 patients in the Any UPA 15 mg group and 73 patients in the Any UPA 30 mg group had been exposed to upadacitinib for ≥18 months.

With longer duration of exposure, no malignancy, adjudicated MACE, adjudicated VTE, retinal detachment, adjudicated GI perforations, serious hypersensitivity, anaemia, opportunistic infection, or herpes zoster were reported in adolescent patients. EAER for serious infections was 0 E/100 PY and 2.8 E/100 PY for the Any UPA 15 mg and Any UPA 30 mg groups, respectively, compared with no events in the All treated 52-week analysis set. Overall, the EAERs with longer duration of exposure for serious infections, hepatic disorders, neutropenia, lymphopenia, bone fractures and elevated CPK were consistent with those reported in the All treated 52-week analysis set. The updated safety data in terms of AESIs for adolescents in the AA indication is largely consistent with the data in the overall population for the AA indication and with the adolescent AD population.

Growth and development assessments for adolescents

Increases in weight and height have been observed across all treatment groups, with minimal changes in BMI. At the end of the 24-week period, inappropriate Tanner stage was reported in 2 patients on UPA 15 mg and 1 patient on placebo; all 3 patients had Tanner stage 3. No TEAEs related to abnormal growth or growth deficiency have been reported.

Although the data do not indicate a clinically relevant effect of upadacitinib on growth and development, assessment of this data is limited by the relatively short observation period, i.e., 6 months. The MAH indicates that height will be monitored in adolescents continuing in the AA clinical program. While this is supported, also the impact on weight, BMI and Tanner stage should continue to be monitored as part of the proposed additional pharmacovigilance activities in the RMP.

Proposed warnings & precautions language (Section 4.4 of the SmPC).

Class warnings, including a boxed warning, were introduced during the Article 20 procedure for JAK inhibitors used in the treatment of chronic inflammatory disorders (EMEA/H-A20/1517/C/004760/0017) state that upadacitinib should only be used if no suitable treatment alternatives are available in patients over 65 years of age, patients with cardiovascular risk factors or patients with malignancy risk factors.

The MAH proposed to indicate that these limitations, regarding suitable alternatives, do not apply to patients treated for severe AA. In order to support the proposed change, the MAH referred to Litfulo (ritlecitinib) a medicinal product inhibiting irreversibly and selectively JAK3 and the TEC family, approved for the treatment of severe alopecia areata after the outcome of the Article 20 procedure. The SmPC of this medicinal product contains warnings and precautions for use regarding patients with cardiovascular and malignancy risk factors introduced following consideration of the conclusions of the Article 20 procedure on JAK inhibitors and data available at the time of marketing authorisation for this medicinal product. The product information does not specify that ritlecitinib should only be used if no suitable treatment alternatives are available.

Further, the MAH considered that the boxed warning should not apply for the AA indication in view of the low incidence of patients with risk factors in the patient population with severe AA.

The CHMP considered the following conclusions of the Article 20 procedure when assessing the MAH's proposal:

- Until more data has been identified, it was considered that the main serious safety events of concerns are general JAKi class effects for the products included in the Article 20 procedure.
- Regarding the treatment of severe AA, it was acknowledged that this patient group generally has less risk factors for the main serious safety outcomes compared with e.g. RA patients, as they are at least not associated to the underlying disease. Nevertheless, if a patient has risk factors in any of the authorised indications, the patient would be equally at risk for the safety findings being the focus of the Article 20 procedure.

Since the serious safety events are considered class effects for the products included in the Article 20 procedure and because the risk factors for these events can emerge in populations treated with any of the JAKis reviewed in the Article 20 procedure, it was concluded that these serious safety concerns are relevant to all approved indications including the AA population.

The CHMP also clarified that the class warnings regarding use of suitable treatment alternatives is only applicable to the subset of patients with risk factors and not to the AA patients without risk factors.

In the absence of additional data provided by the MAH on upadacitinib that would support a change to these conclusions, the proposed amendment of the warning label for the AA population was not endorsed by the CHMP.

In response to the request for supplementary information, the MAH maintained its position that the current wording in SmPC section 4.4 for Rinvoq introduced after the Article 20 referral procedure should be modified considering the differential labelling between upadacitinib and ritlectinib. In order to address this issue, the MAH proposed to add the following text in several parts of section 4.4 of the SmPC. This proposal applied for all already approved indications of Rinvoq as well as for the new claimed AA indication: "*In the statement within the box above, suitable treatment alternatives do not include other systemic JAK inhibitors"*.

In order to support the above proposal, the MAH provided indirect comparative safety data (including rates of MACE, VTE, malignancy excluding NMSC, and NMSC) of upadacitinib and ritlecitinib development programmes for AA. Further, the MAH provided a discussion on the role of the JAK isoforms on the occurrence of these adverse events and submitted real world evidence for ritlecitinib in AA. The MAH concluded that, taking into account the similar safety profiles of upadacitinib and ritlecitinib and upadacitinib's numerically better efficacy, upadacitinib's benefit-risk balance appears more favourable, and is at least equivalent, to that of ritlecitinib. Further, the MAH considered that their proposed wording is consistent with the 2009 SmPC Guideline and stated that the guideline makes explicit provision for the scenario where class labelling exists.

However, each medicinal product is assessed on its own merit, hence, no firm conclusion could be made by the CHMP based on the comparative safety data between the two products and the real-world evidence for ritlecitinib. Regarding upadacitinib, the data submitted in the current procedure were reviewed by the CHMP and indicate that the safety profile of upadacitinib observed in patients with severe AA is consistent with that in patients with AD. Of note, Rinvoq was approved for the treatment of AD during the Article 20 procedure and class warnings were applied for this indication. Hence, the class warnings applied during the Article 20 procedure were considered applicable to the severe alopecia areata indication. Regarding the JAK isoforms of upadacitinib, there were no new elements submitted by the MAH that would allow a different conclusion than the one reached in the Article 20 procedure.

In addition, a PRAC advice was requested by the CHMP on this topic (see Section 2.6 of this assessment report). The PRAC considered that the agreed wording of SmPC section 4.4 implemented during the Article 20 procedure, including the boxed warning, should be maintained for upadacitinib for the new indication of AA, as the concerned risks are primarily driven by patient-related risk factors and exposure to the JAK inhibitor rather than by the underlying disease. Further, based on the evaluation of the data submitted in this procedure, the PRAC concluded that there is no new upadacitinib-specific evidence submitted by the MAH justifying an update of the class warning for the new AA indication.

On the proposed wording of SmPC to amend section 4.4, the CHMP considered the wording inconsistent with the information included in the product information of other products of the JAK inhibitor class that do not bear the boxed warning and was therefore considered not acceptable.

The CHMP also noted that that the proposed addition is not specific to the newly sought AA indication but also applied to all other approved indications for Rinvoq.

Overall, considering all the data submitted by the MAH in writing during this procedure and in an oral explanation, the CHMP concluded that the precautionary measures recommended in the Article 20 procedure are applicable for the new AA indication for Rinvoq and that that there is no sufficient evidence to justify an update of the warnings for upadacitinib as proposed by the MAH.

Following the oral explanation, the MAH amended the scope of this variation application to remove the proposed amendment to the SmPC Section 4.4.

2.5.2. Conclusions on clinical safety

The size of the overall safety database in the indication of severe alopecia areata is considered adequate. The size of the safety database in terms of adolescent patients in the sought indication is considered adequate, with support of safety data in adolescent patients in the atopic dermatitis indication.

The frequency for the commonly reported AEs as well as for AESIs such as serious infections and herpes zoster was higher with the 30 mg dose compared with 15 mg. Most AEs were mild or moderate in severity and no relevant difference in discontinuation rate was observed between both dose groups, indicating that AEs were generally manageable. Nevertheless, the proposed recommendation in section 4.2 of the SmPC to use the lowest effective dose for maintenance of response is supported.

