27 February 2025
EMA/103192/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rinvoq

International non-proprietary name: upadacitinib

Procedure No. EMEA/H/C/004760/II/0056

Note

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

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

Table of contents

List of abbreviations

AD	atopic dermatitis
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aRMM	additional risk minimization measure
AS	ankylosing spondylitis
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
BMI	body mass index
CD	Crohn's disease
CI	confidence interval
Cmax	maximum plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease – 2019 (coronavirus SARS-CoV-2)
CPK	creatine phosphokinase
CRP	C-reactive protein
CS	corticosteroid(s)
CSE	Clinical Summary of Efficacy
CSS	Clinical Summary of Safety
CSR	clinical study report
CS-T	corticosteroid taper
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CV	cardiovascular
CYP	cytochrome P450
D	Distribution coefficient
DVT	deep vein thrombosis
E	event
EAER	exposure-adjusted event rate
EAIR	exposure-adjusted incidence rate
EMA	European Medicines Agency
E-R	exposure-response

ERA	Environmental risk assessment
ESR	erythrocyte sedimentation rate
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
Fpen	Market penetration factor based on prevalence of substance use
GCA	giant cell arteritis
GCP	Good Clinical Practice
HDL-C	high-density lipoprotein cholesterol
hsCRP	high sensitivity C-reactive protein
ICH	International Council for Harmonisation
IFN	interferon
IIV	inter-individual variability
IL	interleukin
ISV	inter-subject variability
JAK	Janus kinase
LDL-C	low-density lipoprotein cholesterol
LLOQ	lower limit of quantification
Log	Logaritmic
MACE	major adverse cardiovascular event
MPA	Medical Products Agency
NE	not evaluable
NMSC	non-melanoma skin cancer
nr-axSpA	non radiographic axial spondyloarthritis
OATP	organic anion transporting polypeptide
PBO	placebo
PBT	Persistent, bioaccumulative and toxic
PCS	physical component summary
pcVPC	prediction-corrected visual predictive check
PEC	Predicted environmental concentration
PEC_{sw}	Predicted environmental concentration in surface water
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency

PMR	polymyalgia rheumatica
PNEC	Predicted no effect concentration
popPK	Population pharmacokinetics
Pow	Partition coefficient for octanol/water
PRO	patient-reported outcome
PsA	psoriatic arthritis
PT	preferred term
PY	patient-year
QD	once daily
QoL	quality of life
RA	rheumatoid arthritis
RSE	relative standard error
SAE	serious adverse event
SAP	Statistical Analysis Plan
SF-36	Short Form 36
SS1	Safety Analysis Set in Period 1
SS_LT	Long-Term Safety Analysis Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TSLD	time since last dose
TSQM	Treatment Satisfaction Questionnaire for Medication
UC	ulcerative colitis
UPA	upadacitinib
US	United States
vs.	versus
VTE	venous thromboembolic event
WK or Wk	week

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 June 2024 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of giant cell arteritis (GCA) in adult patients for Rinvoq based on final results from study M16-852. This is a phase 3, global, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of upadacitinib in subjects with GCA. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 15.0 of the RMP has also been submitted.

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(s) on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH sought Scientific Advice at the CHMP EMEA/H/SA/3190/6/2017/II.

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 June 2024
Start of procedure:	20 July 2024
CHMP Rapporteur Assessment Report	9 September 2024
PRAC Rapporteur Assessment Report	18 September 2024
PRAC members comments	25 September 2024
Updated PRAC Rapporteur Assessment Report	26 September 2024
PRAC Outcome	03 October 2024
CHMP members comments	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 October 2024
Request for supplementary information	17 October 2024
MAH's responses submitted to the CHMP on:	28 November 2024
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	20 December 2024
CHMP members comments	n/a
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	22 January 2025
2nd Request for supplementary information	30 January 2025
MAH's responses submitted to the CHMP on:	03 February 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	07 February 2025
CHMP members comments	n/a
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	18 February 2025
Opinion	27 February 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Giant cell arteritis (GCA, also known as temporal arteritis) is a systemic vasculitis of the large vessels, with a predilection for the cranial branches of the aorta. GCA affects women to men in a 3:1 ratio and almost exclusively occurs in those over age 50. The course of GCA is characterized by a relatively abrupt onset followed by chronic vascular and systemic inflammation. The characteristic symptoms of

GCA include those related to vascular ischemia such as temporal headache, jaw pain related to use (jaw claudication), ocular symptoms, and stroke. Ocular symptoms occur in up to 30% of GCA patients and can include diplopia or vision loss, with 15% of patients manifesting permanent unilateral or bilateral loss of vision. There is a significant overlap between GCA and PMR with approximately 50% of patients with GCA also diagnosed with polymyalgia rheumatica (PMR).

Claimed therapeutic indication

The MAH applied to include the following indication: “Rinvoq is indicated for the treatment of giant cell arteritis in adult patients” with the posology “The recommended dose of upadacitinib is 15 mg once daily in combination with a tapering course of corticosteroids. Based upon the chronic nature of giant cell arteritis, upadacitinib 15 mg once daily can be continued as monotherapy following discontinuation of corticosteroids”.

Clinical presentation, diagnosis

In line with clinical guidelines (e.g. the 2018 Update of the EULAR recommendations for the management of large vessel vasculitis[1]), the GCA diagnosis is suspected on typical symptoms, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and confirmed by imaging or histology (temporal artery biopsy).

Management

Corticosteroid (CS) therapy is the current mainstay of treatment for GCA. Initial high dose CS therapy is followed by a prolonged period of dose tapering. The MAH put forward that during this tapering phase, between 50% and 80% of GCA patients experience a disease flare. Tocilizumab was approved in the European Union in 2017 for the treatment of adults with GCA. Tocilizumab is administered subcutaneously in combination with a steroid taper.

The MAH stated that despite the available therapies, there continues to be a need for additional therapies in GCA. The MAH also stated that oral targeted therapies for the treatment of GCA are not currently available and are preferred over injectables by patients.

2.1.2. About the product

Rinvoq (upadacitinib) is a JAK inhibitor that is approved for various indications within rheumatology (including rheumatoid arthritis), gastroenterology and dermatology, as indicated in the agreed SmPC.

2.2. Non-clinical aspects

An updated environmental risk assessment is provided but no new non-clinical data have been submitted in this application.

2.2.1. Ecotoxicity/environmental risk assessment

The ERA was updated with regard to predicted environmental concentration (PEC) and resulting risk ratios, however, no new study data for the ERA were included with this application. The ERA was

[1] Hellmich B, Agueda A, Monti S, et al. Ann Rheum Dis 2020;79:19–30

updated from the original ERA of the MAA for Rheumatoid Arthritis (RA) approval, and the subsequently updated ERAs to support the indications psoriatic arthritis (PsA), ankylosing spondylitis (AS), atopic dermatitis (AD), active ulcerative colitis (UC), non-Radiographic Axial Spondylarthritis (nr-axSpA), and Crohn´s disease (CD) in adult patients.

In the original ERA the results of the Phase I assessment triggered a Phase II Tier A assessment and the standard suite of fate and effect studies were completed. Upadacitinib is very persistent in sediment according to the OECD 308 study. A Phase II Tier B extended effects on water sediment was thus triggered.

Phase I: Updated predicted environmental concentration (PEC)

The surface water PEC (PEC_{SW}) for GCA was calculated using equation 1 (see below).

$$PEC_{SURFACE\ WATER}\ [mg/L] = \frac{Dose_{ai} * Fpen}{WASTEWinhab * Dilution}$$

Equation 1. Formula used to calculate the predicted environmental concentration in surface water (PEC_{SW}). $Dose_{ai}$ = maximum dose. Fpen = market penetration factor based on prevalence of substance use. WASTEWinhab = default wastewater volume of 200 L per inhabitant. Dilution = default dilution factor of 10.

The maximum daily dose for the indication GCA is 15 mg/day, resulting in $PEC_{SURFACEWATER}$ (PEC_{SW}) value of 0.075 µg/L. For each of the indications RA, PsA, AS and nr-axSpA with the maximum daily dose of 15 mg/day, the PEC_{SW} values was 0.075 µg/L, for the indication AD with the maximum daily dose of 30 mg/day, the PEC_{SW} value was 0.15 µg/L and for the indications UC and CD with the maximum daily dose of 45 mg/day, the PEC_{SW} values were 0.225 µg/L, when using the default Fpen value of 0.01. Combining all eight indications, an updated PEC_{SW}-TOTAL was calculated to 0.975 µg/L.

According to the original ERA, the Log Pow and Log D were 2.50 (pH 7) using the shake flask method (OECD 107). Since the values were below the trigger value 3, no assessment for potential classification as persistent, bioaccumulative and toxic (PBT) was needed.

Phase II Tier A and B: Updated risk ratios (PEC/PNEC)

New phase II risk ratios are based on the updated PEC_{SW}-TOTAL (0.975 µg/L) and the values for predicted no effect concentration (PNEC) that were presented for the original ERA submitted for the MAA. In the tables below the updated risk ratios are presented.

Phase II Tier A

Compartment	PEC	PNEC	PEC/PNEC (action limit)
Surface water	0.9 µg/L	63 µg/L	0.015 (<1)
Groundwater	0.23 µg/L	160 µg/L	0.0015 (<1)
Microorganism	0.9 µg/L	100000 µg/L	0.00000975 (<0.1)

Phase II Tier B

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

Compartment	PEC	PNEC	PEC/PNEC (action limit)
Sediment	1.02 mg/kg	15.6 mg/kg	0.071 (<1)

The updated risk ratios remain below the action limits. Therefore, the clinical use of upadacitinib for the eight indications (RA, PsA, AS, AD, UC, nr-axSpA, CD and GCA) considered in the present report is not expected to pose a risk for the environment.

2.2.2. Discussion on non-clinical aspects

An updated environmental risk assessment was provided but no new non-clinical data submitted in this application, which is considered acceptable to the CHMP given that the clinical dose intended for treatment of the new indication (GCA) is the same as for previously authorised indications. Therefore, the non-clinical data available for the previously authorised product are adequate to support the current application. Hence, the CHMP agreed that no changes in SmPC sections 4.6 and 5.3 are needed.

The MAH has calculated an updated PECsw-TOTAL value (0.975 µg/L) for upadacitinib based on the new indication GCA combined with seven previously authorised indications (RA, PsA, AS, AD, UC, nr-axSpA, and CD). The risk ratios (PEC/PNEC) were subsequently re-calculated based on the updated PECSW-TOTAL and the PNEC values that were presented for the original ERA submitted for the MAA. The resulting risk ratios remain below the action limits. Therefore, it was concluded that the use of upadacitinib for the eight indications (RA, PsA, AS, AD, UC, nr-axSpA, CD and GCA) is not expected to pose a risk for the environment. This is agreed by the CHMP.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application lead to a significant increase in environmental exposure further to the use of upadacitinib. Considering the above data, upadacitinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

The global GCA clinical programme consists of an ongoing single Phase 3 Study: Study M16-852.

2.3.2. Pharmacokinetics

Phase 1 studies that characterized upadacitinib pharmacokinetics after single and multiple doses, absorption, distribution, metabolism, excretion characteristics, drug-drug interaction potential, and pharmacokinetics in special populations were included in the original regulatory submission dossier for the use of upadacitinib in the treatment of RA (EMEA/H/C/004760/0000). No new Phase 1 clinical pharmacology studies are presented within this regulatory application for the use of upadacitinib in the treatment of GCA.

Analytical methods

A salt-assisted liquid/liquid extraction followed by LC-MS/MS analytical method was used for the determination of upadacitinib concentration in human plasma in Study M16-852. The analytical method is the same as used in the original application (EMEA/H/C/004760/0000).

Population pharmacokinetic data analysis

Population pharmacokinetic (popPK) analyses were performed using data from Study M16-852 (Table 1). Results from prior popPK analyses using data from healthy subjects and subjects with RA (EMEA/H/C/004760/0000), were leveraged to inform upadacitinib PK parameters in subjects with GCA.

Table 1: Summary of data included in the population pharmacokinetic and exposure-response analyses for efficacy and safety

Study ($n_{subjects}$)	Dosing regimens[a] (n)	Subjects in analysis (n)	Assessment time points	Data for Exposure-Efficacy analyses	Data for Exposure-safety analyses
M16-852: 428	Placebo: 112 7.5 mg QD: 107 15 mg QD: 209	PK: 292 Efficacy: 428 Safety: 428[b]	PK: Baseline; Weeks 12, 24, 44, and 52 Efficacy: Week 12 and Week 52 Safety: At and through Week 52	Sustained remission at Week 52, sustained complete remission at Week 52, and cumulative corticosteroid exposure through Week 52.	Select adverse events and changes in laboratory parameters at or through Week 52

[a] Extended-release tablets.
[b] n=425 for "> 2 g/dL decrease in haemoglobin" safety endpoint, n=356 for "cumulative CS exposure" safety endpoint.

The popPK analysis dataset included 982 valid concentration records after the first and < 168 hours after the previous dose of upadacitinib.

The lower limit of quantification (LLOQ) of the assay of plasma samples of Study M16-852 was 0.0505 ng/mL. A total of 1.43% (14/982) of the records were below the LLOQ. The first upadacitinib concentration value below the LLOQ after each dose was set to one-half of the LLOQ. All subsequent concentrations below the LLOQ recorded after the last dose were excluded from the modelling exercise.

A total of 87.9% (957/982) upadacitinib concentration records were included in the popPK analysis, with reasons for exclusion detailed in Table 2.

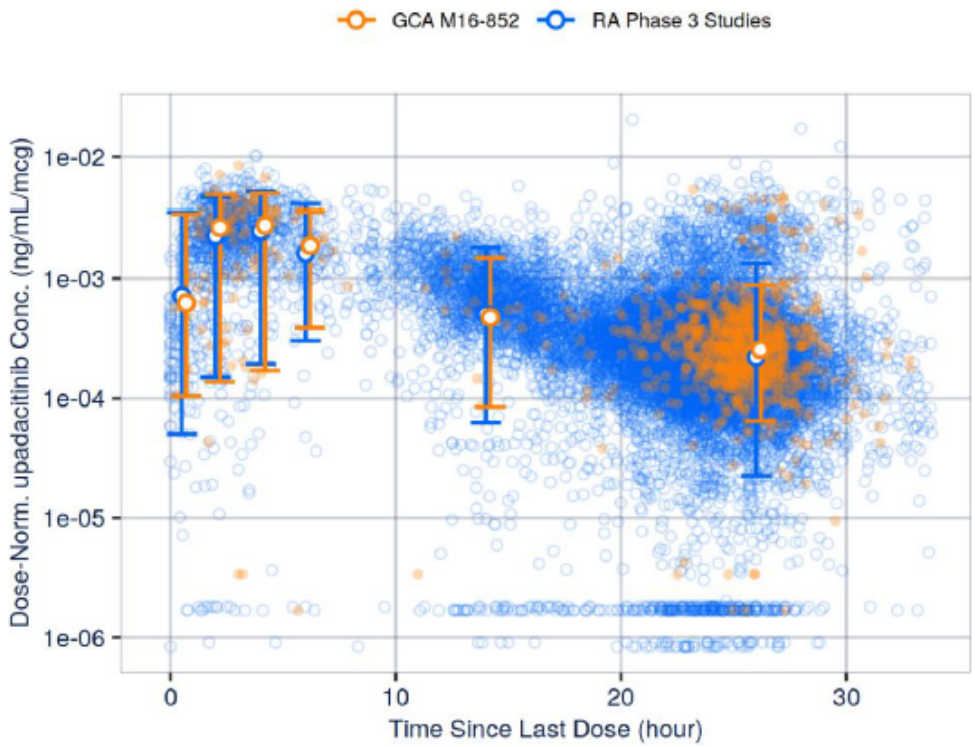
Table 2: Summary of observations excluded from population pharmacokinetic modelling

Reason for Exclusion	Frequency Count	Percent
No Exclusion	957	87.9
No Dose/Concentration	29	2.66
Record Before/At First Dose	1	0.0918
Outlier Rule	25	2.30
Protocol Deviation	2	0.184
TSLD > 168 hours	75	6.89

Graphical assessment

In Figure 1, the dose-normalized observed upadacitinib concentration versus time-since-last-dose profiles in subjects with GCA (M16-852) are compared to dose-normalized concentrations in subjects with RA (Phase 3 Studies M13-549, M15-555, M14-465, M13-545 and M14-663).

Figure 1: Dose-normalised observed upadacitinib concentrations in subjects with RA in Phase 3 studies compared to subjects from Study M16-852 with GCA.



Orange circles represent observed dose-normalised upadacitinib concentrations from GCA subjects. Blue circles represent observed dose-normalised upadacitinib concentrations from RA subjects from Phase 3 studies included in the previous model (EMEA/H/C/004760/0000). Framed circles with error bars represent the median and 5–95th percentiles for the binned (0.5, 2, 4, 6, 14, and 26 hours since last dose) observed data in RA, or GCA subjects.

Model

The popPK model developed in the initial application (EMEA/H/C/004760/0000) was used to describe observed upadacitinib plasma concentrations from the Phase 3 Study M16-852 using a post hoc approach (FOCEI MAXEVAL=0 in NONMEM).

In this previous model, upadacitinib PK were described by a two-compartment model with mixed zero- and first-order absorption with lag time for the upadacitinib extended-release formulation.

The parameter estimates for fixed effects (THETAs) and residual error (SIGMAs) from the previous model are provided in Table 3. Statistically significant covariates identified in the previous model included subject/patient population (patients versus healthy volunteers), creatinine clearance, body weight on CL/F, and body weight on V_c/F. For this popPK modelling exercise of upadacitinib in subjects with GCA, the Applicant claims that fixed-effects parameters were left unchanged from the previous model and were not re-estimated. The random-effects parameters were re-estimated, and the results are displayed in Table 3 and Table 4.

Table 3: Fixed-effects parameters used in the post hoc analysis of upadacitinib PK in subjects with GCA. Random unexplained variabilities (RUV) from the previous model and current model are also displayed here.

Parameter	Previous model (%RSE[a])	Current model
CL/F (L/h)	40.9 (1.6)	Fixed
Vc/F (L)	156 (1.7)	Fixed
Extended-Release KA (1/h)	0.0523 (6.0)	Fixed
Extended-Release Absorption Lag Time (h)	0.154 (3.9)	Fixed
Fraction of Extended-Release Dose Absorbed through Zero-Order Process	0.745 (1.7)	Fixed
Zero-Order Absorption Duration (h)	3.29 (1.7)	Fixed
Immediate-Release KA (1/h)	2.77 (7.4)	Fixed
Immediate-Release Absorption Lag Time (h)	0.200 (3.9)	Fixed
Bioavailability of the Extended-Release Formulation Relative to the Immediate-Release Formulation	0.762 (1.4)	Fixed
Q/F (L/h)	3.22 (5.8)	Fixed
Vp/F (L)	68.0 (7.2)	Fixed
CL/F Ratio of Patients Compared to Healthy Subjects[b]	0.754 (1.7)	Fixed
Covariate Exponent of Creatinine Clearance on CL/F	0.256 (10.0)	Fixed
Covariate Exponent of Weight on Vc/F	0.804 (8.0)	Fixed
Covariate Exponent of Weight on CL/F	0.132 (28.7)	Fixed
Additive Error	0.0858 (38.6)	0.00736
Proportional Error in Phase 2/3	0.543 (9.9)	0.295

[a] RSE% as estimated in the previous model.
[b] In the previous model, the patients were RA patients. In this procedure, the patients are GCA patients.

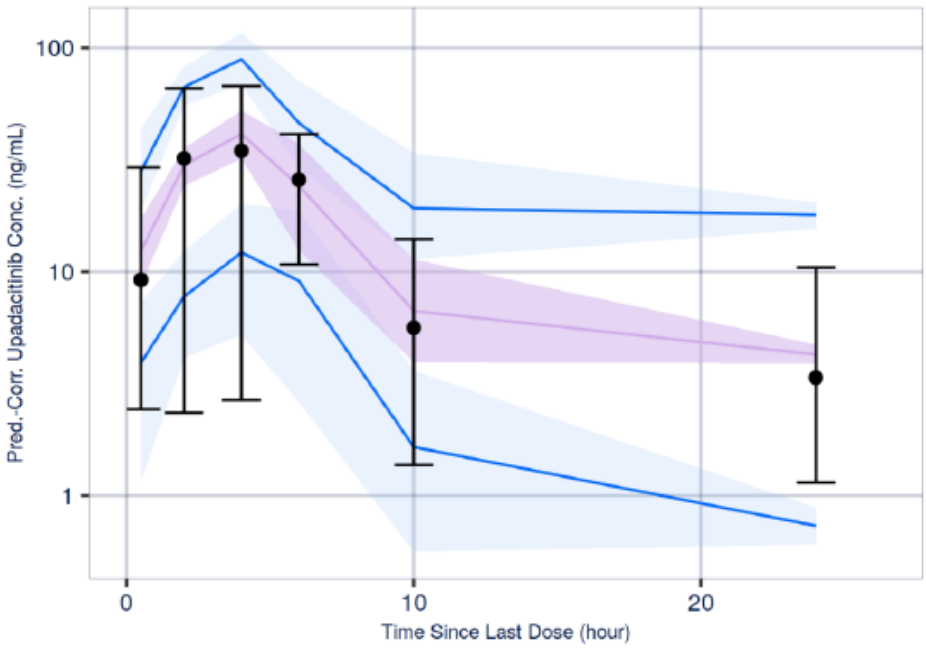
Table 4: Re-estimated inter-individual variability (IIV)

Parameter	Population Estimate	%CV	%Shrinkage
IIV on Extended-Release KA	0.446	75.0	62.6
IIV on CL/F in Phase 2/3	0.133	37.7	33.6
IIV on Vc/F in Phase 2/3	0.281	57.0	60.2

%RSE was calculated as the standard error of the estimate divided by the absolute value of the mean of the estimate multiplied by 100. %CV was calculated as SQRT((exp(ω^2)-1)*100. %Shrinkage was calculated as 100*(1-SD(ETA)/SQRT(ω)), with non-influential ETAs removed.

A prediction corrected visual predictive check (pcVPC) is presented in Figure 2.

Figure 2: Prediction-corrected visual predictive check of upadacitinib concentration in subjects with GCA in Study M16-852.



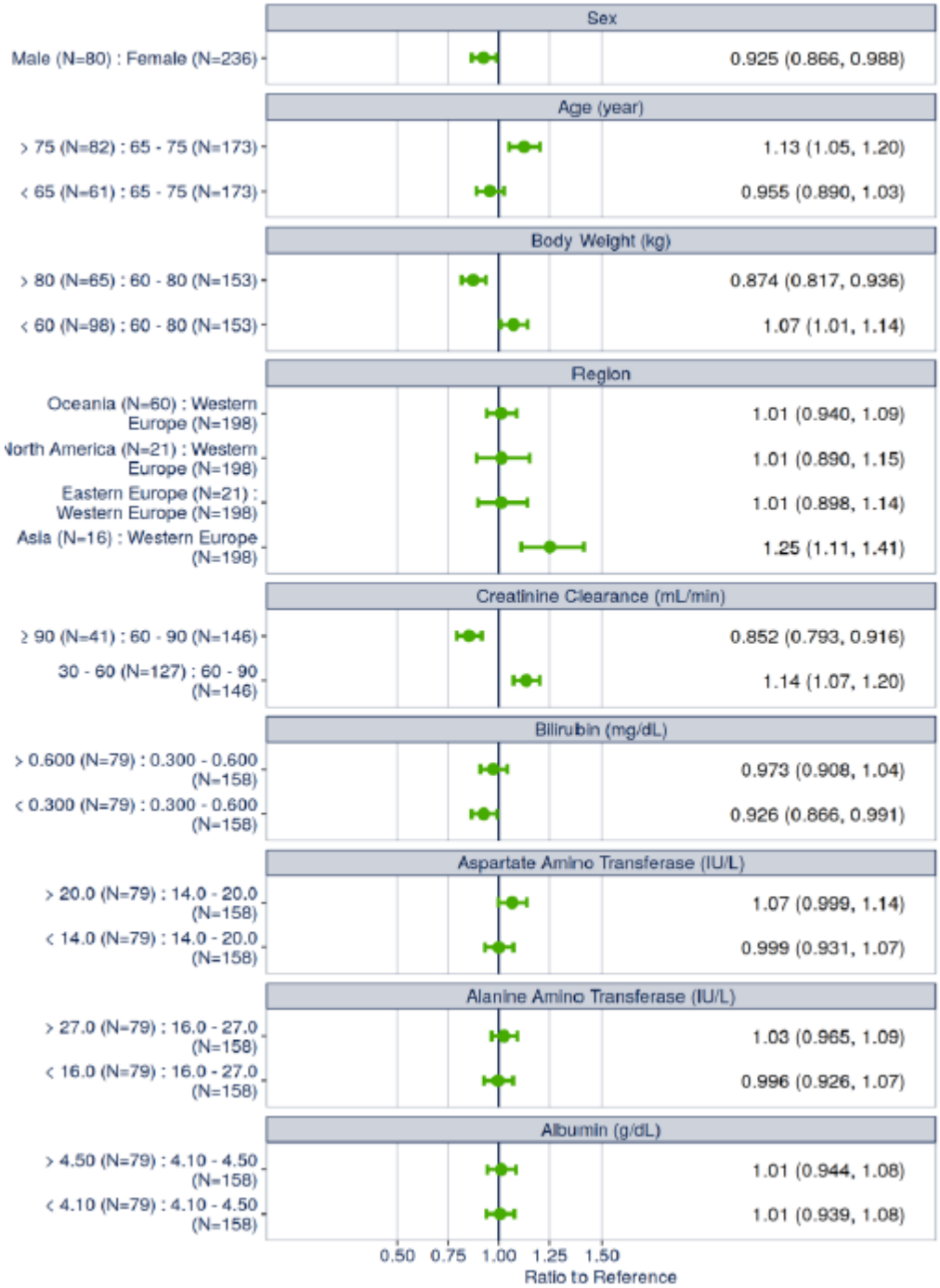
The blue lines represent the 90% prediction-interval (PI) of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. The black dots and error bars represent the median and 90% inter-percentile range (5–95th percentile) of the observed data, respectively. Time bins were chosen 0.5, 2, 4, 6, 10, and 24 hours since last dose.

Special populations

The dose-normalized, model-predicted steady-state exposure (C_{avg}) of upadacitinib was compared across specific demographic (Figure 3) and disease-related (Figure 4) subgroups using forest plots. The prediction was done using the individual post hoc PK parameters for the PK population of

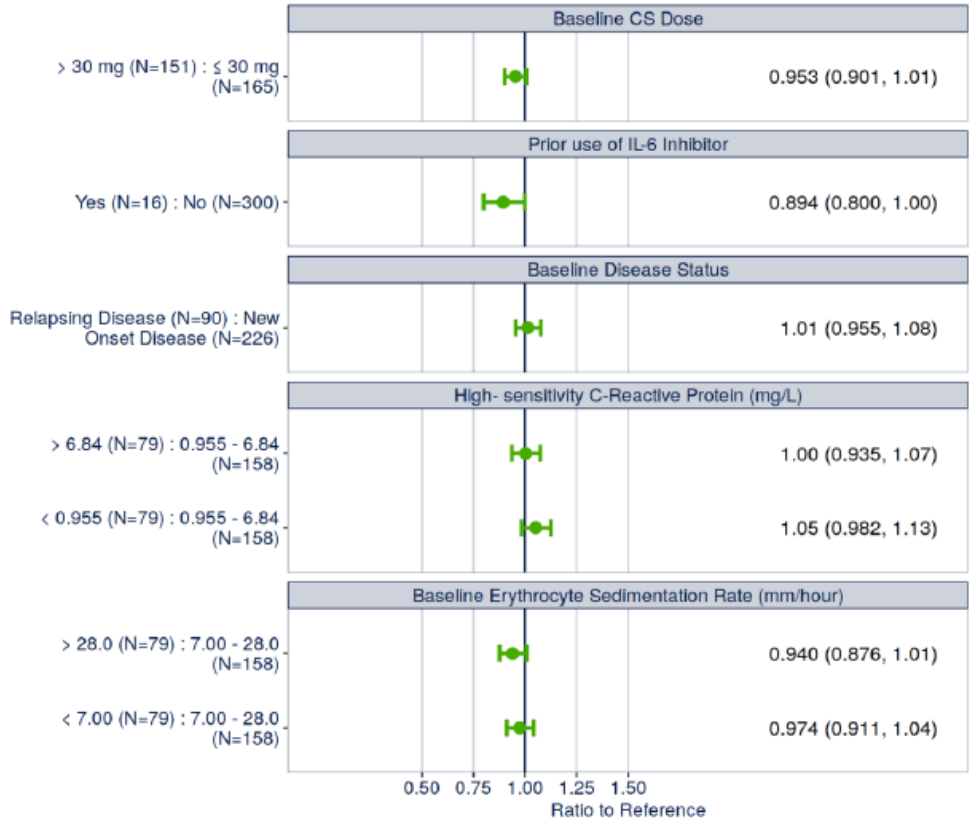
Study M16-852. The estimated geometric mean ratio (GMR) and its 95% CI for each covariate stratum were presented relative to the reference stratum.

Figure 3: Model-predicted demographic related covariate effects on dose-normalized upadacitinib C_{avg} in subjects with GCA



Dots and error bars represent geometric mean ratio and its 95% CI of model-predicted dose-normalized Cavg relative to reference groups. The vertical black line shows the exposure ratio of 1 relative to the reference group. Female subjects, age 65 - 75 years, body weight 60 - 80 kg, Western Europe, creatinine clearance 60 - 90 mL/min, subjects within the 25th to 75th range of bilirubin, AST, ALT and albumin were chosen as reference covariate categories.

Figure 4: Model-predicted disease-specific covariate effects on dose-normalized upadacitinib Cavg in subjects with GCA in Study M16-852.



Dots and error bars represent geometric mean ration 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. Corticosteroid dose ≤ 30 mg, subjects with no IL-6 inhibitor, new onset disease, subjects within the 25–75th range of hsCRP and ESR were chosen as reference covariate categories.

Pharmacokinetic interaction studies

No new drug-drug interaction studies have been submitted in this application. Potential interactions with concomitant medications have been described previously.

