10 December 2020
EMA/708066/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rinvoq

International non-proprietary name: upadacitinib

Procedure No. EMEA/H/C/004760/II/0004

Note

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

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List of abbreviations

ACR	American College of Rheumatology
ACR20/50/70	American College of Rheumatology 20%, 50%, 70% response
ADA	adalimumab
AE(s)	adverse event(s)
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Anti-CCP	anti-cyclic citrullinated peptide
AO	As Observed
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	aspartate aminotransferase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	biologic disease-modifying antirheumatic drug
BID	twice a day
BMI	body mass index
BSA	body surface area
CAC	Cardiovascular Adjudication Committee
CASPAR	Classification Criteria for Psoriatic Arthritis
cDMARDs	conventional disease-modifying anti-rheumatic drugs
CI	confidence interval
CMH	Cochran-Mantel-Haenszel test
CMQ	company MedDRA query
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CRO	contract research organization
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying anti-rheumatic drug
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DAPSA	Disease Activity in Psoriatic Arthritis
DAS	disease activity score
DAS28	disease activity score (28 joints)
Diff	difference
DMARD	disease-modifying anti-rheumatic drug
DMARD-IR	disease-modifying anti-rheumatic drug-intolerant or inadequate responder
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
E	events
E/100 PY	events per 100 patient-year
EAER	exposure-adjusted event rate
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
EOW	every other week

EQ-5D-5L	EuroQoL-5 Dimensions – 5 Levels
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
F	female
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
GCP	Good Clinical Practice
GI	gastrointestinal
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire – Disability Index
Hb	Haemoglobin
HBV	hepatitis B virus
HCQ	hydroxychloroquine
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein-cholesterol
HRU	Health Resource Utilization
hsCRP	high-sensitivity C-reactive protein
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
INH	isoniazid
IR	inadequate response
IRB	institutional review board
JAK	Janus kinase
JSN	joint space narrowing
LDI	Leeds Dactylitis Index
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol
LEI	Leeds Enthesitis Index
LS	least square
M	male
MACE	major adverse cardiac event
Max	maximum
MCS	Mental Component Summary of the SF-36™ Health Status Survey
MDA	minimal disease activity
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
Min	minimum
MMRM	Mixed-Effects Model Repeated Measures
mTSS	modified Total Sharp Score
MTX	methotrexate
NAPF	National Psoriasis Foundation
NI	non-inferiority
NMSC	non-melanoma skin cancer
NRI	Non-Responder Imputation
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
PASDAS	Psoriatic Arthritis Disease Activity Score

PASI	Psoriasis Area Severity Index
PASI 75/90/100	75, 90, 100 percent improvement in Psoriasis Area and Severity Index
PCS	Physical Component Summary
PE	pulmonary embolism
PGA	physician's global assessment
PPD	packs per day
Ps	psoriasis
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
PT	preferred term
PtGA	Patient's Global Assessment
PY	patient-year
QD	once daily
RA	rheumatoid arthritis
RF	rheumatoid factor
Rx	study drug
SAE	serious adverse event
SAP	statistical analysis plan
SAPS	Self-Assessment of Psoriasis Symptoms
SD	standard deviation
SF-36	36-Item Short Form Health Survey
SF-36 PCS	36-Item Short Form Health Survey Physical Component Score
SF-36 MCS	36-Item Short Form Health Survey Mental Component Score
SIR	standard incidence ratios
SHS	Sharp/van der Heijde Score
sIGA	static Investigator Global Assessment
sIGA 0/1	sIGA of psoriasis of 0 or 1 and at least a 2-point improvement from baseline
SJC	swollen joint count
SMQ	standardized MedDRA query
SOC	system organ class
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	sulfasalazine
STAT	signal transducer and activator of transcription
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumour necrosis factor
ULN	upper limit of normal
UNK	unknown
US	United States
vs.	versus
VTE	venous thromboembolic event
WPAI	Work Productivity and Activity Impairment

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 psoriatic arthritis in adult patients for Rinvoq; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Minor updates were made to the Annex II. Version 2.0 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 26 January 2017 (EMEA/H/SA/3190/3/2016/II)15 June 2017 (EMEA/H/SA/3190/3/2016/II)13 February 2017 (EMEA/H/SA/3190/3/2016/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Co-Rapporteur: Outi Mäki-Ikola

Timetable	Actual dates
Submission date	1 June 2020
Start of procedure:	20 June 2020
CHMP Rapporteur Assessment Report	14 August 2020
CHMP Co-Rapporteur Assessment Report	14 August 2020
PRAC Rapporteur Assessment Report	20 August 2020
PRAC Outcome	4 September 2020
CHMP members comments	07 September 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 September 2020
Request for supplementary information (RSI)	17 September 2020
CHMP Rapporteur Assessment Report	10 November 2020
PRAC Rapporteur Assessment Report	13 November 2020
PRAC members comments	18 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

Psoriatic arthritis (PsA) is a chronic systemic inflammatory disease classified as a sub type of spondyloarthritis (SpA) and characterized by the association of arthritis and psoriasis. It comprises both musculoskeletal as well as non-musculoskeletal manifestations; the latter particularly include the skin and the nails, but also potentially the gut (inflammatory bowel disease) or the eyes (uveitis). Active chronic PsA also associates with cardiovascular, psychological and metabolic comorbidities, which add a significant impact on quality of life (QoL) and increased mortality. About 40%−60% of patients develop erosive and deforming joint complications (Liu JT et al., 2014[1]). Joint damaging

[1] Liu, Jung-Tai, et al. "Psoriatic arthritis: epidemiology, diagnosis, and treatment." World journal of orthopedics 5.4 (2014): 537.

complications cause reduced articular function, affecting also the patients' ability to work and their social relationships. The major clinical features of PsA are spondylitis (18%-46%), inflammatory neck pain (23%-39%), thoracic inflammatory pain (13%-21%), and axial symptoms (25%-50%).

State the claimed the therapeutic indication

The MAH proposed the following indication:

Psoriatic arthritis

RINVOQ is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. RINVOQ may be used as monotherapy or in combination with non-biologic DMARDs.

The proposed posology is the same as currently approved for rheumatoid arthritis: 15 mg once daily.

Epidemiology

The incidence and prevalence of PsA vary markedly between different geographical areas. The reasons for the observed difference of PsA morbidity between countries and continents are unclear. In a recent systematic review, the prevalence of psoriasis varied from 0.14 % (95 % uncertainty interval 0.05 % to 0.40 %) in East Asia to 1.99 % (0.64 % to 6.60 %) in Australasia. The prevalence of psoriasis was also high in Western Europe (1.92 %, 1.07 % to 3.46 %), central Europe (1.83 %, 0.62 % to 5.32 %), North America (1.50 %, 0.63 % to 3.60 %), and high income southern Latin America (1.10 %, 0.36 % to 2.96 %). Since psoriasis is usually a lifetime disease, the prevalence increases with age.

The epidemiology of PsA depends on that of psoriasis and is therefore also variable across geographical areas. The exact prevalence of PsA is not known, but estimates vary from 0.3 % to 1 % of the population. Around 20% of patients with psoriasis develop psoriatic arthritis, however, in patients with moderate-to-severe disease the proportion of patients with psoriatic arthritis is higher, about 25 %. In a recent meta-analysis, the prevalence of PsA in European patients with psoriasis was 22.7 %.

Diagnosis of PsA is symptomatic. Clinical features associated with PsA as compared with uncomplicated skin psoriasis are higher extent of psoriasis; psoriasis involvement of the scalp and inter-gluteal area; and nail lesions.

The Classification Criteria for PsA (CASPAR) criteria, used in the Phase 3 studies of upadacitinib, is a diagnostic tool for specialists of rheumatology, since the criteria are based on the stem of inflammatory musculoskeletal disease. However, multiple other questionnaire-based screening tools have also been used in the literature. These tools have moderate accuracy to identify PsA among psoriasis patients.

Aetiology and pathogenesis

PsA is a highly heritable polygenic disease. Hereditary factors include certain HLA-classes and their subtypes as well as polymorphism of genes encoding interleukin-23 receptor,(IL23R), variants in nuclear factor κB (NF κB) gene expression, (TNIP1) and signaling (TNFAIP3), TNF expression, as well as risk alleles in interleukin 12A (IL12A), interleukin-12B (IL12B), IL23R, and genes that regulate NF-κB. Environmental factors increasing risk for PsA include obesity, trauma or deep lesions at sites of trauma, and severe psoriasis. The interaction between genetic and environmental factors triggers an inflammatory response at multiple sites.

Key cytokines involved in PsA pathogenesis, such as interleukin (IL)-6, IL-7, IL-22, IL-23 and interferon, signal through the Janus kinase (JAK) pathway. Some of these cytokines activate Th1 and Th17 cells, which in turn release further pro-inflammatory cytokines, including IL-1, IL-17, IL-21, IL-22 and tumour necrosis factor.

As JAK inhibitors mediate signals of multiple pro-inflammatory cytokines in various immune cell types, targeting these intra-cellular kinases can be an effective approach to reduce inflammatory responses by directly and indirectly inhibiting key cytokines involved in the pathogenesis of PsA (See Section Clinical aspects, subsection Pharmacodynamics of this assessment report).

Clinical presentation, diagnosis

Patients with PsA are usually affected with psoriasis before signs of joint disease have developed. The mean time to onset of PsA is 10 years after the first signs of psoriasis appear. PsA affects men and women equally. PsA can be distinguished from other inflammatory arthritic diseases by its clinical and radiographic features; especially by the presence of other manifestations of psoriasis. Skin involvement occurs most often the scalp, nails, trunk, elbows, and knees. In general, PsA affects fewer joints than rheumatoid arthritis (RA), and it often has an asymmetrical distribution of the affected joints rather than the symmetrical pattern seen in RA. Spinal involvement (sacroiliac joints, lumbar, thoracic or cervical spine) occurs in more than 40% or patients with PsA but is uncommon in rheumatoid arthritis. Enthesitis is common, affecting 30% to 50 % of patients with PsA. Reumafactor is usually negative. One in four patients with PsA are HLA-B27-positive.

Untreated PsA may lead to progressive joint damage and disability, causing absenteeism from work. The life expectancy of PsA patients has been reported to be decreased due to cardiovascular diseases.

Management

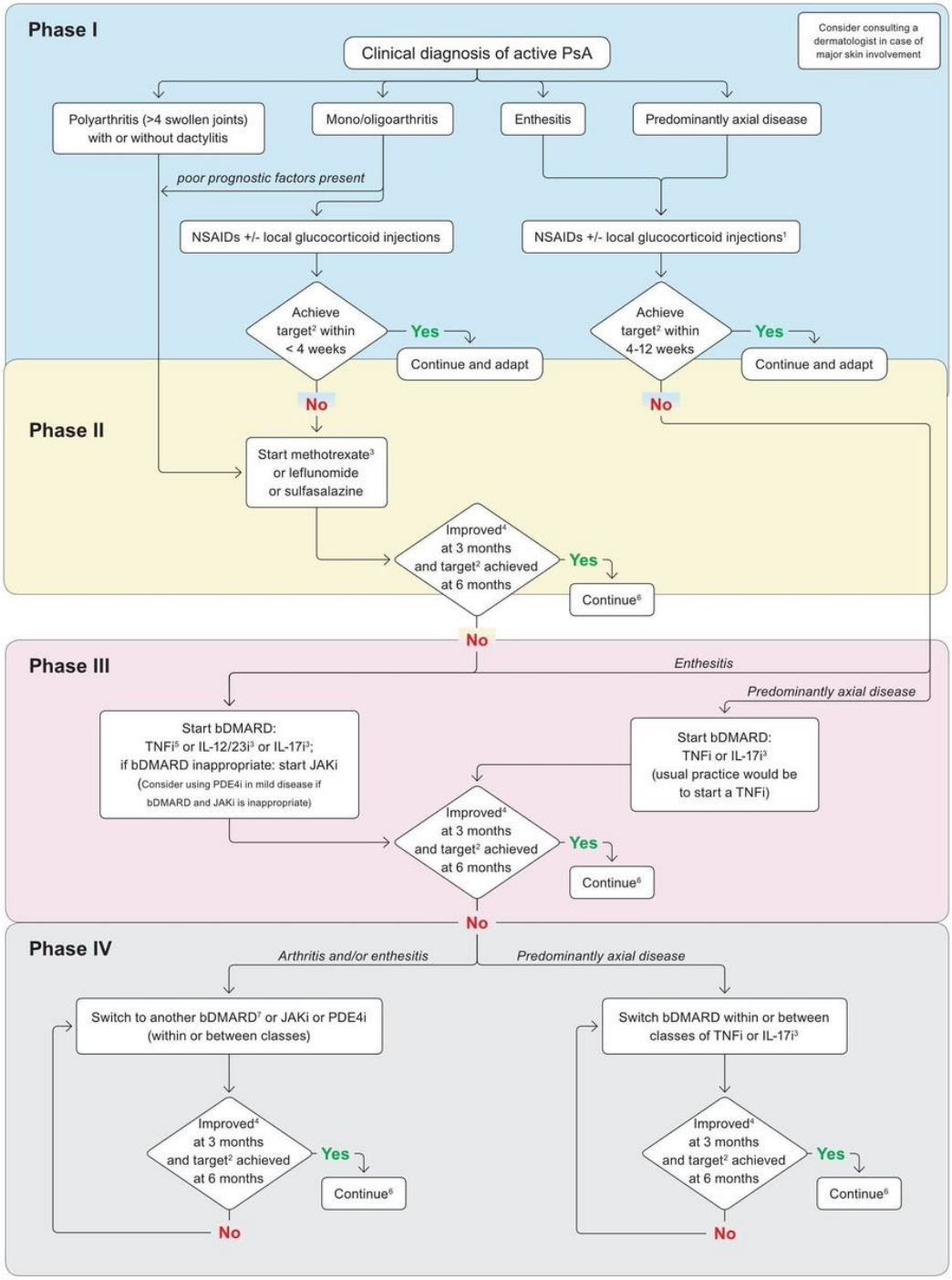
The management of patients with PsA includes non-pharmacological as well as pharmacological interventions. The latest European League Against Rheumatism (EULAR) recommendations for the pharmacological treatment of PsA state that the primary goal of treating patients with psoriatic arthritis is to maximise health-related quality of life, through control of symptoms, prevention of structural damage, normalisation of function and social participation; abrogation of inflammation is an important component to achieve these goals. Furthermore, the EULAR recommendation states that non-musculoskeletal manifestations (skin, eye and gastrointestinal tract) should be taken into account; comorbidities such as metabolic syndrome, cardiovascular disease or depression should also be considered when managing patients with psoriatic arthritis.

The updated recommendation puts forward the treat-to-target approach in the treatment of PsA: remission or low disease activity should be targeted, with the deletion of the previously stated term of minimal disease activity (which refers to a score allowing the assessment of low disease activity rather than to a target). Remission in PsA is difficult to define. Remission should be seen as abrogation of inflammation.

Figure 1 shows the summary of EULAR recommendations for the management of PsA at each phase. As the figure shows, after initial treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and local glucocorticoid injections, systemic pharmacological treatment is recommended to be started in non-responders. Systemic corticosteroids should be used with caution at the lowest effective dose for a short time. Treatment algorithm has been revised to contain a different path for patients with oligoarticular and polyarticular disease, the latter having five or more active swollen joints, as demonstrated in Figure below.

Systemic medications for PsA include corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate (MTX) , sulfasalazine (SSZ), leflunomide (LEF), or cyclosporine; targeted synthetic DMARDs, such as phosphodiesterase-4 inhibitors like apremilast; and biologic DMARDs, such as tumour necrosis factor (TNF) inhibitors, interleukin-12/23 inhibitors, and interleukin-17 inhibitors. Tofacitinib was the first JAK inhibitor (JAKi) approved for use in PsA.

The current recommendation is to consider starting a JAKi in patients with peripheral arthritis and an inadequate response to at least one csDMARD and at least one bDMARD, or when a bDMARD is not appropriate. Of the currently marketed JAKi's (tofacitinib, baricitinib, and upadacitinib), only tofacitinib has been approved for treatment of PsA, only in combination with MTX.



bDMARDs, biological disease-modifying antirheumatic drugs; EULAR, European League Against Rheumatism; IL-12/23i, interleukin-12/23 inhibitor; IL-17i, interleukin-17 inhibitor; JAKi, Janus kinase inhibitor; NSAIDs, non-steroidal anti- inflammatory drugs; PDE4i, phosphodiesterase-4 inhibitor; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor.

Figure 1 The EULAR 2019 algorithm for treatment of PsA with pharmacological non-topical treatments.

Unmet medical need

Despite the beneficial results achieved with the available biologic agents, a marked proportion of PsA patients do not achieve clinical remission after 1 year of treatment or sustained remission for at least 1

year. Polyarticular disease, increased inflammatory marker levels, progressive radiographical changes and concomitant diabetes and cardiovascular diseases indicate poor prognosis. In a recent study, based on clinical practice (Lubrano E, Perrotta FM, Scriffignano S, Coates LC, Helliwell P. Sustained Very Low Disease Activity and Remission in Psoriatic Arthritis Patients. Rheumatol Ther. 2019 Dec;6(4):521-528. doi: 10.1007/s40744-019-00171-w. Epub 2019 Aug 19. PMID: 31428989; PMCID: PMC6858418.), a sustained very low disease activity (VLDA) was achieved in only 17.5% and a sustained remission according to the Disease Activity index for Psoriatic Arthritis (DAPSA) criteria in only 30% of patients with PsA.

Since a substantial proportion of patients with PsA do not have a sustained response to current treatment regimens, there remains a medical need for additional therapeutic options in PsA for patients with inadequate response to or intolerance to currently available therapies.

2.1.2. About the product

The mechanism of action of upadacitinib is inhibition of JAKs, intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, haematopoiesis and immune surveillance. The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and TYK2 which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation, in turn, modulates gene expression and cellular function. JAK1 is important in inflammatory cytokine signals while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function. 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 (Rinvoq) has been approved in the EU on 18 December 2019 for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Rinvoq may be used as monotherapy or in combination with methotrexate.

The initial approval was based primarily on the efficacy, safety, and immunogenicity data from five pivotal Phase 3 studies and clinical pharmacology data from 22 Phase 1 studies, 2 supportive dose ranging Phase 2 studies, 1 supportive Phase 2b/3 dose ranging study in Japanese subjects.

The current submission presents data to support the use of upadacitinib in adult patients with active PsA. The submission includes one bioavailability study and two controlled pivotal randomized, double-blind, Phase 3 studies: one study in subjects with inadequate response (IR) to non biologic disease-modifying anti-rheumatic drugs (DMARDs), "DMARD-IR" subjects (Study M15-572) and one study in subjects with IR to biologic DMARDs, "bDMARD-IR" subjects (Study M15-554).

The clinical development programme of upadacitinib in PsA was designed to demonstrate the efficacy of upadacitinib in reducing the musculoskeletal and cutaneous signs and symptoms of PsA, inhibiting the progression of structural joint damage, and improving physical function and health-related quality of life (QoL) outcomes. The global Phase 3 development programme for PsA evaluated the efficacy and safety of 2 doses of upadacitinib, 15 mg QD and 30 mg QD extended-release formulation, in combination with non biologic DMARDs or as monotherapy in adults with moderately to severely active PsA, including those who are non-biologic DMARD-IR or bDMARD-IR.

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

In addition to rheumatoid arthritis and PsA, upadacitinib is being developed for the treatment of other immune-mediated inflammatory diseases such as Crohn's disease, ulcerative colitis, atopic dermatitis, ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (SpA), polyarticular course juvenile idiopathic arthritis, Takayasu arteritis, and giant cell arteritis.

Upadacitinib is also being developed for paediatric population from 1 to less than 18 years of age for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, spondyloarthritis and juvenile idiopathic arthritis). A waiver has been granted for paediatric population from birth to less than 1 year of age.

Scientific advice (SA) was given by the CHMP on 26 January 2017 (EMEA/H/SA/3190/3/2016/II) and clarifications on the same SA procedure on 13 February 2017 and 15 June 2017. The SA concerned the Phase 3 trials in PsA. The advice pertained to the inclusion criteria, endpoints, the planned duration of placebo treatment, and rescue medication.

- The MAH was advised to foresee and detail the handling of missing data detailed in the final protocols.
- The CHMP commented that placebo subjects will be randomized at baseline to either 15 mg QD or 30 mg QD and switched blindly to one of the doses of upadacitinib after Week 24 regardless of clinical response. The reason for this was not obvious to the CHMP and the CHMP commented that it is expected that the switched treatment groups after Week 24 will not be of similar size. In the final protocol, subjects who were assigned to placebo at baseline are preassigned to receive either upadacitinib 15 mg QD or upadacitinib 30 mg QD starting at Week 24 in a 1:1 ratio.
- The CHMP advised on determination of the non-inferiority (NI) margin for the comparison with adalimumab in study M15-572 based on all data available on the effect size of adalimumab in PsA for determination of the NI margin.
- The CHMP was asked if all primary and ranked secondary endpoints of the studies could be included in section 5.1 of the SmPC, if statistically significant. The CHMP stated that inclusion of the end-points will be based on results. Further, since this section should only include limited information relevant to the prescriber, only main results, statistically compelling and clinically relevant results are foreseen to be included in accordance with SmPC guideline.
- The CHMP stated that the Phase 3 programme is overall comprehensive and in line with the EMA PsA guideline.

2.1.4. General comments on compliance with GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH, and the sponsor has provided audit reports for the audits performed by the sponsor.

No regulatory inspections on the Phase 3 studies are reported in the submission. Since no problems concerning GCP have been identified during assessment, this is not considered an issue by the CHMP.

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 submitted an Environmental Risk Assessment (ERA) to evaluate the risks associated with patient use of upadacitinib in support of the Marketing Authorisation Application (MAA) for treatment of rheumatoid arthritis (RA) by upadacitinib (15 mg/day). The experimentally determined n-octanol-buffer distribution coefficient (log Kow) of 2.5 for upadacitinib does not indicate the potential for bioaccumulation, therefore a persistence, bioaccumulation and toxicity (PBT) screening was not required. The ERA Phase I and II studies were conducted in accordance with the European Medicines Agency's (EMA) 'Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use' and supporting questions and answers on the EMA Guidance, as well as Organization for Economic Cooperation and Development (OECD) and European Chemicals Agency (ECHA) guidance documents. In the original ERA submitted for the MAA for RA approval, a Phase I assessment was completed and the PECSURFACEWATER RA was calculated with a dose of 15 mg/day and the default Fpen value of 0.01. The resulting PECSURFACEWATER RA was 0.075 µg/L.

To support the MAA seeking approval of upadacitinib for the treatment of psoriatic arthritis (PsA) the original ERA was completed. Therefore, as part of the Phase I assessment, the PECSURFACEWATER PsA was calculated using a dose of 15 mg/day and the default Fpen value of 0.01, resulting in a PECSURFACEWATER value of 0.075 µg/L for PsA. To support the request to extend the indications for upadacitinib to include both RA and PsA and to assess the potential impact of patient use of upadacitinib for both indications the PECSURFACEWATER value was recalculated involving both RA and PSA PECSURFACEWATER values, both being 0.075 µg/L. The PEC value that includes both RA and PsA is the PECSW-TOTAL of 0.15 µg/L. Phase I and Phase II Tier A assessment studies have already been completed and no additional studies were needed for the updated ERA. The PECSW-TOTAL value of 0.15 µg/L was used to recalculate the PEC/Predicted No Effect Concentration (PNEC) ratios for the Phase II Tier A risk assessments. All of the PEC/PNEC risk assessment ratios remained less than one, indicating that patient use of upadacitinib for both RA and PsA is unlikely to represent a risk to the aquatic environment.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application lead to a significant increase in environmental exposure further to the use of upadacitinib.

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Type of Study	Study ID	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
BA	M20-017	Part 1: Assess BA of UPA market-image formulation (15 mg) relative to reference 15 mg strength Phase 3 formulation after a high-fat/high-calorie meal and under fasting conditions. Part 2: Assess BA of UPA market-image formulation (30 mg) relative to the reference 30 mg strength Phase 3 formulation after a high-fat/high-calorie meal and under fasting conditions.	Single-dose, open-label, randomized, 4-period, 4-sequence, 2-part crossover study	Part 1: UPA Phase 3 15 mg tablet (ER17Y) and upadacitinib market-image 15 mg tablet (ER17) Part 2: UPA Phase 3 30 mg tablet (ER18Y) and upadacitinib market-image 30 mg tablet (ER18)	80	Healthy adult subjects	Part 1: Four single-doses of UPA 15 mg separated by 4 days Part 2: Four single-doses of UPA 30 mg separated by 4 days

Type of Study	Study ID	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
Efficacy and Safety	M15-554	Period 1: Compare the efficacy, safety, and tolerability of UPA 15 mg QD and 30 mg QD vs PBO Period 2: Evaluate the long-term safety, tolerability, and efficacy of UPA 15 mg QD and 30 mg QD in subjects who have completed Period 1	Period 1: Randomized, DB, parallel-group, PBO-controlled Period 2: Long-term extension	UPA 15 mg and 30 mg QD Matching PBO	642	Adult subjects with moderately to severely active PsA who have had an inadequate response or intolerance to biologic DMARDs	Period 1: 56 weeks; Period 2: Up to 3 years (or until local regulatory approval and/or applicable local reimbursement approval of the study drug if approval occurs after Week 152)

Type of Study	Study ID	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
Efficacy and Safety	M15-572	Period 1: Compare the efficacy (signs and symptoms), safety, and tolerability of UPA 15 mg QD and 30 mg QD vs PBO and ADA and compare the efficacy of UPA 15 mg QD and 30 mg QD vs PBO for the prevention of structural progression Period 2: Evaluate the long-term safety, tolerability, and efficacy of UPA 15 mg QD and 30 mg QD in subjects who have completed Period 1	Period 1: Randomized, DB, parallel-group, PBO- and active comparator-controlled study Period 2: Long-term extension.	UPA 15 mg and 30 mg QD ADA 40 mg eow SC Matching PBO	1705	Adult subjects with moderately to severely active PsA who have had an inadequate response or intolerance to nonbiologic DMARDs	Period 1: 56 weeks; Period 2: Up to 5 years

2.3.2. Pharmacokinetics

Analytical methods

For the applied indication extension, the same prolonged-release formulations of upadacitinib marketed for treatment of patients with RA is proposed for the treatment of adult patients with active PsA. The formulation of the product used for clinical studies in the application is manufactured at another site and shows some differences in its outfit compared to the commercial one. Bioanalytical methods were used for the bioequivalence study and two efficacy and safety studies of the formulations. The bioequivalence of the extended-release (ER) formulation used in PsA Phase 3 studies and the commercial formulation was tested in study M20-017.

The same bioanalytical methods that were used in the regulatory application for the use of upadacitinib in the treatment of RA were used for the analysis of plasma samples in the current submission. The validation of the method, including stability at various stages of the analysis, has been assessed as part of the application for RA. Assuming that the different patient groups do not affect the analytical performance of the method, this validation can be considered valid also for determinations of plasma samples obtained from PsA patients.

The performance of the method in the bioanalytical phase of the bioequivalence study was followed by quality criteria for calibrations, use of quality control samples in the analytical batches and incurred sample reanalysis (more than 10% of the total number of samples that fulfils the EMA recommendation given in the *Guideline on bioanalytical method validation*). Some quality indicating data are listed in Table below.

Table 1 Performance indicating parameters for bioanalysis of upadacitinib in human plasma in study M20-017

	Results
Mean bias (RE %) and CV% of calibration samples	-1.7 - 2.3 % (RE), CV% ≤ 5.3%
Quality control samples, mean bias (RE %) and CV% 0.136 ng/mL 3.16 ng/mL 39.9 ng/mL 79.0 ng/mL	 0,7% (RE), 6.9% (CV) -0.6% (RE), 3.8% (CV) 3.0% (RE), 3.2% (CV) 3.2% (RE), 4.1% (CV)
Incurred sample reanalysis	Difference -23.8% - 18.2%, 635 of 637 met the acceptance criteria

A total of 5088 samples were assayed in 57 analytical batches (including batches for ISR) for the clinical study. The back-calculated concentrations of calibration samples, the reproducible slope and high r2 values for the calibration curves, the results obtained for quality control samples and incurred sample reanalysis reported do not raise immediate concerns concerning the sufficient quality of the bioanalytical results.

The bioanalytical method was also used for determination of upadacitinib in plasma samples from the efficacy and safety studies M15-554 and M15-572. The performance of the method in the laboratories performing the determinations in these studies have been reported in interim reports.

For study M15-572, the bioanalyses were performed in two laboratories. The performance of the methods have been controlled by quality criteria for the calibrations and quality control samples. Incurred sample reanalysis from these studies were not used to assess the reproducibility of the method, except for the determinations done by WuXi AppTec. Some quality indicating data for Study M15-554 are summarized in Table below.

Table 2 Performance indicating parameters for bioanalysis of upadacitinib in human plasma in study M15-554

	Results
Mean bias (RE %) and CV% of calibration samples, calibrations March 2018 - October 2018	-5.0 - 4.0 % (RE), CV% ≤ 5.4%
Mean bias (RE %) and CV% of calibration samples, calibrations December 2018 - April 2019	-2.7 - 3.1 % (RE) CV% ≤ 4.3%
Mean bias (RE %) and CV% of calibration samples, calibrations October 2019 - December 2019	-2.2 - 2.9 % (RE) CV% ≤ 4.5%
Quality control samples, mean bias (RE %) and CV% , March 2018 - October 2018 0.12 ng/mL 3.76 ng/mL 79.0 ng/mL	 5.0% (RE), 7.8% (CV) 4.5% (RE), 4.8% (CV) -2.5% (RE), 7.0% (CV)
Quality control samples, mean bias (RE %) and CV% , December 2018 - April 2019 0.136 ng/mL 3.16 ng/mL 79.0 ng/mL	 1.5% (RE), 5.7% (CV) 0.6% (RE), 3.9%(CV) 1.0% (RE), 5.4% (CV)
Quality control samples, mean bias (RE %) and CV% , October 2019 - December 2019 0.136 ng/mL 3.16 ng/mL 79.0 ng/mL	 2.2% (RE), 5.1% (CV) 0.3% (RE), 2.7% (CV) 2.8% (RE), 1.8% (CV)

The slope of the calibration curves between December 2018 and April 2019 varied between 0.122 and 0.331.

In studies M15-554 and M15-572, the CHMP noted a big variability in the slope of the calibration curves. According to the MAH responses, instrument responses can be varied from mass spectrometer to mass spectrometer and from day to day. Therefore, the slope may vary depending on mass spectrometers used and time of injection. The variability observed is obviously caused by the use of different mass spectrometers and times of injection. The explanation was considered acceptable to the CHMP.

In the interim report from AbbVie, the calibration data shows a low bias and intra-day precision for the back-calculated standards. Quality control samples of three concentrations were analysed in the analytical batches; the maximum bias of the mean for all quality controls was 3.5%, indicating good enough intra-day accuracy and precision.

In the interim report from VuXi AppTec, the calibration data for back-calculated concentrations of calibration samples show a low bias and inter-day variability. The slope of the calibration curve from 24.12.2019 (0.17) differs significantly from the general trend (abut 0.26). VuXi AppTech used 5 QC samples of 5 concentrations. The highest value for bias of these QC runs was 1.4% and the maximum CV% of the QC samples was 8.7%, n=20 (at 0.15 ng/mL), indicating good enough accuracy and inter-day precision in using the method. Incurred sample reanalysis was done on 60 selected samples - 100% of these met the acceptance criteria.

In the BE-study M20-017, QC samples of four concentrations were analyzed. In the WuXi AppTec laboratory, five different concentrations were used for QC samples in study M15-572. During the review, the CHMP asked the MAH to clarify why the concentration was in the middle range of the concentration range not included in the analyses of samples from study M15-554. The MAH clarified that three levels: low, mid (geometric mean) and high QCs are the three levels used. The low QC concentration must be within three times the lower limit of quantitation (LLOQ) concentration. The mid QC concentration must be close to the geometric mean of the low and high QCs. The high QC concentration must be within 75% of the upper limit of quantitation (ULOQ) concentration. Three concentration levels are considered enough by the CHMP and the response was considered acceptable.

Bioequivalence

Study M20-017

Study M20-017 was a Phase 1 single-dose, open-label, randomized, four-period, four-sequence, two-part crossover design to assess the bioavailability of upadacitinib 15 and 30 mg market-image formulations relative to the reference 15 and 30 mg Phase 3 formulations used in Phase 3 studies M15-554 and M15-572 after high-fat/high-calorie meal and under fasting conditions.

Part 1

In Part 1, the bioavailability of upadacitinib market-image formulation (15 mg) relative to the reference 15 mg strength Phase 3 formulation after a high-fat/high-calorie meal and under fasting conditions was evaluated in 39 healthy subjects. The schematic of study M20-017 Part 1 (15 mg dose) is shown in Figure below.

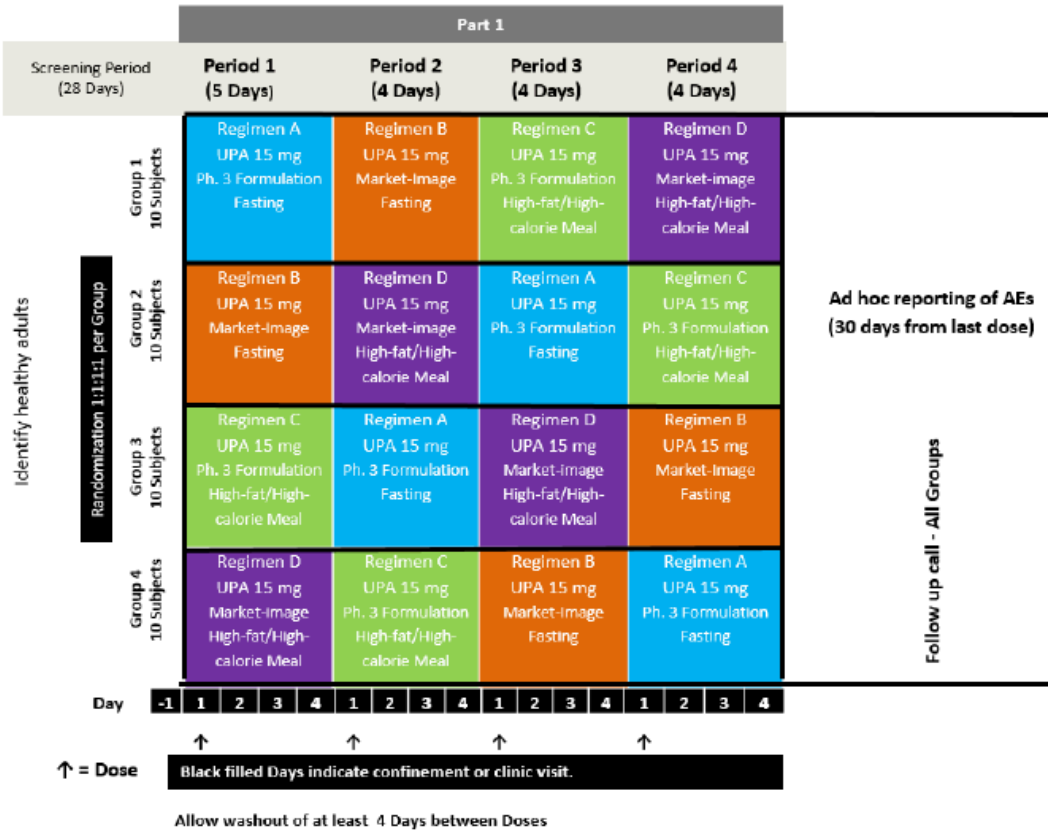


Figure 2 Study M20-017 Part 1: Design Schematic

A washout interval of 4 days separated the doses between the four study periods. Blood samples for assay of upadacitinib were collected for 72 hours after dosing in each period.

Subjects were confined to the study site and supervised for approximately 17 days. Confinement in each period began on Day –1 of Period 1 and ended after the collection of the 72-hour blood samples and completion of scheduled procedures on Day 4 of Period 4.

In all periods, each dose of study drug was taken orally with ~240 mL of water on Day 1 (Table 3). For Regimens C and D, study drug was taken ~30 minutes after starting a high-fat/high-calorie breakfast (Table 4). For Regimens A and B, each dose of study drug was taken after a minimum 10-hour fast and ~4 hours before lunch. Subjects within each regimen received standardized meals during confinement. The upadacitinib formulations used in study M20-017 Part 1 are presented in Table 5.

Table 3 Study M20-017 Part 1: Summary of dosing regimens.

Regimen A	Single 15 mg dose of upadacitinib **Phase 3 formulation (ER17Y)** administered under **fasting conditions** (Reference for B).
Regimen B	Single 15 mg dose of upadacitinib **market-image formulation (ER17)** administered under **fasting conditions** (Test for A).
Regimen C	Single 15 mg dose of upadacitinib **Phase 3 formulation (ER17Y)** administered after **high-fat/high-calorie meal** (Reference for D).
Regimen D	Single 15 mg dose of upadacitinib **market-image formulation (ER17)** administered after **high-fat/high-calorie meal** (Test for C).

Table 4 Study M20-017 Part 1: Content and composition of the high-fat/high-calorie breakfast.

Menu	**Meal composition**
breakfast croissant (3 oz), sliced cheddar cheese (0.5 oz), hard fried egg, sliced ham (1 oz), Swiss cheese (0.75 oz), peanut butter, apple	826 Kcal; 51.5% calories from fat, 33.6% calories from carbohydrates, and 15% calories from protein

Table 5 Study M20-017 Part 1: Identity of Investigational Products

	Upadacitinib Formulations (15 mg)	
	Phase 3 Formulation (Reference)	Market-Image Formulation (Test)
Dosage Form	Tablet	Tablet
Formulation	ER17Y	ER17
Strength (mg)	15	15
MMID	20014313	20015270
Bulk Product Lot Number	1000298099	1000186478
Finishing Lot Number	19-003629	19-003630
Retest Date	31-December-2022	31-March-2021

MMID = Material Master Identification

PK parameters: Blood samples for assay of upadacitinib were collected prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after dosing in each period. Values for the pharmacokinetic parameters of upadacitinib were estimated using noncompartmental methods. PK parameters were defined in the protocol as follows:

1. The C_{max} and T_{max} were determined directly from the plasma concentration-time data.
2. The value of the apparent terminal phase elimination rate constant (β) was obtained from the slope of the least squares linear regression of the logarithms of the plasma concentration versus time data from the terminal log-linear phase of the profile. The range of concentration-time data points selected for the calculation of β was identified by the maximum adjusted R^2 value from the regressions of all the possible ranges of data points, beginning with the last three data points with non-zero concentrations, and then testing additional data points up to but not including T_{max}. In addition, the data points that were selected by the algorithm were evaluated by visual inspection; when appropriate, data points were removed or added and the regression rerun. The actual times used for each subject are listed in the tables of the

calculated pharmacokinetic parameters. The terminal phase elimination half-life (t½) was calculated as ln(2)/β.

3. The area under the plasma concentration-time curve (AUC) from time 0 to the time of the last measurable concentration (AUC_t), AUC from time 0 to 12 hours after dosing (AUC_{0-12}), and AUC from 12 hours after dosing to time of last measurable concentration (AUC_{12-t}) were calculated by the linear trapezoidal rule. The AUC was extrapolated to infinite time by dividing the last measurable plasma concentration (C_t) by β. Denoting the extrapolated portion of the AUC by AUC_{ext}, the AUC from time 0 to infinite time (AUC_{inf}) was calculated as follows:

   $AUC_{inf} = AUC_t + AUC_{ext}$

4. The percentage of the contribution of AUC_{ext} to the overall AUC_{inf} was calculated by dividing the AUC_{ext} by the AUC_{inf} and multiplying this quotient by 100.

Statistical Methods: For each part, a linear mixed effects analysis was performed for the natural logarithms of C_{max}, AUC_t, AUC_{inf}, AUC_{0-12} and AUC_{12-t} using SAS PROC MIXED. The model included effects for sequence, period, and regimen. Within the mixed modeling framework, each test regimen was compared to the corresponding reference regimen.

The bioavailability of a test regimen relative to that of the corresponding reference regimens (market-image versus Phase 3 formulation and high-fat/high calorie meal versus fasting condition) was assessed by point estimates of the central values and corresponding 90% confidence intervals (CI) obtained from the analyses of the natural logarithms of C_{max}, AUC_t, AUC_{inf}, AUC_{0-12} and AUC_{12-t}. These CIs were obtained by taking the antilogarithm of the upper and lower limits of CIs for the difference of the least squares (LS) means on the logarithmic scale within the framework of mixed effects models.

Conduct of the study: In Part 1, all PK samples collected 5 hours or less after dosing were obtained within 10% of the protocol-scheduled times; all samples collected more than 5 hours after dosing were obtained within 30 minutes of the protocol-scheduled times. The scheduled times were used in the calculations of the PK parameters. No protocol deviations were reported in study M20-017.

Data set analysed: 40 subjects were randomised in Part 1. One subject discontinued study drug due to an adverse event (cholelithiasis) after receiving Regimen D in Period 3 and did not receive Regimen B in Period 4. Therefore, only data for Regimens A, C, and D from this subject were included in the linear mixed effects analyses of PK parameters. In addition, one subject was lost to follow up after completing all 4 periods of the study. Prior to enrolment in the study, each subject was judged to be in good health based on review of his/her medical history, a physical examination, vital signs, 12-lead ECG and laboratory tests. A summary of the demographic data is presented in Table below.

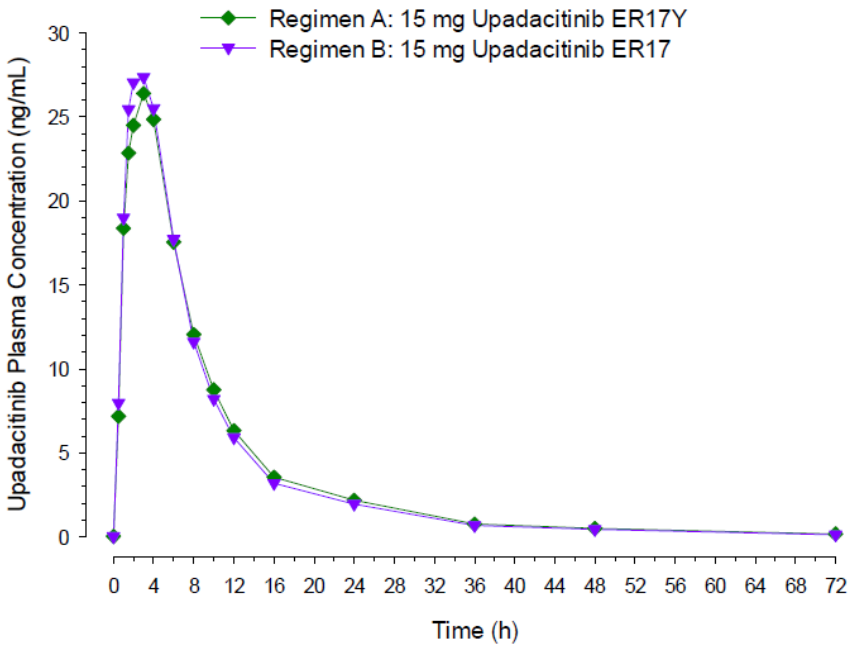
Table 6 Study M20-017 Part 1: Demographic Summary (N=40)

	Mean ± SD (Minimum to Maximum)
Age (years)	38.0 ± 9.65 (19 to 56)
Weight (kg)	81.4 ± 11.5 (55.1 to 101)
Height (cm)	176 ± 9.33 (152 to 193)
BMI (kg/m^2)	26.2 ± 2.59 (19.5 to 29.4)
Sex	35 Males (88%), 5 Females (13%)[a]
Race[a]	13 White (33%), 20 Black (50%), 1 Asian (3%), 6 Multiple (15%)
BMI = Body Mass Index a. Due to rounding over 100% is reported.	

PK results:

Part 1

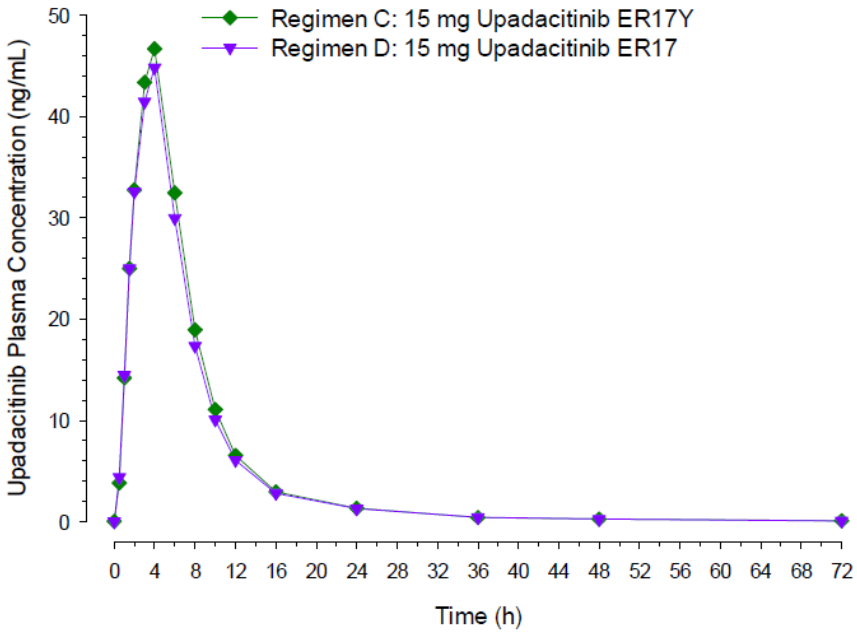
The mean upadacitinib plasma concentration-time profiles by study drug regimens are presented in Figure 3 and Figure 4. The point estimates for relative bioavailability and the corresponding 90% confidence intervals from the linear mixed effects analysis are presented in Table 7. The results demonstrated that the 15 mg upadacitinib commercial formulation is bioequivalent to the 15 mg formulation used in PsA Phase 3 studies under fasting conditions and after a high-fat/high-calorie meal.



Regimen A: Single 15 mg dose of upadacitinib Phase 3 formulation (ER17Y) administered under fasting conditions (N = 40).

Regimen B: Single 15 mg dose of upadacitinib market-image formulation (ER17) administered under fasting conditions (N = 39).

Figure 3 Study M20-017 Part 1: Mean Upadacitinib Plasma Concentrations vs Time Profiles Following Administration of Upadacitinib 15 mg Market-Image Formulation (ER17) and Phase 3 Formulation (ER17Y) Under Fasting Conditions.



Regimen C: Single 15 mg dose of upadacitinib Phase 3 formulation (ER17Y) administered after high-fat/high-calorie meal (N = 40).

Regimen D: Single 15 mg dose of upadacitinib market-image formulation (ER17) administered after high-fat/high-calorie meal (N = 40).

Figure 4 Study M20-017 Part 1: Mean Upadacitinib Plasma Concentrations vs Time Profiles Following Administration of Upadacitinib 15 mg Market-Image Formulation (ER17) and Phase 3 Formulation (ER17Y) After a High-Fat/High-Calorie Meal.

Table 7 Study M20-017 Part 1: Point Estimates and 90% Confidence Intervals for the Bioavailability of Upadacitinib 15 mg Commercial Formulation Relative to the Upadacitinib Phase 3 Formulation under Fasting Conditions and after High Fat/High Calorie Meal.

Regimens Test vs. Reference	Pharmacokinetic Parameter (units)	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen B vs. A	C_{max} (ng/mL)	29.1	28.1	1.038	0.936 – 1.150
	AUC_t (ng•h/mL)	250	256	0.973	0.919 – 1.031
	AUC_{inf} (ng•h/mL)	254	265	0.960	0.907 – 1.015
	AUC_{0-12} (ng•h/mL)	184	184	1.003	0.938 – 1.072
	AUC_{12-t} (ng•h/mL)	62.7	70.3	0.892	0.823 – 0.968
Regimen D vs. C	C_{max} (ng/mL)	47.4	48.4	0.980	0.915 – 1.049
	AUC_t (ng•h/mL)	318	335	0.949	0.906 – 0.994
	AUC_{inf} (ng•h/mL)	323	339	0.952	0.910 – 0.997
	AUC_{0-12} (ng•h/mL)	267	281	0.949	0.897 – 1.004
	AUC_{12-t} (ng•h/mL)	49.1	51.4	0.956	0.882 – 1.036

*Exponentiation of the least squares means for logarithm values

Regimen A: Single 15 mg dose of Phase 3 formulation (ER17Y) administered under fasting conditions (reference for B).

Regimen B: Single 15 mg dose of market-image formulation (ER17) administered under fasting conditions (test for A).

Regimen C: Single 15 mg dose of Phase 3 formulation (ER17Y) administered after a high fat/high calorie meal (reference for D).

Regimen D: Single 15 mg dose of market-image formulation (ER17) administered after a high fat/high calorie meal (test for C).

Part 2

In Part 2, the bioavailability of upadacitinib market-image formulation (30 mg) relative to the reference 30 mg strength Phase 3 formulation after a high-fat/high-calorie meal and under fasting conditions was evaluated in 40 healthy subjects.

Results for Part 2 indicated bioequivalence between upadacitinib 30 mg ER tablet market-image formulation and 30 mg ER tablet Phase 3 formulation under fasting conditions and after a high-fat/high-calorie meal. An application to extend the marketing authorisation for the 30 mg strength was not applied. Therefore, details of study M20-017 Part 2 are not presented.

2.3.3. Pharmacodynamics

Mechanism of action and primary pharmacology

No new studies on pharmacodynamics of upadacitinib are presented within this application. The mode of action of upadacitinib is described below based on published literature.

JAKs are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, haematopoiesis and immune surveillance. The JAK family is composed of 4 members: JAK 1, 2, 3, and tyrosine kinase 2 (Tyk2). These cytoplasmic tyrosine kinases act in tandem to activate the Signal Transducer and Activator of

Transcription (STAT) that transduces cytokine-mediated signals, and are associated with multiple membrane cytokine receptors such as common gamma-chain (CGC) receptors and the glycoprotein 130 (gp130) trans-membrane proteins. Interleukin-6 (IL-6), a pro-inflammatory cytokine, propagates its signalling through the IL-6 receptor and gp130 which in turn results in activation of JAK1, JAK2 and Tyk2 with possible preferential usage of JAK1. JAK3 and JAK1 are components of the CGC cytokine receptor complexes that are responsible for the signalling of the inflammatory cytokines interleukin (IL)-2, -4, -7, -9, -15 and -21; whereas IL-12 and IL-23 signal through JAK2 and Tyk2. Propagation of these signals is important in the amplification of inflammatory responses.

The phosphorylated STATs (pSTATs) form either homo- or heterodimers, which translocate into the nucleus where they bind their cognate promoter elements to regulate transcription of target genes and modulate, in turn, gene expression and cellular function. As the antigen presenting cell engages with the T cell receptor, several cytokines are released to promote the differentiation of various T cell subtypes. Each cytokine involved in T cell differentiation and function have particular JAKs that mediate the signalling. Differentiated T cells produce cytokines that contribute to various immune responses and are implicated in inflammatory and autoimmune diseases.

The exact pathophysiology of psoriasis and PsA has not been fully elucidated. Dysregulated functions of immune cells, mainly dendritic cells and Th17 and Th1, and keratinocyte proliferation/differentiation are involved. In PsA, immune cells, such as activated T cells, dendritic cells, macrophages, and innate lymphoid cells, infiltrate peripheral or axial joints, entheses, and tenosynovial sheaths. The inflammatory cytokines driving the infiltration include IL-1β, IL-2, IL-10, interferon gamma (IFN-γ), and tumour necrosis factor alpha (TNF-α). These mediators can further recruit and stimulate the proliferation of immune cells contributing to synovial hypertrophy and bone destruction. Many of these cytokines and immune cell responses are regulated by JAK/STAT signalling pathways.

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 induces a dose-, and concentration-dependent inhibition of IL-6 (JAK1/JAK2) - induced STAT3 and IL-7 (JAK1/JAK3)-induced STAT5 phosphorylation, oncostatin M, IL-2 and IFNγ. The exact mode of action at involved sites is not fully clear. However, alleviation of the inflammatory JAK/STAT signalling pathways is the overall mode of action of upadacitinib in the treatment of PsA.

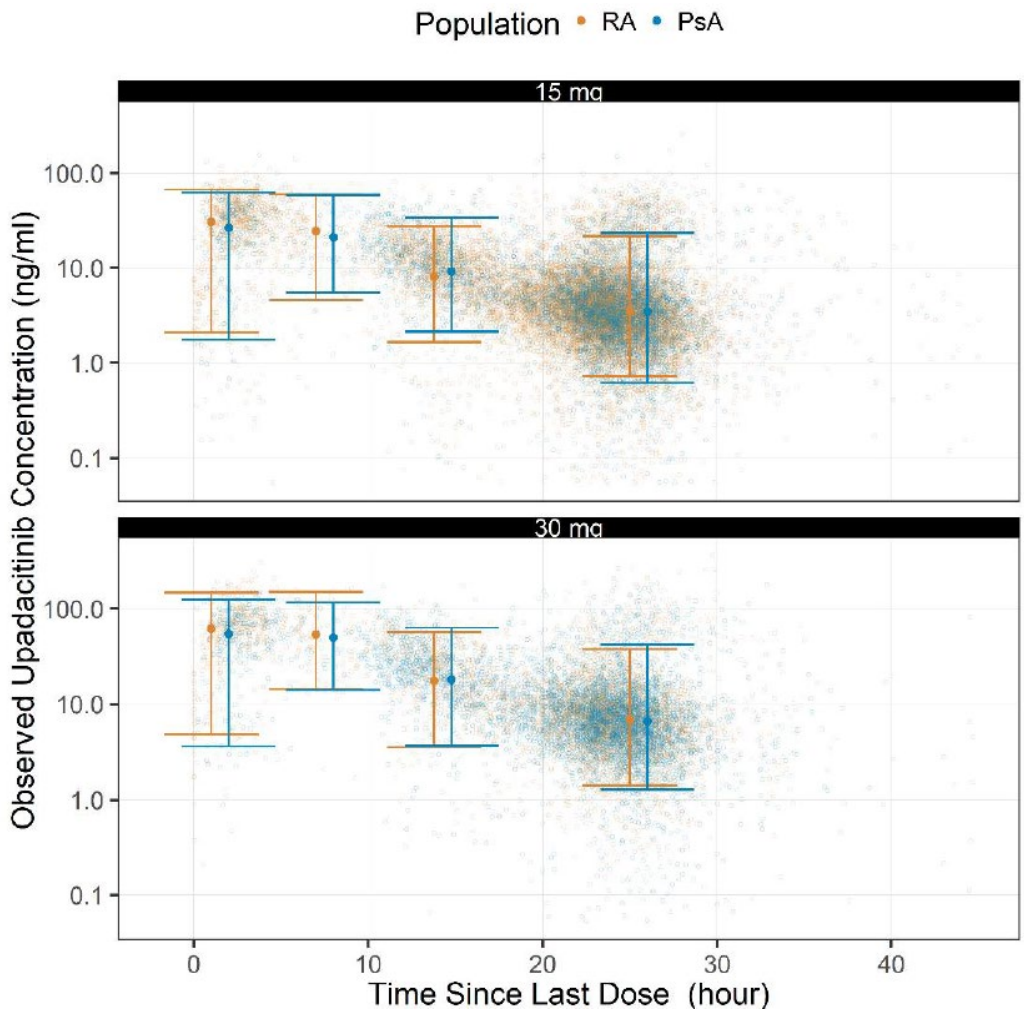
2.3.4. PK/PD modelling

Population pharmacokinetic analysis

Population pharmacokinetic (PPK) analysis in patients with PsA was performed using data from Study M15-554 Period 1 and Study M15-572 Period 1 (up to 24 Weeks). The objective of PPK analysis was to characterize the population PK of upadacitinib in subjects with moderate to severe PsA. Individual predicted upadacitinib exposures based on the PPK model were subsequently used in exposure-response analyses.

Results from prior PPK analyses in healthy subjects and patients with RA were leveraged to inform upadacitinib PK parameters in subjects with PsA. The observed binned plasma concentration versus time profiles of upadacitinib between subjects with RA and subjects with PsA were comparable (Figure 5). Therefore, a Bayesian PK modeling approach was implemented using prior information from the previous upadacitinib PPK model (hereafter "*PPK model 1*" based on 4170 subjects; 96% subjects with RA and 4% healthy subjects), which was assessed within the Rinvoq marketing authorisation application. Specifically, the structural, statistical (inter- and intra-individual variability) and covariate components of the previous model were maintained. Population parameter estimates, the variance-

covariance matrix of the fixed effects and estimates for the random effects (inter- and intra-individual variability) from the PPK model 1 were used as priors via the $PRIOR TNPRI function in NONMEM. All model parameters were re-estimated using the data in subjects with PsA from studies M15-554 and M15-572.



Orange circles: Observed upadacitinib concentrations from subjects with RA in Phase 3 studies.
Blue circles: Observed upadacitinib concentrations from PsA patients.
Closed cycles and error bars represent median and 5th and 95th percentiles for the binned observed data.

Figure 5 Observed Upadacitinib Concentrations vs Time after Last Dose in Subjects with RA and PsA in Phase 3 Studies

Continuous covariates were included in the model using power functions centred on the median value of each covariate in the dataset. Categorical covariates were tested with a multiplicative model. Inter-subject variability (IIV) was modeled assuming a log-normal distribution and residual variability was modeled using a combination of additive and proportional error terms.

PK datasets

Data from 1694 patients with PsA who received upadacitinib and had at least one measurable upadacitinib concentration were included in the PPK analysis of studies M15-554 and M15-572. This includes patients initially randomised to placebo and assigned to upadacitinib at week 24. PK data up to week 56 were used in the PPK analysis. Samples collected before administration of the first

upadacitinib dose were excluded. Sampling times represented actual sampling times. PK sample collections that did not have a sampling time recorded were not included in the analysis.

PsA patients were typically female (916/1694; 54.1%) and white (88.8%). Mean (SD) age, weight and creatinine clearance were 51.5 (12.2) years, 86.8 (20.8) kg and 127 (42.1) ml/min, respectively.

Upadacitinib concentrations were measured at two sites, AbbVie laboratory and WuXi laboratory (samples collected in China). Based on a cross-validation analysis, upadacitinib concentrations measured at WuXi site in China were systematically higher compared to samples analysed at AbbVie, by an average of 11%. To account for the analytical difference between the two laboratories, all upadacitinib plasma concentrations for samples analysed at WuXi, upadacitinib exposure were adjusted (decreased) in the dataset by 11% in the PPK analysis.

Outlier identification and data exclusion rules were the same as those used in the PPK model 1 analysis.

The dataset included 10,691 concentrations with 396 records (3.7%) below the LLOQ. The first observed upadacitinib concentration value below the LLOQ was set to one-half of the LLOQ and flagged with '1' in the BLQ column. All subsequent concentrations below the LLOQ recorded after the last dose were flagged with '2' in the BLQ column and ignored in the analysis.

Two hundred (200) concentration records were excluded due to lack of dosing records being associated with sampling times. Additionally, 105 observations recorded more than 168 hours after the last dose were excluded from the model. Finally, 235 concentration records were flagged as outliers. These records were excluded from the PPK model development, but the final model was rerun on the full dataset including the outliers to evaluate the impact of outliers on parameter estimates.

PPK model development

In the PPK model 1, the PK of upadacitinib were characterized by a two-compartment model with mixed zero and first order absorption with lag time for the extended-release formulation, and linear elimination. Statistically significant covariates were patient population (patients versus healthy), creatinine clearance, and baseline bodyweight on CL/F; and body weight on Vc/F. These covariates were retained in the model and were re-estimated with current data.

The fixed and random effect parameter estimates from the final model updated with data from subjects with PsA were comparable to the prior parameter estimates from the model developed using data from healthy subjects and subjects with RA. Likewise, the 95% CI for the estimates of the covariate effects parameters in the updated model did not include no effect value (zero for continuous covariates and one for categorical covariates) indicating that the previously identified covariates were statistically significant in the model updated with data from PsA studies (Table 8). The CL/F ratio of patients compared to healthy subjects was comparable for PsA and RA patients (0.756 and 0.754, respectively). The parameter estimates were not markedly changed when the model updated with PsA data was re-run with the outlier observations that were excluded during the model development, which supported the robustness of the model.

Table 8 Parameter Estimates and Variability for Upadacitinib Population PK: Model Updated with Data from Subjects with PsA Compared to Prior Model (PPK model 1)

Parameter	Model Updated with PsA Studies		PPK model 1
	Population Estimate	95% Confidence Interval	Population Estimate
CL/F (L/h)[a]	41.3	40.0 - 42.6	40.9
V_C/F (L)[a]	156	151 - 161	156
Extended-Release KA (1/h)	0.0539	0.0489 - 0.0595	0.0523
Extended-Release Lag time (h)	0.153	0.131 - 0.178	0.154
Fraction of ER Dose Absorbed through Zero-Order Process (%)	73.1	70.5 - 75.6	74.5
Zero-Order Infusion Duration (h)	3.32	3.21 - 3.43	3.29
Immediate-Release KA (1/h)	2.75	2.37 - 3.18	2.77
Immediate-Release Lag time (h)	0.200	0.185 - 0.216	0.200
Bioavailability of the ER Formulation Relative to the IR Formulation (%)	76.0	73.9 - 78.0	76.2
Q/F (L/h)[a]	3.22	2.88 - 3.60	3.22
Vp/F (L)[a]	67.4	58.7 - 77.3	68.0
CL/F Ratio of diseased Patients Compared to Healthy Subjects[b]	0.756	0.730 - 0.782	0.754
Covariate Exponent of Creatinine Clearance on CL/F[b]	0.258	0.214 - 0.302	0.256
Covariate Exponent of Weight on V_C/F[b]	0.864	0.744 - 0.984	0.804
Covariate Exponent of Weight on CL/F[b]	0.123	0.0569 - 0.189	0.132
ISV on CL/F in Phase 1 (%)	20.5	18.5 - 22.3	20.5
ISV on V_C/F in Phase 1 (%)	24.2	20.6 - 27.4	24.4
ISV on Extended-Release KA (%)	63.8	56.8 - 70.1	66.8
ISV on CL/F in Phase 2/3 (%)	36.3	34.6 - 38.0	36.5
ISV on V_C/F in Phase 2/3 (%)	60.7	51.3 - 68.9	53.0
Proportional Error in Phase 1 SD	0.345	0.325 - 0.364	0.344
Additive Error SD (ng/mL)	0.0809	0.0529 - 0.101	0.0858
Proportional Error in Phase 2/3 SD	0.559	0.550 - 0.568	0.543

CL/F = apparent clearance; **CrCL** = creatinine clearance; **ER** = extended-release; **IR** = immediate-release; **ISV** = inter-subject variability; **KA** = absorption rate constant; **PsA** = psoriatic arthritis; **Q/F** = apparent inter-compartmental clearance; **RA** = rheumatoid arthritis; **SD** = standard deviation; **Vc/F** = apparent volume of distribution of central compartment; **Vp/F** = apparent volume of distribution of peripheral compartment.

%ISV was calculated as SQRT(ω^2) × 100

a. Estimates are for the immediate release (based on immediate release bioavailability).

b. Typical clearance and volume of central compartment with particular covariate combination:

$$CL/F = \begin{cases} 41.3 * \left(\frac{CRCL[mL/min]}{108.7\ mL/min}\right)^{0.258} * \left(\frac{WTKG[kg]}{74\ kg}\right)^{0.123} \frac{L}{h} & \text{for healthy subjects} \\ 41.3 * \left(\frac{CRCL[mL/min]}{108.7\ mL/min}\right)^{0.258} * \left(\frac{WTKG[kg]}{74\ kg}\right)^{0.123} * 0.756\ \frac{L}{h} & \text{for PsA and RA patients} \end{cases}$$

$$V_c/F = 156 * \left(\frac{WTKG[kg]}{74\ kg}\right)^{0.864} \text{L}$$

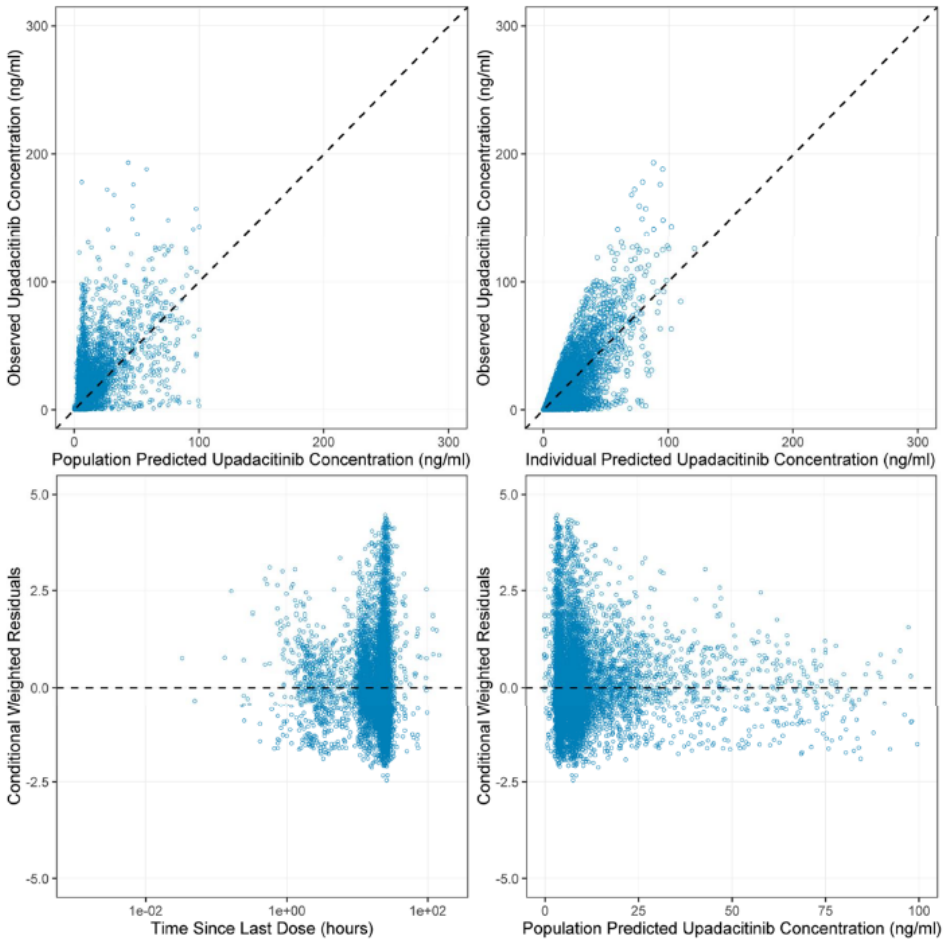
The following additional covariates were investigated for influence on upadacitinib PK in subjects with PsA by graphical analyses of post hocs vs covariates:

- For CL/F: age, sex, race, (White, Black, Hispanic, Asian), country (Taiwan, Japan, China, South Korea), baseline serum bilirubin, baseline aspartate transaminase (AST), baseline alanine transaminase (ALT), baseline hsCRP, concomitant use of non-biologic DMARDs, concomitant use of any pH-modifying agents, concomitant use of moderate or strong CYP3A inhibitors, and concomitant use of strong CYP3A inducers

- For Vc/F: sex, race (White, Black, Hispanic, Asian), and country (Taiwan, Japan, China, South Korea)
- For absorption rate of the ER formulation: upadacitinib dose, concomitant use of antacids, concomitant used of H2 receptor antagonists, concomitant use of proton pump inhibitors, concomitant use of any pH-modifying agents, concomitant use of moderate or strong CYP3A inhibitors, and concomitant use of strong CYP3A inducers

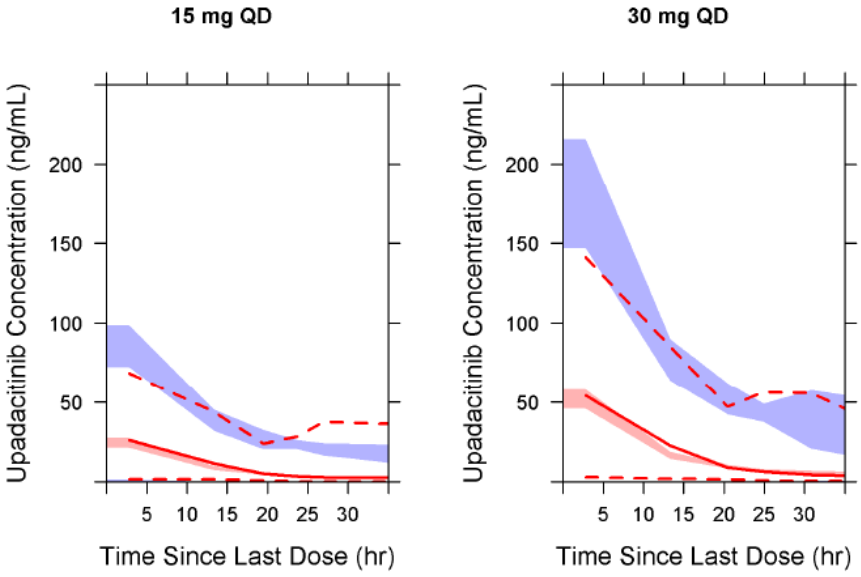
In the exploratory plots, a trend for decrease in CL/F with age was present. No clear trend was observed for any other tested covariate. Age was tested as a covariate on CL/F but it was not statistically significant (decreased OFV by only one point). Therefore, age was not included as a covariate and the model summarised in Table 8 was selected as the final model.