The safety profile of upadacitinib in the proposed indication of treatment of severe alopecia areata in adults and adolescents 12 years and older is largely consistent with the known safety profile of upadacitinib.

Long-term safety in the paediatric population in terms of the important identified and potential risks as well as data on growth and development is recommended to be monitored as part of the proposed additional pharmacovigilance activities in the context of the RMP.

2.5.3. PSUR cycle

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

2.6. PRAC advice

At the June 2026 PRAC plenary meeting, the PRAC discussed the CHMP request for PRAC advice for Rinvoq (upadacitinib) on the applicability to the new alopecia areata (AA) indication of the class warning, implemented during the Article 20 procedure Janus kinase inhibitors (JAKi) (EMEA/H-A20/1517/C/004760/0017), stating that upadacitinib should only be used if no suitable treatment alternatives are available in patients over 65 years of age, patients with cardiovascular risk factors or patients with malignancy risk factors.

The PRAC concluded the following:

1. The PRAC considered that the previously agreed class warning in section 4.4 of the SmPC implemented during the Article 20 procedure for JAKi (EMEA/H-A20/1517/C/004760/0017), including the boxed warning with recommendation to use upadacitinib in patients with risk factors only if no suitable treatment alternatives are available, is also applicable for upadacitinib in the newly proposed indication of AA.

As per the conclusions of the Article 20 procedure, the serious adverse events of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), malignancies and serious infections are considered class effects for the JAKis included in the procedure, applicable across all the approved indications. To minimise these risks, an approach focused on identifiable individual risk factors has been implemented. Although the incidence of patients with risk factors for these safety events might be lower in the AA population, the data submitted by the MAH in the ongoing extension of indication,

including indirect comparisons with ritlecitinib, do not allow conclusion that such patients with risk factors are at lower risk of developing these adverse reactions when compared to patients with risk factors in any other approved indication of upadacitinib. The PRAC further noted that the AA indication was part of the Article 20 procedure, and that the class warning was also applied for this indication at that time.

In conclusion, the PRAC considers that the agreed wording of section 4.4 of the SmPC implemented during the Article 20 procedure, including the boxed warning, should be maintained for upadacitinib for the new indication of AA, as the concerned risks are primarily driven by patient-related risk factors and exposure to the JAK inhibitor rather than by the underlying disease.

2. Based on the evaluation of the data submitted in the extension of indication procedure for Rinvoq in the treatment of AA, the PRAC concluded that there is no new upadacitinib-specific evidence justifying an update of the warnings for the new AA indication. Hence, the PRAC concluded that it is not warranted to adapt the currently present warning in section 4.4 of the SmPC on risks of serious infection, malignancy, MACE, VTE and use in patients 65 years of age and older.

2.7. Risk management plan

The MAH submitted an updated RMP version 20.0 with this application.

The main proposed RMP changes were the following:

- Added information on AA as proposed indication.
- Updated pregnancy data.
- Revised presentation of safety concerns and updated data for approved indications
- Added Study M23-716 as an additional pharmacovigilance activity.
- Revised presentation of milestone dates for additional pharmacovigilance activities throughout the document, specifically those for clinical trials, to align with the current RMP company template which follows EMA RMP standards and GVP Module XVI – Risk Minimisation Measures Rev
- Removed Study M13-538 from Final protocols not reviewed or synopsis/protocols not approved:
- Removed completed commitment for Study M15-554
- Renamed Missing information "Long-term safety in adolescents with AD" to "Long-term safety in adolescents"

Clinical Trial Exposure

Updated exposure data

Post-Authorization Exposure

Updated exposure data.

Additional Risk Minimization Measures

Removal of one-time distribution of DHPC

Annex 4

Included the latest versions of adverse drug reaction follow-up forms

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

The PRAC considered that the risk management plan version 20.0 is acceptable. The CHMP endorsed the Risk Management Plan version 20.0.

Safety concerns

Table 53. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Serious and opportunistic infections including TB • Herpes zoster • NMSC • GI perforation
Important potential risks	• Malignancies excluding NMSC • MACE • VTEs (deep venous thrombosis and pulmonary embolus) • DILI • Fetal malformation following exposure in utero • Fractures
Missing information	• Use in very elderly (≥ 75 years of age) • Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C • Use in patients with moderate hepatic impairment • Use in patients with severe renal impairment • Long-term safety • Long-term safety in adolescents

Pharmacovigilance plan

Table 54. Ongoing and Planned Additional Pharmacovigilance Activities

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable	--	--	--	--
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable	--	--	--	--
Category 3 – Required additional pharmacovigilance activities				
Study P19-150 Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe/Ongoing	The primary objectives are to assess comparability across users of upadacitinib and other select systemic treatments for RA through in-depth assessments of drug utilization and patient characteristics at baseline; to describe the incidence of the following safety outcomes in patients with RA treated with upadacitinib: malignancy excluding non-melanoma skin cancer, including malignancy by type, NMSC, MACE, VTE, serious and opportunistic infections (including herpes zoster and TB), GI perforations, liver injury (including DILI), bone fractures, and all-cause mortality; if a suitable comparator is identified, to describe and compare (when feasible) the incidence of the above safety outcomes in patients with RA treated with upadacitinib relative to those treated other select systemic RA treatments (excluding other JAK inhibitors).	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures	• Draft protocol • Progress report • Interim report • Final study report	• Submitted 16 March 2020 • Submitted in 2022 and 2023. No longer needed per EMA advice. • Submitted 19 September 2025 • Estimated Q1 2030

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	Secondary objectives are to describe the incidence of the safety outcomes mentioned under the primary objective among the following patient subcohorts of upadacitinib users: the very elderly (≥ 75 years of age), patients with moderate hepatic impairment (when possible using proxy measures available within a given data source), patients with severe renal impairment (when possible using proxy measures available within a given data source), and patients with evidence of chronic infection with HBV or HCV; if a suitable comparator is identified, to describe the incidence of the safety outcomes mentioned under primary objectives in the following patient subcohorts of other select systemic RA treatments: the very elderly (≥ 75 years of age), patients with moderate hepatic impairment (when possible using proxy measures available within a given data source), and patients with severe renal impairment (when possible using proxy measures available within a given data source) and patients with evidence of chronic infection with HBV or HCV.	Missing Information: use in very elderly (≥ 75 years of age); use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C; use in patients with moderate hepatic impairment; use in patients with severe renal impairment; long-term safety		

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P19-141 Long-Term Safety Study of Upadacitinib Use in RA Patients in the US/Ongoing	The primary objective is to compare the incidence of malignancy (excluding NMSC), NMSC, MACE, VTE, serious infection events, and all-cause mortality in adults with RA who receive upadacitinib in the course of routine clinical care relative to those who receive biologic therapy for the treatment of RA. Secondary objectives are to describe the incidence rates of herpes zoster, opportunistic infections, active TB, GI perforations, evidence of DILI, and fractures; to describe the incidence of the above outcomes in very elderly patients (aged ≥ 75 years); and to describe the incidence rates of events in primary and secondary objectives in the following subgroups of interest: patients with moderate hepatic impairment at the time of Rinvoq or biologic therapy start; patients with evidence of chronic infection with HBV or HCV at the time of Rinvoq or biologic therapy start; and patients with severe renal impairment at the time of Rinvoq or biologic therapy start. An exploratory objective is to describe the distribution of risk factors for VTE in those treated with Rinvoq and those treated with biologic therapy, and in those who do and do not experience VTE during follow-up, in a subset of participating patients providing laboratory samples.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures Missing information: use in very elderly (≥ 75 years of age); long-term safety; use in patients with moderate hepatic impairment; use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C; use in patients with severe renal impairment.	• Draft protocol • Progress report • Update on prevalence of baseline biomarkers and clinical risk factors within PSUR • Interim report • Final study report	• Submitted 16 March 2020 • Submitted in 2022 and 2023. No longer needed per EMA advice. • Annually for the first 2 years and thereafter in accordance with the PSUR reporting schedule • Estimated Q2 2029 • Estimated Q1 2030

