10 December 2020
EMA/708068/2020
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Rinvoq

International non-proprietary name: upadacitinib

Procedure No. EMEA/H/C/004760/II/0005

## Note

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

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# List of abbreviations

| | |
|---|---|
| Δ | change from Baseline |
| ADR | adverse drug reaction |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| AO | as observed |
| AS | ankylosing spondylitis |
| ASAS | Assessment of SpondyloArthritis international Society |
| ASDAS | Ankylosing Spondylitis Disease Activity Score |
| ASQoL | Ankylosing Spondylitis Quality of Life |
| AST | aspartate aminotransferase |
| AUC | Area under the time concentration curve |
| $AUC_{inf}$ | total drug exposure across time |
| BASDAI | Bath Ankylosing Spondylitis Disease Activity Index |
| BASFI | Bath Ankylosing Spondylitis Functional Index |
| BASMI | Bath Ankylosing Spondylitis Metrology Index |
| bDMARD | biologic disease-modifying antirheumatic drug |
| BMI | body mass index |
| CHF | congestive heart failure |
| CHMP | Committee for Human Medicinal Products |
| CI | confidence interval |
| CL/F | oral clearance |
| $C_{max}$ | maximum observed concentration |
| CMH | Cochran-Mantel-Haenszel |
| CMQ | company MedDRA query |
| CNS | central nervous system |
| CPK | creatine phosphokinase |
| CRF | case report form |
| CRP | C-reactive protein |
| cs | conventional-synthetic |
| csDMARD | conventional synthetic disease-modifying antirheumatic drug |

| | |
|---|---|
| LS | least squares |
| MA | Marketing Authorization |
| MACE | major adverse cardiac event |
| MASES | Maastricht Ankylosing Spondylitis Enthesitis Score |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | mixed effect model repeated measurement |
| MPA | (Swedish) Medical Products Agency |
| 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 |
| OMERACT | Outcome Measures in Rheumatology |
| PCS | potentially clinically significant |
| PE | pulmonary embolism |
| PGA | physician's global assessment |
| PR | partial remission |
| PsA | psoriatic arthritis |
| PT | preferred term |
| PtGA | Patient's Global Assessment of Disease Activity |
| PY | patient-year |
| QD | once daily |
| QoL | quality of life |
| R&D | research and development |
| RA | rheumatoid arthritis |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SI | sacroiliac |
| SIR | standard incidence ratio |
| SmPC | Summary of Product Characteristics |
| SMQ | standardized MedDRA query |

# 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 1 June 2020 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, II and IIIB |

C.I.6 (Extension of indication) - Extension of indication to include the treatment of active ankylosing spondylitis in adult patients for Rinvoq; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Minor editorial changes to the SmPC and Annex II are also proposed. Version 3.0 of the RMP has also been submitted.

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

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0322/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0322/2019 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 13 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 Co-Rapporteur: n/a

| Timetable | Actual dates |
|---|---|
| Submission date | 1 June 2020 |
| Start of procedure: | 20 June 2020 |
| CHMP Rapporteur Assessment Report | 14 August 2020 |
| PRAC Rapporteur Assessment Report | 20 August 2020 |
| PRAC Outcome | 4 September 2020 |
| CHMP members comments | 7 September 2020 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 10 September 2020 |
| Request for supplementary information (RSI) | 17 September 2020 |
| CHMP Rapporteur Assessment Report | 09 November 2020 |
| PRAC Rapporteur Assessment Report | 13 November 2020 |
| PRAC members comments | 19 November 2020 |
| Updated PRAC Rapporteur Assessment Report | 19 November 2020 |
| PRAC Outcome | 26 November 2020 |
| CHMP members comments | 30 November 2020 |
| Updated CHMP Rapporteur Assessment Report | 03 December 2020 |
| Opinion | 10 December 2020 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

### *Disease or condition*

Spondyloarthritis (SpA) is a group of diseases that share common clinical, radiographic, and genetic features. These include Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), reactive arthritis, enteropathic or inflammatory bowel disease (IBD)-related arthritis, and undifferentiated Spondyloarthritis. A more universally consistent way of categorizing SpA patients is to define them by their primary and predominant clinical manifestation of axial or peripheral SpA.

Axial SpA encompasses a spectrum of disease manifestations, which has been split into two categories, AS (also called radiographic axial spondyloarthritis) and non-radiographic axial SpA (nr-axSpA), based on the 1984 modified New York criteria, which require the presence of sacroiliitis on plain conventional radiographs for the classification of AS. 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 axial SpA in the United States of approximately up to 1% or even higher in the overall population.

*Claimed the therapeutic indication*The MAH applied for the following indication:

*"Ankylosing spondylitis*

*RINVOQ is indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy."*

The recommended dose of upadacitinib was 15 mg once daily.

### *Management*

In 2016, the ASAS and European League Against Rheumatism (EULAR) published updated treatment recommendations for axial SpA, and in 2019 the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (SPARTAN) published updated axial SpA treatment recommendations. 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-17 inhibitor (IL-17i) is recommended. Despite recent advances in the treatment of axial SpA, there remains a significant unmet medical need, as only approximately 45% to 50% of patients in the studies of TNFi showed an ASAS40 response, and only approximately 15% to 20% achieved a state of remission.

## 2.1.2. About the product

The JAK family is composed of 4 family members: JAK1, 2, 3, and Tyrosine kinase 2 (Tyk2). Activation of JAK pathways initiates expression of survival factors, cytokines, chemokines, and other molecules that facilitate leukocyte cellular trafficking and cell proliferation, which contribute to inflammatory and autoimmune disorders. Hence, the JAK family has evoked interest in the area of inflammatory diseases, leading to the development of various JAK inhibitors with different selectivity profiles against JAK1, JAK2, JAK3, and Tyk2.

Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.

Upadacitinib (ABT-494) (Rinvoq) is a Janus kinase (JAK) inhibitor that was approved for the treatment of moderately to severely active rheumatoid arthritis (RA) in the United States (US) on 16 August 2019, by the European Commission on 18 December 2019, and has since been approved in multiple other countries.

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

Scientific Advice was received from CHMP in June 2019, the following issues of relevance for the current application were discussed:

- Whether Study M16-098 could be regarded as a pivotal study for this application; this was considered a matter of assessment.

- The omission of an active control arm in the axSpA study; this was considered acceptable
- Reducing or stopping treatment; the MAH was encouraged to develop an approach for studying dose reduction and/or stopping treatment with upadacitinib 15 mg QD, in patients with an extended period of low disease activity/near remission. It is recommended to implement this in the long follow-up phase of patients with active nr-axSpA and with Ankylosing Spondylitis in the clinical study program.

Adherence to the given Advice is commented throughout the report.

### 2.1.4. General comments on compliance with GCP

According to the MAH, the pivotal clinical phase 2/3 study M16-098 supporting this Application, is being conducted in accordance with the International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and relevant regulatory requirements. Subjects are accorded all rights granted by the Declaration of Helsinki. All protocols received approval by the appropriate governing investigational review board, ethics committee, or similar authority.

## *2.2. Non-clinical aspects*

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

### 2.2.1. Ecotoxicity/environmental risk assessment

The MAH has provided an ERA, but 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, to support the new indication PsA (ongoing procedure), and to support the new indication AS (present procedure).

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

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

***Phase 1***

The daily dose for the indications RA, PsA and AS is 15 mg/day, resulting in $PEC_{SURFACEWATER}$ values of 0.075 µg/L for each of the indications when using the default Fpen value of 0.01.

A $PEC_{SW\text{-}TOTAL}$ was calculated (0.23 µg/L) and was used to re-calculate the Phase II Tier A and Tier B PEC/PNEC ratios.

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

***Phase II***

For this application, the same PNEC values were presented as for the original ERA submitted for the MAA. In the table below the updated PEC/PNEC ratios are presented, based on the PEC value obtained for all three 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 | 0.23 µg/L | 63 µg/L | 0.004 (<1) |
| Groundwater | 0.0575 µg/L | 160 µg/L | 0.0004 (<1) |
| Microorganism | 0.23 µg/L | 100000 µg/L | 0.000002 (<0.1) |

***Phase II Tier B***

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

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

### 2.2.2. Conclusion on the non-clinical aspects

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 overview 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 | M16-098 | 5.3.5.1 | Period 1: Compare the efficacy, safety, and tolerability of UPA 15 mg QD vs PBO<br>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<br>Period 2: OL, long-term extension | UPA 15 mg<br>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 Week 64) |

AS = ankylosing spondylitis; BA = bioavailability; bDMARD = biologic disease-modifying antirheumatic drug; CSR = clinical study report; DB = double-blind; ER = extended release; NSAIDs = nonsteroidal anti-inflammatory drugs; OL = open-label; PBO = placebo; PO = orally; UPA = upadacitinib; QD = once daily

## 2.3.2. Pharmacokinetics

The objectives of the clinical pharmacology programme supporting the application for ankylosing spondylitis (AS) were to characterize the population pharmacokinetics of upadacitinib in patients with AS and to evaluate the relationships between upadacitinib plasma exposures and efficacy as well as safety in subjects with active AS using data from Phase 2/3 Study M16-098.

In total, 92 subjects with active AS who had at least one measurable upadacitinib concentration were included in the population pharmacokinetic (PK) analysis and 187 subjects [93 subjects administered upadacitinib 15 mg once daily (QD) and 94 subjects administered placebo] were included in the exposure-response 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 M16-098 (N = 187) | Phase 2/3 Adult subjects with active AS who have an inadequate response to NSAIDs | 15 mg QD, Extended-Release | *Pharmacokinetics:* Weeks 2, 4, 8, 12, and 14<br>*Efficacy and Safety Assessments:* Weeks 0, 2, 4, 8, 12, and 14 | Exposure-response for ASAS20 and ASAS40, at Week 14 | Select adverse events and changes in laboratory parameters at Week 14 |

AS = Ankylosing Spondylitis; NSAID = Nonsteroidal Anti-inflammatory Drug; ASAS = Assessment of SpondyloArthritis international Society

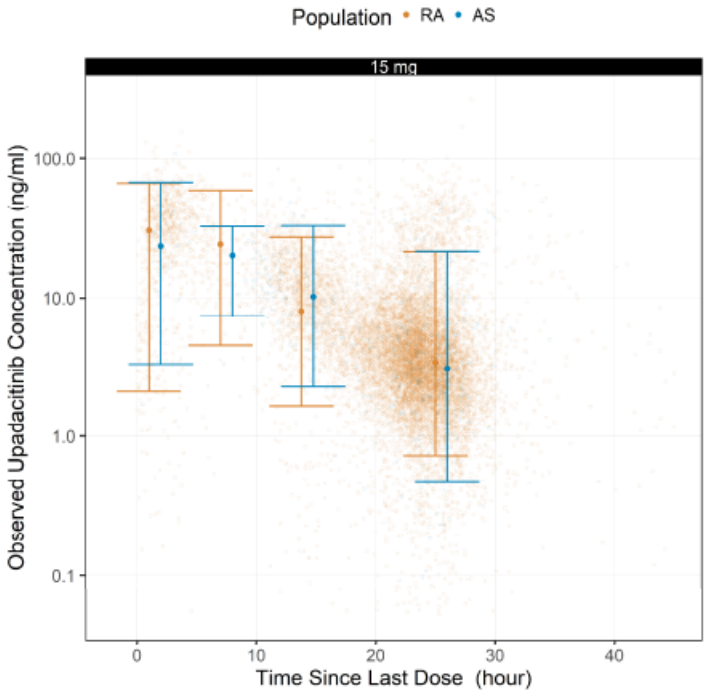
a. N is the total number of subjects enrolled in the study.

### *Analytical method*

Plasma concentrations of upadacitinib were determined using a previously assessed (EMEA/H/C/004760/0000) validated liquid chromatography method with tandem mass spectrometric detection. The lower limit of quantitation (LLOQ) of the assay of plasma samples of Study M16-098 for the determination of upadacitinib concentrations is 0.0505 ng/mL. The bioanalytical method was found to be adequately validated.

## *Population pharmacokinetic analysis*

Parameters from the previously built model in healthy volunteers and subjects with rheumatoid arthritis (RA) were fixed and the model was re-run on the AS dataset by only re-estimated inter-subject variability (IIV) and residual error terms using the nonlinear mixed effects modeling software, nonlinear mixed-effects model (NONMEM). It was further evaluated if subjects with AS have significantly different pharmacokinetics from subjects with RA by estimating apparent oral clearance (CL/F) and apparent volume of distribution of central compartment (Vc/F) using the AS dataset and assessing if the objective function value and visual predictive checks are significantly improved.




Open points show observed concentrations per indication, filled points and error bars show median concentration and $5^{th}/95^{th}$ quantiles of the observed data per time bin.

*Figure 1. Observed upadacitinib Concentrations Versus Binned Time After Last Dose in AS and RA Populations*

### *Results*

The pharmacokinetic analyses included 452 concentration records with 12 records (2.7%) below the LLOQ. One subject (Subject 10291005) was excluded from the analyses because of having discontinued treatment after 4 days and having only one concentration measurement, which was BLQ. Given the small fraction of concentration below the LLOQ, the M5 imputation method was used by imputing BLQ concentrations with the LLOQ/2. Four upadacitinib concentrations (< 1%) were flagged as outliers.

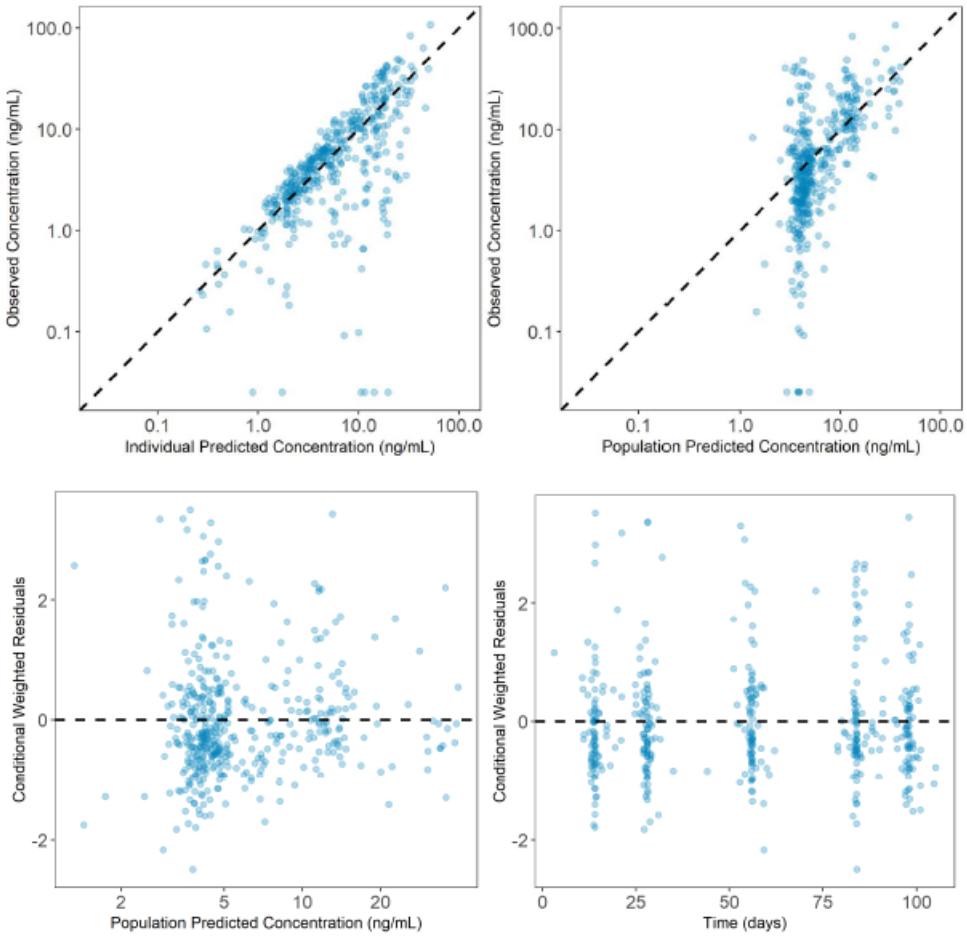
The re-estimation of upadacitinib CL/F and Vc/F using data from subjects with AS did not result in a significant change in OFV (model run002, OFV 1762). A model with re-estimated Vc/F only did not result in a significant change in OFV from run001 (model run002b OFV 1763) but was found to be more stable in terms of successful estimation and covariance steps. This model was hence used to obtain the individual Bayesian estimates to derive exposures for the exposure-response analyses. The population estimate for Vc/F (171 L) was similar to that obtained from the previously developed RA model (156 L).

Parameter estimates of this model (run002b) are provided in Table 3. The additive error term is estimated to be very small (7.16E-6) but was kept in the model for consistency with the RA model. Random effect distributions by covariates did not indicate that trends exist for the AS population.

*Table 3. Final Population Pharmacokinetic Parameter Estimates and Variability for upadacitinib from Subjects with AS*

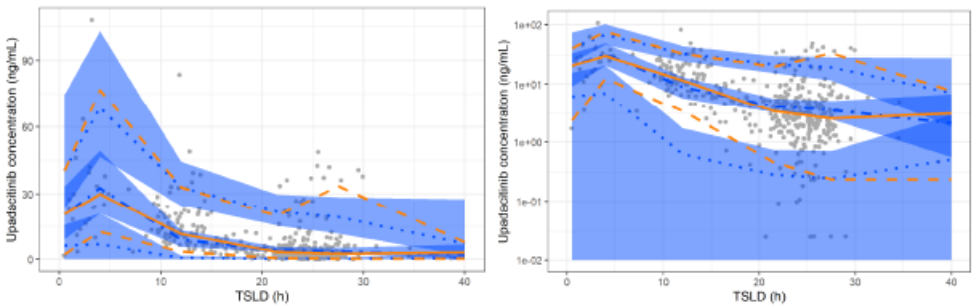
| Parameter | Population Estimate (%RSE) | 95% Confidence Interval |
|---|---|---|
| CL/F (L/h) | 40.9 (FIX) | -- |
| Vc/F (L) | 171 (25.5) | 128 – 227 |
| Extended-Release KA (1/h) | 0.0523 (FIX) | -- |
| Extended-Release Lag time (h) | 0.154 (FIX) | -- |
| Fraction of Extended-Release Dose Absorbed 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; SEE = standard error of estimate; Vc/F = apparent volume of distribution of central compartment; $V_p/F$ = apparent volume of distribution of peripheral compartment; %IIV was calculated as SQRT($\omega^2$)*100




Dashed lines show the line of unity (upper panels) or indicate the zero reference (lower panels).

*Figure 2. Goodness of Fit-Plots for Final Population Pharmacokinetic Model*




TSLD = Time since last dose

The gray dots represent observed data, the orange lines represent median (solid) and 5th and 95th quantiles (dashed) for observed data, and the blue lines and bands represent median (dashed-dotted) and 5th and 95th quantiles (dotted) with 95% prediction bands for simulations.

*Figure 3. VPC for Final Population Pharmacokinetic Model Using Linear and Log-Linear Scales*

Cavg and AUCss,24 were calculated from the individual Bayesian estimates. Trough plasma concentration (Ctrough) and Cmax were obtained by steady-state simulations over 21 days. Model-estimated plasma exposures were very similar to those previously reported in subjects with RA for the 15 mg QD dose (median Cmax, Cavg, and Ctrough of 41.1, 15.1, and 3.82 ng/mL in RA compared to 39.6, 14.5 and 3.50 ng/mL in AS, respectively).

## 2.3.3. Pharmacodynamics

Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.

## 2.3.4. PK/PD modelling

Model-estimated upadacitinib average plasma concentration (Cavg) in subjects with AS in the active treatment arm were derived using empirical Bayesian estimates from the population pharmacokinetics analysis. Exploratory exposure-response quartile plots were first evaluated for the efficacy and safety endpoints to identify the efficacy and safety variables that have a clear relationship with upadacitinib Cavg. Only efficacy and safety variables identified to exhibit a clear relationship with upadacitinib Cavg were evaluated further using exposure-response models.

Models describing the relationship between upadacitinib Cavg and efficacy as well as safety variables were constructed as logistic regression models using R version 3.5.2 or later. For each of the evaluated efficacy and safety variables, models with and without a drug effect function were compared to determine if there is a statistically significant effect of upadacitinib exposures on the probability of occurrence of each variable. Model selection was based on the Akaike Information Criterion (AIC) since non-nested models were compared for base model development.

The covariates specified for potential investigation for influence on clinical response included the following: demographics (age, body weight, sex, race.), baseline disease characteristics (baseline PtGA, baseline BASDAI, baseline BASFI, baseline inflammation (based on the mean of Questions 5 and 6 of BASDAI assessment), baseline CRP level, concomitant medication(s), geographic region and duration of disease.

The covariates specified for potential investigation for influence on safety events included the following: demographics (age, body weight, sex, race, etc.), geographical region and baseline laboratory measurements.

### *Exposure-efficacy*

Exposure-efficacy quartile plots for the percentage of subjects who achieved ASAS20 or ASAS40 response at Week 14 versus upadacitinib Cavg are presented in Figure 4. upadacitinib Cavg values associated with 15 mg QD dose (7 to 33 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.

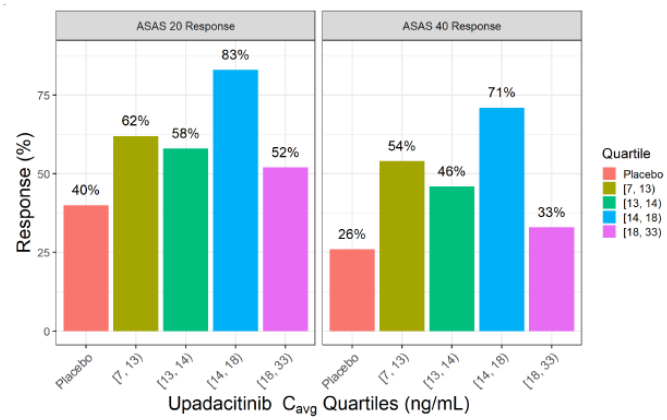


*Figure 4. Exposure-Response Quartile Plots for ASAS20 and ASAS40 at Week 14 in Subjects with AS*

Logistic regression analyses were conducted for ASAS20 and ASAS40 responses to confirm observed trends in the exposure-response quartile plots. Linear and non-linear logistic exposure-response regression models were compared to models with only intercept and treatment effect terms (placebo or upadacitinib 15 mg) for describing each efficacy variable. ASAS20 and ASAS40 responses were best described by models with only an intercept and treatment effect parameters, versus models with exposure-driven responses (i.e., using Cavg), based on lower AIC values.

## *Exposure-safety*

Exposure-safety 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 cases of serious infections or neutropenia (Grade 3 or higher: < 1 × 109/L) at Week 14. Only one variable (> 1 g/dL decrease in haemoglobin from baseline) showed a trend between upadacitinib Cavg and percent of subjects experiencing the event at Week 14 (Figure 5).

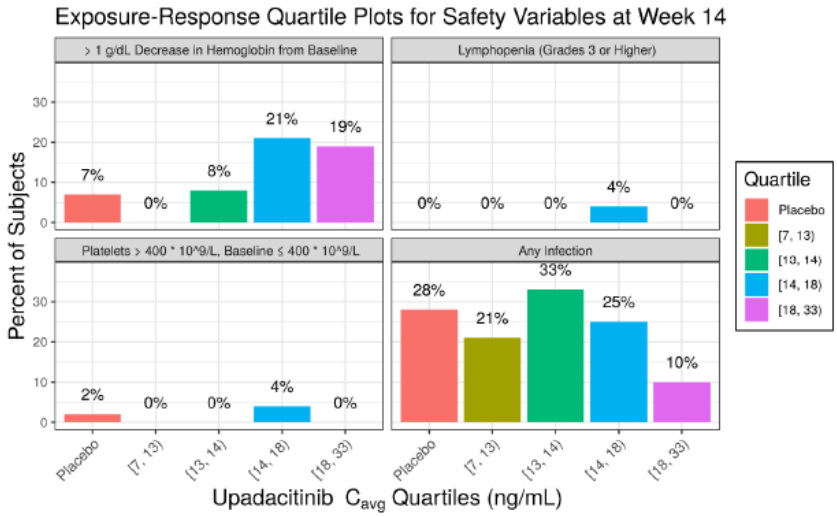



*Figure 5. Exposure-Response Quartile Plots for Safety Variables at Week 14 in Subjects with AS*

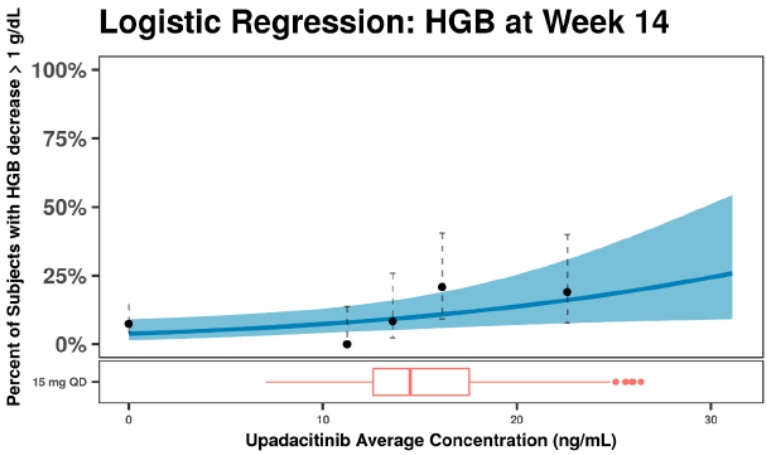
Logistic regression modelling was performed for the relationship between upadacitinib Cavg and the percentage of subjects experiencing > 1 g/dL decrease in haemoglobin from baseline at Week 14. There was a statistically significant relationship between increasing upadacitinib Cavg and the percentage of subjects experiencing > 1 g/dL decrease in haemoglobin from baseline at Week 14. This was based on the lower AIC value for the logistic regression model with an exposure effect compared to the model without any drug effect (AIC: 118.204, p-value of likelihood ratio compared to model without drug effect: 0.039). A logistic regression model with a linear drug effect function best described the probability of experiencing a > 1 g/dl decrease in haemoglobin from baseline at Week 14. The estimated slope parameter for the base linear logistic regression model describing the relationship for decrease in haemoglobin from baseline was 0.070.