The goodness-of-fit plots for the final model are depicted in Figure 6 for the data from Phase 3 PsA studies. Visual predictive checks (VPCs) with 250 replicates for the upadacitinib concentrations in subjects with PsA were plotted against time since last dose and stratified by dose group (Figure 7). Median and 5th and 95th percentiles of observed exposures lie within the 95% prediction bands for these percentiles for most of the bins shown in the plots indicating that the model adequately describes the pharmacokinetics of upadacitinib in subjects with PsA.



Goodness-of-fit plots for the individual predicted and population predicted versus observed concentrations (top left and right, respectively) from upadacitinib PsA Phase 3 studies and conditional weighted residuals versus time since last dose and population predicted concentrations (bottom left and right, respectively).

Figure 6 Goodness-of-Fit Plots of Upadacitinib PPK Model (Data from Phase 3 PsA Studies)



The shaded blue areas represent the 95% prediction interval of the 2.5th and 97.5th percentiles of simulated concentrations, the red shaded areas represent the 95% prediction interval of the 50th percentile of simulated concentrations, the solid red line represents median of the observed concentrations and dashed red lines represent the 2.5th and 97.5th percentile of the observed concentrations.

Figure 7 Visual Predictive Checks of Upadacitinib Concentration Plotted Versus Time Since Last Dose for PsA Patients Stratified by Dose.

Impact of Statistically Significant Covariates on Upadacitinib Exposures

The influence of statistically significant covariates identified in the PPK analyses on upadacitinib steady-state area under the plasma concentration-time curve from time zero to 24 hours (AUC_{24h}) and steady-state maximum observed plasma concentration (C_{max}) following administration of the 15 mg and 30 mg extended-release dose are presented in Figure 8. The test and reference groups for the assessment of covariate effects were as follows:

Body Weight:

- Test groups: < 60 kg and > 100 kg
- Reference group: 60 - 100 kg

Creatinine clearance (CrCL):

- Test groups: 60 to < 90 mL/min [mild renal impairment] and 30 to < 60 mL/min [moderate renal impairment]
- Reference group: ≥ 90 mL/min

Based on the simulations, subjects with PsA with bodyweight <60 kg or >100 kg were predicted to have 5% higher or 4% lower AUC on average, and 20% higher or 16% lower C_{max}, on average, respectively, compared to subjects with bodyweight 60 - 100 kg. Subjects with mild (CrCL 60 to < 90 mL/min) or moderate (30 to < 60 mL/min) renal impairment are predicted to have approximately 15% and 26% higher AUC and 8% and 13% higher C_{max}, respectively, compared to subjects with normal renal function.

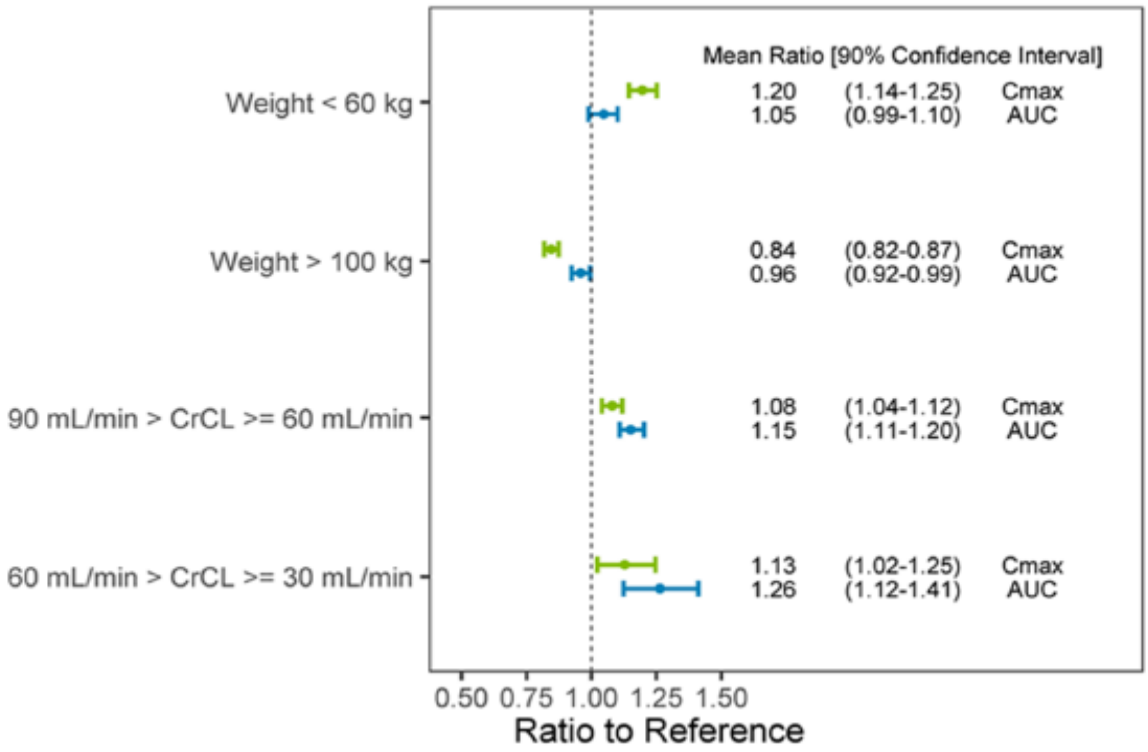


Figure 8 Model-Predicted Covariate Effect on Upadacitinib Cmax and AUC24h for Different Subpopulations Relative to the Reference Population.

The vertical dashed line shows the exposure ratio of 1 relative to the reference group. The reference group for bodyweight was 60 to100 kg and for creatinine clearance was ≥ 90 mL/min.

Effect of Commonly Used DMARDs on Upadacitinib Exposures

In the Phase 3 Studies M15-554 and M15-572, upadacitinib was given as monotherapy or concomitantly with disease-modifying anti-rheumatic drugs (DMARDs). The percentages and number of subjects in the PPK dataset who were administered concomitant DMARDs is presented in Table 9.

Table 9 Concomitantly used disease-modifying anti-rheumatic drugs in the population PK dataset.

		15 mg QD (N = 841)	30 mg QD (N = 853)	ALL SUBJECTS (N = 1694)
Any concomitant DMARD	No	168 (20.0%)	161 (18.9%)	329 (19.4%)
	Yes	673 (80.0%)	692 (81.1%)	1365 (80.6%)
Methotrexate	No	329 (39.1%)	358 (42.0%)	687 (40.6%)
	Yes	512 (60.9%)	495 (58.0%)	1007 (59.4%)
Apremilast	No	813 (96.7%)	829 (97.2%)	1642 (96.9%)
	Yes	28 (3.3%)	24 (2.8%)	52 (3.1%)
Chloroquine	No	841 (100.0%)	851 (99.8%)	1692 (99.9%)
	Yes	0 (0.0%)	2 (0.2%)	2 (0.1%)
Ciclosporin	No	840 (99.9%)	852 (99.9%)	1692 (99.9%)
	Yes	1 (0.1%)	1 (0.1%)	2 (0.1%)
Hydroxy-choloroquine	No	832 (98.9%)	845 (99.1%)	1677 (99.0%)
	Yes	9 (1.1%)	8 (0.9%)	17 (1.0%)
Iguratimod	No	839 (99.8%)	852 (99.9%)	1691 (99.8%)
	Yes	2 (0.2%)	1 (0.1%)	3 (0.2%)
Leflunomide	No	800 (95.1%)	799 (93.7%)	1599 (94.4%)
	Yes	41 (4.9%)	54 (6.3%)	95 (5.6%)
Sulfasalazine	No	781 (92.9%)	789 (92.5%)	1570 (92.7%)
	Yes	60 (7.1%)	64 (7.5%)	124 (7.3%)
Mycophenolate mofetil	No	840 (99.9%)	853 (100.0%)	1693 (99.9%)
	Yes	1 (0.1%)	0 (0.0%)	1 (0.1%)

Summary statistics of model-estimated upadacitinib steady state C_{avg}, C_{min} and C_{max} from the final PPK model were summarized for the different DMARDs, which were used by at least 1% of all subjects included in the PPK analysis; these DMARDs were methotrexate, apremilast, hydroxychloroquine, sulfasalazine, and leflunomide. As demonstrated in Table 10, upadacitinib plasma exposures were similar between subjects who were co-administered apremilast, hydroxychloroquine, sulfasalazine, and leflunomide, and subjects who did not receive these DMARDs, indicating lack of effect of these DMARDs on upadacitinib pharmacokinetics.

Table 10 Summary Statistics of Model-Estimated Upadacitinib Plasma Exposures for 15 mg and 30 mg QD in Phase 3 PsA Studies Stratified by DMARD Use

Treatment	csDMARD	Use	N (%)	Cavg (ng/mL) Median (90% CI)	Cmax (ng/mL) Median (90% CI)	Cmin (ng/mL) Median (90% CI)
15 mg QD	Methotrexate	Yes	512 (60.9%)	15.4 (9.76 - 28.9)	37.9 (27.8 - 49.7)	4.42 (1.46 - 19.5)
		No	329 (39.1%)	14.8 (9.52 - 28.3)	36.8 (26.5 - 47.9)	4.16 (1.55 - 19.2)
	Apremilast	Yes	28 (3.3%)	14.2 (9.35 - 26.5)	35.6 (29.4 - 41.9)	4.03 (1.69 - 18.5)
		No	813 (96.7%)	15.2 (9.59 - 28.7)	37.7 (27.1 - 49.3)	4.26 (1.49 - 19.6)
	Sulfasalazine	Yes	60 (7.1%)	15.2 (9.38 - 31.9)	37.3 (25.9 - 53.0)	4.20 (1.68 - 18.9)
		No	781 (92.9%)	15.2 (9.60 - 28.6)	37.6 (27.2 - 49.3)	4.27 (1.48 - 19.4)
	Leflunomide	Yes	41 (4.9%)	13.8 (9.58 - 19.4)	36.2 (26.8 - 47.2)	3.56 (1.37 - 10.0)
		No	800 (95.1%)	15.3 (9.59 - 28.8)	37.6 (27.2 - 49.3)	4.33 (1.56 - 19.6)
	Hydroxy-chloroquine	Yes	9 (1.1%)	14.6 (10.7 - 36.0)	31.9 (30.1 - 48.2)	4.71 (2.13 - 26.0)
		No	832 (98.9%)	15.2 (9.58 - 28.7)	37.6 (27.1 - 49.3)	4.24 (1.48 - 19.3)
30 mg QD	Methotrexate	Yes	495 (58.0%)	28.7 (19.5 - 53.2)	74.5 (57.0 - 96.9)	7.82 (3.21 - 33.2)
		No	358 (42.0%)	29.2 (18.6 - 55.9)	73.1 (54.8 - 98.9)	8.13 (2.83 - 36.7)
	Apremilast	Yes	24 (2.8%)	31.4 (20.9 - 46.9)	71.8 (56.4 - 87.7)	8.79 (4.67 - 25.5)
		No	829 (97.2%)	28.8 (19.1 - 54.9)	74.0 (55.6 - 97.9)	7.92 (2.92 - 34.6)
	Sulfasalazine	Yes	64 (7.5%)	26.5 (18.6 - 49.0)	76.8 (53.4 - 93.3)	6.57 (2.79 - 28.0)
		No	789 (92.5%)	29.0 (19.3 - 55.0)	73.8 (56.1 - 98.1)	8.13 (3.03 - 35.6)
	Leflunomide	Yes	54 (6.3%)	28.1 (18.6 - 57.1)	76.9 (59.9 - 106)	7.08 (2.38 - 38.5)
		No	799 (93.7%)	29.0 (19.3 - 53.5)	73.8 (55.4 - 96.9)	8.06 (2.97 - 34.2)
	Hydroxy-chloroquine	Yes	8 (0.9%)	27.8 (23.8 - 57.9)	82.3 (71.3 - 95.7)	6.23 (4.93 - 36.6)
		No	845 (99.1%)	29.0 (19.1 - 54.5)	73.9 (55.5 - 97.4)	8.06 (2.95 - 34.4)

Exposure-response analyses for efficacy

The objective of efficacy E-R analyses of Studies M15-554 and M15-572 was to characterize the relationships between upadacitinib plasma exposures and efficacy in subjects with moderate to severe PsA. Data from 1916 subjects who received placebo or upadacitinib were included in the efficacy E-R analyses. The following efficacy endpoints were used:

- ACR20 at Weeks 12 and 24
- ACR50 at Weeks 12 and 24
- ACR70 at Weeks 12 and 24
- PASI75 (for subjects with ≥ 3% BSA psoriasis at baseline) at Weeks 16 and 24
- sIGA (0/1) and at least a 2-point improvement from baseline (for subjects with baseline sIGA ≥ 2) at Weeks 16 and 24

For missing efficacy variables, Non-Responder Imputation (NRI) were used. In NRI, subjects who prematurely discontinued study drug were considered to be non-responders on or after discontinuation date.

Methods

Upadacitinib plasma exposures (C_{avg}) in subjects with PsA who received the ER dosing regimens were derived using the individual predicted upadacitinib exposures based on the population PK model.

The relationships between upadacitinib C_{avg} and efficacy endpoints were first explored using quartile plots. Additionally, stepwise logistic regression analyses were constructed to test for relationship between each endpoint and upadacitinib C_{avg} in subjects with PsA.

For each of the evaluated efficacy variables, logistic regression models with treatment effect and exposure effect function were first evaluated to determine if there was a statistically significant effect

of upadacitinib exposures on the probability of occurrence of each efficacy and safety variable. The logistic regression model described in Equation 5 was used to test for the statistical significance of treatment and/or plasma exposure effect as follows:

$$log\left(\frac{P(Y_i = 1)}{1 - P(Y_i = 1)}\right) = \alpha + \beta_{\exp} \times \text{Exposure}_i + \beta_{trt} \times \text{Treatment}_i \quad \text{Equation 5}$$

where $P(Y_i = 1)$ is the probability that the observation Y from subject i is equal to 1, with 1 indicating the event of interest occurred, α is the intercept parameter (reflecting placebo response), β_{exp} is the slope for the exposure metric (i.e., C_{avg}), $Exposure_i$ is the exposure metric in subject i, β_{trt} is the estimated magnitude of treatment effect, $Treatment_i$ is the study arm in subject i.

Only efficacy endpoints exhibiting a statistically significant exposure effect (p-value < 0.01 for β_{exp}) were evaluated further using separate exposure-response models. Different drug effect functions such as linear (Equation 8), maximum response (E_{max}; Equation 9), and sigmoid E_{max} (Equation 10) were evaluated to determine the best model describing the effect of upadacitinib plasma exposures on the probability of each efficacy outcome.

Equivalent to Equation 5 the logit of the probabilities to reach the endpoint was described as:

$$\ln\frac{P(Y = 1)}{1 - P(Y = 1)} = f(C) \quad \text{Equation 7}$$

Here, Y denotes the binary variable of response being reached (or not), with $P(Y = 1)$ representing the probability of the response being reached. Different link functions for correlation with upadacitinib plasma exposures were explored to obtain optimal fits to observed data.

$$f(C) = Intercept + Slope * C \quad \text{Equation 8}$$

$$f(C) = Intercept + \frac{E_{MAX} * C}{EC_{50} + C} \quad \text{Equation 9}$$

$$f(C) = Intercept + \frac{E_{MAX} * C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}} \quad \text{Equation 10}$$

where *Intercept* represents the logit-transformed probability at zero concentration (placebo-treated subjects), *C* represents the exposure metric (C_{avg}) and *Slope* is the slope parameter for linear drug effect models. E_{max}, EC_{50} and γ represent the maximum response, the upadacitinib concentration associated with half E_{max} and the Hill factor in the sigmoid E_{max} models in the logit domain, respectively. These parameters are to be interpreted on the logistic scale. Exposure-response model selection was based on the Akaike Information Criterion (AIC) and graphical assessment of the adequacy of the models to describe the observed data. Additionally, model stability and precision of parameter estimates were used in the model selection process.

Covariate modelling Univariate analysis (evaluating one covariate at a time) was first performed. If more than one covariate was statistically significant, a multivariate assessment was performed. Covariates were tested for statistical significance using the likelihood ratio test by the stepwise forward-inclusion-backward-elimination procedure with p-value thresholds of $p < 0.01$ and $p < 0.001$, respectively.

Continuous covariates were centered at their median and included in the model as follows:

$$P_i = P + (COV_i - COV_{med}).\theta_{cov} \qquad \text{Equation 11}$$

where P_i is the parameter value for individual *i* with covariate value COV_i, COV_{med} is the median value of the covariate, *P* is the typical value of the parameter (when $COV_i = COV_{med}$) and θ_{cov} is the estimated slope of the covariate relationship.

Binary covariates were included in the model as follows:

$$P_i = P + COV_i.\theta_{cov} \qquad \text{Equation 12}$$

where θ_{cov} is the estimated slope of the covariate relationship and COV_i denotes the binary covariate value of 0 or 1 for individual *i*, and *P* is the typical value (reference subject with covariate value of zero) of the parameter.

For each significant covariate in the final model, model predictions for the 15 and 30 mg QD regimen were carried out via bootstrapping and stratified by pre-specified categories (e.g., subject age was categorized into < 52 y, ≥ 52 y, subject BMI into < 29.6 and ≥ 29.6 and hsCRP into ≤ upper limit of normal [2.87 mg/L] and > upper limit of normal). Finally, median and 90% confidence intervals were calculated for response for each covariate category and shown in forest plots.

The final logistic regression models developed for efficacy endpoints were used to conduct simulations to predict the probabilities of the efficacy endpoints following treatment with placebo, upadacitinib 15 mg QD, and upadacitinib 30 mg QD regimens.

The simulations incorporated inter-individual variability in upadacitinib PK and covariate distributions by resampling exposures and covariates from the subjects enrolled in the Phase 3 Studies M15-554 and M15-572. The variabilities associated with the precision of the parameter estimates in the logistic regression models were also included in the simulations by sampling the parameters from a multivariate random normal distribution with means and covariance terms that were estimated in the logistic regression models. All simulations were conducted with 500 replicates for N = 300 subjects at each treatment group. The percentage of subjects predicted to achieve each of the efficacy endpoints were then calculated for each replicate, and median and 95% CI were calculated across all the replicates.

Results: ACR responses

Exploratory exposure-response quartile plots for ACR20/50/70 at Week 12 and Week 24 are shown in Figure 9.

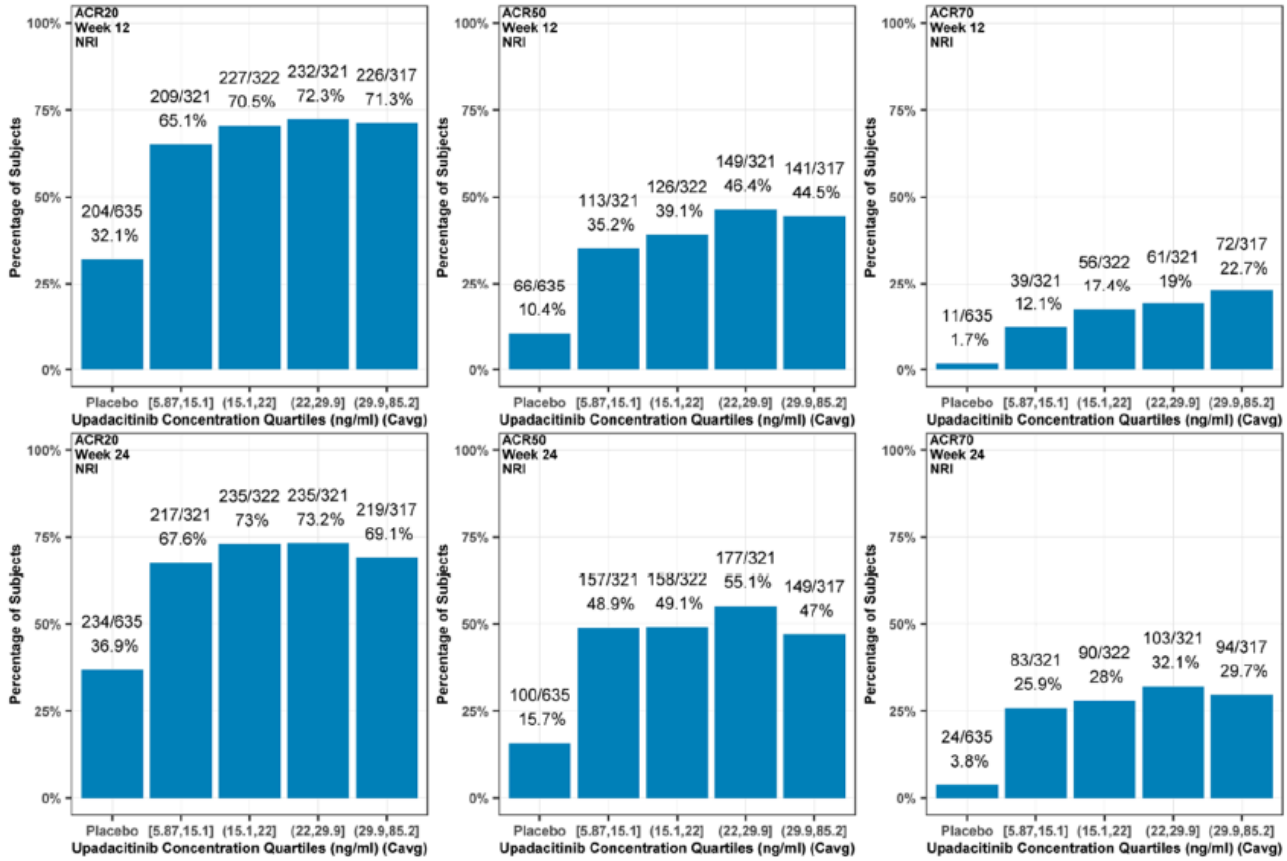


Figure 9 Observed ACR20, ACR50 and ACR70 Responses (NRI) versus predicted Upadacitinib Cavg Quartiles at Week 12 and Week 24

For ACR20 (the primary efficacy endpoint in studies M15-572 and M15-554), a statistically significant treatment effect was present at Week 12 and Week 24, but no statistically significant exposure-response relationship was present at either Week 12 or Week 24. For ACR50 and ACR70, logistic regression analyses revealed statistically significant treatment effect for each endpoint at both Week 12 and Week 24, while significant exposure-response relationships were only present at Week 12.

Therefore, only ACR50 and ACR70 at Week 12 were evaluated further through exposure-response modeling given that these endpoints exhibited statistically significant exposure-response relationship (p-value < 0.01). An E_{max} with intercept model was chosen as the most appropriate model for both endpoints based on AIC and assessment of the observed and predicted responses.

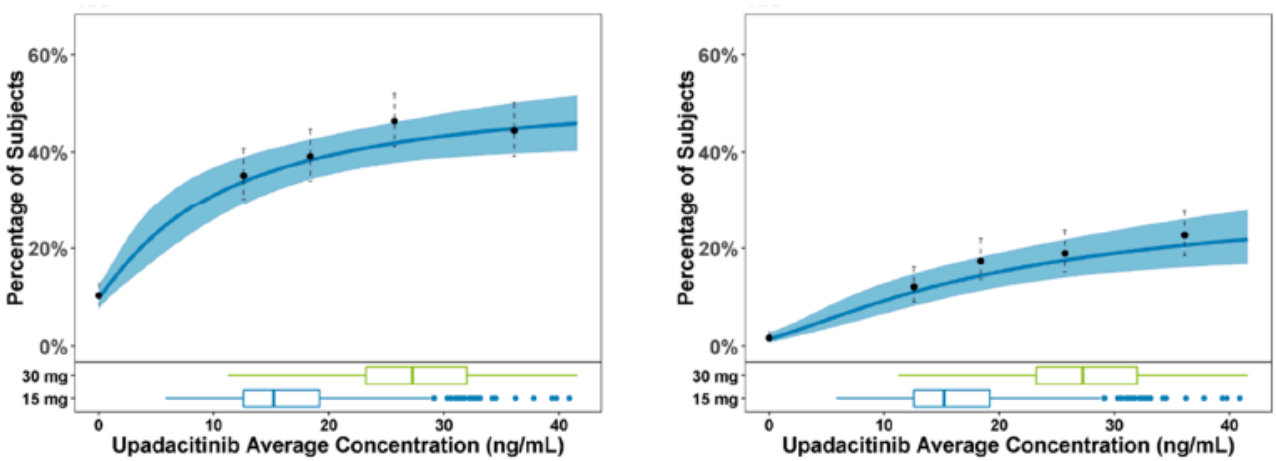
The following covariates were identified in the forward inclusion process with none removed in the backward elimination step:

- ACR50 at Week 12: Age, BMI and population [history of an inadequate response to non-biologic DMARDs (DMARD-IR) vs history of an inadequate response to biologic DMARDs (bDMARD-IR)] on the intercept; hsCRP on E_{max}
- ACR70 at Week 12: Age, sex and population on the intercept; hsCRP on E_{max}

Final model parameters are shown in Table 11 and final model fit is shown in Figure 10. Figure 11 summarizes the final model simulated ACR50 and ACR70 responses for upadacitinib 15 mg QD, 30 mg QD regimens and placebo at Week 12 stratified by the significant covariates in the final ACR model.

Table 11 Final Model Parameter Estimates for Logistic Regression Models for the Relationship between Upadacitinib C_{avg} and ACR50 and ACR70 Efficacy Endpoints at Week 12

Parameter	Estimate	95% CI
ACR50		
Intercept	−2.42	−2.73; −2.12
Emax	2.41	1.93; 3.00
EC_{50}	6.79	2.95; 15.7
hsCRP on Emax	0.15	0.10; 0.21
BMI on Intercept	−0.04	−0.06; −0.02
Relative additive effect of DMARD-IR on Intercept	0.38	0.15; 0.61
Age on Intercept	−0.02	−0.02; −0.01
ACR70		
Intercept	−4.83	−5.51; −4.15
Emax	3.53	2.77; 4.49
EC_{50}	8.50	3.95; 18.3
hsCRP on Emax	0.10	0.05; 0.15
Relative additive effect of Male on Intercept	0.63	0.34; 0.92
Age on Intercept	−0.02	−0.03; −0.01
Relative additive effect of DMARD-IR on Intercept	0.53	0.19; 0.86



Left: ACR50 response. **Right**: ACR70 response. **Blue solid line**: Median predicted response. **Blue shaded area**: 95% confidence intervals of the predicted response. **Dots and error bars**: Median and 95% binomial CIs of binned observed rates.

Observed and Model-Predicted ACR50 and ACR70 Responses (NRI) at Week 12 vs predicted Upadacitinib C_{avg}

Figure 10 Observed and Model-Predicted ACR50 and ACR70 Responses (NRI) at Week 12 vs predicted Upadacitinib Cavg

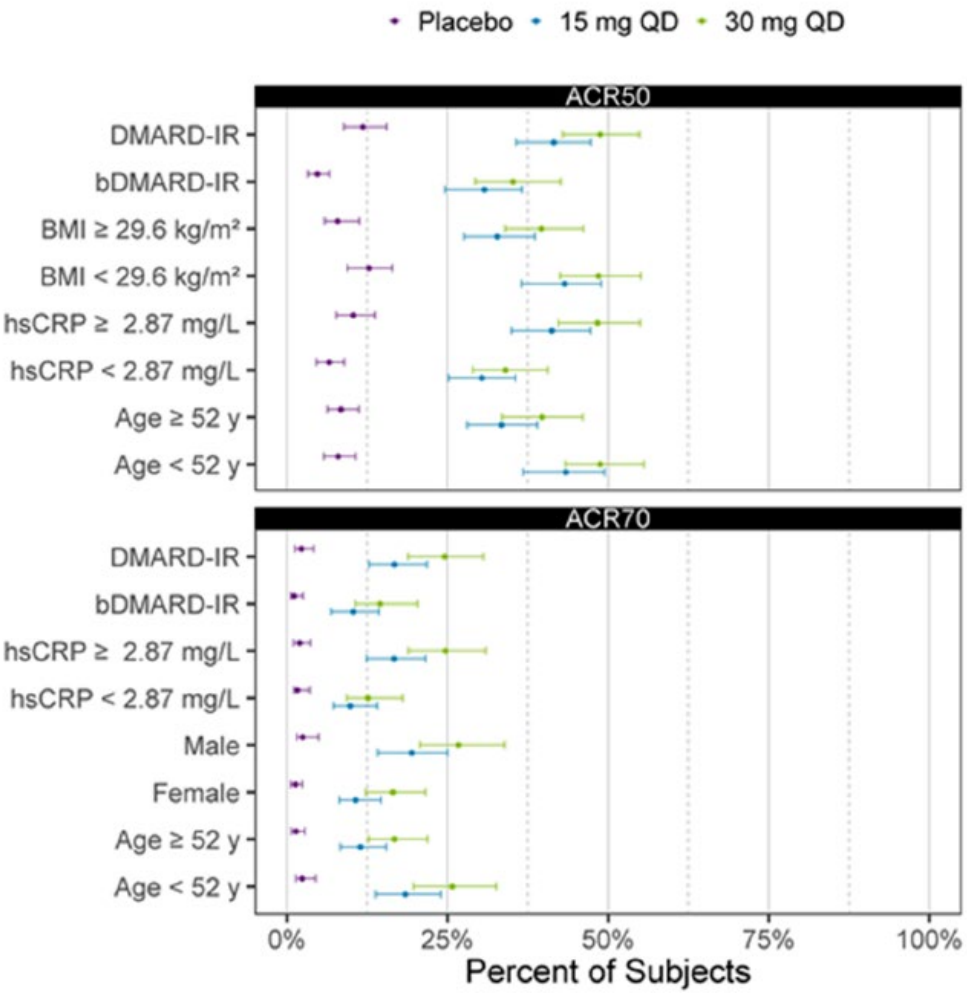


Figure 11 Model-Predicted ACR50 and ACR70 Responses for 15 mg QD, 30 mg QD Regimens and Placebo at Week 12 Stratified by Covariate Subgroups

Results: PASI75 response

The percentage of subjects with ≥ 3% BSA psoriasis at baseline who achieved PASI 75 response was plotted against predicted upadacitinib C_{avg} quartiles at Week 16 and Week 24 (Figure 12). There was a statistically significant treatment effect but no significant exposure-response relationship for PASI75 at either Week 16 or Week 24. Therefore, no exposure-response modeling was conducted for PASI75.

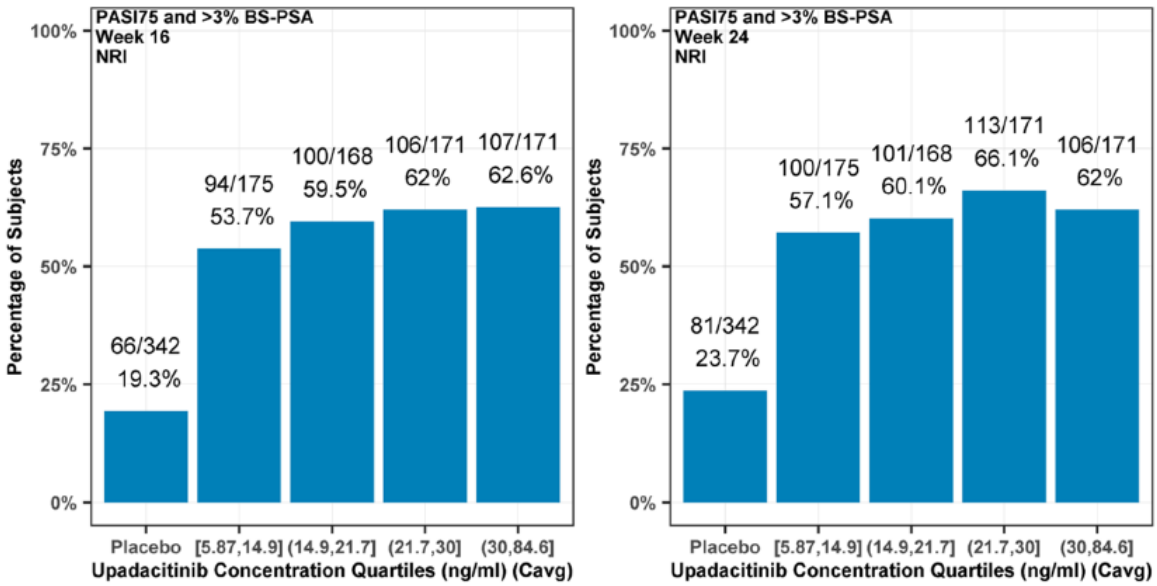


Figure 12 Observed PASI75 Responses (NRI) versus predicted Upadacitinib Cavg Quartiles at Week 16 and Week 24

Results: sIGA 0/1 response

The percentage of subjects achieving sIGA 0/1 and at least a 2-point improvement from baseline (for subjects with baseline sIGA ≥ 2) was plotted against predicted upadacitinib C_{avg} quartiles at Week 16 and Week 24 (Figure 13).

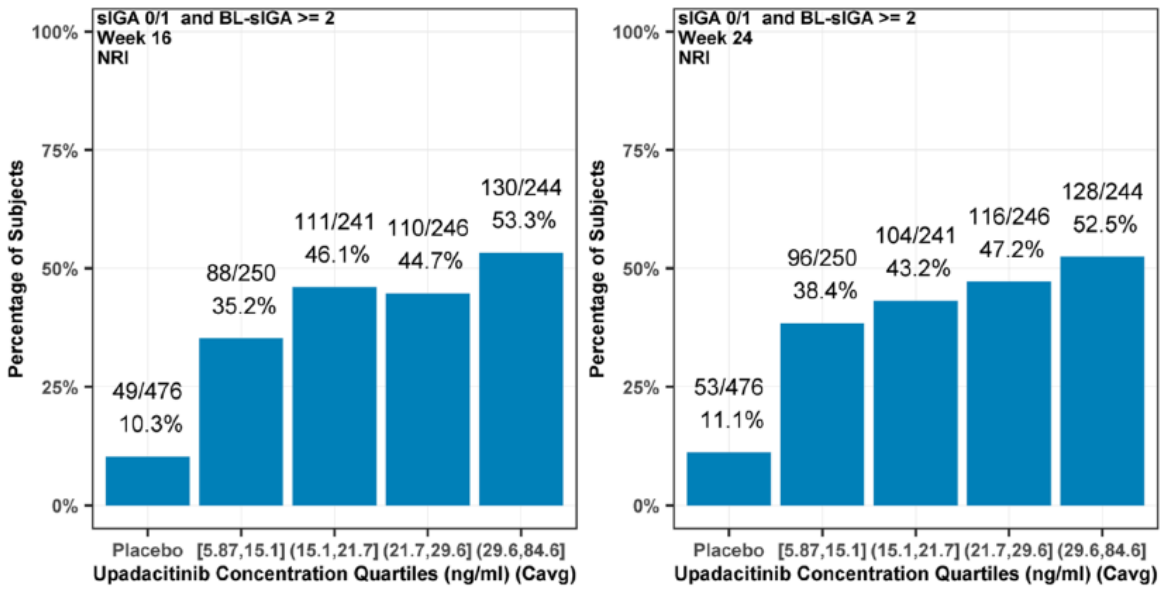


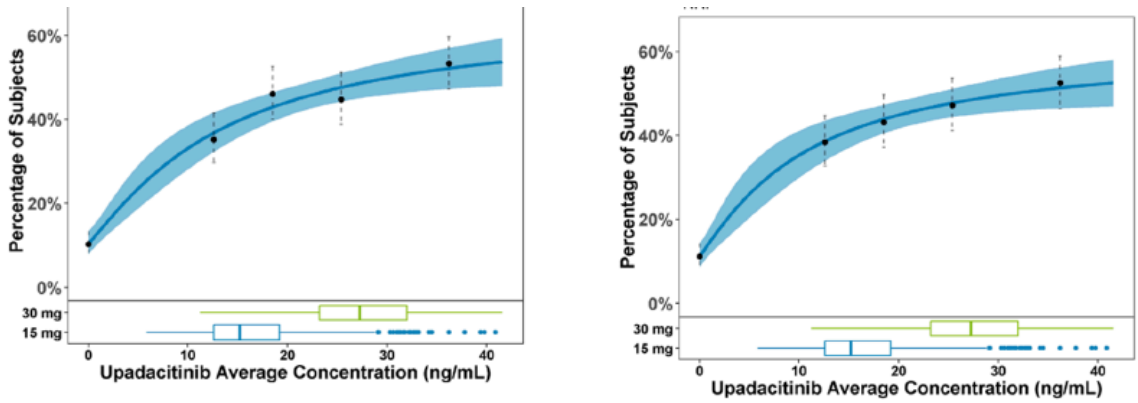
Figure 13 Observed sIGA 0/1 Responses (NRI) versus predicted Upadacitinib Cavg Quartiles at Week 16 and Week 24

Logistic regression analysis revealed that at Week 16 and Week 24 a statistically significant treatment effect was present. In addition, a significant exposure-response relationship for this efficacy endpoint was present at Week 16 and Week 24. The relationship between upadacitinib C_{avg} and the percentage of subjects achieving sIGA 0/1 at Week 16 and Week 24 was best described by E_{max} with intercept model.

Covariate analysis was performed on intercept, EC_{50} and E_{max} for the sIGA base model. Body weight was identified as a significant covariate in the forward inclusion process but was then removed in the backward elimination step due to failing to meet the statistically significant threshold (p-value < 0.001). Hence, the base model without covariates was chosen as the final model. Summary of the final model parameters are presented in Table 12, while the final model fit is shown in Figure 14.

Table 12 Final Model Parameter Estimates for Logistic Regression Models for the Relationship Between Upadacitinib Cavg and sIGA 0/1 at Week 16 and Week 24

Parameter	Estimate	95% CI
sIGA 0/1 Week 16		
Intercept	−2.17	−2.46; −1.87
Emax	2.83	2.23; 3.59
EC50	9.37	4.30; 20.4
sIGA 0/1 Week 24		
Intercept	−2.08	−2.36; −1.79
Emax	2.57	2.03; 3.26
EC50	7.43	3.12; 17.7



Left: sIGA 0/1 response at Week 16. **Right**: sIGA 0/1 response at Week 24. **Blue solid line**: Median predicted response. **Blue shaded area**: 95% confidence intervals of the predicted response. **Dots and error bars**: Median and 95% binomial CIs of binned observed rates.

Figure 14 Observed and Model-Predicted sIGA 0/1 Responses at Week 16 and Week 24 vs predicted Upadacitinib Cavg

Exposure-response analyses for safety

The objective of safety E-R analyses of Studies M15-554 and M15-572 was to characterize the relationships between upadacitinib plasma exposures and select safety parameters in subjects with moderate to severe PsA. Data from 1916 subjects who received placebo or upadacitinib were included in the safety E-R analyses.

The adverse events (AEs) and changes in laboratory parameters evaluated for relationships with upadacitinib exposures were:

- Neutropenia Grade 3 or higher (total neutrophils count < 1 × 10^9/L) at Week 24 (LOCF)
- Lymphopenia Grade 3 or higher (total lymphocytes count < 1 × 10^9/L) at Week 24 (LOCF)
- Lymphopenia Grade 4 (total lymphocytes count < 0.5 × 10^9/L) at Week 24 (LOCF)

- Haemoglobin decrease from baseline by > 2 g/dL (LOCF)
- Haemoglobin decrease from baseline by > 2 g/dL and < lower limit for normal [females: 11.5 g/dL and males: 12.5 g/dL] at Week 24 (LOCF)
- Haemoglobin < 8 g/dL at Week 24 (LOCF)
- Herpes Zoster infection anytime through 24 weeks
- Serious infections anytime through 24 weeks
- Pneumonia anytime through 24 weeks

Missing laboratory parameter values at Week 24 were imputed using the LOCF method. If there was no reportable value at any time (i.e., LOCF imputation cannot be applied), the laboratory parameter was flagged as missing ("–99") and excluded from the analysis.

Methods

As with efficacy endpoints, the relationships between upadacitinib exposures and safety endpoints were first explored using quartile plots followed by logistic regression analyses (Equation 5). Upadacitinib C_{avg} was used as the exposure metric. Safety endpoints exhibiting a statistically significant exposure effect were evaluated further using separate exposure-response models (linear, E_{max} and sigmoid E_{max}).

In addition to using C_{avg} as the upadacitinib exposure parameter in the logistic regression models, parameters of the final statistically significant models for safety endpoints were re-estimated using upadacitinib C_{max} (individual estimates from the PPK model) to enable simulation of the effect of changes in upadacitinib C_{max} on the probability of occurrence of the different adverse events or changes in laboratory parameters. Adequacy of model fits with C_{max} as exposure metric was confirmed before simulations.

Covariate modelling for safety endpoints was conducted as with efficacy endpoints.

The final logistic regression models developed for safety were used to conduct simulations to predict the percentage of subjects experiencing each of the safety endpoints following treatment with placebo, upadacitinib 15 mg QD, and upadacitinib 30 mg QD regimens and for scenarios of 25%, 50%, and 75% increase from target 15 mg QD and 30 mg QD exposures.

As with efficacy analyses, the simulations incorporated inter-individual variability in upadacitinib PK and covariate distributions by resampling exposures and covariates from the subjects enrolled in the Phase 3 Studies M15-554 and M15-572. The variabilities associated with the precision of the parameter estimates in the logistic regression models were also included in the simulations by sampling the parameters from a multivariate random normal distribution with means and covariance terms that were estimated in the logistic regression models. All simulations were conducted with 500 replicates for N = 300 subjects at each treatment group. The percentage of subjects predicted to experience each of the safety endpoints were then calculated for each replicate, and median and 95% CI were calculated across all the replicates.

Results

Exploratory E-R quartile plots for the safety endpoints are shown in Figure 15. Subjects were binned according to their individual predicted C_{avg} into quartiles, and the percent of subjects with specific safety events/laboratory changes were plotted in each quartile.

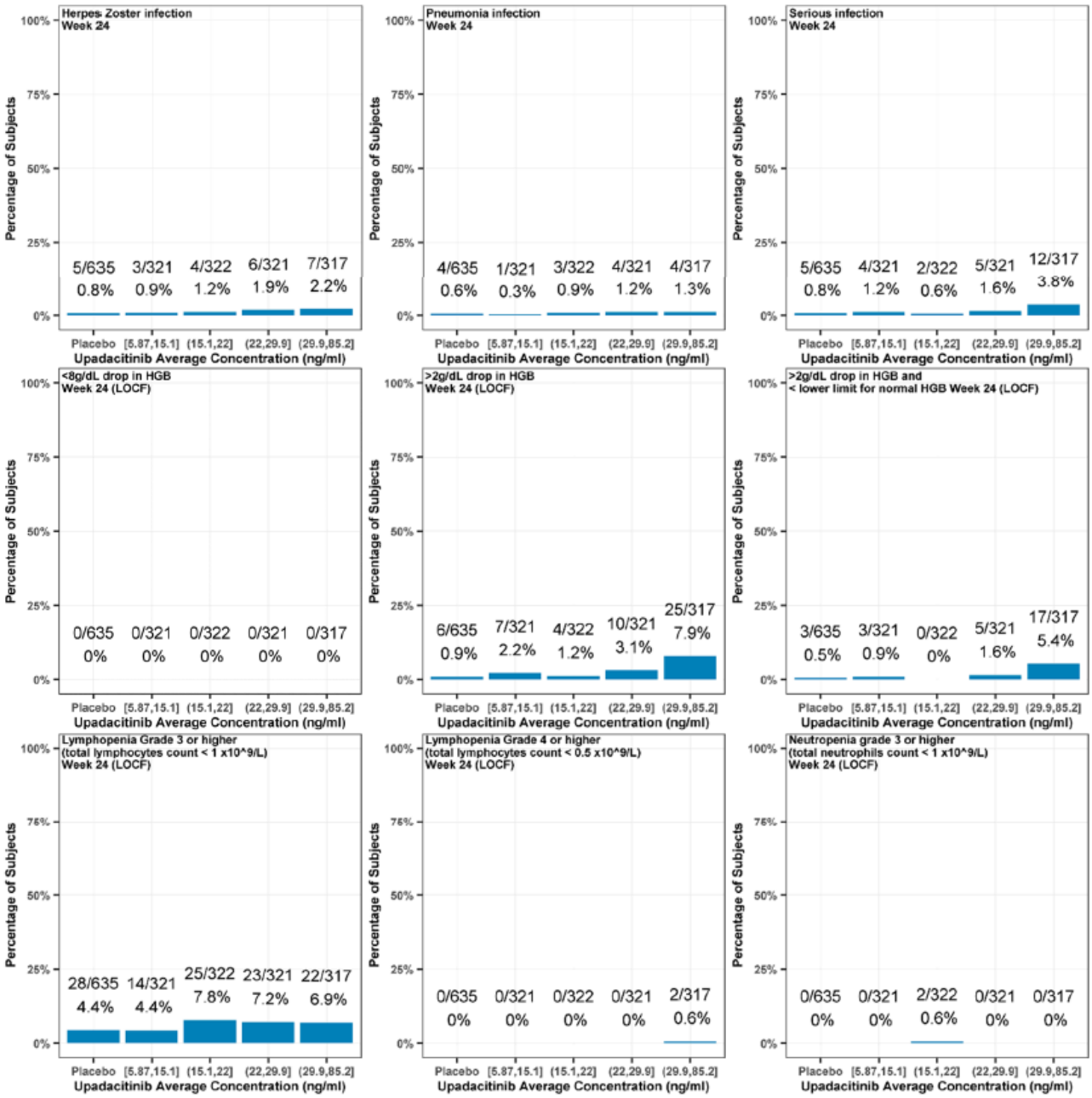


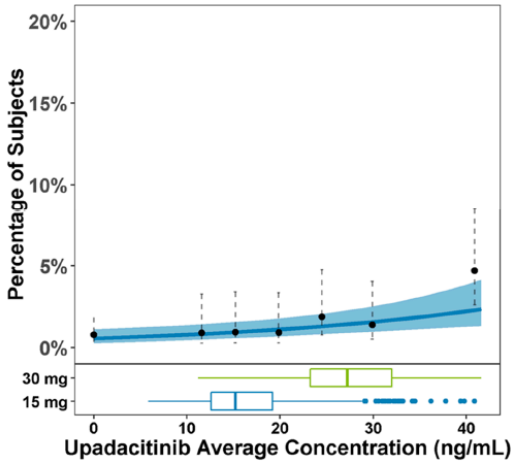
Figure 15 Exploratory Quartile Plots for Observed Safety Endpoints at Week 24 vs Predicted Upadacitinib Cavg

For the following endpoints, a logistic regression model could not be fitted due to lack of observations: haemoglobin < 8 g/dL at Week 24, lymphopenia Grade 4, and neutropenia Grade 3 or higher. No statistically significant relationship was observed between upadacitinib C_{avg} and the percentage of subjects who experienced herpes zoster infection, pneumonia or lymphopenia Grade 3 or higher at Week 24; hence, these endpoints were not analysed further.

There was a statistically significant relationship between upadacitinib C_{avg} and the percentage of subjects who experienced serious infections up to Week 24, > 2 g/dL haemoglobin decrease from baseline at Week 24, or > 2 g/dL haemoglobin decrease from baseline with haemoglobin < lower limit for normal at Week 24; these endpoints were evaluated further.

The relationship between upadacitinib C_{avg} and the percentage of subjects experiencing serious infection was best described by a linear model with intercept. Covariate analysis demonstrated that

subject's age is a significant covariate on intercept. Final model fit is shown in Figure 16 and summary of the model parameters are shown in Table 13.



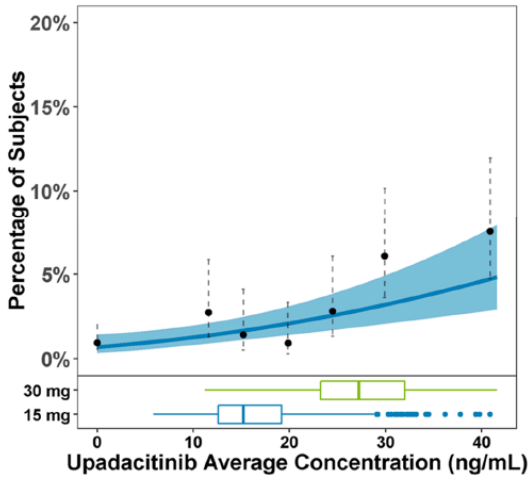
Blue solid line: Median predicted response. **Blue shaded area**: 95% confidence intervals of the predicted response. **Dots and error bars**: Median and 95% binomial CIs of binned observed rates.

Figure 16 Observed and Model-Predicted Percentage of Subjects with Serious Infections up to Week 24 vs predicted upadacitinib Cavg.

Table 13 Final Model Parameter Estimates of the Logistic Regression Model for the Relationship between Predicted Upadacitinib C_{avg} and Serious Infection up to Week 24

Parameter	Estimate	95% CI
Intercept	–5.19	–5.90; –4.49
Slope	0.04	0.01; 0.06
Age on Intercept	0.07	0.03; 0.10

The relationship between upadacitinib C_{avg} and the percentage of subjects experiencing > 2 g/dL decrease in haemoglobin from baseline was best described by an E_{max} with intercept model. Covariate analysis demonstrated that baseline haemoglobin was a significant covariate on intercept and subject's age was a statistically significant covariate on EC_{50}. Final model fit is shown in Figure 17 and final model parameters are shown in Table 14.



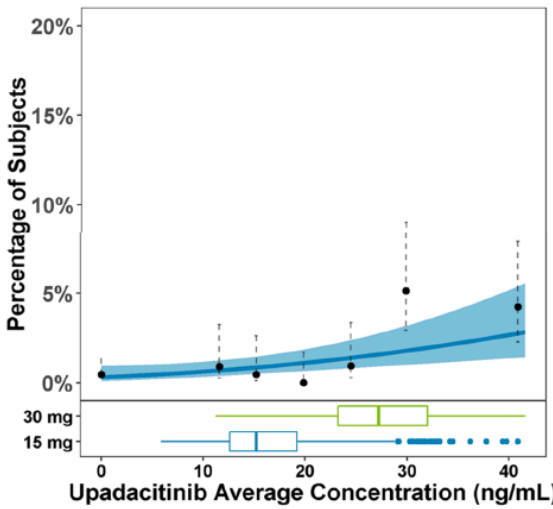
Blue solid line: Median predicted response. **Blue shaded area**: 95% confidence intervals of the predicted response. **Dots and error bars**: Median and 95% binomial CIs of binned observed rates.

Figure 17 Observed and Model-Predicted Percentage of Subjects with > 2 g/dL Decrease in Haemoglobin up to Week 24 vs predicted upadacitinib Cavg.

Table 14 Final Model Parameter Estimates of the Logistic Regression Model for the Relationship between Predicted Upadacitinib C_{avg} and Subjects with Decrease > 2 g/dL in Haemoglobin up to Week 24

Parameter	Esti	95% CI
Intercept	−4.97	−5.71; −4.23
E_{max}	6.84	2.48; 18.8
EC_{50}	102	19.2; 539
Age on EC_{50}	−2.51	−4.39; −0.63
Baseline HBG on Intercept	0.50	0.28; −0.71

The relationship between upadacitinib C_{avg} and the percentage of subjects with PsA experiencing haemoglobin (Hb) decrease from baseline > 2 g/dL with Hb < lower limit for normal at Week 24 was best described by E_{max} with intercept model. Covariate analysis demonstrated that subject's age on EC_{50} was the only statistically significant covariate of this model. Final model fit is shown in Figure 18 and final model parameters are shown in Table 15.



Blue solid line: Median predicted response. **Blue shaded area**: 95% confidence intervals of the predicted response. **Dots and error bars**: Median and 95% binomial CIs of binned observed rates.

Figure 18 Observed and Model-Predicted Percentage of Subjects with Haemoglobin Decrease from Baseline > 2 g/dL with Hb < Lower Limit for Normal up to Week 24 vs predicted upadacitinib Cavg.

Table 15 Final Model Parameter Estimates of the Logistic Regression Model for the Relationship Between Predicted Upadacitinib C_{avg} and Subjects with Haemoglobin Decrease from Baseline > 2 g/dL with Haemoglobin < Lower Limit for Normal up to Week 24

Parameter	Estimate	95% CI
Intercept	–5.79	–6.94; –4.65
Emax	6.95	2.92; 16.6
EC_{50}	86.5	16.2; 463
Age on EC_{50}	–2.82	–5.16; –0.48

Exposure-Safety Models with C_{max}

Each of the three safety final C_{avg} logistic regression analyses were re-run with upadacitinib C_{max} and all parameters were re-estimated. Observed and model-predicted percentage of subjects experiencing each of the three safety events versus upadacitinib C_{max} are shown in Figure 19. Summary of the model parameters are shown in Table 16.

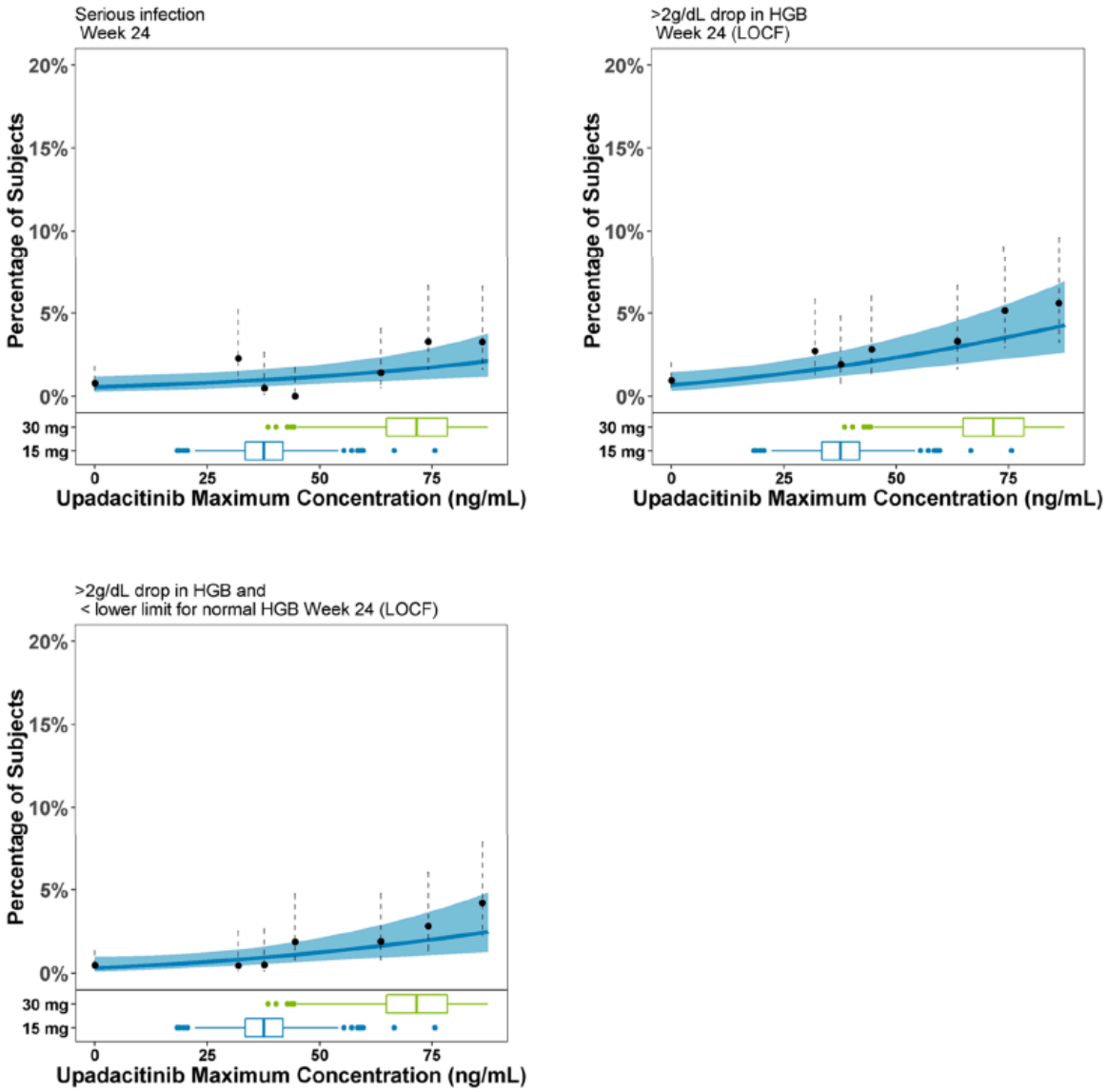


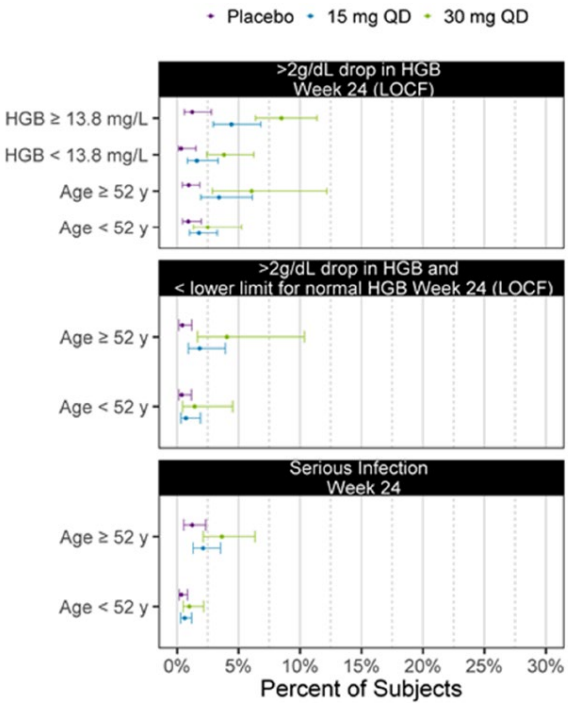
Figure 19 Observed and Model-Predicted Percentage of Subjects with Serious Infections, Hb Decrease >2 g/dL and Decrease in Hb from Baseline by >2 g/dL with Hb< Lower Limit for Normal up to Week 24

Table 16 Final Model Parameter Estimates for Logistic Regression Models of Predicted Upadacitinib C_{max} and Safety Variables at Week 24

Parameter	Estimate	95% CI
Serious Infection		
Intercept	–5.20	–5.96; –4.43
Slope	0.02	0.005; 0.03
Age on Intercept	0.07	0.03; 0.10
Hemoglobin Decrease > 2 g/dL from Baseline		
Intercept	–4.99	–5.76; –4.21
E_{max}	5.68	1.89; 17.1
EC_{50}	177	28.7; 1095
Age on EC_{50}	–2.74	–5.05; –0.42
Baseline HBG on Intercept	0.51	0.29; 0.73
Hemoglobin Decrease > 2 g/dL from Baseline and Hemoglobin < Lower Limit for Normal		
Intercept	–5.80	–6.99; –4.61
E_{max}	6.29	2.25; 17.6
EC_{50}	172	26.5; 1113
Age on EC_{50}	–3.04	–5.89; –0.18

Simulations

The final logistic regression models were used to predict the probability of serious infections and haemoglobin decreases for placebo, upadacitinib 15 mg and 30 mg QD regimen at Week 24 stratified by the significant covariates in the final logistic regression models (Figure 20).



Dots = median response; **Lines** = 90% CI. Continuous covariates are split by median values.

Figure 20 Model-predicted Probability of Serious Infections and Decreases in Haemoglobin for Placebo, 15 mg and 30 mg QD Regimen at Week 24 Stratified by Covariate Subgroups

Furthermore, final logistic regression models for serious infections and haemoglobin decreases were also employed to perform simulations to predict the occurrence of the safety occurrences following 15 mg QD and 30 mg QD regimen of upadacitinib at Week 24. The simulated percentage of subjects for each endpoint following treatment with placebo, upadacitinib 15 mg QD, and upadacitinib 30 mg QD are shown in Table 17.

Table 17 Model-Simulated Percentage of Subjects Experiencing Clinically Relevant Decreases in Haemoglobin or Serious Infections at Week 24

		Simulated Percentage of Subjects Based on Modeling	
Scenario	**Median C_{avg} (ng/mL)**	**Median**	**90% CI**
Percentage of Subjects with > 2 g/dL Decrease from Baseline in Hemoglobin			
Placebo	0	1%	(0% – 2%)
15 mg QD	15	3%	(1% – 4%)
30 mg QD	29	4%	(2% – 7%)
Percentage of Subjects with > 2 g/dL Decrease from Baseline in Hemoglobin and < Normal Hemoglobin levels			
Placebo	0	0%	(0% – 2%)
15 mg QD	15	1%	(0% – 3%)
30 mg QD	29	3%	(1% – 6%)
Percentage of Subjects with Serious Infections			
Placebo	0	1%	(0% – 2%)
15 mg QD	15	2%	(0% – 3%)
30 mg QD	29	2%	(1% – 4%)

The exposure-response models for safety were utilized to simulate the effects of increase in upadacitinib plasma exposures due to different intrinsic and extrinsic factors on the percentage of subjects with serious infections and decreases in haemoglobin > 2 g/dL at Week 24. Scenarios for increases in exposures by 25% to 75% were simulated which cover the effects of all evaluated intrinsic and extrinsic factors (75% reflect increase in exposures with strong CYP3A inhibitors). The simulations were conducted for increases in upadacitinib C_{avg} and C_{max} (Table 18). The results are overall consistent with previous analyses in RA patients.

Table 18 Model-Simulated Percentage of Subjects Experiencing Safety Outcomes with Increased Upadacitinib C_{avg} or C_{max} Relative to 15 mg QD Dose.

Scenario	Median Cavg or Cmax (ng/mL)	Simulated Percentage of Subjects	
		Median	90% Confidence Interval
Percentage of Subjects with > 2 g/dL Decrease from Baseline in Haemoglobin			
Cavg			
15 mg QD	15	2.6%	(0.7% - 4.4%)
25% Higher Upadacitinib C_{avg}	19	3.3%	(1.5% - 5.6%)
50% Higher Upadacitinib C_{avg}	23	3.7%	(1.9% - 5.9%)
75% Higher Upadacitinib C_{avg}	27	4.8%	(2.2% - 7.8%)
Cmax			
15 mg QD	38	2.6%	(1.1% - 4.5%)
25% Higher Upadacitinib C_{max}	47	3.0%	(1.1% - 5.2%)
50% Higher Upadacitinib C_{max}	56	3.3%	(1.5% - 5.9%)
75% Higher Upadacitinib C_{max}	66	4.1%	(1.5% - 7.8%)
Percentage of Subjects with > 2 g/dL Decrease from Baseline in Haemoglobin and < Normal Haemoglobin Levels			
Cavg			
15 mg QD	15	1.1%	(0.4% - 3.0%)
25% Higher Upadacitinib C_{avg}	19	1.5%	(0.4% - 3.3%)
50% Higher Upadacitinib C_{avg}	23	1.9%	(0.4% - 4.1%)
75% Higher Upadacitinib C_{avg}	27	2.6%	(0.7% - 4.8%)
Cmax			
15 mg QD	38	1.1%	(0.4% - 2.6%)
25% Higher Upadacitinib C_{max}	47	1.5%	(0.4% - 3.3%)
50% Higher Upadacitinib C_{max}	56	1.9%	(0.4% - 3.7%)
75% Higher Upadacitinib C_{max}	66	2.2%	(0.7% - 4.8%)
Percentage of subjects with Serious Infection			
Cavg			
15 mg QD	15	1.5%	(0.4% - 3.0%)
25% Higher Upadacitinib C_{avg}	19	1.5%	(0.4% - 3.0%)
50% Higher Upadacitinib C_{avg}	23	1.9%	(0.7% - 3.7%)
75% Higher Upadacitinib C_{avg}	27	2.2%	(0.7% - 4.1%)
Cmax			
15 mg QD	38	1.5%	(0.4% - 3.0%)
25% Higher Upadacitinib C_{max}	47	1.5%	(0.4% - 3.0%)
50% Higher Upadacitinib C_{max}	56	1.9%	(0.7% - 3.3%)
75% Higher Upadacitinib C_{max}	66	2.2%	(0.7% - 3.7%)

2.3.5. Discussion on clinical pharmacology

Analytical methods

The analytical phase of bioanalysis in the BE-study were acceptable to the CHMP. This conclusion is also applicable to the plasma concentrations determined for studies M15-554 and M15-572.

Bioequivalence

Results of study M20-017 Part 1 demonstrated bioequivalence between upadacitinib 15 mg extended-release (ER) tablet market-image formulation (formulation currently marketed Rinvoq 15 mg

prolonged-release tablet) and 15 mg ER tablet Phase 3 formulation (formulation used in Phase 3 PsA studies) under fasting conditions and after a high-fat/high-calorie meal.

Bioequivalence was demonstrated not only for conventional primary PK parameters C_{max}, AUC_t and AUC_{inf}, but also for partial AUCs (AUC_{0-12} and AUC_{12-t}). Although AUC_{0-12} and AUC_{12-t} were not pre-specified PK parameters in the protocol, they are recommended parameters in EMA guidance (*Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms* EMA/CHMP/EWP/280/96 Rev1) and provide supportive evidence for conclusion of bioequivalence between the formulations. Demonstration of bioequivalence in a multiple dose study is not required for upadacitinib 15 mg ER tablet, because the mean AUC_t after a single dose covers more than 90% of mean AUC_{inf}, and consequently a low extent of accumulation is expected (see EMA/CHMP/EWP/280/96 Rev1 and assessment reports for Rinvoq marketing authorisation application). In addition, results for AUC_{0-12} and AUC_{12-t} support the conclusion of bioequivalence.

The PK sampling scheme adequately covered the absorption and elimination phases: C_{max} was not observed at the first sample for any subject and extrapolated AUC was less than 20% for each subject.

An interval of 4 days separated the doses between the four study periods. The washout period should have been longer because pre-dose upadacitinib concentrations were observed in a few subjects (up to 0.2, 0.3, 0.3, and 0.3 ng/mL after administration of Regimen A, B, C and D, respectively; approximately 0.6 to 1.0 % of mean C_{max}). This is not expected to affect the overall conclusions of the study and further analyses were not requested by the CHMP. However, the MAH is recommended to plan future studies more carefully.

Population PK analysis

The methodology for development of the population PK model for patients with PsA is appropriate.

The covariates previously identified in patients with RA were statistically important also in PsA population: patient population (patients versus healthy), creatinine clearance (CrCL), and baseline bodyweight on CL/F; and body weight on Vc/F. No additional covariates were identified. Weight and CrCL are correlated, which can influence the estimated covariate effects. The CHMP did not pursue this point; it is reasonable to use the same model structure as in the previous model (in patients with RA) to facilitate the comparison of the two populations. However, in future population PK analyses, the MAH should consider to re-parametrise the model to avoid correlation between CrCL and body weight. The CL/F ratio of patients compared to healthy subjects was comparable for PsA and RA patients (0.756 and 0.754, respectively), which supports the statement in the product information that upadacitinib pharmacokinetics are consistent between RA and PsA patients.

Interactions

The population PK analysis suggested no effect by DMARDs methotrexate, apremilast, hydroxychloroquine, sulfasalazine, and leflunomide on PK of upadacitinib. This conclusion is supported by the MAH's review on mechanistic plausibility of pharmacokinetic DDI between upadacitinib and the aforementioned DMARDs.

Exposure-response analyses

Logistic regression models with treatment effect and exposure effect function were used to describe the efficacy and safety of upadacitinib. Predicted upadacitinib C_{avg} was used as the primary exposure parameter, predicted C_{max} was also tested in the safety analyses.