2.3.3. Pharmacodynamics

Mechanism of action

In line with Rinvoq SmPC Section 5.1, upadacitinib is a selective and reversible JAK inhibitor. JAKs are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, hematopoiesis, and immune surveillance. The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and TYK2 which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation, in turn, modulates gene expression and cellular function. JAK1 is important in inflammatory cytokine signals while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function.

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.

The MAH indicates that through modulation of proinflammatory cytokine pathways, upadacitinib offers the potential for effective treatment of immune-mediated inflammatory conditions and has the potential to target several pathways involved in GCA pathogenesis (IL6, IFNγ).

2.3.1. Exposure-response modelling

Table 1 describes the data used for exposure-response (E-R) analyses. Only efficacy and safety endpoints with > 10 events were evaluated further using E-R models. Data from 428 subjects with GCA, enrolled in Study M16-852 (Period 1) were included in the E-R analyses.

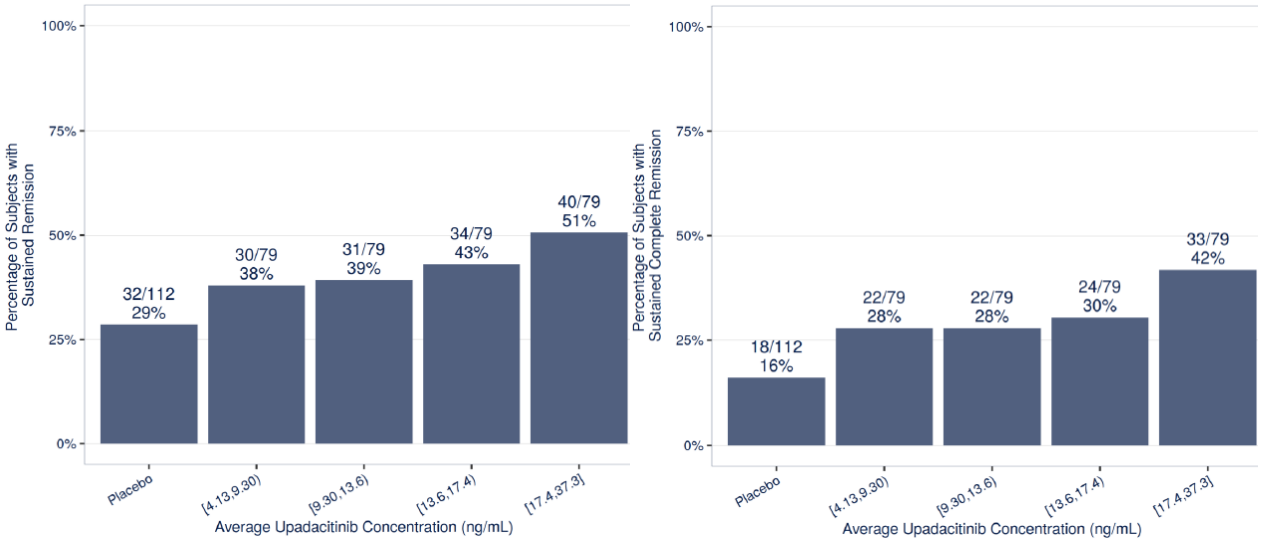
Quartile plots were used to assess the E-R relationships for upadacitinib in terms of efficacy and safety parameters through Week 52, with the exposure metric being the model-predicted inter-dose C_{avg} at steady-state. All subjects receiving placebo were included in the E-R analyses with C_{avg} set to 0.

Logistic and Gaussian regression analyses were conducted to characterize the relationship between upadacitinib C_{avg}, as the predictor variable, and various endpoints. A treatment effect model comparing upadacitinib to placebo, with and without an E-R relationship, was evaluated alongside different drug effect E-R models to identify the best fit for describing upadacitinib's impact on the probability of each efficacy and safety outcome.

Exposure-efficacy

Model-predicted C_{avg} compared to the observed percentages of subjects achieving sustained remission and sustained complete remission at Week 52 for the overall population are shown in Figure 5. There was an apparent increase in response with increasing upadacitinib plasma exposures.

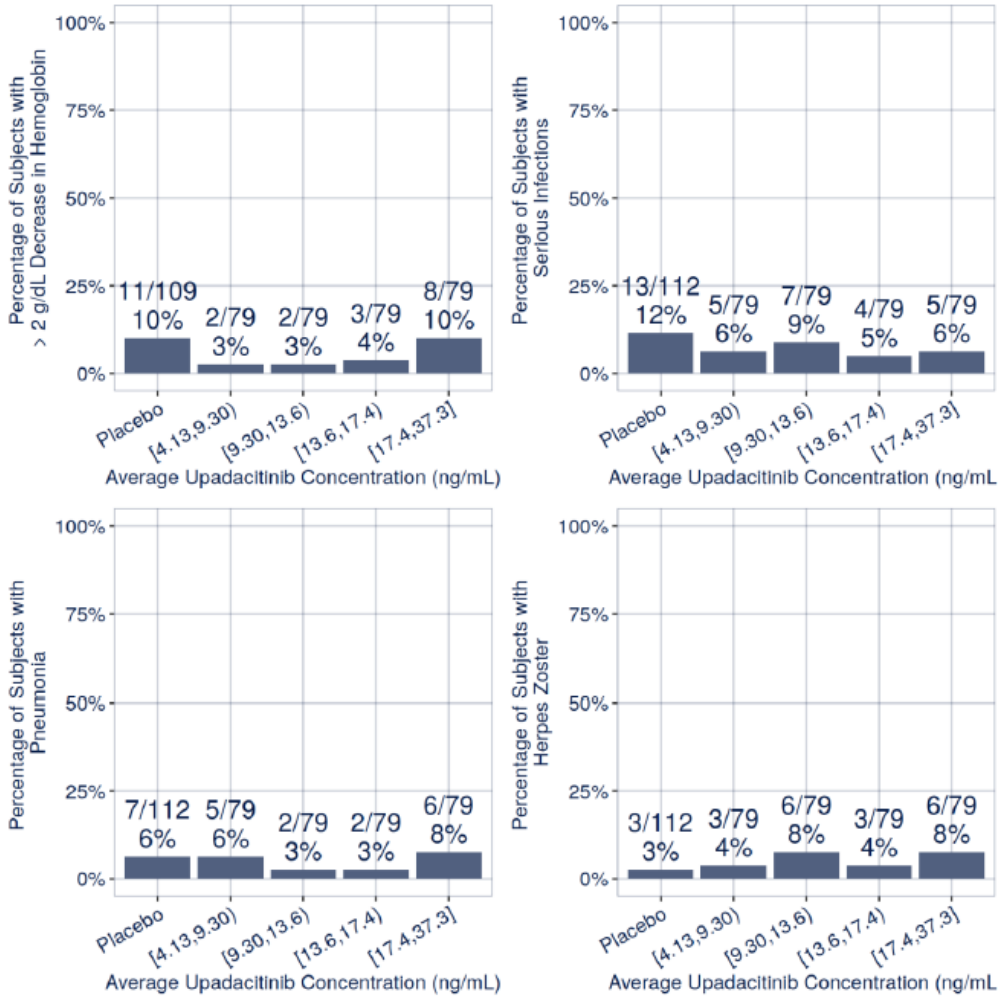
Figure 5: Exposure-response quartile plots of observed percentage of subjects with GCA achieving sustained remission (left) and sustained complete remission (right) at Week 52.



Exposure-safety

No significant exposure-safety relationship was seen in the analyses for any of the safety endpoints (Figure 6).

Figure 6: Exposure-response quartile plots of the relationship between model-predicted upadacitinib C_{avg} and safety endpoints with **>10** events, in subjects with GCA



2.3.2. Discussion on clinical pharmacology

The analytical method used to determine upadacitinib concentration in human plasma is the same as in the initial RA application (EMEA/H/C/004760/0000). The method has previously been assessed and found acceptable.

Dose-normalised observed upadacitinib concentrations in GCA subjects from Study M16-852 were compared to those in RA subjects (Phase 3 studies). The results indicate that dose-normalised exposure is comparable between the two conditions.

A PopPK analysis was conducted using data from Study M16-852. Results from the initial popPK analysis (EMEA/H/C/004760/0000) were used to inform the upadacitinib pharmacokinetic (PK) parameters in patients with GCA. No testing of new covariates was done. The THETA parameters are identical to the previous model. However, it is evident from the report that the values of OMEGAs and SIGMAs differ from those in the previous submission (EMEA/H/C/004760/0000). The CHMP considered that this discrepancy has minimal impact on the overall assessment, hence this issue was not further pursued.

The pcVPC shows that the model adequately describes the upadacitinib PK data from GCA subjects.

To explore differences in PK between special populations, a post hoc assessment of exposure differences between subgroups was done. Overall, the PK appears comparable across the evaluated subgroups, and across previous indications.

The narrow dose range in this application makes the overall E-R analysis inconclusive. However, there is an apparent exposure-efficacy trend based on the observed data, although no trend is observed for safety endpoints. This offers support (although weak) for the 15 mg QD regimen of upadacitinib over the 7.5 mg QD regimen, with the impact of this analysis being limited.

2.3.3. Conclusions on clinical pharmacology

The CHMP concludes that the PK of upadacitinib appears comparable between GCA and RA patients and is sufficiently characterised.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dedicated dose-response studies in GCA were conducted.

The pivotal clinical study M16-852 evaluated 2 doses of upadacitinib (7.5 and 15 mg) using the once-daily extended-release tablet formulation. The upadacitinib 15 mg QD regimen was selected based on the results from the exposure-response relationships characterized in Phase 2 studies in RA (Studies M13-537 and M13-550), and the Phase 3 clinical trials in RA (Studies M13-549 [SELECT-NEXT] and M13-542 [SELECT-BEYOND]). Upadacitinib 15 mg QD was expected to be the effective dose for GCA. Upadacitinib 7.5 mg QD, in conjunction with the 15 mg QD arm, was considered to allow characterization of the exposure-response relationship.

2.4.2. Main study

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Giant Cell Arteritis: SELECT-GCA

Methods

Study M16-852, is global, multicenter, randomized, double-blind and placebo-controlled, including adult subjects of at least 50 years of age with a diagnosis of new onset or relapsing GCA.

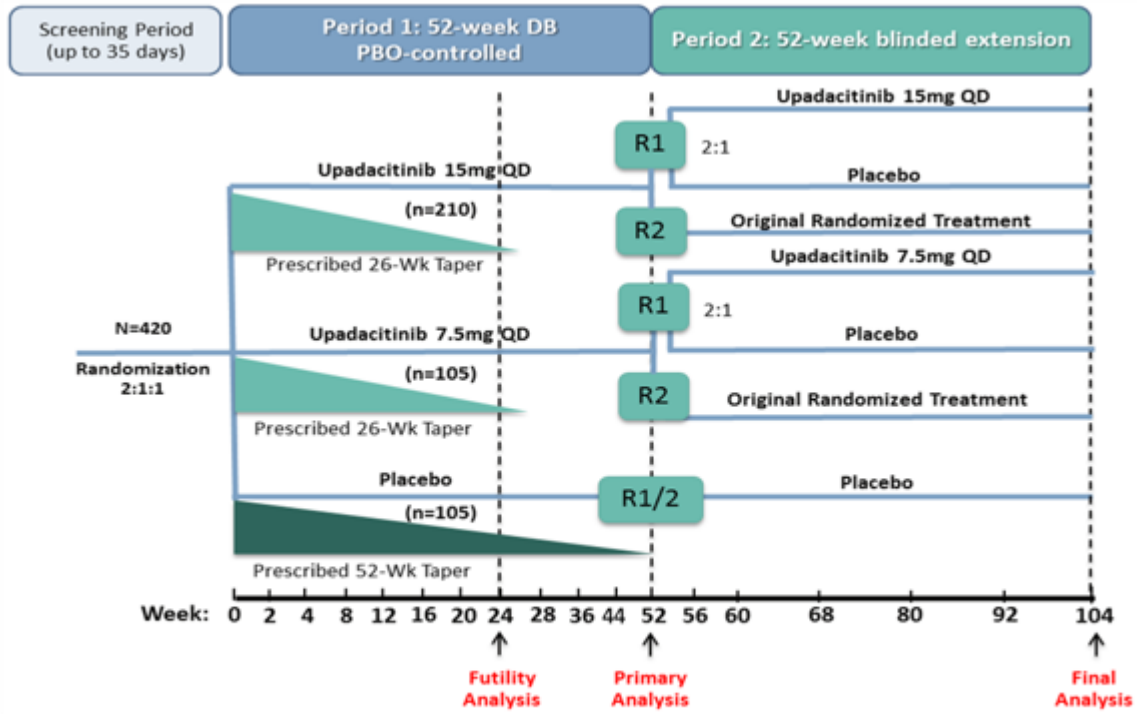
Study M16-852 has two periods. Period 1 evaluated the efficacy of upadacitinib 15 mg QD and 7.5 mg QD in combination with a 26-week CS taper regimen compared to placebo in combination with a 52-week CS taper regimen, as measured by the proportion of subjects in sustained remission at Week 52 and assessed the safety and tolerability of upadacitinib in subjects with GCA. Period 2 is ongoing and evaluates the safety of upadacitinib in all subjects who entered Period 2, and the efficacy of continuing or withdrawing upadacitinib in maintaining remission in subjects who achieved remission in Period 1 for at least 24 consecutive weeks prior to Week 52.

The MAH has submitted the Primary Analysis of Study M16-852 and the efficacy data for all subjects who completed the Week 52 visit or prematurely discontinued from the study prior to Week 52 in

Period 1. The interim database lock for the Primary Analysis was based on a data cutoff date of 06 February 2024.

The study duration includes a 35-day maximum Screening Period; a 52-week randomized, double-blind, parallel-group treatment period (Period 1); a 52-week blinded extension period (Period 2); and a 30-day follow-up period. Subjects who achieved remission at or prior to the Week 52 Visit (at the end of Period 1) were eligible to continue to Period 2. Please see below figure.

Figure 7: Study Schematic of Study M16-852



R1 = sustained remission for 24 consecutive weeks prior to Week 52; R2 = remission at Week 52 but not achieving sustained remission for at least 24 consecutive weeks prior to the Week 52 Visit

Study participants

Table 5 describes the study population.

Table 5: Study population of Study M16-852

Subjects who meet the following criteria:
Diagnosis of GCA according to the following criteria: • Adult male or female, at least 50 years of age • History of ESR ≥ 50 mm/hour or hsCRP/CRP ≥ 1.0 mg/dL • Presence of at least one of the following: o Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication), or

o Unequivocal symptoms of PMR (shoulder and/or hip girdle pain associated with inflammatory morning stiffness). • Presence of at least one of the following: o Temporal artery biopsy revealing features of GCA, or o Evidence of large vessel vasculitis by angiography or cross-sectional imaging such as MRI, CT or PET, assessed by a qualified radiologist experienced in evaluating large vessel vasculitis, or ultrasound of temporal arteries assessed by a qualified physician experienced in evaluating large vessel vasculitis.
Active new onset or relapsing GCA with active disease within 8 weeks of Baseline. Active disease is defined by the presence of at least one of the following: unequivocal cranial symptoms of GCA, unequivocal symptoms of PMR, or other features judged by the investigator to be consistent with GCA or PMR flares, AND an ESR ≥ 30 mm/hr or hsCRP/CRP ≥ 1 mg/dL.
Subjects must have received treatment with ≥ 40 mg prednisone (or equivalent) at any time prior to Baseline and must have been receiving prednisone (or prednisolone) 20 mg, 30 mg, 40 mg, 50 mg, or 60 mg QD at Baseline.
Subjects must have had GCA that, in the opinion of the investigator, was clinically stable to allow the subject to safely initiate the protocol-defined CS taper regimen.

Treatments

Study drug includes the investigational product (IP) of upadacitinib and matching upadacitinib placebo as well as CS therapy (open label or blinded prednisone/prednisolone and matching CS placebo) included as part of the protocol-defined CS taper. Study drug was to be taken orally once daily beginning on Day 1 (Baseline) and was to be taken at approximately the same time each day, with or without food.

Starting at Baseline, all subjects switched from CS obtained outside of the study to open-label oral prednisone or prednisolone provided by the Sponsor at a dose of 20, 30, 40, 50, or 60 mg QD. The initial dose of prednisone or prednisolone was at the discretion of the investigator, based on disease severity and comorbid medical conditions, but was a minimum of 20 mg QD at Baseline. At Baseline, if a subject was on a dose other than 20, 30, 40, 50, or 60 mg QD, the dose was rounded up or down, as clinically indicated per investigator discretion, to the nearest of these doses. Subjects followed a CS Tapering Schedule, completing the open-label phase and transitioning to the blinded phase of tapering depending on the CS dose at baseline (i.e., subjects starting on 20 mg/day transitioned to the double-blind phase of tapering more quickly than patients starting on 60 mg/day).

Subjects were instructed to return all drug containers (even if empty) to the study site personnel at each study visit and the study site personnel was to document compliance. The MAH supplied upadacitinib, matching upadacitinib placebo, as well as open-label and blinded CS therapy (prednisone or prednisolone) and matching CS placebo included as part of the protocol-defined CS taper.

Objectives

The study objectives of period 1 of Study M16852 are to evaluate the efficacy of upadacitinib 7.5 mg QD and 15 mg QD in combination with a 26-week CS taper regimen compared to placebo in combination with a 52-week CS taper regimen, as measured by the proportion of subjects in sustained remission at Week 52, and to assess the safety and tolerability of upadacitinib in subjects with GCA.

Outcomes/endpoints

The primary endpoint of Study M16-852 is:

- the proportion of subjects achieving sustained remission at Week 52, defined as having achieved the absence of GCA signs and symptoms from Week 12 through Week 52 and adherence to the protocol defined CS taper regimen. Subjects who adhered to the protocol-defined CS taper regimen would be CS-free at Week 52.

The multiplicity-controlled secondary endpoints are:

1. Proportion of subjects achieving sustained complete remission from Week 12 through Week 52
2. Cumulative CS exposure through Week 52.
3. Time to first GCA flare through Week 52.
4. Proportion of subjects who experience at least 1 GCA flare through Week 52.
5. Proportion of subjects in complete remission at Week 52.
6. Proportion of subjects in complete remission at Week 24.
7. Change from Baseline in the 36-item SF-36 PCS at Week 52.
8. A group of four endpoints:
    - Number of GCA flares per subject during Period 1.
    - Change from Baseline in FACIT-Fatigue at Week 52.
    - Assessment of TSQM patient global satisfaction subscale at Week 52.
    - Rate of CS-related AEs through Week 52.

The primary and multiplicity-controlled secondary endpoints were tested in the specified order and began with testing the primary endpoint for upadacitinib 15 mg dose using α of 0.05. Continued testing followed a pre-specified α transfer path which includes downstream transfer along the endpoint sequence within each dose as well as cross-dose transfer. Adjusted P values for the primary and multiplicity-controlled secondary endpoints were provided based on the testing procedure.

The remission-related endpoints are assessed based on the following concepts at specific timepoints or periods:

- Remission

Absence of GCA signs and symptoms

Adherence to the protocol-defined CS taper regimen

- Sustained Remission

Sustained remission at Week 52 is defined as having achieved remission from Weeks 12 through 52.

- Complete Remission

Complete remission is defined as having achieved all of the following:

- Remission (as defined above).
- Normalization of ESR (to ≤ 30 mm/hr); if ESR > 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met.
- Normalization of hsCRP to < 1 mg/dL.

- Sustained complete remission from Week 12 through Week 52

Sustained complete remission from Week 12 though Week 52 is defined as having achieved all of the following:

- Sustained remission.
- Normalization of ESR (to ≤ 30 mm/hr; if ESR > 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met) from Week 12 through Week 52.
- Normalization of hsCRP (to < 1 mg/dL without elevation [on 2 consecutive visits] to ≥ 1 mg/dL) from Week 12 through Week 52.

GCA flare is a composite endpoint that is defined as an event determined by the investigator to represent recurrence of GCA signs or symptoms or an ESR > 30 mm/hr (attributable to GCA) and requiring an increase in CS dose. In order to meet the GCA flare criteria, a subject must first achieve a "flare-free" status, defined by satisfying all the following elements: absence of recurrence of GCA signs and symptoms, normalization of ESR, and no increase in CS dose. Subjects who never achieved 'flare-free' status were considered as having GCA flare at Baseline.

The following QoL and ePRO instruments were used:

- SF-36

SF-36 is a generic health-related quality-of-life instrument that can be used across age, disease and treatment groups and includes 8 domains: physical functioning; role limitations due to physical health problems; role limitations due to emotional health problems; social functioning; pain; energy/fatigue; emotional well-being; and general health problems. Two summary scores, PCS and MCS, are generated based on the eight domains. All items, scales, and summary measures have a score range of 0-100 with higher scores indicating better outcomes.

The sponsor conducted qualitative research to provide patient-reported evidence of content validity for the SF-36, specifically that this PRO instrument measures concepts relevant to patients with GCA and that patients with GCA are able to interpret and respond to the items on this questionnaire. Further, the sponsor conducted a set of quantitative analyses using data from Study M16-852 to evaluate the psychometric performance and score interpretation of the SF-36 PCS score.

- FACIT-Fatigue

FACIT-Fatigue is a 13-item ePRO that evaluates fatigue/tiredness and its impact on daily activities and functioning, which has been validated in the general population and in other chronic diseases. This instrument includes items such as tiredness, weakness, listlessness, lack of energy, and the impact of these feelings on daily functioning (e.g., sleeping, and social activities).

The sponsor conducted qualitative research to provide patient-reported evidence of content validity for the FACIT-Fatigue, specifically that this PRO instrument measures concepts relevant to patients with GCA and that patients with GCA are able to interpret and respond to the items on this questionnaire.

Further, the sponsor conducted a set of quantitative analyses using data from Study M16-852 to evaluate the psychometric performance and score interpretation of FACIT-Fatigue.

- TSQM

TSQM is a generic ePRO measure of treatment satisfaction, developed to compare treatment satisfaction between medication types and conditions (Atkinson 2004[2]).

TSQM version 1.4 consists of 14 items that result in 4 specific domains: Effectiveness, Side Effects, Convenience, and one global scale item, Global Satisfaction. Scores for each of the 4 domains range from 0 to 100, with higher scores corresponding to higher satisfaction.

Sample size

The planned total sample size of 420 subjects with a 2:1:1 ratio (upadacitinib 15 mg QD + 26-week CS taper: upadacitinib 7.5 mg QD + 26-week CS taper: placebo QD + 52-week CS taper) was determined to have at least 90% power to detect a 20% difference in sustained remission rate at Week 52 between the upadacitinib 15 mg arm and the placebo arm (assuming a response rate of 40% in the placebo arm), using Fisher's exact test, with an overall two-sided alpha = 0.05.

Randomisation

Subjects were randomized in a 2:1:1 ratio (upadacitinib 15 mg + 26-week CS taper regimen, upadacitinib 7.5 mg + 26-week CS taper regimen, or PBO + 52-week CS taper regimen).

Randomization was stratified by Baseline CS dose (prednisone or prednisolone > 30 mg, prednisone or prednisolone ≤ 30 mg), prior use of an IL-6 inhibitor (yes, no), and Baseline disease status (new onset disease, relapsing disease). No stratification was utilized for randomization in Japan, although data on all three stratification factors will be collected for Japanese patients.

A fixed block size of 8 was used according to the randomization schedule (dated 29-Aug-2018).

Blinding (masking)

The investigator, study site personnel, and the subject were blinded to each subject's treatment throughout the study.

Open-label prednisone or prednisolone was provided until the dose is tapered to less than 20 mg/day. Subsequently, blinded CS therapy and/or matching CS PBO was provided for the remaining blinded taper regimen. While receiving blinded CS therapy, subjects received 1 carton containing 3 bottles of CS study drug per week and were instructed to take 1 capsule per bottle per day; the 3 capsules combined were equivalent to the weekly dose according to the CS tapering schedule.

To maintain the blind, upadacitinib tablets and matching PBO tablets as well as CS capsules and matching PBO capsules were identical in appearance.

All personnel with direct oversight of the conduct and management of the trial (with the exception of Drug Supply Management Team) were blinded to each subject's treatment until the last subject completed the Week 52 visit.

[2] Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12.

Statistical methods

Analysis sets

The Full Analysis Set in Period 1 (FAS1) was used for all efficacy analyses and baseline analyses except for the analysis of CS-related AEs, which was based on the Safety Analysis Set in Period 1 (SS1). The FAS1 included all randomized subjects who received at least 1 dose of study drug in Period 1, and subjects were grouped according to treatment as randomized. The SS1 consisted of all subjects who received at least 1 dose of study drug in Period 1, but subjects were assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

Statistical models

The primary endpoint and other binary endpoints (except for proportion of subjects with at least one GCA flare) were analyzed using the Cochran-Mantel-Haenszel to test for common risk difference. The strata include stratification factors (Baseline CS dose [prednisone or prednisolone > 30 mg, prednisone or prednisolone ≤ 30 mg], and baseline disease status [new onset disease, relapsing disease]). The stratification factor of prior use of an IL-6 inhibitor was not included in the models for all analyses due to the small number of prior IL-6 inhibitor users enrolled.

For the proportion of subjects with at least one GCA flare, the point estimate of flare rate at Week 52 from the Kaplan-Meier estimate for each stratum was used to derive the stratified disease flare rate according to Sun R et al[3]. Point estimate, p-value, and 95% CI for the odds ratio between each upadacitinib group and placebo was provided.

For the continuous change from baseline endpoints, of SF-36 PGA and FACIT-Fatigue, comparisons between the upadacitinib treatment groups and the PBO group will be carried out using the Mixed-Effect Model Repeat Measurement (MMRM) model with treatment group, visit, treatment-by-visit interaction, and stratification factors as the fixed factors and the corresponding baseline values as the covariates. An unstructured variance covariance matrix was used. A similar model was used for the endpoint of TSQM, but without adjustment for the baseline value.

For cumulative CS exposure, which was likely non-normally distributed, van Elteren test stratified by stratification factors was used. The median total cumulative CS exposure over the 52 weeks for each treatment group, p-value and the corresponding 95% CI (based on order statistics) for the median was presented.

For the time to event endpoint (i.e., time to first disease flare), treatment comparisons were conducted using stratified log-rank test stratified by stratification factors. Median time for each treatment group was provided based on Kaplan-Meier estimate. Subjects who never achieve the three criteria required before disease flare is considered during the treatment period was censored at Baseline. Subjects who achieved the three criteria required before disease flare but never experience disease flare were censored at the last assessment in Period 1. Analyses using Cox proportional hazards model with stratification factors as covariates were also performed. Corresponding p-values, hazard ratios and 95% CIs were reported.

For count endpoints (i.e., number of disease flare per subject and CS-related AEs), comparisons between each upadacitinib treatment group and the placebo group were carried out using Poisson regression model with stratification factors as covariates, adjusted by the duration of study participation (or duration of study drug exposure for CS-related AEs). Robust standard error was used.

Intercurrent events

[3] Sun R, McCaw Z, Tian L, et al. Moving beyond conventional stratified analysis to assess the treatment effect in a comparative oncology study. J Immunother Cancer. 2021;9:e003323.

Intercurrent Events (ICEs):

- ICE1: Premature discontinuation from study treatment
- ICE2: Investigator-initiated CS escape therapy
- ICE3: Received more than 100 mg prednisone (or equivalent) systemic CS for a non-GCA indication

For the primary analysis of the primary efficacy endpoint, estimand with composite and hypothetical strategy were used. For ICE1: subjects were considered as nonresponders after ICE1. ICE2 is not applicable for the primary endpoint. For ICE3: data after ICE3 were handled by multiple imputation (MI).

For the primary analysis of the multiplicity-controlled secondary binary remission related efficacy endpoints, estimands with composite and hypothetical strategy were used. For ICE1: subjects were considered as non-responders after ICE1. ICE2 is not applicable for remission related endpoints. For ICE3: data after ICE3 were handled by MI.

For the primary analysis of the secondary binary efficacy endpoint of proportion of subjects who experience at least 1 disease flare through Week 52, estimand with treatment policy strategy to handle ICEs were used: data collected were used regardless of ICE1 or ICE3. ICE2 is not applicable for the endpoint of proportion of subjects who experience at least 1 disease flare.

For the primary analysis of the secondary continuous efficacy endpoints (except for cumulative CS exposure), estimands with treatment policy and hypothetical strategy to handle ICEs were used: data collected were used regardless of ICE1 or ICE3. Data collected after ICE2 were excluded and missing data were handled by mixed effect model repeat measurement (MMRM).

For the primary analysis of secondary endpoint of cumulative CS exposure, estimand with treatment policy strategy to handle ICEs were used: data collected were used regardless of ICE1, ICE2, or ICE3.

For the primary analysis of secondary time-to-event endpoint (i.e., time-to-first disease flare), estimand with treatment policy strategy to handle ICEs were used: data were used regardless of ICE1 or ICE3. ICE2 is not applicable for the endpoint of time-to-first disease flare.

For the primary analysis of secondary count endpoint (i.e., number of disease flares per subject), estimand with treatment policy strategy to handle ICEs were used: data were used regardless of ICE1 or ICE3. ICE2 is not applicable for the endpoint of number of disease flares per subject.

For the primary analysis of the secondary efficacy endpoint of rate of CS-related AEs, estimand with treatment policy strategy to handle ICEs were used: data collected were used regardless of ICE1, ICE2, or ICE3.Missing data

Non-Responder Imputation incorporating multiple imputation (NRI-MI) was the primary approach to handle missing data for binary primary and secondary endpoints (except for the endpoints of proportion of subjects who experience least 1 disease flare). The NRI-MI categorized any subject who does not have an evaluation during a pre-specified visit window (either due to missing assessment, early withdrawal from the study, or due to intercurrent event) as a non-responder for the visit. The only exceptions were: 1) when a subject is a responder both before and after the visit window, the subject was categorized as a responder for the visit 2) missing data due to COVID-19 logistical restriction were handled by MI. The MI assumes data are missing at random (MAR). In total, 30 datasets were imputed, and results from the 30 datasets were synthesized following Rubin's formula.

In as observed (AO) analyses, missing evaluations were not imputed. Thus, a subject who does not have an evaluation on a scheduled visit was excluded from the AO analysis for that visit. All observed

data were used in the analysis. AO analysis was the primary approach to analyze disease flare endpoints (including proportion of subjects who experience at least 1 disease flare through Week 52, time to first disease flare through Week 52, and number of disease flares per subject through Week 52), cumulative CS exposure, and rate of CS-related AEs.