Covariates were tested on the exposure-safety base model for decreases in haemoglobin. Only baseline haemoglobin was retained as a covariate on the intercept of the model (Table 4). Higher baseline haemoglobin values were associated with a higher percentage of subjects, independent of upadacitinib treatment, experiencing a > 1 g/dL decrease from baseline haemoglobin at Week 14.

Visual predictive check demonstrates that the final logistic regression model for change in haemoglobin adequately described the observed data (Figure 6).

*Table 4. Final Model Parameter Estimates for Logistic Regression Model of upadacitinib Cavg and Probability of Experiencing > 1 g/dL Decrease from Baseline in Haemoglobin*

| Week | Parameter | Estimate | 95% Confidence Interval |
|---|---|---|---|
| | > 1 g/dL Decrease from Baseline in Hemoglobin | | |
| Week 14 | Intercept | –3.24 | –4.18, –2.30 |
| Week 14 | Slope | 0.070 | 0.013, 0.127 |
| Week 14 | Baseline Hemoglobin on Intercept | 0.651 | 0.233, 1.07 |




Upper Part: The blue line denotes model-predicted median (and the blue shaded area denotes the 5th and 95th percentiles) of percentage of subjects experiencing > 1 g/dl decrease in hemoglobin from baseline at Week 14; the dots denote the binned observed median (and the dashed lines the 5th and 95th percentiles) of percentage of subjects experiencing > 1 g/dl decrease in hemoglobin from baseline at Week 14. Lower Part (upadacitinib $C_{avg}$ in the 15 mg QD treatment arm): The band inside the box is the median. The lower and upper hinges correspond to the 25th and 75th percentiles. Whiskers represent 1.5 IQR. The data beyond the end of the whiskers are plotted individually.

*Figure 6. Visual Predictive Check for Final Logistic Regression Model for Change in Haemoglobin from Baseline at Week 14*

## 2.3.5. Discussion on clinical pharmacology

The objectives of the clinical pharmacology programme supporting the application for AS were to characterize the population pharmacokinetics of upadacitinib and to evaluate the relationships between upadacitinib plasma exposures and efficacy as well as safety in subjects with active AS using data from Phase 2/3 Study M16-098. The data were evaluated using population PK analysis, graphical evaluation and exposure-response (logistic regression) analysis.

**Population pharmacokinetic model**

The population PK model previously developed in subjects with RA was determined to adequately characterize upadacitinib pharmacokinetics. However, there was high shrinkage (50%) on V2/F, which means that Cmax was shrunk towards the population mean.

The MAH chose to evaluate if the PK between the AS and RA population were similar by re-estimating the IIV and subsequently also central volume of distribution. The MAH did not present results when only IIVs were re-estimated. The %RSEs are high on IIV (26-110%). The shrinkage values for IIV on CL/F and V/F were moderate to low. As expected, the shrinkage value for IIV on the extended release

absorption (Ka) was high. Nonetheless, the individual exposure predictions are considered reliable. 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 since last dose. Overall, upadacitinib pharmacokinetics appear to be similar in subjects with AS and RA, and the model estimated Cavg were 14.5 ng/mL and 15.1 ng/mL, respectively.

**Exposure-response**

In the exposure-efficacy analyses of upadacitinib on the probability of achieving ASAS20 and ASAS40 at Week 14, there was a statistically significant treatment effect observed between the placebo and upadacitinib 15 mg QD arms. The was no trend towards increased responses with increasing upadacitinib exposures within the 15 mg QD arm.

With increasing upadacitinib exposures, a relationship was found in the percentage of patients experiencing decreases in haemoglobin of ≥ 1 g/dL from baseline. No patient experienced changes of ≥ 2 g/dL decreases in haemoglobin from baseline. No statistically significant trend was found for the probability of experiencing any infection, changes in platelet count, or lymphopenia (Grade 3 or higher at Week 14) and increasing upadacitinib exposure.

## 2.3.6. Conclusions on clinical pharmacology

The CHMP considered that adequate methods have been used to evaluate the PK and exposure-response in AS patients. The exposure-efficacy analyses of upadacitinib support the 15 mg QD dosing regimen. The CHMP concluded that upadacitinib pharmacokinetics are consistent between rheumatoid arthritis and ankylosing spondylitis patients. Section 5.2 of the SmPC was updated accordingly.

# *2.4. Clinical efficacy*

## 2.4.1. Dose response study

According to the MAH, the selection of the upadacitinib 15 mg QD dose for evaluation in the AS pivotal phase 2/3 Study M16-098 was informed by the upadacitinib exposure-response analyses conducted using results from 4 RA studies: two Phase 2 studies (Studies M13-537 and M13-550) and two Phase 3 studies (Studies M13-549 and M13-542), as well as published results for a Phase 2b AS study of another JAKi, tofacitinib (van der Heijde D, Deodhar A, Wei JC, et al. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. Ann Rheum Dis. 2017;76(8):1340-7).

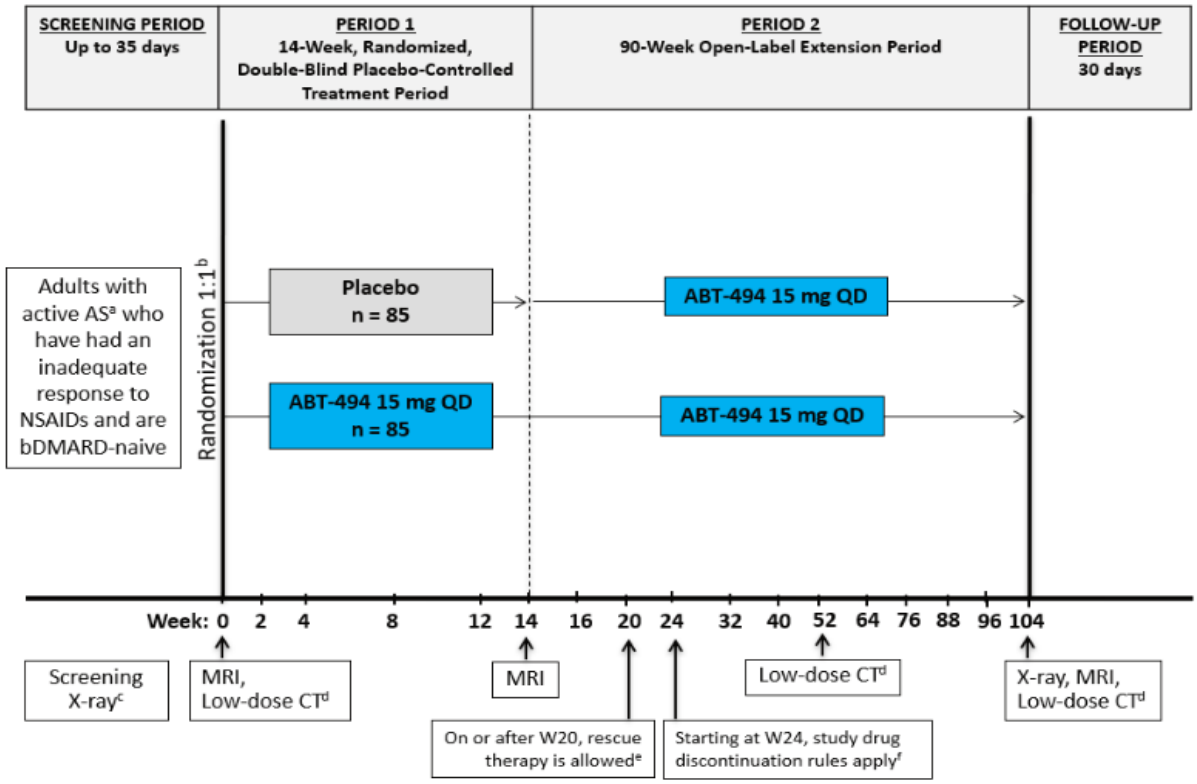
Exposure-response analyses using data from upadacitinib Phase 2 and Phase 3 studies in subjects with RA demonstrated that plasma exposures associated with a dose of upadacitinib 15 mg QD maximized upadacitinib efficacy. Furthermore, exposure-response analyses showed that doses lower than 15 mg QD (e.g., 7.5 mg QD) are expected to provide sub-optimal efficacy in the treatment of axial spondyloarthritis (axSpA). Using data across Phase 2 and 3 RA studies, exposure-response relationships for different safety measures (across 7.5, 15, and 30 mg dose range) showed no exposure-dependent increase in occurrence of the following events at either Week 12/14 or Week 24/26: pneumonia, herpes zoster infection, changes in platelet count (platelets ≥ 600 × 109/L with baseline ≤ 400 × 109/L, platelets > 400 × 109/L with baseline ≤ 400 × 109/L), lymphopenia (grade 4 or higher), and neutropenia (grade 3 or higher upadacitinib exposures of 30 mg QD or higher were associated with significantly higher incidences of hemoglobin decrease from baseline (> 1 g/dL and > 2 g/dL) at Week 12/14 and at Week 24/26 compared with placebo and upadacitinib 15 mg QD).

## 2.4.2. Main study

## M16-098 A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of upadacitinib in Subjects with Active Ankylosing Spondylitis

### *Methods*

The design of the pivotal M16-098 Study is presented in the figure below.




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

*Figure 7: The design of M16-098 Study*

## Study participants

Inclusion criteria:

1. Male or female ≥ 18 years of age.
2. Subject with a clinical diagnosis of AS and meeting the modified New York Criteria for AS.
3. Subject must have baseline disease activity as defined by having a 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.
4. Subject has had an inadequate response to at least two 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.
5. Women of childbearing potential, must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Baseline Visit prior to study drug dosing. Note: subjects with borderline serum pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result and the subject can be enrolled into the study in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.
6. If female, subject must be postmenopausal, OR permanently surgically sterile, OR for women of childbearing potential practicing at least one protocol-specified method of birth control, that is effective from Study Day 1 through at least 30 days after the last dose of study drug. (Additional local requirements may apply).
7. If male, and subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through 30 days after the last dose of oral study drug, to practice the protocol-specified contraception. (Additional local requirements may apply).
8. If entering the study on concomitant MTX, leflunomide, SSZ, and/or hydroxychloroquine, subject must be on a stable dose of MTX (≤ 25 mg/week) and/or SSZ (≤ 3 g/day) and/or hydroxychloroquine (≤ 400 mg/day) or leflunomide (≤ 20 mg/day) for at least 28 days prior to the Baseline Visit. A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide.
9. If entering the study on concomitant oral corticosteroids, subject must be on a stable dose of prednisone (≤ 10 mg/day), or oral corticosteroid equivalents, for at least 14 days prior to the Baseline Visit.
10. If entering the study on concomitant NSAIDs, tramadol, combination of acetaminophen and codeine or hydrocodone, and/or non-opioid analgesics, subject must be on stable dose(s) for at least 14 days prior to the Baseline Visit.
11. Object is judged to be in good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, CXR, and a 12-lead ECG performed at the Screening Visit.

12. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study- specific procedures. For subjects in Japan only: In case of subjects under 20 years of age, the subjects and their parents or legal guardians must voluntarily sign and date an informed conse

Exclusion criteria:

1. Prior exposure to any JAK inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).
2. Prior exposure to any biologic therapy with a potential therapeutic impact on SpA.
3. Subject has been treated with any investigational drug within 30 days or five half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study.
4. Intra-articular joint injections, spinal/paraspinal injection(s), or parenteral administration of corticosteroids within 28 days prior to the Baseline Visit. Inhaled or topical corticosteroids are allowed.
5. Subject on any other DMARDs (other than those allowed), thalidomide, or apremilast within 28 days or five half-lives (whichever is longer) of the drug prior to the Baseline Visit.
6. Subject on opioid analgesics (except for combination acetaminophen/codeine or acetaminophen/hydrocodone which are allowed) or use of inhaled marijuana within 14 day s prior to the Baseline Visit.
7. Subject has a history of inflammatory arthritis of different etiology other than axial SpA (including but not limited to RA, PsA, mixed connective tissue disease, systemic lupus erythematosus, reactive arthritis, scleroderma, polymyositis, dermatomyositis, fibromyalgia), or any arthritis with onset prior to 17 years of age.
8. Subject with extra-articular manifestations (e.g., psoriasis, uveitis, or IBD) that are not clinically stable for at least 30 days prior to study entry.
9. Subject has total spinal ankylosis.
10. Subject has undergone spinal or joint surgery at joints to be assessed within this study within 60 days prior to the Baseline Visit or subject has been diagnosed with a spinal condition that may interfere with study assessments (i.e., disc herniation, degenerative spine disease, etc.) in the opinion of the Investigator.
11. Subject is permanently wheelchair-bound or bedridden.
12. Receipt of any live vaccine within 4 weeks (8 weeks in Japan) prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4weeks (8 weeks in Japan) after the last dose of study drug.
13. Systemic use of known strong cytochrome P450 (CYP)3A inhibitors or strong CYP3A inducers from Screening through the end of the study (refer to Table 1 for examples of commonly used strong CYP3A inhibitors and inducers).
14. Use of oral traditional Chinese medicine within 4 weeks prior to the Baseline visit.

15. Any active, chronic or recurrent viral infection that, based on the Investigator's clinical assessment, makes the subject an unsuitable candidate for the study, including hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated (even a single episode) herpes zoster, disseminated (even a single episode) herpes simplex, or human immunodeficiency virus (HIV). HBV, HCV, and HIV infections are defined as:
    a. HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for Hepatitis B core antibody (HBc Ab) positive (+) subjects (and for Hepatitis B surface antibody (HBs Ab) positive [+] subjects in Japan only);
    b. HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCVantibody (HCV Ab).
    c. HIV: confirmed positive anti-HIV antibody (HIV Ab) test.
16. Subject has active TB or meets TB exclusionary parameters
17. Active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior the first dose of study drug.
18. History of any malignancy except for successfully treated NMSC or localized carcinoma in situ of the cervix.
19. History of gastrointestinal perforation (other than appendicitis or penetrating injury), diverticulitis or significantly increased risk for gastrointestinal perforation per Investigator judgment.
20. Conditions that could interfere with drug absorption including but not limited to short bowel syndrome.
21. Subject has been a previous recipient of an organ transplant.
22. History of recent (within past 6 months) cerebrovascular accident, myocardial infarction, or coronary stenting.
23. History of any condition which, in the opinion of the Investigator, would put the subject at risk by participating in the protocol.
24. History of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months.
25. History of an allergic reaction or significant sensitivity to constituents of the studydrug(s) (and their excipients) and/or other products in the same class.
26. Subject has contraindication to MRI or any condition that would interfere with the ability to perform an MRI.
27. Female subject who is breastfeeding or considering becoming pregnant during the study.
28. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug: Serum aspartate transaminase (AST) > 2 $\times$ ULN, serum alanine transaminase (ALT) > 2 $\times$ ULN, estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73m2, hemoglobin < 10 g/dL, total white blood cell count (WBC) < 2,500/$\mu$L, absolute neutrophil count (ANC) < 1,500/$\mu$L, absolute lymphocyte count < 800/$\mu$L, platelet count < 100,000/$\mu$L.

29. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.
30. For Japan subjects only: positive result of beta-D- glucan.

## Treatments

Eligible patients were randomized in a ratio 1:1 to either upadacitinib 15 mg or placebo. The tablet was taken orally daily beginning on Day 1 (Baseline) at approximately the same time each day, with or without food.

After week 14, all patients were to receive upadacitinib 15 mg open label.

Rescue therapy: Starting at Week 16, subjects who do not achieve at least an ASAS 20 response at two consecutive visits will 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(after assessments have been performed). Change in dose or addition of DMARDs other than MTX or SSZ is not permitted for rescue. Starting at Week 24, subjects who still do not achieve at least an ASAS 20 response at two consecutive visits will be discontinued from study drug treatment. ASAS 20 calculation for rescue and discontinuation criteria no longer applies post Week 104

## Objectives

Period 1

To evaluate the efficacy of upadacitinib compared with placebo on reduction of signs and symptoms as measured by the proportion of subjects who achieve an ASAS 40 response at Week 14 in subjects with active AS who have had an inadequate response to at least 2 non-steroidal anti-inflammatory drugs (NSAIDs) or intolerance to or a contraindication for NSAIDs, and who are naïve to biologic disease-modifying anti-rheumatic drugs (bDMARD).

To assess the safety and tolerability of upadacitinib in subjects with active AS who have had an inadequate response to at least 2 NSAIDs or intolerance to or a contraindication for NSAIDs, and who are bDMARD-naïve.

Period 2

To evaluate the safety, tolerability, and efficacy of upadacitinib through up to 2 years of treatment in subjects who have completed Period 1.

## Outcomes/endpoints

**Primary efficacy endpoint:** ASAS40 response at Week 14.

**Multiplicity-controlled key secondary endpoints (at Week 14):**

Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) based on CRP.

Change from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) MRI spine score

Subjects achieving at least 50% improvement in BASDAI (BASDAI50)

Change from baseline in ankylosing spondylitis quality of life (ASQoL)

Subjects achieving ASAS partial remission,

Change from baseline in the following outcomes:

- BASFI,
- linear Bath Ankylosing Spondylitis Metrology Index (BASMIlin),
- Maastricht Ankylosing Spondylitis Enthesitis Score (MASES),
- work productivity and activity impairment (WPAI)
- ASAS Health Index.

Additional key secondary endpoints included ASAS20 response at Week 14 and change from baseline in SPARCC MRI sacroiliac joint score at Week 14

Definition of endpoints

ASAS40 response: at least 40% improvement and an absolute improvement of at least 2 units on a numerical rating scale of 0– 10 from baseline in at least 3 of the following 4 domains, with no worsening in the remaining domain: Patient's Global Assessment of Disease Activity, Patient's Assessment of Total Back Pain, Bath Ankylosing Spondylitis Functional Index (BASFI), and inflammation defined as the mean of the BASDAI questions on severity and duration of morning stiffness (see below for definitions of BASDAI and BASFI).

ASAS Partial Remission: Absolute score of $\leq$ 2 units for each of the 4 domains identified above.

Ankylosing Spondylitis Disease Activity Score (ASDAS)(CRP): The ASDAS is a 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 high-sensitivity C-reactive protein (hsCRP). Higher scores indicate more active disease.

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

- ASDAS Inactive Disease: ASDAS < 1.3
- ASDAS Low Disease Activity: ASDAS < 2.1
- ASDAS Major Improvement: a change from baseline $\leq$ -2.0)
- ASDAS Clinically Important Improvement: change from baseline $\leq$ -1.1

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.

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 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 (duration and severity). 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 at least 50% improvement from Baseline in the BASDAI score.

Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire: The ASQoL is an 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.

The Bath Ankylosing Spondylitis Functional Index (BASFI): The BASFI assesses functional limitations in 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 (mean of the 10 item scores) ranges from 0 to 10, with higher scores indicating worse functioning.

BASMI: The BASMI assesses spinal mobility in patients with AS. The Linear BASMI (BASMIlin) composite score was 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.

The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES tool) is used to assess enthesitis in AS. The presence or absence of enthesitis at 13 different sites, noting the subjects' responses, is assessed. The following left and right locations were graded for presence (1) or absence (0) of enthesitis: 1st Costochondral joint, 7th Costochondral joint, Posterior Superior Iliac Spine, Anterior Superior Iliac Spine, Iliac Crest, Proximal Insertion of Achilles tendon; the 5th Lumbar Spinous process was also graded for enthesitis yielding a total score ranging 0 – 13.

Work Productivity and Activity Impairment (WPAI): A patient-reported measure of work productivity including presenteeism, absenteeism, overall work productivity loss, and daily activity impairment.

ASAS Health Index (HI): The ASAS HI is an instrument for use in patients with all forms of axSpA. 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.

## Sample size

The planned total sample size of 170, 85 in each treatment arm, was expected to provide at least 90% power to detect a 26% difference in ASAS 40 response rates at Week 14 assuming a placebo ASAS 40 response rate of 20%, using a two-sided $\alpha = 0.05$ and accounting for 10% dropout rate.

## Randomisation

Subjects who met eligibility criteria were to be randomised at day 1 (baseline) in a 1:1 ratio to one of the two treatment arms, upadacitinib 15 mg QD or placebo, using IRT (Interactive Response Technology).

Randomisation was stratified by screening high sensitivity C-reactive protein (hsCRP) (≤ upper limit of normal [ULN] vs. > ULN) and geographic region (United States [US]/Canada, Japan, Rest of the World [RoW]).

## Blinding (masking)

Period 1 was double-blind. In order to achieve and maintain the blind, upadacitinib tablets and placebo tablets provided for the study were to be identical in appearance. Period 2 is an open label long-term extension in which all subjects are treated with open label upadacitinib 15 mg QD. An unblinded analysis was planned once all subjects had completed Period 1 (Week 14) or discontinued prior to Week 14. Study sites and subjects were to remain blinded to the treatment assignment in Period 1 for the duration of the study. All sponsor personnel with direct oversight of the conduct and management of the trial (with the exception of Drug Supply Management Team) were to remain blinded to each subject's treatment throughout Period 1.

## Statistical methods

The primary analysis was conducted, as had been planned, after all subjects had completed Week 14 or discontinued prior to Week 14.

The SAP (version 2.0) was dated 20 Dec 2018 and the primary database lock for Period 1 (Week 0-14) was conducted on 05 February 2019 (the cut-off date was 21 Jan 2019).

All the efficacy analyses were performed using the Full Analysis Set which included all subjects who had been randomised and had received at least one dose of study drug. In addition, a PP Set and a Safety Set was pre-defined. The PP Set was a subset of the FAS and consisted of all FAS subjects who did not have any major protocol deviations up to Week 14. The Safety Analysis Set consisted of all subjects who received at least one dose of study drug with subjects analysed "as treated".

All efficacy analyses were performed adjusting for the stratification factor of hsCRP level collected at screening visit. No adjustment was made for multiple centres, and no summaries by study site are provided.

*The primary estimand*

The primary estimand was defined as the difference in the proportion of AS patients who achieved ASAS 40 response at Week 14 and did not discontinue study drug by Week 14, comparing those who were randomised to the upadacitinib 15 MG QD group and received study drug to those who were randomised to placebo and received study drug.

For binary key secondary efficacy endpoints, the primary estimand was defined as for the primary endpoint.

For continuous key secondary efficacy endpoints, the estimand was defined as the difference in mean change from baseline at Week 14 under the assumption that patients with missing data including those due to premature discontinuation of study drug could have their measurements at Week 14 predicted by their observed data and the observed data for other patients for their respective assessments during follow-up. The comparison was upadacitinib 15 mg QD vs placebo for patients randomised and treated with at least one dose of study drug.

*Handling of missing data and intercurrent events*

NRI

For binary endpoints, including the primary endpoint, a non-responder imputation approach was applied. Subjects who prematurely discontinued from study drug were considered as non-responders for all subsequent visits after discontinuation. In addition, any subject with any missing value for binary variables at a specific visit was to be treated as non-responder for that visit.

MMRM

Analyses of continuous endpoints were performed using a MMRM model based on the assumption of missing at random. For the MMRM analysis, any data collected after premature discontinuation of study drug were excluded.

As Observed (AO)

The AO data handling implied that no imputation of missing evaluations was performed, and a subject who did not have an evaluation on a scheduled visit was excluded from the AO analysis for that visit. Regardless of premature discontinuation of study drug, all observed data was used in the analysis.

*Primary efficacy analysis*

The primary efficacy endpoint was ASAS 40 response at Week 14. Comparisons between upadacitinib and placebo was performed using the Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factor of hsCRP level (≤ ULN vs. > ULN). Point estimate, 95% CI using normal approximation and p-value for the treatment comparison was presented. In addition, point estimate and 95% CI using normal approximation was provided for the response rate for each treatment group.

The number and percentage of non-responders for ASAS40 was to be summarized into three categories:

1. Subjects who discontinued study drug by Week 14

2. Subjects who didn't discontinue study drug but had missing Week 14 ASAS 40 measurements

3. Subjects with ASAS 40 measurements observed and on study drug at Week 14 but didn't meet ASAS 40 response criteria

*Analysis of Key Secondary Endpoints:*

For binary key secondary efficacy endpoints, the primary estimand was defined as for the primary endpoint and used the same analysis approach. Frequencies and percentages were reported for each treatment group and comparisons between the two treatment groups were performed using the Cochran-Mantel-Haenszel test, adjusting for main stratification factor of screening hsCRP level (> upper limit of normal [ULN] vs ≤ ULN).