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P20-199 Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA/ Ongoing	This study aims to evaluate the use of upadacitinib in routine clinical care through the following specific objectives: to describe the baseline characteristics of new users of, and in a similar manner, to describe new users of a selected bDMARD for comparison; to evaluate prescribers' adherence to the upadacitinib aRMMs, specifically: compliance to recommendations for patient screening and laboratory monitoring prior to and during treatment; compliance to recommendations for limitations of use, including: Use in patients with risk factors for GI perforation; use in patients with risk factors for VTE; use in the patients aged 65 years and older; use in patients with risk factors for CVD; use in patients with risk factors for malignancy; use in patients with risk factors for serious infections; and contraindicated use (active TB and pregnancy); and to describe changes in the utilisation of upadacitinib following the updated recommendations and limitations for use implemented after the Article 20 referral procedure.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; and fetal malformation following exposure in utero	• Draft protocol • Progress reports • Final study report	• Submitted 16 March 2020) • Submitted Q2 2022, Q1 2023; next estimated Q1 2024, Q2 2025 • Estimated Q3 2026
Study P20-390 Long-Term Safety Study of Upadacitinib Use in AD Patients/ Ongoing	To evaluate and characterise the important identified and potential risks of upadacitinib and missing information on the safety of upadacitinib. Primary objectives: To assess comparability across upadacitinib and other select systemic treatments for AD through in-depth assessments of treatment pattern and patient disposition at baseline;	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTE; DILI; fractures	• Draft protocol • Progress report • Interim report • Final Study Report	• Submitted 18 March 2021 • Annually starting 2023, except 2028 • Estimated Q4 2028 • Estimated Q4 2033

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	To describe the incidence of the following safety outcomes in adolescent and adult individuals with AD treated with upadacitinib: malignancy (excluding NMSC) including malignancy by type, NMSC, MACE, VTE, serious infections (incl. OI), HZ, EH/ KVE, active TB, GI perforation, DILI, fractures, and all-cause mortality; If a suitable comparator is identified: to describe and compare (when feasible) the incidence of the above safety outcomes in adolescent and adult individuals with AD treated with upadacitinib, relative to those treated with other selected systemic AD treatments. Secondary objectives: To describe the incidence of the outcomes above in upadacitinib users by: dose of upadacitinib (15 mg and 30 mg); age group (adolescents 12 – 17 years, 18 – 64 years, 65 – 74 years and ≥ 75 years) at the time of upadacitinib initiation; history of moderate hepatic impairment at the time of upadacitinib initiation; history of chronic infection with HBV or HCV at the time of upadacitinib initiation; history of severe renal impairment at the time of upadacitinib initiation. • If a suitable comparator is identified, to describe the incidence of the outcomes above in adolescent and adult individuals with AD treated with other selected systemic AD treatments by: age group (adolescents 12 – 17 years, 18 – 64 years, 65 – 74 years and ≥ 75 years) at the time of treatment initiation; history of moderate hepatic impairment at the time of treatment initiation; history of chronic infection with HBV or HCV at the time of treatment initiation; history of severe renal impairment at the time of treatment initiation.	Missing information: use in very elderly (≥ 75 years of age); long-term safety; use in patients with moderate hepatic impairment at the time of initiation of upadacitinib or other systemic drug therapies; use in patients with evidence of chronic infection with HBV or HCV at the time of initiation of upadacitinib or other systemic drug therapies; use in patients with severe renal impairment at the time of initiation of upadacitinib or other systemic drug therapies; long-term safety in adolescents		
Study P21-825 Drug Utilization Study Evaluating Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe/ Ongoing	To evaluate the use of upadacitinib in individuals with AD through the following objectives: To describe the baseline characteristics of individuals with AD who are new users of upadacitinib; To the extent measurable, evaluate healthcare utilization in routine clinical care as an indicator of physician adherence to the aRMMs among individuals with AD who are new users of upadacitinib, by: a) Quantifying the compliance to recommendations for posology (average daily dose) and by describing the duration of use; b) Quantifying the compliance to recommendations for the use among individuals who have risk factors for GI perforation, serious infections, malignancy, MACE, and VTE; c) Quantifying the compliance to the recommendations for the use among patients aged 65 years and older; d) Quantifying the compliance to the recommendations for contraindicated use including pregnancy, and active TB; e) Quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark, Germany, and Spain only).	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC, GI perforation Important potential risks: MACE; VTEs; malignancies excluding NMSC; and fetal malformation following exposure in utero	• Draft protocol • Progress Report 1 • Progress Report 2 • Final Study Report	• Submitted 27 May 2021 • Submitted 13 December 2024 • 19 September 2025 • Q3 2026
	To describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure, specifically: a) Describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections; b) Describe the use of upadacitinib among patients aged 65 years and older; c) Describe the use of upadacitinib 30 mg.			

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P21-824 A Study of Growth in Adolescents with AD Who Receive Upadacitinib/Ongoing	To evaluate the growth, development, and maturation in North American (US and Canada)-residing adolescents with moderate to severe AD who receive upadacitinib vs. biologic and other non-biologic, non-JAKi systemic comparators in routine clinical care. Where feasible, a cohort of European-residing adolescents with moderate to severe AD will also be evaluated. The primary objective is to compare differences in changes from baseline in height SDS and weight SDS, age at peak height velocity, age at Tanner stage progression, and incidence of bone fractures in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD. The secondary objectives of the study are to describe changes from baseline in standing height, height percentiles, height velocity, height velocity SDS, weight, weight percentiles, BMI, BMI percentiles, and BMI SDS, as well as the frequency of delayed puberty in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD.	Important potential risk: fractures Missing information: long-term safety in adolescents	• Draft Protocol • Annual reports • Interim report 1 • Interim report 2 • Final study report	• Submitted 27 May 2021 • Annually starting Q4 2024 • Estimated Q4 2027 • Estimated Q4 2030 • Estimated Q4 2033

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P24-343 Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe /Ongoing	Primary Objectives: To describe and compare the incidence of GI perforation in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy; To describe and compare, where possible, the incidence of fractures and DILI in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy. Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for incidence comparison of fractures and DILI. Secondary objectives: To describe and compare, where possible, the incidence of the following secondary safety outcomes in adults with UC or CD treated with upadacitinib, relative to those treated with biological drug therapies at a similar line of therapy for UC and CD in the course of routine clinical care: malignancy excluding NMSC (stratified by type), NMSC, MACE, VTE, serious infections (defined as all infections that require hospitalization, including opportunistic infections), herpes zoster, active TB, and all-cause mortality. Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures Missing Information: use in very elderly (≥ 75 years of age); long-term safety; use in patients with: moderate hepatic impairment at the time of initiation of upadacitinib or other systemic drug therapies; evidence of chronic infection with HBV or HCV at the time of initiation of upadacitinib or other systemic drug therapies; severe renal impairment at the time of initiation of upadacitinib or other systemic drug therapies.	• Draft protocol • Progress report • Interim study report • Final study report	• Submitted 09 August 2023 • Annually starting Q4 2025, except 2029 • Estimated Q4 2029 • Estimated Q2 2035

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for the incidence comparison of the secondary outcomes. In addition, incidence of the primary and secondary safety outcomes will be described in patients with UC or CD who receive upadacitinib by dosing pattern (45 mg induction followed by 15 mg and/or 30 mg maintenance dosing). When possible, the occurrence of the safety outcomes will be described in the following subgroups of interest, with limited or missing information from the clinical development program: very elderly (aged ≥ 75 years) at the time of treatment initiation; patients with moderate hepatic impairment at the time of treatment initiation; patients with severe renal impairment at the time of treatment initiation; patients with evidence of chronic infection with HBV or HCV at the time of treatment initiation.			

