25 June 2026
EMADOC-1700519818-3190821
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rinvoq

International non-proprietary name: upadacitinib

Procedure No. EMA/VR/0000325958

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event(s) of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aRMM	additional risk minimization measure
AST	aspartate aminotransferase
BL	Baseline
BMI	body mass index
BSA	body surface area
CHMP	Committee for Human Medicinal Products
CI	confidence interval
ClinRO	Clinician-Reported Outcome
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CPK	creatine phosphokinase
CSE	Clinical Summary of Efficacy
CSR	Clinical study report
CSS	Clinical Summary of Safety
CYP	cytochrome P450
Diff	difference
DVT	deep vein thrombosis
EAER	exposure-adjusted event rate
EAIR	exposure-adjusted incidence rate
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
F-VASI	Facial Vitiligo Area Scoring Index
GCP	Good Clinical Practice
GI	gastrointestinal
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN	interferon
IL	interleukin
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT_A	Intent-to-treat population in Period A
ITT_B	Intent-to-treat population in Period B
IV	intravenous(ly)
JAK	Janus kinase

LS	least square
MACE	major adverse cardiovascular event
MAR	missing at random
Max	maximum
MI	multiple imputation
Min	minimum
MTX	methotrexate
NB-UVB	Narrowband Ultraviolet B
NMSC	non-melanoma skin cancer
NRI	Non-Responder Imputation
NRI-MI	Non-Responder Imputation incorporating multiple imputation
NSV	non-segmental vitiligo
PaGIC-V	Patient's Global Impression of Change-Vitiligo
PBO	placebo
PCI	potentially clinically important
PhGIC-V	Physician's Global Impression of Change – Vitiligo
PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PRO	patient-reported outcome
PUVA	Psoralen + Ultraviolet A
PT	preferred term
PY	patient year(s)
QD	once daily
QoL	quality-of-life
RMP	Risk Management Plan
RTB	return-to-Baseline
RTB-MI	return-to-Baseline multiple imputation
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TB	tuberculosis
TBL	total bilirubin
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
T-VASI	Total Vitiligo Area Scoring Index
ULN	upper limit of normal
UPA	upadacitinib
US	United States

UV	ultraviolet
VNS	Vitiligo Noticeability Scale
vs.	versus
VTE	venous thromboembolic event

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 28 January 2026 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.6.a	C.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 non-segmental vitiligo in adults and adolescents 12 years and older who are candidates for systemic therapy, for Rinvoq, based on results from the two replicate Phase 3 studies M19-044: study 1 (R&D/25/1342) and study 2 (R&D/25/1343), as well as from integrated long-term safety data. Study 1 and study 2 are Phase 3, global, randomized, double-blind, placebo-controlled multi-center studies that evaluate the safety and efficacy of upadacitinib in adult and adolescent patients with non-segmental vitiligo. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated in accordance. Version 19.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI. 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 and 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/0383/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0383/2023 was not yet completed as some measures were deferred.

A positive outcome for the partial PIP compliance check (EMA/PE/0000314098) was received on 30 January 2026, which confirms compliance with the agreed PIP for upadacitinib for the condition 'treatment of vitiligo (PIP P/0383/2023).

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 2	Compliance confirmed	Double-blind, randomised, placebo-controlled trial to evaluate safety and efficacy of upadacitinib in children

		from 12 years to less than 18 years of age (and adults) with nonsegmental vitiligo
Study 3	Compliance confirmed	Double-blind, randomised, placebo-controlled trial to evaluate safety and efficacy of upadacitinib in children from 12 years to less than 18 years of age (and adults) with nonsegmental vitiligo
Study 5	Compliance confirmed	Modelling and simulation study to evaluate the use of upadacitinib in children from 12 years to less than 18 years of age with nonsegmental vitiligo

Information relating to orphan market exclusivity

N/A

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.

Scientific advice

The MAH received Scientific Advice from the CHMP on 20 July 2023 (EMA/SA/0000121195). The Scientific Advice pertained to clinical aspects of the dossier.

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	28 January 2026
Start of procedure:	21 February 2026
CHMP Rapporteur's preliminary assessment report circulated on:	17 April 2026
PRAC Rapporteur's preliminary assessment report circulated on:	22 April 2026
PRAC Rapporteur's updated assessment report circulated on:	30 April 2026
PRAC Outcome	07 May 2026
CHMP Rapporteur's updated assessment report circulated on:	13 May 2026
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:	10 June 2026
PRAC Rapporteur's preliminary response assessment report on the MAH's responses circulated on:	11 June 2026
PRAC comments	n/a
CHMP comments	n/a
PRAC Rapporteur's updated response assessment report on the MAH's responses circulated on:	17 June 2026
CHMP Rapporteur's updated response assessment report on the MAH's responses circulated on:	18 June 2026
CHMP opinion:	25 June 2026
The CHMP adopted a report on the significant clinical benefit for Rinvoq in comparison with existing therapies (Appendix 1)	25 June 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

This application pertains to the extension of indication for Rinvoq (upadacitinib) in the treatment of non-segmental vitiligo.

Disease or condition

Vitiligo is a chronic autoimmune disease characterized by depigmented skin lesions due to loss of melanocytes in the epidermis. The natural course of the disease is often progressive and unpredictable,

and it can lead to a decline in quality of life, self-esteem, and amplify social stigma.[1,2] Among all cases of vitiligo, non-segmental vitiligo (NSV) is the predominant type, accounting for an estimated 81% to 97% of cases).[3,4,5] In general, the term vitiligo is used to encompass all forms of NSV, including acrofacial, mucosal, generalized, universal, mixed, and rare variants.

State the claimed the therapeutic indication

The proposed therapeutic indication is:

"Rinvoq is indicated for the treatment of non-segmental vitiligo in adults and adolescents 12 years and older who are candidates for systemic therapy." with the posology "The recommended dose of upadacitinib is 15 mg once daily for adults and adolescent patients 12 years of age and older weighing at least 30 kg."

Epidemiology

Vitiligo is the most common depigmenting disorder, with a prevalence of approximately 0.5% to 1% in the world population.[1,3,6] Since vitiligo can present at any age and seldom goes into complete remission, the prevalence increases with age. [1]Almost half of patients develop vitiligo before 20 years of age.[2] The disease appears to be equally distributed in men and women and affect people of all skin types and races with no predilection. [2,7]

Aetiology and pathogenesis

Although the exact aetiology is unknown, the autoimmune theory proposes that activated CD8+ T-cells mediate destruction of melanocytes via the release of IFN-γ, which activates JAK/STAT via CXCR3-CXCL9/10.[8] Once a sufficient number of melanocytes are destroyed, noticeable depigmentation occurs due to the inability to replenish the melanin content in the skin. The natural history of vitiligo is characterized by cycles of flare-ups, stabilization, and repigmentation. Environmental factors, such as UV light exposure or certain chemicals, may trigger immune responses leading to the destruction of melanocytes and development of depigmented patches.[9] Vitiligo lesions are classified as stable (unchanged for 6 months or more) or actively spreading (increasing in size). Signs of active disease include new lesions after skin trauma (Koebner phenomenon), trichrome appearance, inflammation at the border, and confetti-like small, depigmented spots.[10]

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[1] Haulrig al. (2024), The global epidemiology of vitiligo: A systematic review and meta-analysis of the incidence and prevalence. *JEADV Clinical Practice*, 3: 1410–1419
[2] Taïeb, A. and Picardo, M. (2009), Vitiligo. *New England Journal of Medicine*, 360: 160–169.
[3] Gandhi et al. (2022), Prevalence of vitiligo among adults in the United States. *JAMA Dermatology*, 158: 43–50.
[4] Ingordo, et al. (2014), Circulating autoantibodies and autoimmune comorbidities in vitiligo patients: A multicenter Italian study. *Dermatology*, 228: 240–249.
[5] Mazereeuw-Hautier et al. (2010), Segmental and nonsegmental childhood vitiligo have distinct clinical characteristics: A prospective observational study. Journal of the American Academy of Dermatology, 62: 945–949.
[6] Akl et al. (2024), Estimating the burden of vitiligo: A systematic review and modelling study. *The Lancet Public Health*, 9: e386–e396.
[7] Alikhan, A., Felsten, L. M., Daly, M., & Petronic-Rosic, V. (2011).
Vitiligo: A comprehensive overview. Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. *Journal of the American Academy of Dermatology, 65*(3), 473–491.
[8] Rodrigues, M., Ezzedine, K., Hamzavi, I., Pandya, A. G., & Harris, J. E. (2017). New discoveries in the pathogenesis and classification of vitiligo. *Journal of the American Academy of Dermatology, 77*(1), 1–13.
[9] Ezzedine, K., Eleftheriadou, V., Whitton, M., & van Geel, N. (2015). Vitiligo. *The Lancet, 386*(9988), 74–84. https://doi.org/10.1016/S0140-6736(14)60763-7.
[10] Ezzedine, K., Tannous, R., Pearson, T. F., & Harris, J. E. (2025).
Recent clinical and mechanistic insights into vitiligo offer new treatment options for cell-specific autoimmunity. *Journal of Clinical Investigation, 135*(2)

Clinical presentation, diagnosis

The clinical presentation of vitiligo typically involves asymptomatic depigmented patches and macules, without clinical signs of inflammation. Classification is based on the Vitiligo Global Issues Consensus Conference (2012), which defined two broad categories: non-segmental (NSV) and segmental vitiligo (SV). The two other categories are mixed (SV and NSV), and unclassified. NSV is further categorised into generalised, acro / acrofacial, focal, mucosal, or universal subtypes; the first being the most prevalent. SV typically occurs in a (quasi)dermatomal pattern, most frequently along the trigeminal nerve. It is less common than NSV and presents most often in childhood.

The clinical course of vitiligo is unpredictable, with stable disease, slow progression over years, flares, etc. Progression is more common in patients with a family history of NSV, longer disease duration, Koebner phenomenon, or mucosal involvement. Diagnosis is usually quite straightforward, based on clinical presentation of well-demarcated, uniformly white macules surrounded by normal skin in the absence of inflammatory signs. The differential diagnosis is extensive and comprises chemically induced leukoderma, topical or systemic drug-induced depigmentation, post-inflammatory hypopigmentation, neoplasm-related hypomelanoses, idiopathic hypomelanosis, congenital hypomelanosis, and other conditions. The diagnosis may be facilitated by using a Wood's lamp or dermoscopy. A skin biopsy is rarely necessary but can be useful in certain cases. Histological examination typically reveals a complete or near complete loss of epidermal pigmentation and an absence of melanocytes in the basal layer. Other findings may be vacuolar degeneration of keratinocytes, spongiosis, and dermal lymphocyte infiltration. Immunohistochemical staining shows a predominance of CD8+ positive T-lymphocytes.

Management

There are currently few available topical and systemic treatment options, with most not approved for NSV or having limited efficacy. Topical corticosteroids (TCS) are recommended for NSV, particularly for extrafacial locations and more limited treatment areas. Moreover, topical calcineurin inhibitors (TCI) are considered first-line treatment in adults and children with limited involvement, especially for lesions involving the face, neck, and body folds with thin skin (e.g., axillary and inguinal regions). Phototherapy remains a key tool in the treatment of vitiligo, with narrowband UVB (NB-UVB) being the preferred first-line therapy for widespread or rapidly progressive disease.[11]

Methotrexate, cyclosporine, azathioprine, and minocycline can be used in patients with progressive NSV, although strong evidence for efficacy and safety is lacking. Oral mini-pulses of corticosteroids twice weekly on 2 consecutive days per week are recommended, with careful consideration of the risks and benefits, for the treatment of rapidly progressive NSV to stop disease progression. The recommended duration of use is up to 3 months, with a maximum of 6 months due to the risk of adverse effects.

Opzelura (ruxolitinib, a topical JAK inhibitor) is the first treatment approved for the repigmentation of NSV. It was granted a marketing authorisation by a European Commission decision on 19 April 2023 for the treatment of NSV with facial involvement in adults and adolescents 12 years of age and older. There is currently no approved systemic medical therapy for NSV.

In conclusion, there is a high unmet need for adolescent and adult patients with NSV for a systemic therapeutic option with a positive benefit-risk profile that provides and maintains re-pigmentation and helps to alleviate the impaired QoL and high psychosocial burden associated with NSV.

[11] Seneschal et al. (2023) Worldwide expert recommendations for the diagnosis and management of vitiligo: Position statement from the international Vitiligo Task Force—Part 2: Specific treatment recommendations. *Journal of the European Academy of Dermatology and Venereology, 37*(11), 2185–2195.

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, 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.

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

Development programme

The upadacitinib NSV clinical development programme includes two replicate Phase 3 studies, Study 1 and Study 2, and the optional, exploratory Study 3, all under a single protocol (M19-044). For Study 1 and Study 2, the study duration included a 35-day screening period; a 48-week placebo-controlled, double-blind treatment period (Period A); a 112-week open-label extension period (Period B); and a 30-day follow-up period. The NSV clinical development programme also included a dose-ranging Phase 2 study in NSV (M19-051) that has been completed.

The pivotal 48-week placebo-controlled, double-blind treatment period M19-044 Study 1 and Study 2 period A are both complete. The data cutoff date for analyses presented in this submission is 24 September 2025. For participant details please refer to 'Participant flow and numbers analysed' section of this report. At the time of the CHMP opinion, the MAH committed to submit the final Clinical Study Reports (CSRs) from Period B of Study 1 and Study 2 (112-week open-label extension period) in Q2 2028. These studies are classified as Category 3 studies and are included in the Risk Management Plan (RMP).

Scientific advice

Scientific advice from regulatory agencies, including the US FDA, CHMP, Swedish MPA and Japan PMDA, was sought on the upadacitinib NSV Phase 3 clinical development programme. Key scientific advice feedback from FDA and EMA for the M19-044 studies (1 and 2) and resulting changes to the study designs are summarized in Table 1.

Table 1. Key Feedback Incorporated in Protocol M19-044 After Scientific Advice

Agency	Scientific Advice	Key Changes Following Scientific Advice
Adolescents:		
EMA	• It is recommended to aim at a minimum of 50 adolescents (n = 33 on upadacitinib and n = 17 on placebo), increasing the precision of the point estimate in this subgroup.	• The number of adolescents enrolled was increased.
Endpoints:		
FDA	• The proposed co-primary endpoints of "the proportion of subjects achieving ≥ 50% reduction from Baseline in T-VASI (T-VASI 50) at Week 48" and "the proportion of subjects achieving ≥ 75% reduction from Baseline in F-VASI (F-VASI 75) at Week 48" are acceptable. • The proposed secondary endpoints of F-VASI 75 at Week 24, F-VASI 90 at Week 48, T-VASI 75 at Week 48 are acceptable. • We consider the endpoints related to the Physician's Global Impression of Change-Vitiligo (PhGIC-V) and Patient's Global Impression of Change Vitiligo (PaGIC-V) scales as exploratory efficacy endpoints. The PhGIC-V and PaGIC-V can be used as anchors to interpret meaningful within patient score changes in the target clinical outcome assessment endpoints. • We do not agree with the proposed ranked secondary endpoints based on the Vitiligo Noticeability Scale (VNS), and sun sensitivity and itch items.	• FDA comments were acknowledged. • Secondary endpoints were revised accordingly.

Agency	Scientific Advice	Key Changes Following Scientific Advice
Endpoints:		
EMA	• The use of F-VASI 75 at Week 48 as the primary endpoint and the use of T-VASI 50 at Week 48, F-VASI 50 at Week 48, PaGIC-V and PhGIC-V at Week 48, VNS at Week 48, F-VASI 75 at Week 24 as ranked secondary outcomes is agreed.	• EMA comments were acknowledged. Subsequently T-VASI 50 at Week 48 was added as a co-primary endpoint.
	• However, considering 'a little better' to already indicate a response in PaGIC-V and in PhGIC-V is not supported. Similarly, it is not supported to include 'slightly less noticeable' as indicating response for the VNS but VNS response of 'a lot less noticeable' or 'no longer noticeable' would be acceptable. Inclusion of improvement in sun sensitivity and/or itch at lesion sites in the ranked secondary endpoints is not supported. Instead of these, it is strongly recommended to include an endpoint relevant to the broader target population, such as VitiQoL. From the perspective of validity testing, the inclusion of the 3D digital imaging at Week 24 (Study 1 only) is endorsed. Further addition of continuous measures on repigmentation as secondary endpoints, e.g., F-VASI and T-VASI, is recommended for obtaining a more accurate assessment of effect size.	• Secondary and additional endpoints were revised accordingly.
Safety:		
FDA	• We recommend that the safety database in the treatment of vitiligo consists of at least 300 subjects exposed for 1 year at the to-be-marketed dose.	• The data of 339 subjects with NSV exposed to upadacitinib 15 mg for at least 52 weeks are included in the safety data set provided with the dossier.

Agency	Scientific Advice	Key Changes Following Scientific Advice
EMA	• The proposed size of the safety database is likely to be sufficient for review in terms of number of subjects exposed as well as duration of exposure, provided unexpected safety signals do not emerge during the conduct of the clinical trials.	• EMA comments were acknowledged.
Statistics:		
FDA	• FDA agreed with the planned multiple imputation approach to handling missing data and recommended the SAP clearly specify the types of missing data that "can reasonably be assumed to be Missing at Random" to ensure that the approach is adequately prespecified.	• The SAP was updated to clearly specify the types of missing data that "can reasonably be assumed to be Missing at Random."
	• FDA requested to include ethnicity in the efficacy subgroup analyses.	• The SAP was updated to include ethnicity in the efficacy subgroup analyses.
	• FDA recommended the proposed ISS analyses in the SAP include the following: ○ For age subgroup analysis, include analyses for subjects < 65 and ≥ 65 years of age	• The ISS SAP was updated to include the suggested age subgroup analysis for subjects < 65 and ≥ 65 years of age.
EMA	• Efficacy assessment should continue beyond study treatment discontinuation; otherwise, it is not possible to analyze "regardless of discontinuation." The confounding medications triggering "non-response" should be clearly defined and the decision to start these medications should be strongly indicative of unfavorable outcome. In these situations, dichotomized endpoints can be analyzed "non-response." For the continuous endpoints, the Applicant's hypothetical scenario of return-to-baseline is not understood.	• EMA comments were acknowledged, and protocol and SAPs were revised. For continuous endpoints, missing data after treatment discontinuation due to lack of efficacy were updated to be handled by "return-to-baseline", which was consistent with the hypothetical scenarios assumed to handle the intercurrent events.

2.1.4. General comments on compliance with GCP

The MAH declared that studies of the M19-044 protocol and the M19-051 Study are being and have been conducted in accordance with Good Clinical Practice and ethical principles that have their origin in the Declaration of Helsinki and are consistent with European and ICH guidelines on drug development.

2.2. Non-clinical aspects

No new clinical data have been submitted, but in support to this application, updated safety margins of all pivotal nonclinical studies was provided. The safety margins were based on therapeutic $AUC_{0\text{-}24hr}$ of 0.396 µgxh/mL and 0.780 µg•hr/mL at 15 and 30 mg QD, respectively, in RA patients and to the $AUC_{0\text{-}24hr}$ of 1.068 µg•hr/mL for the 45 mg QD dose in UC and CD patients. In general, no critical issues were identified from the nonclinical studies. However, teratogenicity in rats and rabbits was observed within the range of upadacitinib therapeutic exposures. This is reflected sufficiently in the SmPC.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH has provided an updated ERA to include the new indication of vitiligo, however no new data for the environmental risk assessment were included, and the update is based on the original ERA submitted for the iMAA for RA approval, and the subsequent extension of indications (PsA, AS, AD, UC, nr-axSpA, CD, GCA, pcJIA and AA.)

In the original ERA submitted as part of the iMAA 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 of vitiligo is 15 mg/day, resulting in PEC_{SW} value of 0.075 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 indications of AD and AA with the maximum daily dose of 30 mg/day, the PEC_{SW} values was 0.15µg/L and for the indications of UC and CD with the maximum daily dose of 45 mg/day, the PEC_{SW} values was 0.225 µg/L, when using the default Fpen value of 0.01.

A $PEC_{SW\text{-}TOTAL}$ was calculated (1.2 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 eleven indications. These ratios remain far below 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	0.001275 mg/L	0.063 mg/L	0.020 (<1)
Groundwater	0.00026 mg/L	0.0063mg/L	0.041 (<1)
Microorganism	0.0105 mg/L	100 mg/L	0.000105 (<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	1.43 mg/kg	15.6 mg/kg	0.092 (<1)

Summary table of main study results: Phase I

Substance (INN/Invented Name):	Upadacitinib		
CAS-number (if available):	2050057-56-0		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Pow	OECD 107	1.81 *at pH 3* 2.50 *at pH 5* 2.48 *at pH 7*	Potential PBT: *N*

Phase I			
Parameter	**Value**	**Unit**	**Conclusion**
PEC_{sw}, default Fpen	1.2	µg/L	≥ 0.01 threshold: *Y*
Other concerns (e.g. chemical class)			N

Summary table of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	203 ± 6.0 mg/L mg/L at 20 ± 1°C	
Dissociation in Water	OECD 112	$pK_{a,\ 1}$ = 4.7 ± 0.0 (base) $pK_{a,\ 2}$ = 12.8 ± 0.0 (acid)	
Adsorption-Desorption Soil 1 = Sandy Loam	OECD 106	$K_{FOC,\ soil\ 1}$ = 5.58×10^3 L/kg	No trigger of terrestrial studies as <10000L/kg.
Soil 2 = Clay Loam		$K_{FOC,\ soil\ 2}$ = 1.18×10^4 L/kg	
Soil 3 = Loamy Sand		$K_{FOC,\ soil\ 3}$ = 2.31×10^4 L/kg	
Sludge 1 = ASS, Denton WWTP		$K_{FOC,\ sludge\ 1}$ = 118 L/kg_{oc}	
Sludge 2 = ASS, Easton WWTP		$K_{FOC,\ sludge\ 2}$ = 129 L/kg_{oc}	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = Brandywine Creek	OECD 308	$DT_{50,\ water\ 1}$ = 5.6d/12d $DT_{50,\ sediment\ 1}$ = 347d/741d $DT_{50,\ whole\ system\ 1}$ = 234d/499d CO_2 = 1.7 % NER_{total} = 98.7 % $NER_{type\ I}$ = 36.8%	20°C/12°C CO_2 and NER values at test end
Sediment 2 = Choptank River		$DT_{50,\ water\ 2}$ = 13d/28d $DT_{50,\ sediment\ 2}$ = 110d/235d $DT_{50,\ whole\ system\ 2}$ = 138d/295d CO_2 = % NER_{total} = 77.1% $NER_{type\ I}$ = 29.3%	20°C/12°C CO_2 and NER values at test end
Transformation products		>10% = Y TP1 (max) =7.6%	sed. Brandywine Creek

		DT_{50} TP1: 150d			
Phase II Aquatic effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/Psuedokirchneriea subcapitata)	OECD 201	NOEC EC_{10}	31.3 36.7	mg/L	growth rate
Daphnia sp. Reproduction Test/ Daphnia magna	OECD 211	NOEC EC_{10}	1.6 3.09	mg/L	effect of on the survival, growth, and reproductive output
Fish, Pimephales promelas	OECD 210	NOEC EC_{10}	0.63 1.8	mg/L	effect on hatchability, time to hatch, fry survival, sublethal effects, and growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC EC_{10}	1000	mg/L	total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/Chironomus riparius	OECD 218	NOEC EC_{10}	390 402	mg/kg_{dw}	o.c. content 2.5%
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**		**Conclusion**
Surface water	0.001275 mg/L	0.063 mg/L	0.020 (<1)		No risk
Groundwater	0.00026 mg/L	0.0063 mg/L	0.041 (<1)		No risk
Microorganism	0.0105 mg/L	100 mg/L	0.000105 (<1)		No risk
Sediment	1.43 mg/kg	15.6 mg/kg	0.092 (<1)		No risk

Considering the above data from Phase I and Phase II, upadacitinib is not expected to pose a risk to the environment when used in the requested extended indication.

2.2.2. Discussion on non-clinical aspects

The non-clinical aspects of upadacitinib were thoroughly evaluated during the original approval procedure. The MAH provided an updated ERA to include the new indication of vitiligo, however, no new data for the environmental risk assessment were included. No new non-clinical studies were submitted in support of the present application. This is acceptable.

2.2.3. Conclusion on the non-clinical aspects

Overall, the non-clinical data package available for the non-clinical profile of upadacitinib is considered sufficient by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

Tabular overview of clinical studies

The upadacitinib clinical development programme for adults and adolescents 12 years and older with NSV is composed of 3 clinical studies (Table 2). These include two pivotal and replicate Phase 3 studies (M19-044 Study 1 and Study 2), performed in the target population of adults and adolescent patients 12 years and older who are candidates for systemic therapy. A dose-ranging study has been performed (M19-051), from which a dose in the range of the highest doses was carried forward to phase 3 studies.

Table 2. Tabular listings of clinical studies

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	M19-051	5.3.5.1	The primary objective of this study was to evaluate the safety and efficacy of UPA for the treatment of adult subjects with NSV.	Multicenter, randomized, double-blinded, parallel-group, PBO-controlled dose-ranging; 24-week PBO-controlled DB period (Period 1), 28-week blinded LTE (Period 2), and a 30-day follow-up period.	6 mg UPA (Period 1 and 2 Group 3), 11 mg UPA (Period 1 and 2 Group 2, Period 2 Group 5), 22 mg UPA (Period 1 and 2 Group 1, Period 2 Group 4), or PBO (Period 1 Group 4 and 5) QD PO	Period 1: 185 Period 2: 166	Female and male adult subjects ≥ 18 to 65 years of age with a documented clinical diagnosis of NSV. At Screening and Baseline visits, subjects must have ≥ 0.5 F-VASI AND ≥ 5 T-VASI.	Period 1: 24 weeks Period 2: 28 weeks	Completed; Final CSR

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	M19-044 Study 1	5.3.5.1	The primary objective of Study 1 is to evaluate the efficacy, safety, and tolerability of UPA for the treatment of adults and adolescents with NSV who are eligible for systemic therapy.	Global, randomized, DB, PBO-controlled, multicenter; 48-week PBO-controlled DB period (Period A), 112-week OLE period (Period B), and a 30-day follow-up period.	Period A: 15 mg UPA or PBO QD PO Period B: 15 mg UPA QD PO	Period A: 308 Period B: 209	Female and male adult and adolescent subjects ≥ 12 years old with a documented clinical diagnosis of NSV who satisfy at least 1 of the following criteria: ≥ 0.5 F-VASI and 5 ≤ T-VASI < 50 AND have failed at least 1 topical corticosteroid and/or at least 1 topical calcineurin inhibitor for vitiligo; or ≥ 0.5 F-VASI and 5 ≤ T-VASI < 50 AND have a sign of actively progressing vitiligo; or ≥ 0.5 F-VASI and 10 ≤ T-VASI < 50.	Period A: 48 weeks Period B: 112 weeks	Ongoing; Week 48 Interim CSR

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	M19-044 Study 2	5.3.5.1	The primary objective of Study 2 is to evaluate the efficacy, safety, and tolerability of UPA for the treatment of adults and adolescents with NSV who are eligible for systemic therapy.	Global, randomized, DB, PBO-controlled, multicenter; 48-week PBO-controlled DB period (Period A), 112-week OLE period (Period B), and a 30-day follow-up period.	Period A: 15 mg UPA or PBO QD PO Period B: 15 mg UPA QD PO	Period A: 306 Period B: 221	Female and male adult and adolescent subjects ≥ 12 years old with a documented clinical diagnosis of NSV who satisfy at least 1 of the following criteria: ≥ 0.5 F-VASI and 5 ≤ T-VASI < 50 AND have failed at least 1 topical corticosteroid and/or at least 1 topical calcineurin inhibitor for vitiligo; or ≥ 0.5 F-VASI and 5 ≤ T-VASI < 50 AND have a sign of actively progressing vitiligo; or ≥ 0.5 F-VASI and 10 ≤ T-VASI < 50.	Period A: 48 weeks Period B: 112 weeks	Ongoing; Week 48 Interim CSR

CSR = clinical study report; DB = double-blind; F-VASI = Facial Vitiligo Area Scoring Index; LTE = long term extension; NSV = non-segmental vitiligo; PBO = placebo; PO = orally; QD = once daily; T-VASI = Total Vitiligo Area Scoring Index; UPA = upadacitinib

2.3.2. Pharmacokinetics

Exposure data on upadacitinib in patients with non-segmental vitiligo (NSV) from the Phase 2 Study M19-051 and Phase 3 M19-044 Study 1 and Study 2, submitted in this variation, were analysed with population pharmacokinetics (popPK) modelling, in order to characterise the pharmacokinetics (PK) of upadacitinib in adult and adolescent subjects with NSV, quantify covariate effects in the population, and to generate individual exposure metrics for use in the exposure-response (ER) analyses.

Methods – analysis of data submitted

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.

Evaluation and qualification of models

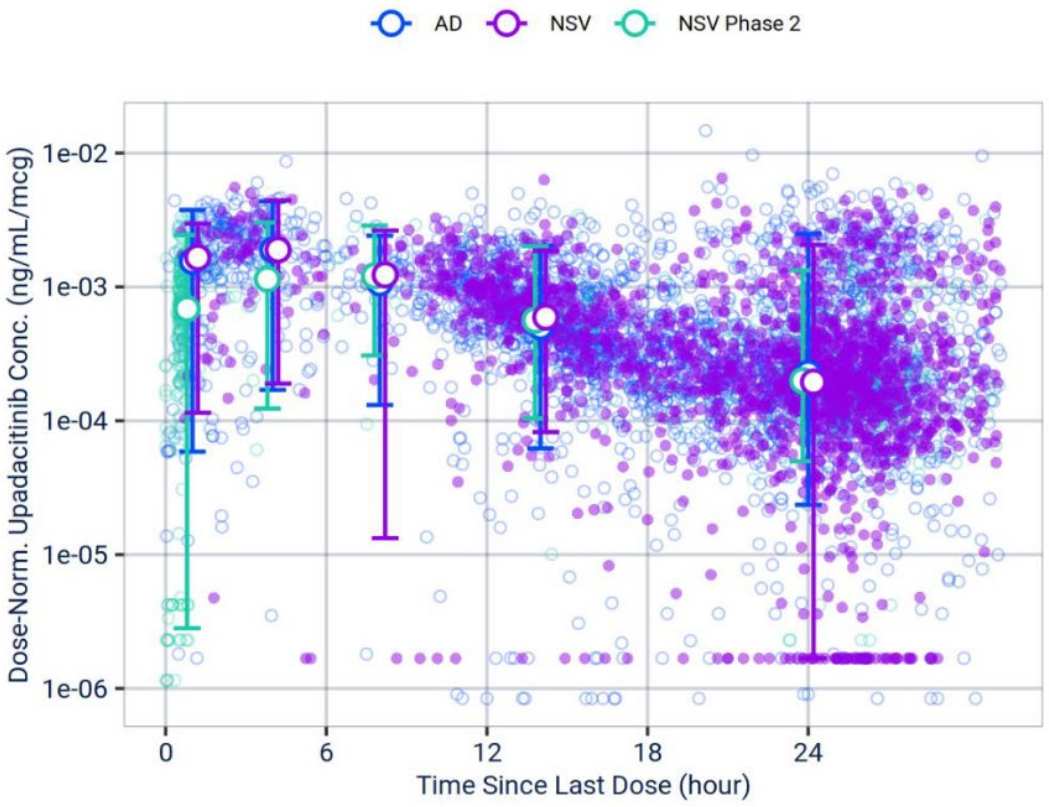
Population PK analysis

This section describes the poPK analysis to define upadacitinib concentrations in subjects with NSV, using a *post hoc* approach based on previously developed population PK model(s) across multiple indications.

Data

Comparable dose-normalised upadacitinib concentration versus time-since last dose (TSLD) was observed between subjects with NSV from Phase 3, subjects with NSV from Phase 2 and subjects with AD, justifying the use of this previously developed model to characterise the PK of upadacitinib in NSV (Figure 1).

Figure 1. Dose-Normalized Observed Upadacitinib Concentrations in Phase 3 Subjects with NSV Compared to Phase 2 Subjects with NSV and Subjects with AD



Circles represent observed upadacitinib concentrations (normalized by the most recent prior dose). Framed circles with error bars represent the median and 5th to 95th percentiles for the binned observed data.

The dataset for characterizing PK of upadacitinib in subjects with NSV from the Phase 2 dose ranging Study M19-051 included all subjects in the Phase 2 study who received upadacitinib and had at least one measurable upadacitinib concentration greater than LLOQ (n=138 subjects). PK samples collected before first dose or sampled > 140 hours (to account for 10-times the half-life) after last dose, were excluded from the analysis. 24 outliers were identified and excluded, using ANOVA to set the upper and lower limit to exclude no more than 5% and 1% of the high and low concentrations, respectively. A total of 593 concentration records were included in the PK analysis. A total of 28 of records were below the LLOQ of 0.0503 ng/mL.

A summary of demographics and other baseline characteristics for subjects with NSV from Study M19-051 who were included in the population PK analyse are presented in Table 3.

Table 3. Demographic and Baseline Characteristics of Subjects with NSV from Phase 2 Study M19-051 Included in the Population Pharmacokinetic Analysis

Characteristic	6 mg QD (N = 49)	11 mg QD (N = 47)	22 mg QD (N = 42)	All Subjects (N = 138)
Sex, n (%)				
Male	23 (47%)	13 (28%)	17 (40%)	53 (38%)
Female	26 (53%)	34 (72%)	25 (60%)	85 (62%)
Body Weight (kg)				
Mean (SD)	81.5 (19.2)	76.9 (22.7)	78.5 (18.0)	79.0 (20.1)
Median	81.2	71.6	79.1	77.3
Min, Max	47.8, 137	48.0, 187	44.0, 117	44.0, 187
Age (year)				
Mean (SD)	45 (12)	45 (12)	48 (11)	46 (12)
Median	45	45	50	48
Min, Max	19, 66	22, 65	19, 65	19, 66
Race, n (%)				
White	35 (71%)	36 (77%)	32 (76%)	103 (75%)
Black	3 (6%)	3 (6%)	1 (2%)	7 (5%)
Asian	6 (12%)	7 (15%)	6 (14%)	19 (14%)
Other/Multiple	5 (10%)	1 (2%)	3 (7%)	9 (7%)
Creatinine Clearance (mL/min)				
Mean (SD)	116 (32.9)	113 (33.8)	110 (33.2)	113 (33.2)
Median	124	106	106	109
Min, Max	61.8, 191	56.6, 242	60.9, 213	56.6, 242
Alanine Amino Transferase (IU/L)				
Mean (SD)	23.1 (16.5)	18.7 (10.4)	23.3 (15.8)	21.7 (14.5)
Median	20.0	17.0	19.5	19.0
Min, Max	7.00, 112	5.00, 56.0	5.00, 95.0	5.00, 112
Aspartate Amino Transferase (IU/L)				
Mean (SD)	21.4 (7.34)	20.0 (6.26)	21.1 (6.38)	20.8 (6.67)
Median	19.0	19.0	19.5	19.0
Min, Max	11.0, 46.0	10.0, 40.0	12.0, 37.0	10.0, 46.0
Albumin (g/dL)				
Mean (SD)	4.73 (0.279)	4.60 (0.276)	4.62 (0.212)	4.65 (0.264)
Median	4.80	4.60	4.60	4.60
Min, Max	4.10, 5.30	4.10, 5.50	4.00, 5.30	4.00, 5.50
Bilirubin (mg/dL)				
Mean (SD)	0.424 (0.192)	0.453 (0.216)	0.521 (0.319)	0.463 (0.246)
Median	0.400	0.400	0.400	0.400
Min, Max	0.200, 1.00	0.175, 1.30	0.175, 1.64	0.175, 1.64

The dataset for characterizing PK of upadacitinib in adult and adolescent subjects with NSV from the Phase 3 Study M19-044 included all subjects who received upadacitinib and had at least one measurable upadacitinib concentration greater than LLOQ (n=398 subjects). PK sample collections before first dose or sampled > 168 hours after last dose were excluded from the analysis. 15 observations were excluded, due to missing information about dose or concentration. A total of 1828 concentration records were included in the PK analysis and 76 (4.16%) of records were below the LLOQ of 0.0503 ng/mL.

A summary of demographics and other baseline characteristics for subjects with NSV from Study M19-044 who were included in the population PK analyse are presented in Table 4.

Table 4. Demographic and Baseline Characteristics of Subjects with NSV from Study M19-044 Included in the Population Pharmacokinetic Analysis

Characteristic	M19-044 (N = 398)
Age (year)	
Mean (SD)	44 (15)
Median	46
Min, Max	12, 78
Body Weight (kg)	
Mean (SD)	73.6 (16.9)
Median	71.5
Min, Max	37.7, 128
eGFR (mL/(min · 1.73 m²))	
Mean (SD)	99.4 (15.9)
Median	101
Min, Max	51.2, 153
Baseline Disease Duration (year)	
Mean (SD)	16.0 (13.3)
Median	12.6
Min, Max	0.0301, 64.7
Baseline F-VASI	
Mean (SD)	1.07 (0.635)
Median	0.820
Min, Max	0.500, 3.00
Baseline T-VASI	
Mean (SD)	17.6 (10.9)
Median	14.8
Min, Max	5.00, 49.9
Sex, n (%)	
Male	188 (47%)
Female	210 (53%)
Race, n (%)	
Missing	6 (2%)
White	313 (79%)
Black	11 (3%)
Asian	64 (16%)
Other	4 (1%)
Region, n (%)	
North America	166 (42%)
Europe	156 (39%)
Rest of World	76 (19%)
Baseline Disease Status, n (%)	
No Active NSV	149 (37%)
Active NSV	249 (63%)
Fitzpatrick Skin Type, n (%)	
1-3	269 (68%)
4-5	129 (32%)

All observed plasma concentrations below LLOQ were set to LLOQ/2 and flagged. The first 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).

Model

PK Meta-Analysis model

A PK meta-analysis model to describe upadacitinib across indications was developed using an iterative *post hoc* approach. An initial model, using data from healthy subjects and subjects with RA, was developed used as a basis. 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.

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.

The final meta-analysis model was subsequently used as a starting point for the analysis of the data from the NSV Phase 3 Study M19-044.

PopPK analysis for subjects with NSV Phase 2 Study M19-051

A previously developed population pharmacokinetic model) that described upadacitinib pharmacokinetics in healthy subjects and subjects with RA, AD, UC, and CD was evaluated to describe observed upadacitinib plasma concentrations from Phase 2 Study M19-051 using a *post hoc* approach. The population parameter estimates of the fixed effects and estimates for IIV of the previously established popPK model were used to generate individual *post hoc* estimates ($ESTIMATION MAXEVAL=0 in NONMEM) for subjects in Study M19-051.

Statistically significant covariates identified in the previous model were subject population (subjects with RA compared to subjects with other indications and healthy subjects), CrCL and sex on CL/F, as well as sex and body weight on Vc/F. These were retained in the model for the current analysis. None of the model parameters were re-estimated.

PopPK analysis for subjects with NSV Phase 3 Study M19-044

The PK meta-analysis model, as depicted above, was utilized to describe observed upadacitinib concentrations in NSV Phase 3 Study M19-044 using a *post hoc* approach. The population parameter estimates of the fixed effects and estimates for IIV of the Meta-Analysis model were used to generate individual *post hoc* estimates ($ESTIMATION MAXEVAL=0 in NONMEM) for subjects in Study M19-044.

Statistically significant covariates identified in the previous model were patient population (patient versus healthy) on CL/F, 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.