For continuous key secondary efficacy endpoints between group comparisons were carried out using a mixed model for repeated measures (MMRM). The least squares mean change from baseline and 95% confidence interval were reported. The mixed model included treatment group, visit, and treatment-by-visit interaction as fixed effects, and the corresponding baseline values and the main stratification factor of screening hsCRP level (>ULN vs ≤ ULN) as the covariates. An unstructured variance covariance matrix was used. The parameter estimations were based on the assumption of data being missing at random and using the method of restricted maximum likelihood (REML).

*Supplementary and sensitivity analyses*

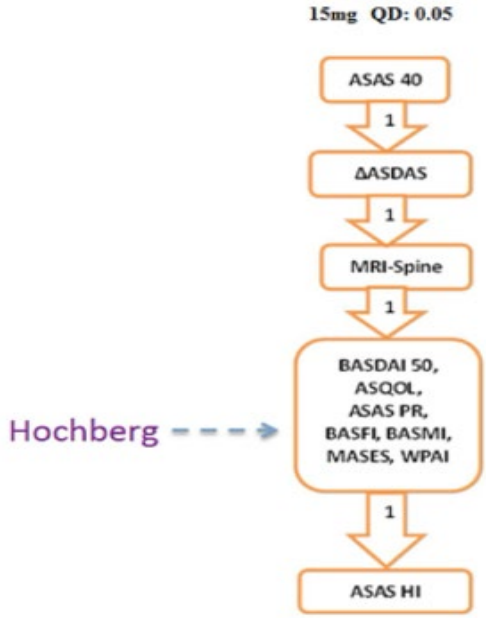
For the primary efficacy endpoint, the CMH analysis was repeated using As Observed (AO) data handling without any imputation. This analysis was conducted on the FAS based on randomised treatment groups. The corresponding estimand for the supplementary analysis was defined as the difference in the proportion of AS patients who achieved ASAS40 response at Week 14, regardless of whether the subject had discontinued study drug by Week 14, comparing upadacitinib 15 MG QD vs placebo for those who were randomised, received study drug and had a efficacy measurement at Week 14 visit.

Supplementary estimands were defined also for key secondary endpoints and aligned analyses using AO data handling were conducted.

*Handling of Multiplicity*

The overall type I error rate of the primary and multiplicity-adjusted key secondary endpoints was strongly controlled at 0.05 level using a fixed testing sequence where statistical significance could be claimed for a lower ranked endpoint only if the previous endpoint in the sequence met the requirements of significance. As a node in the fixed testing sequence, a group of multiple endpoints (including proportion of subjects with BASDAI 50 response, proportion of subjects with ASAS partial remission, changes from baseline in ASQoL, BASFI, BASMIlin, MASES, and WPAI) was tested using the Hochberg procedure at 0.05 level, conditional on significance of higher-ranked endpoints.

Graphical multiple testing procedure;




*Efficacy Subgroup Analysis*

The primary efficacy endpoint was further examined in the following subgroups:

| Subgroup Factor | Categories |
|---|---|
| Age | < 40, [40, 65), ≥ 65 |
| Sex | Male or Female |
| BMI | < 25, ≥ 25 |
| Race | White vs non-White |
| Geographic Region | North America, Europe, Other |
| hsCRP level at screening | ≤ ULN vs > ULN |

Treatment differences between upadacitinib and placebo were presented in a Forest plot with the point estimate and a 95% confidence interval using normal approximation.

*Long-Term Efficacy*

Long-term efficacy by time point was summarized based on observed data only (As Observed). The As Observed (AO) data handling implied that no imputation of values for missing evaluations were performed and thus, subjects without an evaluation on a scheduled visit were excluded from the AO analysis for that visit. Regardless of premature discontinuation of study drug, all observed data were used in the analysis.

Analyses were performed by randomised treatment group sequence:

1. Placebo → upadacitinib 15 mg QD

2. upadacitinib 15 mg QD → upadacitinib 15 mg QD

There was no statistical testing; descriptive statistics were provided for each randomised treatment group sequence. These included the number of observations, mean, standard deviation, 95% CI, median, minimum, Q1, Q3 and maximum for continuous endpoints; and frequencies and percentages with 95% CI using normal approximation for binary endpoints. Plots by randomised treatment group sequence over time were provided for the primary endpoint and all ranked (key) secondary endpoints.

At the cut-off date for the interim study report, all subjects had either discontinued prematurely or had completed 64 weeks of the study.

## ***Results***

## Participant flow

A total of 187 subjects were randomized (please refer to tables below). A total of 89 subjects in each treatment group completed Period 1 on study drug and entered Period 2 on study drug. One subject completed Period 1 study participation after discontinuing study drug. Adverse event was the most frequent primary reason for discontinuing study drug in the placebo group (3 subjects); in the upadacitinib group, adverse event and withdrawal by subject each accounted for 2 subjects.

Adverse events and withdrawal by subjects were also the most frequent reasons for discontinuation from study participation in Period 1. Up to the data cut-off date, 28 subjects who entered Period 2 on study drug discontinued study drug; the most frequent primary reason for discontinuation of study drug was lack of efficacy.

*Table 5: Subject Accountability (All Randomized Subjects), M16-098 Study*

| | Placebo N | Upadacitinib 15 mg QD N | Total N |
|---|---|---|---|
| Randomized | 94 | 93 | 187 |
| Treated | 94 | 93 | 187 |
| Full Analysis Set (FAS) | 94 | 93 | 187 |
| Per Protocol Analysis Set | 86 | 82 | 168 |
| Safety Analysis Set | 94 | 93 | 187 |
| Completed Period 1 Study Participation | 90 | 89 | 179 |
| Entered Period 2 | 90 | 89 | 179 |
| Completed Period 1 on Study Drug | 89 | 89 | 178 |
| Entered Period 2 on Study Drug | 89 | 89 | 178 |

*Table 6: Subject Final Status and Reasons for Study Drug Discontinuation -Period 1 (All Randomized Subjects), M16-098 Study*

| Discontinuation Due to | Placebo (N = 94) n (%) | Upadacitinib 15 mg QD (N = 93) n (%) | Total (N = 187) n (%) |
|---|---|---|---|
| All Reasons[a] | 5 (5.3) | 4 (4.3) | 9 (4.8) |
| Adverse Event | 3 (3.2) | 2 (2.2) | 5 (2.7) |
| Withdrawal by Subject | 1 (1.1) | 2 (2.2) | 3 (1.6) |
| Lost to Follow-up | 1 (1.1) | 0 | 1 (0.5) |
| Other | 1 (1.1) | 1 (1.1) | 2 (1.1) |
| Primary Reason | 5 (5.3) | 4 (4.3) | 9 (4.8) |
| Adverse Event | 3 (3.2) | 2 (2.2) | 5 (2.7) |
| Withdrawal by Subject | 1 (1.1) | 2 (2.2) | 3 (1.6) |
| Lost to Follow-up | 1 (1.1) | 0 | 1 (0.5) |

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.

*Table 7: Subject Final Status and Reasons for Study Participation Discontinuation –Period 1, M16-098 Study*

| Discontinuation Due to | Placebo (N = 94) n (%) | Upadacitinib 15 mg QD (N = 93) n (%) | Total (N = 187) n (%) |
|---|---|---|---|
| All Reasons[a] | 4 (4.3) | 4 (4.3) | 8 (4.3) |
| Adverse Event | 1 (1.1) | 2 (2.2) | 3 (1.6) |
| Withdrawal by Subject | 3 (3.2) | 1 (1.1) | 4 (2.1) |
| Lost to Follow-up | 1 (1.1) | 0 | 1 (0.5) |
| Other | 0 | 2 (2.2) | 2 (1.1) |
| Primary Reason | 4 (4.3) | 4 (4.3) | 8 (4.3) |
| Adverse Event | 1 (1.1) | 1 (1.1) | 2 (1.1) |
| Withdrawal by Subject | 2 (2.1) | 1 (1.1) | 3 (1.6) |
| Lost to Follow-up | 1 (1.1) | 0 | 1 (0.5) |
| Other | 0 | 2 (2.2) | 2 (1.1) |

a. Subjects who discontinued study participation 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.

*Table 8: Subject Final Status and Reasons for Study Drug Discontinuation -Period 2 (Subjects Who Entered Period 2 on Study Drug), M16-098 Study*

| Discontinuation Due to | Upadacitinib 15 mg QD (N = 178) n (%) |
|---|---|
| All Reasons[a] | 28 (15.7) |
| Adverse Event | 9 (5.1) |
| Withdrawal by Subject | 6 (3.4) |
| Lost to Follow-up | 1 (0.6) |
| Lack of Efficacy | 12 (6.7) |
| Other | 3 (1.7) |
| Primary Reason | 28 (15.7) |
| Adverse Event | 8 (4.5) |
| Withdrawal by Subject | 5 (2.8) |
| Lost to Follow-up | 1 (0.6) |
| Lack of Efficacy | 11 (6.2) |
| Other | 3 (1.7) |

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

62 sites in 20 countries: Australia, Belgium, Canada, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Japan, Netherlands, New Zealand, Poland, Portugal, Republic of Korea, Spain, Sweden, United Kingdom, United States.

First Subject First Visit: 24 October 2017

Last Subject Last Visit: 31 January 2020

## Conduct of the study

At the time of the data cut-off for this interim clinical study report, the original protocol (12 April 2017, 0 subjects enrolled) had 2 global amendments, 2 global administrative changes, 4 country- or region-specific amendments, and 2 country-specific administrative changes.

The amendments and number of subjects enrolled under each global amendment were as follows:

- Amendment 1 (12 September 2017, 187 subjects)
- Amendment 2 (20 December 2019, 0 subjects)

Global Amendment 1:

- Removed the upadacitinib 30 mg QD dose from the study design.
- Updated the study phase description from Phase 2b/3 to Phase 2/3.
- Modified the description of an inadequate response to NSAIDs required for study participation.
- Updated the approximate number of sites from 120 to 107.
- Updated the approximate sample size from 228 to 170 subjects.
- Modified the study design for Period 2 from blinded to open-label design with only one open-label dose (15 mg) in Period 2.
- Allowed earlier consideration of rescue therapy at Week 16 instead of Week 20 for concomitant pain medications and Week 20 instead of Week 24 for certain concomitant csDMARDs.
- Allowed earlier discontinuation of study drug treatment (at Week 24 instead of Week 32), including calculation of Assessment of Spondylo-Arthritis international Society (ASAS) 20 score beginning at Week 16 to determine subject response.
- Updated results from other clinical studies in support of benefit and risk assessment.
- Update references to spondyloarthritis to specify axial manifestation, where not previously defined. Removed the statement on subject enrollment after target number has been reached to allow all subjects in screening to enroll if otherwise eligible.
- Updated tuberculosis testing and prophylaxis information.
- Updated the schedule for premature discontinuation (PD) visits for those subjects still participating in the study but no longer taking study drug.
- Updated contraception information for female subjects who become surgically sterile or post-menopausal during the course of the study.
- Updated reader assignments and information on purpose of evaluation for x- ray measurements.
- Updated the visit window and information on the purpose of evaluation magnetic resonance imaging (MRI) measurements.
- Updated information on the purpose of evaluation for low-dose computed tomography (CT) measurements.
- Updated assessment information for x-ray, MRI, and low-dose CT measurements.

- Updated the requirements for use of local hsCRP testing.
- Updated Hepatitis B infection definition and testing requirements.
- Clarified the impact of corticosteroid injections on swollen joint count (SJC) and dactylitis assessments.
- Added "embolic and thrombotic events" to the Adverse Events of Special Interest and added a Supplemental electronic case report form (eCRF) for embolic and thrombotic events.
- Updated the list of Adverse Events of Special Interest.
- Updated adverse event severity assessment and laboratory and vital sign change assessment to reference Common Terminology Criteria for Adverse Events (CTCAE) criteria.
- Updated the instructions on collection of adverse event information after subject premature discontinuation for subjects who continued in the study but were off study drug.
- Updated supplemental information to be collected for certain cardiovascular, herpes zoster, and thrombotic/embolic adverse events reported during the study.
- Updated Suspected Unexpected Serious Adverse Reactions (SUSAR) event reporting reference.
- Updated information to be collected on pregnancies reported during the study.
- Updated toxicity criteria for potentially serious gastrointestinal (GI) events reported during the study.
- Updated toxicity management guidelines for serum creatinine laboratory values.
- Updated toxicity management guidelines for creatine phosphokinase (CPK)laboratory values.
- Updated the timeframe for product complaint reporting from 24 hours to 1 business day.
- Updated the planned statistical analyses for multiplicity control.
- Updated the statistical power for the primary endpoint from 80% to 90%.

Global Amendment 2:

- Added events of deep vein thrombosis (DVT)and pulmonary embolism (PE) to the adverse events that have been observed in subjects who receive JAK inhibitors, including upadacitinib
- Added management of thrombosis events.
- Added management of herpes zoster and a recommendation for periodic skin examination for subjects who are at increased risk for skin cancer.
- Amended the wording for subjects who experience a study drug interruption > 7 consecutive days during Weeks 1 through 14 (Period 1) or > 30 consecutive days during Period2 to allow the Investigator to decide if the drug should be re-started; previous wording required that upadacitinib be permanently discontinued if interruptions of those lengths occurred

A summary of ICH-Defined Protocol Deviations is provided in the table below.

*Table 9: Summary of ICH-Defined Protocol Deviations (All Randomized Subjects), M16-098 Study*

| Criteria Category | Placebo (N = 94) n (%) | Upadacitinib 15 mg QD (N = 93) n (%) | Total (N = 187) n (%) |
|---|---|---|---|
| Category 1: Subject entered into the study even though she/he did not satisfy entry criteria | | | |
| Inclusion Criteria | | | |
| 3 | 9 (9.6) | 11 (11.8) | 20 (10.7) |
| Exclusion Criteria | | | |
| 6 | 0 | 1 (1.1) | 1 (0.5) |
| Any Inclusion Criterion Not Met | 9 (9.6) | 11 (11.8) | 20 (10.7) |
| Any Exclusion Criterion Met | 0 | 1 (1.1) | 1 (0.5) |
| Any Inclusion/Exclusion Criterion Violated | 9 (9.6) | 12 (12.9) | 21 (11.2) |
| Category 2: Subject who developed withdrawal criteria during the study and were not withdrawn | 2 (2.1) | 0 | 2 (1.1) |
| Category 3: Subject who received wrong treatment or incorrect dose | 0 | 1 (1.1) | 1 (0.5) |
| Category 4: Subject who received excluded or prohibited concomitant treatment | 5 (5.3) | 1 (1.1) | 6 (3.2) |

## Baseline data

*Table 10: Key Demographic Characteristics of All Randomized Subjects at Baseline (FAS), M16-098 Study*

| | Placebo (N = 94) | Upadacitinib 15 mg QD (N = 93) | Total (N = 187) |
|---|---|---|---|
| Sex - n (%) | | | |
| Female | 25 (26.6) | 30 (32.3) | 55 (29.4) |
| Male | 69 (73.4) | 63 (67.7) | 132 (70.6) |
| Ethnicity - n (%) | | | |
| Hispanic or Latino | 5 (5.3) | 4 (4.3) | 9 (4.8) |
| Not Hispanic or Latino | 89 (94.7) | 89 (95.7) | 178 (95.2) |
| Race - n (%) | | | |
| White | 76 (80.9) | 79 (84.9) | 155 (82.9) |
| Black or African American | 2 (2.1) | 1 (1.1) | 3 (1.6) |
| Asian | 16 (17.0) | 13 (14.0) | 29 (15.5) |
| Age (Years) | | | |
| Mean (SD) | 43.7 (12.07) | 47.0 (12.78) | 45.4 (12.50) |
| Median | 44.0 (22, 67) | 48.0 (21, 74) | 46.0 (21, 74) |
| Age group (Years) - n (%) | | | |
| < 40 | 39 (41.5) | 28 (30.1) | 67 (35.8) |
| 40 - 64 | 53 (56.4) | 56 (60.2) | 109 (58.3) |
| ≥ 65 | 2 (2.1) | 9 (9.7) | 11 (5.9) |
| Weight (kg) | | | |
| Mean (SD) | 80.2 (17.23) | 79.0 (18.30) | 79.6 (17.73) |
| Median (min, max) | 77.7 (55, 157) | 77.0 (47, 149) | 77.6 (47, 157) |
| Weight (kg) - n (%) | | | |
| < 60 | 6 (6.4) | 14 (15.1) | 20 (10.7) |
| ≥ 60 | 88 (93.6) | 79 (84.9) | 167 (89.3) |
| Body Mass Index ($kg/m^2$) | | | |
| Mean (SD) | 26.9 (5.05) | 26.6 (4.88) | 26.8 (4.96) |
| Median (min, max) | 26.1 (19, 42) | 26.2 (17, 44) | 26.1 (17, 44) |

| | | | |
|---|---|---|---|
| Body Mass Index category ($kg/m^2$) - n (%) | | | |
| < 25 | 40 (42.6) | 37 (39.8) | 77 (41.2) |
| ≥ 25 | 54 (57.4) | 56 (60.2) | 110 (58.8) |
| Region - n (%) | | | |
| North America | 10 (10.6) | 9 (9.7) | 19 (10.2) |
| Western Europe | 33 (35.1) | 30 (32.3) | 63 (33.7) |
| Eastern Europe | 34 (36.2) | 36 (38.7) | 70 (37.4) |
| Asia[a] | 14 (14.9) | 12 (12.9) | 26 (13.9) |
| Other[b] | 3 (3.2) | 6 (6.5) | 9 (4.8) |
| Tobacco/Nicotine Use - n (%) | | | |
| Current | 37 (39.4) | 32 (34.4) | 69 (36.9) |
| Former | 15 (16.0) | 18 (19.4) | 33 (17.6) |
| Never | 42 (44.7) | 43 (46.2) | 85 (45.5) |
| Alcohol Use – n (%) | | | |
| Current | 63 (67.0) | 55 (59.1) | 118 (63.1) |
| Former | 9 (9.6) | 9 (9.7) | 18 (9.6) |
| Never | 22 (23.4) | 29 (31.2) | 51 (27.3) |

SD = standard deviation

a. 13 subjects each were from Japan and the Republic of Korea.

b. Australia and New Zealand.

Note: Numbers of subjects for each variable are the same as shown in the column header unless otherwise noted. 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.

*Table 11: Disease-Related Baseline Characteristics, M16-098 Study*

| | Placebo (N = 94) | Upadacitinib 15 mg QD (N = 93) | Total (N = 187) |
|---|---|---|---|
| Duration (Years) of AS Symptoms | | | |
| n | 94 | 93 | 187 |
| Mean (SD) | 14.0 (9.86) | 14.8 (11.64) | 14.4 (10.76) |
| Median (min, max) | 12.3 (0.5, 41.4) | 10.3 (0.8, 51.9) | 10.6 (0.5, 51.9) |
| Duration (Years) since AS Diagnosis | | | |
| n | 94 | 93 | 187 |
| Mean (SD) | 6.0 (6.79) | 7.8 (10.64) | 6.9 (8.94) |
| Median (min, max) | 3.5 (0.1, 30.6) | 2.9 (0.1, 40.9) | 3.5 (0.1, 40.9) |
| Duration (Years) since AS Diagnosis - n (%) | | | |
| < 5 | 55 (58.5) | 55 (59.1) | 110 (58.8) |
| ≥ 5 | 39 (41.5) | 38 (40.9) | 77 (41.2) |
| HLA-B27 - n (%) | | | |
| Positive | 73 (77.7) | 70 (75.3) | 143 (76.5) |
| Negative | 20 (21.3) | 21 (22.6) | 41 (21.9) |
| Missing | 1 (1.1) | 2 (2.2) | 3 (1.6) |
| Key Disease History at Screening[a] - n (%) | | | |
| Psoriasis | 3 (3.2) | 4 (4.3) | 7 (3.7) |
| Inflammatory bowel disease | 2 (2.1) | 2 (2.2) | 4 (2.1) |
| Anterior uveitis | 24 (25.5) | 16 (17.2) | 40 (21.4) |
| Patient's Global Assessment of Disease Activity NRS score 0 - 10 | | | |
| n | 94 | 91 | 185 |
| Mean (SD) | 6.8 (1.66) | 6.6 (1.81) | 6.7 (1.73) |
| Median (min, max) | 7.0 (1, 10) | 7.0 (1, 10) | 7.0 (1, 10) |

| | | | |
|---|---|---|---|
| Patient's Assessment of Total Back Pain NRS score 0 - 10 | | | |
| n | 94 | 92 | 186 |
| Mean (SD) | 6.7 (1.78) | 6.8 (1.77) | 6.8 (1.78) |
| Median (min, max) | 7.0 (2, 10) | 7.0 (2, 10) | 7.0 (2, 10) |
| Patient's Assessment of Back Pain (BASDAI Question 2 NRS Score 0 - 10) | | | |
| n | 94 | 92 | 186 |
| Mean (SD) | 7.3 (1.53) | 7.1 (1.83) | 7.2 (1.69) |
| Median (min, max) | 7.0 (3, 10) | 7.0 (2, 10) | 7.0 (2, 10) |
| Patient's Global Assessment of Pain NRS score 0 - 10 | | | |
| n | 94 | 91 | 185 |
| Mean (SD) | 6.9 (1.58) | 6.8 (1.58) | 6.9 (1.58) |
| Median (min, max) | 7.0 (1, 10) | 7.0 (1, 10) | 7.0 (1, 10) |
| BASDAI | | | |
| n | 94 | 92 | 186 |
| Mean (SD) | 6.5 (1.56) | 6.3 (1.76) | 6.4 (1.66) |
| Median (min, max) | 6.7 (2, 10) | 6.6 (1, 10) | 6.7 (1, 10) |
| Inflammation (mean of Questions 5 and 6 of BASDAI NRS scores 0 - 10) | | | |
| n | 94 | 92 | 186 |
| Mean (SD) | 6.7 (1.90) | 6.5 (1.99) | 6.6 (1.94) |
| Median (min, max) | 6.5 (1, 10) | 6.5 (1, 10) | 6.5 (1, 10) |
| Function - Represented by the BASFI score 0 - 10 | | | |
| n | 94 | 91 | 185 |
| Mean (SD) | 5.5 (2.17) | 5.4 (2.36) | 5.4 (2.26) |
| Median (min, max) | 5.9 (0, 9) | 6.0 (1, 10) | 5.9 (0, 10) |
| ASDAS(CRP) | | | |
| n | 94 | 91 | 185 |
| Mean (SD) | 3.7 (0.74) | 3.5 (0.76) | 3.6 (0.76) |
| Median (min, max) | 3.6 (2, 5) | 3.5 (1, 5) | 3.6 (1, 5) |
| MRI SPARCC Score (Spine)[b] | | | |

| | | | |
|---|---|---|---|
| n | 81 | 84 | 165 |
| Mean (SD) | 11.9 (14.52) | 10.4 (14.36) | 11.2 (14.41) |
| Median (min, max) | 4.5 (0, 49) | 3.5 (0, 68) | 4.5 (0, 68) |
| MRI SPARCC Score (SI Joint)[b] | | | |
| n | 80 | 84 | 164 |
| Mean (SD) | 5.4 (8.55) | 7.9 (10.91) | 6.6 (9.88) |
| Median (min, max) | 0.0 (0, 33) | 1.0 (0, 40) | 0.5 (0, 40) |
| BASMI | | | |
| n | 94 | 93 | 187 |
| Mean (SD) | 3.5 (1.48) | 3.7 (1.45) | 3.6 (1.46) |
| Median (min, max) | 3.2 (1, 7) | 3.5 (1, 7) | 3.4 (1, 7) |
| Presence of Enthesitis[c] | | | |
| Yes | 55 (58.5) | 54 (58.1) | 109 (58.3) |
| No | 39 (41.5) | 39 (41.9) | 78 (41.7) |
| MASES | | | |
| n | 55 | 54 | 109 |
| Mean (SD) | 3.7 (2.71) | 3.9 (2.79) | 3.8 (2.74) |
| Median (min, max) | 3.0 (1, 12) | 3.0 (1, 13) | 3.0 (1, 13) |
| ASAS HI | | | |
| n | 94 | 91 | 185 |
| Mean (SD) | 8.2 (3.84) | 8.6 (4.12) | 8.4 (3.97) |
| Median (min, max) | 8.0 (1, 17) | 8.0 (0, 17) | 8.0 (0, 17) |
| WPAI-S3 Overall Work Impairment (0-100)[d] | | | |
| n | 66 | 64 | 130 |
| Mean (SD) | 53.3 (24.64) | 54.3 (28.10) | 53.8 (26.30) |
| Median (min, max) | 50.0 (0, 100) | 60.0 (0, 100) | 57.8 (0, 100) |
| ASQoL | | | |
| n | 94 | 91 | 185 |
| Mean (SD) | 10.3 (4.65) | 10.0 (5.27) | 10.1 (4.96) |
| Median (min, max) | 10.5 (0, 18) | 9.0 (0, 18) | 10.0 (0, 18) |

| | | | |
|---|---|---|---|
| hsCRP (mg/L) at Screening | | | |
| n | 94 | 93 | 187 |
| Mean (SD) | 11.7 (11.11) | 9.6 (12.57) | 10.7 (11.88) |
| Median (min, max) | 8.0 (0.2, 47.7) | 6.0 (0.2, 78.4) | 7.4 (0.2, 78.4) |
| hsCRP Level at Screening - n (%) | | | |
| > ULN | 68 (72.3) | 67 (72.0) | 135 (72.2) |
| ≤ ULN | 26 (27.7) | 26 (28.0) | 52 (27.8) |
| Physician's Global Assessment of Disease Activity NRS score 0 - 10 | | | |
| n | 88 | 90 | 178 |
| Mean (SD) | 6.9 (1.43) | 6.7 (1.58) | 6.8 (1.51) |
| Median (min, max) | 7.0 (3, 10) | 7.0 (1, 10) | 7.0 (1, 10) |

ASQoL = AS quality of life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; HI = health index; HLA-B27 = human leukocyte antigen-B27; hsCRP = high sensitivity C-reactive protein; NRS = numeric rating scale; SD = standard deviation; SPARCC = Spondyloarthritis Research Consortium of Canada; ULN = upper limit of normal; WPAI = Work Productivity and Activity Impairment

a. These diseases are not mutually exclusive.

b. Includes baseline MRI data up to 3 days post first dose of study drug.

c. Based on MASES > 0 at baseline.

d. Including subjects currently employed according to WPAI S0.