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P24-344 Effectiveness Evaluation of aRMMs for Upadacitinib in UC/Ongoing	To evaluate the use of upadacitinib in routine clinical care for UC through the following specific objectives: To describe the baseline characteristics of UC patients who are new users of upadacitinib; To the extent measurable, evaluate healthcare utilization in routine clinical care as indicator of physician adherence to the aRMMs among patients with UC who are new users of upadacitinib, by: a) Quantifying the compliance to recommendations for posology (average daily dose) and duration of use; b) Quantifying the compliance to recommendations for the use among patients who have risk factors for GI perforation, malignancy, MACE, VTE, and serious infections; c) Quantifying the compliance to the recommendations for the use among patients aged 65 years and older; d) Quantifying the compliance to the recommendations for contraindicated use including pregnancy and active TB; e) Quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark and Spain only).	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: MACE; VTEs; malignancies excluding NMSC; and fetal malformation following exposure in utero	• Draft protocol • Progress report • Final study report	• Submitted 21 October 2022 • Annually starting 2024 • Estimated Q3 2027

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	To describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure (Sweden only), specifically: a) Describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections; b) Describe the use of upadacitinib among patients aged 65 years and older; Describe the use of higher maintenance dose of upadacitinib 30 mg.			
Long-Term Extension Portion of Study M14-465/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety	• Final report submission	• 30 November 2028

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M15-572/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety	• Final report submission	• 31 December 2025
Long-Term Extension Portion of Study M19-944 (Study 1)/ Ongoing	To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active bDMARD-IR AS (Study 1), who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI, fractures; fetal malformation following exposure in utero Missing Information: long-term safety	• Final report submission	• Q3 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M19-944 (Study 2)/ Ongoing	To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active nr-axSpA (Study 2), who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI, fractures, fetal malformation following exposure in utero Missing Information: long-term safety	• Final report submission	• Q3 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M16-045/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in adolescent and adult subjects with AD who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents	• Final report submission	• Q2 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M16-047/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in combination with TCS in adolescent and adult subjects with AD who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents	• Interim report submission • Final report submission	• Q3 2026 • Q2 2031

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M18-891/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in adolescent and adult subjects with AD who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents	• Final report submission	• Q2 2026
Long-Term Extension Study M14-533/ Ongoing	To evaluate the long-term safety and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with UC who were nonresponders in Study M14-234 Substudy 1, subjects who lost response during Study M14-234 Substudy 3, and subjects who completed Study M14-234 Substudy 3	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety	• Final report submission	• Q3 2027

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M14-430/ Ongoing	To evaluate safety and efficacy of long-term administration of upadacitinib in subjects with moderately to severely active CD who participated in the Phase 3 upadacitinib induction and maintenance studies.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety	• Final report submission	• Q2 2028
Long-Term Extension Portion of Study M16-852/ Ongoing	To evaluate the safety and efficacy of continuing versus withdrawing upadacitinib in maintaining remission in subjects with GCA who achieved remission in Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: use in very elderly (≥ 75 years of age), long-term safety	• Final report submission	• Q2 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Protocol M23-716 Long-term Extension Portions of Study 1, 2, and 4; and Long-term Extension Study 3/Ongoing	To assess long-term efficacy and safety of continuous upadacitinib 15 mg QD, continuous upadacitinib 30 mg QD, dose escalation to upadacitinib 30 mg QD, and dose reduction to upadacitinib 15 mg QD in subjects with severe AA	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety, long-term safety in adolescents	Final report submission	Q1 2029

Risk minimisation measures

Table 55. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Serious and opportunistic infections including TB	Routine risk communication: • SmPC Section 4.4 summarizes the risk and provides guidance on ways to reduce the risk. • SmPC Section 4.4 includes a statement on dose dependency of upadacitinib on reports of serious infection. • SmPC Section 4.4 specifies a higher incidence of infections in the elderly and diabetic populations. • The PL warns when patients 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. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 outlines lymphocyte and neutrophil counts 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 chronic or recurrent infections. • 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. • 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. • SmPC Section 4.4 specifies patient populations for which upadacitinib should be used with caution. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Herpes zoster	Routine risk communication: • 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 describes 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. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 advises that prior to initiating upadacitinib patients be brought up to date with all immunizations including herpes zoster according to current immunization guidelines. • SmPC Section 4.4 advises that if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves.

	Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
NMSC	Routine risk communication: • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 indicates that NMSCs have been reported in patients treated with upadacitinib and includes a statement on dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 advises on periodic skin examination. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
GI perforation	Routine risk communication: • SmPC Section 4.4 informs on reports of diverticulitis and GI perforation in clinical trials and from post-marketing sources. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 advises to use with caution in patients who may be at risk for GI perforation and prompt evaluation if specific signs/symptoms occur. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Malignancies excluding NMSC	Routine risk communication: • SmPC Section 4.4 indicates that malignancies have been reported in patients receiving JAK inhibitors, including upadacitinib, and includes a statement on upadacitinib dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 specifies when the 15 mg dose is recommended.

	• SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
MACE	Routine risk communication: • 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 indicates that events of MACE were observed in clinical trials for upadacitinib. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
VTEs (deep venous thrombosis and pulmonary embolus)	Routine risk communication: • SmPC Section 4.4 indicates that events of deep vein thrombosis and pulmonary embolism have been reported in clinical trials for upadacitinib. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get certain symptoms. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies in patients with VTE risk factors other than cardiovascular or malignancy risk factors, use upadacitinib with caution. Examples of the risk factors which may put a patient at higher risk for VTE are provided. • SmPC Section 4.4 on re-evaluation of VTE risk and to promptly evaluate patients with signs and symptoms of VTE and discontinue upadacitinib in patients with suspected VTE, regardless of dose.

	Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
DILI	Routine risk communication: SmPC Section 4.4 describes the effect of upadacitinib on transaminases. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 recommends prompt investigation of the cause of 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. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Fetal malformation following exposure in utero	Routine risk communication: • SmPC Section 4.6 describes the teratogenic effects observed in animals receiving upadacitinib and state 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. Routine risk minimization activities recommending specific clinical measures to address the risk: • 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 pediatric 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. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Fractures	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription only medicine

Safety Concern	Routine Risk Minimization Activities
Use in very elderly (≥ 75 years of age)	Routine risk communication: • SmPC Section 4.2 states that there are limited data in patients 75 years of age and older. • SmPC Section 4.4 indicates that there is an increased risk of adverse reactions with upadacitinib 30 mg in patients 65 years of age and older. • SmPC Section 4.4 specifies increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomized study of tofacitinib (another JAK inhibitor). Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 specifies that upadacitinib 15 mg is recommended in patients 65 years of age and older. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine

Safety Concern	Routine Risk Minimization Activities
Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C	Routine risk communication: • 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. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 describes the need for screening and consultation with a hepatologist if HBV DNA is detected. Other routine risk minimization measures: Prescription only medicine

Safety Concern	Routine Risk Minimization Activities
Use in patients with moderate hepatic impairment	Routine risk communication: • SmPC Section 4.2 describes use in patients with hepatic impairment. Routine risk minimization activities recommending specific clinical measures to address the risk: • 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. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Use in patients with severe renal impairment	Routine risk communication: • SmPC Section 4.2 describes use in patients with renal impairment. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 states that upadacitinib should be used with caution in patients with severe renal impairment. • SmPC Section 4.2 specifies that for RA, PsA, AS, nr-axSpA, AD, GCA, and AA, the recommended dose is 15 mg QD for patients with severe renal impairment and that for UC and CD, the recommended dose is 30 mg QD for induction treatment and 15 mg QD for maintenance treatment for patients with severe renal impairment. Other routine risk minimization measures: Prescription only medicine.
Safety Concern	**Routine Risk Minimization Activities**
Long-term safety	Routine risk communication: • SmPC Section 4.4 indicates that upadacitinib clinical data on malignancies are currently limited and long-term studies are ongoing. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription only medicine.
Long-term safety in adolescents	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription only medicine.