Several efficacy endpoints were tested, including ACR20/50/70 at week 12 and 24, PASI75 at week 16 and 24, and sIGA at weeks 16 and 24. Time-effect was not formally evaluated as separate models were developed for week 12/16 and 24 data. However, the methodology is sufficient for the intended

use. The treatment effect (use of upadacitinib compared with placebo) was robustly associated with better clinical response. Of note, higher exposure was only modestly or not at all associated with better clinical response.

Several safety endpoints were included in the exposure-response analyses. A statistically significant relationship between upadacitinib C_{avg} (and upadacitinib C_{max}) and the percentage of subjects who experienced serious infections up to Week 24, > 2 g/dL haemoglobin decrease from baseline at Week 24, or > 2 g/dL haemoglobin decrease from baseline with haemoglobin < lower limit for normal at Week 24. No statistically significant relationship was observed between predicted upadacitinib concentration and the percentage of subjects who experienced herpes zoster infection, pneumonia or lymphopenia Grade 3 or higher. There were too few (n ≤ 2) cases of haemoglobin < 8 g/dL at Week 24, lymphopenia Grade 4, and neutropenia Grade 3 or higher to conduct E-R analyses for these safety endpoints.

Exposures achieved with upadacitinib 15 mg QD are approximately at the plateau for the majority of evaluated efficacy endpoints. Clinically meaningful improvement of efficacy is not expected with the higher upadacitinib dose (30 mg QD). On the other hand, the probability of occurrence of serious infections and decrease in haemoglobin was increased with increasing exposure to upadacitinib. The MAH concluded that the dose of 15 mg QD provides the optimal benefit-risk balance in subjects with PsA and the higher dose (30 mg) tested in the Phase 3 clinical studies is not applied for. The CHMP was of the opinion that the clinical pharmacology data support those conclusions.

2.3.6. Conclusions on clinical pharmacology

Upadacitinib pharmacokinetics are consistent between rheumatoid arthritis and psoriatic arthritis patients.

The proposed dose regimen of upadacitinib 15 mg QD was considered appropriate to the CHMP.

2.4. Clinical efficacy

2.4.1. Dose response study

No specific dose-response studies were performed for treatment of PsA. The currently approved dose in the treatment of rheumatoid arthritis is 15 mg QD.

The dosages studied in the pivotal studies for PsA, upadacitinib 15 mg and upadacitinib 30 mg QD, are the same doses as in the pivotal studies for rheumatoid arthritis.

The MAH proposes the same ER formulation of upadacitinib 15 mg QD for the treatment of adult patients with active PsA, which is marketed for treatment of patients with RA.

2.4.2. Main studies

The clinical development pivotal programme supporting the efficacy of upadacitinib in PsA is composed of 2 randomized, multi-centre, double-blind, parallel-group Phase 3 studies.

- **Study M15-572** investigates upadacitinib in subjects who have an inadequate response or intolerance to non-biologic DMARDs (conventional synthetic DMARDs [csDMARDs] and/or targeted synthetic disease-modifying anti-rheumatic drug [tsDMARDs]) or had a contraindication for non-biologic DMARDs. Study M15-572 evaluates upadacitinib versus (vs.)

placebo and adalimumab, with or without background non-biologic DMARDs, in a non-biologic DMARD-IR population. Radiographic assessment was included in Study M15-572 to evaluate the effect of upadacitinib treatment on progression of structural joint damage in a non-biologic DMARD-IR population.

- **Study M15-554** evaluates upadacitinib in subjects who have an inadequate response or intolerance to biologic disease-modifying anti-rheumatic drugs (bDMARDs). Study M15-554 is a placebo-controlled study. Study M15-554 evaluates upadacitinib with or without background non-biologic DMARDs in a bDMARD-IR population without regard to the nature and number of prior bDMARDs.

Long-term efficacy is assessed in each individual study.

An overview of the Phase 3 studies is given in Table 19.

Table 19 Overview of Upadacitinib Clinical Development Program for PsA – Pivotal Phase 3 Studies

	M15-572 (Select PsA1)	M15-554 (Select PsA2)
Population	non-biologic DMARD-IR[a]	bDMARD-IR
Background	≤ 2 non-biologic DMARDs[b]	≤ 2 non-biologic DMARDs[b]
Comparator	adalimumab, placebo	placebo
Upadacitinib Dose (Extended-Release Formulation)	15 mg QD 30 mg QD	15 mg QD 30 mg QD
Duration	Period 1: 56 weeks (24 weeks placebo-controlled and 56 weeks adalimumab-controlled) Period 2: Long-term extension (adalimumab-controlled) (up to a total treatment duration of approximately 3 years)	Period 1: 56 weeks (24 weeks placebo-controlled) Period 2: Long-term extension (up to a total treatment duration of approximately 3 years)
Study Blind	Double-blind through Week 24 followed by an additional 32 weeks of blinded active comparator-controlled treatment (Weeks 24 – 56). Sponsor was unblinded after Week 24 database lock. Sites and subjects remain blinded until the last subject completes Week 56 in Period 1.	Double-blind through Week 24 followed by an additional 32 weeks of blinded treatment (Weeks 24 – 56). Sponsor was unblinded after Week 24 database lock. Sites and subjects remain blinded until the last subject completes Week 56 in Period 1.
Number of subjects randomized/exposed to at least 1 dose of study drug	1705/1704	642/641
Number of subjects randomized to each treatment group	upadacitinib 15 mg QD: N = 430 upadacitinib 30 mg QD: N = 423 adalimumab (40 mg every other week [eow]): N = 429 placebo: N = 423	upadacitinib 15 mg QD: N = 211 upadacitinib 30 mg QD: N = 219 placebo: N = 212
Primary Efficacy Endpoint	ACR20 response at Week 12[c]	ACR20 response at Week 12[c]
Status	Ongoing	Ongoing

a. Prior exposure to any biologic immunomodulation agent was not permitted.

b. Background non-biologic DMARD therapy is not required during the study.

c. ACR20 response rate was determined based on 20% or greater improvement in tender joint count (TJC) and swollen joint count (SJC) and ≥ 3 of the 5 measures of Patient's Assessment of Pain (Numeric Rating Scale [NRS]), Patient's Global Assessment of Disease Activity (PtGA) (NRS), Physician's Global Assessment (PGA) (NRS), HAQ-DI, and hsCRP.

Since both studies were ongoing at time of submission, interim CSRs are provided in the submission as outlined in Table 20.

Table 20 Upadacitinib PsA Individual Study Efficacy Data

Study	CSRs Included in Submission		Data Included in ISE	
	Data	Cutoff Date	Data	Cutoff Date
	Pivotal Phase 3 Studies			
M15-572 (non-biologic DMARD-IR) Select PsA1	Data through Week 24 from all subjects and long-term data (through Week 56) from available subjects	13 December 2019	Data through Week 24 from all subjects who received upadacitinib, adalimumab, or placebo (only upadacitinib or placebo for integrated analyses)	Same as CSR
M15-554 (bDMARD-IR) Select PsA2	Data through Week 24 from all subjects and long-term data (through Week 56) from available subjects	09 October 2019	Data through Week 24 from all subjects who received upadacitinib or placebo	Same as CSR

The MAH provided during the procedure a revised interim CSR for study M15-554, dated 16 June 2020. The purpose of the revised CSR is to correct the text describing subjects with disseminated herpes zoster.

After the original submission, all subjects in both Phase 3 Studies M15-572 and M15-554 reached Week 56 or prematurely discontinued. Results through Week 56 were provided for all endpoints proposed for labelling during the procedure.

Methodology

The methodology is described together for both Phase 3 studies. Results of the studies are described separately for each study and integrated efficacy analyses are also presented.

Study designs

Study M15-572

A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (DMARD) – SELECT – PsA 1.

Study design is presented in Figure 21.

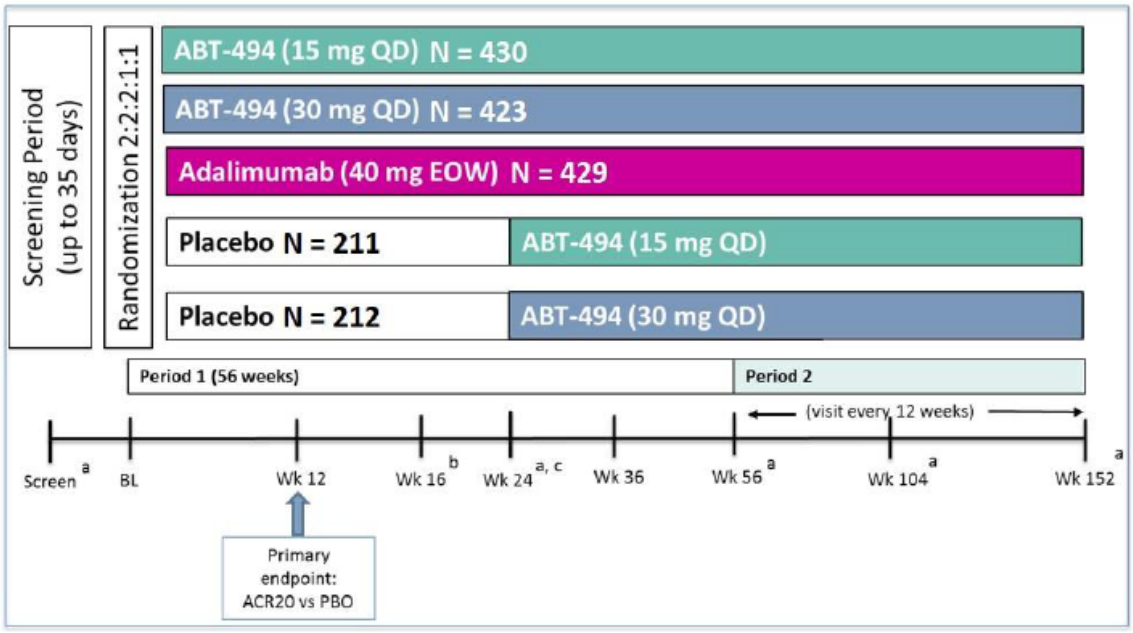
The study includes

- a 35-day screening period;
- a 56-week blinded period which includes 24 weeks of randomized, double-blind, placebo-controlled and active comparator-controlled treatment followed by 32 weeks of active comparator-controlled upadacitinib (Period 1);
- a long-term extension period of up to a total treatment duration of approximately 3 years ([blinded until the last subject completes the last visit of Period 1] Period 2); and

- a 30-day follow-up call or visit; and a 70-day follow-up call.

Period 1 is designed to compare the safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo and versus ADA for the treatment of signs and symptoms of PsA, including the prevention of structural progression, in subjects with moderately to severely active PsA who are DMARD-IR.

Period 2 is an open-label (blinded until the last subject completes the last visit of Period 1), long-term extension of up to a total treatment duration of approximately 3 years to evaluate the safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.



ABT-494 = upadacitinib; ACR20 = American College of Rheumatology 20% response; BL = baseline; PBO = placebo; QD = once daily; Wk = week

a. All subjects will receive x-rays of hands and feet at screening, Wk 24, Wk 56, Wk 104, and Wk 152/PD.

b. At Week 16, rescue therapy will be offered to subjects classified as non-responders (defined as not achieving at least 20% improvement in either or both tender joint count (TJC) and swollen joint count (SJC) at both Week 12 and Week 16) as described in Protocol Section 5.2.3.4.

c. At Week 24, all placebo subjects will switch to upadacitinib 15 mg QD or 30 mg QD (1:1 ratio) regardless of response.

Note: Sample sizes represent actual number of subjects randomized to each treatment sequence.

Figure 21 Study design of study M15-572

Study M15-554

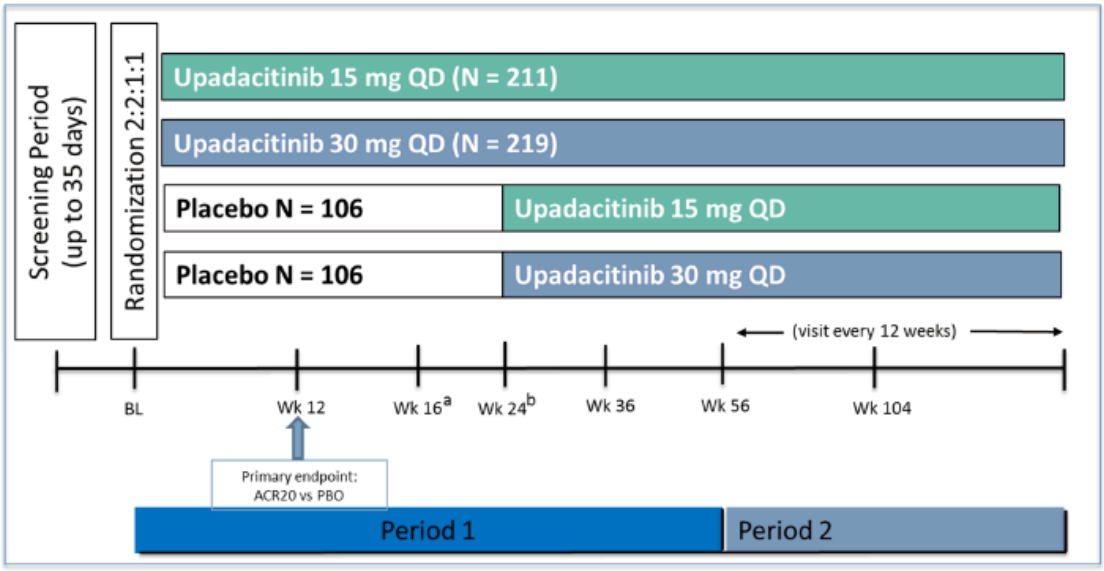
A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease-Modifying Anti-Rheumatic Drug (bDMARD) – SELECT – PsA 2

Study design is presented in Figure 22.

The study includes the following periods:

- a 35-day screening period;

- a 24-week blinded randomized, double-blind, parallel-group, placebo-controlled period followed by an additional 32 weeks of blinded upadacitinib treatment (Weeks 24 – 56) (Period 1);
- a long-term extension period of up to a total treatment duration of approximately 3 years (blinded until the last subject completes the last visit of Period 1 - Period 2); and
- a 30-day follow-up call or visit.



ACR20 = American College of Rheumatology 20% response; BL = baseline; PBO = placebo; QD = once daily; Wk = week

a. At Week 16, rescue therapy was to be offered to subjects classified as non-responders (defined as not achieving at least 20% improvement in either or both tender joint count (TJC) and swollen joint count (SJC) at both Week 12 and Week 16) as described in Protocol Section 5.2.3.4.

b. At Week 24, all placebo subjects were to switch to upadacitinib 15 mg QD or 30 mg QD (1:1 ratio) regardless of response.

Figure 22 Study design of study M15-554

Since the original submission of the variation application, Study M15-572 protocol has been amended to extend its long-term extension period from 3 years to 5 years (Protocol Amendment Version 6, dated 15 May 2020, Voluntary Harmonisation Procedure (VHP) approval on 10 July 2020).

Study M15-554 protocol has been amended in selected countries (Belgium, Czech Republic, France, Greece, Hungary, Japan, New Zealand, and Portugal) in order to provide continued upadacitinib therapy after Week 152 until regulatory approval, and/or applicable local reimbursement approval of the study drug, or at such time that development or pursuit of regulatory approval is discontinued (Protocol Amendment Version 7.1, dated 23 July 2020). Hence, final results for both studies are anticipated to be submitted in year 2025. The submission of the results for the long term extension for both studies is included in the RMP.

Study participants

Both pivotal, Phase 3 studies enrolled adult male or female subjects at least 18 years old who were diagnosed with PsA with symptom onset at least 6 months prior to the Screening Visit and had moderately to severely active disease. Stable doses of NSAIDs, acetaminophen/paracetamol, low-

potency opiates (tramadol or combination of acetaminophen and codeine or hydrocodone), oral corticosteroids (equivalent to prednisone ≤ 10 mg/day) were allowed. Changes in the upadacitinib dose were not permitted during either study in order to avoid confounding of interpretation of the safety results.

Study M15-572 evaluates upadacitinib in subjects who have an inadequate response (IR) or intolerance to non-biologic DMARDs (conventional synthetic DMARDs [csDMARDs] and/or tsDMARDs) or had a contraindication for non-biologic DMARDs as follows: IR to ≥ 1 non-biologic DMARD (MTX, sulfasalazine [SSZ], leflunomide, cyclosporine, apremilast, bucillamine or iguratimod) or an intolerance to or contraindication for DMARDs as defined by the investigator prior to the screening visit. Subjects were not to have had prior exposure to any biologic immunomodulation agents, JAK inhibitors, current treatment with > 2 non-biologic DMARDs or use of DMARDs other than protocol-specified DMARDs.

In study M15-572, at screening, subjects were to have had either ≥ 1 erosion on x-ray as determined by central imaging review or high-sensitivity C-reactive protein (hs-CRP) > laboratory defined upper limit of normal (ULN). The requirements for existing erosions in X-rays and/or higher CRP levels were selected for this study only in order to enrol a population appropriate for assessment of radiographic progression and to increase the power for detection of a treatment effect for upadacitinib on the radiographic endpoints.

Study M15-554 evaluates upadacitinib in subjects who have an IR or intolerance to biologic disease-modifying anti-rheumatic drugs (bDMARDs) as follows: IR (lack of efficacy after a minimum 12 week duration of therapy) or intolerance to treatment with at least 1 bDMARD.

Subjects must have discontinued all bDMARDs prior to the first dose of study drug. Subjects who need to discontinue bDMARDs prior to the Baseline Visit to comply with this inclusion criterion must follow the procedure specified below or at least five times the mean terminal elimination half-life of a drug: ≥ 4 weeks for etanercept; ≥ 8 weeks for adalimumab, infliximab, certolizumab, golimumab, abatacept, tocilizumab, and ixekizumab;≥ 16 weeks for secukinumab;≥ 12 weeks for ustekinumab; ≥ 1 year for rituximab OR ≥ 6 months if B cells have returned to pre-treatment level or normal reference range (local lab) if pre-treatment levels are not available. Subject who is on current treatment with concomitant non-biologic DMARDs at study entry must be on ≤ 2 non-biologic DMARDs (except the combination of MTX and leflunomide) at the following doses: MTX (≤ 25 mg/week), SSZ (≤ 3000 mg/day), leflunomide (LEF) (≤ 20 mg/day), apremilast (≤ 60 mg/day), HCQ (≤ 400 mg/day), bucillamine (≤ 300 mg/day) and iguratimod (≤ 50 mg/day) for ≥ 12 weeks and at stable dose for ≥ 4 weeks prior to the Baseline Visit. No other DMARDs are permitted during the study.

In both studies, subjects were to have had active disease at baseline defined as ≥ 3 tender joints (based on 68 joint counts) and ≥ 3 swollen joints (based on 66 joint counts) at screening and baseline visits. Clinical diagnosis of PsA was to include symptom onset at least 6 months prior to the screening visit and fulfilment of the Classification Criteria for PsA (CASPAR) criteria. Diagnosis of active plaque psoriasis or documented history of plaque psoriasis was also required.

In both studies, exclusion criteria included current treatment with > 2 non-biologic DMARDs or use of DMARDs other than MTX, SSZ, LEF, apremilast, HCQ, bucillamine or iguratimod or use of MTX in combination with LEF at Baseline. Subjects with prior exposure to JAKi were excluded.

Subjects were to have no history of fibromyalgia; any arthritis with onset prior to age 17 years; or current diagnosis of inflammatory joint disease other than PsA; prior history of reactive arthritis or axial SpA including ankylosing spondylitis and non-radiographic axial SpA were permitted if documentation of change in diagnosis to PsA or additional diagnosis of PsA was made.

Patients with current or past history of infection were excluded in both studies: history of recurrent or disseminated (even a single episode) herpes zoster; disseminated (even a single episode) herpes simplex; known invasive infection (e.g., listeriosis and histoplasmosis); active human immunodeficiency virus (defined as confirmed positive anti-HIV antibody (HIV Ab) test) or immunodeficiency syndrome ; active TB or meets TB exclusionary parameters; active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the Baseline Visit; chronic recurring infection and/or active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study; active HBV or HCV. For subjects in Japan only: Positive result of beta-D-glucan or two consecutive indeterminate results of beta-D-glucan (screening for pneumocystis jiroveci infection).

Subjects with history or current underlying medical diseases or problems including but not limited to the following were excluded: moderate to severe congestive heart failure; recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting; uncontrolled hypertension; recipient of an organ transplant which requires continued immunosuppression; gastrointestinal perforation (other than appendicitis or penetrating injury), diverticulitis, or significantly increased risk for GI perforation per investigator judgment; conditions that could interfere with drug absorption including but not limited to short bowel syndrome; any malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix; demyelinating disease such as Multiple Sclerosis or neurologic symptoms suggestive of demyelinating disease (including myelitis); clinically significant medical conditions or any other reason which in the opinion of the investigator would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug or would put the subject at risk.

Other exclusion criteria included e.g. to following:

- Use of the following concomitant psoriasis treatments within the specified timeframe: Oral retinoids within 4 weeks of the Baseline visit; Fumarates within 1 week of the Baseline Visit: Psoralens and Ultraviolet A (PUVA) within 4 weeks of the Baseline visit; Ultraviolet A (UVA) or Ultraviolet B (UVB); or Laser therapy within 2 weeks of the Baseline visit; All topical psoriasis treatments, including medicated shampoos, within 2 weeks of the Baseline visit. The following exceptions are allowed: Bland (without beta or alpha hydroxy acids, urea or salicylic acids) emollients, and low potency (Class VI or VII) topical corticosteroids on the palms, soles, face, inframammary area and groin only; and topical anti-itch treatment with no expected effect on psoriatic skin lesions.
- Systemic use of known strong cytochrome P450 (CYP) 3A inhibitors or strong CYP3A inducers from Screening through the last dose of the study drug
- Receipt of any live vaccine within 4 weeks (8 weeks in Japan) prior to the Baseline Visit, or expected need of live vaccination during study participation including at least 4 weeks (8 weeks in Japan) after the last dose of oral study drug, and including at least 70 days after the last dose of subcutaneous study drug.
- Subject has received oral or parenteral Traditional Chinese Medicines within 4 weeks prior to Baseline, has received opioid analgesics (except for tramadol or combination of acetaminophen and codeine or hydrocodone which are allowed) within 1 week prior to Baseline, or use of inhaled marijuana within 2 weeks prior to Baseline.
- History of an allergic reaction or significant sensitivity to constituents of the study drugs (including adalimumab or its excipients) and/or other products in the same class.

- History of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months preceding the Baseline Visit.
- Laboratory values meeting the following criteria within the Screening period:

  Serum aspartate transaminase (AST) > 2 × ULN; Serum alanine transaminase (ALT) > 2 × ULN; Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73 m2; Total white blood cell count (WBC) < 2,500/µL; Absolute neutrophil count (ANC) < 1,500/µL; Platelet count < 100,000/µL; Absolute lymphocyte count < 800/µL; Haemoglobin < 10 g/dL.
- Active skin disease other than psoriasis that would interfere with the assessment of psoriasis.
- Subject with extra-articular manifestations of PsA (e.g., PsO, uveitis, or IBD) that are not clinically stable for at least 30 days prior to study entry.
- Subject has had joint surgery at joints to be assessed within this study or has been treated with intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the preceding 8 weeks prior to the Baseline visit.
- Consideration by the Investigator, for any reason, that the subject is an unsuitable candidate to receive upadacitinib or adalimumab or subject has any contraindication to adalimumab, according to the local label.

Treatments

Study M15-572

Active study drugs in this study are upadacitinib and adalimumab. The different phases of the study and administration of study medication is given earlier in this AR in Figure 21 and later under the heading of Randomisation.

Study M15-554

The active study drug in this study is upadacitinib (see Figure 22 for the different phases of the study).

Objectives

The objectives of both studies are listed below. The studies were on-going at the time of the submission and the efficacy results were only available up to week 24 of both studies. During the procedure, results up to Week 56 were submitted.

Study M15-572

Period 1

Primary Objective

To compare the efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo and versus adalimumab (ADA) for the treatment of signs and symptoms of PsA in subjects with moderately to severely active PsA who have an inadequate response or intolerance to 1 or more non-biologic DMARD (DMARD-IR).

Secondary Objective

To compare the efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo for the prevention of structural progression in subjects with moderately to severely active PsA who have an inadequate response or intolerance to 1 or more non-biologic DMARD (DMARD-IR).

To compare the safety and tolerability of upadacitinib 15 mg QD and 30 mg QD versus placebo and versus adalimumab in subjects with moderately to severely active PsA who and have an inadequate response or intolerance to 1 or more non-biologic DMARD (DMARD-IR).

Period 2

To evaluate the long-term safety, tolerability and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.

Period 2 is ongoing and planned to last up to ~5 years for evaluation of long-term maintenance of efficacy and safety.

Study M15-554

Period 1

1. To compare the efficacy of upadacitinib 15 mg once daily (QD) and 30 mg QD versus placebo for the treatment of signs and symptoms in subjects with moderately to severely active PsA who have had an inadequate response or intolerance to bDMARDs (Bio-IR), and

2. To compare the safety and tolerability of upadacitinib 15 mg QD and 30 mg QD versus placebo in subjects with moderately to severely active PsA who have had an inadequate response or intolerance to bDMARDs.

The objective of ***Period 2*** is to evaluate the long-term safety, tolerability and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.

Period 2 is ongoing and planned to last up to ~3 years for evaluation of long-term maintenance of efficacy and safety.

Outcomes/endpoints

Primary efficacy endpoint

The primary efficacy endpoint in both studies is the proportion of subjects achieving ACR 20% response (ACR20) at Week 12.

- ACR20: standard criteria of American College of Rheumatology to evaluate the effectiveness of investigation drug in RA clinical trials reflecting improvement of response outcomes. ACR20 is defined as at least 20% improvement (compared to baseline values) in tender and swollen joint counts and at least 20 improvement in 3 of the remaining 5 core set measures (subject global assessment of pain, subject global assessment of disease activity, physician global assessment of disease activity, subject assessment of physical function and acute phase reactant hsCRP).

The multiplicity-adjusted primary and ranked key secondary endpoints for both studies are given in Table 21. The key multiplicity adjusted secondary efficacy endpoints are for each dose of upadacitinib vs. combined placebo unless noted otherwise.

Table 21 Primary and Ranked Key Secondary Endpoints for Pivotal Phase 3 Studies (Multiplicity-Adjusted)

	Study M15-572	Study M15-554
Primary Efficacy Endpoints	ACR20 response at Week 12	ACR20 response at Week 12
Ranked Key Secondary Efficacy Endpoints		
Ranking		
1	ΔHAQ-DI at Week 12	ΔHAQ-DI at Week 12
2	sIGA 0/1 at Week 16	sIGA 0/1 at Week 16
3	PASI 75 response at Week 16	PASI 75 response at Week 16
4	ΔSHS at Week 24[a]	ΔSF-36 PCS at Week 12
5	MDA at Week 24	ΔFACIT-F at Week 12
6	Resolution of enthesitis (LEI = 0) at Week 24	MDA at Week 24
7	ACR20 response at Week 12 (non-inferiority of upadacitinib vs. adalimumab)	ΔSAPS at Week 16
8	ΔSF-36 PCS at Week 12	
9	ΔFACIT-F at Week 12	
10	ACR20 response at Week 12 (superiority of upadacitinib vs. adalimumab)	
11	Resolution of dactylitis (LDI = 0) at Week 24	
12	ΔPatient's Assessment of Pain NRS at Week 12 (superiority of upadacitinib vs. adalimumab)	
13	ΔHAQ-DI at Week 12 (superiority of upadacitinib vs. adalimumab)	
14	ΔSAPS at Week 16	

ACR20 = American College of Rheumatology 20%; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; MDA = minimal disease activity; NRS = Numeric Rating Scale; PASI = Psoriasis Area Severity Index; PCS = Physical Component Summary; SAPS = Self-Assessment of Psoriasis Symptoms; SF-36 = 36-Item Short Form Health Survey; SHS = Sharp/van der Heijde Score (equivalent to van der Heijde modified Total Sharp Score [mTSS]); sIGA 0/1 = Static Investigator Global Assessment of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline; vs. = versus

Additional key secondary efficacy endpoints

Studies M15-572 and M15-554: ACR 50%/70% response (ACR50/70) at Week 12 and ACR20 response at Week 2.

Additional efficacy analyses included the following endpoints obtained at multiple scheduled time points during the course of the study:

Study M15-572

- Proportion of subjects with no radiographic progression defined as:
  - Change from baseline in SHS ≤ 0;
  - Change from baseline in SHS ≤ 0.5;
- Change from baseline in joint space narrowing (JSN) score and joint erosion score;

- Change from baseline in individual components of ACR response;
  - ○ Change from baseline in Tender Joint Count (TJC) (0 - 68);
  - ○ Change from baseline in Swollen Joint Count (SJC) (0 - 66);
  - ○ Change from baseline in Physician Global Assessment (PGA) - Disease Activity (NRS);
  - ○ Change from baseline in Patient's Global Assessment (PtGA) - Disease Activity (NRS);
  - ○ Change from baseline in Patient's Assessment of Pain Numerical Rating Scale (NRS);
  - ○ Change from baseline in Health Assessment Questionnaire - Disability Index (HAQ-DI);
  - ○ Change from baseline in high-sensitivity C-reactive protein (hs-CRP);
- ACR 20/50/70 response rates;
- Proportion of subjects achieving MDA;
- Change from baseline in Leeds Dactylitis Index (LDI) (for subjects with baseline LDI > 0);
- Change from baseline in dactylitis count (for subjects with baseline LDI > 0);
- Proportion of subjects with resolution of dactylitis (for subjects with baseline LDI > 0);
- Change from baseline in Leeds Enthesitis Index (LEI) (for subjects with baseline LEI > 0);
- Proportion of subjects with resolution of enthesitis defined as LEI = 0 (for subjects with baseline LEI > 0);
- Change from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index (for subjects with baseline SPARCC Enthesitis Index > 0);
- Proportion of subjects with resolution of enthesitis defined as SPARCC Enthesitis Index = 0 (for subjects with baseline SPARCC Enthesitis Index > 0);
- Change from baseline in total enthesitis count (for subjects with baseline total enthesitis count > 0);
- Proportion of subjects with resolution of enthesitis defined as total enthesitis count = 0 (for subjects with baseline total enthesitis count > 0);
- Psoriasis Area Severity Index 75, 90, 100 (PASI 75/90/100) response rates (for subjects with ≥ 3% BSA psoriasis at baseline);
- Proportion of subjects achieving sIGA 0/1 (for subjects with baseline sIGA ≥ 2);
- Change from baseline in BSA-Ps (for subjects with baseline BSA-Ps > 0);
- Modified Psoriatic Arthritis Response Criteria (PsARC) response rate;
- Change from baseline in Disease Activity Score (DAS) 28 joints (DAS28) (C-reactive protein [CRP]);
- Change from baseline in DAS28 (erythrocyte sedimentation rate [ESR]);
- Change from baseline in PsA DAS (PASDAS);
- Change from baseline in Disease Activity in Psoriatic Arthritis (DAPSA) score;
- Change from baseline in Short Form 36 (SF-36) Health Questionnaire;
- Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Questionnaire;

- Change from baseline in EuroQoL - 5 Dimensions - 5 Levels (EQ-5D-5L) Questionnaire and visual analogue scale score;
- Change from baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire;
- Health Resource Utilization (HRU);
- Change from baseline in SAPS Questionnaire;
- Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (out of subjects with presence of psoriatic spondylitis at baseline);
- BASDAI 50 response rates (out of subjects with psoriatic spondylitis);
- Change from baseline in morning stiffness (mean of BASDAI Questions 5 and 6);
- Change from baseline in morning stiffness severity 0 - 10 (BASDAI Question 5);
- Change from baseline in morning stiffness duration 0 - 10 (BASDAI Question 6);
- Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) (out of subjects with presence of psoriatic spondylitis);
- Proportion of subjects with ASDAS Inactive Disease (out of subjects with presence of psoriatic spondylitis);
- Proportion of subjects with ASDAS Major Improvement (out of subjects with presence of psoriatic spondylitis);
- Proportion of subjects with ASDAS Clinically Important Improvement (out of subjects with presence of psoriatic spondylitis);
- Proportion of subjects achieving a clinically meaningful improvement in HAQ-DI ($\geq$ 0.35).

Study M15-554:

- Change from baseline in individual components of ACR response;
- ACR20/50/70 response rates;
- Change from baseline in Leeds Dactylitis Index (LDI)
- Change from baseline in dactylitis count;
- Proportion of subjects with resolution of dactylitis;
- Change from baseline in Leeds Enthesitis Indices (LEI);
- Proportion of subjects with resolution of enthesitis sites included in the LEI;
- Change from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index;
- Proportion of subjects with resolution of enthesitis sites included in the SPARCC Enthesitis Index;
- Change from baseline in total enthesitis count;
- Proportion of subjects with resolution of enthesitis;
- PASI 75/90/100 response rates (for subjects with $\geq$ 3% BSA psoriasis at baseline);
- Proportion of subjects achieving a sIGA score of 0 or 1 and at least a 2-point improvement from baseline;

- Change from baseline in body surface area - psoriasis (BSA-Ps) (for subjects with BSA-PS > 0);
- Modified Psoriatic Arthritis Response Criteria (PsARC) response rate;
- Change from baseline in Disease Activity Score 28 joints (DAS28) (C-reactiveprotein [CRP]);
- Change from baseline in DAS28 (erythrocyte sedimentation rate [ESR]);
- Change from baseline in PsA Disease Activity Score (PASDAS);
- Change from baseline in Disease Activity in Psoriatic Arthritis (DAPSA) score;
- Change from baseline in SF-36 PCS;
- Change from baseline in FACIT-Fatigue (FACIT-F);
- Change from baseline in EuroQoL-5 Dimensions - 5 Levels (EQ-5D-5L);
- Change from baseline in Work Productivity and Activity Impairment (WPAI);
- Health Resource Utilization (HRU);
- Proportion of subjects achieving MDA;
- Change from baseline in SAPS;
- Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (among subjects with psoriatic spondylitis);
- 50% improvement of the initial BASDAI (BASDAI 50) response rates (among subjects with psoriatic spondylitis);
- Change from baseline in morning stiffness (mean of BASDAI Questions 5 and 6);
- Change from baseline in morning stiffness duration;
- Change from baseline in morning stiffness severity;
- Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) (among subjects with psoriatic spondylitis);
- Proportion of subjects with ASDAS Inactive Disease (among subjects with psoriatic spondylitis);
- Proportion of subjects with ASDAS Major Improvement (among subjects with psoriatic spondylitis);
- Proportion of subjects with ASDAS Clinically Important Improvement (among subjects with psoriatic spondylitis);
- Proportion of subjects achieving a clinically meaningful improvement in HAQ-DI ($\geq$ 0.35).

Sample size

Study M15-572

The planned sample size of approximately 1640 for this study (with 2:2:2:1:1 randomization ratio for upadacitinib 15 mg, upadacitinib 30 mg, adalimumab and placebo subjects) was estimated to provide at least 90% power for a 20% difference in ACR20 response rate (assuming a placebo ACR20 response rate of 30%). It was estimated to also provide at least 90% power for the majority of the key secondary endpoints. With the given sample size, the MAH states that there is approximately 90% power to detect a standardized effect size of 0.26 in change from baseline in SHS for each upadacitinib dose group versus the combined placebo group at Week 24. This sample size was calculated to also provide at least 85%

power for evaluating noninferiority for each upadacitinib dose group vs. ADA in ACR20 response rate at Week 12 assuming 50% ACR20 response rates for ADA and upadacitinib and 30% ACR20 response rates for placebo. All power and sample size calculations were performed at two-sided significance level of 0.025 and accounting for a 10% dropout rate. The pre-specified approach to testing NI of each upadacitinib dose versus ADA for ACR20 response rate at Week 12 was based on the placebo-subtracted treatment difference using Koch's 3-arm test statistic. The test aims to show that upadacitinib preserves at least 50% of the placebo-subtracted adalimumab effect. If statistical significance is achieved for the non-inferiority assessment, superiority of upadacitinib versus adalimumab will be tested for ACR20.

Study M15-554

According to the MAH, the planned total sample size of 630 for this study provides at least 90% power for a 20% difference in ACR20 response rate (assuming a placebo ACR20 response rate of 20%). It will also provide at least 90% power for the majority of the key secondary endpoints. All power and sample size calculations are performed at a two-sided significance level of 0.025 and accounting for a 10% dropout rate.

Randomisation

Study M15-572

Subjects who met eligibility criteria were stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA), current use of at least 1 DMARD, presence of dactylitis, and presence of enthesitis, except for subjects from China and Japan, where randomization for each country was stratified by extent of psoriasis (≥ 3% BSA or < 3% BSA) only, and then randomized in a 2:2:2:1:1 ratio to one of five treatment groups:

- Group 1: Upadacitinib 15 mg QD (N = 410)
- Group 2: Upadacitinib 30 mg QD (N = 410)
- Group 3: ADA 40 mg every other week (EOW) (N = 410)
- Group 4: Placebo followed by upadacitinib 15 mg QD (N = 205)
- Group 5: Placebo followed by upadacitinib 30 mg QD (N = 205)

No more than approximately 15% of subjects were to be enrolled with concomitant use of hydroxychloroquine (HCQ), sulfasalazine (SSZ), bucillamine, or iguratimod.

Study M15-554

Subjects were stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA), current use of at least 1 DMARD (Yes or No), and number of prior failed biologic DMARDs (1 vs > 1), except for subjects from Japan, for which randomization was stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA) only.

No more than approximately 40% of subjects will be enrolled with < 3% BSA extent of psoriasis and no more than approximately 30% of subjects were to be enrolled with prior failure of more than 1 biologic DMARD.

Blinding (masking)

In both studies, MAH's personnel with direct oversight of the conduct and management of the trial (with the exception of Drug Supply Management Team), the Investigator, study site personnel, and the subject will remain blinded to each subject's treatment. In order to maintain the blind, the upadacitinib/placebo tablets and adalimumab/matching placebo syringes provided for the study are identical in appearance.

After the last subject completed the Week 24 visit, an unblinded analysis was conducted for the purpose of regulatory submission. Study sites and subjects will remain blinded until all subjects have reached Week 56 (end of Period 1).

An independent external Data Monitoring Committee (DMC) is used to review unblinded safety data at regular intervals during the conduct of the studies.

Statistical methods

Since the available CSR for both Phase 3 studies only coversed the first 24 weeks of the study at the time of original submission, the statistical methodology is presented mainly for Period 1 of the studies.

The data cut-off date for the interim analyses are for study M15-572 13 December 2019 and for study 15-554 09 October 2019.

There were five protocol amendments and one administrative change in study M15-572 and six amendments and two administrative changes in the protocol for study M15-554. All of these were dated prior to data cut-off. There was an update of the statistical analysis plan (SAP) for the integrated summary of efficacy dated 01 October 2019, also before data cut-off dates.

Analysis populations

Full Analysis Set (FAS)

The FAS includes all randomized subjects who received at least one dose of study drug. The FAS is used for all efficacy and baseline analyses.

Per Protocol Analysis Set

The Per Protocol Analysis Set represents a subset of the FAS and consists of all FAS subjects who did not meet any major protocol deviations that are determined to have a potential impact on the primary efficacy endpoint up to Week 12 in Period 1 of the study. Additional analysis of the primary efficacy endpoint are conducted on the Per Protocol analysis set, in order to evaluate the impact of major protocol deviations.

Safety Analysis Set

The Safety Analysis Set consists of all subjects who received at least one dose of study drug. For the Safety Analysis Set, subjects are analysed "as treated," regardless of the treatment randomized. "As treated" is determined by the treatment the subject received during the majority of the subject's drug exposure time in the analysis period.

Analysis of results

Demographic and baseline characteristics information were collected at the Baseline and summarized for the FAS. The number of observations, mean, standard deviation, median, minimum and maximum were summarized for continuous variables. Categorical or discrete variables were summarized via frequencies and percentages. Summary statistics were computed for each treatment group and overall.

No statistical comparison was performed for medical history reporting.

Prior and concomitant medications were summarized by each randomized treatment group as well as overall for FAS.

Protocol deviations based on ICH deviation criteria, summarized and listed by treatment group, are categorized as follows:

1. Those who entered the study even though they did not satisfy the entry criteria

2. Those who developed withdrawal criteria during the study and were not withdrawn

3. Those who received the wrong treatment or incorrect dose, and

4. Those who received an excluded or prohibited concomitant medication.

Patient disposition

The following will be summarized by randomized treatment group as well as overall: number of subjects randomized; number of subjects included in key analysis populations (FAS and Per Protocol Analysis Set for efficacy analysis, Safety Analysis Set for safety analysis); number of subjects who completed Period 1 study participation; number of subjects who entered Period 2; number of subjects who completed overall study (Period 1 and Period 2) participation (if applicable).

Premature discontinuation details will be further summarized separately for Period 1 and Period 2. The number and percentage of subjects completed Period 1 and prematurely discontinued in Period 1 are summarized by randomized treatment group, separately by study drug and study participation completion/discontinuation, with the reason for discontinuation collected from CRF by the following categories: Adverse event (AE), Withdrew consent, Lost to follow-up, Lack of efficacy, Other.

Study drug exposure

For short term up to Week 24, the duration of exposure to study drug is summarized for the safety analysis set by the randomized treatment groups.

Study drug compliance was summarized for each treatment group at Week 24. The summary was performed for UPA/PBO tablets and ADA/PBO injections separately.

Efficacy analysis

Of the two sets of planned efficacy analysis: efficacy analysis through Week 24 and long-term efficacy analysis, this AR focuses on the analysis through Week 24, for which period results are available. Unless otherwise noted, all efficacy analyses were carried out using the FAS population.

Efficacy Analysis by Week 24

Standard efficacy analysis by randomized treatment groups (upadacitinib 15 mg QD, upadacitinib 30 mg QD, adalimumab 40 mg EOW and the combined placebo groups) was performed on efficacy data up to Week 24.

For ACR20 response at Week 12 of study M15-572, analysis was conducted to assess the non-inferiority of each upadacitinib dose versus adalimumab on the placebo-subtracted treatment difference using Koch's 3-arm test statistic (described in Appendix C of the statistical analysis plan). The test aims to show that upadacitinib preserves at least 50% of the placebo-subtracted adalimumab effect.

Since statistical significance was achieved for the non-inferiority assessment of ACR20 response at Week 12 compared with adalimumab for both upadacitinib doses, superiority of upadacitinib versus adalimumab was tested for ACR20 subsequently.

- Multiple Imputation and tipping point analysis:

Tipping point analysis was performed for the primary endpoint (ACR20 at Week 12) by multiple imputations using logistic regression, allowing the imputed ACR response rate to systematically vary from 0% to 100% in both upadacitinib and placebo, respectively. Supportive analysis was also conducted on the Per Protocol Analysis Set.

Tipping point analysis was performed also for the key secondary non-radiographic continuous endpoints.

Adjustment for Covariates

All efficacy analyses were performed adjusting for the stratification factor of current DMARD use. Continuous variables were also analysed adjusting for baseline values. No other adjustment for covariates was performed.

Missing data handling included

- Non-responder imputation (NRI) for binary endpoints: subjects who prematurely discontinued from study drug were considered as non-responders for all subsequent visits after discontinuation; and any subject with any missing value for the binary endpoints at a specific visit was treated as non-responder for that visit.

- As observed (AO): The AO data handling does not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the AO analysis for that visit. Regardless of premature discontinuation of study drug or use of rescue medication, all observed data will be used in the analysis. The intention-to-treat (ITT) principle for the analysis using AO data, AO (with imputation), where additional missing data will be imputed as non-responders, is used for the supplementary analysis of the primary and key secondary binary endpoints.

- Mixed-Effect Model Repeat Measurement (MMRM): The repeated measure analysis was conducted using mixed models including observed data at all visits. For the MMRM analysis, data collected after premature discontinuation of study drug was excluded. The mixed model includes the categorical fixed effects of treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) and the continuous fixed covariates of baseline measurement. An unstructured variance covariance matrix was used. The parameter estimations were based on the assumption of data being missing at random (MAR) and using the method of restrictive maximum likelihood (REML). MMRM will be used for the primary estimand of the non-radiographic continuous endpoints.

Linear extrapolation will be used to facilitate the primary estimand for radiographic endpoints. The multiple imputation model was used for radiographic continuous endpoints. The model for the change from baseline in SHS score was based on the linearity assumption for the subjects with missing data including those due to premature discontinuation of study drug or meeting the rescue criteria. The regression method used imputed missing Week 24 observations by regression upon all previous visits including baseline and Week 16, stratified by treatment group. The imputation model included baseline demographics and key baseline characteristics as appropriate. Analysis of covariance (ANCOVA) was performed on each of the multiple imputed datasets.

Handling of multiplicity

The overall type I error rate of the primary and ranked key secondary endpoints for the two doses was controlled using a graphical multiple testing procedure. The graph for the testing procedures is provided for each study in Figures 23 and 24. In the graphs, the arrows specify the α transfer paths. Once an endpoint is rejected (i.e., deemed significant) at its assigned significance level, its significance level will be transferred to subsequent endpoint(s) following the arrow(s). The numbers on the arrows denote the weights for transferring significance levels. Specifically, the weight 1 denotes 100% transfer of significance level. (Note: in the Figure 23, 'Humira' denotes the adalimumab product used in the study).

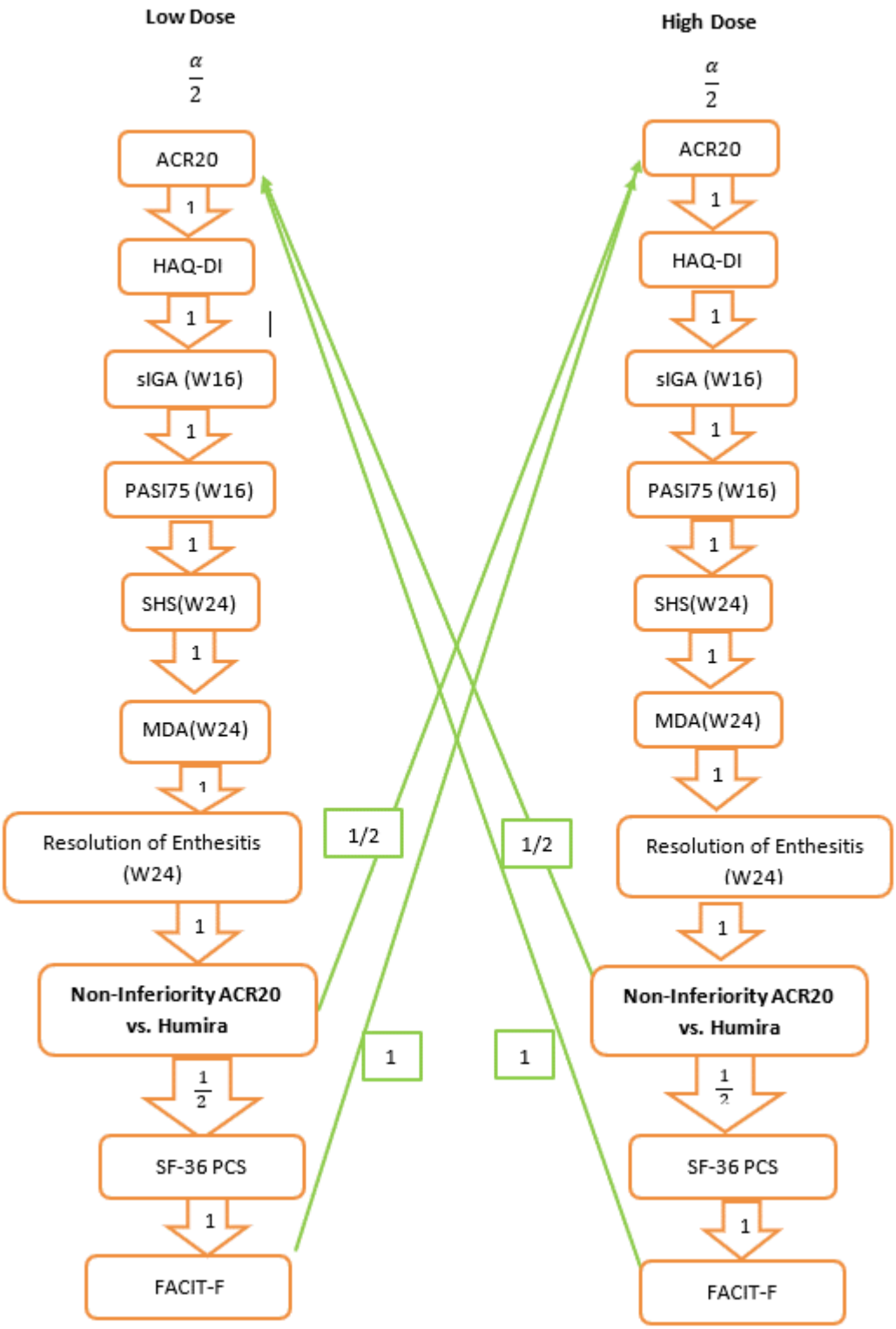


Figure 23 Graphical Multiple Testing Procedure (Study M15-572)

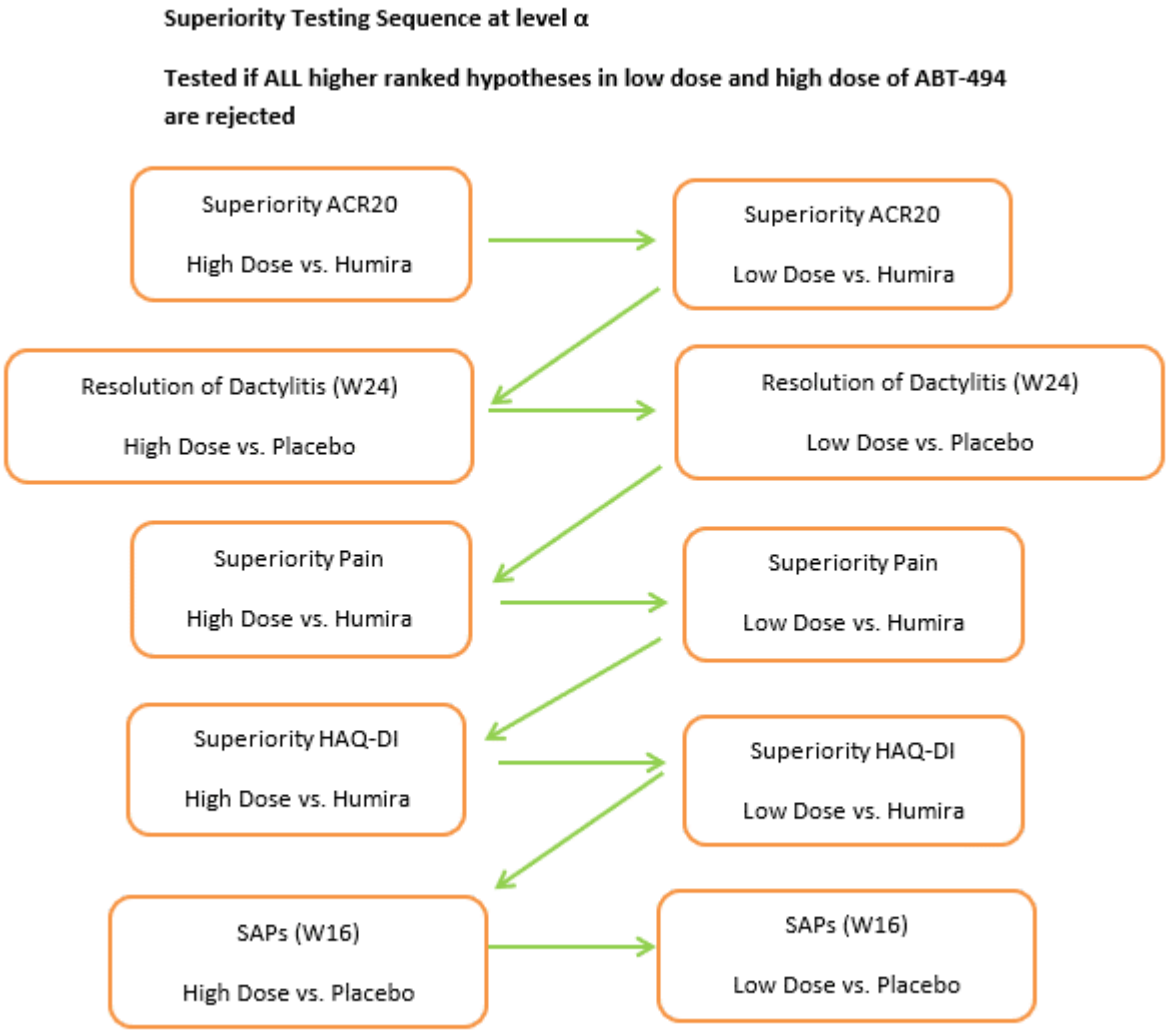


Figure 24 Graphical Multiple Testing Procedure (Study M15-572)

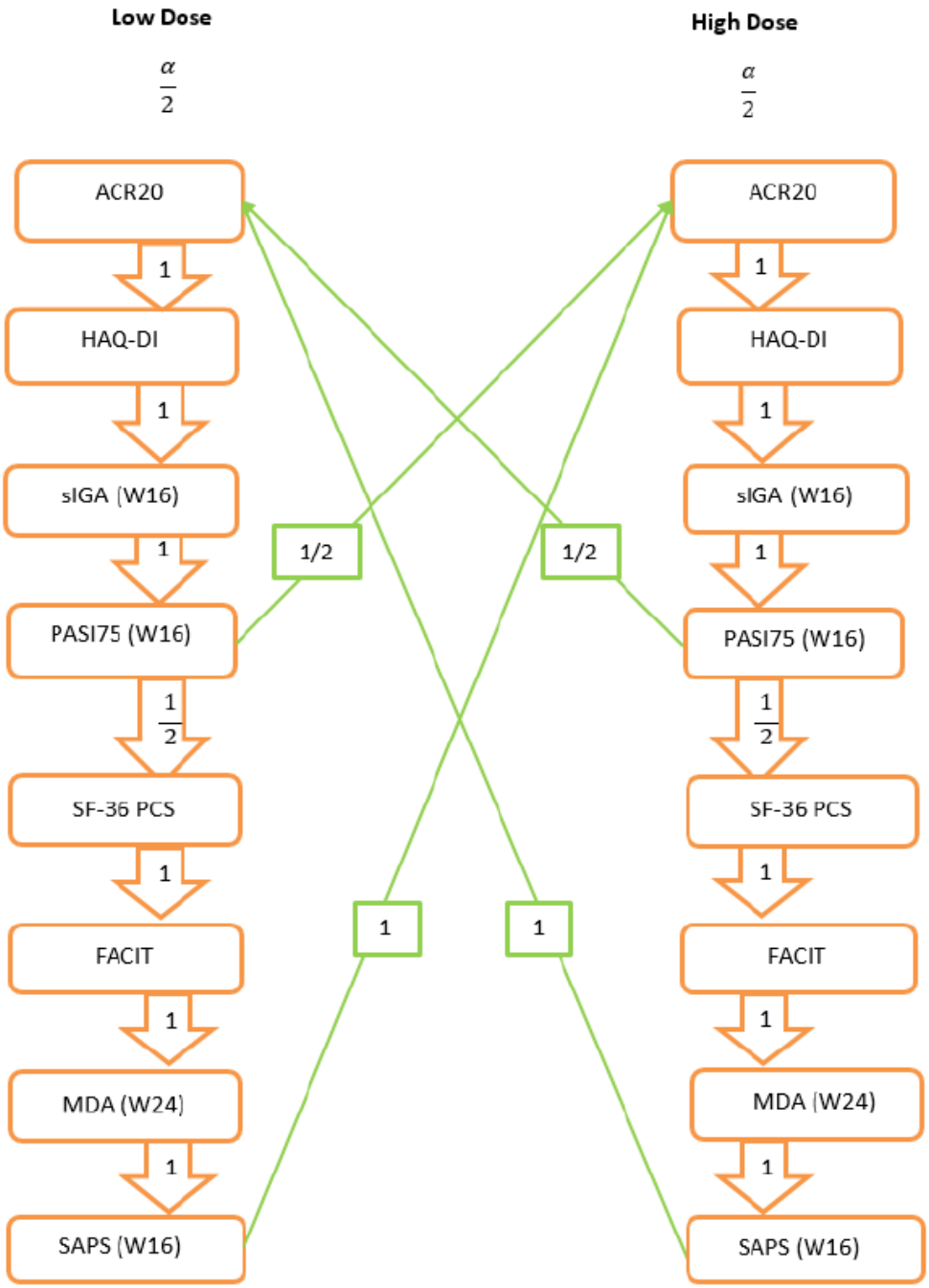


Figure 25 Graphical Multiple Testing Procedure (Study M15-554)

Subgroup analyses

Table 22 presents the subgroups in study M15-572 for efficacy analyses on the primary efficacy endpoint. Treatment difference between each upadacitinib dose and the combined placebo group is presented with point estimate and 95% confidence interval using normal approximation. No p-value is provided for subgroup analyses.

In study M15-554, the same subgroups were analysed as in M15-572, except that instead of the subgroup "Number of prior non-biologic DMARDs" the subgroup "Number of prior failed biologic DMARDs [= 1, >1] was analysed.

Table 22 Subgroups for efficacy analysis (Study M15-572)

Subgroup Factor	Categories
Age	< 65, ≥ 65 - < 75, ≥ 75 years (if sample size allows)
Sex	Male or Female
BMI	< 25 kg/m^2 or ≥ 25 kg/m^2
Race	White, Non-white
Geographic region	North America, Western Europe and Oceania, Eastern Europe, Latin-America, Asia, and Other
Duration of PsA diagnosis	≤ 5, > 5 - ≤ 10, > 10 years
Baseline hsCRP	≤ ULN or > ULN
Number of prior non-biologic DMARDs	≤ 1, > 1
Current use of non-biologic DMARDs	Yes or No

Methodology of integrated efficacy analyses

The integrated summary of efficacy (ISE) of the dossier presents short-term integrated analyses conducted on the 24 week placebo-controlled period data from the two pivotal Phase 3 global trials Study M15-554 and Study M15-572.

The main objectives of the ISE were 1) to assess the efficacy of upadacitinib on key endpoints in the integrated dataset; 2) to assess the efficacy in subgroups defined by demographic and baseline disease characteristics in the integrated dataset; 3) to examine the efficacy of upadacitinib as monotherapy vs in combination with background non-biologic DMARDs; and 4) to examine the efficacy of upadacitinib in combination with methotrexate (MTX) vs with other non-biologic DMARDs respectively.

Data from the three treatment arms of upadacitinib 15 mg QD, upadacitinib 30 mg QD, and placebo were included. All analyses for ISE were to be performed on the FAS population, which includes all randomized subjects who have received at least one dose of study drug. Data from the FAS is presented by the treatment group assigned at the time of randomization, even if the subject did not receive the correct treatment or did not follow the protocol until completion.

Demographic and baseline characteristics were summarized for the ISE.

Table 23 summarises the efficacy analyses conducted for the ISE.

Table 23 Overview of Integrated Efficacy Analysis

Analyses Outline
Analysis of Key Efficacy Endpoints ACR20/50/70, HAQ-DI, sIGA, PASI75, and MDA Dactylitis and Enthesitis related endpoints
Subgroup Analysis for ACR20 Assessment of efficacy in subgroups by demographic and baseline disease characteristics
Upadacitinib monotherapy vs in combination with background non-biologic DMARDs Examine the efficacy of upadacitinib as monotherapy vs. in combination with background non-biologic DMARDs
Upadacitinib in combination with MTX vs with other background non-biologic DMARDs Examine the efficacy of upadacitinib in combination with different types of background non-biologic DMARDs

The MAH informs that handling of missing data and intercurrent events is consistent with the primary estimand and primary analysis in the individual studies. Analyses in the ISE are considered by the MAH to be supportive of the efficacy results obtained from the individual studies and are not intended to be interpreted without this context.

For binary endpoints, the point estimate and 95% CI for the response rate for each group as well as the point estimate, 95% CI and p-value for the treatment difference between each upadacitinib group and placebo are provided using the Cochran-Mantel-Haenszel analysis adjusting for study as a stratification factor.

For continuous endpoints, the LS mean and 95% CI for each group as well as the LS mean treatment difference, the associated 95% CI and the p-value for the treatment difference between each upadacitinib group and placebo is provided using MMRM model adjusting for study as a stratification factor. Additionally, the MI analysis based on all data as observed (AO) has been performed as supplementary analysis.

No multiplicity adjustment was planned or conducted for any ISE analyses.

Results

Study M15-572

Participant flow

A total of 1705 subjects were randomized at 281 sites located in 44 countries, of whom 1704 subjects received study drug. Number of screened subjects is not available.

A total of 1,626 subjects (95.4%) and 1,548 subjects (90.8%) were continuing the study drug at Week 12 (primary endpoint) and Week 24 (cut-off for interim CSR), respectively.

The most frequent primary reason for study drug discontinuation by Week 24 was withdrawal by subject for the placebo group, AE and withdrawal by subject for the upadacitinib 15 mg group, and AE for the upadacitinib 30 mg and adalimumab (ADA) groups (table 24). As of the data cut-off date of the CSR, 649 subjects (38.1%) had completed Period 1 (Week 56) study drug, 240 subjects (14.1%) had discontinued study drug during Period 1, and 816 subjects were ongoing in Period 1. However, the MAH provided in the response to the RSI the 56 week results for all efficacy endpoints proposed by the

MAH to be included in the PI, since all subjects had reached Week 56 or were prematurely discontinued by submission of the response (see assessment in ancillary analysis section).

Table 24 Study Drug Disposition of Subjects (All Randomized Subjects)

	Placebo (N = 423)	ADA 40 mg EOW (N = 429)	Upadacitinib 15 mg QD (N = 430)	Upadacitinib 30 mg QD (N = 423)	Overall Total (N = 1705)
Randomized, n	423	429	430	423	1705
FAS, n	423	429	429	423	1704
Per Protocol Analysis Set, n	413	424	402	394	1633
Safety Analysis Set, n	423	429	429	423	1704
Completed study drug up to Week 12, n (%)	399 (94.3)	410 (95.6)	412 (95.8)	405 (95.7)	1626 (95.4)
Discontinued study drug (primary reason), n (%)	24 (5.7)	19 (4.4)	18 (4.2)	18 (4.3)	79 (4.6)
Adverse event	9 (2.1)	8 (1.9)	5 (1.2)	12 (2.8)	34 (2.0)
Withdrawal by subject	9 (2.1)	7 (1.6)	7 (1.6)	5 (1.2)	28 (1.6)
Lost to follow up	2 (0.5)	1 (0.2)	4 (0.9)	0	7 (0.4)
Lack of efficacy	1 (0.2)	2 (0.5)	0	0	3 (0.2)
Other	3 (0.7)	1 (0.2)	2 (0.5)	1 (0.2)	7 (0.4)
Completed study drug up to Week 24, n (%)	377 (89.1)	388 (90.4)	395 (91.9)	388 (91.7)	1548 (90.8)
Discontinued study drug (primary reason), n (%)	44 (10.4)	36 (8.4)	31 (7.2)	34 (8.0)	145 (8.5)
Adverse event	11 (2.6)	18 (4.2)	10 (2.3)	19 (4.5)	58 (3.4)
Withdrawal by subject	19 (4.5)	10 (2.3)	10 (2.3)	10 (2.4)	49 (2.9)
Lost to follow up	3 (0.7)	3 (0.7)	5 (1.2)	2 (0.5)	13 (0.8)
Lack of efficacy	7 (1.7)	3 (0.7)	1 (0.2)	0	11 (0.6)
Other	4 (0.9)	2 (0.5)	5 (1.2)	3 (0.7)	14 (0.8)

ADA = adalimumab; EOW = every other week; FAS = Full Analysis Set; QD = once daily

Recruitment

The first subject first visit occurred on 27 April 2017. The submitted interim CSR presents efficacy results up to Week 24 in Period 1, short-term safety results up to Week 24, and long-term safety results up to the data cut-off date of 13 December 2019.

Study M15-572 was designed to enrol approximately 1640 subjects at approximately 350 study centres worldwide. Finally, the study is being conducted in 281 sites in 44 participating countries.

Conduct of the study

There were five protocol amendments and one administrative change in study M15-572, all dated prior to data cut-off. Each amendment contained multiple updates, mostly clarifications on inclusion and exclusion criteria, permitted concomitant treatments and their dose changes, administrative changes, contraception recommendations, and linguistic changes. Some amendments were performed due to the concerns on increased thrombosis risk associated to the JAKi class.

According to the MAH, all studies were conducted in accordance with GCP and applicable local laws and regulations. Three investigative site audits were conducted by the sponsor. No regulatory inspections are reported in the submission.

Protocol deviations were defined in accordance with the ICH guidelines and included but were not limited to: inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. In addition, all non-ICH deviations were reviewed. Deviations were assessed for their impact on analyses and data integrity or subject safety. Subjects judged to have deviations with a potential impact on the primary variable were excluded from the PP analysis set. The deviations were not considered by the MAH to have affected the overall study outcome or interpretation of the study results or conclusions.

Baseline data

Demographic characteristics were generally balanced across the upadacitinib, ADA, and placebo groups (Table 25). The mean age of study subjects was 50.8 years, they had been diagnosed with PsA for a mean of 6.1 years, and experienced symptoms of PsA for a mean of 9.2 years. There were slightly more women than men. Subjects had active disease as indicated by mean TJC68 of 20.0, mean SJC66 of 11.2, and 49.6% of subjects had psoriasis with BSA ≥ 3%.

Table 25 Demographic characteristics (FAS)

	Placebo (N = 423)	ADA 40 mg EOW (N = 429)	Upadacitinib 15 mg QD (N = 429)	Upadacitinib 30 mg QD (N = 423)	Total (N = 1704)
Sex, n (%)					
Female	211 (49.9)	222 (51.7)	238 (55.5)	236 (55.8)	907 (53.2)
Male	212 (50.1)	207 (48.3)	191 (44.5)	187 (44.2)	797 (46.8)
Age (years)					
Mean (SD)	50.4 (12.21)	51.4 (12.04)	51.6 (12.19)	49.9 (12.41)	50.8 (12.22)
Median (min, max)	50.0 (20.0, 81.0)	52.0 (21.0, 77.0)	52.0 (22.0, 83.0)	51.0 (19.0, 82.0)	51.0 (19.0, 83.0)
Age (years), n (%)					
< 65	367 (86.8)	362 (84.4)	367 (85.5)	371 (87.7)	1467 (86.1)
65 - < 75	52 (12.3)	61 (14.2)	52 (12.1)	46 (10.9)	211 (12.4)
≥ 75	4 (0.9)	6 (1.4)	10 (2.3)	6 (1.4)	26 (1.5)
Race					
White	377 (89.1)	375 (87.4)	386 (90.0)	377 (89.1)	1515 (88.9)
Black or African American					
American Indian/Alaska Native					
Native Hawaiian or other Pacific Islander					
Asian	37 (8.7)	41 (9.6)	37 (8.6)	34 (8.0)	149 (8.7)
Multiple	3 (0.7)	7 (1.6)	5 (1.2)	6 (1.4)	21 (1.2)

Ethnicity					
Hispanic or Latino	66 (15.6)	65 (15.2)	59 (13.8)	53 (12.5)	243 (14.3)
Not Hispanic or Latino	357 (84.4)	364 (84.8)	370 (86.2)	370 (87.5)	1461 (85.7)
Weight (kg)					
Mean (SD)	87.4 (21.36)	87.8 (21.90)	84.8 (18.89)	85.5 (18.83)	86.4 (20.32)
Median (min, max)	85.0 (41.0, 168.6)	85.0 (43.0, 217.2)	83.0 (46.3, 160.1)	84.0 (44.2, 143.0)	84.0 (41.0, 217.2)
Height (cm)					
Mean (SD)	169.5 (10.29)	169.2 (10.01)	167.8 (9.12)	168.7 (10.05)	168.8 (9.89)
Median (min, max)	169.0 (144.0, 200.7)	170.0 (144.7, 193.0)	167.6 (145.1, 194.5)	168.0 (139.0, 199.0)	168.0 (139.0, 200.7)
Body mass index (kg/m^2)					
Mean (SD)	30.4 (6.79)	30.7 (7.24)	30.1 (6.40)	30.1 (6.77)	30.3 (6.81)
Median (min, max)	29.5 (15.6, 61.9)	29.8 (16.5, 87.0)	29.1 (17.9, 56.0)	29.3 (16.7, 57.3)	29.5 (15.6, 87.0)
Body mass index (kg/m^2), n (%)					
< 25	94 (22.2)	95 (22.1)	87 (20.3)	104 (24.6)	380 (22.3)
Tobacco/nicotine use,[a] n (%)					
Current	74 (17.5)	85 (19.8)	82 (19.1)	64 (15.1)	305 (17.9)
Former	84 (19.9)	78 (18.2)	85 (19.8)	91 (21.5)	338 (19.8)
Never	265 (62.6)	266 (62.0)	262 (61.1)	268 (63.4)	1061 (62.3)
Alcohol use, n (%)					
Current	160 (37.8)	187 (43.6)	161 (37.6)	156 (36.9)	664 (39.0)
Former	36 (8.5)	23 (5.4)	38 (8.9)	40 (9.5)	137 (8.0)
Never	227 (53.7)	219 (51.0)	229 (53.5)	227 (53.7)	902 (53.0)
Unknown	0	0	1	0	1

ADA = adalimumab; EOW = every other week; Max = maximum; min = minimum; QD = once daily; SD = standard deviation

a. A subject that was a current user of any type of tobacco is counted under "current." Otherwise, a subject that was a former user of any type of tobacco is counted under "former." A subject who had never used any tobacco is counted under "never."

