EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2022
EMA/659973/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RINVOQ

International non-proprietary name: upadacitinib

Procedure No. EMEA/H/C/004760/II/0016

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
AST	aspartate aminotransferase
axSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
	BASMIlin = Linear Bath Ankylosing Spondylitis Metrology Index
bDMARD	biologic disease-modifying antirheumatic drug
bDMARD-IR	biologic DMARD-inadequate responders
	CI = Confidence Interval
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
DMARD	disease-modifying antirheumatic drug
EAER(s)	exposure-adjusted event rate(s)
EAIR	exposure-adjusted incidence rate
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	full analysis set
HDL-C	high-density lipoprotein cholesterol
hsCRP	high-sensitivity C-reactive protein
IL	interleukin
IR	inadequate response
JAK	Janus kinase
LDA	Low Disease Activity
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiac event
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed-effect model repeated measurements
MRI	magnetic resonance imaging
MTX	methotrexate
NMSC	non-melanoma skin cancer
nr-axSpA	non-radiographic axial spondyloarthritis
NRI	non-responder imputation

NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
OLE	Open-label extension
OMERACT	Outcome Measures in Rheumatology
PCS	potentially clinically significant
PR	partial remission
PsA	psoriatic arthritis
PT	preferred term
PtGA	Patient's Global Assessment of Disease Activity
PYs	patient-years
QD	once daily
QoL	quality of life
RA	rheumatoid arthritis
SAE	serious adverse event
SF-36 PCS	36-Item Short Form Health Survey Physical Component Summary
SI	sacroiliac
SJC	swollen joint count
SMQ	standardized MedDRA query
SOC	system organ class
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SPARTAN	Spondyloarthritis Research and Treatment Network
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumor necrosis factor
TNFi	tumor necrosis factor alpha inhibitor
ULN	upper limit of normal
VTE	venous thromboembolic event

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 22 December 2021 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 the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation who have responded inadequately to NSAIDs or other conventional therapy, based on the final clinical study report from the pivotal study M19-944 Study 2 (nr-axSpA); a randomized, double-blind, phase III study evaluating the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with nr-axSpA who completed the double-blind period on study drug. As a consequence, SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2 have been updated and the Package Leaflet has been updated in accordance. A revised RMP version 8.0 was also 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 P/0510/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001741-PIP01-14-M05 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH received Scientific Advice from the CHMP on 27 June 2019 (EMEA/H/SA/3190/8/2019/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder

Timetable	Actual dates
Submission date	22 December 2021
Start of procedure:	23 January 2022
CHMP Rapporteur Assessment Report	15 March 2022
PRAC Rapporteur Assessment Report	22 March 2022
PRAC members comments	30 March 2022
Updated PRAC Rapporteur Assessment Report	30 March 2022
PRAC Outcome	7 April 2022
CHMP members comments	11 April 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 April 2022
Request for supplementary information (RSI)	22 April 2022
CHMP Rapporteur Assessment Report	07 June 2022
CHMP members comments	13 June 2022
Updated CHMP Rapporteur Assessment Report	15 June 2022
Opinion	23 June 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Spondyloarthritis (SpA) is represented by a group of diseases that share common genetic, clinical, and radiographic features. Adult SpA patients are commonly categorized by the two predominant manifestations of disease: axial SpA, which primarily involves the spine and sacroiliac (SI) joints, or peripheral SpA, which primarily involves peripheral joints. Further, axial SpA encompasses a spectrum of inflammatory conditions involving the axial skeleton with two distinct entities, ankylosing spondylitis (AS), which requires the presence of sacroiliitis on plain conventional radiographs as defined by the modified New York criteria and non-radiographic axial spondyloarthritis (nr-axSpA), which does not meet the 1984 modified New York imaging criteria. Patients with nr axSpA and AS share common epidemiological, genetic, and clinical disease characteristics, including disease activity, and similar response to treatment however, presence (AS) or absence (nr-axSpA) of radiographic findings serve as an important differentiating characteristic between the two categories of axSpA.

The prevalence of AS differs between regions and has been estimated to be up to 0.5% with similar estimated prevalence rates for nr-axSpA, resulting in an overall prevalence for axSpA in the US and in the EU of approximately up to 1% or higher.

The MAH applied for the following indication: "*RINVOQ is indicated for the treatment of active non-radiographic axial spondyloarthritis (nr-axSpA) in adult patients with objective signs of inflammation who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)*."

Management

In 2016, the Assessment of SpondyloArthritis international Society (ASAS) and European League Against Rheumatism (EULAR) published updated treatment recommendations for axial SpA. The first-line treatment of axial SpA consists of nonsteroidal anti inflammatory drugs (NSAIDs). In patients with persistently high disease activity despite a course of two NSAIDs given over a total of at least 4 weeks, initiation of a bDMARD is recommended, and current practice is to start with a tumor necrosis factor alpha inhibitor (TNFi). If TNFi therapy fails, switching to another TNFi or an interleukin (IL)-17 inhibitor (IL-17i) is recommended.

Overall, available treatment options remain limited, particularly for nr-axSpA as compared to other rheumatic diseases such as RA or PsA. In axSpA, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and long-term corticosteroids are not efficacious and therefore not recommended for treatment of axial symptoms. Once patients have an inadequate response to NSAIDs, and more advanced systemic therapies are required, available biologics are all administered either subcutaneous (SQ) or intravenous. To date, there have been no oral targeted therapies approved for the treatment of nr axSpA. However, upadacitinib was recently approved for the AS indication in the EU, as an additional treatment option based on the Phase 2/3 study in AS bDMARD-naïve subjects (Study M16-098, SELECT-AXIS 1).

2.1.2. About the product

Rinvoq (upadacitinib) is a selective and reversible Janus kinase (JAK) inhibitor. As per the approved EU SmPC, it is currently authorized for Rheumatoid arthritis (RA), Psoriatic arthritis (PsA), Ankylosing spondylitis, Atopic dermatitis (AD) and has received a positive opinion during the May 2022 CHMP for Ulcerative Colitis (UC).

For Rheumatoid arthritis, Psoriatic arthritis, Ankylosing spondylitis, the recommended dose is, according to section 4.2 of the SmPC, 15 mg once daily. For Atopic dermatitis, the recommended dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation. For Ulcerative Colitis, the recommended dose is 45mg for the induction phase once daily and 15 mg or 30 mg once daily for the maintenance phase.

The proposed dose for the new indication is 15 mg once daily.

EMA's safety committee, PRAC, has started a review of the safety of Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis and atopic dermatitis).

The review was prompted by the final results from a clinical trial (study A3921133) of the JAK inhibitor Xeljanz (tofacitinib). The results showed that patients taking Xeljanz for rheumatoid arthritis and who were at risk of heart disease were more likely to experience a major cardiovascular problem (such as heart attack, stroke or death due to cardiovascular disease) and had a higher risk of developing cancer than those treated with medicines belonging to the class of TNF-alpha inhibitors. The study also

showed that compared with TNF-alpha inhibitors, Xeljanz was associated with a higher risk of death due to any cause, serious infections, and blood clots in the lungs and in deep veins (venous thromboembolism, VTE).

In addition, preliminary findings from an observational study involving another JAK inhibitor, Olumiant (baricitinib), also suggest an increased risk of major cardiovascular problems and VTE in patients with rheumatoid arthritis treated with Olumiant compared with those treated with TNF-alpha inhibitors.

In the treatment of inflammatory disorders, Olumiant and other JAK inhibitors work in a similar way to Xeljanz. PRAC is therefore carrying out a review to determine whether these risks are associated with all JAK inhibitors authorised in the EU for the treatment of inflammatory disorders and whether the marketing authorisations for these medicines should be amended.

The review of JAK inhibitors in the treatment of inflammatory disorders has been initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004 and is currently on-going.

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

A Scientific Advice, with implications for the present Application was received from the CHMP in 2019 (EMEA/H/SA/3190/8/2019/II). Compliance with the Scientific Advice is commented on throughout the report.

2.1.4. General comments on compliance with GCP

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

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

The MAH has provided an ERA to include the new indication of non-Radiographic Axial Spondylarthritis (nr-axSpA); however, no new data for the environmental risk assessment were included with this application. The submitted ERA was updated from the original ERA submitted for the MAA for RA approval, and the updates to support the indications psoriatic arthritis, ankylosing spondylitis, atopic dermatitis and active ulcerative colitis.

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

The maximum daily dose for the indication nr-axSpA is 15 mg/day, resulting in $PEC_{SURFACEWATER}$ values of 0.075 µg/L, for each of the indications RA, PsA and AS, with the maximum daily dose of 15 mg/day, the $PEC_{SURFACEWATER}$ values was 0.075 µg/L, for the indication AD with the maximum daily dose of 15 mg/day, the $PEC_{SURFACEWATER}$ values was 0.15 µg/L and for the indication UC with the maximum daily

dose of 45 mg/day, the $PEC_{SURFACEWATER}$ values was 0.225 µg/L when using the default Fpen value of 0.01.

A $PEC_{SW-TOTAL}$ was calculated (0.68 µg/L) and was used to re-calculate the Phase II Tier A and Tier B PEC/PNEC ratios.

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

Phase II

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

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

Compartment	**PEC**	**PNEC**	**PEC/PNEC (action limit)**
Surface water	0.68 µg/L	63 µg/L	0.011 (<1)
Groundwater	0.17 µg/L	160 µg/L	0.0011 (<1)
Microorganism	0.68 µg/L	100000 µg/L	0.0000068 (<0.1)

Phase II Tier B

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

Compartment	**PEC**	**PNEC**	**PEC/PNEC (action limit)**
Sediment	0.76 mg/kg	15.6 mg/kg	0.049 (<1)

Conclusion

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

2.2.2. Conclusion on the non-clinical aspects

The non-clinical aspects of upadacitinib were thoroughly evaluated during the original approval procedure for Rinvoq. No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

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.

- Tabular overview of clinical studies

Table 1: Tabular Listing of Clinical Studies

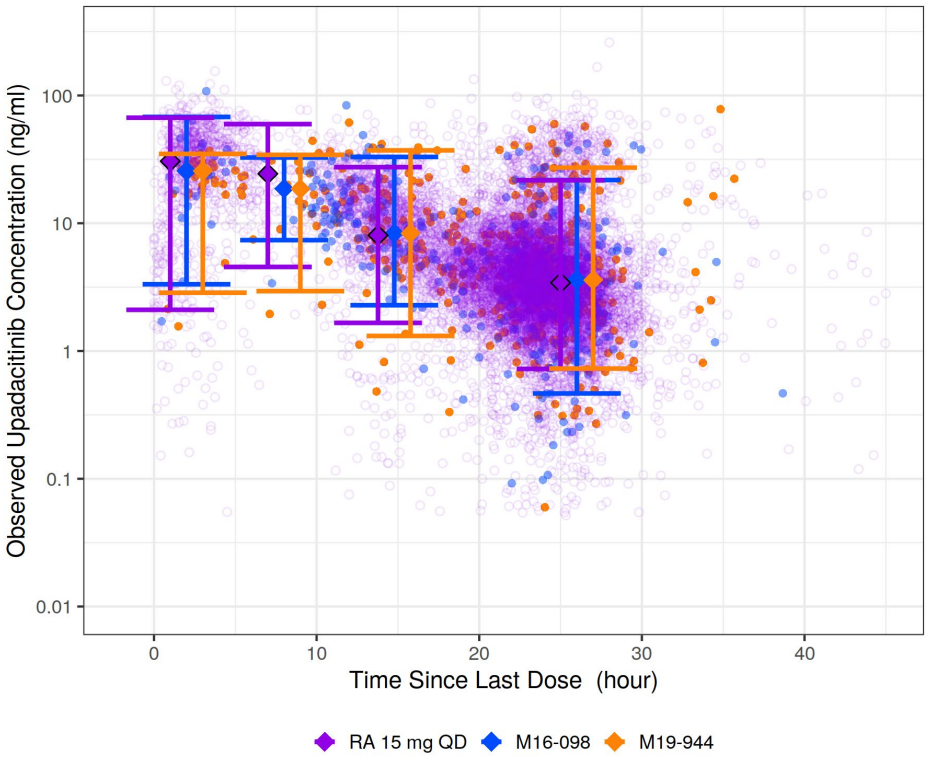
Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration (if not PO)	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	M19-944 Study 2	5.3.1.2	DB Period: Evaluate efficacy of UPA compared with PBO on reduction of signs and symptoms in adult subjects with active nr-axSpA OLE Period: Evaluate the safety and tolerability of extended treatment in subjects who completed DB Period Remission-Withdrawal: Evaluate maintenance of disease control after withdrawal of upadacitinib	DB Period: Multicenter, randomized, DB, PBO-controlled, parallel-group OLE Period: Open-label Remission-Withdrawal: Treatment withdrawal; retreatment in event of flare	Upadacitinib 15 mg QD and matching placebo	DB Period: 314 OLE Period: 60 Remission-Withdrawal: No subjects had entered at the interim data cutoff date.	Adult male and female subjects with clinical diagnosis of nr-axSpA fulfilling the 2009 ASAS classification criteria for axSpA but not meeting the radiologic criterion of the modified New York criteria for AS.	Up to 152 weeks globally[a]	Ongoing; Interim Full CSR
Efficacy and Safety	M16-098	5.3.5.1	Period 1: Compare the efficacy, safety, and tolerability of UPA 15 mg QD vs PBO Period 2: Evaluate the safety, tolerability, and efficacy of UPA 15 mg QD in subjects who have completed Period 1	Period 1: Randomized, DB, parallel-group, PBO-controlled Period 2: Open-label, long-term extension	UPA 15 mg Matching PBO	187	Adult subjects with active AS who have had an inadequate response, intolerance to, or contraindication for NSAIDs and who are bDMARD-naïve	Period 1: 14 weeks; Period 2 (globally): 90 weeks	Ongoing; Interim Full CSR (up to Year 2)

AS = ankylosing spondylitis; ASAS40 = Assessment of SpondyloArthritis international Society 40; ASDAS = Ankylosing Spondylitis Disease Activity Score; bDMARD = biologic disease-modifying antirheumatic drug; CSR = clinical study report; DB = double-blind; ER = extended release; IL = interleukin; nr-axSpA = non-radiographic axial spondyloarthritis; NSAIDs = nonsteroidal anti-inflammatory drugs; OLE = open-label extension; PBO = placebo; PO = orally; TNF = tumor necrosis factor; UPA = upadacitinib; QD = once daily

a. Study duration up to Week 152 for subjects who enter the remission withdrawal period and do not flare; study duration may vary depending on occurrence and timepoint of flare.

2.3.2. Pharmacokinetics

Upadacitinib is proposed to be used in nr-axSpA, at dose of 15 mg QD using the extended-release formulation. Pharmacokinetic samples were collected in 36% of the subjects from Study 1 (bDMARD-IR AS) and 47% of the subjects from Study 2 (nr-axSpA) of Study M19-944. Summary of upadacitinib pharmacokinetics in Study M19-944, and a comparison of upadacitinib pharmacokinetics to subjects with AS, who are bDMARD naïve, and subjects with RA are presented in Figure 1.



Circles show observed concentrations per indication, diamonds and error bars show median concentration and 5th/95th quantiles of the observed data per time bin.

Figure 1. Observed Upadacitinib Concentrations Versus Binned Time Since Last Dose in RA, bDMARD-Naïve AS (Study M16-098) and bDMARD-IR AS/nr-axSpA (Study M19-944) Populations

Upadacitinib pharmacokinetics in subjects in Study 2 (nr-axSpA) were characterized through population pharmacokinetics approach using data from the Phase 3 Study M19-944 (Study M19-944 PopPK Report). Data from Study M19-944 were also used to characterize the relationships between upadacitinib plasma exposures and efficacy as well as safety in subjects with nr-axSpA.

Methods

Quantification of upadacitinib

Specific and sensitive bioanalytical assays, developed and validated using high performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) for the quantitation of upadacitinib in human plasma have been described in the regulatory application for the use of upadacitinib in the treatment of RA.

Population pharmacokinetic analysis

Population pharmacokinetic analyses were performed using data from Study M19-944 (Study 1 and Study 2, *Table 2*). Results from prior population pharmacokinetic analyses using data from healthy subjects, subjects with RA, and subjects with AS, who are bDMARD-naïve, were leveraged to inform upadacitinib pharmacokinetic parameters in subjects with AS, who are bDMARD-IR, and subjects with nr-axSpA.

Pharmacokinetic samples were collected in approximately 30% of the subjects with AS, who are bDMARD-IR, and subjects with nr-axSpA in Study M19-944. All pharmacokinetic data collected before first dose or > 168 hours after last dose were excluded from the analyses.

Table 2. Summary of Data Included in the Population Pharmacokinetics and Exposure-Response Analyses for Efficacy and Safety

Study (N)[a]	Phase/ Population	Upadacitinib Regimen, Formulation	Pharmacokinetic Sampling and Assessment Time Points	Data for Exposure-Response Analyses of Efficacy	Data for Exposure-Response Analyses of Safety
Study M19-944 (Study 1) (N = 420)	Phase 3 Adult subjects with active bDMARD-IR AS	15 mg QD, Extended-Release	*Pharmacokinetics:* Weeks 2, 8, 12, and 14 in approximately 30% of subjects and at select sites *Efficacy and Safety Assessments:* Weeks 0, 1, 2, 4, 8, 12, and 14	Exposure-response for ASAS40 and ASAS20 at Week 14	Select adverse events and changes in laboratory parameters at Week 14
Study M19-944 (Study 2) (N = 313)	Phase 3 Adult subjects with active nr-axSpA	15 mg QD, Extended-Release	*Pharmacokinetics:* Weeks 2, 8, and 14, in approximately 30% of subjects and at select sites *Efficacy and Safety Assessments:* Weeks 0, 1, 2, 4, 8, 12, and 14	Exposure-response for ASAS40 and ASAS20 at Week 14	Select adverse events and changes in laboratory parameters at Week 14

AS = Ankylosing Spondylitis; ASAS = Assessment of SpondyloArthritis international Society; axSpA = axial spondyloarthritis; bDMARD-IR = biologic disease-modifying antirheumatic drug inadequate responder; nr-axSpA = non-radiographic axial spondyloarthritis

a. N is the total number of subjects enrolled in the study.

Due to differences in bioanalytical assay between AbbVie bioanalysis and the bioanalytical lab in China (used only for samples collected in China), upadacitinib concentrations measured at WuXi lab in China were systematically higher compared to samples analyzed at AbbVie, by an average of 11%; based on a cross-validation analysis. To account for the analytical difference between the two laboratories, all upadacitinib plasma concentrations for samples collected in China and for all samples analyzed at WuXiAppTec Co., upadacitinib exposure were adjusted (decreased) in the dataset by 11% in the population pharmacokinetics analysis.

The lower limit of quantitation (LLOQ) of the assay of plasma samples of Study M19-944 for the determination of upadacitinib concentrations is 0.05 ng/mL. 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 modeling exercise. A total of 13 records (2.9%) were below the LLOQ.

A previously built population pharmacokinetic model for upadacitinib in healthy volunteers, subjects with RA and AS (first presented in variation EMEA/H/C/004760/II/0005), who are bDMARD-naïve,1 was leveraged for this analysis. No new covariates were investigated and the covariate model from this original model was used. To assess adequacy of the established population pharmacokinetics model to describe upadacitinib pharmacokinetics in subjects with AS who are bDMARD-IR and subjects with nr-axSpA, a visual predictive check (VPC) was performed using the parameter estimates for fixed and random effects from the previous model. After positive evaluation of the VPC, the population parameter estimates of the fixed effects and estimates for the random effects (inter-individual variability) of the previously established population pharmacokinetic model were used to generate individual post hoc estimates ($ESTIMATION MAXEVAL=0 in NONMEM) for subjects in Study M19-944.

Standard model selection criteria and figures and summary statistics for evaluation of the model were used.

Final model

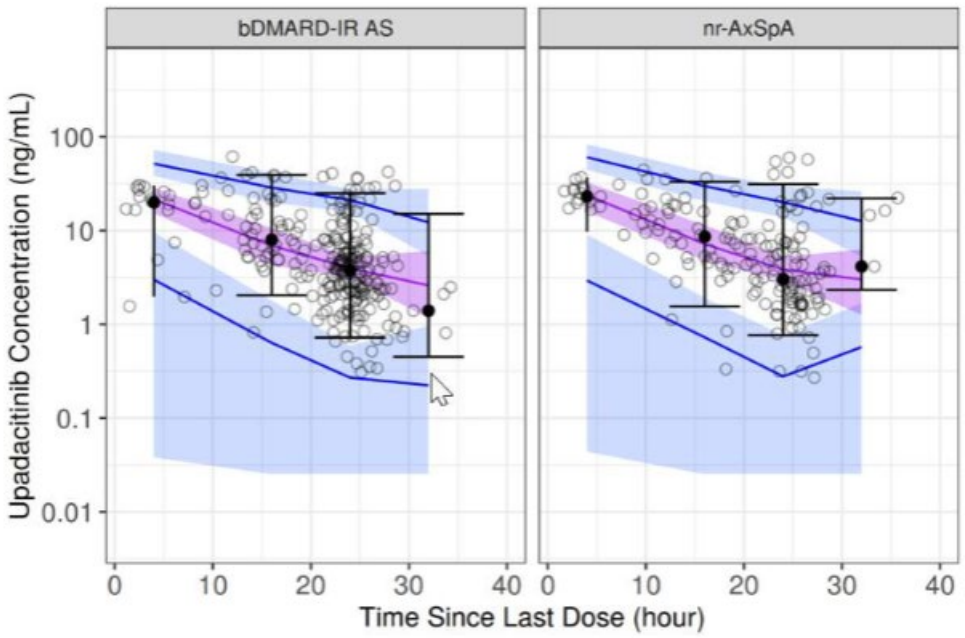
Upadacitinib pharmacokinetics were described by a two-compartment model with first-order absorption for the immediate release formulation, mixed zero- and first-order absorption with lag time for the extended-release formulation, and linear first-order elimination. The parameter estimates for fixed and random effects from the AS model are in *Table 3.*

Statistically significant covariates identified in the final AS model included subject/patient population (RA/AS versus healthy), creatinine clearance, body weight on CL/F, and body weight on Vc/F. For this population PK modeling exercise of upadacitinib in subjects with AS, who are bDMARD-IR, and in subjects with nr-axSpA, the model parameters were left unchanged from the final AS model and were not re-estimated.

Table 3. Final Population Pharmacokinetic Parameter Estimates and Variability for Upadacitinib AS Model (R&D/20/0181)

Parameter	Population Estimate (%RSE)	95% Confidence Interval
CL/F (L/h)	40.9 (FIX)	--
Vc/F (L)	171 (25.5)	128 – 227
Extended-Release KA (1/h)	0.0523 (FIX)	--
Extended-Release Lag time (h)	0.154 (FIX)	--
Fraction of Extended-Release Dose Absorbed through Zero-Order Process (%)	74.5 (FIX)	--
Zero-Order Infusion Duration (h)	3.29 (FIX)	--
Immediate-Release KA (1/h)	2.77 (FIX)	--
Immediate-Release Lag time (h)	2.00 (FIX)	--
Bioavailability of the Extended-Release Formulation Relative to the Immediate-Release Formulation (%)	76.2 (FIX)	--
Q/F (L/h)	3.22 (FIX)	--
Vp/F (L)	68.0 (FIX)	--
CL/F Ratio of RA/AS Patients Compared to Healthy Subjects	0.754 (FIX)	--
Covariate Exponent of Creatinine Clearance on CL/F	0.256 (FIX)	--
Covariate Exponent of Weight on Vc/F	0.804 (FIX)	--
Covariate Exponent of Weight on CL/F	0.132 (FIX)	--
IIV on CL/F (%)	33 (56)	--
IIV on Vc/F (%)	77 (70)	--
IIV on Extended-Release KA (%)	80 (57)	--
Proportional Error SD in Phase 3	0.559 (26)	--
Additive Error SD (ng/mL)	0.00244 (110)	--

CL/F = apparent oral clearance; CrCL = creatinine clearance; IIV = inter-subject variability; KA = absorption rate constant; Q/F = apparent inter-compartmental clearance; RA = rheumatoid arthritis; AS = axial spondyloarthritis; RSE = relative standard error; SD = Standard Deviation; Vc/F = apparent volume of distribution of central compartment; V_p/F = apparent volume of distribution of peripheral compartment; %IIV was calculated as SQRT(ω^2)*100



AS = ankylosing spondylitis; bDMARD-IR = biologic disease-modifying antirheumatic drug inadequate responder; nr-AxSpA = non-radiographic axial spondyloarthritis

Figure 2. Visual predictive check of Upadacitinib Concentrations Versus Time Since Last Dose stratified on bDMARD-IR AS and nr-axSpA (Study M19-944) Population (observed concentrations are included as points in the figure)

2.3.3. PK/PD modelling

The objectives of these analyses were to evaluate the relationships between upadacitinib plasma exposures and efficacy and safety in subjects with nr-axSpA. Model-estimated upadacitinib average plasma concentration (Cavg) in the active treatment arms were derived using empirical Bayesian estimates from the population PK analysis.

The efficacy/safety dataset contained Assessment of SpondyloArthritis international Society (ASAS40 and ASAS20) response at Week 14, laboratory safety variables at Week 14, upadacitinib average plasma concentration (Cavg) generated from the empirical Bayesian individual estimates from the population PK model, bDMARD-IR status, baseline disease activity measures, and baseline laboratory parameters (hemoglobin, neutrophils, platelets and lymphocyte count).

Exposure-response quartile plots, with upadacitinib Cavg as the exposure metric, were generated for the efficacy and safety endpoints. No exposure-response modeling was conducted, and therefore the covariate effects on exposure-response relationships with efficacy and safety were not evaluated.

Exposure-efficacy analysis (only Study 2)

Exposure-response quartile plots for the percentage of subjects with nr-axSpA, who were included in the exposure-response analyses and achieved ASAS20 or ASAS40 response at Week 14 versus upadacitinib Cavg are presented in *Figure 3*. Upadacitinib Cavg values associated with 15 mg QD dose (9.08 to 38.2 ng/mL) were associated with higher ASAS20 and ASAS40 response rates compared to placebo. Within the upadacitinib 15 mg QD treatment arm, no clear trends for exposure-response relationship were observed for ASAS20 or ASAS40.

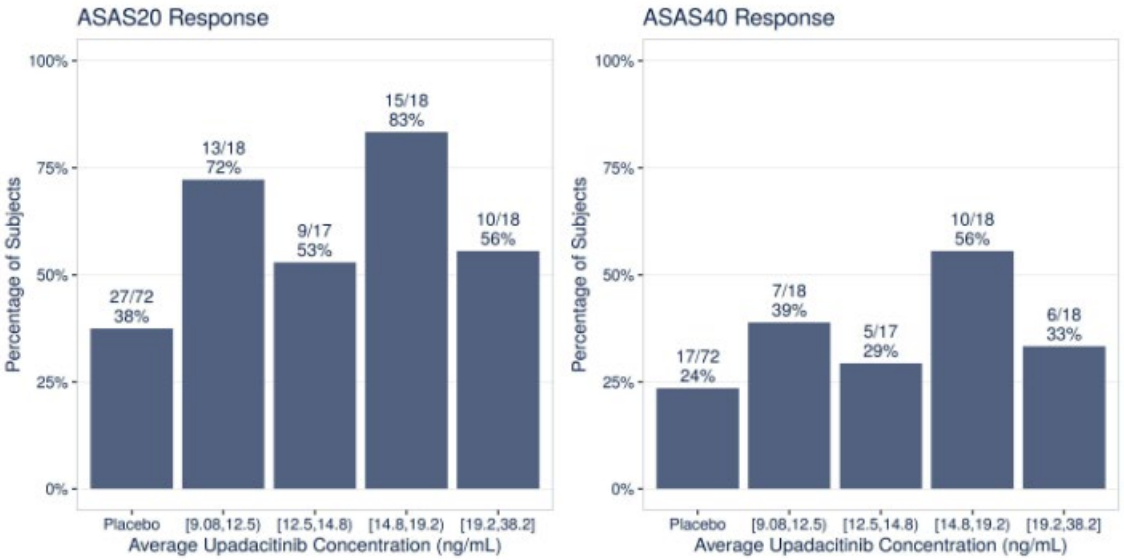


Figure 3. Exposure-Response Quartile Plots for ASAS20 and ASAS40 at Week 14 in Subjects with nr-axSpA (Study 2)

Exposure-safety analysis (only Study 2)

Exposure-response quartile plots were generated to identify safety variables demonstrating upadacitinib exposure-dependent changes. Subjects were binned according to their individual model-predicted plasma exposures into quartiles, and the percent of subjects with specific safety events/laboratory changes were plotted for each quartile.