Note: hsCRP ULN = 2.87 mg/L.

There were approximately 71% males and 29% females. The mean duration of AS symptoms at Baseline was 14.4 years (median = 10.6 years), and the mean duration since AS diagnosis was 6.9 years (median = 3.5 years). Mean and median Baseline values for PtGA, Patient's Assessment of Total Back Pain, Patient's Global Assessment of Pain, BASDAI, inflammation (mean of BASDAI Q5 and Q6), which use a 0 to 10 NRS, were 6.4 to 7.0. The mean hsCRP was 10.7 mg/L (median = 7.4 mg/L; upper limit of normal [ULN] = 2.87 mg/L). The mean MRI SPARCC scores for spine and sacroiliac joints were 11.2 (mean = 4.5) and 6.6 (median =0.5), respectively

The most frequently reported conditions (≥ 5% of total subjects) in the medical history were hypertension (18.2%), osteoarthritis (13.4%), seasonal allergy (9.1%), latent tuberculosis (8.0%), asthma (7.0%), vitamin D deficiency (7.0%), foot deformity (5.9%), depression (5.3%), and spinal pain (5.3%). All subjects had prior NSAID use except for 1 subject who had a contraindication to NSAID use (186/187). Approximately 37% to 38% of subjects in each group had prior conventional-synthetic (cs) DMARD use, and approximately 18% to 19% of subjects in each group had prior corticosteroid use.

During Period 1, 86.2% of subjects in the placebo group and 76.3% of subjects in the upadacitinib group took ≥ 1 concomitant NSAID. In the placebo group, 12.8% of subjects took ≥ 1 concomitant corticosteroid compared with 6.5% of subjects in the upadacitinib group and 18.1% in the placebo group and 14.0% in the upadacitinib group received concomitant csDMARD therapy.

## Numbers analysed

A total of 187 subjects were randomized in the study, 94 in the placebo group and 93 in the upadacitinib group.

All randomised subjects received at least one dose of randomised treatment and were thereby included in the Full Analysis Set. This was the primary analysis set to be used for all efficacy analyses. For number of subjects included in each analysis set, see below excerpt from Table 5 in the Participant flow section (above).

*Table 12 Number of subjects included in each analysis set*

| | Placebo N | Upadacitinib 15 mg QD N | Total N |
|---|---|---|---|
| Randomized | 94 | 93 | 187 |
| Treated | 94 | 93 | 187 |
| Full Analysis Set (FAS) | 94 | 93 | 187 |
| Per Protocol Analysis Set | 86 | 82 | 168 |
| Safety Analysis Set | 94 | 93 | 187 |

## Outcomes and estimation

Period 1 data were analysed using the primary database (05 February 2019). Long-term data were analysed using the 1-year database (13 February 2020).

*Outcome of the Primary Endpoint*

A statistically significant difference vs placebo was achieved for upadacitinib treatment based on the primary endpoint ASAS40 at Week 14 using NRI.

*Table 13: Analysis of ASAS40 at Week 14 (NRI; FAS), M16-098 Study*

| | | Responder | Response Rate | Response Rate Diff (Upadacitinib - Placebo) | | |
|---|---|---|---|---|---|---|
| Treatment | N | n (%) | (95% CI)[a] | Point Estimate | (95% CI)[b] | *P*-Value[c] |
| Placebo | 94 | 24 (25.5) | 25.5 (16.7, 34.3) | | | |
| Upadacitinib 15 mg QD | 93 | 48 (51.6) | 51.6 (41.5, 61.8) | 26.1 | (12.6, 39.5) | < 0.001 |

CI = confidence interval

a. 95% CIs for response rate are calculated based on normal approximation to the binomial distribution.

b. 95% CIs for response rate difference are calculated based on normal approximation using PROC FREQ.

c. Nominal *P*-value is constructed using Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor of screening hsCRP level.

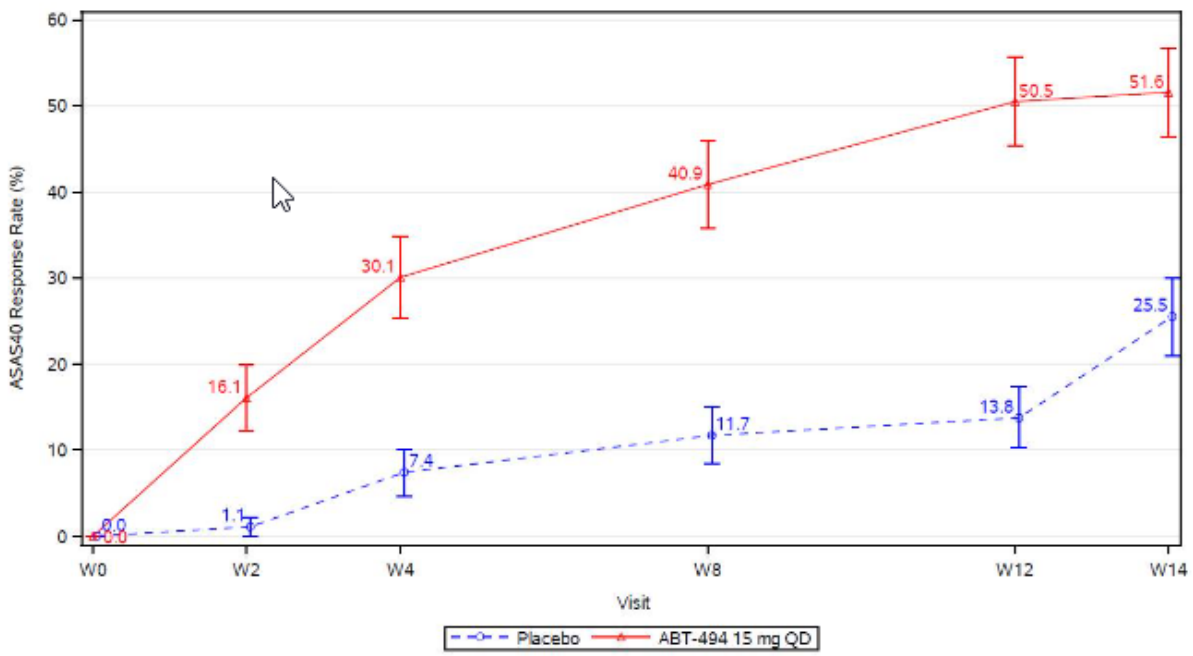
The majority of the ASAS40 non-responders were based on observed data. Out of the 14 subjects imputed as non-responders, 5 were due to missing measurements, and 9 were due to study drug discontinuation prior to Week 14; see the table below.

*Table 14: ASAS Response at week 14 by Intercurrent Events, M16-098 Study*

ASAS20/40 Response at Week 14 by Intercurrent Events (NRI)
(Full Analysis Set)

| | Placebo | ABT-494 15 mg QD |
|---|---|---|
| ASAS 40 | | |
| N | 94 | 93 |
| Responders n (%) | 24 (25.5) | 48 (51.6) |
| Non-Responders n (%) | 70 (74.5) | 45 (48.4) |
| Discontinued study drug | 5 (5.3) | 4 (4.3) |
| Missing measurements | 3 (3.2) | 2 (2.2) |
| Observed | 62 (66.0) | 39 (41.9) |
| ASAS 20 | | |
| N | 94 | 93 |
| Responders n (%) | 38 (40.4) | 60 (64.5) |
| Non-Responders n (%) | 56 (59.6) | 33 (35.5) |
| Discontinued study drug | 5 (5.3) | 4 (4.3) |
| Missing measurements | 2 (2.1) | 2 (2.2) |
| Observed | 49 (52.1) | 27 (29.0) |

*Table 15: ASAS40 Response Rate by Visit in Period 1 (NRI, FAS), M16-098 Study*




*Outcome of the ranked secondary endpoints*

In the table presenting ranked key secondary endpoints "N" had not been explained and for the continuous endpoints' "N" was consistently smaller than the number of subjects included in FAS (placebo:94 and upadacitinib:93). Upon request from the CHMP, the MAH confirmed that all subjects included in the FAS was also included in the analyses of ranked key secondary continuous endpoints and that "N" in Table 15 represents the number of subjects with change from baseline measurements at Week 14.

*Table 16; Summary of Ranked Secondary Efficacy Endpoint Results (FAS), M16-098 Study*

| Endpoint[a] Treatment | N | Within Group Point Estimate (95% CI) | Between Group Difference (Upadacitinib - Placebo) Point Estimate (95% CI) | Nominal *P*-Value | Multiplicity Adjusted Results[b] |
|---|---|---|---|---|---|
| ASDAS(CRP) Change from Baseline at Week 14 | | | | | |
| Placebo | 84 | –0.54 (–0.71, –0.37) | | | |
| Upadacitinib | 84 | –1.45 (–1.62, –1.28) | –0.91 (–1.14, –0.68) | < 0.001 | Significant |
| SPARCC Score - Spine[c] Change from Baseline at Week 14 | | | | | |
| Placebo | 60 | –0.22 (–2.01, 1.57) | | | |
| Upadacitinib | 68 | –6.93 (–8.58, –5.28) | –6.71 (–9.01, –4.41) | < 0.001 | Significant |
| BASDAI 50 Response Rate at Week 14[d] | | | | | |
| Placebo | 94 | 23.4 (14.8, 32.0) | | | |
| Upadacitinib | 93 | 45.2 (35.0, 55.3) | 21.8 (8.5, 35.0) | 0.002 | Significant |
| ASQoL Change from Baseline at Week 14[d] | | | | | |
| Placebo | 88 | –2.67 (–3.58, –1.75) | | | |
| Upadacitinib | 88 | –4.20 (–5.12, –3.29) | –1.54 (–2.78, –0.30) | 0.016 | Not significant |
| ASAS Partial Remission (PR) Response Rate at Week 14[d] | | | | | |
| Placebo | 94 | 1.1 (0.0, 3.1) | | | |
| Upadacitinib | 93 | 19.4 (11.3, 27.4) | 18.3 (10.0, 26.6) | < 0.001 | Significant |
| BASFI Change from Baseline at Week 14[d] | | | | | |
| Placebo | 86 | –1.30 (–1.74, –0.86) | | | |
| Upadacitinib | 86 | –2.29 (–2.73, –1.85) | –1.00 (–1.60, –0.39) | 0.001 | Significant |
| BASMI Change from Baseline at Week 14[d] | | | | | |
| Placebo | 89 | –0.14 (–0.29, 0.01) | | | |
| Upadacitinib | 89 | –0.37 (–0.52, –0.21) | –0.22 (–0.43, –0.02) | 0.030 | Not significant |
| MASES (for Subjects with Baseline Enthesitis) Change from Baseline at Week 14[d] | | | | | |
| Placebo | 51 | –1.41 (–2.02, –0.80) | | | |
| Upadacitinib | 50 | –2.25 (–2.86, –1.64) | –0.84 (–1.68, –0.00) | 0.049 | Not significant |
| WPAI Overall Work Impairment[e] Change from Baseline at Week 14[d] | | | | | |
| Placebo | 53 | –12.60 (–19.04, –6.15) | | | |
| Upadacitinib | 55 | –18.11 (–24.73, –11.50) | –5.52 (–13.82, 2.78) | 0.190 | Not significant |
| ASAS Health Index (HI) Change from Baseline at Week 14 | | | | | |
| Placebo | 88 | –1.38 (–2.11, –0.65) | | | |
| Upadacitinib | 88 | –2.75 (–3.48, –2.02) | –1.37 (–2.37, –0.37) | 0.007 | Not significant[f] |

a. Results for binary endpoints are based on non-responder imputation. Results for continuous endpoints are based on MMRM model.

b. Multiplicity adjusted results are obtained via the sequential multiple testing procedure with the group of endpoints denoted with "d" tested using the Hochberg procedure as one node in the sequence. The testing procedure controls the overall type I error rate of all primary and ranked secondary endpoints at the 0.05 level.

c. Baseline includes MRI data up to 3 days post first dose of study drug and Week 14 includes MRI data up to first dose of Period 2 study drug.

d. Variables in the Hochberg procedure.

e. Includes subjects currently employed according to WPAI S0.

f. Result is designated as not significant because the chain was broken before ASAS HI, and therefore it was not evaluated.

*Additional Efficacy analysis*

*Table 17: Clinical Response to upadacitinib 15 mg QD: ASAS20, BASDAI, and ASDAS Results in Study M16-098 at Week14 (Full Analysis Set), M16-098 Study*

| Endpoint | Placebo N = 94 | Upadacitinib 15 mg QD N = 93 | Nominal *P*-value[a] |
|---|---|---|---|
| ASAS20 response rate | 40.4% | 64.5% | 0.001 |
| ASAS PR response rate | 1.1% | 19.4% | < 0.001[b] |
| BASDAI50 response rate | 23.4% | 45.2% | 0.002[b] |
| BASDAI[c] | –1.63 | –2.75 | < 0.001 |
| ASDAS(CRP)[d] | –0.54 | –1.45 | < 0.001[b] |
| ASDAS Low Disease Activity, % | 10.6% | 49.5% | < 0.001 |
| ASDAS Inactive Disease, % | 0 | 16.1% | < 0.001 |
| ASDAS Clinically Important Improvement, % | 18.1% | 52.7% | < 0.001 |
| ASDAS Major Improvement, % | 5.3% | 32.3% | < 0.001 |

ASAS = Assessment in SpondyloArthritis international Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index

a. Results for proportion of subjects (binary endpoints) are based on non-responder imputation analysis. Results for continuous endpoints (change from baseline) are based on mixed effect model repeated measurement analysis.

b. Statistically significant results in the multiplicity-adjusted analyses obtained via the sequential multiple testing procedure with one node of group of endpoints tested in the Hochberg procedure.

c. n = 86 for each treatment group.

d. n = 84 for each treatment group.

## Long-Term Efficacy Results

The MAH states that the long-term efficacy data were analysed on as observed data for each randomized treatment group sequence.

According to the MAH, in long-term data through Week 64, ASAS40 response rates and component scores were consistently maintained and continued to improve over time for subjects who were randomized to upadacitinib. Subjects who were randomized to placebo and switched to upadacitinib at Week 14 showed a similar response to upadacitinib in terms of speed of onset and magnitude of improvement after switching. Each ASAS component had a similar pattern of continued improvement in subjects who were randomized to upadacitinib and rapid onset of improvement after switching.

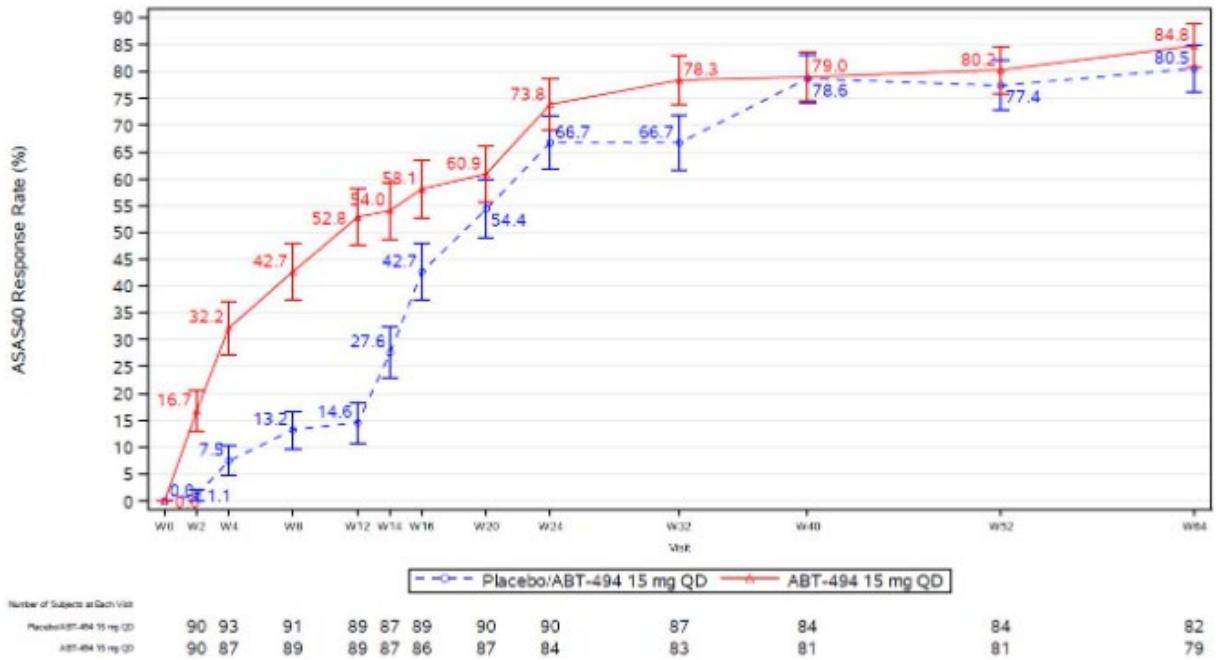



*Figure 8: ASAS40 Response Rate, Weeks 0 to 64 (AO, FAS), M16-098 Study*

## Ancillary analyses

Outcome was analysed according to the following subgroups (please refer to outcome in figure below).

- Age group: < 40, 40 to 65, ≥ 65
- Gender: male, female
- BMI: < 25, ≥ 25
- Race: white, non-white
- Geographic Region: North America, Europe, Other
- hsCRP level at screening: ≤ ULN, > ULN

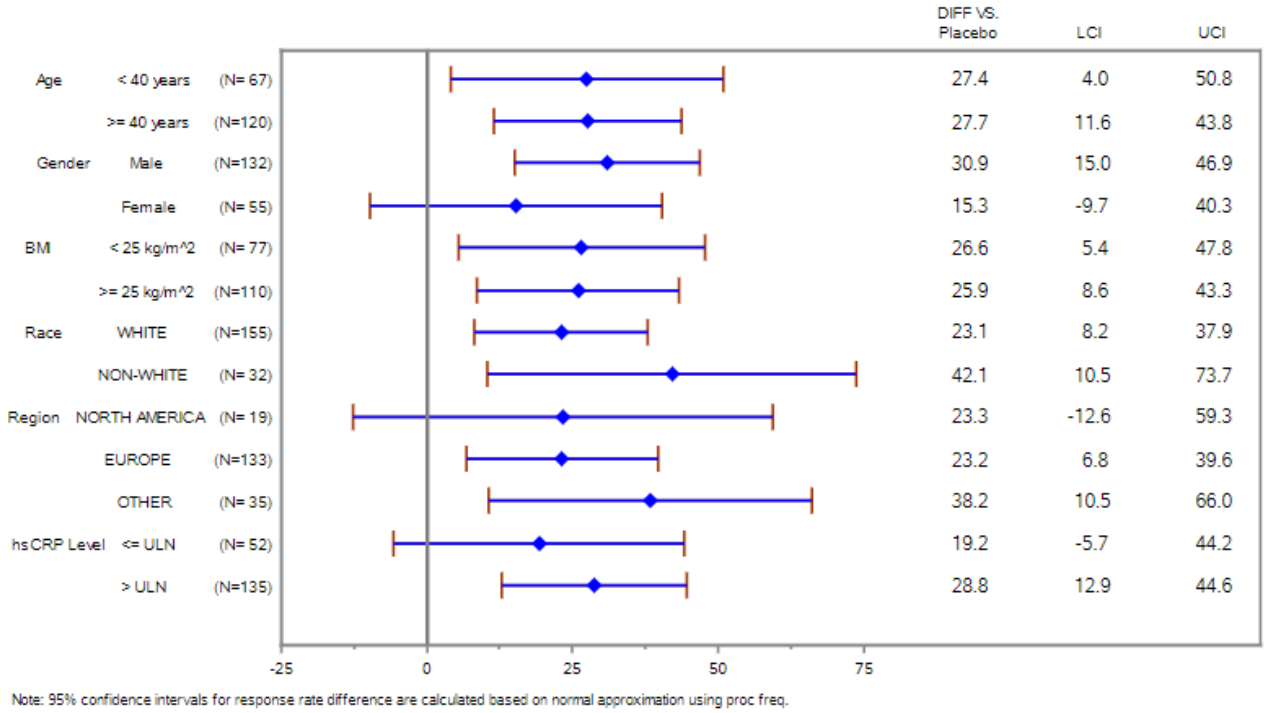



*Figure 9: Forest Plot of ASAS40 Response Rate at Week 14 by Subgroups (NRI) (Full Analysis Set), M16-098 Study*

Post hoc analyses of ASAS40 response rates at Week 14 were performed for the following subgroups, per the presubmission meeting feedback from the Swedish Medical Products Agency: AS symptom duration (≤ 5 years, > 5 and <10 years, ≥ 10 years); history of enthesitis (yes/no); concomitant csDMARD use (yes/no), baseline BASDAI (<6.7 vs ≥ 6.7; median split)

*Table 18: Subgroup Analyses of ASAS40 at Week 14 –Additional Subgroups (NRI; FAS), M16-098 Study*

| Subgroup | | | | Response Rate Diff (Upadacitinib - Placebo) | |
|---|---|---|---|---|---|
| Treatment | N | Responder n (%) | Response Rate (95% CI)[a] | Point Estimate | (95% CI)[b] |
| **Symptom Duration** | | | | | |
| ≤ 5 years | | | | | |
| Placebo | 20 | 7 (35.0) | 35.0 (14.1, 55.9) | | |
| Upadacitinib 15 mg QD | 18 | 10 (55.6) | 55.6 (32.6, 78.5) | 20.6 | (–10.5, 51.60) |
| > 5 to < 10 years | | | | | |
| Placebo | 22 | 6 (27.3) | 27.3 (8.7, 45.9) | | |
| Upadacitinib 15 mg QD | 28 | 16 (57.1) | 57.1 (38.8, 75.5) | 29.9 | (3.7, 56.0) |
| ≥ 10 years | | | | | |
| Placebo | 52 | 11 (21.2) | 21.2 (10.1, 32.3) | | |
| Upadacitinib 15 mg QD | 47 | 22 (46.8) | 46.8 (32.5, 61.1) | 25.7 | (7.6, 43.7) |
| **History of Enthesitis** | | | | | |
| Yes | | | | | |
| Placebo | 55 | 15 (27.3) | 27.3 (15.5, 39.0) | | |
| Upadacitinib 15 mg QD | 54 | 26 (48.1) | 48.1 (34.8, 61.5) | 20.9 | (3.1, 38.7) |
| No | | | | | |
| Placebo | 39 | 9 (23.1) | 23.1 (9.9, 36.3) | | |
| Upadacitinib 15 mg QD | 39 | 22 (56.4) | 56.4 (40.8, 72.0) | 33.3 | (12.9, 53.8) |
| **Concomitant csDMARDs Use** | | | | | |
| Yes | | | | | |
| Placebo | 17 | 6 (35.3) | 35.3 (12.6, 58.0) | | |
| Upadacitinib 15 mg QD | 13 | 5 (38.5) | 38.5 (12.0, 64.9) | 3.2 | (–31.7, 38.0) |
| No | | | | | |
| Placebo | 77 | 18 (23.4) | 23.4 (13.9, 32.8) | | |
| Upadacitinib 15 mg QD | 80 | 43 (53.8) | 53.8 (42.8, 64.7) | 30.4 | (15.9, 44.8) |

| | | | | | |
|---|---|---|---|---|---|
| **Baseline BASDAI** | | | | | |
| < 6.7 | | | | | |
| Placebo | 45 | 8 (17.8) | 17.8 (6.6, 28.9) | | |
| Upadacitinib 15 mg QD | 47 | 25 (53.2) | 53.2 (38.9, 67.5) | 35.4 | (17.3, 53.5) |
| ≥ 6.7 | | | | | |
| Placebo | 49 | 16 (32.7) | 32.7 (19.5, 45.8) | | |
| Upadacitinib 15 mg QD | 45 | 23 (51.1) | 51.1 (36.5, 65.7) | 18.5 | (–1.2, 38.1) |

a. 95% CIs for response rate are calculated based on normal approximation to the binomial distribution.

b. 95% CIs for response rate difference are calculated based on normal approximation using PROC FREQ.

Note: One subject in the upadacitinib 15 mg QD group did not have a baseline value.