MMRM was the primary approach for the analysis of continuous variables with more than one post Baseline assessment, except for the endpoint of cumulative CS exposure. The parameter estimations were based on the assumption of data being missing at random.Interim analysis

An interim analysis for futility to assess lack of efficacy was conducted by DMC when the first 145 randomized and dosed subjects either completed Week 24 visit or discontinued the study prior to Week 24. The DMC recommendation for this interim analysis for futility was that the study may continue without modification.

The interim futility analysis was based on the conditional power of 15 mg dose group compared to placebo for proportion of subjects achieving sustained remission at Week 24. If the conditional power was below the pre-specified threshold of 15%, the entire study would stop; otherwise, the entire study would move forward without modification. Since the entire study would be either continued without modification or terminated based on the futility analysis results, there was no alpha spending due to the futility analysis.

Type I error control

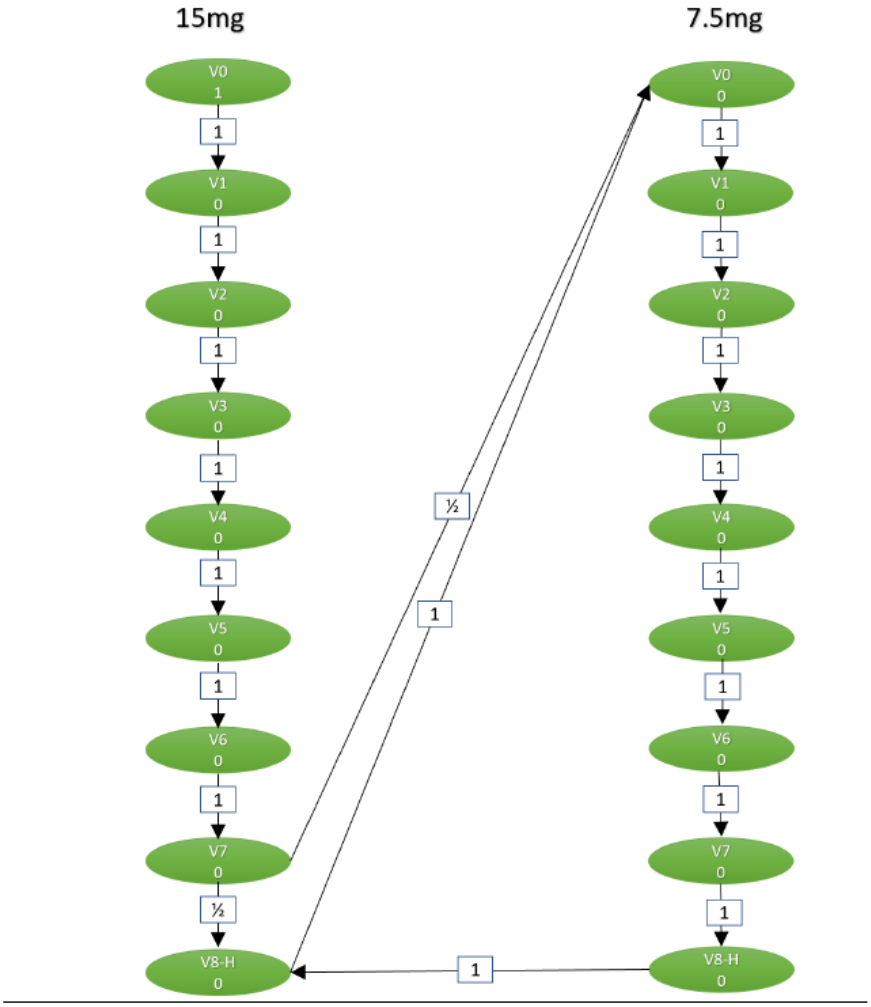
The overall type I error rate of the primary and ranked key secondary endpoints for the 2 upadacitinib doses was strongly controlled using a graphical multiple testing procedure. The ranking is presented in the table below.

Table 6: List of primary and secondary endpoints for regulatory purpose (FAS1)

Name	Variable
V0	Proportion of subjects achieving sustained remission at Week 52
V1	Proportion of subjects achieving sustained complete remission from Week 12 through Week 52
V2	Cumulative CS exposure through Week 52
V3	Time to first disease flare through Week 52
V4	Proportion of subjects who experience at least 1 disease flare through Week 52
V5	Proportion of subjects in complete remission at Week 52
V6	Proportion of subjects in complete remission at Week 24
V7	Change from Baseline in the 36-item Short Form Quality of Life Questionnaire (SF-36) Physical Component Score (PCS) at Week 52
V8-H	• Number of disease flares per subject through Week 52 • Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) at Week 52 • Assessment of Treatment Satisfaction Questionnaire for Medication (TSQM) patient global satisfaction subscale at Week 52 • Rate of CS-related AEs through Week 52

The graphical testing procedure is provided the figure below. The arrows specify the α transfer paths. Once a null hypothesis of an endpoint is rejected (i.e., deemed significant) at its assigned significance level, its significance level will be transferred to subsequent endpoint(s) following the arrow(s). The numbers on the arrows denote the weights for transferring and (possibly) splitting significance levels. Specifically, the weight 1 and 1/2 denotes 100% and 50% transfer of significance level, respectively. The primary and multiplicity-controlled secondary endpoints (V1-V7) are tested sequentially. The remaining multiplicity-controlled secondary endpoints re grouped together (V8-H) and tested using Hochberg procedure.

Table 7: Graphical multiple testing procedure for regulatory purpose (FAS1)



Results

Participant flow

A total of 428 subjects were randomized and received at least one dose of study drug (upadacitinib 15 mg, upadacitinib 7.5 mg, or placebo) in Period 1 at 100 sites located in 23 countries. Overall, 348 (81.3%) subjects completed Period 1. In Period 1, the most frequent primary reasons (reported in ≥ 5% subjects in any treatment group) for discontinuing the study across the treatment groups were AEs and withdrawal of consent.

Table 8: Subject Disposition in Period 1 in Study M16-852 (FAS1)

	PBO + 52 WK CS-T (N=112) n (%)	UPA 7.5 mg + 26 WK CS-T (N=107) n (%)	UPA 15 mg + 26 WK CS-T (N=209) n (%)	UPA Total (N=316) n (%)	Overall Total (N=428) n (%)
Received randomized study drug	112 (100)	107 (100)	209 (100)	316 (100)	428 (100)
Completed Period 1	86 (76.8)	85 (79.4)	177 (84.7)	262 (82.9)	348 (81.3)
Ongoing in Period 1	0	0	0	0	0
Discontinued study in Period 1	26 (23.2)	22 (20.6)	32 (15.3)	54 (17.1)	80 (18.7)
Primary reason for discontinuation					
Adverse event	13 (11.6)	11 (10.3)	17 (8.1)	28 (8.9)	41 (9.6)
Withdrew consent	5 (4.5)	6 (5.6)	10 (4.8)	16 (5.1)	21 (4.9)
Lost to follow-up	0	0	0	0	0
COVID-19 infection	0	0	0	0	0
COVID-19 logistical restrictions	1 (0.9)	0	0	0	1 (0.2)
Failure to meet continuation criteria	2 (1.8)	0	0	0	2 (0.5)
Other	5 (4.5)	5 (4.7)	5 (2.4)	10 (3.2)	15 (3.5)
Completed study drug in Period 1	71 (63.4)	73 (68.2)	155 (74.2)	228 (72.2)	299 (69.9)
Ongoing study drug in Period 1	0	0	0	0	0
Discontinued study drug in Period 1	41 (36.6)	34 (31.8)	54 (25.8)	88 (27.8)	129 (30.1)
Primary reason for discontinuation					
Adverse event	23 (20.5)	18 (16.8)	32 (15.3)	50 (15.8)	73 (17.1)
Withdrew consent	3 (2.7)	7 (6.5)	8 (3.8)	15 (4.7)	18 (4.2)
Lost to follow-up	0	0	0	0	0
Lack of efficacy	8 (7.1)	4 (3.7)	7 (3.3)	11 (3.5)	19 (4.4)
COVID-19 infection	0	0	0	0	0
COVID-19 logistical restrictions	1 (0.9)	0	0	0	1 (0.2)
Other	6 (5.4)	5 (4.7)	7 (3.3)	12 (3.8)	18 (4.2)

PBO + 52 WK CS-T = PBO + 52 Weeks Corticosteroid Taper; UPA 7.5 + 26 WK CS-T = UPA 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 + 26 WK CS-T = UPA 15 mg + 26 Weeks Corticosteroid Taper

Note: Subject 236101 was randomized by error and never dosed.

Methods

Recruitment

First Subject First Visit: 06 February 2019

Last Subject Last Visit (Week 52): 06 February 2024

Conduct of the study

List of protocol changes

The original protocol i.e. Version 1.0 (27 March 2018, 0 subjects) had 7 versions/amendments and 2 administrative changes. The versions/amendments and number of subjects enrolled under each version/amendment were as follows:

- Version 2.0 (05 September 2018, 24 subjects)

Clarified that sustained remission is defined as having achieved both of the primary endpoint components.

Increased the amount of time that subjects should be in remission before enrolling in Period 2 from 8 to 16 weeks.

- Version 2.1 (VHP) (13 February 2019, 3 subjects)

Allowed subjects experiencing a flare to be treated with standard-of-care therapies, including TCZ, after 2 weeks of open label CS escape therapy if investigator believes it is medically necessary for them to permanently discontinue study drug and make this treatment switch.

Clarified role of Data Monitoring Committee.

- Version 3.0 (28 March 2019, 83 subjects)

Clarified that SF-36 PRO endpoint is related to the PCS.

Added patient global satisfaction subscale of TSQM at Week 52 as a multiplicity-adjusted secondary endpoint.

Increased the amount of time that subjects should be in remission before enrolling in Period 2 from 16 to 24 weeks.

Added provision for subjects who achieve remission but not sustained remission at Week 52 to enter Period 2 by staying on their originally randomized treatment.

Clarified that last 4 multiplicity-controlled secondary endpoints will be considered as a group.

Defined and added instructions for subjects experiencing a flare in Period 2

Added nomenclature of FAS1 and FAS2.

- Version 4.0 (27 March 2020, 94 subjects)

Clarified that subjects should stay in the study until the end of the current Period, even after they permanently discontinue study drug.

Decreased the requirement for IV CS from 6 weeks to 4 weeks from Baseline.

- Version 5.0 (09 December 2020, 154 subjects)

Added and updated COVID-19-related language

- Version 6.0 (29 March 2022, 70 subjects)

Added to Benefits and Risks section that MACE and thrombosis have been observed with JAK inhibition.

Updated exclusion criterion #2 changing the time period for having active GCA from within 6 weeks to Baseline to within 8 weeks of Baseline.

- Version 7.0 (31 May 2023, 0 subjects)

Added to Benefits and Risks section the results of ORAL Surveillance study.

Clarified several of the secondary endpoints and explained that secondary endpoints will be multiplicity controlled.

Clarified that the Sponsor will be unblinded at the time of primary analysis for subjects entering into Period 2, while investigators, study site personnel, and subjects will remain blinded to each subject's treatment throughout the study.

Statistical Changes

There were no changes to the planned analyses after finalization of the SAP Version 2.

Protocol deviations

Eighteen subjects received the incorrect treatment or dose of study drug; all of these were related to prednisone/prednisolone, and none were related to upadacitinib/placebo.

Deviations were assessed for their impact on analyses and data integrity or subject safety. None of the deviations were considered to have affected the study outcome or interpretation of the study results or conclusions.

Baseline data

In Period 1, demographic characteristics were generally balanced across the upadacitinib and placebo treatment groups. Overall, the majority of subjects were female, white, not Hispanic nor Latino, non-users of tobacco, and were ≥ 65 years of age (49.1% were ≥ 65 and < 75 years old; and 32.7% were ≥ 75 years old). Mean (SD) BMI for the overall study population in Period 1 was 25.3946 (4.6832) kg/m^2.

Baseline disease characteristics were, according to the MAH, generally balanced across the upadacitinib and placebo treatment groups. The majority of subjects had new onset disease at Baseline and were not prior users of IL-6 inhibitors. The mean CS dose at Baseline in prednisone equivalents was approximately 35 mg across the treatment groups. A similar proportion of subjects in the upadacitinib and placebo treatment groups had CS dose ≤ 30 mg at Baseline. The median (range) disease duration since diagnosis was 41 (14 to 4903) days in the upadacitinib (total) treatment group and 42 (15 to 2993) days in the placebo treatment group.

At Baseline, the mean CRP was 6.479 mg/L in the upadacitinib (total) group and 5.701 mg/L in the placebo group; the mean ESR was 19.7 mm/hr in the upadacitinib (total) group and 21.7 mm/hr in the placebo group.

Numbers analysed

The following population sets were used for the main analyses included in this interim CSR:

- The FAS in Period 1 (FAS1) consisted of all randomized subjects who received at least 1 dose of study drug in Period 1. N=428.
- The Per-Protocol Analysis Set was defined to represent a subset of the FAS1 subjects without any major protocol violations during the study which are expected to impact the primary endpoint. The final criteria and the exclusion of subjects for the Per-Protocol Analysis Set was finalized before the database lock for Primary Analysis. The Per-Protocol Analysis Set was used to analyze the primary efficacy endpoint as a supplementary analysis. N=378.

- The Safety Analysis Set in Period 1 (SS1) consisted of all subjects who received at least 1 dose of study drug in Period 1.
- The Long-Term Safety Analysis Set (SS_LT) consisted of all subjects who received at least one dose of study drug in Period 1 and received the same study drug in Period 2.

Outcomes and estimation

Primary Endpoint (Sustained Remission at Week 52)

The outcome for the primary endpoint is summarized in Table 9.

Table 9: Primary Endpoint: Proportion of Subjects Achieving Sustained Remission at Week 52 (NRI-MI; FAS1)

		Responder			Response Rate Diff Compared to PBO			
Strata Treatment	N	n (%)	[95% CI][&]	Number of Subjects Imputed by MI n	Diff (%)	Adjusted Diff (%)	[95% CI][#]	P-value[@]
All								
PBO + 52 WK CS-T	112	33 (29.0)	[20.6, 37.5]	1				
UPA 7.5 + 26 WK CS-T	107	44 (41.1)	[31.8, 50.4]	2	12.1	12.1	[-0.4, 24.6]	0.0579
UPA 15 + 26 WK CS-T	209	97 (46.4)	[39.6, 53.2]	6	17.4	17.1	[6.3, 27.8]	0.0019**

PBO + 52 WK CS-T = placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 + 26 WK CS-T = upadacitinib 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 + 26 WK CS-T = upadacitinib 15 mg + 26 Weeks Corticosteroid Taper

& 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 logistic restriction or data after subject received more than 100 mg systemic CS (prednisone or equivalent) for a non-GCA indication. Otherwise, it is based on the normal approximation to the binomial distribution.

@ Across the strata, 95% CI for adjusted difference and p-value are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (Baseline CS dose (prednisone or prednisolone > 30 mg or ≤ 30 mg) and disease status (new onset or relapsing disease)) for the comparison of two treatment groups. Within each stratum, 95% CI for difference are calculated using normal approximation to the binomial distribution. The calculations are based on non-responder imputation incorporating multiple imputation or non-responder imputation only if there are no missing data due to COVID-19 logistic restrictions.

* P-value ≤ 0.05.

** P-value ≤ 0.01.

*** P-value ≤ 0.001.

The analysis of components of sustained remission is provided in the table below.

Table 10: Analysis of Components of Sustained Remission at Week 52 (FAS1)

Analysis of Components of Sustained Remission at Week 52
(FAS1)

Endpoint/Component Treatment	N	Responder n (%)	Responder [95% CI] &	Missing Due to COVID-19 n $	Response Rate Diff Compared to Placebo Diff(%)	Response Rate Diff Compared to Placebo Adjusted Diff(%)	Response Rate Diff Compared to Placebo [95% CI] #	Response Rate Diff Compared to Placebo P-value @
Sustained Remission at Week 52 (NRI-MI)								
PBO + 52 WK CS-T	112	33 (29.0)	[20.6, 37.5]	0				
UPA 7.5 + 26 WK CS-T	107	44 (41.1)	[31.8, 50.4]	0	12.1	12.1	[-0.4, 24.6]	0.0579
UPA 15 + 26 WK CS-T	209	97 (46.4)	[39.6, 53.2]	0	17.4	17.1	[6.3, 27.8]	0.0019**
Absence of GCA signs and Symptoms from Week 12 through Week 52 (NRI-MI)								
PBO + 52 WK CS-T	112	33 (29.8)	[21.3, 38.3]	0				
UPA 7.5 + 26 WK CS-T	107	45 (42.1)	[32.7, 51.4]	0	12.3		[-0.4, 24.9]	
UPA 15 + 26 WK CS-T	209	97 (46.3)	[39.5, 53.1]	0	16.5		[5.6, 27.4]	
Adherence to CS Taper Regimen (NRI)								
PBO + 52 WK CS-T	112	44 (39.3)	[30.2, 48.3]					
UPA 7.5 + 26 WK CS-T	107	51 (47.7)	[38.2, 57.1]		8.4		[-4.7, 21.5]	
UPA 15 + 26 WK CS-T	209	122 (58.4)	[51.7, 65.1]		19.1		[7.8, 30.3]	

Note: & 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 logistic restriction or data after subject received more than 100 mg systemic CS (prednisone or equivalent) for a non-GCA indication. Otherwise, it is based on the normal approximation to the binomial distribution.
$ Only count assessment missing due to COVID-19 and imputed by MI.
# @ For all endpoints, 95% CI for adjusted difference and p-value are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (Baseline CS dose (prednisone or prednisolone > 30 mg or <= 30 mg) and disease status (new onset or relapsing disease)) for the comparison of two treatment groups. For each component, 95% CI for difference are calculated using normal approximation to the binomial distribution. The calculations are based on non-responder imputation incorporating multiple imputation or non-responder imputation only if there are no missing data due to COVID-19 logistic restrictions.
For Adherence to CS Taper Regimen, non-Responder Imputation is used.
PBO + 52 WK CS-T = Placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 + 26 WK CS-T = Upadacitinib 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 + 26 WK CS-T = Upadacitinib 15 mg + 26 Weeks Corticosteroid Taper.
* P-value <= 0.05; ** P-value <= 0.01; *** P-value <= 0.001.

Complementary information on the reason for non-responder for “Proportion of Subjects Achieving Sustained Remission at Week 52” was provided. Of note, if a subject met multiple criteria leading to non-responder status at different visits, they were classified according to the category that was met first.

Table 11: Reason for Non-responder in Endpoint Proportion of Subjects Achieving Sustained Remission at Week 52 by Each Component (FAS1)

	PBO + 52 WK CS-T (N=112)	UPA 7.5 + 26 WK CS-T (N=107)	UPA 15 + 26 WK CS-T (N=209)
Number of subjects who were non-responders	79 (70.5)	63 (58.9)	111 (53.1)
Due to premature discontinuation from study treatment	22 (19.6)	19 (17.8)	42 (20.1)
Due to missing assessment	1 (0.9)	1 (0.9)	1 (0.5)
Due to not meeting Absence of GCA signs and symptoms from Week 12 through Week 52	45 (40.2)	34 (31.8)	58 (27.8)
Due to not meeting Adherence to the protocol-defined CS taper regimen	39 (34.8)	29 (27.1)	41 (19.6)

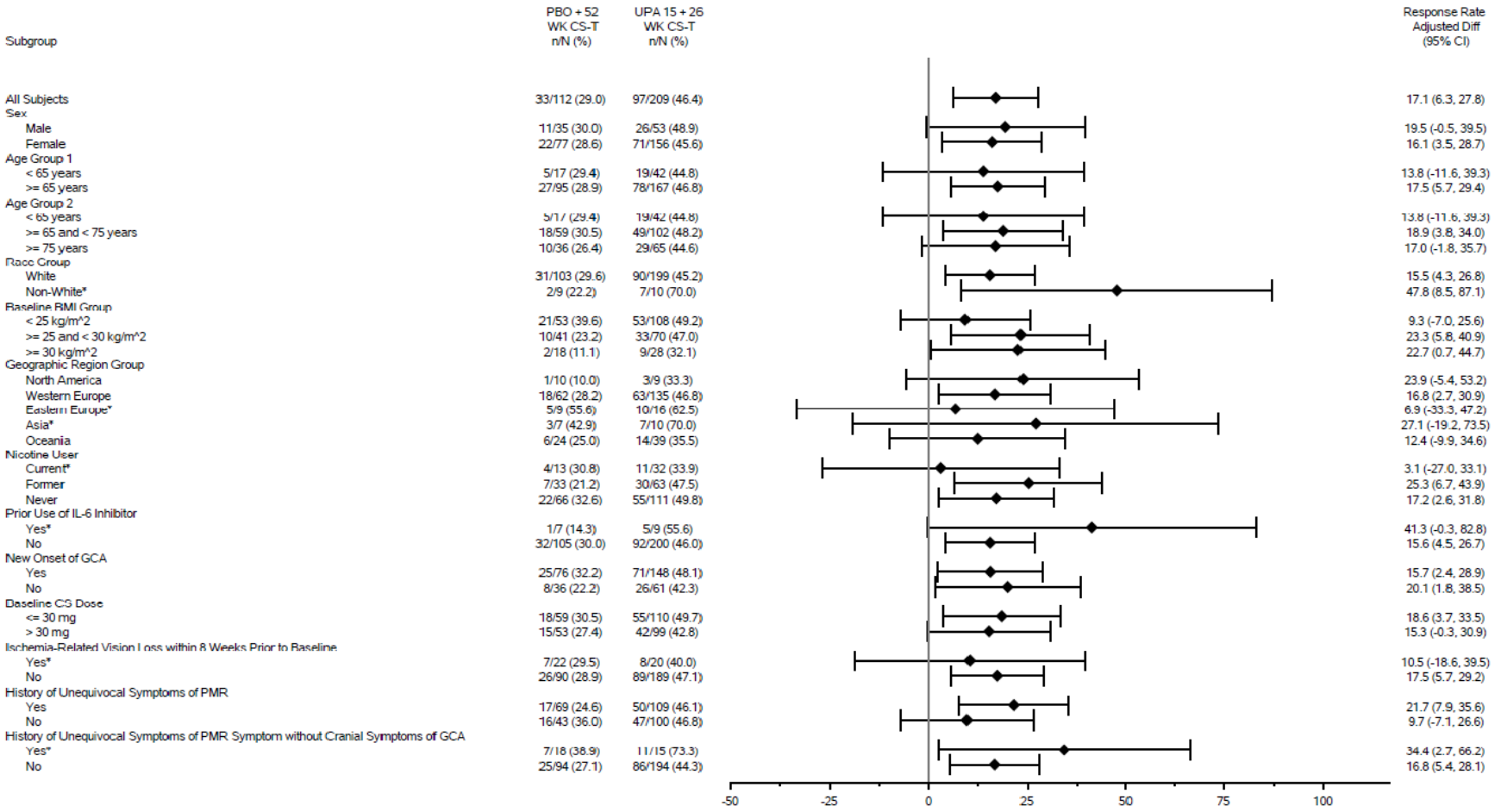
Note: Subjects are classified into the category that was met first. If subjects failed to meet both components—absence of GCA signs and symptoms from Week 12 through Week 52 and adherence to the protocol-defined CS taper regimen at the same time—subjects are classified into both categories.

For UPA 15 arm, number of subjects who were non-responders does not include the one non-responder due to ICE 3 [Received more than 100 mg prednisone (or equivalent) systemic CS for a non-GCA indication] handling by multiple imputation.

PBO + 52 WK CS-T = Placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 + 26 WK CS-T = Upadacitinib 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 + 26 WK CS-T = Upadacitinib 15 mg + 26 Weeks Corticosteroid Taper.

The proportion of subjects achieving sustained remission in upadacitinib 15 mg Group at Week 52 by subgroup is provided in Figure 8.

Figure 8: Proportion of Subjects Achieving Sustained Remission in Upadacitinib 15 mg Group at Week 52 by Subgroup (NRI-MI; FAS1)



PBO + 52 WK CS-T = placebo + 52 Weeks Corticosteroid Taper; UPA 15 + 26 WK CS-T = upadacitinib 15 mg + 26 Weeks Corticosteroid Taper
Note: 95% CI for adjusted difference and P-value were calculated according to the CMH test adjusted for strata (Baseline CS dose [prednisone or prednisolone > 30 mg or ≤ 30mg] and disease status [new onset or relapsing disease]) for the comparison of 2 treatment groups, with the excepts: 1) Baseline CS dose was stratified by disease status(new onset or relapsing disease); 2) Disease status was stratified by Baseline CS dose (prednisone or prednisolone > 30 mg or ≤ 30 mg). The calculations were based on non-responder imputation incorporating multiple imputation or non-responder imputation only if there were no missing data due to COVID-19 logistic restrictions.

* Model was not adjusted by stratification factors due to zero subject in a stratum, and 95% CI for difference was calculated using normal approximation to the binomial distribution

Secondary Endpoints

The secondary endpoint results for Period 1 are summarized in the Table 12.

Table 12: Summary of Secondary Endpoint Results (FAS1)

Endpoint[#]		Within Group	Between Group (UPA vs PBO)		
Treatment	N	PE [95% CI]	PE [95% CI][$]	P-value	Statistical Significance[@]
Proportion of subjects achieving sustained complete remission from Week 12 through Week 52 (%)					
PBO + 52 WK CS-T	112	16.1 [9.3, 22.9]			
UPA 7.5 + 26 WK CS-T	107	26.2 [17.8, 34.5]	9.9 [-0.8, 20.6]	0.0699	Not Significant
UPA 15 + 26 WK CS-T	209	37.1 [30.5, 43.7]	20.7 [11.3, 30.2]	<0.0001***	Significant
Cumulative CS exposure through Week 52 (median, mg)					
PBO + 52 WK CS-T	90	2882.0 [2762.00, 3253.00]			
UPA 7.5 + 26 WK CS-T	86	1905.0 [1615.00, 2265.00]		<0.0001***	Not Significant
UPA 15 + 26 WK CS-T	180	1615.0 [1615.00, 1635.00]		<0.0001***	Significant
Time to first GCA flare through Week 52 (days)					
PBO + 52 WK CS-T	112	323.0 [249.00, NE]			
UPA 7.5 + 26 WK CS-T	107	NE [316.00, NE]	0.75 [0.499, 1.136]	0.1778	Not Significant
UPA 15 + 26 WK CS-T	209	NE [NE, NE]	0.57 [0.399, 0.826]	0.0025**	Significant
Proportion of subjects who experience at least 1 GCA flare through Week 52 (%)					
PBO + 52 WK CS-T	112	55.6 [42.9, 69.2]			
UPA 7.5 + 26 WK CS-T	107	41.3 [32.2, 51.7]	0.60 [0.35, 1.03]	0.0633	Not Significant
UPA 15 + 26 WK CS-T	209	34.3 [27.4, 42.4]	0.47 [0.29, 0.74]	0.0014**	Significant
Proportion of subjects in complete remission at Week 52 (%)					
PBO + 52 WK CS-T	112	19.6 [12.3, 27.0]			
UPA 7.5 + 26 WK CS-T	107	43.0 [33.6, 52.4]	23.5 [11.7, 35.3]	<0.0001***	Not Significant
UPA 15 + 26 WK CS-T	209	50.2 [43.4, 57.1]	30.3 [20.4, 40.2]	<0.0001***	Significant
Proportion of subjects in complete remission at Week 24 (%)					
PBO + 52 WK CS-T	112	36.1 [27.2, 45.1]			
UPA 7.5 + 26 WK CS-T	107	39.3 [30.0, 48.5]	3.2 [-9.6, 16.0]	0.6276	Not Significant
UPA 15 + 26 WK CS-T	209	57.2 [50.5, 64.0]	20.8 [9.7, 31.9]	0.0002***	Significant
Change from Baseline in the SF-36 PCS at Week 52					
PBO + 52 WK CS-T	44	-1.2892 [-3.3093, 0.7309]			
UPA 7.5 + 26 WK CS-T	49	1.3202 [-0.6553, 3.2957]	2.6094 [-0.1841, 5.4028]	0.0670	Not Significant
UPA 15 + 26 WK CS-T	123	2.4634 [1.1707, 3.7561]	3.7526 [1.3932, 6.1119]	0.0019**	Significant

Endpoint[#]		Within Group	Between Group (UPA vs PBO)		
Treatment	N	PE [95% CI]	PE [95% CI][$]	P-value	Statistical Significance[@]
Number of GCA flares per subject through Week 52					
PBO + 52 WK CS-T	112	0.7 [0.5, 0.9]			
UPA 7.5 + 26 WK CS-T	107	0.6 [0.4, 0.7]	0.8 [0.6, 1.2]	0.2722	Not Significant
UPA 15 + 26 WK CS-T	209	0.4 [0.3, 0.5]	0.6 [0.4, 0.8]	0.0010***	Significant
Change from Baseline in FACIT-Fatigue at Week 52					
PBO + 52 WK CS-T	45	-2.4 [-4.71, -0.07]			
UPA 7.5 + 26 WK CS-T	49	1.1 [-1.17, 3.37]	3.5 [0.27, 6.70]	0.0338*	Not Significant
UPA 15 + 26 WK CS-T	123	1.7 [0.18, 3.14]	4.0 [1.33, 6.76]	0.0036**	Significant
Assessment of TSQM patient global satisfaction subscale at Week 52					
PBO + 52 WK CS-T	45	68.8428 [63.8310, 73.8547]			
UPA 7.5 + 26 WK CS-T	52	74.2644 [69.4483, 79.0805]	5.4216 [-1.4269, 12.2701]	0.1203	Not Significant
UPA 15 + 26 WK CS-T	126	71.5753 [68.3375, 74.8131]	2.7325 [-3.1020, 8.5670]	0.3573	Not Significant
Rate of CS-related AEs through Week 52 (mean number per subject per PY)^					
PBO + 52 WK CS-T	112	1.7 [1.3, 2.3]			
UPA 7.5 + 26 WK CS-T	107	1.7 [1.2, 2.2]	0.9 [0.6, 1.4]	0.7749	Not Significant
UPA 15 + 26 WK CS-T	209	2.0 [1.7, 2.4]	1.1 [0.8, 1.6]	0.4371	Not Significant

PBO + 52 WK CS-T = PBO + 52 Weeks Corticosteroid Taper; UPA 7.5 + 26 WK CS-T = UPA 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 + 26 WK CS-T = UPA 15 mg + 26 Weeks Corticosteroid Taper

Results for categorical endpoints (except for proportion of subjects who experience at least 1 GCA flare) were based on CMH with non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-MI).