There were no clear trends in the exposure-response relationships with upadacitinib Cavg and any infections, changes in platelet counts, and >1g/dL increase in haemoglobin. Among the subjects included in the exposure-response analysis, there were no events of serious infection, no events of neutropenia ≥ Grade 3, no events of lymphopenia ≥ Grade 3, no events of platelets ≥ 600 × 109/L, 2 events of herpes zoster infection, 1 event of pneumonia, and 2 events of > 2 g/dL decrease in hemoglobin.

2.3.4. Discussion on clinical pharmacology

The analytical method has been validated and accepted previously (see EPAR for the initial marketing authorisation application). Satisfactory method performance during study sample analysis was demonstrated.

The objectives of the clinical pharmacology program were to evaluate the pharmacokinetics of upadacitinib in the nr-axSpA population and derive individual average concentrations, subsequently used to evaluate the relationships between upadacitinib plasma exposures and efficacy as well as safety using data from Study 2 in study M19-944. All subjects received 15 mg QD treatment. The data were evaluated using population PK analysis, and graphical evaluation of exposure-response.

Population pharmacokinetic model

The MAH used the already developed population PK model to evaluate the pharmacokinetics of upadacitinib in subjects with AS who are bDMARD-IR and in subjects with nr-axSpA. A small trend in the GOF plots indicates that the model has problems capturing some of the lower observed concentrations. The VPCs show a similar trend at the later timepoints (time since last dose). Given the purpose of the model, the model adequately captures the exposure in subjects with AS and nr-AxSpA.

The model estimated Cavg (used in exposure response analysis), for nr-axSpA subjects was 14.8 (10.5 - 25.5) ng/mL, respectively. The stratified figures show that the pharmacokinetics are consistent within the axial spondyloarthritis population.

Exposure-response

The exposure-efficacy analyses on achieving ASAS20 and ASAS40 at Week 14 demonstrated a higher response for the upadacitinib 15 mg QD arm compared to placebo for the nr-axSpA population (Study 2). There was no trend toward higher response rates with increasing upadacitinib plasma exposures within the 15 mg QD arm.

The exposure-safety analyses showed no clear trends for the probability of experiencing any infections, changes in platelet counts, or >1g decrease in hemoglobin from baseline, with increasing upadacitinib exposures. Other safety variables were not analysed due to too low number events. The MAH did not pool the exposure safety analysis for the AS and nr-AxSpA population; however, as the safety with a 15 mg dose is established, this issue was not further pursued by the CHMP.

2.3.5. Conclusions on clinical pharmacology

Adequate methods have been used to evaluate the PK and exposure-response in subjects with nr-axSpA. See 2.4.3. for further discussion on the dose.

The CHMP concluded that the application was approvable from a clinical pharmacology perspective.

2.4. Clinical efficacy

The support for the efficacy of upadacitinib for the new indication nr-axSpA is primarily derived from the pivotal study M19-944 in nr-axSpA. Supportive data is claimed from study M16-098 in a related condition i.e. bDMARD-naïve AS.

2.4.1. Dose response study

No dedicated dose response study was conducted for this application.

Exposure-response analyses comparing 15 mg dose to placebo were conducted to characterize the relationships between upadacitinib plasma exposures and clinical efficacy and safety in subjects with nr-axSpA using data from Study M19-944 Study 2. The efficacy endpoints evaluated for relationships with upadacitinib exposures included ASAS20 and ASAS40 response at Week 14. No trends towards increased efficacy with increasing upadacitinib exposures were observed for ASAS20 or ASAS40; however, only 15 mg was given. Results of the exposure-safety analyses through Week 14 showed no clear trends for the probability of experiencing any infections (including serious infections, herpes zoster, and pneumonia), lymphopenia, neutropenia, changes in platelet counts, and decrease in hemoglobin from Baseline, with increasing upadacitinib exposures.

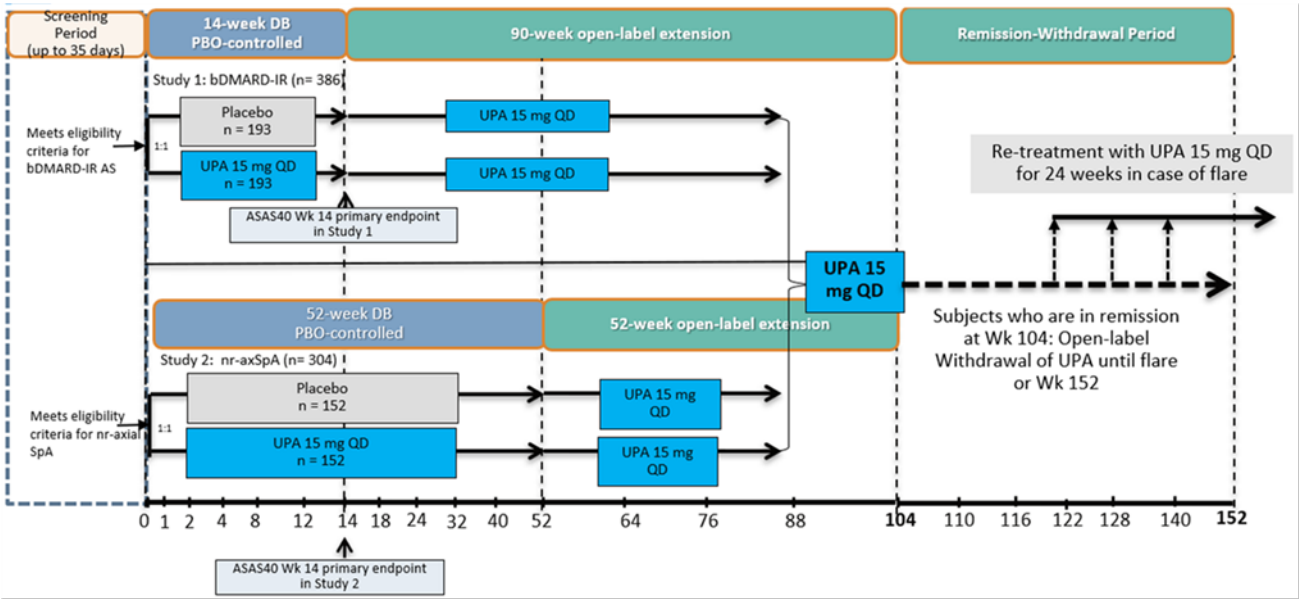
The MAH states that in the exposure-response analyses for the effect of upadacitinib on the probability of achieving ASAS20 and ASAS40 at Week 14, there was no evidence for increased efficacy responses with increasing upadacitinib exposures within the 15 mg QD arm. These results indicate that exposures associated with 15 mg QD maximize efficacy in treatment of patients with nr-axSpA. In the exposure-response analyses for safety through Week 14 in subjects with nr-axSpA, there were no trends observed between upadacitinib exposures and changes in laboratory parameters or adverse events (AEs). These safety-exposure relationships are consistent with previous analyses conducted in subjects with bDMARD-naïve AS. Overall, the results of these population pharmacokinetic and

exposure-response analyses support a favourable benefit risk profile of upadacitinib 15 mg QD for treatment of patients with nr-axSpA.

The MAH states that dose selection was also informed by results from the exposure-response analyses conducted based on data from upadacitinib Phase 2 and Phase 3 studies in RA. The extended-release tablet formulation of upadacitinib was evaluated in the pivotal Study M19-944.

Methods

Study M19-944 Study 2 (nr-axSpA) is an ongoing multicenter study with an overall design as outlined in the figure below.



AS = ankylosing spondylitis; ASAS = Assessment of SpondyloArthritis international Society; bDMARD-IR = biologic disease-modifying antirheumatic drugs inadequate responder; DB = double-blind; IR = inadequate response; nr-axSpA = non-radiographic axial spondyloarthritis; PBO = placebo; QD = once daily; UPA = upadacitinib; Wk = week

Figure 4: Study M19-944 Study 2 Design Schematic

Study M19-944 utilizes a "master protocol" that includes 2 independent studies for subjects with active axSpA: biologic DMARD-inadequate responders (bDMARD-IRs) AS (Study 1) and nr-axSpA (Study 2). While this protocol includes a common screening platform and other operational elements for Study 1 and Study 2, randomization and data collection are conducted for each study independently. There is no overlap in subject population, nor is there a shared control group. Each study has its own objective, hypothesis testing, and adequate power for primary and secondary endpoints. The analyses and reporting for the 2 studies are therefore separate and each study represents a standalone study for regulatory purposes.

The Clinical Study Report (CSR) presents the complete 14-week results from Study 2 in subjects with active nr-axSpA. Efficacy data are presented up to Week 14. Safety data and subject disposition are presented up to the cut-off date (26 August 2021), which includes summaries of all data up to Week 14, summaries of available data up to Week 52, as well as summaries of available long-term data up to the cut-off date.

As apparent from the above figure, Study 2 includes a 35-day Screening Period; a 52-week Double-Blind Period, a 52-week Open-Label Extension (OLE) Period and a 30-day F/U Visit. A 30-day F/U

phone call may be performed in place of a visit to determine the status of any ongoing adverse events (AEs)/serious adverse event (SAE) or the occurrence of any new AEs/SAEs is required; these subjects will be considered as having completed the study (see further below). Subjects with that meet protocol defined remission criteria are eligible for the open-label Remission-Withdrawal Period (see further below).

According to the MAH, data from the OLE Period and Remission-Withdrawal Period will be reported in subsequent summaries/submissions.

Study participants

According to the Clinical Overview, the study includes subjects with:

- Clinical diagnosis of nr-axSpA fulfilling the 2009 ASAS classification criteria for axSpA but who did not meet the radiologic criterion of the modified New York criteria for AS;
- With or without prior bDMARD exposure
- Active disease defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 and a Patient's Assessment of Total Back Pain score ≥ 4 based on a 0 – 10 numeric rating scale (NRS) at the Screening and Baseline Visits and;
- Objective signs of active inflammation consistent with axSpA on magnetic resonance imaging (MRI) of SI joints or high-sensitivity C-reactive protein (hsCRP) > upper limit of normal (ULN) at Screening.

Eligibility criteria was detailed in the study protocol and these included the following additional information:

- Additional eligibility criteria: inadequate response to at least 2 NSAIDs over an at least 4-week period in total at maximum recommended or tolerated doses, or subject has an intolerance to or contraindication for NSAIDs as defined by the Investigator.
- Subjects who have had lack of efficacy to both a TNF inhibitor and IL-17 inhibitor are not eligible
- Subject must not have been exposed to any JAK inhibitor
- Concomitant treatment: wash-out periods for biologics drugs (prohibited medication), csDMARD generally allowed if on stable dose, po steroids allowed in stable and low dos (prednisone ≤ 10 mg/day or oral corticosteroid equivalent for at least 14 days prior to the baseline visit)
- Exclusion criteria regarding laboratory values and subject history including infections, cardiovascular disease, malignancy, inflammatory arthritis of different etiology other than axial SpA and Fibromyalgia (currently with active symptoms) and some prohibited concomitant treatments (including intra-articular joint injections of corticosteroids within 28 days prior to the baseline visit)

Treatments

Study drug

Subjects who met the eligibility criteria are randomized in a 1:1 ratio to receive upadacitinib 15 mg QD or placebo, up to the Week 52 (Double-Blind period).

Subjects in the placebo group are switched to upadacitinib 15 mg QD at Week 52 in the OLE Period. The OLE Period is a 52-week open-label extension to evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in subjects with nr-axSpA who completed Double-Blind Period on study drug. All subjects are to receive upadacitinib 15 mg QD during the OLE Period.

The MAH study team was unblinded to perform the Week 14 primary analysis. The unblinding took place after all subjects in the study completed the Week 14 visit or prematurely discontinued prior to Week 14. Sites and subjects will remain blinded to the Double Blind Period treatment assignments for the duration of the study.

Remission-Withdrawal Period: Subjects that meet protocol defined remission criteria are eligible for the open-label Remission-Withdrawal Period.

Subjects who are not in remission at Week 104 will complete the study after the 30 day follow-up visit OR, if applicable, will have the option to enter open-label treatment with upadacitinib until a predefined time period only per local country requirements.

Study drug includes the investigational product of upadacitinib and matching upadacitinib placebo. Study drug is to be taken orally QD, beginning on Day 1 (Baseline), and is to be taken at approximately the same time each day, with or without food.

Prohibited medications

As per the study protocol, prohibited medications include any other JAK inhibitor, biologic drugs and high potency opiates.

Allowed Therapies

Methotrexate, sulfasalazine (SSZ), hydroxychloroquine, chloroquine, leflunomide, oral corticosteroids, NSAIDs, tramadol,combinationof acetaminophen/paracetamoland codeine or combination of acetaminophen/paracetamoland hydrocodone,and/or non-opioid analgesics are allowed during the study.

Addition or Modification of Medication for axSpA

The below figure, extracted from the Study Protocol, presents the Rescue Therapy and Permanent Study Drug Discontinuation Parameters.

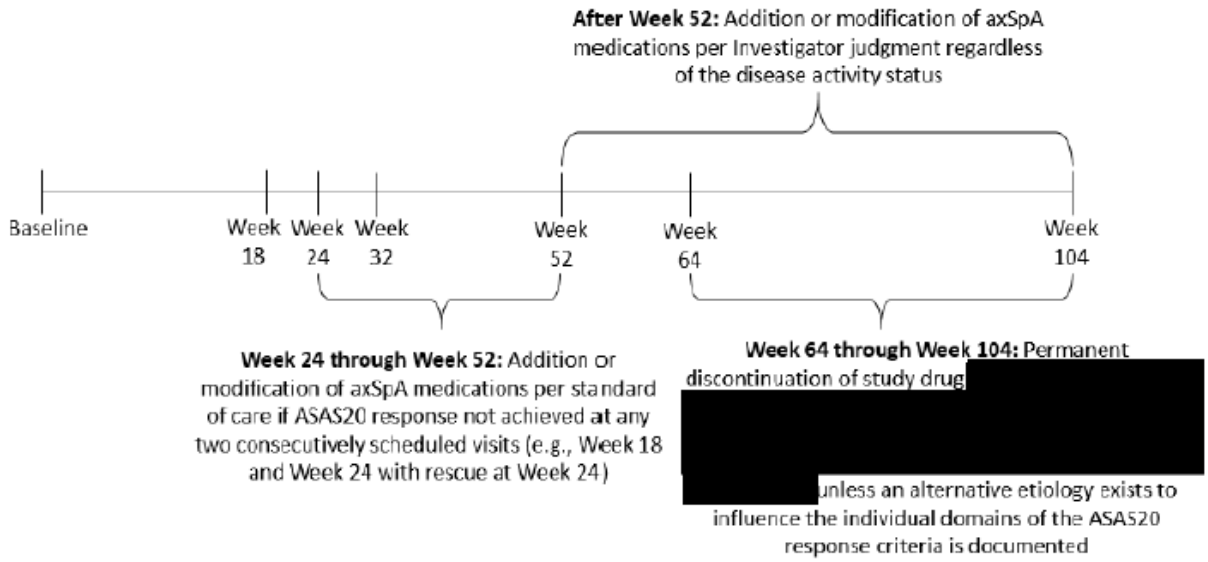


Figure 5: Study 2 (nr-axSpA): Rescue Therapy and Permanent Study Drug Discontinuation Parameters

After visit assessments have been performed at Week 24 and through Week 52, subjects who do not achieve an ASAS20 response at any 2 consecutively scheduled visits should be rescued with standard of care (e.g., Week 18 and Week 24 with rescue at Week 24; or Week 32 and Week 40 with rescue at Week 40).

Objectives

The overall study objectives are the following:

Double-Blind Period

- To evaluate the efficacy of upadacitinib compared with placebo on reduction of signs and symptoms in adult subjects with active axSpA including bDMARD-IR AS (Study 1) and nr-axSpA (Study 2);
- To assess the safety and tolerability of upadacitinib in adult subjects with active axSpA including bDMARD-IR AS (Study 1) and with nr-axSpA (Study 2).

Open-Label Extension Period

To evaluate the safety and tolerability of upadacitinib in extended treatment in adult subjects with active axSpA including bDMARD-IR AS who have completed the Double-Blind Period (Study 1) and with nr-axSpA who have completed the Double-Blind Period (Study 2).

Remission-Withdrawal Period

To evaluate the maintenance of disease control after withdrawal of upadacitinib in those subjects who achieved remission.

Outcomes/endpoints

Primary endpoint

The primary endpoint for Study 2 was the proportion of subjects with ASAS40 response at Week 14, defined as at least 40% improvement and an absolute improvement of ≥ 2 units (on a scale of 0 to 10) from Baseline in at least 3 of the following 4 domains, with no worsening at all in the remaining domain:

- Patient's Global Assessment of Disease Activity (PtGA) - Represented by the PtGA NRS score (0 to 10)
- Pain - Represented by the Patient's Assessment of Total Back Pain NRS score (0 to 10)
- Function - Represented by the Bath Ankylosing Spondylitis Functional Index; BASFI score (0 to 10)
- Inflammation - Represented by the mean of the two morning stiffness-related BASDAI items (Questions 5 and 6 NRS scores [0 to 10])

Multiplicity-controlled secondary endpoints

The multiplicity-controlled secondary endpoints *at Week 14 unless otherwise specified* were:

1. Change from Baseline in ASDAS (CRP)

2. Change from Baseline in MRI Spondyloarthritis Research Consortium of Canada; SPARCC score SI joints

3. Bath Ankylosing Spondylitis Disease Activity Index; BASDAI 50 response (defined as at least 50% improvement in the BASDAI)

4. ASDAS (CRP) Inactive Disease (ID) (ASDAS score < 1.3)

5. Change from Baseline in Patient's Assessment of Total Back Pain NRS (Score 0 – 10)

6. Change from Baseline in Patient's Assessment of Nocturnal Back Pain NRS (Score 0 – 10)

7. ASDAS (CRP) Low Disease Activity (LDA) (ASDAS score < 2.1)

8. ASAS partial remission (PR) (an absolute score of ≤ 2 units for each of the 4 domains identified in ASAS40);

9. Change from Baseline in BASFI

10. Change from Baseline in Ankylosing Spondylitis Quality of Life; ASQoL

11. Change from Baseline in ASAS Health Index

12. ASAS20 response

13. Change from Baseline in Linear Bath Ankylosing Spondylitis Metrology Index; BASMIlin

14. Change from Baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) for subjects with baseline Enthesitis; MASES > 0)

15. ASAS40 response at Week 52 (for EU/European Medicines Agency [EMA] regulatory purposes).

Change from Baseline in MRI SPARCC score (spine) was an additional secondary endpoint at Week 14.

Please refer to section "Statistical methods" for testing sequence.

Additional endpoints

Additional endpoints included change from Baseline in MRI SPARCC score of the spine at Week 14, ASAS components, ASAS20 Response Rate and ASAS Partial Remission Rate by visit and ASDAS (CRP) Components. Also, ASDAS LDA, ASDAS Clinically Important Improvement, and ASDAS Major Improvement over time, BASDAI 50 Response Rate, Change from Baseline in Measures of Inflammation and Change from Baseline in Measures of Pain by Visit, Patient-Reported Outcomes over time, number of tender joint and number of swollen joints at week 14 and Physician's Global Assessment of Disease Activity NRS were reported.

MAH's descriptions of the outcome measures used for study endpoints multiplicity-controlled secondary and additional endpoints

ASAS20 Response: Improvement of ≥ 20% and absolute improvement of ≥ 1 unit (on a scale of 0 to 10) from Baseline in ≥ 3 of the above mentioned 4 domains (see description of primary endpoint), with no deterioration in the remaining domain (defined as a worsening of ≥ 20% and a net worsening of ≥ 1 unit).

ASAS Partial Remission: Absolute score of ≤ 2 units for each of the 4 domains mentioned above.

Patient's Global Assessment of Disease Activity (PtGA) (NRS score 0 – 10): Subject rated axSpA/AS disease activity, measured on a 0 to 10 NRS, where higher scores indicate higher disease activity.

BASDAI: The BASDAI assesses disease activity levels and consists of 6 questions measured on a 0 to 10 NRS pertaining to the 5 major symptoms of axSpA/AS: fatigue; spinal pain (neck, back, hips); peripheral joint pain/swelling; areas of localized tenderness (also called enthesitis, or inflammation of tendons and ligaments); and morning stiffness (severity and duration). The overall BASDAI score ranges from 0 to 10, with higher scores indicating greater disease activity. Questions 1 through 5 have responses that can range from 0 (none) to 10 (very severe); Question 6 has a response range from 0 (0 hours) to 10 (2 or more hours), and 5 represents 1 hour.

BASDAI50: BASDAI50 response is defined as ≥ 50% improvement from Baseline in the BASDAI score.

Ankylosing Spondylitis Disease Activity Score (ASDAS)(CRP): The ASDAS is a validated composite index that combines the following 5 disease activity variables: spinal pain (BASDAI Question 2; NRS score 0 – 10), peripheral joint pain/swelling (BASDAI Question 3; NRS score 0 – 10), duration of morning stiffness (BASDAI Question 6; NRS score 0 – 10), PtGA, and hsCRP. Higher scores indicate more active disease.

ASDAS (CRP) Disease Activity States and Response Categories: The ASDAS is categorized into the following ASDAS disease activity states and response categories:

- ASDAS ID: ASDAS < 1.3
- ASDAS LDA: ASDAS < 2.1
- ASDAS Major Improvement: a change from baseline ≤ -2.0
- ASDAS Clinically Important Improvement: a change from baseline ≤ -1.1

High-sensitivity C-reactive protein (hsCRP): A laboratory measurement for evaluation of an acute phase reactant of inflammation in peripheral blood. A decrease in the level of hsCRP indicates reduction in systemic inflammation.

Patient-reported measure of inflammation (mean of BASDAI Questions 5 and 6): severity of morning stiffness from 0 (none) to 10 (very severe) and duration of morning stiffness 0 = 0 hours, 5 = 1 hour, 10 = 2 or more hours.

Patient's Assessment of Total Back Pain (NRS score 0 – 10): No pain is indicated by 0 and most severe pain by 10.

Back pain, including neck, back, hips (BASDAI Question 2): Patient's assessment of overall level of axSpA/AS neck, back or hip pain, from 0 (none) to 10 (very severe).

Patient's Assessment of Nocturnal Back Pain: Measures the amount of back pain at night on a 0 – 10 NRS, with a score of 0 indicating "no pain" and a score of 10 indicating "worst possible pain."

Peripheral joint pain/swelling (BASDAI Question 3): Patient's assessment of overall level of pain/swelling in joints, other than neck, back, or hip pain, from 0 (none) to 10 (very severe).

Patient's Global Assessment of Pain (NRS score 0 – 10): No pain is indicated by 0 and severe pain by 10.

Bath Ankylosing Spondylitis Functional Index (BASFI): BASFI assesses functional limitations in axSpA/AS. It consists of 10 items measured on a 0 to 10 NRS, with 0 = easy and 10 = impossible, and assesses the subject's ability to perform activities such as dressing, bending, reaching, turning, and climbing steps. The total score ranges from 0 to 10, with higher scores indicating worse functioning.

Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire: ASQoL is an axSpA/AS specific QoL measure that consists of 18 items and evaluates concepts such as ability to perform activities of daily living, emotional functioning, pain, fatigue, and sleep problems. Each item on the ASQoL is given a score of "1" or "0," where a score of "1" is given when an item is affirmed, indicating adverse QoL. Total scores range from 0 to 18, with higher scores representing worse QoL.

ASAS Health Index (HI): ASAS HI is an instrument for use in patients with axSpA/AS. It consists of 17 items measuring aspects of global functioning and health that are typical and relevant for axSpA patients. Items are scored dichotomously (0 = do not agree; 1 = agree) and assess pain, emotional function, sleep, sexual function, mobility, self-care, and community life. Total scores range from 0 to 17, with lower scores indicating better health.

36-Item Short Form Health Survey (SF-36): Generic health-related QoL instrument consisting of 8 domains: physical functioning, role limitations due to physical health problems, role limitations due to emotional health problems, social functioning, bodily pain, vitality, mental health, and general health. Range for each domain is 0 – 100; higher scores indicate better outcomes. Two summary scores are derived from the 8 domains: the SF-36 Physical Component Summary (SF-36 PCS) score and the SF-36 Mental Component Summary (SF-36 MCS) score.

Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F): 13-item patient-reported measure of fatigue. Score ranges from 0 – 52; higher scores represent less fatigue.

Fatigue/Tiredness (BASDAI Question 1): Patient's assessment of overall fatigue tiredness from 0 (none) to 10 (very severe).

MASES: MASES assesses enthesitis in patients with axSpA/AS. The presence (score = 1) or absence (score = 0) of enthesitis is clinically assessed at 13 pre-defined sites: Bilateral 1st Costochondral joint, 7th Costochondral joint, Posterior Superior Iliac Spine, Anterior Superior Iliac Spine, Iliac Crest, and Proximal Insertion of Achilles tendon; the 5th Lumbar Spinous process was also graded for enthesitis, yielding a total score ranging 0 – 13.

BASMI: BASMI assesses spinal mobility in patients with axSpA/AS. The linear BASMI (BASMIlin) composite score is calculated using the BASMI components: lateral lumbar flexion; tragus to wall distance, lumbar flexion, intermalleolar, and cervical rotation. Scores for each assessment range from

0 to 10, and the BASMIlin total score is the average of the 5 assessment scores. Higher scores indicate decreased spinal mobility.

MRI SPARCC of SI joint score: Scoring is conducted on 6 consecutive slices of the short-tau inversion recovery image sequence. Each consecutive slice is scored separately for the right and left joint in all 4 quadrants of the SI joint. The maximum possible score for any individual slice is 12, with a maximum score for all 6 slices being 72.

MRI SPARCC Spine score: In total, 23 discovertebral units (DVUs) are assessed by a reviewer per subject and time point, and the 6 most severely affected DVUs are selected by each reviewer and used to calculate the MRI Spine SPARCC score. The maximum score for all 6 DVUs is 108.

High-sensitivity C-reactive protein: An objective laboratory measure of inflammation is hsCRP (ULN is 2.87 mg/L), described above as part of the ASDAS (CRP) composite score.

Physician's Global Assessment of Disease Activity: Physician assessment of the subject's current disease activity using a 0 – 10 NRS, with a score of 0 indicating absence of disease activity and a score of 10 indicating severe activity

Estimand

As per the study protocol, the primary efficacy analysis will use the composite estimand framework, where the Week 14 primary endpoint for both studies is defined as a composite endpoint that is achieved if a subject fulfils the following 2 components: 1) Remain in the study and on study drug through 14 weeks; and 2) Achieve an ASAS40 response at Week 14.

Corresponding to this estimand, in the primary analysis, subjects who discontinue study drug prior to Week 14 will be treated as non-responders. Missing data due to COVID-19 will be imputed using Multiple Imputation and additional missing data due to other reasons will be treated as non-responders.