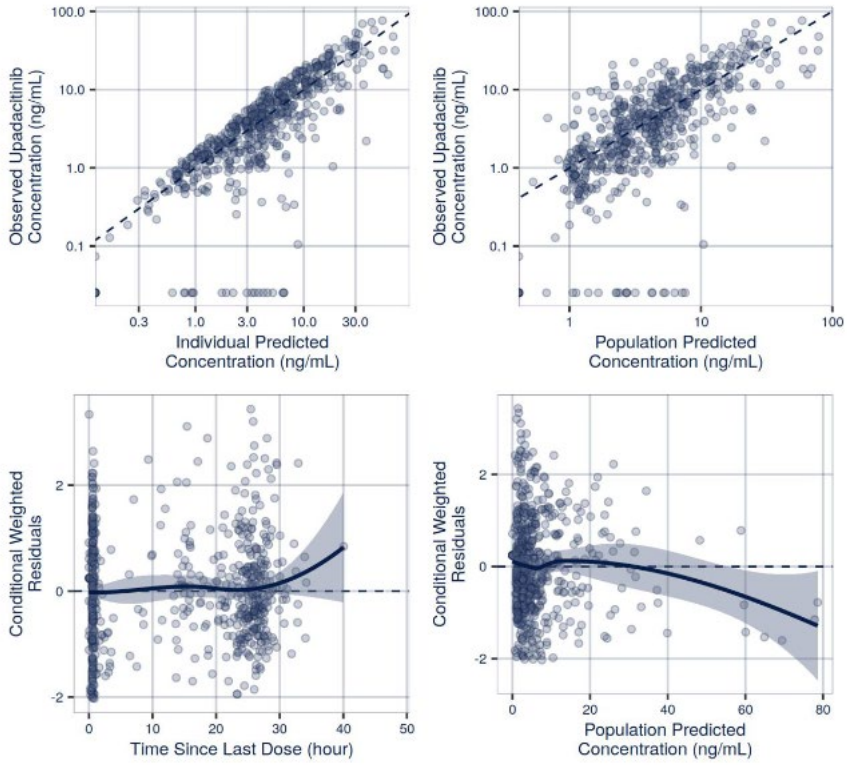
Results

PopPK analysis for subjects with NSV Phase 2 Study M19-051

GOF plots and pcVPCs to evaluate the ability of the model to describe the observed upadacitinib concentrations in subjects with NSV in the Phase 2 Study M19-051 are displayed in Figure 2 and Figure 3, respectively.

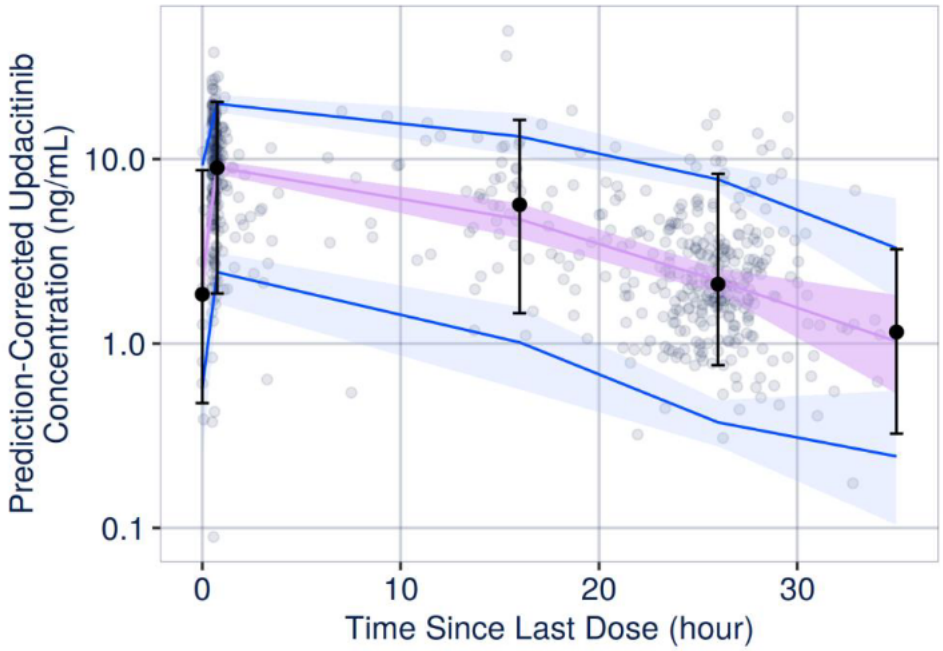
The shrinkage on CL/F, Vc/F, and KA were 17.8, 33.4, and 45.1, respectively.

Figure 2. Goodness-of-Fit Plots of Upadacitinib Pharmacokinetic Final Model for Subjects in Phase 2 Study M19-051



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).

Figure 3. Prediction-Corrected Visual Predictive Checks of Upadacitinib Concentration in Subjects with NSV in Phase 2 Study M19-051



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. Circles denote observed concentrations. Time bins were chosen at 0, 0.75, 16, 26, 35 hours since last dose.

PopPK analysis for subjects with NSV Phase 3 Study M19-044

Estimates of the PK parameters and their associated variability for the final model utilized to describe upadacitinib in in subjects with NSV in the Phase 3 Study M19-044 are shown in Table 5. The shrinkages for upadacitinib KA, CL/F and Vc/F were 53.4%, 0.406%, and 38.9%, respectively.

GOF plots and pcVPCs to evaluate the ability of the model to describe the observed upadacitinib concentrations in the NSV population (Phase 3) are displayed in Figure 4, Figure 5 and Figure 6, respectively.

Table 5. Parameter Estimates and Variability of Upadacitinib Pharmacokinetics in Subjects with NSV

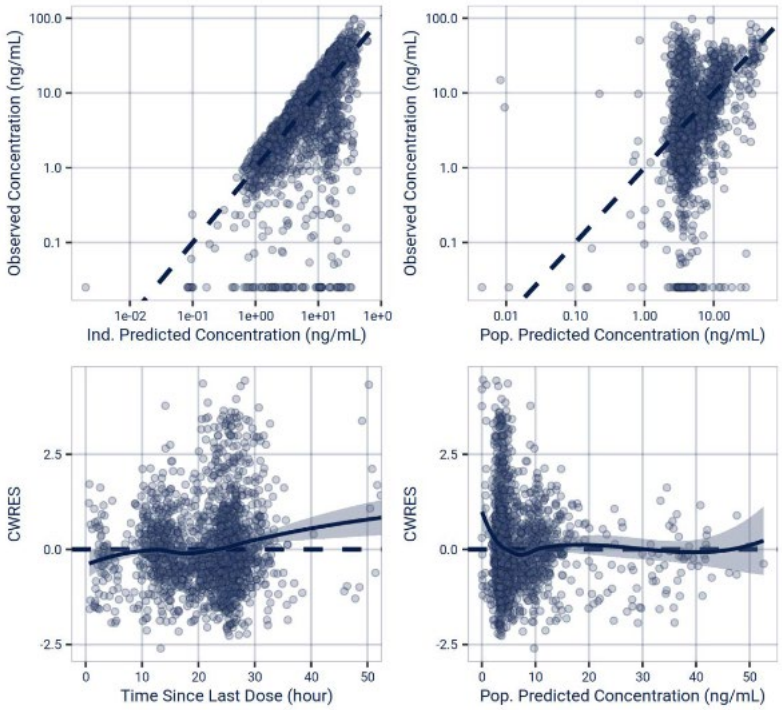
Parameter	Population Estimate	%RSE	95% Confidence Interval
CL/F (L/h)	43.0	--	--
Vc/F (L)	166	--	--
ER KA (1/h)	0.0822	--	--
ER Absorption Lag Time (h)	0.140	--	--
Fraction of ER Dose Absorbed through Zero-Order Process (%)	65.9	--	--
Zero-Order Absorption Duration (h)	3.27	--	--
IR KA (1/h)	2.69	--	--
IR Absorption Lag Time (h)	0.200	--	--
Bioavailability of the ER Tablet Formulation Relative to the IR Capsule Formulation (%)	73.9	--	--
Q/F (L/h)	3.09	--	--
Vp/F (L)	65.0	--	--
Ratio of CL/F in Rheumatic Subjects Compared to Healthy Subjects	0.732	--	--
Covariate Exponent of eGFR (Capped at 90 mL/(min · 1.73 m2)) on CL/F[a]	0.525	--	--
Covariate Exponent of Weight on CL/F	0.291	--	--
Ratio of Vc/F in Female Compared to Male Subjects	0.881	--	--
Covariate Exponent of Weight on Vc/F	0.666	--	--
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	--	--
Bioavailability of the IR Oral Solution Formulation Relative to the IR Capsule Formulation (%)	117	--	--
Additive Error (ng/mL)	0.00544	--	--
Proportional Error in Phase 2/3	0.314	--	--

Parameter	Population Estimate	%CV	%Shrinkage
IIV on ER KA	0.336	63.2	53.4
IIV on CL/F in Phase 2/3	0.144	39.3	0.406
IIV on Vc/F in Phase 2/3	0.335	63.1	38.9

%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).

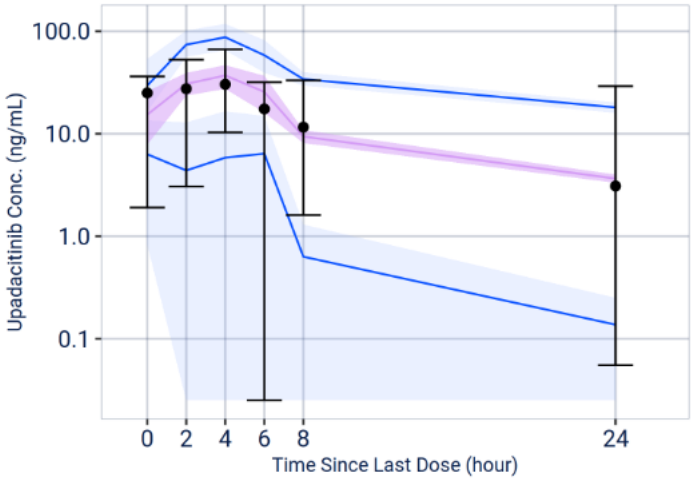
a. For eGFR a piecewise, normalized power model was used: min($eGFR_i$, 90 mL/(min · 1.73 m^2)) / 90 mL/(min · 1.73 m^2))$^{\theta eGFR}$, where $eGFR_i$ is the individual eGFR and θ_{eGFR} the estimated exponent.

Figure 4. Goodness-of-Fit Plots of Upadacitinib Pharmacokinetic Final Model for Subjects in Phase 3 Study M19-044



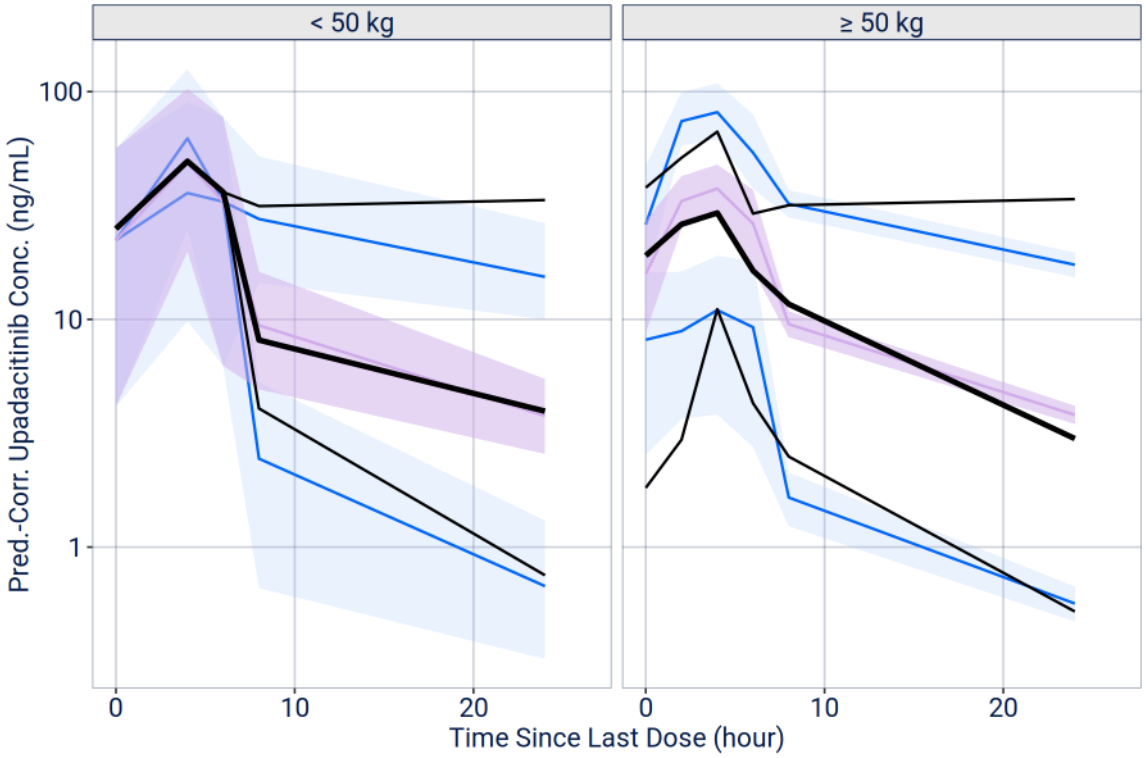
Goodness-of-fit plots for the individual predicted and population predicted versus observed concentrations (top left and right, respectively) and CWRES versus TSLD and population prediction (bottom left and right, respectively) with loess smooth (95% CI).

Figure 5. Visual Predictive Checks of Upadacitinib Concentration in Subjects with NSV in Study M19-044



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 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 0, 2, 4, 6, 8, and 24 hours since last dose.

Figure 6. Prediction-Corrected Visual Predictive Checks of Upadacitinib Concentration in All Subjects with NSV in Study M19-044



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 0, 2, 4, 6, 8, and 24 hours since last dose.

Absorption

Bioequivalence between the commercial and Phase 3 formulations for 15 mg was demonstrated in Study M20-017, which was previously included in the regulatory dossier to support the approvals of PsA and AD.

Upadacitinib was administered without regard to food in M19-044 Study 1 and Study 2. The effect of food was previously described in RA Submission. For the upadacitinib commercial formulation, a high-fat meal increased upadacitinib AUC by 29% and C_{max} by 39%.

Dose proportionality and time dependencies

Model-predicted upadacitinib C_{avg} at steady-state indicates a proportional increase in concentrations with dose in the Phase 2 Study M19-051 study (Table 6). Comparable exposure of upadacitinib was predicted for the subject in the Phase 3 Study M19-044 study (Table 7).

Table 6. Summary Statistics (Median and 5th/95th Percentile) of Individual Predictions of Steady-State C_{avg} for Upadacitinib, Using the Final Population Pharmacokinetic Model

Treatment	Number of Subjects	Model-Predicted Steady-State C_{avg} (ng/mL)	Simulated Steady-State C_{avg} (ng/mL)
6 mg QD	49	5.82 (3.75, 11.7)	--
11 mg QD	47	13.2 (8.33, 19.6)	--
15 mg QD	400	--	15.8 (8.45, 29.3)
22 mg QD	42	22.5 (14.1, 35.9)	--
30 mg QD	400	--	31.8 (18.6, 59.5)

Table 7. Summary Statistics of Model-Predicted Steady-State Exposures for Upadacitinib, Using the Final Population Pharmacokinetic Model

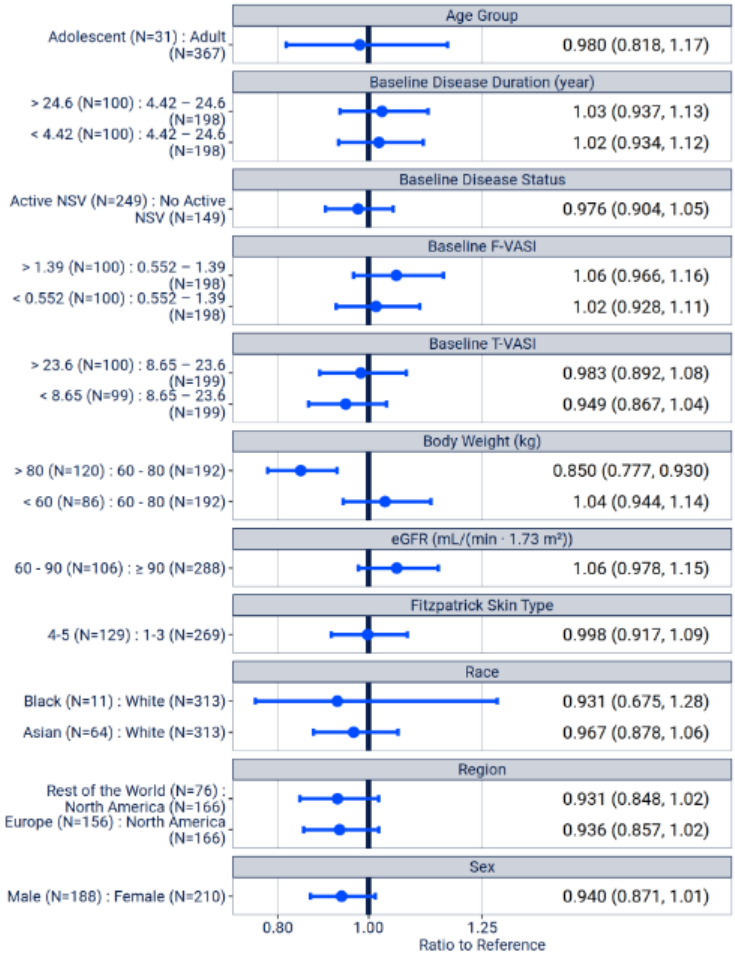
Regimen	Number of Subjects	AUC_{24} (ng·hr/mL) Median (5^{th} to 95^{th} Percentile)	C_{avg} (ng/mL) Median (5^{th} to 95^{th} Percentile)	C_{max} (ng/mL) Median (5^{th} to 95^{th} Percentile)	C_{trough} (ng/mL) Median (5^{th} to 95^{th} Percentile)
15 mg QD	398	364 (229, 796)	15.2 (9.55, 33.2)	43.3 (33.0, 56.5)	3.90 (1.13, 22.4)

Special populations

The dose-normalized, model-predicted steady-state exposure (C_{avg}) of upadacitinib was compared across specific demographic and disease-related subgroups (Figure 7). 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 the phase 3 Study M19-044.

Overall, the impact of these covariates on the dose-normalized steady-state C_{avg} of upadacitinib was ≤15% relative to their reference groups. No relevant covariate effects of race, sex, or body weight were thus identified in the population pharmacokinetics analyses in subjects with NSV, in accordance with original regulatory application for the use of upadacitinib in the treatment of RA.

Figure 7. Model-Predicted Covariate Effects on Dose-Normalized Upadacitinib C_{avg} in Subjects with NSV



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. The reference population comprised adult, female, subjects enrolled in North America, of White race, Fitzpatrick skin types 1-3, without active NSV at Baseline, with body weight 60–80 kg, and an eGFR ≥ 90 mL/(min · 1.73 m²). For baseline disease duration, baseline F-VASI, and baseline T-VASI, the inter-quartile range was used as the reference category.

In addition to the results shown in Figure 7, 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 8 and Table 9).

Table 8. Summary Statistics (Median [5th to 95th Percentile]) of Model-Predicted Upadacitinib Steady-State Exposures Following the 15 mg QD Regimen Stratified by Japanese versus Non-Japanese Subjects

Population	Number of Subjects	AUC_{24} (ng•hr/mL)	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
Japanese	14	404 (283, 476)	16.8 (11.8, 19.8)	44.5 (38.4, 51.2)	4.50 (2.46, 8.05)
Non-Japanese	384	363 (229, 804)	15.1 (9.55, 33.5)	43.3 (32.8, 56.7)	3.89 (1.11, 22.5)

Cross reference: R&D/25/2325 Table 7

Table 9. Summary Statistics (Median [5th to 95th Percentile]) of Model-Predicted Upadacitinib Steady-State Exposures Following the 15 mg QD Regimen Stratified by Chinese versus Non-Chinese Subjects

Population	Number of Subjects	AUC_{24} (ng•hr/mL)	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
Chinese	35	329 (265, 589)	13.7 (11.0, 24.6)	44.7 (35.7, 53.3)	3.01 (1.38, 15.6)
Non-Chinese	363	369 (229, 807)	15.4 (9.54, 33.6)	43.1 (32.6, 56.7)	3.98 (1.10, 23.3)

Cross reference: R&D/25/2325 Table 8

Adolescent Population

The number of adolescents subjects included in the PK analysis from the M19-044 study was 31. The PK dataset covered subjects, from 37.7 kg, with 3 subjects between 35-45 kg

Upadacitinib popPK model-predicted steady-state plasma exposure (C_{avg}, C_{max} and C_{trough}) in adolescent and adult subjects with NSV are compared in Table 10. Based on the model predictions, the exposure in adolescents was comparable to adults.

Table 10. Summary Statistics (Median [5th to 95th Percentile]) of Model-Predicted Upadacitinib Steady-State Exposures Following the 15 mg QD Regimen Stratified by Age Group

Age Group	Number of Subjects	AUC_{24} (ng•h/mL)	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
Adolescent	31	363 (203, 969)	15.1 (8.44, 40.4)	47.0 (38.0, 60.2)	3.42 (0.892, 27.9)
Adult	367	364 (233, 777)	15.2 (9.71, 32.4)	43.1 (32.7, 55.5)	3.91 (1.23, 22.3)

Cross reference: R&D/25/2325 Table 6

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 NSV, AA, AD, and pcJIA, is provided in Table 11. 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 11. Summary Statistics of Model-Predicted Steady-State Exposures for Upadacitinib in Paediatric Age Groups, Stratified by Body Weight, Using the Final Population Pharmacokinetic Model

					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)
NSV (R&D/25/2325)	15 mg QD	12 to < 18 years	30 kg - < 40 kg	1	777 (777, 777)	32.4 (32.4, 32.4)	59.6 (59.6, 59.6)
		12 to < 18 years	≥ 40 kg	30	359 (201, 986)	15.0 (8.37, 41.1)	46.3 (38.0, 59.7)
AA (R&D/25/1571)		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 (R&D/20/0641)	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)
AD (R&D/22/1451)	7.5 mg QD	6 to < 12 years	30 kg - < 40 kg	1	193 (193, 193)	8.04 (8.04, 8.04)	30.5 (30.5, 30.5)
	15 mg QD	6 to < 12 years	≥ 40 kg	1	344 (344, 344)	14.3 (14.3, 14.3)	57.2 (57.2, 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 (R&D/25/0393)	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, only 3 out of 24 subjects and in the ≥ 40 kg only 1 out of 48 subjects received the oral solution. The data were included for completeness.

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. Depigmentation in vitiligo is driven by autoreactive CD8+ T-cells that target and destroy melanocytes. This immune response is amplified by increased levels of proinflammatory cytokines (e.g., IFN-γ, IL-15, IL-7, CXCL9, CXCL10), which activate the JAK/STAT pathway and promote inflammatory signalling that leads to melanocyte loss. As a selective and reversible JAK inhibitor, upadacitinib may interrupt JAK-dependent inflammatory pathways that contribute to the immunopathogenesis of NSV. There is clinical evidence with other topically applied JAK inhibitors that also support the investigation of upadacitinib in the treatment of NSV.

2.3.4. PK/PD modelling

Exposure-Response Analysis

Exposure-Response (E-R) model analyses was conducted to characterise the relationships between upadacitinib plasma exposures and clinical efficacy and safety in adolescent and adult subjects with NSV using data from the Phase 2 M19-051 study and Phase 3 M19-044 study.

Exploratory exposure-response quartile plots were first evaluated for the efficacy and safety endpoints to identify the efficacy and safety variables that have a clear relationship with upadacitinib C_{avg}. Only efficacy and safety variables with > 10 events were evaluated further using exposure-response models.

Non-linear and linear logistic regression models for efficacy and safety were evaluated to characterize the relationship between upadacitinib C_{avg} as a predictor variable and the binary endpoints including achievement of F-VASI ≥75% and T-VASI ≥50% from Baseline. Gaussian a regression models was constructed relating average upadacitinib concentration to percent change from Baseline in T-VASI (Total Vitiligo Area Scoring Index) and F-VASI (Facial Vitiligo Area Scoring Index) at Week 24 and at 52 (Phase 2) or week 48 (Phase 3).

Safety endpoints included: Neutropenia Grade ≥ 3, Lymphopenia Grade ≥ 3, Anaemia (haemoglobin < 8 g/dL), 2 g/dL decrease in haemoglobin from baseline and Serious infection, Herpes zoster or Pneumonia.

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, Age at screening and Baseline status of active NSV. The following pre-specified variables were included in the safety exposure-response models: baseline haemoglobin, baseline lymphocyte count, baseline neutrophil count, serious infections, pneumonia, herpes zoster infections and age.

The effect of significant covariates (including demographics, geographic region, baseline disease duration, Fitzpatrick skin type (1-3, 4-6) and Prior topical therapy (TCS/TCI) 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.

The developed Logistic and Gaussian regression models for efficacy were used to conduct simulations to predict the responses of the efficacy endpoints at different treatments (placebo, upadacitinib 6, 11, 15, 22 and 30 mg QD from the Phase 2 analysis, and placebo, upadacitinib 15 mg QD for the Phase 3 analysis.

Exposure-Response for Subjects with NSV in the Phase 2 Study M19-051

Data from 184 subjects with NSV from Phase 2 Study M19-051 who received placebo or who received upadacitinib were included in the efficacy and safety exposure-response analyses (Table 12). Upadacitinib individual average plasma concentrations over a dosing interval at steady state (C_{avg}), derived using empirical Bayesian estimates from the population PK model, were used as the exposure metrics.

Table 12. Demographic and Baseline Characteristics of Subjects with NSV from Phase 2 Study M19-051 Included in the Exposure-Response Analyses

Characteristic	Placebo (N = 46)	6 mg QD (N = 49)	11 mg QD (N = 47)	22 mg QD (N = 43)	All Subjects (N = 185)
Pooled Age Group, n (%)					
≤ 50 Years	26 (57%)	28 (57%)	28 (60%)	25 (58%)	107 (58%)
> 50 Years	20 (43%)	21 (43%)	19 (40%)	18 (42%)	78 (42%)
Active Vitiligo, n (%)					
No Active Vitiligo	12 (26%)	16 (33%)	15 (32%)	11 (26%)	54 (29%)
Active Vitiligo	34 (74%)	33 (67%)	32 (68%)	32 (74%)	131 (71%)
Baseline Disease Severity, n (%)					
T-VASI ≥ 15	26 (57%)	29 (59%)	27 (57%)	25 (58%)	107 (58%)
T-VASI < 15	20 (43%)	20 (41%)	20 (43%)	18 (42%)	78 (42%)
Race, n (%)					
White	34 (74%)	35 (71%)	36 (77%)	33 (77%)	138 (75%)
Black	4 (9%)	3 (6%)	3 (6%)	1 (2%)	11 (6%)
Asian	6 (13%)	6 (12%)	7 (15%)	6 (14%)	25 (14%)
Other/Multiple	2 (4%)	5 (10%)	1 (2%)	3 (7%)	11 (6%)
Fitzpatrick Skin Type, n (%)					
1 - 3	31 (67%)	31 (63%)	35 (74%)	32 (74%)	129 (70%)
4 - 6	15 (33%)	18 (37%)	12 (26%)	11 (26%)	56 (30%)

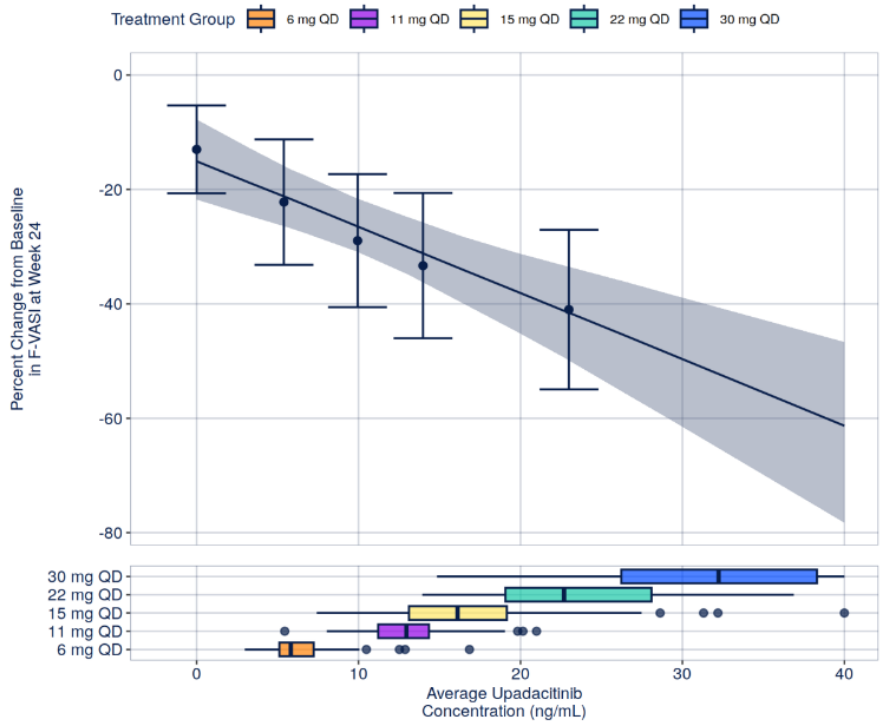
Characteristic	Placebo (N = 46)	6 mg QD (N = 49)	11 mg QD (N = 47)	22 mg QD (N = 43)	All Subjects (N = 185)
Region US, n (%)					
Non-US	23 (50%)	23 (47%)	23 (49%)	22 (51%)	91 (49%)
US	23 (50%)	26 (53%)	24 (51%)	21 (49%)	94 (51%)
Region Asia, n (%)					
Non-Asian	41 (89%)	47 (96%)	43 (91%)	39 (91%)	170 (92%)
Asian	5 (11%)	2 (4%)	4 (9%)	4 (9%)	15 (8%)
Sex, n (%)					
Male	17 (37%)	23 (47%)	13 (28%)	17 (40%)	70 (38%)
Female	29 (63%)	26 (53%)	34 (72%)	26 (60%)	115 (62%)
Prior Topical Therapy (TCS/TCI), n (%)					
No	23 (50%)	29 (59%)	27 (57%)	25 (58%)	104 (56%)
Yes	23 (50%)	20 (41%)	20 (43%)	18 (42%)	81 (44%)
Age (year)					
Mean (SD)	47 (10)	45 (12)	45 (12)	48 (11)	46 (11)
Median	48	45	45	49	48
Min, Max	18, 64	19, 66	22, 65	19, 65	18, 66
Body Weight (kg)					
Mean (SD)	77.8 (23.4)	81.5 (19.2)	76.9 (22.7)	78.5 (17.8)	78.7 (20.8)
Median	73.3	81.2	71.6	79.0	76.3
Min, Max	40.4, 161	47.8, 137	48.0, 187	44.0, 117	40.4, 187
Baseline Disease Duration (year)					
Mean (SD)	18.5 (13.8)	16.0 (11.4)	17.9 (13.9)	14.7 (13.7)	16.8 (13.2)
Median	14.2	14.2	14.0	10.9	13.5
Min, Max	0.235, 50.6	1.01, 45.1	0.126, 48.8	0.211, 55.0	0.126, 55.0
Baseline F-VASI					
Mean (SD)	1.04 (0.609)	1.15 (0.765)	1.02 (0.578)	1.16 (0.659)	1.09 (0.656)
Median	0.805	0.800	0.810	0.990	0.900
Min, Max	0.250, 2.50	0.150, 3.00	0.500, 2.70	0.500, 3.00	0.150, 3.00
Baseline T-VASI					
Mean (SD)	21.0 (17.0)	21.0 (16.0)	22.3 (18.2)	21.8 (15.9)	21.5 (16.7)
Median	16.7	16.4	18.1	17.4	16.7
Min, Max	5.10, 90.6	5.00, 66.8	5.00, 74.7	5.00, 67.2	5.00, 90.6

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

The exposure-response relationships for efficacy during the 24-week placebo-controlled period showed a decrease in percent change from baseline in F-VASI (primary endpoint, Figure 8) and T-VASI, with increasing upadacitinib average plasma concentration. A linear exposure-response relationship best described the observed data for both of these endpoints, and the association between F-VASI 75 at Week 24 and C_{avg} was significant ($p<0.05$) across the evaluated range of exposures.

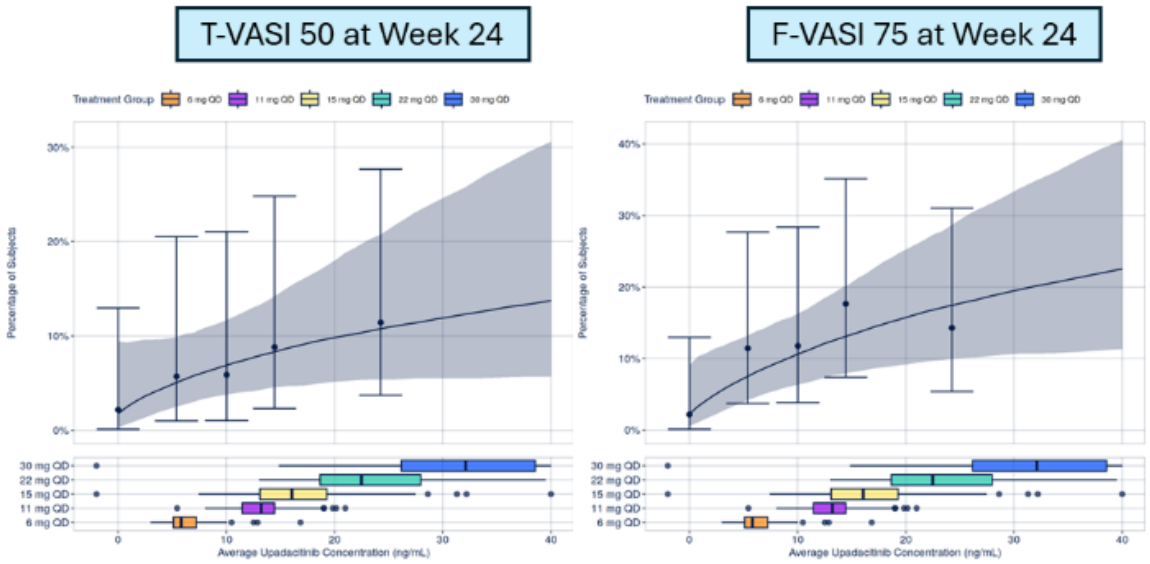
Also, there was an increase in response with increasing upadacitinib average plasma concentration for ≥ 75% improvement in facial Vitiligo Area Scoring Index from Baseline (F-VASI 75) and ≥ 50% improvement in total Vitiligo Area Scoring Index from Baseline (T-VASI 50), with a logarithmic exposure-response relationship best describing the observed data (Figure 9).

Figure 8. Observed and Model-Predicted Percent Change from Baseline in F-VASI at Week 24



The solid line represents the median predicted response and the shaded area represents the 95% CIs of the response. Dots and error bars represent the mean and 95% CIs of the binned observed response. Horizontal boxplots show the median, 25th to 75th percentiles (IQR) of the model-predicted exposures by treatment group. Whiskers represent the 1.5-fold of the IQR.

Figure 9. Observed and Model-Predicted Percentage of Subjects with Achievement of F-VASI 75 and Achievement of T-VASI 50 at Week 24.

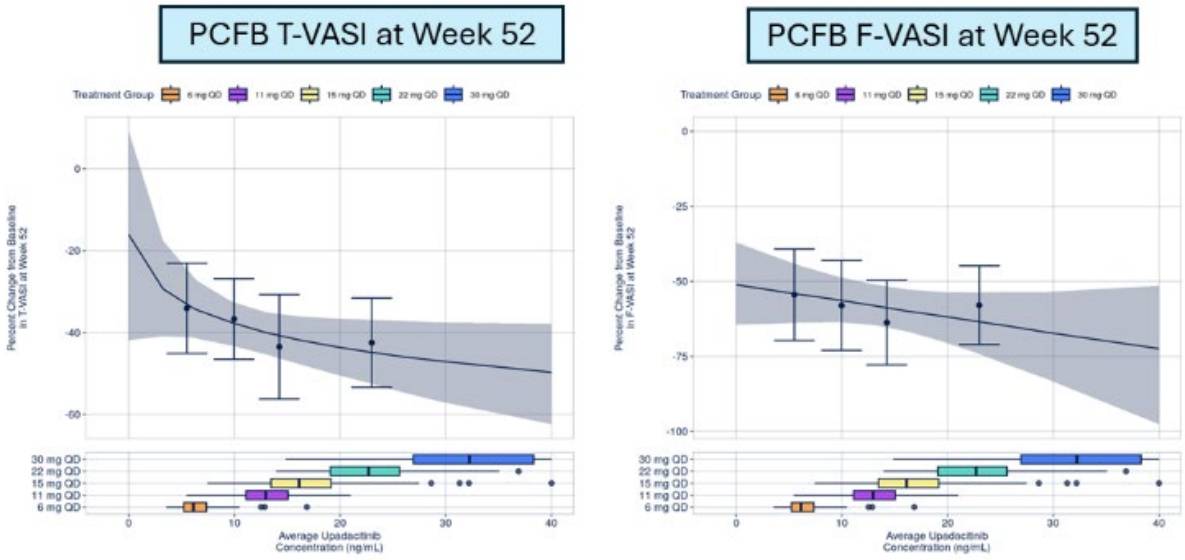


The exposure-response relationships for efficacy at Week 52 (blinded extension) showed a trend of a decrease in percent change from baseline in F-VASI and T-VASI with increasing upadacitinib

average plasma concentration, with the response approaching a plateau at plasma exposures associated with the 15 mg QD regimen (Figure 10).

None of the tested covariates were identified as being a significant predictor for any of the endpoints.

Figure 10. Observed and Model-Predicted Percent Change from Baseline in F-VASI and Percent Change from Baseline in T-VASI at Week 52



Exposure-Response for Subjects with NSV in the Phase 3 M19-044

Data from subjects in Period A of in the Study M19-044 (Study 1 and Study 2, safety population) who received placebo (n=202) or upadacitinib (n=410) were included in the exposure-response analysis (Table 13). Upadacitinib individual average plasma concentrations over a dosing interval at steady state (C_{avg}), derived using empirical Bayesian estimates from the population pharmacokinetic model, were used as the exposure metrics.

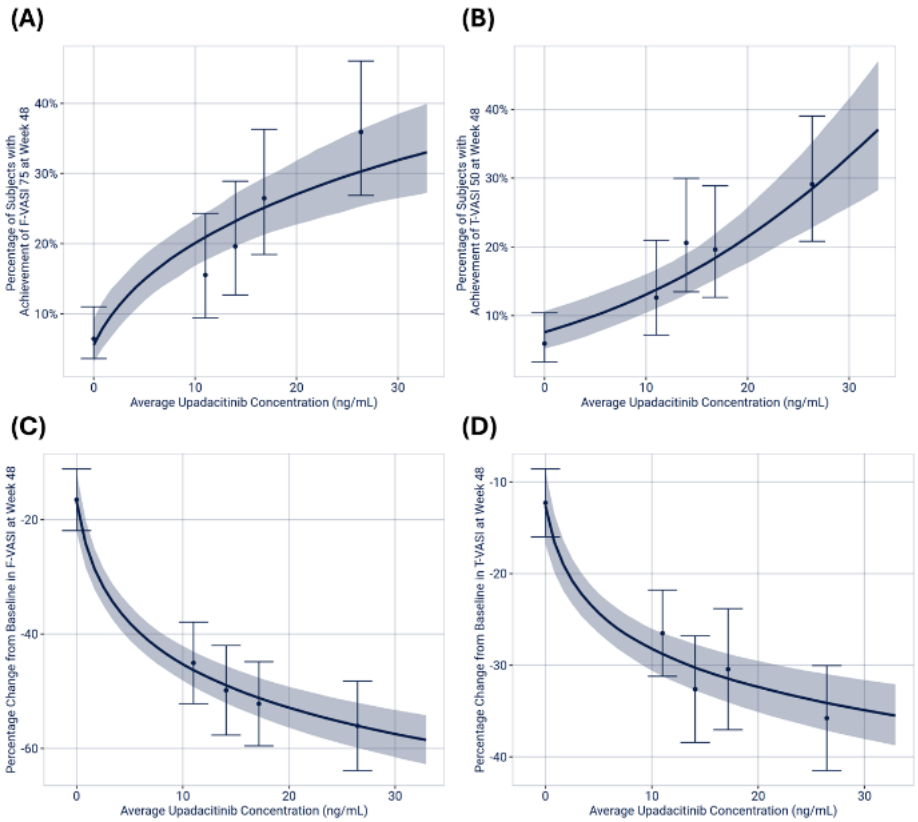
Table 13. Demographic and Baseline Characteristics of Subjects with NSV from Study M19-044 Included in the Exposure-Response Analyses

Characteristic	Placebo (N = 202)	15 mg QD (N = 410)	All Subjects (N = 612)
Body Weight (kg)			
Mean (SD)	75.9 (15.4)	74.1 (17.2)	74.7 (16.6)
Median	75.9	71.7	73.0
Min, Max	39.0, 113	37.7, 128	37.7, 128
Baseline Disease Duration (year)			
Mean (SD)	16.2 (13.3)	16.2 (13.7)	16.2 (13.6)
Median	12.3	12.6	12.6
Min, Max	0.0301, 58.6	0.0301, 64.7	0.0301, 64.7
Sex, n (%)			
Male	110 (54%)	196 (48%)	306 (50%)
Female	92 (46%)	214 (52%)	306 (50%)
Race Asian, n (%)			
Non-Asian	169 (84%)	346 (84%)	515 (84%)
Asian	33 (16%)	64 (16%)	97 (16%)
Race Black, n (%)			
Non-Black	194 (96%)	395 (96%)	589 (96%)
Black	8 (4%)	15 (4%)	23 (4%)
Race White, n (%)			
Non-White	44 (22%)	89 (22%)	133 (22%)
White	158 (78%)	321 (78%)	479 (78%)
Region, n (%)			
North America	86 (43%)	176 (43%)	262 (43%)
Europe	74 (37%)	158 (39%)	232 (38%)
Rest of World	42 (21%)	76 (19%)	118 (19%)
Prior Topical Therapy for NSV, n (%)			
No	84 (42%)	175 (43%)	259 (42%)
Yes	118 (58%)	235 (57%)	353 (58%)
Prior Phototherapy Therapy for NSV, n (%)			
Yes	18 (9%)	41 (10%)	59 (10%)
No	184 (91%)	369 (90%)	553 (90%)
Fitzpatrick Skin Type, n (%)			
1-3	145 (72%)	273 (67%)	418 (68%)
4-5	57 (28%)	137 (33%)	194 (32%)

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

An exposure-response relationship between all evaluated efficacy endpoints and upadacitinib exposures was found, in the range of exposures associated with 15 mg QD. A logarithmic shape function best described the exposure-response relationship for achievement of F-VASI 75 at Week 48, percent change from Baseline in F-VASI at Week 48, and percent change from Baseline in T-VASI at Week 48. A linear shape function best described the exposure-response relationship for achievement of T-VASI 50 at Week 48 (Figure 11).