Number of GCA flares per subject and rate of CS-related AEs were assessed as events per patient-years based on Poisson model adjusted by stratification factors, with log (duration of study participation in years) as an offset. Robust standard error was used in inference.

Results for continuous endpoints (except for cumulative CS exposure) were based on MMRM. Cumulative CS exposure was assessed using van Elteren test stratified by stratification factors. Time to first GCA flare was based on KM Method and p-values are based on stratified log-rank test.

$ Point estimate and 95% CI for treatment difference were based on CMH for categorical endpoints, MMRM for continuous endpoints (except for cumulative CS exposure), Cox model for time to first GCA flare, and Poisson model for Number of GCA flares per subject and Rate of CS-related AEs.

@ Statistical significance was determined via the graphical multiple testing procedure controlling the overall Type I error rate of all primary and secondary endpoints at the 0.05 level.

^ This endpoint was based on SS1.

* P-value ≤ 0.05.

** P-value ≤ 0.01.

*** P-value ≤ 0.001.

Note: Within-group estimate: Percentage for categorical endpoints, median for cumulative CS exposure and time to first GCA flare, least squares mean for continuous endpoints, and mean number of event rate per patient-year for number of GCA flares per subject and rate of CS-related AEs. Between-group estimate: HR for time to first GCA flare, odds ratio for proportion of subjects who experience at least 1 GCA flare, difference in least squares means for continuous endpoints, difference in percentages for categorical endpoints.

The analysis of the components of the first secondary endpoint is provided in Table 13.

Table 13: Analysis of Components of Sustained Complete Remission from Week 12 through Week 52

(FAS1)

Endpoint/Component Treatment	N	Responder n (%)	Responder [95% CI] &	Missing Due to COVID-19 n $	Response Rate Diff Compared to Placebo Diff(%)	Adjusted Diff(%)	[95% CI] #	P-value @
Sustained Complete Remission from Week 12 through Week 52 (NRI-MI)								
PBO + 52 WK CS-T	112	18 (16.1)	[9.3, 22.9]	0				
UPA 7.5 + 26 WK CS-T	107	28 (26.2)	[17.8, 34.5]	0	10.1	9.9	[-0.8, 20.6]	0.0699
UPA 15 + 26 WK CS-T	209	78 (37.1)	[30.5, 43.7]	2	21.0	20.7	[11.3, 30.2]	<0.0001***
Absence of GCA signs and Symptoms from Week 12 through Week 52 (NRI-MI)								
PBO + 52 WK CS-T	112	33 (29.8)	[21.3, 38.3]	0				
UPA 7.5 + 26 WK CS-T	107	45 (42.1)	[32.7, 51.4]	0	12.3		[-0.4, 24.9]	
UPA 15 + 26 WK CS-T	209	97 (46.3)	[39.5, 53.1]	0	16.5		[5.6, 27.4]	
Normalization of ESR from Week 12 through Week 52 (NRI-MI)								
PBO + 52 WK CS-T	112	27 (23.8)	[15.9, 31.8]	1				
UPA 7.5 + 26 WK CS-T	107	41 (38.3)	[29.1, 47.5]	0	14.5		[2.3, 26.6]	
UPA 15 + 26 WK CS-T	209	98 (47.0)	[40.1, 53.8]	0	23.1		[12.7, 33.6]	
Normalization of hsCRP from Week 12 through Week 52 (NRI-MI)								
PBO + 52 WK CS-T	112	28 (25.0)	[17.0, 33.0]	0				
UPA 7.5 + 26 WK CS-T	107	41 (37.9)	[28.7, 47.2]	0	12.9		[0.7, 25.2]	
UPA 15 + 26 WK CS-T	209	110 (52.6)	[45.9, 59.4]	0	27.6		[17.1, 38.1]	
Adherence to CS Taper Regimen (NRI)								
PBO + 52 WK CS-T	112	44 (39.3)	[30.2, 48.3]					
UPA 7.5 + 26 WK CS-T	107	51 (47.7)	[38.2, 57.1]		8.4		[-4.7, 21.5]	
UPA 15 + 26 WK CS-T	209	122 (58.4)	[51.7, 65.1]		19.1		[7.8, 30.3]	

Note: & 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 logistic restriction or data after subject received more than 100 mg systemic CS (prednisone or equivalent) for a non-GCA indication. Otherwise, it is based on the normal approximation to the binomial distribution.
$ Only count assessment missing due to COVID-19 and imputed by MI.
# @ For all endpoints, 95% CI for adjusted difference and p-value are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (Baseline CS dose (prednisone or prednisolone > 30 mg or <= 30 mg) and disease status (new onset or relapsing disease)) for the comparison of two treatment groups. For each component, 95% CI for difference are calculated using normal approximation to the binomial distribution. The calculations are based on non-responder imputation incorporating multiple imputation or non-responder imputation only if there are no missing data due to COVID-19 logistic restrictions.
For Adherence to CS Taper Regimen, non-Responder Imputation is used.
PBO + 52 WK CS-T = Placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 + 26 WK CS-T = Upadacitinib 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 + 26 WK CS-T = Upadacitinib 15 mg + 26 Weeks Corticosteroid Taper.
* P-value <= 0.05; ** P-value <= 0.01; *** P-value <= 0.001.

Complementary information on the reason for non-responder in endpoint “Proportion of Subjects Achieving Sustained Complete Remission at Week 52” (secondary endpoint) were provided. Of note, if a subject met multiple criteria leading to non-responder status at different visits, they were classified according to the category that was met first.

Table 14: Reason for Non-responder in Endpoint Proportion of Subjects Achieving Sustained Complete Remission at Week 52 by Each Component (FAS1)

	PBO + 52 WK CS-T (N=112)	UPA 7.5 + 26 WK CS-T (N=107)	UPA 15 + 26 WK CS-T (N=209)
Number of subjects who were non-responders	94 (83.9)	79 (73.8)	131 (62.7)
Due to premature discontinuation from study treatment	19 (17.0)	20 (18.7)	39 (18.7)
Due to missing assessment	6 (5.4)	2 (1.9)	8 (3.8)
Due to not meeting Absence of GCA signs and symptoms from Week 12 through Week 52	29 (25.9)	28 (26.2)	50 (23.9)
Due to not meeting Normalization of ESR	22 (19.6)	21 (19.6)	30 (14.4)
Due to not meeting Normalization of hsCRP	30 (26.8)	14 (13.1)	9 (4.3)
Due to not meeting Adherence to the protocol-defined CS taper regimen	29 (25.9)	25 (23.4)	34 (16.3)

Note: Subjects are classified into the first category they met. If subjects failed to meet more than one component—absence of GCA signs and symptoms from Week 12 through Week 52, normalization of ESR, normalization of hsCRP, and adherence to the protocol-defined CS taper regimen—subjects are classified under all applicable criteria.

PBO + 52 WK CS-T = Placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 + 26 WK CS-T = Upadacitinib 7.5 mg + 26 Weeks CorticosteroidTaper; UPA 15 + 26 WK CS-T = Upadacitinib 15 mg + 26 Weeks Corticosteroid Taper.

Ancillary analyses

None

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15: Summary of Efficacy for Study M16-852

Title: A Multicenter, Randomized, Double-Blind, Placebo- Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Giant Cell Arteritis: SELECT-GCA (Period 1)			
Study identifier	EU CT: 2023-505476-29-00		
Design	Randomized, double blind, placebo-controlled, multicenter study		
	Period 1; 52-week randomized, double-blind, parallel-group period that investigated upadacitinib 15 mg QD or 7.5 mg QD in combination with a 26-week CS taper regimen compared to placebo in combination with a 52-week CS taper regimen. (Period 2 is an ongoing 52-week blinded extension period)		First Subject First Visit: 06 February 2019 Last Subject Last Visit (Week 52): 06 February 2024
Hypothesis	Superiority		
Treatments groups	Upadacitinib 15 mg QD + 26-week CS taper regimen		number randomized that received study drug: 209
	Upadacitinib 7.5 mg QD + 26-week CS taper regimen		number randomized that received study drug: 107
	Placebo QD + 52-week CS taper regimen		number randomized that received study drug: 112
Endpoints and definitions	Primary endpoint	Sustained remission at week 52	Sustained remission is defined as having achieved both of the following: 1) Absence of GCA signs and symptoms from Week 12 through Week 52; 2) Adherence to the protocol-defined CS taper regimen.
	Secondary	Sustained complete remission from Week 12 through Week 52	Sustained remission+ Normalization of ESR and hsCRP from Week 12 through Week 52.
	Secondary	Cumulative corticosteroid exposure through Week 52 (median)	Cumulative CS (mg) exposure through Week 52
Database lock	The interim database lock for the Primary Analysis was based on a data cutoff date of 06 February 2024		
Results and Analysis			
Analysis description	Primary Analysis		

Analysis population and time point description	The Full Analysis Set in Period 1 (FAS1) was used for all efficacy analyses and baseline analyses except for the analysis of CS-related AEs. The FAS1 included all randomized subjects who received at least 1 dose of study drug in Period 1, and subjects were grouped according to treatment as randomized.			
Descriptive statistics and estimate variability	Treatment group	Upadacitinib 15 mg QD + 26-week CS taper regimen	Upadacitinib 7.5 mg QD + 26-week CS taper regimen	Placebo QD + 52-week CS taper regimen
	Number of subject	209	107	112
	Sustained remission at week 52	46.4	41.1	29.0
	95% CI (primary endpoint)	39.6, 53.2	31.8, 50.4	20.6, 37.5
	Sustained complete remission from Week 12 through Week 52 (secondary endpoint)	37.1	26.2	16.1
	95% CI	30.5, 43.7	17.8, 34.5	9.3, 22.9
	Cumulative corticosteroid exposure through Week 52 (median, mg) (secondary endpoint)*	1615.0	1905.0	2882.0
	95% CI	1615.00, 1635.00	1615.00, 2265.00	2762.00, 3253.00
Effect estimate per comparison	Sustained remission at week 52 (primary endpoint)	Upadacitinib 15 mg QD + 26-week CS taper regimen vs Placebo QD + 52-week CS taper regimen		
		Treatment difference	17.1%	
		95% CI	6.3, 27.8	
		P-value	p⩽0.01	
	Sustained complete remission from Week 12 through Week 52 (secondary endpoint)	Upadacitinib 15 mg QD + 26-week CS taper regimen vs Placebo QD + 52-week CS taper regimen	20.7%	
		Treatment difference	11.3, 30.2	
		95% CI		
		P-value	p⩽0.001	
	Cumulative corticosteroid exposure through Week 52 (median, mg) (secondary endpoint)	Upadacitinib 15 mg QD + 26-week CS taper regimen vs Placebo QD + 52-week CS taper regimen		
		Treatment difference	Not reported	
		variability statistic	Not reported	
		P-value	p⩽0.001	

Notes	CS=corticosteroid(s), QD=once daily
Analysis description	* The comparison of cumulative steroid dose between the upadacitinib arms and the placebo arm is hampered by the different rules for steroid tapering in the active arms vs the placebo arm.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This is an extension of the Rinvoq indication to encompass the new indication “Rinvoq is indicated for the treatment of giant cell arteritis in adult patients”. The posology, as initially proposed, was:

“*The recommended dose of upadacitinib is 15 mg once daily in combination with a tapering course of corticosteroids.*

Based upon the chronic nature of giant cell arteritis, upadacitinib 15 mg once daily can be continued as monotherapy following discontinuation of corticosteroids.”

The application is supported by a single pivotal phase 3 study, Study M16-852, which is a global, multicenter, randomized, double-blind and placebo-controlled including adult subjects of at least 50 years of age with a diagnosis of new onset or relapsing GCA. The studied population is in line with the applied indication of adult patients with GCA. The indication does not include an age threshold, which is agreed as GCA almost exclusively occurs in patients 50 years and older. This is reflected in the ACR/EULAR classification criteria that lists age≥50 years at time of diagnosis as an absolute requirement for the diagnosis (Ponte et al, 2022[4]).

Study M16-852 has two periods. Period 1 evaluated upadacitinib 15 mg QD and 7.5 mg QD in combination with a 26-week CS taper regimen compared to placebo in combination with a 52-week CS taper regimen. Period 2 is ongoing and evaluates the safety of upadacitinib in all subjects who entered Period 2, and the efficacy of continuing or withdrawing upadacitinib in maintaining remission in subjects who achieved remission in Period 1 for at least 24 consecutive weeks prior to Week 52.

The submitted Summary of Clinical Efficacy describes the primary analysis of Study M16-852 and includes the efficacy data for all subjects who completed the Week 52 visit or prematurely discontinued from the study prior to Week 52 in Period 1. The interim database lock for the primary analysis was based on a data cutoff date of 06 February 2024.

Eligible subjects were randomized in a 2:1:1 ratio to 1 of 3 treatment groups: upadacitinib 15 mg QD + 26-week CS taper regimen, upadacitinib 7.5 mg QD + 26-week CS taper regimen, or placebo QD + 52-week CS taper regimen. Randomization at Baseline of all subjects, except for those in Japan, was stratified by Baseline CS dose (prednisone or prednisolone > 30 mg or ≤ 30 mg), prior use of an IL-6 inhibitor, and whether entering the study with new onset or relapsing disease.

The primary endpoint was the proportion of subjects achieving sustained remission at Week 52, defined as having achieved the absence of GCA signs and symptoms from Week 12 through Week 52 and adherence to the protocol defined CS taper regimen. Subjects who adhered to the protocol-defined CS taper regimen would be CS-free at Week 52.

The multiplicity-controlled secondary endpoints were:

[4] Ponte, Cristina, et al. "2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis." *Annals of the Rheumatic Diseases* 81.12 (2022): 1647-1653.

1. Proportion of subjects achieving sustained complete remission from Week 12 through Week 52

- Sustained remission
- Normalization of ESR (to ≤ 30 mm/hr; if ESR > 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met) from Week 12 through Week 52.
- Normalization of hsCRP (to < 1 mg/dL without elevation [on 2 consecutive visits] to ≥ 1 mg/dL) from Week 12 through Week 52.

2. Cumulative CS exposure through Week 52.

3. Time to first GCA flare through Week 52.

4. Proportion of subjects who experience at least 1 GCA flare through Week 52.

5. Proportion of subjects in complete remission at Week 52.

6. Proportion of subjects in complete remission at Week 24.

7. Change from Baseline in the 36-item SF-36 PCS at Week 52.

8. A group of four endpoints:

- Number of GCA flares per subject during Period 1.
- Change from Baseline in FACIT-Fatigue at Week 52.
- Assessment of TSQM patient global satisfaction subscale at Week 52.
- Rate of CS-related AEs through Week 52.

The design of the study and the endpoint selection was discussed with the CHMP in a previous scientific advice procedure and the recommendations given by the CHMP have largely been adhered to.

The pivotal study included both active new onset or relapsing GCA, but subjects must have received treatment with ≥ 40 mg prednisone (or equivalent) at any time prior to Baseline and must have been receiving prednisone (or prednisolone) 20 mg, 30 mg, 40 mg, 50 mg, or 60 mg QD at Baseline. Further, subjects must have GCA that, in the opinion of the investigator, was clinically stable to allow the subject to safely initiate the protocol-defined CS taper regimen. Therefore, upon the CHMP's request, the MAH agreed to update the posology in SmPC Section 4.2 to indicate that upadacitinib monotherapy should not be used for the treatment of acute relapses. A warning is also included in SmPC Section 4.4 stating that upadacitinib monotherapy should not be used for the treatment of acute relapses as efficacy in this setting has not been established.

The posology is also updated to state that treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

Methodological/statistical considerations for study M16-852

It was initially unclear whether the statistical analysis was fully prespecified. In the MAH's initial submission, version 2.0 of the statistical analysis plan (dated 14 February 2024) was provided. However, version 2.0 was finalised 8 days after the data cutoff date for the primary analysis (data cutoff date was the date of the last subject's last visit on 6 February 2024). Upon the CHMP's request, the MAH provided version 1.0 of the statistical analysis plan (dated 27 March 2018). The MAH also clarified that unblinding and database lock for the primary analysis at week 52 took place on 18 March 2024, approximately one month after finalisation of the statistical analysis plan. Therefore, the analysis was fully prespecified and the issue was considered resolved by the CHMP.

The study adhered to the planned sample size, and it was appropriately randomised and double blinded. The type I error was controlled at 5% (two-sided) across endpoints and the two upadacitinib doses using a graphical testing procedure. One protocol-specified interim analysis was conducted to assess futility, at which the data monitoring committee recommended continuing the trial.

The data analysis followed the protocol and the statistical analysis plan. Standard statistical models were used to analyse the data (Kaplan-Meier curves, the stratified log-rank test, the Cochran–Mantel–Haenszel test, the van Elteren test, Poisson regression, and mixed models for repeated measures). It was initially unclear how the odds ratio, p-value, and 95% confidence interval for the endpoint of 'proportion of subjects with at least one GCA flare' were calculated, but the MAH clarified that standard methods had been used.

One of the stratification factors used in the randomisation procedure – prior use of an IL-6 inhibitor (yes, no) – was not controlled for in the analyses. The decision to exclude this factor was specified in the statistical analysis plan, and the reason was the small number of IL-6 inhibitor users enrolled in the trial (23 out of 428 patients). This is acceptable to the CHMP.

The MAH initially provided contradictory information about the analysis sets used for the analysis of the following secondary endpoints:

- Proportion of subjects who experience at least 1 disease flare through Week 52
- Cumulative CS exposure by week through Week 52
- Number of disease flares per subject through Week 52

The study protocol and the statistical analysis plan stated that all primary and key secondary endpoints should be analysed in the full analysis set or the safety analysis set (which turned out to be identical, as all randomised patients received at least 1 dose of their assigned treatment). However, a contradictory statement in the statistical analysis plan indicated that an 'as observed' analysis should be used for the above-mentioned endpoints, meaning that patients with missing data should be excluded. The clinical study report did not clarify which approach was used, and the results table in the clinical study report suggested that all randomised patients were included in the analyses of 2 of the endpoints, the exception being the analysis of 'cumulative CS exposure'. Upon the CHMP's request, the MAH clarified that all randomised patients were included in the analyses of the two flare-related endpoint ('proportion with at least one disease flare' and 'number of disease flares'). This analysis set is appropriate and consistent with the protocol and statistical analysis plan.

The MAH has also clarified that 'cumulative CS exposure' was analysed in the 'as observed set,' meaning that patients with missing data at week 52 were excluded. However, the CHMP pointed out that such analysis set is generally discouraged because it biases the results unless the data are missing completely at random and that imputation of missing data is typically preferable. Nevertheless, the CHMP acknowledged the difficulties of selecting a suitable imputation method, especially when none was pre-specified and agreed that imputation was not required. The information on cumulative CS dose included in SmPC Section 5.1 was updated to clearly state that only patients who completed 52 weeks of follow up were included in the analysis. Further, caution should be given when interpreting the results for 'cumulative CS exposure' because these results are already biased by the study design in favour of the upadacitinib arms (the upadacitinib arms had a faster CS taper than the placebo arm, 26 weeks instead of 52 weeks). This is appropriately reflected in SmPC Section 5.1.

For the primary endpoint and other binary endpoints, missing data were primarily handled using non-response imputation. If data were missing due to COVID-19 restrictions, multiple imputation was used instead. This approach is acceptable to the CHMP.

For continuous endpoints, missing data were handled under a missing-at-random assumption in MMRM models. However, one of the continuous endpoints ('cumulative CS exposure') was analysed using the van Elteren test, which is acceptable to the CHMP.

There were technically no missing data for the count endpoints of 'number of disease flares per subject' and 'CS-related AEs' because these were analysed as event rates (number of events/time in study). For the time-to-event endpoint of 'time to first disease flare', missing data were handled using censoring. Both of these methods assume that patients who withdrew from the trial were similar to those who remained in the trial (independent censoring/missing-at-random), which may not be true. However, this issue was not pursued and the endpoints are not included in the SmPC.

Treatment discontinuations were handled differently for different endpoints. Non-response imputation (a composite strategy) was used for all but one binary endpoint. The exception was the endpoint of 'proportion of subjects who experience at least 1 disease flare', for which treatment discontinuations were ignored (a treatment policy strategy). Treatment discontinuations were also ignored for all other endpoints. The MAH did not justify the use of different strategies for different endpoints, but a reanalysis was not requested for the endpoints for which a treatment policy was used because there were more treatment discontinuations in the placebo group, so the treatment policy strategy would be more conservative (disadvantage the upadacitinib groups) than the composite strategy.

Efficacy data and additional analyses

A total of 428 subjects were randomized and received at least one dose of study drug (upadacitinib 15 mg, upadacitinib 7.5 mg, or placebo) in Period 1. Overall, 348 (81.3%) subjects completed Period 1.

The proportion of subjects that discontinued study in Period 1 was rather high (18.7%) with a somewhat uneven distribution between the study arms: 15.3% in the upadacitinib 15 mg +26-week CS taper arm vs 23.2% in the PBO+52-week CS taper arm. In both groups "adverse event" was the most common primary reason for discontinuation of study: 8.1% in the upadacitinib 15 mg +26-week CS taper arm vs 11.6% in the PBO+52-week CS taper arm. The proportion that discontinued study drug in Period 1 was 25.8% in the upadacitinib 15 mg +26-week CS taper arm vs 36.6% in the PBO+52-week CS taper arm. In both the groups, "adverse event" was the most common primary reason for discontinuation of study drug: 15.3% in the upadacitinib 15 mg+26-week CS taper arm and 20.5% in the PBO+52-week CS taper arm. These data have been taken into consideration for the overall interpretation of study findings.

A statistically significantly greater proportion of subjects achieved the primary endpoint of sustained remission at Week 52 (having achieved both the absence of GCA signs and symptoms from Week 12 through Week 52 and adherence to the protocol-defined corticosteroid taper regimen) in the upadacitinib 15 mg group (46.4%) compared with the placebo group (29.0%). The adjusted difference between upadacitinib 15 mg vs. placebo was 17.1% (P = 0.0019). Results from the subgroup analysis for the primary endpoint indicated consistency of efficacy of upadacitinib 15 mg across important subgroups (eg. sex, race, BMI).

A numerically greater proportion of subjects achieved the primary endpoint of sustained remission at Week 52 in the upadacitinib 7.5 mg group (41.1%) compared with the placebo group (29.0%). The adjusted difference for upadacitinib 7.5 mg vs. placebo was 12.1% (nominal P = 0.0579) and did not reach statistical significance.

For upadacitinib 15 mg+26-week steroid taper vs placebo+52-week steroid taper, not only the primary endpoint but also almost all secondary, multiplicity-controlled, endpoints were met. The exceptions were assessment of TSQM patient global satisfaction subscale at Week 52 and rate of CS-related AEs

through Week 52. For the secondary endpoint sustained complete remission at Week 52 (having achieved absence of GCA signs and symptoms from Week 12 through Week 52, normalization of ESR from Week 12 through Week 52, normalization of hsCRP from Week 12 through Week 52, and adherence to the protocol-defined corticosteroid taper regimen), the difference between the two groups was 20.7%.

Results for each component of sustained remission at Week 52 and sustained complete remission from Week 12 through Week 52 were consistent with that of the respective composite endpoints.

Regarding the secondary endpoint cumulative corticosteroid exposure through Week 52 (median), it was 1615.0 mg in the upadacitinib 15 mg+26-week steroid taper and 2882.0 mg in the placebo+52-week steroid taper group. The CHMP noted that the comparison of cumulative steroid dose between the upadacitinib arms and the placebo arm is hampered by the different rules for steroid tapering in the active arms vs the placebo arm (as discussed above under methodology). The limitations are adequately reflected in the SmPC Section 5.1.

The efficacy results were initially considered difficult to interpret for the binary endpoints because it was unclear why patients had been classified as not achieving remission (e.g., presence of GCA signs, non-adherence to corticosteroid taper, treatment discontinuation, or missing data). Upon the CHMP's request, the MAH provided information on the reason for non-responder in the endpoints "Proportion of Subjects Achieving Sustained Remission at Week 52" and "Proportion of Subjects Achieving Sustained Complete Remission at Week 52". This information were found adequate to support the final efficacy assessment. In order to provide relevant information to the prescriber, the proportion of patients classified as non-responders because of premature treatment discontinuation or missing assessment for the primary endpoint of sustained remission at week 52 is included in SmPC Section 5.1.

The study had an overall 52-week completion rate of 81%, but data for SF-36 PCS and FACIT-Fatigue were only available for 59% (n=123/209) of patients in the 15 mg group and 39-40% (n=44 or 45/112) of patients in the placebo group. This large amount of missing data was handled under a missing-at-random assumption in the MMRM model. There appeared to be more missing data for the SF-36 PCS and FACIT endpoints than there were withdrawals in the study. The MAH explained that this was due to the handling of the 'corticosteroid escape treatment' using a hypothetical strategy, which meant that post-escape-treatment data had been deleted and assumed to be missing-at-random.

Upon the CHMP's request request, the MAH submitted an additional analysis of SF-36 GCS and FACIT-Fatigue that used a treatment-policy strategy for all intercurrent events and jump-to-reference for missing data. This analysis confirmed the statistically significant effect on SF-36 PCS seen in the pre-specified analysis (least-squares mean change: +1.36 for upadacitinib 15 mg versus -1.07 for placebo; p-value for difference: 0.0173) but not on FACIT-Fatigue (least-squares mean change: +1.2 for upadacitinib 15 mg versus -0.5 for placebo; p-value: 0.1278).

The CHMP believed that it is difficult to say which strategy – a treatment policy or hypothetical strategy – is more appropriate for handling the intercurrent event of 'escape corticosteroid treatment.' The choice is ultimately subjective, as the strategies reflect different clinical questions. Therefore, the MAH's hypothetical strategy was considered acceptable.

In the pre-specified analysis, the hypothetical strategy for SF-36 PCS and FACIT-Fatigue was implemented assuming that the post-escape-treatment scores were missing at random (in a mixed model for repeated measures). The CHMP considered this implementation inappropriate because it is equivalent to assuming that patients had not needed – rather than not having used – escape therapy, which is an unrealistic scenario. However, the MAH provided a sensitivity analysis in which the post-escape-treatment scores were imputed with the patient's worst pre-escape-treatment score. The CHMP agreed that this was more appropriate, despite being a single-imputation method. This sensitivity

analysis showed a statistically significant effect on both SF-36 PCS (least-squares mean change: +1.16 for upadacitinib 15 mg versus -1.57 for placebo; p-value for difference: 0.0078) and on FACIT-Fatigue (least-squares mean change: +1.0 for upadacitinib 15 mg versus -1.4 for placebo; p-value for difference: 0.0289). The reported effect size of SF-36 PCS and FACIT-Fatigue for upadacitinib 15 mg+26-week steroid taper (vs placebo+52-week steroid taper) was considered clinically relevant even though close to the limit for what could be considered clinically relevant. Therefore, the CHMP considered the efficacy of upacaditinib on SF-36 PCS and FACIT-Fatigue sufficiently demonstrated to be included in the SmPC Section 5.1.

The analysis of 'time to first disease flare', in which patients were censored upon withdrawing from the study, assumes that patients withdrew from the study at random. Although this may not be true, there were more withdrawals in the placebo arm than in the upadacitinib arms. Hence, the analysis should be conservative and the issue was not further pursued.

The effect size recorded for upadacitinib 15 mg is considered of clinical relevance; both in terms of the ability to induce remission and its likely steroid-sparing potential.

2.4.4. Conclusions on the clinical efficacy

The efficacy data presented are sufficient to support the extension of the indication for the treatment of giant cell arteritis in adult patients.

The available data support the following posology in SmPC section 4.2:

The recommended dose of upadacitinib is 15 mg once daily in combination with a tapering course of corticosteroids. Upadacitinib monotherapy should not be used for the treatment of acute relapses (see section 4.4).

Based upon the chronic nature of giant cell arteritis, upadacitinib 15 mg once daily can be continued as monotherapy following discontinuation of corticosteroids. Treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

2.5. Clinical safety

Introduction

Since its initial approval for the treatment of adults with moderately to severely active RA in 2019, upadacitinib has been approved for the treatment of adults with active AS, nr-axSpA, patients 2 years of age and older with active pJIA, adults and paediatric patients 2 years of age and older with active PsA, adults and adolescents with moderate to severe AD, and adults with moderately to severely active UC and CD. The approved dosage in adults for the different indications spans between doses from 15 mg QD (rheumatic diseases) to 45 mg QD (induction treatments for inflammatory bowel diseases). Some of the known adverse events associated with upadacitinib are infections (sometimes fatal), herpes zoster and other opportunistic infections, transaminase elevations and haematological abnormalities. In addition, as a class effect, treatment of JAK-inhibitors has been associated with an elevated risk of malignancies, MACE and VTE and thus, as a result of the JAKi referral (EMEA/H-A20/1517/C/004760/0017), several updates of the SmPC was made. The updates include a boxed warning that states that upadacitinib should not be used in patients with certain risk factors for these events unless there are no other treatment available.

This submission for the indication of adults with GCA is based on data from the Phase 3 Study M16-852, a Phase 3, global, multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of upadacitinib in subjects with new onset or relapsing GCA.

The following analysis sets were used for the safety analyses:

- The Safety Analysis Set in Period 1 (SS1) consists of all subjects who received at least 1 dose of study drug in Period 1.
- The Long-Term Safety Analysis Set (SS_LT) consists of all subjects who received at least one dose of study drug in Period 1 and received the same dose of study drug in Period 2.

For Safety Analysis Sets (SS1 or SS_LT), subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.
Summaries of safety results from Period 1 (SS1), and long-term safety results across Period 1 and Period 2 are based on SS_LT, in which patients who took the same dose throughout both periods.
Long-term data is presented through the data cutoff date of 06 February 2024.

