17 October 2019
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rinvoq

International non-proprietary name: upadacitinib

Procedure No. EMEA/H/C/004760/0000

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% improvement criteria
ADA	adalimumab
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AO	as observed
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCS	Biopharmaceutical Classification System
bDMARD	biologic disease-modifying antirheumatic drug
BID	twice daily
BMI	body mass index
CAC	Cardiovascular Adjudication Committee
Cavg	average concentration
CCP	cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CI	confidence interval
cMTX	continuing a prior stable dose of MTX
CPK	creatine phosphokinase
CQA	critical quality attribute
CR	clinical remission
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CSR	clinical study report
CSS	Clinical Summary of Safety
CV	cardiovascular
CYP	Cytochrome P450
DAS28	disease activity score (28 joints)
DILI	drug induced liver injury

DMARD	disease-modifying antirheumatic drug
DoE	Design of experiment
DVT	deep vein thrombosis
E	event
EAER	exposure-adjusted event rate
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOW	every other week
EPO	erythropoietin
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Health State Instrument
ER	extended-release
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	full analysis set
FDA	Food and Drug Administration
GC	gas chromatography
GCP	Good Clinical Practice
GI	gastrointestinal
HAQ-DI	Health Assessment Questionnaire Disability Index
HDL-C	high-density lipoprotein-cholesterol
HDPE	high density polyethylene
HPLC	high pressure liquid chromatography
HPMC	Hydroxypropylmethylcellulose (Hypromellose)
hsCRP	high-sensitivity C-reactive protein
ICH	International Council for Harmonisation
ICP-OES	Inductively coupled plasma- Optical Emission Spectrometry
IL	interleukin
INH	isoniazid
IR	infrared spectroscopy
IR	inadequate response
ISE	Integrated Summary of Efficacy

ISS	Integrated Summary of Safety
IVIVC	in vitro-in vivo correlation
JAK	Janus Kinase
LDA	low disease activity
LDL-C	low-density lipoprotein-cholesterol
LDPE	low-density polyethylene
LOCF	last observation carried forward
MACE	major adverse cardiovascular event
MCC	Microcrystalline cellulose
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
mGFR	measured glomerular filtration rate
MI	myocardial infarction
MMRM	mixed effect model repeat measurement
MS	mass spectrometry
mTSS	modified Total Sharp Score
MTX	methotrexate
NAS	new active substance
NI	non-inferiority
NK	natural killer
NMR	nuclear magnetic resonance spectroscopy
NMSC	non-melanoma skin cancer
NMT	not more than
NOR	normal operating ranges
NRI	non-responder imputation
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
OMERACT	Outcome Measures in Rheumatology
OOO	out-of-specifications
OVAT	one variable at time
PAR	process acceptable ranges
PBO	placebo
PCS	physical component summary

PDE	permitted daily exposure
PE	pulmonary embolism
Ph	Phase
PJP	pneumocystis jirovecii pneumonia
Ph. Eur.	European Pharmacopoeia
PRO	patient-reported outcome
PT	Preferred Term
PY	patient-year
QC	quality control
QbD	quality by design
QD	once daily
QTPP	quality target product profile
RA	rheumatoid arthritis
RA-WIS	Rheumatoid Arthritis Work Instability Scale
RH	relative humidity
SAE	serious adverse event
SAP	statistical analysis plan
SDAI	Simplified Disease Activity Index
SEER	Surveillance, Epidemiology, and End Results
SF-36	36-Item Short Form Health Survey
SIR	standard incidence ratio
SJC	swollen joint count
SmPC	Summary of Product Characteristics
SMR	standardized mortality ratio
SOC	System Organ Class
t1/2	terminal phase elimination half-life
TAMC	total aerobic microbial count
TB	tuberculosis
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TJC	tender joint count
TNF	tumor necrosis factor
tsDMARDs	targeted synthetic disease-modifying antirheumatic drugs

Tyk2	tyrosine kinase 2
TYMC	total combined yeasts and molds count
UPA	upadacitinib
USP	United States Pharamacopoeia
US	United States
UV	ultra violet spectrometry
VTE	venous thromboembolic event
W	week
WHO	World Health Organization
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AbbVie Deutschland GmbH & Co. KG submitted on 18 December 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Rinvoq, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 February 2017.

The applicant applied for the following indication:

RINVOQ is indicated 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 or other conventional synthetic DMARDs (csDMARDs).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0363/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0363/2017 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 applicant 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.

New active Substance status

The applicant requested the active substance upadacitinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice on 28 January 2016 (EMEA/H/SA/3190/1/2015/III CORRIGENDUM) and on 23 March 2017 (EMEA/H/SA/3190/4/2017/I and

EMEA/H/SA/3190/1/FU/1/2017/II) for the development programme in question. The Scientific advice pertained to the following Quality, Non-clinical and Clinical aspects:

- Acceptability of the proposed strategy to demonstrate dose proportionality and bioequivalence between the formulation utilized in Phase 3 clinical studies and the commercial formulation
- Appropriateness of the nonclinical programme to support the initiation of Phase 3 studies and to support MAA
- Appropriateness of the clinical pharmacology programme to support the initiation of Phase 3 studies and to support MAA
- Acceptability not to perform a thorough QT study based on dose-response and concentration-response analyses of the QTc data from the Phase 1 single and multiple ascending dose studies
- Acceptability of the proposed rationale for dose selection for Phase 3 based on Phase 2 data
- Appropriateness of the design of study M15-555 for evidence generation to support use as monotherapy
- Appropriateness of the design of study M14-465 for evidence generation to demonstrate activity to inhibit the progression of structural damage
- Appropriateness of the proposed strategy to analyse early non-responder data in study M14-465
- Appropriateness of the proposed Phase 3 program to support the use in the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more csDMARDs or bDMARDs: study populations proposed for the 4 pivotal clinical studies, two primary efficacy endpoints (ACR20 and low disease activity (LDA))
- Acceptability of a primary efficacy endpoint of ACR20 at 12 weeks in the Biologic-IR study (Study M13-542) to demonstrate superiority versus placebo
- Appropriateness of proposed secondary efficacy endpoints on fatigue (FACIT-fatigue), work instability (RA-WIS) and morning stiffness severity (NRS) to capture patient relevant clinical information for potential reflection in the product information
- Adequacy of the proposed non-inferiority margin for ACR50 response at Week 24 in Study M14-465 (MTX-IR population) to assess non-inferiority of ABT-494 versus adalimumab (ADA) for improvement of signs and symptoms
- Acceptability of two primary endpoints of ACR50 and LDA as defined by DAS28(CRP) ≤ 3.2 and ACR50 in the planned post-approval MTX-naïve study (Study M13-545)
- Acceptability of a level of 20% improvement in Tender Joint Count (TJC) and Swollen Joint Count (SJC) in Study M14-465 to define criteria for early conversion to active treatment
- Acceptability of the planned clinical safety monitoring in the Phase 3 clinical trials
- Acceptability of the planned cardiovascular safety monitoring programme in the Phase 3 programme
- Adequacy of the proposed lymphocyte subset investigations in the Phase 3 programme to characterise effects on lymphocytes
- Appropriateness of the designs for extension studies to generate long-term safety data (StudyM13-536 and Study M15-556)

- Adequacy of the proposed number of subjects exposed to ABT-494 and the duration of exposure in Phase 2 and Phase 3 studies to support MAA
- Statistics: a) Adequacy of the proposed multiplicity control on primary and key secondary endpoints; b) Acceptability of an ANCOVA based primary analysis on mean change from baseline of mTSS score for evaluating benefit on structural damage progression; c) Acceptability of the proposed strategies to handle missing data for primary anlyses

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Outi Mäki-Ikola

The application was received by the EMA on	18 December 2018
The procedure started on	30 January 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	3 May 2019
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	16 May 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	29 May 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 July 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	26 August 2019
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	4 September 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 September 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 September 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 September 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	2 October 2019
The Rapporteurs circulated the Joint updated Assessment Report on the	10 October 2019

responses to the List of Outstanding Issues to all CHMP members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rinvoq on	17 October 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant has applied for the following indication: "Rinvoq is indicated 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 or other conventional synthetic DMARDs (csDMARDs)."

2.1.2. Epidemiology

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory autoimmune disease with an estimated prevalence of approximately 1%. RA is more frequent in women. The hallmark feature of RA is polyarticular joint swelling and tenderness caused by progressive inflammatory synovitis, which can result in severe, debilitating disease. Patients with moderately to severely active RA have persistent synovitis with systemic inflammation leading to destruction of articular cartilage and bone, which ultimately interfere with function of the joint. Joint destruction often occurs early in the disease process and accumulates in an inexorable manner, usually affecting up to 80% of patients within 1 year of diagnosis. Over time, the impact of this damage increases until it becomes the dominant factor driving loss of function. Left untreated, or inadequately treated, progressive functional impairment can ultimately lead to significant disability, impaired quality of life, and increased mortality.

2.1.3. Biologic features

Upadacitinib (also known as "ABT-494", "Upadacitinib AbbVie", or "Rinvoq") is an oral JAK inhibitor. Inhibition of Janus Kinase (JAK)-mediated pathways is an established approach for the treatment of patients with rheumatoid arthritis (RA). There are two other already approved JAK-inhibitors in EU: tofacitinib (Xeljanz) and barcitinib (Olumiant).

2.1.4. Clinical presentation, diagnosis

The proposed indication pertains to 2nd line and beyond treatment of RA either as monotherapy or in combination with csDMARD. As described above, RA is a chronic inflammatory, potentially debilitating disease. The diagnosis is based on careful history and clinical examination, guided by additional procedures such as laboratory testing. Erosions detected by X-ray and positivity for anti-CCP or RF are poor prognostic factors.