The disease-related baseline characteristics were overall balanced across the upadacitinib, ADA, and placebo groups, incl. duration of symptoms and diagnosis, RF and anti-CCP status, indicators of disease activity, status of structural changes, and PROs. Dactylitis was present (defined as LDI>0) in 30.3 % and enthesitis (defined as total enthesitis count > 0) in 77.2% of study subjects. One third (31.3 %) of subjects had psoriatic spondylitis at baseline. About half of subjects (49.6 %) had total body surface area affected by psoriasis (BSA-Ps) ≥ 3% at baseline. (Table 26)

The requirement for either at least one erosion on x-ray or elevated hsCRP in inclusion criteria were selected in order to enrol a population appropriate for assessment of radiographic progression and to increase the power for detection of a treatment effect for upadacitinib on the radiographic endpoints. However, less than half (39.2 %9 of study subjects had ≥ 1 erosion at baseline. The mean hsCRP was 11.22 mg/L (median 6.21 mg/L).

Table 26 Disease-Related Baseline Characteristics (FAS)

	Placebo (N = 423) n (%)	ADA 40 mg EOW (N = 429) n (%)	Upadacitinib 15 mg QD (N = 429) n (%)	Upadacitinib 30 mg QD (N = 423) n (%)	Total (N = 1704) n (%)
Duration of PsA symptoms (years)					
n	423	428	429	423	1703
Mean (SD)	9.3 (8.58)	9.1 (8.78)	9.2 (8.63)	9.3 (8.28)	9.2 (8.56)
Median (min, max)	6.4 (0.6, 55.0)	6.0 (0.6, 55.3)	6.7 (0.6, 44.4)	6.7 (0.6, 54.3)	6.4 (0.6, 55.3)
Duration of PsA diagnosis (years)					
Mean (SD)	6.2 (7.01)	5.9 (7.06)	6.2 (7.41)	5.9 (6.37)	6.1 (6.97)
Median (min, max)	3.5 (0.1, 45.0)	3.5 (0.1, 40.9)	3.5 (0.1, 41.0)	3.4 (0.1, 33.2)	3.5 (0.1, 45.0)
RF status, n (%)					
Positive	20 (4.7)	13 (3.0)	15 (3.5)	23 (5.4)	71 (4.2)
Negative	403 (95.3)	416 (97.0)	414 (96.5)	400 (94.6)	1633 (95.8)
Anti-CCP status, n (%)					
Positive	16 (3.8)	11 (2.6)	9 (2.1)	17 (4.0)	53 (3.1)
Negative	406 (96.0)	418 (97.4)	419 (97.7)	405 (95.7)	1648 (96.7)
Missing	1 (0.2)	0	1 (0.2)	1 (0.2)	3 (0.2)
TJC68					
Mean (SD)	20.0 (14.34)	20.1 (13.82)	20.4 (14.72)	19.4 (13.32)	20.0 (14.05)
Median (min, max)	15.0 (3.0, 68.0)	16.0 (3.0, 66.0)	16.0 (2.0, 68.0)	15.0 (3.0, 66.0)	16.0 (2.0, 68.0)
SJC66					
Mean (SD)	11.0 (8.16)	11.6 (8.75)	11.6 (9.31)	10.6 (7.06)	11.2 (8.37)
Median (min, max)	9.0 (3.0, 56.0)	9.0 (3.0, 52.0)	9.0 (3.0, 59.0)	9.0 (1.0, 56.0)	9.0 (1.0, 59.0)
Patient's Assessment of Pain (NRS)					
n	421	428	425	421	1695
Mean (SD)	6.1 (2.14)	6.0 (2.08)	6.2 (2.07)	5.9 (2.05)	6.0 (2.09)
Median (min, max)	6.0 (0.0, 10.0)	6.0 (0.0, 10.0)	6.0 (0.0, 10.0)	6.0 (0.0, 10.0)	6.0 (0.0, 10.0)
PGA – Disease Activity (NRS)					
n	423	429	429	423	1704
Mean (SD)	6.5 (1.64)	6.6 (1.65)	6.7 (1.62)	6.5 (1.68)	6.5 (1.65)
Median (min, max)	7.0 (1.0, 10.0)	7.0 (0.0, 10.0)	7.0 (1.0, 10.0)	7.0 (1.0, 10.0)	7.0 (0.0, 10.0)
PtGA – Disease Activity (NRS)					
n	421	428	425	421	1695
Mean ± SD	6.3 (2.04)	6.3 (2.03)	6.6 (2.03)	6.4 (2.07)	6.4 (2.04)
Median (min, max)	6.0 (0.0, 10.0)	6.0 (1.0, 10.0)	7.0 (0.0, 10.0)	6.0 (0.0, 10.0)	7.0 (0.0, 10.0)
HAQ-DI					
n	421	428	425	421	1695
Mean ± SD	1.12 (0.639)	1.12 (0.626)	1.15 (0.653)	1.09 (0.630)	1.12 (0.637)
Median (min, max)	1.13 (0.00, 2.88)	1.13 (0.00, 3.00)	1.13 (0.00, 2.75)	1.13 (0.00, 2.88)	1.13 (0.00, 3.00)
hs-CRP (mg/L)					
Mean ± SD	11.48 (15.800)	10.91 (15.463)	11.00 (14.910)	11.49 (15.355)	11.22 (15.373)
Median (min, max)	6.34 (0.20, 152.00)	5.40 (0.20, 117.00)	6.66 (0.20, 141.00)	6.89 (0.20, 169.00)	6.21 (0.20, 169.00)
BSA – psoriasis (Ps)					
< 3%	212 (50.1)	218 (50.8)	215 (50.1)	213 (50.4)	858 (50.4)
≥ 3%	211 (49.9)	211 (49.2)	214 (49.9)	210 (49.6)	846 (49.6)
BSA-Ps (for baseline > 0%)					
n	400	397	394	397	1588
Mean ± SD	9.41 (16.108)	7.98 (13.650)	8.29 (15.496)	8.18 (14.095)	8.47 (14.869)
Median (min, max)	3.00 (0.10, 90.00)	3.00 (0.03, 90.00)	3.00 (0.10, 97.00)	3.00 (0.10, 87.00)	3.00 (0.03, 97.00)

sIGA of psoriasis score					
0	24 (5.7)	34 (7.9)	34 (7.9)	21 (5.0)	113 (6.6)
1	86 (20.3)	65 (15.2)	73 (17.0)	78 (18.4)	302 (17.7)
2	167 (39.5)	181 (42.2)	170 (39.6)	173 (40.9)	691 (40.6)
3	119 (28.1)	132 (30.8)	133 (31.0)	128 (30.3)	512 (30.0)
4	27 (6.4)	17 (4.0)	19 (4.4)	23 (5.4)	86 (5.0)
PASI (for baseline BSA-Ps ≥ 3%)					
n	211	211	214	210	846
Mean ± SD	11.21 (11.425)	9.42 (8.535)	9.78 (9.954)	9.45 (8.750)	9.97 (9.746)
Median (min, max)	6.60 (0.10, 57.70)	6.30 (0.10, 53.70)	6.80 (0.10, 70.80)	6.45 (0.10, 47.20)	6.60 (0.10, 70.80)
PASDAS					
n	421	428	425	421	1695
Mean (SD)	6.18 (1.064)	6.15 (1.032)	6.31 (1.046)	6.17 (1.021)	6.20 (1.042)
Median (min, max)	6.14 (2.73, 9.27)	6.07 (3.45, 9.97)	6.21 (2.92, 9.66)	6.15 (2.81, 9.40)	6.14 (2.73, 9.97)
DAS28 (CRP)					
n	421	428	425	421	1695
Mean (SD)	4.90 (1.008)	4.88 (1.063)	4.94 (1.045)	4.88 (0.995)	4.90 (1.028)
Median (min, max)	4.86 (1.86, 7.81)	4.84 (2.01, 8.38)	4.87 (1.86, 8.17)	4.85 (1.84, 7.58)	4.85 (1.84, 8.38)
Presence of ≥ 1 erosion, n (%)					
Yes	161 (38.1)	183 (42.7)	165 (38.5)	159 (37.6)	668 (39.2)
No	227 (53.7)	218 (50.8)	241 (56.2)	234 (55.3)	920 (54.0)
Missing	35 (8.3)	28 (6.5)	23 (5.4)	30 (7.1)	116 (6.8)
Presence of dactylitis (defined as LDI > 0)					
Yes	126 (29.8)	127 (29.6)	136 (31.7)	127 (30.0)	516 (30.3)
No	297 (70.2)	302 (70.4)	293 (68.3)	296 (70.0)	1188 (69.7)
Leeds Dactylitis Index (for baseline LDI > 0)					
n	126	127	136	127	516
Mean (SD)	87.65 (114.764)	99.00 (163.109)	88.99 (106.495)	80.17 (132.391)	88.95 (130.428)
Median (min, max)	39.11 (10.00, 600.04)	52.91 (10.00, 1310.57)	55.96 (10.00, 726.44)	34.92 (10.00, 893.63)	41.88 (10.00, 1310.57)
Presence of enthesitis (defined as Total Enthesitis Count > 0)					
Yes	322 (76.1)	330 (76.9)	333 (77.6)	331 (78.3)	1316 (77.2)
No	101 (23.9)	99 (23.1)	96 (22.4)	92 (21.7)	388 (22.8)
Leeds enthesitis Index (for baseline LEI > 0)					
n	241	265	270	267	1043
Mean (SD)	2.7 (1.52)	2.5 (1.42)	2.6 (1.55)	2.6 (1.49)	2.6 (1.50)
Median (min, max)	2.0 (1.0, 6.0)	2.0 (1.0, 6.0)	2.0 (1.0, 6.0)	2.0 (1.0, 6.0)	2.0 (1.0, 6.0)
Morning Stiffness score[a]					
n	420	427	423	421	1691
Mean (SD)	5.29 (2.536)	5.24 (2.588)	5.65 (2.563)	5.34 (2.631)	5.38 (2.582)
Median (min, max)	5.50 (0.00, 10.00)	5.00 (0.00, 10.00)	6.00 (0.00, 10.00)	5.50 (0.00, 10.00)	5.50 (0.00, 10.00)
Presence of psoriatic spondylitis					
Yes	130 (30.7)	127 (29.6)	139 (32.4)	138 (32.6)	534 (31.3)
No	293 (69.3)	302 (70.4)	290 (67.6)	285 (67.4)	1170 (68.7)
ASDAS (CRP) (among subjects with psoriatic spondylitis)					
n	130	125	138	137	530
Mean (SD)	3.39 (0.999)	3.24 (0.973)	3.43 (0.911)	3.41 (0.911)	3.37 (0.948)
Median (min, max)	3.29 (1.19, 5.92)	3.32 (0.76, 5.75)	3.54 (0.36, 6.05)	3.37 (0.97, 5.75)	3.37 (0.36, 6.05)

BASDAI (among subjects with psoriatic spondylitis)					
n	130	125	138	137	530
Mean (SD)	5.81 (1.863)	5.69 (2.193)	5.94 (2.026)	5.91 (2.119)	5.84 (2.049)
Median (min, max)	5.80 (1.40, 10.00)	5.90 (0.00, 9.80)	6.10 (1.20, 9.50)	6.20 (0.50, 10.00)	6.00 (0.00, 10.00)
SHS					
n	388	401	406	393	1588
Mean (SD)	13.32 (31.211)	14.97 (38.867)	13.14 (42.448)	11.20 (24.539)	13.17 (35.052)
Median (min, max)	1.00 (0.00, 242.50)	1.50 (0.00, 382.00)	1.00 (0.00, 465.00)	1.50 (0.00, 164.00)	1.50 (0.00, 465.00)

ADA = adalimumab; Anti-CCP = anti-cyclic citrullinated peptide; ASDAS = ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BSA = body surface area; CRP = C-reactive protein; DAS28 = Disease Activity Score (28 joints); EOW = every other week; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire - Disability Index; hs-CRP = high-sensitivity C-reactive protein; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; Max = maximum; min = minimum; NRS = Numerical Rating Scale; PASDAS = Psoriatic Arthritis Disease Activity Score; PASI = Psoriasis Area Severity Index; PGA = Physician's Global Assessment; Ps = psoriasis; PsA = psoriatic arthritis; PtGA = Patient's Global Assessment; QD = once daily; RF = rheumatoid factor; SD = standard deviation; SHS = Sharp/van der Heijde Score; sIGA = static Investigator Global Assessment; SJC = Swollen Joint Count; TJC = Tender Joint Count

a. Morning stiffness score is the mean of BASDAI questions 5 and 6.

The study arms were overall similar regarding medical and surgical history.

Prior use of DMARDs

All but 4 subjects had used one or more prior non-biologic DMARDs, including 65.6% of subjects who used 1 prior non-biologic DMARD, 25.4% who used 2 prior non-biologic DMARDs, and 8.8% who had used 3 or more prior non-biologic DMARDs. Methotrexate was the most frequently reported (91.7%) prior non-biologic DMARD overall.

DMARD use concomitantly with study medication

Through Week 24, most subjects (99.0%) reported use of concomitant medications for any indication. The majority (82.3%) of subjects reported concomitant use of non-biologic DMARDs (Table 27), 66.3% of subjects reported concomitant use of NSAIDs, and a minority (20.0%) of subjects reported concomitant use of systemic corticosteroids.

Table 27 Concomitant Non-Biologic DMARDs up to Week 24 (FAS)

					---------UPA---------		
Generic Name (WHO Q1 2018)	Placebo to UPA 15 mg QD (N = 211) n (%)	Placebo to UPA 30 mg QD (N = 212) n (%)	All Placebo (N = 423) n (%)	ADA 40 mg EOW (N = 429) n (%)	15 mg QD (N = 429) n (%)	30 mg QD (N = 423) n (%)	Total (N = 1704) n (%)
Any Concomitant Non-Biologic DMARDs	176 (83.4)	178 (84.0)	354 (83.7)	348 (81.1)	355 (82.8)	346 (81.8)	1403 (82.3)
APREMILAST	9 (4.3)	4 (1.9)	13 (3.1)	9 (2.1)	7 (1.6)	9 (2.1)	38 (2.2)
BUCILLAMINE	0	0	0	0	1 (0.2)	0	1 (<0.1)
CHLOROQUINE	0	1 (0.5)	1 (0.2)	1 (0.2)	0	2 (0.5)	4 (0.2)
CICLOSPORIN	0	1 (0.5)	1 (0.2)	0	1 (0.2)	1 (0.2)	3 (0.2)
HYDROXYCHLOROQUINE	3 (1.4)	3 (1.4)	6 (1.4)	7 (1.6)	8 (1.9)	2 (0.5)	23 (1.3)
IGURATIMOD	1 (0.5)	0	1 (0.2)	0	1 (0.2)	0	2 (0.1)
LEFLUNOMIDE	7 (3.3)	17 (8.0)	24 (5.7)	25 (5.8)	29 (6.8)	29 (6.9)	107 (6.3)
METHOTREXATE	151 (71.6)	145 (68.4)	296 (70.0)	286 (66.7)	299 (69.7)	295 (69.7)	1176 (69.0)
SULFASALAZINE	21 (10.0)	22 (10.4)	43 (10.2)	44 (10.3)	32 (7.5)	38 (9.0)	157 (9.2)

Note: This table includes all medications administered up to Week 24 treatment period. Thus all medications with an end date prior to the first study drug dose or a start date after the first dose date at the Week 24 are excluded. For the subjects who discontinued before Week 24 first dose date, the medications taken within 1 day of the last dose of study drug for the subjects on upadacitinib and placebo, and within 14 day of the last dose of study drug for the subjects on adalimumab, are included.

Through Week 24, mean treatment compliance was 99.4% and 98.7% in the upadacitinib 15 mg and 30 mg groups, respectively, and 98.3% in the ADA group (after two outliers in the upadacitinib groups were excluded who discontinued study drug on the same day or one day after the baseline visit and did not return the study drug).

Outcomes and estimation

Primary endpoint

The primary endpoint was the proportion of subjects achieving ACR20 response at Week 12. A statistically significantly greater percentage of subjects in the upadacitinib 15 mg QD and 30 mg QD groups demonstrated an ACR20 response at Week 12 compared with the placebo group based on the FAS using NRI (Table 28). Results from supplementary analyses using As Observed [AO] on the FAS and Non-Responder Imputation (NRI) on the Per Protocol Analysis Set were consistent with the primary analysis (data not shown in this AR for brevity). The results of the tipping point analysis for ACR20 at Week 12 showed that results of the primary efficacy analysis using NRI data handling are robust to missing data assumptions.

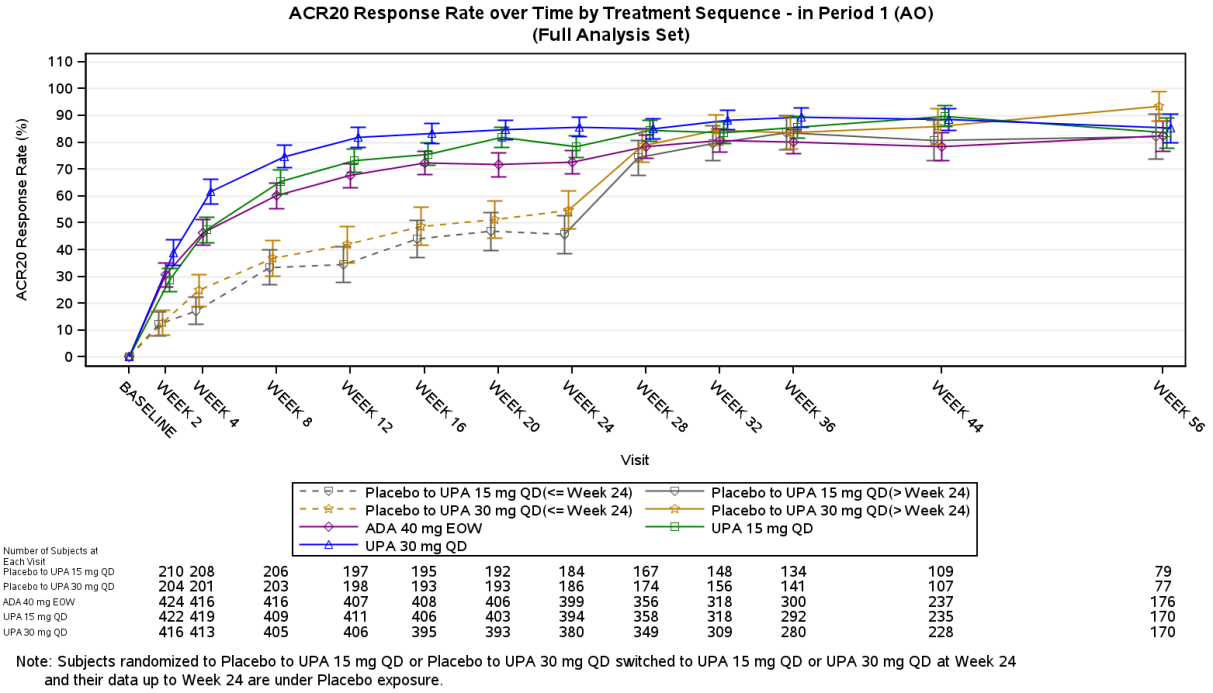
The difference in the response rate was retained up to Week 24, where after the response rate in subjects transferred from placebo arms to upadacitinib achieved the response rate of subjects who had used upadacitinib or adalimumab from the start of the study (Figure 26, results given as observed (AO)). Of note, the study is ongoing, and the results after Week 24 represent the subjects who had already reached the respective time points in the study.

Table 28 ACR20 response at Week 12 (FAS)

Analysis of ACR20 Response Rate at Week 12
(Full Analysis Set)

Imputation Treatment	N	Responder n (%)	Response Rate (95% CI) [A]	---------Response Rate Diff (UPA - Placebo)---------- Point Estimate	95% CI [B]	P-value [C]
NRI						
Placebo	423	153 (36.2)	36.2 (31.6, 40.7)			
ADA 40 mg EOW	429	279 (65.0)	65.0 (60.5, 69.5)			
UPA 15 mg QD	429	303 (70.6)	70.6 (66.3, 74.9)	34.5	(28.2, 40.7)	<0.0001*
UPA 30 mg QD	423	332 (78.5)	78.5 (74.6, 82.4)	42.3	(36.3, 48.3)	<0.0001*
AO						
Placebo	395	151 (38.2)	38.2 (33.4, 43.0)			
ADA 40 mg EOW	407	275 (67.6)	67.6 (63.0, 72.1)			
UPA 15 mg QD	411	301 (73.2)	73.2 (69.0, 77.5)	35.0	(28.6, 41.4)	<0.0001*
UPA 30 mg QD	406	333 (82.0)	82.0 (78.3, 85.8)	43.8	(37.7, 49.9)	<0.0001*
AO (with imputation)						
Placebo	423	151 (35.7)	35.7 (31.1, 40.3)			
ADA 40 mg EOW	429	275 (64.1)	64.1 (59.6, 68.6)			
UPA 15 mg QD	429	301 (70.2)	70.2 (65.8, 74.5)	34.5	(28.2, 40.8)	<0.0001*
UPA 30 mg QD	423	333 (78.7)	78.7 (74.8, 82.6)	43.0	(37.0, 49.0)	<0.0001*

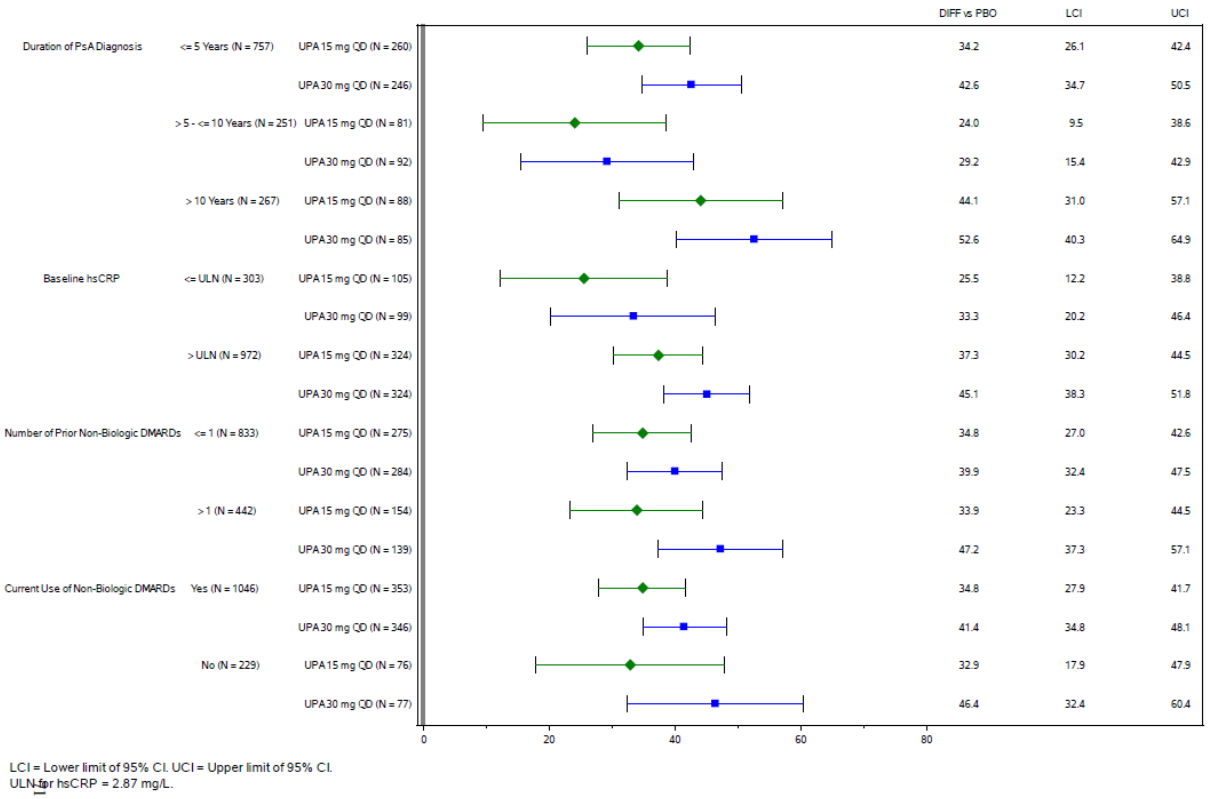
Note: AO (with imputation): Missing evaluations based on as-observed data are imputed as non-responders.
[A]: 95% CI for response rate are calculated based on normal approximation to the binomial distribution.
[B]: 95% CI for response rate difference are calculated based on normal approximation.
[C]: Nominal p-value is constructed using Cochran-Mantel-Haenszel test adjusting for the main stratification factor of current DMARD use (yes/no).
* Statistically significant at 0.05 level.



Note: Subjects randomized to Placebo to UPA 15 mg QD or Placebo to UPA 30 mg QD switched to UPA 15 mg QD or UPA 30 mg QD at Week 24 and their data up to Week 24 are under Placebo exposure.

Figure 26 ACR20 response rate over time by treatment sequence – in Period 1 (AO, FAS)

Results on primary endpoint analysed for demographic subgroups based on age, sex, BMI, race, and geographic region were consistent with the primary analysis. Additionally, the results for different subgroups based on disease characteristics showed benefit for upadacitinib compared with placebo (Figure 27). Neither the number of prior non-biologic DMARDs nor presence of concomitant non-biologic DMARDs had effect on efficacy.



LCI = Lower limit of 95% CI. UCI = Upper limit of 95% CI.
ULN for hsCRP = 2.87 mg/L.

Figure 27 Forest Plot of ACR20 Response Rate (UPA vs PBO) at Week 12 by Disease Characteristic Subgroups (NRI) (FAS)

The ACR20 response rate was of the same order of magnitude in patients using and not using non-biologic DMARDs concomitantly (Table 29).

Table 29 Subgroup Analysis of ACR20 Response Rate at Week 12 by Current Use of Non-Biologic DMARDs (NRI) (FAS)

Subgroup Treatment	N	Responder n (%)	Response Rate (95% CI) [A]	---------Response Rate Diff (UPA - Placebo)---------- Point Estimate	 95% CI [B]
Yes					
Placebo	347	130 (37.5)	37.5 (32.4, 42.6)		
ADA 40 mg EOW	347	223 (64.3)	64.3 (59.2, 69.3)		
UPA 15 mg QD	353	255 (72.2)	72.2 (67.6, 76.9)	34.8	(27.9, 41.7)
UPA 30 mg QD	346	273 (78.9)	78.9 (74.6, 83.2)	41.4	(34.8, 48.1)
No					
Placebo	76	23 (30.3)	30.3 (19.9, 40.6)		
ADA 40 mg EOW	82	56 (68.3)	68.3 (58.2, 78.4)		
UPA 15 mg QD	76	48 (63.2)	63.2 (52.3, 74.0)	32.9	(17.9, 47.9)
UPA 30 mg QD	77	59 (76.6)	76.6 (67.2, 86.1)	46.4	(32.4, 60.4)

[A]: 95% CI for response rate are calculated based on normal approximation to the binomial distribution.
[B]: 95% CI for response rate difference are calculated based on normal approximation.

The proportion of responders and non-responders by study arms and subsets of non-responders is given in Table 30. The number of subjects classified as non-responders due to discontinuation of study drug or missing values was relatively small.

Table 30 ACR20 response at week 12 by intercurrent events (NRI; FAS)

TABLE 14.2 2.5

ACR20 Response at Week 12 by Intercurrent Events (NRI)
(Full Analysis Set)

	Placebo (N = 423)	ADA 40 mg EOW (N = 429)	----------UPA---------- 15 mg QD (N = 429)	 30 mg QD (N = 423)
Responders, n (%)	153 (36.2)	279 (65.0)	303 (70.6)	332 (78.5)
Non-responders, n (%)	270 (63.8)	150 (35.0)	126 (29.4)	91 (21.5)
Discontinued study drug	21 (5.0)	19 (4.4)	16 (3.7)	16 (3.8)
Missing measurements	8 (1.9)	1 (0.2)	3 (0.7)	3 (0.7)
Observed	241 (57.0)	130 (30.3)	107 (24.9)	72 (17.0)

Key secondary endpoints

The results for key secondary endpoints versus placebo were consistent with that of the primary endpoint (Table 31). Upadacitinib 15 mg and 30 mg showed statistically significant efficacy compared with placebo for change in baseline in HAQ-DI, SF-36 PCS, and FACIT-F at Week 12, the proportion of subjects achieving sIGA 0/1 and PASI 75 at Week 16, the change from baseline in SHS and the proportion of subjects achieving MDA and resolution of enthesitis at Week 24. The difference between upadacitinib and placebo in improvement of dactylitis was no statistically significant.

The study also showed statistical significance for the NI of ACR20 response at Week 12 compared with ADA for both upadacitinib doses. The percentages of ADA effect preservation, which was calculated by (upadacitinib – placebo)/(ADA – placebo), were 119.4% (confidence interval [CI]: 98.0, 147.9) and 146.6% (CI: 122.8, 180.4) in upadacitinib 15 mg and 30 mg groups, respectively. For both upadacitinib doses, the lower bound of the 95% CI exceeded the pre-specified NI ratio of at least 50% of the placebo-subtracted ADA effect.

The response rate differences in ACR20 at Week 12 between the upadacitinib 15 and 30 mg doses and ADA using the FAS were 5.6% (CI: –0.6, 11.8) and 13.5% (CI: 7.5, 19.4), respectively. The analysis

on the Per Protocol Analysis Set showed consistent results for both response rate difference and ADA effect preservation.

The ACR20 response was larger already at Week 2 in the upadacitinib arms vs. placebo.

The response in skin symptoms was assessed by the key secondary endpoints 75 percent improvement in Psoriasis Area and Severity Index (PASI75), static Investigator Global Assessment of Psoriasis (sIGA), and Self-Assessment of Psoriasis Symptoms (SAPS). All comparisons except the difference in SAPS response were statistically significant.

Table 31 Summary of Key Secondary Endpoints (FAS)

Endpoint[a] Treatment	N	Within Group Point Estimate (95% CI)	Between Group Difference (Upadacitinib - Control) Point Estimate (95% CI)	Nominal *P*-Value	Adjusted *P*-Value
Change from baseline in HAQ-DI at Week 12					
Placebo	392	–0.14 (–0.18, –0.09)			
Upadacitinib 15 mg	404	–0.42 (–0.47, –0.37)	–0.28 (–0.35, –0.22)	< 0.0001	< 0.0001
Upadacitinib 30 mg	398	–0.47 (–0.52, –0.42)	–0.34 (–0.40, –0.27)	< 0.0001	< 0.0001
sIGA 0/1 at Week 16[b]					
Placebo	313	10.9 (7.4, 14.3)			
Upadacitinib 15 mg	322	41.9 (36.5, 47.3)	31.1 (24.7, 37.5)	< 0.0001	< 0.0001
Upadacitinib 30 mg	324	54.0 (48.6, 59.4)	43.1 (36.7, 49.6)	< 0.0001	< 0.0001
PASI 75 response at Week 16 (for subjects with ≥ 3% BSA psoriasis at baseline)					
Placebo	211	21.3 (15.8, 26.9)			
Upadacitinib 15 mg	214	62.6 (56.1, 69.1)	41.3 (32.8, 49.8)	< 0.0001	< 0.0001
Upadacitinib 30 mg	210	62.4 (55.8, 68.9)	41.1 (32.5, 49.6)	< 0.0001	< 0.0001
Change from baseline in SHS at Week 24					
Placebo	372	0.25 (0.13, 0.36)			
Upadacitinib 15 mg	391	–0.04 (–0.16, 0.07)	–0.29 (–0.44, –0.14)	0.0002	0.0004
Upadacitinib 30 mg	383	0.03 (–0.08, 0.15)	–0.21 (–0.36, –0.06)	0.0069	0.0069
Proportion of subjects achieving MDA at Week 24					
Placebo	423	12.3 (9.2, 15.4)			
Upadacitinib 15 mg	429	36.6 (32.0, 41.2)	24.3 (18.8, 29.8)	< 0.0001	0.0004
Upadacitinib 30 mg	423	45.4 (40.6, 50.1)	33.1 (27.4, 38.8)	< 0.0001	0.0069
Proportion of subjects with resolution of enthesitis at Week 24 (LEI = 0) (For subjects with baseline LEI > 0)					
Placebo	241	32.4 (26.5, 38.3)			
Upadacitinib 15 mg	270	53.7 (47.8, 59.7)	21.3 (13.0, 29.7)	< 0.0001	0.0004
Upadacitinib 30 mg	267	57.7 (51.8, 63.6)	25.3 (16.9, 33.7)	< 0.0001	0.0069
ACR20 response rate at Week 12 (NI of UPA vs. ADA)[c]					
Placebo	423	36.2 (31.6, 40.7)			
ADA 40 mg	429	65.0 (60.5, 69.5)			
Upadacitinib 15 mg	429	70.6 (66.3, 74.9)	119.381 (97.987, 147.942)	< 0.0001	0.0004
Upadacitinib 30 mg	423	78.5 (74.6, 82.4)	146.604 (122.817, 180.398)	< 0.0001	0.0069
SF-36 PCS change from baseline at Week 12					
Placebo	394	3.19 (2.41, 3.96)			
Upadacitinib 15 mg	405	7.86 (7.09, 8.63)	4.67 (3.67, 5.67)	< 0.0001	0.0004
Upadacitinib 30 mg	398	8.90 (8.13, 9.68)	5.72 (4.71, 6.72)	< 0.0001	0.0069

Change from baseline in HAQ-DI at Week 12 (superiority of UPA vs ADA)					
Placebo	392	–0.14 (–0.18, –0.09)			
ADA 40 mg	406	–0.34 (–0.38, –0.29)			
Upadacitinib 15 mg	404	–0.42 (–0.47, –0.37)	–0.08 (–0.15, –0.01)	0.0162 (vs. ADA)	0.8970
Upadacitinib 30 mg	398	–0.47 (–0.52, –0.42)	–0.14 (–0.20, –0.07)	< 0.0001 (vs. ADA)	0.8970
SAPS change from baseline at Week 16					
Placebo	388	–8.2 (–10.2, –6.3)			
Upadacitinib 15 mg	396	–25.3 (–27.3, –23.4)	–17.1 (–19.6, –14.6)	< 0.0001	0.8970
Upadacitinib 30 mg	395	–28.1 (–30.0, –26.1)	–19.8 (–22.3, –17.3)	< 0.0001	0.8970
ACR50 response rate at Week 12					
Placebo	423	13.2 (10.0, 16.5)			
Upadacitinib 15 mg	429	37.5 (32.9, 42.1)	24.3 (18.7, 29.9)	< 0.0001	
Upadacitinib 30 mg	423	51.8 (47.0, 56.5)	38.5 (32.8, 44.3)	< 0.0001	
ACR70 response rate at Week 12					
Placebo	423	2.4 (0.9, 3.8)			
Upadacitinib 15 mg	429	15.6 (12.2, 19.1)	13.3 (9.5, 17.0)	< 0.0001	
Upadacitinib 30 mg	423	25.3 (21.2, 29.4)	22.9 (18.5, 27.3)	< 0.0001	
FACIT-F change from baseline at Week 12					
Placebo	394	2.8 (1.9, 3.7)			
Upadacitinib 15 mg	404	6.3 (5.4, 7.2)	3.5 (2.4, 4.7)	< 0.0001	0.0004
Upadacitinib 30 mg	398	7.1 (6.2, 8.0)	4.3 (3.1, 5.5)	< 0.0001	0.0069
ACR20 response rate at Week 12 (superiority of UPA vs ADA)					
Placebo	423	36.2 (31.6, 40.7)			
ADA 40 mg	429	65.0 (60.5, 69.5)			
Upadacitinib 15 mg	429	70.6 (66.3, 74.9)	5.6 (–0.6, 11.8)	0.0815 (vs. ADA)	0.0815
Upadacitinib 30 mg	423	78.5 (74.6, 82.4)	13.5 (7.5, 19.4)	< 0.0001 (vs. ADA)	0.0069
Proportion of subjects with resolution of dactylitis at Week 24 (LDI = 0) (For subjects with baseline LDI > 0)					
Placebo	126	39.7 (31.1, 48.2)			
Upadacitinib 15 mg	136	76.5 (69.3, 83.6)	36.8 (25.7, 47.9)	< 0.0001	0.0815
Upadacitinib 30 mg	127	79.5 (72.5, 86.5)	39.8 (28.8, 50.9)	< 0.0001	0.0815
Change from baseline in Patient's Assessment of Pain at Week 12 (superiority of UPA vs ADA)					
Placebo	392	–0.9 (–1.2, –0.7)			
ADA 40 mg	406	–2.3 (–2.5, –2.1)			
Upadacitinib 15 mg	404	–2.3 (–2.5, –2.0)	0.0 (–0.3, 0.3)	0.8970 (vs. ADA)	0.8970
Upadacitinib 30 mg	398	–2.7 (–2.9, –2.5)	–0.5 (–0.7, –0.2)	0.0028 (vs. ADA)	0.0815
ACR20 response rate at Week 2					
Placebo	423	12.1 (9.0, 15.2)			
Upadacitinib 15 mg	429	28.2 (23.9, 32.5)	16.1 (10.9, 21.4)	< 0.0001	
Upadacitinib 30 mg	423	38.3 (33.7, 42.9)	26.2 (20.7, 31.8)	< 0.0001	

ACR20/50/70 = American College of Rheumatology 20%, 50%, 70% response; ADA = adalimumab; ANCOVA = analysis of covariance; BSA = body surface area; CI = confidence interval; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire - Disability Index; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; MDA = minimal disease activity; MMRM = Mixed-Effects Model Repeated Measures; NI = non-inferiority; NRI = Non-Responder Imputation; PASI = Psoriasis Area Severity Index; SAPS = Self-Assessment of Psoriasis Symptoms; SF-36 PCS = 36-Item Short Form Health Survey Physical Component Score; SHS = Sharp/van der Heijde Score; sIGA = Static Investigator Global Assessment of Psoriasis; UPA = upadacitinib

a. Results for binary endpoints except for MDA at Week 24 are based on NRI. Results for MDA, resolution of enthesitis, and resolution of dactylitis at Week 24 are based on NRI with additional rescue handling, where subjects rescued at Week 16 is imputed as non-responders. Results for SHS were based on ANCOVA with linear extrapolation for missing data and rescue handling. Results for other continuous endpoints were based on MMRM model.

b. sIGA 0/1 for subjects with baseline sIGA ≥ 2.

c. NI test of UPA vs. ADA was based on three arm NI testing aiming UPA preserves at least 50% of the placebo-subtracted ADA effect.

Adjusted P-values are provided for multiplicity-adjusted endpoints.

In subsequent testing of superiority versus ADA, upadacitinib 30 mg, but not 15 mg, showed superiority versus ADA in the primary endpoint ACR20 at Week 12, with ACR20 response rates of 65.0 (ADA), 70.6 (upadacitinib 15 mg, adjusted P-value against ADA 0.0815), and 78.5 (upadacitinib 30 mg, adj. P-value 0.0069).

Additional efficacy endpoints

Structural changes

Analyses of structural joint damage were conducted based on linear extrapolation as the primary analysis and AO data as a supplementary analysis. In addition, a sensitivity analysis was conducted using a random coefficient model.

At Week 24, inhibition of radiographic progression was observed in the upadacitinib 15 mg and 30 mg groups compared with the placebo group, as shown by a statistically smaller mean increase from baseline in SHS (equivalent to modified Total Sharp Score [mTSS], key secondary endpoint) and nominally smaller increase in Joint Erosion Score and JSN Score at Week 24 (additional secondary endpoints). Consistent results were obtained by linear extrapolation and AO (Table 32). The Random coefficient model gave similar results.

Table 32 Summary of Change from Baseline in SHS, Joint Erosion Score, and JSN Score at Week 24 (Linear Extrapolation and AO; FAS)

Measure Imputation Treatment	N	Baseline Mean	Visit Mean	Change from Baseline Within Group LS Mean (95% CI)[a]	Between Group Comparison (Upadacitinib – Placebo) LS Mean Diff (95% CI)[a]	P-Value[a]
SHS						
Linear Extrapolation						
Placebo	372	13.05	13.31	0.25 (0.13, 0.36)		
ADA 40 mg	384	14.89	14.92	0.01 (–0.11, 0.13)		
Upadacitinib 15 mg	391	13.44	13.42	–0.04 (–0.16, 0.07)	–0.29 (–0.44, –0.14)	0.0002
Upadacitinib 30 mg	383	11.36	11.41	0.03 (–0.08, 0.15)	–0.21 (–0.36, –0.06)	0.0069
AO						
Placebo	365	13.27	13.53	0.24 (0.12, 0.35)		
ADA 40 mg	391	15.31	15.35	0.01 (–0.10, 0.13)		
Upadacitinib 15 mg	387	13.58	13.55	–0.05 (–0.16, 0.07)	–0.28 (–0.43, –0.14)	0.0002
Upadacitinib 30 mg	381	11.22	11.27	0.03 (–0.08, 0.14)	–0.21 (–0.35, –0.06)	0.0061
Joint Erosion Score						
Linear Extrapolation						
Placebo	372	5.95	6.07	0.12 (0.06, 0.17)		
ADA 40 mg	384	6.72	6.74	0.01 (–0.04, 0.07)		
Upadacitinib 15 mg	391	6.19	6.16	–0.03 (–0.08, 0.02)	–0.15 (–0.22, –0.08)	< 0.0001
Upadacitinib 30 mg	383	5.00	5.03	0.03 (–0.03, 0.08)	–0.09 (–0.16, –0.02)	0.0105
AO						
Placebo	365	6.05	6.17	0.12 (0.06, 0.17)		
ADA 40 mg	391	6.88	6.90	0.01 (–0.04, 0.07)		
Upadacitinib 15 mg	387	6.26	6.23	–0.03 (–0.08, 0.02)	–0.15 (–0.22, –0.08)	< 0.0001
Upadacitinib 30 mg	381	4.92	4.96	0.03 (–0.02, 0.08)	–0.09 (–0.15, –0.02)	0.0121
JSN						
Linear Extrapolation						
Placebo	372	7.10	7.22	0.10 (0.04, 0.17)		
ADA 40 mg	384	8.17	8.16	–0.02 (–0.09, 0.04)		
Upadacitinib 15 mg	391	7.24	7.25	0.00 (–0.07, 0.06)	–0.11 (–0.19, –0.02)	0.0159
Upadacitinib 30 mg	383	6.35	6.38	0.01 (–0.06, 0.08)	–0.09 (–0.18, –0.01)	0.0325
AO						
Placebo	365	7.22	7.33	0.10 (0.03, 0.16)		
ADA 40 mg	391	8.44	8.43	–0.02 (–0.08, 0.04)		
Upadacitinib 15 mg	387	7.31	7.32	0.00 (–0.06, 0.06)	–0.10 (–0.18, –0.02)	0.0169
Upadacitinib 30 mg	381	6.29	6.31	0.00 (–0.06, 0.07)	–0.09 (–0.17, –0.01)	0.0251

ANCOVA = analysis of covariance; AO = As Observed; CI = confidence interval; Diff = difference; DMARD = disease-modifying antirheumatic drug; EOW = every other week; FAS = Full Analysis Set; JSN = joint space narrowing; LS = least square; QD = once daily; SHS = Sharp/van der Heijde Score

a. Within group LS mean and 95% CI, and between group LS mean difference and 95% CI and nominal p-value were based on ANCOVA model including treatment and the stratification factor current DMARD use (yes/no) as fixed factors and baseline value as covariate.

Inhibition of progression of structural joint damage was also measured by the *proportion of subjects with no radiographic progression*, defined in 2 ways: as a change from baseline in SHS ≤ 0, and as ≤ 0.5 (additional secondary endpoints) (table 33). It is noteworthy that the nominal difference in proportion of responders to upadacitinib and placebo was less than 5 %.

No difference was seen between upadacitinib and ADA in any of the investigated parameters for structural progression (Table 33).

Table 33 Proportion of Subjects with No Radiographic Progression (Change from Baseline in SHS ≤ 0 or SHS ≤ 0.5) at Week 24 (FAS)

Endpoint Definition Imputation Treatment	N	Responder n (%)	Response Rate Difference (Upadacitinib – Placebo) Point Estimate (95% CI)[a]	P-value[b]	Response Rate Difference (Upadacitinib – Adalimumab) Point Estimate (95% CI)[a]	P-value[b]
SHS ≤ 0						
Linear Extrapolation						
Placebo	372	332 (89.2)				
Adalimumab 40 mg eow	384	357 (93.0)				
Upadacitinib 15 mg QD	391	365 (93.4)	4.1 (0.1, 8.1)	0.0448	0.4 (–3.2, 3.9)	0.8352
Upadacitinib 30 mg QD	383	358 (93.5)	4.2 (0.2, 8.2)	0.0401	0.5 (–3.1, 4.1)	0.7815
As Observed						
Placebo	365	324 (88.8)				
Adalimumab 40 mg eow	391	362 (92.6)				
Upadacitinib 15 mg QD	387	360 (93.0)	4.3 (0.1, 8.4)	0.0427	0.4 (–3.2, 4.1)	0.8202
Upadacitinib 30 mg QD	381	356 (93.4)	4.7 (0.6, 8.8)	0.0263	0.9 (–2.7, 4.5)	0.6378
SHS ≤ 0.5						
Linear Extrapolation						
Placebo	372	342 (91.9)				
Adalimumab 40 mg eow	384	364 (94.8)				
Upadacitinib 15 mg QD	391	376 (96.2)	4.2 (0.9, 7.6)	0.0135	1.4 (–1.6, 4.3)	0.3582
Upadacitinib 30 mg QD	383	364 (95.0)	3.1 (–0.4, 6.6)	0.0861	0.2 (–2.9, 3.4)	0.8753
As Observed						
Placebo	365	336 (92.1)				
Adalimumab 40 mg eow	391	371 (94.9)				
Upadacitinib 15 mg QD	387	371 (95.9)	3.8 (0.4, 7.2)	0.0283	1.0 (–2.0, 3.9)	0.5199
Upadacitinib 30 mg QD	381	363 (95.3)	3.2 (–0.3, 6.7)	0.0745	0.4 (–2.7, 3.4)	0.7967

a. 95% CIs for response rate difference were calculated based on normal approximation.

b. Nominal p-value was constructed using CMH test adjusting for the main stratification factor of current DMARD use (yes/no).

Components of ACR response and ACR response over time

Components of ACR20/50/70 response include TJC68, SJC66, HAQ-DI, PtGA, PGA, Patient's Assessment of Pain, and hsCRP. All of these additional efficacy endpoints demonstrated a greater numerical improvement from baseline in all components of the ACR20/50/70 response at Week 12 compared with placebo. Further improvements were generally observed between Week 12 and Week 24 for subjects in both upadacitinib 15 mg QD and 30 mg QD groups (Table 34). The observed improvement was in general slightly larger with the 30 mg QD dose.

Table 34 Change from Baseline at Week 12 in Components of ACR20/50/70 Response (MMRM; FAS)

	M15-572 (Non-Biologic DMARD-IR)			
ACR Component	**Placebo**	**Adalimumab 40 mg eow**	**Upadacitinib 15 mg QD**	**Upadacitinib 30 mg**
TJC68				
LS mean	–7.1	–10.3	–11.3	–12.6
P-value vs. control			< 0.0001 (vs. placebo) 0.1590 (vs. adalimumab)	< 0.0001 (vs. placebo) 0.0007 (vs. adalimumab)
SJC66				
LS mean	–5.3	–7.6	–7.9	–8.0
P-value vs. control			< 0.0001 (vs. placebo) 0.4167 (vs. adalimumab)	< 0.0001 (vs. placebo) 0.2389 (vs. adalimumab)
HAQ-DI				
LS mean	–0.13	–0.34	–0.42	–0.47
P-value vs. control			< 0.0001 (vs. placebo) 0.0152 (vs. adalimumab)	< 0.0001 (vs. placebo) < 0.0001 (vs. adalimumab)
PtGA NRS				
LS mean	–1.2	–2.6	–2.7	–3.1
P-value vs. control			< 0.0001 (vs. placebo) 0.6300 (vs. adalimumab)	< 0.0001 (vs. placebo) 0.0004 (vs. adalimumab)
PGA NRS				
LS mean	–2.1	–3.4	–3.6	–3.8
P-value vs. control			< 0.0001 (vs. placebo) 0.2590 (vs. adalimumab)	< 0.0001 (vs. placebo) 0.0017 (vs. adalimumab)
Patient's Assessment of Pain NRS				
LS mean	–0.9	–2.3	–2.3	–2.7
P-value vs. control			< 0.0001 (vs. placebo) 0.9005 (vs. adalimumab)	< 0.0001 (vs. placebo) 0.0025 (vs. adalimumab)
hsCRP (mg/L)				
LS mean	–1.3	–7.6	–7.1	–7.4
P-value vs. control			< 0.0001 (vs. placebo) 0.5641 (vs. adalimumab)	< 0.0001 (vs. placebo) 0.8391 (vs. adalimumab)

P-values are for comparisons between upadacitinib groups and placebo and between upadacitinib groups and adalimumab. LS mean is the within group LS mean for change from baseline.

Treatment with upadacitinib 15 mg QD demonstrated a statistically significantly greater improvement from baseline in HAQ-DI at Week 12 and Week 24, PtGA at Week 24, and numerical larger improvement in Patient's Assessment of Pain at Week 24 compared with the adalimumab group (nominal $P < 0.05$).

Additional efficacy endpoints

A great number of other additional efficacy endpoints were studied. The results of these measures of musculoskeletal manifestations (joint, dactylitis, enthesitis, spinal), structural join damage, skin manifestations, physical function, quality of life (QoL) and other patient reported outcomes (PROs) and comprehensive disease control (measured by MDA percentage) are given in table 35. Most comparisons were not multiplicity controlled. The results that were statistically significant in the multiplicity-controlled analysis for upadacitinib vs. placebo are marked with the symbol "~".

Similar improvement was seen with upadacitinib 15 mg and adalimumab on the musculoskeletal manifestations of PsA. Upadacitinib 15 mg was more efficacious than placebo in all comparisons.

All measures of skin manifestations were nominally alleviated by upadacitinib 15 mg when compared with placebo. Significantly better results with upadacitinib than placebo groups, respectively, were obtained at Week 16 by multiplicity-controlled analysis in PASI75: 62.6 % vs. 21.3 %, and sIGA: 0/1 41.9% vs. 10.9%.

In the QoL measures and other PROs, the results were uniformly nominally better in the upadacitinib than placebo group. Multiplicity-controlled analyses gave significantly better results for the upadacitinib 15 mg vs. placebo group, respectively, in the following measures: ΔSF-36 PCS (LS mean 7.86 vs. 3.19) and ΔFACIT-F (LS mean 6.3 vs. 2.8).

In subjects determined by the investigator to have psoriatic spondylitis at baseline (534/1704, 31 %), subjects in the upadacitinib 15 mg group had greater improvement from baseline in BASDAI and ASDAS, and a greater proportion of subjects achieved BASDAI 50, ASDAS inactive disease, ASDAS major improvement, and ASDAS clinically important improvement at Week 12 and Week 24 compared with subjects in the placebo group, with nominal P-values < 0.05. Further improvement in BASDAI and ASDAS scores were observed at Week 24 for both the upadacitinib 15 mg and 30 mg groups. The subjects with psoriatic spondylitis at baseline in the upadacitinib 15 mg group also showed greater nominal improvement from baseline in BASDAI and ASDAS and a greater proportion of subjects achieved ASDAS major improvement and clinically important improvement at Week 24 compared with subjects in the ADA group. The mean baseline BASDAI values were in the range of 5.69 to 5.98 in patients assessed by the investigator to have psoriatic spondylitis. At Week 12, the LS mean change in BASDAI was -1.00 (-1.39, -0.62) in the placebo arm, -2.35 (-2.74, -1.96) in the adalimumab arm, and -2.20 (-2.57, -1.82) in the upadacitinib 15 mg arm. ASDAI showed improvement as well.

Similarly, the results on morning stiffness as measured by overall morning stiffness (mean of BASDAI Questions 5 and 6), morning stiffness severity, and morning stiffness duration at Week 12 and through Week 24 was nominally better in the upadacitinib group compared with subjects in the placebo group (nominal P < 0.05). Subjects in the upadacitinib 30 mg group at Weeks 12 and 24 and subjects in the upadacitinib 15 mg group at Week 12 had greater improvement in overall morning stiffness, morning stiffness severity, and morning stiffness duration compared to the ADA group (nominal P < 0.05).

Table 35 Select Efficacy Results Across PsA Domains Through Week 56 for Study M15-572 (FAS)

Domain Outcome	PBO	ADA	UPA 15 mg	UPA 30 mg	PBO	ADA	UPA 15 mg	UPA 30 mg	PBO to UPA 15 mg[a]	PBO to UPA 30 mg[a]	ADA	UPA 15 mg	UPA 30 mg
Musculoskeletal manifestations (joint, dactylitis, enthesitis, spinal)	Week 12				Week 24				Week 56[b]				
ACR20 (%)	36.2	65.0	70.6~,&	78.5~,&,$	45.2	67.1	73.4*,#	78.5*,#	82.3	93.5	82.4	83.5	85.3
ACR50 (%)	13.2	37.5	37.5*	51.8*,#	18.9	44.3	52.4*,#	60.5*,#	62.0	76.9	61.1	67.6	69.4
ACR70 (%)	2.4	13.8	15.6*	25.3*,#	5.2	22.6	28.7*,#	36.4*,#	31.6	41.8	36.9	44.1	48.2
Modified PsARC (%)	54.6	75.5	78.3*	83.5*,#	59.3	76.7	83.7*,#	82.0*	92.4	93.7	88.6	90.0	92.9
ΔDAPSA (LS mean)	–15.7	–30.0	–30.7*	–33.9*,#	–20.6	–33.6	–36.4*,#	–38.0*,#	–38.9	–44.3	–39.7	–40.9	–42.5
ΔPASDAS (LS mean)	–1.09	–2.13	–2.29*	–2.61*,#	–1.51	–2.58	–2.95*,#	–3.13*,#	–3.06	–3.56	–3.17	–3.40	–3.53
ΔDAS28 (CRP) (LS mean)	–0.90	–1.68	–1.86*,#	–2.13*,#	–1.21	–2.01	–2.32*,#	–2.45*,#	–2.38	–2.82	–2.42	–2.54	–2.65
ΔPatient's Assessment of Pain (NRS) (LS mean)	–0.9	–2.3	–2.3*	–2.7*,#	–1.4	–2.6	–3.0*,#	–3.2*,#	–3.2	–3.8	–3.2	–3.4	–3.4
Resolution of dactylitis (LDI = 0) (%)[c]	42.1	71.7	73.5*	79.5*	39.7	74.0	76.5*	79.5*	80.8	100	91.4	94.4	96.2
Resolution of enthesitis (LEI = 0) (%)[d]	32.8	46.8	47.4*	51.3*	32.4	47.2	53.7~	57.7~,#	61.4	75.6	73.7	72.8	73.5
Resolution of enthesitis (SPARCC Enthesitis Index = 0) (%)[e]	27.6	39.6	36.3*	43.4*	28.2	43.0	47.6*	53.2*,#	66.7	70.0	67.9	62.8	70.0
ΔBASDAI (LS mean)[f]	–1.00	–2.35	–2.20*	–2.60*	–1.70	–2.55	–3.12*,#	–3.16*,#	–2.58	–2.95	–3.15	–3.37	–3.55
BASDAI 50 (%)[f]	15.4	42.5	37.4*	50.7*	26.9	44.1	59.0*,#	52.9*	55.0	50.0	60.4	72.0	75.0
ΔASDAS (LS mean)[f]	–0.38	–1.47	–1.40*	–1.62*	–0.70	–1.41	–1.76*,#	–1.92*,#	–1.55	–1.95	–1.81	–1.88	–2.18
ASDAS inactive disease (%)[f]	6.2	29.9	23.0*	34.1*	13.1	35.4	41.7*	49.3*,#	31.6	42.9	47.8	54.2	60.4
Structural joint damage	Week 12				Week 24				Week 56[b]				
ΔSHS (LS mean)	--	--	--	--	0.25	0.01	–0.04~	0.03~	--	--	--	--	--
ΔJoint erosion score (LS mean)	--	--	--	--	0.12	0.01	–0.03*	0.03*	--	--	--	--	--
ΔJSN score (LS mean)	--	--	--	--	0.10	–0.02	–0.00*,$	0.01*	--	--	--	--	--
No radiographic progression (ΔSHS ≤ 0) (%)	--	--	--	--	89.2	93.0	93.4*	93.5*	--	--	--	--	--
No radiographic progression (ΔSHS ≤ 0.5) (%)	--	--	--	--	91.9	94.8	96.2*	95.0	--	--	--	--	--
Skin manifestations	Week 16				Week 24				Week 56[b]				
PASI 75 (%)[h]	21.3	53.1	62.6~	62.4~	26.5	58.8	64.0*	62.4*	63.9	76.2	71.4	72.9	76.5
PASI 90 (%)[h]	12.3	38.9	38.3*	49.5*,#	16.6	45.0	41.6*	48.1*	52.8	64.3	56.0	54.1	63.0
PASI 100 (%)[h]	7.1	19.9	23.8*	33.8*,#	10.0	27.5	26.6*	38.1*,#	30.6	47.6	34.5	37.6	49.4
sIGA 0/1 (%)[i]	10.9	38.5	41.9~	54.0~,#	11.5	40.6	45.3*	52.5*,#	39.3	58.5	52.2	52.4	64.1
ΔBSA-Ps (LS mean)[j]	–1.66	–5.26	–5.88*	–6.24*	–1.63	–5.74	–6.29*	–6.50*	–5.69	–7.47	–7.03	–6.23	–7.30
ΔSAPS (LS mean)	–8.2	–22.7	–25.3*,#	–28.1*,#	–9.7	–24.4	–28.3*,#	–29.4*,#	–27.7	–33.4	–27.9	–30.8	–33.3

Physical function	Week 12				Week 24				Week 56[b]				
ΔHAQ-DI (LS mean)	–0.14	–0.34	–0.42~,#	–0.47~,#	–0.19	–0.39	–0.51*,#	–0.51*,#	–0.40	–0.53	–0.50	–0.55	–0.55
HAQ-DI clinically meaningful improvement (ΔHAQ-DI ≤ –0.35) (%)	33.4	47.2	57.9*,#	62.0*,#	37.3	51.8	59.8*,#	63.1*,#	58.2	71.4	64.6	69.1	71.5
QoL and other PROs													
ΔSF-36 PCS (LS mean)	3.19	6.82	7.86~,#	8.90~,#	4.26	7.80	9.82*,#	9.85*,#	8.33	10.12	8.60	10.81	10.14
ΔSF-36 MCS (LS mean)	2.21	3.59	3.91*	3.42*	2.44	4.06	4.66*	4.32*	2.28	4.28	4.95	5.77	4.55
ΔEQ-5D-5L index (LS mean)	0.08	0.16	0.16*	0.18*	0.10	0.16	0.18*,#	0.19*,#	0.16	0.21	0.18	0.21	0.20
ΔFACIT-F (LS mean)	2.8	5.7	6.3~	7.1~,#	3.8	6.8	7.9*	8.0*	6.8	9.1	8.1	9.1	8.5
ΔMorning stiffness overall (LS mean)	–0.99	–2.13	–2.41*	–2.66*,#	–1.41	–2.49	–3.02*,#	–3.06*,#	–2.74	–3.32	–2.80	–3.24	–3.33
ΔMorning stiffness severity (LS mean)	–1.1	–2.3	–2.6*	–3.0*,#	–1.7	–2.8	–3.4*,#	–3.5*,#	–3.2	–3.6	–3.2	–3.6	–3.7
ΔMorning stiffness duration (LS mean)	–0.8	–2.0	–2.2*	–2.3*,#	–1.2	–2.2	–2.6*,#	–2.6*,#	–2.3	–3.0	–2.4	–2.8	–2.9
ΔWPAI overall work impairment (LS mean)[k]	–5.04	–17.12	–20.11*	–19.50*	–8.25	–20.33	–23.23*	–22.63*	–18.82	–21.35	–19.63	–23.42	–22.40
Comprehensive disease control													
MDA (%)	6.4	24.9	24.7*	35.5*,#	12.3	33.3	36.6~	45.4~,#	40.5	56.8	46.1	52.3	54.7

ACR20/50/70 = American College of Rheumatology 20/50/70%; ADA = adalimumab; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BSA-Ps = body surface area – psoriasis; CRP = C-reactive protein; DAPSA = Disease Activity in Psoriatic Arthritis; DAS28 = Disease Activity Score 28; EQ-5D-5L = EuroQoL-5 Dimensions-5 Levels; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire - Disability Index; JSN = joint space narrowing; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; LS = least square; MCS = Mental Component Summary; MDA = minimal disease activity; PASDAS = Psoriatic Arthritis Disease Activity Score; PASI = Psoriasis Area Severity Index; PBO = placebo; PCS = Physical Component Summary; PRO = patient-reported outcome; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; QoL = quality of life; SAPS = Self-Assessment of Psoriasis Symptoms; SF-36 = 36-Item Short Form Health Survey; SHS = Sharp/van der Heijde Score (equivalent to van der Heijde mTSS); sIGA 0/1 = Static Investigator Global Assessment of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline; SPARCC = Spondyloarthritis Research Consortium of Canada; UPA = upadacitinib; WPAI = Work Productivity and Activity Impairment

a. Treatment switch was at Week 24.

b. Available efficacy data are presented at Week 56. Through the data cutoff for Study M15-572, 39.7% of subjects completed Week 56 study participation. Data are subject to change when all subjects have completed Week 56 or otherwise prematurely discontinued study participation.

c. For subjects with baseline LDI > 0.

d. For subjects with baseline LEI > 0.

e. For subjects with baseline SPARCC Enthesitis Index > 0.

f. For subjects with psoriatic spondylitis at baseline.

g. Negative sign was omitted from 0.00 value in Study M15-572 CSR Table 10 and Table 14.2__4.3. The value was corrected to –0.00 in this table (i.e., Table 4) as well as Integrated Summary of Efficacy (ISE) Table 1.2__7.8.

h. For subjects with ≥ 3% BSA-Ps at baseline.

i. For subjects with baseline Static Investigator Global Assessment of Psoriasis (sIGA) ≥ 2.

j. For subjects with baseline BSA-Ps > 0.

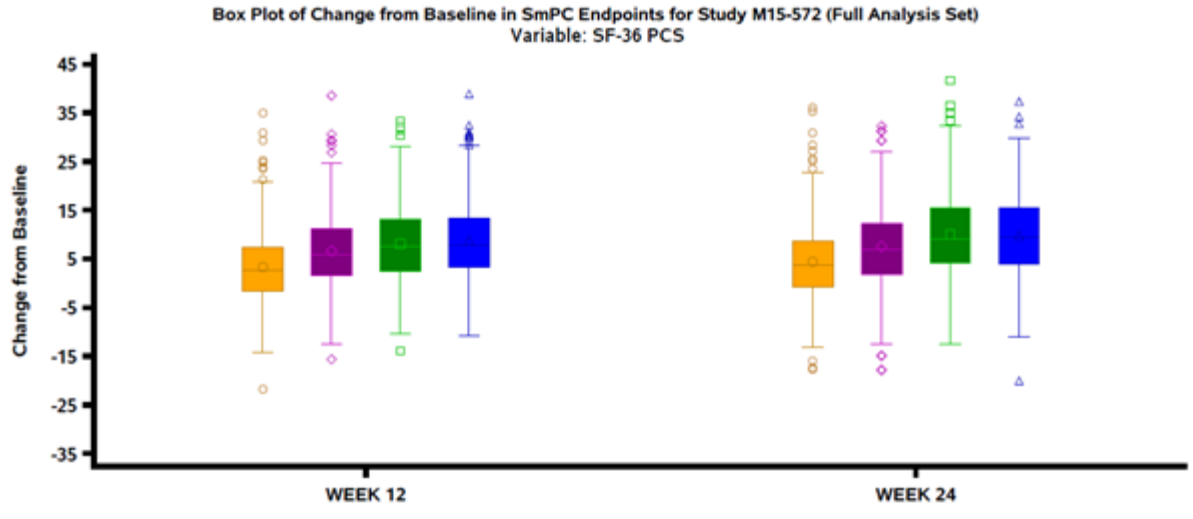
k. For subjects employed at baseline.

* Nominal $P < 0.05$ for upadacitinib vs. placebo.

\# Nominal $P < 0.05$ for upadacitinib vs. adalimumab.

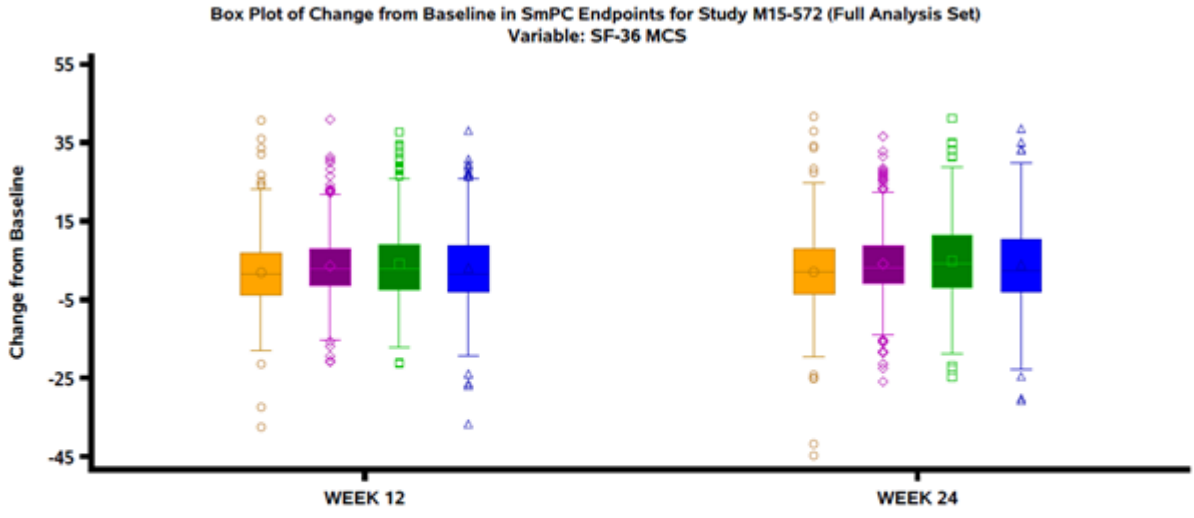
~ Statistically significant in the multiplicity-controlled analysis for upadacitinib vs. placebo.

The data submitted by the MAH in their response results on the SF-36 physical component score (PCS) and mental component score (MCS).



Statistics	Placebo	ADA 40 mg EOW	UPA 15 mg QD	UPA 30 mg QD	Placebo	ADA 40 mg EOW	UPA 15 mg QD	UPA 30 mg QD
Max*	20.80	24.65	28.04	28.21	22.76	27.04	32.35	29.80
Q3	7.40	11.27	13.04	13.31	8.67	12.32	15.45	15.40
Median	2.54	5.92	7.65	7.69	3.71	6.87	9.12	9.57
Mean	3.25	6.63	8.09	8.82	4.31	7.57	10.06	9.81
Q1	-1.56	1.48	2.39	3.30	-0.77	1.84	4.08	3.89
Min*	-14.21	-12.43	-10.31	-10.81	-13.28	-12.43	-12.52	-11.05

*: Max is the maximum observation below Q3 + 1.5*IQR and min is the minimum observation above Q1 - 1.5*IQR.