- The Full Analysis Set for Period 1 (FAS1) consisted of all randomized subjects who received at least 1 dose of study drug in Period 1. FAS1 is used to describe subject disposition, demographics, medical history and Baseline disease characteristics, and prior and concomitant medications.
- Safety data from an age matched subpopulation of the upadacitinib RA programme with and without concomitant corticosteroid use was also provided.

Patient exposure

Table 16: Extent of Exposure in Period 1 (SS1)

		UPA		
	PBO + 52 WK CS-T (N=112)	7.5 mg + 26 WK CS-T (N=107)	15 mg + 26 WK CS-T (N=209)	Total (N=316)
Duration (days)				
n	112	107	209	316
Mean (SD)	289.4 (121.13)	286.9 (125.23)	299.6 (120.49)	295.3 (122.07)
Median	364.0	364.0	364.0	364.0
Min, Max	6.0, 372.0	2.0, 392.0	3.0, 373.0	2.0, 392.0
Duration (weeks) - n (%)				
≥ 1 day	112 (100)	107 (100)	209 (100)	316 (100)
≥ 2 weeks	107 (95.5)	104 (97.2)	207 (99.0)	311 (98.4)
≥ 4 weeks	104 (92.9)	102 (95.3)	203 (97.1)	305 (96.5)
≥ 12 weeks	98 (87.5)	95 (88.8)	183 (87.6)	278 (88.0)
≥ 24 weeks	91 (81.3)	81 (75.7)	167 (79.9)	248 (78.5)
≥ 36 weeks	84 (75.0)	76 (71.0)	162 (77.5)	238 (75.3)
≥ 48 weeks	73 (65.2)	75 (70.1)	157 (75.1)	232 (73.4)
≥ 52 weeks	58 (51.8)	60 (56.1)	122 (58.4)	182 (57.6)

PBO + 52 WK CS-T = placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 mg + 26 WK CS-T = upadacitinib 7.5 mg + 26 Corticosteroid Taper; UPA 15 mg + 26 WK CS-T = upadacitinib 15 mg + 26 Weeks Corticosteroid Taper

Note: Duration of treatment = last dose date - first dose date + 1.

A total of 316 subjects received at least 1 dose of upadacitinib in Period 1 of Study M16-852, representing a total of 266.5 PY of exposure in Period 1, including 209 subjects who received at least 1 dose of upadacitinib 15 mg, representing a total of 178.1 PY of upadacitinib 15 mg exposure.

A total of 92 subjects in the upadacitinib 15 mg group and 39 subjects in the upadacitinib 7.5 mg group received the same dose of study drug in Period 2 as in Period 1, and cumulative safety data (Period 1 and Period 2 data through the data cutoff date) are presented for these subjects in the SS_LT.

Adverse events

Table 17: Overview of Treatment-Emergent Adverse Events and All Deaths Per 100 PYs in Period 1 (SS1)

		UPA			Treatment Difference	
	PBO + 52 WK CS-T (N = 112) (PYs = 94.3) Events (E/100 PY)	7.5 mg + 26 WK CS-T (N = 107) (PYs = 88.5) Events (E/100 PY)	15 mg + 26 WK CS-T (N = 209) (PYs = 178.1) Events (E/100 PY)	Total (N = 316) (PYs = 266.5) Events (E/100 PY)	UPA 7.5 mg - PBO (95% CI&)	UPA 15 mg - PBO (95% CI&)
Any treatment-emergent						
Adverse events (AE)	706 (748.6)	597 (674.8)	1456 (817.7)	2053 (770.3)	-73.8 (-151.1, 3.5)	69.1 (-0.3, 138.4)
AE with reasonable possibility of being related to upadacitinib (or matching placebo)	103 (109.2)	85 (96.1)	247 (138.7)	332 (124.6)	-13.1 (-42.5, 16.2)	29.5 (2.2, 56.8)
AE with reasonable possibility of being related to prednisone/prednisolone (or matching placebo)	171 (181.3)	152 (171.8)	367 (206.1)	519 (194.7)	-9.5 (-48.0, 29.0)	24.8 (-9.6, 59.2)
AE with CTCAE Grade ≥ 3	53 (56.2)	35 (39.6)	99 (55.6)	134 (50.3)	-16.6 (-36.7, 3.4)	-0.6 (-19.3, 18.1)
Serious AE	40 (42.4)	25 (28.3)	65 (36.5)	90 (33.8)	-14.2 (-31.3, 3.0)	-5.9 (-21.8, 9.9)
AE leading to withdrawal of upadacitinib (or matching placebo)	31 (32.9)	27 (30.5)	41 (23.0)	68 (25.5)	-2.4 (-18.7, 14.0)	-9.8 (-23.4, 3.7)
COVID-19 related AE	12 (12.7)	12 (13.6)	33 (18.5)	45 (16.9)	0.8 (-9.7, 11.4)	5.8 (-3.8, 15.4)
AE results in death	2 (2.1)	0	2 (1.1)	2 (0.8)	-2.1 (-5.1, 0.8)	-1.0 (-4.3, 2.3)
All deaths	2 (2.1)	0	3 (1.7)	3 (1.1)	-2.1 (-5.1, 0.8)	-0.4 (-3.9, 3.1)
Occurring ≤ 30 days after last dose of study drug	2 (2.1)	0	2 (1.1)	2 (0.8)	-2.1 (-5.1, 0.8)	-1.0 (-4.3, 2.3)
COVID-19 related	0	0	1 (0.6)	1 (0.4)	0.0	0.6 (-0.5, 1.7)
Occurring > 30 days after last dose of study drug	0	0	1 (0.6)	1 (0.4)	0.0	0.6 (-0.5, 1.7)
COVID-19 related	0	0	0	0	0.0	0.0

E/100 PY = Events per 100 patient-years

Note: Treatment-emergent adverse events in Period 1 are defined as any adverse events with an onset or worsening in severity date on or after the first dose date of study drug and prior to the first dose of study drug in Period 2 or no more than 30 days after the last dose of study drug in Period 1, whichever occurs firstly.

& 95% CI for treatment difference is based on the normal approximation to Poisson distribution.

PBO + 52 WK CS-T = PBO + 52 Weeks Corticosteroid Taper; UPA 7.5 + 26 WK CS-T = UPA 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 + 26 WK CS-T = UPA 15 mg + 26 Weeks Corticosteroid Taper

UPA 7.5 - PBO is the difference of EAER for each AE category between UPA 7.5 mg + 26 Weeks CS Taper group and PBO + 52 Weeks CS Taper group.

UPA 15 - PBO is the difference of EAER for each AE category between UPA 15 mg + 26 Weeks CS Taper group and PBO + 52 Weeks CS Taper group.

Table 18: Overview of Treatment-Emergent Adverse Events and All Deaths per 100 Patient-years (PYs) - Long-Term (SS_LT)

		UPA			Treatment Difference	
	PBO + 52 WK CS-T (N = 43) (PYs = 72.3) Events (E/100 PY)	7.5 mg + 26 WK CS-T (N = 39) (PYs = 72.6) Events (E/100 PY)	15 mg + 26 WK CS-T (N = 92) (PYs = 171.4) Events (E/100 PY)	Total (N = 131) (PYs = 244.0) Events (E/100 PY)	UPA 7.5 mg - PBO (95% CI&)	UPA 15 mg - PBO (95% CI&)
Any treatment-emergent Adverse events (AE)	396 (548.0)	264 (363.6)	874 (509.9)	1138 (466.4)	-184.4 (-253.9, -114.8)	-38.1 (-101.8, 25.6)
AE with reasonable possibility of being related to upadacitinib (or matching placebo)	43 (59.5)	32 (44.1)	145 (84.6)	177 (72.5)	-15.4 (-38.9, 8.0)	25.1 (2.6, 47.6)
AE with reasonable possibility of being related to prednisone/prednisolone (or matching placebo)	63 (87.2)	34 (46.8)	160 (93.4)	194 (79.5)	-40.4 (-67.0, -13.7)	6.2 (-19.8, 32.1)
AE with CTCAE Grade ≥ 3	24 (33.2)	21 (28.9)	42 (24.5)	63 (25.8)	-4.3 (-22.4, 13.9)	-8.7 (-23.9, 6.5)
Serious AE	18 (24.9)	15 (20.7)	26 (15.2)	41 (16.8)	-4.2 (-19.8, 11.3)	-9.7 (-22.6, 3.2)
AE leading to withdrawal of upadacitinib (or matching placebo)	4 (5.5)	2 (2.8)	9 (5.3)	11 (4.5)	-2.8 (-9.4, 3.9)	-0.3 (-6.7, 6.1)
COVID-19 related AE	12 (16.6)	10 (13.8)	29 (16.9)	39 (16.0)	-2.8 (-15.5, 9.9)	0.3 (-10.9, 11.5)
AE results in death	0	0	0	0	0.0	0.0
All deaths	0	0	0	0	0.0	0.0
Occurring ≤ 30 days after last dose of study drug	0	0	0	0	0.0	0.0
COVID-19 related	0	0	0	0	0.0	0.0
Occurring > 30 days after last dose of study drug	0	0	0	0	0.0	0.0
COVID-19 related	0	0	0	0	0.0	0.0

E/100 PY = Events per 100 patient-years

Note: Treatment-emergent adverse events are defined as any adverse events with an onset or worsening in severity date after initiation of study drug and no more than 30 days after the last dose of study drug in the study.

& 95% CI for treatment difference is based on the normal approximation to Poisson distribution.

PBO + 52 WK CS-T = Placebo + 52 Weeks CS Taper / PBO; UPA 7.5 + 26 WK CS-T = UPA 7.5 mg + 26 Weeks CS Taper/UPA 7.5 mg; UPA 15 + 26 WK CS-T = UPA 15 mg + 26 Weeks CS Taper / UPA 15 mg.

UPA 7.5 - PBO is the difference of EAER for each AE category between UPA 7.5 mg + 26 Weeks CS Taper group and PBO + 52 Weeks CS Taper group.

UPA 15 - PBO is the difference of EAER for each AE category between UPA 15 mg + 26 Weeks CS Taper group and PBO + 52 Weeks CS Taper group.

Common Adverse Events

Safety Analysis through Week 52 (Period 1; SS1)

In Period 1, the most frequent TEAEs by SOC in either upadacitinib group were infections and infestations (upadacitinib 15 mg 63.2 %, upadacitinib 7.5 mg 57.0% and placebo 58.9%) followed by musculoskeletal and connective tissue disorders in the upadacitinib 15 mg group and vascular disorders in the upadacitinib 7.5 mg group.

The most common TEAEs (≥ 10% subjects in any treatment group) included worsening of giant cell arteritis, headache, hypertension, COVID-19, arthralgia, urinary tract infection, back pain, nasopharyngitis, and diarrhea. The proportion of subjects with worsening of GCAwas higher in the placebo group compared with the upadacitinib 15 mg and upadacitinib 7.5 mg groups.

Worsening of GCA and urinary tract infection were the most common TEAE (≥ 5% subjects on upadacitinib treatment) considered by the investigator to have a reasonable possibility of being related to upadacitinib (or matching placebo). The common TEAEs considered by the investigator to have a reasonable possibility of being related to prednisone/prednisolone (or matching placebo) included: hypertension, worsening of giant cell arthritis, and urinary tract infection.

Table 19: Subjects with TEAEs Occurring in ≥ 5% Subjects in Active Total by Preferred Term in Period 1 (SS1)

		UPA		
MedDRA 26.1 PT	**PBO + 52 WK CS-T (N = 112) n (%)**	**7.5 mg + 26 WK CS-T (N = 107) n (%)**	**15 mg + 26 WK CS-T (N = 209) n (%)**	**Total (N = 316) n (%)**
Any adverse event	106 (94.6)	102 (95.3)	202 (96.7)	304 (96.2)
Giant cell arteritis	35 (31.3)	28 (26.2)	48 (23.0)	76 (24.1)
Headache	13 (11.6)	16 (15.0)	34 (16.3)	50 (15.8)
Hypertension	13 (11.6)	16 (15.0)	28 (13.4)	44 (13.9)
COVID-19	12 (10.7)	12 (11.2)	28 (13.4)	40 (12.7)
Arthralgia	15 (13.4)	7 (6.5)	29 (13.9)	36 (11.4)
Urinary tract infection	18 (16.1)	15 (14.0)	21 (10.0)	36 (11.4)
Back pain	15 (13.4)	6 (5.6)	25 (12.0)	31 (9.8)
Nasopharyngitis	13 (11.6)	6 (5.6)	18 (8.6)	24 (7.6)
Diarrhoea	12 (10.7)	5 (4.7)	18 (8.6)	23 (7.3)
Fatigue	6 (5.4)	4 (3.7)	19 (9.1)	23 (7.3)
Oedema peripheral	3 (2.7)	7 (6.5)	16 (7.7)	23 (7.3)
Cystitis	3 (2.7)	5 (4.7)	15 (7.2)	20 (6.3)
Constipation	2 (1.8)	8 (7.5)	11 (5.3)	19 (6.0)
Cough	4 (3.6)	5 (4.7)	14 (6.7)	19 (6.0)
Muscle spasms	8 (7.1)	6 (5.6)	13 (6.2)	19 (6.0)
Pain in extremity	6 (5.4)	4 (3.7)	15 (7.2)	19 (6.0)
Upper respiratory tract infection	8 (7.1)	8 (7.5)	11 (5.3)	19 (6.0)
Nausea	4 (3.6)	6 (5.6)	11 (5.3)	17 (5.4)
Cataract	2 (1.8)	6 (5.6)	10 (4.8)	16 (5.1)
Dizziness	6 (5.4)	6 (5.6)	10 (4.8)	16 (5.1)
Myalgia	5 (4.5)	7 (6.5)	9 (4.3)	16 (5.1)
Osteoarthritis	5 (4.5)	3 (2.8)	13 (6.2)	16 (5.1)

Note: Treatment-emergent adverse events in Period 1 are defined as any adverse events with an onset or worsening in severity date on or after the first dose date of study drug and prior to the first dose of study drug in Period 2 or no more than 30 days after the last dose of study drug in Period 1, whichever occurs firstly.

PBO + 52 WK CS-T = Placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 + 26 WK CS-T = Upadacitinib 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 + 26 WK CS-T = Upadacitinib 15 mg + 26 Weeks Corticosteroid Taper.

Subjects are counted once in each row, regardless of the number of events they may have had.

Long-term Analysis Set (SS_LT)

In the long-term data, AE rates in both upadacitinib groups were highest in the SOCs of infections and infestations followed by musculoskeletal and connective tissue disorders. The most common TEAEs (≥ 10 E/100 PY in any treatment group) were COVID-19, headache, arthralgia, hypertension, worsening of giant cell arteritis, back pain, nasopharyngitis, and urinary tract infection. The most common TEAEs are presented in the table below.

Urinary tract infection was the most common TEAE considered by the investigator to have a reasonable possibility of being related to upadacitinib (or matching placebo). None of the TEAEs considered by the investigator to have a reasonable possibility of being related to upadacitinib (or matching placebo) were reported at a rate of > 5 E/100 PY in subjects on upadacitinib (15 mg and 7.5 mg) treatment.

The common TEAEs considered by the investigator to have a reasonable possibility of being related to prednisone/prednisolone (or matching placebo) were hypertension, worsening of giant cell arthritis, and urinary tract infection. None of the TEAEs considered by the investigator to have a reasonable possibility of being related to prednisone/prednisolone (or matching placebo) were reported at a rate of > 5 E/100 PY in subjects on upadacitinib 15 mg treatment.

Table 20: Subjects with TEAEs Occurring ≥ 5 E/100 PY in Active Total by PT - Long-Term (SS_LT)

		UPA		
MedDRA 26.1 PT	**PBO + 52 WK CS-T (N = 43) (PYs = 72.3) Events (E/100 PY)**	**7.5 mg + 26 WK CS-T (N = 39) (PYs = 72.6) Events (E/100 PY)**	**15 mg + 26 WK CS-T (N = 92) (PYs = 171.4) Events (E/100 PY)**	**Total (N = 131) (PYs = 244) Events (E/100 PY)**
Any adverse event	396 (548.0)	264 (363.6)	874 (509.9)	1138 (466.4)
COVID-19	12 (16.6)	9 (12.4)	29 (16.9)	38 (15.6)
Headache	7 (9.7)	11 (15.2)	26 (15.2)	37 (15.2)
Arthralgia	15 (20.8)	3 (4.1)	24 (14.0)	27 (11.1)
Hypertension	5 (6.9)	7 (9.6)	20 (11.7)	27 (11.1)
Giant cell arteritis	13 (18.0)	6 (8.3)	20 (11.7)	26 (10.7)
Back pain	9 (12.5)	3 (4.1)	21 (12.3)	24 (9.8)
Nasopharyngitis	7 (9.7)	8 (11.0)	14 (8.2)	22 (9.0)
Urinary tract infection	16 (22.1)	9 (12.4)	13 (7.6)	22 (9.0)
Pain in extremity	4 (5.5)	1 (1.4)	16 (9.3)	17 (7.0)
Cough	5 (6.9)	3 (4.1)	10 (5.8)	13 (5.3)
Diarrhoea	0	4 (5.5)	9 (5.3)	13 (5.3)
Fatigue	4 (5.5)	3 (4.1)	10 (5.8)	13 (5.3)
Nausea	2 (2.8)	6 (8.3)	7 (4.1)	13 (5.3)
Osteoarthritis	4 (5.5)	1 (1.4)	12 (7.0)	13 (5.3)

E/100 PY = Events per 100 patient-years

Note: Treatment-emergent adverse events are defined as any adverse events with an onset or worsening in severity date after initiation of study drug and no more than 30 days after the last dose of study drug in the study.

PBO + 52 WK CS-T = Placebo + 52 Weeks Corticosteroid Taper/Placebo; UPA 7.5 + 26 WK CS-T = Upadacitinib 7.5 mg + 26 Weeks Corticosteroid Taper/Upadacitinib 7.5 mg; UPA 15 + 26 WK CS-T = Upadacitinib 15 mg + 26 Weeks Corticosteroid Taper/Upadacitinib 15 mg.

Adverse Drug Reactions for Labeling

The determination of ADRs applied for this GCA analysis was the following: AEs that occurred in > 10 subjects (> 5%) in the upadacitinib 15 mg group and have a delta of ≥ 1% difference between the upadacitinib 15 mg and the placebo group were identified in Period 1 (SS1), which was placebo-controlled time period. As a first step in the ADR algorithm, a comparison was made between placebo and the upadacitinib 15 mg dose group. AEs in the 15 mg group meeting the minimum number of events and delta criteria outlined above were then further reviewed, taking into account the upadacitinib 7.5 mg dosing group and any evidence of a dose response.

In addition, the body of evidence for AEs observed at a frequency of < 1% (uncommon and rare events) that were deemed events of medical importance were reviewed. AEs in the upadacitinib groups

that were determined to have a biologic plausibility of causal association with JAK inhibition were also evaluated and considered for inclusion as an ADR. AEs were considered for inclusion in the ADR section of the product information if determined by the sponsor to have a causal relationship to product administration.

Following the assessment process described above, one new event was assessed as an ADR for upadacitinib: peripheral oedema. Based on the Period 1 data (SS1), the incidence was 2.7% in the placebo group, 6.5% in the upadacitinib 7.5 mg group, and 8.6% in the upadacitinib 15 mg group. A dose dependence was observed for this event. A medical review of all cases of peripheral edema was performed to assess possible confounders given the advanced age of the patient population. Potential confounders that were identified were concurrent VTE or patients administered a concomitant calcium channel blocker, for which peripheral oedema is a known ADR.

In addition, the event of headache was found to have a higher frequency category (very common [(≥ 1/10)]) than that found in other indications (common [≥ 1/100 to < 1/10]). Proportions of the event of headache were 11.6% in the placebo group, 15% in the upadacitinib 7.5 mg group, and 16.3% in the upadacitinib 15 mg group. The MAH put forward that while headache is a known ADR for upadacitinib, it is also an event that is anticipated due to the underlying pathology of GCA, which is likely to be a contributor to the higher frequency in the population overall when compared to other populations.

Serious adverse event/deaths/other significant events

Deaths

Safety Analysis through Week 52 (Period 1; [SS1])

There were 4 treatment emergent deaths reported during Period 1 (2 in upadacitinib 15 mg group and 2 in placebo group) and 1 non-treatment emergent death (upadacitinib 15 mg). Of the treatment emergent deaths on upadacitinib 15 mg, 1 was a COVID-19 related death in a patient with medical history of chronic obstructive pulmonary disease, hypertension, leg oedema, obesity, deep vein thrombosis, main pulmonary artery enlargement, pulmonary embolism, pneumonia, hidradenitis suppurative. The event was assessed by the investigator as no reasonable possibility of being related to study drug, and the other was an unexplained death that was assessed by the investigator as possibly related to upadacitinib. On placebo, the 2 deaths resulted from TEAEs of sepsis and acute pancreatitis. The non-treatment emergent death in upadacitinib 15 mg was reported as a stroke and occurred > 30 days after the last dose of study drug.

Long-term Analysis Set (SS_LT)

There were no deaths reported during the long-term safety data.

Other Serious Adverse Events

Safety Analysis through Week 52 (Period 1; SS1)

Table 21: Subjects with Treatment-Emergent Serious Adverse event by System Organ Class and Preferred Term in period 1

MedDRA 26.1 System Organ Class Preferred Term	PBO + 52 WK CS-T (N=112) n (%)	UPA 7.5 + 26 WK CS-T (N=107) n (%)	UPA 15 + 26 WK CS-T (N=209) n (%)	UPA Total (N=316) n (%)
Any adverse event	24 (21.4)	14 (13.1)	48 (23.0)	62 (19.6)
Blood and lymphatic system disorders	0	1 (0.9)	0	1 (0.3)
Anaemia	0	1 (0.9)	0	1 (0.3)
Cardiac disorders	2 (1.8)	1 (0.9)	5 (2.4)	6 (1.9)
Atrial fibrillation	0	0	1 (0.5)	1 (0.3)
Cardiac failure	0	1 (0.9)	1 (0.5)	2 (0.6)
Cardiac failure congestive	0	0	2 (1.0)	2 (0.6)
Endocarditis fibroplastica	1 (0.9)	0	0	0
Mitral valve incompetence	0	0	1 (0.5)	1 (0.3)
Myocardial ischaemia	1 (0.9)	0	0	0
Tricuspid valve incompetence	0	0	1 (0.5)	1 (0.3)
Ear and labyrinth disorders	0	1 (0.9)	0	1 (0.3)
Vertigo	0	1 (0.9)	0	1 (0.3)
Eye disorders	0	0	4 (1.9)	4 (1.3)
Diplopia	0	0	1 (0.5)	1 (0.3)
Eye disorders (cont.)				
Glaucoma	0	0	1 (0.5)	1 (0.3)
Macular oedema	0	0	1 (0.5)	1 (0.3)
Retinal detachment	0	0	1 (0.5)	1 (0.3)
Gastrointestinal disorders	2 (1.8)	3 (2.8)	4 (1.9)	7 (2.2)
Colitis ischaemic	0	0	1 (0.5)	1 (0.3)
Colitis ulcerative	0	0	1 (0.5)	1 (0.3)
Diarrhoea	0	0	1 (0.5)	1 (0.3)
Mallory-Weiss syndrome	0	1 (0.9)	0	1 (0.3)
Pancreatitis	0	1 (0.9)	0	1 (0.3)
Pancreatitis acute	2 (1.8)	0	0	0
Vomiting	0	1 (0.9)	1 (0.5)	2 (0.6)
General disorders and administration site conditions	1 (0.9)	0	3 (1.4)	3 (0.9)
Death	0	0	1 (0.5)	1 (0.3)
Fatigue	0	0	1 (0.5)	1 (0.3)
Oedema peripheral	1 (0.9)	0	1 (0.5)	1 (0.3)
Hepatobiliary disorders	2 (1.8)	0	0	0
Cholecystitis chronic	1 (0.9)	0	0	0
Hepatitis acute	1 (0.9)	0	0	0
Immune system disorders	0	0	1 (0.5)	1 (0.3)
Drug hypersensitivity	0	0	1 (0.5)	1 (0.3)
Infections and infestations	11 (9.8)	6 (5.6)	12 (5.7)	18 (5.7)
COVID-19	0	0	1 (0.5)	1 (0.3)
COVID-19 pneumonia	0	0	2 (1.0)	2 (0.6)
Cystitis	0	0	1 (0.5)	1 (0.3)
Device related infection	0	0	1 (0.5)	1 (0.3)
Erysipelas	0	1 (0.9)	0	1 (0.3)
Febrile infection	0	1 (0.9)	0	1 (0.3)
Gastroenteritis clostridial	0	0	1 (0.5)	1 (0.3)
Genitourinary tract infection	0	0	1 (0.5)	1 (0.3)
Intervertebral discitis	0	0	1 (0.5)	1 (0.3)
Infections and infestations (cont.)				
Ophthalmic herpes zoster	0	0	2 (1.0)	2 (0.6)
Pneumocystis jirovecii pneumonia	0	0	1 (0.5)	1 (0.3)
Pneumonia	5 (4.5)	3 (2.8)	0	3 (0.9)
Pneumonia bacterial	1 (0.9)	0	0	0
Pseudomonal bacteraemia	0	0	1 (0.5)	1 (0.3)
Respiratory syncytial virus infection	0	1 (0.9)	0	1 (0.3)
Respiratory tract infection	0	0	1 (0.5)	1 (0.3)
Salmonellosis	0	0	1 (0.5)	1 (0.3)
Sepsis	1 (0.9)	0	0	0
Septic arthritis streptococcal	0	1 (0.9)	0	1 (0.3)
Staphylococcal sepsis	1 (0.9)	0	0	0
Urinary tract infection	1 (0.9)	0	0	0
Urosepsis	1 (0.9)	0	0	0
Wound infection	1 (0.9)	0	0	0
Injury, poisoning and procedural complications	2 (1.8)	2 (1.9)	2 (1.0)	4 (1.3)

Injury, poisoning and procedural complications (cont.)				
Fall	1 (0.9)	0	1 (0.5)	1 (0.3)
Head injury	0	0	1 (0.5)	1 (0.3)
Hip fracture	0	0	1 (0.5)	1 (0.3)
Infusion related reaction	1 (0.9)	0	0	0
Patella fracture	0	1 (0.9)	0	1 (0.3)
Radius fracture	1 (0.9)	0	0	0
Road traffic accident	0	1 (0.9)	0	1 (0.3)
Spinal fracture	0	1 (0.9)	0	1 (0.3)
Thoracic vertebral fracture	0	1 (0.9)	0	1 (0.3)
Investigations	1 (0.9)	0	1 (0.5)	1 (0.3)
Blood alkaline phosphatase increased	1 (0.9)	0	0	0
Gamma-glutamyltransferase increased	1 (0.9)	0	0	0
Troponin T increased	0	0	1 (0.5)	1 (0.3)
Metabolism and nutrition disorders	0	1 (0.9)	0	1 (0.3)
Hypokalaemia	0	1 (0.9)	0	1 (0.3)
Metabolism and nutrition disorders (cont.)				
Hyponatraemia	0	1 (0.9)	0	1 (0.3)
Musculoskeletal and connective tissue disorders	3 (2.7)	1 (0.9)	4 (1.9)	5 (1.6)
Back pain	1 (0.9)	0	0	0
Intervertebral disc protrusion	1 (0.9)	0	0	0
Lumbar spinal stenosis	0	1 (0.9)	0	1 (0.3)
Meniscal degeneration	0	0	1 (0.5)	1 (0.3)
Osteoarthritis	1 (0.9)	0	2 (1.0)	2 (0.6)
Vertebral foraminal stenosis	0	0	1 (0.5)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.8)	1 (0.9)	3 (1.4)	4 (1.3)
Malignant neoplasm of ampulla of Vater	0	0	1 (0.5)	1 (0.3)
Prostate cancer	1 (0.9)	0	0	0
Squamous cell carcinoma of lung	0	0	1 (0.5)	1 (0.3)
Squamous cell carcinoma of skin	0	1 (0.9)	0	1 (0.3)
Tongue neoplasm malignant stage unspecified	0	0	1 (0.5)	1 (0.3)
Tonsil cancer metastatic	1 (0.9)	0	0	0
Nervous system disorders	5 (4.5)	1 (0.9)	3 (1.4)	4 (1.3)
Cerebellar ataxia	0	0	1 (0.5)	1 (0.3)
Cerebral amyloid angiopathy	1 (0.9)	0	0	0
Cerebral infarction	1 (0.9)	0	0	0
Cerebrospinal fistula	1 (0.9)	0	0	0
Cerebrovascular accident	1 (0.9)	0	0	0
Headache	0	0	1 (0.5)	1 (0.3)
Quadrantanopia	0	0	1 (0.5)	1 (0.3)
Sciatica	0	1 (0.9)	0	1 (0.3)
Syncope	1 (0.9)	0	0	0
Psychiatric disorders	0	0	1 (0.5)	1 (0.3)
Substance-induced psychotic disorder	0	0	1 (0.5)	1 (0.3)
Renal and urinary disorders	1 (0.9)	0	0	0
Acute kidney injury	1 (0.9)	0	0	0
Reproductive system and breast disorders	0	0	1 (0.5)	1 (0.3)
Reproductive system and breast disorders (cont.)				
Cervical dysplasia	0	0	1 (0.5)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	2 (1.8)	2 (1.9)	5 (2.4)	7 (2.2)
Haemothorax	0	1 (0.9)	0	1 (0.3)
Pulmonary embolism	2 (1.8)	1 (0.9)	5 (2.4)	6 (1.9)
Vascular disorders	2 (1.8)	1 (0.9)	10 (4.8)	11 (3.5)
Aortic dissection	0	0	1 (0.5)	1 (0.3)
Aortic thrombosis	0	0	1 (0.5)	1 (0.3)
Arteriosclerosis	1 (0.9)	0	0	0
Deep vein thrombosis	0	0	3 (1.4)	3 (0.9)
Giant cell arteritis	1 (0.9)	1 (0.9)	3 (1.4)	4 (1.3)
Haematoma	0	0	1 (0.5)	1 (0.3)
Peripheral arterial occlusive disease	0	0	1 (0.5)	1 (0.3)
Peripheral embolism	0	0	1 (0.5)	1 (0.3)

Through Week 52 (Period 1), the most frequently reported SAE was pulmonary embolism in the upadacitinib 15 mg group and pneumonia in the upadacitinib 7.5 mg and placebo groups. While 3 subjects reported serious deep vein thrombosis (DVT) in the upadacitinib 15 mg group compared to no subjects in the upadacitinib 7.5 mg and placebo groups, the overall rates for adjudicated VTE (DVT and pulmonary embolism), including serious and nonserious events, were similar between the upadacitinib 15 mg and placebo groups.