Sample size

The planned total sample size of 304 for Study 2 (with a 1:1 randomization ratio for placebo and upadacitinib 15 mg) provides at least 90% power for the primary endpoint ASAS40 response of upadacitinib 15 mg versus placebo using a two-sided Chi-square test at 0.05 level. For ASAS40 at Week 14, the assumed response rates for upadacitinib and placebo are 42% and 17%, respectively. In addition, this sample size provides at least 80% power for several of the multiplicity-controlled secondary endpoints including change from Baseline in ASDAS, change from Baseline in MRI SPARCC score of SI joints, BASDAI 50 response, ASDAS Inactive Disease, change from Baseline in Total Back Pain, change from Baseline in Nocturnal Back Pain, ASDAS Low Disease Activity, ASAS PR, and Week 52 ASAS40 response (multiplicity-controlled for EU/EMA regulatory purpose only).

Randomisation

According to the study protocol, all subjects are to be assigned a unique identification number by the IRT at the screening visit. For subjects who re-screen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie.

Subjects were randomized in a 1:1 ratio to 1 of 2 treatment groups; Group 1: upadacitinib 15 mg QD and Group 2: placebo QD.

Randomization was stratified by magnetic resonance imaging (MRI) and screening high sensitivity C-reactive protein (hsCRP) status (MRI+/hsCRP > upper limit of normal [ULN], MRI+/hsCRP ≤ ULN, and MRI-/hsCRP > ULN) and exposure to bDMARDs (yes versus [vs] no). At least 20%, but not exceeding 35% of subjects with prior exposure to a bDMARD were enrolled in Study 2 (nr-axSpA).

Blinding (masking)

According to the study protocol, for Study 2 in nr-axSpA, all AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) will remain blinded to each subject's treatment until the Week 14 primary analysis, while the Investigator, study site personnel, and the subject will remain blinded to each subject's treatment until after all subjects have completed the Week 52 visit or have prematurely discontinued prior to Week 52.

For Study 1 and Study 2, sites and subjects will remain blinded to the Double-Blind Period treatment assignments for the duration of the respective study. To maintain the blind, the upadacitinib tablets and placebo tablets provided for each study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

Statistical methods

General

There are three sets of planned efficacy analysis:

- efficacy analysis up to Week 14 in the Double-Blind Period
- efficacy analysis up to Week 52 in the Double-Blind Period, and
- long-term efficacy analysis up to Week 104.

Efficacy data are presented up to Week 14. Safety data and subject disposition are presented up to the cutoff date (26 August 2021), which includes summaries of data up to Week 14, summaries of available data up to Week 52, as well as summaries of all available long-term data up to the cutoff date.

Analysis sets

All efficacy analyses were conducted using the Full Analysis Set (FAS), which includes all randomized subjects who received at least 1 dose of study drug. In addition, per-protocol (PP) analysis for the primary endpoint was performed based on PP analysis set, consisting of all FAS subjects who did not have any major protocol violations that impact primary efficacy analysis. The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug.

Primary analyses at Week 14

The primary efficacy endpoint and multiplicity-controlled secondary endpoints were analyzed at Week 14, by methods briefly described in table below.

Endpoints	**Primary Analysis Methods**
Proportion of subjects achieving: • ASAS40 response • BASDAI50 response	• Point estimate, 95% CI, and p-value for the treatment comparison between upadacitinib group and placebo group are based on NRI-MI inference from multiple imputed datasets, where the Cochran-Mantel-Haenszel test adjusting for stratification factor of MRI and screening hsCRP status (MRI+/hsCRP > ULN,

• ASDAS ID • ASDAS LDA • ASAS PR • ASAS20 response	MRI+/hsCRP ≤ ULN, and MRI-/hsCRP > ULN) is used within each imputed dataset. • Imputation: NRI-MI for primary analysis • Analysis Set: FAS
Change from Baseline in: • ASDAS (CRP) • MRI SPARCC SI joint score • Patient's Assessment of Total Back Pain NRS (Score 0 – 10) • Patient's Assessment of Nocturnal Back Pain NRS score 0 – 10 • BASFI • ASQoL • ASAS HI • BASMIlin • MASES	• LS mean, 95% CI and p-values for the treatment comparison between upadacitinib group and the placebo group using MMRM model with fixed effects of treatment, visit and treatment-by-visit interaction, MRI and screening hsCRP status (MRI+/hsCRP > ULN, MRI+/hsCRP ≤ ULN, and MRI–/hsCRP > ULN) and baseline value as covariate. • For the analysis of change from baseline in MRI SPARCC SI joint score, the ANCOVA model also includes the interaction between treatment group and the stratification factor of MRI and screening hsCRP status. • Analysis Set: FAS

Handling of Missing Data and Intercurrent Events

Intercurrent events include discontinuation of study drug and initiation of rescue medication. Missing data and intercurrent events were handled using the following methods for the efficacy analysis.

Binary endpoints

The primary estimand for binary endpoints is the composite estimand. NRI-MI and NRI analysis were used for the primary estimand.

Non-responder imputation in conjunction with multiple imputation (NRI-MI) was used as the primary approach for handling missing data and intercurrent events for the primary estimand. It handles intercurrent events and missing data as follows:

a. Subjects who prematurely discontinue study drug or use rescue therapy are categorized as non-responders for visits after study drug discontinuation or rescue initiation.
b. Missing data due to COVID-19 infection or logistical restriction are handled by multiple imputation.
c. Additional missing data due to other reasons are categorized as non-responders.

For composite binary endpoints such as ASAS40, ASAS20 and ASAS PR, missing values in the continuous component variables were imputed via MI, and the composite binary endpoints were derived from the multiple imputed continuous component variables. Other binary endpoints which are directly dichotomized from a continuous score were handled in a similar way.

Non-Responder Imputation (NRI) was used as a sensitivity analysis for binary endpoints for the primary estimand. It treats intercurrent events and missing data as non-responders (i.e., subjects who prematurely discontinue study drug or use rescue therapy are categorized as non-responders for visits after study drug discontinuation or rescue initiation; additional missing data including those due to COVID-19 infection or logistical restriction are also categorized as non-responders).

As Observed (AO) data handling was used in a supplementary analysis (following treatment policy strategy). By OA data handling, all observed data are used regardless of premature discontinuation of

study drug or use of rescue therapy, while missing data are categorized as non-responders. Sensitivity analyses for missing data handling using MI and tipping point were also conducted.

Continuous endpoints

The primary estimand for continuous endpoints is the treatment policy estimand, where all observed data were used, regardless of premature discontinuation of study drug. MMRM was used as the primary approach for handling missing data, and MI was used as a sensitivity analysis.

Mixed-Effect Model Repeat Measurement (MMRM) was utilized for the treatment policy estimand. The mixed model included the categorical fixed effects of treatment, visit and treatment-by-visit interaction, main stratification factor of MRI and screening hsCRP level status (MRI+/hsCRP > ULN, MRI+/hsCRP ≤ ULN, and MRI-/hsCRP > ULN) and the continuous fixed covariates of baseline measurement.

Multiple Imputation (MI) was used for a sensitivity analysis of the treatment policy estimand. Treatment group was included in the MI model to enable stratified sampling. Additionally, the imputation model included demographics variables and baseline disease characteristics, as well as longitudinal response observed at any other visits. To assess the impact of potential departures from the MAR assumption, tipping point analyses was also conducted to as a sensitivity check for multiplicity-controlled secondary continuous endpoints.

Primary analysis

The primary efficacy endpoint was ASAS40 response at Week 14. The attributes of the primary estimand corresponding to the primary efficacy endpoint are as follows:

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Intercurrent Events (IE)**	**Statistical Summary**
Primary: Composite Estimand	Upadacitinib 15 mg QD vs. placebo	Achievement of ASAS40 at Week 14, remain in the study and on study drug through 14 weeks.	Full Analysis Set	IE: premature discontinuation of study drug. Subjects will be considered as non-responders at visits after IE.	Difference in the proportion of subjects achieving the endpoint

Handling of missing data for the primary endpoint

For the primary estimand, NRI-MI data handling was used. Subjects who prematurely discontinue study drug prior Week 14 were categorized as non-responders for visits after study drug discontinuation. Missing data due to COVID-19 infection or logistic restriction were handled by MI. Additional missing ASAS40 response due to other reasons was categorized as non-responders.

To facilitate the interpretation of the estimand, ASAS40 response was summarized into the following categories for each randomized treatment group:

1. Subjects who prematurely discontinue study drug by Week 14;
2. Subjects who did not discontinue study drug but are missing Week 14 ASAS40 measurements due to COVID-19 infection or logistical restriction;
3. Subjects who did not discontinue study drug but are missing Week 14 ASAS40 measurements due to other reasons;
4. Subjects with ASAS40 measurements observed and on study drug at Week 14.

Sensitivity analysis for the primary estimand was performed using NRI data handling, and the same CMH analysis as described for the primary analysis.

Supplementary analysis for the primary efficacy endpoint under the treatment policy estimand, the same CMH method was repeated using As Observed (AO) data, regardless of adherence to study drug. Subjects with missing ASAS40 response were categorized as non-responders.

For the treatment policy estimand, additional sensitivity analyses using AO data were also conducted using MI to handle missing ASAS40 responses. In order to assess the deviation from missing at random (MAR) assumptions, tipping point analysis was also conducted for the primary endpoint.

Supportive analyses were also conducted on the Per Protocol Analysis Set using the same CMH model and NRI-MI data handling as the primary analysis.

The primary efficacy endpoint was examined in the pre-specified subgroups.

Secondary analyses

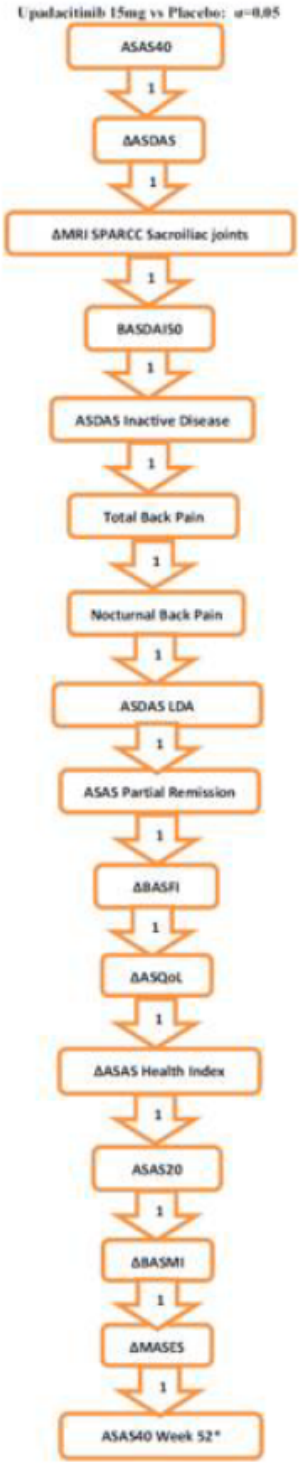
For binary endpoints, the primary estimand and analysis method are the same as that for the primary efficacy endpoint. NRI-MI and NRI data handling were used to analyze the primary estimand.

For continuous efficacy endpoints, the primary analyses were performed using all data as observed, regardless of adherence to study drug, using the treatment policy estimand framework. The statistical inference was conducted using the MMRM model and the associated data handling, with the main stratification factor of MRI and screening hsCRP status (MRI+/hsCRP > ULN, MRI+/hsCRP ≤ ULN, and MRI–/hsCRP > ULN). For the analysis of change from baseline in MRI SPARCC SI joint score at Week 14, the ANCOVA model also included the interaction between treatment group and the stratification factor of MRI and screening hsCRP status, to account for the potential differences between the MRI+ and MRI- strata. The LS mean and 95% CI were reported for each randomized treatment group; the LS mean treatment difference and associated 95% CI and p-value were reported comparing upadacitinib with the placebo group. For this estimand, additional sensitivity analyses were conducted using MI under MAR assumption for multiplicity controlled secondary continuous endpoints. To assess deviations from MAR, the tipping point analyses was also conducted as additional sensitivity analyses.

Multiplicity

A multiple testing procedure was used to provide strong control of the type I error rate at $\alpha = 0.05$ (2-sided) across analyses with respect to the primary endpoint and selected secondary endpoints. The test starts with the primary endpoint using two-sided $\alpha = 0.05$; significance can be claimed for a lower ranked endpoint only if the previous endpoints in the sequence meet the requirement of significance. The testing sequence is shown in figure below. Endpoints at Week 14 were tested at the primary database lock. The last ranked endpoint ASAS40 at Week 52 (for EU/EMA) will be tested at the Week 52 database lock.

The primary endpoint and multiplicity controlled secondary endpoints at Week 14 were analyzed after all subjects had completed the Week 14 visit of the Double-Blind Period or had discontinued study by Week 14 in the Double-Blind Period and the database had been locked.



* ASAS40 response at Week 52 is part of the testing sequence for EU/EMA regulatory purposes. For US/FDA regulatory purposes, the testing sequence stops at ΔMASES.

Note: The primary endpoint and multiplicity-controlled secondary endpoints will be assessed at Week 14 unless otherwise noted.

Interim analysis

No interim analysis was planned for efficacy endpoints. An independent external Data Monitoring Committee (DMC) was used to review unblinded safety data at regular intervals during the conduct of

the study. When needed, high-level unblinded efficacy data may also be requested by the DMC and be reviewed so that the DMC can assess benefit:risk of any emerging safety differences. Since there were no efficacy analyses for early stopping, no alpha adjustment was needed.

Safety analysis

Safety data are presented up to the cutoff date (26 August 2021), which includes summaries of data up to Week 14, summaries of available data up to Week 52, as well as summaries of all available long-term data up to the cutoff date.

Changes from the analyses

According to the MAH, the SAP version 4.0, which was dated 15 Sep 2021, was finalized prior to the Week 14 database lock and analyses.

The SAP Version 3.0 was dated 19 Aug 2021 and included, among others, changes to align with the Protocol Version 5.0 (which included the updated order of multiplicity-controlled secondary endpoints, and addition of the remission-withdrawal period), updated methods for handling missing data and intercurrent events to address regulatory feedback, updated efficacy subgroup analyses categories, etc.

Changes to the statistical analyses and order of multiplicity-controlled secondary endpoints were also made in the SAP Version 2 (dated 8 Jan 2021) to align with the Protocol Version 4.0.

Changes to the planned analyses after finalization of the SAP version 4.0 included the following: per regulatory feedback, additional supplementary analyses were conducted for exposure-adjusted event rates and incidence rates for overview of TEAE and AESI. The supplementary analyses applied patient exposure calculation reflecting the subjects' time at risk, following the definition of the treatment-emergent period for AEs, which is up to 30 days after the last dose of study drug.

Results

Participant flow

Study disposition is presented in the two below tables. In summary, one subject in the placebo group decided not to participate after randomization and discontinued the study before receiving study drug and a total of 145 subjects (92.9%) in the upadacitinib group and 150 subjects (95.5%) in the placebo group completed study drug up to Week 14. Up to Week 52, 29 subjects (18.6%) in the upadacitinib group and 31 subjects (19.7%) in the placebo group completed study drug.

Table 4: Subject Accountability in Double-Blind Period (All Randomized Subjects)

	Placebo N	Upadacitinib 15 mg QD N
Randomized	158	156
Treated	157[a]	156
Week 14		
Completed study drug	150	145
Discontinued study drug	8	11
Completed study	149	142
Discontinued study	9	14
Week 52		
Completed study drug	31	29
Discontinued study drug	22	26
Completed study	31	31
Discontinued study	16	22

QD = once daily

a. One subject in the placebo group (Subject 841015) decided not to participate after randomization and discontinued the study without receiving study drug.

Table 5: Reasons for Study Drug Discontinuation – Double Blind Period

Discontinuation Due to	Placebo (N = 157) n (%)	Upadacitinib 15 mg QD (N = 156) n (%)	Total (N = 313) n (%)
By Week 14			
All Reasons[a]	7 (4.5)	11 (7.1)	18 (5.8)
Adverse Event	2 (1.3)	4 (2.6)	6 (1.9)
Withdrawal by Subject	1 (0.6)	3 (1.9)	4 (1.3)
Lost to Follow-up	0	0	0
Lack of Efficacy	3 (1.9)	3 (1.9)	6 (1.9)
COVID-19 Infection	0	0	0
COVID-19 Logistical Restrictions	0	1 (0.6)	1 (0.3)
Other	1 (0.6)	1 (0.6)	2 (0.6)
Primary Reason	7 (4.5)	11 (7.1)	18 (5.8)
Adverse Event	2 (1.3)	4 (2.6)	6 (1.9)
Withdrawal by Subject	1 (0.6)	2 (1.3)	3 (1.0)
Lost to Follow-up	0	0	0
Lack of Efficacy	3 (1.9)	3 (1.9)	6 (1.9)
COVID-19 Infection	0	0	0
COVID-19 Logistical Restrictions	0	1 (0.6)	1 (0.3)
Other	1 (0.6)	1 (0.6)	2 (0.6)
By Week 52			
All Reasons[a]	21 (13.4)	26 (16.7)	47 (15.0)
Adverse Event	4 (2.5)	6 (3.8)	10 (3.2)
Withdrawal by Subject	6 (3.8)	6 (3.8)	12 (3.8)
Lost to Follow-up	0	2 (1.3)	2 (0.6)
Lack of Efficacy	8 (5.1)	5 (3.2)	13 (4.2)
COVID-19 Infection	0	0	0
COVID-19 Logistical Restrictions	0	1 (0.6)	1 (0.3)
Other	6 (3.8)	7 (4.5)	13 (4.2)

Discontinuation Due to	Placebo (N = 157) n (%)	Upadacitinib 15 mg QD (N = 156) n (%)	Total (N = 313) n (%)
By Week 52 (continued)			
Primary Reason	21 (13.4)	26 (16.7)	47 (15.0)
Adverse Event	4 (2.5)	6 (3.8)	10 (3.2)
Withdrawal by Subject	5 (3.2)	5 (3.2)	10 (3.2)
Lost to Follow-up	0	2 (1.3)	2 (0.6)
Lack of Efficacy	8 (5.1)	5 (3.2)	13 (4.2)
COVID-19 Infection	0	0	0
COVID-19 Logistical Restrictions	0	1 (0.6)	1 (0.3)
Other	4 (2.5)	7 (4.5)	11 (3.5)

COVID-19 = coronavirus disease of 2019; QD = once daily

a. Subjects who discontinued study drug are counted under each reason given for discontinuation, therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.

Recruitment

The first subject first visit occurred 26 November 2019. The last subject last visit occurred 02 September 2021 (Week 14).

According to the CSR, the report focuses on and presents the complete 14-week results from Study 2 in subjects with active nr-axSpA. Efficacy data are presented up to Week 14. Safety data and subject disposition are presented up to the cut-off date (26 August 2021).

According to the study protocol, study M19-944 includes approximately 230 sites in approximately 25 countries between 2 studies. The planned number to be enrolled is approximately 386 subjects with AS who are bDMARD-IR (Study 1) and approximately 304 subjects with nr-axSpA (Study 2).

According to the study protocol, the database lock for the primary analysis will occur after all Study 2 subjects have completed the Week 14 visit or have prematurely discontinued prior to Week 14.

Conduct of the study

Protocol changes

The original protocol (Protocol Version 1.0, 23 August 2019, 01 subjects) had 4 amendments, 1 country-specific amendment, and 1 administrative change. The amendments and number of subjects enrolled under each amendment were as follows (summary of presentation provided in CSR with focus on amendments of relevance for efficacy assessment of Study 2):

Global Protocol Version 2.0 (13 September 2019, 32 subjects)

- Stated that active inflammation must be consistent with axSpA and that the hsCRP criterion is based on levels at Screening.

Global Protocol Version 3.0 (01 February 2020, 274 subjects)

- Revised key secondary endpoints for Study 1 and Study 2.
- Added that subjects with fibromyalgia are excluded from the study.

- Added that subjects with extra-articular manifestations that are not clinically stable for at least 30 days prior to study entry are excluded.
- Added that subjects with a history of inflammatory arthritis of different etiology other than axial SpA or any arthritis with onset prior to 17 years of age are excluded.
- Clarified when subjects should be discontinued due to abnormal labs and ASAS20 non-response.
- Clarified that at Week 32 and through Week 104, subjects without an ASAS20 response at any 2 consecutively scheduled visits will be permanently discontinued from study drug treatment unless an alternative etiology exists to influence the individual domains of the ASAS20 response criteria.
- Updated wording on eligibility criteria to clarify that subject must have discontinued the bDMARD due to lack of efficacy (after at least 12 weeks of treatment with a bDMARD at an adequate dose) or intolerance (irrespective of treatment duration) and no more than 30% of subjects can enter the study if prior exposure to a 2nd bDMARD is stopped due to lack of efficacy.
- Updated wording on eligibility criteria to clarify that subject must have discontinued the bDMARD due to lack of efficacy (after at least 12 weeks of treatment with a bDMARD at an adequate dose) or intolerance (irrespective of treatment duration).
- Added study visit windows for Double-Blind and Open-Label periods of each study.

Global Protocol Version 4.0 (29 December 2020, 07 subjects)

- Moved primary endpoint in Study 2 for US/Food and Drug Administration (FDA) regulatory purposes from Week 52 to Week 14. A common primary endpoint at Week 14 will be used for both US/FDA and EU/EMA regulatory purposes, with primary analyses conducted at Week 14.
- Removed statement that primary analyses will be conducted separately for EU/EMA regulatory purposes and US/FDA regulatory purposes for Study 2.
- Removed "proportion of subjects" from description of primary, secondary, and additional efficacy endpoints.
- Switched the ranking order of BASMIlin and MASES for Study 1 and Study 2.
- Added ASAS40 response at Week 52 as a multiplicity-controlled secondary endpoint and ASDAS Major Improvement, ASDAS ID, and ASDAS LDA at Week 52 as additional secondary endpoints in Study 2 for EU/EMA regulatory purposes.
- Added BASDAI 50 response as an additional endpoint for both Study 1 and Study 2.
- Revised when AbbVie study team will be unblinded to perform the primary analysis for Study 2.
- For the 30-day F/U Visit, revised and clarified when a phone call may be used in place of a visit.
- Clarified that for Study 1, subjects must have been previously exposed to 1 or 2 bDMARDs.
- Revised the percentage of subjects with prior exposure to a bDMARD who may be enrolled in Study 2.

- Added that parenteral corticosteroids and systemic corticosteroids include intramuscular and IV injections.
- Added new subsection on Opiates in Prohibited Medications and Therapy.
- Updated when an elective surgery is allowed in Study 2.
- Added how long subjects should stay on their stable background csDMARD therapy and that at any time, the csDMARD dose may be decreased for safety reasons. Added language on allowance of peripheral joint corticosteroid injections.
- Added details on when the procedures for the Premature Discontinuation (PD) Visit should be completed.
- Updated several sections in Statistical Methods and Determination of Sample Size to align with protocol updates.
- Revised when the database lock for the primary analysis of Study 2 will occur and when the SAP for Study 2 will be finalized. Added that an additional analysis will be conducted for Study 2 for regulatory purposes after all subjects have completed the Week 52 visit or have prematurely discontinued prior to Week 52.
- Updated primary efficacy analysis to handle missing data due to COVID-19 infection or logistical reasons. Made corresponding updates to sensitivity and supplementary analyses for the primary, secondary, and additional efficacy endpoints, where needed, as a result of changes to the primary analysis.
- Updated sections in Statistical Methods and Determination of Sample Size to align with protocol updates.

Protocol Version 4.1 (Voluntary Harmonization Procedure countries only) (02 March 2021, 0 subjects):

- Updated applicability of study modifications to the COVID-19 pandemic.

Global Protocol Version 5.0 (12 July 2021, 0 subjects)

- Added the Remission-Withdrawal Period and design and requirements for that period.
- Updated the statistical methods for handling of missing data and intercurrent events to address regulatory feedback.
- Switched the ranking order of ASAS20 and BASFI for Study 2
- Added appendix to include information on the overall study design and plan for applicable countries in the open-label extension period.

According to the MAH, the protocol changes described in the amendments and administrative change did not affect the interpretation of study results.

Protocol deviations

Protocol deviations were defined in accordance with the ICH guidelines and ICH-defined categories included but were not limited to the following: eligibility criteria violation, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. In Study 2 (nr-axSpA), eligibility criteria violation was the most frequent deviation, see below table.

Table 6: Protocol Deviations (All Randomized Subjects)

Category	Placebo (N = 158) n (%)	Upadacitinib 15 mg QD (N = 156) n (%)	Total (N = 314) n (%)
Subjects with at least one protocol deviation	35 (22.2)	33 (21.2)	68 (21.7)
Subjects who entered the study even though they did not satisfy the entry criteria	31 (19.6)	23 (14.7)	54 (17.2)
Eligibility criteria not met	31 (19.6)	22 (14.1)	53 (16.9)
3	1 (0.6)	0	1 (0.3)
4	2 (1.3)	0	2 (0.6)
5	7 (4.4)	5 (3.2)	12 (3.8)
6	1 (0.6)	1 (0.6)	2 (0.6)
9	8 (5.1)	6 (3.8)	14 (4.5)
10	0	1 (0.6)	1 (0.3)
14	1 (0.6)	0	1 (0.3)
16	2 (1.3)	0	2 (0.6)
18	3 (1.9)	2 (1.3)	5 (1.6)
21	3 (1.9)	2 (1.3)	5 (1.6)
22	0	2 (1.3)	2 (0.6)
24	0	1 (0.6)	1 (0.3)
27	8 (5.1)	3 (1.9)	11 (3.5)
28	2 (1.3)	2 (1.3)	4 (1.3)
Subjects who developed withdrawal criteria during the study but were not withdrawn	0	0	0
Subjects who received the wrong treatment or incorrect dose	0	0	0
Subjects who received an excluded concomitant treatment	5 (3.2)	11 (7.1)	16 (5.1)

QD = once daily

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

According to the MAH, all protocol deviations including non-ICH deviations and all deviations related to COVID-19 were reviewed and assessed for their impact on analyses, data integrity, and/or subject safety. The totality of the protocol deviations incurred during the study did not affect the study outcomes, interpretation of study results and/or conclusions.

Treatment compliance

According to the CSR, compliance was defined as the number of tablets taken divided by the number of tablets that should have been taken. In Study 2, mean treatment compliance by Week 14 was 97.4% for both groups.

Baseline data

Demographics

Please see below table.