## *Summary of main study*

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

*Table 19: Summary of Efficacy for trial M16-098*

| **Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of upadacitinib in Subjects with Active Ankylosing Spondylitis** | | | |
|---|---|---|---|
| Study identifier | M16-098 [R&D/19/1043 | | |
| Design | Multicenter, Randomized, Double-Blind, Placebo-Controlled Study | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 14 weeks<br>not applicable<br>90 weeks (data on 52/64 weeks included in the current submission) |
| Hypothesis | Superiority to placebo | | |
| Treatments groups | upadacitinib 15 mg | | upadacitinib 15 mg po QD, N=93. |
| | Placebo | | Placebo po QD, N=94 |
| Endpoints and definitions | Primary endpoint | ASAS40 response at Week 14 | Improvement of ⩾40% and ⩾2 units on a scale of 10 in at least three of the four ASAS scale main domains and no worsening at all in the remaining domain, at week 14 |
| | Secondary endpoint | Change from baseline in ASDAS-CRP at week 14 | Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) based on CRP at week 14 |
| | Secondary endpoint | Change from baseline in SPARCC MRI spine score | Change from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) MRI spine score at week 14. |
| | Secondary endpoint | BASDAI50 response at week 14 | Subjects achieving at least 50% improvement in BASDAI (BASDAI50) at week 14 |

| | | | |
|---|---|---|---|
| | Secondary endpoint | Change from baseline in ASQoL at week 14 | Change from baseline in ankylosing spondylitis quality of life (ASQoL) at week 14 |
| | Secondary endpoint | ASAS partial remission response at week 14 | Subjects achieving ASAS partial remission, a value not exceeding 2 (on a scale from 0 to 10) in each of the ASAS scale main domains, at week 14 |
| | Secondary endpoint | Change from baseline in BASFI, | Change from baseline in BASFI |
| | Secondary endpoint | Change from baseline in BASMIlin | Change from baseline in linear Bath Ankylosing Spondylitis Metrology Index (BASMIlin), |
| | Secondary endpoint | Change from baseline in MASES | Change from baseline inMaastricht Ankylosing Spondylitis Enthesitis Score (MASES), |
| | Secondary endpoint | Change from baseline in WPAI | Change from baseline in work productivity and activity impairment (WPAI) |
| | Secondary endpoint | Change from baseline in ASAS Health Index. | Change from baseline in ASAS Health Index. |
| Database lock | Primary database lock 05 February 2019. Long-term data were analysed using the 1-year database (DBL 13 February 2020) | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | | |
|---|---|---|---|---|
| Analysis population and time point description | Full Analysis set (randomised, received at least one dose of study drug)<br>Week 14 | | | |
| Descriptive statistics and estimate variability | Treatment group | upadacitinib 15 mg | Placebo | |
| | Number of subjects | 93 | 94 | |
| | ASAS40 response % (95% CI) | 51.6 (41.5, 61.8) | 25.5 (16.7, 34.3) | |
| | Number of subjects | 84 | 84 | |
| | Change from baseline in ASDAS-CRP units (95% CI) | -1.45 (-1.62, -1.28) | -0.54 (-0.71,-0.37) | |
| | Number of subjects | 68 | 60 | |
| | Change from baseline in SPARCC MRI spine score | -6.93 (-8.58, -5.28) | -0.22 (-2.01, 1.57) | |
| | units (95% CI) | | | |
| | Number of subjects | 93 | 94 | |
| | BASDAI50 response % (95% CI) | 45.2 (35.0, 55.3) | 23.4 (14.8, 32.0) | |
| | Number of subjects | 88 | 88 | |

| | | | | |
|---|---|---|---|---|
| | Change from baseline in ASQoL units (95% CI) | -4.20 (-5.12, -3.29) | -2.67 (-3.58, -1.75) | |
| | Number of subjects | 93 | 94 | |
| | ASAS partial remission % (95% CI) | 19.4 (11.3, 27.4) | 1.1 (0.0, 3.1) | |
| | Number of subjects | 86 | 86 | |
| | Change from baseline in BASFI units (95% CI) | -2.29 (-2.73, -1.85) | | |
| | Number of subjects | 89 | 89 | |
| | Change from baseline in BASMIlin units (95% CI) | -0.37 (-0.52, -0.21) | -0.14 (-0.29, 0.01) | |
| | Number of subjects | 50 | 51 | |
| | Change from baseline in MASES units (95% CI) | -2.25 (-2.86, -1.64) | -1.41 (-2.02, -0.80) | |
| | Number of subjects | 55 | 53 | |
| | Change from baseline in WPAI Units (95% CI) | -18.11 (-24.73, -11.50) | -12.60 (-19.04, -6.15) | |
| | Number of subjects | 88 | 88 | |
| | Change from baseline in ASAS Health Index. units (95% CI) | -2.75 (-3.84, -2.02) | -1.38 (-2.11, -0.65) | |
| Effect estimates per comparison | Primary endpoint ASAS40 response | Comparison groups | upadacitinib 15 mg vs Placebo | |
| | | % difference in response rate | 26.1 | |
| | | 95% CI | 12.6, 39.5 | |
| | | P-value | <0.001 | |
| | Secondary endpoint Change from baseline in ASDAS-CRP | Comparison groups | upadacitinib 15 mg vs Placebo | |
| | | LS Mean Diff | -0.91 | |
| | | 95% CI | -1.14, -0.68 | |
| | | P-value | <0.001 | |
| | Secondary endpoint Change from baseline in SPARCC MRI spine score | Comparison groups | upadacitinib 15 mg vs Placebo | |
| | | LS Mean Diff | -6.71 | |
| | | 95% CI | -9.01, -4.41 | |
| | | P-value | <0.001 | |
| | Secondary endpoint BASDAI50 response | Comparison groups | upadacitinib 15 mg vs Placebo | |
| | | Difference resp rate | 21.8 | |
| | | 95% CI | 8.5, 35.0 | |
| | | P-value | 0.002 | |

| | | | |
|---|---|---|---|
| | Secondary endpoint Change from baseline in ASQoL | Comparison groups | upadacitinib 15 mg vs Placebo |
| | | LS Mean Diff | -1.54 |
| | | 95% CI | -2.75, -0.30 |
| | | P-value | 0.016 (not significant) |
| | Secondary endpoint ASAS partial remission | Comparison groups | upadacitinib 15 mg vs Placebo |
| | | Difference resp rate | 18.3 |
| | | 95% CI | 10.0, 26.6 |
| | | P-value | <0.001 |
| | Secondary endpoint Change from baseline in BASFI | Comparison groups | upadacitinib 15 mg vs Placebo |
| | | LS Mean Diff | -1.00 |
| | | 95% CI | -1.60, -0.39 |
| | | P-value | 0.001 |
| | Secondary endpoint Change from baseline in BASMIlin | Comparison groups | upadacitinib 15 mg vs Placebo |
| | | LS Mean Diff | -0.22 |
| | | 95% CI | -0.43, -0.02 |
| | | P-value | 0.030 (not significant) |
| | Secondary endpoint Change from baseline in MASES | Comparison groups | upadacitinib 15 mg vs Placebo |
| | | LS Mean Diff | -0.84 |
| | | 95% CI | -1.68, -0.00 |
| | | P-value | 0.049 (not significant) |
| | Secondary endpoint Change from baseline in WPAI | Comparison groups | upadacitinib 15 mg vs Placebo |
| | | LS Mean Diff | -5.52 |
| | | 95% CI | -13.82, 2.78 |
| | | P-value | 0.190 (not significant) |
| | Change from baseline in ASAS Health Index | Comparison groups | upadacitinib 15 mg vs Placebo |
| | | LS Mean Diff | -1.37 |
| | | 95% CI | -2.37, -0.37 |
| | | P-value | 0.007 (not significant) |

## 2.4.3. Discussion on clinical efficacy

## Design and conduct of clinical studies

With this submission, the MAH seeks to add a new indication for Rinvoq (upadacitinib) for the treatment of adult patients with active AS who have responded inadequately to conventional therapy. This application is supported by data from one phase 2/3 multicenter study, M16-098, that is currently ongoing. The first part of the study (Period 1) is a 14-week randomized, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 15 mg once daily

(QD) versus placebo. The second part of the study (Period 2) is an open-label, long-term extension to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects who have completed Period 1. The study duration included a 35-day screening period; a 14-week randomized, double-blind, placebo-controlled period (Period 1); a 90-week open-label extension period (Period 2); and a 30-day follow-up visit.

The MAH has followed most of the advice in the Guideline on the Clinical Investigation of Medicinal products for the treatment of Axial Spondyloarthritis (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1*). The guideline states that products belonging to new therapeutic classes may need also comparison against an accepted active comparator (e.g. anti TNF treatments) for the target population. A three-arm trial is therefore recommended, particularly in the case when biological naive patients are to be studied. This topic was discussed in the Scientific Advice received from the CHMP (EMA/CHMP/SAWP/340675/2019) and the study design was considered acceptable. However, today several biological therapies with the same indication exist; hence, the MAH was invited to provide a critical discussion comparing the benefits and risks of upadacitinib vs. TNF inhibitors and IL-17 inhibitors previously approved for the treatment of AS to put the results into context. Acknowledging the limitation of judging from head-to-head studies in RA and PsA and based on the data provided by the MAH, the treatment effects observed with upadacitinib in Study M16-098 are within the range of those observed with approved targeted therapies for AS, such as TNF inhibitors or IL-17 inhibitors. However, the rates of herpes zoster and CPK elevations seem to be higher in subjects on upadacitinib compared to those on the TNF-inhibitor adalimumab.

The EMA guideline states that specific dose response studies should be performed in patients with axSpA since there are several antecedents of different response to medicinal products in patients with AS compared to the same product in other rheumatic diseases or other AS-related non-articular disorders. The initial study protocol aimed to compare two different doses of upadacitinib (15 mg and 30 mg) but this approach was abandoned with amendment 1. Instead, only the 15 mg dose is used in the current study based on exposure-response analyses conducted using results from 4 RA studies and a review of a published phase 2 study in another JAK-inhibitor. As stated in the CHMP Advice from June 2019, "*The dose i.e. 15 mg QD seems an appropriate based on exposure-response analyses conducted in RA. From a pragmatic point of view the dose justification is less relevant as study M16-098 is already completed with the intended dose*". In the exposure-efficacy analyses of upadacitinib on the probability of achieving ASAS20 and ASAS40 at Week 14, there was no trend towards increased responses with increasing upadacitinib exposures within the 15 mg QD arm but with increasing upadacitinib exposures, a relationship was found in the percentage of patients experiencing decreases in haemoglobin of $\geq$ 1 g/dL from baseline. Taken together, although the support for the proposed posology in the AS indication is not completely in line with the relevant EMA guidelines, with the efficacy and safety data generated by the proposed dose at hand, the justification for the proposed dose is considered acceptable to the CHMP.

As stated in the EMA guideline and also discussed in the SA, once resolution of inflammation has been achieved, the possibility of using a reduced dose, or an increased dosing interval or even to stop treatment while maintaining disease control, may be valuable information for prescribers and its investigation is encouraged. The MAH plans to study treatment withdrawal in related patient populations (AS-patients that are bDMARD-inadequate responders and non-radiographic axial SpA patients).

The inclusion and exclusion criteria of the pivotal clinical study adequately defined the intended population for the indication. Subjects in the study were to be adults (≥ 18 years of age) and have a clinical diagnosis of AS meeting the modified New York Criteria for AS. The subjects were to have an active disease defined by having a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score

≥ 4 and a Patient's Assessment of Total Back Pain score ≥ 4. In addition, they should have an inadequate response to at least 2 NSAIDs over an at least 4-week period in total at maximum recommended or tolerated doses or had an intolerance to or contraindication for NSAIDs as defined by the Investigator. They also had to be bDMARD naïve but could have received or be on concomitant csDMARD treatment. The CHMP considered that the inclusion and exclusion criteria were adequate and reflected the intended population in the proposed indication text: "*RINVOQ is indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy*".

Eligible patients were randomized in a ratio 1:1 to either upadacitinib 15 mg extended release tablet once daily or placebo. After week 14, all patients were to receive upadacitinib 15 mg open label. Rescue therapy was allowed after week 16 if the patients had not achieved at least ASAS20 response at two consecutive visits. Rescue therapy included adding or modifying doses of NSAIDs, acetaminophen/paracetamol or low potency opioid medications (tramadol or combination of acetaminophen and codeine or hydrocodone) (after week 16) and/or modify dose of MTX or SSZ (after week 20).

The primary endpoint ASAS40 is considered the preferred ASAS response criterion in the current EMA Guideline and is supported by the CHMP. The study has in addition several defined multiplicity-controlled key secondary endpoints evaluating not only symptomatic features, but also spinal mobility (BASMI), structural damage (SPARCC, evaluating MRI spine inflammation), enthesitis (MASES), and quality of life (ASQoL). The chosen endpoints are endorsed by the CHMP.

**Statistical considerations**

Study M16-098 was initially designed as a placebo-controlled three-arm study to assess two doses of upadacitinib; 15 mg QD and 30 mg QD. The study design was revised within a protocol amendment before the first subject's first visit; with no subjects enrolled under the original protocol version. Hence, the CHMP did not raise any concern. The planned sample size was 170 (1:1). Although the sample size is considered limited given the clinical context, the sample size estimation was appropriate. It was based on the primary endpoint and was for the purpose of showing a difference versus placebo in ASAS 40 response rate shown to be sufficient. At randomisation subjects were stratified by baseline hsCRP (≤ ULN vs. > ULN) and geographic region (US/Canada, Japan, Rest of the World). In the efficacy analyses only hsCRP was adjusted for and the MAH was requested to justify this point during the review. The rationale for not taking region into account in the analysis was the expected few subjects within a stratum. An analysis of the primary endpoint adjusting for both stratification factors was nonetheless provided and compared with the primary analysis in which region was omitted, the CMH p-values were shown to be similar. The majority of subjects were enrolled at sites in Europe (71.1%) and the geographic regions used in subgroup analyses were North America, Europe and Other, and hence do not match the strata used for randomisation. This was acceptable to the CHMP since the difference will be minor due to that the majority of subjects in the RoW stratum emanated from Europe. In addition, the number of subjects randomised in Japan was very limited (n=13). Within the RoW stratum, 14/17 countries were European which implied that balance between randomised arms was nonetheless achieved irrespective of strata used.

The primary analysis was conducted, as had been planned, after all subjects had completed Week 14 or discontinued prior to Week 14. The SAP (version 2.0) was dated 20 Dec 2018 and the primary database lock for Period 1 (Week 0- 14) was conducted on 05 February 2019 (the cut-off date was 21 Jan 2019). The majority of subjects completed period 1 on study drug: 95.7% (89/93) in the upadacitinib 15 mg QD arm and 94.7% (89/94) in the placebo arm.

All randomised subjects received at least one dose of randomised treatment and were thereby included in the Full Analysis Set. This was the primary analysis set to be used for all efficacy analyses.

The multiple testing procedure for the primary and the 10 ranked key secondary endpoints is considered to have implied strong control of the type I error rate at the 0.05 level.

The open label phase in the second period of the study hampers the assessment of long-term efficacy. However, overall, the statistical analysis methods were considered acceptable to the CHMP.

The primary estimand was defined as the difference in the proportion of (randomised and treated) AS patients who achieved ASAS 40 response at Week 14 and did not discontinue study drug by Week 14. Albeit the notation "intercurrent events" has been used, intercurrent events were not explicitly defined or discussed. In the analysis of the primary endpoint, subjects who prematurely discontinued from study drug were considered as non-responders for all subsequent visits after discontinuation. In addition, a non-responder imputation was used for those subjects with a missing assessment at the week 14 visit. Rescue therapy was not allowed until week 16; hence, need of rescue should not have been expected to have any impact on the primary analysis. The missing data approach was considered acceptable to the CHMP and considered to be aligned with the estimand definition. For binary key secondary efficacy endpoints, the estimand was defined as for the primary endpoint and used the same analysis approach. Binary endpoints were analysed using a CMH test stratified by hsCRP providing a p-value for the difference. The point estimate for the difference and corresponding 95% CI was estimated using normal approximation.

For continuous key secondary efficacy endpoints, the estimand was defined as the difference in mean change from baseline at Week 14 under the assumption that patients with missing data including those due to premature discontinuation of study drug could have their measurements at Week 14 predicted by their observed data and the observed data for other patients for their respective assessments during follow-up. Analyses of continuous endpoints were performed using a MMRM model based on, in alignment with how the estimand had been defined, the assumption of missing at random without any explicit imputation in case data was missing. For the MMRM analysis, any data collected after premature discontinuation of study drug was excluded.

Estimand definitions and hence the approach to the handling of missing data did thereby differ depending on whether an endpoint was continuous or binary. Since continuous endpoint assessment implies an assumption of continued benefit after treatment discontinuation and/or missed visits, additional analyses were requested during the review (see further below).

A supplemental estimand was defined implying for both binary and continuous endpoints that all available data at week 14 were to be accounted for regardless of premature discontinuation of study drug. For the primary endpoint, the primary CMH analysis was repeated using As Observed data handling without any imputation. Contrary to the primary analysis, to be included a subject had to have an assessment week 14 albeit ignoring whether the subject was still on randomised treatment or not. The lack of an imputation approach in the supplemental analysis was not supported by the CHMP. Given the requirement to have an observed value at week 14, the clinical interpretation of this estimand was found difficult to understand. Additional analyses were performed post-hoc based on regulatory feedback (FDA); among them an analysis of the primary endpoint based on a treatment policy estimand, hence ignoring any intercurrent events, using the full analysis set and a non-responder imputation (NRI) approach to impute the missing ASAS40 responses at Week 14. The CHMP considered that this analysis supports the primary outcome and was robust.

With regard to long-term efficacy analyses, there was no statistical testing planned; only descriptive statistics and confidence intervals have been provided. This is agreed by the CHMP. The analyses of long-term efficacy were performed using an As Observed (AO) analysis approach which implied that all

observed data was included in the analyses irrespective of whether a subject stayed on randomised study drug or not. This approach is not necessarily sufficiently conservative in estimating efficacy within each randomised treatment group sequence. Further, they were considered not to be very transparent. Hence, the results were difficult to interpret and additional analyses of long-term efficacy were requested during the review (see below).

## Efficacy data and additional analyses

A total of 187 patients were randomized, 94 patients to the placebo group and 93 patients to the upadacitinib group. During the first study period (the 14 weeks placebo-controlled period), 9 participants (4.8%) discontinued the study drug, 5 patients in the placebo group and 4 patients in the upadacitinib group. The main reasons for discontinuation were adverse events in the placebo group (3/5) and adverse events and withdrawal by subjects in the upadacitinib group (2 patient each).

A total of 178 (95.2%) patients continued to the second period and received OL upadacitinib (89 participants from the placebo group and 89 participants from the upadacitinib group). During the OL period, 28 patients (15.7%) discontinued study drug. The primary reason for study drug discontinuation was lack of efficacy (N=11, 6.2%) and adverse events (N=8, 4.5%). The number of subjects who permanently discontinued study drug in Period 2 was the same (each n = 14) for the two treatment group sequences.

The majority of the included patients were male (70.6%), white (82.5%) and European (71.1%). The mean age was 45.4 years, mean duration of AS symptoms was 14.4 years, and the mean duration since AS diagnosis was 6.9 years.

The included patients had an active disease indicated by a median (min, max) value of 7.0 (1,10) in Patient's Assessment of Total Back Pain and a median value of 6.7 (2,10) in BASDAI. It is noted that some patients had a lower disease activity than what was postulated by the inclusion criterion (e.g. <4); however, this did not differ between the placebo and upadacitinib group and was addressed by an additional analysis excluding the 20 patients (10.7%) who did not meet the eligibility criteria related to disease activity (see below).

All subjects had prior NSAID use except for 1 subject who had a contraindication to NSAID use. Approximately 37% to 38% of subjects in each group had prior conventional-synthetic (cs)DMARD use and approximately 18% to 19% of subjects in each group had prior corticosteroid use.

There were some slight imbalances between the two study groups during the placebo-controlled period; a numerically higher proportion of subjects in the placebo-group than the upadacitinib group took $\geq$ 1 concomitant NSAID (86.2% vs 76.3%), concomitant csDMARD (18.1% vs 14.0%) and concomitant corticosteroids (12.8% vs 6.5%). Otherwise, baseline demographic characteristics were generally balanced across treatment groups.

A statistically significant higher proportion of patients in the upadacitinib group reached ASAS40 at week 14 in comparison to the placebo group (51.6% vs 25.5%, p<0.001). The point estimate for the difference was 26.1% (95% CI: 12.6%, 39.5%) which is very close to what had been assumed at the planning stage (26%). In a post-hoc analysis aligned with a treatment policy estimand the difference between the treatments was 25.0% (95% CI: 11.6%, 38.5%) supporting that the primary endpoint outcome can be considered robust. Contributing to this conclusion is that the majority of the ASAS 40 non-responders, 87.8% (101/115), are stated to have been based on observed data and that the 14 subjects imputed as non-responders was balanced across the two randomised treatments arms (upadacitinib: 6, placebo: 8).

An additional analysis for the primary endpoint excluding the 20 patients (10.7%) who did not meet the eligibility criteria related to disease activity demonstrated that 56.1% of the patients in the upadacitinib group and 28.2% in the placebo group achieved ASAS40 at Week 14 i.e. results were consistent with those of the primary analysis.

Treatment with upadacitinib 15 mg resulted in improvements in individual ASAS components (patient global assessment of disease activity, total back pain assessment, inflammation, and function) and other measures of disease activity, including hsCRP, at week 14 compared to placebo.

The difference between treatment groups seems to be observed already at week 2. Results for the key secondary endpoints supported the outcome of the primary endpoint, showing statistically significant better effect in the upadacitinib group compared to placebo in changes from baseline to Week 14 in ASDAS(CRP), SPARCC MRI spine, and BASFI, and proportion of subjects who had BASDAI50 and an ASAS partial remission at week 14.

Of a total of 10 ranked key secondary endpoints, five succeeded whereof the majority were among those highest ranked (according to MAH). Among the endpoints that failed three were PROs (ASQoL, ASAS(HI) and WPAI Overall Work Impairment). For ASQoL and ASAS(HI) there were numerically differences favouring upadacitinib and having used another multiple testing procedure, they could eventually have succeeded, at least statistically (nominally p= 0.016 for ASQoL and nominally p= 0.007 for ASAS(HI)). For the analysis of MASES and WPAI Overall Work Impairment it was considered by the CHMP that it could, at least in part, be a question of power and eventually an underestimation of the number of subjects that where to contribute with data.

Across key ranked secondary endpoints, the CHMP considered that there was an uncertainty for several of the endpoints due to the amount of missing data. For the binary endpoint analyses, all randomised subjects had an assessment at week 14, if not observed, subjects were assigned a value (0 referring to failure) but for the analyses of change from baseline, no explicit imputation method was applied. A rather high proportion of subjects was not included in the analysis of the MRI of the spine and sacroiliac joints score, the MAH clarified that only subjects with MRIs that were performed within the pre-specified analysis window were part of the primary MRI analysis. These answers were considered acceptable to the CHMP.

Among continuous endpoints for which a statistically significant difference in favour of upadacitinib was demonstrated, the "N" for ASDAS (CRP) and BASFI represented approximately 90% of randomised subjects and was also similar in the two arms. For SPARCC-Score Spine, it is acknowledged that the number of subjects in this respect was much lower and also unbalanced between randomised arms: 60/94 (63.8%) in the placebo arm and 68/93 (73.1%) in the upadacitinib arm.

Considering the assumption of missing at random in the primary analysis and the requirement of having an assessment week 14 in the supplemental analysis of continuous endpoints, additional analyses of all ranked key continuous secondary endpoints were requested during the review. They were to be based on all subjects in the FAS using multiple imputation (MI) and a jump to reference approach. Sensitivity analyses for all ranked key secondary continuous endpoints were provided. They are considered to offer more conservative estimates of the treatment efficacy of upadacitinib in comparison with placebo albeit have no impact on study conclusions. For the key secondary endpoint change from baseline in ASDAS (CRP) at Week 14, the presentation of outcomes in the Section 5.1 of the SmPC from the primary analysis was agreed given the small differences in the estimates and the convincing statistically evidence.

During the first 14 weeks, it is noticed that a plateau seems to be reached at week 12-14 in the upadacitinib group although results from the long term analysis provided by the MAH seems to indicate additional improvement beyond this timepoint. While clinical response is generally achieved with

upadacitinib treatment within 14 to 16 weeks, response rates further improve with continued treatment beyond Week 16, particularly for endpoints reflecting greater depth of response, such as remission and low disease activity. However, of the subjects that have not even achieved ASAS20 at week 16, only few additional subjects attain an initial ASAS20 response after this time point. Based on these observations, the MAH proposed to add the following text to section 4.2 of the SmPC:

"*Consideration should be given to discontinuing treatment in patients with ankylosing spondylitis who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks*."

The SmPC-proposal was considered acceptable by the CHMP.

The CHMP noted that many subjects stayed in the study and contributed with data up to at least week 64. However, 28 patients (15.7%) discontinued study drug treatment during the OLE period, the primary reason being lack of efficacy (n=11, 6.2%). Presentation of study drug discontinuations in period 2 was only summarised for all subjects combined and a new table was requested describing subjects' status and reasons for study drug discontinuation in period 2 by randomised treatment group sequence (upadacitinib – upadacitinib and placebo – upadacitinib). In addition, the MAH was requested to summarize e.g. need of rescue during period 2. The MAH clarified that per the data cutoff date (31 January 2020) the number of subjects ongoing in Period 2 on drug without having received rescue medication (among subjects entering period 2 on drug) was high in both groups and also very similar; 69/89 (77.5%) in the placebo-upadacitinib group and 68/89 (76.4%) in the upadacitinib- upadacitinib group. At the time, only a few subjects (4 and 3 respectively) had completed period 2 / week 104 all on study drug and without having received rescue.