Additional Risk Minimization:

Although the risks for upadacitinib are familiar to prescribers, consistent with marketed JAK inhibitor products, additional risk minimization will consist of an educational program targeted to both HCPs and patients.

Health Care Professional-Directed Measure – Health Care Professional Educational Guide

Objectives:

Overall objective for the HCP measure: To increase awareness of HCPs on the following upadacitinib risks: serious and opportunistic infections including TB, herpes zoster, fetal malformation (pregnancy risk), MACE, VTEs, malignancy, and GI perforation and ways to manage these risks.

The HCP measure will also serve to remind HCPs on clinical measures which are relevant in reducing each risk.

The HCP measure will also remind HCPs on key points to discuss with their patients and importance of the patient card.

Patient-Directed Measure – Patient Card

Objectives:

Overall objective for the patient card:

- To increase awareness of patients and caregivers on the following upadacitinib risks: serious and opportunistic infections including TB, herpes zoster, fetal malformation (pregnancy risk), MACE, VTEs, malignancy, and GI perforation and signs/symptoms to be aware of in order to alert their doctor.
- To communicate these risks to other treating HCPs (i.e., non upadacitinib prescribing HCPs in emergency or other settings)

Rationale for the Additional Risk Minimization Activity (Health Care Professional Educational Guide and Patient Card):

Consistent with already marketed JAK inhibitor products in the EU, additional risk minimization will be used. The targeted risks are serious and opportunistic infections including TB, herpes zoster, fetal malformation, MACE, VTEs, malignancy, and GI perforation. Reinforcement of awareness for these risks is deemed important, especially since all of these risks have specific clinical measures which may be used to help reduce the risk. In addition, awareness of the patient of these risks is important in order for the patient to know when to seek medical attention and why particular laboratory parameters are being following during treatment with upadacitinib.

Implementation Plan (Including Target Audience and Planned Distribution Path):

Health Care Professional Measure

Depending on local regulatory regulations, the HCP measure will be distributed to HCPs who prescribe upadacitinib for RA, PsA, AS, nr-axSpA, AD, UC, CD, GCA, or AA (i.e., rheumatologists, dermatologists, gastroenterologists, and others, depending on the local area) via multiple methods (i.e., delivery via the sales force, mail, email). If applicable, the measure will have information on how to access the same information but in digital format.

Depending on local regulatory regulations, the HCP measure is available on the local health authority website and/or the specific upadacitinib website, or other websites, if available in local countries.

Patient Card

Depending on local regulatory regulations, the patient measure will be distributed to HCPs who would then distribute the patient card to patients who are prescribed upadacitinib. Patient support programs or inclusion in medication packs may be used. If applicable, the patient measure will have information on how to access the same information but in digital format.

Depending on local regulatory regulations, the patient card is available on the local health authority website, AbbVie Care website, and/or the specific upadacitinib website, or other websites, if available in local countries.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success (Health Care Professional Educational Guide and Patient Card):

Effectiveness of the additional risk minimization program will be performed using Category 3 PASS – Drug utilization patterns and evaluation of the extent to which recommendations for patient screening and laboratory monitoring targeted by the additional risk minimization program are followed in RA, AD, and UC populations (see Part III.2 for additional details).

To assess the effectiveness of messaging contained in the HCP educational guide, outcome indicators will be described for patients who are treated with upadacitinib, including the following:

- Drug utilization of upadacitinib in populations of special interest which are targeted by messaging in the HCP educational guide:
    - Patients who are currently being treated for active TB;
    - Patients who are at high risk for VTEs (deep venous thrombosis and/or pulmonary embolus);
    - Patients who are pregnant at the time of initiation or become pregnant while taking upadacitinib;
    - Additional objectives to evaluate changes to aRMM (EMA procedure under Article 20 of Regulation (EC) 726/2004 [EMEA/H-A20/1517/C/004760/0017]) will be added based on feasibility.
- The extent to which recommendations for patient screening and laboratory monitoring are followed, including the following recommendations:
    - Assess lipid levels 12 weeks after starting upadacitinib; monitor and manage lipid levels during treatment: Occurrence of lipid testing;
    - Screen for viral hepatitis and monitor for reactivation in accordance with clinical guidelines: Occurrence of viral hepatitis screening;
    - Monitor patients for herpes zoster infections;
    - Check absolute lymphocyte count (ALC) and absolute neutrophil count (ANC) before and during upadacitinib treatment: Occurrence of lymphocyte and neutrophil screening;
    - No use of live, attenuated vaccines during, or immediately prior to starting upadacitinib treatment: Occurrence of live vaccination receipt;
    - Discontinue upadacitinib treatment in the event a patient experiences a deep venous thrombosis and/or pulmonary embolus;

- Additional objectives to evaluate changes to aRMM (EMA procedure under Article 20 of Regulation (EC) 726/2004 [EMEA/H-A20/1517/C/004760/0017]) will be added based on feasibility.

Removal of Additional Risk Minimization Activity:

Not applicable.

Overall conclusion on the RMP

☒ The changes to the RMP are acceptable.

2.8. Update of the Product information

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

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- The strength, pharmaceutical form, and route of administration are the same as for the currently approved indications.
- Data from the pivotal AA clinical studies demonstrate that overall, the safety profile of Rinvoq observed in adults & adolescents with severe AA was consistent with that for the existing approved indications.
- The revisions now proposed to the PL (i.e., those relevant to the AA indication) do not represent major changes.
- The general design and layout of the proposed PL has not changed.

3. Benefit-Risk Balance

3.1. Therapeutic Context

This application concerns an extension of indication to include the treatment of severe AA in adult and adolescents 12 years and older for Rinvoq (upadacitinib). The proposed posology is 15 mg or 30 mg once daily based on individual patient presentation for patients weighing at least 30 kg. A dose of 30 mg once daily may be appropriate for patients with high disease burden or patients with an inadequate response to 15 mg once daily. For patients 65 years of age and older, the recommended dose is 15 mg once daily.

Upadacitinib is a selective and reversible Janus kinase (JAK) inhibitor. Janus kinases are intracellular enzymes that transmit signals from cytokine or growth factor-receptor interactions on the cellular membrane to influence immune cell functions and haematopoiesis.

The mechanisms leading to alopecia areata are not fully understood. Insights into the immunopathogenesis of AA began with recognizing the hair follicle as an immune-privileged site like the eye and testes.[5] Disruption of this immune privilege occurs upon follicular influx by auto-reactive CD8+ T cells, leading to increases in major histocompatibility complex (MHC) Class I and II antigens and inflammation disrupting hair follicle biology.[1,6] Activation of the pathogenic T cells leads to IFNY production, which contributes both to enhanced MHC class I and II antigens and interleukin-15 (IL 15) [1,6] accompanied by additional cytokines including IL 2, IL-13, IL-23, and thymic stromal lymphopoietin.[7] All these inflammatory-related cytokines are dependent on JAK/STAT signalling, and of note, IFNY utilizes JAK1 and JAK2.

3.1.1. Disease or condition

Alopecia areata is an autoimmune disease characterized by patches of non-scarring hair loss. Severe AA is defined as scalp hair loss > 50% using the Severity of Alopecia Tool (SALT). Severe AA is recognized as a significant autoimmune condition with emotional and psychosocial distress, including high prevalence of depression and anxiety. Although up to 50% of patients with patchy alopecia areata experience spontaneous hair regrowth within one year, most will relapse months or years after remission.