Figure 11. Observed and Model-Predicted Percentage of Subjects with Achievement of F-VASI 75 at Week 48 (A), Percentage of Subjects with Achievement of T-VASI 50 at Week 48 (B), Percent Change from Baseline in F-VASI at Week 48 (C), and Percent Change from Baseline in T-VASI at Week 48 (D)



The solid lines represent median predicted response and the shaded areas represent 95% CIs of the response. The dots and error bars represent the proportion and 95% binomial CIs (A and B) or mean and 95% CIs (C and D) of the binned observed response.

Cross reference: R&D/25/2325 Figure 6; Figure 9, Figure 12, Figure 15

No covariates were identified as significant predictors for achievement of T-VASI 50 or achievement of F-VASI 75 and at Week 48. Fitzpatrick skin type was identified as a significant predictor of percentage change from Baseline in F-VASI at Week 48. Sex, Asian race and region were identified as significant predictors of percentage change from Baseline in T-VASI at Week 48.

Age at Screening [12 to < 18 years; ≥18 years], included as one of the pre-defined stratification factors, did not have any significant influence on the E-R relationship for any of the endpoints.

Exposure-safety analyses

There were not sufficient number of events for 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) to enable adequate assessment of exposure-response relationships.

2.3.5. Discussion on clinical pharmacology

The MAH has submitted PK data from the phase 2-study M19-051 and the phase 3-studies M19-044 Study 1 and Study 2 in adult and adolescent patients with NSV. A popPK model analysis approach was used to describe the upadacitinib exposure in the NSV population and to compare it to the exposure for previous characterised populations, including AD patients. The models were subsequently used to derive individual exposure metrics to evaluate that the exposures are comparable between subgroups, including adolescent vs adults.

Moreover, individual average steady state upadacitinib concentrations were derived from the popPK models to evaluate the relationships between upadacitinib plasma exposures and efficacy as well as safety, using data from the Phase 3 M19-051 study and the Phase 3 M19-044 studies.

The analytical methods were validated and accepted previously as satisfactory.

Two previously developed popPK models, based on data on various of indications, were utilised to describe upadacitinib concentrations in NSV and the strategy to use these as starting points for describing the upadacitinib PK in subjects with NSV is supported. This approach was justified by showing comparable observed dose-normalized upadacitinib concentrations versus time since the last dose (TSLD) in the NSV study populations 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 the Phase 2 Study M19-051 and Phase 3 M19-044.

In the PK datasets <2% of the samples were BLQ, which were handled using the M6 method. Samples with TSLD > 140 hours (168 hours for phase 2), or sampled before dosing, were excluded from the analysis. Additionally, for the phase 2 dataset, 24 outliers were excluded, as they were outside of the upper and lower boundaries set by ANOVA (excluding no more than 5% and 1% of the high and low concentrations, respectively). Overall, the handling of BLQ samples and the exclusion criteria are acceptable and the potential effect on the analysis is negligible.

PcVPCs on upadacitinib concentration vs TSLD showed an acceptable performance of the model to generally describe the PK of the subjects with NSV from both studies, except for some difficulties in capturing the lower variability. 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. The shrinkage on CL/F for both modelling analyses were < 20% and thus acceptable for the application to generate individual C_{avg} for exposure response analyses.

Based on the provided results, the model gives overall acceptable description of the observed PK data for general NSV 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 20 subjects. The larger variability in this body weight group could thus be expected.

Nevertheless, the model appears to give a sufficient 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 M19-044 study.

To assess differences in PK between special populations, a *post hoc* assessment of exposure differences between subgroups was made. The results indicated ≤15% impact of these covariates on the dose-normalized steady-state C_{avg} of upadacitinib relative to their reference groups. No relevant covariate effects were identified in the population pharmacokinetics analyses in subjects with NSV, 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 NSV to adults with NSV, in the M19-044 1 and 2 studies. No significant differences could be detected when comparing the model-predicted upadacitinib exposures between adolescents and adults at steady-state ($AUC_{24,ss}$, C_{avg}, C_{max} and C_{trough}). The dataset from the M19-044 1 and 2 studies covered subjects from 37.7 kg, with only 3 subjects between 35-45 kg. An acceptable exposure for upadacitinib from 30 kg could however be confirmed by additional data for subjects <40 kg with pcJIA, AA and AD.

Upadacitinib was previously approved from 12 years in patients with AD, with the max dose of 30 mg QD. Model predicted upadacitinib exposures in adolescents with NSV from the M19-044 1 and 2 studies are compared to predicted exposures for adolescents in AD. 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 NSV 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 NSV.

In the SmPC section 5.2, the statement on a similar PK and steady-state concentrations for adults and adolescents 12 to 17 years of age with atopic dermatitis and non-segmental vitiligo is endorsed.

A clear exposure-response relationship was identified, with an increase in response for all endpoints with increasing exposures of upadacitinib, best described with either linear or logarithmic shape functions in the studied range of exposures.

Data from three dose levels and placebo were available from the Phase 2 study. The use of E-R analysis to support the dose selection to Phase 3 is endorsed and the selected dose of 15 mg lies within the studied dose range. The data set was however limited and there were not sufficient number of safety variables of interest to enable adequate assessment of exposure-response relationships. Also, a substantial overlap of the confidence intervals for both the observed and predicted responses for the dose groups are shown, and the confidence intervals are wide in relation to the response size.

In Phase 3, one dose (+ placebo) was evaluated, corresponding to the selected therapeutic dose (15 mg QD). The observed relationship between concentration and response endpoints is consistent with Phase 2 findings and supports the exposure–response relationship at clinically relevant exposures.

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

2.3.6. Conclusions on clinical pharmacology

PK-data were presented from in total 536 patients with NSV, from Phase 2 Study M19-051 (6, 11 and 22 mg QD) and from Phase 3 Studies M19-044 Study 1 and Study (15 mg QD). The PK-data were analysed using PopPK modelling. The exposure of upadacitinib in the general NSV patient population was adequately described, showing similar PK in NSV as in the populations of previous

accepted indications. Additionally, comparable exposure (C_{avg}) of upadacitinib for adolescents with NSV and adolescents with AD is shown. Safety data from adolescents with AD can thus be used as supportive information for the sought posology in adolescents from 30 kg with NSV.

2.4. Clinical efficacy

The support of the efficacy of upadacitinib as a treatment for the new indication NSV (adults and adolescents, 12 years of age and older) is primarily derived by two ongoing Phase 3 studies, M19-044 Study 1 and Study 2. Period A of M19-044 Study 1 and Study 2 48-week placebo-controlled, double-blind treatment period has been completed. Phase B, a 112-week open-label extension period, is ongoing and the final CSRs will be submitted in Q2 2028. The completed Phase 2 dose-ranging study (Study M19-051) is also included as supportive data for the dosing recommendation. A tabular overview of the pivotal clinical studies is provided below (Table 14).

Table 14. Description of Clinical Efficacy and Safety Studies – Pivotal

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed Period A	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Co-Primary Endpoints
M19-044 Study 1/69/ AR, BE, BG, CA, CN, FR, DE, IL, NL, PL, PT, KR, ES, US/DB: 48 weeks; OLE: 112 weeks	19 Dec 2023 first subject screened, 24 Sep 2025 total enrollment 308 subjects/ 270 subjects enrollment goal	Global, randomized, double-blind, placebo-controlled, multicenter; 48-week, placebo-controlled, DB treatment period (Period A); = 112-week OLE period (Period B); and a 30-day follow-up period	DB Period: UPA 15 mg or placebo QD PO; OLE Period: UPA 15 mg QD PO	The primary objective of Study 1 is to evaluate the efficacy, safety, and tolerability of upadacitinib for the treatment of adults and adolescents with NSV who are eligible for systemic therapy	PBO: 102/87 UPA 15 mg: 206/172	49.4% Male 50.6% Female Median Age (Range) 46.0 (12, 77)	Adults and adolescents ≥ 12 years of age at Screening who have a documented clinical diagnosis of NSV who satisfy at least 1 of the following criteria at Screening and Baseline: • ≥ 0.5 F-VASI and 5 ≤ T-VASI < 50 AND have failed at least 1 topical corticosteroid and/or at least 1 topical calcineurin inhibitor for vitiligo; or • ≥ 0.5 F-VASI and 5 ≤ T-VASI < 50 AND have a sign of actively progressing vitiligo; or • ≥ 0.5 F-VASI and 10 ≤ T-VASI < 50	• Achievement of T-VASI 50 (≥ 50% reduction in T-VASI from Baseline) at Week 48 • Achievement of F-VASI 75 (≥ 75% reduction in F-VASI from Baseline) at Week 48

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed Period A	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Co-Primary Endpoints
M19-044 Study 2/65/ AR, BE, BG, CA, CN, FR, DE, IT, JP, NL, PL, SK, KR, ES, US/ DB: 48 weeks; OLE: 112 weeks	08 Jan 2024 first subject screened, 23 Sep 2025 total enrollment 306 subjects/270 subjects enrollment goal	Global, randomized, double-blind, placebo-controlled, multicenter; 48-week, placebo-controlled, DB treatment period (Period A); 112-week OLE period (Period B); and a 30-day follow-up period	DB Period: 15 mg UPA or placebo QD PO; OLE Period: 15 mg UPA QD PO	The primary objective of Study 2 is to evaluate the efficacy, safety, and tolerability of upadacitinib for the treatment of adults and adolescents with NSV who are eligible for systemic therapy	PBO: 101/81 UPA 15 mg: 205/177	50.7% Male 49.3% Female Median Age (Range) 46.0 (12, 78)	Adults and adolescents ≥ 12 years of age at Screening who have a documented clinical diagnosis of NSV who satisfy at least 1 of the following criteria at Screening and Baseline: • ≥ 0.5 F-VASI and 5 ≤ T-VASI < 50 AND have failed at least 1 topical corticosteroid and/or at least 1 topical calcineurin inhibitor for vitiligo; or • ≥ 0.5 F-VASI and 5 ≤ T-VASI < 50 AND have a sign of actively progressing vitiligo; or • ≥ 0.5 F-VASI and 10 ≤ T-VASI < 50	• Achievement of T-VASI 50 (≥ 50% reduction in T-VASI from Baseline) at Week 48 • Achievement of F-VASI 75 (≥ 75% reduction in F-VASI from Baseline) at Week 48

2.4.1. Dose response study

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Non-Segmental Vitiligo (M19-051)

Objectives

The primary objective of this study was to evaluate the safety and efficacy of upadacitinib for the treatment of adult subjects with non-segmental vitiligo (NSV).

Design

Study M19-051 was a Phase 2, multicenter, randomized, double-blinded, parallel-group, placebo-controlled dose-ranging study to evaluate the safety and efficacy of upadacitinib in adult subjects with NSV (Figure 12). Subjects enrolled in this study were adults (male and female) between 18 and 65 years old with a clinical diagnosis of NSV and no segmental or localized vitiligo, with all of the following at Screening and Baseline Visits: ≥ 0.5 Facial Vitiligo Area Scoring Index (F-VASI) and ≥ 5 Total Vitiligo Area Scoring Index (T-VASI). Subjects with other skin conditions that would interfere with evaluation of vitiligo, subjects with uncontrolled thyroid disease, and subjects with > 33% leukotrichia on the face or > 33% leukotrichia on the body (including face) were not eligible to enroll in this study.

The study was comprised of a 35-day Screening Period, a 24-week double-blind treatment period (Period 1), a 28-week blinded long-term extension (Period 2), and a 30-day Follow-up Period. Subjects who met the eligibility criteria at Baseline were randomized in a 2:2:2:1:1 ratio to one of five treatment groups:

- Group 1: upadacitinib 22 mg once daily (QD) (Period 1) → upadacitinib 22 mg QD (Period 2)
- Group 2: upadacitinib 11 mg QD (Period 1) → upadacitinib 11mg QD (Period 2)
- Group 3: upadacitinib 6 mg QD (Period 1) → upadacitinib 6 mg QD (Period 2)
- Group 4: placebo (Period 1) → upadacitinib 22 mg QD (Period 2)
- Group 5: placebo (Period 1) → upadacitinib 11 mg QD (Period 2)

At Week 24, subjects who were randomized to placebo at Baseline were switched to either 22 mg (Group 4) or 11 mg (Group 5) upadacitinib in a blinded fashion per pre-specified randomization assignments.

Efficacy analyses were conducted in the ITT Population in each period (ITT_1 and ITT_2). All tests were 2-sided at an alpha level of 0.1. In Period 1, the ITT Population (ITT_1) included all randomized subjects.

The primary endpoint was the percent (%) change from Baseline in F-VASI at Week 24. Secondary endpoints included: achievement of F-VASI 75 (≥75% improvement in F-VASI from Baseline) at Week 24, achievement of F-VASI 50 (≥50% improvement in F-VASI from Baseline) at Week 24, achievement of T-VASI 50 (≥50% improvement in T-VASI from Baseline) at Week 24, and percent (%) change from Baseline in T-VASI at Week 24.

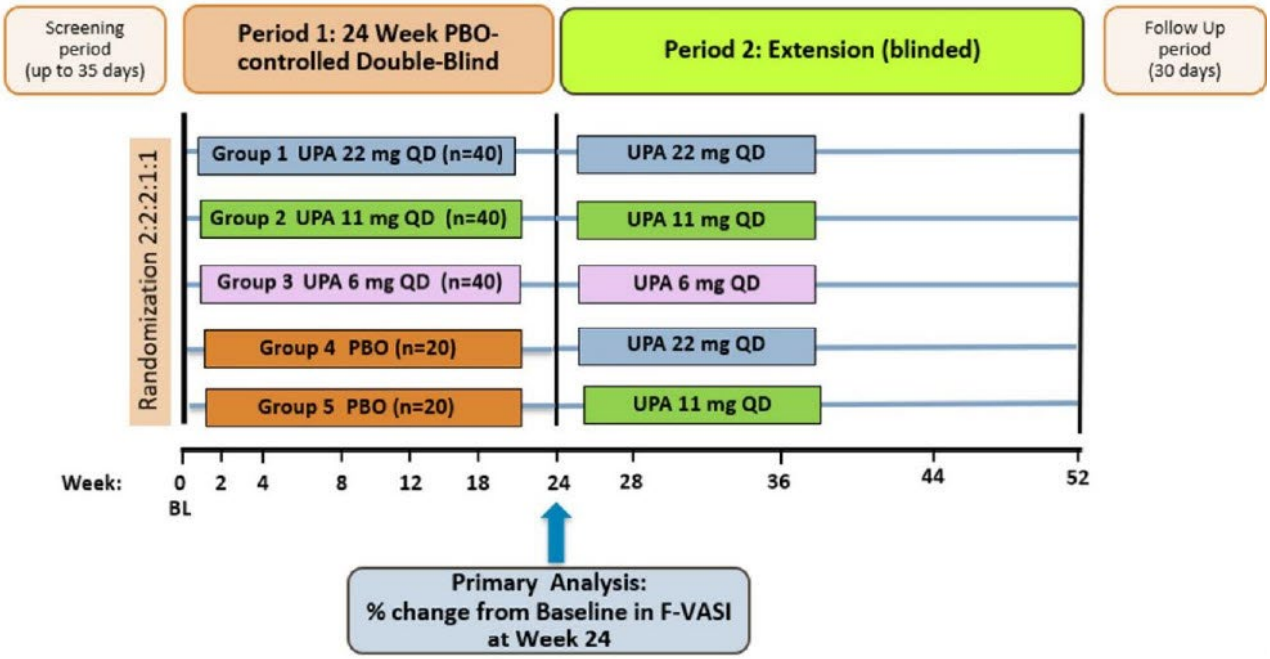
Approximately 160 subjects were planned to be randomized to three upadacitinib treatment groups and placebo in a ratio of 2:2:2:1:1. The sample size for this study was based on the percent change in F-VASI from Baseline at Week 24. The approach provided more than 90% power to detect the treatment difference of 40% reduction (assuming a standard deviation of 54.8%) in at least 1 upadacitinib group

versus placebo using a 2-sided significance level of 0.1 based on the two sample t-test. Multiplicity from multiple comparisons was not adjusted in this Phase 2 study.

For continuous variables, comparisons of change and/or percent change from Baseline will be made between upadacitinib and placebo based on the Mixed Model Repeated Measures (MMRM) adjusting for treatment, visit, treatment-by-visit interaction, and stratification factors derived by the actual value (age group [≤ 50 and > 50], Baseline disease severity [T-VASI < 15 and ≥ 15], and status of active vitiligo [Yes/No]) as fixed factors, and Baseline value as a covariate. The MMRM will be the primary approach to handle missing values for continuous endpoints.

For categorical variables, comparisons will be made between upadacitinib and placebo using the Cochran-Mantel-Haenszel (CMH) test, adjusting for the stratification factors derived by the actual value: age group (≤ 50 and > 50), Baseline disease severity (T-VASI < 15 and ≥ 15), and status of active vitiligo (Yes/No). Non-Responder Imputation incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-MI) will be the primary approach to handle missing values for categorical endpoints.

Figure 12. Study Design, Study M19-051



UPA=upadacitinib; PBO=placebo; QD=once daily; F-VASI= Facial Vitiligo Area Scoring Index

Results

A total of 185 subjects were randomized and received the study drug (upadacitinib or PBO) in Period 1. Overall, 173 (93.5%) subjects completed Period 1, and 166 (89.7%) subjects completed the study drug in Period 1. In Period 1, the most frequent reasons for discontinuing the study across the treatment groups were withdrawal by subjects and lost to follow-up, and the most frequent reasons for discontinuing the study drug across the treatment groups were withdrawal from treatment by subjects, AEs, lost to follow-up, and progressive disease.

A total of 166 subjects entered Period 2 and received randomized study drug. Of those, 147 (88.6%) completed Period 2, and 145 (87.3%) subjects completed the study drug. In Period 2, the most frequent reasons for discontinuing the study across the treatment groups were lost to follow up and withdrawal

from treatment by subjects. The most frequent reasons for discontinuing the study drug across the treatment groups were lost to follow up, withdrawal of consent by subjects, AEs, and progressive disease.

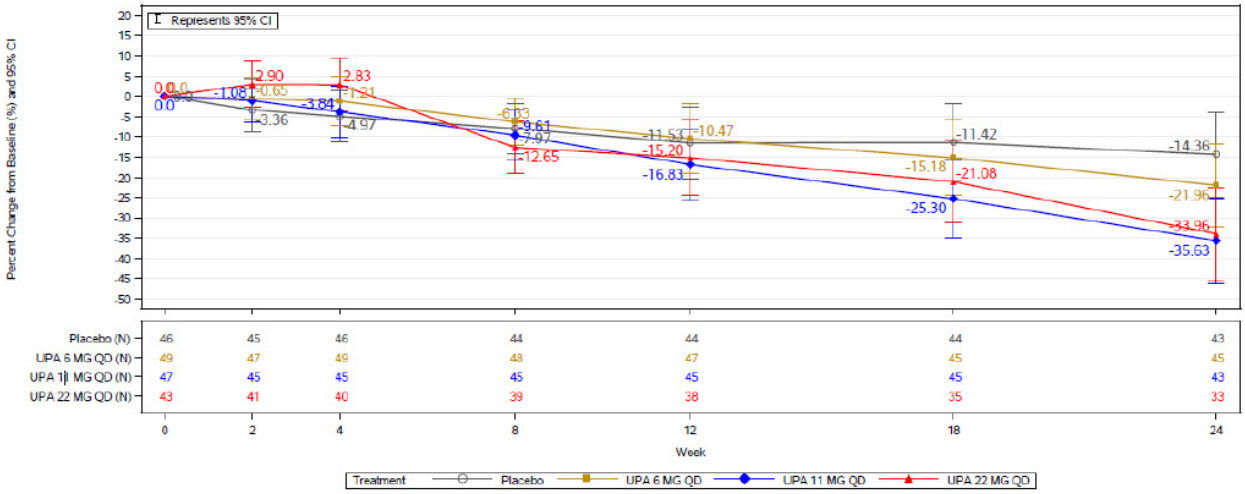
Participants had a mean (range) age of 46.3 years (18-66), and most participants (57.8%) were ≤50 years of age, white (76.2%), not Hispanic or Latino (89.2%), and 62.2% were female. Overall, the mean (SD) vitiligo disease duration since diagnosis was 16.8 (13.19) years. At Baseline, most subjects were reported to have active vitiligo (70.8%) and T-VASI score >10 (68.1%). Overall, 41.1% of the subjects used prior medications for vitiligo: topical therapy (34.6%), phototherapy (18.9%), topical vitamin D (5.9%), systemic corticosteroids (4.3%), and antioxidants (3.8%).

Twenty-two (11.9%) participants had at least one protocol deviation; inclusion/exclusion criteria violation (n=11[5.9%]), development of withdrawal criteria without being withdrawn (n=3 [1.6%]), and use of prohibited concomitant medications (n=8 [4.3%]). Deviations were assessed for their impact on analyses and data integrity or subject safety. The MAH states that none of the deviations were considered to have affected the study outcome or interpretation of the study results or conclusions.

For the primary efficacy endpoint, upadacitinib 11 mg and upadacitinib 22 mg showed a greater mean reduction in percent change from Baseline in F-VASI at Week 24 (difference vs. placebo: -21.27, P = 0.005 and -19.60, P = 0.013, respectively) than placebo (Figure 13). No significant reduction in mean percentage change from Baseline in F-VASI at Week 24 was observed for upadacitinib 6 mg treatment compared to placebo (difference vs. placebo: -7.60; P = 0.304). Results from the subgroup analysis for the primary endpoint indicated consistency of efficacy of upadacitinib 22 mg and upadacitinib 11 mg across a range of prespecified demographic and Baseline disease characteristics, with treatment differences in favour of upadacitinib 22 mg and upadacitinib 11 mg compared to placebo. No notable differences were observed between upadacitinib 6 mg and placebo treatment groups in the subgroup analysis for the primary endpoint.

Upadacitinib 11 mg and upadacitinib 22 mg showed better efficacy compared to placebo for 4 out of 5 secondary efficacy endpoints: achievement of F-VASI 75, T-VASI 50, and F-VASI 50, at Week 24; and percent change from Baseline in T-VASI at Week 24.

Figure 13. Percent change from Baseline in F-VASI by Visit in Period 1 (MMRM; ITT_1 Population)



UPA=upadacitinib; PBO=placebo; QD=once daily
Source: Figure 14.2__16.1.1

For subjects initially randomized to upadacitinib treatment in Period 1 and continued with the same upadacitinib treatment in Period 2, mean percent change from Baseline in F-VASI, response rates of F-VASI 75, T-VASI 50, and F-VASI 50, and mean percent change from Baseline in T-VASI continued to improve through Week 52. For subjects initially randomized to placebo in Period 1 and switched to upadacitinib 11 mg or upadacitinib 22 mg in Period 2 mean percent change from Baseline in F-VASI, the responses rates of F-VASI 75, T-VASI 50, and F-VASI 50, and mean percent change from Baseline in T-VASI improved after receiving upadacitinib treatment.

2.4.2. Main studies

A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy, Safety, and Tolerability of Upadacitinib in Adult and Adolescent Subjects with Non-Segmental Vitiligo Who Are Eligible for Systemic Therapy (M19-044 Study 1 and Study 2)

Objectives

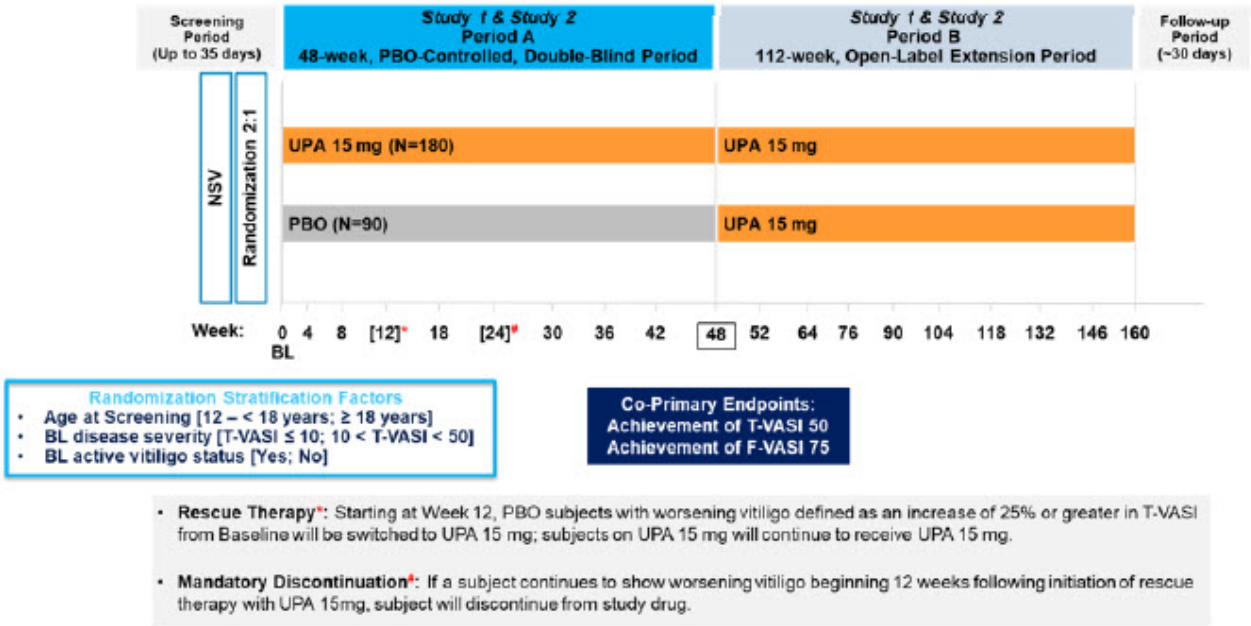
The main objectives were to evaluate the efficacy, safety, and tolerability of upadacitinib for the treatment of adults and adolescents with non-segmental vitiligo (NSV) who are eligible for systemic therapy.

Design

The two pivotal studies, M19-044 Study 1 and Study 2, are Phase 3, global, randomized, double-blind, placebo-controlled, multicenter studies and are identical in objectives and design (Figure 14). Studies 1 and 2 were carried out at different sites with different subjects. Both Study 1 and Study 2 comprised a 35-day Screening Period; a 48-week, double-blind, **placebo-controlled treatment period** (Period A); a 112-week **open-label extension period** (Period B); and a 30-day follow-up period. Subjects who completed Period A of Study 1 or Study 2 and failed to achieve T-VASI 90 at Study 1 or Study 2 Week 48 were provided the opportunity to enter the optional, exploratory Study 3. Subjects who were unable, unwilling, or not eligible to participate in Study 3 continued into Period B of Study 1 or Study 2 to receive

open-label upadacitinib 15 mg daily as monotherapy. Period B is ongoing and the has MAH committed to submit the final CSRs from Period B of Study 1 and Study 2 (112 week open label extension period) in Q2 2028. These studies are classified as Category 3 studies and are included in the Risk Management Plan (RMP).

Figure 14. Study Design, M19-044 (Study 1 and Study 2)



UPA=upadacitinib; PBO=placebo; BL=Baseline; T-VASI=Total Vitiligo Area Scoring Index; F-VASI= Facial Vitiligo Area Scoring Index

Study participants

Male and female adult (≥ 18 years of age at Screening) and adolescent subjects (≥ 12 and < 18 years of age at Screening) with a documented clinical diagnosis of NSV and no segmental or localized vitiligo, and who met all eligibility criteria and none of the exclusion criteria were enrolled in Study 1 and Study 2. Subjects with a baseline T-VASI score ≤ 10 will be enrolled up to 30% of each study's total population. Subjects with a sign of actively progressing vitiligo will be enrolled to approximately 60% of the total population.

Main inclusion and exclusion criteria

The inclusion/exclusion criteria were similar for the Phase 3 M19-044 Study 1 and Study 2. Subjects who met the following criteria were **included**:

- Adults and adolescent individuals ≥ 12 years of age at Screening
- Documented clinical diagnosis of NSV
- At Screening and Baseline Visits, subject must have satisfied at least one of the following criteria:
    - ≥ 0.5 Facial Vitiligo Area Scoring Index (F-VASI) and 5 ≤ T-VASI < 50 and have failed at least 1 topical corticosteroid and/or at least 1 topical calcineurin inhibitor for vitiligo; or
    - ≥ 0.5 F-VASI and 5 ≤ T-VASI < 50 and have a sign of actively progressing vitiligo; or
    - ≥ 0.5 F-VASI and 10 ≤ T-VASI < 50
- Body weight must be ≥ 30 kg at Baseline Visit for subjects who are ≥ 12 and < 18 years of age

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

- Had segmental or localized vitiligo.
- Had a history of active skin disease other than vitiligo that could interfere with the assessment of vitiligo
- Had > 33% leukotrichia in areas of vitiligo on the face or > 33% leukotrichia in areas of vitiligo on the body (including the face)
- Had been treated:
    - with any systemic JAK inhibitor
    - with any permanent skin bleaching agents
    - for any indication with any systemic therapy that can be used for vitiligo (e.g., methotrexate (MTX), mycophenolate mofetil, corticosteroids) or supplemental vitiligo therapy (antioxidants, vitamins, herbal medicine, traditional medicine) within 30 days or five half-lives (whichever is longer) prior to the first dose of study drug
    - for any indication with a topical non-JAK inhibitor that can be used to treat vitiligo within 60 days prior to the first dose of study drug
    - with any topical JAK inhibitor within 60 days prior to the first dose of study drug
    - with any photochemotherapy or phototherapy, including excimer and other forms of laser therapy, for any indication, within 84 days prior to the first dose of study drug
    - with temporary tattoos (excluding vinyl adhesive tattoos) within the vitiligo lesions within a minimum of 30 days prior to first dose of study drug or had been treated previously with any permanent tattoo or transplant (skin graft or melanocyte – keratinocyte transplant) within the vitiligo lesions

Discontinuation

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

- The subject requests withdrawal from study drug or the study
- Abnormal laboratory results or AEs that either met the criteria for discontinuation of study drug or ruled out safe continuation of the study drug
- Serious infection (e.g., sepsis) which could not 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 (DVT), pulmonary embolus, or non-cardiac, non-neurologic arterial thrombosis
- Subject was non-compliant with TB prophylaxis (as applicable) or developed active TB at any time during the study
- Subject develops any malignancy including localized non-melanoma skin cancer (NMSC) or carcinoma in situ of the cervix
- The subject continued to demonstrate worsening of vitiligo (defined by an increase of $\geq$ 25% in T-VASI from Baseline) beginning 12 weeks following initiation of rescue therapy

- Subject developed a GI perforation (other than due to appendicitis or mechanical injury)
- The subject experienced a serious hypersensitivity reaction without an alternative etiology
- Pregnancy

Treatments

Upadacitinib and matching placebo were supplied as shown in Table 15.

Table 15. Description of Study Drug.

Investigational Product	Mode of Administration	Dosage Form	Strength	Masking	Frequency
Upadacitinib (ABT-494)	Oral	Extended-release tablets	15 mg	Blinded, Period A	QD
Upadacitinib (ABT-494)	Oral	Extended-release tablets	15 mg	Unblinded, Rescue Therapy and Period B	QD
Placebo for Upadacitinib (ABT-494)	Oral	Film-coated tablets	Not applicable	Blinded, Period A	QD

Treatment compliance

Treatment compliance was defined as the number of tablets actually taken (i.e., the difference between the number of tablets dispensed and the number of tablets returned) divided by the number of tablets that should have been taken.

Concomitant treatments

The routine use of photoprotective measures, including but not limited to protective clothing and topical sunscreens, was allowed. The use of oral supplements for the purpose of photoprotection, including but not limited to Polypodium leucotomos, was prohibited throughout the study.

Rescue treatment

Rescue therapy will not be permitted prior to Week 12. Starting at Week 12 through Week 42, subjects (receiving either placebo or upadacitinib 15 mg in Period A) who show worsening vitiligo, defined as an increase of $\geq$ 25% in T-VASI from Baseline at a given scheduled visit, rescue therapy with upadacitinib 15 mg QD was offered. Subjects who underwent rescue therapy with upadacitinib 15 mg QD would continue upadacitinib 15 mg QD for the remainder of the study. Subjects and sites would remain blinded to preceding treatment assignment for the duration of the study. If a subject continued to demonstrate worsening of vitiligo (defined by an increase of $\geq$ 25% in T-VASI from Baseline) beginning 12 weeks following initiation of rescue therapy, the subject must be discontinued from study drug.

Objectives

Outcomes/endpoints

For M19-044 Study 1 and Study 2, the co-primary endpoints, the multiplicity-controlled secondary endpoints, and the additional endpoints were the same for both studies.

Co-primary endpoints

The co-primary endpoints of Study 1 and Study 2 were achievement of T-VASI 50 (≥ 50% reduction in T-VASI from Baseline) and F-VASI 75 (≥ 75% reduction in F-VASI from Baseline) at Week 48.

Ranked secondary endpoints

1. Achievement of F-VASI 50 (≥ 50% reduction in F-VASI from Baseline) at Week 48;
2. Achievement of F-VASI 75 (≥ 75% reduction in F-VASI from Baseline) at Week 24;
3. Percent change from Baseline in F-VASI at Week 24;
4. Percent change from Baseline in T-VASI at Week 48;
5. Achievement of F-VASI 90 (≥ 90% reduction in F-VASI from Baseline) at Week 48;
6. Achievement of PhGIC-V of "Much better (1)" at Week 48;
7. Achievement of VNS score of "A lot less noticeable (4)" or "No longer noticeable (5)" at Week 48;
8. Achievement of PaGIC-V of "Much better (1)" at Week 48;
9. Achievement of no increase from Baseline in T-VASI at both Week 8 and Week 12 among subjects with actively progressing vitiligo at Baseline.

Additional efficacy endpoints

Additional efficacy endpoints were measured and are noted in the study protocol.

Physician Assessments

Descriptions of the clinician reported outcome (ClinRO) assessments used to evaluate the efficacy of upadacitinib are summarized below.

Total Vitiligo Area Scoring Index (T-VASI) and Facial Vitiligo Area Scoring Index (F-VASI)

The Vitiligo Area Scoring Index (VASI) is a ClinRO that assesses affected BSA and level of depigmentation analogous to the PASI as used in psoriasis.[12] It is based on a composite estimate of the overall area of vitiligo patches, measured by the number of hand units (subject's palm plus volar surface of all 5 digits = 1% BSA) multiplied by the degree of depigmentation within each affected area (0%, 10%, 25%, 50%, 75%, 90%, or 100%).

The Total Vitiligo Area Scoring Index (T-VASI) is calculated using a formula that includes contributions from all body regions, with a possible range from 0 to 100. The Facial Vitiligo Area Scoring Index (F-VASI) includes contributions from the face, with a possible range from 0 to 3. For assessing F-VASI, the area of the face includes the forehead to the original anterior hairline, temples, around the eyes (including eyelids), nose, cheeks (mid and lateral), and around the mouth (including the cutaneous lips and chin). The 'face' excludes the vermillion lips, ears, and scalp. To facilitate measurement of T-VASI or F-VASI scoring, a qualified investigator or designee can measure the area of vitiligo patches by the number of thumb units (subject's thumb from distal tip to metacarpophalangeal joint = 0.1% BSA) as well as the number of hand units (1% BSA).

[12] Hamzavi, I., Jain, H., McLean, D., Shapiro, J., Zeng, H., & Lui, H. (2004). Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: The Vitiligo Area Scoring Index. Archives of Dermatology, 140(6), 677–683.

Physician Global Impression of Change – Vitiligo (PhGIC-V)

The investigator rates the overall change in the subject's vitiligo by comparing the severity of vitiligo right now with the severity of vitiligo since the subject started the study treatment. Responses range from 1 = "Much better" to 5 = "Much worse."

A qualified investigator collected vitiligo history at Screening and Baseline Visits and documented all areas of the body with actively progressing vitiligo lesions.

Patient reported outcomes (PROs)

Descriptions of selected clinical response measures and health-related PRO measures used to evaluate the efficacy of upadacitinib are summarized below.

Patient Global Impression of Change – Vitiligo (PaGIC-V)

The PaGIC-V asks subjects to rate the overall change in their vitiligo by comparing the severity of their vitiligo right now with the severity of their vitiligo since they started the study treatment.

Vitiligo Noticeability Scale (VNS)

The VNS is a single-item, validated questionnaire used in clinical trials to assess the noticeability of vitiligo lesions following therapy.

Sample size

Approximately 270 adult and adolescent subjects were to be randomized to upadacitinib 15 mg or placebo in each of Study 1 and Study 2 (Period A) (180 subjects to upadacitinib 15 mg and 90 subjects to placebo). Approximately 50 adolescents were to be enrolled across both studies. Assuming a Week 48 T-VASI 50 response rate of 6% and an F-VASI 75 response rate of 6% in the placebo group and T-VASI 50 of 28.8% and F-VASI 75 of 37.7% for the UPA 15 mg group, the sample size was expected to provide more than 90% power to simultaneously detect a treatment difference of 22.8% and 31.7% for T-VASI 50 and F-VASI 75, respectively, in the upadacitinib 15 mg group versus placebo using 2-sided test at a 0.05 significance level.

Randomisation

In Period A of Study 1 and Study 2, subjects were randomized 2:1 to receive 15 mg upadacitinib or placebo once daily. Randomization was stratified by age at Screening (12 to < 18 years; ≥ 18 years), Baseline disease severity (T-VASI ≤ 10; 10 < T-VASI < 50) and Baseline status of actively progressing vitiligo (Yes; No). Subjects were classified as having actively progressing vitiligo at Baseline if they fulfilled at least 1 of the following criteria:

- Documented evidence of the occurrence of new lesions or the progression (enlargement) of existing lesions within 6 months prior to Baseline
- Presence of at least 1 lesion of confetti-like depigmentation, trichrome pattern, and/or Koebner phenomenon type 2B.

Blinding (masking)

In Study 1 and Study 2, the treatment assignment was double-blinded in Period A. Period B was open label (all patients received upadacitinib 15 mg during Period B). Study sites and subjects remained

blinded to treatment assignments in Period A for the duration of the study. To maintain the blind, 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.

The final version of the Statistical Analysis Plan (version 4.0) is dated 13 October 2025.

Database lock took place on 20 October 2025 for both Study 1 and Study 2.

Analysis population

The ITT populations were used for all efficacy analyses of Study 1 and Study 2 and were defined as:

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

The Safety Populations were defined as:

- 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.

In addition, safety summaries were provided for the following population:

- ALL_UPA: All randomized subjects who received at least 1 dose of upadacitinib in the study.

Hypothesis testing

For the primary analysis of each co-primary endpoint, comparison between upadacitinib and placebo was done using the Cochran-Mantel-Haenszel test, adjusting for the actual values of the 3 stratification factors: age at Screening [12 – < 18 years; ≥ 18 years], Baseline disease severity [T-VASI ≤ 10; 10 < T-VASI < 50], and Baseline status of actively progressing vitiligo [Yes; No].