After week 14, all the patients were to receive upadacitinib open label. The data provided by the MAH seems to imply that the percentage of patients receiving ASAS 40 response were still increasing after week 14, and at week 52 as many as 80% of the patients had received ASAS 40 response. This finding is quite remarkable (even if figures are somewhat overestimated, see below) and still unexplained. However, it does not seem to be driven by the use of rescue medication. Up to the data cut-off date, rescue medication was provided to only 8 subjects; 3 subjects in the placebo-to-upadacitinib group and 5 subjects in the upadacitinib group. In this small subgroup, the addition of rescue medication resulted in only a few subjects achieving an ASAS40 response at Week 52: 1 in the placebo-to-upadacitinib group and 2 in the upadacitinib group. In the analyses of long-term efficacy, an "As observed" (AO) data handling was used. The AO implied that no imputation of values for missing evaluations were performed and thus, subjects without an evaluation on a scheduled visit were excluded from the AO analysis for that visit. Further, all observed data was included in the analysis regardless of premature discontinuation of study drug. Hence, additional analyses of ASAS40 were requested by the CHMP. The number of observed and imputed non-responders together with reason in case NRI was applied were presented. Based on these analyses, the outcomes initially presented based on data "as observed" implied that efficacy at later time-points have been overestimated. In the FAS (NRI) analysis performed in response to the CHMP, the week 52 response rate among those initially randomised to upadacitinib 15 mg was estimated to be 67.7% (63/93). The CHMP recognised that in the week 52 analysis, few had received rescue or had missing visits and also, that it was not that many in the upadacitinib arm who had discontinued treatment with study drug (12.9% (12/93)). Based on the additional analyses performed, the CHMP considered that there is support of a continued benefit of treatment with upadacitinib beyond week 14 and currently, there is data available up to week 64.

A treatment effect vs placebo was seen across the investigated subgroups including subgroups based on concomitant use of NDAIDs and steroids.

### 2.4.4. Conclusions on the clinical efficacy

A clinically relevant effect as measured by ASAS40 has been demonstrated for upadacitinib 15 mg in the target population of subjects with active AS and inadequate response or intolerance/ contraindication to NSAIDs. Overall, there is also support from secondary endpoints measuring different aspects of the disease.

Although there is still an uncertainty with regards to the precise magnitude of the long-term efficacy, the CHMP agreed that there is support of a continued benefit of treatment with upadacitinib beyond week 14.

Hence, the indication for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy was considered acceptable to the CHMP from an efficacy perspective. The proposed dosing regimen of 15mg once daily was also supported by the CHMP.

## *2.5. Clinical safety*

### *Introduction*

Safety data from the randomized, controlled Phase 2/3 study (Study M16-098) in subjects with active AS was submitted along with supportive safety data from upadacitinib rheumatoid arthritis (RA) and psoriatic arthritis (PsA) clinical programs.

### *Patient exposure*

A total of 182 subjects received ≥ 1 dose of upadacitinib 15 mg in the Phase 2/3 Study M16-098, representing 237.6 patient years (PYs). In the 14-week placebo-controlled period, subjects in the upadacitinib and placebo groups each had a mean exposure of approximately 95 days (~13.6 weeks). Up to the data cutoff date, 160 of the 182 subjects (87.9%) had exposure to upadacitinib for ≥ 12 months.

*Table 20: Extent of Exposure to Study Drug –Lon*

| | Upadacitinib 15 mg QD (N = 182) |
|---|---|
| Duration (Days) | |
| N | 182 |
| Mean (SD) | 476.9 (144.82) |
| Median (min, max) | 507.5 (6, 742) |
| Duration Interval - n (%) | |
| ≥ 2 Weeks | 181 (99.5) |
| ≥ 1 Month | 180 (98.9) |
| ≥ 3 Months | 175 (96.2) |
| ≥ 6 Months | 169 (92.9) |
| ≥ 9 Months | 164 (90.1) |
| ≥ 12 Months | 160 (87.9) |
| ≥ 18 Months | 62 (34.1) |
| ≥ 2 Years | 4 (2.2) |

Notes: Exposure = date of last study medication in Period 1 – date of first study medication in Period 1 + 1.
1 month = 30 days, 3 months = 90 days, 6 months = 180 days, 9 months = 270 days, 12 months = 360 days, 18 months = 540 days, 2 years = 720 days.

*g-Term (Safety Analysis Set)*

## *Adverse events*

A TEAE was defined as any event with onset on or after the first dose of study drug and up to 30 days after the last dose of study drug or up to the cutoff date, whichever came first. Treatment-emergent AEs for the placebo-controlled period were defined as any AE with an onset date that was on or after the first dose of study drug in the placebo-controlled period and prior to the first dose of study drug in Period 2 or up to 30 days after the last dose of study drug, whichever was earlier. Events for which the onset date was the same as the study drug start date were assumed to be treatment-emergent, unless exact times of the events were available. All AEs are treatment-emergent unless otherwise noted. Adverse events were coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

*Placebo-controlled period*

An overview of TEAEs in the placebo-controlled part of the pivotal study is presented in the table below.

*Table 21: Overview of Treatment-Emergent Adverse Events in the Placebo-Controlled Period (Safety Analysis Set), Study M16-098*

| | Placebo (N = 94) n (%) | Upadacitinib 15 mg QD (N = 93) n (%) |
|---|---|---|
| Subjects with any treatment-emergent | | |
| AE | 52 (55.3) | 58 (62.4) |
| AE with reasonable possibility of being drug related[a] | 17 (18.1) | 27 (29.0) |
| Severe AE | 2 (2.1) | 0 |
| Serious AE | 1 (1.1) | 1 (1.1) |
| AE leading to discontinuation of study drug | 3 (3.2) | 2 (2.2) |
| AE leading to death | 0 | 0 |
| Deaths[b] | 0 | 0 |

a. As assessed by the investigator

b. Includes non–treatment-emergent deaths

In the placebo-controlled period, the most frequently reported (≥ 15% of subjects) TEAEs by MedDRA system organ classes (SOC) in the upadacitinib group were Infections and Infestations (20.4%), Gastrointestinal Disorders (19.4%) , and Investigations (16.1%). Infections were reported by 20.4% of subjects in the upadacitinib group and 26.6% of subjects in the placebo group. The most frequently reported infections (≥ 2 subjects) in the upadacitinib group were nasopharyngitis, influenza, and tonsillitis and in the placebo group were nasopharyngitis, rhinitis, upper respiratory tract infection, pharyngitis, urinary tract infection, and viral infection.

In the placebo-controlled period, the most frequently reported TEAEs (≥ 5% of subjects) in the upadacitinib group were blood creatine phosphokinase (CPK) increased, diarrhoea, nasopharyngitis, and headache compared with diarrhoea and nausea in the placebo group. The frequencies of CPK increased and ALT increased were 8.6% and 4.3%, respectively, in the upadacitinib group compared with 2.1% for each event in the placebo group. Nausea was the event most frequently reported in a larger proportion of subjects in the placebo group (5.3%) compared with the upadacitinib group (1.1%).

*Table 22: Treatment-Emergent Adverse Events Reported in ⩾ 2% of Subjects in any Treatment Group in Period 1, by Decreasing Frequency in upadacitinib Group (Safety Analysis Set), Study M16-098*

| MedDRA 21.1 Preferred Term | Placebo (N = 94) n (%) | Upadacitinib 15 mg QD (N = 93) n (%) |
|---|---|---|
| Any adverse event | 52 (55.3) | 58 (62.4) |
| Blood creatine phosphokinase increased | 2 (2.1) | 8 (8.6) |
| Diarrhoea | 5 (5.3) | 5 (5.4) |
| Nasopharyngitis | 4 (4.3) | 5 (5.4) |
| Headache | 2 (2.1) | 5 (5.4) |
| Alanine aminotransferase increased | 2 (2.1) | 4 (4.3) |
| Dyspepsia | 1 (1.1) | 3 (3.2) |
| Abdominal pain upper | 2 (2.1) | 2 (2.2) |
| Aspartate aminotransferase increased | 1 (1.1) | 2 (2.2) |
| Arthralgia | 0 | 2 (2.2) |
| Asthenia | 0 | 2 (2.2) |
| Chalazion | 0 | 2 (2.2) |
| Hypercholesterolaemia | 0 | 2 (2.2) |
| Influenza | 0 | 2 (2.2) |
| Limb injury | 0 | 2 (2.2) |
| Tinnitus | 0 | 2 (2.2) |
| Tonsillitis | 0 | 2 (2.2) |
| Nausea | 5 (5.3) | 1 (1.1) |
| Back pain | 4 (4.3) | 1 (1.1) |
| Rhinitis | 4 (4.3) | 1 (1.1) |
| Upper respiratory tract infection | 3 (3.2) | 1 (1.1) |
| Abdominal discomfort | 2 (2.1) | 1 (1.1) |
| Dermatitis atopic | 2 (2.1) | 1 (1.1) |
| Pharyngitis | 2 (2.1) | 1 (1.1) |
| Urinary tract infection | 2 (2.1) | 1 (1.1) |
| Vomiting | 2 (2.1) | 1 (1.1) |

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

A greater proportion of subjects with AEs assessed by the investigator as having a reasonable possibility of being related to study drug was observed in the upadacitinib group compared with the

placebo group. The most frequently reported study-drug related AE in the upadacitinib group was blood CPK increased.

*Table 23: Treatment-Emergent Adverse Events with a Reasonable Possibility of Being Related to Study Drug Reported in ⩾2% of Subjects in any Treatment Group in Period 1, by Decreasing Frequency in upadacitinib Group (Safety Analysis Set), Study M16-098*

| MedDRA 21.1 System Organ Class<br>Preferred Term | Placebo<br>(N = 94)<br>n (%) | Upadacitinib 15 mg QD<br>(N = 93)<br>n (%) |
|---|---|---|
| Any adverse event | 17 (18.1) | 27 (29.0) |
| Blood creatine phosphokinase increased | 1 (1.1) | 4 (4.3) |
| Alanine aminotransferase increased | 0 | 2 (2.2) |
| Headache | 1 (1.1) | 2 (2.2) |
| Hypercholesterolaemia | 0 | 2 (2.2) |
| Nasopharyngitis | 0 | 2 (2.2) |
| Nausea | 4 (4.3) | 0 |
| Diarrhoea | 2 (2.1) | 0 |
| Haematuria | 2 (2.1) | 0 |

Note: Subjects are counted once in each row, regardless of the number of events they may have had.
Event with unknown relationship to study drug is being counted as having a reasonable possibility of being study drug-related.

*Long-term data*

In the long-term data up to the data cutoff date, 618 AEs (260.1 events [E]/100 PYs) were reported in 182 subjects (237.6 patient-years [PYs]) who received upadacitinib 15mg QD. Among the 182 subjects exposed to upadacitinib, 7 severe AEs (2.9E/100 PYs), 14 SAEs (5.9E/100 PYs) and 15 AEs (6.3E/100 PYs) leading to discontinuation were reported. No deaths were reported

*Table 24: Overview of Treatment-Emergent Adverse Events Per 100 Patient-Years with Long-Term Exposure through 31 January 2020(Safety Analysis Set)*

| | Upadacitinib 15 mg QD (N = 182) (PYs = 237.6) Events (E/100PYs) |
|---|---|
| Exposure-adjusted Event Rate | |
| AE | 618 (260.1) |
| AE with reasonable possibility of being drug related[a] | 186 (78.3) |
| Severe AE | 7 (2.9) |
| Serious AE | 14 (5.9) |
| AE leading to discontinuation of study drug | 15 (6.3) |
| AE leading to death | 0 |
| Deaths[b] | 0 |

a. As assessed by the investigator

b. Includes non–treatment-emergent deaths.

In the long-term data, upadacitinib TEAE rates were highest in the SOC of Infections and Infestations (80.0 E/100 PYs), followed by the SOCs of Musculoskeletal and Connective Tissue Disorders (27.4 E/100 PYs), Gastrointestinal Disorders (26.9E/100 PYs), and Investigations (26.5 E/100 PYs). Among infections, nasopharyngitis and upper respiratory tract infection had the highest event rates, 15.6 and 10.9 E/100 PYs, respectively. Overall, the most frequently reported events (≥ 5 E/100 PY) were nasopharyngitis, blood CPK increased, upper respiratory tract infection, headache, ALT increased, and diarrhea.

*Table 25: Long-Term Data: Treatment-Emergent Adverse Events per 100PY with Frequency ⩾ 2 Events/100 Patient Years by PT by Decreasing Frequency (Safety Analysis Set)*

| MedDRA 22.0 Preferred Term | Any Upadacitinib 15 mg QD (N = 182) (PYs = 237.6) Events (E/100 PYs) |
|---|---|
| Any adverse event | 618 (260.1) |
| Nasopharyngitis | 37 (15.6) |
| Blood creatine phosphokinase increased | 28 (11.8) |
| Upper respiratory tract infection | 26 (10.9) |
| Headache | 16 (6.7) |
| Alanine aminotransferase increased | 12 (5.1) |
| Diarrhoea | 12 (5.1) |
| Ankylosing spondylitis | 11 (4.6) |
| Iridocyclitis | 10 (4.2) |
| Hypertension | 9 (3.8) |
| Gastroenteritis | 8 (3.4) |
| Influenza like illness | 8 (3.4) |
| Respiratory tract infection | 8 (3.4) |
| Aspartate aminotransferase increased | 7 (2.9) |

| MedDRA 22.0 Preferred Term | Any Upadacitinib 15 mg QD (N = 182) (PYs = 237.6) Events (E/100 PYs) |
|---|---|
| Bronchitis | 7 (2.9) |
| Dyspepsia | 7 (2.9) |
| Abdominal pain upper | 6 (2.5) |
| Arthralgia | 6 (2.5) |
| Back pain | 6 (2.5) |
| Latent tuberculosis | 6 (2.5) |
| Neutropenia | 6 (2.5) |
| Urinary tract infection | 6 (2.5) |
| Acne | 5 (2.1) |
| Folliculitis | 5 (2.1) |
| Herpes zoster | 5 (2.1) |
| Influenza | 5 (2.1) |
| Nausea | 5 (2.1) |
| Rhinitis | 5 (2.1) |
| Tonsillitis | 5 (2.1) |
| Weight increased | 5 (2.1) |

A total of 186 AEs (78.3 E/100 PYs) were considered by the investigator to have a reasonable possibility of being related to upadacitinib treatment. Study-drug related AEs with ≥ 5E/100 PYs were blood CPK increased, nasopharyngitis, and upper respiratory tract infection.

*Extra-Articular Manifestations of AS*

Uveitis: In the current AS study, 24 (25.5%) subjects in the placebo group and 16 (17.2%) subjects in the upadacitinib group had anterior uveitis at Baseline (Screening) In the placebo-controlled period, 3 (3.2%) subjects receiving placebo experienced uveitis flares (PT: iridocyclitis; the 3 subjects on placebo had a history of uveitis). No subject receiving upadacitinib experienced uveitis flares.

In the long-term data, 13 uveitis events (PTs of iridocyclitis, iritis, and uveitis) were reported at a rate of 5.5E/100 PY in subjects receiving upadacitinib. All uveitis events with upadacitinib treatment were observed subjects with a history of uveitis.

Inflammatory Bowel Disease**:** In the placebo-controlled period, 1 subject on placebo (without a history of inflammatory bowel disease), and no subject on upadacitinib had a new onset of inflammatory bowel disease. In the long-term data, no new onset or exacerbation of inflammatory bowel disease was observed during upadacitinib treatment.

## *Serious adverse event/deaths/other significant events*

*Deaths*

No deaths occurred up to the data cut-off date.

*Other Serious Adverse Events*

In the placebo-controlled period, 1 SAE of spinal osteoarthritis was reported in a subject in the upadacitinib group, and 1 SAE of cardiovascular disorder was reported in a subject in the placebo group.

In the long-term data, 14 SAEs (5.9 E/100 PYs) were reported in 12 subjects; according to the MAH, there was no discernible pattern to the SAEs reported. Three SAEs were reported in the Musculoskeletal and Connective Tissue Disorders SOC: osteoarthritis, periarthritis, and spinal osteoarthritis. Three SAEs were reported in the Injury, Poisoning, and Procedural Complications SOC: facial bones fracture, multiple fractures, and radius fracture. Other SOCs had ≤ 2 SAEs reported.

*Table 26: Long-Term Data: Treatment-Emergent Serious Adverse Events per 100 PYs (Safety Analysis Set*

| MedDRA 22.0 System Organ Class<br>Preferred Term | Any Upadacitinib 15 mg QD<br>(N = 182)<br>(PYs = 237.6)<br>Events (E/100PYs) |
|---|---|
| Any adverse event | 14 (5.9) |
| Ear and labyrinth disorders | 1 (0.4) |
| Vertigo positional | 1 (0.4) |
| Injury, poisoning and procedural complications | 3 (1.3) |
| Facial bones fracture | 1 (0.4) |
| Multiple fractures | 1 (0.4) |
| Radius fracture | 1 (0.4) |
| Musculoskeletal and connective tissue disorders | 3 (1.3) |
| Osteoarthritis | 1 (0.4) |
| Periarthritis | 1 (0.4) |
| Spinal osteoarthritis | 1 (0.4) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 (0.4) |
| Squamous cell carcinoma of the tongue | 1 (0.4) |
| Nervous system disorders | 2 (0.8) |
| Hemiparaesthesia | 1 (0.4) |
| Syncope | 1 (0.4) |
| Reproductive system and breast disorders | 2 (0.8) |
| Benign prostatic hyperplasia | 1 (0.4) |
| Uterine prolapse | 1 (0.4) |
| Vascular disorders | 2 (0.8) |
| Aortic dilatation | 1 (0.4) |
| Hypertensive emergency | 1 (0.4) |

*Adverse Drug Reactions*

Adverse events were evaluated for inclusion as adverse drug reactions (ADR) based on the totality of the evidence with the following considerations: disproportionate number of reports between placebo and upadacitinib, similar trend among medically-related events, temporal relationship, dechallenge/rechallenge information for relevant event reports, preclinical data, and biological plausibility based on mechanism of action and/or class effect. All currently labeled ADRs for RA and PsA were reviewed against the Study M16-098 safety data to determine whether any meaningful change in the rates for the ADRs had occurred to warrant a frequency change in the presentation in

the ADR table. Following this assessment process, the MAH concludes that no new ADRs were identified based on analysis of AEs and medical review of the placebo-controlled data. In addition, all the currently labeled ADRs had no meaningful change in their rates.

*Adverse Events of Special Interest*

As of the data cut-off date, no events in the following AESI categories were reported in Study M16-098 by any subject: serious infection, NMSC, lymphoma, gastrointestinal perforation, renal dysfunction, active TB, adjudicated major adverse cardiovascular event (MACE) or adjudicated VTE.

Opportunistic Infections

A single subject experienced 2 episodes of non-serious esophageal candidiasis, 1 AE in each study period resulting in temporary interruption of study drug. Both events resolved after treatment. Opportunistic infections are an identified risk of upadacitinib treatment, and a warning regarding this risk is included in the current product information

Herpes Zoster

No herpes zoster AE was reported in the placebo-controlled period.

In the long-term data, 5 events (2.1 E/100 PYs) of herpes zoster were reported in 4 subjects. All herpes zoster AEs were assessed as having a reasonable possibility of being related to study drug. None of the herpes zoster events were serious, but 1 subject discontinued study drug as a result of a herpes zoster AE. All events were mild or moderate in severity and confined to a single dermatome. Herpes zoster is an identified risk for upadacitinib treatment and is described in the current product information. The MAH states that long-term event rate of herpes zoster observed with upadacitinib 15 mg in the AS clinical study was not higher than that observed previously in the RA programme.

Malignancy

No malignancy, including NMSC and lymphoma, was reported in the placebo-controlled period.

In the long-term data, 1 malignancy (0.4 E/100 PYs), a SAE of squamous cell carcinoma of the tongue, was observed. The AE was reported in a former smoker who had < 5 months exposure to upadacitinib. The AE was assessed as having no reasonable possibility of being related to study drug. As an important potential risk, malignancies are included in the warnings and precautions of current product information. The MAH states that an increased risk of malignancy has not been observed with upadacitinib 15 mg therapy during the AS, PsA and RA clinical trials to date. However, malignancies have a long latency to onset, and administration of immunomodulatory drugs may increase a person's susceptibility to develop malignancies.

Hepatic Disorders

In the placebo-controlled period, the proportion of subjects with AEs of hepatic disorders was greater in the upadacitinib group than the placebo group (5.4% versus 2.1%. Seven non-serious AEs of hepatic disorders were reported in 5 subjects in the upadacitinib group. The hepatic disorders in these subjects were all asymptomatic alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increased or hepatic enzymes increased. None of the events led to discontinuation of study drug. Five of 7 events in the upadacitinib group were mild, and 2 were moderate.

At Week 14, greater mean increases from Baseline in ALT and AST (each 5.8 U/L) were observed in subjects in the upadacitinib group vs the placebo group (ALT: −2.7 U/L; AST: −1.4 U/L). The majority of ALT/AST elevations were <3 × ULN.

In the long-term data, 24 hepatic disorders (10.1 E/100 PYs) were reported in 15 subjects who received upadacitinib. No report was serious, and none led to discontinuation of study drug. ALT increased (12 events [5.1E/100 PYs]) and AST increased (7 events [2.9 E/100 PYs]) were the most frequently reported hepatic disorders. Eight AEs of ALT increased, and 4 AEs of AST increased were assessed as having a reasonable possibility of being related to study drug. Through Week 64, greater mean changes from Baseline in ALT, AST, and bilirubin upadacitinib therapy were observed in subjects who received upadacitinib. Two subjects had potentially clinically significant Grade 3 ALT/ AST increases. Both ALT and AST values decreased to normal ranges or Baseline levels without study drug discontinuation. No cases met the biochemical criteria for Hy's law. Increases in ALT and AST are listed as ADRs in the current product information. The MAH states that the nature and severity of ALT and AST elevations observed with upadacitinib 15 mg in the AS patient population, as judged by the assessment of the reported laboratory values, were similar to that reported previously in the RA programme. Due to the observation of transaminase elevations with upadacitinib treatment, potential for drug induced liver injury remains an important potential risk for upadacitinib.

Anemia

No AE of anemia was reported in the placebo-controlled period. At Week 14, mean changes from Baseline in hemoglobin were for the upadacitinib group 0.1 g/L and for the placebo group –0.2 g/L. No Grade 3 hemoglobin value was reported in the placebo or upadacitinib group.

In the long-term data, 3 events (1.3 E/100 PYs) of anemia were reported. No event was serious, severe, or led to study drug discontinuation. According to the MAH, through Week 64, mean hemoglobin values were essentially unchanged in subjects who received upadacitinib. No subjects had ≥ Grade 3 decreases in hemoglobin. Recommendations for dose interruption of upadacitinib for low hemoglobin are provided in the current product information. The MAH states that overall, no clinically meaningful impact on hemoglobin levels was observed with upadacitinib 15 mg treatment in the AS clinical studies. The long-term rate of anemia observed was, according to the MAH, not higher than that reported previously in the RA program.

Lymphopenia

In the placebo-controlled period, no AE of lymphopenia was reported.

At Week 14, a numerically greater mean increase from Baseline in lymphocyte count was observed in subjects in the upadacitinib group vs the placebo group ($0.139 \times 10^9$/L vs $0.015 \times 10^9$/L). No≥ Grade 3 lymphocyte count decrease was reported in the placebo or upadacitinib group. In the long-term data, 2 events (0.8 E/100PYs) of lymphopenia were reported. Neither event was serious, severe, or led to study drug discontinuation. The MAH states that overall, lymphocyte mean changes from Baseline were small in subjects receiving upadacitinib through Week 64, and lymphocyte values tended to fluctuate between increases and decreases. No subject had a post-Baseline Grade ≥ 3 lymphocyte count decrease. Recommendation for dose interruption of upadacitinib for low absolute lymphocyte count is provided in the current product information. According to the MAH, overall, no clinically meaningful impact on lymphocyte counts was observed with upadacitinib 15 mg treatment in the AS clinical studies. The long-term rate of lymphopenia observed was not higher than that reported previously in the RA programme.

Neutropenia

In the placebo-controlled period, 1 AE of neutropenia (Grade 2 neutrophil count decreased) assessed as having no reasonable possibility of being related to study drug was reported in the upadacitinib group. Study drug was interrupted for 5 days and re-started. A numerically greater mean decrease from Baseline in neutrophil count was observed in the upadacitinib group vs the placebo group at Week

14 ($-0.595 \times 10^9$/L vs $-0.052 \times 10^9$/L). In addition, a larger proportion of subjects in the upadacitinib group compared with the placebo had shifts from high or normal at Baseline to low post-Baseline values in neutrophil count (16.5% compared with 4.3%, respectively. In the long-term data, 7 (2.9 E/100 PYs) AEs of neutropenia were reported, the majority of these events were not associated with infections. Five neutropenia AEs were assessed as having a reasonable possibility of being related to study drug. Most events were mild, no event was serious, and no subject discontinued study drug as a result of an AE of neutropenia. The MAH states that neutrophil mean changes from Baseline were small through Week 64. Two subjects (1.1%) experienced Grade 3 neutrophil count decreases. Neutropenia is listed as an ADR for upadacitinib, and the recommendation for dose interruption of upadacitinib for low absolute neutrophil count is also provided in the current product information. The long-term rate and severity of the neutropenia in the AS clinical studies were, according to the MAH, similar to that observed previously in the RA programme.