Table 7 Demographics

	Placebo (N = 157)	Upadacitinib 15 mg QD (N = 156)	Total (N = 313)
Sex - n (%)			
Female	94 (59.9)	89 (57.1)	183 (58.5)
Male	63 (40.1)	67 (42.9)	130 (41.5)
Ethnicity - n (%)			
Hispanic or Latino	15 (9.6)	24 (15.4)	39 (12.5)
Not Hispanic or Latino	142 (90.4)	132 (84.6)	274 (87.5)
Race - n (%)			
White	127 (80.9)	134 (85.9)	261 (83.4)
Black or African American	1 (0.6)	2 (1.3)	3 (1.0)
Asian	28 (17.8)	19 (12.2)	47 (15.0)
American Indian or Alaska native	0	1 (0.6)	1 (0.3)
Multiple	1 (0.6)	0	1 (0.3)
Age (Years)			
Mean (SD)	42.5 (12.44)	41.6 (12.00)	42.1 (12.21)
Median (min, max)	42.0 (20, 70)	41.0 (19, 79)	41.0 (19, 79)
Age group (Years) - n (%)			
< 40	67 (42.7)	72 (46.2)	139 (44.4)
40 - ≤ 65	84 (53.5)	81 (51.9)	165 (52.7)
≥ 65	6 (3.8)	3 (1.9)	9 (2.9)
Weight (kg)			
Mean (SD)	79.2 (17.54)	81.6 (19.36)	80.4 (18.48)
Median (min, max)	77.9 (42, 136)	82.0 (47, 144)	79.5 (42, 144)
Weight (kg) - n (%)			
< 60	21 (13.4)	24 (15.4)	45 (14.4)
60 - 79	66 (42.0)	49 (31.4)	115 (36.7)
≥ 80	70 (44.6)	83 (53.2)	153 (48.9)
Body Mass Index (kg/m^2)			
Mean (SD)	27.7 (5.23)	28.2 (6.39)	28.0 (5.83)
Median (min, max)	27.2 (16.5, 47.9)	27.0 (16.8, 47.6)	27.2 (16.5, 47.9)

	Placebo (N = 157)	Upadacitinib 15 mg QD (N = 156)	Total (N = 313)
Body Mass Index category (kg/m^2) - n (%)			
< 25	50 (31.8)	57 (36.5)	107 (34.2)
≥ 25	107 (68.2)	99 (63.5)	206 (65.8)
Region - n (%)			
North America	19 (12.1)	26 (16.7)	45 (14.4)
South/Central America	13 (8.3)	12 (7.7)	25 (8.0)
Western Europe	19 (12.1)	24 (15.4)	43 (13.7)
Eastern Europe	72 (45.9)	68 (43.6)	140 (44.7)
Asia[a]	27 (17.2)	19 (12.2)	46 (14.7)
Other[b]	7 (4.5)	7 (4.5)	14 (4.5)
Tobacco - n (%)			
Current	26 (16.6)	25 (16.0)	51 (16.3)
Former	25 (15.9)	28 (17.9)	53 (16.9)
Never	106 (67.5)	103 (66.0)	209 (66.8)
Alcohol - n (%)			
Current	78 (49.7)	60 (38.7)	138 (44.2)
Former	8 (5.1)	8 (5.2)	16 (5.1)
Never	71 (45.2)	87 (56.1)	158 (50.6)
Unknown	0	1	1

FAS = Full Analysis Set; max = maximum; min = minimum; QD = once daily; SD = standard deviation

a. China, Taiwan, South Korea, and Japan.

b. Australia and Israel.

Note: Percentages calculated on non-missing values. A subject may be a current user of one type of tobacco, a former user of another type of tobacco and never used another type of tobacco. A subject will be counted in the category closest to user.

Baseline Disease Characteristic

Table 8: Baseline Disease Characteristics – General (FAS)

	Placebo (N = 157)	Upadacitinib 15 mg QD (N = 156)	Total (N = 313)
Duration (Years) since nr-axSpA symptoms			
n	156	155	311
Mean (SD)	9.2 (8.12)	9.0 (7.86)	9.1 (7.98)
Median (min, max)	6.8 (0.3, 41.1)	7.2 (0.2, 40.7)	6.9 (0.2, 41.1)
Duration (Years) since nr-axSpA diagnosis			
n	157	156	313
Mean (SD)	4.4 (5.83)	4.5 (5.54)	4.4 (5.68)
Median (min, max)	2.4 (0.1, 31.2)	2.5 (0.1, 32.4)	2.4 (0.1, 32.4)
Duration (Years) since nr-axSpA diagnosis categories - n (%)			
< 5	115 (73.2)	100 (64.1)	215 (68.7)
≥ 5 - < 10	26 (16.6)	36 (23.1)	62 (19.8)
≥ 10	16 (10.2)	20 (12.8)	36 (11.5)
Duration (Years) since nr-axSpA symptoms categories - n (%)			
< 5	57 (36.5)	58 (37.4)	115 (37.0)
≥ 5 - < 10	47 (30.1)	40 (25.8)	87 (28.0)
≥ 10	52 (33.3)	57 (36.8)	109 (35.0)
Missing	1	1	2
HLA-B27 - n (%)			
Positive	93 (59.6)	90 (58.8)	183 (59.2)
Negative	63 (40.4)	63 (41.2)	126 (40.8)
Missing[a]	1	3	4

	Placebo (N = 157)	Upadacitinib 15 mg QD (N = 156)	Total (N = 313)
Proportion of prior bDMARD use - n (%)			
Yes	54 (34.4)	49 (31.4)	103 (32.9)
No	103 (65.6)	107 (68.6)	210 (67.1)
Discontinuation reason of prior bDMARD(s) - n (%)			
Intolerance (without lack of efficacy and regardless of other reasons)	12 (7.6)	8 (5.1)	20 (6.4)
Lack of efficacy (without intolerance and regardless of other reasons)	39 (24.8)	37 (23.7)	76 (24.3)
Lack of efficacy to TNF-inhibitor therapy	29 (18.5)	32 (20.5)	61 (19.5)
Lack of efficacy to IL-17-inhibitor therapy	10 (6.4)	5 (3.2)	15 (4.8)
Opioid use at Baseline – n (%)			
Yes	18 (11.5)	6 (3.8)	24 (7.7)
No	139 (88.5)	150 (96.2)	289 (92.3)
NSAID score at Baseline			
n	157	156	313
Mean (SD)	58.0 (47.20)	63.8 (48.16)	60.9 (47.70)
Median (min, max)	53.4 (0.0, 160.3)	71.3 (0.0, 213.8)	64.1 (0.0, 213.8)

bDMARD = biologic disease-modifying antirheumatic drug; HLA-B27 = human leukocyte antigen-B27; IL = interleukin; max = maximum; min = minimum; nr-axSpA = non-radiographic axial spondyloarthritis; NSAID = nonsteroidal anti-inflammatory drug; QD = once daily; SD = standard deviation; TNF = tumor necrosis factor

a. Tests were completed but genotypes could not to be assigned for 2 subjects in the upadacitinib group.

As apparent from the above table, 49 subjects (31.4%) in the upadacitinib group and 54 subjects (34.4%) in the placebo group had prior exposure to at least 1 bDMARD. Among the subjects with prior bDMARD exposure, a total of 44 and 43 subjects were exposed to at least 1 tumor necrosis factor (TNF) inhibitor (TNFi) in the upadacitinib and placebo groups, respectively, while 5 and 14 subjects were exposed to at least 1 IL-17 inhibitor (IL-17i) in the upadacitinib and placebo groups, respectively.

A total of 44.9% in the upadacitinib group and 51.6% in the placebo group had prior csDMARD use. All subjects had prior NSAID use and 98.4% of them at least 2 prior NSAID use.

Up to Week 14 in the Double-Blind Period, 78.2% and 73.2% of subjects in the upadacitinib and placebo groups, respectively, took one or more concomitant NSAID. A total of 26.3% of subjects in the upadacitinib group and 31.8% of subjects in the placebo group received concomitant csDMARD therapy. In total 29.1% (across treatment groups) received concomitant csDMARD therapy. A total of 11.5% of subjects each in the upadacitinib and placebo group took one or more concomitant oral corticosteroid.

High-sensitivity CRP > ULN and > 5 mg/L was reported for 79.6% (80.3% placebo group, 78.8% upadacitinib group) and 58.5% (53.5% in placebo group, 63.5% in upadacitinib group) of subjects at screening, respectively; MRI inflammation status at screening was positive for 43.5% of subjects (42.0% in the placebo group, 44.9% in the upadacitinib group).

Endpoint related baseline disease characteristics were also tabulated and presented in the CSR. As stated in the CSR, subjects had moderately to severely active disease, as indicated by mean BASDAI of 6.86 (6.91 in the placebo-group and 6.82 in the upadacitinib group) and ASDAS (CRP) of 3.63 (3.65 in the placebo group and 3.61 in the upadacitinib group).

Regarding medical history, according to the CSR, in Study 2 (nr-axSpA), the most frequently reported conditions (≥ 5% of total subjects) in the medical history were hypertension (18.5%), osteoarthritis (10.5%), gastroesophageal reflux disease (10.2%), depression (9.9%), anxiety (8.6%), drug hypersensitivity (8.6%), back pain (8.0%), latent TB (7.7%), obesity (7.7%), seasonal allergy (7.7%), intervertebral disc protrusion (7.0%), menopause (7.0%), vitamin D deficiency (6.7%), hypothyroidism (6.1%), tonsillitis (6.1%), appendicitis (5.4%), insomnia (5.4%), migraine (5.4%), post menopause (5.4%), and osteochondrosis (5.1%).

Numbers analysed

Data sets analyzed

Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects who received at least 1 dose of study drug. Subjects will be included in the analysis based on the treatment group as randomized. The FAS is used for all efficacy and Baseline analyses.

The FAS included 313 subjects; 157 in the placebo-group and 156 in the upadacitinib group (one randomized subject in the placebo group discontinued without receiving study drug, see table under heading "Participant flow").

Per Protocol Analysis Set

The Per Protocol Analysis Set represents a subset of the FAS and consists of all FAS subjects who did not have any major protocol violations that impact primary efficacy analysis. The primary endpoint is analyzed in the Per Protocol Analysis Set as a sensitivity analysis. The Per Protocol Analysis Set is determined prior to the primary analysis database lock.

The number of subjects excluded from the Per Protocol Analysis Set were: 24 in the placebo group and 21 in the Upadacitinib group.

Safety Analysis Set

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. For the Safety Analysis Set, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized. Subjects who received at least one dose of upadacitinib in the Double-Blind Period are considered to be in the upadacitinib group for safety analysis.

The number of subjects in the Safety Analysis Set was identical to the number in the Full Analysis Set i.e. 157 in the placebo group and 156 in the upadacitinib group.

Outcomes and estimation

Primary endpoint

A statistically significantly greater percentage of subjects achieved the primary endpoint of ASAS40 at Week 14 in the upadacitinib group (44.9%) compared with the placebo group (22.5%), resulting in a placebo adjusted difference of 22.2% ($P < 0.0001$) using non-responder imputation (NRI) incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-MI), please see below table.

Table 9: Primary Endpoint: Analysis of ASAS40 Response Rate at Week 14 (NRI-MI; Full Analysis Set)

		Responder		Missing Due to		Response Rate Diff (Compared to Placebo[c])		
Treatment	N	n[a] (%)	(95% CI)[b]	COVID-19 n	Other n	Diff (%)	(95% CI)[c]	*P*-Value
Placebo	157	35 (22.5)	[16.0, 29.1]	1	1			
UPA 15 mg QD	156	70 (44.9)	[37.1, 52.7]	0	4	22.2	[12.1, 32.3]	< 0.0001

ASAS = Assessment of SpondyloArthritis international Society; CI = confidence interval; COVID-19 = coronavirus disease of 2019; Diff = difference; MI = multiple imputation; NRI = non-responder imputation; QD = once daily; UPA = upadacitinib

a. n is calculated by N and MI-aggregated response rate (%).

b. Construction of CIs for response rate is based on MI inference. The response rate and standard error (SE) are estimated within each imputed 'complete' dataset, then Rubin's rule is used to combine the response rate and SE estimates from 30 imputed 'complete' datasets to get aggregated rate and CIs.

c. Treatment difference, associated CI and *P*-value for test of difference between upadacitinib group and placebo group is constructed based on the MI inference. Risk difference and SE is estimated using Cochran-Mantel-Haenszel (CMH) test and screening magnetic resonance imaging (MRI) and screening high sensitivity C-reactive protein (hsCRP) status as stratification factor within each imputed 'complete' dataset, then Rubin's rule is used to combine the results from 30 imputed 'complete' datasets to get aggregated treatment difference, associated confidence interval, and *P*-value.

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

According to the CSR, results from sensitivity analysis using NRI, supplementary analyses using as observed (AO), AO-NRI, AO-MI, and the Per Protocol Analysis (NRI-MI) were consistent with the primary NRI-MI analysis. Results from the tipping point analysis were consistent with the primary analysis and demonstrated that the primary analysis is robust to the missing not at random (MNAR) assumption.

To facilitate the interpretation of the primary analysis using NRI-MI, a breakdown of the ASAS40 response at Week 14 by intercurrent events and missing data was provided, se below table.

Table 10: ASAS40 Response at Week 14 by Intercurrent Events (NRI-MI; Full Analysis Set)

Intercurrent Events	Placebo (N = 157) n (%)	Upadacitinib 15 mg QD (N = 156) n (%)
Subjects without any intercurrent events	149 (94.9)	144 (92.3)
With observed measurement	147 (93.6)	140 (89.7)
Responder	35 (22.3)	70 (44.9)
Non-responder	112 (71.3)	70 (44.9)
With missing measurement	2 (1.3)	4 (2.6)
Due to COVID-19[a]	1 (0.6)	0
COVID-19 infection	1 (0.6)	0
Responder	0	0
Non-responder	1 (0.6)	0
COVID-19 logistical restrictions	0	0
Responder	0	0
Non-responder	0	0
Due to other reasons (non-responder)	1 (0.6)	4 (2.6)
Subjects with premature discontinuation of study drug (non-responder)	8 (5.1)	12 (7.7)

ASAS = Assessment of SpondyloArthritis international Society; COVID-19 = coronavirus disease of 2019; MI = multiple imputation; NRI = non-responder imputation; QD = once daily

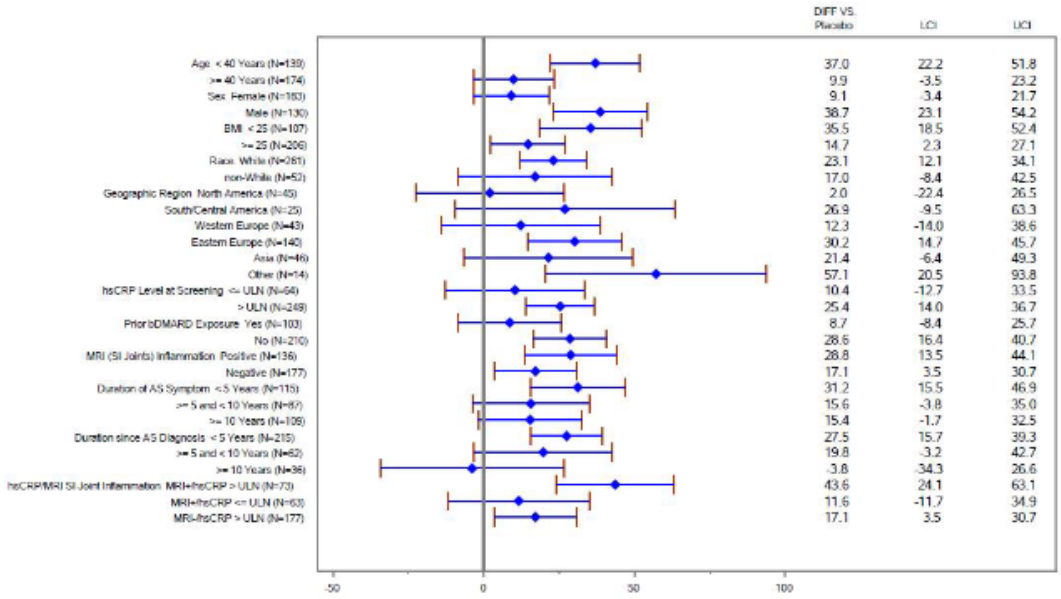
a. For subjects with missing measurement due to COVID-19, the response is imputed by multiple imputation. The number of responders and non-responders are calculated by N and MI-aggregated response rates (%).

Note: Intercurrent event by Week 14 means discontinuation of study drug.

ASAS40 Subgroup Analyses at Week 14

According to the CSR, treatment effects in pre-specified subgroups were generally consistent in favour of upadacitinib vs placebo. Subgroup data was summarized in Forest plots in the Clinical Summary of Efficacy, please see below figure.

Figure 6: Study M19-944 Study 2 (nr-axSpA): Forest Plot of Placebo-Adjusted Difference of ASAS40 at Week 14, by Subgroup (NRI-MI, FAS



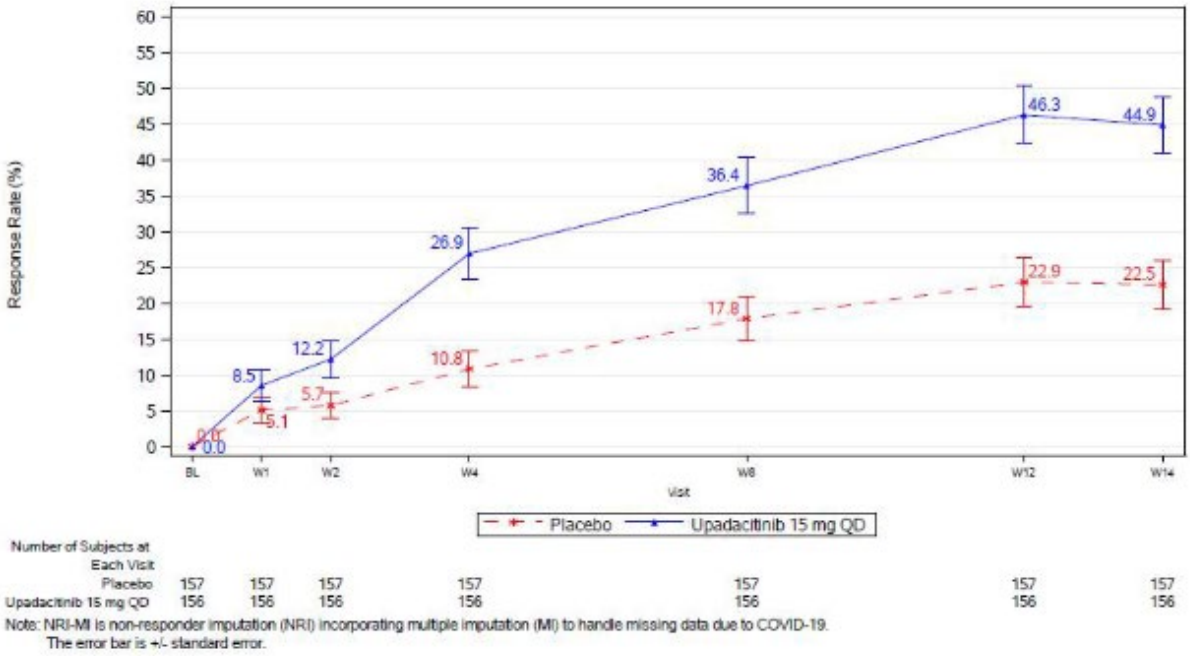
Note: NRI-MI is non-responder imputation (NRI) incorporating multiple imputation (MI) to handle missing data due to COVID-19.

According to the MAH, most of the subgroup covariates were not stratification factors at randomization and have imbalances in demographic and clinically relevant baseline characteristics between the treatment groups within each subgroup. To account for the confounding effects of these imbalances, logistic regression for ASAS40 response at Week 14 was conducted adjusting for the most influential baseline factors (sex, BMI, and HLA-B27 status, identified by logistic regression with stepwise selection). According to the MAH, the re-analysis showed consistent treatment effects in all subgroups in favour of upadacitinib vs placebo (data not shown).

ASAS40 Time Course Weeks 1 – 14

A figure of ASAS40 Time Course Weeks 1 – 14 was provided (see below) along with a statement that higher proportion of subjects in the upadacitinib group consistently achieved ASAS40 compared with the placebo group from Week 2 onwards.

Figure 7: ASAS40 Response Rate by Visit – By Week 14 in Double-Blind Period (NRI-MI, FAS)



Multiplicity-adjusted secondary endpoints

Statistical significance was achieved in the first 12 of the 14 multiplicity-controlled secondary endpoints for upadacitinib compared with placebo, see below table.

Endpoint[a] Treatment	N	Within Group Point Estimate (95% CI)	Between Group Difference		
			Point Estimate (95% CI)	*P*-value[b]	Statistical Significance[c]
ASDAS (CRP) Change from Baseline					
Placebo	156	-0.71 [-0.85, -0.56]			
Upadacitinib	154	-1.36 [-1.50, -1.21]	-0.65 [-0.85, -0.45]	< 0.0001	Significant
MRI SPARCC Score (SI Joint) Change from Baseline					
Placebo	148	0.57 [-0.17, 1.30]			
Upadacitinib	140	-2.49 [-3.22, -1.77]	-3.06 [-4.08, -2.04]	< 0.0001	Significant
BASDAI 50 Response %					
Placebo	157	22.1 [15.5, 28.6]			
Upadacitinib	156	42.3 [34.6, 50.1]	20.1 [10.1, 30.1]	0.0001	Significant

Endpoint[a] Treatment	N	Within Group Point Estimate (95% CI)	Between Group Difference		
			Point Estimate (95% CI)	*P*-value[b]	Statistical Significance[c]
ASDAS (CRP) ID %					
Placebo	157	5.2 [1.7, 8.7]			
Upadacitinib	156	14.1 [8.6, 19.6]	8.8 [2.5, 15.2]	0.0063	Significant
Patient's Assessment of Total Back Pain Change from Baseline					
Placebo	156	-2.00 [-2.35, -1.65]			
Upadacitinib	154	-2.91 [-3.27, -2.56]	-0.92 [-1.42, -0.41]	0.0004	Significant
Patient's Assessment of Nocturnal Back Pain Change from Baseline					
Placebo	154	-1.84 [-2.23, -1.44]			
Upadacitinib	151	-2.96 [-3.36, -2.56]	-1.12 [-1.68, -0.55]	0.0001	Significant
ASDAS (CRP) LDA %					
Placebo	157	18.3 [12.2, 24.4]			
Upadacitinib	156	42.3 [34.6, 50.1]	23.8 [14.2, 33.4]	< 0.0001	Significant
ASAS PR %					
Placebo	157	7.6 [3.5, 11.8]			
Upadacitinib	156	18.6 [12.5, 24.7]	10.9 [3.6, 18.3]	0.0035	Significant
BASFI Change from Baseline					
Placebo	156	-1.47 [-1.79, -1.15]			
Upadacitinib	154	-2.61 [-2.94, -2.29]	-1.14 [-1.60, -0.68]	<0.0001	Significant
ASQoL Change from Baseline					
Placebo	154	-3.15 [-3.87, -2.43]			
Upadacitinib	151	-5.38 [-6.11, -4.65]	-2.23 [-3.26, -1.21]	< 0.0001	Significant
ASAS HI Change from Baseline					
Placebo	154	-1.48 [-2.02, -0.93]			
Upadacitinib	150	-3.26 [-3.81, -2.70]	-1.78 [-2.56, -1.00]	< 0.0001	Significant
ASAS20 Response %					
Placebo	157	43.8 [36.0, 51.5]			
Upadacitinib	156	66.7 [59.3, 74.1]	22.8 [12.2, 33.4]	< 0.0001	Significant
$BASMI_{lin}$ Change from Baseline					
Placebo	148	-0.19 [-0.29, -0.08]			
Upadacitinib	144	-0.29 [-0.40, -0.18]	-0.10 [-0.25, 0.05]	0.1781	Not Significant

Endpoint[a] Treatment	N	Within Group Point Estimate (95% CI)	Between Group Difference		
			Point Estimate (95% CI)	*P*-value[b]	Statistical Significance[c]
MASES (for Subjects with Baseline Enthesitis) Change from Baseline					
Placebo	125	-1.6 [-2.0, -1.2]			
Upadacitinib	124	-2.3 [-2.7, -1.9]	-0.7 [-1.3, -0.1]	0.0193	Not Significant

ASAS = Assessment of SpondyloArthritis international Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; $BASMI_{lin}$ = Linear Bath Ankylosing Spondylitis Metrology Index; CI = confidence interval; CRP = C-reactive protein; FAS = Full Analysis Set; HI = Health Index; ID = Inactive Disease; LDA = Low Disease Activity; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = magnetic resonance imaging; PR = partial remission; SI = sacroiliac; SPARCC = Spondyloarthritis Research Consortium of Canada

a. For categorical endpoints, Cochran-Mantel-Haenszel (CMH) test is used with non-responder imputation (NRI) incorporating multiple imputation (MI) to handle missing data due to coronavirus disease of 2019 (COVID-19) (NRI-MI). For continuous endpoints, mixed-effect model repeated measurements (MMRM) are used and N is number of unique subjects contributing to MMRM model estimates.

b. *P*-value is unadjusted.

c. Results are obtained via the sequential multiple testing procedure controlling the overall type I error rate of all primary and multiplicity-controlled secondary endpoints at the significance level of 0.05 (two-sided).

The above table does not include the outcome of ASAS40 response at Week 52 that was included last in the testing sequence for EU/ EMA. As stated above, the submitted CSR only presents efficacy data up to Week 14.

According to the CSR, for the multiplicity-controlled secondary endpoints, results from the corresponding sensitivity and/or supplementary analyses were consistent with the primary analyses. Results from the tipping point analyses were consistent with that of the primary analyses and in general are robust to the MNAR assumption.

Other endpoints

The outcome of additional endpoints was also included in the CSR. These data included change from Baseline in MRI SPARCC score of the spine at Week 14, ASAS components, ASAS20 Response Rate and ASAS Partial Remission Rate by visit and ASDAS (CRP) Components. Also the outcome of ASDAS LDA, ASDAS Clinically Important Improvement, and ASDAS Major Improvement over time, BASDAI 50 Response Rate, Change from Baseline in Measures of Inflammation and Change from Baseline in Measures of Pain by Visit, Patient-Reported Outcomes over time, number of tender joint and number of swollen joints at week 14 and Physician's Global Assessment of Disease Activity NRS were reported/commented on.

The below table provides a descriptive summary of components of ASAS at Baseline and at Week 14.

Table 11: Components of ASAS: Mean and Standard Deviation at Baseline and Week 14 (AO; FAS)

Parameter Visit Treatment	N	Mean	SD
Patient's Assessment Total Back Pain NRS			
Baseline			
Placebo	157	7.29	1.39
Upadacitinib 15 mg QD	156	7.23	1.55
Week 14			
Placebo	148	5.27	2.36
Upadacitinib 15 mg QD	143	4.29	2.49
Patient's Global Assessment of Disease Activity NRS			
Baseline			
Placebo	157	7.30	1.38
Upadacitinib 15 mg QD	156	6.99	1.62
Week 14			
Placebo	148	5.35	2.31
Upadacitinib 15 mg QD	143	4.16	2.38
BASFI			
Baseline			
Placebo	157	5.99	2.14
Upadacitinib 15 mg QD	156	5.89	2.08
Week 14			
Placebo	148	4.47	2.42
Upadacitinib 15 mg QD	143	3.33	2.39
Inflammation (Mean of BASDAI Q5 and Q6)			
Baseline			
Placebo	157	6.68	1.67
Upadacitinib 15 mg QD	156	6.60	1.83
Week 14			
Placebo	148	4.69	2.36
Upadacitinib 15 mg QD	143	3.48	2.51

AO = as observed; ASAS = Assessment of SpondyloArthritis international Society; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; FAS = Full Analysis Set; NRS = numerical rating scale; QD = once daily; SD = standard deviation

According to the CSR, there was a greater improvement in the number of tender joints in favour of upadacitinib vs placebo based on change from Baseline in TJC68 at Week 14 (-4.2 in the upadacitinib group and -2.7 in the placebo group) (nominal P = 0.0178). Further, there was a greater improvement in the number of swollen joints in favour of upadacitinib vs placebo based on change from Baseline in SJC66 at Week 14 (-1.7 in the upadacitinib group and -1.1 in the placebo group) (nominal P = 0.0028).

The below table (from the CSR) presents the hsCRP Mean Change by Visit during the study.