For the binary ranked secondary endpoints, similar analysis as the co-primary endpoints were conducted using Cochran-Mantel-Haenszel test as described above.

The ranked continuous secondary endpoints were analyzed using an ANCOVA model including treatment groups, the actual values of the 3 stratification factors (age at Screening [12 to < 18 years; ≥ 18 years], Baseline disease severity [T-VASI ≤ 10; T-VASI > 10], and Baseline status of actively progressing vitiligo [Yes; No]), and the Baseline value.

Intercurrent events

Intercurrent events were defined as:

- The use of confounding treatment for NSV that could impact the evaluation of the respective endpoint. Confounding treatments include two types: 1. Rescue therapy if upadacitinib 15 mg; 2. Other pre-specified confounding treatments for vitiligo.

These events were handled using non-response imputation (a composite variable strategy) for binary endpoints. For continuous endpoints, return-to-baseline multiple imputation (hypothetical strategy) was used.

Missing data

For binary endpoints, Non-Responder Imputation (NRI) while incorporating Multiple Imputation (MI) approach (NRI-MI) was used to handle any missing values. In NRI-MI approach, the missing data were categorised as a non-responder for the visit, with two exceptions:

1. When the subject is a responder both before and after the visit window, the subject will be categorized as a responder for the visit.
2. Any missing data that could reasonably assumed to be missing-at-random (MAR), in cases such as due to a pandemic, significant natural disaster, or a geopolitical conflict, will be handled by MI.

As a sensitivity analysis for the binary co-primary endpoints, missing values due to all causes were imputed using MI under the MAR assumption. A tipping-point analyses were also conducted.

For the continuous endpoints, Multiple Imputation was the primary approach for handling the missing data, except that missing data after treatment discontinuation due to lack of efficacy was handled by "Return-to-Baseline"(RTB).

Type-I error control

The statistical comparisons of upadacitinib versus placebo for co-primary efficacy endpoints and the ranked secondary endpoints was carried out in a hierarchical order under a 2-sided significance level of 0.05.

Results

Participant flow *and numbers analysed*

Across the two pivotal studies, a total of 614 participants aged 12 to 78 years at Baseline (including 53 adolescent subjects) were randomized in the double-blind, placebo-controlled Period A (Table 16, Table 17). Of these, 411 participants were randomized to treatment with upadacitinib 15 mg (206 in Study 1 and 205 in Study 2) and 203 participants with placebo (102 in Study 1 and 101 in Study 2) once daily (Figure 15, Figure 16). In accordance with the inclusion criteria, subjects enrolled had a documented clinical diagnosis of NSV.

A total of 83.9% completed study treatment in Period A (258 participants [83.8%] in Study 1 and 257 participants [84.3%] in Study 2). In the adolescent population, 92.5% completed the study treatment in Period A (22 participants [95.7%] in Study 1 and 27 participants [90%] in Study 2). A total of 430 subjects including 48 adolescents continued into Period B as of the data cutoff date of 24 September 2025. Period B is ongoing and the final CSRs will be submitted in Q2 of 2028.

In total, 97 subjects (15.8%) discontinued study treatment in Period A. Across studies, the most frequent (primary) reason for study treatment discontinuation in Period A was withdrawal from treatment by subject. Subjects who discontinued study treatment were encouraged to remain in the study to complete all scheduled visits for all safety and efficacy assessments as per protocol. Across studies, a higher percentage of subjects in the placebo group (n=29) received **rescue treatment** with open-label upadacitinib 15 mg QD in Period A compared to the upadacitinib 15 mg group (n=18).

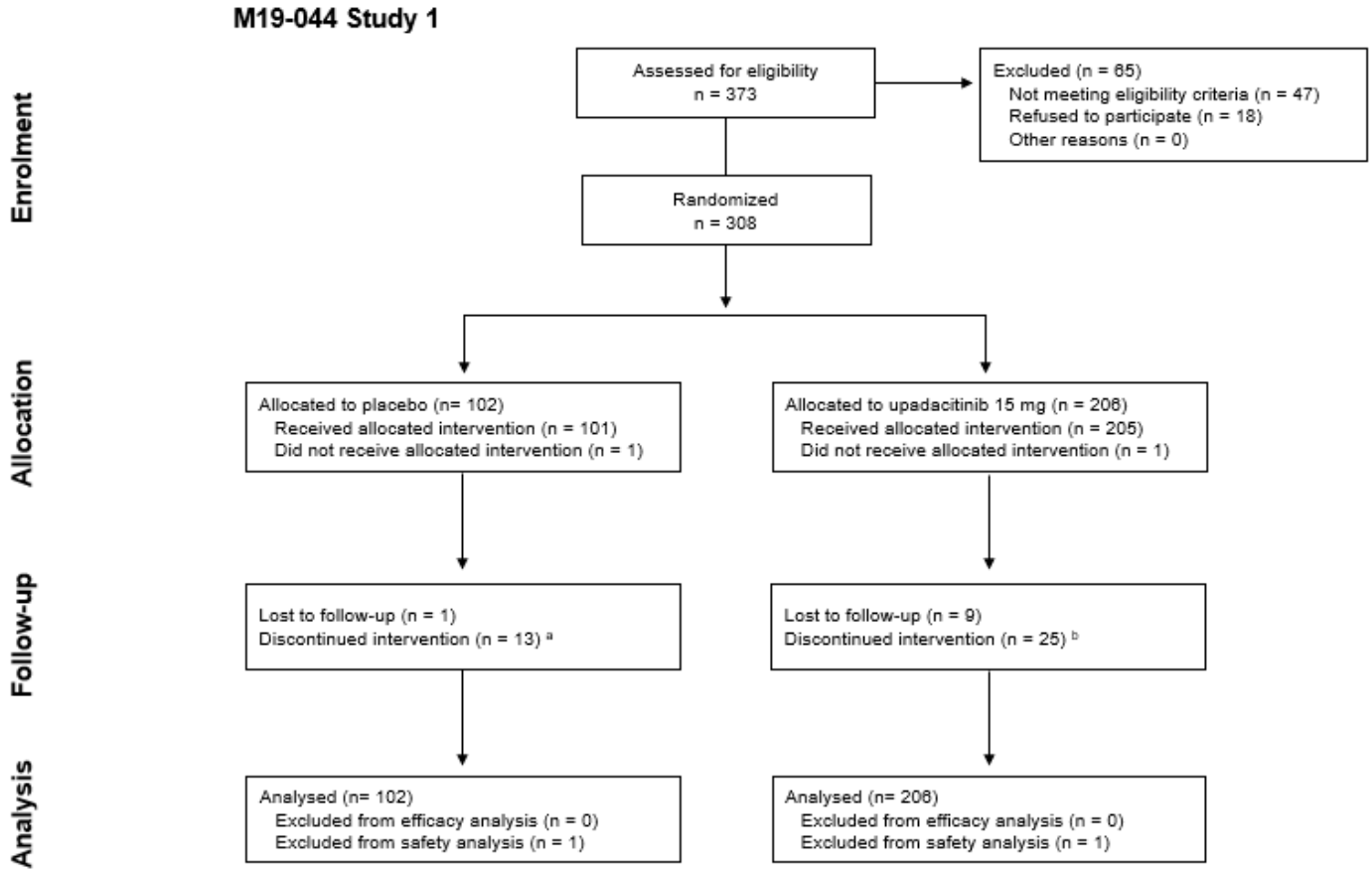
Table 16. Subject Disposition in M19-044 Study 1, ITT_A Population

		Overall		Adolescents		
Status	PBO (N = 102) n (%)	UPA 15 mg (N = 206) n (%)	Overall (N = 308) n (%)	PBO (N = 8) n (%)	UPA 15 mg (N = 15) n (%)	Overall (N = 23) n (%)
Subjects randomized in Period A	102 (100)	206 (100)	308 (100)	8 (100)	15 (100)	23 (100)
Subjects who took at least one dose of study treatment in Period A	101 (99.0)	205 (99.5)	306 (99.4)	8 (100)	15 (100)	23 (100)
Subjects who took confounding treatment in	19 (18.6) Period A	14 (6.8)	33 (10.7)	1 (12.5)	0	1 (4.3)
Subjects who were rescued by Open-label	19 (18.6) UPA 15	11 (5.3)	30 (9.7)	1 (12.5)	0	1 (4.3)
mg in Period A						
Subjects who took other confounding treatment in Period A	0	3 (1.5)	3 (1.0)	0	0	0
Subjects who completed Period A	87 (85.3)	172 (83.5)	259 (84.1)	8 (100)	14 (93.3)	22 (95.7)
Subjects who prematurely discontinued study in Period A	15 (14.7)	34 (16.5)	49 (15.9)	0	1 (6.7)	1 (4.3)
Primary reason for discontinuation						
Death	0	0	0	0	0	0
Lost to follow-up	1 (1.0)	9 (4.4)	10 (3.2)	0	1 (6.7)	1 (4.3)
Withdrawal by subject	13 (12.7)	23 (11.2)	36 (11.7)	0	0	0
Study terminated by sponsor	0	0	0	0	0	0
Other	1 (1.0)	2 (1.0)	3 (1.0)	0	0	0
Subjects who completed study treatment in Period A	87 (85.3)	171 (83.0)	258 (83.8)	8 (100)	14 (93.3)	22 (95.7)
Subjects who prematurely discontinued study treatment in Period A	14 (13.7)	34 (16.5)	48 (15.6)	0	1 (6.7)	1 (4.3)
Primary reason for discontinuation						
Adverse event	5 (4.9)	6 (2.9)	11 (3.6)	0	0	0
Lost to follow-up	1 (1.0)	9 (4.4)	10 (3.2)	0	1 (6.7)	1 (4.3)
Progressive disease	0	0	0	0	0	0
Lack of efficacy	0	0	0	0	0	0
No longer clinically benefiting	0	0	0	0	0	0
Symptomatic deterioration	0	0	0	0	0	0
Withdrawal from treatment by subject	6 (5.9)	17 (8.3)	23 (7.5)	0	0	0
Study terminated by sponsor	0	0	0	0	0	0
Other	2 (2.0)	2 (1.0)	4 (1.3)	0	0	0
Mandatory discontinuation for progressing vitiligo	2 (2.0)	1 (0.5)	3 (1.0)	0	0	0
Other reasons	0	1 (0.5)	1 (0.3)	0	0	0

Table 17. Subject Disposition in M19-044 Study 2, ITT_A Population

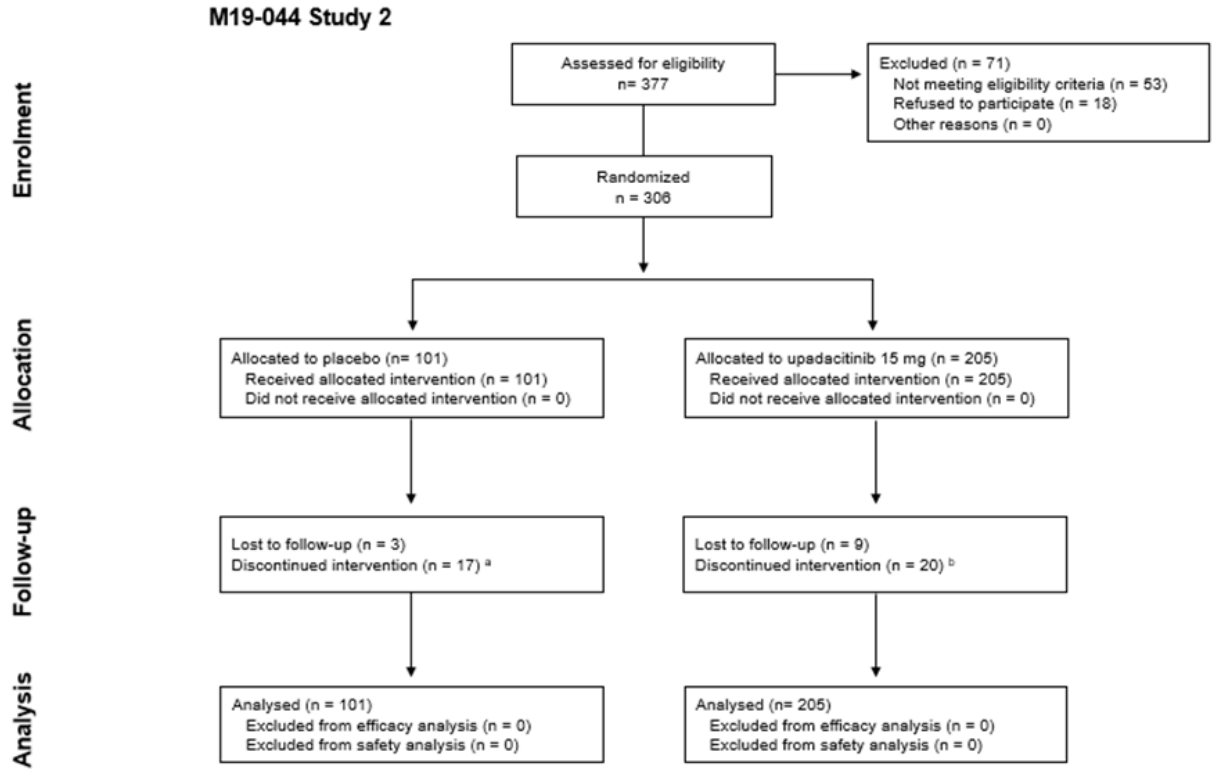
Status	Overall			Adolescents		
	PBO (N = 101) n (%)	UPA 15 mg (N = 205) n (%)	Overall (N = 306) n (%)	PBO (N = 8) n (%)	UPA 15 mg (N = 22) n (%)	Overall (N = 30) n (%)
Subjects randomized in Period A	101 (100)	205 (100)	306 (100)	8 (100)	22 (100)	30 (100)
Subjects who took at least one dose of study treatment in Period A	101 (100)	205 (100)	306 (100)	8 (100)	22 (100)	30 (100)
Subjects who took confounding treatment in Period A	10 (9.9)	10 (4.9)	20 (6.5)	1 (12.5)	2 (9.1)	3 (10.0)
Subjects who were rescued by open-label UPA 15 mg in Period A	10 (9.9)	7 (3.4)	17 (5.6)	1 (12.5)	2 (9.1)	3 (10.0)
Subjects who took other confounding treatment in Period A	0	3 (1.5)	3 (1.0)	0	0	0
Subjects who completed Period A	81 (80.2)	177 (86.3)	258 (84.3)	6 (75.0)	21 (95.5)	27 (90.0)
Subjects who entered Study 3	12 (11.9)	23 (11.2)	35 (11.4)	0	1 (4.5)	1 (3.3)
Subjects who prematurely discontinued study in Period A	20 (19.8)	28 (13.7)	48 (15.7)	2 (25.0)	1 (4.5)	3 (10.0)
Primary reason for discontinuation						
Death	1 (1.0)	0	1 (0.3)	0	0	0
Lost to follow-up	3 (3.0)	9 (4.4)	12 (3.9)	0	1 (4.5)	1 (3.3)
Withdrawal by subject	15 (14.9)	18 (8.8)	33 (10.8)	2 (25.0)	0	2 (6.7)
Study terminated by sponsor	0	0	0	0	0	0
Other	1 (1.0)	1 (0.5)	2 (0.7)	0	0	0
Subjects who completed study treatment in Period A	81 (80.2)	176 (85.9)	257 (84.0)	6 (75.0)	21 (95.5)	27 (90.0)
Subjects who prematurely discontinued study treatment in Period A	20 (19.8)	29 (14.1)	49 (16.0)	2 (25.0)	1 (4.5)	3 (10.0)
Primary reason for discontinuation						
Adverse event	4 (4.0)	4 (2.0)	8 (2.6)	0	0	0
Lost to follow-up	3 (3.0)	9 (4.4)	12 (3.9)	0	1 (4.5)	1 (3.3)
Progressive disease	1 (1.0)	0	1 (0.3)	0	0	0
Lack of efficacy	1 (1.0)	0	1 (0.3)	0	0	0
No longer clinically benefiting	0	0	0	0	0	0
Symptomatic deterioration	0	0	0	0	0	0
Withdrawal from treatment by subject	11 (10.9)	14 (6.8)	25 (8.2)	2 (25.0)	0	2 (6.7)
Study terminated by sponsor	0	0	0	0	0	0
Other	0	2 (1.0)	2 (0.7)	0	0	0
Mandatory discontinuation for progressing vitiligo	0	1 (0.5)	1 (0.3)	0	0	0
Other reasons	0	1 (0.5)	1 (0.3)	0	0	0

Figure 15. Subject Disposition M19-044 Study 1 – Period A (ITT_A Population)



[a] Reasons for discontinued intervention: 2 subjects due to Mandatory discontinuation for progressing vitiligo; 5 subjects due to Adverse event; 6 subjects due to Withdrawal from treatment by subject.
[b] Reasons for discontinued intervention : 1 subject due to Mandatory discontinuation for progressing vitiligo; 6 subjects due to Adverse event; 17 subjects due to Withdrawal from treatment by subject; 1 subject due to Other reason (Investigator decision due to non-compliance with protocol requirements).

Figure 16. Subject Disposition M19-044 Study 2 – Period A (ITT_A Population)



[a] Reasons for discontinued intervention : 4 subjects due to Adverse event; 1 subject due to Progressive disease; 1 subject due to Lack of efficacy; 11 subjects due to Withdrawal from treatment by subject;
[b] Reasons for discontinued intervention : 4 subjects due to Adverse event; 14 subjects due to Withdrawal from treatment by subject; 1 subject due to Mandatory discontinuation for progressing vitiligo; 1 subject due to Other reason (Protocol deviations due to concomitant use of prohibited medications).

Recruitment

The first subject's first visit was on 18 January 2024 for Study 1 and on 17 January 2024 for Study 2. The last subject's last visit (Week 48, corresponding to end of Period A) was on 24 September 2025 for Study 1 and on 23 September 2025 for Study 2. Subjects were enrolled in Period A at 134 sites located in 17 countries worldwide.

Conduct of the study

The original protocol (Version 1.0, 09 August 2023) had 2 global amendments and 3 country-specific amendments (EU only).

Protocol deviations were defined in accordance with the ICH guidelines and included: inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study treatment, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. In M19-044 Study 1, a total of 51 subjects (16.6%) had at least 1 protocol deviation in Period A, with the most common deviation being 'subject received excluded concomitant treatment' (Table 18). In M19-044 Study 2, a total of 30 subjects (9.8%) had at least 1 protocol deviation in Period A, with the most common deviation being 'subject received excluded concomitant treatment' (Table 19).

Table 18. Protocol deviation in Study 1 Period A (ITT_A Population)

Category	PBO (N=102) n (%)	UPA 15 mg (N=206) n (%)	Overall (N=308) n (%)
Subjects with at least one protocol deviation	22 (21.6)	29 (14.1)	51 (16.6)
Subject entered into the study even though did not satisfy entry criteria	8 (7.8)	13 (6.3)	21 (6.8)
Inclusion criteria not met	1 (1.0)	2 (1.0)	3 (1.0)
Criterion number 1	0	2 (1.0)	2 (0.6)
Criterion number 5	1 (1.0)	0	1 (0.3)
Exclusion criteria met	7 (6.9)	10 (4.9)	17 (5.5)
Criterion number 5	7 (6.9)	7 (3.4)	14 (4.5)
Criterion number 16	0	1 (0.5)	1 (0.3)
Criterion number 19	0	2 (1.0)	2 (0.6)
Subject developed withdrawal criteria during the study but was not withdrawn	3 (2.9)	0	3 (1.0)
Subject received wrong treatment or incorrect dose of study treatment	0	1 (0.5)	1 (0.3)
Subject received excluded concomitant treatment	13 (12.7)	16 (7.8)	29 (9.4)

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 19. Protocol deviation in Study 2 Period A (ITT_A Population)

Category	PBO (N=101) n (%)	UPA 15 mg (N=205) n (%)	Overall (N=306) n (%)
Subjects with at least one protocol deviation	10 (9.9)	20 (9.8)	30 (9.8)
Subject entered into the study even though did not satisfy entry criteria	3 (3.0)	9 (4.4)	12 (3.9)
Inclusion criteria not met	0	0	0
Exclusion criteria met	3 (3.0)	9 (4.4)	12 (3.9)
Criterion number 5	3 (3.0)	6 (2.9)	9 (2.9)
Criterion number 6	0	2 (1.0)	2 (0.7)
Criterion number 19	0	1 (0.5)	1 (0.3)
Subject developed withdrawal criteria during the study but was not withdrawn	0	1 (0.5)	1 (0.3)
Subject received wrong treatment or incorrect dose of study treatment	1 (1.0)	0	1 (0.3)
Subject received excluded concomitant treatment	6 (5.9)	11 (5.4)	17 (5.6)

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.

Baseline data

Patient Demographics

Baseline demographic characteristics from M19-044 Study 1 and Study 2 are presented in Table 20. Across studies, most subjects were white and in the age group ≥ 40 years of age, and an equal proportion of males and females were enrolled.

Baseline Disease Characteristics

In accordance with the inclusion criteria, subjects enrolled had a documented clinical diagnosis of NSV. Baseline disease characteristics were generally balanced across treatment groups in M19-044 Study 1 and Study 2 (Table 21). The mean (SD) F-VASI score was 1.053 (0.6335), and the mean (SD) T-VASI score was 19.377 (12.0976). There were 204 subjects (66.2%) with actively progressing vitiligo (defined as having documented evidence of the occurrence of new lesions or the progression [enlargement] of existing lesions within 6 months prior to baseline and/or the presence of at least 1 lesion of confetti-like depigmentation, trichrome pattern, and/or Koebner phenomenon type 2B at Baseline), and the majority (222 subjects [72.1%]) had T-VASI values between 10 and 50 (10 < T-VASI < 50) at Baseline. The mean (SD) vitiligo disease duration since diagnosis was 16.709 (14.6252) years for all subjects and 5.955 (3.7276) years for adolescents.

Prior and concomitant therapy

There were 193 subjects (62.7%) in Study 1 and 203 subjects (66.3%) in Study 2 that had previously received NSV treatment. The most frequently reported prior medication for treatment of NSV was tacrolimus (126 subjects in Study 1 and 105 subjects in Study 2). A total of 28 subjects in Study 1 and 31 subjects in Study 2 had previously received phototherapy for vitiligo. There were 246 subjects (79.9%) in Study 1 and 253 subjects (82.7%) in Study 2 who reported use of any concomitant medications in Period A. In Study 1, concomitant medication usage in Period A was similar but slightly higher in the upadacitinib 15 mg group (170 subjects [82.5%]) compared to placebo group (76 subjects [74.5%]). In Study 2, the concomitant medication usage was comparable across treatment groups in Study 2. In each of the two studies, a total of 3 subjects received confounding treatment in Period A; all were in the upadacitinib 15 mg group and received systemic corticosteroids.

Table 20. Overall Baseline Demographic Characteristics (ITT_A Population, M19-044 Study 1 and Study 2)

	M19-044 Study 1			M19-044 Study 2		
	PBO (N = 102)	**UPA 15 mg (N = 206)**	**Overall (N = 308)**	**PBO (N = 101)**	**UPA 15 mg (N = 205)**	**Overall (N = 306)**
Age (years)						
Mean (SD)	43.6 (14.66)	44.9 (15.38)	44.5 (15.13)	45.6 (15.71)	44.1 (15.31)	44.6 (15.43)
Median	45.0	47.0	46.0	46.0	46.0	46.0
Min, Max	13, 69	12, 77	12, 77	12, 75	12, 78	12, 78
Age group (years) - n (%)						
≥ 12 to < 18	8 (7.8)	15 (7.3)	23 (7.5)	8 (7.9)	22 (10.7)	30 (9.8)
≥ 18 to < 40	24 (23.5)	53 (25.7)	77 (25.0)	21 (20.8)	46 (22.4)	67 (21.9)
≥ 40	70 (68.6)	138 (67.0)	208 (67.5)	72 (71.3)	137 (66.8)	209 (68.3)
Sex - n (%)						
Male	54 (52.9)	98 (47.6)	152 (49.4)	57 (56.4)	98 (47.8)	155 (50.7)
Female	48 (47.1)	108 (52.4)	156 (50.6)	44 (43.6)	107 (52.2)	151 (49.3)
Ethnicity - n (%)						
Hispanic or Latino	21 (20.6)	60 (29.1)	81 (26.3)	33 (32.7)	67 (32.7)	100 (32.7)
Not Hispanic or Latino	81 (79.4)	146 (70.9)	227 (73.7)	68 (67.3)	138 (67.3)	206 (67.3)
Race - n (%)						
White	74 (72.5)	152 (74.5)	226 (73.9)	85 (84.2)	170 (84.6)	255 (84.4)
Asian	23 (22.5)	41 (20.1)	64 (20.9)	10 (9.9)	23 (11.4)	33 (10.9)

	M19-044 Study 1			M19-044 Study 2		
	PBO (N = 102)	**UPA 15 mg (N = 206)**	**Overall (N = 308)**	**PBO (N = 101)**	**UPA 15 mg (N = 205)**	**Overall (N = 306)**
Black	2 (2.0)	9 (4.4)	11 (3.6)	6 (5.9)	6 (3.0)	12 (4.0)
Other	3 (2.9)	2 (1.0)	5 (1.6)	0	2 (1.0)	2 (0.7)
Missing	0	2	2	0	4	4
Weight (kg)						
Mean (SD)	74.058 (14.7993)	74.235 (17.2131)	74.176 (16.4290)	77.775 (15.7709)	73.918 (17.0957)	75.191 (16.7430)
Median	73.255	72.642	72.642	80.000	71.100	73.500
Min, Max	39.01, 111.20	37.74, 127.60	37.74, 127.60	45.00, 113.00	40.00, 126.10	40.00, 126.10
Weight (kg)						
< 60	17 (16.7)	43 (20.9)	60 (19.5)	18 (17.8)	43 (21.0)	61 (19.9)
≥ 60	85 (83.3)	163 (79.1)	248 (80.5)	83 (82.2)	162 (79.0)	245 (80.1)
BMI (kg/m^2)						
Mean (SD)	25.95 (4.254)	26.30 (5.711)	26.18 (5.269)	26.78 (5.238)	25.86 (5.060)	26.16 (5.128)
Median	25.52	25.63	25.55	26.59	25.47	26.03
Min, Max	16.4, 38.2	16.1, 48.3	16.1, 48.3	16.2, 44.1	16.3, 42.8	16.2, 44.1
BMI (kg/m^2) - n (%)						
< 25	46 (45.1)	96 (46.6)	142 (46.1)	35 (35.0)	99 (48.3)	134 (43.9)
≥ 25 to < 30	37 (36.3)	65 (31.6)	102 (33.1)	39 (39.0)	68 (33.2)	107 (35.1)
≥ 30	19 (18.6)	45 (21.8)	64 (20.8)	26 (26.0)	38 (18.5)	64 (21.0)

	M19-044 Study 1			M19-044 Study 2		
	PBO (N = 102)	**UPA 15 mg (N = 206)**	**Overall (N = 308)**	**PBO (N = 101)**	**UPA 15 mg (N = 205)**	**Overall (N = 306)**
Missing	0	0	0	1	0	1

Note: Percentages are calculated based on non-missing values.

Table 21. Overall Baseline Disease Characteristics (ITT_A Population, M19-044 Study 1 and Study 2)

	M19-044 Study 1			M19-044 Study 2		
	PBO (N = 102)	**UPA 15 mg (N = 206)**	**Overall (N = 308)**	**PBO (N = 101)**	**UPA 15 mg (N = 205)**	**Overall (N = 306)**
Baseline status of active vitiligo - n (%)						
Yes	63 (61.8)	141 (68.4)	204 (66.2)	59 (58.4)	119 (58.0)	178 (58.2)
No	39 (38.2)	65 (31.6)	104 (33.8)	42 (41.6)	86 (42.0)	128 (41.8)
Baseline disease severity – n (%)						
T-VASI ≤ 10	28 (27.5)	57 (27.7)	85 (27.6)	33 (32.7)	64 (31.2)	97 (31.7)
10<T-VASI < 50	73 (71.6)	149 (72.3)	222 (72.1)	68 (67.3)	141 (68.8)	209 (68.3)
T-VASI ≥ 50	1 (1.0)	0	1 (0.3)	0	0	0
Baseline F-VASI						
Mean (SD)	1.089 (0.6765)	1.035 (0.6120)	1.053 (0.6335)	1.041 (0.5553)	1.086 (0.6558)	1.071 (0.6239)
Median	0.800	0.865	0.800	0.830	0.810	0.810
Min, Max	0.50, 3.00	0.50, 3.00	0.50, 3.00	0.50, 2.60	0.50, 3.00	0.50, 3.00
Baseline F-VASI - n (%)						
< Median	49 (48.0)	97 (47.1)	146 (47.4)	48 (47.5)	102 (49.8)	150 (49.0)
≥ Median	53 (52.0)	109 (52.9)	162 (52.6)	53 (52.5)	103 (50.2)	156 (51.0)
Baseline T-VASI						
Mean (SD)	20.695 (12.8935)	18.725 (11.6608)	19.377 (12.0976)	17.551 (11.5619)	16.496 (10.0618)	16.844 (10.5731)

	M19-044 Study 1			M19-044 Study 2		
	PBO (N = 102)	**UPA 15 mg (N = 206)**	**Overall (N = 308)**	**PBO (N = 101)**	**UPA 15 mg (N = 205)**	**Overall (N = 306)**
Median	17.365	14.905	15.975	14.700	14.500	14.650
Min, Max	5.16, 57.50	5.00, 49.85	5.00, 57.50	5.00, 49.97	5.00, 49.35	5.00, 49.97
Baseline T-VASI - n (%)						
< Median	46 (45.1)	108 (52.4)	154 (50.0)	50 (49.5)	103 (50.2)	153 (50.0)
≥ Median	56 (54.9)	98 (47.6)	154 (50.0)	51 (50.5)	102 (49.8)	153 (50.0)
Fitzpatrick skin types - n (%)						
Type I - Alway burn, never tans	1 (1.0)	4 (1.9)	5 (1.6)	5 (5.0)	8 (3.9)	13 (4.2)
Type II - Burns easily, tans minimally	16 (15.7)	38 (18.4)	54 (17.5)	33 (32.7)	72 (35.1)	105 (34.3)
Type III - Sometimes burns, tans moderately	47 (46.1)	79 (38.3)	126 (40.9)	43 (42.6)	72 (35.1)	115 (37.6)
Type IV - Burns minimally, tans easily	31 (30.4)	64 (31.1)	95 (30.8)	15 (14.9)	41 (20.0)	56 (18.3)
Type V - Rarely burns, tans deeply	6 (5.9)	15 (7.3)	21 (6.8)	5 (5.0)	10 (4.9)	15 (4.9)
Type VI - Never burns, tans deeply	1 (1.0)	6 (2.9)	7 (2.3)	0	2 (1.0)	2 (0.7)

	M19-044 Study 1			M19-044 Study 2		
	PBO (N = 102)	**UPA 15 mg (N = 206)**	**Overall (N = 308)**	**PBO (N = 101)**	**UPA 15 mg (N = 205)**	**Overall (N = 306)**
Fitzpatrick skin types - n (%)						
≤ II	17 (16.7)	42 (20.4)	59 (19.2)	38 (37.6)	80 (39.0)	118 (38.6)
III	47 (46.1)	79 (38.3)	126 (40.9)	43 (42.6)	72 (35.1)	115 (37.6)
> III	38 (37.3)	85 (41.3)	123 (39.9)	20 (19.8)	53 (25.9)	73 (23.9)
Prior topical therapy for vitiligo - n (%)						
With	54 (52.9)	117 (56.8)	171 (55.5)	64 (63.4)	118 (57.6)	182 (59.5)
Without	48 (47.1)	89 (43.2)	137 (44.5)	37 (36.6)	87 (42.4)	124 (40.5)
Prior phototherapy for vitiligo - n (%)						
With	11 (10.8)	17 (8.3)	28 (9.1)	7 (6.9)	24 (11.7)	31 (10.1)
Without	91 (89.2)	189 (91.7)	280 (90.9)	94 (93.1)	181 (88.3)	275 (89.9)
Baseline vitiligo disease diagnosis duration in years						
Mean (SD)	16.747 (14.4084)	16.690 (14.7662)	16.709 (14.6252)	15.561 (11.9949)	15.731 (12.6075)	15.675 (12.3892)
Median	11.504	12.408	11.929	12.860	13.240	13.050
Min, Max	0.03, 58.56	0.03, 64.67	0.03, 64.67	0.72, 49.38	0.05, 62.24	0.05, 62.24

	M19-044 Study 1			M19-044 Study 2		
	PBO (N = 102)	**UPA 15 mg (N = 206)**	**Overall (N = 308)**	**PBO (N = 101)**	**UPA 15 mg (N = 205)**	**Overall (N = 306)**
Duration of vitiligo since diagnosis in years - n (%)						
< Median	53 (52.0)	101 (49.0)	154 (50.0)	51 (50.5)	102 (49.8)	153 (50.0)
≥ Median	49 (48.0)	105 (51.0)	154 (50.0)	50 (49.5)	103 (50.2)	153 (50.0)

Note: Prior topical therapy includes topical corticosteroids and topical calcineurin inhibitors; prior phototherapy includes phototherapy, photochemotherapy, and laser (phototherapy equivalent). Percentages are calculated based on non-missing values.

Outcomes and estimation

Co-primary endpoints

Both co-primary endpoints, achievement of T-VASI 50 (≥50% reduction in T-VASI from Baseline) and F-VASI 75 (≥75% reduction in F-VASI from Baseline) at Week 48, were met for each individual study (Table 22). A numerically greater proportion of subjects achieved the primary endpoint of F-VASI 75 at Week 48 in the upadacitinib 15 mg group (24.3%) vs. the placebo group (6.4%), resulting in a placebo-adjusted difference of 17.8% (nominal P-value ≤0.001) using the CMH test with adjustment for actual values of stratification factors and study (Study 1 and Study 2). Adolescent response rates at Week 48 for upadacitinib 15 mg (21.6%) were generally consistent with the overall population (24.3%). However, due to a smaller samples size of the placebo groups, the results for adolescents should be interpreted with caution. A numerically greater proportion of subjects achieved the primary endpoint of T-VASI 50 at Week 48 in the upadacitinib 15 mg group (20.4%) vs. the placebo group (5.9%), resulting in a placebo-adjusted difference of 13.9% (nominal P-value ≤0.001) using the CMH test with adjustment for actual values of stratification factors and study (Study 1 and Study 2). Sensitivity analyses of the co-primary endpoints, including MI, showed consistent results with the primary approach (NRI-MI), with nominal P-value ≤ 0.001. Supplementary analysis of the co-primary endpoints by OC showed results consistent with the primary approach, with a numerically greater proportion of subjects treated with upadacitinib 15 mg achieving F-VASI 75 at Week 48 compared to placebo and a numerically greater proportion of subjects treated with upadacitinib 15 mg achieving T-VASI 50 at Week 48 compared to placebo.

Ranked secondary endpoints (multiplicity-controlled)

The ranked secondary endpoints for the EU/EMA and the US/FDA respectively, are described in the table below. Across both pivotal studies, all pre-specified multiplicity-controlled ranked secondary endpoints for EMA were met.

F-VASI

In Period A, upadacitinib 15 mg demonstrated a numerically greater proportion of subjects achieving each F-VASI 50, F-VASI 75, and F-VASI 90 (corresponding to achievement of ≥50%, ≥75% and ≥90% repigmentation of facial vitiligo, respectively) versus placebo at Week 48. Responses to upadacitinib 15 mg were observed as early as Week 8, in which a numerically greater proportion of subjects achieved F-VASI 75 compared to placebo (Figure 17), and numerically greater proportions of subjects achieved each F-VASI 50 and F-VASI 90 compared to placebo (nominal P-value ≤ 0.001).

In Period A, upadacitinib 15 mg demonstrated a numerically greater improvement (reduction) from Baseline in F-VASI vs. placebo at Week 24 (Figure 9). Responses to upadacitinib 15 mg were observed as early as Week 8, where numerically greater improvement from Baseline in F-VASI was observed compared to placebo (nominal P-value ≤ 0.001) (Figure 18). Results were generally consistent for adolescents.

Table 22. Primary and Secondary Endpoints in M19-044 Study 1 and Study 2 (ITT_A population)

	M19-044 Study 1		M19-044 Study 2	
Endpoints[a]	**PBO (N = 102)**	**UPA 15 mg (N = 206)**	**PBO (N =101)**	**UPA 15 mg (N =205)**
Co-Primary				
T-VASI 50 at Week 48 – n (%)[#,$]	6 (5.9%)	40 (19.4%)[~,*]	6 (5.9%)	44 (21.5%)[~,*]
F-VASI 75 at Week 48 – n (%)[#,$]	6 (5.9%)	52 (25.2%)[~,*]	7 (6.9%)	48 (23.4%)[~,*]
Ranked Secondary[a]				
F-VASI 50 at Week 48 – n (%)[#,$]	13 (12.7%)	99 (48.1%)[~,*]	13 (12.9%)	89 (43.4%)[~,*]
F-VASI 75 at Week 24 – n (%)[#,$]	2 (2.0%)	31 (15.0%)[~,*]	1 (1.0%)	23 (11.2%)[~,*]
Percent change from Baseline in F-VASI at Week 24 (LS Mean [SE])[#,$]	-12.97 (5.092)	-42.39 (4.424) [~,*]	-1.68 (4.464)	-27.85 (3.483) [~,*]
Percent change from Baseline in T-VASI at Week 48 (LS Mean [SE])[#,$]	-9.14 (4.667)	-28.55 (4.029) [~,*]	-12.55 (4.231)	-32.95 (3.196) [~,*]
F-VASI 90 at Week 48 – n (%)[#,$]	2 (2.0%)	32 (15.5%)[~,*]	3 (3.0%)	25 (12.2%)[~,*]
T-VASI 75 at Week 48 – n (%)[#]	3 (2.9%)	10 (4.9%)	2 (2.0%)	10 (4.9%)
3D Imaging Facial Vitiligo 40 at Week 48 – n (%)[#]	(N = 23) 1 (4.3%)	(N = 52) 12 (23.1%)	---	---
PhGIC-V of "Much better (1)" at Week 48 – n (%)[$]	6 (5.9%)	41 (19.9%)[*]	1 (1.0%)	34 (16.6%)[*]
VNS score of "A lot less noticeable (4)" or "No longer noticeable (5)" at Week 48 – n (%)[$]	2 (2.0%)	26 (12.6%)[*]	1 (1.0%)	30 (14.6%)[*]
PaGIC-V of "Much better (1)" at Week 48 – n (%)[$]	4 (3.9%)	32 (15.5%)[*]	1 (1.0%)	37 (18.0%)[*]
No increase from Baseline in T-VASI at both Week 8 and Week 12 among subjects with actively progressing vitiligo at Baseline – n (%)[#,$]	(N = 63) 38 (60.3%)	(N = 141) 107 (75.9%)[*]	(N = 59) 36 (61.0%)	(N = 119) 90 (75.6%)[*]

Multiplicity-controlled for US/FDA purposes.

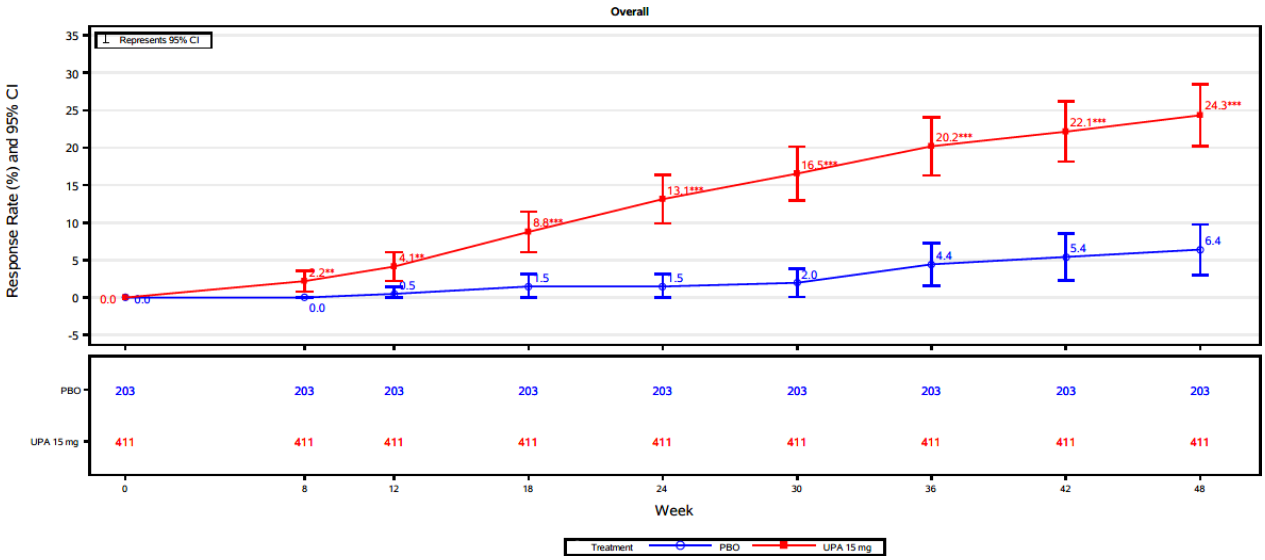
$ Multiplicity-controlled for EU/EMA purposes.