Creatine Phosphokinase Elevation

In the placebo-controlled period, a larger proportion of subjects who received upadacitinib (8 [8.6%] subjects) had AEs of CPK elevation compared with placebo (2 [2.1%] subjects). Events in 4 subjects who received upadacitinib and 1 subject who received placebo were mild and assessed as having a reasonable possibility of being related to study drug. No subjects had severe events. At Week 14, subjects in the upadacitinib group had a numerically greater mean increase in CPK versus placebo group (upadacitinib 58.5U/L vs placebo –57.8 U/L). A Grade3 (> 5 – 10 × ULN) increased CPK value was reported in 1(1.1%) subject in each of the placebo and upadacitinib groups

In the long-term data, 28 AEs of CPK elevation (11.8 E/100 PYs), none severe, were reported in 23 subjects (19 male; 4 female) who received upadacitinib. Sixteen events were assessed as having a reasonable possibility of being related to study drug. All events were non-serious, and none led to discontinuation of study drug). Mean CPK values increased from Baseline to Week 4 for subjects who received upadacitinib group and then generally stabilized through Week 64. Most CPK elevations were <4 × ULN, and the majority of subjects were asymptomatic. "Exercise or other vigorous physical activity" was reported by more than 50% of subjects who had increased CPK. Five (2.7%) Grade 3 and 2 (1.1%) Grade 4 elevations were reported). Most of the Grade 3 and Grade 4 CPK elevations occurred at 1 time point only followed by normalization at subsequent testing. All Grade3 or 4 CPK elevations occurred in young male subjects; 86% (6 of 7) did not lead to study drug interruption or discontinuation. Two CPK increases were reported as AEs. No event of rhabdomyolysis was reported. The MAH concludes that CPK elevation is an identified ADR for upadacitinib and is considered to pose minimal clinical impact due to most elevations being asymptomatic and drug discontinuations related to CPK elevations being uncommon. In addition, the AS population has a predominance of males who have a greater muscle mass than females, which may contribute to a higher rate of CPK elevations being observed in the AS study compared to the RA clinical programme. However, the nature (e.g., nonseriousness, few leading to study drug discontinuation, lack of associated symptoms) and severity of CPK elevations in the AS program was, according to the MAH, similar to that observed previously in the RA programme.

Renal Dysfunction

No AEs of renal dysfunction were reported up to the data cut-off date. At Week 14, subjects in the upadacitinib group had a numerically greater mean increase from Baseline in serum creatinine versus the placebo group. According to the MAH, through Week 64, minimal mean increases from Baseline in serum creatinine were observed for subjects receiving upadacitinib. No Grade ≥ 3 value for creatinine was reported. The MAH states that overall, no clinically meaningful impact on creatinine levels was observed with upadacitinib 15 mg treatment in the AS clinical studies.

*Other Areas of Safety Interest*

Lipids

Mean values for total cholesterol, HDL-C and LDL-C increased for subjects receiving upadacitinib through Week 64. In the long-term data, 5.0%, 6.1%, and 15.5% of subjects had shifts from low or normal at Baseline to high final post-Baseline values for LDL-C, total cholesterol, and HDL-C, respectively. In total, 4 (2.2%) subjects had Grade 3 and 2 (1.1%) subjects had Grade 4 triglyceride increases; 1 (0.5%) subject had Grade 3 increase of total cholesterol. Two nonserious events of hypertriglyceridemia were reported. Current upadacitinib information in RA, advises prescribers to assess lipid parameters at approximately 12 weeks following initiation of treatment and manage patients according to applicable clinical guidelines for hyperlipidemia.

## *Laboratory findings*

*Additional Clinical Laboratory Measurements*

Evaluation of mean changes over time and potentially clinically significant abnormalities in hemoglobin values and neutrophil and lymphocyte counts, as well as transaminases and CPK were evaluated and reported in the section for the respective associated AESIs. The MAH states that other than that discussed in the AESI sections above, evaluation of changes in hematology and clinical chemistry values did not identify any significant safety concerns with upadacitinib treatment.

At Week 14, the mean increase from Baseline in platelets was 8.4 × 109/L in the upadacitinib group versus 1.0 × 109/L in the placebo group. No subject had a post Baseline platelet value meeting ≥ Grade 3 values (during the placebo-controlled period or in the long-term data).

For most hematology and chemistry parameters, small numbers of subjects shifted from high or normal at Baseline to low post-Baseline or from low or normal at Baseline to high post-baseline. In long-term data, ≥ 10% of subjects shifted from high or normal at baseline to low post-baseline for hemoglobin and neutrophil counts and from low or normal at baseline to high post-baseline for ALT, AST, bilirubin, BUN, albumin, cholesterol, HDL cholesterol, and LDL cholesterol.

*Vital Signs*

According to the MAH, through Week 64, few subjects had potentially clinically significant (PCS) vital sign values for increased or decreased systolic or diastolic blood pressure, increased or decreased pulse, or increased or decreased respiratory rate; no subject had increased temperature.

In the long-term data, eight subjects (4.4%) had decreased weight > 7% from Baseline, and 40 subjects (22.0%) experienced a weight increase > 7%. Weight gain is an ADR for upadacitinib and is listed in the current product information. The weight changes observed in the AS clinical study is according to the MAH similar to those reported in the RA clinical development programme.

## *Safety in special populations*

*Pregnancy*

There were no pregnancies reported to date in female subjects in the AS program.

The MAH has provided information about pregnancies in the other study programmes. As of 15 February 2020, there were a total of 39 pregnancies reported in female subjects conservatively considered to have been exposed to upadacitinib in clinical studies of RA, PsA, atopic dermatitis, ulcerative colitis, and CD. Of the 39 pregnancies, 13 were live births in women exposed to upadacitinib

during the first 4 to 8 weeks of pregnancy with no congenital anomalies reported. There were 12 spontaneous abortions identified in pregnant females with various risk factors (e.g., age > 35 years of age, MTX exposure during pregnancy) and the resulting rate of spontaneous abortion was consistent with what has been reported in patients with rheumatic diseases on MTX. Four elective terminations did not report any foetal defects. There was 1 ectopic pregnancy, 1 unknown outcome, and 8 pregnancies were ongoing as of the data cut off (15 February 2020).

*Other safety data in special populations*

According to the MAH, safety in Special Groups Subgroup analyses of AE data for E/100 PYs, AESI/100 PYs, AEs by SOC and PT were performed for age, sex, race and body mass index (BMI) groups; analyses did not reveal a clinically relevant increased risk for upadacitinib treatment based on these intrinsic subject factors. Given this assessment, no special considerations for upadacitinib 15 mg treatment based on the age, sex, race, BMI, or age are warranted beyond those already described for the RA patient population. For the extrinsic factor of csDMARD use, < 20% of subjects were on concomitant csDMARDs during the study. As a result, no conclusions can be made regarding increased risk of AEs when upadacitinib is used in combination with csDMARDs. However, the MAH states that based on the analysis of data from the upadacitinib PsA programme with a larger sample size, the safety profile was generally similar between the upadacitinib monotherapy and upadacitinib combination therapy, with the exception of higher rates of serious infections, hepatic disorder, and CPK elevation in the combination therapy. Of note, csDMARDs have generally not been demonstrated to be effective in AS and are not part of the overall treatment recommendations.

## *Discontinuation due to adverse events*

In the placebo-controlled period, the proportion of subjects with AEs leading to discontinuation of study drug was similar in subjects receiving upadacitinib (2 [2.2%] subjects) and placebo (3[3.2%] subjects) Events of dyspepsia, blood CPK increased, and atlantoaxial instability were each reported in 1 subject in the placebo group, and events of otitis media and myalgia were each reported in 1 subject in the upadacitinib group. The subject with myalgia did not have a concurrent CPK increase. There were no laboratory AEs in a subject receiving upadacitinib that led to discontinuation of study drug.

*Table 27: Long-Term Data: Treatment-Emergent Adverse Events Leading to Discontinuation, E/100 PYs (Safety Analysis Set)*

| MedDRA 22.0 System Organ Class<br>Preferred Term | Any Upadacitinib15 mg QD<br>(N = 182)<br>(PYs = 237.6)<br>Events (E/100PYs) |
|---|---|
| Any adverse event | 15 (6.3) |
| Ear and labyrinth disorders | 1 (0.4) |
| Vertigo | 1 (0.4) |
| Eye disorders | 1 (0.4) |
| Iridocyclitis | 1 (0.4) |
| Gastrointestinal disorders | 2 (0.8) |
| Aphthous ulcer | 1 (0.4) |
| Diarrhoea | 1 (0.4) |
| General disorders and administration site conditions | 1 (0.4) |
| Treatment noncompliance | 1 (0.4) |
| Infections and infestations | 2 (0.8) |
| Herpes zoster | 1 (0.4) |
| Otitis media | 1 (0.4) |
| Musculoskeletal and connective tissue disorders | 2 (0.8) |
| Intervertebral disc protrusion | 1 (0.4) |
| Myalgia | 1 (0.4) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 (0.4) |
| Squamous cell carcinoma of the tongue | 1 (0.4) |
| Nervous system disorders | 3 (1.3) |
| Headache | 2 (0.8) |
| Hemiparaesthesia | 1 (0.4) |
| Reproductive system and breast disorders | 1 (0.4) |
| Benign prostatic hyperplasia | 1 (0.4) |
| Vascular disorders | 1 (0.4) |
| Vasculitis | 1 (0.4) |

## *Post marketing experience*

Upadacitinib 15 mg daily dose was first approved for the treatment of RA on 16 August 2019 (international birth date [IBD]) in the United States. Through 31 January 2020, upadacitinib has been approved in 41 countries with estimated cumulative exposure of 3,138 patient treatment years across 9 countries.

The overall safety of upadacitinib 15 mg QD therapy was evaluated through review of post-marketing reports (spontaneous, solicited, literature) received from 16 August 2019 through 15 February 2020.

Search of the AbbVie global safety database retrieved 1,573 reports. Overall, 90% of the reports were considered nonserious and 95% were from solicited source. The most frequently reported MedDRA SOC was Infections and Infestations, in which nasopharyngitis, sinusitis, and URTI had the greatest number of reports. Among all the reports, the most common AEs reported included headache (7%), nausea (7%), drug ineffective (6%), fatigue (6%), and arthralgia (5%) The most commonly reported SAE was pneumonia (1%), and the remaining SAEs were reported in less than 0.5% of the retrieved reports. Generally, the type and pattern of SAEs reported were, according to the MAH, similar to what has been observed in the RA clinical trials for upadacitinib. Causality could not be assessed for the few reports describing events of hypersensitivity/anaphylactic reactions due to limited information in these reports. Review of the post-marketing reports did not identify any new safety risks for the marketed upadacitinib in treating patients with moderately to severely active RA.

## 2.5.1. Discussion on clinical safety

**Extent of exposure and overview of adverse events**

A total of 182 AS subjects received ≥ 1 dose of upadacitinib 15 mg and up to the data cut-off date, 160 of the 182 subjects had exposure to upadacitinib for ≥ 12 months. Although the extent of exposure for the patient population targeted by the new indication sought is limited, it is considered acceptable to the CHMP as safety information can largely be extrapolated from the approved RA-indication. This was discussed also the CHMP SA in which it was stated: *"It is agreed that the safety experience of upadacitinib can be further supported by information from trials performed in other rheumatology indications i.e. RA and in PsA".*

As stated in the Rinvoq EPAR, important observed adverse events in the RA population are infections, haematological disturbances, elevated liver enzymes and CPK elevations. The risk for malignancy and cardiovascular disorder are to be further addressed in post-authorization studies. Further, use in patients with severe renal impairment is listed as a safety concern in the RMP. Upadacitinib is contraindicated in active tuberculosis (TB) or active serious infections, severe hepatic impairment and pregnancy. upadacitinib should not be used during breast-feeding.

In the 14-week placebo-controlled period, 62.4 % of the subjects in the upadacitinib group and 55.3 % in the placebo group had any AEs. No patients in the upadacitinib group had any severe AE and similar proportions of subjects in the placebo and upadacitinib groups had ≥ 1 SAEs (1.1% in each group) and AEs leading to discontinuation (2.2% in the upadacitinib group and 3.2% in the placebo group).

Infections were reported by 20.4% in the upadacitinib group and 26.6% in the placebo group. The most frequently reported infections (≥ 2 subjects) in the upadacitinib group were nasopharyngitis, influenza, and tonsillitis. No serious infections were reported by any subject in this study.

In the placebo-controlled period, the most frequently reported TEAEs (≥ 5% of subjects) in the upadacitinib group were increased blood CPK, diarrhea, nasopharyngitis, and headache compared with diarrhea and nausea in the placebo group. The frequencies of CPK increased and ALT increased were 8.6% and 4.3%, respectively, in the upadacitinib group compared with 2.1% for each event in the placebo group.

In the long-term data up to the data cut-off date, 618 AEs (260.1 events [E]/100 PYs) were reported in 182 subjects (237.6 patient-years [PYs]) who received upadacitinib 15mg QD. Seven (7) severe AEs (2.9E/100 PYs), 14 SAEs (5.9E/100 PYs) and 15 AEs (6.3E/100 PYs) leading to discontinuation were reported. No deaths were reported.

For comparison, it can be noted that according to the Rinvoq EPAR, in the short-term placebo-controlled safety set in the development programme for RA, the frequency for infections and

infestations was 27.2% in the upadacitinib 15 mg group and 20.6% in the placebo group. According to the EPAR, in both the short-term and long-term RA datasets, adverse events were most frequently reported in the Infectious and Infestations SOC. The incidence of AEs for upadacitinib 15 mg monotherapy (over 48 weeks) was 345.4/100 PY while the incidence of serious infections for upadacitinib 15 mg in combination with MTX (over 48 weeks) was 4.1/100 PY.

**Adverse events of special interest**

No events in the following AESI categories were reported by any subjects in the study: serious infection, NMSC, lymphoma, gastrointestinal perforation, renal dysfunction, active TB, adjudicated MACE or adjudicated VTE. It is noted that there were no exclusion criteria for VTE in the original protocol, and it is noted that the only patients with contraindication for NSAID in the study were due to previous VTE. In addition, 8% of the patients had latent TB.

Opportunistic Infections

A single subject experienced 2 episodes of non-serious esophageal candidiasis, 1 AE in each study period resulting in temporary interruption of study drug. Both events resolved after treatment. Opportunistic infections are an identified important risk of upadacitinib treatment, and a warning in SmPC section 4.4 regarding this risk is included in the current product information. This is adequate also for the new AS indication.

Herpes Zoster

In the long-term data, 5 events (2.1 E/100 PYs) of herpes zoster were reported in 4 subjects, leading to discontinued study drug in one patient. All events were mild or moderate in severity and confined to a single dermatome. Herpes zoster is an identified important risk for upadacitinib treatment and is described in section 4.8 of the SmPC as uncommon. In addition, multidermatomal herpes zoster is mentioned in the section 4.4 of the SmPC. The long-term event rate of herpes zoster observed with upadacitinib 15 mg in the AS clinical study was not higher than that observed previously in the RA program (4.3 E/100 PYs).

Malignancy

One malignancy (0.4 E/100 PYs), a SAE of squamous cell carcinoma of the tongue, was observed. The AE was reported in a former smoker who had < 5 months exposure to upadacitinib. The AE was assessed as having no reasonable possibility of being related to study drug. Malignancies are safety concerns included in the RMP and also included in section 4.4 of the SmPC. This is adequate also for the AS population.

Hepatic Disorders

In the placebo-controlled period of the AS study, the proportion of subjects with AEs of hepatic disorders was greater in the upadacitinib group than the placebo group (5.4% versus 2.1%). The hepatic disorders in these subjects were all asymptomatic alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increased or hepatic enzymes increased. None of the events led to discontinuation of study drug. In the long-term data, 24 hepatic disorders (10.1 E/100 PYs) were reported in 15 subjects who received upadacitinib. No report was serious, and none led to discontinuation of study drug. Two subjects had potentially clinically significant Grade 3 ALT/ AST increases but both ALT and AST values decreased to normal ranges or Baseline levels without study drug discontinuation. In both cases there were confounding factors (co-medication, alcohol).

Increases in ALT and AST are listed as common ADRs (corresponds to ≥ 1/100 to <1/10) in the current product information. According to the Rinvoq EPAR, in the previous studies in RA programme, upadacitinib 15 mg was associated with a small (about 5 U/L) increase in mean ALT and AST levels in

short-term analyses, and ALT increases of 5*ULN or greater were seen in about 1.5% of subjects compared to less than 0.5% of subjects on placebo. This small increase persisted on long-term treatment. Two subjects in the long-term "Any Ph 3 UPA 15" analysis set met biochemical criteria for Hy's Law, but both subjects had alternative aetiologies (malignant melanoma, and concomitant use of INH). In the long-term Any Ph 3 UPA 15 analysis set, the exposure-adjusted event rate (EAER) of treatment-emergent hepatic disorders was 14.4 E/100 PY, most events being transaminase elevations. Elevations were usually asymptomatic and transient even in the setting of continued treatment; the EAER of hepatic disorders leading to study drug discontinuation was 0.8 E/100 PY.

Overall, the nature and severity of ALT and AST elevations observed with upadacitinib 15 mg in the AS patient population appear broadly similar to that reported previously in the RA programme. Due to the observation of transaminase elevations with upadacitinib treatment, potential for drug induced liver injury remains an important potential risk for upadacitinib. Section 4.4 of the SmPC describes the effect of upadacitinib on transaminases and advices the prescriber on how to proceed in cases of liver enzyme elevation. This is considered relevant also for the new indication that this application targets.

Anemia

In the Exposure-response analysis submitted with this application, it was noted that with increasing upadacitinib exposures, a relationship was found in the percentage of patients experiencing decreases in haemoglobin of ≥ 1 g/dL from baseline. This is consistent with information from the RA population from the Rinvoq EPAR, in which it is stated that overall there was very little effect on mean haemoglobin with the 15 mg dosage of upadacitinib but the 30 mg dosage did induce a more observable decrease in haemoglobin.

Reassuringly, judging from the provided clinical safety data, also in the AS population, the 15 mg dose seemed to be associated with very limited influence on Hb. No AE of anemia was reported in the placebo-controlled period. At Week 14, mean changes from Baseline in hemoglobin were minimal for the upadacitinib (0.1 g/L) and placebo groups (−0.2 g/L). In the long-term data, 3 events (1.3 E/100 PYs) of anemia were reported. No event was serious, severe, or led to study drug discontinuation. Through Week 64, mean hemoglobin values were essentially unchanged in subjects who received upadacitinib.

The current SmPC text, including the recommendations for dose interruption of upadacitinib for low hemoglobin is considered appropriate also for the new AS indication.

Lymphopenia

In the placebo-controlled period, no AE of lymphopenia was reported. At Week 14, a numerically greater mean increase from Baseline in lymphocyte count was observed in subjects in the upadacitinib group vs the placebo group. In the long-term data, 2 events (0.8 E/100PYs) of lymphopenia were reported. Neither event was serious, severe, or led to study drug discontinuation. Overall, lymphocyte mean changes from Baseline were small in subjects receiving upadacitinib through Week 64, and lymphocyte values tended to fluctuate between increases and decreases. No subject had a post-Baseline Grade ≥ 3 lymphocyte count decrease. Recommendation for dose interruption of upadacitinib for low absolute lymphocyte count is provided in the current product information which is considered adequate also for the new AS indication.

Neutropenia

In the placebo-controlled period, 1 AE of neutropenia (Grade 2 neutrophil count decreased) assessed as having no reasonable possibility of being related to study drug was reported in the upadacitinib group. Study drug was interrupted for 5 days and re-started. A numerically greater mean decrease from Baseline in neutrophil count was observed in the upadacitinib group vs the placebo group at Week

14. In addition, a larger proportion of subjects in the upadacitinib group compared with the placebo had shifts from high or normal at Baseline to low post-Baseline values in neutrophil count (16.5% compared with 4.3%, respectively. In the long-term data, 7 (2.9 E/100 PYs) AEs of neutropenia were reported, the majority of these events were stated not to be associated with infections. Five neutropenia AEs were assessed as having a reasonable possibility of being related to study drug. Most events were mild, no event was serious, and no subject discontinued study drug as a result of an AE of neutropenia. Neutrophil mean changes from Baseline were small through Week 64. Two subjects (1.1%) experienced Grade 3 neutrophil count decreases.

In the current SmPC, neutropenia is listed as common adverse reaction (frequency ≥ 1/100 to < 1/10) and it is stated that in placebo-controlled RA studies with background DMARDs, for up to 12/14 weeks, decreases in neutrophil counts below 1,000 cells/mm3 in at least one measurement occurred in 1.1% and <0.1% of patients in the upadacitinib 15 mg and placebo groups, respectively. Mean neutrophil counts decreased over 4 to 8 weeks. The decreases in neutrophil counts remained stable at a lower value than baseline over time including with extended therapy. The SmPC also includes a recommendation for dose interruption of upadacitinib for low absolute neutrophil count. The CHMP agreed that this recommendation is appropriate also for the new AS indication.

Creatine Phosphokinase Elevation

In the placebo-controlled period, a larger proportion of subjects who received upadacitinib (8 [8.6%] subjects) had AEs of CPK elevation compared with placebo (2 [2.1%] subjects). It is noted that only half of the events in the respective groups were according to the MAH assessed as having a reasonable possibility of being related to study drug (4/8 in the upadacitinib group and 1/2 in the placebo group). No subjects had severe events. At Week 14, subjects in the upadacitinib group had a numerically greater mean increase in CPK versus placebo group (upadacitinib 58.5U/L vs placebo −57.8 U/L). A Grade 3 (> 5 − 10 × ULN) increased CPK value was reported in 1(1.1%) subject in each of the placebo and upadacitinib groups.

In the long-term data, 28 AEs of CPK elevation (11.8 E/100 PYs), none severe, were reported in 23 subjects who received upadacitinib. Sixteen events were assessed as having a reasonable possibility of being related to study drug. All events were non-serious, and none led to discontinuation of study drug. Mean CPK values increased from Baseline to Week 4 for subjects who received upadacitinib group and then generally stabilized through Week 64. Most CPK elevations were <4 × ULN, and the majority of subjects were asymptomatic. "Exercise or other vigorous physical activity" was reported by more than 50% of subjects who had increased CPK. Five (2.7%) Grade 3 and 2 (1.1%) Grade 4 elevations were reported. Most of the Grade3 and Grade 4 CPK elevations occurred at 1 time point only followed by normalization at subsequent testing. All Grade 3 or 4 CPK elevations occurred in young male subjects; 86% (6 of 7) did not lead to study drug interruption or discontinuation. Two CPK increases were reported as AEs. No event of rhabdomyolysis was reported.

According to the current SmPC, in placebo-controlled studies with background DMARDs in the RA population (for up to 12/14 weeks) increases in CPK values were also observed. CPK elevations > 5 x upper limit of normal (ULN) were reported in 1.0% and 0.3% of RA patients over 12/14 weeks in the upadacitinib 15 mg and placebo groups, respectively. Blood CPK increased is listed as a common (frequency ≥ 1/100 to < 1/10) adverse reaction in the SmPC. According to the Rinvoq EPAR, CPK elevations were observed in 2.8% of RA patients treated with upadacitinib 15 mg (vs 0.6% in placebo treated subjects, both in combination with csDMARDs) during the first 3 months. Across the five phase 3 RA studies, the incidence of any CPK elevation was 10.1/100 PYs in the group that received upadacitinib 15 mg in combination with a non-MTX csDMARD and 4.8/100 PY in the group that received upadacitinib 15 mg in combination with MTX alone.

The MAH believes that the predominance of males in the AS population (with males generally having greater muscle mass than females), may contribute to a higher rate of CPK elevations being observed in the AS study compared to the RA clinical programme. This might be the case but it should also be noted that as the estimate is based on rather few patients and events, it is expected to have a rather low precision, hampering the comparative conclusions that can be drawn. In any way, the nonseriousness of the observed events, the few events leading to study drug discontinuation and lack of associated symptoms indicates that this observation is not likely to pose large clinical impact. Thus, no further action was considered warranted by the CHMP.

Renal Dysfunction

No AEs of renal dysfunction were reported up to the data cut-off date. At Week 14, subjects in the upadacitinib group had a numerically greater mean increase from Baseline in serum creatinine versus the placebo group. According to the MAH, through Week 64, minimal mean increases from Baseline in serum creatinine were observed for subjects receiving upadacitinib. No Grade ≥ 3 value for creatinine was reported. The CHMP agreed that no update to the SmPC was required for the new AS indication.

Other Areas of Interest

*Lipids*

Mean values for total cholesterol, HDL-C and LDL-C increased for subjects receiving upadacitinib through Week 64. In the long-term data, 5.0%, 6.1%, and 15.5% of subjects had shifts from low or normal at Baseline to high final post-Baseline values for LDL-C, total cholesterol, and HDL-C, respectively. In total, 4 (2.2%) subjects had Grade 3 and 2 (1.1%) subjects had Grade 4 triglyceride increases; 1 (0.5%) subject had Grade 3 increase of total cholesterol. Two nonserious events of hypertriglyceridemia were reported. Current advice for prescribers on the product information for upadacitinib in RA is to assess lipid parameters at approximately 12 weeks following initiation of treatment and manage patients according to applicable clinical guidelines for hyperlipidemia. The same advice is applicable to AS.