Table 12: Analysis of hsCRP Mean Change by Visit - by Week 14 in Double Blind Period (AO-MMRM) (Full Analysis Set)

Visit / Treatment	N_OBS	Baseline Mean	Visit Mean	Within Group Change from Baseline Mean	Within Group Change from Baseline SD	Missing Due to COVID -19 n	MMRM Results $ N^	Within Group Change from Baseline Mean Estimates	Within Group Change from Baseline [95% CI]	Between Groups Difference UPA - PBO Mean Estimates	Between Groups Difference UPA - PBO [95% CI]	Between Groups Difference UPA - PBO P-value
Week 1												
Placebo	145	8.69	7.40	-1.29	10.997	1	156	-1.80	(-3.78, 0.17)			
Upadacitinib 15 mg QD	142	9.72	4.40	-5.32	19.365	1	154	-4.89	(-6.87, -2.90)	-3.09	(-5.88, -0.29)	0.0308*
Week 2												
Placebo	145	8.74	7.45	-1.29	11.554	3	156	-1.70	(-2.84, -0.56)			
Upadacitinib 15 mg QD	147	9.49	2.61	-6.89	14.244	2	154	-6.61	(-7.75, -5.47)	-4.91	(-6.52, -3.29)	<0.0001***
Week 4												
Placebo	148	8.37	7.41	-0.96	11.937	2	156	-1.29	(-2.53, -0.05)			
Upadacitinib 15 mg QD	150	9.88	2.53	-7.35	15.068	0	154	-6.77	(-8.01, -5.53)	-5.48	(-7.23, -3.73)	<0.0001***
Week 8												
Placebo	147	8.67	7.12	-1.55	11.790	1	156	-1.80	(-2.88, -0.73)			
Upadacitinib 15 mg QD	144	9.55	2.15	-7.39	15.869	3	154	-6.94	(-8.02, -5.86)	-5.14	(-6.67, -3.62)	<0.0001***

$ Mixed Effect Model Repeated Measurement (MMRM) analysis includes treatment, visit and treatment-by-visit interaction as fixed factors and baseline value as covariate. Main stratification factors MRI and screening hsCRP status are also included in the model. Data up to 14 week are included in the model.
^ Number of unique subjects contributing to MMRM model estimates: subjects with at least one available change from baseline value and no missing data for the factors and covariates in the model. The MMRM N is not visit-specific and is displayed for model estimates for all visits.
* P-value <=0.05; **P-value <=0.01; ***P-value <=0.001.

Visit / Treatment	N_OBS	Baseline Mean	Visit Mean	Within Group Change from Baseline Mean	Within Group Change from Baseline SD	Missing Due to COVID -19 n	MMRM Results $ N^	Within Group Change from Baseline Mean Estimates	Within Group Change from Baseline [95% CI]	Between Groups Difference UPA - PBO Mean Estimates	Between Groups Difference UPA - PBO [95% CI]	Between Groups Difference UPA - PBO P-value
Week 12												
Placebo	148	8.43	7.21	-1.22	12.060	1	156	-1.76	(-2.86, -0.66)			
Upadacitinib 15 mg QD	143	9.78	2.58	-7.20	16.645	3	154	-6.75	(-7.86, -5.64)	-4.99	(-6.55, -3.43)	<0.0001***
Week 14												
Placebo	144	8.34	7.25	-1.09	12.389	1	156	-1.45	(-2.73, -0.18)			
Upadacitinib 15 mg QD	136	9.61	2.84	-6.77	15.124	0	154	-6.50	(-7.79, -5.21)	-5.04	(-6.86, -3.23)	<0.0001***

$ Mixed Effect Model Repeated Measurement (MMRM) analysis includes treatment, visit and treatment-by-visit interaction as fixed factors and baseline value as covariate. Main stratification factors MRI and screening hsCRP status are also included in the model. Data up to 14 week are included in the model.
^ Number of unique subjects contributing to MMRM model estimates: subjects with at least one available change from baseline value and no missing data for the factors and covariates in the model. The MMRM N is not visit-specific and is displayed for model estimates for all visits.
* P-value <=0.05; **P-value <=0.01; ***P-value <=0.001.

Summary of main study(ies)

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

Table 13 ***Summary of Efficacy for trial M19-944 Study 2 [nr-axSpA]***

Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Program to Evaluate Efficacy and Safety of Upadacitinib in Adult Subjects with Axial Spondyloarthritis Followed by a Remission-Withdrawal Period		
Study identifier	M19-944	
Design	RCT, double-blind, PBO-controlled	
	Duration of main phase:	Study 2 (nr-axSpA) is composed of a 52-week randomized, double-blind, placebo-controlled period and
	Duration of Extension phase:	52-week open-label, long-term extension period and a 30-day follow-up (F/U) Visit
Hypothesis	Superiority	

Treatments groups	Upadacitinib 15 mg QD		See above
	Placebo		See above
Endpoints and definitions (in total 15 Secondary endpoints, the outcome of 14 of these are presented within the current submission, please refer to above section of the AR).	Primary endpoint	ASAS40 Response Rate at Week 14	
	Secondary endpoint	ASDAS (CRP) LDA at week 14	
	Secondary endpoint	BASFI Change from Baseline at week 14	
Database lock	Database lock and unblinding for the Week 14 data occurred on 22 September 2021		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set, week 14			
Descriptive statistics and estimate variability	Treatment group	Upadacitinib	Placebo	
	Number of subject	156	157	
	ASAS40 week 14	44.9%	22.5%	
	95% CI	[37.1, 52.7]	[16.0, 29.1]	
	ASDAS (CRP) LDA w14	42.3	18.3	
	95% CI	[34.6, 50.1]	[12.2, 24.4]	
	BASFI Change from Baseline w14 95% CI	-2.61 [-2.94, -2.29]	-1.47 [-1.79, -1.15]	(n=154/156)

Effect estimate per comparison	Primary endpoint: ASAS40 week 14	Comparison group: Upadacitinib vs placebo	
		Difference, Point estimate	22.2
		Difference, 95% CI	[12.1, 32.3]
		P-value	<0.0001
	Secondary endpoint: ASDAS (CRP) LDA w14	Comparison groups: Upadacitinib vs placebo	
		Difference, Point Estimate	23.8 %
		Difference, 95% CI	[14.2, 33.4]
		P-value	< 0.0001
	Secondary endpoint: BASFI Change from Baseline w14	Comparison groups Upadacitinib vs placebo	
		Difference, Point estimate	-1.14
		Difference, 95% CI	[-1.60, -0.68]
		P-value	<0.0001

Notes	*a. n is calculated by N and MI-aggregated response rate (%).* *b. Construction of CIs for response rate is based on MI inference. The response rate and standard error (SE) are estimated within each imputed 'complete' dataset, then Rubin's rule is used to combine the response rate and SE estimates from 30 imputed 'complete' datasets to get aggregated rate and CIs.* *c. Treatment difference, associated CI and P-value for test of difference between upadacitinib group and placebo group is constructed based on the MI inference. Risk difference and SE is estimated using Cochran-Mantel-Haenszel (CMH) test and screening magnetic resonance imaging (MRI) and screening high sensitivity C-reactive protein (hsCRP) status as stratification factor within each imputed 'complete' dataset, then Rubin's rule is used to combine the results from 30 imputed 'complete' datasets to get aggregated treatment difference, associated confidence interval, and P-value.* *NRI-MI is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19*

Clinical studies in special populations

The pivotal clinical study included only 9 subjects who were ≥65 years: 6 in the PBO-group and 3 in the upadacitinib group.

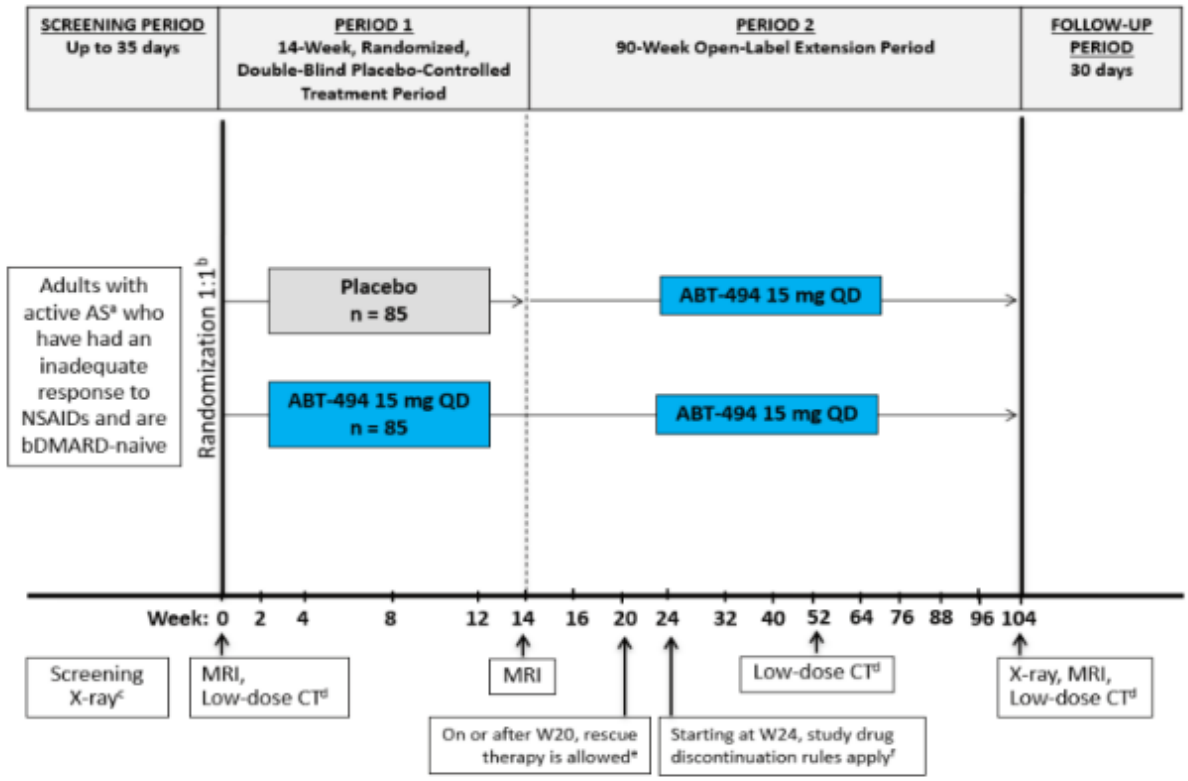
Supportive study

Long-term efficacy data (data beyond week 14)

According to the Clinical Overview (p.37), in addition to the 14-week efficacy results from Study M19-944 Study 2 (nr-axSpA), accumulated 2-year efficacy data from Study M16-098 (SELECT-AXIS 1) of the related AS population showed that the benefits of upadacitinib in improving clinical responses, pain, function, quality of life, and inflammation can be maintained for the long-term. Non-radiographic axSpA and AS are part of the same spectrum of axial SpA and share common epidemiological, genetic, and clinical disease characteristics, including similar disease burden, similar response to treatment, and common treatment guidelines. Thus, the 2-year long-term efficacy data from Study M16-098 in bDMARD-naïve AS patients can be used as supplementary information to support the long-term benefit of upadacitinib in the treatment of patients with active nr-axSpA.

Study M16-098 was the pivotal study supporting approval of the AS indication for upadacitinib (please refer to EPAR for EMEA/H/C/004760/II/0005 and approved SmPC). The study design is depicted in the below figure from the EPAR.

Figure 8: The design of M16-098 Study



AS = ankylosing spondylitis; ASAS = Assessment of Spondylo Arthritis international Society; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; bDMARD = biologic disease-modifying antirheumatic drugs; CT = computer tomography; hsCRP = high sensitivity C-reactive protein; MRI= magnetic resonance imaging; NRS = numeric rating scale; NSAIDs = nonsteroidal anti-inflammatory drugs; QD= once daily; SSZ = Sulfasalazine;ULN = upper limit of normal; W = week

a. Clinical diagnosis of AS and meeting the modified New York Criteria for AS. Subject must have had Baseline disease activity as defined by having BASDAI score ≥ 4 and Patient's Assessment of Total Back Pain score ≥4 based on a 0 – 10 NRS at the Screening and Baseline Visit
b. Stratified by geographic region (US/Canada, Japan, rest of world) and hsCRP (≤ ULN vs. > ULN).
c. The x-rays of the spine and pelvis were required during the Screening Period if the subject had a previous anteroposterior pelvis x-ray and lateral spine x-rays within 90 days of the Screening Period, provided that the x-rays were confirmed to be adequate for the required evaluations and were deemed acceptable by the central imaging vendor
d. For subjects at select sites who consented to participation in the low-dose CT scan substudy.
e. Starting at Week 16, subjects who did not achieve at least an ASAS20 response at two consecutive visits were to have the option to add or modify doses of NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol or combination of acetaminophen and codeine or hydrocodone), and/or modify dose of MTX or SSZ at Week 20 or thereafter..
f. Starting at Week 24, subjects who still did not achieve at least an ASAS20 response at two consecutive visits were to be discontinued from study drug treatment

The MAH considers that improvement in AS in subjects who received upadacitinib 15 mg QD in both study periods was maintained from Week 14 to Week 104 on all measures of clinical response and that subjects who switched from placebo in the placebo-controlled period to upadacitinib at Week 14 improved rapidly and maintained response through Week 104, see below table.

Table 14: Study M16-098: Clinical Response to Upadacitinib 15 mg QD – ASAS, BASDAI, and ASDAS (CRP) Results at Week 14, Week 52, and Week 104 (AO, FAS)

	Week 14				Week 52				Week 104			
	Placebo		Upadacitinib 15 mg QD		Placebo		Upadacitinib 15 mg QD		Placebo/ Upadacitinib 15 mg QD		Upadacitinib 15 mg QD/ Upadacitinib 15 mg QD	
Endpoint	N	n (%) or Mean Change	N	n (%) or Mean Change	N	n (%) or Mean Change	N	n (%) or Mean Change	N	n (%) or Mean Change	N	n (%) or Mean Change
ASAS40, %	87	24 (27.6)	87	47 (54.0)	84	65 (77.4)	81	65 (80.2)	71	63 (88.7)	71	61 (85.9)
ASAS20, %	87	37 (42.5)	87	59 (67.8)	84	79 (94.0)	81	71 (87.7)	71	69 (97.2)	71	64 (90.1)
ASAS PR, %	87	1 (1.1)	88	17 (19.3)	84	38 (45.2)	82	41 (50.0)	71	31 (43.7)	72	37 (51.4)
BASDAI50, %	87	22 (25.3)	87	42 (48.3)	84	64 (76.2)	81	63 (77.8)	71	60 (84.5)	71	63 (88.7)
ASDAS LDA, %	84	10 (11.9)	86	46 (53.5)	82	67 (81.7)	78	67 (85.9)	66	54 (81.8)	68	59 (86.8)
ASDAS ID, %	84	0 (0.0)	86	15 (17.4)	82	34 (41.5)	78	36 (46.2)	66	34 (51.5)	68	31 (45.6)
ASDAS Clinically important improvement, %	84	17 (20.2)	85	49 (57.6)	82	74 (90.2)	77	66 (85.7)	66	57 (86.4)	67	60 (89.6)
ASDAS Major improvement, %	84	5 (6.0)	85	30 (35.3)	82	43 (52.4)	77	43 (55.8)	66	33 (50.0)	67	37 (55.2)
BASDAI, Δ (Mean)	87	–1.80	87	–2.79	84	–4.42	81	–4.29	71	–4.58	71	–4.56
ASDAS, Δ (Mean)	84	–0.62	85	–1.44	82	–2.12	77	–2.05	66	–2.11	67	–2.10

AO = as observed; ASAS = Assessment of SpondyloArthritis international Society; ASAS40 = ASAS 40 response; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; Δ = change from Baseline; FAS = full analysis set; ID = Inactive Disease; LDA = Low Disease Activity; PR = partial remission; QD = once daily

Note: All ASDAS outcomes are based on ASDAS (CRP).

The long-term data from Study M16-098 is currently being assessed in the parallel variation EMEA/H/C/004760/II/0015/G. Please refer to this variation for the complete assessment of those data.

2.4.2. Discussion on clinical efficacy

The JAK-inhibitor upadacitinib was recently approved for the ankylosing spondylitis (AS) indication (EMEA/H/C/004760/II/0005) based on data from study M16-098 (SELECT-AXIS 1) which was conducted in AS bDMARD-naïve subjects. The current procedure aims to extend the indication to subjects with another type of axial spondyloarthritis (axSpA), namely the less advanced form without presence of sacroiliitis on plain conventional radiographs (as defined by the modified New York criteria, required to fulfil the diagnosis for AS).

The MAH submitted the following indication proposal: "*RINVOQ is indicated for the treatment of active non-radiographic axial spondyloarthritis (nr axSpA) in adult patients with objective signs of inflammation who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)*."

The proposed posology was, similar to AS (and also rheumatoid arthritis-RA, psoriatic arthritis-PsA), 15 mg once daily.

The support for the efficacy of upadacitinib for the new indication nr-axSpA is primarily derived from the pivotal study M19-944, study 2 in nr-axSpA. Supportive data, on maintenance of effect, is claimed from study M16-098 in the related condition i.e. AS.

No dedicated dose response study was conducted for the new applied indication. Specific dose response studies should, in line with the EMA axSpA GL (Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis, EMA/CPMP/EWP/4891/03 Rev.1, Corr 1*) be performed in patients with axial SpA. In this case, dose selection is, according to the MAH, informed by results from the exposure-response analyses using data from study M19-944 Study 2 in nr-axSpA but also results from the exposure-response analyses conducted based on data from

upadacitinib Phase 2 and Phase 3 studies in RA. The possible uncertainty pertaining to whether optimal daily dose has been identified for nr-axSpA has not been pursued by the CHMP. The MAH's approach was considered acceptable.

Design and conduct of clinical studies

Pivotal study M19-944, study 2 in nr-axSpA

Overall design

Study M19-944 utilizes a "master protocol" that includes 2 independent studies for subjects with active axSpA: Study 1 in biologic DMARD-inadequate responders (bDMARD-IRs) AS and Study 2 in nr-axSpA. The latter study is the pivotal study for the current application. The approach was agreed to in previous CHMP Advice (EMEA/H/SA/3190/8/2019/II).

Study 2 includes a 52-week randomized, double-blind, parallel-group, placebo-controlled period followed by a 52-week open-label, long-term extension (OLE) period. The primary endpoint for efficacy is analysed at week 14. The study is still on-going and the MAH submitted Clinical Study Report (CSR) with efficacy data up to Week 14. Safety data and subject disposition are presented up to the cut-off date (26 August 2021). The approach to submit the variation based on primarily week 14 efficacy data and submit efficacy-data from the beyond the week 14 timepoint post-approval was overall accepted in the previous CHMP Advice in which it was stated: "*The MAH proposes an interim database lock of the 14 week data, to support submission of the nr-axSpA indication following an AS indication. This may be acceptable on the understanding that one year data and two year data are submitted post-approval, and given that there are no limiting uncertainties regarding maintenance of efficacy and of safety for AS and nr-AxSpA*."

A placebo-controlled parallel group design is, according to EMA axSpA GL acceptable for trials in axSpA, both for those including subjects with insufficient response to NSAIDs and those including subjects with insufficient response to biological medicinal products. However, according to the EMA GL, products belonging to new therapeutic classes may need also comparison against an accepted active comparator (e.g. anti TNF treatments) for the target population, in order to properly assess the relative benefit risk balance of the new product. In the current case, information on comparative efficacy could be extrapolated from data originating from the development programme of related conditions e.g. PsA. It is noted that the PsA development programme included one active-controlled study in which upadacitinib was compared against adalimumab (please refer to EPAR for EMEA/H/C/004760/II/0004 for details). With the totality of data at hand, the CHMP decided that the issue of efficacy relative an active comparator for the nr-axSpA indication will not be further pursued.

The 52-week OLE will be followed by an open-label Remission-Withdrawal Period for which subjects with sufficiently low disease activity are eligible. The importance of this was discussed already in the procedure leading to the AS approval (please refer to EPAR for EMEA/H/C/004760/II/0005 for details).

Study population

Study 2 includes subjects with nr-axSpA diagnosis, who do not meet the radiologic criterion for AS, which are NSAID-inadequate responders/cannot tolerate NSAIDs which may or may not have previous exposure to bDMARDs. Objective signs of active inflammation on MRI of SI joints or hsCRP > ULN at Screening are required. Further, active disease as reflected by BASDAI score ≥ 4 and a Patient's Assessment of Total Back Pain score ≥ 4 based on a 0 - 10 NRS at Baseline is mandatory. Randomization is stratified by MRI and screening hsCRP status and exposure to bDMARDs.

Overall, the study population expected to be captured with the eligibility criteria is in line with comments in previous CHMP Advice and EMA axSpA GL. As underlined in GL, traditional non-biological

disease modifying antirheumatic drugs have limited value for the treatment of the spinal involvement in patients with SpA. Thus, it is supported that csDMARD is allowed in the study if in stable dose but that there are no requirements for such treatment. Further, while the eligibility criteria do not specify a minimum duration of active disease before study inclusion, the fact that subjects have inadequate response to at least two NSAIDs over a period of at least 4 weeks prior to screening mean that there is still a requirement for a minimum time with active disease. The approach is considered to comply with the EMA guideline. On the contrary, the fact that physical therapy is not required prior to study entry is considered a limitation. However, this issue was not further pursued.

During the evaluation, the CHMP requested the MAH to specify the objective signs of inflammation in the indication wording. The MAH submitted an updated SmPC in which the indication statement has been revised as requested:

RINVOQ is indicated for the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

With the current criteria, the CHMP considered that the study population would overall be expected to be consistent with the revised indication.

Endpoints and estimand

The primary endpoint for Study 2 is the proportion of subjects with ASAS40 response at Week 14. This is in line with the relevant EMA axSpA GL and was also agreed in the CHMP Advice.

As per the relevant EMA GL, the goals of therapy for axSpA includes improvement of symptoms and signs such as pain and stiffness, improvement of physical function and slowing or prevention of structural damage with acceptable endpoints including ASAS response criteria, ASDAS, BASDAI, assessments of spinal mobility e.g the composite BASMI, PROs e.g. ASQoL, acute phase reactants, assessment of peripheral joints and entheseal involvement. This is considered adequately well reflected in the selection of primary and secondary endpoints in the main study. According to the EMA GL, prevention of structural damage is considered a relevant endpoint to be assessed but not a requirement for approval and further, SPARCC is acceptable for measurement of MRI changes.

The primary efficacy analysis uses the composite estimand framework. This is overall in line with comments in the CHMP Advice.

Statistical methods

The statistical methods applied were largely acceptable and in line with the scientific advice given by the CHMP. The primary composite estimand, sensitivity analysis and the supplementary treatment policy estimand, analyses of the primary and ranked secondary endpoints, as well as the handling of missing data due to COVID-19, were all agreed to by the CHMP prior to submission of the MAA.

The stepwise multiple testing procedure provides strong control of the type I error rate at 0.05 alpha (2-sided) across analyses of the primary endpoint and 15 secondary endpoints. The primary and the multiplicity controlled secondary endpoints (except for the last endpoint in the testing sequence) were observed at Week 14. The efficacy analysis up to Week 14, which is presented in this report, is the first set of 3 planned analyses. However, no multiplicity adjustment is necessary due to repeated analyses, since all subjects had completed the Week 14 visit or had discontinued the study prior to Week 14. The data cutoff date for the report is 26 August 2021.

The efficacy analysis up to Week 52 in the double-blind study period will be reported when data becomes available. However, with the present report of positive treatment outcome at Week 14 it is

reasonable to assume that patient retention in the placebo group might be lower for the remaining part of the study period, which may have negative impact on quality of Week 52 data.

The primary and first 12 secondary endpoints were statistically significant, which implies that the last ranked endpoint ASAS40 at Week 52 (for EU/EMA) which will be tested at the Week 52 database lock, will give nominal p-value. Several updates of the SAP were made during the course of the study, mainly to align with the new protocol versions. The major statistical changes included addition of the remission-withdrawal period and methods for handling missing data due to COVID-19 and regulatory feedback, but also change in order of the multiplicity-controlled secondary endpoints. The rationale for switching the order in the multiple testing procedure was ”emerging external literature data and clinical relevance”, as explained in the Protocol Appendix E. The effective SAP version 4.0 was finalized prior to the Week 14 database lock.

No interim efficacy analysis for early stopping was planned. An independent external Data Monitoring Committee (DMC) was used to regularly review unblinded safety data, and when needed, also had right to request high-level unblinded efficacy data.

Participant flow, recruitment and conduct of the study

In total 314 subjects were randomized; 158 in the placebo group and 156 in the upadacitinib group. One subject in the placebo group decided not to participate after randomization and discontinued the study before receiving study drug, thus 313 subjects were included in the Full Analysis Set (FAS) used for all efficacy analyses. Further, a total of 145 subjects (92.9%) in the upadacitinib group and 150 subjects (95.5%) in the placebo group in the FAS completed study drug up to Week 14 (i.e. the timepoint for the analysis of the primary endpoint). Further, 149/157 (94.3%) of the subjects in the FAS in placebo group and 142/156 (91.0%) in the upadacitinib group completed study up to that timepoint. The most frequent primary reason for discontinuation of study drug up to week 14 was AE in the upadacitinib group and lack of efficacy in the placebo group.

The drop-out rate up to week 14 is acceptable in total number and distribution between the groups. As commented above, the primary efficacy analysis will use the composite estimand framework. Corresponding to this estimand, in the primary analysis, subjects who discontinue study drug prior to Week 14 will be treated as non-responders.

The last subject last visit occurred 02 September 2021 (Week 14) while the cut-off date for the CSR is stated to be 26 August 2021. The MAH clarified that it was due to rescheduling of 1 subject and this was considered acceptable to the CHMP.

Substantial amendments were made during the course of this pivotal confirmatory study. The amendments included changes to the eligibility criteria and multiplicity-adjusted endpoints including the order of these endpoints. The majority of the subjects were enrolled under Global Protocol Version 3.0 and after that, the changes to the eligibility criteria do not seem substantial and further seem to constitute clarifications rather than complete revisions meaning that the population included in the study is probably not too heterogenous. Throughout the study, changes to study endpoints and statistics were conducted. The MAH has confirmed that changes to eligibility criteria and multiplicity-adjusted endpoints in the protocol version (amendments) for M19-944 Study 2 were not influenced by unblinded data from this study.

A rather high number of subjects had at least one protocol deviation (21.7%) and eligibility criteria not met seemed to be an important reason (16.9% of subjects). The 5 most frequent protocol deviation categories related to eligibility criteria not met were presented in a tabulated form. From this presentation follows that the most frequent “Eligibility Criteria Not Met” was “BASDAI score ≥ 4 and Total Back Pain score ≥ 4 requirement at Screening and BL Visits” (n=14; 8 PBO, 6 upa) while the

second most common was "Exposure to at most one bDMARD was permitted" (n=12; 7 PBO, 5 upa). The remaining 3 of the most frequent protocol deviation categories related to eligibility criteria not met, were related to safety criteria. It is agreed with the MAH that the occurrence of these deviations should not have a significant impact on the ability to generalize the study results to the (currently) proposed indication.

The MAH pointed out that the pre-specified sensitivity analysis for the primary endpoint in the Per Protocol Analysis Set, which excludes subjects with relevant protocol deviations (M19-944 Study 2 CSR), showed consistent results with the primary analysis. Further, the MAH put forward that additional post-hoc analyses were performed for the multiplicity-controlled secondary endpoints in the Per Protocol Analysis Set, and the results of those analyses are consistent with the primary analysis of the multiplicity-controlled secondary endpoints. This was generally agreed by CHMP.

Study M16-098 in AS (supportive data)

Study M16-098 was the pivotal study supporting approval of the AS indication for upadacitinib (please refer to EPAR for EMEA/H/C/004760/II/0005 and SmPC). In this procedure, efficacy data up to week 64 was already provided.

The current approach to submit the variation based on primarily week 14 efficacy data and submit efficacy-data from the beyond the week 14 timepoint post-approval was essentially already accepted in the previous CHMP Advice (see above reference). However, as indicated in the EMA GL, although efficacy may be demonstrated in 12-24 weeks trial, maintenance of the effect in longer trials (e.g. ≥1 year) should be demonstrated. Considering that efficacy data up to week 64 was already provided in Study M16-098 (EMEA/H/C/004760/II/0005) and the fact that it is reasonable to extrapolate long-term efficacy between the conditions due to the similarities in disease characteristics, it was considered that overall sufficient data to support the new indication was available.