~ Statistically significant (upadacitinib vs. placebo) in the multiplicity-controlled analysis for US/FDA purposes.

* Statistically significant (upadacitinib vs. placebo) in the multiplicity-controlled analysis for EU/EMA purposes.

a. Results for binary endpoints are based on NRI-MI to handle missing data that can be reasonably assumed to be MAR. There are no missing data observed that can be reasonably assumed to be MAR, so NRI is used instead. Subjects were considered nonresponders at the visits impacted by the intercurrent events. Results for continuous endpoints are based on MI for handling the missing data, except that missing data after treatment discontinuation due to lack of efficacy is handled by RTB. Data impacted by the intercurrent events are considered as RTB.

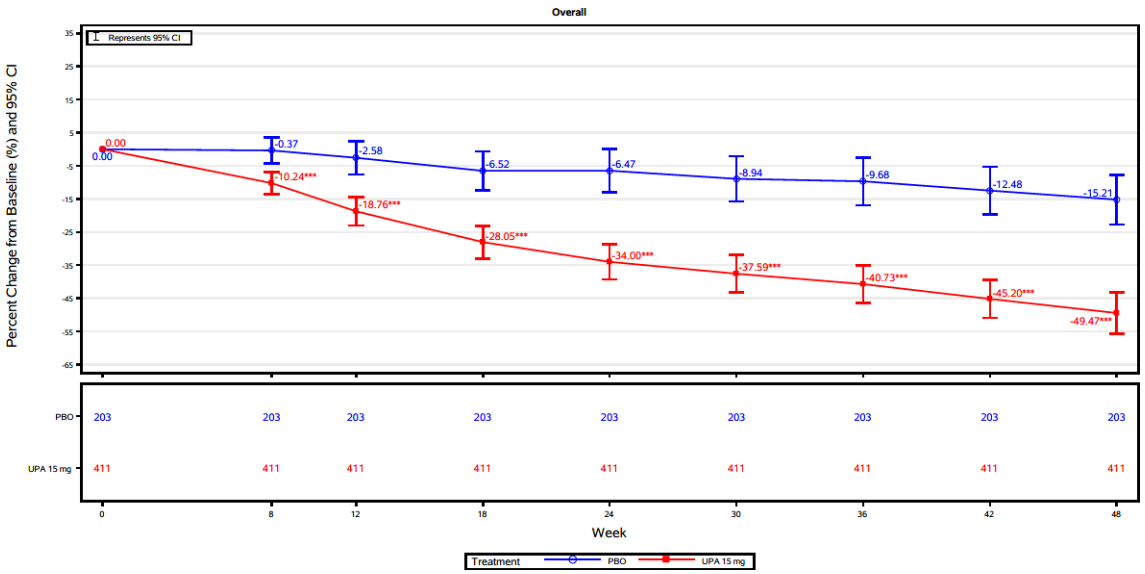
Figure 17. Proportion of subjects achieving F-VASI 75 by Visti in Period A (NRI-MI) (ITT_A population)



*P-value ≤ 0.05; **P-value ≤ 0.01; ***P-value ≤ 0.001.

Notes: NRI-MI is non-responder imputation while incorporating MI to handle missing data that can be reasonably assumed to be MAR. There is no missing data observed that can be reasonably assumed to be MAR, so NRI is used instead. 95% CI for response rate is based on the normal approximation to the binomial distribution.

Figure 18. Percent change from baseline in F-VASI by Visti in Period A (RTB-MI) (ITT_A population)



*P-value ≤ 0.05; **P-value ≤ 0.01; ***P-value ≤ 0.001.

Notes: Results for continuous endpoints are based on MI for handling the missing data, except that missing data after treatment discontinuation due to lack of efficacy is handled by RTB. The values impacted by the intercurrent events are considered as RTB. The LS mean and 95% CI are the synthetic result based on ANCOVA with fixed effects of treatment group an stratification factors (age at Screening [12 to < 18 years; ≥ 18 years], Baseline disease severity [T-VASI ≤ 10; T-VASI > 10], and Baseline

status of actively progressing vitiligo [Yes; No]), Study [Study 1; Study 2], and the Baseline value as covariate from PROC MIANALYZE procedure.

T-VASI

In Period A, upadacitinib 15 mg demonstrated a numerically greater proportion of subjects achieving T-VASI 50 (corresponding to achievement of ≥50% repigmentation of total vitiligo) versus placebo at Week 48 (Figure 19, Table 22). Responses to upadacitinib 15 mg were observed as early as Week 18, in which numerically greater proportions of subjects achieved T-VASI 50 compared to placebo (nominal P-value ≤ 0.05). In Period A, upadacitinib 15 mg demonstrated a numerically greater improvement (reduction) from baseline in T-VASI versus placebo at Week 48 (Figure 20, Table 22). Responses to upadacitinib 15 mg were observed as early as Week 8, where numerically greater improvements from baseline in T-VASI was observed compared to placebo (nominal p-value ≤0.05). Results were generally consistent for adolescents.

Disease activity

Among subjects with actively progressing vitiligo at baseline, a numerically greater proportion of subjects achieved no increase (i.e. no worsening) from baseline in T-VASI at both Week 8 and Week 12 of Period A in the upadacitinib 15 mg group versus placebo. Adolescent response rates for upadacitinib 15 mg (80.8%) were generally consistent with the overall population (75.8%)

Other physician assessments

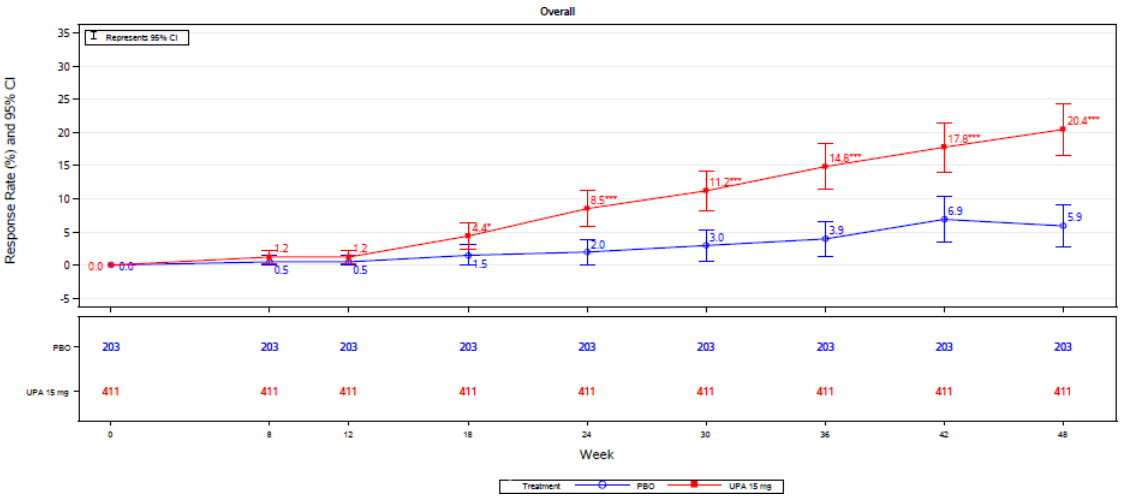
In Period A, a numerically greater proportion of subjects achieved PhGIC-V of "Much better (1)" at Week 48 in the upadacitinib 15 mg group versus the placebo group (nominal p-value ≤0.001). Responses to upadacitinib 15 mg were observed as early as Week 8, where numerically greater proportions of subjects achieved PhGIC-V of "Much better (1)" compared to placebo (nominal P-value ≤ 0.01).

Patient reported noticeability assessments

In Period A, a numerically greater proportion of subjects achieved VNS scores of "A lot less noticeable (4)" or "No longer noticeable (5)" at Week 48 in the upadacitinib 15 mg group vs. the placebo group. Responses to upadacitinib 15 mg were observed as early as Week 24, where numerically greater proportions of subjects achieved VNS scores of "A lot less noticeable (4)" or "No longer noticeable (5)" compared to placebo (nominal P-value ≤ 0.001).

In Period A, a numerically greater proportion of subjects achieved a PaGIC-V score of "Much better (1)" at Week 48 in the upadacitinib 15 mg group vs. the placebo group. Responses to upadacitinib 15 mg were observed as early as Week 12, where numerically greater proportions of subjects achieved a PaGIC-V score of "Much better (1)" compared to placebo (nominal P-value ≤ 0.05). Results were generally consistent for adolescents.

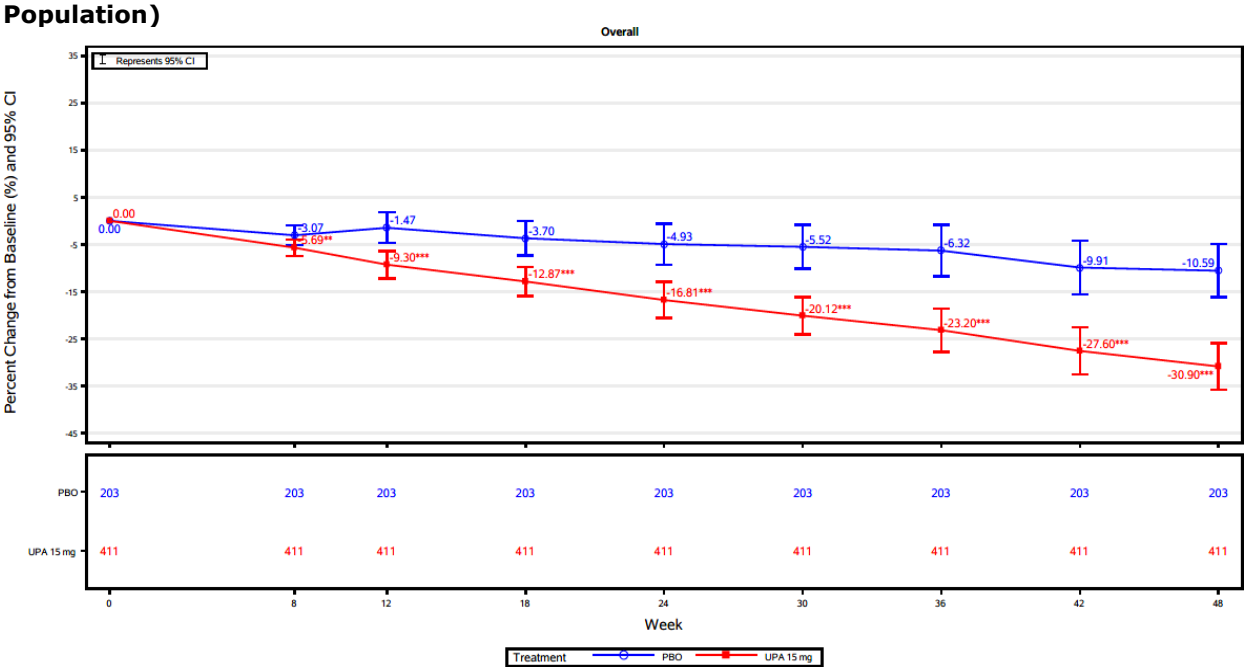
Figure 19. Proportion of Subjects Achieving T-VASI 50 by Visit in Period A (NRI-MI) (ITT_A Population)



*P-value ≤ 0.05; **P-value ≤ 0.01; ***P-value ≤ 0.001.

Notes: NRI-MI is non-responder imputation while incorporating MI to handle missing data that can be reasonably assumed to be MAR. There is no missing data observed that can be reasonably assumed to be MAR, so NRI is used instead. 95% CI for response rate is based on the normal approximation to the binomial distribution.

Figure 20. Percent Change from Baseline in T-VASI by Visit in Period A (RTB-MI) (ITT_A Population)



*P-value ≤ 0.05; **P-value ≤ 0.01; ***P-value ≤ 0.001.

Notes: Results for continuous endpoints are based on MI for handling the missing data, except that missing data after treatment discontinuation due to lack of efficacy is handled by RTB. The values impacted impacted by the intercurrent events are considered as RTB. The LS mean and 95% CI are the

synthetic result based on ANCOVA with fixed effects of treatment group and stratification factors (age at Screening [12 to < 18 years; ≥ 18 years] and Baseline status of actively progressing vitiligo [Yes; No]), Study [Study 1; Study 2], and the Baseline value as covariate from PROC MIANALYZE procedure.

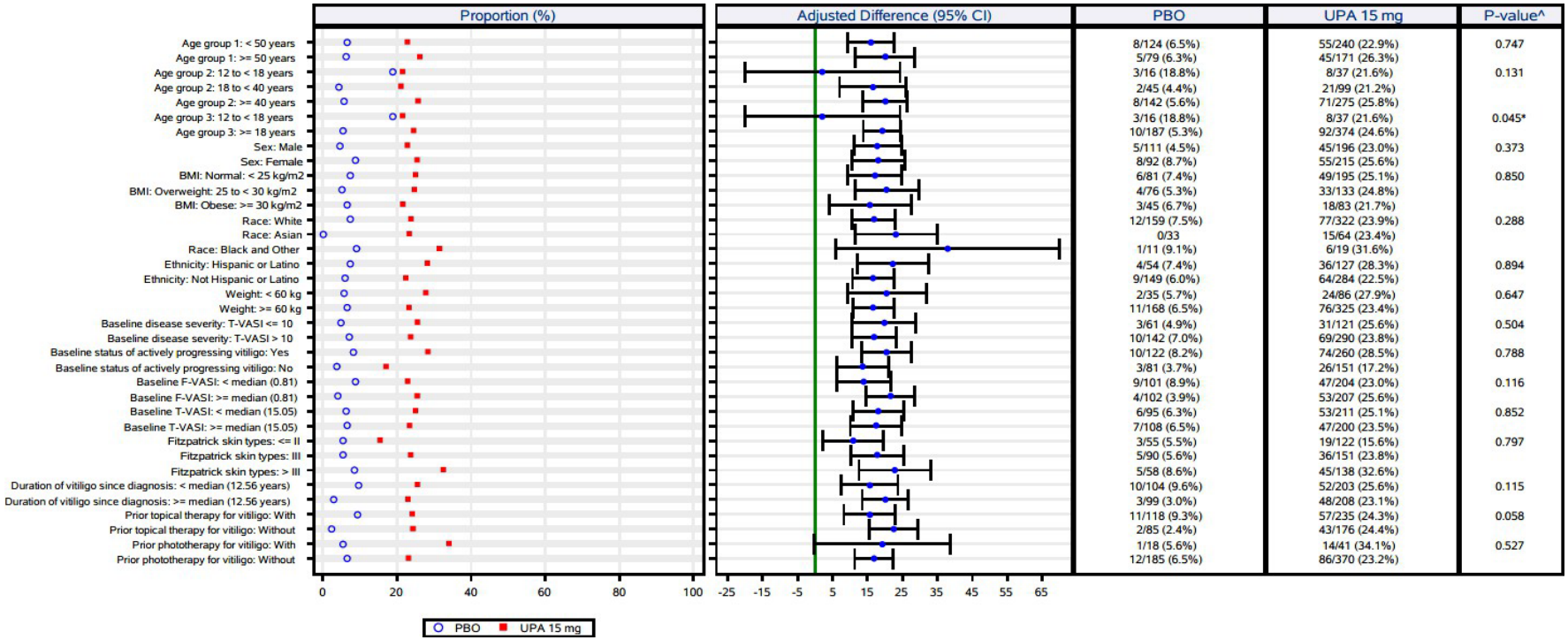
Ancillary analyses

Subgroup analyses

Subgroup analyses were performed for the pooled ITT_A population for M19-044 Study 1 and Study 2 for the following subgroups: age, sex, BMI, race, ethnicity, weight, baseline disease severity, baseline status of actively progressing vitiligo, baseline F-VASI, baseline T-VASI, Fitzpatrick skin types, duration of vitiligo since diagnosis, prior topical therapy for vitiligo, and prior phototherapy for vitiligo. Of note, any subgroup with fewer than 4% of subjects may be combined with the smallest of other subgroups for analyses.

Treatment effects in pre-specified subgroups (across demographic and Baseline characteristics) consistently favoured upadacitinib 15 mg QD compared to placebo in the proportion of subjects achieving each F-VASI 75 at Week 48 and T-VASI 50 at Week 48, with 95% CIs excluding zero in the majority of the subgroups (Figure 21, Figure 22).

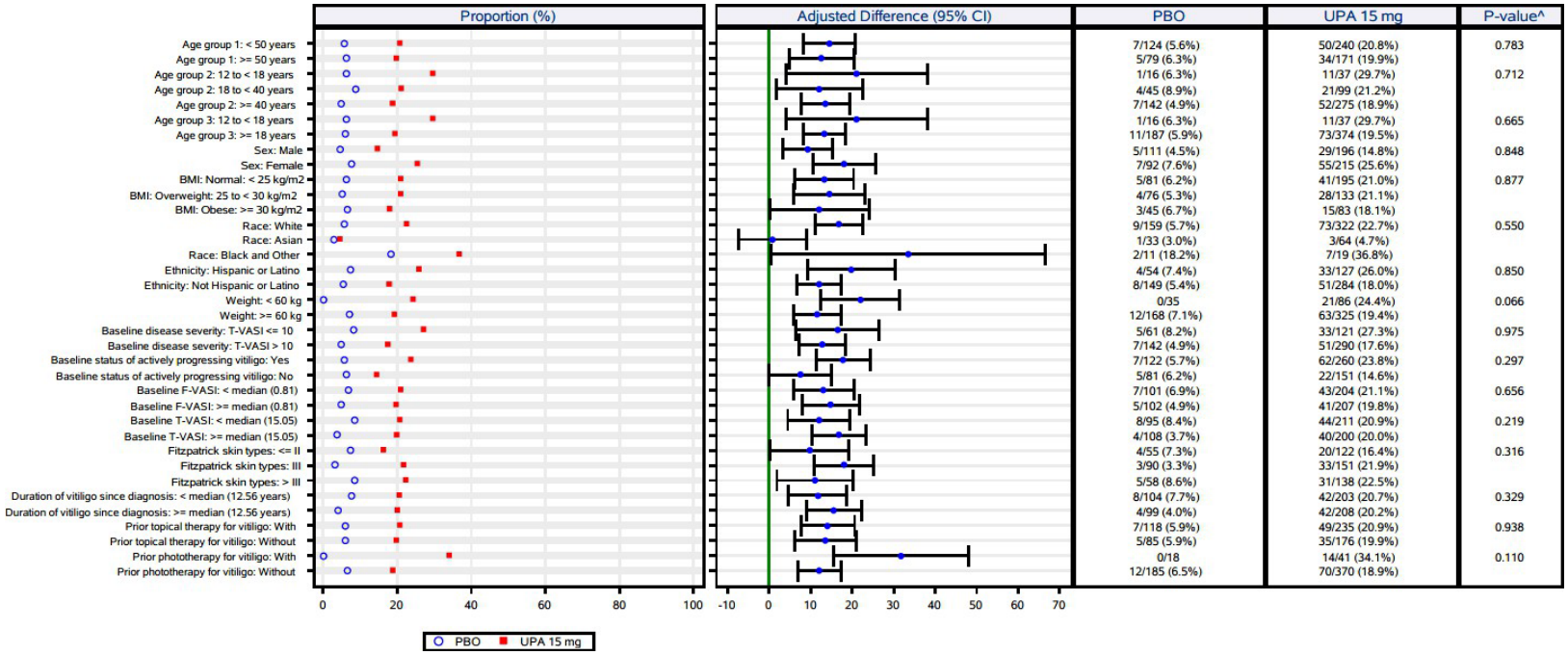
Figure 21. Proportion of subjects achieving F-VASI 75 at Week 48 by subgroup (NRI-MI) (ITT_A population)



*P-value ≤ 0.05; **P-value ≤ 0.01; ***P-value ≤ 0.001.

Notes: NRI-MI is non-responder imputation while incorporating MI to handle missing data that can be reasonably assumed to be MAR. There is no missing data observed that can be reasonably assumed to be MAR, so NRI is used instead. 95% CI for adjusted difference is calculated according to the CMH test adjusted for strata (age at Screening [12 to < 18 years; ≥ 18 years], Baseline disease severity [T-VASI ≤ 10; T-VASI > 10], and Baseline status of actively progressing vitiligo [Yes; No]) and Study [Study 1; Study 2], except that the CMH model does not adjust 1) for age at Screening (12 to < 18 years; ≥ 18 years) for all age groups; 2) for Baseline disease severity (T-VASI ≤ 10; T-VASI > 10) for disease severity subgroups; 3) for Baseline status of actively progressing vitiligo (Yes/No) for Baseline status of actively progressing vitiligo subgroups. P-value is based on Breslow-Day test performed across subgroups.

Figure 22. Proportion of subjects achieving T-VASI 50 at Week 48 by subgroup (NRI-MI) (ITT_A population)



*P-value ≤ 0.05; **P-value ≤ 0.01; ***P-value ≤ 0.001.

Notes: NRI-MI is non-responder imputation while incorporating MI to handle missing data that can be reasonably assumed to be MAR. There is no missing data observed that can be reasonably assumed to be MAR, so NRI is used instead. 95% CI for adjusted difference is calculated according to the CMH test adjusted for strata (age at Screening [12 to < 18 years; ≥ 18 years], Baseline disease severity [T-VASI ≤ 10; T-VASI > 10], and Baseline status of actively progressing vitiligo [Yes; No]) and Study [Study 1; Study 2], except that the CMH model does not adjust 1) for age at Screening (12 to < 18 years; ≥ 18 years) for all age groups; 2) for Baseline disease severity (T-VASI ≤ 10; T-VASI > 10) for disease severity subgroups; 3) for Baseline status of actively progressing vitiligo (Yes/No) for Baseline status of actively progressing vitiligo subgroups. 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 trial M19-044 Study 1

Title: A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy, Safety, and Tolerability of Upadacitinib in Adult and Adolescent Subjects with Non-Segmental Vitiligo Who Are Eligible for Systemic Therapy	
Study Identifier	M19-044
Design	Study 1 and Study 2 are Phase 3, global, randomized, double-blind, placebo-controlled, multicenter studies. Both Study 1 and Study 2 comprised a 35-day Screening Period; a 48-week, placebo-controlled, double-blind treatment period (Period A); a 112-week open-label extension period (Period B); and a 30-day follow-up period. Subjects that completed Period A of Study 1 or Study 2 and failed to achieve T-VASI 90 at Study 1 or Study 2 Week 48 were provided the opportunity to enter into Study 3. Subjects who were unable, unwilling, or not eligible to participate in Study 3 continued into Period B of Study 1 or Study 2 to receive open-label upadacitinib 15 mg daily as monotherapy. Period A: At Baseline, subjects were randomized 2:1 to one of two treatment groups: • Group 1: upadacitinib 15 mg QD (N = 180 subjects/study); • Group 2: placebo QD (N = 90 subjects/study). A total of 53 adolescents were enrolled across both studies. Subjects who met eligibility criteria and had a Baseline T-VASI ≤ 10 were enrolled up to 30% of each study's total population. Subjects who met eligibility criteria and were characterized as having actively progressing vitiligo at Baseline were enrolled up to approximately 60% of the total population. Randomization was stratified by age at Screening [12 to < 18 years; ≥ 18 years], Baseline disease severity [T VASI ≤ 10; 10 < T-VASI < 50], and Baseline status of actively progressing vitiligo [Yes; No]. Subjects were classified as having actively progressing vitiligo at Baseline if they fulfilled at least 1 of the following criteria: • Documented evidence of the occurrence of new lesions or the progression (enlargement) of existing lesions within 6 months prior to Baseline • Presence of at least 1 lesion of confetti-like depigmentation, trichrome pattern, and/or Koebner phenomenon type 2B. Period B: Subjects that completed Period A continued into Period B, consisting of a 112-week, open-label, long-term extension treatment period. The primary analysis for Study 1 and Study 2 was conducted based on the Week 48 database lock (Primary Lock) of each study after all continuing subjects in each corresponding study completed Week 48. This analysis was the final and only analysis for efficacy in Period A for each study (Study 1 and Study 2). Study sites and subjects remain blinded to treatment assignments in Period A for the duration of the study.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	48 weeks (double-blind, placebo-controlled Period A) Not applicable 112 weeks (open-label Period B)
Hypothesis	Superiority of upadacitinib 15 mg QD vs. placebo	
Treatments groups	Placebo (PBO)	Placebo QD for 48 weeks in Period A (N = 102 subjects).
	Upadacitinib 15 mg QD (UPA 15 mg)	Upadacitinib 15 mg QD for 48 weeks in Period A (N = 206 subjects)
Endpoints and definitions	Co-Primary Endpoints	
	T-VASI 50 at Week 48 n (%) [95% CI]	Achievement of T-VASI 50 (≥ 50% reduction in T-VASI from Baseline) at Week 48
	F-VASI 75 at Week 48 n (%) [95% CI]	Achievement of F-VASI 75 (≥ 75% reduction in F-VASI from Baseline) at Week 48
	Ranked Secondary Endpoints	
	F-VASI 50 at Week 48 n (%) [95% CI]	1. Achievement of F-VASI 50 (≥ 50% reduction in F-VASI from Baseline) at Week 48
	F-VASI 75 at Week 24 n (%) [95% CI]	2. Achievement of F-VASI 75 (≥ 75% reduction in F-VASI from Baseline) at Week 24
	Percent change from Baseline in F-VASI at Week 24 LS Mean (SE)	3. Percent change from Baseline in F-VASI at Week 24
	Percent change from Baseline in T-VASI at Week 48 LS Mean (SE)	4. Percent change from Baseline in T-VASI at Week 48
	F-VASI 90 at Week 48 n (%) [95% CI]	5. Achievement of F-VASI 90 (≥ 90% reduction in F-VASI from Baseline) at Week 48
	PhGIC-V of "Much better (1)" at Week 48	6. Achievement of PhGIC-V of "Much better (1)" at Week 48
	VNS score of "A lot less noticeable (4)" or "No longer noticeable (5)" at Week 48 n (%) [95% CI]	7. Achievement of VNS score of "A lot less noticeable (4)" or "No longer noticeable (5)" at Week 48
	PaGIC-V of "Much better (1)" at Week 48 n (%) [95% CI]	8. Achievement of PaGIC-V of "Much better (1)" at Week 48
	No increase from Baseline in T-VASI at both Week 8 and Week 12 among subjects with actively progressing vitiligo at Baseline n (%) [95% CI]	9. Achievement of no increase from Baseline in T-VASI at both Week 8 and Week 12 among subjects with actively progressing vitiligo at Baseline
Data Cut-off date	24 September 2025	

Results and Analysis			
Analysis Description	**Primary Analysis**		
Analysis Population and Time Point Description	The Period A ITT population was defined as: • ITT_A: All subjects who were randomized at Baseline. The ITT_A populations was used for all primary and ranked secondary efficacy analyses. Subjects were analyzed according to treatment as randomized. No subject was excluded from the efficacy analyses.		
	Treatment group	**PBO**	**UPA 15 mg**
	Number of subjects (Number of subjects indicated below if different)	102	206
Descriptive Statistics and Estimate Variability	Co-Primary endpoint: Achievement of T-VASI 50 at Week 48 (NRI-MI) n (%) [95% CI]	6 (5.9) [1.3, 10.4]	40 (19.4) [14.0, 24.8]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	13.1
		95% CI	[6.3, 19.8]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Co-Primary endpoint: Achievement of F-VASI 75 at Week 48 (NRI-MI) n (%) [95% CI]	6 (5.9) [1.3, 10.4]	52 (25.2) [19.3, 31.2]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	18.7
		95% CI	[11.5, 25.9]
		P-value	<0.001
		Statistical Significance	Significant
Analysis Description	**Secondary Analyses**		
	Treatment group	**PBO**	**UPA 15 mg**
	Number of subjects (Number of subjects indicated below if different)	102	206
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #1: Achievement of	13 (12.7) [6.3, 19.2]	99 (48.1) [41.2, 54.9]
Effect Estimate per		Comparison groups	UPA 15 mg vs. PBO

Comparison	F-VASI 50 at Week 48 (NRI-MI) n (%) [95% CI]	Adjusted Difference (%)	33.8
		95% CI	[24.8, 42.9]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #2: Achievement of F-VASI 75 at Week 24 (NRI-MI) n (%) [95% CI]	2 (2.0) [0.0, 4.7]	31 (15.0) [10.2, 19.9]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	13.1
		95% CI	[7.7, 18.5]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #3: Percent change from Baseline in F-VASI at Week 24 (RTB-MI) LS MEAN (SE)	-12.97 (5.092)	-42.39 (4.424)
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		LS Mean	-29.42
		95% CI	[-38.08, -20.77]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #4: Percent change from Baseline in T-VASI at Week 48 (RTB-MI) LS MEAN (SE)	-9.14 (4.667)	-28.55 (4.029)
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		LS Mean	-19.41
		95% CI	[-27.63, -11.19]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #5: Achievement of F-VASI 90 at Week 48 (NRI-MI) n (%) [95% CI]	2 (2.0) [0.0, 4.7]	32 (15.5) [10.6, 20.5]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	13.0
		95% CI	[7.8, 18.3]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #6: Achievement of PhGIC-V of "Much better	6 (5.9) [1.3, 10.4]	41 (19.9) [14.5, 25.4]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	12.8

	(1)" at Week 48 (NRI-MI) n (%) [95% CI]	95% CI	[6.2, 19.4]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #7: Achievement of VNS score of "A lot less noticeable (4)" or "No longer noticeable (5)" at Week 48 (NRI-MI) n (%) [95% CI]	2 (2.0) [0.0, 4.7]	26 (12.6) [8.1, 17.2]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	10.5
		95% CI	[5.3, 15.8]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #8: Achievement of PaGIC-V of "Much better (1)" at Week 48 (NRI-MI) n (%) [95% CI]	4 (3.9) [0.2, 7.7]	32 (15.5) [10.6, 20.5]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	11.2
		95% CI	[5.1, 17.3]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #9: Achievement of no increase from Baseline in T-VASI at both Week 8 and Week 12 among subjects with actively progressing vitiligo at Baseline (NRI-MI) n (%) [95% CI]	[N = 63] 38 (60.3) [48.2, 72.4]	[N = 141] 107 (75.9) [68.8, 82.9]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	15.8
		95% CI	[2.0, 29.7]
		P-value	0.025
		Statistical Significance	Significant
Notes	Percentages with 95% CIs are reported for binary endpoints, and LS means with SEs for continuous endpoints		

CI = confidence interval; F-VASI = Facial Vitiligo Area Scoring Index; ITT = intent-to-treat; LS = least square; MI = multiple imputation; NRI = non-responder imputation; PaGIC-V = Patient's Global Impression of Change – Vitiligo; PBO = placebo; PhGIC-V = Physician's Global Impression of Change – Vitiligo; QD = once daily; RTB = return-to-Baseline; SE = standard error; T-VASI = Total Vitiligo Area Scoring Index; UPA = upadacitinib; VNS = Vitiligo Noticeability Scale

Table 24. Summary of Efficacy for trial M19-044 Study 2

<table>
<tr><td colspan="3">Title: A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy, Safety, and Tolerability of Upadacitinib in Adult and Adolescent Subjects with Non-Segmental Vitiligo Who Are Eligible for Systemic Therapy</td></tr>
<tr><td>Study Identifier</td><td colspan="2">M19-044</td></tr>
<tr><td>Design</td><td colspan="2">Study 1 and Study 2 are Phase 3, global, randomized, double-blind, placebo-controlled, multicenter studies. Both Study 1 and Study 2 comprised a 35-day Screening Period; a 48-week, placebo-controlled, double-blind treatment period (Period A); a 112-week open-label extension period (Period B); and a 30-day follow-up period. Subjects that completed Period A of Study 1 or Study 2 and failed to achieve T-VASI 90 at Study 1 or Study 2 Week 48 were provided the opportunity to enter into Study 3. Subjects who were unable, unwilling, or not eligible to participate in Study 3 continued into Period B of Study 1 or Study 2 to receive open-label upadacitinib 15 mg daily as monotherapy.
Period A:
At Baseline, subjects were randomized 2:1 to one of two treatment groups:
• Group 1: upadacitinib 15 mg QD (N = 180 subjects/study);
• Group 2: placebo QD (N = 90 subjects/study).
A total of 53 adolescents were enrolled across both studies.
Subjects who met eligibility criteria and had a Baseline T-VASI ≤ 10 were enrolled up to 30% of each study's total population.
Subjects who met eligibility criteria and were characterized as having actively progressing vitiligo at Baseline were enrolled up to approximately 60% of the total population.
Randomization was stratified by age at Screening [12 to < 18 years; ≥ 18 years], Baseline disease severity [T VASI ≤ 10; 10 < T-VASI < 50], and Baseline status of actively progressing vitiligo [Yes; No].
Subjects were classified as having actively progressing vitiligo at Baseline if they fulfilled at least 1 of the following criteria:
• Documented evidence of the occurrence of new lesions or the progression (enlargement) of existing lesions within 6 months prior to Baseline
• Presence of at least 1 lesion of confetti-like depigmentation, trichrome pattern, and/or Koebner phenomenon type 2B.
Period B:
Subjects that completed Period A continued into Period B, consisting of a 112-week, open-label, long-term extension treatment period.
The primary analysis for Study 1 and Study 2 was conducted based on the Week 48 database lock (Primary Lock) of each study after all continuing subjects in each corresponding study completed Week 48. This analysis was the final and only analysis for efficacy in Period A for each study (Study 1 and Study 2). Study sites and subjects remain blinded to treatment assignments in Period A for the duration of the study.</td></tr>
<tr><td></td><td>Duration of main phase:

Duration of Run-in phase:
Duration of Extension phase:</td><td>48 weeks (double-blind, placebo-controlled Period A)
Not applicable
112 weeks (open-label Period B)</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Superiority of upadacitinib 15 mg QD vs. placebo</td></tr>
<tr><td>Treatments groups</td><td>Placebo (PBO)</td><td>Placebo QD for 48 weeks in Period A (N = 101 subjects).</td></tr>
</table>

	Upadacitinib 15 mg QD (UPA 15 mg)	Upadacitinib 15 mg QD for 48 weeks in Period A (N = 205 subjects)
Endpoints and definitions	Co-Primary Endpoints	
	T-VASI 50 at Week 48 n (%) [95% CI]	Achievement of T-VASI 50 (≥ 50% reduction in T-VASI from Baseline) at Week 48
	F-VASI 75 at Week 48 n (%) [95% CI]	Achievement of F-VASI 75 (≥ 75% reduction in F-VASI from Baseline) at Week 48
	Ranked Secondary Endpoints	
	F-VASI 50 at Week 48 n (%) [95% CI]	1. Achievement of F-VASI 50 (≥ 50% reduction in F-VASI from Baseline) at Week 48
	F-VASI 75 at Week 24 n (%) [95% CI]	2. Achievement of F-VASI 75 (≥ 75% reduction in F-VASI from Baseline) at Week 24
	Percent change from Baseline in F-VASI at Week 24 LS Mean (SE)	3. Percent change from Baseline in F-VASI at Week 24
	Percent change from Baseline in T-VASI at Week 48 LS Mean (SE)	4. Percent change from Baseline in T-VASI at Week 48
	F-VASI 90 at Week 48 n (%) [95% CI]	5. Achievement of F-VASI 90 (≥ 90% reduction in F-VASI from Baseline) at Week 48
	PhGIC-V of "Much better (1)" at Week 48	6. Achievement of PhGIC-V of "Much better (1)" at Week 48
	VNS score of "A lot less noticeable (4)" or "No longer noticeable (5)" at Week 48 n (%) [95% CI]	7. Achievement of VNS score of "A lot less noticeable (4)" or "No longer noticeable (5)" at Week 48
	PaGIC-V of "Much better (1)" at Week 48 n (%) [95% CI]	8. Achievement of PaGIC-V of "Much better (1)" at Week 48
	No increase from Baseline in T-VASI at both Week 8 and Week 12 among subjects with actively progressing vitiligo at Baseline n (%) [95% CI]	9. Achievement of no increase from Baseline in T-VASI at both Week 8 and Week 12 among subjects with actively progressing vitiligo at Baseline
Data Cut-off date	24 September 2025	
Results and Analysis		
Analysis Description	**Primary Analysis**	
Analysis Population and Time Point Description	The ITT population was defined as: • ITT_A: All subjects who were randomized at Baseline. The ITT_A population was used for all primary and ranked secondary efficacy analyses. Subjects were analyzed according to treatment as randomized. No subject was excluded from the efficacy analyses.	

	Treatment group	PBO	UPA 15 mg
	Number of subjects (Number of subjects indicated below if different)	101	205
Descriptive Statistics and Estimate Variability	Co-Primary endpoint: Achievement of T-VASI 50 at Week 48 (NRI-MI) n (%) [95% CI]	6 (5.9) [1.3, 10.6]	44 (21.5) [15.8, 27.1]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	14.7
		95% CI	[7.5, 21.9]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Co-Primary endpoint: Achievement of F-VASI 75 at Week 48 (NRI-MI) n (%) [95% CI]	7 (6.9) [2.0, 11.9]	48 (23.4) [17.6, 29.2]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	16.9
		95% CI	[9.2, 24.5]
		P-value	<0.001
		Statistical Significance	Significant
Analysis Description	**Secondary Analyses**		
	Treatment group	**PBO**	**UPA 15 mg**
	Number of subjects (Number of subjects indicated below if different)	101	205
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #1: Achievement of F-VASI 50 at Week 48 (NRI-MI) n (%) [95% CI]	13 (12.9) [6.3, 19.4]	89 (43.4) [36.6, 50.2]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	30.1
		95% CI	[20.8, 39.4]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #2:	1 (1.0) [0.0, 2.9]	23 (11.2) [6.9, 15.5]

Effect Estimate per Comparison	Achievement of F-VASI 75 at Week 24 (NRI-MI) n (%) [95% CI]	Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	10.6
		95% CI	[5.8, 15.5]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #3: Percent change from Baseline in F-VASI at Week 24 (RTB-MI) LS MEAN (SE)	-1.68 (4.464)	-27.85 (3.483)
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		LS Mean	-26.17
		95% CI	[-34.39, -17.95]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #4: Percent change from Baseline in T-VASI at Week 48 (RTB-MI) LS MEAN (SE)	-12.55 (4.231)	-32.95 (3.196)
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		LS Mean	-20.40
		95% CI	[-28.74, -12.06]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #5: Achievement of F-VASI 90 at Week 48 (NRI-MI) n (%) [95% CI]	3 (3.0) [0.0, 6.3]	25 (12.2) [7.7, 16.7]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	9.4
		95% CI	[3.7, 15.1]
		P-value	0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #6: Achievement of PhGIC-V of "Much better (1)" at Week 48 (NRI-MI) n (%) [95% CI]	1 (1.0) [0.0, 2.9]	34 (16.6) [11.5, 21.7]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	15.4
		95% CI	[10.2, 20.6]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #7: Achievement of	1 (1.0) [0.0, 2.9]	30 (14.6) [9.8, 19.5]
Effect Estimate per		Comparison groups	UPA 15 mg vs. PBO

Comparison	VNS score of "A lot less noticeable (4)" or "No longer noticeable (5)" at Week 48 (NRI-MI) n (%) [95% CI]	Adjusted Difference (%)	13.9
		95% CI	[8.7, 19.1]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #8: Achievement of PaGIC-V of "Much better (1)" at Week 48 (NRI-MI) n (%) [95% CI]	1 (1.0) [0.0, 2.9]	37 (18.0) [12.8, 23.3]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	16.9
		95% CI	[11.3, 22.5]
		P-value	<0.001
		Statistical Significance	Significant
Descriptive Statistics and Estimate Variability	Ranked Secondary Endpoint #9: Achievement of no increase from Baseline in T-VASI at both Week 8 and Week 12 among subjects with actively progressing vitiligo at Baseline (NRI-MI) n (%) [95% CI]	[N = 59] 36 (61.0) [48.6, 73.5]	[N = 119] 90 (75.6) [67.9, 83.3]
Effect Estimate per Comparison		Comparison groups	UPA 15 mg vs. PBO
		Adjusted Difference (%)	14.9
		95% CI	[0.5, 29.2]
		P-value	0.042
		Statistical Significance	Significant
Notes	Percentages with 95% CIs are reported for binary endpoints, and LS means with SEs for continuous endpoints		

CI = confidence interval; F-VASI = Facial Vitiligo Area Scoring Index; ITT = intent-to-treat; LS = least square; MI = multiple imputation; NRI = non-responder imputation; PaGIC-V = Patient's Global Impression of Change – Vitiligo; PBO = placebo; PhGIC-V = Physician's Global Impression of Change – Vitiligo; QD = once daily; RTB = return-to-Baseline; SE = standard error; T-VASI = Total Vitiligo Area Scoring Index; UPA = upadacitinib; VNS = Vitiligo Noticeability Scale

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The upadacitinib NSV clinical development programme includes two replicate Phase 3 studies, Study 1 and Study 2, and the optional, exploratory Study 3, all under a single protocol (M19-044). The NSV clinical development programme also included a dose-ranging Phase 2 study in NSV (M19-051) that has been completed. In this application, efficacy data was provided from the preliminary analysis of M19-044 Study 1 and Study 2. These two studies are considered the main studies in this application and described

in further detail below. The M19-044 Study 1 and Study 2 are replicate, pivotal, randomized, double-blind, placebo-controlled studies in adults and adolescents with a clinical diagnosis of NSV. Overall, the design of Study 1 and Study 2 is endorsed, and in line with the received CHMP Scientific Advice.