*Weight gain*

Eight subjects (4.4%) had decreased weight > 7% from Baseline, and 40 subjects (22.0%) experienced a weight increase > 7%. Weight gain is an ADR for upadacitinib and is listed in the current product information.

## 2.5.2. Conclusions on clinical safety

Overall, the safety profile of upadacitinib in AS in the proposed posology of 15mg QD, is considered by the CHMP to be consistent with the safety profile in the approved RA-indication and thus covered in the approved SmPC and RMP (see RMP section). The MAH proposed to add a general statement in section 4.8 of the SmPC to inform about the consistency of safety data between the indications, this statement was agreed on by the CHMP.

## 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 3.3 is acceptable.

The CHMP endorsed this advice without changes:

| **Safety Concern** | **Risk Minimization Measures** | **Pharmacovigilance Activities** |
|---|---|---|
| Serious and opportunistic infections including TB | Routine risk minimization measures:<br>• SmPC Section 4.4 summarizes the risk and provides guidance on ways to reduce the risk.<br>• 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.<br>• 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.<br>• SmPC Section 4.2 outlines lymphocyte and neutrophil counts and when not to initiate upadacitinib dosing.<br>• SmPC Section 4.2 outlines interruption guidelines based on ALC and ANC.<br>• SmPC Section 4.3 indicates that upadacitinib is contraindicated in patients with active TB or active serious infections.<br>• 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.<br>• SmPC Section 4.4 advises to consider the risks and benefits of initiating upadacitinib in patients with active, chronic, or recurrent infections.<br>○ A patient who develops a new infection during treatment with upadacitinib should undergo | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>Routine pharmacovigilance activities including follow-up questionnaire for serious and opportunistic infections including TB<br>Additional pharmacovigilance activities:<br>• Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe<br>• Long-Term Safety Study of Upadacitinib Use in RA Patients in the US<br>• Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation<br>• Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545)<br>• Long-term extension portion of Phase 2/3 AS trial (Study M16-098) |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | 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.<br>○ Screening for TB prior to initiation is advised, and upadacitinib should not be given if active TB is diagnosed. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with untreated latent TB or in patients with risk factors for TB infection.<br>Additional risk minimization measures:<br>• HCP educational brochure<br>• PAC<br>Other routine risk minimization measures:<br>Prescription only medicine. | |
| Herpes zoster | Routine risk minimization measures:<br>• SmPC Section 4.4 describes the risk of viral reactivation such as herpes zoster.<br>• SmPC Section 4.8 describes findings from upadacitinib clinical trials.<br>• 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.<br>• 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.<br>• SmPC Section 4.4 advises that if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves.<br>Additional risk minimization measures:<br>• HCP educational brochure<br>• PAC | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>Routine pharmacovigilance activities including follow-up questionnaire for serious infections<br>Additional pharmacovigilance activities:<br>• Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe<br>• Long-Term Safety Study of Upadacitinib Use in RA Patients in the US<br>• Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation<br>• Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545)<br>• Long-term extension portion of Phase 2/3 AS trial (Study M16-098) |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | Other routine risk minimization measures:<br>Prescription only medicine. | |
| Malignancies | Routine risk minimization measures:<br>• 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.<br>• 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.<br>• SmPC Section 4.4 advises that periodic skin examination is recommended for patients who are at increased risk for skin cancer.<br>Additional risk minimization measures:<br>None<br>Other routine risk minimization measures:<br>Prescription only medicine. | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>Routine pharmacovigilance activities including follow-up questionnaire for malignancies<br>Additional pharmacovigilance activities:<br>• Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe<br>• Long-Term Safety Study of Upadacitinib Use in RA Patients in the US<br>• Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545)<br>• Long-term extension portion of Phase 2/3 AS trial (Study M16-098) |
| MACE | Routine risk minimization measures:<br>• SmPC Section 4.4 describes the effect of upadacitinib on lipids and describes that impact on CV morbidity and mortality has not been determined.<br>• SmPC Section 4.4 contains a section on CV risk including a statement on increased CV risk in RA patients and the need for management of CV risk factors as part of usual standard care.<br>• SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib.<br>• 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.<br>Additional risk minimization measures:<br>• HCP educational brochure<br>• PAC<br>Other routine risk minimization measures: | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>Routine pharmacovigilance activities including follow-up questionnaire for MACE<br>Additional pharmacovigilance activities:<br>• Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe<br>• Long-Term Safety Study of Upadacitinib Use in RA Patients in the US<br>• Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation<br>• Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545)<br>• Long-term extension portion of Phase 2/3 AS trial (Study M16-098) |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | Prescription only medicine. | |
| VTEs (deep venous thrombosis and pulmonary embolus) | Routine risk minimization measures:<br>• SmPC Section 4.4 indicates that events of deep vein thrombosis and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib.<br>• 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.<br>• 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 thrombosis/pulmonary embolism, patients undergoing major surgery, and prolonged immobilisation.<br>• 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.<br>Additional risk minimization measures:<br>• HCP educational brochure<br>• PAC<br>Other routine risk minimization measures:<br>Prescription only medicine. | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>Routine pharmacovigilance activities including:<br>• Follow-up questionnaire for VTEs<br>• Monitoring of VTE risk and literature review provided within the PSUR<br>Additional pharmacovigilance activities:<br>• Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe<br>• Long-Term Safety Study of Upadacitinib Use in RA Patients in the US<br>• Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation<br>• Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545)<br>• Long-term extension portion of Phase 2/3 AS trial (Study M16-098) |
| GI perforation | Routine risk minimization measures:<br>None<br>Additional risk minimization measures:<br>None<br>Other routine risk minimization measures:<br>Prescription only medicine. | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>• Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | | • Long-Term Safety Study of Upadacitinib Use in RA Patients in the US<br>• Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545)<br>• Long-term extension portion of Phase 2/3 AS trial (Study M16-098) |
| DILI | Routine risk minimization measures:<br>• SmPC Section 4.4 describes the effect of upadacitinib on transaminases.<br>• SmPC Section 4.4 recommends prompt investigation of the cause of liver enzyme elevation to identify potential cases of DILI.<br>• 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.<br>Additional risk minimization measures:<br>None<br>Other routine risk minimization measures:<br>Prescription only medicine. | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>• Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe<br>• Long-Term Safety Study of Upadacitinib Use in RA Patients in the US<br>• Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545)<br>• Long-term extension portion of Phase 2/3 AS trial (Study M16-098) |
| Foetal malformation following exposure in utero | Routine risk minimization measures:<br>• 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.<br>• 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.<br>• SmPC Section 4.3 and Section 4.6 indicate that upadacitinib is contraindicated during pregnancy.<br>• SmPC Section 4.6 and PL advise on use of effective contraception.<br>Additional risk minimization measures: | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>Routine pharmacovigilance activities including follow-up questionnaires for pregnancies<br>Additional pharmacovigilance activities:<br>• Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation<br>• Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545)<br>• Long-term extension portion of Phase 2/3 AS trial (Study M16-098) |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | • HCP educational brochure<br>• PAC<br>Other routine risk minimization measures:<br>Prescription only medicine. | |
| Use in very elderly (≥ 75 years of age) | Routine risk minimization measures:<br>• SmPC Section 4.2 states that there are limited data in patients aged 75 years and older.<br>• SmPC Section 4.8 states that there was a higher rate of serious infections in patients ≥ 75 years of age, although data are limited.<br>• SmPC Section 4.4 states that as there is a higher incidence of infections in the elderly ≥ 75 years of age, caution should be used when treating this population.<br>Additional risk minimization measures:<br>None<br>Other routine risk minimization measures:<br>Prescription only medicine. | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>• Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe<br>• Long-Term Safety Study of Upadacitinib Use in RA Patients in the US |
| Effect on vaccination efficacy | Routine risk minimization measures:<br>• SmPC Section 4.4 includes language that no data are available on the response to vaccination with live or inactivated vaccines in patients receiving upadacitinib.<br>• SmPC Section 4.4 states that use with live, attenuated vaccines during, or immediately prior to, upadacitinib therapy is not recommended.<br>• SmPC Section 4.4 includes language that prior to initiating upadacitinib, it is recommended that patients be brought up to date with all immunisations in agreement with current immunisation guidelines.<br>Additional risk minimization measures:<br>None<br>Other routine risk minimization measures:<br>Prescription only medicine. | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>Vaccination substudy |
| Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C | Routine risk minimization measures:<br>• SmPC Section 4.4 describes the risk of viral reactivation.<br>• The PL warns that patients who have ever had hepatitis B or hepatitis C | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>None<br>Additional pharmacovigilance activities: |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | should consult their doctor or pharmacist before and during treatment with Rinvoq.<br>• SmPC Section 4.4 describes the need for screening and consultation with a hepatologist if HBV DNA is detected.<br>Additional risk minimization measures:<br>None<br>Other routine risk minimization measures:<br>Prescription only medicine. | Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe |
| Use in patients with moderate hepatic impairment | Routine risk minimization measures:<br>• SmPC Section 4.2 describes use in patients with hepatic impairment.<br>• SmPC Section 4.2 states that upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment.<br>• SmPC Section 4.3 indicates that upadacitinib is contraindicated for use in patients with severe hepatic impairment.<br>• 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.<br>Additional risk minimization measures:<br>None<br>Other routine risk minimization measures:<br>Prescription only medicine. | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe |
| Use in patients with severe renal impairment | Routine risk minimization measures:<br>• SmPC Section 4.2 describes use in patients with renal impairment.<br>• SmPC Section 4.2 states that upadacitinib should be used with caution in patients with severe renal impairment.<br>Additional risk minimization measures:<br>None<br>Other routine risk minimization measures:<br>Prescription only medicine. | Pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe |
| Long-term safety | Routine risk minimization measures:<br>SmPC Section 4.4 indicates that upadacitinib clinical data on malignancies | Pharmacovigilance activities beyond adverse reaction reporting and signal detection: |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | are currently limited and long-term studies are ongoing.<br>Additional risk minimization measures:<br>None<br>Other routine risk minimization measures:<br>Prescription only medicine. | Routine pharmacovigilance activities including follow-up questionnaire for malignancies<br>Additional pharmacovigilance activities:<br>• Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe<br>• Long-Term Safety Study of Upadacitinib Use in RA Patients in the US<br>• Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545)<br>• Long-term extension portion of Phase 2/3 AS trial (Study M16-098) |

ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; aRMMs = additional risk minimization measures; AS = ankylosing spondylitis; AST = aspartate transaminase; CV = cardiovascular; DILI = drug-induced liver injury; DNA = deoxyribonucleic acid; GI = gastrointestinal; HBV = hepatitis B virus; HCP = healthcare professional; JAK = Janus kinase; MACE = major adverse cardiovascular event; PAC = patient alert card; PL = package leaflet; PSUR = periodic safety update report; 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.

Minor editorial changes to Annex IIC are proposed but no changes to Annex IID are suggested.

### 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 style and layout is identical to the leaflet in the initial marketing authorisation application. A full user consultation was performed and assessed during the initial procedure.

No bridging report need to be submitted since no major changes to content or layout are made.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

SpA is a group of diseases that share common clinical, radiographic, and genetic features. This includes AS, PsA, reactive arthritis, enteropathic or IBD-related arthritis, and undifferentiated SpA. A more universally consistent way of categorizing SpA patients is to define them by their primary and predominant clinical manifestation of axial or peripheral SpA. Axial SpA encompasses a spectrum of disease manifestations, which has been split into two categories, AS and nr-axSpA, based on the 1984 modified New York criteria, which require the presence of sacroiliitis on plain conventional radiographs for the classification of AS. AxSpA affects up to 1.4% of the Caucasian adult population worldwide.

AxSpA is characterised by chronic inflammation of the axial skeleton (sacroiliac joint and spine), as well as variable involvement of the peripheral joints. As the disease progresses, it can lead to new bone formation in the form of syndesmophytes and joint ankylosis, primarily in the axial skeleton. Patients with axSpA may also have extra articular manifestations of the disease such as enthesitis, anterior uveitis, psoriasis (Ps), and IBD, as well as comorbidities of aortitis or cardiac conduction abnormalities.

### 3.1.2. Available therapies and unmet medical need

In 2016, the ASAS and European League Against Rheumatism (EULAR) published updated treatment recommendations for axial SpA, and in 2019 the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (SPARTAN) published updated axial SpA treatment recommendations. 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-17 inhibitor (IL-17i) is recommended. As pointed out by the MAH, despite recent advances in the treatment of axial SpA, there remains a significant unmet medical need, as only approximately 45% to 50% of patients in the studies of TNFi showed an ASAS40 response, and only approximately 15% to 20% achieved a state of remission.

### 3.1.3. Main clinical studies

The application is supported by a pivotal clinical phase 2/3 study; M16-098, which is still on-going. The first part of the study (Period 1) is a 14-week randomized, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 15 mg once daily (QD) versus placebo. The second part of the study (Period 2) is a 90-week open-label, long-term extension. A 30-day follow-up visit was also included.

Subjects in the study were adults with a clinical diagnosis of AS meeting the modified New York Criteria for AS. The subjects were to have an active disease defined by having a BASDAI score $\geq$ 4 and a Patient's Assessment of Total Back Pain score $\geq$ 4. In addition, they should have an inadequate response to at least 2 NSAIDs over an at least 4-week period in total at maximum recommended or tolerated doses or had an intolerance to or contraindication for NSAIDs as defined by the Investigator. They also had to be bDMARD naïve but could have received or be on concomitant csDMARD treatment.

A total of 187 patients were randomized, 94 patients to the placebo group and 93 patients to the upadacitinib group.

The primary estimand was defined as the difference in the proportion of (randomised and treated) AS patients who achieved ASAS 40 response at Week 14 and did not discontinue study drug by Week 14. ASA40 is an EMA guideline-preferred responder index which incorporates improvement in Patient Global Assessment, Pain Assessment, Function (BASFI) and inflammation.

## *3.2. Favourable effects*

A statistically significant higher proportion (95% CI) of patients in the upadacitinib group reached ASAS40 at week 14 in comparison to the placebo group: 51.6 (41.6, 61.8) % vs 25.5 (16.7, 34.3) % ($p<0.001$). The difference between treatment groups seems to be observed as early as week 2.

Results for the key secondary endpoints generally supported the outcome of the primary endpoint. Five of the 10 ranked, secondary endpoints showed a statistically significant better effect in the upadacitinib group compared to placebo, these were: changes from baseline to Week 14 in ASDAS(CRP), SPARCC MRI spine and BASFI and the respective proportions of subjects who had BASDAI50 and an ASAS partial remission at week 14. ASDAS (CRP) and BASDAI are measures of disease activity while SPARCC while SPARCC is a scoring system for active inflammatory lesions detected by MRI and BASFI is a functional index.

The change from baseline in ASDAS-CRP (95% CI) was -1.45 (-1.62, -1.28) in the upadacitinib group and -0.54 (-0.71,-0.37) in the Placebo group ($p<0.001$). The change from baseline in SPARCC MRI spine score (95% CI) was -6.93 (-8.58, -5.28) in the Upadacitib group and -0.22 (-2.01, 1.57) in the Placebo group ($p<0.001$). The change from baseline in BASFI (95% CI) was -2.29 (-2.73, -1.85) in the Upadacintib group and -1.30 (-1.74,-0.86) in the Placebo group ($p=0.001$). The BASDAI50 response % (95% CI) was 45.2 (35.0, 55.3) in the upadacitinib group and 23.4 (14.8, 32.0) in the Placebo group ($p=0.002$). The ASAS partial remission % (95% CI) was 19.4 (11.3, 27.4) in the Upadacitib group and 1.1 (0.0, 3.1) in the Placebo group ($p<0.001$).

## *3.3. Uncertainties and limitations about favourable effects*

Among the endpoints that failed three were PROs (ASQoL, ASAS(HI) and WPAI Overall Work Impairment): for ASQoL and ASAS(HI) there were numerically differences favouring upadacitinib and having used another multiple testing procedure, they could eventually have succeeded, at least statistically (nominally $p= 0.016$ for ASQoL and nominally $p= 0.007$ for ASAS(HI)). For the analysis of MASES and WPAI Overall Work Impairment it was considered by the CHMP that it could, at least in part, be a question of power and eventually an underestimation of the number of subjects that where to contribute with data. The issue was therefore not further pursued by CHMP.

Although there is still an uncertainty with regards to the precise magnitude of the long-term efficacy, the CHMP agreed that there is support of a continued benefit of treatment with upadacitinib beyond week 14.

Among the subjects that have not even achieved ASAS20 at week 16, only few additional subjects attain an initial ASAS20 response after this time point. Section 4.2 of the SmPC states that consideration should be given to discontinuing treatment in patients with ankylosing spondylitis who have shown no response after 16 weeks of treatment.

## 3.4. Unfavourable effects

In the placebo-controlled period, 62.4 % of the subjects in the upadacitinib group and 55.3 % in the placebo group had any AEs. No patients in the upadacitinib group had any severe AE and similar proportions of subjects in the placebo and upadacitinib groups had ≥ 1 SAEs (1.1% in each group) and AEs leading to discontinuation (2.2% in the upadacitinib group and 3.2% in the placebo group).

Infections were reported by 20.4% in the upadacitinib group and 26.6% in the placebo group. The most frequently reported infections (≥ 2 subjects) in the upadacitinib group were nasopharyngitis, influenza, and tonsillitis. As of the data cut-off date, no events of serious infections were reported from the study.

In the placebo-controlled period, the most frequently reported TEAEs (≥ 5% of subjects) in the upadacitinib group were increased blood creatine phosphokinase (CPK), diarrhea, nasopharyngitis, and headache compared with diarrhea and nausea in the placebo group. The frequencies of CPK increased and ALT increased were 8.6% and 4.3%, respectively, in the upadacitinib group compared with 2.1% for each event in the placebo group.

In the long-term data up to the data cut-off date, 618 AEs (260.1 events [E]/100 PYs) were reported in 182 subjects (237.6 patient-years [PYs]) who received upadacitinib 15mg QD. Seven (7) severe AEs (2.9E/100 PYs), 14 SAEs (5.9E/100 PYs) and 15 AEs (6.3E/100 PYs) leading to discontinuation were reported. No deaths were reported.

## 3.5. Uncertainties and limitations about unfavourable effects

The safety data base in AS is rather limited. A total of 182 subjects received ≥ 1 dose of upadacitinib 15 mg, representing 237.6 patient years (PYs). Up to the data cut-off date, 160 of the 182 subjects had exposure to upadacitinib for ≥ 12 months. However, as safety data can to a large extent be extrapolated from the approved RA-indication, this is considered acceptable by the CHMP.

## 3.6. Effects Table

*Table 28 Effects Table for upadacitinib in the AS indication*

| Effect | Short description | Unit | upadacitinib 15mg | Placebo | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| ASAS40 Wk 14 | % patients achieving ASAS40 response at Week 14 | % | 51.6% | 25.5% | Difference in response 26.1 (p<0.001) | Study M16-098 |
| ASDAS-CRP change Wk 14 | Change from baseline to week 14 in Ankylosing Spondylitis Disease Activity Score (ASDAS) based on CRP. | | - 1.45 | - 0.54 | p<0.001 for comparison vs placebo | Study M16-098 |
| SPARCC MRI Spine score change Wk 14 | Change from baseline in Spondyloarthritis Research Consortium of Canada | | -6.93 | -0.22 | p<0.001 for comparison vs placebo | Study M16-098 |

| Effect | Short description | Unit | upadacitinib 15mg | Placebo | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| | (SPARCC) MRI spine score | | | | | |
| BASDAI50 Wk 14 | Subjects achieving at least 50% improvement in BASDAI (BASDAI50) | % | 45.2% | 23.4% | P=0.002 for comparison vs placebo | Study M16-098 |
| ASAS partial remission wk14 | Subjects achieving ASAS partial remission, | % | 19.4% | 1.1% | p<0.001 for comparison vs placebo | Study M16-098 |
| BASFI change Wk 14 | Change from baseline BASFI | | -2.29 | -1.30 | P=0.001 for comparison vs placebo | Study M16-098 |
| **Unfavourable Effects** | | | | | | |
| AEs | Frequency Adverse events in the placebo controlled study period | % | 62.4% | 55.3 % | | Study M16-098 |
| SAE | Frequency Serious Adverse events in the placebo controlled study period | % | 1.1% | 1.1% | | Study M16-098 |
| Infections | Frequency in the placebo controlled study period | % | 20.4% | 26.6% | | Study M16-098 |
| Serious Infections | Frequency in the placebo controlled study period | % | 0 | 0 | | Study M16-098 |

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

A clinically relevant and robust effect as measured by ASAS40 has been demonstrated for upadacitinib 15 mg in the target population of subjects with active AS and inadequate response or intolerance/contraindication to NSAIDs. Overall, there are support from secondary endpoints measuring different aspects of the disease.

The safety findings in the AS development programme were generally consistent with the findings in the RA development programme and thus adequately described in the currently approved PI and RMP. The safety database in AS is limited; however, as safety data can to a large extent be extrapolated from the approved RA-indication, this is considered acceptable to the CHMP.

### 3.7.2. Balance of benefits and risks

No important limitations regarding the favourable effects remain. Although there is still an uncertainty with regards to the precise magnitude of the long-term efficacy, the CHMP agreed that there is support of a continued benefit of treatment with upadacitinib beyond week 14.

The safety profile of upadacitinib in AS in the proposed posology, is considered broadly similar to the safety profile in the approved RA-indication and thus generally covered in the approved SmPC and RMP.

## *3.8. Conclusions*

The overall B/R of Rinvoq in the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy is positive.

# 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, II and IIIB |

Extension of indication to include the treatment of active ankylosing spondylitis in adult patients for Rinvoq; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Minor editorial changes to the SmPC and Annex II are also agreed. Version 3.3 of the RMP has been adopted.

The variation leads to amendments to the Summary of Product Characteristics, Annex II 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, II and IIIB and to the Risk Management Plan are recommended.

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

## Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and

any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

## Additional risk minimisation measures

Prior to launch of RINVOQ in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The objective of the programme is to increase awareness of HCPs and patients on the risks of serious and opportunistic infections including TB, herpes zoster, foetal malformation (pregnancy risk), MACE, and VTEs and how to manage these risks.

The MAH shall ensure that in each Member State where RINVOQ is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use RINVOQ have access to/are provided with the following educational package:

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- Patient Alert Card (PAC)

The Guide for healthcare professionals shall contain the following key elements:

- General introductory language that the HCP measure contains important information to assist the discussion with patients when prescribing upadacitinib. The brochure also informs on steps which can be taken to reduce a patient's risk for key safety aspects of upadacitinib.
- Language for HCPs to inform patients of the importance of the PAC
- Risk of serious and opportunistic infections including TB

o Language on the risk of infections during treatment with upadacitinib

o Details on how to reduce the risk of infection with specific clinical measures (what laboratory parameters should be used to initiate upadacitinib, screening for TB, and getting patients immunised as per local guidelines, and interruption of upadacitinib if an infection develops)

o Language on avoidance of live vaccines (i.e., Zostavax) prior to and during upadacitinib treatment

o Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.

- Risk of herpes zoster

o Language on the risk of herpes zoster during treatment with upadacitinib

o Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.

- Risk of foetal malformation

o Language on teratogenicity of upadacitinib in animals

o Details on how to reduce the risk of exposure during pregnancy for women of childbearing potential based on the following: upadacitinib is contraindicated during pregnancy, women of childbearing potential should be advised to use effective contraception both during treatment and for 4 weeks after the final dose of upadacitinib treatment, and to advise patients to inform their HCP immediately if they think they could be pregnant or if pregnancy is confirmed.

- Risk of MACE

o Language on the increased risk of MACE in patients with immune-mediated inflammatory diseases and the need to consider typical CV risk factors (e.g., hypertension, hyperlipidaemia) when treating patients

o Language on the risk of MACE during treatment with upadacitinib

o Language on the risk of hyperlipidaemia during upadacitinib therapy

o Details on monitoring of lipid levels and management of elevated lipid levels per clinical guidelines

- Risk of VTE

o Examples of the risk factors which may put a patient at higher risk for VTE and in whom caution is needed when using upadacitinib.

o Language on the risk of VTE during treatment with upadacitinib

o Language on need for discontinuation of upadacitinib, evaluation, and appropriate treatment for VTE if clinical features of deep venous thrombosis or pulmonary embolism develop

- Instructions for how to access digital HCP information

- Instructions on where to report AEs

The patient information pack should contain:

- Patient information leaflet

- A patient alert card

- The patient alert card shall contain the following key messages:

o Contact details of the upadacitinib prescriber

o Language that the PAC should be carried by the patient at any time and to share it with HCPs involved in their care (i.e., non-upadacitinib prescribers, emergency room HCPs, etc.)

o Description of signs/symptoms of infections the patient needs to be aware of, so that they can seek attention from their HCP:

- Language to advise patients and their HCPs about the risk of live vaccinations when given during upadacitinib therapy

o Description of targeted risks for awareness by the patient and for HCPs involved in their care including:

- Elevations in plasma lipids and the need for monitoring and lipid lowering treatment
- A reminder to use contraception, that upadacitinib is contraindicated during pregnancy, and to notify their HCPs if they become pregnant while taking upadacitinib

o Description of signs/symptoms of deep venous thrombosis or pulmonary embolism which the patient needs to be aware of, so that they can seek attention from an HCP.

# 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/0005"

# Attachments

1. SmPC, Annex II, Package Leaflet (changes highlighted) as adopted by the CHMP on 10 December 2020