The long-term data from Study M16-098, which may provide further support of long-term benefit, is currently being assessed in the parallel variation EMEA/H/C/004760/II/0015/G. Please refer to this variation for the complete assessment of those data.

Efficacy data and additional analyses

Pivotal study M19-944, study 2 in nr-axSpA

Baseline data

Baseline data on general demographics and disease characteristics were overall similar in the two treatment groups and the included population is also generally representative for the population covered by the indication. Further, the proposed section 5.1 of the SmPC wording on baseline characteristics is acceptable in relation to the data available.

In both treatment groups somewhat more females than males are included; 58.5% females in total. In a population of AS a male predominance would have been expected but it is known that for nr-axSpA the sex distribution is more even. In the light of this, these baseline findings are not considered to have a negative impact on the generalisability of the study results.

All subjects had prior NSAID use and 98.4% of them at least 2 prior NSAID use (which was stipulated by eligibility criteria). Further, it is noted that 49 subjects (31.4%) in the upadacitinib group and 54 subjects (34.4%) in the placebo group had prior exposure to at least 1 bDMARD. Among the subjects with prior bDMARD exposure, a total of 44 and 43 subjects were exposed to at least 1 TNFi in the upadacitinib and placebo groups, respectively.

Subjects had moderately to severely active disease, as indicated by mean BASDAI of 6.86 (Mild 1-3, Moderate 4-7 and Severe 8-10). High-sensitivity CRP > ULN was reported for 79.6% of subjects at screening and MRI inflammation status at Screening was positive for 43.5% of subjects. At baseline, patients had symptoms of non radiographic axial spondyloarthritis for an average of 9.1 years.

Outcome of the primary endpoint: ASAS40 at week 14

The study met its primary endpoint as a statistically significantly greater percentage of subjects achieved ASAS40 at Week 14 in the upadacitinib group (44.9%, 70/156) compared with the placebo group (22.5%, 35/157), resulting in a placebo adjusted difference of 22.2% (P < 0.0001) using non-responder imputation (NRI) incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-MI). From the breakdown of the ASAS40 response at Week 14 by intercurrent events and missing data provided, it is apparent that the vast majority of non-responders in both treatment groups were non-responders based on observed measurements. As a minor clarification, the MAH was requested to explain why the proportion of responders in the CSR and SmPC in the placebo group is reported to be 22.5% as 35/157=22.3%. In response to the RSI, it was clarified that this relates to the analysis approached used and the approach is considered acceptable.

For ASAS40, numerical difference between treatment groups was observed at all timepoints from week 2 to week 14. This has been included in the SmPC.

Regarding the outcome in subgroups, across subgroups based on age, sex, BMI, race, region, hsCRP level at screening, prior bDMARD Exposure, duration of nr-axSpA Symptoms, MRI (SI joints) inflammation at screening, MRI inflammation/hsCRP level at screening, there was a numerical difference between treatment groups favouring upadacitinib treatment although effect size and 95% CI was fluctuating (NRI-MI, FAS). But for the subgroup of subjects with duration since nr-axSpA diagnosis>10 years (n=16 in the placebo group and 20 in the upadacitinib group), the response rate difference was -3.8% i.e. in favour of placebo. This finding is of some interest, as it can be speculated that it would reflect some kind of "window of opportunity" for upadacitinib early in the course of the disease. However, as it is based on data from a rather small group of patients, as duration since nr-axSpA diagnosis was not a stratification factor in the study, the CHMP concluded that it does not (without having been replicated) merit inclusion in the product information.

It is further noted that the response rate difference vs placebo was highest in the stratum which was both MRI and hsCRP+ as compared to being positive for one of the factors. For the MRI+/hsCRP>ULN stratum, the response rate difference was 43.6% as compared to 11.6% in the MRI+/hsCRP<=ULN stratum and 17.1% in the MRI-/hsCRP>ULN stratum (the largest of the three strata). Further, the response rate difference was higher in subjects without previous bDMARD exposure as compared to subjects with such experience: 28.6% vs 8.7%.

Overall, the proposed subgroup statement in the product information i.e. "*The efficacy of upadacitinib 15 mg was demonstrated across subgroups including gender, baseline BMI, symptom duration of non-radiographic axial spondyloarthritis, baseline hsCRP, MRI sacroiliitis, and prior use of bDMARDs*." was considered acceptable.

Outcome of Multiplicity-adjusted secondary endpoints and additional, other endpoints

Statistical significance was achieved in the first 12 of the 14 presented multiplicity-controlled secondary endpoints for upadacitinib compared with placebo. The presentation did not include the outcome of ASAS40 response at Week 52 that is placed last in the testing sequence for EU/ EMA. As stated above, the submitted CSR only presents efficacy data up to Week 14.

The endpoints for which statistical significance was achieved thus included: ASAS40 at Week 14 (the primary endpoint), Change from Baseline in ASDAS (CRP) at week 14, Change from Baseline in MRI

SPARCC) score (SI joints) at week 14, BASDAI) 50 response at week 14, ASDAS (CRP) Inactive Disease (ID) (ASDAS score < 1.3) at week 14, Change from Baseline in Patient's Assessment of Total Back Pain NRS (Score 0 – 10) at week 14, Change from Baseline in Patient's Assessment of Nocturnal Back Pain NRS (Score 0 – 10) at week 14, ASDAS (CRP) Low Disease Activity (LDA) (ASDAS score < 2.1) at week 14, ASAS partial remission (PR) (an absolute score of ≤ 2 units for each of the 4 domains identified in ASAS40) at week 14, Change from Baseline in BASFI at week 14, Change from Baseline in ASQoL at week 14, Change from Baseline in ASAS Health Index at week 14 and ASAS20 response at week 14.

Statistical significance was not met for: Change from Baseline in BASMIlin at week 14 and Change from Baseline in MASES for subjects with baseline Enthesitis (MASES > 0) at week 14. Consequently, neither will the endpoint included last in the testing sequence i.e. ASAS40 response at Week 52 be able to achieve statistical significance.

The results indicate some effect also on tender and swollen joint count and hsCRP although these outcome measures were not included among the multiplicity-adjusted secondary endpoints precluding firm conclusions. Regarding the components of the primary endpoint i.e. ASAS, numerical differences in favour of the active arm were noted for all the components when compared with placebo.

Overall, the outcome of the study indicates that 14-week treatment with upadacitinib have an effect on symptoms and signs of nr axSpA (as measured by e.g. ASAS40, ASAS20, ASDAS [CRP]) physical function (as measured by BASFI) and other patient-reported outcomes (as measured by ASQoL, ASAS Health Index). Further, upadacitinib has an effect on typical MRI-findings indicative of inflammation attributed to the target disease.

Judging from the outcome on the primary endpoint i.e. ASAS40 at week 14, although the limitations of comparisons between trials are acknowledged, the effect size appears similar as the effect size of upadacitinib in the treatment of AS (difference from placebo 22.5% for nr-axSpA and, according to the approved SmPC, 26.1% for AS).

Efficacy data in elderly

Available efficacy data was not reported separately for patients aged 65-74, 75-85 and 85 and older. However, the pivotal clinical study included only 9 subjects who were ≥65 years: 6 in the PBO-group and 3 in the upadacitinib group. No meaningful information is expected to be yielded by presenting efficacy data in this subgroup separately and even less by presenting data split into further age subcategories. Thus, the issue was not further pursued by the CHMP.

Study M16-098 in AS (supportive data)

Study M16-098 was the pivotal study supporting approval of the AS indication for upadacitinib (EMEA/H/C/004760/II/0005) and, in this procedure, efficacy data up to week 64 was already provided as reflected by the following statement in the approved SmPC:

"*In SELECT-AXIS 1, a significantly greater proportion of patients treated with upadacitinib 15 mg achieved an ASAS40 response compared to placebo at week 14 (*Table 10*). A numerical difference between treatment groups was observed at week 2 and response was maintained through week 64*"

Thus, although the additional data that is to be assessed in EMEA/H/C/004760/II/0015/G will provide further information on the efficacy in axSpA up to 2 years, maintenance of ASAS40 response for at least 1 year has already been demonstrated.

In conclusion, as it is considered reasonable to extrapolate long-term efficacy from AS to nr-axSpA due to the similarities in disease characteristics, the CHMP agreed that the M16-098 1-year data supports a maintained treatment effect of upadacitinib in subjects with nr-axSpA.

As the conclusions on long-term efficacy in nr-axSpA are based on extrapolation between the conditions, the statement in Section 4.2 of the SmPC on when to consider discontinuing treatment was updated to include nr-axSpA at the CHMP's request: *"Consideration should be given to discontinuing treatment in patients with axial spondyloarthritis who have shown no clinical response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks."*

2.4.3. Conclusions on the clinical efficacy

The pivotal, confirmatory study in nr-axSpA met its primary endpoint and the first 12 of the 14 presented multiplicity-controlled secondary endpoints. Overall, the outcome of the study indicates that 14-week treatment with upadacitinib has an effect on symptoms and signs of nr axSpA (as measured by e.g. ASAS40, ASAS20, ASDAS [CRP]) physical function (as measured by BASFI) and other patient-reported outcomes (as measured by ASQoL, ASAS Health Index). Further, upadacitinib has an effect on typical MRI-findings indicative of inflammation.

Judging from the outcome on the primary endpoint i.e. ASAS40 at week 14, the effect size appears similar as the effect size of upadacitinib in the treatment of AS. The effect size is considered clinically relevant.

The current submission does not include any efficacy data from the pivotal nr-axSpA study beyond 14 weeks. Instead, maintenance of effect is supported by extrapolation from long-term data from study M16-098 that was the pivotal study supporting approval of upadacitinib in a related condition i.e. AS (EMEA/H/C/004760/II/0005). In the AS procedure efficacy data up to week 64 was already assessed as reflected in the approved SmPC. Thus, the maintenance of ASAS40 response for at least 1 year in AS has already been demonstrated and the CHMP considered that it was acceptable to extrapolate long-term efficacy from AS to nr-axSpA due to the similarities in disease characteristics. The CHMP therefore agreed that the M16-098 1-year data supports a maintained treatment effect of upadacitinib in subjects with nr-axSpA. Additional M16-098-data up to 2 years is currently assessed in the separate on-going procedure EMEA/H/C/004760/II/0015/G. Please refer to this variation for the complete assessment of those data.

The CHMP concluded that the data supported the following extension of indication with a dosage of 15 mg once daily:

"Non-radiographic axial spondyloarthritis (nr-axSpA)

RINVOQ is indicated for the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)."

2.5. Clinical safety

Introduction

The safety profile for Rinvoq includes infections, neutropenia, anaemia, increased liver enzymes, increased CPK and lipid derangements.

Patient exposure

Through the data cutoff (26 August 2021), a total of 187 subjects received at least 1 dose of upadacitinib (mean duration of exposure was 227.8 days).

Table 15 Extent of exposure in study M19.944

	Upadacitinib 15 mg QD (N = 187)
Duration (Days)	
N	187
Mean (SD)	227.8 (131.18)
Median (min, max)	234.0 (3, 520)
Duration Interval – n (%)	
≥ 2 Weeks	182 (97.3)
≥ 1 Month	179 (95.7)
≥ 3 Months	155 (82.9)
≥ 6 Months	114 (61.0)
≥ 9 Months	75 (40.1)
≥ 12 Months	35 (18.7)
≥ 18 Months	0

Adverse events

Adverse events are tabulated by the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class SOC and PTs as listed below:

- Week 14: number and percent of subjects experiencing TEAEs by treatment group
- Week 52: number and percent of subjects experiencing TEAEs and events per 100 PYs of study drug exposure by treatment group
- Long-term: events per 100 PYs of study drug exposure for all subjects who received at least one dose of upadacitinib

A TEAE was defined as an adverse event with an onset date that is after the first dose of study drug, and no more than 30 days after the last dose of study drug.

An overview of adverse events during the placebo-controlled period is shown below.

Table 16. Study M19-944 Study 2 (nr-axSpA): Overview of Treatment-Emergent Adverse Events and All Deaths – By Week 14 in the Double-Blind Period (Safety Analysis Set)

	Placebo (N = 157) n (%)	Upadacitinib 15 mg QD (N = 156) n (%)	Upadacitinib – Placebo (95% CI)[a]
Any treatment-emergent			
AE	72 (45.9)	75 (48.1)	2.2 (-8.8, 13.3)
AE with reasonable possibility of being related to study drug[b]	30 (19.1)	29 (18.6)	-0.5 (-9.2, 8.1)
Severe AE	3 (1.9)	8 (5.1)	3.2 (-0.9, 7.3)
SAE	2 (1.3)	4 (2.6)	1.3 (-1.7, 4.3)
AE leading to discontinuation of study drug	2 (1.3)	4 (2.6)	1.3 (-1.7, 4.3)
Any AE leading to death	0 (0.0)	0 (0.0)	0.0
COVID-19 related AE[c]	10 (6.4)	8 (5.1)	-1.2 (-6.4, 3.9)
All deaths	0 (0.0)	0 (0.0)	0.0

AE = adverse event; CI = confidence interval; COVID-19 = coronavirus disease 2019; QD = once daily; SAE = serious adverse event

a. The point estimate and 95% CI are calculated based on the normal approximation and separate group variance.

b. As assessed by investigator.

c. Based on investigator assessment of AEs associated with COVID-19 and not limited to preferred terms of COVID-19.

An overview of adverse events in the 52-week double-blind period is shown below.

Table 17. Study M19-944 Study 2 (nr-axSpA): Overview of Treatment-Emergent Adverse Events and All Deaths per 100 PYs – By Week 52 in the Double-Blind Period (Safety Analysis Set)

	Placebo (N = 157) (PYs= 111.4) (E/100 PYs) (95% CI)[a]	**Upadacitinib 15 mg QD (N = 156) (PYs= 106.2) (E/100 PYs) (95% CI)[a]**	**Upadacitinib – Placebo (95% CI)[a]**
Exposure-adjusted event rate			
AE	254 (227.9) (200.7, 257.7)	276 (260.0) (230.2, 292.5)	32.1 (-9.5, 73.6)
AE with reasonable possibility of being related to study treatment[b]	54 (48.5) (36.4, 63.2)	82 (77.2) (61.4, 95.9)	28.8 (7.7, 49.9)
Severe AE	11 (9.9) (4.9, 17.7)	12 (11.3) (5.8, 19.7)	1.4 (-7.2, 10.1)
SAE	6 (5.4) (2.0, 11.7)	6 (5.7) (2.1, 12.3)	0.3 (-6.0, 6.5)
AE leading to discontinuation of study treatment	4 (3.6) (1.0, 9.2)	9 (8.5) (3.9, 16.1)	4.9 (-1.7, 11.4)
Any AE leading to death	0 (0.0)	0 (0.0)	0.0
COVID-19 related AE[c]	20 (17.9) (11.0, 27.7)	18 (17.0) (10.0, 26.8)	-1.0 (-12.1, 10.1)
All deaths	0 (0.0)	0 (0.0)	0.0

AE = adverse event; CI = confidence interval; COVID-19 = coronavirus disease 2019; E = event; E/100 PYs = events per 100 patient-years; PYs = patient years; QD = once daily; SAE = serious adverse event

a. The point estimate and 95% CI are using the Poisson assumption and normal approximation.

b. As assessed by investigator.

c. Based on investigator assessment of AEs associated with COVID-19 and not limited to preferred terms of COVID-19.

Common adverse events

Up to Week 14, the most frequently reported (≥ 5% of subjects) TEAEs by MedDRA system organ classes (SOC) in the upadacitinib group were Infections and Infestations, Gastrointestinal Disorders, Nervous System Disorders, Musculoskeletal and Connective Tissue Disorders, Investigations, and Skin and Subcutaneous Tissue Disorders.

The most frequently reported (≥ 2% of subjects) TEAEs by PT in the upadacitinib group were headache, COVID-19, nasopharyngitis, nausea, abdominal pain, diarrhoea, and neutropenia. In the placebo group, the most frequently reported TEAEs (≥ 2% of subjects) were COVID-19, nasopharyngitis, oral herpes, headache, abdominal pain upper, pain in extremity, and upper respiratory tract infection (Table 18). Higher frequencies were observed for the upadacitinib group compared with the placebo group for headache, nausea, abdominal pain, diarrhoea, and neutropenia.

Table 18. Study M19-944 Study 2 (nr-axSpA): Treatment-Emergent Adverse Events Reported in ≥ 2% of Subjects in any Treatment Group up to Week 14, by Decreasing Frequency in the Upadacitinib Group (Safety Analysis Set)

MedDRA 24.0 Preferred Term	Placebo (N = 157) n (%)	Upadacitinib 15 mg QD (N = 156) n (%)
Any adverse event	72 (45.9)	75 (48.1)
Headache	4 (2.5)	9 (5.8)
COVID-19	9 (5.7)	6 (3.8)
Nasopharyngitis	7 (4.5)	5 (3.2)
Nausea	3 (1.9)	5 (3.2)
Abdominal pain	1 (0.6)	4 (2.6)
Diarrhoea	3 (1.9)	4 (2.6)
Neutropenia	0	4 (2.6)
Oral herpes	5 (3.2)	3 (1.9)
Abdominal pain upper	4 (2.5)	1 (0.6)
Pain in extremity	4 (2.5)	1 (0.6)
Upper respiratory tract infection	4 (2.5)	0

COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily

Serious adverse event/deaths/other significant events

Up to Week 14, SAEs were reported in 6 subjects: 4 subjects (2.6%) in the upadacitinib group and 2 subjects (1.3%) in the placebo group (Table 16). COVID-19 pneumonia, pyelonephritis, foot fracture, and osteoarthritis were each reported in 1 subject in the upadacitinib group, and pancreatitis and haemorrhagic fever with renal syndrome were each reported in 1 subject in the placebo group.

Up to Week 52, 4 additional SAEs were reported in 4 subjects in the placebo group: meniscus injury, femur fracture, cataract, and acute pancreatitis. Two additional SAEs were reported in the upadacitinib group: nasal polyps and ureterolithiasis were reported in 1 subject each. Up to Week 52, the EAER of SAEs was similar in both treatment groups: 5.7 E/100 PYs in the upadacitinib group and 5.4 E/100 PYs in the placebo group. No new SAEs were reported beyond the double-blind period (i.e., after Week 52).

There were no deaths up to the current data cut-off.

Adverse events of special interest

Adverse events of special interest were identified based on safety concerns reported for other Janus kinase (JAK) inhibitor products, as well as upadacitinib data from preclinical studies and the RA development program, and customary regulatory concerns for novel small molecule drugs.

Up to Week 14, events were reported in the AESI categories listed in Table 19. A notably higher proportion of subjects in the upadacitinib group reported neutropenia compared with the placebo group. No events were reported in the AESI categories of opportunistic infection, lymphoma, adjudicated gastrointestinal (GI) perforation, renal dysfunction, active TB, adjudicated MACE, or adjudicated VTE in the upadacitinib group up to Week 14 (Table 19).

Table 19. Study M19-944 Study 2 (nr-axSpA): Treatment-Emergent Adverse Events of Special Interest Reported up to Week 14 (Safety Analysis Set)

	Placebo (N = 157) n (%)	Upadacitinib 15 mg QD (N = 156) n (%)	Upadacitinib - Placebo (95% CI)[a]
Subjects with any treatment-emergent			
Serious infection	1 (0.6)	2 (1.3)	0.6 (-1.5, 2.8)
Malignancy	1 (0.6)	0 (0.0)	-0.6 (-1.9, 0.6)
Non-melanoma skin cancer (NMSC)	1 (0.6)	0 (0.0)	-0.6 (-1.9, 0.6)
Hepatic disorder	5 (3.2)	4 (2.6)	-0.6 (-4.3, 3.1)
Anemia	0 (0.0)	1 (0.6)	0.6 (-0.6, 1.9)
Neutropenia	0 (0.0)	5 (3.2)	3.2 (0.4, 6.0)
Herpes zoster	1 (0.6)	2 (1.3)	0.6 (-1.5, 2.8)

CI = confidence interval; QD = once daily

a. The point estimate and 95% CI are calculated based on the normal approximation and separate group variance.

Up to Week 52, the EAERs of neutropenia (8.5 E/100 PYs), hepatic disorder (7.5 E/100 PYs), serious infection (1.9 E/100 PYs), anemia (0.9 E/100 PYs), and herpes zoster (3.8 E/100 PYs) were numerically higher in the upadacitinib group compared with the placebo group (see below).

Table 20. Treatment-Emergent Adverse Events of Special Interest Reported up to Week 52 (Safety Analysis Set)

	Placebo (N=157) (PYs=111.4) Events (E/100PYs) (95% CI) [A]	Upadacitinib 15 mg QD (N=156) (PYs=106.2) Events (E/100PYs) (95% CI) [A]
Exposure-adjusted Event Rate		
Infection	78 (70.0) (55.3,87.3)	84 (79.1) (63.1,98.0)
Serious infection	1 (0.9) (0.0,5.0)	2 (1.9) (0.2,6.8)
Opportunistic infection excluding tuberculosis and herpes zoster	0 (0.0)	0 (0.0)
Possible malignancy	1 (0.9) (0.0,5.0)	0 (0.0)
Malignancy	1 (0.9) (0.0,5.0)	0 (0.0)
Non-melanoma skin cancer (NMSC)	1 (0.9) (0.0,5.0)	0 (0.0)
Malignancy other than NMSC	0 (0.0)	0 (0.0)
Lymphoma	0 (0.0)	0 (0.0)
Hepatic disorder	7 (6.3) (2.5,12.9)	8 (7.5) (3.3,14.8)
Adjudicated gastrointestinal perforation	0 (0.0)	0 (0.0)
Anemia	0 (0.0)	1 (0.9) (0.0,5.2)
Neutropenia	1 (0.9) (0.0,5.0)	9 (8.5) (3.9,16.1)
Lymphopenia	0 (0.0)	0 (0.0)
Herpes zoster	1 (0.9) (0.0,5.0)	4 (3.8) (1.0,9.6)
Serious herpes zoster	0 (0.0)	0 (0.0)
Renal dysfunction	0 (0.0)	0 (0.0)
Active tuberculosis	0 (0.0)	0 (0.0)
Adjudicated MACE*	0 (0.0)	0 (0.0)
Adjudicated venous thromboembolic events**	1 (0.9) (0.0,5.0)	0 (0.0)

**MACE; Major adverse cardiovascular events, defined as cardiovascular death (includes acute myocardial infarction, sudden cardiac death, heart failure, cardiovascular procedure-related death, death due to cardiovascular hemorrhage, fatal stroke, pulmonary embolism and other cardiovascular causes), non-fatal myocardial infarction and non-fatal stroke.*

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

Serious infections

Up to Week 14, 2 subjects (1.3%) in the upadacitinib group and 1 subject (0.6%) in the placebo group had a treatment-emergent serious infection. Serious infections were reported in 1 subject each and

included COVID-19 pneumonia and pyelonephritis in the upadacitinib group and hemorrhagic fever with renal syndrome in the placebo group. Up to Week 52, there were no additional treatment-emergent serious infections reported.

Herpes zoster

Up to Week 14, 2 subjects (1.3%) in the upadacitinib group, and 1 subject (0.6%) in the placebo group had TEAEs of herpes zoster. According to the MAH, no TEAE of herpes zoster was serious, and no subjects discontinued study drug as a result of a herpes zoster. Up to Week 52, there were 2 additional TEAEs of herpes zoster reported in the upadacitinib group, also these reported as mild or moderate and limited to one single dermatome. There were no new herpes zoster TEAEs reported after the 52-week Double-Blind Period. Through the data cutoff, a total of 4 TEAEs of herpes zoster (3.4 E/100 PYs) were reported in 4 subjects who received ≥ 1 dose of upadacitinib.

Malignancy

Up to Week 14, 1 subject in the placebo group experienced a malignancy (basal cell carcinoma). No additional malignancies were reported up to current data cut-off.

Hepatic disorders

At Week 14, subjects in the upadacitinib group had a greater mean increase from baseline in ALT and AST (ALT: 3.4 U/L; AST: 2.3 U/L) compared with the placebo group (ALT: -0.3 U/L; AST: -0.7 U/L). Up to Week 14, the proportion of subjects with hepatic disorders was similar in the upadacitinib and placebo groups. By Week 52, the EAER of hepatic disorder was higher in the upadacitinib group compared with the placebo group. No events led to discontinuation of study drug. No events were serious, and all events were mild to moderate in severity.

Lymphopenia

At Week 14, subjects in the upadacitinib group had numerically greater mean increases from Baseline in lymphocyte count compared with the placebo group (0.132×10^9/L versus 0.026×10^9/L). Three Grade 3 lymphocyte count decreases were reported, 1 in the placebo group and 2 in the upadacitinib group. Up to Week 52, no TEAEs of lymphopenia were reported.

Anaemia

At Week 14, mean changes from Baseline in hemoglobin were -0.7 g/L for the upadacitinib group and -0.1 g/L for the placebo group. Up to Week 14, anaemia was reported in 1 subject in the upadacitinib group only. The event was assessed as having a reasonable possibility of being related to study drug, was considered a mild TEAE, resolved without study drug interruption and did not lead to discontinuation of study drug. No additional events of anaemia were reported up to current data cut-off.

Neutropenia

At Week 14, subjects in the upadacitinib group had a numerically greater mean decrease from Baseline in neutrophil count versus the placebo group (-0.670×10^9/L vs. -0.156×10^9/L. Up to Week 14, 5 subjects in the upadacitinib group had TEAEs of neutropenia (none in the placebo group). Of these TEAEs, 2 were mild, 2 were moderate, and 1 was severe. Study drug was not interrupted except for the severe case that occurred on Day 1. Up to Week 52, 4 additional events (9 events cumulatively) of neutropenia were reported in subjects treated with upadacitinib. Most events were mild or moderate, and no subject discontinued study drug as a result of TEAEs of neutropenia. Two of the neutropenia TEAEs in the upadacitinib group were considered severe, and none were considered serious. There

were no new neutropenia events reported since Week 52. Overall, the cumulative EAER of neutropenia events was 7.7 E/100 PYs.

Thrombotic events

In Study M19-944 Study 2, by Week 14, no adjudicated VTEs were reported in subjects in either treatment group. Up to Week 52, 1 subject in the placebo group had 1 non-fatal event of DVT. Up to current cut-off date, there have been no cases of VTE in the upadacitinib group.

Laboratory findings

Regarding liver enzymes and haematology, please refer to adverse events of special interest above.

Lipids

In Study M19-944 Study 2 (nr-axSpA), up to Week 14, upadacitinib therapy was associated with an increase of lipids compared to the placebo group. At Week 14, the mean changes from Baseline for the upadacitinib versus placebo groups were: high-density lipoprotein cholesterol (HDL-C): 0.191 mmol/L versus -0.017 mmol/L; low-density lipoprotein cholesterol (LDL-C): 0.253 mmol/L versus 0.025 mmol/L; total cholesterol (TC): 0.457 mmol/L versus -0.034 mmol/L. In the upadacitinib group, LDL increases were observed up to Week 4 and generally stabilized at Week 8 through Week 14.

However, the ratios of the TC:HDL-C and the LDL-C:HDL-C, used to assess the overall atherogenic potential, generally remained unchanged in both groups.

Creatinine

At Week 14, subjects in the upadacitinib group had a small mean increase from Baseline in serum creatinine compared to a small mean decrease observed in the placebo group (upadacitinib 3.5 µmol/L versus placebo -0.2 µmol/L). No ≥ Grade 3 creatinine increases were reported in any subject (Study M19-944 Study 2) in the long-term data.