2.1.5. Management

According to EULAR recommendations (EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update), treatment should be initiated as soon as the RA diagnosis is made. Treatment should be aimed at reaching a target of sustained low disease activity. Methotrexate (MTX) should be the first treatment strategy. In patients with contraindications to MTX (or early intolerance), leflunomide or sulfalazine should be considered as the (first) line treatment strategy. If there is no improvement by at most 3 months after start of treatment or the target has not been reached by 6 months, therapy should be adjusted. Depending on whether poor prognostic factors are present or not, other csDMARD or addition of a

bDMARD (biologic DMARD) or tsDMARD (targeted synthetic DMARD) could then be considered. JAK-inhibitors are tsDMARD.

Despite the recent advances in this therapeutic field, there all still patients who either cannot tolerate or do not respond to the available treatment options.

About the product

Upadacitinib is a new JAK-inhibitor intended for 2nd line and >2nd line treatment of RA either as monotherapy or in combination with csDMARD (see above for the complete claimed indication). The proposed posology is 15 mg once daily.

Type of Application and aspects on development

Article 8.3 of Directive 2001/83/EC - complete and independent application: The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The product has not been granted eligibility to PRIME.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a prolonged-release, film-coated tablet containing 15 mg of upadacitinib as active substance.

Other ingredients are: microcrystalline cellulose, hypromellose, mannitol, tartaric acid, silica colloidal anhydrous, magnesium stearate, polyvinyl alcohol, macrogol, talc, titanium dioxide (E171), black iron oxide (E172) and red iron oxide (E172), as described in SmPC section 6.1.

The product is available in HDPE bottles with desiccant and propylene caps or polyvinyl chloride/ polyethylene/ polychlorotrifluoroethylene- aluminium blisters, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of upadacitinib is (3*S*,4*R*)-3-Ethyl-4-(3*H*-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin- 8-yl)-*N*-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrate (2:1). It corresponds to the molecular formula $C_{17}H_{19}F_3N_6O \times ½\ H_2O$, its relative molecular mass is 389.38 g/mol (hemihydrate) (380.38 g/mol (anhydrate)) and it has the structure shown in Figure 1.

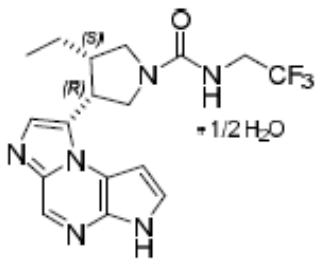


Figure 1. Structure of upadacitinib

The structure of the active substance was elucidated by a combination of elemental analysis, mass spectrometry (MS), infrared spectroscopy (IR), 1D and 2D ^{1}H- and ^{13}C- nuclear magnetic resonance spectroscopy (NMR) and X-ray crystallography.

Upadacitinib appears as a white to light brown non-hygroscopic crystalline powder. It is freely soluble in water and ethanol. Its partition coefficient (LogP) was determined to be 2.5 and two pKa values were determined to be pKa1: 4.7 (nitrogen of the imidazole) and pKa2: 12.8 (amide nitrogen).

Upadacitinib has two chiral centers and is manufactured as a single stereoisomer. Enantiomeric purity is achieved through chiral controls in the manufacturing process and is considered acceptable.

Upadacitinib exhibits polymorphism. Screening studies identified two forms relevant to the manufacturing process of upadacitinib; the hemihydrate form is manufactured by the commercial process. XRPD diffraction patterns, have been provided.

Based on the information provided by the applicant, upadacitinib is considered to be a New Active Substance (NAS).

Manufacture, characterisation and process controls

The synthesis of upadacitinib comprises six stages and three defined starting materials. The intermediates have been defined. Sufficient information regarding the starting material synthesis and relevant impurities has been provided for all of them and all three are considered acceptable and are controlled by suitable specifications as requested by the CHMP.

The manufacturing process is well described in the dossier and details of in-process controls and proven acceptable ranges (PARs) are listed for each manufacturing step. The critical process parameters (CPPs) and in-process controls (IPCs) are also indicated.

For all isolated intermediates acceptable specifications were provided. Structures for specified and known, unspecified impurities were presented in the dossier. Intermediates from different batches may be combined and used in subsequent steps. No recovered materials or solvents are used in the process.

Critical steps of the synthesis have been described and sufficient in process controls are applied. The parameters controlling the reaction parameters are presented as set-points or ranges and were established by DoE. However, no design spaces are claimed. The manufacturing process and the control strategy is described in sufficient detail. Reprocessing would only be undertaken if it can be ensured that the reprocessed material would meet the approved specification. In the event of reprocessing, the process and sequence of the steps would be repeated as described above.

The manufacturing process has evolved during the process development. The change of crystallization method has been sufficiently investigated and discussed. The different processes produced active substance batches that were of comparable quality.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. A thorough discussion of the source, formation and control of impurities, including impurities in the regulatory starting materials, impurities generated during the manufacturing process (side-products, reagent residues, etc.) and intentionally added catalysts and solvents was presented. No Class I solvents are used during the manufacturing process; however,

benzene may be present as an impurity in some solvents used in the manufacturing process. The control of benzene is acceptable.

Stereoisomerism is sufficiently controlled during the synthesis and a test for chiral purity in the commercial upadacitinib active substance specification is not considered required to control the quality of upadacitinib.

Upadacitinib active substance is packaged in double low-density polyethylene (LDPE) bags sealed with nylon cable ties. The inner plastic bag material meets EU Regulation No. 2002/72/EC and subsequent amendments as well as EU Pharmacopoeial requirements. Acceptable specifications for the materials were presented.

Specification

The active substance specification includes appropriate tests and limits for description (visual), clarity and colour of solution (Ph. Eur.), identification (IR and HPLC), chiral identification (chiral HPLC), crystal form (XRPD), assay (HPLC), residual solvents (GC), impurities (HPLC; 4 methods), mutagenic impurities (HPLC-MS), sulfated ash (Ph. Eur.), elemental impurities (ICP-OES), water content (Ph. Eur.), particle size distribution (laser diffraction) and microbiological quality (TAMC and TYMC - Ph. Eur.).

Mutagenic impurities are acceptably controlled according to ICH M7. Upon request of the CHMP, the applicant adjusted the limits for all specified impurities according to ICH Q3A. The limit for individual unspecified impurities is also set in line with ICH Q3A. ICH Q3C limits are applied for residual solvents.

For mutagenic impurities, the acceptable intake is 1.5 µg/day, considering possible treatment periods longer than 10 years. Based on a 60 mg/day maximum dose of upadacitinib, the 1.5 µg/day limit corresponds to 25 ppm for each mutagenic or potentially mutagenic impurity. The active substance specification limit for mutagenic impurities is 20 ppm.

Upadacitinib batches from the proposed process were tested for Class 1 and Class 2A elemental impurities identified in ICH Q3D Guideline. Based on the results, a test for Class 1 and 2A elemental impurities in the commercial active substance specification is not required to control the quality of upadacitinib. The only specified elemental impurity, is acceptably controlled according to ICH Q3D.

As shown by batch data and based on synthesis considerations, a test for chiral purity in the commercial upadacitinib active substance specification is not considered necessary.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch data from 28 batches of varying size, including commercial scale batches, used for clinical studies and in the stability program, was presented. The batches were manufacture by the commercial method or the second most recent manufacturing method. The batches were tested according to the current specification at the time of their manufacture. Although different analytical methods have been used, the presented results show little variation. The batch data provided is considered to be sufficient. Consistency and uniformity of the active substance quality have been demonstrated.

Stability

Stability data on six production scale batches of active substance stored in the intended commercial packaging for up to 12 months under long term conditions 30 °C / 75 % RH, and for up to 6 months under accelerated conditions 40 °C / 75 % RH was provided. Additional stability data from three

further commercial batches manufactured at the development site stored for up to 9 months under long-term conditions 30 °C / 75 % RH and 6 months under accelerated conditions 40 °C / 75 % was also provided. The stability conditions were according to the ICH guidelines except for the relative humidity during long-term studies, which was set at 75 % instead of 65 %. The first six stability batches (primary) were manufactured with the proposed synthesis but with slightly different crystallization parameters; the additional three stability batches were manufactured with the proposed route with optimized crystallization. The stability batches were packaged in the commercial primary packaging.

The following parameters were evaluated: description, crystal form, assay, impurities, water content and microbiological quality (TAMC and TYMC). The methods were the same as for release. The reported results show no trends, only minor fluctuations, and remain essentially unchanged over the studied time points currently available (long-term and accelerated, respectively). The results from long-term and accelerated studies are similar. However, for one batch a decreasing assay value has been reported during accelerated conditions, but the lower value was still within the assay specification limits at the time.

A photostability study was conducted according to ICH Q1B on three commercial scale batches. No significant degradation was observed; the results support the conclusion that the active substance does not need protection from light.

Stress testing was performed on samples in solid state and in solution that were subjected to stressed conditions (UV light, oxidation, acid, base, heat and humidity). No significant degradation was observed in forced degradation studies and primarily occurred in samples exposed to acidic, basic or oxidation conditions. The analytical methods were shown to be stability indicating.

Based on the provided data, the proposed retest period of 24 months, with storage in the proposed commercial container closure system at or below 30 °C, is accepted.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as an oblong, biconvex film-coated prolonged-release tablet containing 15 mg of upadacitinib. The tablet has a purple colour and the dimensions are 14.0 mm x 8.0 mm. The tablet debossed "a15" on one side.

A systematic quality risk based approach has been followed during development. The quality target product profile (QTPP) has been defined and relating critical quality parameters (CQAs) were presented.

Considering the potential CQAs, risk assessments were performed to evaluate the impact on CQAs of risk factors related to formulation, process and packaging. The risk assessment was revisited after completion of development. Potential risks have been identified, assessed and actions have been taken, where needed, to reduce the risks to an acceptable level. The proposed control strategy is considered satisfactory. The CQA identified for upadacitinib tablets were: identity, purity, assay, uniformity of dosage units, degradation products, dissolution, microbiological quality, water content, appearance.

Upadacitinib is classified as highly soluble substance according to BCS. The choice of the crystalline free base hemihydrate form for development has been justified. All the excipients used are common in tablet formulations as well as the film-coating agents. The excipients including those of the film-coating agent are of compendial quality. The function of each excipient was discussed and justified.