Long-term Analysis Set (SS_LT)

The event rate of SAEs was higher in the placebo group compared to the upadacitinib 15 mg and upadacitinib 7.5 mg groups. The SAEs most frequently reported on upadacitinib (15 mg and 7.5 mg) treatment were pneumonia, atrial fibrillation, and cardiac failure. The remainder of the SAEs were not reported more than once in any treatment group.

Bone Fractures

Safety Analysis through Week 52 (Period 1; SS1)

The EAIRs of TEAEs of bone fracture was slightly higher on upadacitinib treatment as compared to placebo. Three subjects in the upadacitinib 15 mg group had 2 bone fractures each, and 1 subject in the upadacitinib 7.5 mg group had 4 bone fractures. Of the 19 subjects on upadacitinib treatment, 12 of the fractures were due to trauma. All the subjects with spinal fractures were female, and most had a medical history of osteopenia or osteoporosis. Most bone fractures were considered by the investigator as having no reasonable possibility of being related to the study drug. Five events of bone fracture were considered serious; 1 event in the upadacitinib 15 mg group (hip fracture), 3 events in the upadacitinib 7.5 mg group (thoracic vertebral fracture, spinal fracture, and patella fracture), and 1 event in the placebo group (radius fracture). None of the serious fractures were considered related to study drug and one (spinal fracture) led to study drug discontinuation.

Table 22: Subjects with treatment-emergent bone fracture in period 1

MedDRA 26.1 System Organ Class Preferred Term	PBO + 52 WK CS-T (N=112) n (%)	UPA 7.5 + 26 WK CS-T (N=107) n (%)	UPA 15 + 26 WK CS-T (N=209) n (%)	UPA Total (N=316) n (%)
Any adverse event	6 (5.4)	6 (5.6)	13 (6.2)	19 (6.0)
Injury, poisoning and procedural complications	6 (5.4)	6 (5.6)	13 (6.2)	19 (6.0)
Avulsion fracture	0	0	1 (0.5)	1 (0.3)
Craniofacial fracture	0	1 (0.9)	0	1 (0.3)
Foot fracture	1 (0.9)	0	1 (0.5)	1 (0.3)
Hip fracture	0	0	1 (0.5)	1 (0.3)
Humerus fracture	0	1 (0.9)	0	1 (0.3)
Lower limb fracture	0	0	1 (0.5)	1 (0.3)
Lumbar vertebral fracture	0	1 (0.9)	0	1 (0.3)
Patella fracture	0	1 (0.9)	1 (0.5)	2 (0.6)
Radius fracture	1 (0.9)	0	0	0
Rib fracture	0	0	2 (1.0)	2 (0.6)
Scapula fracture	1 (0.9)	0	0	0
Spinal compression fracture	2 (1.8)	1 (0.9)	5 (2.4)	6 (1.9)
Spinal fracture	0	1 (0.9)	1 (0.5)	2 (0.6)
Stress fracture	1 (0.9)	1 (0.9)	0	1 (0.3)
Thoracic vertebral fracture	0	1 (0.9)	0	1 (0.3)
Upper limb fracture	0	1 (0.9)	0	1 (0.3)
Wrist fracture	0	0	1 (0.5)	1 (0.3)

Note: Treatment-emergent adverse events in Period 1 are defined as any adverse events with an onset or worsening in severity date on or after the first dose date of study drug and prior to the first dose of study drug in Period 2 or no more than 30 days after the last dose of study drug in Period 1, whichever occurs firstly.
Subjects are counted once in each row, regardless of the number of events they may have had.
PBO + 52 WK CS-T = Placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 + 26 WK CS-T = Upadacitinib 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 + 26 WK CS-T = Upadacitinib 15 mg + 26 Weeks Corticosteroid Taper.

Long-term Analysis Set (SS_LT)

The EAIR of TEAEs of bone fracture was higher in the placebo group (5.8/100 PY) compared to the upadacitinib treatment groups (4.3/100 PY in 7.5 mg upadacitinib and 3.7/100 PY in 15 mg UPA) in the long-term analysis set. One serious event of foot fracture led to study drug discontinuation in the upadacitinib 15 mg group. None of the bone fractures were considered by the investigator as having a reasonable possibility of being related to the study drug.

Retinal detachment

Safety Analysis through Week 52 (Period 1; SS1)

The EAIRs of TEAEs of retinal detachment was higher in the placebo group compared to the upadacitinib groups. Most events were nonserious and mild or moderate, with no events leading to discontinuation of study drug. Only 1 serious event of retinal detachment occurred in the upadacitinib 15 mg group and resolved without study drug discontinuation. None of the events were considered by the investigator to have a reasonable possibility of being related to upadacitinib (or matching placebo).

Long-term Analysis Set (SS_LT)

In the long-term analysis set, EAIR of TEAEs of retinal detachment continued to be higher in the placebo group compared to the upadacitinib groups.

Ocular Complications

Given the higher risk of ocular complications in patients with GCA, a summary of these events is presented below. Medical review of the PTs observed during Period 1 and long-term data was performed for this ad-hoc analysis and identified the following PTs: diplopia, vision blurred, visual acuity reduced, visual field defect, visual impairment and quadrantanopia.

Safety Analysis through Week 52 (Period 1; SS1)

TEAEs of ocular complications were reported in all treatment groups, with 26 reported in total and 19 on both upadacitinib treatments. Each ocular complication is listed below by PT with rates presented in the table below.

Table 23: Ocular Complications of GCA by PT in Period 1

		UPA	
MedDRA 26.1 PT	PBO + 52 WK CS-T (N = 112) (PYs = 94.3) Events (E/100 PY)	7.5 + 26 WK CS-T (N = 107) (PYs = 88.5) Events (E/100 PY)	15 + 26 WK CS-T (N = 209) (PYs = 178.1) Events (E/100 PY)
Diplopia	0	0	2 (1.1)
Vision blurred	4 (4.2)	6 (6.8)	6 (3.4)
Visual acuity reduced	1 (1.1)	0	1 (0.6)
Visual field defect	0	0	2 (1.1)
Visual impairment	2 (2.1)	0	1 (0.6)
Quadrantanopia	0	0	1 (0.6)

Ocular events were primarily nonserious and mild, except for 2 events which were serious (PTs: diplopia and quadrantanopia). Two nonserious events (PTs: ocular discomfort and vision blurred) in the same subject who received upadacitinib 7.5 mg led to the study drug discontinuation. None of these events led to permanent partial or total blindness.

Long-term Analysis Set (SS_LT)

No new ocular events were reported in any treatment group.

Adverse Events of Special Interest (AESIs)

No treatment-emergent AESIs of active TB, lymphoma, or adjudicated GI perforation were reported through Week 52 or through the cutoff date for subjects in the long-term analysis set. All other AESIs are described in the following sections.

Safety Analysis through Week 52 (Period 1; SS1)

AESIs for Period 1 are listed in the table below:

Table 24: Overview of Treatment-Emergent AESIs per 100 PY in Period 1 (SS1)

		UPA		
Any Treatment-emergent	**PBO + 52 WK CS-T (N = 112) Events (E/100 PY)**	**7.5 mg + 26 WK CS-T (N = 107) Events (E/100 PY)**	**15 mg + 26 WK CS-T (N = 209) Events (E/100 PY)**	**Total (N = 316) Events (E/100 PY)**
EAER	Events (E/100 PY)			
	(PYs = 94.3)	(PYs = 88.5)	(PYs = 178.1)	(PYs = 266.5)
Serious infections	12 (12.7)	7 (7.9)	14 (7.9)	21 (7.9)
Opportunistic infection excluding TB and herpes zoster	1 (1.1)	0	4 (2.2)	4 (1.5)
Herpes zoster	4 (4.2)	4 (4.5)	13 (7.3)	17 (6.4)
Active TB	0	0	0	0
Adjudicated GI perforation	0	0	0	0
Anemia	3 (3.2)	3 (3.4)	15 (8.4)	18 (6.8)
Neutropenia	1 (1.1)	0	0	0
Lymphopenia	0	1 (1.1)	4 (2.2)	5 (1.9)
Renal dysfunction	3 (3.2)	0	4 (2.2)	4 (1.5)
Hepatic disorder	6 (6.4)	2 (2.3)	13 (7.3)	15 (5.6)
CPK elevation	0	0	6 (3.4)	6 (2.3)
EAIR	n/PY (n/100 PY)			
Malignancy	3/93.5 (3.2)	1/88.4 (1.1)	9/174.8 (5.1)	10/263.2 (3.8)
NMSC	2/93.7 (2.1)	1/88.4 (1.1)	5/176.1 (2.8)	6/264.5 (2.3)
Malignancy excluding NMSC	2/94.0 (2.1)	0/88.5	4/176.8 (2.3)	4/265.3 (1.5)
Lymphoma	0/94.3	0/88.5	0/178.1	0/266.5
Adjudicated MACE[a]	2/94.2 (2.1)	0/88.5	0/178.1	0/266.5
Adjudicated embolic and thrombotic events (non-cardiac, non-CNS)	4/93.6 (4.3)	4/87.3 (4.6)	8/177.3 (4.5)	12/264.6 (4.5)
VTE[b]	4/93.6 (4.3)	4/87.3 (4.6)	7/177.4 (3.9)	11/264.7 (4.2)
Other venous thrombosis	0/94.3	0/88.5	0/178.1	0/266.5
Arterial thromboembolic events	0/94.3	0/88.5	2/177.9 (1.1)	2/266.4 (0.8)

a. MACE is defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

b. VTE includes deep vein thrombosis and pulmonary embolism (fatal and non-fatal).

Note: EAIRs (n/PY [n/100 PY]) are reported for the following AESIs: malignancies (NMSC, malignancy excluding NMSC, and lymphoma), adjudicated MACE and adjudicated embolic and thrombotic events.

Long-term Analysis Set (SS_LT)

Similar trends to Period 1 data were generally observed with the long-term data (see table below).

Table 25: Overview of Treatment-Emergent AESIs per 100 PY - Long-Term (SS_LT)

Any Treatment-emergent	PBO + 52 WK CS-T (N = 43) Events (E/100 PY)	UPA 7.5 mg + 26 WK CS-T (N = 39) Events (E/100 PY)	UPA 15 mg + 26 WK CS-T (N = 92) Events (E/100 PY)	UPA Total (N = 131) Events (E/100 PY)
EAER	Events (E/100 PY)			
	(PYs = 72.3)	(PYs = 72.6)	(PYs = 171.4)	(PYs = 244.0)
Serious infections	5 (6.9)	3 (4.1)	5 (2.9)	8 (3.3)
Opportunistic infection excluding TB and herpes zoster	1 (1.4)	0	1 (0.6)	1 (0.4)
Herpes zoster	2 (2.8)	4 (5.5)	7 (4.1)	11 (4.5)
Active TB	0	0	0	0
Adjudicated GI perforation	0	0	0	0
Anemia	4 (5.5)	4 (5.5)	12 (7.0)	16 (6.6)
Neutropenia	0	0	0	0
Lymphopenia	0	0	1 (0.6)	1 (0.4)
Renal dysfunction	1 (1.4)	0	0	0
Hepatic disorder	3 (4.2)	1 (1.4)	7 (4.1)	8 (3.3)
CPK elevation	0	0	8 (4.7)	8 (3.3)
EAIR	n/PY (n/100 PY)			
Malignancy	2/71.4 (2.8)	2/71.7 (2.8)	6/166.1 (3.6)	8/237.8 (3.4)
NMSC	2/71.4 (2.8)	0/72.6	5/167.8 (3.0)	5/240.5 (2.1)
Malignancy excluding NMSC	0/72.3	2/71.7 (2.8)	2/169.2 (1.2)	4/240.9 (1.7)
Lymphoma	0/72.3	0/72.6	0/171.4	0/244.0
Adjudicated MACE[a]	0/72.3	0/72.6	0/171.4	0/244.0
Adjudicated embolic and thrombotic events (non-cardiac, non-CNS)	0/72.3	0/72.6	1/171.4 (0.6)	1/244.0 (0.4)
VTE[b]	0/72.3	0/72.6	1/171.4 (0.6)	1/244.0 (0.4)
Other venous thrombosis	0/72.3	0/72.6	0/171.4	0/244.0
Arterial thromboembolic events	0/72.3	0/72.6	0/171.4	0/244.0

a. MACE is defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

b. VTE includes deep vein thrombosis and pulmonary embolism (fatal and non-fatal).

Note: EAIRs (n/PY [n/100 PY]) are reported for the following AESIs: malignancies (NMSC, malignancy excluding NMSC, and lymphoma) adjudicated MACE and adjudicated embolic and thrombotic events.

Serious infections

Safety Analysis through Week 52 (Period 1; SS1)

The frequency of serious infections over 52 weeks was 5.7% in the upadacitinib 15 mg group and 10.7% in the placebo group. The EAER of TEAEs of serious infections were similar in the upadacitinib groups, both of which were lower than the placebo group. By PT, no more than 1 subject reported an event for any given treatment group, except for pneumonia (5 subjects in the placebo group and 3 subjects in the upadacitinib 7.5 mg group), and COVID-19 pneumonia and ophthalmic herpes zoster (2 subjects each in the upadacitinib 15 mg group). Approximately half of the serious infections were

considered by the investigator as having a reasonable possibility of being related to upadacitinib (or matching placebo).

Two treatment-emergent serious infections (sepsis in the placebo group and COVID-19 in the upadacitinib 15 mg group) resulted in death.

The types of treatment-emergent serious infections reported were generally consistent with what has been reported in other upadacitinib indications.

Long-term Analysis Set (SS_LT)

Similar trends to Period 1 data were generally observed with the long-term data with a lower rate of TEAEs of serious infections in the upadacitinib groups compared to the placebo group.

Opportunistic infections excluding TB and herpes zoster

Safety Analysis through Week 52 (Period 1; SS1)

The frequency of opportunistic infection (excluding tuberculosis and herpes zoster) over 52 weeks was 1.9% in the upadacitinib 15 mg group and 0.9% in the placebo group. Treatment-emergent opportunistic infections excluding TB and herpes zoster were only reported in the upadacitinib 15 mg and placebo groups. Oral fungal infection (2 subjects) and esophageal candidiasis and pneumocystis jirovecii pneumonia (PJP) (1 subject each) were reported in the upadacitinib 15 mg group; and esophageal candidiasis (1 subject) in the placebo group. The oral fungal infection and PJP were considered by the investigator as having a reasonable possibility of being related to upadacitinib. The PJP was serious and severe and led to discontinuation of the study drug. No other events were serious, severe, or led to discontinuation of the study drug.

Long-term Analysis Set (SS_LT)

Similar to Period 1 data, opportunistic infections excluding TB and herpes zoster were only reported in the upadacitinib 15 mg (1 event of esophageal candidiasis) and placebo (1 event of aspergillus infection) groups with the long-term data. The aspergillus infection was serious and severe and led to discontinuation of study drug. According to the MAH, the esophageal candidiasis was nonserious, moderate, and did not result in discontinuation of study drug.

Herpes zoster

Safety Analysis through Week 52 (Period 1; SS1)

In the placebo-controlled clinical study, the frequency of herpes zoster over 52 weeks was 5.3% in the upadacitinib 15 mg group and 2.7% in the placebo group. The rate of TEAEs of herpes zoster was higher on upadacitinib 15 mg as compared to placebo and upadacitinib 7.5 mg groups which had similar rates. Two events of ophthalmic herpes zoster were reported, both in the upadacitinib 15 mg group, were serious and severe; 1 of the 2 events led to discontinuation of the study drug. No other events were serious or severe and 3 subjects discontinued the study drug due to HZ events. The majority of events were considered by the investigator as having a reasonable possibility of being related to upadacitinib (or matching placebo). For those subjects with extent of involvement reported, the majority of HZ events involved 1 dermatome. Four subjects had events involving 2 or 3 dermatomes, 1 had ophthalmic involvement, and no events involved CNS, liver, or lung. Of the subjects with a prior history of HZ, no subjects on upadacitinib had an event of HZ. Of the subjects who had received HZ vaccination, 3 subjects reported an event of HZ.

Long-term Analysis Set (SS_LT)

The rates of TEAEs of HZ were higher in the upadacitinib treatment groups compared to placebo. Overall, the extent of involvement of the HZ events were similar to that reported for Period 1.

Malignancies

Safety Analysis through Week 52 (Period 1; SS1)

TEAEs of malignancies excluding NMSC were only reported in the upadacitinib 15 mg and placebo groups. The malignancies excluding NMSC reported were the following: 1 subject each with lentigo maligna, malignant neoplasm of ampulla of Vater, squamous cell carcinoma of lung, and tongue neoplasm malignant stage unspecified in the upadacitinib 15 mg group, and 1 subject each with prostate cancer and metastatic tonsil cancer in the placebo group. All events were considered by the investigator as having no reasonable possibility of being related to the study drug and resulted in discontinuation of the study drug (except for lentigo maligna). No event of lymphoma was reported.

Of the 6 subjects with malignancy excluding NMSC, the age range was 70-74 years and all except 1 subject on placebo (prostate cancer) were either former or current smokers. All malignancy excluding NMSC events on upadacitinib were diagnosed within the first 4 months of the study drug treatment except for 1 event which occurred after approximately 8 months on upadacitinib. The MAH states that given the long latency time of malignancies, upadacitinib is unlikely to have caused the events that occurred within the first 6 months of treatment.

The EAIRs of TEAEs of NMSC were similar in the upadacitinib 15 mg and placebo groups and lower in the upadacitinib 7.5 mg group. The events reported were squamous cell carcinoma (3 subjects in the upadacitinib 15 mg group and 1 subject in the upadacitinib 7.5 mg group) and basal cell carcinoma (2 subjects in the upadacitinib 15 mg group and 2 subjects in the placebo group). The majority of the events were considered by the investigator as having no reasonable possibility of being related to the study drug, and no events led to discontinuation of the study drug. Of the 8 subjects with NMSC, the age range was 71-80 years and all were Caucasian. Time to onset ranged from 69-379 days with 1 case occurring in < 6 months (69 days) and the remainder occurring after 8 months on upadacitinib treatment.

Long-term Analysis Set (SS_LT)

TEAEs of malignancies excluding NMSC were only reported in the upadacitinib groups with a higher incidence rate in the upadacitinib 7.5 mg group. Malignancies excluding NMSC included 1 event each of lentigo maligna (same event described above under Period 1 summary) and prostate cancer in the upadacitinib 15 mg group, and 1 event each of lung adenocarcinoma and papillary thyroid cancer in the upadacitinib 7.5 mg group. None of the events was considered by the investigator as having a reasonable possibility of being related to upadacitinib. All events resulted in discontinuation of the study drug with the exception of the lentigo maligna (as mentioned in Period 1 summary) and lung adenocarcinoma. In the 3 additional subjects with malignancy excluding NMSC, the ages ranged from 71 to 75 years and the 2 subjects with lung adenocarcinoma and prostate cancer had a risk factor of being former smokers. These 3 cases occurred within 13-24 months of upadacitinib treatment.

TEAEs of NMSC were only reported in the upadacitinib 15 mg and placebo groups, at similar incidence rates. Events reported were squamous cell carcinoma of the skin (5 events in the upadacitinib 15 mg group) and basal cell carcinoma (2 events in the placebo group and 1 event in the upadacitinib 15 mg group). The majority of the events were considered by the investigator as having no reasonable possibility of being related to upadacitinib (or matching placebo), and no events led to discontinuation of the study drug. Subjects age ranged from 65 to 74 years and time to onset of the NMSC events ranged from approximately 12-20 months.

Hepatic disorder

Safety Analysis through Week 52 (Period 1; SS1)

At Week 52, subjects in the upadacitinib treatment groups had a greater mean increase from Baseline in AST compared with the placebo group. Overall, mean ALT values generally decreased through 52 weeks of upadacitinib treatment.

Table 26: Subject with treatment emergent hepatic disorder by SOC and PT in period 1 (SS1)

		UPA	
MedDRA 26.1 SOC PT	PBO + 52 WK CS-T (N = 112) n (%)	7.5 mg + 26 WK CS-T (N = 107) n (%)	15 mg + 26 WK CS-T (N = 209) n (%)
Hepatobiliary disorders	3 (2.7)	1 (0.9)	5 (2.4)
Drug-induced liver injury	1 (0.9)	0	0
Hepatic cyst	0	0	1 (0.5)
Hepatic cytolysis	1 (0.9)	0	1 (0.5)
Hepatic function abnormal	0	0	1 (0.5)
Hepatic lesion	1 (0.9)	0	1 (0.5)
Hepatic steatosis	0	1 (0.9)	0
Hepatitis acute	1 (0.9)	0	0
Hepatomegaly	0	0	1 (0.5)
Investigations	2 (1.8)	1 (0.9)	7 (3.3)
Alanine aminotransferase increased	0	0	3 (1.4)
Aspartate aminotransferase increased	0	0	1 (0.5)
Blood bilirubin increased	0	0	1 (0.5)
Gamma-glutamyl transferase increased	1 (0.9)	0	0
Liver function test abnormal	0	0	2 (1.0)
Liver function test increased	1 (0.9)	0	0
Transaminases increased	0	1 (0.9)	1 (0.5)

PBO + 52 WK CS-T = placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 mg + 26 WK CS-T = upadacitinib 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 mg + 26 WK CS-T = upadacitinib 15 mg + 26 Weeks Corticosteroid Taper.
TEAEs in Period 1 were defined as any AEs with an onset or worsening in severity date on or after the first dose date of study drug and prior to the first dose of study drug in Period 2 or no more than 30 days after the last dose of study drug in Period 1, whichever occurred firstly.
Subjects were counted once in each row, regardless of the number of events they may have had.

The EAERs of TEAEs of hepatic disorder were slightly higher in the upadacitinib 15 mg (7.3 E/100 PY), group compared to placebo (6.4 E/100 PYs) and higher than upadacitinib 7.5 mg (2.3 E/100 PY). Two events were serious and severe (acute hepatitis and gamma-glutamyltransferase increased, both in the placebo group); the acute hepatitis led to discontinuation of the study drug. No other event was serious, 1 other event was severe (hepatic steatosis [upadacitinib 7.5 mg group], and 2 other events led to discontinuation of study drug (transaminases increased [upadacitinib 7.5 mg group]) and drug-induced liver injury [placebo group]). Overall, the majority of events were considered by the investigator as having no reasonable possibility of being related to upadacitinib (or matching placebo). TEAEs of AST increased or ALT increased were mild or moderate. One moderate event of transaminase increased resulted in discontinuation of the study drug.

The percentage of subjects with ALT > 3 × ULN or AST > 3 × ULN, ALT > 5 × ULN or AST > 5 × ULN, and ALT > 10 × ULN or AST > 10 × ULN were higher on placebo than on the upadacitinib treatment groups. No subject in any treatment group reported an ALT > 20 × ULN or AST > 20 × ULN.

Two subjects met biochemical criteria for Hy's Law during Period 1 (SS1), 1 on upadacitinib 15 mg treatment and 1 on placebo. According to the MAH, upon medical review, neither case was considered a true Hy's Law as both had alternate etiologies (malignant neoplasm of the ampulla of Vater on upadacitinib 15 mg and acute hepatitis with acute pancreatitis leading to death on placebo.

Long-term Analysis Set (SS_LT)

Continued treatment with upadacitinib on the same dose resulted in increased mean AST levels and decreased mean ALT levels from Baseline. The EAERs of TEAEs of hepatic disorder were similar in the upadacitinib 15 mg (4.1 E/100 PY) and placebo groups (4.2 E/100 PYs), both of which were higher than upadacitinib 7.5 mg (1.4 E/100 PYs). No additional event was serious or severe or led to discontinuation of the study drug beyond the events described in the Period 1 summary above. Although infrequent, AST/ALT > 3 × ULN and AST/ALT > 5 × ULN occurred only on the upadacitinib treatment groups, with the majority on upadacitinib 15 mg. No event was identified as meeting biochemical Hy's Law criteria.

Anaemia

Safety Analysis through Week 52 (Period 1; SS1)

During Period 1, hemoglobin LS mean decreases from Baseline generally decreased with treatment to Week 52 with the highest decreases on upadacitinib 15 mg.

The rate of TEAEs of anaemia was highest in the upadacitinib 15 mg group and similar in the upadacitinib 7.5 mg and placebo groups. Serious events and events leading to discontinuation of study drug were rare (1 event each), as were severe events (2 events). The majority of events were mild in severity and considered by the investigator as having no reasonable possibility of being related to upadacitinib (or matching placebo). One laboratory Grade 3 haemoglobin decrease occurred in the placebo and upadacitinib 15 mg groups each, and 2 occurred in the upadacitinib 7.5 mg group.

Long-term Analysis Set (SS_LT)

Similar trends to Period 1 data were observed with the long-term data, with the highest rate in the upadacitinib 15 mg group and similar rates observed in the upadacitinib 7.5 mg and placebo groups. One subject had a laboratory Grade 3 hemoglobin decrease in each treatment arm.

Neutropaenia

Safety Analysis through Week 52 (Period 1; SS1)

According to the MAH, mean decreases from Baseline in neutrophil count by Week 16 were observed with upadacitinib treatments, which appeared to be dose related. No TEAEs of neutropaenia were reported in the upadacitinib groups. One transient Grade 3 laboratory abnormality of neutrophil count decreased occurred on upadacitinib 15 mg without study drug discontinuation with no concomitant infection reported. No Grade 4 laboratory abnormality of neutrophil count decreased occurred on either dose of upadacitinib.

Long-term Analysis Set (SS_LT)

No TEAEs of neutropeania were reported. According to the MAH, mean decreases in neutrophil count stabilized in the long-term. One Grade 3 laboratory abnormality of neutrophil count decreased

occurred on upadacitinib 15 mg and no Grade 4 laboratory abnormality of neutrophil count decreased occurred on either dose of upadacitinib.

Lymphopaenia

Safety Analysis through Week 52 (Period 1; SS1)

During Period 1, mean increases in lymphocyte count were observed within the first 8 weeks of upadacitinib treatment which did not appear to be dose related. The mean increases were followed by decreases, resulting in small mean dose-dependent changes from Baseline at Week 52. TEAEs of lymphopaenia were only reported in the upadacitinib 15 mg and 7.5 mg groups. All events were nonserious and mild or moderate, and the majority of events were considered by the investigator as having a reasonable possibility of being related to upadacitinib. All events resolved without discontinuation of the study drug. Rates of Grade 3 laboratory abnormalities of lymphocyte decreased were uncommon in all 3 treatment groups. There were no Grade 4 laboratory abnormalities of lymphocyte decreased.

There were two Grade 3 laboratory abnormalities of decreased lymphocyte count on upadacitinib treatments associated with an infection (1 subject with nonserious penile ulceration) or a serious infection (1 subject with serious PJP).

Long-term Analysis Set (SS_LT)

No TEAEs of lymphopaenia were reported in the upadacitinib 7.5 mg and placebo groups. One TEAE of lymphopenia was reported in the upadacitinib 15 mg group. The event was nonserious, severe, considered by the investigator as having a reasonable possibility of being related to upadacitinib, and resolved without discontinuation of the study drug. Two Grade 3 laboratory abnormalities of lymphocyte count decreased occurred on upadacitinib 15 mg and no Grade 4 laboratory abnormalities of lymphocyte count decreased occurred on an upadacitinib treatment. One Grade 3 laboratory abnormalities of decreased lymphocyte count on upadacitinib treatment was associated with an infection (1 subject with nonserious viral infection).

Creatine Phosphokinase Elevation

Safety Analysis through Week 52 (Period 1; SS1)

During Period 1, a dose dependent increase in LS mean for CPK occurred with upadacitinib treatment through Week 52. TEAEs of CPK elevation were only reported in the upadacitinib 15 mg group. According to the MAH, all events were nonserious and the majority were mild or moderate. No subject discontinued study drug due to an event of CPK elevation. The majority of the events were considered by the investigator as having a reasonable possibility of being related to upadacitinib. No event of rhabdomyolysis was reported. Only 1 laboratory abnormality of CPK increased occurred on upadacitinib 15 mg and none occurred in the other treatment groups. No Grade 4 laboratory abnormality of CPK increased occurred on any treatment group.

Long-term Analysis Set (SS_LT)

Similar trends to Period 1 data were observed with the long-term data. Continued treatment with upadacitinib resulted in a dose dependent increase in LS mean creatine kinase values through Week 104. TEAEs of CPK elevation were only reported in the upadacitinib 15 mg group. No event of rhabdomyolysis was reported. As described in Period 1, 1 laboratory abnormality of CPK increases occurred on upadacitinib 15 mg and none on the other treatment groups. No Grade 4 laboratory abnormality of CPK increased occurred on any treatment group.

Renal Dysfunction

Safety Analysis through Week 52 (Period 1; SS1)

During Period 1, generally a small increase was observed in creatinine values following upadacitinib treatment. Small mean increases from Baseline to Week 8 in both upadacitinib groups which were similar to placebo were observed. TEAEs of renal dysfunction were only reported in the upadacitinib 15 mg and placebo groups. Events included acute kidney injury (3 subject in the placebo group and 2 subjects in the upadacitinib 15 mg group), renal failure and renal impairment (1 subject each in the upadacitinib 15 mg group). One event was serious and severe (acute kidney injury in the placebo group). No other event was serious, and the majority of the other events were mild. No subject discontinued the study drug due to the event. Most events were considered by the investigator as having no reasonable possibility of being related to upadacitinib (or matching placebo). Grade 3 increases in creatinine were not observed in the upadacitinib treatment groups, and no Grade 4 increase was reported in any treatment group.