Statistics	Placebo	ADA 40 mg EOW	UPA 15 mg QD	UPA 30 mg QD	Placebo	ADA 40 mg EOW	UPA 15 mg QD	UPA 30 mg QD
Max*	23.12	21.78	25.90	25.84	24.62	22.39	28.87	29.70
Q3	6.94	7.86	9.03	8.66	8.00	8.69	11.28	10.39
Median	1.54	2.75	2.78	1.48	1.99	3.04	4.29	2.40
Mean	1.86	3.55	3.97	3.09	2.11	4.12	4.80	3.88
Q1	-3.86	-1.53	-2.39	-3.13	-3.60	-0.76	-1.99	-2.99
Min*	-18.10	-15.31	-17.15	-19.39	-19.64	-14.05	-18.88	-22.69

*: Max is the maximum observation below Q3 + 1.5*IQR and min is the minimum observation above Q1 - 1.5*IQR.

Figure 28 Change from baseline in SF-36 PCS and MCS (full analysis set)

Study M15-554

Participant flow and numbers analysed

A total of 642 subjects were randomized at 123 sites located in 16 countries, of whom 641 subjects received study drug. Number of screened subjects is not available. A total of 591 subjects (92.1 %)

and 543 subjects (84,6 %) completed study drug by Week 12 (primary endpoint) and Week 24, respectively.

The most frequent primary reason for study drug discontinuation by Week 24 was lack of efficacy for the placebo group, and AE for the upadacitinib group (table 36). As of the data cut-off date for this CSR, 297 subjects (46.3%) had completed Period 1 (Week 56), 182 subjects (28.3%) had discontinued study drug during Period 1, and 163 subjects were ongoing in Period 1. Of the 182 subjects who discontinued by data cut-off, the most frequent primary reason for study drug discontinuation was lack of efficacy for the placebo and upadacitinib 15 mg groups, and AE for the upadacitinib 30 mg group.

The MAH provided in the response to the RSI 56 week, results for all efficacy endpoints. All study subjects had reached Week 56 or were prematurely discontinued by submission of the response.

Table 36 Study Drug Disposition of Subjects (All Randomized Subjects)

	Placebo (N = 212)	Upadacitinib 15 mg QD (N = 211)	Upadacitinib 30 mg QD (N = 219)	Overall Total (N = 642)
Randomized, n	212	211	219	642
FAS, n	212	211	218	641
Per Protocol Analysis Set, n	203	192	196	591
Safety Analysis Set, n	212	211	218	641
Completed study drug up to Week 12, n (%)	183 (86.3)	202 (95.7)	206 (94.1)	591 (92.1)
Discontinued study drug (primary reason), n (%)	29 (13.7)	9 (4.3)	13 (5.9)	51 (7.9)
Adverse event	6 (2.8)	4 (1.9)	6 (2.7)	16 (2.5)
Withdrawal by subject	12 (5.7)	0	3 (1.4)	15 (2.3)
Lost to follow up	4 (1.9)	3 (1.4)	1 (0.5)	8 (1.2)
Lack of efficacy	7 (3.3)	0	1 (0.5)	8 (1.2)
Other	0	2 (0.9)	2 (0.9)	4 (0.6)
Completed study drug up to Week 24, n (%)	169 (79.7)	185 (87.7)	189 (86.3)	543 (84.6)
Discontinued study drug (primary reason), n (%)	43 (20.3)	26 (12.3)	30 (13.7)	99 (15.4)
Adverse event	9 (4.2)	15 (7.1)	16 (7.3)	40 (6.2)
Withdrawal by subject	13 (6.1)	0	7 (3.2)	20 (3.1)
Lost to follow up	5 (2.4)	4 (1.9)	1 (0.5)	10 (1.6)
Lack of efficacy	14 (6.6)	5 (2.4)	2 (0.9)	21 (3.3)
Other	2 (0.9)	2 (0.9)	4 (1.8)	8 (1.2)

FAS = Full Analysis Set; QD = once daily

Recruitment

The first subject first visit occurred 01 May 2017 and the last subject last visit for the Period 1 up to 24 weeks was 09 October 2019. Discussion of results for the remainder of Period 1 (Weeks 24 through 56) is not included in the interim CSR, however, some data are presented for the remainder of Period 1 (24 to 56 weeks). All study subjects had reached Week 56 or were prematurely discontinued by submission of the response to the RSI; hence, the results were submitted by the MAH (see assessment in Ancillary Analyses of this AR).

Conduct of the study

There were six protocol amendments and two administrative changes in the protocol for study M15-554. All of these were dated prior to data cut-off. Each amendment contained multiple updates, mostly clarifications on inclusion and exclusion criteria, permitted concomitant treatments and their dose changes, administrative changes, contraception recommendations, measures to ensure safety of study subjects, and linguistic changes.

According to the MAH, all studies were conducted in accordance with GCP and applicable local laws and regulations. Two investigative site audits were conducted by the sponsor. No regulatory inspections are reported in the submission.

Receipt of excluded or prohibited medications was the most common protocol deviation. A total of 77 (12.0%) subjects had such a deviation. However, after the database lock for the interim report, 10 of these 77 subjects were deemed to have been erroneously included in this category. These 10 subjects all received corticosteroids > 10 mg/day of prednisone or equivalent after implementation of Amendment 3, which did not state that such doses of corticosteroids were prohibited after Week 36. These protocol deviations will according to the MAH be removed from the database prior to the final clinical study report for the study.

Baseline data

Demographic characteristics were generally balanced across the upadacitinib 15 mg, 30 mg, and placebo groups (Table 37). The mean age of the study subjects was 53.4 years, with a small majority of females.

Table 37 Demographic characteristics (FAS)

	Placebo (N = 212)	Upadacitinib 15 mg QD (N = 211)	Upadacitinib 30 mg QD (N = 218)	Total (N = 641)
Sex, n (%)				
Female	120 (56.6)	113 (53.6)	115 (52.8)	348 (54.3)
Male	92 (43.4)	98 (46.4)	103 (47.2)	293 (45.7)
Age (years)				
Mean ± SD	54.1 (11.53)	53.0 (12.02)	53.0 (11.94)	53.4 (11.83)
Median (min, max)	55.0 (22.0, 83.0)	54.0 (25.0, 80.0)	53.0 (26.0, 79.0)	54.0 (22.0, 83.0)
Age (years), n (%)				
< 65	170 (80.2)	174 (82.5)	173 (79.4)	517 (80.7)
65 - < 75	37 (17.5)	31 (14.7)	38 (17.4)	106 (16.5)
≥ 75	5 (2.4)	6 (2.8)	7 (3.2)	18 (2.8)
Race				
White	186 (87.7)	183 (86.7)	196 (89.9)	565 (88.1)
Black or African American	7 (3.3)	5 (2.4)	5 (2.3)	17 (2.7)
American Indian/Alaska Native				
Native Hawaiian or other Pacific Islander				
Asian	17 (8.0)	19 (9.0)	16 (7.3)	52 (8.1)
Multiple				
Ethnicity				
Hispanic or Latino	53 (25.0)	36 (17.1)	50 (22.9)	139 (21.7)
Not Hispanic or Latino	159 (75.0)	175 (82.9)	168 (77.1)	502 (78.3)
Weight (kg)				
Mean ± SD	90.0 (23.02)	89.3 (23.56)	87.1 (21.71)	88.8 (22.76)
Median (min, max)	87.5 (43.0, 180.3)	86.6 (47.2, 188.2)	86.1 (41.9, 181.8)	86.6 (41.9, 188.2)
Height (cm)				
n	211	211	218	640
Mean ± SD	168.2 (10.87)	168.1 (9.99)	167.9 (9.21)	168.1 (10.02)
Median (min, max)	169.0 (140.0, 198.1)	167.6 (145.0, 200.7)	167.6 (144.0, 196.0)	167.6 (140.0, 200.7)
Body mass index (kg/m^2)				
n	211	211	218	640
Mean ± SD	31.8 (7.47)	31.5 (7.37)	30.8 (7.00)	31.3 (7.28)
Median (min, max)	30.5 (15.8, 61.7)	30.3 (17.5, 64.9)	30.0 (16.3, 61.1)	30.4 (15.8, 64.9)
Body mass index (kg/m^2), n (%)				
< 25	39 (18.4)	40 (19.0)	39 (17.9)	118 (18.4)
≥ 25	172 (81.1)	171 (81.0)	179 (82.1)	522 (81.4)
missing	1 (0.5)	0	0	1 (0.2)
Tobacco/nicotine use,[a] n (%)				
Current	49 (23.1)	56 (26.5)	50 (22.9)	155 (24.2)
Former	54 (25.5)	56 (26.5)	76 (34.9)	186 (29.0)
Never	109 (51.4)	99 (46.9)	92 (42.2)	300 (46.8)
Alcohol use,[a] n (%)				
Current	114 (53.8)	106 (50.2)	126 (57.8)	346 (54.0)
Former	18 (8.5)	22 (10.4)	11 (5.0)	51 (8.0)
Never	80 (37.7)	83 (39.3)	81 (37.2)	244 (38.1)

Max = maximum; min = minimum; QD = once daily; SD = standard deviation

a. A subject that was a current user of any type of tobacco is counted under "current." Otherwise, a subject that was a former user of any type of tobacco is counted under "former." A subject who had never used any tobacco is counted under "never."

At baseline, the disease-related characteristics were generally balanced across the upadacitinib and placebo arms, including duration of symptoms and diagnosis, RF and anti-CCP status, indicators of disease activity, status of psoriasis, and PROs (Table 38). Subjects had been diagnosed with PsA for a mean of 10.1 years, and experienced symptoms of PsA for a mean of 13.4 years. Subjects had active disease as indicated by mean TJC68 of 24.8 and mean SJC66 of 12.1.

Table 38 Disease-Related Baseline Characteristics (FAS)

	Placebo (N = 212) n (%)	Upadacitinib 15 mg QD (N = 211) n (%)	Upadacitinib 30 mg QD (N = 218) n (%)	Total (N = 641) n (%)
Duration of PsA symptoms (years)				
n	209	211	217	637
Mean ± SD	14.6 ± 11.70	12.2 ± 8.81	13.3 ± 10.84	13.4 ± 10.54
Median (min, max)	10.8 (0.7, 59.2)	10.3 (0.8, 47.2)	10.1 (0.8, 52.4)	10.4 (0.7, 59.2)
Duration of PsA diagnosis (years)				
Mean ± SD	11.0 ± 10.33	9.6 ± 8.36	9.7 ± 8.71	10.1 ± 9.18
Median (min, max)	7.6 (0.1, 54.8)	7.5 (0.1, 47.2)	7.0 (0.1, 42.9)	7.3 (0.1, 54.8)
RF status, n (%)				
Positive	6 (2.8)	11 (5.2)	8 (3.7)	25 (3.9)
Negative	206 (97.2)	200 (94.8)	210 (96.3)	616 (96.1)
Anti-CCP status, n (%)				
Positive	10 (4.7)	7 (3.3)	5 (2.3)	22 (3.4)
Negative	202 (95.3)	203 (96.2)	213 (97.7)	618 (96.4)
Missing	0	1 (0.5)	0	1 (0.2)
TJC68				
Mean ± SD	25.3 ± 17.62	24.9 ± 17.27	24.2 ± 15.87	24.8 ± 16.91
Median (min, max)	21.0 (3.0, 68.0)	20.0 (3.0, 68.0)	20.0 (3.0, 68.0)	20.0 (3.0, 68.0)
SJC66				
Mean ± SD	12.0 ± 8.85	11.3 ± 8.19	12.9 ± 9.41	12.1 ± 8.85
Median (min, max)	10.0 (3.0, 56.0)	9.0 (3.0, 57.0)	10.0 (3.0, 57.0)	10.0 (3.0, 57.0)
Patient's Assessment of Pain (NRS)				
n	209	208	218	635
Mean ± SD	6.6 ± 2.12	6.4 ± 2.13	6.2 ± 2.21	6.4 ± 2.16
Median (min, max)	7.0 (0.0, 10.0)	7.0 (0.0, 10.0)	6.0 (1.0, 10.0)	7.0 (0.0, 10.0)
PGA – Disease Activity (NRS)				
Mean ± SD	6.5 ± 1.76	6.5 ± 1.80	6.6 ± 1.73	6.5 ± 1.76
Median (min, max)	7.0 (2.0, 10.0)	7.0 (1.0, 10.0)	7.0 (0.0, 10.0)	7.0 (0.0, 10.0)
PtGA – Disease Activity (NRS)				
n	209	208	218	635
Mean ± SD	6.8 ± 2.04	6.8 ± 1.91	6.7 ± 2.15	6.8 ± 2.04
Median (min, max)	7.0 (0.0, 10.0)	7.0 (2.0, 10.0)	7.0 (0.0, 10.0)	7.0 (0.0, 10.0)
HAQ-DI				
n	209	208	218	635
Mean ± SD	1.23 ± 0.69	1.10 ± 0.61	1.19 ± 0.66	1.17 ± 0.66
Median (min, max)	1.25 (0.00, 3.00)	1.13 (0.00, 2.50)	1.13 (0.00, 2.63)	1.13 (0.00, 3.00)
hs-CRP (mg/L)				
Mean ± SD	10.40 ± 18.46	11.16 ± 18.55	10.53 ± 17.21	10.69 ± 18.05
Median (min, max)	4.06 (0.20, 135.00)	3.95 (0.22, 128.00)	4.24 (0.20, 107.00)	4.08 (0.20, 135.00)
BSA – psoriasis (Ps)				
< 3%	81 (38.2)	81 (38.4)	87 (39.9)	249 (38.8)
≥ 3%	131 (61.8)	130 (61.6)	131 (60.1)	392 (61.2)
BSA-Ps (for baseline > 0%)				
n	198	202	202	602
Mean ± SD	12.76 ± 18.39	9.95 ± 15.73	10.03 ± 15.76	10.90 ± 16.68
Median (min, max)	4.00 (0.10, 95.00)	3.50 (0.20, 83.00)	4.00 (0.10, 80.00)	4.00 (0.10, 95.00)
sIGA of psoriasis score				
0	17 (8.0)	9 (4.3)	16 (7.3)	42 (6.6)
1	32 (15.1)	31 (14.7)	38 (17.4)	101 (15.8)
2	59 (27.8)	82 (38.9)	78 (35.8)	219 (34.2)
3	88 (41.5)	78 (37.0)	77 (35.3)	243 (37.9)
4	16 (7.5)	11 (5.2)	9 (4.1)	36 (5.6)
PASI (for baseline BSA-Ps ≥ 3%)				
n	131	130	131	392
Mean ± SD	11.68 ± 11.43	10.13 ± 9.20	8.91 ± 9.09	10.24 ± 10.00
Median (min, max)	8.30 (0.30, 64.80)	6.55 (0.20, 48.10)	5.80 (0.20, 47.50)	6.80 (0.20, 64.80)

PASDAS				
n	209	207	217	633
Mean ± SD	6.38 ± 1.22	6.26 ± 1.07	6.28 ± 1.15	6.31 ± 1.15
Median (min, max)	6.23 (3.54, 9.63)	6.13 (3.20, 9.89)	6.25 (3.01, 9.69)	6.20 (3.01, 9.89)
DAS28 (CRP)				
n	209	208	218	635
Mean ± SD	5.15 ± 1.03	5.14 ± 0.99	5.13 ± 1.13	5.14 ± 1.05
Median (min, max)	5.11 (2.59, 7.63)	5.03 (1.77, 8.10)	5.03 (2.01, 7.85)	5.05 (1.77, 8.10)
Presence of dactylitis (defined as LDI > 0)				
Yes	64 (30.2)	55 (26.1)	50 (22.9)	169 (26.4)
No	148 (69.8)	156 (73.9)	168 (77.1)	472 (73.6)
Leeds Dactylitis Index (for baseline > 0)				
n	64	55	50	169
Mean ± SD	124.19 ± 178.76	96.27 ± 97.87	98.38 ± 153.43	107.47 ± 148.66
Median (min, max)	64.00 (10.00, 1056.47)	68.77 (10.00, 477.75)	52.16 (10.00, 947.64)	59.58 (10.00, 1056.47)
Presence of enthesitis (defined as Total Enthesitis Count > 0)				
Yes	173 (81.6)	173 (82.0)	181 (83.0)	527 (82.2)
No	39 (18.4)	37 (17.5)	36 (16.5)	112 (17.5)
Missing	0	1 (0.5)	1 (0.5)	2 (0.3)
	Placebo (N = 212) n (%)	**Upadacitinib 15 mg QD (N = 211) n (%)**	**Upadacitinib 30 mg QD (N = 218) n (%)**	**Total (N = 641) n (%)**
Leeds Enthesitis Index (for baseline > 0)				
n	144	133	152	429
Mean ± SD	3.3 ± 1.70	3.0 ± 1.64	2.9 ± 1.57	3.0 ± 1.64
Median (min, max)	3.0 (1.0, 6.0)	2.0 (1.0, 6.0)	2.0 (1.0, 6.0)	3.0 (1.0, 6.0)
ASDAS (CRP) (among subjects with psoriatic spondylitis)				
n	74	75	68	217
Mean ± SD	3.44 ± 1.02	3.31 ± 0.93	3.26 ± 1.10	3.34 ± 1.01
Median (min, max)	3.40 (1.24, 5.69)	3.25 (1.06, 5.54)	3.31 (0.62, 5.62)	3.29 (0.62, 5.69)
BASDAI (among subjects with psoriatic spondylitis)				
n	74	75	68	217
Mean ± SD	6.54 ± 1.88	5.90 ± 2.14	6.04 ± 2.41	6.16 ± 2.15
Median (min, max)	7.00 (1.10, 9.80)	6.20 (1.20, 10.00)	6.10 (0.00, 10.00)	6.40 (0.00, 10.00)
Morning Stiffness score (NRS)[a]				
n	208	208	218	634
Mean ± SD	5.84 ± 2.53	5.97 ± 2.46	5.70 ± 2.70	5.84 ± 2.57
Median (min, max)	6.00 (0.00, 10.00)	6.00 (0.00, 10.00)	5.50 (0.00, 10.00)	6.00 (0.00, 10.00)
Presence of psoriatic spondylitis				
Yes	75 (35.4)	76 (36.0)	68 (31.2)	219 (34.2)
No	137 (64.6)	135 (64.0)	149 (68.3)	421 (65.7)
Missing	0	0	1 (0.5)	1 (0.2)

Anti-CCP = anti-cyclic citrullinated peptide; ASDAS = ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BSA = body surface area; CRP = C-reactive protein; DAS28 = Disease Activity Score (28 joints); FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire - Disability Index; hs-CRP = high-sensitivity C-reactive protein; LDI = Leeds Dactylitis Index; Max = maximum; min = minimum; NRS = Numerical Rating Scale; PASDAS = Psoriatic Arthritis Disease Activity Score; PASI = Psoriasis Area Severity Index; PGA = Physician's Global Assessment; Ps = psoriasis; PsA = psoriatic arthritis; PtGA = Patient's Global Assessment of Disease Activity; QD = once daily; RF = rheumatoid factor; SD = standard deviation; sIGA = Static Investigator Global Assessment of Psoriasis; SJC66 = number of swollen joints out of 66 assessed joints; TJC68 = number of tender joints out of 68 assessed joints

a. Morning stiffness score is the mean of BASDAI questions 5 and 6.

The study arms were overall similar regarding medical and surgical history.

Overall, 61.0% of subjects had failed 1 prior bDMARD, 18.1% had failed 2 prior bDMARDs, and 12.9% had failed 3 or more prior bDMARDs. Of the subjects, 8 % entered the study after intolerance but not failure of a prior bDMARD. Adalimumab was the most frequently reported (46.6%) prior bDMARD overall.

Background non-biologic DMARD therapy is optional this study; subjects are permitted to use up to 2 concomitant non-biologic DMARDs, and subjects who are on non-biologic DMARD therapy at baseline are to remain on a stable dose through Week 36. In total, 53.8% of subjects reported no concomitant use of non-biologic DMARDs at baseline. The use of concomitant non-biologic DMARD was similar across groups (Table 39). Methotrexate was used concomitantly by 39.3 % of subjects. Concomitant use of other non-biologic DMARDs was much lower. Any systemic corticosteroids were used by 15.3%

of study subjects: 19.8 % in the placebo arms, 15.6 % in the upadacitinib 15 mg arm, and 10.6 % in the upadacitinib 30mg arm.

Table 39 Concomitant Non-Biologic DMARDs up to Week 24 (FAS)

Generic Name (WHO Q1_2018)	Placebo to UPA 15 mg QD (N = 106) n (%)	Placebo to UPA 30 mg QD (N = 106) n (%)	All Placebo (N = 212) n (%)	UPA 15 mg QD (N = 211) n (%)	UPA 30 mg QD (N = 218) n (%)	Total (N = 641) n (%)
Any Concomitant Non-Biologic DMARDs	60 (56.6)	53 (50.0)	113 (53.3)	101 (47.9)	99 (45.4)	313 (48.8)
APREMILAST	5 (4.7)	6 (5.7)	11 (5.2)	11 (5.2)	9 (4.1)	31 (4.8)
HYDROXYCHLOROQUINE	0	1 (0.9)	1 (0.5)	0	3 (1.4)	4 (0.6)
IGURATIMOD	0	1 (0.9)	1 (0.5)	1 (0.5)	0	2 (0.3)
LEFLUNOMIDE	4 (3.8)	7 (6.6)	11 (5.2)	3 (1.4)	7 (3.2)	21 (3.3)
METHOTREXATE	51 (48.1)	41 (38.7)	92 (43.4)	82 (38.9)	78 (35.8)	252 (39.3)
MYCOPHENOLIC ACID	0	0	0	1 (0.5)	0	1 (0.2)
SULFASALAZINE	5 (4.7)	2 (1.9)	7 (3.3)	11 (5.2)	11 (5.0)	29 (4.5)
TACROLIMUS	1 (0.9)	0	1 (0.5)	0	0	1 (0.2)

Note: This table includes all medications administered up to Week 24 treatment period. Thus all medications with an end date prior to the first study drug dose or a start date after the first dose date at Week 24 are excluded.

Through Week 24, the mean treatment compliance was 98.7% and 97.1% in the upadacitinib 15 mg and 30 mg groups, respectively.

Outcomes and estimation

Primary endpoint

The primary endpoint was change in ACR20 at Week 12. A statistically significantly greater percentage of subjects achieved an ACR20 response in the upadacitinib 15 mg and 30 mg groups compared with the placebo group. Table 40 presents the results for FAS, AO and AO with imputation. The results on the per protocol analysis set were consistent with the primary analysis (Table 41).

The results of the tipping point analysis for ACR20 at Week 12 showed that results of the primary efficacy analysis using Non-Responder Imputation (NRI) data handling are robust.

Table 40 ACR20 Response Rate at Week 12 (FAS)

Treatment	N	Responder n (%)	Response Rate (95% CI)[a]	Response Rate Difference (Upadacitinib - Placebo) Point Estimate	95% CI[b]	*P*-Value[c]
FAS, NRI						
Placebo	212	51 (24.1)	24.1 (18.3, 29.8)			
Upadacitinib 15 mg	211	120 (56.9)	56.9 (50.2, 63.6)	32.8	(24.0, 41.6)	< 0.0001
Upadacitinib 30 mg	218	139 (63.8)	63.8 (57.4, 70.1)	39.7	(31.1, 48.3)	< 0.0001
FAS, AO						
Placebo	185	50 (27.0)	27.0 (20.6, 33.4)			
Upadacitinib 15 mg	205	119 (58.0)	58.0 (51.3, 64.8)	31.0	(21.7, 40.3)	< 0.0001
[redacted]						

Table 41 ACR20 Response Rate at Week 12 (Per Protocol Analysis Set)

The mean difference in the response rate was retained up to Week 24, where after the response rate in subjects transferred from placebo arms to upadacitinib achieved the response rate of subjects who had used upadacitinib already from the start of the study (Figure 29, results given as observed (AO) up to end of Period 1, 56 weeks). Of note, the study is ongoing, and the results after Week 24 represent the proportion of subjects who had already reached the respective study time points.

Table 49 Radiographic changes in study M15-572 (SELECT-PsA 1)

Treatment Group	PBO	UPA 15 mg	ADA 40 mg
Modified Total Sharp Score, mean change from baseline (95% CI)			
Week 24	0.25 (0.13, 0.36)	-0.04 (-0.16, 0.07)[c]	0.01 (-0.11, 0.13)
Week 56[a]	0.39 (0.23, 0,55)	-0.06 (–0.22, 0.10)[d]	-0.07 (-0.22, 0.09)
Proportion of patients with no radiographic progression[b], % (95% CI)			
Week 24	92 (89, 95)	96 (94, 98)[e]	95 (93, 97)
Week 56[a]	89 (86, 92)	97 (96, 99)[d]	94 (92, 97)

Abbreviations: ADA = adalimumab; PBO = placebo; UPA= upadacitinib

a. All placebo data at week 56 derived using linear extrapolation
b. No progression defined as mTSS change ≤0.5
c. multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison
d. nominal p≤0.001 upadacitinib vs placebo comparison
e. nominal p<0.05 upadacitinib vs placebo comparison

The proportion of patients with no radiographic progression is still very high at week 56 in all study arms (Table 50). However, the CIs are narrow for this measure, and the CIs of the placebo and upadacitinib groups no more overlap at week 56.

The onset of response was variable, with some patients achieving ACR20 at 2 weeks and some only at 56 weeks (Figures 33 and 34). Most subjects who were responders remained responders. Some subjects were obviously close to the margin of response, since they fluctuated between being non-responders and responders. The rate of achieving response appears to be similar after initiation of upadacitinib treatment for those who started treatment in the beginning of the studies and those who switched from placebo to upadacitinib at week 24.

The time to skin response as measured by PASI75 was also individual (data not shown for brevity). The treatment effect on skin improved markedly still after 24 weeks from initiation of upadacitinib in both Phase 3 studies; hence, the proportion of patients with PASI75 response at week 56 was somewhat lower in patients who had initially been in the placebo group than in patients who received upadacitinib from the beginning of the studies.

The PROs HAQ-DI, SF-36 PCS and MCS, FACIT-Fatigue showed mostly clinically relevant improvement in the change from baseline to weeks 12 and 56 in both phase 3 studies. However, the SF-36 MCS results, which were statistically non-significant (not controlled for multiplicity) were also clinically modest in comparison with the multiplicity-controlled SF-36 PCS results.

Results from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were given for patients with active spondylitis at baseline. The BASDAI score ranges from 0 (no disease activity) to 10 (maximal disease activity). A cut-off of 4 is used to define active disease. The LS mean change (95% CI) in BASDAI at week 56 was -3.06 (-3.57, -2.55), -2.84 (-3.23, -2.44), and -3.27 (-3.66, -2.89) in the placebo to upadacitinib 15 mg, adalimumab, and upadacitinib 15 mg groups, respectively. Concordant results were seen for the TJC and SJC.

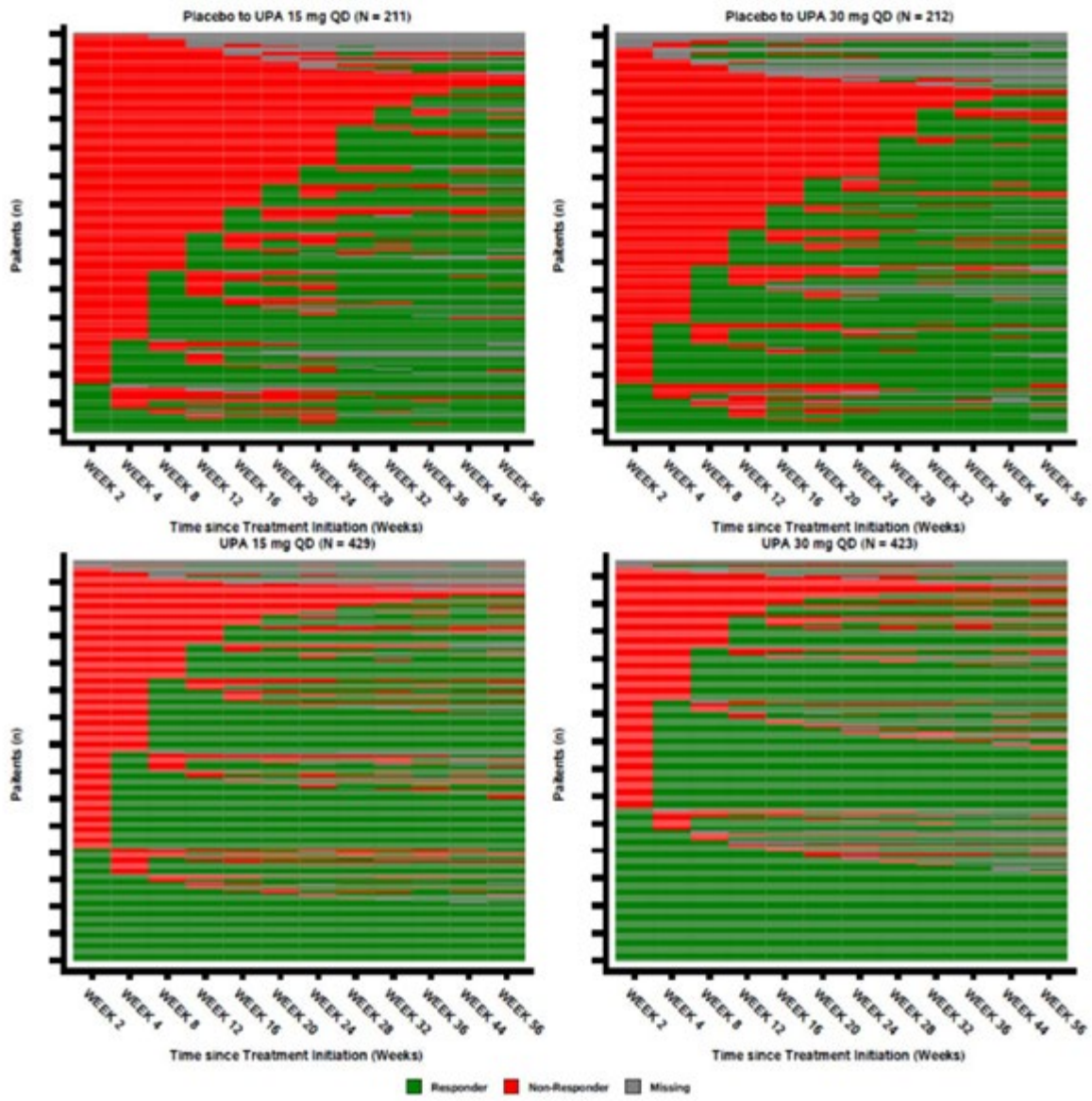


Figure 33 ACR20 response per patient in study M15-572

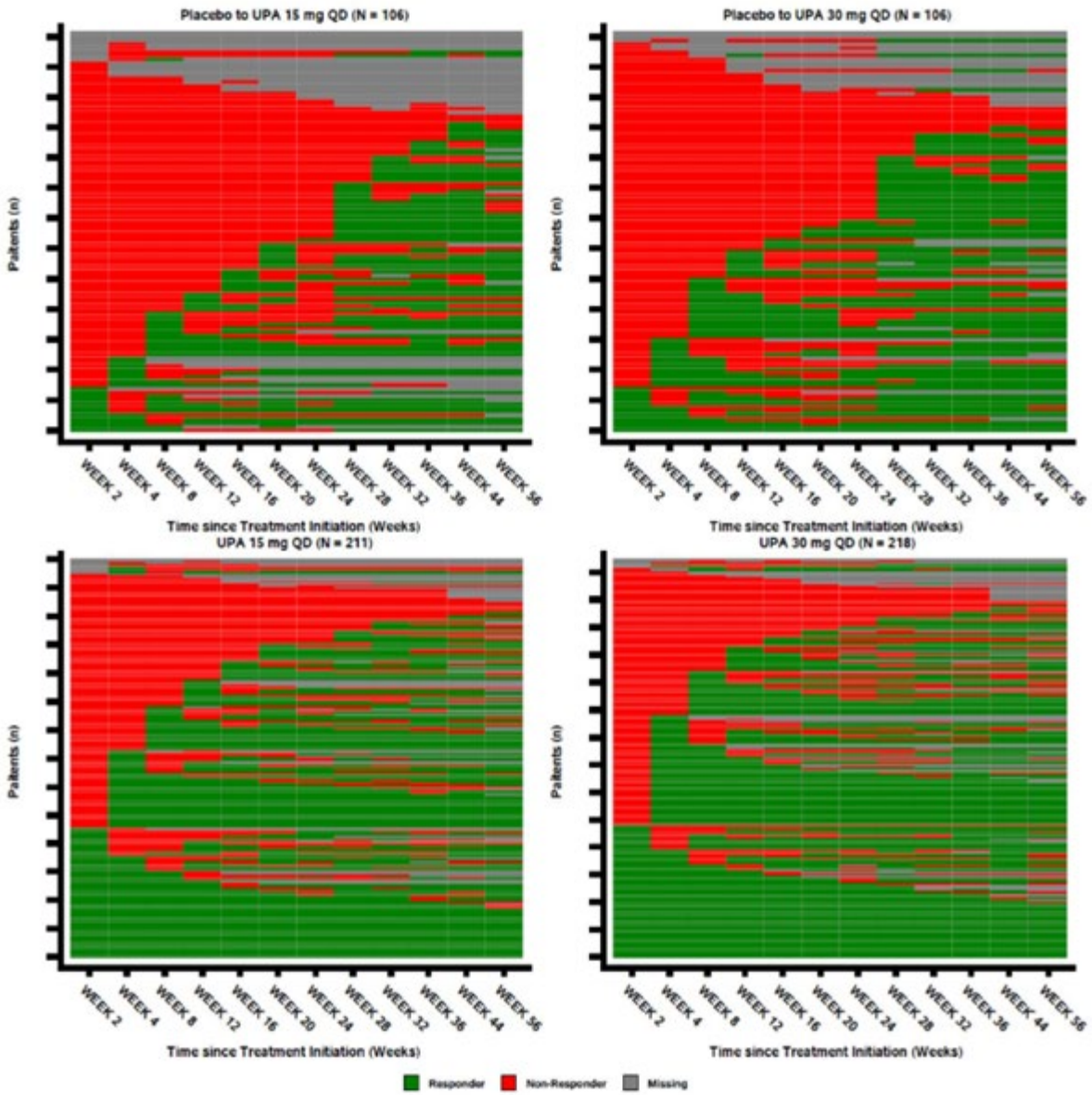


Figure 34 ACR20 response per patient in study M15-554

Efficacy in subgroups using upadacitinib as monotherapy and as combined with methotrexate

With the response to the 1st RSI, the MAH submitted efficacy results analysed for subgroups of subjects using upadacitinib 15 mg QD as monotherapy vs. subjects using the combination of upadactinib 15 mg and methotrexate.

Across all treatment groups, ~ 30% of subjects in the PBO-Controlled Analysis Set reported no concomitant use of non-biologic DMARDs at baseline compared to ~70% of subjects who reported concomitant use of non-biologic DMARDs at baseline; 60% of subjects reported concomitant MTX with or without another non-biologic DMARD and 56% of subjects reported concomitant use of only MTX. The distribution of background non-biologic DMARD use per study is presented in Table 50.

Table 50 Distribution of Background Non-Biologic DMARD Use in Studies M15-572 and M15-554

	M15-572 (SELECT PsA-1) N = 1704				M15-554 (SELECT PsA-2) N = 641		
	PBO N=423	UPA 15 mg N=429	UPA 30 mg N=423	ADA 40 mg N=429	PBO N=212	UPA 15 mg N=211	UPA 30 mg N=218
	N (%)						
Any non-biologic DMARD	347 (82)	353 (82)	346 (82)	347 (81)	100 (47)	98 (46)	98 (45)
MTX Only	267 (63)	279 (65)	268 (63)	270 (63)	75 (35)	74 (35)	73 (34)
MTX + Another Any non-biologic DMARD	26 (6.1)	20 (4.7)	27 (6.4)	61 (14.2)	7 (3)	6 (2.8)	5 (2.3)
Any MTX[a]	293 (69)	299 (70)	295 (70)	331 (77)	82 (39)	80 (38)	78 (36)

Source: M15-572 CSR Table 14.1__3.3, M15-554 CSR Table 14.1__3.3

a. The Any MTX group includes subjects treated with MTX with or without another non-biologic DMARD.

Across endpoints, consistent point estimates of the placebo-subtracted treatment effect and associated overlapping CIs were observed between subjects who were on UPA 15 mg monotherapy and those who were on combination therapy with MTX only. Results from this analysis support the use of UPA with or without concomitant MTX (Figure 35 Figure 36).

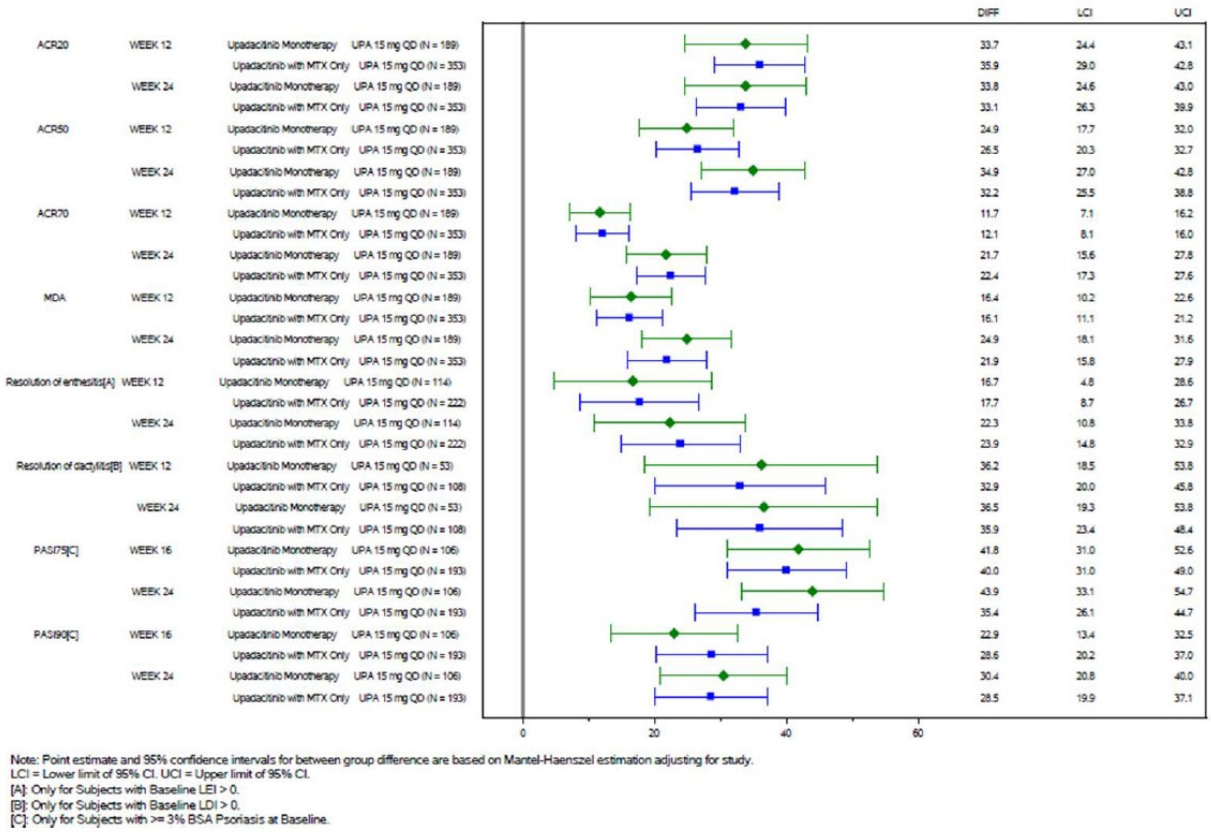


Figure 35 Forest Plot for Key Binary Endpoints by Upadacitinib 15 mg QD Monotherapy vs. Upadacitinib 15 mg QD with Methotrexate Only (NRI)

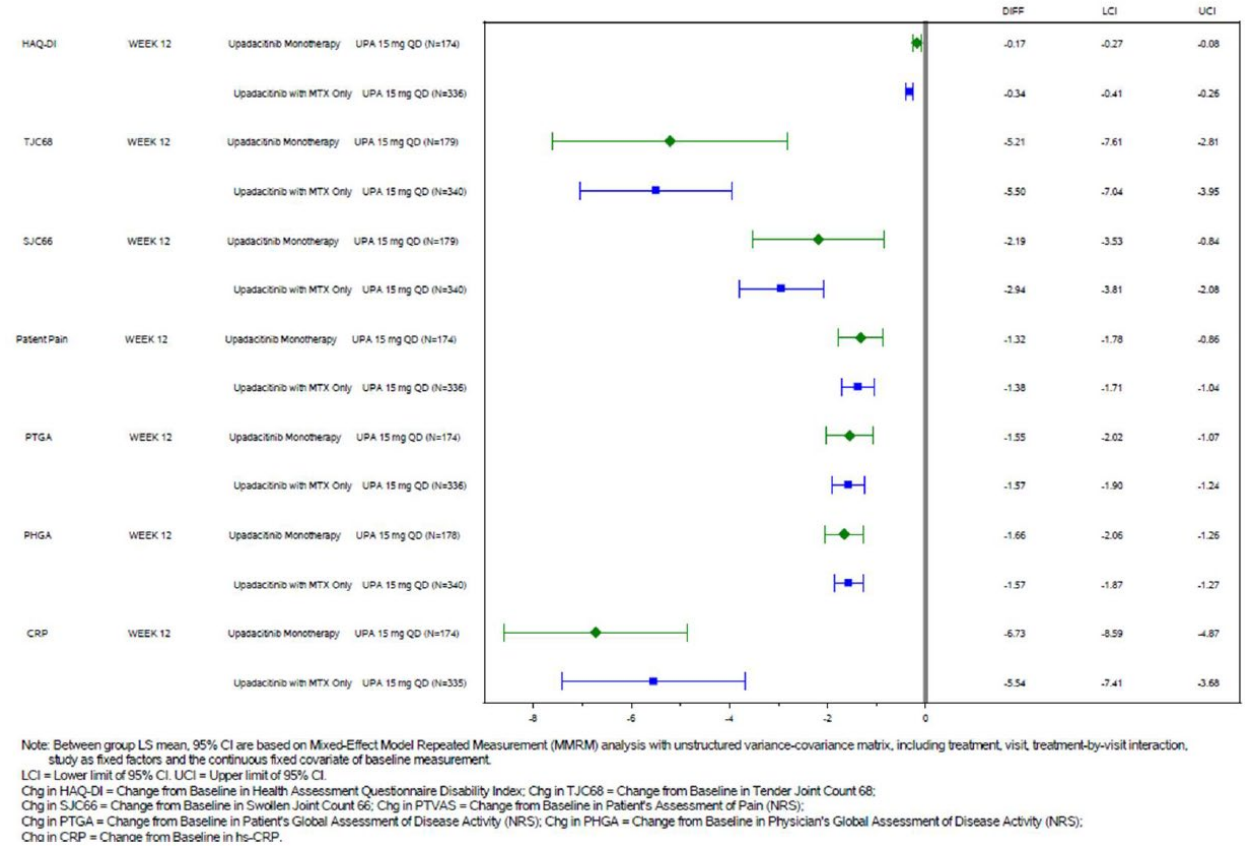


Figure 36 Forest Plot for Components of ACR Response by Upadacitinib 15 mg QD Monotherapy vs. Upadacitinib 15 mg QD with Methotrexate Only (MMRM)

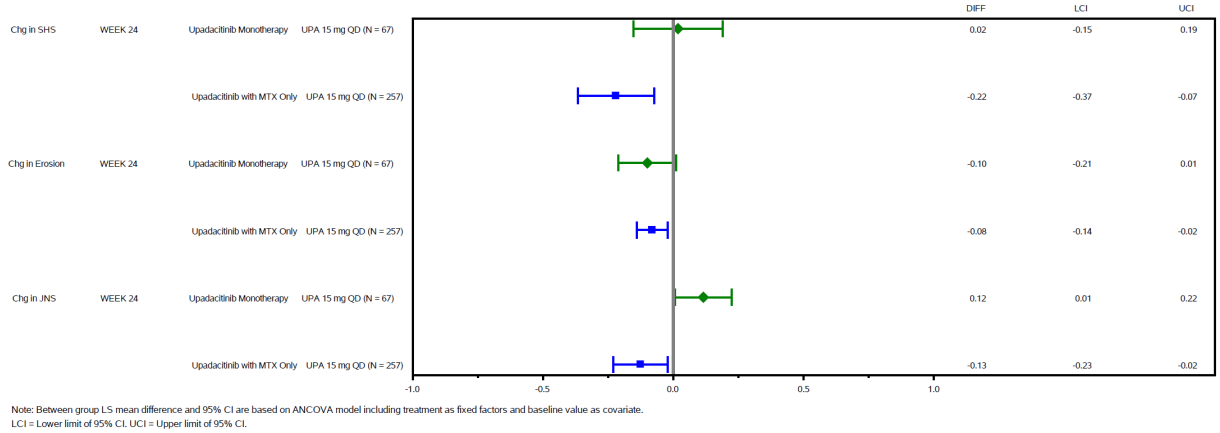


Figure 37 Forest Plot for Radiographic Endpoints by Upadacitinib 15 mg QD Monotherapy vs. Upadacitinib 15 mg QD with MTX Only (Linear Extrapolation) (M15-572)

A vast majority of all patients had no change in radiographic endpoints during the study. Therefore, Figure 37 should not be overinterpreted to indicate true difference in the monotherapy and combination therapy groups.

Summary of main studies

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

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

Table 51 Summary of Efficacy for trial M15-572

Title: A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib to Placebo and to Adalimumab in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (DMARD) – *SELECT – PsA 1*		
Study identifier	M15-572 (EudraCT number: 016-004130-24)	
Design	This is a Phase 3 multicenter study that includes two periods. Period 1 is 56 weeks in duration and includes a 24-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled period followed by an additional 32 weeks of blinded, active comparator-controlled treatment (Weeks 24 – 56). Period 1 is designed to compare the safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo and versus adalimumab 40 mg every other week (eow) in subjects with moderately to severely active PsA and have an inadequate response to non-biologic DMARDs (DMARD-IR). Period 1 is also designed to compare the efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo for the prevention of structural progression. Period 2 is an open-label (blinded until the last subject completes the last visit of Period 1), long-term extension of up to a total treatment duration of approximately 3 years to evaluate the safety, tolerability and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.	
	Duration of double-blind, placebo-controlled period: Duration of double-blind active-controlled period: Duration of extension period:	24 weeks 56 weeks Up to Week 260
Hypothesis	Superiority (upadacitinib vs placebo); Non-inferiority (upadacitinib vs adalimumab) and Superiority (upadacitinib vs adalimumab)	
Treatments groups	Upadacitinib 15mg	Upadacitinib 15mg QD for up to 5 years; n = 430
	Upadacitinib 30mg	Upadacitinib 30mg QD for up to 5 years; n = 423
	Adalimumab 40mg	Adalimumab 40mg EOW for 5 years; n = 429
	Placebo	Placebo for 24 weeks; Total n = 423 After week 24: Placebo to UPA 15mg; n = 211 Placebo to UPA 30mg; n = 212
Endpoints and definitions	Primary endpoint (Upadacitinib 15 and 30 mg vs placebo)	Proportion of subjects achieving ACR20 response at Week 12
	Ranked key secondary endpoints (at Week 12 unless otherwise specified)	<u>The key multiplicity adjusted secondary efficacy endpoints (each dose of upadacitinib versus placebo unless noted) are:</u> 1. Change from baseline in HAQ-DI; 2. Proportion of subjects achieving a static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16;

	Ranked key secondary endpoints (at Week 12 unless otherwise specified)	3. Psoriasis Area Severity Index (PASI) 75 response at Week 16 (for subjects with ≥ 3% BSA psoriasis at baseline);4. Change from baseline in SHS at Week 24; 5. Proportion of subjects achieving MDA at Week 24; 6. Proportion of subjects with resolution of enthesitis (LEI = 0) at Week 24; 7. ACR 20 response rate (non-inferiority of upadacitinib vs adalimumab); 8. Change from baseline in SF-36 PCS; 9. Change from baseline in FACIT-Fatigue Questionnaire; 10. ACR 20 response rate (superiority of upadacitinib vs. adalimumab); 11. Proportion of subjects with resolution of dactylitis (LDI = 0) at Week 24; 12. Change from baseline in Patient's Assessment of Pain NRS (superiority of upadacitinib vs. adalimumab); 13. Change from baseline in HAQ-DI (superiority of upadacitinib vs. adalimumab); 14. Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire at Week 16
Database lock	Week 24 database lock: 21 JAN 2020 (Data Cutoff Date 13 DEC 2019)	

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	**Week 12 (unless otherwise specified), Full Analysis Set** (includes all randomized subjects who received at least one dose of study drug)				
Effect Estimate per Comparison	**Treatment Group**	**Placebo**	**Adalimumab 40 mg EOW**	**Upadacitinib 15 mg QD**	**Upadacitinib 30mg QD**
	Number of subjects	423	429	429	423
	Primary Endpoint:				
	ACR20 % responders Diff. (95% CI) p-value	36.2	65.0	70.6 UPA vs Placebo 34.5 (28.2, 40.7) < 0.0001*	78.5 UPA vs Placebo 42.3 (36.3, 48.3) < 0.0001*
	Ranked Key Secondary Endpoints:				
	HAQ-DI change from baseline LS Mean	−0.14	−0.34	−0.42	−0.47

Effect Estimate per Comparison	Treatment Group	Placebo	Adalimumab 40 mg EOW	Upadacitinib 15 mg QD	Upadacitinib 30mg QD
	Diff. (95% CI) p-value			UPA vs Placebo −0.28 (−0.35, −0.22) < 0.0001* UPA vs ADA −0.08 (−0.15, −0.01) 0.0162	UPA vs Placebo −0.34 (−0.40, −0.27) < 0.0001* UPA vs ADA −0.14 (−0.20, −0.07) < 0.0001
	sIGA 0/1 at Week 16[a] % responders Diff. (95% CI) p-value	10.9	38.5	41.9 UPA vs Placebo 31.1 (24.7, 37.5) < 0.0001* UPA vs ADA 3.4 (−4.1, 11.0) 0.3857	54.0 UPA vs Placebo 43.1 (36.7, 49.6) < 0.0001* UPA vs ADA 15.5 (8.0, 23.1) < 0.0001
	PASI75 at Week 16[b] % responders Diff. (95% CI) p-value	21.3	53.1	62.6 UPA vs Placebo 41.3 (32.8, 49.8) < 0.0001* UPA vs ADA 9.5 (0.2, 18.9) 0.0528	62.4 UPA vs Placebo 41.1 (32.5, 49.6) < 0.0001* UPA vs ADA 9.3 (−0.1, 18.7) 0.0516
	Modified PsA Sharp/van der Heijde Score (mTSS) change from baseline at Week 24 LS Mean Diff. (95% CI) p-value	0.25	0.01	−0.04 UPA vs Placebo −0.29 (−0.44, −0.14) 0.0002*	0.03 UPA vs Placebo −0.21 (−0.36, −0.06) 0.0069*
Effect Estimate per Comparison	**Treatment Group**	**Placebo**	**Adalimumab 40 mg EOW**	**Upadacitinib 15 mg QD**	**Upadacitinib 30mg QD**
	MDA at Week 24 % responders	12.3	33.3		
	Diff. (95% CI) p-value				

				36.6 UPA vs Placebo 24.3 (18.8, 29.8) < 0.0001* UPA vs ADA 3.3 (−3.1, 9.6) 0.3218	45.4 UPA vs Placebo 33.1 (27.4, 38.8) < 0.0001* UPA vs ADA 12.1 (5.5, 18.6) 0.0003
	Resolution of Enthesitis at Week 24[c] % responders Diff. (95% CI) p-value	32.4	47.2	53.7 UPA vs Placebo 21.3 (13.0, 29.7) < 0.0001* UPA vs ADA 6.5 (−1.9, 15.0) 0.1500	57.7 UPA vs Placebo 25.3 (16.9, 33.7) < 0.0001* UPA vs ADA 10.5 (2.1, 18.9) 0.0169
	ACR20 % responders Diff. (95% CI) p-value	36.2	65.0	70.6 UPA vs ADA 5.6 (−0.6, 11.8) Non-inferiority: < 0.0001* Superiority: 0.0815	78.5 UPA vs ADA 13.5 (7.5, 19.4) Non-inferiority: < 0.0001* Superiority: < 0.0001*
	SF-36 PCS change from baseline LS Mean Diff. (95% CI) p-value	3.19	6.82	7.86 UPA vs Placebo 4.67 (3.67, 5.67) < 0.0001* UPA vs ADA 1.00 (0.01, 2.00) 0.0475	8.90 UPA vs Placebo 5.72 (4.71, 6.72) < 0.0001* UPA vs ADA 2.08 (1.09, 3.08) < 0.0001
	FACIT-F change from baseline LS Mean Diff. (95% CI)	2.8	5.7	6.3 UPA vs Placebo 3.5 (2.4, 4.7) < 0.0001* UPA vs ADA 0.7	7.1 UPA vs Placebo 4.3 (3.1, 5.5) < 0.0001* UPA vs ADA 1.4

Effect Estimate per Comparison	Treatment Group	Placebo	Adalimumab 40 mg EOW	Upadacitinib 15 mg QD	Upadacitinib 30mg QD
	p-value			(–0.5, 1.8) 0.2678	(0.3, 2.6) 0.0157
	Resolution of dactylitis at Week 24[d] % responders Diff. (95% CI) p-value	39.7	74.0	76.5 UPA vs Placebo 36.8 (25.7, 47.9) < 0.0001 UPA vs ADA 2.5 (–8.0, 12.9) 0.5615	79.5 UPA vs Placebo 39.8 (28.8, 50.9) < 0.0001 UPA vs ADA 5.5 (-4.9, 15.9) 0.2792
	Patient's Assessment of Pain change from baseline LS Mean Diff. (95% CI) p-value	–0.9	–2.3	–2.3 UPA vs Placebo –1.3 (–1.6, –1.0) < 0.0001 UPA vs ADA 0.0 (–0.3, 0.3) 0.8970	–2.7 UPA vs Placebo –1.8 (–2.1, –1.5) < 0.0001 UPA vs ADA –0.5 (–0.7, –0.2) 0.0028
	SAPS change from baseline at Week 16 LS Mean Diff. (95% CI) p-value	–8.2	–22.7	–25.3 UPA vs Placebo –17.1 (–19.6, –14.6) < 0.0001 UPA vs ADA –2.5 (–5.0, –0.0) 0.0498	–28.1 PA vs Placebo –19.8 (–22.3, –17.3) < 0.0001 UPA vs ADA –5.2 (–7.7, –2.7) < 0.0001
Notes	p-values with * are statistically significant in the multiplicity adjusted analysis, under strong control of the overall type I error. a. In patients with sIGA ≥ 2 at baseline (n = 313, 330, 322, and 324, respectively). b. In patients with ≥ 3% BSA psoriasis at baseline (n = 211, 211, 214, and 210, respectively). c. In patients with enthesitis at baseline (n = 241, 265, 270, and 267, respectively). d. In patients with dactylitis at baseline (n = 126, 127, 136, and 127, respectively).				

Table 52 Summary of Efficacy for trial M15-554

Title: A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) – SELECT – PsA 2		
Study identifier	Study M15-554 (EudraCT Number: 2016-004152-30)	
Design	A Phase 3 multicenter study that includes two periods. Period 1 is 56-weeks in duration and includes a 24-week randomized, double-blind, parallel-group, placebo-controlled period followed by an additional 32 weeks of blinded treatment (Weeks 24 – 56). Period 1 is designed to compare the safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo in subjects with moderately to severely active PsA who have an inadequate response to bDMARDs (Bio-IR). Period 2 is an open label (blinded until the last subject completes the last visit of Period 1) long-term extension of up to a total treatment duration of approximately 3 years (or until approval in certain countries) to evaluate the safety, tolerability and efficacy of upadacitinib 15 mg QD, and 30 mg QD, in subjects with PsA who have completed Period 1.	
	Duration of double-blind, placebo-controlled period: Duration of additional blinded treatment period: Duration of open-label extension period:	24 weeks 32 weeks Up to 2 years
Hypothesis	Superiority	
Treatments groups	Upadacitinib 15 mg	Upadacitinib 15 mg QD for up to 3 years, n = 211
	Upadacitinib 30 mg	Upadacitinib 30 mg QD for up to 3 years, n = 219
	Placebo	Placebo for 24 weeks; Total n = 212 After Week 24: Placebo to UPA 15mg; n = 106 Placebo to UPA 30mg; n = 106
Endpoints and definitions	Primary endpoint (Upadacitinib 15 and 30 mg vs placebo)	Proportion of subjects achieving ACR20 response at Week 12
	Ranked key secondary endpoints (at Week 12 unless otherwise specified)	<u>The key multiplicity adjusted secondary efficacy endpoints (each dose of upadacitinib versus placebo) are:</u> 1. Change from baseline in HAQ-DI 2. Static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16 (For Subjects with Baseline sIGA ≥ 2) 3. Psoriasis Area Severity Index (PASI) 75 response at Week 16 (for subjects with ≥ 3% BSA psoriasis at baseline) 4. Change from baseline in SF-36 PCS 5. Change from baseline in FACIT-Fatigue Questionnaire

		6. Proportion of subjects achieving Minimal Disease Activity (MDA) at Week 24 7. Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire at Week 16
Database lock	Week 24 interim database lock: Oct 23, 2019 (Data Cutoff Date 09 OCT 2019)	
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	**Week 12, Full Analysis Set** (includes all randomized subjects who received at least one dose of study drug)	

Effect Estimate per Comparison	**Treatment Group**	**Placebo**	**Upadacitinib 15 mg QD**	**Upadacitinib 30 mg QD**
	Number of subjects	212	211	218
	Primary endpoint:			
	ACR20 at Week 12 % responders vs placebo: Diff. (95% CI) p-value	24.1	56.9 32.8 (24.0, 41.6) < 0.0001*	63.8 39.7 (31.1, 48.3) < 0.0001*
	Ranked Key Secondary Endpoints:			
	HAQ-DI change from baseline at Week 12 LS Mean vs placebo: Diff. (95% CI) p-value	−0.10	−0.30 −0.21 (−0.30, −0.12) < 0.0001*	−0.41 −0.31 (−0.40, −0.22) < 0.0001*
	sIGA 0/1 at Week 16[a] % responders vs placebo: Diff. (95% CI) p-value	9.2	36.8 27.6 (19.2, 36.1) < 0.0001*	40.2 31.0 (22.3, 39.8) < 0.0001*
	PASI75 at Week 16[b] % responders vs placebo: Diff. (95% CI) p-value	16.0	52.3 36.3 (25.6, 46.9) < 0.0001*	56.5 40.5 (29.9, 51.0) < 0.0001*

Effect Estimate per Comparison	**Treatment Group**	**Placebo**	**Upadacitinib 15 mg QD**	**Upadacitinib 30 mg QD**
	SF-36 PCS change from baseline at Week 12 LS Mean vs placebo: Diff. (95% CI) p-value	1.62	5.15 3.52 (2.07, 4.98) < 0.0001*	7.06 5.44 (3.99, 6.88) < 0.0001*
	FACIT-Fatigue change from baseline at Week 12 LS Mean vs placebo: Diff. (95% CI) p-value	1.3	5.0 3.7 (2.0, 5.4) < 0.0001*	6.1 4.8 (3.1, 6.4) < 0.0001*
	Minimal Disease Activity (MDA) at Week 24 % responders vs placebo: Diff. (95% CI) p-value	2.8	25.1 22.3 (16.0, 28.6) < 0.0001*	28.9 26.1 (19.7, 32.5) < 0.0001*

	Self-Assessment of Psoriasis Symptoms (SAPS) at Week 16 LS Mean	−1.5	−24.4 −22.9 (−27.4, −18.4) < 0.0001*	−29.7 −28.2 (−32.7, −23.8) < 0.0001*
	vs placebo: Diff. (95% CI) p-value			
Notes	p-values with * are statistically significant in the multiplicity adjusted analysis, under strong control of the overall type I error. a. In patients with sIGA ≥ 2 at baseline (n = 163, 171, and 164, respectively). b. In patients with ≥ 3% BSA psoriasis at baseline (n = 131, 130, and 131, respectively).			

Analysis performed across trials (pooled analyses and meta-analysis)

Integrated efficacy analyses

One integrated analysis set of the Phase 3 studies was defined for the purpose of short-term integrated efficacy analyses. The integrated analysis set combines efficacy data during the 24-week placebo-controlled period from Study M15-572 (non-biologic DMARD-IR) and Study M15-554 (bDMARD-IR). The integrated analysis set is referred to as the 'Placebo-Controlled Analysis Set'. Subjects receiving upadacitinib 15 mg QD, upadacitinib 30 mg QD, or placebo were included in this analysis set. The randomization ratio between upadacitinib and control is the same in both studies being integrated.

The following integrated efficacy analyses were conducted using the Placebo-Controlled Analysis Set: ACR20/50/70, HAQ-DI, sIGA 0/1, PASI 75/90/100, and MDA.

The following key efficacy endpoints were examined at the specified time points: ACR20/50/70 response rates at Week 12; Change from baseline in HAQ-DI at Week 12; Proportion of subjects achieving sIGA 0/1 at Week 16 (for subjects with baseline sIGA ≥ 2); PASI 75/90/100 response rates at Week 16 (for subjects with ≥ 3% BSA-Ps at baseline); and proportion of subjects achieving MDA at Weeks 16 and 24.

For MDA and additional secondary endpoints related to dactylitis and enthesitis, results were also evaluated at Week 16 in addition to point Week 24 to assess MDA prior to the initiation of potential rescue therapies.

Overall, the results of the above-mentioned integrated analyses are concordant with the results of the individual studies. Therefore, the results are not shown here except for the primary endpoint in different treatment combinations.

Primary endpoint in different DMARD combinations

Primary endpoint (ACR20 response rate at Week 12) results in the specific subgroups with different combinations of upadacitinib, MTX and other non-biologic DMARDs in the "placebo-controlled upadacitinib 15 mg and 30 mg analysis set" are given in Table 53.

Table 53 ACR20 Response Rate at Week 12 by Upadacitinib with MTX vs. Upadacitinib with Other Non-Biologic DMARDs (Placebo-Controlled Upadacitinib 15 mg and 30 mg Analysis Set)

Parameter Subgroup Treatment	N	Responder n (%)	Response Rate (95% CI) [A]	Adjusted by Study [B] -Between Group Comparison (UPA - Placebo)- Response Rate Diff (95% CI)
ACR20				
Upadacitinib with MTX				
Placebo	375	126 (33.6)	33.6 (28.8, 38.4)	
UPA 15 mg QD	379	267 (70.4)	70.4 (65.9, 75.0)	36.8 (30.2, 43.4)
UPA 30 mg QD	373	282 (75.6)	75.6 (71.2, 80.0)	41.9 (35.5, 48.3)
With MTX Alone				
Placebo	342	120 (35.1)	35.1 (30.0, 40.1)	
UPA 15 mg QD	353	251 (71.1)	71.1 (66.4, 75.8)	35.9 (29.0, 42.8)
UPA 30 mg QD	341	254 (74.5)	74.5 (69.9, 79.1)	39.3 (32.5, 46.1)
With MTX and Other Non-Biologic DMARDs				
Placebo	33	6 (18.2)	18.2 (5.0, 31.3)	
UPA 15 mg QD	26	16 (61.5)	61.5 (42.8, 80.2)	43.2 (20.7, 65.6)
UPA 30 mg QD	32	28 (87.5)	87.5 (76.0, 99.0)	69.5 (52.3, 86.7)

[A]: 95% confidence intervals for response rate are calculated based on normal approximation to the binomial distribution.
[B]: Point estimate and 95% confidence intervals for between group difference are based on Mantel-Haenszel estimation adjusting for study.

Parameter Subgroup Treatment	N	Responder n (%)	Response Rate (95% CI) [A]	Adjusted by Study [B] -Between Group Comparison (UPA - Placebo)- Response Rate Diff (95% CI)
ACR20 (Cont.)				
Upadacitinib with Other Non-Biologic DMARDs				
Placebo	72	31 (43.1)	43.1 (31.6, 54.5)	
UPA 15 mg QD	72	45 (62.5)	62.5 (51.3, 73.7)	19.4 (3.8, 35.1)
UPA 30 mg QD	71	50 (70.4)	70.4 (59.8, 81.0)	28.0 (12.8, 43.3)
Any APREMILAST without MTX				
Placebo	16	3 (18.8)	18.8 (0.0, 37.9)	
UPA 15 mg QD	15	9 (60.0)	60.0 (35.2, 84.8)	
UPA 30 mg QD	13	8 (61.5)	61.5 (35.1, 88.0)	
Any LEFLUNOMIDE without MTX				
Placebo	29	16 (55.2)	55.2 (37.1, 73.3)	
UPA 15 mg QD	30	20 (66.7)	66.7 (49.8, 83.5)	
UPA 30 mg QD	35	28 (80.0)	80.0 (66.7, 93.3)	
Any SULFASALAZINE without MTX				
Placebo	26	9 (34.6)	34.6 (16.3, 52.9)	
UPA 15 mg QD	22	15 (68.2)	68.2 (48.7, 87.6)	
UPA 30 mg QD	24	15 (62.5)	62.5 (43.1, 81.9)	

[A]: 95% confidence intervals for response rate are calculated based on normal approximation to the binomial distribution.
[B]: Point estimate and 95% confidence intervals for between group difference are based on Mantel-Haenszel estimation adjusting for study.

Supportive studies

Health economics and outcomes research reports

Short-Form Health Survey Version 2 (SF-36v2)

To evaluate the extent to which upadacitinib improves HRQoL among patients with PsA, the MAH evaluated the change in SF-36v2 questionnaire score from baseline to Week 12 was in studies M15-572 and M15-554, of upadacitinib in adults with active PsA. The SF-36v2 includes 36 items across eight subscales that assess functional health and well-being: physical functioning, bodily pain, vitality, social functioning, mental health, general health perceptions, and role limitations due to physical problems (hereafter referred to as role-physical) and emotional problems. Additionally, a Physical Component Summary (PCS), Mental Component Summary (MCS), and preference-based health utility index can be derived from the SF-36v2.

The modified version of the original questionnaire, the SF-36v2, was created in 1996. The content validity of the SF-36v2 is supported by qualitative and quantitative study findings published in the literature, which document that HRQoL impacts as measured by the SF-36v2 are important and relevant to the PsA experience.

The SF-36v2 is fit for the purpose of evaluating the Phase 3 efficacy hypotheses that upadacitinib improves HRQoL associated with PsA.

Functional Assessment of Chronic Illness Therapy- Fatigue

PsA can result in fatigue, which has been reported in the literature and noted in clinical trials to be important and relevant to patients with PsA.

The FACIT-Fatigue's items assess fatigue experience and fatigue impact (i.e., severity, impacts to daily activities, emotional impacts) on a five-point scale ranging from 0 ("not at all") to 4 ("very much") with a recall period of the "past 7 days. A total score is calculated by summing the item scores, after reversing items that are worded in the negative direction, resulting in a maximum score of 52 and a minimum score of 0; lower scores indicate greater fatigue. The MAH evaluated the mean change in FACIT-Fatigue total scores from Baseline to Week 12 between secondary endpoint for fatigue upadacitinib and the combined placebo group. These results are consistent with other studies of the FACIT-Fatigue scores in PsA patient populations as reported in the scientific literature. Data generated from this study M15-554 were used to create clinically important difference (CID) and clinically important response (CIR) estimates. These values can be compared with results from Cella et al. (2019), which indicated a CID of 3.1 points for the FACIT-Fatigue total score in a PsA patient population and a responder definition estimated as a 4-point improvement in total score.

Patient Reported Outcomes Evidence for Fatigue as a Clinically Meaningful Symptom of Psoriatic Arthritis and a Unique Endpoint in AbbVie's Phase 3 Measurement Strategy - Position Paper

This report addresses the FDA's concerns regarding the clinical meaningfulness of fatigue in PsA, and its redundancy with other endpoints, in an effort to support the FACIT-Fatigue as a key secondary endpoint in the Phase 3 trials of upadacitinib in adults ≥18 years of age with active PsA.

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) – Outcome Measures in Rheumatology (OMERACT) PsA working group includes fatigue as one of the core outcomes of PsA treatment. Conclusion: Improvement in fatigue captures a treatment benefit that is both meaningful from the patient and physician perspectives, and unlike any other primary and secondary endpoints in the MAH outcome measurement strategy.