The development of three strengths is described (7.5, 15 and 30 mg), but only the 15 mg strength is intended for marketing.

In PhI and PhII clinical trials, immediate release capsule formulations with an upadacitinib salt were used. For PhIII, a prolonged release tablet based on the earlier capsule formulations was targeted to allow for once daily dosing. One of the formulations evaluated was selected on the basis of its PK profile for further development of the PhIII 7.5, 15 mg and 30 mg tablet formulations. HPMC level in the final formulation was defined so that it enables comparable exposure to the IR capsules used in PhI/PhII clinical studies. Several changes were done to the PhIII product in the establishment of the proposed commercial formulation and these were clearly presented and justified. The pivotal bioequivalence study (Study M15-878) has been conducted to evaluate the bioavailability of the commercial formulation compared to the formulation used in Phase 3 studies. The tested formulations were found bioequivalent.

Discoloration (mottling) of the tablet surface has been observed over storage but this is not due to the active substance as the same occurs to placebo tablets stored under similar conditions to the active containing tablets. Except for a change in appearance, the stability of the drug product is unaffected by the appearance of mottling. Water content limits of the tablets are specified to minimize the occurrence of mottling. Protection from water was found to prevent mottling of the final product. Desiccant is incorporated in all bottle packaging. To limit water uptake in blisters, a more water-protective grade of blister material has been utilized.

Dissolution method development and IVIVC
The development of the proposed dissolution method intended for quality control (QC) has been sufficiently described. The proposed method is basket apparatus, 100rpm, 900 ml 0.05M sodium phosphate, pH 6.8.

The sensitivity of dissolution method with regard to changes in the properties of HPMC was assessed using different lots of HPMC in the extragranular portion of the tablet. Particle size, viscosity and substitution percentage of hydroxypropoxy groups and methoxy groups were also investigated.

A level A *in vitro-in vivo correlation* (IVIVC) was successfully developed for the product on the 30 mg strength. Four formulations were tested to investigate the relationship between *in vitro* dissolution and the corresponding *in vivo* performance. The formulation had similar compositions except for the proportion of the rate controlling polymer (HPMC) and the mannitol content used to compensate for the difference in HPMC amount. A non-linear model was developed based on the QC dissolution method. The discriminating power of the dissolution method is considered to be shown by the successful establishment of a level A IVIVC. Therefore, no additional studies were performed to further demonstrate discriminating power of the method against either formulation or manufacturing parameters. With the establishment of the IVIVC, the dissolution test has been demonstrated to be predictive of *in vivo* performance (clinically relevant) and during development it has been used to assess drug product performance when changes are made to material attributes and manufacturing process parameters.
The IVIVC model showed acceptable predictability of the plasma concentration-time curves. Furthermore, internal and external validation resulted in prediction errors within the acceptance criteria defined in the EMA guideline. It can be concluded that the proposed dissolution method is suitable for use as part of the overall analytical testing for assessing the quality of the drug product, is predictive of in vivo performance, is clinically relevant and can be used as a surrogate for bioavailability in obtaining bioavailability/ bioequivalence waivers.

The IVIVC established for the 30 mg strength it has been shown to be applicable also to the 15 mg product and therefore applicable for evaluation of future changes to the product. Thus, it would be

possible to use dissolution data to establish bioequivalence of formulations provided that the change results in a product dissolution profile within the studied range and does not involve any modifications of the parameters governing the release mechanism of the product – i.e. the diffusion/erosion.

Effect of alcohol on product performance
The risk of dose dumping due to the presence of alcohol was assessed. Drug release was slowed down by the presence of alcohol and based on this dose dumping from consumption of alcohol by the patient is not expected.

Manufacturing process development
The manufacturing process changes from PhIII clinical trial material to the proposed commercial process has been presented. The commercial scale manufacturing process was developed in laboratory and pilot scale at a development site whilst the commercial development was concluded at the proposed site. Bioequivalence between the PhIII and commercial tablets has however been demonstrated. Changes in the process between the manufacture of stability batches and commercialization have been discussed and the stability batches are considered to be representative.

Process operating ranges for selected parameters were presented and their establishment discussed. QbD principles have been applied and both OVAT and DoE methodologies used. The process is operated with PARs for milling, blending and tableting unit operations and with design spaces for granulation and film-coating. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces.

The product is packaged either in HDPE bottles with desiccant, induction sealed and child resistant propylene cap, or in polyvinyl chloride/ polyethylene/ polychlorotrifluoroethene polymer blisters with push through aluminium foil. Specifications were provided for all packaging materials and compliance with relevant EU legislation has been confirmed for the blister packaging materials and the bottle pack. It has also been confirmed that the bottle with child resistant closure complies with ISO8317.

Manufacture of the product and process controls

The manufacturing process consists of six unit operations: granulation, milling, blending, tableting, coating and packaging. The process concerns a modified release formulation but it has been accepted as a standard process based on the experience of the proposed manufacturing site with similar products and processes, as per the Process Validation guideline.

Critical steps have been appropriately identified. The in-process controls and their applied limits are specified and adequately explained. Design spaces have been proposed for the granulation and coating steps of the manufacturing process of the medicinal product. The design spaces have been developed at commercial scale and are accepted.

The overall control strategy for Rinvoq tablets is considered satisfactory and ensures sufficient control of the process which is expected to produce tablets with consistent quality.

Process hold times have been established for the milled granulate, final blend, uncoated and coated tablets based on relevant stability studies. The packaging materials have been described. Additionally, a 1-year bulk hold time is proposed. The applicant has confirmed that the hold times are included in the product shelf life in line with 'Note for Guidance on Start of Shelf-Life of the Finished Dosage Form' (CPMP/QWP/072/96) and this is accepted.

With regard to process validation, it has been argued and accepted that, based on previous experience with similar products, the gained knowledge of the specific product during development and the

manufacturing site previous experience with the specific process, the process validation can be completed before commercialisation. An acceptable protocol has been presented.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), identification (UV, HPLC), assay (HPLC), degradation products (HPLC), water content (Ph. Eur.), dissolution (Ph. Eur.) and Uniformity of Dosage (Ph. Eur.).

The specifications are in accordance with ICH Q6A. The acceptance criteria are set based on a combination of batch data, clinical experience, manufacturing and analytical aspects, knowledge gained during development and regulatory guidelines. The justifications provided are acceptable. Limits for degradation products are in line with ICH Q3B and thus no further qualification in non-clinical/clinical studies is warranted.

The risk assessment for elemental impurities based on ICH Q3D option 2b and a maximum daily dose of one tablet shows that the estimated maximum daily exposure levels of all potential elemental impurities were less than the ICH Q3D control threshold level (30% of the PDE). The risk assessment is supported by batch data from twelve representative production scale batches of upadacitinib tablets. It is therefore accepted that no controls of elemental impurities are needed in the finished product specification.

Microbial limits, residual solvents and mutagenic impurities are not included in the finished product specification. These quality attributes will instead be ensured through upstream controls. Also based on the presented development data, control of polymorphic form in the finished product specification is not needed.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data of 5 commercial scale batches of 15 mg tablets manufactured at the proposed commercial manufacturing site have been provided. Supportive data from13 smaller scale batches were also presented. Based on the batch analysis data the finished product meets the proposed specifications and therefore indicate consistent manufacture of the finished product.

Stability of the product

Stability data on three commercial scale batches of Rinvoq tablets 15 mg stored in the proposed blisters and bottles packaging for up to 18 months under long-term conditions at 30 °C ± 2 °C / 75% ± 5% RH and at 25 °C ± 2 °C / 60% ± 5% RH and under accelerated conditions 40 °C ± 2 °C / 75% ± 5% RH for six months has been presented according to ICH guideline.
Supportive stability data from three batches of each strength (7.5 mg, 15 mg and 30 mg) manufactured at least at one-fourth the commercial scale at the development facility were also presented and these are regarded representative of the commercial process. These batches were stored both in blisters and bottles for up to 24 months under long-term conditions at 30 °C ± 2 °C / 75% ± 5% RH and at 25 °C ± 2 °C / 60% ± 5% RH and for six months under accelerated conditions 40 °C ± 2 °C / 75% ± 5% RH according to ICH guideline.
Storage at 30°C/75% RH is considered as worst case compared to ICH 25°C/60% RH or 30°C/65% RH. Samples have been tested against the product specification. No significant changes in any of the quality attributes monitored were seen after storage at either long term or accelerated conditions. Some out of specifications results have been satisfactorily investigated and the root cause has been

identified. It is not considered that any concern remains about the stability of the product in relation to these observations. The analytical methods adequately support the product specifications.

It has been shown that the change in appearance does not occur under the proposed storage conditions and does not affect any other product quality attributes.

Photostability
The ICH photostability studies as per ICH Q1B were performed for 3 commercial scale batches of each tablet strength. The samples were tested for description, degradation products, assay, water content, and dissolution. No meaningful change was observed for tablets exposed without the primary packaging. The product does not need protection from light.

In-use stability
In-use stability was performed for the bottle pack using commercial bottles and caps. One study was performed on the commercial scale batches. A second study was performed with supportive batches. The samples were tested for description, degradation products, assay, water content, and dissolution. Periodic testing of microbiological quality (TAMC and TYMC) was also performed. Water content increased in the study where the desiccant had been removed. With no desiccant present, a known degradation product was formed. The increase in water content (with desiccant present) did not impact stability, quality or performance of the tablets as measured by the other tested attributes and a one month in-use shelf life is therefore supported.