Long-term Analysis Set (SS_LT)

In the long-term analysis set, continued treatment with upadacitinib was generally associated with small increases in mean serum creatinine in both upadacitinib groups which were similar to placebo. At Week 104, mean creatinine increases from Baseline remained small for the upadacitinib 15 mg and 7.5 mg groups. No TEAEs of renal dysfunction were reported in the upadacitinib 15 mg and 7.5 mg groups in the long-term analysis set. One TEAE of renal dysfunction (acute kidney injury) was reported in the placebo group and is included in the Period 1 summary above. No laboratory abnormalities of Grade 2, 3 or Grade 4 increases in creatinine were reported in both upadacitinib and placebo groups

Adjudicated MACE and Other Cardiovascular Events

Safety Analysis through Week 52 (Period 1; SS1)

No treatment-emergent adjudicated MACE were reported in the upadacitinib groups. Two treatment-emergent adjudicated MACE (cerebrovascular accident and myocardial ischemia) were reported in the placebo group. The cerebrovascular accident was serious and moderate and led to discontinuation of study drug. The event of myocardial ischemia was serious and severe and did not lead to discontinuation of study drug. Both subjects had at least 1 cardiovascular risk factor.

The proportion of subjects with TEAEs adjudicated as other cardiovascular events were similar across the upadacitinib 15 mg, upadacitinib 7.5 mg, and placebo groups. The majority of the adjudicated other cardiovascular events were considered by the investigator as having no reasonable possibility of being related to study drug

Long-term Analysis Set (SS_LT)

No treatment-emergent adjudicated MACE was reported.

The rates of TEAEs adjudicated as other cardiovascular events were similar in the upadacitinib 15 mg, upadacitinib 7.5 mg, and placebo groups.

Other Adjudicated Cardiovascular Events

Rates of other adjudicated CV events reported were low in the upadacitinib GCA program. The majority of the adjudicated other cardiovascular events were considered by the investigator as having no reasonable possibility of being related to study drug.

Adjudicated Embolic and Thrombotic Events

Safety Analysis through Week 52 (Period 1; SS1)

Table 27: Subjects with Treatment-Emergent Adjudicated Embolic and Thrombotic Events by Adjudicated Term in Period 1 (SS1)

Event Category Adjudicated Term	PBO + 52 WK CS-T (N = 112) n (%)	UPA 7.5 mg + 26 WK CS-T (N = 107) n (%)	UPA 15 mg + 26 WK CS-T (N = 209) n (%)
Any adjudicated thrombotic events	4 (3.6)	4 (3.7)	8 (3.8)
Venous Thromboembolic Events	4 (3.6)	4 (3.7)	7 (3.3)
Venous thromboembolic events (fatal)	0	0	0
Venous thromboembolic events (non-fatal)	4 (3.6)	4 (3.7)	7 (3.3)
Deep vein thrombosis	2 (1.8)	2 (1.9)	4 (1.9)
Pulmonary embolism	2 (1.8)	2 (1.9)	6 (2.9)
DVT and PE (concurrent)	0	0	3 (1.4)
Other venous thrombosis (non-fatal)	0	0	0
Arterial thromboembolic events (non-cardiac, non-neurologic) (non-fatal)	0	0	2 (1.0)

PBO + 52 WK CS-T = placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 mg + 26 WK CS-T = upadacitinib 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 mg + 26 WK CS-T = upadacitinib 15 mg + 26 Weeks Corticosteroid Taper.

TEAEs in Period 1 were defined as any AEs with an onset or worsening in severity date on or after the first dose date of study drug and prior to the first dose of study drug in Period 2 or no more than 30 days after the last dose of study drug in Period 1, whichever occurred firstly.

TEAEs of adjudicated VTEs were reported in all treatment groups, and the EAIRs were similar across the upadacitinib 15 mg, upadacitinib 7.5 mg, and placebo groups. Three subjects in the upadacitinib 15 mg group had concurrent DVT and PE and 1 subject in the upadacitinib 15 mg group had a concurrent arterial thromboembolic event and a PE. The majority of events were serious and severe, resulted in discontinuation of the study drug, and were considered by the investigator as having a reasonable possibility of being related to study drug.

The age range of subjects with VTE was 62-83 years, with the majority of subjects in the ≥ 75 year age range and few < 65 years of age. All subjects except one had at least 1 risk factor for VTE (including hypertension, hyperlipidemia, recent surgery, immobility, smoking, and history of previous VTE). The range of time to onset in subjects on upadacitinib with a VTE was 33-198 days (mean 96 days). Time to onset of VTE for subjects on placebo was 2, 4, 6 and 227 days.

In addition, adjudicated arterial thromboembolic events were reported in 2 subjects (on upadacitinib 15 mg); peripheral artery embolism (concurrent with PE, reported above) and aortic thrombosis. Both subjects had risk factors for thromboembolism (obesity, smoking, hyperlipidemia, hypertension, and previous peripheral vascular disease).

Long-term Analysis Set (SS_LT)

No adjudicated VTEs were reported in the upadacitinib 7.5 mg and placebo groups. One adjudicated VTE (pulmonary embolism) was reported in the upadacitinib 15 mg group and the subject had multiple risk factors for VTE and a time to onset of 745 days (5 days after study last visit). The event was serious and severe and did not result in discontinuation of study drug. The investigator considered the event as having a reasonable possibility of being related to upadacitinib.

No TEAEs were adjudicated as arterial thromboembolic events.

Laboratory findings

Hematology and clinical chemistry

According to the MAH, there were no clinically relevant trends in chemistry parameters in any treatment group over time and overall, chemistry parameter results from the long-term analysis were generally consistent with the results from Period 1.

Lipid Effects

Safety Analysis through Week 52 (Period 1; SS1)

Similar to observations in subjects from other upadacitinib clinical programs, upadacitinib treatment in subjects with GCA was associated with an increase in lipid parameters (cholesterol, HDL-C, and LDL-C) in relation to placebo. While total lipids did increase, the atherogenic index did not show a significant increase as assessed by ratios of TC/HDL-C and LDL-C/HDL-C. The mean changes were generally small and according to the MAH probably due to natural variations that occur among the population analyzed.

Potentially clinically important laboratory values are defined as CTCAE Grade 3 or 4 laboratory abnormalities, for PCI, few Grade 3 cholesterol and no triglyceride increases occurred on upadacitinib treatments. There was 1 subject on upadacitinib 7.5 mg who had a Grade 2 cholesterol value at Baseline that worsened to Grade 3 worst post-Baseline, and 2 subjects on upadacitinib 15 mg who had a Grade 0 cholesterol value at Baseline that worsened to Grade 3 worst post-Baseline during Period 1. No other Grade 3 or above worst post-Baseline values cholesterol or triglycerides were reported in any treatment group.

Long-term Analysis Set (SS_LT)

Overall, lipid parameter shift analysis results from the long-term analysis set were generally consistent with the results from Period 1.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Through Week 52 (Period 1; SS1)

According to the MAH, mean changes in vital signs from Baseline to the end of Period 1 (Week 52) were small and not considered to be clinically meaningful. The most frequently observed PCS vital sign values (> 10% of subjects in any treatment group) were weight increase > 7% from Baseline (slightly higher on upadacitinib 15 mg than placebo or upadacitinib 7.5 mg) and systolic blood pressure ≥ 160 mm Hg and increase ≥ 20 mm Hg from Baseline (similar in upadacitinib 7.5 mg and placebo and higher in upadacitinib 15 mg). TEAEs with the PT hypertension were more frequent in the upadacitinib 7.5 mg compared to the upadacitinib 15 mg and placebo groups. All the events were nonserious and did not lead to discontinuation of study drug. In addition, there was 1 event of a nonserious hypertensive crisis in the upadacitinib 15 mg group that did not lead to discontinuation of study drug. According to the MAH, these observations in the GCA study are not unexpected given GCA patients frequently have traditional cardiovascular risk factors, particularly hypertension and use of chronic CS. Background incidence rates of hypertension in GCA patients were 14.1 E/100 PY (Mohammad 2017[5]), which is higher than the general population. In addition, hypertension and weight gain are examples of common and long-term side effects of treatment with glucocorticoids.

[5] Mohammad AJ, Englund M, Turesson C, et al. Rate of Comorbidities in Giant Cell Arteritis: A Population-based Study. J Rheumatol. 2017;44(1):84-90.

Long-term Analysis Set (SS_LT)

Overall, vital sign results from the long-term analysis set were similar to results from Period 1.

Safety in special populations

Intrinsic Factors

Age

Table 28: Overview of treatment-emergent adverse events and all deaths in period 1 by age group <65 years (SS1)

	< 65 Years			
		UPA		
	PBO + 52 WK CS-T (N=17) n (%)	7.5 + 26 WK CS-T (N=19) n (%)	15 + 26 WK CS-T (N=42) n (%)	Total (N=61) n (%)
Subjects with any treatment-emergent				
Adverse events (AE)	16 (94.1)	18 (94.7)	41 (97.6)	59 (96.7)
AE with reasonable possibility of being related to upadacitinib (or matching placebo)	7 (41.2)	11 (57.9)	22 (52.4)	33 (54.1)
AE with reasonable possibility of being related to prednisone/prednisolone (or matching placebo)	9 (52.9)	12 (63.2)	28 (66.7)	40 (65.6)
AE with CTCAE Grade >=3	2 (11.8)	1 (5.3)	12 (28.6)	13 (21.3)
Serious AE	1 (5.9)	0	9 (21.4)	9 (14.8)
AE leading to withdrawal of upadacitinib (or matching placebo)	2 (11.8)	1 (5.3)	8 (19.0)	9 (14.8)
COVID-19 related AE	4 (23.5)	4 (21.1)	8 (19.0)	12 (19.7)
AE results in death	0	0	0	0
All deaths	0	0	0	0
Occurring <= 30 days after last dose of study drug	0	0	0	0
COVID-19 related	0	0	0	0
Occurring > 30 days after last dose of study drug	0	0	0	0
COVID-19 related	0	0	0	0

Note: Treatment-emergent adverse events in Period 1 are defined as any adverse events with an onset or worsening in severity date on or after the first dose date of study drug and prior to the first dose of study drug in Period 2 or no more than 30 days after the last dose of study drug in Period 1, whichever occurs firstly.
Subjects are counted once in each row, regardless of the number of events they may have had.
PBO + 52 WK CS-T = Placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 + 26 WK CS-T = Upadacitinib 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 + 26 WK CS-T = Upadacitinib 15 mg + 26 Weeks Corticosteroid Taper.

Table 29: Overview of treatment-emergent adverse events and all deaths in period 1 by age group >65 years (SS1)

	>= 65 Years			
		UPA		
	PBO + 52 WK CS-T (N=95) n (%)	7.5 + 26 WK CS-T (N=88) n (%)	15 + 26 WK CS-T (N=167) n (%)	Total (N=255) n (%)
Subjects with any treatment-emergent				
Adverse events (AE)	90 (94.7)	84 (95.5)	161 (96.4)	245 (96.1)
AE with reasonable possibility of being related to upadacitinib (or matching placebo)	42 (44.2)	31 (35.2)	88 (52.7)	119 (46.7)
AE with reasonable possibility of being related to prednisone/prednisolone (or matching placebo)	56 (58.9)	47 (53.4)	110 (65.9)	157 (61.6)
AE with CTCAE Grade >=3	29 (30.5)	19 (21.6)	53 (31.7)	72 (28.2)
Serious AE	23 (24.2)	14 (15.9)	39 (23.4)	53 (20.8)
AE leading to withdrawal of upadacitinib (or matching placebo)	27 (28.4)	22 (25.0)	28 (16.8)	50 (19.6)
COVID-19 related AE	8 (8.4)	8 (9.1)	22 (13.2)	30 (11.8)
AE results in death	2 (2.1)	0	2 (1.2)	2 (0.8)
All deaths	2 (2.1)	0	3 (1.8)	3 (1.2)
Occurring <= 30 days after last dose of study drug	2 (2.1)	0	2 (1.2)	2 (0.8)
COVID-19 related	0	0	1 (0.6)	1 (0.4)
Occurring > 30 days after last dose of study drug	0	0	1 (0.6)	1 (0.4)
COVID-19 related	0	0	0	0

Note: Treatment-emergent adverse events in Period 1 are defined as any adverse events with an onset or worsening in severity date on or after the first dose date of study drug and prior to the first dose of study drug in Period 2 or no more than 30 days after the last dose of study drug in Period 1, whichever occurs firstly.
Subjects are counted once in each row, regardless of the number of events they may have had.
PBO + 52 WK CS-T = Placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 + 26 WK CS-T = Upadacitinib 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 + 26 WK CS-T = Upadacitinib 15 mg + 26 Weeks Corticosteroid Taper.

Table 30: Overview of treatment-emergent adverse events and all deaths in period 1 by age group >75 years

TABLE 14.3__1.1.1.3

Overview of Treatment-Emergent Adverse Events and All Deaths in Period 1 by Age Group 2
(SS1)

	>= 75 Years			
		UPA		
	PBO + 52 WK CS-T (N=36) n (%)	7.5 + 26 WK CS-T (N=39) n (%)	15 + 26 WK CS-T (N=65) n (%)	Total (N=104) n (%)
Subjects with any treatment-emergent				
Adverse events (AE)	34 (94.4)	37 (94.9)	60 (92.3)	97 (93.3)
AE with reasonable possibility of being related to upadacitinib (or matching placebo)	15 (41.7)	17 (43.6)	36 (55.4)	53 (51.0)
AE with reasonable possibility of being related to prednisone/prednisolone (or matching placebo)	21 (58.3)	23 (59.0)	37 (56.9)	60 (57.7)
AE with CTCAE Grade >=3	16 (44.4)	10 (25.6)	22 (33.8)	32 (30.8)
Serious AE	11 (30.6)	9 (23.1)	18 (27.7)	27 (26.0)
AE leading to withdrawal of upadacitinib (or matching placebo)	10 (27.8)	11 (28.2)	13 (20.0)	24 (23.1)
COVID-19 related AE	4 (11.1)	3 (7.7)	8 (12.3)	11 (10.6)
AE results in death	2 (5.6)	0	1 (1.5)	1 (1.0)
All deaths	2 (5.6)	0	1 (1.5)	1 (1.0)
Occurring <= 30 days after last dose of study drug	2 (5.6)	0	1 (1.5)	1 (1.0)
COVID-19 related	0	0	0	0
Occurring > 30 days after last dose of study drug	0	0	0	0
COVID-19 related	0	0	0	0

The rest of the subgroup analyses did not reveal a clinically relevant increased risk of AEs on upadacitinib treatment based on sex, race group, nicotine use, BMI, and geographic region. Given this assessment, the MAH states that no special considerations for upadacitinib treatment based on the age, sex, race, BMI, nicotine use, or geographic region are warranted beyond those already described in the label.

Extrinsic Factors

A similar proportion of subjects in the upadacitinib (total) and placebo treatment groups had CS dose ≤ 30 mg at Baseline. No clinically meaningful differences were observed in subjects who had a CS dose ≤ 30 mg at Baseline compared to subjects who had a CS dose > 30 mg at Baseline. Due to the small sample size of subjects with prior use of an IL-6 inhibitor, no conclusions can be made.

Rheumatoid Arthritis: Long-Term Upadacitinib 15 mg Safety Data

Upadacitinib 15 mg has been approved for the treatment of various inflammatory diseases, including RA which shares similar mechanistic pathways with GCA, with common cytokines being targeted by effective therapies. RA has a similar patient population to GCA given the older age of the RA patients and use of glucocorticoids, albeit a lower dose.

Long-term data through 15 February 2024 in age-matched (≥ 50 years) patients in the upadacitinib RA Phase 3 clinical development program (studies included: M13-545, M13-549, M14-465, M15-555, M13-542, and M15-925) who received upadacitinib 15 mg were summarized by the MAH as supportive information for use of upadacitinib 15 mg in GCA patients. The data are only inclusive of patients with RA 50 years of age and older thus providing data in a population similar in age to the GCA population.

The matched population from the RA studies included 2200 patients (7970 PYs). Of these, only 101 patients were above 75 years.

Long-term RA data in subjects 50 years of age and older include the following subgroups:

- Stratified by Baseline CS use or without CS-use.
- Age Group 1: stratified by 50 - < 65 years and 65 years and above, irrespective of CS use.

- Age Group 2: stratified by 50 - < 65 years and 65 years - < 75 years and 75 years and above, irrespective of CS use.

The age group analysis primarily focuses on Age Group 1 (Table 31) given the relatively small sample size of the ≥ 75-year-old subjects in Age Group 2.

Table 31: Overview of Treatment-Emergent Adverse Events and All Deaths Per 100 PY in Upadacitinib 15 mg RA Data

	≥ 50 Years and With and Without CS Use		Age Group 1		
	CS Use at Baseline Y (N = 1157) (PYs = 4328.4) Events (E/100 PY)	CS Use at Baseline N (N = 1043) (PYs = 3641.8) Events (E/100 PY)	50 - < 65 Years (N = 1557) (PYs = 5909.9) Events (E/100 PY)	≥ 65 Years (N = 643) (PYs = 2060.2) Events (E/100 PY)	Total (N = 2200) (PYs = 7970.2) Events (E/100 PY)
Any treatment-emergent					
Adverse events (AE)	8963 (207.1)	7833 (215.1)	12013 (203.3)	4783 (232.2)	16796 (210.7)
AE with reasonable possibility of being related to upadacitinib (or matching placebo) as assessed by investigator	2678 (61.9)	2137 (58.7)	3474 (58.8)	1341 (65.1)	4815 (60.4)
AE with CTCAE Grade ≥ 3 (severe AE)	629 (14.5)	511 (14.0)	729 (12.3)	411 (19.9)	1140 (14.3)
Serious AE	624 (14.4)	550 (15.1)	704 (11.9)	470 (22.8)	1174 (14.7)
AE leading to withdrawal of upadacitinib (or matching placebo)	233 (5.4)	227 (6.2)	259 (4.4)	201 (9.8)	460 (5.8)
COVID-19 related AE	206 (4.8)	151 (4.1)	269 (4.6)	88 (4.3)	357 (4.5)
AE results in death	57 (1.3)	31 (0.9)	44 (0.7)	44 (2.1)	88 (1.1)
EAIR:					
All deaths	68/4358.4 (1.6)	29/3649.3 (0.8)	48/5938.6 (0.8)	49/2069.0 (2.4)	97/8007.7 (1.2)
Occurring ≤ 30 days after last dose of study drug and COVID-19 related	13/4328.8 (0.3)	10/3642.1 (0.3)	10/5910.2 (0.2)	13/2060.7 (0.6)	23/7970.9 (0.3)
Occurring > 30 days after last dose of study drug and COVID-19 related	4/4328.9 (< 0.1)	3/3645.9 (< 0.1)	6/5914.5 (0.1)	1/2060.3 (< 0.1)	7/7974.8 (< 0.1)

E/100 PY = Events per 100 patient-years

EAERs of AESIs of serious infection, anaemia, and HZ and EAIRs of MACE and fractures were higher in the ≥ 75 year age group than 50 - < 65 or 65 - < 75 year groups.

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

Safety Analysis through Week 52 (Period 1; SS1)

During Period 1, the rates of TEAEs leading to study drug discontinuation were lower in the upadacitinib 15 mg and upadacitinib 7.5 mg treatment groups compared to the placebo group. The TEAEs leading study drug discontinuation reported in ≥ 1% of subjects in any treatment group in Period 1 are provided in Table 32, no other TEAE leading study drug discontinuation was reported in > 1% subjects in any treatment group. Giant cell arteritis was the most frequent TEAE leading study drug discontinuation in Period 1.

Table 32: Subjects with TEAEs Leading to Discontinuation of Study Drug Reported in ≥ 1% Subjects in Any Treatment Group by PT in Period 1 (SS1)

		UPA	
MedDRA 26.1 PT	PBO + 52 WK CS-T (N=112) n (%)	7.5 mg + 26 WK CS-T (N=107) n (%)	15 mg + 26 WK CS-T (N=209) n (%)
Any adverse event	29 (25.9)	23 (21.5)	36 (17.2)
Deep vein thrombosis	1 (0.9)	1 (0.9)	2 (1.0)
Giant cell arteritis	7 (6.3)	6 (5.6)	5 (2.4)
Pneumonia	3 (2.7)	2 (1.9)	0
Polymyalgia rheumatica	2 (1.8)	1 (0.9)	0
Pulmonary embolism	2 (1.8)	2 (1.9)	4 (1.9)
Substance-induced psychotic disorder	0	0	2 (1.0)

PBO + 52 WK CS-T = placebo + 52 Weeks Corticosteroid Taper; UPA 7.5 mg + 26 WK CS-T = upadacitinib 7.5 mg + 26 Weeks Corticosteroid Taper; UPA 15 mg + 26 WK CS-T = upadacitinib 15 mg + 26 Weeks Corticosteroid Taper

Note: TEAEs in Period 1 were defined as any AE with an onset or worsening in severity date on or after the first dose date of study drug and prior to the first dose of study drug in Period 2 or no more than 30 days after the last dose of study drug in Period 1, whichever occurred first.

Subjects were counted once in each row, regardless of the number of events they may have had.

Long-term Analysis Set (SS_LT)

The EAER of TEAEs leading study drug discontinuation was similar in the upadacitinib 15 mg and placebo groups and lower in the upadacitinib 7.5 mg group.

Post marketing experience

Please refer to the above heading “Rheumatoid Arthritis: Long-Term Upadacitinib 15 mg Safety Data”.

2.5.1. Discussion on clinical safety

This submission for the indication of adults with GCA is based on data from the Phase 3 Study M16-852, a Phase 3, global, multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of upadacitinib in subjects with new onset or relapsing GCA. Study M16-852 has two periods. Period 1 evaluated the efficacy, safety and tolerability of upadacitinib 15 mg QD and 7.5 mg QD in combination with a 26-week CS taper regimen compared to placebo in combination with a 52-week CS taper regimen. Period 2 is ongoing and evaluates the safety of upadacitinib in all subjects who entered Period 2, and the efficacy of continuing or withdrawing upadacitinib in maintaining remission in subjects who achieved remission in Period 1 for at least 24 consecutive weeks prior to Week 52.

The study included 428 subjects who were randomised and received at least one dose of study drug in period 1. The study population were mainly females and the majority above 65 years old (49.1% were ≥ 65 and < 75 years old; and 32.7% were ≥ 75 years old), thus representing an elderly study population, hence particular caution with respect of safety events was warranted.

The following analysis sets were used for the safety analyses:

- The Safety Analysis Set in Period 1 (SS1) consisting of all subjects who received at least 1 dose of study drug in Period 1.

- The Long-Term Safety Analysis Set (SS_LT) consisting of all subjects who received at least one dose of study drug in Period 1 and received the same dose of study drug in Period 2.

Based on efficacy data, the 15 mg dose was chosen by the MAH for the GCA indication. A total of 209 subjects received at least one dose of upadacitinib 15mg, representing a total of 178 PY of upadacitinib 15 mg exposure in period 1. A total of 167 and 122 subjects have been exposed to upadacitinib 15 mg for 24 weeks and 52 weeks respectively. Hence, the CHMP considers the exposure sufficient to support approval of the new indication and in line with the ICH recommendation for one year of safety data. Safety data beyond one year are scarce, provided from only 92 subjects on 15 mg upadacitinib who received the same dose of study drug in Period 2 as in Period 1. However, since the proposed dose 15 mg already are in use for rheumatic diseases, the MAH provided additional supportive data from a RA-cohort with similar age (>50) and with and without use of corticosteroids.

Common adverse events in the GCA study were mostly in line with previous known AEs, thus, the most frequent TEAEs by SOC were infections and infestations (upadacitinib 15 mg 63.2 % and placebo 58.9%). The most frequently reported TEAEs in the upadacitinib 15 mg group were GCA, headache, hypertension, COVID 19, arthralgia, urinary tract infection, back pain, nasopharyngitis. The TEAE 'GCA' was, however, more common in the placebo group and may reflect lack of efficacy rather than a true adverse event.

Regarding headache, the frequency was higher in the GCA population (very common) than previously reported in other indications (common). As the MAH stated, the higher frequency is not unexpected in the GCA population due to the underlying pathology of GCA. The MAH has included a footnote in the SmPC Section 4.8 table to express this higher frequency. This is acceptable to the CHMP.

One additional adverse event was reported in the GCA studies, namely peripheral oedema, which was seen in 2.7% in the placebo group and 8.6% in the upadacitinib 15 mg group. According to the MAH, there were some potential confounders identified, such as concurrent VTE or treatment with calcium channel blockers, but peripheral oedema is included in the SmPC as a common ADR of another JAK-inhibitor. Hence, it seems plausible that this is an ADR also for upadacitinib. The SmPC Section 4.8 is therefore updated to include peripheral oedema as adverse reaction (frequency common). This is agreed by the CHMP.

There were 5 deaths during the study, 2 in the placebo group (sepsis and acute pancreatitis) and 3 in the upadacitinib (UPA) 15 mg group (unexplained, COVID-19, stroke). The COVID-19 related death was not considered related to the study drug. The stroke case was regarded as non-treatment emergent since it occurred around 60 days after treatment stop. This is agreed by the CHMP. Upon the CHMP's request, the MAH also provided a summary of the unexplained death in the upadacitinib 15 mg group. The death case concerned an 80-year-old male with several co-morbidities. After almost a year of treatment with upadacitinib, he had acute abdominal pain, nausea, vomiting that was worsening during the night. Emergency team was called but unable to resuscitate the patient. No autopsy was done. The investigator evaluated these events as possibly related to the study drug; however, it is agreed with the MAH that the case lacks sufficient information for a meaningful assessment. This case does not evoke any further concerns.

Serious events (SAE) were slightly more common in the placebo group (42.4 E/100 PY) than the upadacitinib 15mg group (36.5 E/100 PY). Infections and infestation were the most common reported SOC in all groups. No more than 2 subjects reported SAEs in any treatment groups, with the exception of pneumonia (5 subjects in the placebo group, and 3 subjects in upadacitinib 7.5 mg group), pulmonary embolism (5 subjects in the upadacitinib 15 mg group), DVT (3 subjects in the upadacitinib 15 mg group) and worsening of giant cell arteritis (3 subjects in the upadacitinib 15 mg group). Regarding VTE, these events are discussed further below.

Fractures are listed as an important potential risk in the RMP. There was a slightly higher rate of bone fractures in especially the upadacitinib 15 mg treatment group compared to placebo (6.2% for the upadacitinib 15 mg and 5.4% for the placebo group, respectively). According to the MAH, most fractures occurred in post-menopausal females and in subjects in > 65 years old. Of the 19 subjects on upadacitinib treatment, 12 of the fractures were due to trauma. Some of the fractures were non-traumatic spinal fractures or spinal compression fractures likely due, according to the MAH, to decreased bone density in the context of the elderly patient population on high dose and prolonged exposure of corticosteroids. However, since the patients on upadacitinib 15 mg were supposed to taper the corticosteroids faster than the placebo group, and thus receive a lower cumulative dose (as confirmed by the efficacy data on cumulative steroid dose in the Section 2.4. of the assessment report), the finding was considered worrisome. Six total events of bone fracture during the study were serious, and 2 events of bone fracture led to the study drug discontinuation. Additional information provided by the MAH did however show that the patients treated with upadacitinib 15 mg also had slightly more risk factors for osteoporosis, including a longer base-line corticosteroid treatment period. Fractures are already listed as a potential risk in the RMP and the CHMP concluded that no further updates are needed based on the findings from this study.

Regarding the adverse events of special interest, there were no events of active TB, lymphoma, or adjudicated GI perforation reported through Week 52 or through the cut-off date for subjects in the long-term analysis set. Serious infections were more common in the placebo group (12.7 E/100 PY) than the upadacitinib groups (7.9 E/100 PY in both the 7.5 mg and the 15 mg groups). The types of treatment-emergent serious infections reported were generally consistent with events that has been reported in other upadacitinib indications, such as pneumonia. Two serious infections (one in the placebo group and one in the 15 mg upadacitinib group) resulted in deaths. Regarding opportunistic infections, the TEAEs were slightly higher in the upadacitinib 15 mg group (4 events, 2.2 E/100 PY), than the placebo group (1 event, 1.1 E/100 PY), during period 1. The TEAE of herpes zoster were also higher in the upadacitinib 15 mg group (13 events, 7.3 E/100 PY) than the placebo group (4 events, 4.2 E/100 PY). The SmPC currently includes a warning in Section 4.4 with information regarding serious infections, opportunistic infections and herpes zoster, with description of selected types of manifestations and also a statement that caution should be used when treating the elderly. It is also highlighted that in patients 65 years of age and older, upadacitinib should only be used if no suitable treatment alternatives are available. In addition, both herpes zoster and pneumonia are included in SmPC Section 4.8 as common ADRs. Therefore, there is no need to update the SmPC regarding infections. However, a short summary of the frequency of serious infections, opportunistic infections and herpes zoster in the GCA population was, upon the CHMP's request, included in the SmPC Section 4.8.

The malignancies excluding NMSC reported in period 1 were reported in one subject each (lentigo maligna, malignant neoplasm of ampulla of Vater, squamous cell carcinoma of lung, and tongue neoplasm malignant in the upadacitinib 15 mg group; and prostate cancer and metastatic tonsil cancer in the placebo group). In the long-term, one additional malignancy was seen in the upadacitinib 15 group (prostate cancer) and 2 malignancies in the upadacitinib 7.5 mg group (lung adenocarcinoma and papillary thyroid cancer). All events were considered as having no relation to the study drug by the investigator and considering the short time between the start of the treatment and the event of most of the malignancies.

In period 1, the EAIRs of TEAEs of NMSC were similar in the upadacitinib 15 mg and placebo groups and lower in the upadacitinib 7.5 mg group. In the long term analysis, TEAEs of NMSC were only reported in the upadacitinib 15 mg and placebo groups, at similar incidence rates. NMSC are already included as a common ADR in SmPC Section 4.8, with basal cell carcinoma and squamous cell carcinoma of skin identified as the most common manifestations. The type of events and frequency of

malignancies are similar in the GCA population as previously reported and no updates of the SmPC is warranted.

The EAERs of TEAEs of hepatic disorder were slightly higher in the upadacitinib 15 mg (7.3 E/100 PY), group compared to placebo (6.4 E/100 PYs) and higher than UPA 7.5 mg (2.3 E/100 PY). Two subjects met the biochemical criteria for Hy's Law during Period 1, one patient on upadacitinib 15 mg and 1 on placebo. Upon medical review, neither case was considered a true Hy's Law event as both had alternate aetiologies (malignant neoplasm of the ampulla of Vater on upadacitinib 15 mg and acute hepatitis with acute pancreatitis leading to death on placebo). Increases in ALT and AST are listed as common ADRs in the current SmPC Section 4.8 and a warning included in SmPC Section 4.4. In addition, upadacitinib is contraindicated in severe hepatic impairment. Therefore, there is no need to update the SmPC.