Both children and adults may develop AA, and the disorder occurs at similar rates in males and females.[1] AA has a lifetime prevalence of approximately 2%.[6,24,25] The mean age for diagnosis of AA is predicted at 32 years in males and 36 years in females.[26]

3.1.2. Available therapies and unmet medical need

Baricitinib (Olumiant, inhibitor of JAK 1 and 2) and ritlecitinib (Litfulo, JAK3 and TEC inhibitor) are both centrally approved in the EU for the treatment of severe AA in adolescents (from age of 12 years) and adults. Some authorized medicines (e.g. methylprednisolone and triamcinolone intra-lesion injections) are available in individual member states.

Topical treatments (e.g. corticosteroids and minoxidil) are frequently used in AA. However, according to European expert consensus statement on the systemic treatment of AA, a SALT score equal to or greater than 20 constitutes a commonly accepted indication for systemic therapy in AA.[9] Systemic medicines used off-label in AA include glucocorticosteroids, cyclosporine, methotrexate and azathioprine. Oral minoxidil is considered an adjuvant therapy with limited data confirming its possible efficacy.[9]

Off-label treatments for AA in adults are used empirically for adolescent patients. Current treatments for children <10 years of age include topical corticosteroid (Class I–III) monotherapy or in combination with topical retinoids, topical anthralin, and rarely systemic steroids (pulse therapy).[10,11] Treatment in children >10 years of age may also include topical sensitisers and intralesional corticosteroids if tolerated (the latter treatment is locally approved in several European countries).[10,11] Methotrexate, hydroxychloroquine, azathioprine and other immunomodulators are used, despite limited efficacy data in this population.[9] Use of minoxidil is controversial both due to lack of efficacy [9] and tolerability concerns (lightheadedness, adherence issues) in children.[11]

[24] Wasserman et al. (2007), Alopecia areata. International Journal of Dermatology, 46: 121–131.
[25] Korta et al. (2018), Alopecia areata is a medical disease. Journal of the American Academy of Dermatology, 78: 832–834.
[26] Mirzoyev S.A et al. (2014), Lifetime incidence risk of alopecia areata estimated at 2.1% by Rochester Epidemiology Project, 1990–2009. Journal of Investigative Dermatology, 134: 1141–1142.

The limited authorized treatment options that exist for patients with AA, and the large psychosocial burden, present a high unmet need, especially in the adolescent population.

3.1.3. Main clinical studies

The application is supported by interim results from 2 replicate, pivotal, Phase 3 studies (M23-716 Study 1 and Study 2). The studies are randomized, double blind, placebo-controlled, multi-center studies of upadacitinib evaluating the efficacy and safety of upadacitinib 15 mg QD and 30 mg QD versus placebo for the treatment of severe AA.

Key eligibility criteria for the pivotal studies were age ≥12 years and < 64 years, body weight ≥ 30 kg, and diagnosis of severe AA (with SALT score ≥50 scalp hair loss, no spontaneous scalp hair regrowth over the past 6 months, and a current episode of AA < 8 years). Overall, the inclusion/exclusion criteria are representative of the targeted population.

A total of 1399 subjects (including 118 adolescents) with severe AA were enrolled in the studies. Eligible adult or adolescent subjects were randomized in a 2:2:1 ratio to 1 of 3 treatment groups: upadacitinib 15 mg QD (N = 559), upadacitinib 30 mg QD (N = 560), or matching placebo QD (N=280).

The primary endpoint of Study 1 and Study 2 was the achievement of SALT score ≤ 20 at Week 24, defined as less than or equal to 20% scalp hair loss.

3.2. Favourable effects

The primary efficacy endpoint, achievement of SALT score ≤20 at week 24, was met in both the upadacitinib 15 mg and 30 mg groups compared to the placebo group. In Study 1, the proportion of subjects achieving a SALT score ≤20 in the upadacitinib 15 mg group was 45.2% vs 1.5% in the placebo group, with an unadjusted difference of 43.8 (95% CI 37.6 to 49.9). The upadacitinib 30 mg group achieved a response rate of 55.0% vs 1.5% in the placebo group, with an unadjusted difference of 53.5 (95% CI 47.4 to 59.5) in the full population. The corresponding results obtained in Study 2 were 44.6% vs 3.4% for the 15 mg group, with an unadjusted difference of 41.0 (95% CI 34.9 to 47.1), and 54.3% vs 3.4% for the 30 mg group, with an unadjusted difference of 50.7 (95% CI 44.3 to 57.0).

Overall, the key multiplicity-controlled secondary endpoints support the effectiveness of upadacitinib in treatment of AA (upadacitinib 15 mg, upadacitinib 30 mg, placebo):

- Proportion of subjects achieving SALT ≤ 10 at week 24; (35.2%, 45.8% vs 0,7% [Study 1] and 36.0%, 47.1% vs 1.4% [Study 2]; p<0.001)
- Proportion of subjects achieving SALT 0 at week 24; (14.1%, 20.3% vs 0% [Study 1] and 13.1%, 22.5% vs 0.7% [Study 2]; p<0.001)
- Proportion of subjects achieving ClinRO Eyebrow Hair Loss score of 0 or 1 at Week 24 with a ≥2-point improvement from Baseline among subjects with Baseline score of ≥2; (40.6%, 61.8% vs 1.1% [Study 1] and 41.7%, 58.9% vs 3.2% [Study 2]; p<0.001)
- Proportion of subjects achieving ClinRO Eyelash Hair Loss score of 0 or 1 at Week 24 ≥2-point improvement from Baseline among subjects with Baseline score of ≥2; (43.7%, 58.6% vs 5.6% [Study 1] and 42.8%, 61.4% vs 3.7% [Study 2]; p<0.001)
- Baseline Change in Skindex-16 AA Emotions Domain scores; (-30.1%, -36.2% vs -14.6% [Study 1] and -31.3%, -34.4% vs -10.4% [Study 2]; p<0.001)

- Baseline Change in Skindex-16 AA Functioning Domain scores; (-21.5%, -24.6% vs -9.3% [Study 1] and -22.5%, -23.4% vs -7.1% [Study 2]; p<0.001)

The proportion of patients achieving a SALT score ≤ 20 from week 8 onwards showed a gradual increase over time. The SALT assessments at earlier timepoints overall suggest a relatively early onset of treatment benefit.

Results from subgroup analysis consistently favoured both upadacitinib doses over placebo, with all 95% confidence intervals excluding zero, indicating consistency in efficacy across subgroups. The subgroups prespecified included, but were not limited to, age, gender, AA severity, AA episode duration, and prior systemic AA treatment and prior AA treatment failure. Notably, the 30 mg dose appeared to show higher efficacy than the 15 mg dose, particularly in patients with very severe AA, but these results were only descriptive. The proportion of subjects achieving SALT score ≤ 20 at week 24 in the adolescent population was 56.3% in the upadacitinib 15 mg group and 80.9% in the 30 mg group vs 4.3% in the placebo group. The plasma exposure of upadacitinib in patients with AA seams comparable between adults and adolescent and in line with previous indications.

3.3. Uncertainties and limitations about favourable effects

Data on treatment extension up to 52 weeks is important in assessment of the overall long-term efficacy. The MAH has agreed to submit the CSRs for Study 1 and Study 2 Period B, Study 3, and Study 4 in Q1 2029. These Category 3 studies are expected to further characterise efficacy beyond 24 weeks.