Forced degradation studies
Forced degradation studies were performed on the 7.5 and 30 mg tablet. Samples were exposed to heat, heat/humidity, light, hydrolysis (acid and base) and oxidation.
Some cases of mass balance discrepancies in the results were satisfactorily explained. A greater impact on overall mass balance is seen for the lower strength tablet due to a more extensive degradation. No significant degradation was observed under light. Upon exposure to oxidative, acid and base conditions, the total impurities were slightly increased. Degradation was more prominent for heat and heat/humidity stress conditions. The major degradant under heat, heat/humidity, acid and base stress conditions were found to be two known impurities. The methods were shown to be stability indicating

Temperature cycling
One batch per strength per package type was exposed to temperature cycling experiments comprising 5 cycles shifting between -20 °C and 50 °C followed by storage for 6 months at 30 °C / 75% RH. Testing included description, degradation products, assay, water content and dissolution. No meaningful changes were observed during the temperature cycling period. After the additional 6 months storage, the 7.5 mg strength product packaged in blisters showed some degradation which was not observed in the other product strengths. Based on the stability data, temperature cycling of -20°C for 15 days, and 50°C for 15 days is not cause of concern for the quality for upadacitinib tablets stored in film blisters and bottles with desiccant.

Based on the data presented, the proposed shelf-life of 2 years and without any special temperature storage conditions and "Store in an original package" in order to protect from moisture, is acceptable (SmPC sections 6.3 and 6.4).

Adventitious agents

No excipient or materials of animal or human origin are used. Magnesium stearate are derived from vegetable source.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. Design spaces have been proposed for two steps in the manufacture of the finished product. The design spaces have been adequately verified.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

The pivotal toxicology and safety pharmacology studies were conducted in accordance with GLP regulations and ICH guidelines.

CHMP scientific advice have been given to the nonclinical development of upadacitinib (see Section 1). The given advices have been in general followed.

2.3.2. Pharmacology

Mechanism of action

In rheumatoid arthritis the pathogenic role of inflammatory cytokines is well known. The JAK family is composed of 4 family members: JAK1, JAK2, JAK3, and Tyrosine kinase 2 (TYK2). These cytoplasmic tyrosine kinases are associated with membrane cytokine receptors to mediate signalling downstream of multiple cytokines and growth factors. Activation of JAK pathways initiates expression of survival factors and enhances production of additional cytokines, chemokines, and other molecules that facilitate leukocyte cellular trafficking and cell proliferation, all of which contribute to the pathogenesis of multiple inflammatory and autoimmune disorders. Hence, inhibitors of JAK are of interest for the treatment rheumatoid arthritis (RA) as well as for the treatment of other immune-mediated inflammatory disorders.

Primary pharmacodynamic studies

Primary pharmacodynamics in vitro

The potency of upadacitinib on recombinant JAK family kinase domains was determined in isolated human enzyme complexes using biochemical assays *in vitro* with adenosine-5′-triphosphate (ATP) as a competitive inhibitor (0.1 mM ATP). The results indicated that upadacitinib is a reversible ATP competitive inhibitor and upadacitinib inhibited JAK1 and JAK2 with IC50 of 0.043 µM and 0.12 µM,

while exhibiting less potent activity against JAK3 (IC50 = 2.3 μM) and TYK2 (IC50 =4.7 μM) complexes, respectively. Thus, the potency of upadacitinib on JAK1 and JAK2 at the enzyme level was relatively similar. Both JAK1 and JAK2 could therefore potentially be targeted at clinical exposure level (Cmax = 105 nM).

Effects and cellular potency of upadacitinib on JAK inhibition was investigated in three different human cell lines. In human T-blast cells, upadacitinib inhibited IL-2 induced phosphorylation of STAT5 (JAK1/3 dependent readout) with EC50 of 13 nM. Moreover, upadacitinib inhibited IL-6 induced phosphorylation of STAT3 (JAK1/JAK2 dependent readout) in human erythroleukaemia TF-1 cells with an EC50 value of 9 nM. To evaluate the effects of upadacitinib on JAK2 inhibition in a cellular context, inhibition of EPO-induced phosphorylation of STAT5 in the human EPO dependent megakaryoblastic leukemic UT-7 cells was studied. Upadacitinib inhibited EPO induced phosphorylation STAT5 with an EC50 of 628 nM.

Primary pharmacodynamics in vivo

Potency of upadacitinib *in vivo* was evaluated in acute concanavalin A (Con A) induced IFNγ in male Lewis rats, which is considered a JAK1 dependent mechanism by the applicant. However, it's noted that Con A-induced IFNγ release may also trigger activation of JAK2 dependent mechanisms. Single oral administration of upadacitinib (0.1-10 mg/kg, 30 min prior to Con A; 10 mg/kg, IV) was shown to dose-dependently inhibit the release of IFNγ in rat plasma with an ED50 and ED80 of 0.4 mg/kg and 5.8 mg/kg, respectively. The efficacy of upadacitinib to reduce inflammation was assessed in an adjuvant-induced arthritis (AIA) model in female Lewis rats in vivo. Oral doses of upadacitinib (0.1 to 10 mg/kg twice daily for 10 days) resulted in a dose and exposure-dependent reduction in paw swelling and bone erosion at an efficacious total plasma concentration of 85 ng•hr/mL ($AUC_{0\text{-}12hr}$), which is approximately 5-fold lower compared to the clinical steady state exposure of 420 ng*h/ml ($AUC_{0\text{-}24hr}$) in RA patients. In conclusion, the in vivo results demonstrate that oral dosing of upadacitinib is able to inhibit an inflammatory phenotype after induction of experimental arthritis in rats.

To evaluate the *in vivo* selectivity of upadacitinib, the level of JAK inhibition in rat whole blood samples ex vivo was investigated following IL-7 stimulation of STAT5 phosphorylation. In female rats, orally dosed upadacitinib (1-100 mg/kg, PO) inhibited IL-7 induced pSTAT5, a JAK1 and JAK 3 mechanistic endpoint, with an IC50 value of about 20 nM. Furthermore, the ability of repeated oral dosing of upadacitinib (0.3-30 mg/kg, PO, BID for two weeks) to inhibit circulating NK cells numbers, due to inhibition of JAK3 activity, was studied in Spraque Dawley rats. Orally dosed upadacitinib for two weeks reduced circulating NK cells numbers, a PD biomarker for JAK3 inhibition, by 50 % with an $AUC_{0\text{-}12hr}$ of 520 ng•hr/mL. Taken together, the presented data indicate that, at clinically relevant exposure, upadacitinib is an inhibitor of JAK1 and JAK3 dependent signalling *in vivo*. Functional selectivity of upadacitinib over TyK2 was not evaluated in an in vivo setting. Although upadacitinib was designed to selectively inhibit JAK1 activity, while minimizing effects on JAK2 and JAK3, its selectivity profile for the JAK family is questionable. At the enzyme level the potency of upadacitinib on JAK1 and JAK2 was relatively similar and upadacitinib was able to inhibit JAK3 dependent activity at clinically relevant exposure. In addition, similar to findings reported for other non-selective JAK inhibitors, the results from the toxicity studies, including effects on the hematologic system (decreased lymphocytes and RBC mass) at concentration at or slightly above clinical exposure, indicate a broad JAK inhibitory effect of upadacitinib.

Secondary pharmacodynamics

Binding selectivity of upadacitinib against a panel of over 70 human protein kinases was investigated in a broad kinome selectivity screen. Of the kinases in the panel, six non-JAK kinases showed an IC_{50}

below 5 µM, and two non-JAK kinases had IC_{50}s equal to or below 1 µM (Rock1 at 1 µM and Rock2 at 0.42 µM). Thus, upadacitinib appears to be selective against a number of different non-JAK kinases and upadacitinib seems unlikely to interact with the tested kinases at clinically relevant exposures (C_{max} =105 nM).

Upadacitinib was profiled for its off-target activity against a broad panel of 79 different receptors, ion channels, enzymes and transporters. Upadacitinib (10 µM) did not affect control specific binding by greater than 50% at any of the different receptors, ion channels or transporters tested. The results indicate a low risk for off target activity with upadacitinib at therapeutic plasma concentrations (clinical C_{max} = 105 nM).

Safety pharmacology

Upadacitinib was assessed in a series of GLP compliant safety pharmacology studies *in vitro* and *in vivo*. The CNS/neurobehavioral safety profile was evaluated in rats. In a Functional Observational Battery (FOB) assay in female rats, upadacitinib (10, 50, 100 mg/kg, PO) did not induce any neurobehavioral effects at the oral doses of 10 mg/kg (C_{max} = 0.47 µg/mL) and 50 mg/kg (Cmax = 5.2 µg/mL, yielding an exposure margin of 126-fold above clinical C_{max}. At the highest dose of 100 mg/kg (Cmax = 13.5 µg/mL), upadacitinib produced a significant decrease in locomotor activity.

The respiratory effects of upadacitinib were investigated in the rat using whole body plethysmography. After a single oral gavage administration of upadacitinib (10, 50, 100 mg/kg, PO) in male rats, there was no effect on respiratory rate, tidal volume or minute volume through 100 mg/kg (C_{max} = 3.9 µg/mL, providing an exposure margin of 95-fold above clinical C_{max} (41 ng/mL).

In the hERG assay, upadacitinib was evaluated in stably transfected HEK293 cells at concentrations of 6.7, 20 and 60 µg/mL, which produced concentration-dependent inhibition of hERG tail current from 15 to 59%. The IC_{50} for hERG blockade was 39.5 µg/mL, which is several hundred-fold above clinical plasma concentrations.

In vivo cardiac safety pharmacology (telemetry) studies were performed in conscious dogs. Oral dosing of upadacitinib (0.5, 1.5 and 5 mg/kg, PO) had no effects on electrophysiological parameters (heart rate, PR, QRS and QTc intervals) or mean arterial blood pressure at 0.5 mg/kg (NOAEL, Cmax = 0.09 µg/mL; exposure margins of 2-fold above clinical C_{max}). At higher doses of 1.5 mg/kg (Cmax = 0.42 µg/mL) and 5 mg/kg, upadacitinib dose-dependently decreased mean arterial blood pressure (~15% and ~19%, respectively). At the highest dose of 5 mg/kg (Cmax = 1.3 µg/mL), upadacitinib increased heart rate by ~30%. In addition, in a non-GLP compliant cardiac safety pharmacology study in the anesthetized dog, intravenous infusion of upadacitinib (0.06, 0.19 and 0.58 mg/kg, IV) for 30 minutes produced no cardiovascular effects through 0.25 µg/mL (exposure margins of 6-fold above clinical C_{max}). At a higher plasma concentration of 0.64 µg/mL, upadacitinib reduced systemic vascular resistance (13%) and increased heart rate (14 beats per minute).

Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies were performed with upadacitinib. This is considered acceptable by CHMP.

2.3.3. Pharmacokinetics

Methods of analysis

Upadacitinib was quantified by a common salt-assisted liquid-liquid extraction technique prior to high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) analysis of plasma samples of mouse, rat, rabbit, and dog from GLP compliant toxicity studies. Metabolites in plasma, urine, feces, bile, hepatocyte and liver microsomes and hepatocytes from mouse, rat and dog ADME studies were separated by HPLC and identified and structurally elucidated by MS/MS. Radiometric methods used to measure [^{14}C]upadacitinib-derived radioactivity in samples from *in vivo* studies (bile, urine, feces and plasma) and from in vitro studies (liver microsomes and hepatocyte incubations) were fit for the purpose.

The validations of the bioanalytical methods used for quantification of upadacitinib in pivotal toxicity studies appear not to have been performed according to GLP. At the CHMP's request, the applicant clarified that the bioanalytical method validation was, in general, conducted in accordance with regulatory guidelines for bioanalytical method and appeared to have followed GLP standards with exception for a signed GLP compliant statements and some limitations in QA inspections regarding the validation process. However, the QA unit reviewed all aspects of the implementation of the analytical methods used in the toxicology studies. Thus, the deviations are not considered by the CHMP to have impact on the results in the pivotal GLP toxicity studies.

Absorption

The single dose pharmacokinetics of upadacitinib were characterised in mouse, rats, dogs and cynomolgus monkeys following IV or oral dosing. Upadacitinib was rapidly absorbed after a single oral dose, with mean T_{max} in plasma ranging from 1 to 2 h in rats, dogs and monkeys, which is similar to T_{max} in humans (mean of 1.2 h). Mean oral bioavailability was moderate in rat (30.5%) and higher in monkey (59.3%) and in dog (76.8%). Oral bioavailability was not reported in humans.

The plasma clearance following single intravenous administration were high in rat (CL 2.0 L/hr•kg), but lower in monkey (1.2 L/hr•kg) and dog (0.66 L/hr•kg). The mean plasma elimination half-lives ranged from 1.3 hours in monkey to ~3 hours in rat and dog following single oral dosing of upadacitinib. Volumes of distribution (Vss) were high in all species (1.6-2.6 L/kg).

Following repeated daily oral dosing in mice, rats, rabbits and dogs the exposures (AUC) were not different from that measured on Day 1 in all species. There were no significant sex differences in upadacitinib exposures in mice and dogs, but in rats, AUC values in females were consistently higher than in males. In all species, the upadacitinib exposure (C_{max} and AUC value) were greater than proportional to the administered oral doses. The observed nonlinearity in non-clinical species was hypothesized by the applicant to be dose related mechanisms of absorption.

Distribution

The tissue distribution of total radioactivity in pigmented rats following single oral administration of [^{14}C]upadacitinib was evaluated by quantitative whole-body autoradiography (QWBA).

Upadacitinib derived radioactivity was widely and rapidly distributed to most tissues with highest tissue concentrations between 0.5- and 4-hours postdose. Liver, uveal tract and adrenal gland contained some of the highest concentrations of radioactivity observed. The elimination of radioactivity from most tissues was complete by 24 hours postdose, with exceptions for the arterial wall, cecum, uveal tract, eye, intervertebral discs, kidney, large intestine, liver and pigmented skin having measurable levels of radioactivity between 48 and 168 hours postdose. Radioactivity concentrations were below measurable levels in the CNS tissues and the lens of the eye at all collection times throughout the study. Radioactivity was present in the uveal tract through 192 hours postdose and a slower clearance in pigmented skin indicating an apparent affinity for melanin.

Plasma protein binding of upadacitinib was low in all species and independent of concentration from 0.1 to 100 µM, as determined by equilibrium dialysis. The mean unbound fraction (fu) at 1 µM was 0.28, 0.41, 0.69, 0.47 and 0.48 in mouse, rat, dog, monkey and human, respectively.

Upadacitinib partitioning into red blood cells was slightly higher in rat, dog and monkey (blood to plasma ratios 1.28, 1.18 and 1.31, respectively), with no preferential distribution in mouse and human (blood to plasma ratios of 0.99 and 1.00, respectively).

In pregnant rats, upadacitinib was transferred through the placenta of pregnant rats with measurable concentrations observed in foetal blood and liver through 4 hours following oral dosing. Concentrations in foetal blood were 1 to 10% of the concentration in maternal blood up to 4 hours post-dose and then above the maternal blood concentration up to the last sampling at 72 hours post-dose.

In lactating rats upadacitinib was excreted in milk with measurable concentrations of radioactivity observed in milk through the 24-hour time point with a half-life of 2.8 hours. The concentration of upadacitinib-derived radioactivity in milk was approximately 31 times higher than in plasma.

Metabolism

The *in vitro* metabolism of upadacitinib was evaluated in liver microsomes and hepatocytes of mouse, rat, dog, monkey and human and *in vivo* in rat, dog and human, respectively.

In vitro

The metabolic stability of upadacitinib was evaluated in hepatocytes across species at a single 1 µM concentration. The scaled intrinsic clearance of upadacitinib was 25.6, 4.07, 0.413, 0.415 and 0.366 L/h/kg in mouse, rat, monkey, dog and human hepatocytes, respectively. Metabolite enzyme phenotyping in vitro using incubations with a panel of recombinant human cytochrome P450 enzymes (CYPs) and flavin monooxygenases (FMOs) showed that upadacitinib (2 µM) was metabolized by CYP3A4, and to a lesser extent by CYP2D6 and CYP3A5.

Whereas the metabolism of upadacitinib was thoroughly investigated in vitro in microsomes hepatocytes of mouse, rat, dog, monkey and human and *in vivo* in rat, dog and human, there are no metabolism data in rabbit. As rabbit is used for the embryo-foetal developmental (EFD) studies the applicant was asked by CHMP to justify why such data have not been presented. The applicant has provided results on the metabolism of upadacitinib in rabbit liver microsomes. In line with the in vitro data obtained in other non-clinical species (rat and dog) as well as in humans, there was a low turnover of upadacitinib in rabbits and the oxidative rabbit metabolites M2, M6 and M10 (A-1745477) replicate those found in rat, dog and human. The applicant has not identified any new upadacitinib-related metabolites in rabbit liver microsomes as compared to the metabolites that had previously been identified in rat, dog or human. The justification was considered acceptable to the CHMP.

In vivo

Following a single oral dose in human of [^{14}C]upadacitinib (30 mg) unchanged compound was the major radiochemical component of drug-related material in plasma, representing 79.4% of total radioactivity. M4 and M11 were identified in plasma, representing 13.4% and 7.1% of total plasma radioactivity, respectively. The glucuronide metabolite M4 was characterized as a major metabolite in human plasma, whereas M11 was a minor human metabolite. No further evaluation is warranted for the metabolite M4 since the M4 metabolite is a Phase II conjugate which is not a chemically reactive acyl glucuronide.

Following oral dosing in rats of [^{14}C]upadacitinib (3 mg/kg, PO), 56.3% of the dose was recovered as parent (18.5% in bile, 8.9% in urine, 7.5% in cage wash, 21.4% in feces), while 37.4% of the dose was excreted as metabolites. These data suggest that both metabolism and excretion of parent drug contribute equally to the elimination of upadacitinib.

In male beagle dogs, parent drug was the major radiochemical component in plasma (87.7%) following a single 5 mg/kg oral dose of [^{14}C]upadacitinib.

Upadacitinib was metabolized primarily by CYP3A4, and to a lesser extent by CYP2D6 and CYP3A5. Parent drug was major component in plasma (82.8%) in lactating rats, with low concentrations of M1, M2, M11 and M22.

Excretion

Majority of upadacitinib is excreted as intact in the all species (61% in rats, 56% in dogs). Mass balance data were obtained from rats, dogs and humans. Overall, the results indicate that elimination pathways for upadacitinib in non-clinical species and humans (for details see Clinical Pharmacokinetics) are similar; the majority of absorbed drug-related radioactivity being eliminated by excretion into biliary/fecal or renal routes whereas hepatic metabolism plays a secondary role. In bile cannulated rats, 49.7% of an intravenous dose was recovered in the bile, with 23.7% of the dose recovered in the urine. In dog, drug related radioactivity was eliminated in feces (54.6%) and urine (46.9%). In the human radiolabeled mass balance study which administered the immediate release solution formulation, a mean of 53.4% of the dose was recovered in feces and 42.6% was recovered in urine.

Pharmacokinetic drug interactions

Please refer to Section 2.4.2.

2.3.4. Toxicology

Relevance of animal models

The Sprague Dawley rat and Beagle dog were selected as the main rodent and non-rodent species in the general toxicity studies. The Sprague Dawley rat and Tg(HRAS) mouse were selected for the carcinogenicity studies. The reproductive and developmental toxicity studies were conducted in Sprague Dawley rat and New Zealand White rabbit.

The selection was based on the systemic exposure in rats and dogs which was much higher than in other investigated species. As discussed in the pharmacokinetics section, these species were shown to have similar elimination pathways and metabolic profiles of upadacitinib as in humans and are thus considered adequate for safety evaluation of upadacitinib. There are however no metabolism data presented in the rabbit, which is used in a pivotal EFD study. See further discussion in the pharmacokinetic section.

Repeat-dose toxicity

Upadacitinib was evaluated in repeat-dose toxicity studies in mice (4 weeks with no recovery), rats (4 weeks with 4 weeks recovery, and 26 weeks with no recovery), and dogs (4 weeks with 4 weeks recovery, and 39 weeks with no recovery).