The data from the 24-week dose-ranging study M19-051 in adult patients with NSV support the choice of the upadacitinib 15 mg QD dose used in the two pivotal studies. Further support for the chosen dose comes from its use as the main dose in other inflammatory conditions, like atopic dermatitis (approved for adolescents), and its well-known safety profile.

Considering the chronic nature of the disease, it is anticipated that patients may require treatment beyond 48 weeks (duration of period A in the studies). Therefore, data on treatment extension beyond 48 weeks and up to 160 weeks is important for the assessment of overall long-term efficacy. As outlined in the RMP, the MAH has agreed to submit the final CSRs data from Study 1 and Study 2 Period B when finalised in Q2 2028 as a category 3 study.

The MAH proposed not to include a recommendation regarding the treatment duration once a stable response has been achieved in the SmPC. This was based on that the vitiligo clinical programme did not evaluate the duration of treatment to maintain a given response nor the outcome of upadacitinib treatment discontinuation after achieving treatment response. It is acknowledged that the design of the vitiligo clinical programme has not included evaluations necessary to support a recommendation for treatment duration. The MAH noted that as per recent vitiligo guidelines and expert recommendations, there is a strong consensus that maintenance therapy may mitigate the risk of disease relapse. Based on this statement, it is considered appropriate to await the finalised results of the long-term data (Period B of M19-044 Study 1 and Study 2), which are expected Q2 2028, before providing a recommendation in the product information regarding treatment duration once a stable response has been achieved.

Patient population

Eligible adult or adolescent subjects who were at least 12 years of age with a documented clinical diagnosis of NSV were randomized in a 2:1 ratio to 1 of 2 treatment groups: upadacitinib 15 mg QD (n=411) or matching placebo QD (n=203). Across the two pivotal studies, a total of 53 adolescent subjects were enrolled, which was consistent with the planned adolescent sample size (n=50). Of these, 37 subjects were randomized to the upadacitinib 15 mg QD group, and 16 were randomized to the placebo-group.

Overall, the inclusion/exclusion criteria are representative of the target population. Moreover, the proposed indication wording adequately reflects the study population. Given that initial therapeutic approaches for inflammatory skin conditions often involve topical treatments, the inclusion of a statement regarding line of treatment in the indication is considered appropriate as it ensures proper context and guidance for prescribers.

The Phase 3 studies M19-044 Study 1 and Study 2 are part of the agreed PIP for vitiligo, corresponding to Study 2 and Study 3 as outlined in the PIP. The inclusion criteria for these two studies, including body weight and VASI scores, align with the predetermined measures specified in the PIP. Furthermore, the adolescent population enrolled in the two studies corresponds to the PIP's predefined study population and subset definition.

Given than no additional NSV therapies were permitted during the pivotal studies, the lack of information regarding concomitant medications in the SmPC is deemed acceptable. The routine use of photoprotective measures, which was allowed during the study, is not expected to significantly impact the progression of NSV in a way that would introduce bias into the study results. It is acknowledged that current interim data (beyond 48 weeks) are limited, and hence, a recommendation to discontinue upadacitinib treatment

in patients who show no evidence of therapeutic benefit after 48 weeks of treatment is implemented in the SmPC.

Endpoints and outcomes

The co-primary endpoints of Study 1 and Study 2 were achievement of T-VASI 50 (≥ 50% reduction in T-VASI from Baseline) and F-VASI 75 (≥ 75% reduction in F-VASI from Baseline) at Week 48and is in line with other clinical programs for vitiligo and therefore follows regulatory expectations.

The pivotal studies included several multiplicity-controlled ranked secondary endpoints (see above sections). The inclusion of these endpoints is in line with previous NSV programmes and were endorsed during the CHMP scientific advice

Based on the CHMP's evaluation of the overall clinical data, section 5.1 of the SmPC was updated to reflect the co-primary and multiplicity controlled secondary endpoints outlined in Table 22 which is considered adequate.

Sample size

Both pivotal studies randomised more than the target number of 270 adult and adolescent patients in each study; 308 patients in Study 1 and 306 patients in Study 2. Of these, 53 patients were adolescents across the two studies, which was similar to the target number of 50 adolescent patients. Notably, the efficacy outcomes were highly statistically significant ($p < 0.001$), which suggests that the studies were appropriately powered to detect significant effects, and alleviates potential concerns regarding over-recruitment to obtain smaller p-values.

Analysis sets

All randomised patients were included in the efficacy analyses, which is appropriate.

Hypothesis testing

The co-primary endpoints were analysed using the Cochran-Mantel-Haenszel test, adjusted for the randomisation strata and baseline status of actively progressing vitiligo (yes or no). The ranked continuous secondary endpoints were analysed using an ANCOVA model including covariates for treatment groups, the randomisation strata, and the baseline value. These analysis methods are appropriate, and they were pre-specified in the protocol.

Type-1-error control

To control the type-1 error, the Applicant analysed secondary endpoints hierarchically. This hierarchy was pre-specified in the protocol, with exception of the last endpoint in the hierarchy ('Achievement of no increase from Baseline in T-VASI at both Week 8 and Week 12 among subjects with actively progressing vitiligo at Baseline'), which was added in the last version of the Statistical Analysis Plan (version 4.0, dated 13 October 2025). This version was issued before database lock (20 October 2025 in both studies), so the testing hierarchy was pre-specified.

Missing data

The amount of missing endpoint data was not clearly reported, but the number of patients who prematurely discontinued follow up was substantial. In study 1, 17% of participants in the upadacitinib arm and 15% in the placebo arm prematurely discontinued follow up. In Study 2, 14% in the upadacitinib arm and 20% in the placebo arm prematurely discontinued follow up. These numbers imply that there was a substantial amount of missing data.

For the primary endpoints (and the binary secondary endpoints), missing data were handled using non-response imputation, which is reasonable for the primary analysis. According to the protocol, multiple imputation would be used for data that could reasonably be assumed to be missing at random, but there were no such missing data in studies. Sensitivity analyses were performed in which missing data were handled using multiple imputation (under a missing-at-random assumption). Tipping-point analysis were also performed.

For continuous secondary endpoints, missing data were handled using multiple imputation under a missing-at-random assumption. Although is unclear whether this assumption holds, it is unlikely that the efficacy results are substantially biased given that the two studies showed similar results despite having different patterns of dropout (the upadacitinib arm had more dropouts than the placebo arm in Study 1 but fewer dropouts in Study 2).

Intercurrent events

The Applicant considered one intercurrent event – the use of confounding medication – and defined this as receiving either open-label upadacitinib (15 mg) as rescue medication or receiving another treatment for vitiligo. The use of confounding medication was handled using a composite strategy (non-response imputation) for binary endpoints and a hypothetical strategy (return-to-baseline imputation) for continuous endpoints.

Almost all of the confounding medication used in Studies 1 and 2 was open-label upadacitinib, and it was more common in the placebo arms than in the upadacitinib arms (Study 1: 19% placebo versus 5% upadacitinib. Study 2: 10% placebo versus 3% upadacitinib). The criterion for offering open-label upadacitinib as rescue medication was that a patient's T-VASI score at weeks 12 to 42 was at least 25% worse than a baseline. Since this criterion was pre-specified, and since it represents a clear worsening of symptoms, it is reasonable that a composite strategy (non-response imputation) was used. The Applicant also received support for a composite strategy in scientific advice (EMA/SA/0000121195).

A smaller (more conservative) estimate of the effect on the primary endpoints might have been obtainable if the use of open-label upadacitinib had been ignored in the analysis (similar to a treatment-policy strategy). However, such an analysis might also underestimate the treatment effect. Furthermore, the use of non-response imputation is a reasonable estimate of a clinically relevant scenario in which the rescue treatment had not been offered (patients whose vitiligo worsened are unlikely to become responders spontaneously). To establish efficacy, it was also considered reassuring that the results for the co-primary endpoints favoured the upadacitinib arms before rescue medication became available to patients at week 12.

The use of a hypothetical strategy (return-to-baseline imputation) to handle the use of confounding medications for continuous endpoints is reasonable, as patients are likely to have remained non-responders even if rescue medication had not been given.

Premature treatment discontinuation was not a pre-specified intercurrent event. Those participants who prematurely discontinued treatment appear not to have been followed up afterwards, given that the number of patients who discontinued treatment is similar to the number who discontinued follow-up. This is unfortunate because it leads to more missing data.

The Applicant did not consider deaths as an intercurrent event, but only 1 death occurred in the studies, so this event will not have affected the results.

Protocol amendments

There were only minor protocol amendments after the studies had begun.

Efficacy data and additional analyses

The co-primary endpoints in the pivotal studies (M19-044 Study 1 and Study 2) were the binary response status of T-VASI 50 (≥ 50% reduction in T-VASI from Baseline) and the binary response status of F-VASI 75 (≥ 75% reduction in F-VASI from Baseline) at Week 48; both endpoints were met in both pivotal studies. The results for the co-primary outcomes of both studies were similar. All 9 ranked secondary endpoints, encompassing various VASI-derivatives and disease perception tools (PhGIC-V, VNS score and PaGIC-V), were met while being corrected for multiplicity. The treatment effects in both primary endpoints and in the ranked secondary endpoints are valued as clinically relevant for the treatment of NSV. Overall, additional secondary endpoints that were not corrected for multiplicity, are considered supportive for the findings in the co-primary and ranked secondary endpoints.

The proportion of patients with F-VASI 75 at Week 48 was significantly higher (nominal p≤0.001) in the upadacitinib 15 mg treatment group compared to placebo (24.3% vs. 6.4%). Similarly, the proportion of patients with T-VASI 50 at Week 48 was significantly higher (nominal p≤0.001) in the upadacitinib 15 mg treatment group compared to placebo (20.4% vs. 5.9%). Overall, the ranked multiplicity-controlled secondary endpoints are supporting the effectiveness of upadacitinib in the treatment of NSV.

Until Week 48, which was the end of the double-blind period (Period A), data was complete. This means that the co-primary endpoints, ranked secondary endpoints, as well as the additional endpoints that were up until Week 48 were based on complete data. The MAH has provided results for several endpoints beyond Week 48 (the treatment extension phase, Period B), based on incomplete data as Period B of the pivotal studies are still ongoing at the date of data cut-off. Interpretation of these results is therefore precluded by the incomplete data and limited sample size.

Vitiligo is a chronic disease, and it is therefore anticipated that patients may require treatment beyond 48 weeks. Data on treatment extension beyond 48 weeks and up to 160 weeks is important for the assessment of overall long-term efficacy. As outlined in the RMP, the MAH has agreed to submit the final CSRs from Study 1 and Study 2 Period B in Q2 2028 as a category 3 study.

Adolescents

For the co-primary and ranked secondary endpoints, analyses were performed by stratification factors used for randomization, including age at screening (12-<18 years; ≥18 years). The results of the adolescent population (12-<18 years) did not demonstrate any notable differences in response rates for the co-primary endpoint F-VASI 75 at Week 48. For the other co-primary endpoint T-VASI 50 at Week 48, the response rates were nominally significant (nominal P-value 0.015) favouring the upadacitinb 15 mg treatment. The results for the co-primary endpoints in the adolescent subgroup will be further discussed in the section 'Ancillary analyses' below.

Although the adolescent population did not demonstrate significant responses to upadacitinib 15 mg versus placebo for the predefined levels of repigmentation of the face (F-VASI 50, F-VASI 75, and F-VASI 90), the population did show improvement in facial repigmentation for the endpoint percent change in F-VASI from baseline by Week 24. Moreover, these results were supported by a higher proportion of patients achieving PhGIC-V scores of "Much better" or "A little better" at Weeks 36 and 48. Significant responses were also observed in the ranked secondary patient-reported outcomes, including VNS scores of 4 or 5 and PaGIC-V of "Much better (1)", with higher proportions of patients reporting improvements in the upadacitinib 15 mg group.

<u>Ancillary analyses (with particular emphasis on adolescents)</u>

Subgroup analyses were conducted only for the co-primary endpoints. Treatment effects in the pre-specified subgroups consistently favoured upadacitinib 15 mg QD compared to placebo in the proportion

of subjects achieving each F-VASI 75 and T-VASI 50 at week 48, with 95% Cis excluding zero in most subgroups. These results are descriptive but indicate consistency in efficacy across subgroups.

The adolescent population exhibited a seemingly modest upadacitinib treatment effect for the co-primary endpoint F-VASI 75 (non-significant), likely attributed to the limited placebo group size (n=16). Although not significant, the proportion of adolescent patients in the upadacitinib 15 mg group achieving F-VASI 50, F-VASI 75, and F-VASI 90, respectively, at Week 24 and Week 48 followed a similar trend to the overall population. Given similar pathophysiological mechanism of vitiligo in adolescents and adults, it is reasonable to suggests that extrapolation of efficacy data from adult populations to adolescents may be justified. Therefore, primarily based on the T-VASI 50 co-primary endpoint, the response rates in the adolescent population are considered to be generally consistent with the overall study population. This assumption is supported by findings from the secondary endpoints for adolescents including PhGIC-V, PaGIC-V and VNS score. The adolescent subgroup results were not type-1-error controlled and therefore are considered supportive. However, baseline characteristics in Study 1 and Study 2 are assessed as reasonably similar between adults and adolescents and it is therefore considered that efficacy data can be extrapolated from the adult NSV population. In addition, section 5.1 of the SmPC, was updated with the following statement on observed consistency with the overall population, "Treatment effects at week 48 in adolescents 12 to 17 years of age were consistent with the results observed in the overall study population".

2.4.4. Conclusions on the clinical efficacy

In the pivotal studies in adult and adolescent patients 12 years and older with NSV, upadacitinib 15 mg QD was more effective than placebo in reducing signs and symptoms of NSV. The study population is representative of the target population with NSV. To emphasize the importance of evaluating the need for systemic treatment prior to initiation of upadacitinib therapy, the proposed indication is restricted to patients who are candidates for systemic therapy. The co-primary endpoints, achievement of F-VASI 75 and T-VASI 50 by Week 48, were met ($p < 0.001$) in both pivotal studies (M19-044 Study 1 and Study 2). The results for the co-primary outcomes were comparable across the two studies. Overall, all ranked multiplicity-controlled secondary endpoints (for EU) were met in the two studies and are supportive of the effectiveness of upadacitinib 15 mg QD in the treatment of NSV compared to placebo.

Similar trends of responses to upadacitinib 15 mg QD were observed in the adolescent population as shown in the adult population. The SmpC has been adequately updated.

2.5. Clinical safety

Introduction

The safety data submitted in support of the current variation is derived from two ongoing phase 3 studies, M19-044 Study 1 and Study 2, and the optional exploratory study M19-044 Study 3. Period A (48-week placebo-controlled, double-blind treatment period) of M19-044 Study 1 and 2, as well as Study 3, have been completed. Period B, a 112 week open label extension, is ongoing, and the final CSRs will be submitted in Q2 2028Study 1 and Study 2 are replicate, pivotal, global, double-blind, placebo-controlled, multicenter studies in adults and adolescents. Refer to the efficacy part for a detailed description of the study design. Study 3 is an ongoing, optional, exploratory, open-label 112-week study for adult subjects that completed Period A of Study 1 or Study 2 and failed to achieve T-VASI 90 at week 48. The study includes a re-randomized treatment period comparing upadacitinib 15 mg daily with upadacitinib 15 mg

daily in combination with whole body NB-UVB phototherapy twice weekly during the initial 28 weeks, after which point all subjects receive upadacitinib 15 mg daily.

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, a committee of physician experts was utilized to assess and adjudicate potential gastrointestinal (GI) perforation events.

Data is presented as integrated safety data from M19-044 Study 1 and Study 2. Long-term integrated safety data are presented through the data cutoff date of 24 September 2025 for M19-044 Study 1, Study 2 and Study 3. 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 2025) is included as supportive data.

Patient exposure

Table 25. Number and Percentage of Subjects Exposed to Study Treatment by Duration Intervals (PBO-controlled 48-week Safety Analysis Set, Overall and Adolescents).

	Overall			Adolescents		
Status	PBO (N=202)	UPA 15 mg QD (N=410)	Total (N=612)	PBO (N=16)	UPA 15 mg QD (N=37)	Total (N=53)
Mean duration (SD) (weeks)	40.0 (14.42)	43.1 (12.17)	42.1 (13.03)	44.0 (10.02)	45.2 (9.68)	44.8 (9.71)
Mean duration (SD) (PY)	0.8 (0.28)	0.8 (0.23)	0.8 (0.25)	0.8 (0.19)	0.9 (0.19)	0.9 (0.19)
≥ 1 dose	202 (100)	410 (100)	612 (100)	16 (100)	37 (100)	53 (100)
≥ 4 weeks	200 (99.0)	405 (98.8)	605 (98.9)	16 (100)	36 (97.3)	52 (98.1)
≥ 8 weeks	196 (97.0)	396 (96.6)	592 (96.7)	16 (100)	36 (97.3)	52 (98.1)
≥ 12 weeks	187 (92.6)	384 (93.7)	571 (93.3)	15 (93.8)	36 (97.3)	51 (96.2)
≥ 16 weeks	172 (85.1)	377 (92.0)	549 (89.7)	15 (93.8)	36 (97.3)	51 (96.2)
≥ 20 weeks	166 (82.2)	369 (90.0)	535 (87.4)	15 (93.8)	35 (94.6)	50 (94.3)
≥ 24 weeks	165 (81.7)	364 (88.8)	529 (86.4)	15 (93.8)	34 (91.9)	49 (92.5)
≥ 40 weeks (about 9 months)	150 (74.3)	346 (84.4)	496 (81.0)	13 (81.3)	33 (89.2)	46 (86.8)
≥ 48 weeks (double-blind period)	112 (55.4)	248 (60.5)	360 (58.8)	9 (56.3)	26 (70.3)	35 (66.0)

Cross-reference: ISS Table 2.3_1.1.1; ISS Table 2.3_1.1.2

Table 26. Number and Percentage of Subjects Exposed to Study Treatment by Duration Intervals (All Treated Long-term Safety Analysis Set, Overall and Adolescents).

	Overall				Adolescents			
Status	PBO/UPA 15 mg QD w/o NB-UVB (N = 153)	UPA 15 mg QD/UPA 15 mg QD w/o NB-UVB (N = 319)	Any UPA 15 mg QD w/o NB-UVB (N = 540)	Any UPA 15 mg (N = 582)	PBO/UPA 15 mg QD w/o NB-UVB (N = 14)	UPA 15 mg QD/UPA 15 mg QD w/o NB-UVB (N = 34)	Any UPA 15 mg QD w/o NB-UVB (N = 51)	Any UPA 15 mg (N = 52)
Mean duration (SD) (weeks)	20.2 (13.01)	63.8 (7.28)	46.2 (23.56)	46.2 (23.61)	9.2 (5.71)	57.2 (7.46)	41.3 (23.73)	41.7 (23.62)
Mean duration (SD) (PY)	0.4 (0.25)	1.2 (0.14)	0.9 (0.45)	0.9 (0.45)	0.2 (0.11)	1.1 (0.14)	0.8 (0.45)	0.8 (0.45)
Cumulative treatment duration - n (%)								
≥ 1 dose	153 (100)	319 (100)	540 (100)	582 (100)	14 (100)	34 (100)	51 (100)	52 (100)
≥ 4 weeks	150 (98.0)	319 (100)	532 (98.5)	574 (98.6)	12 (85.7)	34 (100)	48 (94.1)	49 (94.2)
≥ 8 weeks	144 (94.1)	319 (100)	517 (95.7)	558 (95.9)	6 (42.9)	34 (100)	42 (82.4)	43 (82.7)
≥ 12 weeks	109 (71.2)	319 (100)	472 (87.4)	509 (87.5)	4 (28.6)	34 (100)	40 (78.4)	41 (78.8)
≥ 16 weeks	77 (50.3)	319 (100)	435 (80.6)	467 (80.2)	2 (14.3)	34 (100)	37 (72.5)	38 (73.1)
≥ 20 weeks	57 (37.3)	319 (100)	411 (76.1)	442 (75.9)	1 (7.1)	34 (100)	35 (68.6)	36 (69.2)
≥ 24 weeks	36 (23.5)	319 (100)	386 (71.5)	415 (71.3)	0	34 (100)	34 (66.7)	35 (67.3)
≥ 40 weeks (about 9 months)	15 (9.8)	319 (100)	348 (64.4)	375 (64.4)	0	34 (100)	34 (66.7)	35 (67.3)
≥ 48 weeks (double-blind period)	10 (6.5)	318 (99.7)	330 (61.1)	357 (61.3)	0	33 (97.1)	33 (64.7)	34 (65.4)
≥ 52 weeks (about 1 year)	7 (4.6)	304 (95.3)	312 (57.8)	339 (58.2)	0	23 (67.6)	23 (45.1)	24 (46.2)
≥ 78 weeks (about 18 months)	0	15 (4.7)	15 (2.8)	17 (2.9)	0	0	0	0
≥ 104 weeks (about 2 years)	0	0	0	0	0	0	0	0

Cross reference: ISS Table 2.3__2.1.1, Table 2.3__2.1.2

Adverse events

Table 27. Overview of Number and Percentage of Subjects with TEAEs (PBO-controlled 48-week Safety Analysis Set, Overall and Adolescents).

	Overall		Adolescents	
	PBO (N = 202) n (%) [SSA%]	UPA 15 mg QD (N = 410) n (%) [SSA%]	PBO (N = 16) n (%) [SSA%]	UPA 15 mg QD (N = 37) n (%) [SSA%]
Any TEAE	124 (61.4) [61.4]	309 (75.4) [75.4]	7 (43.8) [41.3]	27 (73.0) [73.3]
Any TEAE with reasonable possibility of being related to study treatment according to the investigator	50 (24.8) [24.8]	160 (39.0) [39.0]	4 (25.0) [21.7]	18 (48.6) [48.6]
Any severe TEAE	9 (4.5) [4.5]	26 (6.3) [6.3]	0	1 (2.7) [2.9]
Any serious TEAE	5 (2.5) [2.5]	12 (2.9) [2.9]	0	0
Any TEAE leading to discontinuation of study treatment	9 (4.5) [4.5]	10 (2.4) [2.4]	0	0
Any TEAE leading to death	1 (0.5) [0.5]	0	0	0
All deaths[a]	1 (0.5) [0.5]	0	0	0
Deaths occurring ≤ 30 days after last dose of study treatment	1 (0.5) [0.5]	0	0	0
Deaths occurring > 30 days after last dose of study treatment	0	0	0	0

a. Includes both treatment-emergent and non-treatment-emergent deaths.

Notes: TEAEs on and after the use of rescue treatment are not included in the summary for Period A.
Subjects are counted once in each row, regardless of the number of events they may have had.
An event with unknown severity was counted as severe, and an event with unknown relationship to study treatment was counted as having a reasonable possibility of being study treatment-related.

Cross reference: ISS Table 2.4__1.1.1, Table 2.4__1.7.1

Common TEAEs

Table 28. Summary of Most Frequent (≥2% Subjects in Any Treatment Group) TEAEs by Decreasing Frequency in the UPA 15 mg Group (PBO-controlled 48-week Safety Analysis Set,Overall).

MedDRA 27.1 Preferred Term	PBO (N = 202) n (%) [SSA%]	UPA 15 mg QD (N = 410) n (%) [SSA%]
Nasopharyngitis	22 (10.9) [10.9]	57 (13.9) [13.9]
Upper respiratory tract infection	19 (9.4) [9.4]	49 (12.0) [12.0]
Acne	8 (4.0) [4.0]	47 (11.5) [11.5]
Headache	10 (5.0) [5.0]	35 (8.5) [8.5]
COVID-19	5 (2.5) [2.5]	19 (4.6) [4.6]
Influenza	5 (2.5) [2.5]	18 (4.4) [4.4]
Urinary tract infection	4 (2.0) [2.0]	16 (3.9) [3.9]
Back pain	2 (1.0) [1.0]	15 (3.7) [3.7]
Folliculitis	0	15 (3.7) [3.7]
Diarrhoea	8 (4.0) [4.0]	13 (3.2) [3.2]
Gastroenteritis	5 (2.5) [2.5]	12 (2.9) [2.9]
Hypercholesterolaemia	3 (1.5) [1.5]	12 (2.9) [2.9]
Hypertension	1 (0.5) [0.5]	12 (2.9) [2.9]
Oral herpes	2 (1.0) [1.0]	11 (2.7) [2.7]
Pyrexia	1 (0.5) [0.5]	11 (2.7) [2.7]
Nausea	2 (1.0) [1.0]	10 (2.4) [2.4]
Sinusitis	5 (2.5) [2.5]	10 (2.4) [2.4]
Influenza like illness	3 (1.5) [1.5]	9 (2.2) [2.2]
Oropharyngeal pain	2 (1.0) [1.0]	9 (2.2) [2.2]
Fatigue	4 (2.0) [2.0]	8 (2.0) [2.0]
Hyperlipidaemia	0	8 (2.0) [2.0]
Weight increased	3 (1.5) [1.5]	8 (2.0) [2.0]
Alanine aminotransferase increased	4 (2.0) [2.0]	6 (1.5) [1.5]
Aspartate aminotransferase increased	4 (2.0) [2.0]	4 (1.0) [1.0]
Asthenia	4 (2.0) [2.0]	2 (0.5) [0.5]

Notes: TEAEs on and after the use of rescue treatment are not included in the summary for Period A.
Subjects are counted once in each row, regardless of the number of events they may have had.

Cross reference: ISS Table 2.4__1.3.7

Table 29. Summary of Most Frequent (≥10% Adolescents in Any Treatment Group) TEAEs by Decreasing Frequency in the UPA 15 mg Group (PBO-controlled 48-week Safety Analysis Set, Adolescents).

MedDRA 27.1 Preferred Term	PBO (N = 16) n (%) [SSA%]	UPA 15 mg QD (N = 37) n (%) [SSA%]
Nasopharyngitis	1 (6.3) [5.4]	9 (24.3) [23.5]
Acne	3 (18.8) [16.3]	8 (21.6) [20.9]
Upper respiratory tract infection	2 (12.5) [12.5]	5 (13.5) [13.5]
Headache	0	5 (13.5) [13.2]
Influenza like illness	0	4 (10.8) [10.3]

Notes: TEAEs on and after the use of rescue treatment are not included in the summary for Period A.
Subjects are counted once in each row, regardless of the number of events they may have had.

Cross reference: ISS Table 2.4__1.10.7

Treatment-related TEAEs

Table 30. Summary of Most Frequent (≥2% Subjects in Any Treatment Group) TEAEs with a Reasonable Possibility of Relationship to Study Treatment by Decreasing Frequency in the UPA 15 mg Group (PBO-controlled 48-week Safety Analysis Set, Overall).

MedDRA 27.1 Preferred Term	Placebo (N = 202) n (%) [SSA%]	UPA 15 mg QD (N = 410) n (%) [SSA%]
Any TEAE	50 (24.8) [24.8]	160 (39.0) [39.0]
Acne	4 (2.0) [2.0]	36 (8.8) [8.8]
Nasopharyngitis	6 (3.0) [3.0]	18 (4.4) [4.4]
Headache	2 (1.0) [1.0]	15 (3.7) [3.7]
Upper respiratory tract infection	6 (3.0) [3.0]	15 (3.7) [3.7]
Folliculitis	0	13 (3.2) [3.2]
Oral herpes	2 (1.0) [1.0]	9 (2.2) [2.2]
Hypercholesterolaemia	3 (1.5) [1.5]	8 (2.0) [2.0]

Notes: TEAEs on and after the use of rescue treatment are not included in the summary for Period A.
Subjects are counted once in each row, regardless of the number of events they may have had.

Cross reference: ISS Table 2.4__1.3.4

TEAEs by severity

In the overall study population in the PBO-controlled 48-week Safety Analysis Set, the most frequent severe TEAE by preferred term (PT) (≥1% of subjects in any treatment group) was hypertriglyceridemia. In the adolescent subgroup, 1 severe TEAE was reported (hand fracture in the upadacitinib group). In the overall study population in the All Treated Long-term Safety Analysis Set, the most frequent severe TEAE by PT in the any upadacitinib 15 mg cohort (≥1 E/100 PY) was hypertriglyceridemia. In the adolescent subgroup, no severe TEAE was reported aside from the 1 severe TEAE of hand fracture described above for the PBO-controlled 48-week Safety Analysis Set.

Adverse drug reactions (ADRs)

For the determination of ADRs, PTs were grouped into medical concepts (grouped terms) for acne, abdominal pain, anaemia, bone fracture, herpes simplex, herpes zoster, hypercholesterolemia, hypertriglyceridemia, hyperlipidaemia, lymphopenia, neutropenia, pneumonia, rash, upper respiratory tract infection, GI infection, and urinary tract infection. PTs and grouped terms were considered for ADR determination if they occurred in at least 3.0% of subjects in the upadacitinib group and there was a difference of ≥1.0% over placebo. AEs observed in < 3.0% of subjects were also screened for potential underlying rare or sentinel ADR.

In the NSV clinical programme, the sample size includes 410 subjects in the upadacitinib group and 202 subjects in the placebo group (approximately 2:1 ratio). While in the AD population, the minimum threshold for ADR determination was set as ≥1% of subjects in the upadacitinib 15 mg OR upadacitinib 30 mg groups, given the smaller sample size in NSV, it has been deemed appropriate to set the minimum threshold in NSV at a rate of ≥3.0% (≥13 subjects) in the upadacitinib 15 mg group.

The PTs and grouped terms that were identified as ADRs following the assessment process described above are shown in Table 31. All PTs and grouped terms that were identified as ADRs have been previously determined to be ADRs for upadacitinib treatment, and the frequency of occurrence of these ADRs seen in the NSV clinical programme is consistent with frequency categories in the upadacitinib

SmPC in the AD indication with the following exception: The frequency of hypercholesterolemia in the AD clinical studies has been considered uncommon (i.e., ≥1/1,000 to < 1/100), but was determined as having a common frequency (i.e., ≥1/100 to < 1/10) upon review of the NSV clinical data. No new ADRs for upadacitinib treatment were identified in the safety data from the NSV clinical programme.

Table 31. Number and Percentage of Subjects with TEAEs with ADR Grouped Terms (Placebo-Controlled 48-Week Safety Analysis Set).

Adverse Drug Reaction[a] MedDRA 27.1 Preferred Term	PBO (N = 202) n (%)	UPA 15 mg QD (N = 410) n (%)
Folliculitis	0	15 (3.7)
Headache	10 (5.0)	35 (8.5)
Influenza	5 (2.5)	18 (4.4)
Grouped Term: Hypercholesterolemia	4 (2.0)	14 (3.4)
Blood cholesterol increased	1 (0.5)	2 (0.5)
Hypercholesterolaemia	3 (1.5)	12 (2.9)
Grouped Term: Neutropenia	4 (2.0)	13 (3.2)
Neutropenia	1 (0.5)	6 (1.5)
Neutrophil count decreased	3 (1.5)	7 (1.7)
Grouped Term: Upper Respiratory Tract Infection	48 (23.8)	112 (27.3)
Acute sinusitis	0	1 (0.2)
Chronic sinusitis	0	1 (0.2)
Laryngitis	2 (1.0)	3 (0.7)
Nasopharyngitis	22 (10.9)	57 (13.9)
Pharyngitis	2 (1.0)	5 (1.2)
Pharyngitis streptococcal	1 (0.5)	1 (0.2)
Respiratory tract infection	0	3 (0.7)
Rhinitis	2 (1.0)	1 (0.2)
Sinusitis	5 (2.5)	10 (2.4)
Tonsillitis	1 (0.5)	1 (0.2)
Tonsillitis bacterial	0	1 (0.2)
Upper respiratory tract infection	19 (9.4)	49 (12.0)
Viral upper respiratory tract infection	1 (0.5)	0
Grouped Term: Acne	8 (4.0)	50 (12.2)
Acne	8 (4.0)	47 (11.5)
Dermatitis acneiform	0	3 (0.7)
Grouped Term: Herpes Simplex	3 (1.5)	14 (3.4)
Herpes simplex	1 (0.5)	4 (1.0)
Oral herpes	2 (1.0)	11 (2.7)

a. ADRs that are not designated grouped terms are individual PTs.

Notes: TEAEs on and after the use of rescue treatment are not included in the summary for Period A.
Subjects are counted once in each row, regardless of the number of events they may have had.

Cross reference: ISS Table 2.4__1.5.13

Serious adverse event/deaths/other significant events

Deaths

One death occurred in an adult subject who received placebo and was due to TEAE of drowning and was considered by the investigator as having no reasonable possibility of being related to study treatment. No deaths occurred in adults or adolescents in the upadacitinib group.

SAEs

Table 32. Number and Percentage of Subjects with Treatment-Emergent SAEs by Primary MedDRA SOC and PT (Placebo-Controlled 48-Week Safety Analysis Set, Overall).

MedDRA 27.1 System Organ Class Preferred Term	Placebo (N = 202) n (%) [SSA%]	UPA 15 mg QD (N = 410) n (%) [SSA%]
Ear and labyrinth disorders	0	1 (0.2) [0.2]
Vertigo	0	1 (0.2) [0.2]
Gastrointestinal disorders	2 (1.0) [1.0]	2 (0.5) [0.5]
Diarrhoea haemorrhagic	1 (0.5) [0.5]	0
Large intestine polyp	1 (0.5) [0.5]	0
Small intestinal obstruction	0	1 (0.2) [0.2]
Upper gastrointestinal haemorrhage	0	1 (0.2) [0.2]
General disorders and administration site conditions	1 (0.5) [0.5]	0
Drowning	1 (0.5) [0.5]	0
Hepatobiliary disorders	1 (0.5) [0.5]	0
Cholecystitis acute	1 (0.5) [0.5]	0
Infections and infestations	0	3 (0.7) [0.7]
Bronchitis	0	1 (0.2) [0.2]
Complicated appendicitis	0	1 (0.2) [0.2]
Influenza	0	1 (0.2) [0.2]
Parainfluenzae virus infection	0	1 (0.2) [0.2]
Injury, poisoning and procedural complications	0	1 (0.2) [0.2]
Airway burns	0	1 (0.2) [0.2]
Investigations	1 (0.5) [0.5]	0
Weight decreased	1 (0.5) [0.5]	0
Musculoskeletal and connective tissue disorders	0	2 (0.5) [0.5]
Jaw cyst	0	1 (0.2) [0.2]
Os odontoideum	0	1 (0.2) [0.2]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5) [0.5]	2 (0.5) [0.5]
Genital neoplasm malignant female	0	1 (0.2) [0.2]
Haemangioma	0	1 (0.2) [0.2]
Ovarian adenoma	1 (0.5) [0.5]	0
Nervous system disorders	0	1 (0.2) [0.2]
Transient global amnesia	0	1 (0.2) [0.2]
Reproductive system and breast disorders	0	1 (0.2) [0.2]
Genital haemorrhage	0	1 (0.2) [0.2]
Ovarian cyst	0	1 (0.2) [0.2]
Respiratory, thoracic and mediastinal disorders	0	1 (0.2) [0.2]
Acute respiratory failure	0	1 (0.2) [0.2]
Asthma	0	1 (0.2) [0.2]
Vascular disorders	0	1 (0.2) [0.2]
Hypertensive crisis	0	1 (0.2) [0.2]

Notes: TEAEs on and after the use of rescue treatment are not included in the summary for Period A.
Subjects are counted once in each row, regardless of the number of events they may have had.

Cross reference: ISS Table 2.4__1.3.2

PBO-controlled 48-week Safety Analysis Set

Overall, the percentage of subjects with treatment-emergent SAEs were similar between treatment groups. By PT, all SAEs were reported in 1 subject each.

One adult subject in the upadacitinib group reported treatment-emergent SAEs of transient global amnesia, hypertensive crisis, and haemangioma between Day 154 and Day 191. The subject did not receive any corrective treatment for the events, study treatment continued, and these events had a duration of between 1 to 3 days. A CT scan did not reveal evidence of a stroke. Notably, the subject had a mild elevation of blood pressure since Baseline (140/90 mmHg). The events were assessed by the investigator as having no reasonable possibility of being related to study treatment.

An SAE of upper GI haemorrhage was reported on Day 56 of upadacitinib treatment in an elderly subject with a medical history of gastritis who was a long-term aspirin user. A CT scan of the abdomen showed no evidence of active arterial bleeding, and no corrective treatment was provided. Study treatment was withdrawn. The event resolved and was assessed by the investigator as having no reasonable possibility of being related to study treatment.

In the adolescent subgroup, no SAEs were reported.

All Treated Long-term Safety Analysis Set

Overall, the exposure-adjusted event rate (EAER) of treatment-emergent SAEs was 4.5 E/100 PY in the any upadacitinib 15 mg cohort. By PT, all SAEs in the any upadacitinib 15 mg cohort were reported in 1 subject each. In the adolescent subgroup, no SAEs were reported.

Adverse events of special interest

Table 33. Overview of Number and Percentage of Subjects with Treatment-Emergent AESI (PBO-controlled 48-week Safety Analysis Set, Overall and Adolescents).

	Overall		Adolescents	
	PBO (N = 202) n (%) [SSA%]	UPA 15 mg QD (N = 410) n (%) [SSA%]	PBO (N = 16) n (%) [SSA%]	UPA 15 mg QD (N = 37) n (%) [SSA%]
Serious infections	0	3 (0.7) [0.7]	0	0
Herpes zoster	1 (0.5) [0.5]	7 (1.7) [1.7]	0	1 (2.7) [2.6]
Hepatic disorder	6 (3.0) [3.0]	11 (2.7) [2.7]	0	0
Anemia	1 (0.5) [0.5]	5 (1.2) [1.2]	0	0
Neutropenia	4 (2.0) [2.0]	13 (3.2) [3.2]	0	2 (5.4) [5.1]
Lymphopenia	2 (1.0) [1.0]	5 (1.2) [1.2]	0	0
Malignancy	2 (1.0) [1.0]	1 (0.2) [0.2]	0	0
Malignancy excluding NMSC	2 (1.0) [1.0]	1 (0.2) [0.2]	0	0
Bone fractures	1 (0.5) [0.5]	8 (2.0) [2.0]	1 (6.3) [5.4]	2 (5.4) [5.8]

Notes: TEAEs on and after the use of rescue treatment are not included in the summary for Period A.
Subjects are counted once in each row, regardless of the number of events they may have had.
No treatment-emergent AESIs of opportunistic infections (excluding TB and herpes zoster), active TB, adjudicated GI perforation, renal dysfunction, NMSC, lymphoma, retinal detachment, serious hypersensitivity reactions, adjudicated MACE, and adjudicated VTE were reported.

Cross reference: ISS Table 2.4__1.2.1, Table 2.4__1.8.1

Table 34. Overview of Treatment-Emergent AESI Per 100 PY (All Treated Long-term Safety Analysis Set, Overall and Adolescents).