Self-Assessment of Psoriasis Symptoms (SAPS)

Specific to the present dossier, the effect of upadacitinib on patient-reported psoriasis signs and symptoms in patients with active PsA was evaluated, hypothesizing that greater improvement in patient-reported

psoriasis symptoms, as measured by the SAPS total score from Baseline to Week 16, would be observed in patients treated with upadacitinib compared to placebo (ranked secondary endpoint).

The SAPS is an 11-item patient-reported outcome (PRO) questionnaire that assesses pain, itching, redness, scaling, flaking, bleeding, burning, stinging, tenderness, cracking, and joint pain at their worst in the 24 hours prior to the assessment on an 11-point NRS ranging from 0 ("no [sign/symptom] at all") to 10 ("worst possible [sign/symptom]"). A total score is computed by summing the item scores. The SAPS score ranges from 0 to 110, where higher scores represent more severe signs and symptoms.

Development and content validity: Informed by best measurement development practices, as well as the FDA PRO Guidance, the SAPS was developed based on concepts identified as relevant to plaque psoriasis in the peer-reviewed literature, clinical experts in the field of dermatology (N=3), and concept elicitation interviews with patients with chronic plaque psoriasis (N=40; including those with concomitant PsA [n=15]). Following its development, confirmation of the relevance of item-concepts and evaluation of the readability and comprehensibility of the questionnaire were conducted in a patient population of adults with chronic plaque psoriasis (N=20). The results indicated that the concepts measured by the SAPS are relevant to the condition, and the items themselves are presented in ways that respondents can easily read and understand and to which they can provide meaningful responses.

Measurement properties: The measurement properties of the SAPS were studied in the MAH's Phase 3 clinical study for PsA, M15-554 (SELECT-PsA 2) (N=638). Data generated from these participants at Baseline, Week 16, and Week 24 were used to evaluate the psychometric performance of the SAPS total score when collected during the Phase 3 study. Quality of completion of the SAPS items, an indicator of compliance with assessment, was high at all time points, with no missing items for more than 99.0% of participants across all time points. Descriptive data at Baseline for item scores generated by the SAPS demonstrated that respondents used the entire range of the response scale. The findings from the psychometric evaluation demonstrated that the SAPS produced a total score that was reliable (with high internal consistency reliability and test-retest reliability), valid in terms of measuring the construct it is intended to measure, capable of distinguishing between groups known to be clinically different, and sensitive to change over time. These conclusions are supported by results from AbbVie's Phase 2 clinical study of ABT-122 in PsA, M14-197 (N=240), in which the measurement properties of the SAPS were also studied.

Interpretation of scores: Interpretation of scores produced by the SAPS total score was also examined in the MAH's Phase 3 clinical study for PsA, M15-554 (SELECT-PsA 2), and supported by results from M14-197. Data generated from these clinical studies were used to create clinically important difference (CID) and clinically important response (CIR) estimates that could be used to facilitate the meaning of observed differences and within-person change, respectively, in the SAPS total score. In M15-554, distribution- based statistics were produced for the SAPS total score at Baseline. Anchor-based analyses produced mean change in SAPS total score from Baseline to Weeks 16 and 24 for each anchor group, cumulative distribution functions, probability distribution functions, and receiver operating characteristic curves to specify the change score that optimally discriminates between each group defined by the anchors. Distribution-based and anchor-based methods were used to determine a CID and a CIR for the SAPS total score. These interpretations are supported by results from M14-197.

Conclusion by the MAH: The SAPS is according to the MAH fit for the purpose of evaluating the Phase 3 efficacy hypotheses that upadacitinib improves patient-reported psoriasis signs and symptoms among adult patients with active PsA. This conclusion is supported by evidence of the content validity of the SAPS (i.e., the items measure concepts that are important and relevant to patients with PsA and does so in ways that respondents can understand and to which they can provide meaningful responses), measurement characteristics (i.e., the instrument generate scores that are reliable, valid, and sensitive to change), and interpretability (i.e., identified changes in scores can clearly be distinguished as meaningful from the perspective of the patient seeking treatment).

2.4.3. Discussion on clinical efficacy

Based on the clinical data and PPK modelling, the MAH concluded that the dose of 15 mg QD provides the optimal benefit-risk balance in subjects with PsA, with only modestly increased efficacy and decreased safety compared with the 30 mg QD dose. The higher dose tested in the Phase 3 clinical studies is not applied for. Therefore, the discussion focuses on the results obtained with the 15 mg QD dose.

Clinical studies in PsA include two Phase 3 trials (M15-572 and M15-554).

The two Phase 3 trials were conducted in subjects with moderate to severe PsA who had not responded adequately or were intolerant to prior treatment: M15-572 in patients with prior non-biologic DMARD treatment, and Study M15-554 in patients with prior bDMARDs. Due to the inclusion criteria, patients had moderate to severe PsA, since they were required to have active joint disease defined as ≥ 3 tender joints (based on 68 joint counts) and ≥ 3 swollen joints (based on 66 joint counts) at baseline, symptom onset at least 6 months prior to screening, fulfilment of the CASPAR criteria, and diagnosis of active plaque psoriasis or documented history of plaque psoriasis. In study M15-572, additionally, subjects were required to have had either ≥ 1 erosion on x-ray as determined by central imaging review or high-sensitivity C-reactive protein (hs-CRP) > laboratory defined upper limit of normal (ULN).

The proposed indication does not include any statement on the degree of severity of PsA. No universally agreed definition for mild, moderate and severe PsA exist. According to treatment guidelines, pharmacological treatment of PsA is initiated with anti-inflammatory medications and local corticosteroid injections in affected joints and insertions of tendons, ligaments and joint capsule fibres. Treatment with DMARDs is only started for subjects not responding adequately to the above-mentioned treatments; therefore, it is acceptable to CHMP that subjects with mild disease that can be controlled without DMARDs were not included. In absence of a universally agreed definition of moderate or severe PsA it is considered appropriate to the CHMP that disease severity is not included in the indication.

Both phase 3 studies are still ongoing, and the initial MA submission includes the data for first 24 weeks of Period 1 (56 weeks) of the studies. With the response to the 1st RSI, results up to week 56 were received for all outcomes proposed to be included in the SmPC.

Design and conduct of clinical studies

The clinical development pivotal programme supporting the efficacy of upadacitinib in PsA is considered in principle adequate to the CHMP. Both Phase 3 studies are randomized, multi-centre, double-blind, parallel-group studies with a 35-day screening period, a 56-week blinded period, and a long-term extension period of up to a total treatment duration of approximately 3 years. Both studies are ongoing, and efficacy results up to 24 weeks of the 56-week double-blind Period 1 are included in the clinical study reports, with some incomplete results up to 56 weeks in the clinical overview and clinical efficacy summary. Further 56-week data was received with the MAH's response, at which time all subjects had reached Week 56 or were prematurely discontinued by submission of the response.

Study M15-572 evaluates upadacitinib in subjects who have an inadequate response or intolerance to non-biologic DMARDs (conventional synthetic DMARDs [csDMARDs] and/or tsDMARDs) or had a contraindication for non-biologic DMARDs.

Study M15-554 evaluates upadacitinib in subjects who have an inadequate response or intolerance to biologic disease-modifying anti-rheumatic drugs (bDMARDs).

Using ACR20 as primary endpoint is in line with the Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis (CHMP/EWP/438/04) and considered acceptable to the CHMP. The time point of 12 weeks for the primary endpoint is considered relatively early; however, this has been accepted in the SA and shows difference of effect. Long-term effects on maintenance of effect will be seen with completion of the ongoing trials. Efficacy results up to 56 weeks have been provided. Furthermore, supportive data from RA are available which is of relevance since the mode of action is expected to be similar in PsA as in RA.

There are multiple and partly overlapping secondary efficacy endpoints for investigation of activity of psoriatic arthritis (e.g., ACR20/50/70, MDA, DAS28, DAPSA, several measures on resolution of dactylitis and enthesitis, and in study M15-572, radiographic progression of joint disease); skin involvement (sIGA, PASI, SAPS), spondyloarthropathy (BASDAI, ASDAS), and PROs (HAQ-DI, FACIT-F, SF-36 PCS, patient's assessment of pain, morning stiffness, EQ-5D-5L, pain, WPAI, etc). Inclusion of all endpoints in the studies is for the MAH to choose and, therefore, acceptable to the CHMP. However, only multiplicity-controlled and/or clinically relevant outcomes should be included in the SmPC. In line with this statement, the MAH was requested to shorten the proposed Section 5.1 of the SmPC during the review. The MAH accepted the CHMP's requests and submitted an updated SmPC accordingly; see details below.

The MAH has under development a tool (questionnaire) the Self-Assessment of Psoriasis Symptoms (SAPS) to evaluate signs and symptoms of psoriasis. The SAPS is an 11-item patient-reported outcome (PRO) questionnaire that assesses pain, itching, redness, scaling, flaking, bleeding, burning, stinging, tenderness, cracking, and joint pain at their worst in the 24 hours prior to the assessment on an 11-point NRS ranging from 0 to 10. A total score is computed by summing the item scores. The SAPS score ranges from 0 to 110, where higher scores represent more severe signs and symptoms. As signs and symptoms of psoriasis are an important and relevant treatment outcome in PsA, the MAH evaluated the change in SAPS total score from Baseline to Week 16 between upadacitinib and the combined placebo group in the course of its clinical trials. Measurement properties and the interpretation of the scores, including clinically important response estimates, were evaluated in the MAH PsA development programme.

The CHMP was of the opinion that it wasn't possible at this stage to determine whether this was an appropriate tool in general or to support improved assessment of psoriasis signs and symptoms in PsA or fit for any labelling purposes. For example, lack of comparative data with validated standard instruments are, to date, scarce/lacking. Thus, it was considered premature to include any data on this instrument in the SmPC.

There were several protocol amendments, which did not concern major aspects of the study plans and occurred prior to data cut-off.

The statistical plans are overall considered acceptable by the CHMP. Number of subjects with missing data at various time points was overall small and is adequately described. Variation was large for most outcomes within each treatment group, hence, responses were partly overlapping. Additionally, the onset of efficacy was variable with some subjects reaching the primary endpoint ACR20 already at 2 weeks and some only by 56 weeks from onset of upadacitinib treatment. Only statistically significant and clinically relevant results qualify for inclusion in the SmPC. Therefore, the MAH was requested to update the proposed Section 5.1 of the SmPC during the review. The MAH accepted the CHMP's requests and submitted an updated SmPC accordingly.

The efficacy analyses were conducted for the FAS, which includes all randomized subjects who received at least 1 dose of study drug; instead of the recommended ITT population. Since these populations

only differ by 1 subject in the 15 mg and 1 subject in the 30 mg upadacitinib group, this is not deemed to affect the results.

Doses selection of upadacitinib 15 mg and 30 mg was the same as for studies in RA. The observed binned plasma concentration versus time profiles of upadacitinib between subjects with RA and subjects with PsA were comparable. The choice of adalimumab as active control in Study M15-572 is deemed appropriate, and the adalimumab dose, 40 mg subcutaneous EOW, is the dose approved for treatment of patients with PsA.

The MAH has confirmed that the studies were conducted in accordance with ICH and GCP guidelines.

Efficacy data and additional analyses

A total of 2347 subjects were randomized and 2345 received at least 1 dose of study drug in the global pivotal Phase 3 studies, including 640 subjects who were initially randomized to and received at least 1 dose of upadacitinib 15 mg QD. More than 90% of subjects continued the study up to the primary endpoint (12 weeks) in both studies: 95.4% and 92.1% in studies M15-572 and M15-554, respectively. Most common reasons for discontinuation were lack of efficacy (M15-572) and withdrawal by subject (M15-554) in the placebo groups and AEs in the active-treated groups.

At baseline, the participants in both Phase 3 studies had active joint disease, with mean (SD) TJC68 of 20.0 (14.05) in study M15-572 and 24.8 (16.91) in study M15-554. The corresponding SJC66 was 11.2 (837) and 12.1 (8.85) in studies M15-572 and M15-554, respectively. The proportion of subjects with dactylitis at baseline was 30.3% and 26.4 %, with enthesitis 77.2 % and 82.2 %, and with psoriatic spondylitis 31.3 % and 34.2 % in studies M15-572 and M15-554, respectively. There were slightly more women in both studies. The studies represent different steps in the treatment algorithm for PsA: participants in study M15-572 were required to be intolerant or have inadequate response or contraindication to non-biologic DMARDs, whereas the participants in M15-554 are intolerant or have inadequate response or contraindication to biologic DMARDs. The mean duration of PsA diagnosis was consequently shorter in M15-572 (6.1 years), than in M15-554 (10.1 years).

Both Phase 3 studies met the primary endpoint at Week 12, with a statistically significantly greater percentage of subjects achieving an ACR20 response in the upadacitinib 15 mg and 30 mg QD groups compared with the placebo group. The 30 mg dose showed numerically somewhat more effect than the 15 mg dose. Since only the 15 mg dose is applied for, this discussion focuses on the results for the 15 mg dose.

In study M15-572, ACR 20 response was obtained at 12 weeks by 70.6 % of subjects in the upadacitinib 15 mg arm, 65.0 % in the adalimumab 40 mg EOW arm, and 36.2 % in the placebo arm. The difference between ACR20 response rate in the upadacitinib 15 mg and placebo groups was 34.5 (28.2, 40.7, $p<0.0001$ in the multiplicity-adjusted analysis). Upadacitinib 15 mg QD was non-inferior to adalimumab 40 mg EOW in the primary endpoint: the percentage of adalimumab effect preservation, which was calculated by (upadacitinib – placebo)/(adalimumab – placebo), was 119.4% (confidence interval [CI]: 98.0, 147.9) in the upadacitinib 15 mg group, exceeding the lower bound of the 95% CI of the pre-specified NI ratio of at least 50% of the placebo-subtracted adalimumab effect.

Ranked key secondary endpoints of study M15-572 included comparison of non-inferiority of upadacitinib vs. adalimumab at Week 12 in the primary endpoint, ACR20 response rate, and superiority of upadacitinib vs, adalimumab in ACR20 response rate, change from baseline in Patient's Assessment of Pain NRS, and change in HAQ-DI at Week 12. Non-inferiority in the primary endpoint was met. However, upadacitinib 15 mg was not statistically superior to adalimumab in any of the above-mentioned multiplicity-controlled comparisons. Hence, the nominal differences in HAQ-DI and

pain between upadacitinib 15 mg and adalimumab are not eligible to be included in the SmPC, as originally proposed by the MAH. It is acceptable to include in the SmPC the information that upadacitinib 15 mg was non-inferior to adalimumab. In addition, further justifications for inclusion of some additional secondary endpoints in the SmPC were requested by the CHMP and the SmPC was modified with the omission of improvement in Patient's Assessment of Pain NRS compared to adalimumab (as statistically non-significant), the non-multiplicity controlled endpoints change from baseline in ASDAS and PASI 100 response, and the multiplicity-controlled endpoints sIGA 0/1 response and SAPS.

In study M15-554, ACR 20 response was obtained at 12 weeks by 23.6 % of subjects in the placebo arm and 56.8 % in the upadacitinib 15 mg arm. The difference in the response rate was 33.1 (95 % CI 24.0, 42.3), and the difference was in multiplicity-adjusted analysis statistically significant ($p<0.0001$).

For study M15-554, the ACR20 response rate at Week 12 for subjects with exclusively intolerance to prior bDMARDs and with inadequate response to prior bDMARDs was in the upadacitinib 15 mg vs. placebo arms, respectively, 73.3 % vs. 38.9 % for the patients with intolerance and 55.4 % vs. 22.7 % for patients with inadequate response. Hence, the patients with prior inadequate response were more treatment-resistant, but the improvement with upadacitinib compared to placebo was of similar clinically relevant magnitude. The MAH has not submitted corresponding subgroup analyses for study M15-572, which recruited patients with intolerance, inadequate response or contraindication to prior non-biologic DMARDs. However, there is no reason to assume differential effects in these subgroups in M15-572; hence, this issue was not pursued further by the CHMP.

Additionally, MDA at week 24 showed significant improvement in the upadacitinib 15 mg group than placebo group in both Phase 3 trials. The proportion of subjects achieving MDA was in study M15-572, 36.6 % vs. 12.3 % (between-group difference 24.3, 95 % CI 18.8, 29.9) and in study M15-554, 25.1 % vs. 2.8% (between-group difference 22.3, 95 % CI 16.0, 28.6).

In both studies, the results were significantly better with upadacitinib vs. placebo irrespective of the number of prior DMARDs used by the patient (1 or >1). Other prespecified subgroup results gave as well consistent results with those obtained for the primary endpoint.

Subgroup analyses for subjects using upadacitinib as monotherapy vs. in combination with background non-biologic DMARDs were conducted in the integrated placebo-controlled analysis sets (separately for both upadacitinib doses). The number of subjects with monotherapy or combination therapy in the integrated set with placebo or upadacitinib 15 mg was the following: for monotherapy, placebo (n = 188), upadacitinib 15 mg (n = 189) and for combination therapy, placebo (n = 447), upadacitinib 15 mg (n = 452). These analyses were performed for the following endpoints: ACR20/50/70 response rate at Week 12, change from baseline in HAQ-DI at Week 12, proportion of subjects with sIGA 0/1 at Week 16 (for subjects with baseline sIGA $\geq$ 2), PASI 75/90/100 response rate at Week 16 (for subjects with $\geq$ 3% BSA-Ps at baseline), proportion of subjects achieving MDA at Week 16 and Week 24, and proportion of subjects achieving resolution of dactylitis (LDI = 0) (for subjects with baseline LDI > 0) and resolution of enthesitis (LEI = 0) (for subjects with baseline LEI > 0) at Week 24. The response rate (%, 95% CI) in monotherapy for ACR20 at week 12 was 25.0 (18.8, 31.2) in the placebo group and 58.7 (51.7, 65.7) in the upadacitinib 15 mg group. The respective results in combination therapy were 35.1 (30.7, 39.5) in the placebo and 69.2 (64.9, 73.4) in the upadacitinib 15 mg group. The other endpoints analysed separately for monotherapy and combination therapy also demonstrated better effect of upadacitinib vs. placebo independent of the treatment mode (monotherapy or combination therapy).

The numbers of subjects using other non-biologic DMARDs than MTX in combination with upadacitinib are relatively low in the integrated placebo-controlled data set. For the upadacitinib 15 mg group for

which the indication is applied, there were 15 subjects with the combination of upadacitinib and aprelimast, 30 subjects with upadacitinib + leflunomide, and 22 subjects with upadacitinib + sulfasalazine. Other DMARDs were used by an even lower number of subjects, some medications only by one or two subjects. In addition, the response rate difference vs. placebo in ACR20 is lower in the non-MTX combination therapy (19.4; 95 % CI 3.8, 35.1) than when upadacitinib is used with MTX (36.8; 95% CI 30.2, 43.4), with wider variation, the lower limit for 95% CI being only 3.8. Therefore, the data on the different combination treatments is not considered currently sufficient for the indication on combination treatments except for combination upadacitinib with MTX, also taking into consideration the worse safety profile with these non-MTX combinations. A major objection was raised during the review and the MAH agreed to modify the indication to limit the concomitant use of upadacitinib to methotrexate. This was considered acceptable to the CHMP.

The response in skin symptoms was assessed by the key secondary endpoints 75 percent improvement in PASI75, sIGA, and SAPS. All measures showed improvement in skin condition with upadacitinib 15 mg vs. placebo, and the differences were statistically significant except for SAPS. In the integrated efficacy analysis population, the proportion of responders defined by PASI75 (%, 95 % CI) at Week 16 was 58.7 (53.5, 63.9) in the upadacitinib 15 mg group and 19.3 (15.1, 23.5) in the placebo group.

Presence of dactylitis and enthesitis were stratification factors only in study M15-572; and resolution of enthesitis and dactylitis were multiplicity-controlled key outcome measures in study M15-572. In both studies, change in measures of enthesitis and dactylitis were conducted only on the proportion of patients with these symptoms at baseline; and in both studies, the proportion of subjects with dactylitis and enthesitis decreased numerically more in the upadacitinib 15 mg arm than placebo arm. In study M15 572, proportion of subjects with resolution of enthesitis (LEI = 0; %, 95 % CI) at Week 24 was 53.7 (47.8, 59.7) in the upadacitinib 15 mg group and 32.4 (26.5, 38.3) in the placebo group. Resolution of dactylitis at Week 24 was achieved in M15-572 by 76.5 % (69.3, 83.6) and 39.7 % (31.1, 48.2) in the upadacitinib 15 mg and placebo groups, respectively. In study M15-554, the corresponding figures were in the same order of magnitude as in study M15-572 for enthesitis and dactylitis.

Improvement in activity of spondylitis was evaluated by BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS (Ankylosing Spondylitis Disease Activity Score Based on CRP) were examined in subjects with psoriatic spondylitis at baseline (study M15-572: 31 %, study M15-554:35.4 %). In both studies, subjects in the upadacitinib 15 mg group had greater improvement from baseline in BASDAI and ASDAS, and a greater proportion of subjects achieved BASDAI 50, ASDAS inactive disease, ASDAS major improvement, and ASDAS clinically important improvement at Week 12 compared with subjects in the placebo group. The MAH justified the inclusion of the results for BASDAI in the SmPC as inclusion of one measure of efficacy of spondylitis is clinically relevant for prescribers. This was acceptable to the CHMP. At the CHMP's request, the MAH removed ASDAS from the SmPC since the two measures are largely overlapping.

In both pivotal Phase 3 studies, treatment with upadacitinib 15 mg QD and 30 mg QD demonstrated a numerically greater improvement from baseline in all the individual components of the ACR20/50/70 (TJC68, SJC66, HAQ-DI, PtGA, PGA, Patient's Assessment of Pain, and hsCRP) response at Week 12 compared with placebo. Multifaceted function of the subjects was evaluated by change from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 12, 36-Item Short Form Health Survey Physical Component Summary (SF-36 PCS), and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue in multiplicity-adjusted analyses. In line with results for the primary endpoint, these measures demonstrated statistically significant improvement by upadacitinib 15 mg compared with placebo in multiplicity-controlled analyses. E.g., the HAQ-DI index decreased (improved) from 1.15 at baseline to 0.74 at Week 12 in the upadacitinib 15 mg group and from 1.11 at baseline to 0.98

at Week 12 in the placebo group (LS mean difference between upadacitinib 15 mg and placebo -0.28, 95% CI 0.35, -0.22, p <0.0001) in Study M15-572. Corresponding figures for Study M15-554 were change from 1.08 to 0.79 in the upadacitinib 15 mg group and from 1.23 to 1.12 in the placebo group (LS mean difference between upadacitinib 15 mg and placebo -0.21, 95% CI -0.30, -0.12, p <0.0001). However, the effect of upadacitinib on mental health was considered to be very modest in comparison with that on physical health based on the SF-36 MCS and PCS. Therefore, at the CHMP's request, the MAH removed from the SmPC the non-multiplicity-controlled and clinically non-relevant results of SF-36 MCS.

The ACR20 response was in both studies statistically significantly better with upadacitinib 15 mg vs. placebo already at 2 weeks and the effect was retained up to 24 weeks in both studies. Efficacy results for 56 weeks confirmed maintenance of effect of upadacitinib up to 56 weeks. The data were deemed acceptable for inclusion of these results in the SmPC. However, within-group variation in response was marked for several outcome measures, as was onset of efficacy which varied e.g. for the primary endpoint from 2 weeks to 56 weeks. A large amount of data from patients with RA have demonstrated sustainable effect by upadacitinib. It is therefore plausible that the effect would be maintained also in PsA.

The MAH initially provided only 24-week data on radiographic progression in one of the PsA-studies (M15 572), with PsA-population intended to be enriched with patients with active joint disease (at least 1 X-ray erosion at baseline or increased CRP). The final study population included only 39.2 % of subjects with at least one joint erosion. Even though 75.1 % of subjects had hsCRP > upper limit of normal, the mean and median level of hsCRP was only 11.22 and 6.21 mg/L, respectively, with a range of 0.20 to 169 mg/L. Hence, the population did not have very active joint erosive disease in general. The change from baseline in SHS (equivalent to modified Total Sharp Score [mTSS]), Joint Erosion Score, and JSN Score at Week 24 all showed improvement by upadacitinib 15 mg compared with placebo. The difference in SHS (with the predefined primary linear extrapolation analysis) is small for the comparison of upadacitinib 15 mg with placebo (LS mean, 95% CI): -0.29 (-0.44, -0.14). No difference was seen in the comparison of upadacitinib 15 mg and adalimumab. The MAH has used in their sample size calculation the value 0.26 as a "standardized effect size in change from baseline in SHS versus placebo at week 24". This effect size was met. Most subjects had no radiographic progression at week 24: 89.2% in the placebo group, 93.0% in the adalimumab group and 93.4 % in upadacitinib 15 mg group (with linear extrapolation and change from baseline in SHS <0). Although the time when a patient would develop radiographic progression can vary in PsA, it is reported that up to two thirds of patients will experience progressive joint damage, which can subsequently result in functional loss and disability. Therefore, current EULAR guidelines recommend a treat-to-target approach, similarly to the approach in rheumatoid arthritis management, even though the mechanism causing joint damage in PsA is not well defined. It is important that radiographic progression is investigated for sufficiently long period. Current EMA guidelines state that the observation period needed is not less than two years, showing sustained effects for the effects after the first year. The proportion of patients with no radiographic progression was still very high at week 56 in all study arms: 89 % (95% CI 86, 92) even for patients who received placebo for 24 week before switching to upadacitinib, 97 % (96, 99) for subjects who received upadacitinib 15 mg from the beginning, and 94 % (92, 97) for patients who received ADA from the beginning up to 56 weeks. However, the CIs are narrow for this measure, and the CIs of the placebo and upadacitinib groups no more overlap at week 56. Thus, even though there seemed to be radiographically slower progression with upadacitinib when measured by the change in SHS, the proportions of subjects who had no progression of structural damage is a more robust parameter from a clinical perspective. Contrary to the SHS-scores, the proportions of subjects who had no progression of structural damage showed very small difference (4.2 %) between placebo and upadacitinib treatment arms, potentially due to the fact that most

subjects had no radiographic progression during this time period. This may reflect the importance of longer-term radiographic data in showing benefit in radiographic measures. Nevertheless, the CHMP concluded that the completed 56-week efficacy data supports the inclusion of the radiographic results in the SmPC.

2.4.4. Conclusions on the clinical efficacy

The 24-week data from the two phase 3 studies, one in subjects intolerant or with inadequate response to non-biologic DMARDs and one in subjects intolerant or with inadequate response to bDMARDs, show that upadacitinib 15mg compared with placebo was robustly associated with better clinical efficacy for the treatment of the 3 major manifestations of psoriatic disease (joint, soft tissue and skin), and provided improvement of physical function and health-related quality of life in adults with active psoriatic arthritis. Higher exposure by upadacitinib 30 mg QD vs. 15 mg QD was only modestly or not at all associated with better clinical response in efficacy as observed in the clinical trials and according to the population PK analysis. Upadacitinib 15 mg QD was non-inferior to adalimumab 40 mg EOW in the treatment of patients with inadequate response or intolerance to non-biologic DMARDs.

Based on the totality of the efficacy data and analyses, the same posology as for RA is supported for PsA, i.e. 15 mg once daily. The MAH's proposal to use upadacitinib concomitantly with a non-MTX non-biologic DMARD in the treatment of PsA was not endorsed by the CHMP as the efficacy of combination of upadacitinib 15mg with another non-biologic DMARD than MTX was considered insufficient due to scarcity of subjects administered these combinations. In addition, the use of upadacitinib concomitantly with a non-MTX non-biologic DMARD seems to be associated with a higher frequency of adverse events, including serious and severe events. Since the number of subjects are small, there are considerable remaining uncertainties regarding the safety profile when upadacitinib is used concomitantly with non-MTX agents or with a combination of MTX and a non-MTX agent. The MAH agreed to modify the therapeutic indication in the treatment of psoriatic arthritis in monotherapy or in combination with methotrexate. This was considered acceptable to the CHMP as the efficacy of upadacitinib used as monotherapy and in combination with methotrexate was shown to be comparable.

Long-term data up to 56 weeks for all phase 3 study subjects confirm the maintenance of the therapeutic effect.

The CHMP considered that the efficacy of upadacitinib in the following indication is supported by the data submitted by the MAH: "*RINVOQ is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. RINVOQ may be used as monotherapy or in combination with methotrexate*."

2.5. Clinical safety

Introduction

Upadacitinib was authorised for its original RA indication in the United States in August 2019, by the European Commission in December 2019, and has also been authorised in multiple other countries. Within the RA studies, the most commonly reported adverse drug reactions (ADRs) were upper respiratory tract infections, bronchitis, nausea, blood creatine phosphokinase (CPK) increased and cough. The most common serious adverse reactions were serious infections. The current SmPC includes special warnings and precautions for conditions including serious infections, viral reactivation, malignancies, haematological abnormalities, cardiovascular risk and lipids, hepatic transaminase elevations and venous thromboembolism. Upadacitinib

is contraindicated in patients with hypersensitivity to the active substance or excipients, in patients with active tuberculosis or active serious infections, in severe hepatic impairment, and during pregnancy.

To support the current variation application, upadacitinib was studied in 2 pivotal randomised, double-blind, Phase 3 studies in PsA patients. Study M15-572 was a placebo- and adalimumab -controlled study in non-biologic DMARD-IR patients, and study M15-554 was a placebo-controlled study in biologic DMARD-IR patients. Whereas 2 doses of upadacitinib (15 mg and 30 mg QD) were evaluated in the studies, only the 15 mg dose is being proposed for marketing authorisation. The treatment groups and numbers of enrolled patients are depicted in Table 54.

Table 54 Pivotal Phase 3 PsA Studies (Safety Analysis Set)

	M15-572	M15-554
Population	non-biologic DMARD-IR	bDMARD-IR
Treatment Groups (N)	Upadacitinib 15 QD (430) Upadacitinib 30 QD (423) Placebo (423) Adalimumab 40 EOW (429)	Upadacitinib 15 QD (211) Upadacitinib 30 QD (218) Placebo (212)
Placebo/Active Comparator Duration (Weeks)	24 (placebo) 152 (adalimumab)	24 (placebo)

bDMARD = biologic disease-modifying antirheumatic drug; DMARD-IR = disease-modifying antirheumatic drug-intolerant or inadequate responder; EOW = every other week; IR = inadequate response; PsA = psoriatic arthritis; QD = once daily

Data cut-offs were 09 October 2019 for study 554 and 13 December 2019 for study 572. These cut-off dates enable inclusion of all data from all subjects through Week 24, and long-term data is included through the respective cut-off date for each study into the clinical study reports and integrated analyses.

For purposes of safety assessment, safety data from the two studies were integrated into two analysis sets as outlined in Table 55. Data presentations include frequency tables by treatment group as well as exposure-adjusted event rates and/or incidence rates. Although not part of the formal integrated analysis, data from subjects treated with adalimumab in study 572 is displayed within the tabulations to enable comparison with an authorised active control.

Table 55 Integrated Safety Analysis Sets

Analysis Set	Analysis Set Rationale and Description	Analyses	Pooled Studies	Summarized Treatment Group(s)	Treatment Comparison(s)[b]
PBO-controlled Analysis Set	This analysis set assesses short-term safety through 24 weeks of upadacitinib 15 mg QD and upadacitinib 30 mg QD versus placebo. It includes subjects who received upadacitinib 15 mg QD, upadacitinib 30 mg QD, and placebo during the 24-week placebo-controlled period in Studies M15-554 and M15-572.	Short-term (24 weeks)	M15-554 M15-572	• Upadacitinib 15 mg QD • Upadacitinib 30 mg QD • Placebo	• Upadacitinib 15 mg QD versus placebo • Upadacitinib 30 mg QD versus placebo
Any Upadacitinib Analysis Set[a]	This analysis set is to assesses long-term safety of upadacitinib 15 mg QD and upadacitinib 30 mg QD. It includes all subjects who received upadacitinib 15 mg QD or upadacitinib 30 mg QD from Studies M15-554 and M15-572. This analysis set was based on all cumulative exposure.	Long-term (All exposure)	M15-554 M15-572	• Upadacitinib 15 mg QD (No Cross-over from Placebo)[c] • Upadacitinib 30 mg QD (No Cross-over from Placebo)[c] • Any Upadacitinib 15 mg QD[d] • Any Upadacitinib 30 mg QD[d]	• Upadacitinib 30 mg QD (No Cross-over from Placebo) versus UPA 15 mg QD (No Cross-over from Placebo) • Any Upadacitinib 30 mg QD versus Any Upadacitinib 15 mg QD

PBO = placebo; QD = once daily; UPA = upadacitinib

a. All subjects who received at least one dose of upadacitinib.

b. Treatment comparison for overview of treatment-emergent adverse event (TEAE), overview of treatment-emergent AESI, and potentially clinically significant (PCS) laboratory values.

c. Included any UPA 15 mg QD/30 mg QD exposure of subjects starting on UPA 15 mg QD/30 mg QD at randomization.

d. Included any UPA 15 mg QD/30 mg QD exposure of subjects starting on UPA 15 mg QD/30 mg QD at randomization and subjects switched from placebo to UPA 15 mg QD/30 mg QD.

In both studies, subjects initially randomised to placebo switched to blinded upadacitinib 15 mg or 30 mg (based on pre-specified treatment assignment at Baseline) at Week 24. Switching between upadacitinib doses was not permitted at any stage in either study.

To further characterise the safety profile of long-term upadacitinib exposure, cumulative long-term safety data from the RA programme (comprising 11,201.0 PY of exposure among a total of 5,579 subjects), with a data cut-off date of 31 December 2019, and a summary of post-marketing experience until 31 January 2020 (with cumulative exposure of about 3,100 PY), were provided as supportive information for the current submission.

Patient exposure

Extent of exposure

A total of 1,827 subjects received at least 1 dose of upadacitinib (15 mg QD or 30 mg QD) in the Phase 3 studies, with a total of approximately 1,639 patient-years (PY) of upadacitinib exposure included in the safety analyses. Between the 2 studies, 907 subjects received at least 1 dose of upadacitinib 15 mg, representing a total of 816.9 PY of upadacitinib exposure. At the time of data cut-off, 359 subjects had been treated with upadacitinib 15 mg for at least 12 months (Table 56).

Table 56 Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (Any Upadacitinib Analysis Set)

	Upadacitinib			
Days	15 mg QD (No Cross-Over from Placebo) (N = 640) n (%)	30 mg QD (No Cross-Over from Placebo) (N = 641) n (%)	Any 15 mg QD (N = 907) n (%)	Any 30 mg QD (N = 920) n (%)
≥ 2 weeks	636 (99.4)	637 (99.4)	897 (98.9)	909 (98.8)
≥ 1 month	628 (98.1)	633 (98.8)	866 (95.5)	882 (95.9)
≥ 3 months	605 (94.5)	603 (94.1)	796 (87.8)	800 (87.0)
≥ 6 months	564 (88.1)	553 (86.3)	701 (77.3)	701 (76.2)
≥ 9 months	401 (62.7)	397 (61.9)	490 (54.0)	491 (53.4)
≥ 12 months	303 (47.3)	299 (46.6)	359 (39.6)	363 (39.5)
≥ 18 months	128 (20.0)	128 (20.0)	142 (15.7)	143 (15.5)
≥ 2 years	28 (4.4)	28 (4.4)	29 (3.2)	28 (3.0)
Mean duration (days)	372.0	368.7	329.0	326.4

QD = once daily

Notes: Duration of exposure to study drug in this analysis is Period 1 and Period 2 combined exposure. Exposure is presented by treatment actually received.

Subjects could be included in more than one treatment column.

Exposure to upadacitinib 15 mg = date of last study medication of upadacitinib 15 mg – date of first study medication of upadacitinib 15 mg + 1.

Exposure to upadacitinib 30 mg = date of last study medication of upadacitinib 30 mg – date of first study medication of upadacitinib 30 mg + 1.

Demographic and baseline characteristics

In the PBO-controlled Analysis Set, demographic characteristics were generally balanced across the upadacitinib and placebo groups. Across the treatment groups, 52-55% were female, and about 89% were white. Mean age was 51-52 years and mean BMI was 30-31 kg/m^2. Some 13-14% of patients in each treatment group were >= 65 years of age, but less than 3% were 75 years or older. Whereas 44-50% of enrolled subjects had mild renal impairment (eGFR >= 60 and <90 mL/min/1.73 m^2), the number of patients with moderate renal impairment was small; only 4-6% of subjects across the treatment groups had an eGFR <60 mL/min/1.73 m^2 (subjects with a screening eGFR <40 mL/min/1.73 m^2 were excluded from the studies). The majority of subjects were from Eastern Europe (34-37%) and North America (32-33%).

Apart from the Skin and subcutaneous tissue disorders SOC, the most common medical/surgical history SOCs (≥ 40% in any treatment group) were vascular disorders, metabolism and nutrition disorders, and musculoskeletal and connective tissue disorders (Table 57).

Table 57 Most Common Medical/Surgical History by SOC (≥ 40% in Any Treatment Group) and by PT Within the Most Common SOC (PBO-controlled Analysis Set)

System Organ Class MedDRA 22.0 Preferred Term	Placebo (N = 635) n (%)	Upadacitinib 15 mg QD (N = 640) n (%)	Upadacitinib 30 mg QD (N = 641) n (%)
Metabolism and nutrition disorders	287 (45.2)	288 (45.0)	274 (42.7)
Hyperlipidemia	80 (12.6)	65 (10.2)	83 (12.9)
Obesity	60 (9.4)	69 (10.8)	79 (12.3)
Hypercholesterolemia	57 (9.0)	46 (7.2)	43 (6.7)
Diabetes mellitus	51 (8.0)	50 (7.8)	42 (6.6)
Type 2 diabetes mellitus	37 (5.8)	26 (4.1)	42 (6.6)
Vitamin D deficiency	41 (6.5)	47 (7.3)	42 (6.6)
Hyperuricemia	30 (4.7)	27 (4.2)	29 (4.5)
Dyslipidemia	17 (2.7)	23 (3.6)	21 (3.3)
Glucose tolerance impaired	17 (2.7)	11 (1.7)	8 (1.2)
Overweight	13 (2.0)	5 (0.8)	3 (0.5)
Vascular disorders	301 (47.4)	311 (48.6)	267 (41.7)
Hypertension	283 (44.6)	288 (45.0)	248 (38.7)
Varicose vein	17 (2.7)	15 (2.3)	11 (1.7)
Musculoskeletal and connective tissue disorders	259 (40.8)	257 (40.2)	264 (41.2)
Osteoarthritis	100 (15.7)	87 (13.6)	93 (14.5)
Back pain	42 (6.6)	32 (5.0)	39 (6.1)
Spinal osteoarthritis	35 (5.5)	28 (4.4)	33 (5.1)
Osteoporosis	28 (4.4)	29 (4.5)	32 (5.0)
Intervertebral disc degeneration	21 (3.3)	25 (3.9)	25 (3.9)
Arthralgia	25 (3.9)	21 (3.3)	19 (3.0)
Intervertebral disc protrusion	25 (3.9)	15 (2.3)	18 (2.8)
Rotator cuff syndrome	6 (0.9)	16 (2.5)	18 (2.8)
Osteopenia	15 (2.4)	23 (3.6)	17 (2.7)
Psoriatic arthropathy	18 (2.8)	14 (2.2)	17 (2.7)
Muscle spasms	12 (1.9)	21 (3.3)	15 (2.3)

MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; PT = preferred term; QD = once daily; SOC = system organ class

Note: Percentages calculated on non-missing values.

Concomitant DMARD and corticosteroid use

In the PBO-controlled Analysis Set, approximately 70% of subjects were receiving concomitant therapy with a non-biologic DMARD at Baseline (Table 58). The most commonly used DMARD was MTX, either alone or in combination with another non-biologic DMARD.

Table 58 Concomitant Non-Biologic DMARD at Baseline (PBO-controlled Analysis Set)

Variable	Placebo (N = 635) n (%)	Upadacitinib 15 mg QD (N = 640) n (%)	Upadacitinib 30 mg QD (N = 641) n (%)
MTX alone	342 (53.9)	353 (55.2)	341 (53.2)
MTX and other non-biologic DMARD	33 (5.2)	26 (4.1)	32 (5.0)
Non-biologic DMARD other than MTX	72 (11.3)	72 (11.3)	71 (11.1)
None	188 (29.6)	189 (29.5)	197 (30.7)

DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; PBO = placebo; QD = once daily

Note: Percentages calculated on non-missing values.

When the two studies are compared, one or more background DMARDs were used by 82% of subjects in study 572 (non-biologic DMARD-IR population), compared to 49% in study 554 (biologic DMARD-IR population). According to the MAH, this is expected and explained by more subjects in the non-biologic DMARD-IR population continuing on the last therapy they were on instead of washing it out as compared to the biologic DMARD-IR population. In both studies, MTX was clearly the most commonly used background DMARD (69% in study 572 and 39% in study 554). In study 572, about 9% of subjects were on sulfasalazine and about 6% of patients on leflunomide, whereas in study 554, about 5% of subjects were on apremilast and also about 5% on sulfasalazine.

About 15% of subjects in study 554 and about 20% of subjects in study 572 were using a concomitant systemic corticosteroid at Baseline. In both studies, the most commonly used corticosteroids were prednisone and methylprednisolone.

About 61% of subjects in study 554 and about 66% of subjects in study 572 were using a concomitant NSAID at Baseline. In both studies, most commonly used NSAIDs included acetylsalicylic acid, diclofenac, ibuprofen, meloxicam and naproxen.

Adverse events

Overview of adverse events

An overview of adverse events in the PBO-controlled Analysis Set is displayed in Table 59, and a corresponding display of exposure-adjusted event/incidence rates in the long-term Any Upadacitinib Analysis Set is provided in Table 60.

Table 59 Overview of Subjects with Treatment-Emergent Adverse Events (PBO-controlled Analysis Set)

	Placebo (N = 635) n (%) [SSA %]	Upadacitinib 15 mg QD (N = 640) n (%) [SSA %]	Upadacitinib 30 mg QD (N = 641) n (%) [SSA %]	Adalimumab 40 mg EOW[c] (N = 429) n (%)
Any AE	391 (61.6) [61.6]	422 (65.9) [65.9]	476 (74.3) [74.2]	278 (64.8)
Any SAE	17 (2.7) [2.7]	26 (4.1) [4.1]	44 (6.9) [6.9]	16 (3.7)
Any AE leading to discontinuation of study drug	24 (3.8) [3.8]	28 (4.4) [4.4]	41 (6.4) [6.4]	22 (5.1)
Any severe AE	24 (3.8) [3.8]	34 (5.3) [5.3]	43 (6.7) [6.7]	28 (6.5)
Any AE with reasonable possibility of being related to study drug[a]	173 (27.2) [27.2]	212 (33.1) [33.1]	265 (41.3) [41.4]	168 (39.2)
Any AE leading to death	2 (0.3) [0.3]	0	0	0
Deaths[b]	2 (0.3) [0.3]	0	0	0

AE = adverse event; EOW = every other week; PBO = placebo; QD = once daily; SAE = serious adverse event; SSA = study size adjusted

a. As assessed by investigator.

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

c. Adalimumab was administered only in Study M15-572.

Note: Events with unknown toxicity grade or Grade 3 and above based on CTCAE v5.0 was counted as severe. Events with unknown relationship to study drug was counted as having a reasonable possibility of being related to study drug.

Table 60 Overview of Treatment-Emergent Adverse Events per 100 PY (Any Upadacitinib Analysis Set)

	Upadacitinib				
	15 mg QD (No Cross-Over from Placebo) (N = 640) (PY = 651.8)	30 mg QD (No Cross-Over from Placebo) (N = 641) (PY = 647.1)	Any 15 mg QD (N = 907) (PY = 816.9)	Any 30 mg QD (N = 920) (PY = 822.3)	Adalimumab 40 mg EOW[c] (N = 429) (PY = 394.5)
Exposure-adjusted event rate	E (E/100 PY) [SSA E/100 PY]				E (E/100 PY)
Any AE	2111 (323.9) [323.9]	2638 (407.7) [407.6]	2523 (308.9) [308.8]	3120 (379.4) [379.5]	1294 (328.0)
Any SAE	76 (11.7) [11.6]	98 (15.1) [15.1]	89 (10.9) [10.9]	122 (14.8) [14.8]	43 (10.9)
Any AE leading to discontinuation of study drug	59 (9.1) [9.0]	70 (10.8) [10.8]	69 (8.4) [8.5]	78 (9.5) [9.5]	40 (10.1)
Any severe AE	88 (13.5) [13.5]	118 (18.2) [18.2]	101 (12.4) [12.4]	150 (18.2) [18.2]	51 (12.9)
Any AE with reasonable possibility of being related to study drug[a]	763 (117.1) [117.2]	1087 (168.0) [167.9]	901 (110.3) [110.2]	1256 (152.7) [152.8]	594 (150.6)
Any AE leading to death	1 (0.2) [0.2]	0	1 (0.1) [0.1]	1 (0.1) [0.1]	0
Exposure-adjusted incidence rate	n/PY (n/100 PY) [SSA n/100 PY]				n/PY (n/100 PY)
Deaths[b]	1/652.0 (0.2) [0.2]	1/647.2 (0.2) [0.2]	1/817.1 (0.1) [0.1]	2/822.9 (0.2) [0.2]	0/394.5

AE = adverse event; EOW = every other week; PY = patient-year; QD = once daily; SAE = serious adverse event; SSA = study size adjusted

a. As assessed by investigator.

b. Included both treatment-emergent and non-treatment emergent deaths.

c. Adalimumab was administered only in Study M15-572.

Note: Subjects could be included in more than one treatment column.
Events with unknown toxicity grade or Grade 3 and above based on CTCAE v5.0 will be counted as severe.
Events with unknown relationship to study drug is being counted as having a reasonable possibility of being related to study drug.

Common adverse events

In the PBO-controlled Analysis Set, the most frequent TEAEs (>= 10% of subjects in either upadacitinib group) were in the Infections and infestations, GI disorders, Investigations, and Musculoskeletal and connective tissue disorders SOCs. In the placebo group, the most frequently affected SOCs were Infections and infestations, GI disorders, and Musculoskeletal and connective tissue disorders.

- Within the Infections and infestations SOC, TEAEs were reported in 33.1% of subjects on placebo, 37.0% of subjects on upadacitinib 15 mg, and 45.1% of subjects on upadacitinib 30 mg.
- Within the GI disorders SOC, TEAEs were reported in 11.7% of subjects on placebo, 15.0% of subjects on upadacitinib 15 mg, and 15.8% of subjects on upadacitinib 30 mg.
- Within the Investigations SOC, TEAEs were reported in 7.6% of subjects on placebo, 13.9% of subjects on upadacitinib 15 mg, and 19.7% of subjects on upadacitinib 30 mg.
- Within the Musculoskeletal and connective tissue disorders SOC, TEAEs were reported in 11.5% of subjects on placebo, 10.3% of subjects on upadacitinib 15 mg, and 9.8% of subjects on upadacitinib 30 mg.

At the PT level, the most frequently reported TEAEs were upper respiratory tract infection (URTI) (8.9%) and increased blood CPK (6.6%) in the upadacitinib 15 mg group; URTI (9.7%), increased blood CPK (8.3%), nasopharyngitis (7.2%), and increased ALT (5.5%) in the upadacitinib 30 mg

group; and URTI (6.9%) and nasopharyngitis (6.0%) in the placebo group. The most frequently reported TEAEs are summarised in Table 61.

Table 61 TEAEs Reported in ≥ 2% of Subjects in Any Group by Decreasing Frequency in the Upadacitinib 15 mg Group (PBO-controlled Analysis Set)

MedDRA 22.0 Preferred Term	Placebo (N = 635) n (%) [SSA %]	Upadacitinib 15 mg QD (N = 640) n (%) [SSA %]	Upadacitinib 30 mg QD (N = 641) n (%) [SSA %]
Upper respiratory tract infection	44 (6.9) [6.9]	57 (8.9) [8.9]	62 (9.7) [9.7]
Blood CPK increased	10 (1.6) [1.6]	42 (6.6) [6.5]	53 (8.3) [8.3]
Nasopharyngitis	38 (6.0) [6.0]	31 (4.8) [4.8]	46 (7.2) [7.2]
Urinary tract infection	22 (3.5) [3.5]	27 (4.2) [4.2]	26 (4.1) [4.0]
Bronchitis	14 (2.2) [2.2]	24 (3.8) [3.8]	31 (4.8) [4.8]
Diarrhea	22 (3.5) [3.5]	23 (3.6) [3.6]	26 (4.1) [4.0]
ALT increased	13 (2.0) [2.0]	21 (3.3) [3.3]	35 (5.5) [5.5]
Headache	16 (2.5) [2.5]	21 (3.3) [3.3]	26 (4.1) [4.1]
Hypertension	19 (3.0) [3.0]	20 (3.1) [3.1]	16 (2.5) [2.5]
Influenza	8 (1.3) [1.3]	19 (3.0) [3.0]	17 (2.7) [2.6]
Cough	10 (1.6) [1.6]	16 (2.5) [2.5]	21 (3.3) [3.3]
Psoriatic arthropathy	24 (3.8) [3.8]	16 (2.5) [2.5]	10 (1.6) [1.6]
AST increased	9 (1.4) [1.4]	14 (2.2) [2.2]	22 (3.4) [3.4]
Nausea	15 (2.4) [2.4]	13 (2.0) [2.0]	24 (3.7) [3.7]
Back pain	10 (1.6) [1.6]	12 (1.9) [1.9]	14 (2.2) [2.2]
Sinusitis	15 (2.4) [2.4]	12 (1.9) [1.9]	13 (2.0) [2.0]
Leukopenia	4 (0.6) [0.6]	10 (1.6) [1.6]	13 (2.0) [2.0]
Gastroenteritis	7 (1.1) [1.1]	8 (1.3) [1.3]	19 (3.0) [3.0]
Oral herpes	6 (0.9) [0.9]	7 (1.1) [1.1]	22 (3.4) [3.4]
Herpes zoster	5 (0.8) [0.8]	7 (1.1) [1.1]	13 (2.0) [2.0]
Neutropenia	2 (0.3) [0.3]	6 (0.9) [0.9]	18 (2.8) [2.8]
Pyrexia	5 (0.8) [0.8]	6 (0.9) [0.9]	16 (2.5) [2.5]
Lymphopenia	5 (0.8) [0.8]	5 (0.8) [0.8]	15 (2.3) [2.4]
Anemia	4 (0.6) [0.6]	4 (0.6) [0.6]	20 (3.1) [3.1]
Psoriasis	15 (2.4) [2.4]	4 (0.6) [0.6]	5 (0.8) [0.8]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; QD = once daily; SSA = study size adjusted; TEAE = treatment-emergent adverse event

Also in the long-term Any Upadacitinib Analysis Set, the most common TEAEs (≥ 5 E/100 PY in either upadacitinib group) included URTI, increased blood CPK, nasopharyngitis, urinary tract infection, bronchitis, ALT increased, hypertension, diarrhoea, AST increased, herpes zoster and oral herpes. Apart from hypertension, exposure-adjusted event rate (EAERs) for the events were higher in the 30 mg group than the 15 mg group.

Frequently reported TEAEs in study 572 are displayed in Table 62. Increased blood CPK and herpes zoster were more frequent on upadacitinib, whereas increased ALT and neutropenia as well as injection site reactions were more frequent with adalimumab.

Table 62 Treatment-Emergent Adverse Events Reported in ≥ 5 Events per 100 PY in any Treatment Group by Decreasing Frequency in the Upadacitinib 15 mg Group – Long-Term (Safety Analysis Set; Study M15-572)

MedDRA 22.0 Preferred Term	ADA 40 mg EOW (N = 429) (PY = 394.5) E (E/100 PY)	Upadacitinib 15 mg QD (N = 617) (PY = 524.1) E (E/100 PY)	Upadacitinib 30 mg QD (N = 612) (PY = 526.0) E (E/100 PY)
Blood CPK increased	36 (9.1)	75 (14.3)	113 (21.5)
Upper respiratory tract infection	62 (15.7)	91 (17.4)	98 (18.6)
Nasopharyngitis	52 (13.2)	51 (9.7)	64 (12.2)
ALT increased	44 (11.2)	46 (8.8)	43 (8.2)
Urinary tract infection	18 (4.6)	39 (7.4)	55 (10.5)
AST increased	27 (6.8)	32 (6.1)	30 (5.7)
Headache	25 (6.3)	31 (5.9)	24 (4.6)
Hypertension	13 (3.3)	31 (5.9)	20 (3.8)
Bronchitis	12 (3.0)	30 (5.7)	42 (8.0)
Diarrhea	18 (4.6)	26 (5.0)	28 (5.3)
Herpes zoster	2 (0.5)	16 (3.1)	32 (6.1)
Cough	9 (2.3)	14 (2.7)	28 (5.3)
Oral herpes	15 (3.8)	13 (2.5)	46 (8.7)
Neutropenia	18 (4.6)	12 (2.3)	29 (5.5)
Injection site reaction	24 (6.1)	0	2 (0.4)

ADA = adalimumab; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; EOW = every other week; MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-year; QD = once daily

Note: Subjects in upadacitinib 15 mg or 30 mg group included those who started upadacitinib 15 mg or 30 mg at the beginning of the study and those who switched from placebo to upadacitinib 15 mg or 30 mg at Week 24.

In the PBO-controlled Analysis Set, severe AEs reported in more than 2 subjects in any group comprised pneumonia (4 subjects in the upadacitinib 30 mg group), lymphopenia (3 subjects in the upadacitinib 15 mg group), and ALT increased (3 subjects in the upadacitinib 30 mg group). In the long-term Any Upadacitinib Analysis Set, the most common severe TEAEs (>=0.5 study size adjusted E/100 PY) were lymphopenia and increased blood CPK in the upadacitinib 15 mg group, and anaemia, bronchitis, herpes zoster, pneumonia, increased blood CPK, back pain, and COPD in the 30 mg group.

The MAH analysed the safety data per applicable CIOMS Guidelines (CIOMS III and V) in order to identify any new adverse drug reactions for labelling. Based on this analysis, two new ADR's are proposed to be included in the SmPC, with frequencies based on the PBO-controlled Analysis set:

- Bronchitis (grouped term including bronchitis, bronchitis viral, bronchitis bacterial, and tracheobronchitis): 2.7% in the placebo group vs 3.9% in upadacitinib 15 mg group
- Acne: 0.3% in placebo group vs 1.3% in upadacitinib 15 mg group

Currently labelled ADRs had no significant change in their rates compared with those reported for the RA dataset, with the exception of herpes zoster and herpes simplex, which were observed at a higher

rate (> 1%) in the upadacitinib 15 mg group during the 24-week placebo-controlled period of the PsA studies:

- Herpes zoster: 1.1% in PsA vs 0.7% in RA
- Herpes simplex (grouped term including herpes simplex and oral herpes): 1.4% in PsA vs 0.8% in RA

Adverse events of special interest (AESI)

For identification of AESI, the MAH considered the safety concerns associated with the JAK inhibitor drug class, safety concerns identified from upadacitinib preclinical studies and the RA development programme, as well as those of customary regulatory interest for novel small molecule immunomodulatory products. According to this reasoning, the following AESI were identified and analysed in detail:

- serious infection;
- opportunistic infection excluding TB and herpes zoster;
- herpes zoster;
- active TB;
- malignancy (including malignant tumours, NMSC, malignant tumours excluding NMSC, and lymphoma);
- hepatic disorders;
- adjudicated GI perforation;
- adjudicated MACE (defined as CV death, non-fatal myocardial infarction [MI] and non-fatal stroke);
- adjudicated venous thromboembolic events (VTE), defined as pulmonary embolism (PE) and deep vein thrombosis (DVT) and other venous and arterial thromboembolic events (non-cardiac, non-neurologic);
- anaemia;
- neutropenia;
- lymphopenia;
- renal dysfunction; and
- CPK elevation.

Forest plots of selected AESI for the proposed registration dose of 15 mg are displayed in Figures 38 and 39, and each AESI is discussed below in further detail.

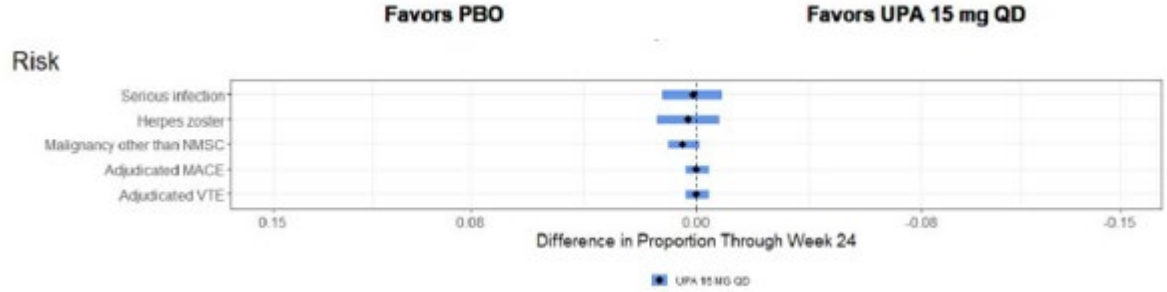


Figure 38 Forest Plot of Risks for Upadacitinib 15 mg QD Compared to Placebo in Non-Biologic DMARD-IR and bDMARD-IR Subjects Through Week 24 (Placebo-Controlled Analysis Set)

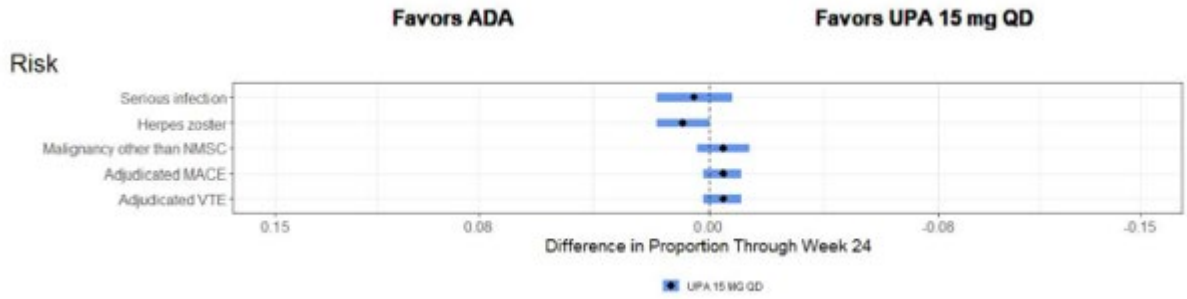


Figure 39 Forest Plot of Risks for Upadacitinib 15 mg QD Compared to Adalimumab in Non Biologic DMARD-IR Subjects Through Week 24 (Study M15-572)

Serious infections

In the PBO-controlled Analysis Set, the percentage of subjects with serious infections was 0.8% for placebo, 0.9% for upadacitinib 15 mg and 2.7% for upadacitinib 30 mg group, and the most frequently reported serious infection was pneumonia (2 events each in the placebo and 15 mg groups, 6 events in the 30 mg group; Table 63). No serious infections were reported as resulting in death.

Table 63 Number and Percentage of Subjects with Treatment-Emergent Serious Infections (PBO-controlled Analysis Set)

System Organ Class MedDRA 22.0 Preferred Term	Placebo (N = 635) n (%) [SSA %]	Upadacitinib 15 mg QD (N = 640) n (%) [SSA %]	Upadacitinib 30 mg QD (N = 641) n (%) [SSA %]
Any adverse event	5 (0.8) [0.8]	6 (0.9) [0.9]	17 (2.7) [2.7]
Anal abscess	0	0	1 (0.2) [0.2]
Appendicitis	1 (0.2) [0.2]	0	1 (0.2) [0.2]
Atypical pneumonia	0	0	2 (0.3) [0.3]
Bacteremia	0	0	2 (0.3) [0.3]
Breast cellulitis	1 (0.2) [0.2]	0	0
Bronchitis	0	0	1 (0.2) [0.2]
Bursitis infective staphylococcal	1 (0.2) [0.2]	0	0
Erysipelas	0	1 (0.2) [0.2]	0
Extradural abscess	0	0	1 (0.2) [0.2]
Laryngitis	0	1 (0.2) [0.2]	0
Lung infection	0	0	1 (0.2) [0.2]
Pneumocystis jirovecii pneumonia	0	0	1 (0.2) [0.2]
Pneumonia	2 (0.3) [0.3]	2 (0.3) [0.3]	6 (0.9) [0.9]
Sepsis	0	2 (0.3) [0.3]	0
Urinary tract infection	0	0	1 (0.2) [0.2]
Urosepsis	0	0	1 (0.2) [0.2]

MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; QD = once daily; SSA = study size adjusted

Note: The sum of the total number of subjects reporting each of the preferred terms should be greater than or equal to the system organ class total. A subject who reported two or more different preferred terms which were in the same system organ class was counted only once in the system organ class total.

In the long-term Any Upadacitinib Analysis Set, the EAERs of serious infections were 2.3 E / 100 PY in the upadacitinib 15 mg group and 6.0 E / 100 PY in the upadacitinib 30 mg group (Table 64). The most common serious infection in the upadacitinib 15 mg group was pneumonia (4 subjects). The most common serious infections in the upadacitinib 30 mg group were pneumonia (8 subjects) and herpes zoster (5 subjects). Two subjects, both in the upadacitinib 30 mg group had Pneumocystis jirovecii pneumonia (PJP).

According to the MAH, an infection was not reported as the cause of death in any subject. However, in Study 554, 1 male subject who received upadacitinib 30 mg experienced events of PJP and CMV infection preceding his death. In addition, in Study 572, 1 subject on upadacitinib 30 mg developed bronchitis followed by unspecified interstitial pneumonitis and dermatomyositis; this subject died several weeks after last dose of study drug.

Table 64 Treatment-Emergent Serious Infection EAERs ≥ 0.2 E/100 PY (In Either Dose Group) (Any Upadacitinib Analysis Set)

System Organ Class MedDRA 22.0 Preferred Term	Upadacitinib 15 mg QD (No Cross-Over from Placebo) (N = 640) (PY = 651.8)	Upadacitinib 30 mg QD (No Cross-Over from Placebo) (N = 641) (PY = 647.1)	Upadacitinib Any 15 mg QD (N = 907) (PY = 816.9)	Upadacitinib Any 30 mg QD (N = 920) (PY = 822.3)
	E (E/100 PY) [SSA E/100 PY]			
Any serious infection	15 (2.3) [2.3]	39 (6.0) [6.0]	19 (2.3) [2.3]	49 (6.0) [6.0]
Infections and infestations				
Appendicitis	1 (0.2) [0.2]	1 (0.2) [0.2]	1 (0.1) [0.1]	2 (0.2) [0.2]
Atypical pneumonia	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Bacteremia	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Bronchitis	1 (0.2) [0.2]	3 (0.5) [0.5]	1 (0.1) [0.1]	3 (0.4) [0.4]
Cellulitis	1 (0.2) [0.2]	1 (0.2) [0.2]	1 (0.1) [0.1]	2 (0.2) [0.2]
Gastroenteritis	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Gastroenteritis viral	1 (0.2) [0.2]	1 (0.2) [0.2]	1 (0.1) [0.1]	2 (0.2) [0.2]
Herpes zoster	1 (0.2) [0.2]	4 (0.6) [0.6]	1 (0.1) [0.1]	5 (0.6) [0.6]
Pneumocystis jirovecii pneumonia	0	1 (0.2) [0.2]	0	2 (0.2) [0.2]
Pneumonia	4 (0.6) [0.6]	6 (0.9) [0.9]	4 (0.5) [0.5]	8 (1.0) [1.0]
Sepsis	2 (0.3) [0.3]	1 (0.2) [0.2]	2 (0.2) [0.2]	1 (0.1) [0.1]
Urinary tract infection	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]

EAER = exposure-adjusted event rate; MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-year; QD = once daily; SSA = study size adjusted

Subgroup analyses based on a number of demographic and baseline characteristics (race, age group, sex, BMI group, baseline renal function status, history of COPD, Type 2 diabetes or cardiovascular events, use of corticosteroids at baseline) did not demonstrate any striking clustering of events; the rate of serious infections was higher among patients >= 65 years in all treatment groups, including placebo. It should however be noted that many of these analyses were impacted by very small sample sizes within several subgroups, precluding robust conclusions.

For both upadacitinib treatment groups, treatment-emergent serious infections were more frequent among subjects on combination therapy than subjects on upadacitinib monotherapy (Table 65). Among subjects on combination therapy, there were no consistent differences between subjects using MTX vs other non-biologic DMARDs; the highest EAERs in the upadacitinib 15 mg group were observed in subjects on both MTX and another non-biologic DMARD, whereas in the upadacitinib 30 mg group, the highest EAERs were observed among subjects on a non-MTX DMARD only (Table 66). Furthermore, the sample sizes for individual non-MTX DMARDs are very small and the overall results should thus be interpreted with caution.

Table 65 Treatment-Emergent Serious Infection EAERs by Upadacitinib Monotherapy vs. Upadacitinib Combination Therapy (Any Upadacitinib Analysis Set)

	Upadacitinib			
	15 mg QD (No Cross-Over from Placebo) Events (E/100 PYs) [SSA E/100 PYs]	30 mg QD (No Cross-Over from Placebo) Events (E/100 PYs) [SSA E/100 PYs]	Any 15 mg QD Events (E/100 PYs) [SSA E/100 PYs]	Any 30 mg QD Events (E/100 PYs) [SSA E/100 PYs]
Upadacitinib monotherapy vs. upadacitinib combination therapy				
Upadacitinib monotherapy	(N = 189, PYs = 192.2)	(N = 197, PYs = 198.3)	(N = 255, PYs = 228.5)	(N = 276, PYs = 253.2)
Any adverse event	1 (0.5) [0.5]	8 (4.0) [3.9]	3 (1.3) [1.3]	11 (4.3) [4.2]
Upadacitinib combination therapy	(N = 451, PYs = 459.7)	(N = 444, PYs = 448.8)	(N = 652, PYs = 588.4)	(N = 644, PYs = 569.1)
Any adverse event	14 (3.0) [3.0]	31 (6.9) [6.9]	16 (2.7) [2.7]	38 (6.7) [6.7]

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of oral study drug, and no more than 30 days after the last dose of upadacitinib and placebo.
E/100 PYs = Events per 100 patient-years. SSA = Study size adjusted.
Patients could be included in more than one treatment group.

Table 66 Treatment-Emergent Serious Infection EAER by Concomitant Non-Biologic DMARD Use at Baseline (Any Upadacitinib Analysis Set)

	Upadacitinib			
	15 mg QD (No Cross-Over from Placebo) Events (E/100 PYs) [SSA E/100 PYs]	30 mg QD (No Cross-Over from Placebo) Events (E/100 PYs) [SSA E/100 PYs]	Any 15 mg QD Events (E/100 PYs) [SSA E/100 PYs]	Any 30 mg QD Events (E/100 PYs) [SSA E/100 PYs]
Concomitant non-biologic DMARDs use at baseline				
MTX alone	(N = 353, PYs = 357.8)	(N = 341, PYs = 344.4)	(N = 516, PYs = 463.3)	(N = 486, PYs = 433.4)
Any adverse event	10 (2.8) [2.8]	24 (7.0) [7.0]	12 (2.6) [2.6]	29 (6.7) [6.7]
MTX and other non-biologic DMARD	(N = 26, PYs = 26.2)	(N = 32, PYs = 33.9)	(N = 37, PYs = 34.7)	(N = 48, PYs = 43.3)
Any adverse event	2 (7.6) [7.1]	1 (3.0) [2.7]	2 (5.8) [5.5]	2 (4.6) [4.9]
Non-biologic DMARD other than MTX	(N = 72, PYs = 75.6)	(N = 71, PYs = 70.5)	(N = 99, PYs = 90.4)	(N = 110, PYs = 92.3)
Any adverse event	2 (2.6) [2.7]	6 (8.5) [8.5]	2 (2.2) [2.2]	7 (7.6) [7.7]
Any APREMILAST without MTX	(N = 15, PYs = 20.5)	(N = 13, PYs = 14.9)	(N = 23, PYs = 25.8)	(N = 18, PYs = 17.4)
Any adverse event	1 (4.9) [5.1]	2 (13.5) [13.9]	1 (3.9) [3.9]	2 (11.5) [11.5]
Any LEFLUNOMIDE without MTX	(N = 30, PYs = 28.9)	(N = 35, PYs = 35.5)	(N = 37, PYs = 33.9)	(N = 56, PYs = 46.7)
Any adverse event	0	4 (11.3) [11.9]	0	5 (10.7) [10.7]
Any SULFASALAZINE without MTX	(N = 22, PYs = 20.9)	(N = 24, PYs = 21.3)	(N = 36, PYs = 27.5)	(N = 33, PYs = 26.0)
Any adverse event	1 (4.8) [4.5]	0	1 (3.6) [3.2]	0
None	(N = 189, PYs = 192.2)	(N = 197, PYs = 198.3)	(N = 255, PYs = 228.5)	(N = 276, PYs = 253.2)
Any adverse event	1 (0.5) [0.5]	8 (4.0) [3.9]	3 (1.3) [1.3]	11 (4.3) [4.2]

Note: Treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of oral study drug, and no more than 30 days after the last dose of upadacitinib and placebo.
E/100 PYs = Events per 100 patient-years. SSA = Study size adjusted.
Patients could be included in more than one treatment group.