The main organs affected in the repeat-dose toxicity studies were primarily those related to JAK inhibition, that is the haematopoietic and immune system.

Morbidity and mortality

Upadacitinib was not tolerated in mice and rats at high doses. In a non-pivotal study in mice several animals were found dead 3-5 hours after administered a dose of 70 or 100 mg/kg. In the 1-month pivotal repeat dose study in rats, all animals in the high dose group (200 mg/kg) were either found dead or euthanized in moribund condition on day 1-3 of the study. Also 5 males in the 100 mg/kg group were euthanized. The animals were observed with reduced activity, weakness, low skin turgor, moderately laboured breathing, and loss of righting reflex. Microscopic evaluation revealed findings in liver, spleen, thymus and kidney. The measured Cmax in the remaining male and female animals in the 100 mg/kg group was 5.72 and 14.9 µg/mL, and the AUC_{0-24} 40.8 and 63.8 µg*hr/mL. This corresponds to at least 140 times the maximum concentration measured in patients (41 ng/mL) and 97 times the exposure based on AUC (420 ng*h/mL). The mortalities can thus be considered of limited clinical relevance although the observed microscopic findings were also observed in lower dose groups, but of a lesser magnitude.

Body weight and food consumption

Administration of upadacitinib was associated with decreased body weight in rats (20 mg/kg/day) at x9 times the systemic exposure compared to exposure in patients. In the carcinogenicity study in rats, body weight decrease was observed also at lower doses.

No effects on body weight or food consumption were observed in the studies in dogs.

Immune system

In all the repeat-dose toxicity studies effects consistent with the inhibition of JAK1/3 were observed. The findings included decreases in circulating lymphocytes and lymphoid depletion in spleen, thymus, and lymph nodes.

After 4 weeks of daily administration in rats, lymphocyte levels had decreased by 70% compared to control values at the highest dose (approximately x100 times the exposure observed in patients), but also at a ten times lower dose (x3 times the clinical exposure) lymphocyte levels was 30-44% lower than in the control animals. In male animals at this dose, neutrophil levels were 20% lower than in controls. In the 6-month study, similar levels of reductions were observed in lymphocytes and eosinophils at approximately clinical relevant exposures. Lymphocyte levels were decreased also in the 1-month dog study (-37%) at systemic exposures corresponding to approximately x10 times the clinical exposure. In the 9-month study the high dose group (approximately x2 the clinical exposure) the white blood cell count was increased. This increase was mainly ascribed to increases in individual neutrophil counts which was consistent with findings of chronic swelling and inflammation correlated with infestation of mites (see below).

At doses from 5 mg/kg (clinical exposure) in rat the weight of the spleen and thymus was decreased. Decreased numbers of lymphocytes in spleen and thymus was observed from 5 mg/kg. Lymphoid depletion from the lymph nodes was observed from 20 mg/kg. These findings were observed at lower doses in male animals compared to female animals.

Altered immune function-secondary effects

In dogs, the main manifestation of immunosuppression was the occurrence of infections. In the 9-month study, demodicosis (Demodex infection) was confirmed in all animals in the high dose group (1.5 mg/kg, x2 clinical exposure). Demodex is a mite considered to be normal flora of the dog skin which is otherwise controlled by innate immune responses. Observations associated with demodicosis

consisted of paw swelling, mixed cell inflammation in the interdigital skin of the paws and in the draining lymph nodes, and an increase in neutrophil counts.

Haemapoietic system

Effects consistent with JAK2 inhibition such as decreases in RBC parameters [red blood cells, haemoglobin, and haematocrit] and reticulocytes were observed in rats and dogs.

In rats, reduced red blood cell parameters were observed at doses from 100 mg/kg (x97 the clinical exposure). In these animals, minimal to mild bone marrow hypocellularity was also observed. Decreased levels of haemoglobin and reticulocytes were observed in the 6-month study at administered doses of 20 and 50 mg/kg (x9 and x29 the clinical exposure).

Decreases in RBC mass was also observed in treated dogs, with greater decreases in male animals than in female.

Adrenal cortex

Vacuolation and/or atrophy of the adrenal cortex were observed in control female dogs and female dogs as well as a single male dog in the 9-month study. The applicant argues that this finding is secondary to stress related to chronic inflammation due to the mite infection observed in the dogs. This explanation is considered acceptable to CHMP.

Kidney

Increased levels of secreted protein and blood in the urine was observed in rats administered 10 mg/kg and above (x3 the clinical exposure). Microscopic evaluation of the kidney in the animals administered 100 mg/kg showed minimal to marked renal tubular epithelial degeneration/regeneration. In the animals exposed to upadacitinib for 6 months minimal to moderate tubular epithelial degeneration/regeneration was observed in the 50 mg/kg group. The observations were more prominent in male animals. There were no kidney related adverse observations in the dog studies.

Liver

In the rats administered 100 mg/kg that were euthanized preterm in morbid state, the microscopic evaluation of the liver showed moderate to marked multifocal, midzonal or diffuse necrosis in the liver. These animals had also an increase in alanine transaminase, aspartate transaminase, and alkaline phosphatase. In the remaining animals in the study administered lower doses, no other observations than an increase in bilirubin and urobilinogen in the urine indicative of hepatic impact by upadacitinib was observed. In the 6-months study in rat in which the animals were administered 50 mg/kg/day at a maximum, no findings related to liver toxicity was observed except variations in the plasma protein levels. There were no observed findings in the dog studies. In the carcinogenicity study in Tg(HRAS) mice, mild periportal hepatocellular single cell necrosis was observed in female mice at approximately 3 times the systemic exposure observed in patients.

Gastro intestinal tract

After 6-months of daily administration of upadacitinib in rats, in the animals in the high dose group (50 mg/kg) the histopathological examination revealed minimal to mild erosion and ulceration or the mucosa primarily at the limiting ridge of the non-glandular stomach with attendant subacute/chronic inflammation, edema and/or epithelial hyperplasia. In the same study it was observed that there was a

minimal to mild mucosal erosion of the tongue, and an inflammation in the submucosa extending to the mucosa in the mid and high dose animals (20 and 50 mg/kg/day, exposure margin x9 to what is observed in patients).

No findings were observed in the studies in dogs.

The rats were administered the test item by gavage in a solution, whereas the dogs were administered a capsule. It is thus possible that the tongue of the rat was directly exposed to the test item in high concentration. The observation of increased salivation in rats administered 50 (males only) and 100 mg/kg supports this possibility. No study of local tolerance has been performed.

The non-glandular stomach of rodents serves as a storage organ and is not present in humans. The clinical relevance of findings in the non-glandular stomach could thus be questioned although it is likely that the squamous mucosa lining the esophagus in species without a forestomach would react similar as the forestomach if the exposure would be equivalent. In the rodent, it is possible that the exposure time to the mucosa is prolonged due to residual upadacitinib in the forestomach. In the patients, upadacitinib is administered in tablets and it is therefore not likely that the mucosa of the human esophagus would be exposed for a prolonged time.

Toxicokinetics

Toxicokinetics of upadacitinib was characterized in all the pivotal repeat dose toxicity studies.

In mice, there was no overall significant difference in plasma exposures between male and female mice. Plasma exposure increased more than dose proportional with an increased dose.

In rats there was a significant difference in plasma concentrations of upadacitinib in male and female rats. Higher Cmax concentrations and AUC values were observed in female animals. In rats, there was a larger than dose proportional increase in exposure with increase in dose. This was more pronounced in the male animals. Also in male rats, toxic findings were more prominent, allowing higher doses of upadacitinib to be administered in female rats in both the carcinogenicity and fertility studies. The reason for this gender difference is not understood, in dogs however, there was no significant difference in exposure between genders. In dogs the exposures increased proportional with increased dose. In the dog studies, the administered doses were however lower. In the 6-month repeat dose toxicity study in rat, the animals tolerated exposures that were 29-52-fold the exposures found in patients. In the 9-month dog study, the animals were at maximum exposed to 2-fold the upadacitinib exposure observed in patients.

Genotoxicity

The genotoxic potential of upadacitinib was characterized by Ames test, a chromosome aberration test in human peripheral blood lymphocytes, and an in vivo rat bone marrow erythrocyte micronucleus test.

The outcome of the bacterial Ames test and the micronucleus test was negative. In the in vitro mammalian chromosome aberration test in human peripheral blood lymphocytes, upadacitinib was found negative for induction of structural chromosome aberrations but positive for induction of numerical chromosome aberration. Since no effect was observed on the structural chromosome breakage and the in vivo micronucleus assay was found negative, this is considered sufficient reassurance of lack of potential for aneuploidy induction. The exposure in the in vivo chromosomal aberration study was considered sufficient (up to 127 times the clinical based on Cmax, and 46 times on AUC for the highest dose tested).

Based on the results of the conducted genotoxicity studies, the overall conclusion is that upadacitinib does not have any genotoxic potential.

Carcinogenicity

The carcinogenic potential of upadacitinib was evaluated in a 6 month study in rasH2 mice and a two year study in Sprague Dawley rats.

Upadacitinib was administered to male and female SD rats (2 year study) daily by oral gavage, and was not carcinogenic at any dose tested. The tested doses were in male 0, 4, 7.5, and 15 mg/kg/day and in female 0, 3, 7.5, and 20 mg/kg/days. The maximum doses were set up based on decreased body weight gain, and findings in the kidney and non-glandular stomach at 50 mg/kg/day in the 26-week repeat dose toxicity study.

In female rats administered 20 mg/kg/day there was an increase in the lungs of alveolar histiocytosis. The incidence was within the historical control range and was not considered treatment related. This was accepted.

No neoplasm was identified following upadacitinib treatment. The exposure multiples for the maximum dose tested in male and female rats relative to the 15 mg clinical dose are 4.0- and 9.9-fold, respectively.

Upadacitinib was administered to male and female HRAS mice (6-month study) daily by oral gavage (at 0, 5, 10, and 20 mg/kg/day) and was not carcinogenic at any dose tested. The maximum dose was set up based on the results from a 4-week repeat dose toxicity study in wild type mice. The incidence of neoplasms in the positive control group was according to the applicant typical of this mouse model.