	Overall				Adolescents			
	PBO/UPA 15 mg QD w/o NB-UVB (N = 153) (PY = 59.3)	UPA 15 mg QD/UPA 15 mg QD w/o NB-UVB (N = 319) (PY = 389.9)	Any UPA 15 mg QD w/o NB-UVB (N = 540) (PY = 478.0)	Any UPA 15 mg (N = 582) (PY = 515.6)	PBO/UPA 15 mg QD w/o NB-UVB (N = 14) (PY = 2.5)	UPA 15 mg QD/UPA 15 mg QD w/o NB-UVB (N = 34) (PY = 37.3)	Any UPA 15 mg QD w/o NB-UVB (N = 51) (PY = 40.4)	Any UPA 15 mg (N = 52) (PY = 41.5)
EAER	**Events (E/100PY)**				**Events (E/100PY)**			
Serious infections	1 (1.7)	2 (0.5)	4 (0.8)	5 (1.0)	0	0	0	0
Herpes zoster	4 (6.7)	7 (1.8)	12 (2.5)	12 (2.3)	0	1 (2.7)	1 (2.5)	1 (2.4)
Hepatic disorder	0	16 (4.1)	16 (3.3)	22 (4.3)	0	0	0	0
Anemia	0	7 (1.8)	9 (1.9)	9 (1.7)	0	0	0	0
Neutropenia	1 (1.7)	16 (4.1)	17 (3.6)	17 (3.3)	0	2 (5.4)	2 (5.0)	2 (4.8)
Lymphopenia	0	9 (2.3)	9 (1.9)	9 (1.7)	0	0	0	0
EAIR	**n/PY (n/100PY)**				**n/PY (n/100PY)**			
Malignancy	0/59.3	0/389.9	1/477.9 (0.2)	1/515.6 (0.2)	0/2.5	0/37.3	0/40.4	0/41.5
Malignancy excluding NMSC	0/59.3	0/389.9	1/477.9 (0.2)	1/515.6 (0.2)	0/2.5	0/37.3	0/40.4	0/41.5
Bone fractures	2/58.8 (3.4)	7/386.1 (1.8)	10/473.0 (2.1)	10/510.6 (2.0)	1/2.4 (41.7)	2/36.4 (5.5)	3/39.5 (7.6)	3/40.6 (7.4)

Note: No treatment-emergent AESIs of opportunistic infections (excluding TB and herpes zoster), active TB, adjudicated GI perforation, renal dysfunction, NMSC, lymphoma, retinal detachment, serious hypersensitivity reactions, adjudicated MACE, and adjudicated VTE were reported.

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), active TB, adjudicated GI perforation, renal dysfunction, NMSC, lymphoma, retinal detachment, serious

hypersensitivity reactions, adjudicated MACE, and adjudicated venous thromboembolic event (VTE) were reported in M19-044 Study 1, Study 2, or Study 3 through the data cut-off date.

Serious infections

PBO-controlled 48-week Safety Analysis Set

Overall, 3 subjects reported a treatment-emergent serious infection in the upadacitinib group compared to none in the placebo group. The serious infections included complicated (phlegmonous) appendicitis and parainfluenza virus infection, both assessed by the investigator as having no reasonable possibility of being related to study treatment, and bronchitis and influenza (same subject), assessed by the investigator as having a reasonable possibility of being related to study treatment. All serious infections resolved without discontinuation of study treatment. In the adolescent subgroup, no serious infections were reported.

All Treated Long-term Safety Analysis Set

Overall, the EAER of serious infection was 1.0 E/100 PY in the any upadacitinib 15 mg cohort. By PT, all serious infections among subjects receiving any upadacitinib were reported in 1 subject each. All serious infections resolved without discontinuation of study treatment. In the adolescent subgroup, no serious infections were reported.

Herpes zoster

PBO-controlled 48-week Safety Analysis Set

Overall, the percentage of subjects with TEAEs of herpes zoster was higher in the upadacitinib group than the placebo group.

All were nonserious and moderate in severity, and none led to discontinuation of study treatment. They involved 1 or 2 dermatomes with no reports of disseminated herpes zoster or events with central nervous system (CNS), lung, or hepatic involvement. One event was reported with ophthalmic involvement in an adult subject on upadacitinib with no varicella or herpes zoster immunization received. The event (PT ophthalmic herpes zoster) resolved after interruption of study treatment and did not recur after study treatment reinitiation. In the adolescent subgroup, 1 TEAE of herpes zoster was reported (upadacitinib group, cutaneous involvement).

All Treated Long-term Safety Analysis Set

Overall, the EAER of herpes zoster was 2.3 E/100 PY in the any upadacitinib 15 mg cohort. All 12 events with exception of one were nonserious, mild or moderate in severity, and involved 1 or 2 dermatomes. There were no herpes zoster events that led to discontinuation of study treatment, were disseminated, or had CNS, lung, or hepatic involvement. Two events were reported with ophthalmic involvement, one of which is summarized above for the PBO-controlled 48-week Safety Analysis Set. The other event with ophthalmic involvement (PT herpes zoster) was serious and severe and occurred in an adult subject with no history of varicella or herpes zoster immunization 384 days after initiation of upadacitinib. This event required hospitalization, involved V1, V2, and C2 adjacent dermatomes (i.e., was determined to be non-disseminated in alignment with the standard definition), and was associated with post-herpetic neuralgia. Study treatment was interrupted, and both the herpes zoster and post-herpetic neuralgia resolved 55-58 days later, were assessed by the investigator as having a reasonable possibility of being related to study treatment, and did not recur after study treatment reinitiation.

In the adolescent subgroup, no TEAEs of herpes zoster were reported aside from the 1 TEAE of herpes zoster with cutaneous involvement described above for the PBO-controlled 48-week Safety Analysis Set.

Most subjects had no prior history of herpes zoster, and the majority had no varicella or herpes zoster vaccination. In subjects with no history of herpes zoster vaccination, the EAER of treatment-emergent herpes zoster was 2.9 E/100 PY in the any upadacitinib 15 mg cohort; 1 subject with a prior history of herpes zoster vaccination reported a TEAE of herpes zoster (2.0 E/100 PY). In subjects with no prior history of herpes zoster, the EAER of treatment-emergent herpes zoster was 2.0 E/100 PY in the any upadacitinib 15 mg cohort. Two events of herpes zoster (11.2 E/100 PY) were reported in subjects with a prior history of herpes zoster infection.

Malignancy

In the *PBO-controlled 48-week Safety Analysis Set*, 2 adult subjects in the placebo group and 1 adult subject in the upadacitinib group reported TEAEs of malignancy excluding NMSC. The events in the placebo group were colon cancer and metastases to liver (same subject); and intraductal proliferative breast lesion. The event in the upadacitinib group was malignant female genital neoplasm. All events in the placebo group resulted in discontinuation of study treatment. The subject in the upadacitinib group withdrew consent and underwent surgical treatment. All events across treatment groups were considered by the investigator as having no reasonable possibility of being related to study treatment. The malignant female genital neoplasm had a relatively short time to onset after start of upadacitinib (46 days). Given the long latency required for induction of solid tumors, a causal association with upadacitinib is implausible in this case. In the adolescent subgroup, no TEAEs of malignancy excluding NMSC were reported.

In the *All Treated Long-term Safety Analysis Set*, the exposure-adjusted incidence rate (EAIR) of malignancy excluding NMSC was 0.2 n/100 PY in the any upadacitinib 15 mg cohort. No TEAEs of malignancy excluding NMSC were reported aside from the 1 event mentioned above for the PBO-controlled 48-week Safety Analysis Set. In the adolescent subgroup, no TEAEs of malignancy excluding NMSC were reported.

No TEAEs of NMSC or lymphoma were reported in the PBO-controlled 48-week Safety Analysis Set or All Treated Long-term Safety Analysis Set.

Hepatic disorder

PBO-controlled 48-week Safety Analysis Set

Overall, the percentages of subjects with TEAEs of hepatic disorder were similar in the upadacitinib and placebo groups. Transaminase elevations accounted for the majority of TEAEs of hepatic disorder. All TEAEs of hepatic disorder were nonserious, and only 1 event (hepatic enzyme increased in the placebo group) led to discontinuation of study treatment. In the adolescent subgroup, no TEAEs of hepatic disorder were reported.

All Treated Long-term Safety Analysis Set

Overall, the EAER of TEAEs of hepatic disorder was 4.3 E/100 PY in the any upadacitinib 15 mg cohort. Transaminase elevations accounted for the majority of the TEAEs of hepatic disorder in this cohort. All TEAEs of hepatic disorder were nonserious and none led to discontinuation of study treatment. In the adolescent subgroup, no TEAEs of hepatic disorder were reported.

Anaemia

PBO-controlled 48-week Safety Analysis Set

Overall, the percentages of subjects with TEAEs of anaemia were similar in the upadacitinib and placebo groups. All events were nonserious, all but 1 event were mild or moderate in severity, and no events led to discontinuation of study treatment. In the adolescent subgroup, no TEAEs of anaemia were reported.

One severe TEAE of anaemia (reported term worsening of iron deficiency anaemia) on Day 57 of upadacitinib treatment occurred in an adult subject with medical history of iron deficiency anaemia and decreased Baseline haemoglobin level. The event was reported concurrently with events of upper GI haemorrhage, duodenal ulcer, and gastritis. Study treatment was interrupted, and the anaemia resolved after transfusion of 1 unit of packed red blood cells. The anaemia was assessed by the investigator as having no reasonable possibility of being related to study treatment.

All Treated Long-term Safety Analysis Set

Overall, the EAER of TEAEs of anaemia was 1.7 E/100 PY in the any upadacitinib 15 mg cohort. All events were nonserious, all but 2 events were mild or moderate in severity, and none led to discontinuation of study treatment. In the adolescent subgroup, no TEAEs of anaemia were reported.

Among the 2 severe events, one is summarized above for the PBO-controlled 48-week Safety Analysis Set. The other severe TEAE was iron deficiency anaemia on Day 345 in an adult subject with medical history of haemorrhoids. Study treatment was interrupted due to the anaemia and the subject later had an event of haemorrhoids (reported term worsening haemorrhoids) on Day 365. The anaemia was ongoing at the time of the data cutoff. The subject received ferrous treatment. The anaemia was assessed by the investigator as having a reasonable possibility of being related to study treatment.

Neutropenia

PBO-controlled 48-week Safety Analysis Set

Overall, the percentage of subjects with TEAEs of neutropenia was higher in the upadacitinib group than the placebo group. All events were nonserious, the majority were mild or moderate in severity, and none led to discontinuation of study treatment.

There were 2 severe TEAEs of neutropenia in the upadacitinib group:

- One severe event of neutrophil count decreased occurred in an adult subject on Day 171 and was associated with a Grade 3 laboratory value decrease in neutrophil count. The subject's neutrophil levels improved at a subsequent test while upadacitinib treatment was ongoing, and the event resolved. Prior to the neutrophil count decrease, the subject experienced nonserious viral gastroenteritis on Day 169. The neutropenia event was assessed by the investigator as having a reasonable possibility of being related to study treatment.
- The second severe event of neutropenia occurred in an adult subject on Day 34 with a history of autoimmune thyroiditis. The subject had transitory Grade 3 laboratory value decreases in neutrophil count and leukocyte count. The subject had concurrent pyrexia and myalgia 5 days prior to the event of neutropenia. Study treatment was interrupted and the neutropenia and leukopenia resolved. The neutropenia event was assessed by the investigator as having a reasonable possibility of being related to study treatment.

In the adolescent subgroup, 2 subjects reported TEAEs of neutropenia, both in the upadacitinib group and moderate in severity. One resolved without interruption of study treatment and the other resolved with interruption of study treatment.

All Treated Long-term Safety Analysis Set

Overall, the EAER of TEAEs of neutropenia was 3.3 E/100 PY in the any upadacitinib 15 mg cohort. All events were nonserious and none led to discontinuation of study treatment. No events were severe aside from the 2 severe events summarized above for the PBO-controlled 48-week Safety Analysis Set. In the adolescent subgroup, no TEAEs of neutropenia were reported aside from the events mentioned above for the PBO-controlled 48-week Safety Analysis Set.

Lymphopenia

PBO-controlled 48-week Safety Analysis Set

Overall, the percentages of subjects with TEAEs of lymphopenia were similar in the upadacitinib and placebo groups. All events were nonserious, the majority were mild or moderate in severity, and none led to discontinuation of study treatment. In the adolescent subgroup, no TEAEs of lymphopenia were reported.

There was 1 severe event of lymphocyte count decreased in the upadacitinib group in a subject with diabetes mellitus type 1 and a decreased lymphocyte count at Baseline. The event occurred on Day 85 and was associated with a Grade 3 lymphocyte count decrease. On Day 97, while treatment continued, the subject's lymphocyte levels improved and the event resolved. The event was assessed by the investigator as having no reasonable possibility of being related to study treatment.

All Treated Long-term Safety Analysis Set

Overall, the EAER of TEAEs of lymphopenia was 1.7 E/100 PY in the any upadacitinib 15 mg cohort. All events were nonserious and none led to discontinuation of study treatment. No events were severe aside from the 1 severe event summarized above for the PBO-controlled 48-week Safety Analysis Set. In the adolescent subgroup, no TEAEs of lymphopenia were reported.

Bone fractures

PBO-controlled 48-week Safety Analysis Set

Overall, the percentage of subjects with TEAEs of bone fracture was higher in the upadacitinib group than the placebo group. All reports of bone fracture were due to trauma, and no TEAEs of bone fracture were considered by the investigator as having a reasonable possibility of being related to study treatment. All events were nonserious, most were mild or moderate in severity, and none led to discontinuation of study treatment. In the adolescent subgroup, TEAEs of bone fracture were reported by 2 subjects in the upadacitinib group (1 with ankle fracture and 1 with hand fracture) and 1 subject in the placebo group (2 events of foot fracture).

All Treated Long-term Safety Analysis Set

Overall, the EAIR of TEAEs of bone fracture was 2.0 n/100 PY in the any upadacitinib 15 mg cohort. Among the 10 bone fractures, 5 were associated with falls, 4 were linked to sports-related injuries, and 1 had no clear trauma history. Among the fall-related cases, three involved slipping; one involved a subject with a history of hypertension, diabetes, and multiple medications that can increase the risk of dizziness or falls (clonazepam, lurasidone, sertraline, and gabapentin) who experienced bradycardia and suspected syncope; and 1 report lacked this specific information. No TEAEs of bone fracture were considered by the investigator as having a reasonable possibility of being related to study treatment. Most events were nonserious, the majority were mild or moderate in severity, and none led to discontinuation of study treatment. In the adolescent subgroup, among the 3 TEAEs of bone fracture, 2 are summarized above for the PBO-controlled 48-week Safety Analysis Set; the other was a scapula fracture.

Table 35. Updated Overview of Treatment-Emergent AESI Per 100 PY (All Treated Long-term Safety Analysis Set, Adolescents).

	Data Cutoff Date 24 September 2025				Data Cutoff Date 05 January 2026			
	PBO/UPA 15 mg QD w/o NB-UVB (N = 14) (PY = 2.5)	UPA 15 mg QD/UPA 15 mg QD w/o NB-UVB (N = 34) (PY = 37.3)	Any UPA 15 mg QD w/o NB-UVB (N = 51) (PY = 40.4)	Any UPA 15 mg (N = 52) (PY = 41.5)	PBO/UPA 15 mg QD w/o NB-UVB (N = 14) (PY = 6.1)	UPA 15 mg QD/UPA 15 mg QD w/o NB-UVB (N = 34) (PY = 46.6)	Any UPA 15 mg QD w/o NB-UVB (N = 51) (PY = 53.3)	Any UPA 15 mg (N = 52) (PY = 54.8)
EAER	**Events (E/100PY)**				**Events (E/100PY)**			
Herpes zoster	0	1 (2.7)	1 (2.5)	1 (2.4)	0	1 (2.1)	1 (1.9)	1 (1.8)
Hepatic disorders	0	0	0	0	0	1 (2.1)	1 (1.9)	1 (1.8)
Neutropenia	0	2 (5.4)	2 (5.0)	2 (4.8)	0	2 (4.3)	2 (3.7)	2 (3.7)
EAIR	**n/PY (n/100PY)**				**n/PY (n/100PY)**			
Bone fractures	1/2.4 (41.7)	2/36.4 (5.5)	3/39.5 (7.6)	3/40.6 (7.4)	1/5.8 (17.3)	3/45.1 (6.7)	4/51.5 (7.8)	4/52.9 (7.6)

Note: No treatment-emergent AESIs of serious infections, opportunistic infections (excluding TB and herpes zoster), active TB, adjudicated GI perforation, anemia, lymphopenia, renal dysfunction, malignancies (all types), retinal detachment, serious hypersensitivity reactions, adjudicated MACE, and adjudicated VTE were reported.

Cross reference: Table 2.4__2.9.2.1, Table 2.4__2.9.2.2; ISS Table 2.4__2.9.2.1, Table 2.4__2.9.2.2

In updated data (cut-off 05 January 2026) for AESI in adolescents 2 additional AESIs were reported, one was a sports-related bone fracture, and another was an event of hepatic disorder which resolved without study treatment interruption.

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 NSV.

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

Compared to individuals without vitiligo or other chronic inflammatory skin conditions, vitiligo patients tend to be younger and show similar or lower prevalence of cardiovascular diseases, obesity, tobacco use, hypertension, dyslipidemia, diabetes, and other major risk factors[13]. Furthermore, among the small proportion of vitiligo patients who also have comorbid RA (approximately 2%)[14] [15] [16], the prevalence of cardiovascular risk factors and all-cause mortality is substantially elevated (approximately 2- to 5-fold higher) compared to vitiligo patients without RA[6], further illustrating the distinct safety risk profile of the vitiligo population.

[13] 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.
[14] Hadi A, Wang JF, Uppal P, Penn LA, Elbuluk N. Comorbid diseases of vitiligo: A 10 year cross-sectional retrospective study of an urban US population. J Am Acad Dermatol. 2020 Mar;82(3):628-633. doi: 10.1016/j.jaad.2019.07.036. Epub 2019 Jul 17. PMID: 31325552.
[15] Zhang Z, Xu SX, Zhang FY, Yin XY, Yang S, Xiao FL, Du WH, Wang JF, Lv YM, Tang HY, Zhang XJ. The analysis of genetics and associated autoimmune diseases in Chinese vitiligo patients. Arch Dermatol Res. 2009 Feb;301(2):167-73.
[16] Cohen NT, Schonmann Y, Kridin K. A bidirectional autoimmune cluster between vitiligo and rheumatoid arthritis: a large-scale population-based study. Arch Dermatol Res. 2024 Jun 8;316(7):366.

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 safety data do not suggest any increased risk, including in comparison to ritlecitinib safety data, as summarised hereafter:

Rates of MACE, VTE, malignancy, malignancy excluding NMSC, and death for upadacitinib Study M19-044 placebo-controlled treatment in period A were presented (Table 36). In addition, rates of MACE, VTE, malignancy, and malignancy excluding NMSC for ritlecitinib and upadacitinib in the AA and NSV long-term development program were presented (Table 37). The MAH 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).

The MAH noted that, in the NSV long-term safety analysis set, incidence rates of malignancy excluding NMSC and MACE for upadacitinib in NSV overall population were low with no evidence of increased risk when compared to placebo treatment group during the 48-week Period A treatment or the background rates[17] [18]. There were no VTE, NMSC events, or deaths in patients treated with upadacitinib in NSV studies.

Table 36 Overview of n(%) of Subjects with Treatment-Emergent MACE, VTE, Malignancy or death reported during PBO-Controlled 48 Week Treatment in Period A M19-044 (Overall Population)

Event	PBO N=202	UPA 15 mg QD N=410
Adjudicated MACE	0	0
Adjudicated VTE	0	0
Malignancy	2 (1.0%)	1 (0.2%)
Malignancy excluding NMSC	2 (1.0%)	1 (0.2%)
Death	1 (0.5%)	0

Ref: SCS Table 7, ISS Table 2.4_1.1.1, SCS Table 13, ISS Table 2.4_1.2.1

[17] Cook K, Elbuluk NM, Adiri R, Lejeune A, Edwards T, Gianfrancesco MA, et al. Risk of Safety Events in Vitiligo Patients: A Retrospective Real-World Data Study in the US. J Dermatol. 2026;53(5):758–73.
[18] King B, Eleftheriadou V, Bristow CC, Conrad DM, Elbuluk N, Wolkerstorfer A, et al. 63465 A Comparison of the Risk of Major Cardiovascular Events, Venous Thromboembolism, Serious Infections, and Malignancies Among Patients With Vitiligo in the United States Using Real-World Data. J Am Acad Dermatol. 2025;93(3):AB8.

Table 37. MACE, VTEs and Malignancy TEAEs observed in Oral Surveillance in the Ritlecitinib and Upadacitinib AA Development Programs, and in All Treated Long-Term Safety Analysis Set of Upadacitinib in NSV (Any UPA 15 mg, Overall) as Compared to Ritlecitinib in AA Development Program (including Ph2b NSV Study B7981019)

Event	AA		AA		AA		AA		NSV	
	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		Any UPA 15 mg QD N=582 PY=653.3 Data cutoff 05 January 2026	
	n	IR	N	IR	n	IR	n	IR	n	IR
MACE	3	0.15	0	0	1	0.1	1	0.06	1*	0.2
VTE	1	0.06	1	0.1	0	0	1	0.06	0	0
Malignancy (excluding NMSC)	7	0.37	1	0.1	1	0.1	2	0.1	1**	0.2
NMSC	5	0.26	0	0	2	0.3	2	0.1	0	0

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

Upadacitinib Safety Update Report, data cutoff 5 January 2026, Table 2.4_2.2.2.1

The data presented is not a direct product comparison

*The TEAE of adjudicated MACE was a subarachnoid hemorrhage in a subject with a history of recurrent migraines. A saccular aneurysm identified at cerebral CT angiography was found as the likely source for the subarachnoid hemorrhage.

**The malignant female genital neoplasm observed in a subject treated with upadacitinib 15 mg, had an event latency of 46 days. Given the long latency required for induction of solid tumors, a causal association with upadacitinib is implausible in this case.

The MAH provided a discussion on the role of the JAK isoforms as follows:

Upadacitinib is a selective JAK1 inhibitor. It preferentially inhibits signaling 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 (XELJANZ: 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,[19] 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."[20]

[19] 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).
[20] Kragstrup, T. W. *et al.* Waiting for JAK inhibitor safety data. *RMD Open* **8**, e002236 (2022).

Other safety topics of interest

Hypoglycemia

PBO-controlled 48-week Safety Analysis Set

Overall, 1 adult in the upadacitinib 15 mg group with a history of diabetes with concomitant use of long-term insulin, reported a TEAE of hypoglycemia. The subject had esophagogastroduodenoscopy and colonoscopy prior to the event of hypoglycemia. Study treatment was interrupted due to colon prep and then hospitalization. The hypoglycemia event was nonserious, moderate in severity, and resolved on the same day. The investigator assessed the event as having no reasonable possibility of being related to study treatment.

All Treated Long-term Safety Analysis Set

Overall, no TEAE of hypoglycemia was reported aside from the 1 event mentioned above from the PBO-controlled 48-week Safety Analysis Set.

All infections

PBO-controlled 48-week Safety Analysis Set

Overall, the percentage of subjects with TEAEs within the infections and infestations SOC was higher in the upadacitinib group (48.0%) compared to the placebo group (32.7%), as were subjects with TEAEs within the infections and infestations SOC considered by the investigator as having a reasonable possibility of being related to study treatment (17.8% for upadacitinib and 11.4% for placebo. Few subjects (≤3 subjects) reported TEAEs within the infections and infestations SOC which were serious, severe, and led to discontinuation of study treatment.

In the adolescent subgroup, similar to the overall study population, the percentage of subjects with TEAEs within the infections and infestations SOC was higher in the upadacitinib group (48.6%) compared to the placebo group (31.3%), as were subjects with TEAEs within the infections and infestations SOC considered by the investigator as having a reasonable possibility of being related to study treatment (29.7% for upadacitinib and 6.3% for placebo). No infection was serious, severe, or led to discontinuation of study treatment.

All Treated Long-term Safety Analysis Set

Overall, the EAER of TEAEs within the infections and infestations SOC was 84.9 E/100 PY in the any upadacitinib 15 mg cohort. The most frequent TEAEs by PT within the infections and infestations SOC (≥5 E/100 PY) were nasopharyngitis and upper respiratory tract infection. The EAERs of TEAEs within the infections and infestations SOC considered by the investigator as having a reasonable possibility of being related to study treatment was 28.3 E/100 PY. The EAERs of TEAEs within the infections and infestations SOC that were serious (1.0 E/100 PY), severe (1.2 E/100 PY), and led to discontinuation of study treatment (0.4 E/100 PY) were infrequent.

In the adolescent subgroup, the EAER of TEAEs within the infections and infestations SOC was 125.3 E/100 PY in the any upadacitinib 15 mg cohort. The most frequent TEAEs by PT within the infections and infestations SOC (≥5 E/100 PY) were nasopharyngitis, upper respiratory tract infection, and ear infection. The EAERs of TEAEs within the infections and infestations SOC considered by the investigator as having a reasonable possibility of being related to study treatment was 77.1 E/100 PY. No infections were serious, severe, or led to discontinuation of study treatment.

Laboratory findings

Haemoglobin

PBO-controlled 48-week Safety Analysis Set

Overall, mean changes from Baseline at Week 48 for haemoglobin were minimal and within the normal laboratory range at Period A visits for the upadacitinib and placebo groups. One subject each in the upadacitinib (0.2%) and placebo (0.5%) groups experienced a Grade 3 laboratory value decrease in haemoglobin. In the adolescent group, no subjects experienced a Grade 3 laboratory value decrease in haemoglobin.

All Treated Long-term Safety Analysis Set

Overall, no subjects experienced a Grade 3 laboratory value decrease in haemoglobin aside from the 1 adult subject mentioned above for the PBO-controlled 48-week Safety Analysis Set.

Neutrophils

PBO-controlled 48-week Safety Analysis Set

Overall, mean changes from Baseline at Week 48 for neutrophils were minimal and within the normal laboratory range at Period A visits for the upadacitinib 15 mg and placebo groups. Four subjects (1.0%) had Grade 3 laboratory value decreases in neutrophil count in the upadacitinib group compared to 1 subject (0.5%) in the placebo group. No Grade 4 laboratory value decreases in neutrophil count were reported in any treatment group. In the adolescent subgroup, no subjects experienced a Grade ≥3 laboratory value decrease in neutrophil count.

Among the 4 subjects with Grade 3 laboratory value decreases in neutrophil count in the upadacitinib group, 2 are described above summarizing AESIs of neutropenia. The remaining 2 subjects are summarized as follows: One report of Grade 3 neutrophil count decrease was in an adult subject who experienced a decreased neutrophil count on Day 173. The neutrophil count decrease resolved at a subsequent test. Upadacitinib treatment continued. Prior to the neutrophil count decrease, the subject experienced nonserious influenza on Day 164. The second report of Grade 3 neutrophil count decrease was in an adult subject who experienced a decreased neutrophil count on Day 337. Prior to the neutrophil count decrease, the subject experienced a nonserious upper respiratory tract infection on Day 330.

All Treated Long-term Safety Analysis Set

Overall, no subjects experienced a Grade ≥3 laboratory value decrease in neutrophil count aside from the 4 adult subjects with Grade 3 decreases mentioned above for the PBO-controlled 48-week Safety Analysis Set.

Lymphocytes

PBO-controlled 48-week Safety Analysis Set

Overall, mean changes from Baseline at Week 48 for lymphocytes were minimal and within the normal laboratory range at Period A visits for the upadacitinib 15 mg and placebo groups. Three subjects (0.7%) had Grade 3 laboratory value decreases in lymphocyte count in the upadacitinib group compared to none in the placebo group. No Grade 4 laboratory value decreases in lymphocyte count were reported in any treatment group. In the adolescent subgroup, no subjects experienced a Grade ≥3 laboratory value decrease in lymphocyte count.

Among the 3 subjects with Grade 3 laboratory value decreases in lymphocyte count in the upadacitinib group, 1 is described above summarizing AESIs of lymphopenia. The remaining 2 subjects are

summarized as follows: One report of Grade 3 lymphocyte count decrease was in an adult subject with history of hypercholesterolemia who experienced a decreased lymphocyte count on Day 254. The lymphocyte count decrease resolved at a subsequent test. The second report of Grade 3 lymphocyte count decrease was in an adult subject with history of chromosome deletion and low lymphocyte levels prior to start of treatment who experienced a decreased lymphocyte count on Day 149. Lymphocyte levels improving at a subsequent visit and returned to normal on Day 254. The subject experienced a concurrent serious parainfluenza virus infection at the time of the Grade 3 lymphocyte count decrease.

All Treated Long-term Safety Analysis Set

Overall, no subjects experienced a Grade ≥3 laboratory value decrease in lymphocyte count aside from the 3 adult subjects with Grade 3 decreases mentioned above for PBO-controlled 48-week Safety Analysis Set.

Platelets

PBO-controlled 48-week Safety Analysis Set

Overall, mean increases from Baseline at Week 48 for platelets were observed in both the upadacitinib and placebo groups. Increases were higher in the upadacitinib group but were not clinically meaningful. No subjects experienced a Grade ≥3 laboratory value decrease in platelet count.

All Treated Long-term Safety Analysis Set

No subjects experienced a Grade ≥3 laboratory value decrease in platelet count.

Liver function tests

PBO-controlled 48-week Safety Analysis Set

Overall, 1 subject each had Grade 3 potentially clinically important (PCI) laboratory abnormalities of increased AST or TBL values in the upadacitinib group, both in adult subjects. No Grade 4 PCI laboratory abnormalities of increased ALT, AST, or TBL values were reported. In the adolescent subgroup, no subjects experienced Grade 3 or Grade 4 PCI laboratory abnormalities. No subjects met DILI criteria.

An adult subject in the upadacitinib group with obesity (BMI = 30.6) experienced AST > 10 × ULN and ALT > 3 × ULN on Day 86 approximately a week after treatment with multiple medicines including paracetamol, ibuprofen, and acetylsalicylic acid in the context of an acute viral infection. The laboratory abnormalities were reported as nonserious TEAEs and were considered by the investigator as having a no reasonable possibility of being related to study treatment. The AST and ALT elevations resolved by Day 126 without study treatment interruption. There was no recurrence with continued treatment. The subject was later diagnosed with hepatic steatosis on Day 429, considered by the investigator as having no reasonable possibility of being related to study treatment.

An adult subject in the upadacitinib group experienced a Grade 3 TBL elevation (> 3.0 to 10.0 × ULN). This subject had elevated bilirubin levels at Baseline (44.5 µmol/L) and had history of Gilbert's syndrome. Levels remained elevated (> 2 × ULN) through the data cutoff. ALT, AST, and ALP levels were normal throughout the study.

All Treated Long-term Safety Analysis Set

Overall, 1 subject each had Grade 3 PCI laboratory abnormalities of increased ALT, AST, and TBL values in the all upadacitinib 15 mg cohort, all in adult subjects. The increased ALT is described below, while the increased AST and TBL are summarized above for the PBO-controlled 48-week Safety Analysis Set. No Grade 4 PCI laboratory abnormalities of increased ALT, AST, or TBL values were reported. One adult subject had an AST value > 10 × ULN; this subject is summarized above for the PBO-controlled 48-week

Safety Analysis Set. In the adolescent subgroup, no subjects experienced Grade 3 or Grade 4 PCI laboratory abnormalities. No subjects met DILI criteria.

An adult subject with obesity (BMI = 31.8) and history of hepatitis B core antibody and surface antibody positive experienced ALT > 5 × ULN and AST > 3 × ULN on Day 365. Prior to the Grade 3 ALT elevation, the subject experienced ALT > 3 × ULN on 2 occasions. Study treatment was interrupted and ALT and AST levels improved but remained elevated (> 3 × ULN) on Day 390 which was the final measurement prior to the data cutoff. ALP and TBL levels were normal throughout the study.

Lipids

PBO-controlled 48-week Safety Analysis Set

Overall, mean changes from Baseline in cholesterol, triglycerides, HDL-C, and LDL-C in the overall study population were generally small with upadacitinib treatment through Week 48. In the adolescent subgroup, no subject experienced Grade 3 or Grade 4 lipid abnormalities.

All Treated Long-term Safety Analysis Set

Overall, Grade 3 laboratory increases in cholesterol and triglycerides were reported in 4 subjects (0.9%) and 8 subjects (1.8%), respectively, in the any upadacitinib 15 mg cohort, all in adult subjects. No Grade 4 laboratory increases in cholesterol or triglycerides were reported. In the adolescent subgroup, no subject experienced Grade 3 or Grade 4 lipid abnormalities.

Of the 4 subjects with Grade 3 laboratory increases in cholesterol, 1 subject also had a Grade 3 laboratory increase in triglycerides and is included in the summary of triglycerides below. The 3 remaining cases of Grade 3 laboratory increases in cholesterol involved an adult with no relevant past medical history, an adult with history of hypercholesterolemia and obesity, and an adult with history of dyslipidaemia and diabetes mellitus type 2.

The Grade 3 laboratory increases in triglycerides occurred in individuals with obesity (BMI over 30), overweight status, and/or metabolic conditions like diabetes and hypercholesterolemia. Three subjects had pre-existing hypercholesterolemia, and 1 of these 3 subjects also had Grade 3 laboratory increases in cholesterol. The remaining 5 subjects did not have relevant medical histories but had BMI values indicating overweight or obesity.

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

Vital signs

In M19-044 Study 1 and Study 2, mean changes from Baseline in vital signs over time were not considered clinically meaningful.

PBO-controlled 48-week Safety Analysis Set

Overall, few subjects (≤2.0% in each treatment group) had PCI vital sign abnormalities of low systolic blood pressure, high systolic blood pressure, low diastolic blood pressure, low pulse rate, and high pulse rate. The percentages of subjects who experienced a PCI vital sign abnormality for high diastolic blood pressure (value ≥100 mmHg and increase ≥10 mmHg from Baseline) was 5.7% in the upadacitinib group and 1.5% in the placebo group. In the adolescent subgroup, results were consistent with the overall study population. Three adolescent subjects (8.1%) experienced a PCI vital sign abnormality for high diastolic blood pressure compared to no subjects in the placebo group. In the overall study population, most subjects with PCI vital sign abnormality for high systolic blood pressure or high diastolic blood pressure had elevated pre-treatment blood pressure measurements. There was no trend for continuous

elevation of blood pressure or heart rate/pulse rate during study treatment, and the measurements reaching PCI values were generally transient.

One elderly subject with a medical history of arterial hypertension discontinued upadacitinib treatment due to TEAE of hypertension (reported term worsening of arterial hypertension). The event was considered ongoing as of the data cutoff date. The investigator assessed the event as having no reasonable possibility of being related to study treatment.

All Treated Long-term Safety Analysis Set

Overall, no TEAE of hypertension led to discontinuation of study treatment aside from the 1 event mentioned above for the PBO-controlled 48-week Safety Analysis Set.

Physical findings

Adults

In the PBO-controlled 48-week Safety Analysis Set, at Week 48, the mean weight increase from Baseline in adult subjects was 0.79 kg in the upadacitinib group and 1.15 kg in the placebo group. The percentages of adult subjects who experienced weight increase (> 7% from Baseline) were 14.9% in the upadacitinib group and 12.7% in the placebo group. The percentages of adult subjects who experienced weight decrease (> 7% from Baseline) were similar in the upadacitinib (4.9%) and placebo (5.5%) groups.

Growth and development assessments for adolescents

Weight

At Week 48, the mean weight increases from Baseline in adolescents were 3.86 kg in the upadacitinib group and 3.50 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 in subjects treated with upadacitinib compared to those treated with placebo.

PCI weight decrease (> 7% from Baseline) was recorded in 1 subject in each treatment group (2.7% of adolescents in the upadacitinib group and 6.3% in the placebo group). Both subjects showed continuous and gradual weight increase during the study treatment, with the exception of 1 lower weight recorded at a single visit. For both subjects, steady increase in weight continued at subsequent visits, suggesting that the sudden weight decrease at the single visit was likely a result of a documentation error. No associated AEs were reported for either of the subjects.

Height and BMI

In the PBO-controlled 48-week Safety Analysis Set, the mean age of adolescents across Study 1 and Study 2 was 15.1 years with a range of 12 to 18 years at the Baseline Visit. Peak height velocity occurs at a mean age of 13.5 years in boys and 11.5 years in girls (Abbassi 1998). At Week 48, mean changes from Baseline in height were generally similar across treatment groups, with too few subjects to draw meaningful conclusions: in female adolescents, mean changes from Baseline in height were 1.22 cm in the upadacitinib group and 3.00 cm in the placebo group; and in male adolescents, 3.41 cm in the upadacitinib group and 5.88 cm in the placebo group. Changes in height z-scores were similar between the upadacitinib and placebo groups. 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, complete data are limited to approximately 1 year of exposure at the time of the data cutoff to measure growth in height. Height will continue to be monitored in adolescents continuing in the NSV clinical programme and results will be reported in future CSRs.

Tanner Staging

During the placebo-controlled period all subjects achieved the appropriate Tanner stage at the applicable visits.

Safety in special populations

Race, age, geographic region, sex

PBO-controlled 48-week Safety Analysis Set

The majority of subjects were white. The sample size for black subjects was too small to draw any conclusions (N = 23 in the PBO-controlled 48-week Safety Analysis Set). In the adolescent subgroup, most patients were white and the sample sizes for other races were too small to draw any conclusions. Across treatment groups, generally similar trends were observed for the percentages of subjects with TEAEs, TEAEs with a reasonable possibility of being related to study treatment, severe TEAEs, and treatment-emergent SAEs across race, age, geographic region, and sex. In female subjects, severe TEAEs and SAEs were more frequently reported in the upadacitinib group than the placebo group. This trend was not observed in male subjects; however, there were too few of events to draw any meaningful conclusions. In subjects ≥65 years of age, the percentages of subjects with TEAEs and TEAEs with a reasonable possibility of being related to study treatment were lower than in subjects <65 years of age. The percentages of subjects with severe and serious TEAEs was higher in subjects ≥65 years of age than in those <65 years of age; however, percentages in subjects ≥65 years of age were lower in the upadacitinib group than the placebo group. No SAEs and TEAEs leading to discontinuation of study treatment were reported in adolescents (<18 years of age) receiving upadacitinib treatment.

Generally similar trends were observed for the percentages of subjects with treatment-emergent AESIs across race, age, geographic region and sex. No AESIs were reported in black subjects. AE 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, in both the upadacitinib and placebo groups, hepatic disorders were more frequently reported in Asian subjects than white subjects and in males than in females; similarly, hepatic disorders were more frequently reported in the Asian geographic region than other geographic regions in both the upadacitinib and placebo groups. The percentages of subjects ≥65 years of age with AESIs was low, and the only AESIs in this population were herpes zoster (1 subject in each treatment group), anaemia (1 subject in the upadacitinib group), malignancy excluding NMSC (1 subject in each treatment group), and bone fracture (1 subject in the upadacitinib group). Due to low numbers, rates cannot be directly compared but are generally consistent with potential effect of age on malignancy and fracture risk. Few AESIs were reported in adolescents to draw any meaningful conclusions, and only in the herpes zoster, neutropenia, and bone fractures categories.

All Treated Long-term Safety Analysis Set

The EAERs of TEAEs, TEAEs with a reasonable possibility of being related to study treatment, severe TEAEs, and treatment-emergent SAEs were generally consistent across race, age, geographic region, and sex in the any upadacitinib 15 mg cohort. No SAEs and TEAEs leading to discontinuation of study

treatment were reported in adolescents receiving upadacitinib treatment. The rate of severe TEAEs was higher in adults than adolescents. The rate of SAEs was higher in females than males.

The EAERs of treatment-emergent AESIs were generally consistent across race, age, geographic region, and sex among subjects receiving any upadacitinib. The rate of hepatic disorders was higher in males than females. The rate of hepatic disorders was higher in the Asian geographic region than other geographic regions. Few AESIs were reported in adolescents to draw any meaningful conclusions, and only in the herpes zoster, neutropenia, and bone fractures categories.

Baseline renal function

Most subjects had normal renal function or mild renal impairment; there were few subjects with moderate renal impairment. 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 48-week Safety Analysis Set, generally similar trends were observed for the percentages of subjects with TEAEs, TEAEs with a reasonable possibility of being related to study treatment, severe TEAEs, treatment-emergent SAEs, and treatment-emergent AESIs for subjects with normal renal function and subjects with mild renal impairment.

Use in pregnancy and lactation

There were no pregnancies that occurred in the NSV clinical development programme through 24 September 2025.

A total of 168 maternal pregnancies have been reported in upadacitinib clinical studies. Of note, a subject may have been included in more than 1 category as described below:

- 5 pregnancies (5 subjects) remain blinded to treatment allocation
- 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; on ABBV-105 in an SLE study, 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 (41), RA (39), UC (16), CD (9), PsA (7), AA (6), HS (2), AS (1), and SLE (1).