Anaemia, neutropaenia and lymphopaenia are listed as common ADRs in the current SmPC Section 4.8. Recommendation for monitoring and for dose interruption if the measurements are below a certain value are also provided in SmPC Section 4.4. In the GCA study, the frequency of anaemia was 8.4 E/100 PY in the upadacitinib 15mg group. No TEAEs of neutropaenia were reported in the upadacitinib groups but one TEAE of neutropaenia was reported in the placebo group. TEAEs of lymphopaenia were only reported in the upadacitinib 15 mg and 7.5 mg groups. According to the MAH, all events were nonserious and mild or moderate and all events resolved without discontinuation of the study drug. However, there were two Grade 3 laboratory abnormalities of decreased lymphocyte count on upadacitinib treatments associated with an infection or a serious infection in period 1, and one Grade 3 laboratory abnormalities of decreased lymphocyte count on upadacitinib treatment was associated with an infection in period 2. The guidance in the SmPC Section 4.4 regarding interruption of treatment when lymphocytes are $<0.5 \times 10^9$ cells/L together with the current information in the SmPC regarding infections and cautious in patients >65 years old is sufficient to mitigate the risk of lymphopaenia in patients with GCA.

Blood CPK increase is a common ADR for upadacitinib (SmPC Section 4.8) and was seen also in the GCA population. Most TEAEs of CPK elevation were mild to moderate in severity and no event of rhabdomyolysis was reported. The CHMP concludes that no SmPC update is needed.

No treatment-emergent MACE was reported in subjects treated with upadacitinib in Period 1 or the long-term analysis set.

TEAEs of adjudicated VTEs were reported in all treatment groups, and the EAIRs were similar across the upadacitinib 15 mg and placebo groups (3.8% and 3.6% respectively). The majority of events were serious and severe, resulted in discontinuation of study drug, and considered by the investigator as having a reasonable possibility of being related to upadacitinib (or matching placebo). Almost all patients had risk factors for thromboembolic disease on top of having a vasculitis, a condition more prone to develop thrombotic events. VTE is considered an important potential risk and a class effect of JAK-inhibition and information regarding VTE and risk factors included in the SmPC Section 4.4. There is no need to update the SmPC based on the results from this study.

Regarding subgroups, the majority of subjects (>80%) in the study were ≥ 65 years and 1/3 >75 years. In general, the rate of AEs, SAEs and AEs leading to withdrawal were lower in the upadacitinib groups than the respectively placebo groups for patient >65 years and >75 years. Among AESIs, the percentages of subjects with serious infections, malignancies, anaemia, hepatic disorder and VTEs were higher in subjects ≥ 65 years compared to < 65 years of age in all groups.

Long term data through 15 February 2024 in age-matched (≥ 50 years) patients in the upadacitinib RA Phase 3 clinical development programme who received upadacitinib 15 mg with or without corticosteroids (to note that the dose was lower than in GCA) showed that AEs in general were higher

in subjects ≥ 65 years of age compared to subjects 50 – 64 years of age. Among the AESIs, no clinically meaningful difference in EAER was observed between subjects with and without CS use. Most AESIs were seen at a higher rate in subjects ≥ 65 years of age compared to subjects 50 – 64 years of age. EAERs of AESIs of serious infection, anaemia, and HZ and EAIRs of MACE and fractures were higher in the ≥ 75 year age group than 50 - < 65 or 65 - < 75 year groups. However, the data on patients above 75 years are still limited. The matched population from the RA studies included 2200 patients (7970 PYs). Of these, only 101 patients were above 75 years. Lack of data in very elderly >75 years and long-term safety are already included as missing information in the RMP. The long-term part of the study M16-852 has been included in the RMP. The SmPC currently includes a boxed warning that highlights that in patients 65 years of age and older, upadacitinib should only be used if no suitable treatment alternatives are available. This statement is also applicable to the GCA population.

2.5.2. Conclusions on clinical safety

The observed data from the GCA study are limited, especially in the long term. However, together with the overall knowledge of upadacitinib gained also from studies in other, already approved indications, do not evoke any concerns for the new GCA indication that are not already covered by the product information or the RMP.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version 16.0 with this application.

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

The PRAC considered that the risk management plan version 16.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 16.0 with the following content:

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 with AD

Pharmacovigilance plan

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. Estimated Q3 2025 • Estimated Q1 2030

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

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

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

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	To 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), HZ, EH/ KVE, active TB, GI perforation, DILI, fractures, and all-cause mortality; If a suitable comparator is identified: to describe and compare (when feasible) the incidence of the above safety outcomes in adolescent and adult individuals with AD treated with upadacitinib, relative to those treated with other selected systemic AD treatments. Secondary objectives: To describe the incidence of the outcomes above in upadacitinib users by: dose of upadacitinib (15 mg and 30 mg); age group (adolescents 12 – 17 years, 18 – 64 years, 65 – 74 years and ≥ 75 years) at the time of upadacitinib initiation; history of moderate hepatic impairment at the time of upadacitinib initiation; history of chronic infection with HBV or HCV at the time of upadacitinib initiation; history of severe renal impairment at the time of upadacitinib initiation. • If a suitable comparator is identified, to describe the incidence of the outcomes above in	Important potential risks: malignancies excluding NMSC; MACE; VTE; 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; 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		

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	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.	drug therapies; long-term safety in adolescents with AD		
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;	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 • Q4 2024 • Q3 2025 • Q3 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	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). To describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure, specifically: a) Describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections; b) Describe the use of upadacitinib among patients aged 65 years and older; c) Describe the use of upadacitinib 30 mg.			

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P21-824 A Study of Growth in Adolescents with AD Who Receive Upadacitinib/Ongoing	To evaluate the growth, development, and maturation in North American (US and Canada)-residing adolescents with moderate to severe AD who receive upadacitinib vs. biologic and other non-biologic, non-JAKi systemic comparators in routine clinical care. Where feasible, a cohort of European-residing adolescents with moderate to severe AD will also be evaluated. The primary objective is to compare differences in changes from baseline in height SDS and weight SDS, age at peak height velocity, age at Tanner stage progression, and incidence of bone fractures in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD. The secondary objectives of the study are to describe changes from baseline in standing height, height percentiles, height velocity, height velocity SDS, weight, weight percentiles, BMI, BMI percentiles, and BMI SDS, as well as the frequency of delayed puberty in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD.	Important potential risk: fractures Missing information: long-term safety in adolescents 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 Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P24-343 Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe /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	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;	• 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
	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 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.	severe renal impairment at the time of initiation of upadacitinib or other systemic drug therapies.		

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; 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	• 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
		exposure in utero Missing Information: long-term safety		
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

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

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities

Serious and opportunistic infections including TB	Routine risk minimization measures: • SmPC Section 4.4 summarizes the risk and provides guidance on ways to reduce the risk. • SmPC Section 4.4 includes a statement on dose-dependency of upadacitinib on reports of serious infection. • SmPC Section 4.4 specifies a higher incidence of infections in the elderly and diabetic populations. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL advises that patients do not take Rinvoq if they have active TB and warns that patients with a history of TB, or who have been in close contact with someone with TB should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.2 outlines lymphocyte and neutrophil counts and when not to initiate upadacitinib dosing. • SmPC Section 4.2 outlines interruption guidelines based on ALC and ANC. • SmPC Section 4.3 indicates that upadacitinib is contraindicated in patients with active TB or active serious infections. • SmPC Section 4.4 states that patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib and that upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection. • SmPC Section 4.4 advises to consider the risks and benefits of initiating upadacitinib in patients with chronic or recurrent infections. • A patient who develops a new infection during treatment with upadacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and upadacitinib should be interrupted if the patient is not responding to therapy. • Screening for TB prior to initiation is advised, and upadacitinib should not be given if active TB is diagnosed. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with untreated latent TB or in patients with risk factors for TB infection. • SmPC Section 4.4 specifies patient populations for which upadacitinib should be used with caution.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for serious and opportunistic infections including TB Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)

	• SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU • Other routine risk minimization measures: • Prescription only medicine.	• Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
Herpes zoster	Routine risk minimization measures: • SmPC Section 4.4 describes the risk of viral reactivation such as herpes zoster. • SmPC Section 4.8 describes findings from upadacitinib clinical trials. • The PL warns that patients who have an infection or who have a recurring infection should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL warns that patients who have had a herpes zoster infection (shingles) should tell their doctor if they get a painful skin rash with blisters as these can be signs of shingles. • SmPC Section 4.4 advises that prior to initiating upadacitinib patients be brought up to date with all immunizations including herpes zoster according to current immunization guidelines. • SmPC Section 4.4 advises that if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. Additional risk minimization measures: • HCP educational guide • Patient card Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for serious infections Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)

		• Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
NMSC	Routine risk minimization measures: • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 indicates that NMSCs have been reported in patients treated with upadacitinib and includes a statement on dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 advises on periodic skin examination. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. aRMMs: • HCP educational guide • Patient card • One-time distribution of DHPC in EU Other routine risk minimization measures: Prescription only medicine	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe

		• P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
GI perforation	Routine risk minimization measures: • SmPC Section 4.4 informs on reports of diverticulitis and GI perforation in clinical trials and from post-marketing sources. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 advises to use with caution in patients who may be at risk for GI perforation and prompt evaluation if specific signs/symptoms occur. Additional risk minimization measures: • HCP educational guide • Patient card Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for GI perforation Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA

		• P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)

Malignancies excluding NMSC	Routine risk minimization measures: • SmPC Section 4.4 indicates that malignancies have been reported in patients receiving JAK inhibitors, including upadacitinib, and includes a statement on upadacitinib dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. aRMMs: • HCP educational guide • Patient card • One-time distribution of DHPC in EU Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD

		trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
MACE	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on lipids and describes that impact on CV morbidity and mortality has not been determined. • SmPC Section 4.4 indicates that events of MACE were observed in clinical trials for upadacitinib. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for MACE Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trials (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)

		• Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
VTEs (deep venous thrombosis and pulmonary embolus)	Routine risk minimization measures: • SmPC Section 4.4 indicates that events of deep vein thrombosis and pulmonary embolism have been reported in clinical trials for upadacitinib. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get certain symptoms. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies in patients with VTE risk factors other than cardiovascular or malignancy risk factors, use upadacitinib with caution. Examples of the risk factors which may put a patient at higher risk for VTE are provided. • SmPC Section 4.4 on re-evaluation of VTE risk and to promptly evaluate patients with signs and symptoms of VTE and discontinue upadacitinib in patients with suspected VTE, regardless of dose. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU Other routine risk minimization measures:	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including: • Follow-up questionnaire for VTEs • Monitoring of VTE risk and literature review provided within the PSUR Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients

	Prescription only medicine.	• P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
DILI	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on transaminases. • SmPC Section 4.4 recommends prompt investigation of the cause of liver enzyme elevation to identify potential cases of DILI. • SmPC Section 4.4 advises that if increases in ALT or AST are observed during routine patient management and DILI is suspected, upadacitinib should be interrupted until this diagnosis is excluded. Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for DILI Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe

	Other routine risk minimization measures: Prescription only medicine.	• P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
Fetal malformation following exposure in utero	Routine risk minimization measures: • SmPC Section 4.6 describes the teratogenic effects observed in animals receiving upadacitinib and states that there are no or limited data from use of upadacitinib in pregnant women. • The PL advises that patients do not take Rinvoq if they are pregnant, that Rinvoq must not be used during pregnancy, and that patients who become pregnant while taking Rinvoq must consult their doctor straight away. • SmPC Section 4.3 and Section 4.6 indicate that upadacitinib is contraindicated during pregnancy.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaires for pregnancies Additional pharmacovigilance activities (see Part III.2): • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA

	• SmPC Section 4.6 and PL advise on use of effective contraception. • SmPC Section 4.6 advises that female pediatric patients and/or their caregivers should be informed about the need to contact the treating physician once the patient experiences menarche. • The PL informs caregivers to let their doctor know if their child has their first menstrual period while using Rinvoq. Additional risk minimization measures: • HCP educational guide • Patient card Other routine risk minimization measures: Prescription only medicine.	• P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
Fractures	Routine risk minimization measures: None Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Follow-up questionnaire for fractures Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of

		Upadacitinib Use in AD Patients • P21-824: A Study of Growth in Adolescents with AD Who Receive Upadacitinib • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)

Use in very elderly (≥ 75 years of age)	Routine risk minimization measures: • SmPC Section 4.2 states that there are limited data in patients 75 years of age and older. • SmPC Section 4.4 indicates that there is an increased risk of adverse reactions with upadacitinib 30 mg in patients 65 years of age and older. • SmPC Section 4.4 specifies increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomised study of tofacitinib (another JAK inhibitor). • SmPC Section 4.2 specifies that upadacitinib 15 mg is recommended in patients 65 years of age and older. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C	Routine risk minimization measures: • SmPC Section 4.4 describes the risk of viral reactivation. • The PL warns that patients who have ever had hepatitis B or hepatitis C should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 describes the need for screening and consultation with a hepatologist if HBV DNA is detected. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe
Use in patients with moderate hepatic impairment	Routine risk minimization measures: • SmPC Section 4.2 describes use in patients with hepatic impairment.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None

	• SmPC Section 4.2 states that upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment. • SmPC Section 4.3 indicates that upadacitinib is contraindicated for use in patients with severe hepatic impairment. • The PL advises that patients do not take Rinvoq if they have severe liver problems and warns that patients should consult their doctor or pharmacist before and during treatment with Rinvoq if their liver does not work as well as it should. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe
Use in patients with severe renal impairment	Routine risk minimization measures: • SmPC Section 4.2 describes use in patients with renal impairment. • SmPC Section 4.2 states that upadacitinib should be used with caution in patients with severe renal impairment. • SmPC Section 4.2 specifies that for RA, PsA, AS, nr-axSpA, AD and GCA, the recommended dose is 15 mg QD for patients with severe renal impairment and that for UC and CD, the recommended dose is 30 mg QD for induction treatment and 15 mg QD for maintenance treatment for patients with severe renal impairment. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe
Long-term safety	Routine risk minimization measures: SmPC Section 4.4 indicates that upadacitinib clinical data on malignancies are currently limited and long-term studies are ongoing. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe

		• P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)

Long-term safety in adolescents with AD	Routine risk minimization measures: None Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Additional pharmacovigilance activities (see Part III.2): • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-824: A Study of Growth in Adolescents with AD Who Receive Upadacitinib • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)

2.7. Update of the Product information

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

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 for the following reasons:

- 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

In this application, the indications of Rinvoq are proposed to be extended to include the treatment of giant cell arteritis in adult patients.Giant cell arteritis (GCA, also known as temporal arteritis) is a systemic vasculitis of the large vessels, with a predilection for the cranial branches of the aorta which almost exclusively occurs in those over age 50. The characteristic symptoms of GCA include those related to vascular ischemia such as temporal headache, jaw claudication, ocular symptoms, and stroke. There is a significant overlap between GCA and PMR.

3.1.2. Available therapies and unmet medical need

Steroid therapy is the current mainstay of treatment for GCA. Initial high dose steroid therapy is followed by a prolonged period of dose tapering. During this tapering phase, between 50% and 80% of GCA patients experience a disease flare.

Tocilizumab (RoActemra) was approved in the European Union in 2017 for the treatment of GCA in adult patients. Tocilizumab is administered subcutaneously in combination with a steroid taper.

As oral targeted therapies for the treatment of GCA are currently not available, there continues to be a need for additional therapies in GCA. .

3.1.3. Main clinical study

The extension of indication for Rinvoq in GCA with the proposed posology of 15 mg QD, is supported by a single pivotal phase 3 study: study M16-852. This is randomized, double-blind and placebo-controlled study including adult subjects of at least 50 years of age with a diagnosis of new onset or relapsing GCA.

Study M16-852 has two periods. Period 1 evaluated upadacitinib 15 mg QD and 7.5 mg QD in combination with a 26-week CS taper regimen compared to placebo in combination with a 52-week CS taper regimen, as measured by the proportion of GCA subjects in sustained remission at Week 52. Period 2 is ongoing and evaluates the safety of upadacitinib in all subjects who entered Period 2 and the efficacy of continuing or withdrawing upadacitinib in maintaining remission.

To support this application, results from the Primary Analysis of Study M16-852 and efficacy data for all subjects who completed the Week 52 visit or prematurely discontinued from the study prior to Week 52 in Period 1 were provided. The interim database lock for the Primary Analysis was based on a data cutoff date of 06 February 2024.

Subjects eligible for Study M16-852 were randomized in a 2:1:1 ratio to 1 of 3 treatment groups: upadacitinib 15 mg QD + 26-week CS taper regimen, upadacitinib 7.5 mg QD + 26-week CS taper regimen, or placebo QD + 52-week CS taper regimen.

The primary endpoint was the proportion of subjects achieving sustained remission at Week 52, defined as having achieved the absence of GCA signs and symptoms from Week 12 through Week 52 and adherence to the protocol defined CS taper regimen. Subjects who adhered to the protocol-defined CS taper regimen would be CS-free at Week 52.

The multiplicity-controlled secondary endpoints were the followings:

1. Proportion of subjects achieving sustained complete remission from Week 12 through Week 52. This was defined as having achieved Sustained remission (see above) and also:

- Normalization of ESR (to ≤ 30 mm/hr; if ESR > 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met) from Week 12 through Week 52.
- Normalization of hsCRP (to < 1 mg/dL without elevation [on 2 consecutive visits] to ≥ 1 mg/dL) from Week 12 through Week 52.

2. Cumulative CS exposure through Week 52.

3. Time to first GCA flare through Week 52.

4. Proportion of subjects who experience at least 1 GCA flare through Week 52.

5. Proportion of subjects in complete remission at Week 52.

6. Proportion of subjects in complete remission at Week 24.

7. Change from Baseline in the 36-item SF-36 PCS at Week 52.

8. A group of four endpoints:

- Number of GCA flares per subject during Period 1.
- Change from Baseline in FACIT-Fatigue at Week 52.
- Assessment of TSQM patient global satisfaction subscale at Week 52.
- Rate of CS-related AEs through Week 52.

3.2. Favourable effects

A significantly greater proportion of subjects achieved the primary endpoint of sustained remission at Week 52 in the upadacitinib 15 mg (+26-week steroid taper) group (46.4%) compared with the placebo (+52-week steroid taper) group (29.0%). The p-value for the difference between the groups was 0.0019. Results from the subgroup analysis for the primary endpoint indicated consistency of efficacy of upadacitinib 15 mg across important subgroups.

For upadacitinib 15 mg (+26-week steroid taper) vs placebo (+52-week steroid taper), not only the primary endpoint but also almost all secondary, multiplicity-controlled, endpoints were met. The exceptions were assessment of TSQM patient global satisfaction subscale at Week 52 and rate of CS-related AEs through Week 52.

As for effect size, the treatment difference (with 95% CI) between upadacitinib 15 mg (+26-week steroid taper) vs placebo (+52-week steroid taper) with regards to achieving the primary endpoint i.e. sustained remission at week 52 (having achieved both the absence of GCA signs and symptoms from Week 12 -Week 52 and adherence to the protocol-defined corticosteroid taper regimen) was 17.1% (6.3, 27.8). For the secondary endpoint sustained complete remission at Week 52 (same requirements as for sustained remission but also normalization of ESR from Week 12- Week 52 and normalization of hsCRP from Week 12 -Week 52), the difference between the two groups was 20.7% (11.3, 30.2).

Results for each component of sustained remission at Week 52 and sustained complete remission from Week 12 through Week 52 were consistent with that of the respective composite endpoints.

The outcome for the secondary endpoint cumulative corticosteroid exposure through Week 52 (median), was 1615.0 mg in the upadacitinib 15 mg (+26-week steroid taper) group and 2882.0 mg in the placebo (+52-week steroid taper) group.

Upadacitinib 15 mg significantly improved the SF-36 PCS and the FACIT-Fatigue score.

3.3. Uncertainties and limitations about favourable effects

A total of 428 subjects were randomized and received at least one dose of study drug (upadacitinib 15 mg, upadacitinib 7.5 mg, or placebo) in Period 1. The proportion of subjects that discontinued study in Period 1 was rather high (18.7%). There was further a somewhat uneven distribution between the study arms: 15.3% in the upadacitinib 15 mg +26-week CS taper arm vs 23.2% in the PBO+52-week CS taper arm. The proportion that discontinued study drug in Period 1 was 25.8% in the upadacitinib 15 mg+26-week CS taper arm vs 36.6% in the PBO+52-week CS taper arm. In both treatment groups, “adverse event” was the most common primary reason for study discontinuation and discontinuation of study drug. The relatively high rate of study discontinuations and study drug discontinuation are limitations that have been considered for the overall interpretation of data. Patients who prematurely discontinued study treatment (upadacitinib or placebo) or had a missing assessment were classified as non-responders. This is reflected accordingly in SmPC Section 5.1.

Finally, the comparison of cumulative steroid dose between the upadacitinib arms and the placebo arm is hampered by the different rules for steroid tapering in the active arms vs the placebo arm i.e. stipulated 26-week corticosteroid taper vs stipulated 52-week taper. This is adequately reflected in the SmPC Section 5.1.

3.4. Unfavourable effects

Common adverse events in the GCA study were mostly in line with previous known AEs in other indications. Thus, the most frequent TEAEs by SOC were infections and infestations. The most frequently reported TEAEs in the upadacitinib 15 mg group were giant cell arteritis, headache, hypertension, COVID 19, arthralgia, urinary tract infection, back pain, nasopharyngitis. One new ADR was reported in the GCA studies, peripheral oedema. This has been included as a common ADR in SmPC Section 4.8.

There were 5 deaths during the study, 2 in the placebo group (sepsis and acute pancreatitis) and 3 in the upadacitinib 15 mg group (unexplained, covid 19, stroke). The COVID-19 related death was not considered related to the study drug. The stroke case was regarded as non-treatment emergent since it occurred around 60 days after treatment stop. The unexplained death was considered related to upadacitinib by the investigator. Additional information provided by the MAH revealed several confounding factors that could have participated in the death and the case did not evoke any further concerns. This is agreed by the CHMP.

SAEs were slightly more common in the placebo group than the upadacitinib groups. Infections and infestation were the most common reported SOC in all groups.

Regarding adverse events of special interest, there were no events of active TB, lymphoma, or adjudicated GI perforation reported. Serious infections were more common in the placebo group than the upadacitinib groups. The types of treatment-emergent serious infections reported were generally consistent with events reported in other upadacitinib indications, such as pneumonia. Two serious infections resulted in deaths. Regarding opportunistic infections, the TEAE were slightly higher in the upadacitinib 15 mg group than the placebo group during period 1. The TEAE of herpes zoster were also higher in the upadacitinib 15 mg group than the placebo group. The warnings included in the SmPC section 4.4 remain adequate inform on the risks of serious infections, opportunistic infections and herpes zoster. It is also highlighted that in patients 65 years of age and older, upadacitinib should only be used if no suitable treatment alternatives are available. Herpes zoster and pneumonia are included in SmPC Section 4.8 as common ADRs. A short summary of the frequency of serious infections, opportunistic infections and herpes zoster in the GCA population are included in the SmPC Section 4.8.

The EAERs of TEAEs of hepatic disorder were slightly higher in the upadacitinib 15 mg, group compared to placebo and higher than upadacitinib 7.5 mg. Upadacitinib is contraindicated in severe hepatic impairment, a warning included in SmPC section 4.4 and ALT and AST are listed as common ADRs. Hence, no further product information is needed.

In the GCA study, the frequency of anaemia was 8.4 E/100 PY in the upadacitinib 15mg group. No TEAEs of neutropaenia were reported in the upadacitinib groups. TEAEs of lymphopaenia were only reported in the upadacitinib 15 mg and 7.5 mg groups. There were three Grade 3 laboratory abnormalities of decreased lymphocyte count on upadacitinib treatments associated with an infection. The guidance in the SmPC regarding interruption of treatment when lymphocytes are <0.5 together with the current information in the SmPC regarding infections and cautious in patients >65 years old are sufficient to mitigate further these risks.

TEAEs of adjudicated VTEs were reported in all treatment groups, and the EAIRs were similar across the upadacitinib 15 mg, upadacitinib 7.5 mg, and placebo groups. The majority of events were serious and severe, resulted in discontinuation of study drug, and considered by the investigator as having a reasonable possibility of being related to the study drug. VTE is an important potential risk and a class effect of JAK-inhibition and information regarding VTE and risk factors is included in the SmPC SmPC 4.4. No further updates are necessary based on the results from this study.

The majority of subjects (>80%) in the study were ≥ 65 years and 1/3 >75 years. In general, the rate of AEs, SAEs and AEs leading to withdrawal were lower in the upadacitinib groups than the respectively placebo groups for patient >65 years and >75 years. Among AESIs, the percentages of subjects with serious infections, malignancies, anaemia, hepatic disorder and VTEs were higher in subjects ≥ 65 years compared to < 65 years of age in all groups.

3.5. Uncertainties and limitations about unfavourable effects

There are limited data regarding long term safety in the GCA population. A total of 209 subjects received at least one dose of upadacitinib 15mg, representing a total of 178 PY of upadacitinib 15 mg exposure in the first year. Safety data beyond one year are provided from only 92 subjects who continued on 15 mg upadacitinib in the long-term part of the study that is currently ongoing. Long term safety is included as missing information in the RMP and the long-term part of the study M16-852 has been included in the RMP. The safety profile of Rinvoq has however been explored in several other indications and doses and there are known risks related to JAK-inhibitors regarding malignancies, infections, VTE and MACE that may have specific impact in the GCA population, where the majority of patients are expected to be >65 years old. The SmPC currently includes a boxed warning that highlights that in patients 65 years of age and older, upadacitinib should only be used if no suitable treatment alternatives are available. This statement is also applicable to the GCA population.

There was a slightly higher rate of bone fractures in especially the upadacitinib 15 mg treatment group compared to placebo. According to the MAH, most fractures occurred in post-menopausal females and in subjects in > 65 years old. Some of the fractures were non-traumatic spinal fractures or spinal compression fractures, according to the MAH, likely due to decreased bone density in the context of the elderly patient population on high dose and prolonged exposure of corticosteroids. However, since the patients on upadacitinib 15 mg were supposed to taper the corticosteroids faster than the placebo group, and thus receive a lower cumulative dose, the finding was found worrisome. Additional information provided by the MAH showed that the patients treated with upadacitinib 15 mg also had slightly more risk factors for osteoporosis, including a longer base-line corticosteroid treatment period. Fractures are already listed as a potential risk in the RMP and no further updates are needed based on the findings from this study.

3.6. Effects Table

Table 33: Effects Table for Rinvoq and indication GCA

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Sustained remission at Week 52 (Primary endpoint)	No GCA signs, symptoms W12-W52 and adherence to corticosteroid taper	%	Upa 15 mg+26 week taper: 46.4%	PBO+52 week taper: 29.0%	p-value for treatment difference between the groups: p≤0.01	Study M16-852
Sustained complete remission at Week 52 (Secondary endpoint)	Sustained remission + normalization ESR and hsCRP W12-W52	%	37.1%	16.1%	p≤0.001	Study M16-852
Complete remission at Week 52 (Secondary endpoint)	No GCA signs and symptoms, normalization of ESR and hsCRP and adherence to corticosteroid taper	%	50.2%	19.6%	p≤0.001	Study M16-852
Cumulative corticosteroid exposure through Week 52 (median) (Secondary endpoint) *		mg	1615.0 mg (n=180)	2882.0 mg (n=90)	p≤0.001	Study M16-852
Unfavourable Effects						
Adverse event	AEs in period 1	E/100 PYs	UPA 15mg 817.7 E/100 PYs	Placebo 748.6 E/100 PYs		Study M16-852
Serious Adverse Events		E/100 PYs	UPA 15mg 36.5 E/100 PYs	Placebo 42.4 E/100 PYs		Study M16-852
Serious Infections		E/100 PYs	UPA 15mg 7.9 E/100 PYs	Placebo 12.7 E/100 PYs		Study M16-852
Opportunistic infections		E/100 PYs	UPA 15mg 2.2 E/100 PYs	Placebo 1.1 E/100 PYs		Study M16-852
Herpes zoster		E/100 PYs	UPA 15mg 7.3 E/100 PYs	Placebo 4.2 E/100 PYs		Study M16-852

Abbreviations: GCA=giant cell arteritis, PBO=placebo, AE=adverse event

Notes: *the comparison of cumulative steroid dose between the upadacitinib arms and the placebo arm is hampered by the different rules for steroid tapering in the active arms vs the placebo arm.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

The effect size recorded for upadacitinib 15 mg is considered of clinical relevance; both in terms of the ability to induce remission and its likely steroid-sparing potential. The relatively high rate of study discontinuations and study drug discontinuation are limitations that have been taken into account for the overall interpretation of data and have been reflected in the SmPC Section 5.1.

Importance of unfavourable effects

The safety profile of Rinvoq has been well characterised through studies in the currently approved indications. The 15 mg dose, proposed for use in GCA, is the same as used in other rheumatic diseases and higher doses are approved for other indications. The short-term safety profile is similar in the GCA population to the already known safety profile with respect to common AEs. Although the majority of the GCA patients are expected to be 65 years or older, and thus at higher risk for known risks related to JAK-inhibitors, no new concerns are evoked that are not already covered by the SmPC or the RMP.

3.7.2. Balance of benefits and risks

The efficacy data presented show clinically relevant effects, hence, support the extension of the Rinvoq indications to GCA in adult patients.

The overall safety profile observed in patients with GCA is generally consistent with that observed in patients with other approved indications.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall Benefit/Risk of Rinvoq is positive in the following indication:

Giant cell arteritis

Rinvoq is indicated for the treatment of giant cell arteritis in adult patients.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and

therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include the treatment of giant cell arteritis (GCA) in adult patients for Rinvoq based on final results from study M16-852. This is a phase 3, global, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of upadacitinib in subjects with GCA. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 16.0 of the RMP is agreed.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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

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

Risk management plan (RMP)

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

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.

Information for upadacitinib use in moderate to severe AD

The 30 mg upadacitinib dose in atopic dermatitis

- Language on dose-dependent increase in serious infections and herpes zoster with upadacitinib.
- Language on dose-dependent increase in 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.

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "steps after the authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘EMEA/H/C/004760/II/0056’.