No neoplasm was identified following upadacitinib treatment. The exposure multiples for the maximum dose tested in male and female mice relative to the 15 mg clinical dose are 2.0- and 3.4-fold, respectively.

In summary, there were no test article related unscheduled deaths or differences in mortality in any of the studies. No neoplastic findings were identified following upadacitinib treatment.

Reproductive and developmental toxicity

Studies were conducted to evaluate the standard reproductive and developmental toxicity profile of upadacitinib: one segment I 'fertility' study (Sprague-Dawley rats), three pivotal segment II 'EFD' studies (Sprague-Dawley rat and New Zealand white rabbits), and one segment III 'prenatal/postnatal study (Sprague Dawley rats). Additionally, one pivotal juvenile toxicity study was conducted in Sprague Dawley rats.

Male and female fertility

Male and female fertility and early embryonic development were evaluated in rats after administration of upadacitinib at 0, 5, 25, 50 (M)/75 (F) mg/kg/day.

The body weight and body weight increase of the male rats was reduced in the mid and high dose treated animals. In the high dose animals (50 mg/kg) reduced weights of epididymides (5%) and prostate (13%) were observed, which correlated with the reduction in body weight. In the repeat-dose toxicity studies, no indications of toxicity to the male or female reproductive organs was observed.

In the dose groups 0, 5, 25, and 50/75 mg/kg/day the male and female mating index was 96%, 100%, 100%, and 92%; fertility index 84%, 92%, 84%, and 76%; and fecundity index 88%, 92%,

84% and 83%. The fertility index was lower in the high dose group (76% vs 84% in control). The applicant argues that this is not upadacitinib-related since the historical control data from the lab ranged from 76% to 100%. In the female rats, six of 19 pregnant animals had litters comprised entirely of resorbed foetuses. Also in the female animals administered the mid dose, increased post-implantation loss was observed (4.8%, 5.8%, 20.4%, and 82.6% in the 0, 5, 25, and 75 mg/kg/day dose groups). The applicant argues that these findings were attributed to the developmental/teratogenic effect of upadacitinib and that the reproductive and fertility parameters in males and females were unaffected by upadacitinib. This is accepted, although it cannot be ruled out that the lower fertility index observed in the high dose group is caused by upadacitinib. Furthermore it should be noted that in the embryo-foetal toxicity study, in which the same dose-levels were administered, there was no increase in the post-implantation loss or change in the litter size. Thus, administration of 75 mg/kg/day upadacitinib from 14 days before pairing until gestational day 7 caused an increase in post-implantation loss whereas administration from GD 6 to 17 did not.

Plasma exposure of upadacitinib was not measured in the study. Instead plasma exposures from the 4 week repeat dose study in rats were used to estimate the exposure margins to patients. Thus considering only the reproductive and fertility parameters the NOAEL was considered 50 mg/kg/day in male rats and 75 mg/kg in females. The exposure (AUC0-24, from 4-weeks study) in males at this dose was 16.8 µg*hr/mL. There was no corresponding dose in females, however the 50 mg/kg/day dose rendered an AUC of 33.2 µg*hr/mL in females. These exposures represent approximately 40 and 80 fold the exposure observed in humans.

Embryo-foetal development

Two embryo-foetal development studies were conducted in rats. In the first study the animals were administered 0, 5, 25, and 75 mg/kg/day and since it was not possible to determine a NOAEL for the observed teratogenicity another study with lower doses (0, 1.5, and 4 mg/kg) was conducted.

There were no observed treatment related effects on implantation sites, viable foetuses, resorption sites or litter size. The foetal body weight was slightly reduced in both male and female foetuses from dams administered 75 mg/kg/day upadacitinib. An increased number of skeletal malformations was observed in all treatment groups, percent foetuses in the 0, 5, 25, and 75 mg/kg/day groups were 0, 1.4, 8, and 35. The skeletal malformations included misshapen humerus and bent scapula, bent, misshapen or shortened long bones of the fore- and hind limbs.

In the second EFD study in rat with lower doses of upadacitinib, skeletal malformations were observed in one fetus in the 4 mg/kg group. Since these malformations were similar as the ones observed in the previous study, they were considered test-article-related. The NOAEL for developmental toxicity was the lowest dose, 1.5 mg/kg/day. The exposure in the dams at gestational day 16 was at this dose 115 ng*hr/mL, which represents 0.27 of the exposure observed in humans.

The embryo-foetal development study in rabbits was conducted at 0, 2.5, 10, and 25 mg/kg. In the rabbits an increase in post-implantation loss was observed (0%, 4.1%, 2.6%, 14.8% in the groups 0, 2.5, 10, and 25 mg/kg/day). There was no apparent increase of skeletal malformations, but an increased incidence of cardiac malformations was observed at 25 mg/kg/day. The NOAEL was considered 10 mg/kg/day and the exposure (AUC0-24) at gestational day 18 was 881 ng*hr/mL, which represents approximately two-fold the exposure observed in humans.

Prenatal and postnatal development

The potential effects of upadacitinib on development, growth, behaviour, reproductive performance and fertility of F1 generation were evaluated in rats after administration of 0, 2.5, 5, and 10

mg/kg/day to F0 females from gestation day 6 through day 20 post-partum. In the study, only F0 dams were administered upadacitinib. The exposure in the pups was not measured in the study. In the previous EFD study it was however shown that the foetuses were exposed to upadacitinib (foetal/dam ratio at 10 mg/kg/day was 0.003). Furthermore, in a study with radiolabelled upadacitinib it was shown that upadacitinib readily transferred to milk in pregnant rats (presented in the section on pharmacokinetics). Thus, it is likely that also the pups were exposed to upadacitinib.

There were no treatment related effects on the F0 generation, including effects on parturition, lactation and maternal behaviour. There were no treatment related effects on the F1 generation in any of the investigated parameters, including viability, body weight, sexual maturation, behavioural testing (acoustic startle habituation, motor activity, and M-shaped water maze), or reproductive endpoints.

The NOAEL for maternal systemic toxicity and F1 development was considered to be 10 mg/kg/day. This corresponds to an exposure margin of 2.6 fold based on AUC and compared to AUC in patients with 15 mg/day.

Juvenile toxicity

In the non-GLP dose-finding study, doses ≥ 100 mg/kg/day resulted in mortality and clinical signs.

In a main GLP study with juvenile Sprague-Dawley rats, accelerated pharmacologic effects on the lymphoid system and exposures similar to those observed in adult rats were evident. A TDAR assay within this study indicated that upadacitinib suppressed a Keyhole Limpet Hemocyanin (KLH)-specific primary IgM and IgG antibody concentrations when administered to juvenile rats from PND 15 through PND 59. This effect was comparable to that of the positive control cyclophosphamide A. Dose-dependent decrease in total T cells, T helper cells, T cytotoxic cells, B cells, NK cells and NKT cells at all doses was revealed by flow cytometric analysis.

Immunotoxicity

Upadacitinib was tested in the T-cell dependent antibody response assay (TDAR) in rats. Upadacitinib suppressed the anti-KLH IgN and IgG T-cell dependent antibody response. Considering the results from the TDAR study and the repeat-dose toxicity studies, it is clear that upadacitinib induces significant immune suppression. This is consistent with the mode of action and as such not unexpected.

Impurities

The potential manufacturing impurities for upadacitinib drug substance, including the starting materials, intermediates, reagents, by-products and potential side products were subjected to two complementary (Q)SAR analysis methodologies (Derek and CASEUltra). The impurities that showed structural alerts for mutagenicity and were subsequently shown to be negative in a bacterial mutation (Ames) testing, are not considered impurities of mutagenic concern.

One impurity was found mutagenic in an Ames test. According to the ICH M7 guideline a maximum daily intake of 1.5 µg of a mutagenic can be considered acceptable for a treatment >10 years. The applicant has calculated the limits on a possible future maximum dose of 60 mg. The acceptable limit would thus be 1.5 µg/60 mg= 25 ppm. A-1653651.0/1 is controlled at 20 ppm which is acceptable.

The bacterial reverse mutation assay was repeated several times using two different batches of another impurity, three times using Lot 1 and two times using Lot 2. It was concluded that Lot 1 was positive. No other positive results were obtained with any of the bacterial strains using standard criteria for a positive response.

Phototoxicity

A neutral red uptake phototoxicity assay was performed to evaluate the phototoxic potential of upadacitinib. Upadacitinib did not have any phototoxic potential in the neutral red uptake bioassay.

2.3.5. Ecotoxicity/environmental risk assessment

In the Phase I exposure assessment, the $PEC_{SURFACEWATER}$ for upadacitinib 0.075 µg/L exceeded the action limit of 0.01 µg/L. Therefore a Phase II Tier A assessment was triggered.

The octanol-water partition coefficient (Log K_{OW}) of upadacitinib was reported to be 2.5 at pH 7.4.

Since the presented value is relatively high (2.5), the Applicant is requested to submit a determination of the n-octanol-buffer distribution coefficient according to OECD 107 post approval (see recommendations). The final conclusions regarding the screening criterion for PBT substance is thus pending.

Upadacitinib is very persistent in sediment according to the OECD 308 study.

Upadacitinib was primarily partitioned to the sediment layers. A Phase II Tier B extended effects on water sediment was thus triggered.

PEC/PNEC ratios are all well below 1.

Table 1 **Table for the assessment report providing relevant endpoints of the environmental risk assessment of human pharmaceuticals**

Substance (INN/Invented Name): Upadacitinib (ABT-494)			
CAS-number (if available): 2050057-56-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	2.5 (Pending, see recommendations)	Potential PBT (Y/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.5 (Pending, see recommendations)	B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability	>180 days	vP
Toxicity	NOEC or CMR		T/not T
PBT-statement :	Pending, see LoQ The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default Fpen	0.075	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	*Soils* *1.* K_{oc} =5.58×10^3 L/kg *2.* K_{oc} =*1.18×10^4* L/kg 3. K_{oc} 2.31×10^4 L/kg Sludges 4. K_{oc} = 1.29×10^2 L/kg 5 K_{oc} = 1.18×10^2 L/kg	1-sandy loam 2-clay loam 3-loamy sand No trigger of terrestrial studies as <10000L/kg.