While a total of 1399 subjects with severe AA were enrolled in the pivotal studies, only 118 of these were adolescent patients. Adolescents showed a numerically better treatment effect (SALT score of ≤20 at week 24) than the overall study population. However, as subgroup results were not type-1-error controlled, they are not statistically compelling and therefore considered supportive. The disease mechanism of AA is regarded to be similar between adults and adolescents. Furthermore, the baseline characteristics in Study 1 and Study 2 are viewed as being reasonably similar between adults and adolescents. In the context of the overall assessment of efficacy in the adolescent population, it is therefore considered that efficacy data can be extrapolated from the adult AA population.

3.4. Unfavourable effects

The safety database in the sought indication and supporting the proposed posology consists of 1372 patients, including 117 adolescents aged 12 to 17 years, and is based on 2 phase 3 studies, M23-716 Study 1 and Study 2, with a similar study design, comprising a double-blind 24-week period (Period A) and a blinded 28-week extension period (Period B).

Mean duration of exposure was 33.9 weeks for the any upadacitinib 15 mg group (n=686) and 33.1 weeks for the any upadacitinib 30 mg group (n=719). A total of 169 patients (12.3%) was exposed to any dose of UPA for at least 52 weeks. In adolescent patients, mean duration of exposure was 34.5 weeks for the any upadacitinib 15 mg group (n=62) and 37.4 weeks for the any upadacitinib 30 mg group (n=57). A total of 17 patients (14.5%) was exposed to any dose of UPA for at least 52 weeks.

Common TEAEs (reported in ≥5% of patients on upadacitinib in the placebo-controlled 24-week period or ≥10 events per 100 PY during the 52-week period) were acne, upper respiratory tract infections, nasopharyngitis and blood CPK increased; in the adolescent population, also cough, folliculitis and gastroenteritis were commonly reported. Most TEAEs were mild or moderate in severity.

No deaths were reported during either study.

The frequency of SAEs in the overall population was higher in the upadacitinib treatment groups (1.6% with upadacitinib 15 mg and 2.3% with upadacitinib 30 mg) compared with placebo (0.4%) and was also higher in the any upadacitinib 30 mg group (6.8%) compared with Any upadacitinib 15 mg (3.4%). SAEs reported in more than 1 patient were CPK increased and rhabdomyolysis, reported in 2 adult patients receiving UPA 30 mg (0.4 E/100 PY, each).

Treatment discontinuations due to TEAEs were reported in 0.9% and 1.4% of patients with upadacitinib 15 mg and upadacitinib 30 mg, respectively, vs. none with placebo in the placebo-controlled 24-week analysis set and in 1.0% and 1.8% of patients in the any upadacitinib 15 mg and any upadacitinib 30 mg group in the 52-week analysis set. In the adolescent population, ALT increased led to treatment discontinuation in a single patient in either analysis set.

In the 52-week analysis set, the adverse events of special interest in terms of serious infections, herpes zoster, hepatic disorder, anaemia, neutropenia, lymphopenia and CPK elevation were reported at a higher rate in the any upadacitinib 30 mg group compared with any upadacitinib 15 mg. Hepatic disorder events concerned increases in transaminases and bilirubin; no events of DILI were reported.

The safety profile in adolescent patients was consistent with the safety profile in the overall population.

3.5. Uncertainties and limitations about unfavourable effects

The size of the overall safety database in the indication of severe alopecia areata is considered adequate. The size of the safety database in terms of adolescent patients in the sought indication is considered adequate, with support of safety data in adolescent patients in the atopic dermatitis indication.

Long-term safety in the paediatric population in terms of the important identified and potential risks as well as data on growth and development is recommended to be monitored as part of the proposed additional pharmacovigilance activities in the context of the RMP.

3.6. Effects Table

Table 56. Effects Table for Rinvoq, severe alopecia areata in adults and adolescents 12 years and older - data cut-off: 08 July 2025 (Study 1) and 13 June 2025 (Study 2)

Effect	Short description	Unit	Placebo	UPA 15 mg	UPA 30 mg	Uncertainties / Strength of evidence	References
Favourable Effects							
SALT ≤20 at week 24 (primary endpoint)	Severity of Alopecia Tool	%	1.5	45.2	55.0	SoE: p < 0.001	Study 1
			3.4	44.6	54.3		Study 2
SALT ≤10 at week 24	Severity of Alopecia Tool	%	0.7	35.2	45.8	SoE: p < 0.001	Study 1
			1.4	36.0	47.1		Study 2
SALT score of 0 at Week 24	Severity of Alopecia Tool	%	0	14.1	20.3	SoE: p < 0.001	Study 1
			0.7	13.1	22.5		Study 2
ClinRO Eyebrow Hair Loss score of 0 or 1 at Week 24	≥2-point improvement from Baseline among subjects with Baseline score of ≥2		1.1	40.6	61.8	SoE: p < 0.001	Study 1
			3.2	41.7	58.9		Study 2
ClinRO Eyelash Hair Loss score of 0 or 1 at Week 24	≥2-point improvement from Baseline among subjects with Baseline score of ≥2		5.6	43.7	58.6	SoE: p < 0.001	Study 1
			3.7	42.8	61.4		Study 2
Baseline Change in Skindex-16 AA Emotions Domain scores	PRO. Measures the effects of AA on a subject's health-related quality of life.		-14.6	-30.1	-36.2	SoE: p < 0.001	Study 1
			-10.4	-31.3	-34.4		Study 2
Baseline Change in Skindex-16 AA Functioning Domain scores	PRO. Measures the effects of AA on a subject's health-related quality of life.		-9.3	-21.5	-24.6	SoE: p < 0.001	Study 1
			-7.1	-22.5	-23.4		Study 2
Unfavourable Effects							
Adverse events of special interest (52-week analysis set)							

Effect	Short description	Unit	Placebo	UPA 15 mg	UPA 30 mg	Uncertainties / Strength of evidence	References
Serious infections	Overall Adolescent	E/100 PY	N/A	0.70	1.30		
Herpes zoster	Overall Adolescent	E/100 PY	N/A	2.00	4.40		
Hepatic disorder	Overall Adolescent	E/100 PY	N/A	7.02.4	12.04.9		
Anaemia	Overall Adolescent	E/100 PY	N/A	1.80	2.20		
Neutropenia	Overall Adolescent	E/100 PY	N/A	4.32.4	8.37.3		
Lymphopenia	Overall Adolescent	E/100 PY	N/A	0.90	2.62.4		
CPK elevation	Overall Adolescent	E/100 PY	N/A	13.34.9	15.514.7		
Malignancy	Overall Adolescent	n/100 PY	N/A	0.20	00		
Adjudicated VTE	Overall Adolescent	n/100 PY	N/A	0.20	00		
Bone fractures	Overall Adolescent	n/100 PY	N/A	1.42.5	1.10		
Retinal detachment	Overall Adolescent	n/100 PY	N/A	0.20	00		

Abbreviations: SoE = strength of evidence, Unc. = Uncertainty, N/A: not applicable, CPK: creatine phosphokinase, VTE: venous thrombotic event

Notes: AESIs are expressed as E/100 PY or n/100 PY (for malignancy, adjudicated VTE, bone fractures and retinal detachment)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The main evidence of efficacy comes from interim results from 2 replicate, pivotal, Phase 3 studies (M23-716 Study 1 and Study 2). Overall, the design of Study 1 and Study 2 is acceptable. The studied population is representing the target population in the proposed indication severe alopecia areata.

Most of the efficacy endpoints chosen for this application are considered clinically relevant and are accepted.

The primary endpoint as well as most of the key secondary endpoints were met in both upadacitinib treatment groups in Study 1 and Study 2. Generally, the proportions of patients achieving the secondary endpoints measured at week 24 were larger for the high-dose upadacitinib compared to the low-dose upadacitinib and placebo.