Creatine phosphokinase (CPK)

Through the data cutoff, there were no AEs of creatine phosphokinase (CPK) elevation reported.

Vital signs, physical findings and other observations related to safety

Up to Week 14, two subjects (1.3%) in the upadacitinib group and three subjects (1.9%) in the placebo group reported hypertension. Up to Week 52, five subjects each in the upadacitinib group (4.7 E/100 PYs) and placebo group (4.5 E/100 PYs) reported hypertension.

In the Double-Blind Period, up to Week 14, a decrease in body weight (> 7% from Baseline) was recorded in 3.2% of subjects in the upadacitinib group and 1.3% of subjects in the placebo group. An increase in body weight (>7% from Baseline) was recorded in 2.6% of subjects in the upadacitinib group and 1.3% of subjects in the placebo group. Weight gain is a known adverse event for upadacitinib.

Safety in special populations

According to the MAH, though based on limited data, the subgroup analyses in Study M19-944 did not reveal a clinically relevant increased risk of AEs on upadacitinib treatment based on age, sex, BMI, or race. An overview of treatment-emergent adverse events per 100 PYs by age is shown below.

Table 21. Overview of treatment-emergent adverse events per 100 PYs by age – long term safety analysis set

	----- <65 ---- Any Upadacitinib 15 mg QD (N=184) (PYs=114.3) Events (E/100PYs)	----- >=65 ----- Any Upadacitinib 15 mg QD (N=3) (PYs=2.3) Events (E/100PYs)
Exposure-adjusted Event Rate		
Adverse event (AE)	287 (251.0)	1 (43.6)
AE with reasonable possibility of being related to study treatment$	82 (71.7)	1 (43.6)
Severe AE	12 (10.5)	0
Serious AE	6 (5.2)	0
AE leading to withdrawal of study treatment	8 (7.0)	1 (43.6)
AE leading to death	0	0
COVID-19 related AE	18 (15.7)	0

Note: Treatment-emergent Adverse Event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study treatment, and no more than 30 days of the treatment after the last dose of study treatment in the study. Any event with an unknown severity will be considered as severe and any AE with an unknown relationship will be considered as drug related.
$ As assessed by investigator.

Due to the relatively small sample size (29.1%) of subjects on concomitant csDMARD therapy, the MAH states that no conclusions can be made regarding increased risk of AEs when upadacitinib is used in combination with csDMARD therapy. Of note, csDMARD therapy is not recommended for the treatment of axial symptoms in international treatment guidelines for AS.

Pregnancy and lactation

There were no pregnancies reported in the study.

Cumulatively, there were a total of 97 pregnancies reported in female subjects in both unblinded and blinded upadacitinib clinical studies with the majority reported in RA studies. Of the 68 pregnancies from unblinded studies in female patients administered upadacitinib, 22 were live births without congenital anomalies (all with exposure to upadacitinib occurred during the first 8 weeks of pregnancy). According to the MAH, the 15 female subjects with pregnancies resulting in spontaneous abortions had various risk factors that may have contributed to the outcome (e.g., age > 35 years of age, concomitant MTX use, previous miscarriage). Additionally, there was 1 ectopic pregnancy, 13 ongoing pregnancies, and 4 lost to follow-up.

No congenital anomaly or fetal defect was observed in pregnancies with a known outcome.

Safety related to drug-drug interactions and other interactions

The potential for drug-drug interactions between upadacitinib and commonly used concomitant medications as well as probe substrates for CYP450 enzymes was characterized in several Phase 1 studies. Based on the results of these studies, strong inducers of CYP3A (e.g., rifampin) reduce upadacitinib plasma exposures by approximately half. Strong CYP3A inhibitors (e.g., ketoconazole) increase upadacitinib AUC by 75% and maximum observed concentration (C_{max}) by 70%. Concomitant administration of strong CYP2D6 inhibitors, OATP1B inhibitors, MTX, pH modifying medications, or statins has no effect on upadacitinib plasma exposures. Upadacitinib has no clinically relevant effects on plasma exposures of MTX, ethinylestradiol, levonorgestrel, statins, or drugs that are substrates for metabolism by CYP1A2, CYP2B6, CYP2D6, CYP2C19, CYP2C9, or CYP3A.

Discontinuation due to adverse events

Up to Week 14, 4 subjects (2.6%) in the upadacitinib group and 2 subjects (1.3%) in the placebo group had TEAE(s) leading to discontinuation of study drug (*Table 16*). In the upadacitinib group, 1

subject withdrew due to nausea and abdominal pain; 2 subjects withdrew due to axial spondyloarthritis; and 1 subject withdrew due to rash, headache, and tremor. According to the MAH, all events were assessed as having no reasonable possibility of being related to study drug by investigators except one event of axial spondyloarthritis and the events of rash and headache. In the placebo group, one subject withdrew due to vomiting, and the other subject withdrew due to axial spondyloarthritis (reported term: flare of axial spondyloarthritis). No laboratory AEs leading to discontinuation of study drug were reported.

Up to Week 52, 2 additional TEAEs leading to discontinuation of study drug were reported each in the upadacitinib group (nasal polyps and malaise) and in the placebo group (axial spondyloarthritis and deep vein thrombosis). Up to Week 52, the EAER of TEAEs leading to discontinuation of study drug was 8.5 E/100 PYs in the upadacitinib group and 3.6 E/100 PYs in the placebo group.

Supportive long-term safety data from study M16-098

In addition to the previously presented data from study M19-944 study 2 (nr-axSpA), accumulated 2-year safety from the AS bDMARD-naïve Study M16-098 were also submitted as supportive information regarding the potential long-term safety of upadacitinib in patients with active nr-axSpA.

As stated by the MAH, non-radiographic axSpA and AS are part of the same spectrum of axial SpA and share common epidemiological, genetic, and clinical disease characteristics, including similar disease burden, and common treatment guidelines. Thus, the 2-year long-term safety data from Study M16-098 in bDMARD-naïve AS patients are proposed to support the long-term benefit of upadacitinib patients with active nr-axSpA. The 2-year long-term data from Study M16-098 in bDMARD-naïve AS patients are being assessed in the on-going variation II/15G. Please refer to this variation for the complete assessment of the data.

In Study M16-098, the original marketing application for upadacitinib for the treatment of AS included safety data from 182 subjects with active AS who received ≥ 1 dose of upadacitinib 15 mg QD, representing an exposure of 237.6 patient-years. According to the MAH, no new safety risks were identified compared to previous upadacitinib data. In the placebo-controlled period, the number of subjects with serious adverse events and AEs leading to discontinuation were comparable between placebo and upadacitinib groups, and there were no deaths up to the data cutoff date (31 January 2020). There was no evidence of a higher rate of adverse events of special interest compared to those previously reported in the RA population. Laboratory changes observed were transient and generally not clinically significant.

Since the original marketing application based on 1-year data, additional data from Study M16-098 are available as of the data cutoff of 26 November 2020. As of this cutoff, 182 subjects had received at least 1 dose of upadacitinib with a cumulative exposure of 308.6 PYs. Evaluation of the updated data compared to that reported in the initial AS submission indicates similar or numerically lower exposure-adjusted rates of overall AEs and AESI (Table 22 and *Table 23*).

Table 22. Study M16-098: Overview of Treatment-Emergent Adverse Events and All Deaths per 100 PYs – Long-Term Data (Safety Analysis Set)

	Study M16-098 Up to 31 January 2020 Any Upadacitinib 15 mg QD (N = 182) (PYs = 237.6) Events (E/100 PYs)	**Study M16-098 Up to 26 November 2020 Any Upadacitinib 15 mg QD (N = 182) (PYs = 308.6) Events (E/100 PYs)**
Exposure-adjusted event rate:		
AE	618 (260.1)	749 (242.7)
AE with reasonable possibility of being related to study drug[a]	186 (78.3)	219 (71.0)
Severe AE	7 (2.9)	12 (3.9)
SAE	14 (5.9)	19 (6.2)
AE leading to discontinuation of study drug	15 (6.3)	17 (5.5)
Any AE leading to death	0	0
Deaths	0	0

AE = adverse event; E = events; PYs = patient-years; QD = once daily; SAE = serious adverse event

a. As assessed by investigator.

Table 23. Study M16-098: Overview of Adverse Events of Special Interest per 100 PYs – Long-Term (Safety Analysis Set)

	Study M16-098 Up to 31 January 2020 Any Upadacitinib 15 mg QD (N = 182) (PYs = 237.6) Events (E/100 PYs)	Study M16-098 Up to 26 November 2020 Any Upadacitinib 15 mg QD (N = 182) (PYs = 308.6) Events (E/100 PYs)
Exposure-adjusted event rate		
Serious infection	0	0
Opportunistic infection excluding tuberculosis and herpes zoster	2 (0.8)	2 (0.6)
Malignancy	1 (0.4)	1 (0.3)
NMSC	0	0
Malignancy other than NMSC	1 (0.4)	1 (0.3)
Lymphoma	0	0
Hepatic disorder	24 (10.1)	32 (10.4)
Anemia	3 (1.3)	5 (1.6)
Neutropenia	7 (2.9)	9 (2.9)
Lymphopenia	2 (0.8)	3 (1.0)
Herpes zoster	5 (2.1)	5 (1.6)
CPK elevation	28 (11.8)	35 (11.3)
Renal dysfunction	0	0
Active tuberculosis	0	0
Adjudicated GI perforation	0	0
Adjudicated MACE	0	0
Adjudicated VTE	0	1 (0.3)

CPK = creatine phosphokinase; E = events; GI = gastrointestinal; MACE = major adverse cardiovascular events; NMSC = nonmelanoma skin cancer; PYs = patient years; QD = once daily; VTE = venous thromboembolic event

No deaths were reported up to the data cutoff for the 2-year report. Overall, SOCs with the highest exposure-adjusted event rates were infections and infestations, gastrointestinal disorders, investigations, and musculoskeletal and connective tissue disorders. At the cutoff date, AEs with ≥ 3 E/100 PYs that were assessed as having a reasonable possibility of being related to study drug were blood CPK increased, nasopharyngitis, and upper respiratory tract infection. Nineteen SAEs (6.2 E/100 PYs) were reported up to the data cutoff in subjects who received ≥ 1 dose of upadacitinib, one of which (CPK increased) was assessed as having a reasonable possibility of being related to study drug. Seventeen events (5.5 E/100 PYs) that led to study drug discontinuation were reported in the long-term data.

No AEs of serious infection, NMSC, lymphoma, adjudicated gastrointestinal perforation, renal dysfunction, active TB, or adjudicated MACE were reported in subjects who received upadacitinib.

AESI that were reported in ≥ 1 subject who received ≥ 1 dose of upadacitinib are summarized below:

- Opportunistic infection was reported in 1 subject who had 2 events (0.6 E/100 PYs) of esophageal candidiasis.

- Five AEs of herpes zoster (1.6 E/100 PYs) were reported in 4 subjects. One subject discontinued study drug as a result. All events were nonserious, mild or moderate in severity, and confined to a single dermatome.
- One malignancy was reported (0.3 E/100 PYs). The AE of squamous cell carcinoma of the tongue was confirmed by biopsy and reported as a stage IVa malignancy (staging T4a N2c MO). It was assessed by the investigator as having no reasonable possibility of being related to study drug. The 60-year-old subject was a former smoker and had less than 5 months of exposure to study drug prior to diagnosis.
- One case of adjudicated VTE was reported. The event was adjudicated as a pulmonary embolism, led to discontinuation of study drug, and was assessed by the investigator as having no reasonable possibility of being related to study drug but to risk factors for thrombosis including prior thrombosis of the lower leg, impaired glucose tolerance, cigarette smoking, sedentary lifestyle, and obesity.
- The rate of hepatic disorders was 10.4 E/100 PYs. None of the hepatic disorders were serious, the majority were mild to moderate, transient asymptomatic transaminase elevations.
- All AEs of neutropenia, anemia, and lymphopenia were nonserious AEs, and none led to discontinuation of study drug.
- The rate of CPK elevation was 11.3 E/100 PYs in subjects receiving upadacitinib. None of the AEs of blood CPK elevation led to study drug discontinuation, and the majority were asymptomatic.

Post marketing experience

Upadacitinib was first approved for the treatment of RA on 16 August 2019 in USA. Through 31 August 2021, the estimated cumulative postmarketing exposure is 102,193 patient treatment years.

The MAH has made a review of postmarketing reports (spontaneous, solicited, literature) received from 16 August 2019 through 15 September 2021. Search of the MAH's global safety database retrieved 51,757 reports. Overall, 89% of the reports were considered nonserious. The most frequently reported MedDRA SOC was General disorders and administration site conditions, in which pain, drug ineffective, and fatigue had the greatest number of reports with this SOC. Among all the reports, the most common AEs reported included rheumatoid arthritis (11%), pain (10%), arthralgia (10%). Indications with the most reported AEs were RA (87%) and Unknown (10%). The remaining indications reported less than 1% of AEs.

The most commonly reported SAE was surgery, which accounted for 3% of all SAEs and 0.5% of all reports. The remaining SAEs were reported in less than 0.5% of all retrieved reports. Generally, the type and pattern of SAEs reported were similar to what has been observed in the clinical trials for upadacitinib.

Most of the postmarketing events were either expected for upadacitinib or commonly seen in the general population or patient populations indicated for upadacitinib. Review of the postmarketing reports did not identify any new safety risks for the marketed upadacitinib in treating patients with active nr-axSpA.

2.5.1. Discussion on clinical safety

Exposure

The exposure for Rinvoq in the nr-axSpA population is limited, since the current submission includes only interim efficacy data up to week 14 (plus additional individual data up to current data cut-off). Only 114/187 patients have been exposed for more than 6 months, and 35 patients for more than 12 months. The final CSR is expected in 2026. Because of this limited exposure, supportive 2-year safety data from Study M16-098 in the ankylosing spondylitis (AS) biologic disease-modifying antirheumatic drug (bDMARD)-naïve population have also been presented within this submission.

This approach was supported in previous scientific advice (EMA/CHMP/SAWP/340675/2019, EMEA/H/SA/3190/8/2019/II): "*The MAH proposes an interim database lock of the 14-week data, to support submission of the nr-axSpA indication following an AS indication. This may be acceptable on the understanding that one year data and two year data are submitted post-approval, and given that there are no limiting uncertainties regarding maintenance of efficacy and of safety for AS and nr-AxSpA*".

Given many well-known similarities between AS and nr-axSpA, this approach is overall considered acceptable. This assessment will include a comparison of the safety data from study M19-944 and the safety data from study M16-098 in patients with active ankylosing spondylitis in order to identify potential new short-term safety concerns in the nr-axSpA population not previously identified in the AS population, which could question such an extrapolation approach.

It needs to be highlighted that there are actually some differences in baseline disease characteristics between these two study populations. The most important differences are that patients in the AS population are generally older and have a longer disease duration than patients in the nr-axSpA population which is expected since nr-axSpA is an earlier stage of AS disease. Further, more patients in the nr-axSpA population were treated with concomitant csDMARDs, distributed as follows: sulfasalazine 17.3%, methotrexate 8.3%, and leflunomide 2.6%. This might impact the safety; however given that no safety concerns are observed in the current study extrapolation from the AS population might still be possible.

Adverse events

During the placebo-controlled 14-week period, the AEs occurred in 75/156 patients (48.1%) in the upadacitinib group and in 72/157 patients (45.9%) in the placebo group. This is lower than what was observed during the placebo-controlled 14-week period in the AS population (UPA: 62.4%, PBO: 55.3%, source: EPAR for variation II/005).

Also serious adverse events were slightly more frequent in the upadacitinib arm (2.6%) than in the placebo arm (1.3%), but the number of events was few. This is in contrast to above slightly higher than what was observed for Rinvoq in the AS study (SAE for UPA: 1.1%); however, of the observed SAEs in the current study only 2/4 events are suspected to be related to Rinvoq (COVID-19 pneumonia, pyelonephritis, foot fracture, and osteoarthritis). There were no deaths in either of the groups.

Throughout the total 52-week period, the pattern was similar with a higher frequency of AEs and SAEs in the upadacitinib than in the placebo group. The EAIR for AEs and SAEs in long-term data is similar (but numerically slightly slower) in the nr-axSpA population compared to the AS population.

The most common adverse events were infections. Higher frequencies were observed for the upadacitinib group compared with the placebo group for headache, nausea, abdominal pain, diarrhoea, and neutropenia. All of these except for diarrhoea is included in section 4.8 of the SmPC; however, the difference in occurrence in diarrhoea is based on only one case and is not considered to be relevant.

The pattern is very similar to the safety profile observed in the AS population, apart from increase in liver enzymes for which there was no difference in frequency of hepatic disorder between the

upadacitinib and placebo arms in the current study. As discussed later in this AR there was a greater mean increase from baseline in liver enzymes for the upadacitinib compared to the placebo group indicating that there are probably no large differences between the populations.

Also up to 52 weeks, headache was the most frequent AE in the upadacitinib group, followed by COVID-19 and neutropenia.

Adverse events of special interest

The most notable difference in occurrence in adverse events of special interest is a higher incidence of neutropenia in the upadacitinib group (8.5E/100PYs) than in the placebo group (0.9E/100PYs). Neutropenia is a known adverse event for Rinvoq, and there are recommendations for monitoring and dose interruption in the SmPC. Also hepatic disorder, serious infection, anaemia, and herpes zoster were numerically higher in the upadacitinib group compared with the placebo group. These are all known risks and no new safety signals were observed.

The EAIR for herpes zoster was slightly higher in the nr-axSpA population (4 events, 3.4E/100 PYs) than in the AS population (5 events, 2.1E/100PYs). Although a higher frequency of concomitant csDMARDs might make these patients more susceptible to herpes, this is likely to be a random finding because of the few actual events. Both studies excluded subjects with recurrent or disseminated herpes zoster infection.

There were no malignancies, gastrointestinal perforations, MACE or thrombotic events in the upadacitinib arm.

In the long-term nr-axSpA data, 8 cumulative events of hepatic disorder (6.9 E/100 PYs) were reported in 5 upadacitinib-treated subjects. This is lower than what was observed in the AS population (10.1 E/100 PYs), despite a higher use of concomitant csDMARDs in the nr-axSpA population which is reassuring.

No relevant differences in anaemia were observed between the nr-axSpA and AS populations.

Overall, there were no new safety concerns observed with regards to adverse events of special interest in this limited nr-axSpA data.

Laboratory findings

Up to Week 14, upadacitinib therapy was associated with an increase of lipids compared to the placebo group. However, the ratios of the TC:HDL-C and the LDL-C:HDL-C generally remained unchanged in both groups. Monitoring recommendations are included in the SmPC, which is appropriate.

At Week 14, subjects in the upadacitinib group had a small mean increase from baseline in serum creatinine compared to a small mean decrease observed in the placebo group, but no $\geq$ Grade 3 creatinine increases were reported in the long-term data and overall, no renal safety concerns were identified.

Through the data cutoff, there were no AEs of creatine phosphokinase (CPK) elevation reported.

Safety in special populations

According to the MAH, though based on limited data, the subgroup analyses in Study M19-944 did not reveal a clinically relevant increased risk of AEs on upadacitinib treatment based on age, sex, BMI, or race.

Due to the relatively small sample size (29.1%) of subjects on concomitant csDMARD therapy, the MAH states that no firm conclusions can be made regarding increased risk of AEs when upadacitinib is used in combination with csDMARD therapy. In the current study, 27/156 patients (17.3%) of

upadacitinib-treated patients received concomitant sulfasalazine. The most prominent finding is that the frequency of hepatic disorders was higher among patients with concomitant sulfasalazine than among patients without any concomitant csDMARD. The MAH argues that this is expected since hepatic disorders are known AEs for both agents, and that this is sufficiently covered in the respective products' SmPCs. This is partly agreed on. Although similar information is included in the Rinvoq SmPC in the description of the safety profile in patients with RA and PsA with/without concomitant methotrexate, the potential difference in the current case is based on very few patients which is a clear limitation. Therefore, the CHMP agreed that no SmPC updates are warranted.

Rinvoq is contraindicated during pregnancy and is not recommended during lactation. There were no pregnancies reported in the current study.

Supportive long-term data from patients with ankylosing spondylitis

The MAH has presented updated data from the AS bDMARD-naïve Study M16-098 to support the long-term safety of upadacitinib in patients with active nr-axSpA. In the 2-year data from study M16-098, there were no deaths and no AEs of serious infection, NMSC, lymphoma, adjudicated gastrointestinal perforation, renal dysfunction, active TB, or adjudicated MACE reported in subjects who received upadacitinib. It is agreed with the MAH that there are no safety signals in the presented data. The 2 years full clinical study report from Study M16-098 is currently being assessed in the parallel variation EMEA/H/C/004760/II/0015/G. Please refer to this variation for the complete assessment of those data.

2.5.2. Conclusions on clinical safety

No new safety signals have been identified in the presented data, and the safety profile of Rinvoq in the nr-axSpA population seems consistent with data from previous indications and the safety profile as described in the SmPC.

The main limitation pertains to the limited long-term data, since this application is based on interim data up to 14 weeks (plus additional individual data up to current data cut-off). Only 114/187 patients have been exposed for more than 6 months, and 35 patients for more than 12 months. However, given many similarities between the nr-ax-SpA population the previously approved AS population, the CHMP agreed that long-term data from the AS population are considered supportive. The 2 years full clinical study report from Study M16-098 is currently being assessed in the parallel variation EMEA/H/C/004760/II/0015/G. Please refer to this variation for the complete assessment of those data.

The CHMP concluded that the safety data was supportive of the extension of indication.

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 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 8.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 8.0 with the following content:

Safety concerns

Table 24. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Serious and opportunistic infections including TB • Herpes zoster
Important potential risks	• Malignancies • MACE • VTEs (deep venous thrombosis and pulmonary embolus) • GI perforation • DILI • Foetal malformation following exposure in utero
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

AD = atopic dermatitis; GI = gastrointestinal; DILI = drug-induced liver injury; MACE = major adverse cardiova1scular event; TB = tuberculosis; VTE = venous thromboembolic event

Pharmacovigilance plan

Table 25. Ongoing and Planned Additional Pharmacovigilance Activities

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable	--	--	--	--
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable	--	--	--	--
Category 3 – Required additional pharmacovigilance activities				
Study P19-150 Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe/ Ongoing	To evaluate the safety of upadacitinib among patients with RA receiving routine clinical care.	Important identified risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; and DILI 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	• Draft protocol • Progress report • Interim report • Targeted submission of interim study report to EMA • Final study report • Targeted submission of final study report to EMA	• Submitted 16 March 2020 • Annually starting in 2022 • Approximately 5 years following market availability (31 March 2025) • 30 June 2025 • Approximately 10 years following market availability (31 March 2030) • 30 June 2030

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	To compare the incidence of malignancy (excluding NMSC), NMSC, MACE, VTE, and serious infection events 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 To describe the incidence rates of herpes zoster, opportunistic infections such as TB, GI perforations, and evidence of DILI. To describe the incidence of the above outcomes in very elderly patients (aged ≥ 75 years). To characterize VTE clinical risk factors and baseline biomarkers in a sub-study of new initiators of upadacitinib and comparator biologic therapies.	Important identified risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; and DILI Missing information: use in very elderly (≥ 75 years of age); long-term safety	• Draft protocol • Progress report • Update on prevalence of baseline biomarkers and clinical risk factors within PSUR • Interim report • Targeted submission of interim study report to EMA • Final study report • Targeted submission of final study report to EMA	• Submitted 16 March 2020 • Annually starting in 2022 • Annually for the first 2 years and thereafter in accordance with the PSUR reporting schedule • Approximately 3 years post-approval (31 March 2023) • 30 June 2023 • Approximately 10 years post-approval (31 March 2030) • 30 June 2030

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P20-199 Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation/ Ongoing	To describe the baseline characteristics of new users of upadacitinib (e.g., demographics, medical history, medical condition associated with upadacitinib use, and concomitant medication use), and in a similar manner, to describe new users of a bDMARD for comparison. To evaluate the effectiveness of the aRMMs, including: • Quantify the occurrence of upadacitinib use among patients who are at high risk for VTEs and among patients who are currently being treated for active TB; • Quantify the number of patients who are pregnant at the time of initiation or become pregnant while taking upadacitinib; and 1. Describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring.	Important identified risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: MACE; VTEs; and foetal malformation following exposure in utero	• Draft protocol • Progress report • Final study report • Targeted submission of final study report to EMA	• Submitted 16 March 2020) • Annually starting in 2022 • 30 September 2024 • 31 December 2024 (estimated)

Study P20-390 Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of AD in Denmark and Sweden/ Planned	To compare the incidence of the following outcomes, in adolescent and adult patients treated with upadacitinib relative to those treated with other alternative systemic drug therapies for AD, in the course of routine clinical care: Malignancy (excluding NMSC), NMSC, MACE, VTE, serious infections, herpes zoster, opportunistic infections, eczema herpeticum/Kaposi's varicelliform eruption, active TB, GI perforations, and evidence of DILI. To describe the incidence of the above adverse events in patients who receive upadacitinib 15 mg and 30 mg. To describe the incidence of the above adverse events by age subgroups (adolescents [12 - 17 years], adults aged 18 - 64 years, and elderly patients aged ≥ 65 years). To describe the incidence rates of the above safety outcomes in the following subgroups of interest, with limited or missing information from the clinical development program: Patients with moderate hepatic impairment at the time of initiation of upadacitinib or other systemic drug therapies. Patients with evidence of chronic infection with HBV or HCV at the time of initiation of upadacitinib or other systemic drug therapies. Patients with severe renal impairment at the time of initiation of upadacitinib or	Important identified risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTE; GI perforation; DILI Missing information: use in very elderly (≥ 75 years of age); long-term safety; use in patients with moderate hepatic impairment at the time of initiation of upadacitinib or other systemic drug therapies; use in patients with evidence of chronic infection with HBV or HCV at the time of initiation of upadacitinib or other systemic drug therapies; use in patients with severe renal impairment at the time of initiation of upadacitinib or other systemic drug therapies; long-term safety in adolescents with AD	• Final Study Report	• Estimated Q4 2033

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	other systemic drug therapies.			
Study P21-825 Effectiveness Evaluation of aRMMs for Upadacitinib in the Treatment of AD/ Planned	To evaluate the effectiveness of the aRMMs for upadacitinib in AD. The specific aims are to: • Quantify the occurrence of upadacitinib use among patients who are at high risk for VTEs and among patients who are currently being treated for active TB; • Quantify the number of patients who are pregnant at the time of initiation or become pregnant while taking upadacitinib; • Describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring.	Important identified risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: MACE; VTEs; and foetal malformation following exposure in utero	• Final Study Report	• Estimated Q2 2026

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/ Planned	To evaluate the growth, development, and maturation in adolescents with moderate to severe AD who receive upadacitinib versus systemic comparators in routine clinical care. The specific objectives are to: • Describe changes in body weight, standing height, height SDS, height velocity, and height velocity SDS in adolescents who received upadacitinib for the treatment of AD from initiation of upadacitinib through adulthood, relative to similar adolescents on other systemic treatments • Describe age at peak height velocity (a somatic maturation milestone) in adolescents who receive upadacitinib for the treatment of AD from initiation of upadacitinib through adulthood (18 years), relative to similar adolescents on other systemic treatments	Missing information: long-term safety in adolescents with AD	• Final study report	• Estimated Q4 2030
Long-Term Extension Portion of Study M13-542/ 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 Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI, and foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 02 January 2023 • 02 April 2023

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M13-549/ 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 risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI, and foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 17 January 2023 • 17 April 2023
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 risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI, and foetal 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
Long-Term Extension Portion of Study M15-555/ 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 risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI, and foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 17 June 2023 • 17 September 2023