In Study 572, the long-term EAERs of treatment-emergent serious infections were 1.5 E/100 PY for adalimumab, 2.1 E/100 PY for upadacitinib 15 mg and 5.5 E/100 PY for upadacitinib 30 mg.

Opportunistic infections (excluding TB and herpes zoster)

In the PBO-controlled Analysis Set, the percentage of subjects with treatment-emergent opportunistic infections excluding TB and herpes zoster was 0.2% (1 subject) in the upadacitinib 15 mg group and 0.6% (4 subjects) in the upadacitinib 30 mg group; none were reported in the placebo group. Treatment-emergent opportunistic infections included candida urethritis in 1 subject in the upadacitinib 15 mg group and candidiasis of trachea, CMV infection, oropharyngeal candidiasis, and PJP in 1 subject each in the upadacitinib 30 mg group; the event of PJP was a serious event and considered by the investigator to have a reasonable possibility of being related to study drug. During the placebo-controlled period, there were no deaths that were considered by the investigators to be related to

opportunistic infections, and no subject had an event of opportunistic infection that led to discontinuation of study drug.

Long-term EAERs for opportunistic infections excluding TB and herpes zoster are summarised in Table 67. The most commonly reported events were related to mucosal candida infections. One subject (0.1 E/100 PY) in the upadacitinib 15 mg group discontinued study drug due to a nonserious opportunistic infection of coccidioidomycosis.

Table 67 Treatment-Emergent Opportunistic Infections Excluding TB and Herpes Zoster EAER per 100 PY (Any Upadacitinib Analysis Set)

	Upadacitinib			
System Organ Class MedDRA 22.0 Preferred Term	15 mg QD (No Cross-Over from Placebo) (N = 640) (PY = 651.8)	30 mg QD (No Cross-Over from Placebo) (N = 641) (PY = 647.1)	Any 15 mg QD (N = 907) (PY = 816.9)	Any 30 mg QD (N = 920) (PY = 822.3)
	E (E/100 PY) [SSA E/100 PY]			
Any opportunistic infection	3 (0.5) [0.5]	7 (1.1) [1.1]	4 (0.5) [0.5]	9 (1.1) [1.1]
Infections and infestations				
Bronchopulmonary aspergillosis	1 (0.2) [0.2]	0	1 (0.1) [0.1]	0
Candida urethritis	1 (0.2) [0.2]	0	1 (0.1) [0.1]	0
Candidiasis of trachea	0	1 (0.2) [0.2]	0	1 (0.1) [0.1]
Coccidioidomycosis	1 (0.2) [0.2]	0	1 (0.1) [0.1]	0
Cytomegalovirus infection	0	1 (0.2) [0.2]	0	2 (0.2) [0.2]
Oesophageal candidiasis	0	0	1 (0.1) [0.1]	0
Oral fungal infection	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Oropharyngeal candidiasis	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Pneumocystis jirovecii pneumonia	0	1 (0.2) [0.2]	0	2 (0.2) [0.2]

EAER = exposure-adjusted event rate; MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-year; QD = once daily; SSA = study size adjusted

In the long-term analysis set, three serious events (0.4 E/100 PY) of opportunistic infections excluding TB and herpes zoster were reported in two subjects in the upadacitinib 30 mg group. In addition to the subject with PJP mentioned above, another subject also had an event of PJP as well as CMV infection; both events were serious and considered to have a reasonable possibility of being related to study drug. Although there were no deaths attributed to opportunistic infections by the investigator, the events of PJP and CMV preceded the death of the subject in question.

In Study 572, the EAERs of treatment-emergent opportunistic infection excluding TB and herpes zoster were 0.4 E/100 PY (N=2) in the upadacitinib 15 mg group and 1.0 E/100 PY (N=5) in the upadacitinib 30 mg group. No events were reported in the adalimumab group.

Herpes zoster

Herpes zoster is an important identified risk for upadacitinib, and subjects with a history of recurrent or disseminated herpes zoster or disseminated herpes simplex were excluded from participating in the global Phase 3 PsA studies with upadacitinib. In these studies, 4.4% and 4.7% in the upadacitinib 15 mg and 30 mg group, respectively, had a history of zoster vaccination.

In the PBO-controlled Analysis Set, the frequencies of herpes zoster were 0.8% for placebo, 1.0% for upadacitinib 15 mg and 2.0% for upadacitinib 30 mg. There were no serious TEAEs of herpes zoster. Events leading to discontinuation of study drug were reported in 1 subject each in the upadacitinib 15 mg and placebo groups and 2 subjects in the upadacitinib 30 mg group,

In the Any Upadacitinib Analysis Set, EAERs for TEAEs of herpes zoster were 3.6 E/100 PY (N=29) in the upadacitinib 15 mg group and 7.9 E/100 PY (N=65) in the upadacitinib 30 mg group. Over 85% of herpes zoster cases in both treatment groups involved a single dermatome or two dermatomes on the same side. About 3% (1/29) of cases with 15 mg and about 12% (8/65) of cases with 30 mg were considered severe in intensity, and one event in the upadacitinib 15 mg and 5 events in the upadacitinib 30 mg group were considered serious. Two events each in the upadacitinib 15 mg and 30 mg groups led to discontinuation of study drug.

Subgroup analyses demonstrated a higher frequency of herpes zoster in Asia compared to other regions, and an increased risk in subjects >= 50 years. Although the number of subjects with a history of zoster vaccination is too small for definite conclusions, a vaccination did not seem to confer reliable protection against a subsequent recurrence.

In Study 572, the EAERs of treatment-emergent herpes zoster were 3.4 E/100 PY in the upadacitinib 15 mg group, 6.5 E/100 PY in the 30 mg group and 0.5 E/100 PY in the adalimumab group.

Active TB

Subjects with evidence of active TB were not permitted to enrol in the Phase 3 PsA clinical studies. However, subjects with latent TB were allowed to enrol in the study after initiation of TB prophylaxis at least 2 weeks prior to first administration of study drug (or per local guidelines, whichever was longer).

In the PsA clinical programme, 4.4%, 4.5%, and 5.1% of subjects in the placebo, upadacitinib 15 mg and upadacitinib 30 mg groups had positive TB test results at Screening. No events of treatment-emergent active TB were reported in the clinical studies.

Malignancy

In the long-term Any Upadacitinib Analysis Set, the EAIRs of malignancy other than NMSC were 0.9 n/100 PY (N=7) for both upadacitinib 15 mg and 30 mg. Other than NMSC, individual malignancy types (per coded PT) were each reported in 1 subject (≤ 0.1 n/100 PY), with the exception of prostate cancer in the upadacitinib 15 mg group and squamous cell carcinoma in the upadacitinib 30 mg group, which were each reported in 2 subjects (although based on medical review, the 2 events of squamous cell carcinoma were determined to represent NMSC). Based on a Kaplan-Meier analysis, the risk of subjects experiencing any malignancy other than NMSC when receiving upadacitinib 15 mg in the global Phase 3 studies did not appear to increase over time.

In Study 572, the EAIR of treatment-emergent malignancy other than NMSC was 0.6 n/100 PY in the upadacitinib 15 mg group, 0.4 n/100 PY in the upadacitinib 30 mg group, and 1.0 n/100 PY in the adalimumab group.

A standard incidence ratios (SIR) analysis for malignancy other than NMSC using age-gender specific malignancy data from the Surveillance, Epidemiology, and End Results 18 Registry Research Data 2000 – 2015 for the general population yielded a SIR estimate for TEAEs of malignancy other than NMSC of 1.17 (95% CI: 0.47 – 2.42) for the upadacitinib 15 mg group and 1.16 (95% CI: 0.47 – 2.39) for the upadacitinib 30 mg group. For both doses, there were 7 observed malignancies other than NSMC, compared to 6 expected.

In the long-term Any Upadacitinib Analysis Set, there were 5 cases of treatment-emergent NMSC in the 15 mg group and 7 cases in the 30 mg group. A Kaplan-Meier analysis did not demonstrate an

increase in NMSC over time. In Study 572, the rate of NMSC was 0.4 n/100 PY in the upadacitinib 15 mg group, 0.8 n/100 PY in the upadacitinib 30 mg group, and 0.5 n/100 PY in the adalimumab group.

No events of lymphoma occurred in the global Phase 3 studies. An abnormal lymphocyte morphology was reported in two subjects; however, these were not reported in subsequent laboratory testing for either subject.

Hepatic disorders

In the PBO-controlled Analysis Set, a modest increase from baseline to Week 24 in ALT and AST was observed for upadacitinib 15 mg (ALT: 6.3 U/L, AST: 6.0 U/L) and upadacitinib 30 mg (ALT: 8.3 U/L, AST: 7.5 U/L), compared to no increase with placebo (ALT: –0.9 U/L, AST: –0.8 U/L). Most cases of transaminase elevations were Grade 2 (i.e. 3 - 5 x ULN). Consistent with this, most TEAEs of hepatic disorders were also related to transaminase elevations. The frequencies of a TEAE of hepatic disorder leading to discontinuation of study drug were 0.2% (N=1) in the placebo group, 0.3% (N=2) in the upadacitinib 15 mg group and 0.9% (N=9) in the upadacitinib 30 mg group.

In the Any Upadacitinib Analysis Set, mean increases from baseline to Week 56 for ALT and AST were observed for both the upadacitinib 15 mg group (7.5 U/L and 6.2 U/L, respectively) and the upadacitinib 30 mg group (11.2 U/L and 8.9 U/L, respectively). The increases developed rapidly, with a plateau observed from Week 2 onward. Similar to the short-term analysis set, most cases of transaminase elevations were Grade 2 (i.e. 3 - 5 x ULN), and most TEAEs of hepatic disorders were related to transaminase elevations. In the long-term analysis set, the EAERs of a TEAE of hepatic disorder leading to discontinuation of study drug were 0.2 E/100 PY (N=2) in the upadacitinib 15 mg group and 1.3 E/100 PY (N=11) in the upadacitinib 30 mg group; most events resolved even when upadacitinib was continued.

There were no serious events of hepatic disorders, and no subjects meeting the biochemical criteria of Hy's Law, with either 15 mg or 30 mg upadacitinib.

In Study 572, Grade 3 increases in ALT and AST were similar across the upadacitinib 15 mg, upadacitinib 30 mg, and adalimumab groups (ALT: 1.2%, 1.0% and 1.2%, respectively, AST: 0.5%, 0.8%, and 0.5%, respectively). The EAER of treatment-emergent hepatic disorders was 22.5 E/100 PY and 24.3 E/100 PY in the upadacitinib 15 mg and 30 mg groups, respectively, and 30.9 E/100 PY in the adalimumab group.

GI perforation

According to the MAH, all potential events of GI perforation in the programme were adjudicated against a pre-specified case definition by internal experts who were independent of the clinical study team and blinded to subject treatment assignment. Subjects with a history of GI perforation (other than appendicitis or penetrating injury), diverticulitis, or significantly increased risk for GI perforation per investigator judgment were excluded from the Phase 3 studies.

In the Any Upadacitinib Analysis Set, there was one treatment-emergent adjudicated GI perforation event (gastric ulcer perforation) reported in a 69-year old male subject who was receiving upadacitinib 15 mg. The event occurred about 9 months after first dose of upadacitinib. The event was serious and led to discontinuation of study drug. The subject was on concomitant NSAIDs and MTX at the time of the event.

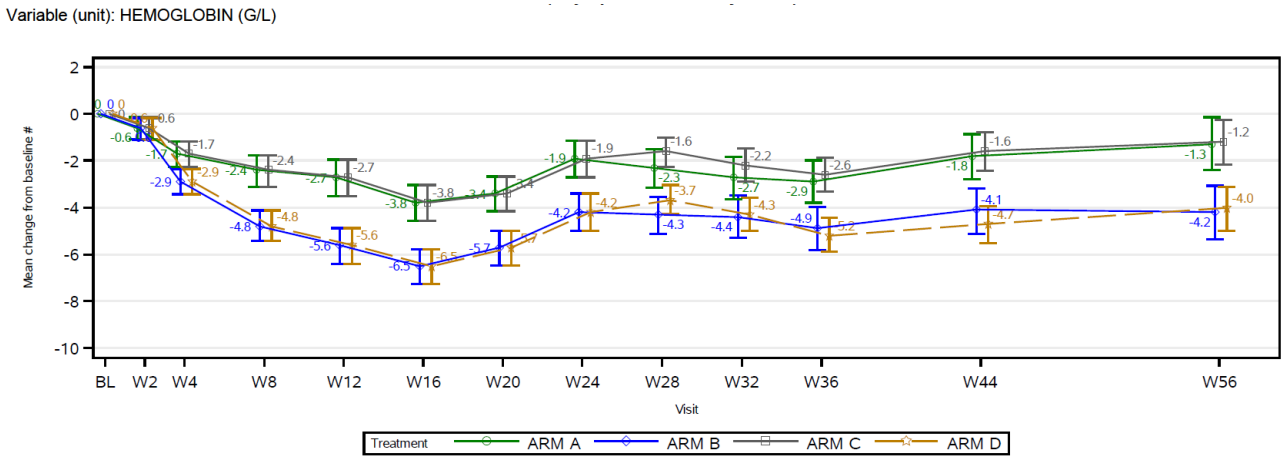
Anaemia

In the PBO-controlled Analysis Set, mean decrease from baseline to Week 24 in haemoglobin was –0.2 g/L in the placebo group, –1.6 g/L in the upadacitinib 15 mg group and –3.6 g/L in the 30 mg group. Grade 2 haemoglobin decreases (i.e. decrease to between 80 and 100 g/L) were reported in 12

subjects (1.9%) on placebo, 10 subjects (1.6%) on 15 mg and 19 subjects (3.0%) on 30 mg. There were 3 subjects (0.5%) with a Grade 3 haemoglobin decrease (i.e. decrease to < 80 g/L) in the upadacitinib 30 mg group.

In the PBO-controlled Analysis Set, a TEAE of anaemia was reported in 0.9% of subjects on placebo, 1.1% of subjects on upadacitinib 15 mg and 5.3% of subjects on upadacitinib 30 mg. One subject in each of the upadacitinib 15 mg and 30 mg groups had a TEAE of anaemia that was considered serious; the event in the upadacitinib 15 mg group led to discontinuation of study drug.

Mean haemoglobin values over time in the Any Upadacitinib Analysis Set are depicted in Figure 40. The pattern is characterised by a dose-related decrease until Week 16 and a partial recovery thereafter. Grade 2 haemoglobin decreases were reported in 16 subjects (1.8%) on 15 mg and 37 subjects (4.1%) on 30 mg, and Grade 3 decreases in 1 subject (0.1%) on 15 mg and 6 subjects (0.7%) on 30 mg. The EAERs of TEAEs of anaemia were 2.8 E/100 PY for 15 mg and 6.9 E/100 PY for 30 mg. A serious TEAE of anaemia was reported for 1 subject on 15 mg and 3 subjects on 30 mg, and anaemia led to study drug discontinuation in 3 subjects in both groups.



Number of Subjects at Each Visit

ARM A	635	616	612	619	598	598	583	574	524	470	438	361	266
ARM B	638	625	624	619	611	598	588	568	529	467	429	357	268
ARM C	878	616	612	619	598	598	583	574	765	686	639	525	388
ARM D	896	625	624	619	611	598	588	568	781	695	644	527	395

ARM A = Upadacitinib 15 mg QD (No Cross-Over from Placebo), ARM B = Upadacitinib 30 mg QD (No Cross-Over from Placebo), ARM C = Any Upadacitinib 15 mg QD, ARM D = Any Upadacitinib 30 mg QD.
Note: Patients could be included in more than one treatment group.
Baseline mean includes subjects with non-missing baseline and at least one post-baseline value.
LS mean is based on ANCOVA model with treatment as a main factor, and baseline and study as covariates.

Figure 40 Plot of Mean Change from Baseline in Haemoglobin Values Over Time (Any Upadacitinib Analysis Set)

In Study 572, the percentages of subjects with a Grade 2 haemoglobin decrease were 0.5%, 1.0% and 4.0% for adalimumab, upadacitinib 15 mg and 30 mg, respectively. A Grade 3 haemoglobin decrease was reported in 0.5%, 0.2% and 0.3% of subjects in the adalimumab, upadacitinib 15 mg and 30 mg groups, respectively. The EAERs of treatment-emergent anaemia were 2.9 E/100 PY and 7.2 E/100 PY in the upadacitinib 15 mg and 30 mg groups, respectively, and 1.5 E/100 PY in the adalimumab group.

Neutropenia

In the PBO-controlled Analysis Set, mean neutrophil counts decreased from baseline to Week 24 in both the upadacitinib 15 mg and 30 mg groups (-0.442 × 10E9/L and -0.758 × 10E9/L, respectively), whereas an increase of 0.018 × 10E9/L from baseline to Week 24 was seen in the placebo group. The decrease in mean values with upadacitinib was evident already at Week 2 and mean values remained stable thereafter.

A summary of neutrophil decreases based on CTC grading is displayed in Table 68. No Grade 4 decreases were seen in any treatment group. The percentage of subjects with a reported TEAE of neutropenia was 0.3% in the placebo group, 0.9% in the upadacitinib 15 mg group and 4.2% in the upadacitinib 30 mg group. No TEAE of neutropenia was serious or led to discontinuation of study drug.

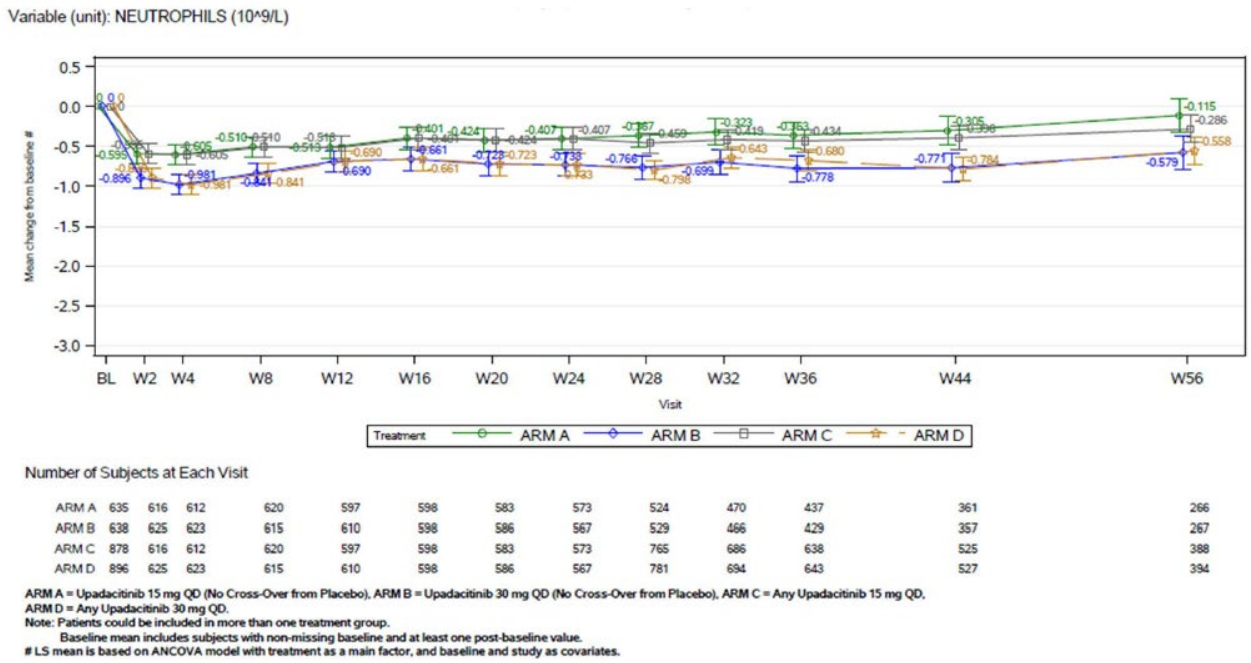
Table 68 Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Values for Neutrophils (PBO-controlled Analysis Set)

Neutrophils (10^9/L)	Placebo (N = 635)	Upadacitinib 15 mg QD (N = 640)	Upadacitinib 30 mg QD (N = 641)
		n/N_OBS (%) [SSA %]	
Grade 2 (1.0 – < 1.5)	5/627 (0.8) [0.8]	20/635 (3.1) [3.2]	43/638 (6.7) [6.7]
Grade 3 (0.5 – < 1.0)	2/627 (0.3) [0.3]	4/635 (0.6) [0.6]	10/638 (1.6) [1.6]
Grade 4 (< 0.5)	0/627	0/635	0/638
≥ Grade 3	2/627 (0.3) [0.3]	4/635 (0.6) [0.6]	10/638 (1.6) [1.6]

CTC = Common Terminology Criteria; NCI = National Cancer Institute; OBS = observed; PBO = placebo; QD = once daily; SSA = study size adjusted

Note: Toxicity grading scale is based on NCI CTC v4.03. Grade must also be more extreme than the baseline grade. N_OBS indicates the number of subjects with both baseline and postbaseline values up to Week 24 for the respective parameter.

Mean neutrophil counts over time in the Any Upadacitinib Analysis Set are depicted in Figure 41. Mean change from baseline to Week 56 was -0.360 × 10E9/L in the upadacitinib 15 mg group and -0.531 × 10E9/L in the upadacitinib 30 mg group. Grade 2 and 3 decreases were seen in 4.4% and 0.7% of subjects in the upadacitinib 15 mg group, and 7.9% and 1.7% of subjects in the upadacitinib 30 mg group. No subjects had Grade 4 decreases in neutrophils. No SAEs of neutropenia were reported and no subjects discontinued study drug permanently due to TEAEs of neutropenia.



ARM A = Upadacitinib 15 mg QD (No Cross-Over from Placebo), ARM B = Upadacitinib 30 mg QD (No Cross-Over from Placebo), ARM C = Any Upadacitinib 15 mg QD, ARM D = Any Upadacitinib 30 mg QD.
Note: Patients could be included in more than one treatment group.
Baseline mean includes subjects with non-missing baseline and at least one post-baseline value.
LS mean is based on ANCOVA model with treatment as a main factor, and baseline and study as covariates.

Figure 41 Plot of Mean Change from Baseline in Neutrophil Count Over Time (Any Upadacitinib Analysis Set)

In Study 572, Grade 3 neutropenias were seen in 0.5% of subjects in the upadacitinib 15 mg and adalimumab groups and 1.7% of subjects in the upadacitinib 30 mg group. There were no Grade 4 neutropenias.

Lymphopenia

In the PBO-controlled Analysis Set, a small increase from baseline to Week 24 in mean lymphocyte count was seen across all treatment groups (0.042 × 10E9/L for placebo, 0.035 × 10E9/L for upadacitinib 15 mg and 0.075 × 10E9/L for upadacitinib 30 mg). On the other hand, Grade 2 to 3 decreases were more frequent with upadacitinib than placebo (Table 69). Most of the Grade 3 decreases in lymphocytes occurred at a single time point (the study protocols mandated study drug interruption if ALC was below 0.5 x 10E9/L). The percentages of subjects with TEAEs of lymphopenia were 0.8% for placebo, 1.3% for upadacitinib 15 mg and 2.7% for upadacitinib 30 mg. Two subjects (0.3%) in both upadacitinib 15 mg and 30 mg groups discontinued study medication permanently due to lymphopenia. No SAEs of lymphopenia were reported.

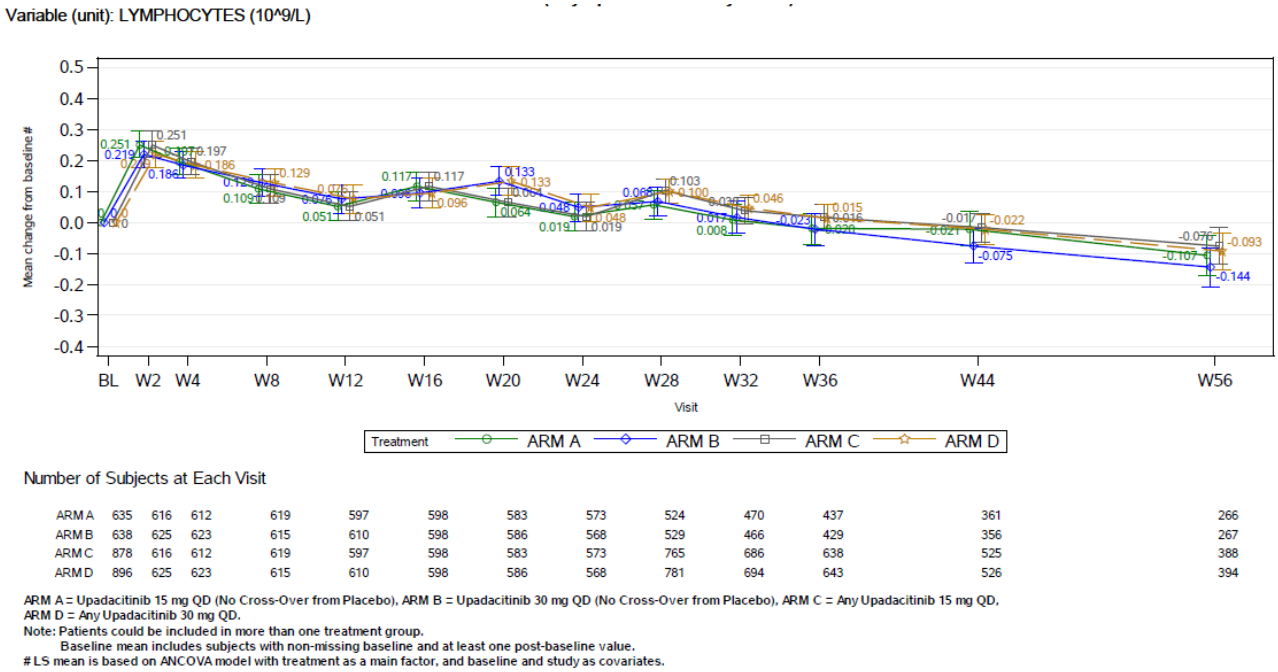
Table 69 Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Values for Lymphocytes (PBO-controlled Analysis Set)

Lymphocytes (10^9/L)	Placebo (N = 635)	Upadacitinib 15 mg QD (N = 640)	Upadacitinib 30 mg QD (N = 641)
		n/N_OBS (%) [SSA %]	
Grade 2 (0.5 – < 0.8)	24/627 (3.8) [3.8]	32/635 (5.0) [5.0]	54/638 (8.5) [8.5]
Grade 3 (0.2 – < 0.5)	1/627 (0.2) [0.2]	5/635 (0.8) [0.8]	11/638 (1.7) [1.7]
Grade 4 (< 0.2)	0/627	0/635	0/638

CTC = Common Terminology Criteria; NCI = National Cancer Institute; OBS = observed; PBO = placebo; QD = once daily; SSA = study size adjusted

Note: Toxicity grading scale is based on NCI CTC v4.03. Grade must also be more extreme than the baseline grade. N_OBS indicates the number of subjects with both baseline and postbaseline values up to Week 24 for the respective parameter.

Mean lymphocyte counts over time in the Any Upadacitinib Analysis Set are depicted in Figure 42. Mean change from baseline to Week 56 was -0.077 × 10E9/L in the upadacitinib 15 mg group and -0.084 × 10E9/L in the upadacitinib 30 mg group. Grade 2 and 3 decreases were seen in 7.4% and 1.3% of subjects in the upadacitinib 15 mg group, and 9.9% and 2.7% of subjects in the upadacitinib 30 mg group. One subject on 30 mg experienced a Grade 4 decrease at Day 540; study drug was temporarily interrupted with the subject experiencing a nonserious event of upper respiratory tract inflammation and a SAE of bronchitis. This subject was treated with antibiotics, MTX dose was decreased, and the subject's lymphocyte count returned to Grade 2 through data cut-off. Two subjects (0.2%) on upadacitinib 15 mg and 3 subjects (0.4%) on upadacitinib 30 mg discontinued study drug permanently due to TEAEs of lymphopenia. No SAEs of lymphopenia were reported.



Number of Subjects at Each Visit

ARM A	635	616	612	619	597	598	583	573	524	470	437	361	266
ARM B	638	625	623	615	610	598	586	568	529	466	429	356	267
ARM C	878	616	612	619	597	598	583	573	765	686	638	525	388
ARM D	896	625	623	615	610	598	586	568	781	694	643	526	394

ARM A = Upadacitinib 15 mg QD (No Cross-Over from Placebo), ARM B = Upadacitinib 30 mg QD (No Cross-Over from Placebo), ARM C = Any Upadacitinib 15 mg QD, ARM D = Any Upadacitinib 30 mg QD.
Note: Patients could be included in more than one treatment group.
Baseline mean includes subjects with non-missing baseline and at least one post-baseline value.
LS mean is based on ANCOVA model with treatment as a main factor, and baseline and study as covariates.

Figure 42 Plot of Mean Change from Baseline in Lymphocytes Over Time (Any Upadacitinib Analysis Set)

In Study 572, Grade 2 lymphopenias were seen in 7.1% of subjects in the upadacitinib 15 mg group, 8.8% of subjects in the upadacitinib 30 mg group and 0.9% of subjects in the adalimumab group; Grade 3 to 4 lymphopenias were seen in 1.2% of subjects in the upadacitinib 15 mg group, 3.7% of subjects in the upadacitinib 30 mg group and no subjects in the adalimumab group.

Creatine phosphokinase elevation

In the PBO-controlled Analysis Set, the mean increases in CPK values from baseline to Week 24 were 111.1 U/L in the upadacitinib 15 mg group and 139.5 U/L in the 30 mg group, compared to 7.5 U/L in the placebo group. In line with this, Grade 2 and Grade 3 CPK increases were more frequent in the upadacitinib groups compared to placebo (Table 70); Grade 4 decreases were infrequent but were seen across all groups including placebo. A TEAE of CPK elevation was reported for 6.6% and 8.3% of subjects in the upadacitinib 15 mg and 30 mg groups, respectively, compared to 1.6% of subjects in the placebo group. There were no serious TEAEs of CPK elevation in any group; discontinuation of study drug was reported in 1 subject (0.2%) in the placebo group and 2 subjects (0.3%) in the upadacitinib 30 mg group.

Table 70 Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Values for CPK (PBO-controlled Analysis Set)

Variable (U/L)	Placebo (N = 635)	Upadacitinib 15 mg QD (N = 640)	Upadacitinib 30 mg QD (N = 641)
		n/N_OBS (%) [SSA %]	
Creatine kinase			
Grade 2 (> 2.5 – 5.0 × ULN)	8/627 (1.3) [1.3]	35/635 (5.5) [5.5]	48/638 (7.5) [7.5]
Grade 3 (> 5.0 – 10.0 × ULN)	4/627 (0.6) [0.6]	7/635 (1.1) [1.1]	12/638 (1.9) [1.9]
Grade 4 (> 10.0 × ULN)	3/627 (0.5) [0.5]	2/635 (0.3) [0.3]	4/638 (0.6) [0.6]
≥ Grade 3	7/627 (1.1) [1.1]	9/635 (1.4) [1.4]	16/638 (2.5) [2.5]

CPK = creatine phosphokinase; CTC = Common Terminology Criteria; NCI = National Cancer Institute; OBS = observed; PBO = placebo; QD = once daily; SSA = study size adjusted; ULN = upper limit of normal

Note: Toxicity grading scale is based on NCI CTC v4.03. Grade must also be more extreme than the baseline grade. N_OBS indicates the number of subjects with both baseline and postbaseline values up to Week 24 for the respective parameter.

In the Any Upadacitinib Analysis Set, mean increases from baseline to Week 56 in CPK values were 82.6 U/L in the upadacitinib 15 mg group and 137.9 U/L in the upadacitinib 30 mg group. The percentage of subjects with Grade 2 increases in CPK levels were 7.7% in the 15 mg group and 11.5% in the 30 mg group. Grade 3 and Grade 4 increases in CPK levels were similar in the upadacitinib 15 mg (1.6% and 0.8%) and 30 mg groups (1.9% and 1.0%). No serious TEAEs of CPK elevations were reported in either group, and the EAERs of discontinuation of study drug due to TEAEs of CPK elevation were similar between the upadacitinib 15 mg and 30 mg groups (0.1 E/100 PY and 0.2 E/100 PY, respectively). No cases of rhabdomyolysis were reported.

In Study 572, Grade 3 increases in CPK values were recorded in 1.9% and 2.0% of subjects in the upadacitinib 15 mg and 30 mg groups, respectively, and 0.5% of subjects in the adalimumab group. Grade 4 increases in CPK values were recorded in 0.7% of subjects in the upadacitinib 15 mg and adalimumab groups, and in 1.5% of subjects in the upadacitinib 30 mg group.

Renal dysfunction / serum creatinine

In the PBO-controlled Analysis Set, small increases from baseline to Week 24 in mean serum creatinine were observed in all treatment groups. From baseline values of approximately 70 umol/L, the increases were 1.8 µmol/L in the placebo group, 4.7 µmol/L in the upadacitinib 15 mg group and 6.0 µmol/L in the upadacitinib 30 mg group. One Grade 3 increase in creatinine was reported in a subject in the upadacitinib 30 mg group on Day 57, and the increase returned to baseline value on Day 72 without interruption or discontinuation of study drug. No Grade 3 increases in creatinine were reported in the upadacitinib 15 mg or placebo groups and there were no Grade 4 increases in creatinine in any treatment group.

In the PBO-controlled Analysis Set, no TEAE of renal dysfunction was reported in the upadacitinib 15 mg group, 1 subject in the upadacitinib 30 mg group had a TEAE of renal dysfunction (acute kidney injury), and 2 subjects in the placebo group had TEAEs of renal dysfunction (1 subject had acute kidney injury and 1 subject had renal failure and acute kidney injury).

The event of acute kidney injury reported in the upadacitinib 30 mg group was considered serious. This case occurred in a 54-year old female subject who had been on study drug for about 5 months. The developed acute kidney injury (serum creatinine was approximately 2 x ULN) in the context of a traumatic hand injury, a systemic staphylococcal infection and a lower back epidural abscess. The investigator assessed the events as being not related to study medication.

According to the MAH, no events of renal dysfunction led to discontinuation of study drug; however, the subject with the serious acute kidney injury was permanently discontinued from the study upon event resolution.

In the Any Upadacitinib Analysis Set, the small increase in mean serum creatinine remained stable through the treatment period. Grade 3 increases were only observed in 2 subjects (0.2%) in the upadacitinib 30 mg group. Beyond the serious acute kidney injury described above, another serious acute kidney injury was reported in 52-year old male subject with a preceding history of abnormal kidney function. The subject had been on upadacitinib 15 mg for about 17 months and also developed the acute kidney injury in the context of an infection (post-traumatic leg cellulitis). The investigator assessed the event as being not related to study medication.

In Study 572, there were no Grade 3 increases in serum creatinine. Grade 4 increases were recorded in 1 subject in the upadacitinib 30 mg group and 2 subjects in the adalimumab group.

Adjudicated MACE and other CV events

MACE are identified as an important potential risk for upadacitinib, although no definite link to an increased risk has been established to date. Subjects with a very high underlying risk of MACE have generally been excluded from studies, but a substantial proportion of the population enrolled in the RA programme as well as the current PsA programme did have pre-existing risk factors such as hypertension, tobacco use, obesity as well as low HDL and/or elevated LDL. The MAH has established an independent external Cardiovascular Adjudication Committee (CAC) to review and adjudicate all potential CV events, including VTEs, as well as all deaths.

In the PBO-controlled Analysis Set, 1 subject each in the upadacitinib 15 mg and placebo groups had a non-fatal MI, and no subjects in the upadacitinib 30 mg group had a treatment-emergent MACE. In the Any Upadacitinib Analysis Set, the EAIR of treatment-emergent MACE was 0.5 n/100 PY (N=4) in the upadacitinib 15 mg group and 0.2 n/100 PY (N=2) in the upadacitinib 30 mg group (Table 71). No fatal events of MACE were reported. According to the MAH, multiple CV risk factors were present in all the subjects who had an event of MACE, including pre-existing CV conditions, hyperlipidaemia, diabetes, smoking, and obesity in addition to the underlying PsA.

Table 71 Treatment-Emergent Adjudicated MACE EAIR per 100 PY (Any Upadacitinib Analysis Set)

	Upadacitinib			
	15 mg QD (No Cross-Over from Placebo) (N = 640)	**30 mg QD (No Cross-Over from Placebo) (N = 641)**	**Any 15 mg QD (N = 907)**	**Any 30 mg QD (N = 920)**
	n/PY (n/100 PY) [SSA n/100 PY]			
MACE[a]	4/649.1 (0.6) [0.6]	1/646.0 (0.2) [0.2]	4/814.2 (0.5) [0.5]	2/821.2 (0.2) [0.2]
CV death	0/651.8	0/647.1	0/816.9	0/822.3
Non-fatal MI	2/650.1 (0.3) [0.3]	1/646.0 (0.2) [0.2]	2/815.2 (0.2) [0.2]	1/821.2 (0.1) [0.1]
Non-fatal stroke	2/650.8 (0.3) [0.3]	0/647.1	2/815.9 (0.2) [0.2]	1/822.3 (0.1) [0.1]

CV = cardiovascular; EAIR = exposure-adjusted incidence rate; MACE = major adverse cardiovascular event; MI = myocardial infarction; OBS = observed; PY = patient-year; QD = once daily; SSA = study size adjusted

a. MACE is defined as CV death, non-fatal MI and non-fatal stroke.

Note: Subjects could be included in more than 1 treatment group.

In study 572, there were 3 treatment-emergent adjudicated MACE events in the adalimumab group, 1 event in the upadacitinib 15 mg group and 3 events in the upadacitinib 30 mg group. No fatal events were reported. The long-term rates of adjudicated MACE were comparable across the treatment groups of upadacitinib 15 mg and 30 mg, and adalimumab (0.6, 0.2, and 0.8 n/100 PY, respectively).

Other adjudicated CV events in the Any Upadacitinib Analysis Set are summarised in Table 72. In study 572, 1 subject in the adalimumab group had a TIA and CV procedure, 1 subject in the upadacitinib 15 mg group had a TIA, and 1 subject in the upadacitinib 30 mg group had a CV procedure.

Table 72 Treatment-Emergent Adjudicated Cardiovascular Events EAIR per 100 PY (Any Upadacitinib Analysis Set)

	Upadacitinib			
	15 mg QD (No Cross-Over from Placebo) (N = 640)	30 mg QD (No Cross-Over from Placebo) (N = 641)	Any 15 mg QD (N = 907)	Any 30 mg QD (N = 920)
	n/PY (n/100 PY) [SSA n/100 PY]			
Other CV events (non-fatal)	0/651.8	4/644.9 (0.6) [0.6]	0/816.9	4/820.1 (0.5) [0.5]
CV procedures	0/651.8	2/645.9 (0.3) [0.3]	0/816.9	2/821.1 (0.2) [0.2]
Unstable angina requiring hospitalization	0/651.8	0/647.1	0/816.9	0/822.3
Hospital based treatment for heart failure	0/651.8	0/647.1	0/816.9	0/822.3
Transient ischemic attack	0/651.8	2/646.1 (0.3) [0.3]	0/816.9	2/821.2 (0.2) [0.2]

CV = cardiovascular; EAIR = exposure-adjusted incidence rate; PY = patient-year; QD = once daily; SSA = study size adjusted

Note: Subjects could be included in more than one treatment column.

Adjudicated thrombotic events

Cases of venous thromboembolism [VTE, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE)] have been observed with all JAK inhibitors including upadacitinib, and VTE is identified as an important potential risk for upadacitinib. As stated above, all VTE events were reviewed and adjudicated as part of the work of the independent external CAC.

In the PBO-controlled Analysis Set, treatment-emergent adjudicated VTEs were reported in 1 subject (0.2%) each in the upadacitinib 15 mg (PE), upadacitinib 30 mg (PE), and placebo (DVT) groups. All events were serious, and the 2 events of PE led to discontinuation of the study drug.

The EAIR of adjudicated VTEs in the Any Upadacitinib Analysis Set are summarised in Table 73. According to the MAH, all subjects who developed VTE had one or more risk factors for VTE, such as a history of hypertension, hyperlipidaemia, obesity, smoking, or concurrent comorbidities (e.g., atrial fibrillation, infections). No fatal adjudicated VTEs were reported.

Table 73 Treatment-Emergent Adjudicated VTE EAIR per 100 PY (Any Upadacitinib Analysis Set)

	Upadacitinib			
	15 mg QD (No Cross-Over from Placebo) (N = 640)	30 mg QD (No Cross-Over from Placebo) (N = 641)	Any 15 mg QD (N = 907)	Any 30 mg QD (N = 920)
	n/PY (n/100 PY) [SSA n/100 PY]			
VTE (fatal and nonfatal)	4/651.1 (0.6) [0.6]	2/647.1 (0.3) [0.3]	4/816.2 (0.5) [0.5]	2/822.3 (0.2) [0.2]
VTE (fatal)	0/651.8	0/647.1	0/816.9	0/822.3
PE	0/651.8	0/647.1	0/816.9	0/822.3
Venous thrombosis	0/651.8	0/647.1	0/816.9	0/822.3
VTE (nonfatal)	4/651.1 (0.6) [0.6]	2/647.1 (0.3) [0.3]	4/816.2 (0.5) [0.5]	2/822.3 (0.2) [0.2]
DVT	2/651.1 (0.3) [0.3]	0/647.1	2/816.2 (0.2) [0.2]	0/822.3
PE	3/651.8 (0.5) [0.5]	2/647.1 (0.3) [0.3]	3/816.9 (0.4) [0.4]	2/822.3 (0.2) [0.2]
DVT and PE (concurrent)	1/651.8 (0.2) [0.2]	0/647.1	1/816.9 (0.1) [0.1]	0/822.3

DVT = deep vein thrombosis; EAIR = exposure-adjusted incidence rate; PE = pulmonary embolism; PY = patient-year; QD = once daily; SSA = study size adjusted; VTE = venous thromboembolic events

In Study 572, there were 2 treatment emergent adjudicated VTE events in the adalimumab group, 3 events in the upadacitinib 15 mg group and 2 events in the upadacitinib 30 mg group. The long-term rates of adjudicated thromboembolic event were comparable across the treatment groups of upadacitinib 15 mg and 30 mg, and adalimumab (0.6, 0.4, and 0.5 n/100 PY).

Other observations related to safety

Consistent with previous experience, upadacitinib did not demonstrate any significant effects on blood pressure or heart rate. In the PBO-controlled Analysis Set, an increase in body weight of 7% or more from baseline to Week 24 was seen in 5.3% of subjects on placebo, 10.4% of subjects on upadacitinib 15 mg, and 12.2% of subjects on upadacitinib 30 mg.

Serious adverse events/deaths/other significant events

Deaths in the PsA programme

All deaths in the PsA clinical development programme were adjudicated by the externally led CAC. A total of 5 deaths were reported within the programme.

In the PBO-controlled Analysis Set, treatment-emergent deaths were reported in 2 subjects who were both in the placebo group.

In the Any Upadacitinib Analysis Set, 3 additional deaths were reported after Week 24. One death in the 30 mg group was treatment-emergent, and the 2 other deaths (1 each in the upadacitinib 15 mg and 30 mg groups) occurred more than 30 days after the last dose of study drug.

Deaths in other programmes

According to the MAH, as of 31 December 2019, 3 deaths have reported in other unblinded studies where the subjects were in the upadacitinib treatment group. The 3 deaths included 2 deaths in a Phase 2 Atopic Dermatitis study (Study M16-048) and 1 death in an open-label Phase 2 Crohn's disease (CD) study (Study M14-327).

Non-fatal serious adverse events

In the PBO-controlled Analysis Set, the numbers and percentages of subjects with SAEs were 26 subjects (4.1%) in the upadacitinib 15 mg group, 44 subjects (6.9%) in the upadacitinib 30 mg group, and 17 subjects (2.7%) in the placebo group. The majority of SAEs were reported in single subjects within a group, except for gastritis erosive, sepsis, psoriatic arthropathy, and nephrolithiasis (2 subjects each in the upadacitinib 15 mg group), atypical pneumonia and bacteraemia (2 subjects each in the upadacitinib 30 mg group), and pneumonia (2 subjects (0.3%) in the upadacitinib 15 mg group, 6 subjects (0.9%) in the upadacitinib 30 mg group, 2 subjects (0.3%) in the placebo group).

In the Any Upadacitinib Analysis Set, the EAERs of SAEs were 10.9 E/100 PY and 14.8 E/100 PY for the upadacitinib 15 mg and 30 mg groups, respectively. The SAE with the highest EAER in the upadacitinib 15 mg and 30 groups was pneumonia (0.5 E/100 PY and 1.0 E/100 PY, respectively). The most frequently reported SAEs (>= 0.2 E/100 PY in any treatment group) are presented in Table 74.

Table 74 Treatment-Emergent Serious Adverse Events Reported in ≥0.2 Events per 100 PY in any Treatment Group by Decreasing Frequency in the Upadacitinib 15 mg Group (Any Upadacitinib Analysis Set)

System Organ Class MedDRA 22.0 Preferred Term	15 mg QD (No Cross-Over from Placebo) (N = 640) (PY = 651.8)	30 mg QD (No Cross-Over from Placebo) (N = 641) (PY = 647.1)	Any 15 mg QD (N = 907) (PY = 816.9)	Any 30 mg QD (N = 920) (PY = 822.3)
	E (E/100 PY) [SSA E/100 PY]			
Pneumonia	4 (0.6) [0.6]	6 (0.9) [0.9]	4 (0.5) [0.5]	8 (1.0) [1.0]
Pulmonary embolism	3 (0.5) [0.5]	2 (0.3) [0.3]	3 (0.4) [0.4]	2 (0.2) [0.2]
Gastritis erosive	2 (0.3) [0.3]	0	2 (0.2) [0.2]	0
Myocardial infarction	2 (0.3) [0.3]	1 (0.2) [0.2]	2 (0.2) [0.2]	1 (0.1) [0.1]
Nephrolithiasis	2 (0.3) [0.3]	1 (0.2) [0.2]	2 (0.2) [0.2]	2 (0.2) [0.2]
Psoriatic arthropathy	2 (0.3) [0.3]	1 (0.2) [0.2]	2 (0.2) [0.2]	1 (0.1) [0.1]
Sepsis	2 (0.3) [0.3]	1 (0.2) [0.2]	2 (0.2) [0.2]	1 (0.1) [0.1]
Uterine prolapse	2 (0.3) [0.3]	0	2 (0.2) [0.2]	0
Appendicitis	1 (0.2) [0.2]	1 (0.2) [0.2]	1 (0.1) [0.1]	2 (0.2) [0.2]
Bronchitis	1 (0.2) [0.2]	3 (0.5) [0.5]	1 (0.1) [0.1]	3 (0.4) [0.4]
Cellulitis	1 (0.2) [0.2]	1 (0.2) [0.2]	1 (0.1) [0.1]	2 (0.2) [0.2]
Gastroenteritis viral	1 (0.2) [0.2]	1 (0.2) [0.2]	1 (0.1) [0.1]	2 (0.2) [0.2]
Herpes zoster	1 (0.2) [0.2]	4 (0.6) [0.6]	1 (0.1) [0.1]	5 (0.6) [0.6]
Osteoarthritis	1 (0.2) [0.2]	1 (0.2) [0.2]	1 (0.1) [0.1]	2 (0.2) [0.2]
Pyrexia	1 (0.2) [0.2]	2 (0.3) [0.3]	1 (0.1) [0.1]	3 (0.4) [0.4]
Atrial fibrillation	0	1 (0.2) [0.2]	0	2 (0.2) [0.2]
Atypical pneumonia	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Bacteremia	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Chronic obstructive pulmonary disease	0	1 (0.2) [0.2]	0	2 (0.2) [0.2]
Duodenal ulcer hemorrhage	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Gastroenteritis	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Osteonecrosis	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Pneumocystis jirovecii pneumonia	0	1 (0.2) [0.2]	0	2 (0.2) [0.2]
Urinary tract infection	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]

MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-year; QD = once daily; SSA = study size adjusted

In study 572, the EAER of SAEs was 8.6 E/100 PY in the upadacitinib 15 mg group, 10.9 E/100 PY in the adalimumab group and 12.9 E/100 PY in the upadacitinib 30 mg group. In the adalimumab group, cellulitis and cerebrovascular accident were each reported in 2 subjects, whereas other SAE terms were only reported in single subjects.

Laboratory findings

Haematology

Consistent with previous experience, upadacitinib had little effect on platelet counts in PsA patients. In the PBO-controlled Analysis Set, mean initial changes from baseline to Week 2 in platelet counts were 2.1 x 10E9/L for placebo, 9.0 x 10E9/L for upadacitinib 15 mg and 14.0 x 10E9/L for upadacitinib 30

mg. Mean changes from baseline to Week 24 were -2.7 x 10E9/L for placebo, 1.3 x 10E9/L for upadacitinib 15 mg and 10.6 x 10E9/L for upadacitinib 30 mg. Grade 2 decreases were recorded in 2 subjects (0.3%) on both upadacitinib 15 mg and upadacitinib 30 mg, and a Grade 3 decrease was recorded in 1 subject (0.2%) on upadacitinib 30 mg.

Effects on haemoglobin and white cells are summarised in other sections of the AR.

Clinical chemistry

In the upadacitinib MAA studies in RA patients, upadacitinib was observed to increase both LDL and HDL cholesterol, but with the effect being of similar magnitude for both types, the LDL/HDL ratio remained quite stable.

In the PBO-controlled Analysis Set, the mean changes in lipid parameters from baseline to Week 24 for placebo, upadacitinib 15 mg and 30 groups were: HDL-C: –0.001, 0.215, 0.247 mmol/L; and LDL-C: 0.018, 0.350, 0.449 mmol/L. At Week 24, for placebo, upadacitinib 15 mg, and 30 mg groups, mean change from baseline in LDL-C/HDL-C ratio was: –0.006, –0.078, –0.013 mmol/L (Figure 43).

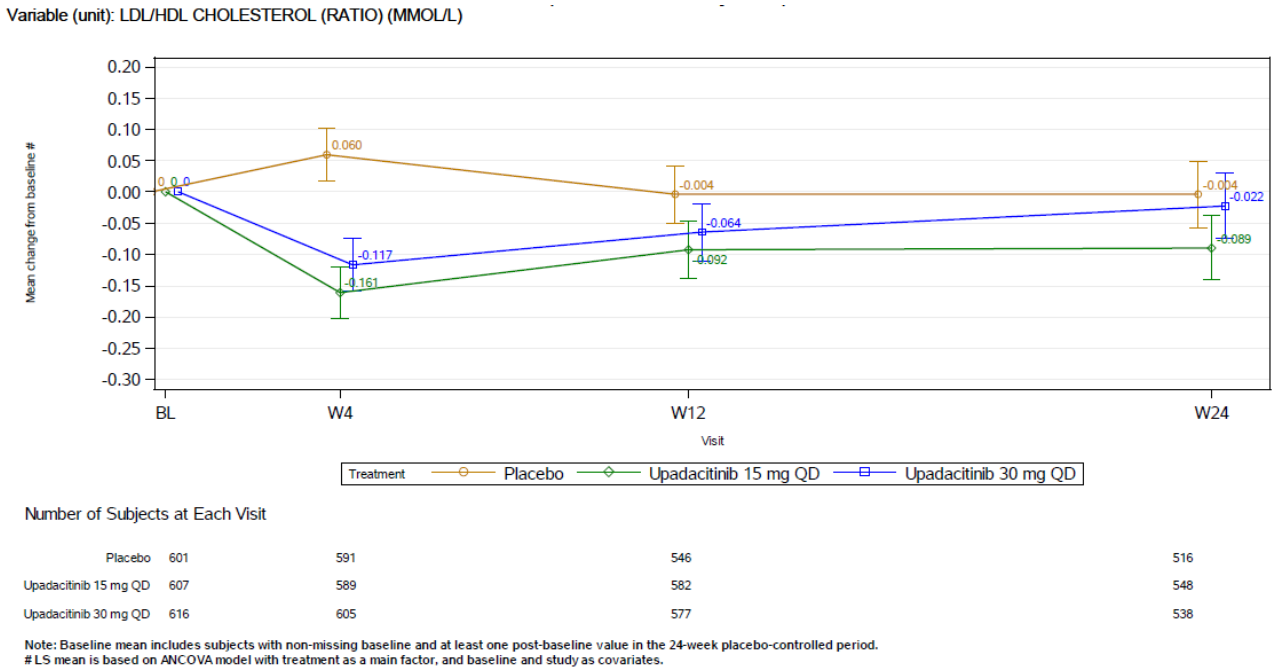


Figure 43 Mean Change from Baseline in LDL/HDL-C Ratio Over Time (PBO-controlled Analysis Set)

During the placebo-controlled period in the Phase 3 studies, statin treatment was initiated post-baseline in 9 subjects in the upadacitinib 15 mg group, 21 in the upadacitinib 30 mg group, and 13 in the placebo group. In this limited sample, a trend could be seen for reversal of mean LDL-C and mean HDL-C toward baseline levels.

Effects on hepatic enzymes, creatine phosphokinase and creatinine are summarised in other sections of the AR.

Safety in special populations

Intrinsic factors

Subgroup analyses based on age, race, sex, baseline BMI and baseline renal impairment were conducted to evaluate their impact on the safety profile.

The analysis based on age is affected by relatively small cell sizes in the 65-75 year age stratum (N=83-89 per treatment group in the PBO-controlled Analysis Set). Moreover, there were only 38 subjects over 75 years in total in the PBO-controlled Analysis Set. In general, an increased frequency of most types of adverse events (any TEAE, serious TEAE, severe TEAE) was seen in the 65-75 year age stratum compared to subjects less than 65 years, although the frequencies were increased in all treatment groups including placebo. The numbers of specific AESIs were generally too small for meaningful conclusions. According to the MAH, an increased rate of serious infections was observed among patients 65 years of age or older as compared to patients < 65 years.

In general, the rates of any TEAE and TEAEs with a reasonable possibility of being related to study drug were higher for non-whites than whites. However, with a 90% white population enrolled, the cell sizes for other races limit the possibility for any robust conclusions.

The overall reporting rates for any TEAE were somewhat higher among female than male subjects, but within each sex, the differences between placebo and upadacitinib were quite similar. In the long-term analysis set, the EAER of urinary tract infection was higher in females compared with males in both upadacitinib doses. The rates of most AESIs were generally similar between males and females.

No noteworthy trends were seen in the subgroup analysis based on BMI. The lowest BMI stratum (<18.5 kg/m^2) had a very small sample size (total N=17 in the PBO-controlled Analysis Set).

No concerning trends were seen in the types of TEAEs or AESIs between subjects with normal renal function compared to subjects with mild renal impairment. Patients with a baseline eGFR < 40 ml/min/1.73m^2 were excluded from the studies, and the study population consequently does not include subjects with severe renal impairment. Furthermore, the number of subjects with moderate renal impairment (i.e. < 60 ml/min/1.73m^2) was small (N=24-38 per treatment group (total N=91) in the PBO-controlled Analysis Set), rendering frequency estimates in this subgroup subject to substantial imprecision.

Extrinsic factors

Upadacitinib monotherapy vs combination therapy with non-biologic DMARDs

Some 70% of subjects in the studies across the treatment groups were using one or more background non-biologic DMARDs, most commonly MTX. In the PBO-controlled Analysis Set, the frequencies of most unique AESI terms were too small for reliable conclusions. In the long-term Any Upadacitinib Analysis Set, the rates of serious infections, hepatic disorders, CPK elevation, neutropenia, anaemia, and lymphopenia were higher in the combination therapy subgroup compared with the monotherapy subgroup in both upadacitinib 15 mg and 30 mg groups (Table 75).

Table 75 Treatment-Emergent AESI EAER per 100 PY by Upadacitinib Monotherapy vs. Upadacitinib Combination Therapy (Any Upadacitinib Analysis Set)

	Upadacitinib Monotherapy			
	Upadacitinib			
	15 mg QD (No Cross-Over from Placebo) (N = 189)	30 mg QD (No Cross-Over from Placebo) (N = 197)	Any 15 mg QD (N = 255)	Any 30 mg QD (N = 276)
Exposure-adjusted event rate:	(PYs = 192.2) Events (E/100 PYs) [SSA E/100 PYs]	(PYs = 198.3) Events (E/100 PYs) [SSA E/100 PYs]	(PYs = 228.5) Events (E/100 PYs) [SSA E/100 PYs]	(PYs = 253.2) Events (E/100 PYs) [SSA E/100 PYs]
Any infections	183 (95.2) [95.3]	270 (136.2) [136.4]	229 (100.2) [100.2]	334 (131.9) [132.0]
Any serious infections	1 (0.5) [0.5]	8 (4.0) [3.9]	3 (1.3) [1.3]	11 (4.3) [4.2]
Any opportunistic infection excluding tuberculosis and herpes zoster	1 (0.5) [0.5]	4 (2.0) [2.1]	1 (0.4) [0.5]	6 (2.4) [2.4]
Any herpes zoster	8 (4.2) [4.2]	17 (8.6) [8.4]	8 (3.5) [3.5]	25 (9.9) [9.7]
Any active tuberculosis	0	0	0	0
Any hepatic disorder	16 (8.3) [8.0]	26 (13.1) [13.2]	18 (7.9) [7.6]	31 (12.2) [12.2]
Any adjudicated gastrointestinal perforation	0	0	0	0
Any anemia	4 (2.1) [2.1]	12 (6.1) [6.0]	5 (2.2) [2.2]	15 (5.9) [5.9]
Any neutropenia	2 (1.0) [1.0]	8 (4.0) [4.1]	2 (0.9) [0.9]	9 (3.6) [3.6]
Any lymphopenia	3 (1.6) [1.6]	4 (2.0) [2.1]	3 (1.3) [1.3]	4 (1.6) [1.7]
Any creatine phosphokinase (CPK) elevation	16 (8.3) [8.0]	23 (11.6) [11.8]	18 (7.9) [7.6]	29 (11.5) [11.6]
Any renal dysfunction	1 (0.5) [0.5]	0	1 (0.4) [0.4]	0

	Upadacitinib Combination Therapy			
	Upadacitinib			
	15 mg QD (No Cross-Over from Placebo) (N = 451)	30 mg QD (No Cross-Over from Placebo) (N = 444)	Any 15 mg QD (N = 652)	Any 30 mg QD (N = 644)
Exposure-adjusted event rate:	(PYs = 459.7) Events (E/100 PYs) [SSA E/100 PYs]	(PYs = 448.8) Events (E/100 PYs) [SSA E/100 PYs]	(PYs = 588.4) Events (E/100 PYs) [SSA E/100 PYs]	(PYs = 569.1) Events (E/100 PYs) [SSA E/100 PYs]
Any infections	479 (104.2) [104.4]	598 (133.2) [133.0]	598 (101.6) [101.8]	713 (125.3) [125.1]
Any serious infections	14 (3.0) [3.0]	31 (6.9) [6.9]	16 (2.7) [2.7]	38 (6.7) [6.7]
Any opportunistic infection excluding tuberculosis and herpes zoster	2 (0.4) [0.4]	3 (0.7) [0.7]	3 (0.5) [0.5]	3 (0.5) [0.5]
Any herpes zoster	15 (3.3) [3.3]	31 (6.9) [7.0]	21 (3.6) [3.6]	40 (7.0) [7.1]
Any active tuberculosis	0	0	0	0
Any hepatic disorder	94 (20.4) [20.8]	128 (28.5) [28.4]	115 (19.5) [19.8]	152 (26.7) [26.7]
Any adjudicated gastrointestinal perforation	1 (0.2) [0.2]	0	1 (0.2) [0.2]	0
Any anemia	17 (3.7) [3.7]	38 (8.5) [8.5]	18 (3.1) [3.1]	42 (7.4) [7.4]
Any neutropenia	13 (2.8) [2.9]	34 (7.6) [7.5]	16 (2.7) [2.7]	42 (7.4) [7.4]
Any lymphopenia	16 (3.5) [3.5]	22 (4.9) [4.9]	17 (2.9) [2.9]	25 (4.4) [4.4]
Any creatine phosphokinase (CPK) elevation	62 (13.5) [13.6]	98 (21.8) [21.7]	75 (12.7) [12.8]	111 (19.5) [19.3]
Any renal dysfunction	1 (0.2) [0.2]	1 (0.2) [0.2]	1 (0.2) [0.2]	1 (0.2) [0.2]

Use with MTX vs other non-biologic DMARDs

As seen in Table 75 above, the majority of subjects on combination therapy were receiving MTX, and the very small cell sizes for individual non-MTX agents severely limit a comparative analysis. Within the Any Upadacitinib 15 mg QD group of the integrated Any Upadacitinib Analysis Set, the total numbers of subjects receiving different non-biologic DMARDs in combination with upadacitinib were as follows: MTX only, N=516; non-MTX non-biologic only, N=99; leflunomide without MTX, N=37; sulfasalazine without MTX, N=36; apremilast without MTX, N=23; MTX+another non-MTX agent, N=37.

A comparison of EAER/EAIRs of TEAEs within subgroups with different types of background medication is displayed in Table 76, and a similar comparison of AESI EAER/EAIRs is displayed in Table 77.

Table 76 TEAE EAER/EAIRs per 100 PY by Concomitant Non-Biologic DMARDs Use at Baseline (Any Upadacitinib Analysis Set, Any 15 mg QD group only)

	Mono	MTX only	non-MTX only	MTX + non-MTX
	Any 15 mg QD (N = 255)	Any 15 mg QD (N = 516)	Any 15 mg QD (N = 99)	Any 15 mg QD (N = 37)
Exposure-adjusted event rate:	(PYs = 228.5) Events (E/100 PYs) [SSA E/100 PYs]	(PYs = 463.3) Events (E/100 PYs) [SSA E/100 PYs]	(PYs = 90.4) Events (E/100 PYs) [SSA E/100 PYs]	(PYs = 34.7) Events (E/100 PYs) [SSA E/100 PYs]
Any adverse event (AE)	721 (315.5) [315.4]	356 (292.7) [293.3]	305 (337.4) [339.1]	141 (406.1) [407.4]
Any serious AE	25 (10.9) [11.0]	41 (8.9) [8.8]	15 (16.6) [16.3]	8 (23.0) [22.6]
Any AE leading to discontinuation of study drug	23 (10.1) [10.3]	26 (5.6) [5.6]	17 (18.8) [18.3]	3 (8.6) [9.2]
Any severe AE	32 (14.0) [14.2]	46 (9.9) [9.9]	13 (14.4) [14.0]	10 (28.8) [28.7]
Any AE with reasonable possibility of being related to study drug$	185 (81.0) [80.1]	550 (118.7) [119.3]	108 (119.5) [121.0]	58 (167.0) [173.2]
Any AE leading to death	0	0	0	1 (2.9) [3.1]
Exposure-adjusted incidence rate:	n/PYs (n/100 PYs) [SSA n/100 PYs]	n/PYs (n/100 PYs) [SSA n/100 PYs]	n/PYs (n/100 PYs) [SSA n/100 PYs]	n/PYs (n/100 PYs) [SSA n/100 PYs]
Deaths#	0/228.5	0/463.3	0/90.4	1/34.9(2.9) [3.0]

Table 77 AESI EAER/EAIRs per 100 PY by Concomitant Non-Biologic DMARDs Use at Baseline (Any Upadacitinib Analysis Set, Any 15 mg QD group only); Table prepared by assessor

	Mono	MTX only	non-MTX only	MTX + non-MTX
	Any 15 mg QD (N = 255)	Any 15 mg QD (N = 516)	Any 15 mg QD (N = 99)	Any 15 mg QD (N = 37)
Exposure-adjusted event rate:	(PYs = 228.5) Events (E/100 PYs) [SSA E/100 PYs]	(PYs = 463.3) Events (E/100 PYs) [SSA E/100 PYs]	(PYs = 90.4) Events (E/100 PYs) [SSA E/100 PYs]	(PYs = 34.7) Events (E/100 PYs) [SSA E/100 PYs]
Any infections	229 (100.2) [100.2]	463 (99.9) [100.0]	94 (104.0) [104.5]	41 (118.1) [117.1]
Any serious infections	3 (1.3) [1.3]	12 (2.6) [2.6]	2 (2.2) [2.2]	2 (5.8) [5.5]
Any opportunistic infection excluding tuberculosis and herpes zoster	1 (0.4) [0.5]	1 (0.2) [0.2]	1 (1.1) [1.0]	1 (2.9) [3.1]
Any herpes zoster	8 (3.5) [3.5]	17 (3.7) [3.7]	3 (3.3) [3.4]	1 (2.9) [2.4]
Any active tuberculosis	0	0	0	0
Any hepatic disorder	18 (7.9) [7.6]	99 (21.4) [21.6]	10 (11.1) [11.2]	6 (17.3) [18.3]
Any adjudicated gastrointestinal perforation	0	1 (0.2) [0.2]	0	0
Any anemia	5 (2.2) [2.2]	17 (3.7) [3.7]	1 (1.1) [1.0]	0
Any neutropenia	2 (0.9) [0.9]	14 (3.0) [3.0]	1 (1.1) [1.1]	1 (2.9) [3.1]
Any lymphopenia	3 (1.3) [1.3]	14 (3.0) [3.1]	2 (2.2) [2.3]	1 (2.9) [2.4]
Any creatine phosphokinase (CPK) elevation	18 (7.9) [7.6]	53 (11.4) [11.5]	15 (16.6) [16.5]	7 (20.2) [19.5]
Any renal dysfunction	1 (0.4) [0.4]	1 (0.2) [0.2]	0	0
Exposure-adjusted incidence rate:	n/PYs (n/100 PYs) [SSA n/100 PYs]	n/PYs (n/100 PYs) [SSA n/100 PYs]	n/PYs (n/100 PYs) [SSA n/100 PYs]	n/PYs (n/100 PYs) [SSA n/100 PYs]
Any possible malignancy	8/227.0(3.5) [3.6]	3/461.7(0.6) [0.7]	1/89.1(1.1) [1.1]	1/34.7(2.9) [3.1]
Any malignancy	8/227.0(3.5) [3.6]	1/463.2(0.2) [0.2]	1/89.1(1.1) [1.1]	1/34.7(2.9) [3.1]
Any non-melanoma skin cancer (NMSC)	3/227.2(1.3) [1.3]	1/463.3(0.2) [0.2]	1/89.1(1.1) [1.1]	0/34.7
Any malignancy other than NMSC	5/228.3(2.2) [2.2]	1/463.2(0.2) [0.2]	0/90.4	1/34.7(2.9) [3.1]
Any lymphoma	1/226.7(0.4) [0.5]	1/463.1(0.2) [0.2]	0/90.4	0/34.7
Any adjudicated MACE*	1/228.1(0.4) [0.4]	3/460.9(0.7) [0.6]	0/90.4	0/34.7
Any adjudicated VTE**	0/228.5	1/462.5(0.2) [0.2]	2/90.4(2.2) [2.2]	1/34.7(2.9) [3.0]

Use in non-biologic DMARD-IR vs biologic DMARD-IR patients

Summaries of AESI in long-term datasets from studies M15-554 (i.e. biologic DMARD-IR subjects) and M15-572 (non-biologic DMARD-IR subjects) are displayed in Table 78 and Table 79, respectively.