The results are considered to be robustly documented and of clinical relevance for the sought indication. Data is only available for 24 weeks treatment which is a limitation considering the chronicity of the condition. However, long term evaluation of safety and efficacy Phase 3 studies are ongoing (Study M23-716 long-term extension portions of Study 1, 2, and 4; and long-term extension Study 3) and are expected to be submitted by Q1 2029 with the objective of further characterizing efficacy beyond 24 weeks.

Results from subgroup analysis consistently favoured both upadacitinib doses over placebo, with all 95% confidence intervals excluding zero, indicating consistency in efficacy across subgroups. The subgroups prespecified included, but were not limited to, age, gender, AA severity, AA episode duration, and prior systemic AA treatment and prior AA treatment failure. Notably, the 30 mg dose appeared to show higher efficacy than the 15 mg dose, particularly in patients with very severe AA, but these results are only descriptive.

The treatment effect (SALT score of ≤20 at week 24) in adolescents seems to be consistent with the results observed in the overall study population. Generally, the same tendency was noted in the proportion of adolescents achieving the secondary endpoints SALT score of ≤10 at week 24, SALT score of ≤20 at week 8 and SALT score of ≤20 at week 12.

There are limited treatment options available for the management of severe AA, especially in the adolescent population. In terms of benefit, upadacitinib provides a significant and clinically meaningful beneficial treatment effect on severe AA in adults and adolescents 12 years and older at week 24, as compared to placebo.

The safety profile in the patient population with severe alopecia areata, including in the subset of adolescent patients, was consistent with the known safety profile of upadacitinib in other indications. No new important safety findings have been identified. Long-term safety in the paediatric population in terms of the important identified and potential risks as well as data on growth and development is recommended to be monitored as part of the additional pharmacovigilance activities in the context of the RMP.

3.7.2. Balance of benefits and risks

The balance of benefits and risks of upadacitinib for the treatment of severe alopecia areata in adults and adolescents 12 years and older, is positive. For adults and adolescent patients 12 years of age and older weighing at least 30 kg, the recommended dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation. Overall, the safety profile in adult and adolescent patients 12 years and older with AA is consistent with that observed for other indications, with no new safety signals identified.

3.8. Conclusions

The overall B/R of Rinvoq is positive in the following indication:

Alopecia areata

RINVOQ is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years and older (see section 5.1).

4. Recommendations

Outcome

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

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

Extension of indication to include the treatment of severe alopecia areata (AA) in adult and adolescents 12 years and older, based on interim results from 2 pivotal, Phase 3 studies (M23-716 Study 1 and Study 2); those are randomized, double blind, placebo-controlled, multi-center studies of Upadacitinib evaluating the efficacy and safety of Upadacitinib 15 mg QD and 30 mg QD versus placebo for the treatment of severe AA in subjects who are at least 12 years of age. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Annex II are updated in accordance. Version 20.0 of the RMP is approvable.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II, IIIB, and to the Risk Management Plan are recommended.

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

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

- **Risk management plan (RMP)**

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

- **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, VTE, and malignancy 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 card

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.
- Indication and posology statements provided to reinforce in whom upadacitinib should be used
- Use in patients 65 years of age and older
    - Language to reinforce risks in these patients and use of the 15 mg dose
- Language for HCPs to inform patients of the importance of the patient card
- *Risk of serious and opportunistic infections including TB*
    - Language on the risk of infections during treatment with upadacitinib
    - Language on increased risk of serious infections in patients 65 years of age and older
    - 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)
    - Language on contraindication in patients with active TB and on consideration of anti-TB therapy in patients with latent TB
    - Language on avoidance of live vaccines (i.e., Zostavax) prior to and during upadacitinib treatment
    - 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*
    - Language on the risk of herpes zoster during treatment with upadacitinib
    - 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*
    - Language on teratogenicity of upadacitinib in animals
    - Details on how to reduce the risk of exposure during pregnancy for female patients of childbearing potential based on the following: upadacitinib is contraindicated during pregnancy, female patients 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*
    - In patients at high risk for MACE upadacitinib should only be used if no suitable treatment alternatives are available, with examples of who may be at high risk.
    - Language on the risk of hyperlipidaemia during upadacitinib therapy
    - Details on monitoring of lipid levels and management of elevated lipid levels per clinical guidelines
- *Risk of VTE*
    - Examples of the risk factors which may put a patient at higher risk for venous thromboembolic event (VTE) and in whom caution is needed when using upadacitinib.
    - Use of caution in patients at high risk during treatment with upadacitinib
    - Language that patients should be periodically reevaluated for changes in VTE risk
    - Language on need for discontinuation of upadacitinib, evaluation, and appropriate treatment for VTE if clinical features of deep venous thrombosis or pulmonary embolism develop
- *Risk of Malignancy*
    - In patients at high risk for malignancy upadacitinib should only be used if no suitable treatment alternatives are available, with examples of who may be at high risk.
    - Reminder about the need for periodic skin examination for patients.
- *Risk of gastrointestinal perforation*
    - Upadacitinib should be used with caution in patients at risk for gastrointestinal perforation with examples of those who may be at risk.
    - Reminder that patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis or gastrointestinal perforation.

The 30 mg upadacitinib dose in moderate to severe atopic dermatitis

- Language on dose-dependent increase in serious infections and herpes zoster with upadacitinib.
- Language on dose-dependent increase in NMSC and malignancy
- Language on dose-dependent increase in plasma lipids with upadacitinib.
- Language that the 30 mg dose is not recommended in certain populations (patients with severe renal impairment and patients taking strong CYP3A4 inhibitors).
- Language to reinforce that the lowest effective dose of upadacitinib should be used for treatment.

The 30 mg upadacitinib dose in severe alopecia areata

- 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 the 30 mg dose is not recommended in certain populations (patients with severe renal impairment and patients taking strong CYP3A4 inhibitors).
- Language to reinforce that the lowest effective dose of upadacitinib should be used for treatment.

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 that if their adolescent patient has not experienced menarche, to inform their adolescent patient or caregiver to let them know when they do.

Information for upadacitinib use in moderate to severe ulcerative colitis (UC) or Crohn's disease (CD)

- Reminder to review induction and maintenance dosing in product labeling.
- Language on dose-dependent increase in serious infections and herpes zoster with upadacitinib
- Language on dose-dependent increase in NMSC and malignancy
- Reminder about induction and maintenance dose in certain populations (patients taking strong CYP3A4 inhibitors and severe renal impairment).
- Language to reinforce that the lowest effective dose of upadacitinib should be used for maintenance treatment

Instructions on where to report AEs will be included.

Instructions for how to access digital HCP information will be included, if applicable.

The patient information pack should contain:

- Package leaflet
- A patient card
- **The patient card** shall contain the following key messages:

- Contact details of the upadacitinib prescriber
- Language that the patient card 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.
    - Language to advise patients to tell their HCP if they have history or have been in contact with TB.

- Description of targeted risks for awareness by the patient and for HCPs involved in their care including:
  - Risk of heart disease:
  - Describe signs/symptoms of heart disease that the patient needs to be aware of, so that they can seek attention from their HCP
  - 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
  - Reminder of the risk of cancer. Regarding skin cancer reminder to let their doctor know if they notice any new growth on the skin.
  - Risk of a hole in the bowel – description of signs/symptoms which the patient needs to be aware of, so that they can seek attention from an HCP

Paediatric data

The requirements for the submitted dossier in relation to paediatrics are described in section 1 of this report.

The Phase 3 studies M23-716 Study 1 and Study 2 submitted as part of this application are not part of the agreed PIP, even though they included adolescent participants. This is because the MAH previously informed PDCO that the adolescent indication would not be based on data from the adult/adolescent studies. The available results of the submitted studies are reflected in sections 4.8, 5.1 & 5.2 of the Summary of Product Characteristics (SmPC).

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Rinvoq-H-C-4760-II-EMAVR0000312506'

Attachments

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