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M13-545/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 7.5 mg QD (for subjects in Japan only), and 15 mg QD in subjects with RA who have completed Period 1	Important identified risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI, and foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 22 September 2023 • 22 December 2023
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 risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI, and foetal 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 risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI, and foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 30 September 2025 • 31 December 2025

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M16-098/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with AS who have completed Period 1.	Important identified risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI, and foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 07 November 2022 • 07 February 2023
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 DB Period.	Important identified risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI, and foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• Q2 2026 • Q3 2026
Long-Term Extension Portion of Study 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 DB Period.	Important identified risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI, and foetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents with AD	• Final study report	• 26 February 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 topical corticosteroids in adolescent and adult subjects with AD who have completed the DB Period.	Important identified risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI, and foetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents with AD	• Final study report	• 04 April 2026
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 DB Period.	Important identified risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI, and foetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents with AD	• Final study report	• 21 April 2026

AD = atopic dermatitis; aRMMs = additional risk minimization measures; AS = ankylosing spondylitis; bDMARD = biologic disease-modifying anti-rheumatic drug; DB = double-blind; DILI = drug-induced liver injury; EMA = European Medicines Agency; GI = gastrointestinal; HBV = hepatitis B virus; HCV = hepatitis C virus; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; nr-axSpA = non-radiographic axial spondyloarthritis; PsA = psoriatic arthritis; PSUR = periodic safety update report; QD = once daily; RA = rheumatoid arthritis; SDS = standard deviation score; TB = tuberculosis; US = United States; VTE = venous thromboembolic event

Risk minimisation measures

Table 26. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious and opportunistic infections including TB	Routine risk minimization measures: • SmPC Section 4.4 summarizes the risk and provides guidance on ways to reduce the risk.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• The PL warns that patients who have an infection or who have a recurring infection should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL advises that patients do not take Rinvoq if they have active TB and warns that patients with a history of TB, or who have been in close contact with someone with TB should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.2 outlines lymphocyte and neutrophil counts and when not to initiate upadacitinib dosing. • SmPC Section 4.2 outlines interruption guidelines based on ALC and ANC. • SmPC Section 4.3 indicates that upadacitinib is contraindicated in patients with active TB or active serious infections. • SmPC Section 4.4 states that patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib and that upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection. • SmPC Section 4.4 advises to consider the risks and benefits of initiating upadacitinib in patients with active, chronic, or recurrent infections. o A patient who develops a new infection during treatment with upadacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and upadacitinib should be interrupted if the patient is not responding to therapy. o Screening for TB prior to initiation is advised, and upadacitinib should not be given	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 • P20-390: Prospective Cohort Study of Long-term safety of Upadacitinib in the treatment of AD in Denmark and Sweden • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in the Treatment of AD • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • 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)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	if active TB is diagnosed. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with untreated latent TB or in patients with risk factors for TB infection. Additional risk minimization measures: • HCP educational brochure • PAC Other routine risk minimization measures: Prescription only medicine.	
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 if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. Additional risk minimization measures: • HCP educational brochure • PAC Other routine risk minimization measures: Prescription only medicine.	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 • P20-390: Prospective Cohort Study of Long-term safety of Upadacitinib in the treatment of AD in Denmark and Sweden • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in the Treatment of AD • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		• Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)
Malignancies	Routine risk minimization measures: • SmPC Section 4.4 describes the risk in patients with RA and indicates that upadacitinib clinical data are currently limited and long-term studies are ongoing. • The PL warns that patients who have cancer, develop a new lesion or any change in the appearance of an area on the skin, or are at high risk of developing skin cancer should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 advises that periodic skin examination is recommended for patients who are at increased risk for skin cancer. Additional risk minimization measures: None Other routine risk minimization measures: 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: Prospective Cohort Study of Long-term safety of Upadacitinib in the treatment of AD in Denmark and Sweden • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • 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)
MACE	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on lipids and describes that impact on CV morbidity and mortality has not been determined. • SmPC Section 4.4 contains a section on CV risk including a statement on increased CV risk in RA patients and need for management of CV risk factors as part of usual standard care.	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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. • The PL warns that patients who have heart problems, high blood pressure, or high cholesterol should consult their doctor or pharmacist before and during treatment with Rinvoq. Additional risk minimization measures: • HCP educational brochure • PAC Other routine risk minimization measures: Prescription only medicine.	• P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • P20-390: Prospective Cohort Study of Long-term safety of Upadacitinib in the treatment of AD in Denmark and Sweden • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in the Treatment of AD • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • 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)
VTEs (deep venous thrombosis and pulmonary embolus)	Routine risk minimization measures: • SmPC Section 4.4 indicates that events of deep vein thrombosis and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib. • The PL warns that patients who have had blood clots in the veins of the legs (deep vein thrombosis) or lungs (pulmonary embolism) should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get a painful swollen leg, chest pain, or shortness of breath. • SmPC Section 4.4 advises that upadacitinib should be used with caution in patients at high risk for deep vein thrombosis/pulmonary embolism. Risk factors that should be considered in determining the patient's risk for deep venous thrombosis/pulmonary embolism include older age, obesity, a medical history of deep venous	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 • P20-390: Prospective Cohort Study of Long-term safety of Upadacitinib in the treatment of AD in Denmark and Sweden

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	thrombosis/pulmonary embolism, patients undergoing major surgery, and prolonged immobilisation. • SmPC Section 4.4 advises that if clinical features of deep vein thrombosis/pulmonary embolism occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment. Additional risk minimization measures: • HCP educational brochure • PAC Other routine risk minimization measures: Prescription only medicine.	• P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in the Treatment of AD • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • 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)
GI perforation	Routine risk minimization measures: None Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (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: Prospective Cohort Study of Long-term safety of Upadacitinib in the treatment of AD in Denmark and Sweden • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • 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)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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 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: Prospective Cohort Study of Long-term safety of Upadacitinib in the treatment of AD in Denmark and Sweden • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • 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)
Foetal malformation following exposure in utero	Routine risk minimization measures: • SmPC Section 4.6 describes the teratogenic effects observed in animals receiving upadacitinib and states that there are no or limited data from use of upadacitinib in pregnant women. • The PL advises that patients do not take Rinvoq if they are pregnant, that Rinvoq must not be used during pregnancy, and that patients who become pregnant while taking Rinvoq must consult their doctor straight away. • SmPC Section 4.3 and Section 4.6 indicate that upadacitinib is contraindicated during pregnancy. • SmPC Section 4.6 and PL advise on use of effective contraception.	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 • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in the Treatment of AD • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• SmPC Section 4.6 advises that female paediatric patients and/or their caregivers should be informed about the need to contact the treating physician once the patient experiences menarche. • The PL informs caregivers to let their doctor know if their child has their first menstrual period while using Rinvoq. Additional risk minimization measures: • HCP educational brochure • PAC Other routine risk minimization measures: Prescription only medicine.	• Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • 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)
Use in very elderly (≥ 75 years of age)	Routine risk minimization measures: • SmPC Section 4.2 states that there are limited data in patients aged 75 years and older. • SmPC Section 4.4 states that as there is a higher incidence of infections in the elderly ≥ 65 years of age, caution should be used when treating this population. 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: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of AD in Denmark and Sweden
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 • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of AD in Denmark and Sweden

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with moderate hepatic impairment	Routine risk minimization measures: • SmPC Section 4.2 describes use in patients with hepatic impairment. • SmPC Section 4.2 states that upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment. • SmPC Section 4.3 indicates that upadacitinib is contraindicated for use in patients with severe hepatic impairment. • The PL advises that patients do not take Rinvoq if they have severe liver problems and warns that patients should consult their doctor or pharmacist before and during treatment with Rinvoq if their liver does not work as well as it should. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of AD in Denmark and Sweden
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 15 mg once daily should be used with caution in patients with severe renal impairment. • SmPC Section 4.2 states that upadacitinib 30 mg once daily is not recommended for patients with severe renal impairment. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of AD in Denmark and Sweden
Long-term safety	Routine risk minimization measures: SmPC Section 4.4 indicates that upadacitinib clinical data on malignancies are currently limited and long-term studies are ongoing. Additional risk minimization measures: None Other routine risk minimization measures:	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):

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Prescription only medicine.	• P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of AD in Denmark and Sweden • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • 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 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): • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • P20-390: Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of AD in Denmark and Sweden • P21-824: A Study of Growth in Adolescents With AD Who Receive Upadacitinib

AD = atopic dermatitis; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; aRMMs = additional risk minimization measures; AS = ankylosing spondylitis; AST = aspartate transaminase; bDMARD = biologic disease-modifying anti-rheumatic drug; CV = cardiovascular; DILI = drug-induced liver injury; DNA = deoxyribonucleic acid; GI = gastrointestinal; HBV = hepatitis B virus; HCP = healthcare professional; JAK = Janus kinase; MACE = major adverse cardiovascular event; nr-axSpA = non-radiographic axial spondyloarthritis; PAC = patient alert card; PL = package leaflet; PsA = psoriatic arthritis; PSUR = periodic safety update report; QD = once daily; RA = rheumatoid arthritis; SmPC = Summary of Product Characteristics; TB = tuberculosis; US = United States; VTE = venous thromboembolic event

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 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:

The proposed leaflet content includes updates to sections 1, 2 and 3 to clearly define the broader indication statement "Axial spondyloarthritis (including non-radiographic axial spondyloarthritis and ankylosing Spondylitis)" to make it clear and understandable to patients. The extension to the AS indication does not change the design formats and layouts (bottle and blister) from the original user tested leaflets for Rheumatoid Arthritis (RA), or subsequent approved bridge reports for the additional indications of Ankylosing Spondylitis (AS)/ Psoriatic Arthritis (PsA), and Atopic Dermatitis (AD).

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Spondyloarthritis (SpA) is represented by a group of diseases that share common genetic, clinical, and radiographic features. Adult SpA patients are commonly categorized by the two predominant manifestations of disease: axial SpA, which primarily involves the spine and sacroiliac (SI) joints, or peripheral SpA, which primarily involves peripheral joints. Further, axial SpA encompasses a spectrum of inflammatory conditions involving the axial skeleton with two distinct entities, AS, which requires the presence of sacroiliitis on plain conventional radiographs as defined by the modified New York criteria and nr-axSpA, which does not meet the 1984 modified New York imaging criteria. Patients with nr-axSpA and AS share common epidemiological, genetic, and clinical disease characteristics, including disease activity, and similar response to treatment however, presence (AS) or absence (nr-axSpA) of radiographic findings serve as an important differentiating characteristic between the two categories of axSpA.

The prevalence of AS differs between regions and has been estimated to be up to 0.5% with similar estimated prevalence rates for nr-axSpA, resulting in an overall prevalence for axSpA in the US and in the EU of approximately up to 1% or higher.

3.1.2. Available therapies and unmet medical need

In 2016, the Assessment of SpondyloArthritis international Society (ASAS) and European League Against Rheumatism (EULAR) published updated treatment recommendations for axial SpA. The first-line treatment of axial SpA consists of nonsteroidal anti inflammatory drugs (NSAIDs). In patients with persistently high disease activity despite a course of two NSAIDs given over a total of at least 4 weeks, initiation of a bDMARD is recommended, and current practice is to start with a tumour necrosis factor alpha inhibitor (TNFi). If TNFi therapy fails, switching to another TNFi or an interleukin (IL)-17 inhibitor (IL-17i) is recommended.

Overall, available treatment options remain limited, particularly for nr-axSpA as compared to other rheumatic diseases such as RA or PsA. In axSpA, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and long-term corticosteroids are not efficacious and therefore not recommended for treatment of axial symptoms. Once patients have an inadequate response to NSAIDs, and more advanced systemic therapies are required, available biologics are administered either subcutaneous (SQ) or intravenous. To date, there have been no oral targeted therapies approved for the treatment of nr-axSpA. However, upadacitinib was recently approved for the AS indication in the EU based on the Phase 2/3 study in AS bDMARD-naïve subjects: Study M16-098, SELECT-AXIS 1 (EMEA/H/C/004760/II/0005). The aim of the current procedure is to extend the Rinvoq indication to nr-axSpA i.e. to include also subjects with the less advanced form without presence of sacroiliitis on plain conventional radiographs.

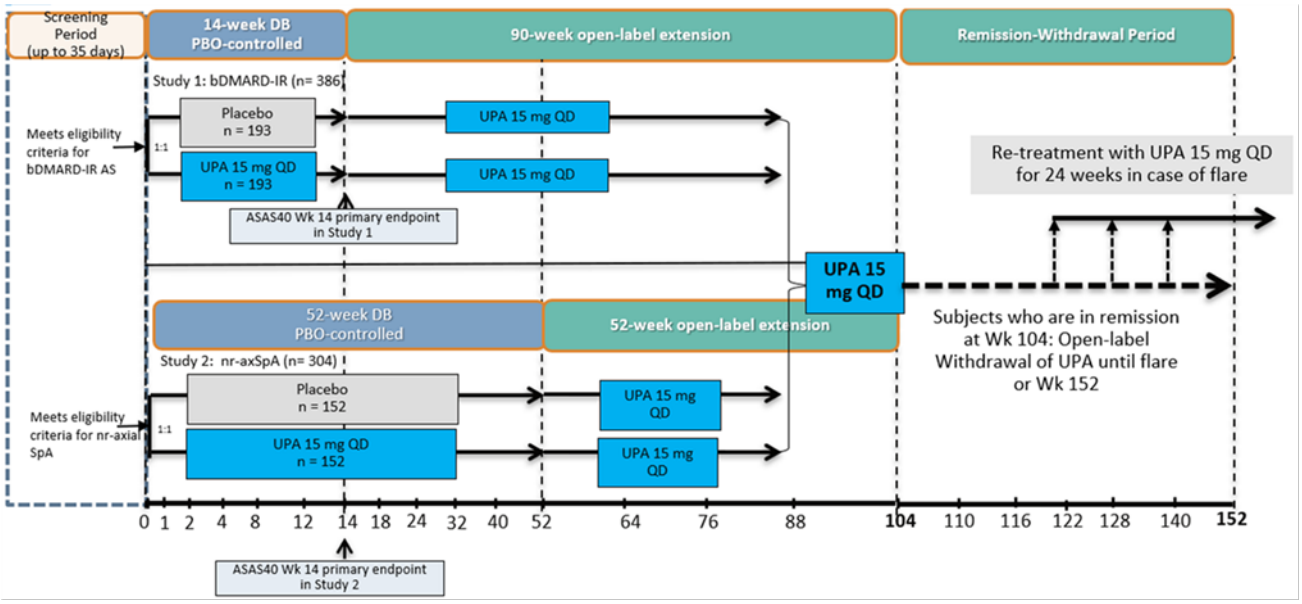
The MAH submitted the following wording for the new indication: "*RINVOQ is indicated for the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).*"

The proposed posology was similar to AS (and also rheumatoid arthritis-RA and psoriatic arthritis-PsA), 15 mg once daily.

3.1.3. Main clinical studies

The support for the efficacy of upadacitinib for the new indication nr-axSpA is primarily derived from the pivotal study M19-944 in nr-axSpA. Supportive data is claimed from study M16-098 in the related condition i.e. bDMARD-naïve AS.

Study M19-944 Study 2 (nr-axSpA) is an ongoing multicenter study with an overall design as outlined in the lower part of the figure below. Study M19-944 utilizes a "master protocol" that includes 2 independent studies for subjects with active axSpA: biologic DMARD-inadequate responders (bDMARD-IRs) AS (Study 1) and nr-axSpA (Study 2).



AS = ankylosing spondylitis; ASAS = Assessment of SpondyloArthritis international Society; bDMARD-IR = biologic disease-modifying antirheumatic drugs inadequate responder; DB = double-blind; IR = inadequate response; nr-axSpA = non-radiographic axial spondyloarthritis; PBO = placebo; QD = once daily; UPA = upadacitinib; Wk = week

Figure 9: Study M19-944 Study 2 Design Schematic

The MAH submitted the complete 14-week results from Study 2 in subjects with active nr-axSpA. Efficacy data are presented up to Week 14. Safety data and subject disposition are presented up to the cut-off date (26 August 2021), which includes summaries of all data up to Week 14, summaries of available data up to Week 52, as well as summaries of available long-term data up to the cut-off date.

The approach to submit the variation based on primarily week 14 efficacy data and submit efficacy-data from the beyond the week 14 timepoint post-approval was overall accepted in the previous CHMP Advice.

The primary endpoint for Study 2 is the proportion of subjects with ASAS40 response at Week 14. This is in line with the relevant EMA axSpA GL and was also agreed in the CHMP Advice.

3.2. Favourable effects

The pivotal, confirmatory study in nr-axSpA met its primary endpoint and the first 12 of the 14 presented multiplicity-controlled secondary endpoints.

A statistically significantly greater percentage of subjects achieved ASAS40 at Week 14 in the upadacitinib group (44.9%, 70/156) compared with the placebo group (22.5%, 35/157), resulting in a placebo adjusted difference of 22.2% ($P < 0.0001$) using non-responder imputation (NRI) incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-MI).

The secondary endpoints for which statistical significance was achieved included: Change from Baseline in ASDAS (CRP) at week 14, Change from Baseline in MRI SPARCC score (SI joints) at week 14, BASDAI 50 response at week 14, ASDAS (CRP) Inactive Disease (ID) (ASDAS score < 1.3) at week 14, Change from Baseline in Patient's Assessment of Total Back Pain NRS (Score 0 – 10) at week 14, Change from Baseline in Patient's Assessment of Nocturnal Back Pain NRS (Score 0 – 10) at week 14, ASDAS (CRP) Low Disease Activity (LDA) (ASDAS score < 2.1) at week 14, ASAS partial remission (PR) (an absolute score of ≤ 2 units for each of the 4 domains identified in ASAS40) at week 14, Change from Baseline in BASFI at week 14, Change from Baseline in ASQoL at week 14, Change from Baseline in ASAS Health Index at week 14 and ASAS20 response at week 14.

3.3. Uncertainties and limitations about favourable effects

The main limitation is that the current submission does not include any efficacy data from the pivotal nr-axSpA study beyond 14 weeks. Instead, maintenance of effect is supported by extrapolation from long-term data from study M16-098 that was the pivotal study supporting approval of upadacitinib in a related condition i.e. AS (EMEA/H/C/004760/II/0005). In the AS procedure efficacy data up to week 64 was already assessed as reflected in the approved SmPC. Thus, the maintenance of ASAS40 response for at least 1 year in AS has already been demonstrated and the CHMP considered that it was acceptable to extrapolate long-term efficacy from AS to nr-axSpA due to the similarities in disease characteristics. The CHMP therefore agreed that the M16-098 1-year data supports a maintained treatment effect of upadacitinib in subjects with nr-axSpA.

The long-term data from Study M16-098, which may provide further support, is currently being assessed in the parallel variation EMEA/H/C/004760/II/0015/G. Please refer to this variation for the complete assessment of those data.

Statistical significance was not met for the following secondary endpoints: Change from Baseline in BASMIlin at week 14 and Change from Baseline in MASES for subjects with baseline Enthesitis (MASES

> 0) at week 14. Consequently, neither will the endpoint included last in the testing sequence i.e. ASAS40 response at Week 52 be able to achieve statistical significance.

3.4. Unfavourable effects

During the placebo-controlled 14-week period, AEs occurred in 75/156 patients (48.1%) in the upadacitinib group and in 72/157 patients (45.9%) in the placebo group. Also serious adverse events were slightly more frequent in the upadacitinib arm (2.6%) than in the placebo arm (1.3%). SAEs among upadacitinib-treated subjects were COVID-19 pneumonia, pyelonephritis, foot fracture, and osteoarthritis.

Throughout the total 52-week period, the pattern was similar with a higher frequency of AEs and SAEs in the upadacitinib group (AEs: 260 E/100PYs, SAEs: 5.7 E/100PYs) than in the placebo group (AEs: 228 E/100PYs, SAEs: 5.4 E/100PYs). There were no deaths up to the current data cut-off.

The most common adverse events were infections. Higher frequencies were observed for the upadacitinib group compared with the placebo group for headache, nausea, abdominal pain, diarrhoea, and neutropenia. Also up to 52 weeks, headache was the most frequent AE in the upadacitinib group, followed by COVID-19 and neutropenia.

The most notable difference in occurrence in adverse events of special interest is a higher incidence of neutropenia in the upadacitinib group (8.5E/100PYs) than in the placebo group (0.9E/100PYs). Also hepatic disorder, serious infection, anaemia, and herpes zoster were numerically higher in the upadacitinib group compared with the placebo group. These are all known risks and no new safety signals were observed.

3.5. Uncertainties and limitations about unfavourable effects

The main limitation pertains to the limited long-term exposure in the nr-axSpA population. Only 114/187 patients have been exposed for more than 6 months, and 35 patients for more than 12 months. Furthermore, the limited size of the study hampers the possibility to evaluate meaningful differences in safety in important subgroups, for example in elderly and in patients treated with concomitant csDMARDs. Long-term safety data will be submitted following the completion of study M19-944 (category 3 study see 2.6.).

Supportive data are gained from study M16-098 in patients with AS, a more advanced form of axial spondylarthritis. It was agreed in the previous scientific advice that these data could support long-term efficacy and safety in the nr-axSpA population "given that there are no limiting uncertainties regarding maintenance of efficacy and of safety for AS and nr-AxSpA". The 2 years full clinical study report from Study M16-098 is currently being assessed in the parallel variation EMEA/H/C/004760/II/0015/G. Please refer to this variation for the complete assessment of those data.

3.6. Effects Table

Table 27. Effects Table for Rinvoq and nr-axSpA (data cut-off: 26 August 2021)

Effect	Short description	Unit	UPA	PBO	Uncertainties / Strength of evidence
ASAS40 w14	ASAS40 Response Rate at Week 14 Primary endpoint	%	44.9	22.5	p< 0.0001

Effect	Short description	Unit	UPA	PBO	Uncertainties / Strength of evidence
ASDAS (CRP) LDA w14	ASDAS LDA rate week 14 Secondary endpoint	%	42.3	18.3	p< 0.0001
BASFI w14	Change from Baseline, Secondary endpoint		-2.61	-1.47	p<0.0001
MRI SPARCC Score (SI Joint) w14	Change from Baseline, Secondary endpoint		-2.49	0.57	p< 0.0001
BASMIlin w14	Change from Baseline Secondary endpoint		-0.29	-0.19	P=0.1781 (Not Significant)
AE	Frequency in the placebo-controlled study period	N (%)	75/156 (48.1)	72/157 (45.9	
SAE	Frequency in the placebo-controlled study period	N (%)	4/156 (2.6)	2/157 (1.3)	
Infections	Frequency kin the placebo-controlled study period	N (%)	35/156 (22.4)	34/157 (21.7)	
Serious infections	Frequency in the placebo-controlled study period	N (%)	2/156 (1.3)	1/157 (0.6)	

Abbreviations*: nr-axSpA (non-radiographic axial spondyloarthritis), UPA: upadacitinib, PBO: placebo, ASAS = Assessment of SpondyloArthritis international Society, ASDAS = Ankylosing Spondylitis Disease Activity Score, BASFI = Bath Ankylosing Spondylitis Functional Index, BASMIlin = Linear Bath Ankylosing Spondylitis Metrology Index, LDA = Low Disease Activity, MRI = magnetic resonance imaging, SI = sacroiliac, SPARCC = Spondyloarthritis Research Consortium of Canada, AE: adverse event, SAE: serious adverse event,*

Notes:

a. For categorical endpoints, Cochran-Mantel-Haenszel (CMH) test is used with non-responder imputation (NRI) incorporating multiple imputation (MI) to handle missing data due to coronavirus disease of 2019 (COVID-19) (NRI-MI). For continuous endpoints, mixed-effect model repeated measurements (MMRM) are used and N is number of unique subjects contributing to MMRM model estimates.

b. P-value is unadjusted.

c. Results are obtained via the sequential multiple testing procedure controlling the overall type I error rate of all primary and multiplicity-controlled secondary endpoints at the significance level of 0.05 (two-sided)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

The outcome of the study indicates that 14-week treatment with upadacitinib has an effect on symptoms and signs of nr axSpA (as measured by e.g. ASAS40, ASAS20, ASDAS [CRP]) physical function (as measured by BASFI) and other patient-reported outcomes (as measured by ASQoL, ASAS Health Index). Further, upadacitinib has an effect on typical MRI-findings indicative of inflammation.

Judging from the outcome on the primary endpoint, i.e. ASAS40 at week 14, the effect size appears similar as the effect size of upadacitinib in the treatment of AS. The effect size is considered clinically relevant.

The main limitation in the assessment of favourable effects is that the current submission does not include any efficacy data from the pivotal nr-axSpA study beyond 14 weeks. Instead, maintenance of effect is supported by extrapolation from long-term data from study M16-098 that was the pivotal study supporting the approval in AS (EMEA/H/C/004760/II/0005). Maintenance of ASAS40 response for at least 1 year in AS has already been demonstrated as reflected in the approved Rinvoq SmPC. The CHMP considered it reasonable to extrapolate long-term efficacy from AS to nr-axSpA due to the similarities in disease characteristics. Thus, although the limitation in the extent of data is acknowledged, the CHMP agreed that the M16-098 1-year data supports a maintained treatment effect of upadacitinib in subjects with nr-axSpA.

The long-term data from Study M16-098, which may provide further support, is currently being assessed in the parallel variation EMEA/H/C/004760/II/0015/G. Please refer to this variation for the complete assessment of those data.

Importance of unfavourable effects

The observed safety data is consistent with the known safety profile of Rinvoq with predominantly infections, headache, nausea, abdominal pain, diarrhoea, and neutropenia. These are all known risks considered to be adequately covered in the current SmPC. Although the short duration of exposure is a clear limitation, it is noted that there were no deaths, MACE or malignancies up to current cut-off.

Long-term safety data will be submitted following the completion of study M19-944 (category 3 study see section 2.6.). Meanwhile, long-term data can be extrapolated from the ankylosing spondylitis population (study M16-098). In the 2-year data from study M16-098, there were no deaths and no AEs of serious infection, NMSC, lymphoma, adjudicated gastrointestinal perforation, renal dysfunction, active TB, or adjudicated MACE reported in subjects who received upadacitinib. Therefore, these data do not raise any concern on the long-term safety of Rinvoq in patients with axial spondyloarthritis. The long-term data from Study M16-098 is currently being assessed in the parallel variation EMEA/H/C/004760/II/0015/G. Please refer to this variation for the complete assessment of those data.

Overall, the safety profile is acceptable; in line with the known safety profile of upadacitinib.

3.7.2. Balance of benefits and risks

During the evaluation, the CHMP requested the MAH to specify the objective signs of inflammation in the indication wording. The MAH submitted an updated SmPC in which the indication statement has been revised as requested:

RINVOQ is indicated for the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

3.7.3. Additional considerations on the benefit-risk balance

EMA's safety committee, PRAC, has started a review of the safety of Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis and atopic dermatitis). Rinvoq is part of the products reviewed in the on-going referral. The review of JAK inhibitors in the treatment of inflammatory disorders has been initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004.

The recommendation on the present application is without prejudice to the final conclusions of the ongoing referral procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data.

3.8. Conclusions

The overall benefit/risk balance of RINVOQ is positive in the following indication:

"Non-radiographic axial spondyloarthritis (nr-axSpA)

RINVOQ is indicated for the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)."

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 active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs), based on the final clinical study report from the pivotal study M19-944 Study 2 (nr-axSpA); a randomized, double-blind, phase III study evaluating the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with nr-axSpA who completed the double-blind period on study drug. As a consequence, SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2 have been updated and the Package Leaflet has been updated in accordance. A revised RMP version 8.0 is adopted.

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.

This recommendation is without prejudice to the final conclusions of the ongoing referral procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data.

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/0016'

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 23 June 2022