Table 78 Overview of AESI per 100 PY in biologic DMARD-IR subjects (Study M-15-554 Long-Term Safety Analysis Set)

	Upadacitinib 15 mg QD (N = 290) (PY = 292.8)	**Upadacitinib 30 mg QD (N = 308) (PY = 296.2)**
Exposure-adjusted event rate	E (E/100 PY)	
Any serious infection	8 (2.7)	20 (6.8)
Any opportunistic infection[a]	2 (0.7)	4 (1.4)
Any herpes zoster	11 (3.8)	31 (10.5)
Any active TB	0	0
Any hepatic disorder	15 (5.1)	55 (18.6)
Any adjudicated GI perforation	0	0
Any anemia	8 (2.7)	19 (6.4)
Any neutropenia	4 (1.4)	12 (4.1)
Any lymphopenia	3 (1.0)	4 (1.4)
Any CPK elevation	18 (6.1)	27 (9.1)
Any renal dysfunction	1 (0.3)	1 (0.3)
Exposure-adjusted incidence rate	n/PY (n/100 PY)	
Any malignancy	7/290.5 (2.4)	6/294.6 (2.0)
Any NMSC	3/290.7 (1.0)	1/295.2 (0.3)
Any malignancy other than NMSC	4/292.6 (1.4)	5/295.6 (1.7)
Any lymphoma	2/290.8 (0.7)	0/296.2
Any adjudicated MACE[b]	1/291.5 (0.3)	1/296.3 (0.3)
Any adjudicated VTE[c]	1/292.8 (0.3)	0/296.2

CPK = creatine phosphokinase; E = events; GI = gastrointestinal; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; PY = patient-years; QD = once daily; TB = tuberculosis; VTE = venous thromboembolic event

a. Excluding TB and herpes zoster.

b. Defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Cardiovascular death includes PE and venous thrombosis, which are also included in the adjudicated VTEs.

c. Includes DVT and PE.

Table 79 Overview of AESI per 100 PY in non-biologic DMARD-IR subjects (Study M-15-572 Long-Term Safety Analysis Set)

	ADA 40 mg EOW (N = 429) (PY = 394.5)	Upadacitinib 15 mg QD (N = 617) (PY = 524.1)	Upadacitinib 30 mg QD (N = 612) (PY = 526.0)
Exposure-adjusted event rate		E (E/100 PY)	
Any serious infection	6 (1.5)	11 (2.1)	29 (5.5)
Any opportunistic infection[a]	0	2 (0.4)	5 (1.0)
Any herpes zoster	2 (0.5)	18 (3.4)	34 (6.5)
Any active TB	0	0	0
Any hepatic disorder	122 (30.9)	118 (22.5)	128 (24.3)
Any adjudicated GI perforation	0	1 (0.2)	0
Any anemia	6 (1.5)	15 (2.9)	38 (7.2)
Any neutropenia	23 (5.8)	14 (2.7)	39 (7.4)
Any lymphopenia	1 (0.3)	17 (3.2)	25 (4.8)
Any CPK elevation	36 (9.1)	75 (14.3)	113 (21.5)
Any renal dysfunction	0	1 (0.2)	0
Exposure-adjusted incidence rate		n/PY (n/100 PY)	
Any malignancy	6/394.0 (1.5)	4/523.5 (0.8)	6/524.3 (1.1)
Any NMSC	2/394.3 (0.5)	2/523.6 (0.4)	4/524.4 (0.8)
Any malignancy other than NMSC	4/394.1 (1.0)	3/524.0 (0.6)	2/525.8 (0.4)
Any lymphoma	0/394.5	0/524.1	0/526.0
Any adjudicated MACE[b]	3/394.3 (0.8)	3/522.7 (0.6)	1/524.9 (0.2)
Any adjudicated VTE[c]	2/392.9 (0.5)	3/523.4 (0.6)	2/526.0 (0.4)

ADA = adalimumab; CPK = creatine phosphokinase; DVT = deep vein thrombosis; E = events; E/100 PY = events per 100 PY; EOW = every other week; GI = gastrointestinal; MACE = major adverse cardiac event; NMSC = non-melanoma skin cancer; PE = pulmonary embolism; PY = patient-year; QD = once daily; TB = tuberculosis; VTE = venous thromboembolic event

a. Excluding TB and herpes zoster.

b. Defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Cardiovascular death includes PE and venous thrombosis, which are also included in the adjudicated VTEs.

c. Includes DVT and PE.

According to the MAH, the higher rates of laboratory related AESI in non-biologic DMARD-IR subjects compared with biologic DMARD-IR subjects are not readily supported by analysis of actual laboratory data (e.g. Grade 3 and/or Grade 4 abnormalities) and may therefore reflect differences in the subjective reporting of laboratory abnormalities as AEs across different countries or investigators in the two studies. Furthermore, the frequency of background DMARD was higher among subjects using 1 or more non-biologic DMARDs in the non-biologic DMARD-IR population as compared with the biologic DMARD-IR population (82.3% versus 48.8%).

A subgroup analysis was also undertaken in study 554 to determine whether the safety profiles differ among subjects with an insufficient response to biologic DMARDs as opposed to intolerance to biologic DMARDs. The number of genuinely biologic DMARD-intolerant subjects is very low (N=25 for Any 15 mg upadacitinib exposure and N=22 for Any 30 mg upadacitinib exposure in the Safety Analysis Set for study M15-554) and mostly results in only single events being reported across most AESI

categories. Whereas this limitation should be taken into account, there is no direct evidence of an overt safety issue in this small subgroup.

Use in pregnancy

According to the MAH, 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 (AD), ulcerative colitis (UC), and CD. Of the 39 pregnancies, 3 occurred in females participating in PsA clinical studies with pregnancy outcomes of ectopic pregnancy, spontaneous abortion, and pregnancy still ongoing.

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 are ongoing.

In addition to the clinical trial cases described above, there was one post-marketing spontaneous report of a pregnancy in a 34-year-old with a medical history of "juvenile RA and IBD"; the pregnancy is ongoing and the timing of exposure to upadacitinib was not reported.

A total of 12 male subject partner pregnancies have been reported through 15 February 2020; all were from clinical trials and in the following indications: 3 RA, 6 CD, 2 PsA, and 1 ankylosing spondylitis. Nine of the 12 subjects are known to have been assigned to upadacitinib at the time of partner pregnancy. Among these 9 subjects, the outcomes are: 4 live births without congenital anomalies, 2 ongoing pregnancies, 1 each of spontaneous abortion, subject lost to follow up and unknown outcome.

Regarding lactation reports, it should be recognised that upadacitinib clinical study protocols exclude breastfeeding women and reference documents provide guidance to avoid breastfeeding while on upadacitinib. In a search of the MAH's safety database, two post-marketing reports from the United States were identified. No neonatal AEs were reported. Both reports contained minimal information.

Other observations

According to the MAH, there have been no reported cases of overdose, drug abuse or dependence, and there is no evidence for and no anticipation of upadacitinib to affect the ability to drive or operate machinery, or to otherwise impair mental ability.

Safety related to drug-drug interactions and other interactions

According to the MAH, upadacitinib plasma exposures in Phase 3 PsA studies were similar between subjects who were co-administered apremilast, hydroxychloroquine, sulfasalazine, leflunomide, and MTX and subjects who did not receive these DMARDs, indicating lack of effect of these DMARDs on upadacitinib pharmacokinetics. See Section on PK/PD modelling of the AR for details.

Discontinuation due to adverse events

In the PBO-controlled Analysis Set, the percentage of subjects with TEAEs leading to discontinuation of study drug was 3.8% in the placebo group, 4.4% in the upadacitinib 15 mg group and 6.4% in the upadacitinib 30 mg group. Most TEAEs leading to discontinuation of study drug were reported in 1-2 subjects in any group; ALT increased was reported in 3 subjects on upadacitinib 30 mg and psoriatic arthropathy was reported in 5 subjects on upadacitinib 15 mg.

In the Any Upadacitinib Analysis Set, the EAERs of TEAEs leading to discontinuation of study drug were 8.4 E/100 PY and 9.5 E/100 PY for the upadacitinib 15 mg and 30 mg groups, respectively. The TEAE leading to discontinuation of study drug with the highest EAER was psoriatic arthropathy in the upadacitinib 15 mg group (5 events [0.6 E/100 PY]) and pyrexia in the upadacitinib 30 mg group (4 events [0.5 E/100 PY]). The most frequently reported TEAEs leading to discontinuation of study drug (>= 0.2 E/100 PY in any treatment group) are presented in Table 80.

Table 80 Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug Reported in ≥ 0.2 Events per 100 PY in any Treatment Group by Decreasing Frequency in the Upadacitinib 15 mg Group (Any Upadacitinib Analysis Set)

System Organ Class MedDRA 22.0 Preferred Term	15 mg QD (No Cross-Over from Placebo) (N = 640) (PY = 651.8)	30 mg QD (No Cross-Over from Placebo) (N = 641) (PY = 647.1)	Any 15 mg QD (N = 907) (PY = 816.9)	Any 30 mg QD (N = 920) (PY = 822.3)
	E (E/100 PY) [SSA E/100 PY]			
Psoriatic arthropathy	5 (0.8) [0.8]	0	5 (0.6) [0.6]	0
Herpes zoster	2 (0.3) [0.3]	2 (0.3) [0.3]	2 (0.2) [0.2]	2 (0.2) [0.2]
Prostate cancer	1 (0.2) [0.2]	0	2 (0.2) [0.2]	0
Psoriasis	1 (0.2) [0.2]	0	2 (0.2) [0.2]	0
Pulmonary embolism	2 (0.3) [0.3]	2 (0.3) [0.3]	2 (0.2) [0.2]	2 (0.2) [0.2]
Sepsis	2 (0.3) [0.3]	0	2 (0.2) [0.2]	0
White blood cell count decreased	2 (0.3) [0.3]	0	2 (0.2) [0.2]	0
Blood creatine phosphokinase increased	0	2 (0.3) [0.3]	1 (0.1) [0.1]	2 (0.2) [0.2]
Bronchitis	0	2 (0.3) [0.3]	1 (0.1) [0.1]	2 (0.2) [0.2]
Lymphopenia	1 (0.2) [0.2]	3 (0.5) [0.5]	1 (0.1) [0.1]	3 (0.4) [0.4]
Pneumonia	1 (0.2) [0.2]	2 (0.3) [0.3]	1 (0.1) [0.1]	2 (0.2) [0.2]
Pyrexia	1 (0.2) [0.2]	3 (0.5) [0.5]	1 (0.1) [0.1]	4 (0.5) [0.5]
Alanine aminotransferase increased	0	3 (0.5) [0.5]	0	3 (0.4) [0.4]
Chronic obstructive pulmonary disease	0	1 (0.2) [0.2]	0	2 (0.2) [0.2]
Diarrhea	0	3 (0.5) [0.5]	0	3 (0.4) [0.4]
Folliculitis	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Hepatic enzyme increased	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Urinary tract infection	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]

MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-year; QD = once daily; SSA = study size adjusted

In long-term data from study 572, the EAER of TEAEs leading to discontinuation of study drug were 5.9 E/100 PY for upadacitinib 15 mg, 7.4 E/100 PY for upadacitinib 30 mg, and 10.1 E/100 PY for adalimumab. TEAEs leading to discontinuation of study drug reported in more than 1 subject in any treatment group are presented in Table 81.

Table 81 Treatment-Emergent Adverse Events Leading to Discontinuation Reported in ≥ 2 Events in any Treatment Group by Decreasing Frequency in the Upadacitinib 30 mg QD Group – Long Term (Safety Analysis Set; Study M15-572)

MedDRA 22.0 Preferred Term	Upadacitinib 15 mg QD (N = 617) (PY = 524.1) E (E/100 PY)	Upadacitinib 30 mg QD (N = 612) (PY = 526.0) E (E/100 PY)	ADA 40 mg EOW (N = 429) (PY = 394.5) E (E/100 PY)
Any adverse event	31 (5.9)	39 (7.4)	40 (10.1)
Lymphopenia	1 (0.2)	3 (0.6)	0
Pyrexia	1 (0.2)	3 (0.6)	0
Bronchitis	0	2 (0.4)	0
Folliculitis	0	2 (0.4)	0
Pulmonary embolism	1 (0.2)	2 (0.4)	0
ALT increased	0	1 (0.2)	2 (0.5)
Alopecia	0	0	2 (0.5)
AST increased	0	0	2 (0.5)
Herpes zoster	2 (0.4)	0	0
Psoriasis	0	0	3 (0.8)
Sepsis	2 (0.4)	0	0

ADA = adalimumab; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EOW = every other week; MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-year; QD = once daily

Note: Subjects in upadacitinib 15 mg or 30 mg group included those who started upadacitinib 15 mg or 30 mg at the beginning of the study and those who switched from placebo to upadacitinib 15 mg or 30 mg at Week 24.

Post marketing experience

Upadacitinib was approved for rheumatoid arthritis in the United States on 16 August 2019 (international birth date) and in the European Union on 18 December 2019. 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 MAH has been continuing to monitor potential new safety signals through its ongoing routine pharmacovigilance that includes weekly review of all post-marketing reports, serious and non-serious, received from all sources (including literature) and SAEs from clinical trials; quarterly review of data mining scores generated from FDA's Adverse Event Reporting System database; periodic reports (Periodic Safety Update Report, development safety update reports, periodic adverse drug experience reports, etc.) with inclusion of sections outlining findings for AEs of interest, per mandated timelines, and post-marketing studies.

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 MAH's global safety database retrieved 1,573 reports. Overall, 90% of the reports were considered non-serious 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%). Most of the post-marketing events were either expected for upadacitinib or commonly seen in the general population or patients with RA. Although drug ineffective is listed as one of the most frequently reported events, it is also not unexpected for a product once reaching market.

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 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 marketing of upadacitinib in treating patients with moderate to severe active RA.

Supportive analyses from clinical studies in RA

To support the current application, the MAH provided an overview of long-term safety data from the RA global clinical studies, with a data cut-off of 31 December 2019. The RA studies included in this analysis are 8 ongoing Phase 3 studies, 2 completed Phase 2 dose-ranging studies, and 1 ongoing Phase 2 open-label extension study.

The population of subjects in the Any upadacitinib analysis set (N=5,579) is about 80% female, and about 79% of subject are white. The number of subjects aged 75 to <85 years is 182, and the number of subjects aged 85 years older is 8. About 34%, 31% and 35% of subjects are in the BMI categories <25 kg/m^2, 25 - <30 kg/m^2 and >=30 kg/m^2, respectively. At baseline, 34% of subjects did not use any concomitant csDMARDs; 52% were on MTX, 6.5% were on MTX + another csDMARD, and 8.1% were on a non-MTX csDMARD only.

In the upadacitinib RA clinical development programme, a total of 5,579 subjects have received at least 1 dose of upadacitinib in the Phase 2 or Phase 3 RA studies, for a mean duration of 733.3 days and 11,201 PY of total exposure including over 6,815 PY of upadacitinib 6 mg BID/15 mg QD exposure and over 2,949 PY of upadacitinib 12 mg BID/30 mg QD exposure. The extent of exposure is summarised in Table 82.

Table 82 Number and Percentage of Subjects Exposed to Study Drug in the RA Development Programme by Duration Intervals

	Any RA Phase 3 Upadacitinib 15 mg Analysis Set		**Any RA Phase 3 Upadacitinib 30 mg Analysis Set**		**Any RA Upadacitinib Analysis Set**	
	Upadacitinib 15 mg QD (N = 3209) n (%)		**Upadacitinib 30 mg QD (N = 1204) n (%)**		**Any Upadacitinib (N = 5579) n (%)**	
Duration						
≥ 4 weeks (28 days)	3168	(98.7)	1182	(98.2)	5493	(98.5)
≥ 12 weeks (84 days)	3081	(96.0)	1131	(93.9)	5296	(94.9)
≥ 24 weeks (168 days)	2760	(86.0)	1058	(87.9)	4835	(86.7)
≥ 36 weeks (252 days)	2485	(77.4)	1026	(85.2)	4458	(79.9)
≥ 48 weeks (336 days)	2265	(70.6)	979	(81.3)	4111	(73.7)
≥ 72 weeks (504 days)	1986	(61.9)	926	(76.9)	3527	(63.2)
≥ 96 weeks (672 days)	1830	(57.0)	863	(71.7)	3272	(58.6)
Mean duration (days)	676.9		821.5		733.3	

QD = once a day; RA = rheumatoid arthritis

An overview of EAERs for TEAEs, providing a side-by-side comparison of data in the initial RA submission and the updated dataset of 31 December 2019, is displayed in Table 83.

Table 83 Overview of Treatment-Emergent Adverse Events Per 100 PY – Long Term All Exposure

	Any RA Phase 3 Upadacitinib 15 mg Analysis Set		Any RA Phase 3 Upadacitinib 30 mg Analysis Set		Any RA Upadacitinib Analysis Set	
	Data Cutoff[a]	Initial RA Submission	Data Cutoff[a]	Initial RA Submission	Data Cutoff[a]	Initial RA Submission
	(N = 3209) (PY = 5947.1)	(N = 2630) (PY = 2655.1)	(N = 1204) (PY = 2708.0)	(N = 1204) (PY = 1365.0)	(N = 5579) (PY = 11201.0)	(N = 4443) (PY = 5263.5)
Exposure-adjusted event rate	E (E/100 PY)					
Any AE	14465 (243.2)	7852 (295.7)	8084 (298.5)	5033 (368.7)	29380 (262.3)	15598 (296.3)
Any SAE	784 (13.2)	399 (15.0)	536 (19.8)	291 (21.3)	1697 (15.2)	827 (15.7)
Any AE leading to discontinuation of study drug	368 (6.2)	224 (8.4)	255 (9.4)	182 (13.3)	825 (7.4)	502 (9.5)
Any severe AE	719 (12.1)	397 (15.0)	440 (16.2)	270 (19.8)	1496 (13.4)	759 (14.4)
Any AE with reasonable possibility of being related to study drug[b]	4735 (79.6)	2676 (100.8)	2699 (99.7)	1755 (128.6)	9781 (87.3)	5179 (98.4)
Any AE leading to death	30 (0.5)	20 (0.8)	26 (1.0)	18 (1.3)	62 (0.6)	43 (0.8)
Exposure-adjusted incidence rate	n/PY (n/100PY)					
Deaths	23/5947.6 (0.4)	11/2655.1 (0.4)	17/2708.4 (0.6)	11/1365.0 (0.8)	44/11201.9 (0.4)	25/5263.5 (0.5)

AE = adverse event; PY = patient-year; RA = rheumatoid arthritis; SAE = serious adverse event

a. Data cutoff = 31 December 2019

b. As assessed by investigator.

Most deaths continued to be considered cardiovascular deaths in subjects with known risk factors, followed by malignancies, infectious deaths, and traumatic deaths. Since the initial RA submission, one suicide has been reported in the upadacitinib 15 mg dose group. This was a non-treatment-emergent death by hanging and occurred approximately 15 months after the last dose of upadacitinib (no further information was available). In the initial RA submission, there was one fatal report of meningitis in a subject receiving upadacitinib 30 mg. In the updated dataset, there are 2 additional fatal events of meningitis reported. The first report concerns a listeria meningitis in a 50-year-old male subject on upadacitinib 15 mg QD. The second report concerns a case of recurrent polymicrobial meningitis in the context of an undefined gastrointestinal condition in a 63-year-old male on upadacitinib 15 mg QD.

The MAH also performed a standard mortality ratio (SMR) analysis using World Health Organization country-age-gender specific death data for the general population that yielded an SMR estimate of 0.42 (95% CI: 0.30, 0.56) for the treatment-emergent deaths in the upadacitinib treatment groups. The expected number of deaths on upadacitinib was 105 compared to 44 observed.

Since the initial RA submission, one serious case of severe angioedema has been reported in a 55-year-old male who received upadacitinib 15 mg. The investigator and MAH assessed the event of angioedema as possibly related to study drug. According to the MAH, no other cases of serious hypersensitivity reactions have been reported in the upadacitinib clinical development programme that were attributed to upadacitinib treatment.

An overview of EAERs for AESI in the updated dataset of 31 December 2019 is displayed in Table 84. According to the MAH, the event rates across the different AESI have remained constant compared to the initial RA submission, and the analyses did not reveal any new safety risks. Compared to long-term AESI event/incidence rates with upadacitinib 15 mg in RA patients, higher rates with upadacitinib 15 mg among PsA patients were observed for the following categories (values are E/100 PY or N/100 PY): Any opportunistic infection excluding tuberculosis and herpes zoster (0.5 for PsA vs. 0.3 for RA); Any herpes zoster (3.6 vs. 3.5); Any hepatic disorder (16.9 vs. 12.4); Any lymphopenia (2.6 vs. 1.8); Any CPK elevation (11.4 vs. 5.3); Any malignancy (1.5 vs. 1.0); Any NMSC (0.7 vs. 0.3); Any malignancy other than NMSC (0.9 vs. 0.8); Any adjudicated MACE (0.5 vs. 0.4).

Table 84 Overview of Treatment-Emergent AESI Per 100 PY – Long Term All Exposure

	Any RA Phase 3 Upadacitinib 15 mg Analysis Set (N = 3209) (PY = 5947.1)	Any RA Phase 3 Upadacitinib 30 mg Analysis Set (N = 1204) (PY = 2708.0)	Any RA Upadacitinib Analysis Set (N = 5579) (PY = 11201.0)
Exposure-adjusted event rate		**E (E/100 PY)**	
Any serious infection	188 (3.2)	145 (5.4)	449 (4.0)
Any opportunistic infection excluding TB and herpes zoster	18 (0.3)	6 (0.2)	39 (0.3)
Any herpes zoster	208 (3.5)	169 (6.2)	546 (4.9)
Any active TB	5 (< 0.1)	3 (0.1)	9 (< 0.1)
Any hepatic disorder	738 (12.4)	309 (11.4)	1320 (11.8)
Any adjudicated GI perforation	5 (< 0.1)	5 (0.2)	14 (0.1)
Any anemia	211 (3.5)	121 (4.5)	416 (3.7)
Any neutropenia	147 (2.5)	130 (4.8)	347 (3.1)
Any lymphopenia	108 (1.8)	83 (3.1)	276 (2.5)
Any CPK elevation	314 (5.3)	250 (9.2)	699 (6.2)
Any renal dysfunction	18 (0.3)	18 (0.7)	39 (0.3)
Exposure-adjusted incidence rate		**n/PY (n/100PY)**	
Any malignancy	61/5924.8 (1.0)	47/2681.0 (1.8)	135/11136.6 (1.2)
Any NMSC	17/5932.2 (0.3)	20/2683.8 (0.7)	44/11149.8 (0.4)
Any malignancy other than NMSC	47/5938.8 (0.8)	30/2704.8 (1.1)	100/11180.2 (0.9)
Any lymphoma	3/5946.2 (< 0.1)	1/2707.8 (< 0.1)	7/11199.6 (< 0.1)
Any adjudicated MACE[a]	24/5930.7 (0.4)	19/2697.3 (0.7)	55/11166.8 (0.5)
Any adjudicated VTE[b]	30/5936.7 (0.5)	9/2701.3 (0.3)	52/11171.9 (0.5)

CPK = creatine phosphokinase; CV = cardiovascular; DVT = deep vein thrombosis; GI = gastrointestinal; MACE = major adverse cardiac event; MI = myocardial infarction; NMSC = non-melanoma skin cancer; PE = pulmonary embolism; PY = patient-year; RA = rheumatoid arthritis; TB = tuberculosis; VTE = venous thromboembolism

a. Defined as CV death, non-MI, and non-fatal stroke.

b. Includes DVT and PE.

2.5.1. Discussion on clinical safety

Safety data is presented from two pivotal Phase 3 studies in PsA patients, of which one also included an authorised active control (adalimumab). Safety data was integrated into two datasets, where the short-term (24 week) dataset enables assessment against placebo, and the long-term dataset provides a snapshot of all available safety data. To support the safety assessment, the MAH also provided a summary of cumulative long-term safety data from the RA programme (comprising 11,201.0 PY of exposure among a total of 5,579 subjects) and a summary of post-marketing data (with cumulative exposure of about 3,100 PY).

In the pivotal studies, over 1,800 subjects were exposed to upadacitinib, and 359 subjects were treated for 12 months or longer at the proposed registration dose of 15 mg QD. Total exposure within the PsA programme amounts to 1,639 PY. The exposure is considered sufficient for adequate safety assessment.

The studies enrolled a primarily white population with approximately equal gender distribution. Mean BMI was over 30 kg/m^2, and considerable proportions of subjects had underlying hypertension or a metabolic disorder.

About 70% of subjects were using a background non-biologic DMARD at baseline; use was more frequent among non-biologic DMARD-IR subjects (82% in study 572) than among biologic DMARD-IR subjects (49% in study 554). MTX was clearly the most common background DMARD in both populations, whereas the use patterns of non-MTX DMARDs was slightly different between the two populations. The majority of subjects in both studies were on a concomitant NSAID, and 15-20% of subjects were using a concomitant systemic corticosteroid.

In the PBO-controlled Analysis Set, SAEs, AEs leading to discontinuation, and severe AEs were more frequent on upadacitinib than placebo, and more frequent on 30 mg than 15 mg. Reporting rates in subjects receiving adalimumab in study 572 were comparable to those in the integrated upadacitinib 15 mg dataset. There were two deaths, both reported in the placebo group.

In the long-term Analysis Set, exposure-adjusted event rates for AEs, SAEs, AEs leading to discontinuation, severe TEAEs and treatment-related AEs were higher for 30 mg than 15 mg. Exposure-adjusted event rates in subjects receiving adalimumab in study 572 were comparable to those in the integrated upadacitinib 15 mg dataset. Three deaths were reported; one death in the 30 mg group was treatment-emergent, and the 2 other deaths (1 each in the upadacitinib 15 mg and 30 mg groups) occurred more than 30 days after the last dose of study drug.

In the PBO-controlled Analysis Set, the pattern of common TEAEs was consistent with the known safety profile for upadacitinib. An increased frequency vs. placebo, and a dose response relationship between the 15 and 30 mg upadacitinib doses, could be seen e.g. for URTI, increased blood CPK, herpes zoster, as well as leukopenia and neutropenia. For anaemia and lymphopenia, an increased frequency compared to placebo was only seen in the 30 mg group. Psoriasis and psoriatic arthropathy were most frequently reported in the placebo group. The pattern of common events remained consistent with long-term exposure.

Based on the MAH's analysis, two new ADRs (bronchitis and acne) are proposed to be included in the Tabulated list of ADRs with a frequency common in Section 4.8 of the SmPC; furthermore, the frequency categories for herpes zoster and herpes simplex are proposed to be changed from uncommon to common. The MAH's proposals were endorsed by the CHMP.

In short-term placebo-controlled analyses, the frequency of serious infections with 15 mg upadacitinib was similar to placebo. However, similar to the original MAA studies with upadacitinib in RA, serious infections were more frequent with the higher 30 mg dose of upadacitinib, and this increased frequency with the 30 mg dose was also observed in long-term data. Most subgroup analyses based on demographic and baseline characteristics were hampered by small sample sizes across several cells, but with this caveat, no obvious clustering was noted. The MAH has proposed a change in Section 4.4 of the SmPC to indicate that there is a higher incidence of infections among patients aged 65 and older (previously 75 and older); this change was acceptable to the CHMP. In general, treatment-emergent serious infections seemed more frequent among subjects on combination therapy than subjects on upadacitinib monotherapy, but small sample sizes for individual non-biologic DMARDs other than MTX prevent any reliable comparison of individual agents.

Opportunistic infections are an important identified risk for upadacitinib. Although they were reported infrequently, some evidence of a dose-related increase in reporting rates can be seen. The SmPC contains adequate information concerning the risk of an atypical infection associated with this class of agents. Consistent with previous experience, the risk of herpes zoster was dose-dependently increased, and higher with upadacitinib than with adalimumab. No cases of active TB were reported in the studies.

In the current dataset, the overall incidence rate of malignancies other than NMSC was consistent with that expected in the general population. Considering the limited follow-up time for a large proportion of subjects, it is recognised that the dataset is not sensitive for detection of rare events with typically long latencies.

Consistent with observations in the RA studies, upadacitinib was associated with a modest increase in transaminase levels; in most cases, these elevations were self-limiting and there is no signal of potential for actual hepatic toxicity.

GI perforation is identified as an important potential risk for upadacitinib. However, with only one confounded case reported in the PsA programme, no further conclusions can be drawn about this important potential risk.

Inhibition of JAK2 is known to be associated with reduced erythropoietin signalling, and the dose-related decrease in haemoglobin was already previously observed in the RA studies with upadacitinib. The current SmPC includes adequate provisions for management of clinically relevant haemoglobin decreases.

The 10-15% decrease seen in mean neutrophil count is consistent with earlier observations in the RA studies. However, cases of severe Grade 4 neutropenia were not reported in the PsA studies, and the current posology section of the SmPC includes appropriate guidelines for management of low neutrophil counts.

Whereas upadacitinib, in line with previous experience, evoked a transient increase in mean lymphocyte counts, transient decreases were also seen quite frequently, and some dose dependency in decreased count frequency was also seen between the 15 and 30 mg doses. In the long-term analysis of Study 572, lymphopenia was clearly more frequent on upadacitinib than adalimumab. Nevertheless, lymphopenias seem to be mostly transient, and where necessary, have been appropriately manageable with protocol-mandated dose interruptions. Similar guidelines are already included in the current SmPC and they remain appropriate and up to date.

An increase in serum creatinine is a common phenomenon with all JAK inhibitors including upadacitinib and was also seen within the current programme, with mean values almost doubling from baseline during treatment. However, it does not seem to bear particular clinical significance, and the SmPC adequately informs prescribers of the phenomenon.

Consistent with the RA studies, upadacitinib was associated with a small increase in mean creatinine that does not seem to be associated with any clinical consequences. Serious cases of decreased renal function were only reported in conjunction with acute infections and were not attributed to upadacitinib.

The EAIRs of MACE in the PsA programme were consistent with those previously seen in the RA programme; no fatal adjudicated MACE were recorded, and no dose relationship was seen between the 15 mg and 30 mg risk. Given the low incidence of MACE events, it remains warranted to continue following this important potential risk in long-term studies.

Similar to the RA programme, VTE events were reported with a low incidence across all treatment groups including placebo and adalimumab. Similar to MACE, given the low incidence as well as the findings across the class of JAK inhibitors, it remains warranted to continue follow-up regarding this potential risk. Given the absence of any new information from the PsA programme, the SmPC remains up to date with respect to VTE. Consistent with previous experience, upadacitinib was not associated with any significant effects on platelet counts.

Upadacitinib does not have significant effect on vital signs. Consistent with weight increase being an adverse reaction already included in the SmPC, a ≥7% increase in body weight was seen in more subjects on upadacitinib than placebo.

The overall number of deaths in the PsA programme was low. A fatal interstitial pneumonitis and dermatomyositis in subject is accounted for as a non-treatment-emergent death, but the sequence of events would also be consistent with a progressively worsening inflammatory cascade that initially started when the subject was exposed to upadacitinib. In light of a potential causative role of upadacitinib and also bearing in mind that interstitial lung disease is considered an important potential risk for another JAK inhibitor, the MAH was requested to provide a more detailed discussion, including

a summary of any previous cases of similar nature. According to the MAH's analysis, the occurrence of interstitial lung disease -type events is infrequent, confined to patients with an underlying rheumatic disorder, and most cases are confounded by a history of smoking and/or concomitant MTX use. The MAH proposes to continue monitoring reports describing interstitial lung disease and dermatomyositis through standardised surveillance activities; this was considered adequate by the CHMP.

The overall frequency of non-fatal SAEs was low, and most event terms were only reported in 1-2 subjects per treatment group. The most frequently reported non-fatal SAE was pneumonia.

Upadacitinib, similar to other JAK kinase inhibitors, induces an increase in plasma lipids, but with the effect size being similar across both LDL and HDL, there was no significant effect on atherogenic indices in the current studies. The SmPC contains adequate information and management guidelines concerning lipid changes associated with upadacitinib treatment.

Subgroup analyses based on several intrinsic factors (age, race, sex, baseline BMI and baseline renal impairment) did not highlight specific concerns. However, sample sizes for some subgroups were small and results should be interpreted with caution. According to the MAH, an increased rate of serious infections was observed in patients 65 years of age or older, and the MAH has proposed a corresponding change in Sections 4.4 and 4.8 of the SmPC. Although the analysis is based on a small number of subjects, the change was considered acceptable to the CHMP.

Given that non-biologic DMARDs, including MTX, are associated with distinct patterns of adverse effects, it is not unexpected that AEs were reported more often on combination therapy. Hence, section 4.8 of the SmPC includes the following statement "*A higher rate of serious infections (2.6 events per 100 patient years and 1.3 events per 100 patient years, respectively) and hepatic transaminase elevations (ALT elevations Grade 3 and higher rates 1.4% and 0.4%, respectively) was observed in patients treated with upadacitinib in combination with MTX therapy compared to patients treated with monotherapy*".

The majority of subjects on combination therapy were using MTX, and a comparison of MTX vs. non-MTX combinations is consequently limited by the small sample sizes. However, within the Any 15 mg QD group of the long-term Any Upadacitinib Analysis Set, the EAERs of serious adverse events, adverse events leading to discontinuation and severe adverse events were clearly higher among subjects on a non-MTX non-biologic DMARD than subjects on MTX. For serious adverse events and severe adverse events, the EAERs were further increased in the group on both MTX and a non-MTX non-biologic DMARD, although the sample size is very small. In the AESI analysis, the numbers of individual AESI in the non-MTX only and MTX+non-MTX groups are generally too small for a meaningful analysis. Nevertheless, the use of upadacitinib concomitantly with a non-MTX non-biologic DMARD seems to be associated with a higher frequency of adverse events, including serious and severe events, and since the subject numbers are small, there are considerable remaining uncertainties regarding the safety profile when upadacitinib is used concomitantly with non-MTX agents or with a combination of MTX and a non-MTX agent. Furthermore, each individual non-MTX non-biologic DMARD is associated with its unique safety profile, but with the small number of patients for each individual non-MTX non-biologic DMARD, it is not possible to adequately assess the safety profile of each individual combination. Lastly, the findings with non-MTX non-biologic DMARDs bear similarities to those in the RA program, where combination therapy with upadacitinib was ultimately restricted to MTX only. As described in the clinical efficacy section, the proposed indication was not endorsed by the CHMP and the MAH consequently agreed to restrict the concomitant use of upadacitinib to methotrexate only.

Whereas combination therapy was used more frequently in the non-biologic DMARD-IR population, slightly elevated rates of serious infections and herpes zoster were seen among biologic DMARD-IR

subjects compared to non-biologic DMARD-IR subjects. The higher frequency of combination therapy in the non-biologic DMARD-IR population could account for a higher rate of laboratory changes being reported in the non-biologic DMARD-IR population, although the MAH indicated that these differences are not completely supported by actual laboratory data. Comparison of profiles of common adverse events between the two subgroups did not identify concerning trends. Overall, the safety profiles can be considered to have been adequately characterised in both biologic DMARD-IR and non-biologic DMARD-IR subjects. The very small number of genuinely biologic DMARD-intolerant subjects enrolled into study 554 (total N=47) precludes reliable analysis of potential specificities in the safety profile in this small subgroup. However, in the absence of any overt safety issues and considering that upadacitinib in RA is already authorised for use in patients who are intolerant to one or more DMARDs (i.e., including biologic DMARDs), a similar wording in the indication is supported by the CHMP in PsA from the safety perspective.

Due to findings of teratogenicity in non-clinical studies, upadacitinib is contraindicated in pregnancy. The absence of reports of congenital abnormalities among offspring of female subjects exposed to upadacitinib during pregnancy is reassuring, but the small number of pregnancies prevents reliable conclusions. No changes to the Product Information are therefore currently warranted.

In the PBO-controlled Analysis Set, AEs leading to discontinuation of study medication were reported in less than 5% of subjects in the placebo and upadacitinib 15 mg groups. Events within the Infections and infestations SOC were the most common reason for discontinuation.

Post-marketing data for upadacitinib in its approved RA indication comprises approximately 3,100 PY of exposure. Based on the MAH's analysis of post-marketing data, no new signals or safety risks have been identified. The most commonly reported serious event was pneumonia.

To support and contextualise the safety findings in PsA patients, the MAH presented a summary of long-term data from the ongoing RA clinical development programme. Compared to the original submission, there was no evidence of an increased exposure-adjusted event rate for any category of overall TEAEs or AESI. Similar to the original submission, the event rates for upadacitinib 30 mg were higher than for the 15 mg dose.

Compared to long-term AESI event/incidence rates with upadacitinib 15 mg in RA patients, higher rates with upadacitinib 15 mg were noted among PsA patients for some AESI categories. However, these differences were generally small and can be accounted for by differences between patient populations, the sizes of the respective databases as well as differences in length of exposure. Overall, no new or unexpected safety issues emerged from the updated RA dataset.

2.5.2. Conclusions on clinical safety

The safety profile of upadacitinib in PsA patients with an insufficient response to DMARDs was evaluated in two placebo-controlled Phase 3 studies. One study was conducted in a non-biologic DMARD-IR population, and the other one in a biologic DMARD-IR population. The first study also included an active control group receiving adalimumab.

In general, the safety profile was consistent with previous experience in RA patients. Based on an analysis of the safety data, the MAH proposed addition of two new ADRs (bronchitis, acne; frequency common) and a change in the frequency categorisation of herpes zoster and herpes simplex from uncommon to common in Section 4.8 of the SmPC. The proposed changes were acceptable to the CHMP.

The use of upadacitinib as monotherapy or in combination with MTX, as well as its use in both non-biologic and biologic DMARD-IR patients is supported by the CHMP. However, the use of upadacitinib in

combination with non-MTX non-biologic DMARDs has been studied in a small number of subjects, precluding adequate assessment of its safety profile with such combinations. Furthermore, within this limited dataset, the use of upadacitinib concomitantly with a non-MTX non-biologic DMARD seemed to be associated with a higher frequency of adverse events, including serious and severe events, than when it was used in combination with MTX. At the CHMP's request, the MAH agreed to restrict the indication to the use as monotherapy or in combination therapy with MTX.

The CHMP considered that the safety of upadacitinib in the following indication is supported by the data submitted by the MAH: "*RINVOQ is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. RINVOQ may be used as monotherapy or in combination with methotrexate.*"

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 2.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.3 with the following content:

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious and opportunistic infections including TB	Routine risk minimization measures: SmPC Section 4.4 summarizes the risk and provides guidance on ways to reduce the risk. The PL warns that patients who have an infection or who have a recurring infection should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. The PL advises that patients do not take Rinvoq if they have active TB and warns that patients with a history of TB, or who have been in close contact with someone with TB should consult their doctor or pharmacist before and during treatment with Rinvoq. SmPC Section 4.2 outlines lymphocyte and neutrophil counts and when not to initiate upadacitinib dosing. SmPC Section 4.2 outlines interruption guidelines based on ALC and ANC. SmPC Section 4.3 indicates that upadacitinib is contraindicated in patients with active TB or active serious infections.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for serious and opportunistic infections including TB Additional pharmacovigilance activities: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe Long-Term Safety Study of Upadacitinib Use in RA Patients in the US Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	SmPC Section 4.4 states that patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib and that upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection. SmPC Section 4.4 advises to consider the risks and benefits of initiating upadacitinib in patients with active, chronic, or recurrent infections. A patient who develops a new infection during treatment with upadacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and upadacitinib should be interrupted if the patient is not responding to therapy. Screening for TB prior to initiation is advised, and upadacitinib should not be given if active TB is diagnosed. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with untreated latent TB or in patients with risk factors for TB infection. Additional risk minimization measures: HCP educational brochure PAC Other routine risk minimization measures: Prescription only medicine.	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Herpes zoster	Routine risk minimization measures: SmPC Section 4.4 describes the risk of viral reactivation such as herpes zoster. SmPC Section 4.8 describes findings from upadacitinib clinical trials. The PL warns that patients who have an infection or who have a recurring infection should consult their doctor or pharmacist before and during treatment with Rinvoq and will describe the risk of viral reactivation. The PL warns that patients who have had a herpes zoster infection (shingles) should tell their doctor if they get a painful skin rash with blisters as these can be signs of shingles. SmPC Section 4.4 advises that if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. Additional risk minimization measures: HCP educational brochure PAC Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for serious infections Additional pharmacovigilance activities: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe Long-Term Safety Study of Upadacitinib Use in RA Patients in the US Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)
Malignancies	Routine risk minimization measures: SmPC Section 4.4 describes the risk in patients with RA and indicates that upadacitinib clinical data are currently limited and long-term studies are ongoing. The PL warns that patients who have cancer, develop a new lesion or any change in the appearance of an area on the skin, or are at high risk of developing skin cancer should consult their doctor or pharmacist before and during treatment with Rinvoq. SmPC Section 4.4 advises that periodic skin examination is recommended for patients who are at increased risk for skin cancer. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe Long-Term Safety Study of Upadacitinib Use in RA Patients in the US Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
MACE	Routine risk minimization measures: SmPC Section 4.4 describes the effect of upadacitinib on lipids and describes that impact on CV morbidity and mortality has not been determined. SmPC Section 4.4 contains a section on CV risk including a statement on increased CV risk in RA patients and need for management of CV risk factors as part of usual standard care. SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. The PL warns that patients who have heart problems, high blood pressure, or high cholesterol should consult their doctor or pharmacist before and during treatment with Rinvoq. Additional risk minimization measures: HCP educational brochure PAC Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for MACE Additional pharmacovigilance activities: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe Long-Term Safety Study of Upadacitinib Use in RA Patients in the US Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)
VTEs (deep venous thrombosis and pulmonary embolus)	Routine risk minimization measures: SmPC Section 4.4 indicates that events of deep vein thrombosis and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib. The PL warns that patients who have had blood clots in the veins of the legs (deep vein thrombosis) or lungs (pulmonary embolism) should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get a painful swollen leg, chest pain, or shortness of breath. SmPC Section 4.4 advises that upadacitinib should be used with caution in patients at high risk for deep vein thrombosis/pulmonary embolism. Risk factors that should be considered in determining the patient's risk for deep venous thrombosis/pulmonary embolism include older age, obesity, a medical history of deep venous thrombosis/pulmonary embolism, patients undergoing major surgery, and prolonged immobilisation. SmPC Section 4.4 advises that if clinical features of deep vein thrombosis/pulmonary embolism occur, upadacitinib treatment should be discontinued and patients should	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including: Follow-up questionnaire for VTEs Monitoring of VTE risk and literature review provided within the PSUR Additional pharmacovigilance activities: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe Long-Term Safety Study of Upadacitinib Use in RA Patients in the US Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	be evaluated promptly, followed by appropriate treatment. Additional risk minimization measures: HCP educational brochure PAC Other routine risk minimization measures: Prescription only medicine.	
GI perforation	Routine risk minimization measures: None Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe Long-Term Safety Study of Upadacitinib Use in RA Patients in the US Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)
DILI	Routine risk minimization measures: SmPC Section 4.4 describes the effect of upadacitinib on transaminases. SmPC Section 4.4 recommends prompt investigation of the cause of liver enzyme elevation to identify potential cases of DILI. SmPC Section 4.4 advises that if increases in ALT or AST are observed during routine patient management and DILI is suspected, upadacitinib should be interrupted until this diagnosis is excluded. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe Long-Term Safety Study of Upadacitinib Use in RA Patients in the US Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)
Foetal malformation following exposure in utero	Routine risk minimization measures: SmPC Section 4.6 describes the teratogenic effects observed in animals receiving upadacitinib and states that there are no or limited data from use of upadacitinib in pregnant women. The PL advises that patients do not take Rinvoq if they are pregnant, that Rinvoq must not be used during pregnancy, and that patients who become pregnant while taking Rinvoq must consult their doctor straight away. SmPC Section 4.3 and Section 4.6 indicate that upadacitinib is contraindicated during pregnancy.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaires for pregnancies Additional pharmacovigilance activities: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	SmPC Section 4.6 and PL advise on use of effective contraception. Additional risk minimization measures: HCP educational brochure PAC Other routine risk minimization measures: Prescription only medicine.	
Use in very elderly (≥ 75 years of age)	Routine risk minimization measures: SmPC Section 4.2 states that there are limited data in patients aged 75 years and older. SmPC Section 4.8 states that there was a higher rate of serious infections in patients ≥ 75 years of age, although data are limited. 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. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe Long-Term Safety Study of Upadacitinib Use in RA Patients in the US
Effect on vaccination efficacy	Routine risk minimization measures: 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. SmPC Section 4.4 states that use with live, attenuated vaccines during, or immediately prior to, upadacitinib therapy is not recommended. 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. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Vaccination substudy

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C	Routine risk minimization measures: SmPC Section 4.4 describes the risk of viral reactivation. The PL warns that patients who have ever had hepatitis B or hepatitis C should consult their doctor or pharmacist before and during treatment with Rinvoq. SmPC Section 4.4 describes the need for screening and consultation with a hepatologist if HBV DNA is detected. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe
Use in patients with moderate hepatic impairment	Routine risk minimization measures: SmPC Section 4.2 describes use in patients with hepatic impairment. SmPC Section 4.2 states that upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment. SmPC Section 4.3 indicates that upadacitinib is contraindicated for use in patients with severe hepatic impairment. The PL advises that patients do not take Rinvoq if they have severe liver problems and warns that patients should consult their doctor or pharmacist before and during treatment with Rinvoq if their liver does not work as well as it should. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe
Use in patients with severe renal impairment	Routine risk minimization measures: SmPC Section 4.2 describes use in patients with renal impairment. SmPC Section 4 states 2 that upadacitinib should be used with caution in patients with severe renal impairment. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Long-term safety	Routine risk minimization measures: SmPC Section 4.4 indicates that upadacitinib clinical data on malignancies are currently limited and long-term studies are ongoing. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe Long-Term Safety Study of Upadacitinib Use in RA Patients in the US Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)

ALC = absolute lymphocyte count; ALT = alanine transaminase; aRMMs = additional risk minimization measures; 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; PsA = psoriatic arthritis; 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, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Minor updates were made to the Annex II.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Rinvoq. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

PsA is a chronic systemic inflammatory disease classified as a sub type of spondyloarthritis and characterized by the association of arthritis and psoriasis. Patients with PsA experience varying combinations of disease manifestations affecting the synovium, tendons, entheses, skin, and bone. Cardiovascular, psychological and metabolic comorbidities associated with PsA add a significant impact on QoL and increased mortality.

Key cytokines involved in SpA pathogenesis like interleukin (IL)-6, IL-7, IL-22, IL-23 and interferon signal through the JAK-STAT pathway. Some of these cytokines activate Th1 and Th17 cells, which in turn release further pro-inflammatory cytokines, including IL-1, IL-17, IL-21, IL-22 and tumour

necrosis factor (TNF). As JAKs mediate signals of multiple pro-inflammatory cytokines in various immune cell types, targeting these intra-cellular kinases can be an effective approach to reduce inflammatory responses by directly and indirectly inhibiting key cytokines involved in the pathogenesis of PsA.

3.1.2. Available therapies and unmet medical need

Treatment of PsA is initiated with NSAIDs and local glucocorticoid injections. Systemic pharmacological treatment is recommended to be started in non-responders. Systemic medications for PsA include corticosteroids – used with caution at the lowest effective dose for a short time – csDMARDs, such as MTX , sulfasalazine, leflunomide, or cyclosporin; targeted synthetic DMARDs, such as phosphodiesterase-4 inhibitors like apremilast; and biologic DMARDs, such as TNF inhibitors, interleukin-12/23 inhibitors, and interleukin-17 inhibitors.

Tofacitinib was the first JAKi approved for use in PsA. The current recommendation is to consider starting a JAKi in patients with peripheral arthritis and an inadequate response to at least one csDMARD and at least one bDMARD, or when a bDMARD is not appropriate.

Despite the beneficial results achieved with the available biologic agents, a marked proportion of PsA patients do not achieve clinical remission after 1 year of treatment or sustained remission for at least 1 year. Polyarticular disease, increased inflammatory marker levels, progressive radiographical changes and concomitant diabetes and cardiovascular diseases indicate poor prognosis. Hence, there remains a medical need for additional therapeutic options in PsA for patients with inadequate response to or intolerance to currently available therapies.

3.1.3. Main clinical studies

Efficacy data are available from 2 controlled clinical studies, both of which are pivotal randomized, double-blind, Phase 3 studies. Study M15-572 is conducted in subjects who have been inadequate responders or were intolerant to non-biologic DMARDs (conventional synthetic disease-modifying anti-rheumatic drugs [csDMARDs] and/or targeted synthetic disease-modifying anti-rheumatic drugs [tsDMARDs]) or had a contraindication for non-biologic DMARDs. Study M15-554 includes subjects who have been inadequate responders or were intolerant to biologic disease-modifying anti-rheumatic drugs (bDMARDs).

Both of these ongoing Phase 3 studies evaluate upadacitinib 15 mg QD and 30 mg QD in combination with non-biologic DMARDs or as monotherapy. Study M15-572 includes also comparison to adalimumab 40 mg EOW. This study also evaluates progression of erosive joint disease, which is not included in study M15-554. Both studies include Period 1, a 56-week blinded controlled period and Period 2, a long-term extension. The submission initially included data up to 24 weeks of the Period 1 of both studies; complete efficacy data up to 56 weeks on endpoints proposed to be included in the SmPC was submitted during the review.

3.2. Favourable effects

In both study populations, patients with inadequate response (IR) or intolerance to non-biologic DMARDs (study M15-572) and bDMARDs (study M15-554), upadacitinib 15 mg was statistically significantly more effective than placebo in reaching the primary endpoint, ACR20 response rate at Week 12. In the upadacitinib 15 mg vs. placebo arm, the proportion of ACR20 responders in study M15-572 at Week 12 was 70.6 vs. 36.2 % in the upadacitinib 15 mg and placebo arms, respectively.

The 12-week ACR20 response rates for study M15-544 are 56.9 % vs. 24.1 % in the upadacitinib 15 mg and placebo arms, respectively. Furthermore, the ARC20 response rate for upadacitinib was non-inferior to adalimumab 40 mg EOW (response rate 65.0 %) in study M15-572 (non-biologic DMARD-IR subjects). These results were adjusted for multiplicity and supported by sensitivity analyses.

The ACR20 results of both studies were independent of the number of previously used DMARDs.

Difference between upadacitinib 15 mg and placebo arms in the proportion of the ACR20 response rate at Week 12 was 34.4 % in patients with intolerance to prior bDMARDs and 32.7 % in patients with inadequate response to prior bDMARDs (study M15-554). However, the overall response to upadacitinib 15 mg was better in intolerant subjects (73.3 %) than in bDMARD-IR subjects (55.4 %).

Structural joint changes were evaluated in study M15-572 at week 24. The change from baseline in SHS (equivalent to modified Total Sharp Score [mTSS]), Joint Erosion Score, and JSN Score at Week 24 all showed improvement by upadacitinib 15 mg compared with placebo. The difference in SHS is small, but statistically significant, in the comparison of upadacitinib 15 mg with placebo (LS mean, 95% CI): -0.29 (-0.44, -0.14). No difference was seen in the comparison of upadacitinib 15 mg and adalimumab.

During the phase 3 studies, methotrexate (MTX) was used concomitantly with study medication by 69 % of subjects in study M15-572 and 39.3 % of subjects in study M15-554. For the upadacitinib 15 mg arms, there were 56 subjects in study M15-572 and 23 subjects in study M15-554 who used a combination of upadacitinib 15 mg and other non-biologic DMARD than MTX by Week 24; these figures include also triple combinations with MTX, since in the integrated data set, the number of subjects on dual combination of upadacitinib 15 mg and non-MTX-non-biologic DMARDs was only 45.

Upadacitinib 15 mg was similarly effective when used as monotherapy or in combination with DMARDs. In the upadacitinib 15 mg group of the placebo-controlled integrated data set, the 12-week ACR20 responder rate was 70.4 % in combination with MTX (n=379), 61.5 % in combination with MTX + other non-biologic DMARDs (n=16) and 62.5 % in combination with non-biologic DMARDs other than MTX (n=45). Other endpoints analysed for monotherapy in the integrated upadacitinib 15 mg database (ACR20/50/70 and change in HAQ-DI at week 12, sIGA response rate and PASI 75/90/100 response at Week 16, proportion of subjects achieving MDA at weeks 16 and 24, proportion of subjects achieving resolution of dactylitis, and proportion of subjects achieving resolution of enthesitis at Week 24) were consistent with the primary endpoint. Additional analyses comparing treatment effect with monotherapy vs. combination of upadacitinib with confirmed overall similar efficacy of the two treatment modalities.

Upadacitinib 15 mg was more effective in improving physical function in PsA as demonstrated by a statistically significantly greater improvement in HAQ-DI and a greater proportion of subjects achieving a clinically meaningful improvement in HAQ-DI (change from baseline in HAQ-DI $\geq$0.35) at Week 12 vs. placebo in both target populations. Also FACIT-F and 36-Item Short Form Health Survey (SF-36) and SF-36 Physical Component Summary (PCS) scores improved statistically significantly more with upadacitinib 15 mg than placebo. Other measures of quality of life and patient reported outcomes evaluated as additional secondary outcomes in both studies (e.g. Mental Component Summary (MCS), and individual domains, EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L), Work Productivity and Activity Impairment (WPAI), and morning stiffness (overall, duration, and severity) at Week 12 improved numerically more by upadacitinib 15 mg vs. placebo; however, these comparisons were not adjusted for multiplicity.

Measures of dactylitis, enthesitis and activity of spondyloarthritis (BASDAI, ASDAS) were evaluated in the subgroups with these symptoms at baseline and showed improvement with upadacitinib 15 mg vs. placebo. However, only the comparisons on dactylitis and enthesitis in study M15-572 were multiplicity

controlled and the results significantly in favour of upadacitinib 15 mg, whereas the other comparisons were numerical. Patients with psoriatic spondylitis treated with upadacitinib 15 mg showed improvements from baseline in BASDAI scores compared to placebo at week 24. Improvements from baseline were maintained through week 56 in both studies.

Activity of skin manifestations was statistically significantly reduced with upadacitinib 15 compared with placebo as assessed by Psoriasis Area and Severity Index (PASI75) and static Investigator Global Assessment of Psoriasis (sIGA). A measure developed by the MAH, Self-Assessment of Psoriasis Symptoms (SAPS) improved numerically with upadacitinib; however, the difference in SAPS compared to placebo was not significant after adjustment for multiplicity.

Available efficacy data are presented through Week 56 for patients having completed the 56-week Period 1 of the studies by the data cut-off dates for the submission (39.7% of subjects in study M15-572 and 49.2% of subjects in study M15-554). The mean ACR20 response appears to be maintained in this subset, up to Week 56.

Overall, the totality of evidence from the clinical studies demonstrates superiority of upadacitinib over placebo, and non-inferiority in comparison with adalimumab, up to 56 weeks.

3.3. Uncertainties and limitations about favourable effects

The difference between placebo and upadacitinib in structural joint changes is small since a great majority of patients in both placebo and active treatment arms experienced no radiographic progression. This may reflect the importance of longer-term radiographic data in showing benefit in radiographic measures. Nevertheless, the CHMP concluded that the completed 56-week efficacy data supports the inclusion of the radiographic results in the SmPC.

The effect of upadacitinib on mental health was considered very modest in comparison with that on physical health based on the SF-36 MCS and PCS.

The MAH originally proposed to include in the SmPC nominal superiority vs. adalimumab in some individual measures. Since comparison of upadacitinib 15 mg with adalimumab in the primary endpoint (ACR20) did not show superiority and the other comparisons were not statistically significant, the MAH removed this information from Section 5.1 of the SmPC at the CHMP's request.

The complete efficacy results for the 56-week period confirmed the sustained efficacy of upadacitinib up to 56 weeks. The data are deemed sufficient for inclusion of these results in the SmPC. However, long-term effects on maintenance of effect will be further assessed when the ongoing trials are completed.

Data are scarce regarding efficacy in combination of upadacitinib 15 mg with other non-biologic DMARDs without MTX due to the overall low number of subjects in this group (n=45 in the integrated placebo-controlled upadacitinib 15 mg data set). Furthermore, several different DMARDs were combined with upadacitinib, with small numbers of combinations of individual other DMARDs with upadacitinib 15 mg. Data on other combinations of upadacitinib with DMARDs expect with MTX was considered insufficient for confirmation of efficacy. A major objection was raised on this issue during the review and the MAH agreed to restrict the indication for use of upadacitinib in PsA to monotherapy or in combination with MTX.

3.4. Unfavourable effects

Overall, SAEs, AEs leading to discontinuation and severe AEs were more frequent on upadacitinib 15 mg than placebo (SAEs, 4.1% upadacitinib vs. 2.7% placebo; AEs leading to discontinuation, 4.4% upadacitinib vs. 3.8% placebo; severe AEs, 5.3% upadacitinib vs. 3.8% placebo). Corresponding frequencies for adalimumab in study 572 were 3.7% for SAEs, 5.1% for AEs leading to discontinuation, and 6.5% for severe AEs.

In the PBO-controlled Analysis Set, the most common AEs with upadacitinib 15 mg included upper respiratory tract infections (8.9%), blood CPK increased (6.5%), nasopharyngitis (4.8%), urinary tract infection (4.2%), bronchitis (3.6%), diarrhoea (3.6%), ALT increased (3.3%), headache (3.3%), hypertension (3.1%) and influenza (3.0%). When 15 mg and 30 mg doses were compared, a dose-related increase in frequency was seen for most of these AEs.

In the PBO-controlled Analysis Set, the frequency of serious infections, most commonly pneumonia, was 0.8% for placebo, 0.9% for 15 mg and 2.7% for 30 mg. Long-term EAERs were 2.3 E / 100 PY for 15 mg and 6.0 E / 100 PY for 30 mg. Serious infections were more frequent among subjects on combination therapy than subjects on monotherapy; long-term EAERs were 2.7 E / 100 PY vs. 1.3 E / 100 PY, respectively, for 15 mg.

The frequency of herpes zoster was also increased in a dose-related manner. In the PBO-controlled Analysis Set, the frequencies of herpes zoster were 0.8% for placebo, 1.0% for 15 mg and 2.0% for 30 mg. Long-term EAERs for herpes zoster were 3.6 E/100 PY for 15 mg and 7.9 E/100 PY for 30 mg. Most events involved a single dermatome.

The safety profile of upadacitinib 15 mg in PsA patients was generally consistent with previous experience gained in the development programme in RA. Based on an analysis of the safety data, the MAH has proposed addition of two new ADRs (bronchitis, acne; frequency common) and a change in the frequency categorisation of herpes zoster and herpes simplex from uncommon to common in Section 4.8 of the SmPC. The proposed changes are considered acceptable to the CHMP.

3.5. Uncertainties and limitations about unfavourable effects

No new information was gained concerning several important potential risks, including malignancies, MACE, VTE and GI perforation. The size of the safety database as well as the limited amount of long-term exposure limits possibilities to detect low-frequency events with sometimes long latencies. However, those risks are adequately addressed in the product information and the RMP.

The small number of subjects on non-MTX non-biologic DMARDs precludes a detailed analysis of the safety profile of these other combinations. However, within the limited dataset, there is some evidence of a potentially less favourable safety profile when upadacitinib was used in combination with non-MTX non-biologic DMARDs as opposed to use in combination with MTX. It should also be borne in mind that combination treatment with upadacitinib in RA is restricted to MTX only. At the CHMP's request, the MAH agreed to restrict the indication to the use as a monotherapy or combination therapy with MTX.

3.6. Effects Table

Table 85 ***Effects Table for upadacitinib 15 mg QD***

(data cut-off: M15-554: 09 Oct 2019), M15-572:13 Dec 2019)

Effect	Short description	Unit	Treatment	Control		Between-group difference	Uncertainties / Strength of evidence	References
Favourable Effects								
		N, within-group point estimate, 95% CI	**UPA 15 mg QD**	**ADA 40 mg EOW**	**PBO**	**UPA vs. placebo LS mean treatment difference (95% CI) Adjusted P-value**		
ACR20	Proportion (%) ≥20% improvement at W12	N, % (95% CI)	429 70.6 (66.3, 74.9)	429 65.0 (60.5, 69.5)	423 36.2 (31.6, 40.7)	34.5 (28.2, 40.7) p<0.0001	Superiority to PBO and non-inferiority to ADA in both studies.	M15-572
		N, % (95% CI)	211 56.9 (50.2, 63.6)	N.A.	212 24.1 (18.3, 29.8)	32.8 (24.0, 41.6) p<0.0001	Superiority not shown for upadacitinib 15 mg vs. ADA.	M15-554
ΔHAQ-DI	Change from BL at W 12	N, LS mean (95% CI)	404 -0.42 (-0.47, -0.37)	406 -0.34 (-0.38, -0.29)	392 -0.14 (-0.18, -0.09)	-0.28 (-0.35, -0.22) p<0.0001	Superiority to PBO in both studies.	M15-572
			199 -0.30 (-0.37, -0.24)	N.A.	180 -0.10 (-0.16, -0.03)	0.21 (-0.30, -0.12) p<0.0001		M15-554
sIGA	Proportion 0 or 1 or >2 improvement from BL at W16	N % LS mean (95% CI)	322 41.9 (36.5, 47.3)	330 38.5 (33.2, 43.7)	313 10.9 (7.4, 14.3)	31.1 (24.7, 37.5) p<0.0001	Superiority to PBO in both studies.	M15-572
			171 36.8 (29.6, 44.1)	N.A.	163 9.2 (4.8, 13.6)	27.6 (19.2, 36.1) p<0.0001		M15-554

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Unfavourable Effects						
AEs	All AEs, 24 weeks vs. PBO	N (%)	422 (65.9)	391 (61.6)		PBO-controlled Analysis Set
AEs	All AEs, 24 weeks vs. ADA	N (%)	287 (66.9)	278 (64.8)		M15-572
SAEs	All SAEs, 24 weeks vs. PBO	N (%)	26 (4.1)	17 (2.7)		PBO-controlled Analysis Set
SAEs	All SAEs, 24 weeks vs. ADA	N (%)	14 (3.3)	16 (3.7)		M15-572
SAEs	Long-term event rate	E/PY (E/100 PY)	89/816.9 (10.9)	--		Any Upadacitinib Analysis Set
Serious infections	Serious infections, 24 weeks vs. PBO	N (%)	6 (0.9)	5 (0.8)		PBO-controlled Analysis Set

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Serious infections	Serious infections, 24 weeks vs. ADA	N (%)	5 (1.2)	3 (0.7)		M15-572
Serious infections	Long-term event rate	E/PY (E/100 PY)	19/816.9 (2.3)			Any Upadacitinib Analysis Set
Herpes zoster	Herpes zoster, 24 weeks vs. PBO	N (%)	7 (1.1)	5 (0.8)		PBO-controlled Analysis Set
Herpes zoster	Herpes zoster, 24 weeks vs. ADA	N (%)	4 (0.9)	0 (0)		M15-572
Deaths	Long-term incidence rate	N/PY (N/100 PY)	1/817.1 (0.1)			Any Upadacitinib Analysis Set

Abbreviations: ADA=adalimumab; AE=adverse event; E=number of events; N=number of subjects; PBO=placebo; PY=patient-years; SAE =serious adverse event; CI=confidence interval; BL=baseline; NI=non-inferiority; QD=once daily, EOW=every other week; ACR20=American College of Rheumatology 20% (ACR20) response:⩾20% or greater improvement in TJC and SJC and ⩾ 3 of the 5 measures of Patient's Assessment of Pain NRS, PtGA-Disease Activity NRS, PGA-Disease Activity NRS, HAQ-DI, or hs-CRP; ∆ HAQ-DI=change from baseline in Health Assessment Questionnaire - Disability Index; sIGA=Static Investigator Global Assessment of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Upadacitinib 15 mg QD was statistically and clinically significantly more effective than placebo in patients with inadequate response (IR) or intolerance to non-biologic DMARDs (study M15-572) and bDMARDs (study M15-554). Efficacy was demonstrated in relevant outcomes measuring treatment response on all main manifestations of psoriasis and psoriatic arthritis, including polyarthritis, axial disease, enthesitis, dactylitis, extent of skin involvement, physical function, and quality of life. The effect was demonstrated in patients at two different stages in the treatment algorithm of psoriatic arthritis: firstly, in patients who had failed both the phase I of EULAR 2019 algorithm (pharmacological treatment with NSAIDs and local glucocorticoid injections) and treatment with one of more non-biologic DMARDs (phase II of EULAR algorithm), and, secondly, in subjects who had additionally been treated with one or more biologic DMRADs but experienced either IR or intolerance (phase III of EULAR algorithm). The submitted results were completed up to 56 weeks in both of the ongoing phase 3 studies. However, the results for long-term efficacy from the ongoing extensions of the phase 3 trials will be important for assessment of benefit and optimal duration of treatment over years in this chronic condition.

Treatment with upadacitinib 15 mg was non-inferior to adalimumab in subjects with intolerance or IR to non-biologic DMARDs in study M15-572. This study also evaluated radiographic changes in structural joint involvement. Even though the radiographic progression in joint disease was statistically significantly decreased in subjects administered upadacitinib or adalimumab compared with placebo, the difference between active treatment and placebo is clinically small, dominated by no change in a great majority of subjects in all study arms. However, a small but statistically significant difference between upadacitinib and placebo was demonstrated up to 56 weeks of therapy. Final evaluation of effects on joint disease will require longer-term experience that will be obtained with the finalisation of the ongoing studies. The submission of the results for the long term extension for both studies is included in the RMP.

The demonstration of efficacy was robust for upadacitinib 15 mg QD as monotherapy and as combined with MTX. However, the numbers of subjects using other non-biologic DMARDs than MTX in

combination were relatively small and divided in subgroups with different DMARDs with various modes of action and individual efficacy and safety profiles. The small number of subjects on non-MTX non-biologic DMARDs precludes a detailed analysis of the efficacy and safety profile of these other combinations. However, within the limited dataset, there is some evidence of a potentially less favourable safety profile when upadacitinib was used in combination with non-MTX non-biologic DMARDs as opposed to use in combination with MTX. It should also be borne in mind that combination treatment with upadacitinib in RA is restricted to MTX only. A major objection was raised on the therapeutic indication during the review and the MAH agreed to modify the indication to monotherapy or combination with MTX.

While there are a number of important identified and potential risks associated with upadacitinib, the current dataset in PsA patients is generally consistent with the previously known safety profile in RA and a number of post-authorisation measures are in place for further characterisation of important identified and potential risks. The Product Information has been adequately updated with new information on PsA and includes adequate warnings and precautions regarding the management of these risks.

3.7.2. Balance of benefits and risks

The proposed indication does not include any statement on the degree of severity of PsA. However, no universally agreed definition for mild, moderate or severe PsA exists. Further, the patients had clearly active disease according to the inclusion criteria and final baseline characteristics (incl. >3 tender and swollen joints). Hence, the wording "active disease" is deemed acceptable to the CHMP without stating mild/moderate/severe disease in the indication, in line with other products for the same indication.

There is robust evidence to allow use of upadacitinib when patients have been intolerant or with inadequate response to both non-biologic and biologic DMARD(s), including patients who have received not only one but also more than one previous DMARD(s). Consequently, the part of indication stating "inadequate response/intolerance to one or more DMARDs" is acceptable to the CHMP. The inclusion criteria of study M15-572 allowed also patients who had contraindication to non-biologic DMARDs to be entered in the study. There is no biological reason to assume differential efficacy of upadacitinib in patients with contraindication to prior DMARDs vs. intolerance to prior DMARDs; hence, the CHMP considered that it would be appropriate that this small group is not specifically mentioned in the wording of the indication.

Finally, the results on upadacitinib monotherapy and combination therapy with MTX show robust efficacy of upadacitinib 15 mg compared to placebo up to 56-weeks. Hence, both the indication for monotherapy and combination therapy with MTX are considered acceptable to the CHMP.

3.8. Conclusions

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

"*Psoriatic arthritis*

RINVOQ is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. RINVOQ may be used as monotherapy or in combination with methotrexate."

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 psoriatic arthritis in adult patients for Rinvoq; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Minor updates were made to the Annex II. Version 2.3 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 Annexes 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*
    - Language on the risk of infections during treatment with upadacitinib
    - 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)
    - Language on avoidance of live vaccines (i.e., Zostavax) prior to and during upadacitinib treatment
    - Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.
- *Risk of herpes zoster*
    - Language on the risk of herpes zoster during treatment with upadacitinib
    - Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.
- *Risk of foetal malformation*
    - Language on teratogenicity of upadacitinib in animals
    - Details on how to reduce the risk of exposure during pregnancy for 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*

- Language on the increased risk of MACE in patients with immune-related inflammatory diseases and the need to consider typical CV risk factors (e.g., hypertension, hyperlipidaemia) when treating patients
- Language on the risk of MACE during treatment with upadacitinib
- Language on the risk of hyperlipidaemia during upadacitinib therapy
- Details on monitoring of lipid levels and management of elevated lipid levels per clinical guidelines

- *Risk of VTE*
  - Examples of the risk factors which may put a patient at higher risk for VTE and in whom caution is needed when using upadacitinib.
  - Language on the risk of VTE during treatment with upadacitinib
  - 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:*
  - Contact details of the upadacitinib prescriber
  - 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.)
  - 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
  - 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

- 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 the Scientific Discussion: Rinvoq EMEA/H/C/4760/II/0004

Attachments

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