AbbVie's The global safety database was searched for all clinical trial reports received through 15 August 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 2025 are summarized in this section as supportive information for upadacitinib in pediatric NSV patients. These studies enrolled adolescents 12 to <18 years of age and evaluated both the 15 and 30 mg QD tablet formulations of upadacitinib. Results of the global Phase 3 AD studies include the data from 541 adolescents, of whom 264 and 265 were subjects who received at least 1 dose of upadacitinib 15 mg and 30 mg, respectively. Overall, subjects had a median duration of 1698.5 days and 1707.0 days exposure to upadacitinib 15 mg

and 30 mg, respectively. Total exposure to upadacitinib 15 mg and 30 mg was 926.1 PY and 986.3 PY, respectively.

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

Skin papilloma was identified as an ADR in the AD adolescent population.

Table 38. 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 = 926.1)	UPA 30 mg QD (N = 265) (PY = 986.3)
EAER (events [E/100 PY])		
TEAE	1689 (182.4)	1879 (190.5)
TEAE with reasonable possibility of being drug-related[a]	504 (54.4)	547 (55.5)
Severe TEAE	108 (11.7)	100 (10.1)
Treatment-emergent SAE	48 (5.2)	45 (4.6)
TEAE leading to discontinuation of study treatment	25 (2.7)	31 (3.1)
TEAE leading to death	0	0
EAIR (n/PY)		
All deaths	0/926.1	0/986.3

a. As assessed by investigator.

Note: Data cutoff = 15 August 2025.

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.

Serious infections occurring more than once were eczema infected, impetigo, and appendicitis. 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. 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 CNS.

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

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 creatine phosphokinase (CPK) elevation. 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 treatment by the investigator.

Table 39. Overview of Treatment-Emergent AESIs per 100 PY (Long-Term Upadacitinib Phase 3 AD Adolescent Analysis Set).

	UPA 15 mg QD (N = 264) (PY = 926.1)	UPA 30 mg QD (N = 265) (PY = 986.3)
EAER (events [E/100 PY])		
Serious infection	17 (1.8)	14 (1.4)
Opportunistic infection (excluding TB and herpes zoster)	13 (1.4)	6 (0.6)
Herpes zoster	17 (1.8)	26 (2.6)
Hepatic disorder	40 (4.3)	27 (2.7)
Anemia	17 (1.8)	7 (0.7)
Neutropenia	16 (1.7)	26 (2.6)
Lymphopenia	3 (0.3)	0
CPK elevation	53 (5.7)	76 (7.7)
Bone fracture	10 (1.1)	18 (1.8)
Serious hypersensitivity reaction	0	5 (0.5)
EAIR (n/PY [n/100 PY])		
Malignancy	1/925.9 (0.1)	0/986.3
Malignancy excluding NMSC	1/925.9 (0.1)	0/986.3

Note: Data cutoff = 15 August 2025.
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 except skin papilloma is an ADR for adolescent AD. Accumulated safety data available from the adolescent AD programme support the regulatory submission for the NSV indication.

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

No AEs leading to discontinuation of study treatment were reported in adolescents receiving upadacitinib treatment.

PBO-controlled 48-week Safety Analysis Set

Overall, the percentage of subjects with TEAEs leading to discontinuation of study treatment was higher in the placebo group than the upadacitinib group. By PT, all TEAEs leading to discontinuation of study treatment were reported in 1 subject each with the exception of hypercholesterolemia (upadacitinib

group: 3 subjects; placebo group: no subjects) and rash (upadacitinib group: 2 subjects; placebo group: no subjects).

Table 40. 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 for Adults (Placebo-Controlled 48-Week Safety Analysis Set).

MedDRA 27.1 System Organ Class Preferred Term	Placebo (N=186) n (%) [SSA%]	UPA 15 mg QD (N=373) n (%) [SSA%]
Adult		
Investigations	3 (1.6) [1.6]	0
Hepatic enzyme increased	1 (0.5) [0.5]	0
Weight decreased	1 (0.5) [0.5]	0
Weight increased	1 (0.5) [0.5]	0
Metabolism and nutrition disorders	0	3 (0.8) [0.8]
Hypercholesterolaemia	0	3 (0.8) [0.8]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.1) [1.1]	0
Colon cancer	1 (0.5) [0.5]	0
Intraductal proliferative breast lesion	1 (0.5) [0.5]	0
Metastases to liver	1 (0.5) [0.5]	0
Nervous system disorders	1 (0.5) [0.5]	1 (0.3) [0.3]
Brain fog	1 (0.5) [0.5]	0
Dizziness	0	1 (0.3) [0.3]
Skin and subcutaneous tissue disorders	0	3 (0.8) [0.8]
Dermatitis acneiform	0	1 (0.3) [0.3]
Skin and subcutaneous tissue disorders (cont.)		
Rash	0	2 (0.5) [0.5]
Vascular disorders	0	1 (0.3) [0.3]
Hypertension	0	1 (0.3) [0.3]

Note: Treatment-Emergent Adverse Events for Week 48 are defined as events occurring after the first dose of study drug and within 30 days after the last administration of study drug in either Period A, or before the first dose of study drug in the next analysis period or study, or database cutoff, whichever occurs first.
SSA = Study-size adjusted.
TEAEs on and after the use of rescue treatment are not included in the summary for Period A.
Subjects are counted once in each row, regardless of the number of events they may have had.

Program Source Code: /SDA/ABT-494/VITILIGO/Integrated_Summaries/ISS/2.4/PCMS_RUN/iss-aesocpt-aa.sas

All Treated Long-term Safety Analysis Set

Overall, the EAER of TEAEs leading to discontinuation of study treatment was 2.9 E/100 PY in the any upadacitinib 15 mg cohort. By PT, all TEAEs leading to discontinuation of study treatment in the any upadacitinib 15 mg cohort were reported in 1 subject each with the exception of hypercholesterolemia (3 events); and dizziness and rash (2 events each).

Table 41. Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug in Exposure-Adjusted Incidence Rate per 100 Patient Years by Primary MedDRA System Organ Class and Preferred Term for Adults (All Treated Long-Term Safety Analysis Set).

MedDRA 27.1 System Organ Class Preferred Term	Placebo/ UPA 15 mg QD w/o NB-UVB (N=139) n/PYs (n/100 PYs)	UPA 15 mg QD/ UPA 15 mg QD w/o NB-UVB (N=285) n/PYs (n/100 PYs)	Any UPA 15 mg QD w/o NB-UVB (N=489) n/PYs (n/100 PYs)	Any UPA 15 mg (N=530) n/PYs (n/100 PYs)
Adult				
Any adverse event	1/56.7 (1.8)	0/352.6	11/436.7 (2.5)	11/473.2 (2.3)
Gastrointestinal disorders	0/56.8	0/352.6	3/437.6 (0.7)	3/474.1 (0.6)
Abdominal distension	0/56.8	0/352.6	1/437.6 (0.2)	1/474.1 (0.2)
Nausea	0/56.8	0/352.6	1/437.6 (0.2)	1/474.1 (0.2)
Upper gastrointestinal haemorrhage	0/56.8	0/352.6	1/437.6 (0.2)	1/474.1 (0.2)
General disorders and administration site conditions	1/56.7 (1.8)	0/352.6	1/437.5 (0.2)	1/474.0 (0.2)
Fatigue	1/56.7 (1.8)	0/352.6	1/437.5 (0.2)	1/474.0 (0.2)
Infections and infestations	0/56.8	0/352.6	2/437.6 (0.5)	2/474.1 (0.4)
COVID-19	0/56.8	0/352.6	1/437.6 (0.2)	1/474.1 (0.2)
Folliculitis	0/56.8	0/352.6	1/437.6 (0.2)	1/474.1 (0.2)
Metabolism and nutrition disorders	0/56.8	0/352.6	3/437.1 (0.7)	3/473.6 (0.6)
Metabolism and nutrition disorders (Cont.)				
Hypercholesterolaemia	0/56.8	0/352.6	3/437.1 (0.7)	3/473.6 (0.6)
Nervous system disorders	1/56.7 (1.8)	0/352.6	2/437.4 (0.5)	2/473.9 (0.4)
Dizziness	1/56.7 (1.8)	0/352.6	2/437.4 (0.5)	2/473.9 (0.4)
Skin and subcutaneous tissue disorders	0/56.8	0/352.6	3/437.6 (0.7)	3/474.1 (0.6)
Dermatitis acneiform	0/56.8	0/352.6	1/437.6 (0.2)	1/474.1 (0.2)
Rash	0/56.8	0/352.6	2/437.6 (0.5)	2/474.1 (0.4)
Vascular disorders	0/56.8	0/352.6	1/437.4 (0.2)	1/473.9 (0.2)
Hypertension	0/56.8	0/352.6	1/437.4 (0.2)	1/473.9 (0.2)

Note: Treatment-Emergent Adverse Events for ISS_LT are defined as occurs within 30 days of the last dose of UPA treatment, or database cutoff, whichever occurs first will be attributed to the last UPA treatment received. TEAEs that occur for placebo subjects will be attributed to placebo up until the minimum of before the first dose of UPA treatment received, or last dose of placebo + 30 days, or database cutoff, whichever occurs first.
n/100 PYs = Number of subjects per 100 patient-years.

Program Source Code: /SDA/ABT-494/VITILIGO/Integrated_Summaries/ISS/2.4/PCMS_RUN/iss-socptpylt-eair-a.sas

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, including 164 postmarketing reports referring to upadacitinib as a treatment for vitiligo.

Among the postmarketing reports across indications, the most common AEs reported included pain (3.5%), arthralgia (3.0%), and drug ineffective (2.9%). The most frequently reported 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 of SAEs reported were similar to what has been observed in the clinical studies for upadacitinib.

Among the 164 postmarketing reports of patients receiving upadacitinib for vitiligo, the most common nonserious PTs reported were off-label use (55.5%), product use in unapproved indication (5.0%), therapeutic product effect incomplete (5.0%), vitiligo (2.8%), and acne (2.3%). SAEs consisted of 5% of all AEs reported in this population.

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 received through 31 July 2025, as well as data analyzed in the Postmarketing Safety Update Report (PSUR) through 15 August 2025, did not identify any new safety signals for upadacitinib.

2.5.1. Discussion on clinical safety

The applied for indication concerns treatment of non-segmental vitiligo (NSV) in adult and adolescent patients aged ≥12 years. The proposed recommended dose is 15 mg once daily.

The safety data in support of this variation is based on 2 phase 3 studies, M19-044 Study 1 and Study 2, and the optional exploratory study M19-044 Study 3.

A total of 582 patients, including 52 adolescents, received at least 1 dose of upadacitinib. At the data cut-off date for Period B, mean duration of exposure was 46.2 weeks for the Any UPA 15 mg group (n=582). A total of 339 patients (58.2%) was exposed to for at least 52 weeks.

In adolescent patients, mean duration of exposure was 41.7 weeks for the Any UPA 15 mg group (n=52). A total of 24 patients (46.2%) was exposed for at least 52 weeks.

The size of the overall safety database for the indication of NSV is considered adequate for the assessment of safety.

It is acknowledged that the safety of upadacitinib has been established previously in other indications, including the dermatologic indication of atopic dermatitis (AD). During the 48-week placebo-controlled period, the overall rate of TEAEs and related TEAEs was higher in the UPA treatment groups compared with placebo. Common TEAEs in the adolescent population (reported in ≥10% of patients on UPA in the placebo-controlled 48-week period or ≥10 events per 100 PY during Period B, including Study 3) were nasopharyngitis and acne, upper respiratory tract infection, headache and influenza like illness. Most TEAEs were mild or moderate in severity. Common TEAEs in adolescents were generally consistent with those in the overall population.

The frequency of SAEs in the overall population was higher in the UPA treatment groups compared with placebo. No SAE was reported in more than 1 patient. In the adolescent population, 1 SAE was reported in the UPA group in the placebo-controlled 48-week safety analysis set, a bone fracture due to trauma. No concern is raised. No other SAEs were reported in adolescents.

Treatment discontinuations due to TEAEs were reported at a low frequency.

There are limited data on safety in the elderly, with only 55 patients ≥65 years included in M19-044 Study 1 and Study 2. One elderly subject with a medical history of gastritis and long-term aspirin use reported an SAE of upper GI haemorrhage assessed by the investigator as having no reasonable possibility of being related to study treatment, and one elderly subject with a medical history of arterial hypertension discontinued upadacitinib treatment due to TEAE of hypertension assessed the event as having no reasonable possibility of being related to study treatment.

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 (2.4%) 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.

No pregnancies occurred in the NSV clinical development programme as of the cut-off date 24 September 2025. Upadacitinib is contraindicated in pregnancy. Section 4.6 of the SmPC includes relevant information, including information specifically addressing paediatric patients.

In the **overall population**, no treatment-emergent AESIs of opportunistic infections (excluding TB and herpes zoster), active TB, adjudicated GI perforation, renal dysfunction, NMSC, lymphoma, retinal detachment, serious hypersensitivity reactions, adjudicated MACE, and adjudicated VTE were reported in the clinical studies. The AESIs of serious infections, herpes zoster, hepatic disorder, anaemia, neutropenia and lymphopenia were reported in the UPA 15 mg cohort. Hepatic disorder events concerned increases in transaminases and bilirubin; no events of DILI were reported. No concerns are raised regarding malignancies and bone fracture. 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, hepatic disorder, anaemia or lymphopenia with upadacitinib were reported. No malignancies were reported.

One nonserious cutaneous TEAE of herpes zoster was reported in an adolescent subject receiving upadacitinib.

Neutropenia events were reported in 2 adolescent patients in the 15 mg UPA group during the 48-week placebo-controlled period. The events were of moderate severity and while one lead to treatment interruption the other resolved without interruption of study treatment.

Three events of bone fracture (ankle fracture, hand fracture, and scapula fracture) were reported in adolescent patients receiving 15 mg UPA. All events were 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 UPA 15 mg (n=264) or UPA 30 mg (n=265). Median duration of exposure was 1698.5 days (926.1 PY) with 15 mg and 1707.0 days (986.3 PY) with 30 mg.

The safety data in terms of AESIs for adolescents in the NSV indication is largely consistent with the AD population. However, interpretation of data is hampered by the considerably shorter duration of exposure for NSV patients. Events in the AD population were reported across a wider range of AESIs, including also serious infections, opportunistic infections, hepatic disorder, anaemia, lymphopenia, CPK elevation, serious hypersensitivity reaction and malignancies (i.e., skin papilloma). The difference in the safety profile in terms of AESIs between both adolescent populations may reflect the difference in sample size and/or the duration of exposure. The MAH has submitted updated data on AESIs in the adolescent population in the NSV indication with a more recent data cut-off date (data cutoff 05 January 2026; Table 35).

As compared to the summary of safety data included in the initial submission, 2 additional AESIs were reported in adolescents, one was a bone fracture and another was an event of hepatic disorder. The updated data revealed no new safety concerns, and the rates of treatment-emergent AESIs were generally similar to those reported in the initial submission.

Increases in weight and height have been observed across all treatment groups, with minimal changes in BMI. At the end of the 48-week placebo-controlled period, all subjects achieved the appropriate Tanner stage at the applicable visit. 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, approximately 1 year. The MAH indicates that height will be monitored in adolescents continuing in the NSV clinical programme. Although 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 NSV.

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 NSV indication in view of the low incidence of patients with risk factors in the patient population with NSV.

The CHMP noted that the current extension of indication concerns the new indication of NSV, which is a chronic inflammatory disorder not specifically assessed during the Article 20 procedure.

However, the CHMP considered the conclusions of the Article 20 procedure when assessing the MAH's proposal and in particular:

- 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.

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 indications reviewed in the Article 20 procedure including the population at lower background risk factors. Hence, although NSV patients generally have less risk factors, the CHMP concluded that the outcome of the Article 20 is also applicable to the NSV indication.

Further, the CHMP clarified that the class warning regarding use of suitable treatment alternatives is only applicable to the subset of patients with risk factors and not to the NSV 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 NSV 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 ritlecitinib. 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 NSV 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, based on the MAH's consideration that NSV and AA are dermatological conditions with similar benefit-risk considerations, they submitted comparative safety data (including rates of MACE, VTE, malignancy excluding NMSC, NMSC and death) between upadacitinib for treatment of NSV and severe AA and ritlecitinib from different studies. Further, the MAH provided a discussion on the role of the JAK isoforms on the occurrence of these adverse events.

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. 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 NSV 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 NSV 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.

On the proposed wording of SmPC to amend section 4.4, the CHMP noted that that the proposed addition is not specific to the newly sought NSV indication but also applied to all other approved indications for Rinvoq. The CHMP noted that the proposed wording is 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.

For the NSV indication, the proposed amendment to section 4.4, specifying that *"suitable treatment alternatives do not include other systemic JAK inhibitors*" lacks justification at this time, as no other systemic JAKi has been approved for the NSV indication.

Overall, considering all the data submitted by the MAH during this procedure, the CHMP concluded that the precautionary measures recommended in the Article 20 procedure are applicable for the new NSV 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. The MAH has 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, including the adolescent population, in the indication of non-segmental vitiligo is considered adequate, with support of safety data in adolescent patients in the atopic dermatitis indication.

The safety profile of upadacitinib in the proposed indication of treatment of non-segmental vitiligo 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.

The SmPC (sec. 4.8) was updated to reflect that safety profile of upadacitinib 15 mg observed in patients with vitiligo was generally consistent with the known safety profile in patients with atopic dermatitis. No new safety findings were identified. A higher incidence of hypercholesterolaemia was observed in patients

with vitiligo treated with upadacitinib 15 mg (3.4%) compared to placebo (2.0%). This is considered adequate.

2.5.3. PSUR cycle

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

2.6. Risk management plan

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

The main proposed RMP changes were the following:

- Added information on NSV as proposed indication.
- Updated pregnancy data.
- Added Protocol M19-044 (Study 1, Study 2, and Study 3) as an additional pharmacovigilance activity.
- Clinical Trial Exposure: Updated exposure data.
- Post-Authorization Exposure: Updated exposure data.
- Presentation of Important Identified Risks and Important Potential Risks: Revised presentation of safety concerns and updated data for approved indications.
- Annex 4: Included the latest versions of adverse drug reaction follow-up forms.
- Renamed Missing information "Long-term safety in adolescents with AD" to "Long-term safety in adolescents"

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 42. 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 43. Summary Table of 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 Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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; 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), herpes zoster, 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.	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
	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 ~~with AD~~		

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P21-825 Drug Utilization Study Evaluating Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe/ Planned	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 • Submitted 19 September 2025 • Q3 2026

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, 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-JAK inhibitor 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 ~~with AD~~	• 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 P24-343 Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe /Planned	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 patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users	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
	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/Planned	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; c) 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 study report • Targeted submission of final study report to EMA	• 30 August 2028 • 30 November 2028

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M15-554/ 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 study report • Targeted submission of final study report to EMA	• 31 December 2024 • 30 April 2025
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 study report • Targeted submission of final study report to EMA	• 30 September 2025 • 31 December 2025

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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 study report • Targeted submission of final study report to EMA	• Q2 2026 • Q3 2026
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 study report • Targeted submission of final study report to EMA	• Q2 2026 • 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 ~~with AD~~	• Targeted submission of final study report to EMA	• 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 ~~with AD~~	• Interim report • Targeted submission of final study report to EMA	• 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 ~~with AD~~	• Targeted submission of final study report to EMA	• 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 study report	• 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 study report • Targeted submission of final study report to EMA	• Q1 2028 • 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 CSR • Target submission of final CSR to EMA	• Q1 2026 • Q2 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study 1 and Study 2 of Protocol M19-044/ Ongoing	Period B: To evaluate the efficacy, safety, and tolerability of upadacitinib for the treatment of adults and adolescents with NSV who are eligible for systemic therapy and completed Period A.	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 2028
Exploratory Study 3 of Protocol M19-044/ Ongoing	To evaluate the efficacy, safety, and tolerability of upadacitinib 15 mg in combination with whole-body NB-UVB phototherapy vs. upadacitinib 15 mg monotherapy for the treatment of adults with NSV who have completed treatment in Period A of M19-044 Study 1 or Study 2 and failed to achieve T-VASI 90.	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	• Q4 2028

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated to include the treatment of non-segmental vitiligo in adults and adolescents 12 years and older who are candidates for systemic therapy.

The Package Leaflet (PL) is updated accordingly.

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

2.7.1. 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 by the CHMP as there have not been revisions that significantly affect the overall readability and design of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This application concerns an extension of indication to include the treatment of non-segmental vitiligo in adult and adolescents 12 years and older for Rinvoq. The new proposed indication is: *'Treatment of non-segmental vitiligo in adults and adolescents 12 years and older who are candidates for systemic therapy.'* The proposed posology is 15 mg once daily for patients weighing at least 30 kg.

Vitiligo is a chronic autoimmune disorder of the skin characterised by depigmented skin lesions due to autoimmune-induced loss of melanocytes in the epidermis. Non-segmental vitiligo (NSV) is the most common form, and develops at all ages, but onset usually occurs between the ages of 10 years and 30 years.[7,9] Vitiligo has a high psychological impact as it significantly impairs the patient's QoL and causes a substantial burden on their daily life.[21,22,23]

Although advances have been made in understanding the pathogenesis of vitiligo, the complete mechanisms leading to vitiligo are not fully understood. Depigmentation is driven by autoreactive CD8+ T-cells that target and destroy melanocytes, the cells responsible for skin pigmentation. This immune response is amplified by increased levels of proinflammatory cytokines, which require JAK/STAT pathway activation for downstream biological activity. Rinvoq (upadacitinib) is a selective and reversible Janus kinase (JAK) inhibitor, that may interrupt the JAK-dependent inflammatory pathways that contribute to the immunopathogenesis of NSV.

3.1.2. Available therapies and unmet medical need

There are no known cures or preventive options for NSV in paediatric or adult patients. The currently used topical and systemic treatment options are mostly used off label for NSV. Evidence for drug

[21] Ezzedine et al. (2021). *Psychosocial effects of vitiligo: A systematic literature review.* American Journal of Clinical Dermatology, 22(6), 757–774.
[22] Morrison, B., Burden-Teh, E., Batchelor, J. M., Mead, E., Grindlay, D., & Ratib, S. (2017). *Quality of life in people with vitiligo: A systematic review and meta-analysis.* British Journal of Dermatology, 177(6).
[23] Grimes, P. E., & Miller, M. M. (2018). *Vitiligo: Patient stories, self-esteem, and the psychological burden of disease.* International Journal of Women's Dermatology, 4(1), 32–37.

therapies used off-label is limited. The current management of vitiligo is empirical and based on consensus guidelines.[11,24,25,26] In general, first-line treatments consist of topical steroids and calcineurin inhibitors, which are most useful for treating limited disease (typically ≤ 10% BSA is treated). Opzelura (ruxolitinib, a topical JAK inhibitor) is the first FDA and EMA approved treatment for the repigmentation of NSV on up to 10% BSA in adults and adolescents 12 years of age and older, and is also an option. Second-line treatments consist of phototherapy (NB-UVB and Psoralen + Ultraviolet A (PUVA)) and systemic steroid treatment, and third-line treatments consist of surgical grafting techniques and depigmenting treatments of neighbouring healthy skin.

Responses to current treatment options vary and have limited durability. Treatments can also be time-intensive and burdensome to the patient and may produce cosmetically unacceptable results. Therefore, an unmet need persists for an effective and well tolerated systemic therapeutic option that halts progression of NSV, while providing and maintaining repigmentation, and alleviating the high psychosocial burden associated with NSV.

3.1.3. Main clinical studies

The application is supported by interim results from 2 replicate, pivotal, Phase 3 studies (M19-044 study 1 and Study 2). The studies are randomized, double-blind, placebo-controlled, multi-centre studies of upadacitinib evaluating the efficacy and safety of upadacitinib 15 mg QD versus placebo for the treatment of NSV.

Key eligibility criteria for the pivotal studies were age ≥12 years, body weight ≥ 30 kg, a clinical diagnosis of NSV, and ≥ 0.5 Facial Vitiligo Area Scoring Index (F-VASI) and 5 ≤ Total Vitiligo Area Scoring Index (T-VASI) < 50 at screening and baseline visits. Overall, the inclusion/exclusion criteria are representative of the targeted population.

A total of 614 patients (including 53 adolescents) with a clinical diagnosis of NSV were enrolled in the pivotal studies. Eligible adult or adolescent subjects were randomized in a 2:1 ratio to 1 of 2 treatment groups: upadacitinib 15 mg QD (n = 411), or matching placebo (n = 203).

The co-primary endpoints of Study 1 and Study 2 were achievement of T-VASI 50 (≥ 50% reduction in T-VASI from Baseline) and F-VASI 75 (≥ 75% reduction in F-VASI from Baseline) at Week 48.

3.2. Favourable effects

The co-primary endpoints, achievement of T-VASI 50 and F-VASI 75 at Week 48, was met in the upadacitinib 15 mg group compared to the placebo group in both pivotal studies. In Study 1, the proportion of subjects achieving a T-VASI 50 score in the upadacitinib 15 mg group was 19.4 % versus 5.9% in the placebo group, with an adjusted difference of 13.1% (95% CI 6.3 to 19.8) using the CMH test adjusting for the actual values of age at screening, baseline disease severity and baseline status of actively progressing vitiligo. The corresponding results for T-VASI 50 in Study 2 were 21.5% versus 5.9% for the upadacitinib 15 mg group versus placebo, with an adjusted difference of 14.7% (95% CI 7.5 to 21.9). In Study 1, the response rates for F-VASI 75 in the upadacitinib 15 mg group was 25.2% versus 5.9% in the placebo group, resulting in an adjusted difference of 18.7% (95% CI 11.5 to 25.9) using the

[24] Taïeb, et al. (2013). *Guidelines for the management of vitiligo: The European Dermatology Forum consensus.* British Journal of Dermatology, 168(1), 5–19.
[25] van Geel, et al.. (2023). *Worldwide expert recommendations for the diagnosis and management of vitiligo: Position statement from the International Vitiligo Task Force. Part 1: Towards a new management algorithm.* Journal of the European Academy of Dermatology and Venereology, 37(11), 2173–2184.
[26] Eleftheriadou et al. (2022) *British Association of Dermatologists guidelines for the management of people with vitiligo 2021.* British Journal of Dermatology, 186(1), 18–29.

CMH test adjusting for actual values of age at Screening, baseline disease severity and baseline status of actively progressing vitiligo. Similarly, the corresponding results for F-VASI 75 in Study 2 were 23.4% versus 6.9% for the upadacitinib 15 mg group versus placebo, with an adjusted difference of 16.9% (95% CI 9.2 to 24.5).

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

- Proportion of subjects achieving F-VASI 50 at Week 48; (48.1% vs 12.7% [Study 1] and 43.4% vs 12.9% [Study 2]; nominal p-value ≤0.001)
- Proportion of subjects achieving F-VASI 75 at Week 24; (15.0% vs 2.0% [Study 1] and 11.2% vs 1.0% [Study 2]; nominal p-value ≤0.001)
- Percent change from Baseline in F-VASI at Week 24; (LS Mean (SE): -42.39 (4.424) vs -12.97 (5.092) [Study 1] and -27.85 (3.483) vs -1.68 (4.464) [Study 2]; nominal p-value ≤0.001)
- Percent change from Baseline in T-VASI at Week 48; (LS Mean (SE): -28.55 (4.029) vs -9.14 (4.667) [Study 1] and -32.95 (3.196) vs -12.55 (4.231) [Study 2]; nominal p-value ≤0.001)
- Proportion of subjects achieving F-VASI 90 at Week 48; (15.5% vs 2.0% [Study 1] and 12.2% vs 3.0% [Study 2]; nominal p-value ≤0.001)
- Proportion of subjects achieving PhGIC-V of "Much better (1)" at Week 48; (19.9% vs 5.9% [Study 1] and 16.6% vs 1.0% [Study 2]; nominal p-value ≤0.001)
- Proportion of subjects achieving VNS score of "A lot less noticeable (4)" or "No longer noticeable (5)" at Week 48; (12.6% vs 2.0% [Study 1] and 14.6% vs 1.0% [Study 2]; nominal p-value ≤0.001)
- Proportion of subjects achieving PaGIC-V of "Much better (1)" at Week 48; (15.5% vs 3.9% [Study 1] and 18.0% vs 1.0% [Study 2]; nominal p-value ≤0.001)
- Proportion of subjects achieving no increase from Baseline in T-VASI at both Week 8 and Week 12 among subjects with actively progressing vitiligo at Baseline; (75.9% vs 60.3% [Study 1] and 75.6% vs 61.0% [Study 2]; nominal p-value ≤0.05)

The proportion of patients achieving F-VASI 75 from week 8 onwards showed a gradual increase over time. The F-VASI assessments at earlier timepoints overall suggest a relatively early onset of treatment benefit.

Results from subgroup analysis consistently favoured upadacitinib 15 mg over placebo, with 95% confidence intervals excluding zero in most subgroups, indicating consistency in efficacy across subgroups. The subgroups prespecified included: age, sex, BMI, race, ethnicity, weight, Baseline disease severity, Baseline status of actively progressing vitiligo, Baseline F-VASI, Baseline T VASI, Fitzpatrick skin types, duration of vitiligo since diagnosis, prior topical therapy for vitiligo, and prior phototherapy for vitiligo. The proportion of subjects achieving F-VASI 75 at Week 48 in the adolescent population across the two studies was 21.6% (8 of 37 subjects) in the upadacitinib 15 mg group vs 18.8% (3 of 16 subjects) in the placebo group (not significant). For T-VASI 50, the response rates in the adolescent population across the two pivotal studies were 29.7% (11 of 37 subjects) in the upadacitinib 15 mg group versus 6.3% (1 of 16 subjects) in the placebo group (nominal p ≤0.015). The plasma exposure of upadacitinib in patients with NSV appeared to be comparable between adults and adolescent subjects and were in line with previous indications.

3.3. Uncertainties and limitations about favourable effects

Given that clinical data are currently limited to 48 weeks, consideration should be given to discontinuing upadacitinib in NSV patients who do not demonstrate a therapeutic benefit by Week 48. As outlined in RMP version 20.0, the MAH has agreed to submit the final CSRs from the ongoing Study 1 and Study 2 Period B in Q2 2028. These Category 3 studies are expected to further characterise efficacy beyond 48 weeks.

The response rates in the adolescent population are considered to be generally consistent with the overall study population. However, as the adolescent subgroup results were not type-1-error controlled are only considered supportive. The disease mechanism of vitiligo is similar in adolescents and adults and baseline characteristics in Study 1 and Study 2 were reasonably comparable between adults and adolescents. In the context of overall assessment of efficacy in the adolescent population, it is therefore considered that efficacy data can be extrapolated from the adult NSV population.

3.4. Unfavourable effects

Mean duration of exposure was 46.2 weeks for the Any UPA 15 mg group (n=582). A total of 339 patients (58.2%) was exposed to any dose of UPA for at least 52 weeks. In adolescent patients, mean duration of exposure was 41.7 weeks for the Any UPA 15 mg group (n=52). A total of 24 patients (46.2%) was exposed to any dose of UPA for at least 52 weeks.

Common TEAEs (reported in ≥5% of patients on UPA in the placebo-controlled 48-week period or ≥10 events per 100 PY during the same period) were nasopharyngitis, upper respiratory tract infection, acne, and headache; in the adolescent population, also influenza-like illness was commonly reported. Most TEAEs were mild or moderate in severity.

One death was reported in the placebo-group of Study 2 due to drowning.

The frequency of SAEs in the overall population was higher in the UPA treatment group (6.3% with UPA 15 mg) compared with placebo (4.5%). No SAEs were reported in more than 1 patient.

Treatment discontinuations due to TEAEs were reported in 2.4% of patients with UPA 15 mg vs. 4.5% with placebo in the placebo-controlled 48-week analysis set and in 1.9% of patients in the Any UPA 15 mg group in all treated long-term analysis set. In the adolescent subgroup, no TEAEs led to discontinuation of study treatment in either analysis set.

In the 48-week analysis set, the adverse events of special interest in terms of serious infections, herpes zoster, hepatic disorder, anaemia, neutropenia and lymphopenia were reported in the Any UPA 15 mg cohort. 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 non-segmental vitiligo, including adolescents, is considered adequate. However, long-term exposure for at least 1 year in the adolescent population is limited. Safety data with a more recent data cut-off date (05 January 2026) has been submitted for the adolescent population, with no new safety concerns.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 44. Effects Table for Rinvoq, non-segmental vitiligo in adults and adolescents 12 years and older

Effect	Short description	Unit	Upadacitinib 15 mg QD	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Co-primary endpoints						
F-VASI 75 at Week 48	Responders	% [95% CI]	25.2 [19.3, 31.2]	5.9 [1.3, 10.4]	SoE: <0.001	Study 1
			23.4 [17.6, 29.2]	6.9 [2.0, 11.9]		Study 2
T-VASI 50 at Week 48	Responders	% [95% CI]	19.4 [14.0, 24.8]	5.9 [1.3, 10.4]	SoE: <0.001	Study 1
			21.5 [15.8, 27.1]	5.9 [1.3, 10.6]		Study 2
Key secondary endpoints						
F-VASI 50 at Week 48	Responders	% [95% CI]	48.1 [41.2, 54.9]	12.7 [6.3, 19.2]	SoE: <0.001	Study 1
			43.4 [36.6, 50.2]	12.9 [6.3, 19.4]		Study 2
F-VASI 75 at Week 24	Early responders	% [95% CI]	15.0 [10.2, 19.9]	2.0 [0.0, 4.7]	SoE: <0.001	Study 1
			11.2 [6.9, 15.5]	1.0 [0.0, 2.9]		Study 2
Percent change from Baseline in F-VASI at Week 24	Responders over time	LS Mean [SE]	-42.39 [-51.06, -33.72]	-12.97 [-22.95, -2.98]	SoE: <0.001	Study 1
			-27.85 [-34.68, -21.02]	-1.68 [-10.44, 7.08]		Study 2

Effect	Short description	Unit	Upadacitinib 15 mg QD	Placebo	Uncertainties / Strength of evidence	References
Percent change from Baseline in T-VASI at Week 48	Responders over time	LS Mean [SE]	-28.55 [-36.46, -20.65]	-9.14 [-18.31, 0.02]	SoE: <0.001	Study 1
			-32.95 [-39.23, -26.68]	-12.55 [-20.87, -4.23]		Study 2
F-VASI 90 at Week 48	Responders	% [95% CI]	15.5 [10.6, 20.5]	2.0 [0.0, 4.7]	SoE: <0.001	Study 1
			12.2 [7.7, 16.7]	3.0 [0.0, 6.3]		Study 2
PhGIC-V of "Much better (1) at Week 48	Responders: Physician's Global Impression of Change - Vitiligo	% [95% CI]	19.9 [14.5, 25.4]	5.9 [1.3, 10.4]	SoE: <0.001	Study 1
			16.6 [11.5, 21.7]	1.0 [0.0, 2.9]		Study 2
VNS score at Week 48	Vitiligo Noticeability Scale score of 4 (a lot less noticeable) or 5 (no longer noticeable)	% [95% CI]	12.6 [8.1, 17.2]	2.0 [0.0, 4.7]	SoE: <0.001	Study 1
			14.6 [9.8, 19.5]	1.0 [0.0, 2.9]		Study 2
PaGIC-V of "Much better (1)" at Week 48	Responders: Patient's Global Impression of Change - Vitiligo	% [95% CI]	15.5 [10.6, 20.5]	3.9 [0.2, 7.7]	SoE: <0.001	Study 1
			18.0 [12.8, 23.3]	1.0 [0.0, 2.9]		Study 2
No increase from Baseline in T-VASI at both Week 8 and Week 12 among subjects with actively progressing vitiligo at Baseline	Halting disease progression	% [95% CI]	75.9 [68.8, 82.9]	60.3 [48.2, 72.4]	SoE: 0.025	Study 1
			75.6 [67.9, 83.3]	61.0 [48.6, 73.5]	SoE: 0.042	Study 2

Effect	Short description	Unit	Upadacitinib 15 mg QD	Placebo	Uncertainties / Strength of evidence	References
Unfavourable Effects						
Adverse events of special interest (all treated long-term safety analysis set)						
Serious infections	Overall Adolescents	E/100PY	1.0 0	N/A		
Herpes zoster	Overall Adolescents	E/100PY	2.3 2.4	N/A		
Hepatic disorder	Overall Adolescents	E/100PY	4.3 0	N/A		
Anaemia	Overall Adolescents	E/100PY	1.7 0	N/A		
Neutropenia	Overall Adolescents	E/100PY	3.3 4.8	N/A		
Lymphopenia	Overall Adolescents	E/100PY	1.7 0	N/A		
Malignancy	Overall Adolescents	n/100PY	0.2 0	N/A		
Bone fractures	Overall Adolescents	n/100PY	2.0 7.4	N/A		

Abbreviations: N/A

Notes: AESIs are expressed as E/100 PY or n/100 PY (for malignancy and bone fractures)

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 (M19-044 Study 1 and Study 2).

In both pivotal studies, the co-primary endpoints, F-VASI 75 and T-VASI 50 at Week 48, were met. The results were further substantiated by the pre-specified, multiplicity-controlled, ranked secondary endpoints, comprising various VASI-derivatives and noticeability scoring metrics (including VNS score, PhGIC-V and PaGIC-V), all of which demonstrated statistically significant results for the upadacitinib 15 mg treated group compared to placebo. Most of the chosen endpoints included in the application are considered clinically relevant and are accepted. The results are robustly documented and of clinical relevance for the sought indication. Data is only available for 48 weeks treatment which is a limitation considering the chronicity of the condition. However, long term evaluation of safety and efficacy is ongoing, the final results from the Study 1 and Study 2 Period B will be submitted in Q2 2028. These studies will further characterise the efficacy upadacitinib beyond 48 weeks in the AA population.

Adolescents (12-18 years; n= 53) are part of the applied indication and comprised about 9% of the total study population, which is rather limited. Analyses of the two co-primary endpoints across the two studies suggest at least a similar effect on F-VASI 75 and T-VASI 50 in adolescents as compared to adults.

In terms of benefit, upadacitinib provides a significant and clinically meaningful beneficial treatment effect on NSV in adults and adolescents 12 years and older at Week 48, as compared to placebo. The safety profile in the patient population with NSV, 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. However, long-term safety data in adolescent patients is limited. The final results from the Study 1 and Study 2 Period B will be submitted in Q2 2028 and will further characterise the safety upadacitinib beyond 48 weeks in the AA population.

3.7.2. Balance of benefits and risks

The balance of benefits and risks of upadacitinib 15 mg for the treatment of NSV in adult and adolescent patients 12 years and older who are candidates for systemic therapy, is positive. Upadacitinib 15 mg is intended as a systemic second-line product. It is considered to fulfil an unmet need in patients for whom standard first-line topical treatments is insufficiently effective and would be particularly beneficial for patients with widespread disease, or without facial involvement for which there are currently no authorised treatment options.

Overall, the safety profile in adult and adolescent patients 12 years and older with NSV is consistent with that observed for other indications, with no new safety signals identified.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

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

Vitiligo

Rinvoq is indicated for the treatment of non-segmental vitiligo in adults and adolescents 12 years and older who are candidates for systemic therapy.

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.6.a	C.6.a) Addition of a new therapeutic indication or modification of an approved one	Variation type II	I, and IIIB.

Extension of indication to include the treatment of non-segmental vitiligo in adults and adolescents 12 years and older who are candidates for systemic therapy, for Rinvoq, based on results from the two replicate Phase 3 studies M19-044: study 1 (R&D/25/1342) and study 2 (R&D/25/1343), as well as from integrated long-term safety data. Study 1 and study 2 are Phase 3, global, randomized, double-blind, placebo-controlled multi-center studies that evaluate the safety and efficacy of upadacitinib in adult and adolescent patients with non-segmental vitiligo. As a consequence, 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 in accordance. Version 20.0 of the RMP is approvable. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the product information.

Amendments to the marketing authorisation

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

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

- **Risk management plan (RMP)**

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

- ## 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.

In this procedure, the CHMP reviewed the available data from the clinical study conducted in accordance with the agreed PIP P/0383/2023, namely PIP studies 2,3 (M19-044 study 1 & 2) and PIP study 5. The available results of these studies are reflected in sections 4.8, 5.1 & 5.2 of the Summary of Product Characteristics (SmPC).

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

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-EMAVR0000325958'

Attachments

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

Appendix

1. CHMP AR on the significant clinical benefit in comparison with existing therapies