Ready Biodegradability Test	OECD 301				Not available, but can be waived because OECD308 is submitted
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Brandywine/Choptank River $DT_{50,\ water}$ = 5.6/13 days $DT_{50,\ sediment}$ = 347/110 days $DT_{50,\ whole\ system}$ = 234/138 days Corrected to 12 °C $DT_{50,\ water}$ = 12/28 days $DT_{50,\ sediment}$ = 741/235 days $DT_{50,\ whole\ system}$ = 499/295 days % shifting to sediment >10%			Results obtained in two river systems; sediment risk assessment triggered.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	EC10 NOEC	36.7 31.3	mg/L	*Psuedokirchneriella subcapitata*)
Daphnia sp. Reproduction Test	OECD 211	EC10 NOEC	3.09 1.6	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	EC10 NOEC	1.8 0.63	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50 and NOEC	>1000	mg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	EC10 NOEC	402 390	mg/kg	*Chironomus riparius*

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed: The applicant should provide the final report describing the n-octanol-buffer distribution coefficient according to OECD 107 and updated environmental risk assessment for upadacitinib by 31/03/2020.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The primary pharmacodynamics program of upadacitinib included *in vitro* cell free (biochemical) and cellular assays and *in vivo* studies in two rodent models of arthritis to determine potency and selectivity of upadacitinib. Specificity has been determined by evaluating upadacitinib against a panel of other kinases, ion channels, transporters and cell surface receptors.

Upadacitinib was developed as an orally active and selective JAK1 inhibitor with functional inhibition of the JAK-STAT pathway demonstrated in several cell-based assay systems using cytokine activators such as IL-6 and IL-2. However, the CHMP did not agree, based on the data provided by the Applicant, that a JAK1 selectivity over JAK3 has been convincingly shown in either cellular assays or under *ex vivo* conditions. For example, in rat ex vivo studies, at clinically relevant plasma exposure (AUC0-24hr = 0,420 µg•hr/mL at 15 mg), inhibition of both JAK1 and JAK3 activity was observed since upadacitinib could inhibit JAK3 activity (as measured by 50% inhibition of circulating NK cells) at an AUC0-12hr of 0.520 µg•hr/mL in rat. Moreover, in clinical ex vivo studies using in IL-6-induced pSTAT3 (as a marker for JAK1 activity) and IL-7-induced pSTAT5 (as a marker for JAK1/3 activity), the estimated EC50

values for inhibition of IL-6-induced phosphorylation were 23.1 ng/mL (60.7 nM) and the EC50 values for inhibition of IL-7-induced pSTAT5 were 47.7 ng/mL (125 nM) for upadacitinib. Both these EC50 values are well covered by the clinical Cmax of upadacitinib in human plasma following the recommended dosing of 15 mg ER QD. Therefore, pharmacological activity at JAK1 and JAK1/3 could be expected at therapeutic plasma concentrations of upadacitinib. The applicant agreed to revise the Section 5.1 of the SmPC accordingly.

The applicant did not submit primary pharmacology data to demonstrate the intended pharmacological activity of upadacitinib in the dog and rabbit, two of the species used in the pivotal toxicology studies. The CHMP asked for clarifications on this point: according to published studies, there is a high sequence conservation of the JAK family across species and JAK inhibition of other, albeit chemical different, JAK inhibitors, do not apparently differ between species. In addition, the pharmacological profile of upadacitinib in the performed toxicity studies, including the dog and the rabbit, is indicative of JAK inhibition. Based on those clarifications, the CHMP agreed that there should be a minimal influence on upadacitinib potencies between different species and all species tested within the non-clinical program (mouse, rat, rabbit and dog)

The in vivo safety pharmacology studies with upadacitinib in dogs demonstrated a decrease in arterial blood pressure at an oral dose equal to or greater than a plasma concentration of Cmax = 0.42 µg/mL and an increase in heart rate at a drug plasma concentration of Cmax= 1.3 µg/ml. These effects in dogs were observed at plasma concentrations approximately 10 times the clinical exposure at the recommended dose of 15 mg. A thorough QT study has not been conducted in clinical trials. However, an exposure-response analysis stated that no QT interval prolongation at therapeutic or supra-therapeutic plasma exposures was observed in healthy subjects. From a non-clinical perspective, no further action is considered necessary with respect to safety pharmacology.

Pharmacokinetics

The pharmacokinetic studies with upadacitinib have been conducted in rats, beagle dogs and cynomolgus monkeys following oral and IV dosing. The rat and dog were chosen as the primary nonclinical species for upadacitinib toxicology studies based on superior exposure relative to mice and monkeys. However, toxicokinetic analysis was also conducted for mouse and rabbit, which were used in toxicology studies. Upadacitinib does not have pharmacologically active metabolites. Formulation of upadacitinib in oral suspensions of tartrate co-crystal or free base resulted in comparable exposures in rats and dogs.

The analytical methods were overall acceptable to the CHMP.

Upadacitinib displays rapid absorption after a single oral dose, with Tmax in plasma ranging from 1 to 2 h in rats, dogs and monkeys. The pharmacokinetics was further characterized by high to moderate plasma clearance in rat and dog, respectively, and high volume of distribution across all species. There was evidence of only limited decrease or accumulation (<2-fold) following multiple daily oral dosing in mice, rats, rabbits and dogs, which is in line with human data.

The in vivo tissue distribution in rat showed that upadacitinib related radioactivity was distributed rapidly into most tissues through 4 hr post-dose, with the liver, uveal tract and adrenal gland having the highest exposure. Lowest exposure was found in the CNS, spinal cord and eye lens. Radioactivity was present in the uveal tract through 192 hours post-dose and a slower clearance in pigmented skin indicating an apparent affinity for melanin. Placental transfer and subsequent foetal exposure to [14C]-upadacitinib-related radioactivity occurred at moderate to low levels. Exposure of [14C]-upadacitinib-related radioactivity was approximately 31-fold greater in milk than in plasma.

Plasma protein binding of upadacitinib was low in all species (fu ranged from 0.41 in rat to 0.69 in dog) and independent of test concentration.

Biotransformation of upadacitinib in nonclinical species (mouse, rat, rabbit, dog) and human was, in general, low and unchanged parent was the primary drug-related component in dog (~88%) and in human (~79%) plasma, whereas unchanged parent represented about 56% of drug-related material in rats. In human plasma, the M4 metabolite was found to be a major metabolite, which was detected as a minor metabolite in rats and dogs. M4 is a Phase II conjugate, a normally non-reactive acyl glucuronide. M11 is considered an artifact resulting from degradation of M10 during sample preparation. Later the Applicant submitted spectroscopic data supporting the amide structure of M11. The mechanism for this transformation (M10 and M11) in vitro, and possibly in vivo, is unknown. M10 is instable under mild conditions in vitro and might be a reactive intermediate in vivo. In the rat plasma M11 was defined as a major metabolite, which may also have indicated a high concentration of the preceding M10 intermediate in the rat plasma. Considering that covalent binding of reactive metabolites to endogenous macromolecules is one of the mechanisms that can lead to hepatoxicity, the applicant was asked to discuss the role of M10 intermediate in different species and its possible implications for liver necrosis reported in four-week repeat-dose toxicity study in rats. Based on the applicant's response, the formation, structure and fate of intermediates M10 and M11 in metabolism and radiolabeled ADME studies do not support a hypothesis of a potential reactive intermediate/covalent binding as causality for the liver necrosis. Furthermore, liver necrosis was not observed in other repeat-dose rat studies of longer duration.

The probability of chiral interconversion of upadacitinib in vivo is low, given that the observed metabolic pathways are consistent across species with no metabolic transformation observed in the chiral centres of upadacitinib in man and only low levels of the M1/M2 metabolites were detected also in animals.

All human metabolites, including the major metabolite M4, were observed in one or more animal species.

The species selected for the toxicology studies (rat, dog and rabbit) were shown to have similar elimination pathways and metabolic profiles of upadacitinib as in humans and are thus considered adequate for safety evaluation of upadacitinib.

Toxicology

The toxicological profile of upadacitinib has been evaluated in non-clinical studies in agreement with relevant guidelines. Also, a number of process intermediates/impurities have been studied. Overall, the toxicity profile of upadacitinib has been characterized via repeat dose toxicity (up to 6 months in rats and 9 months in dogs; no recovery period), genotoxicity, carcinogenicity studies in rats and Tg(HRAS) mice, reproductive and developmental toxicity studies in rats and rabbits, juvenile toxicity, immunotoxicity, and phototoxicity studies.

The oral route of administration was utilized in all toxicology studies to match the intended clinical administration route.

In four-week repeat dose toxicity study in rats, there were decreased white blood cell counts (up to 65% in males and -61% in females) and lymphocyte counts (up to -71% in males and females) at 10, 50, and 100 mg/kg/day that were dose-dependent with partial recovery after four weeks. RBC parameters were decreased relative to control, including RBC count (to -13%), hemoglobin concentration (to -12%), and hematocrit (to -14%) in females at 100 mg/kg/day.

Degeneration/regeneration of the renal tubular epithelium occurred in the 26-week repeat-dose oral toxicity study in rats at dose level of 50 mg/kg/day. At 50 mg/kg/day, moderate decreases in lymphocyte counts were observed for males and females on Week 13 (up to -70%) and at the end of dosing (up to -58%). In the four-week repeat-dose oral toxicity study in rats, peripheral blood

lymphocyte immunophenotyping assay was conducted to study immunotoxicity/abnormal immunophenotype profiles because of upadacitinib administration. However, in the 26-week rat study immunophenotyping was not performed. The CHMP agreed that the four weeks dosing period was sufficient for recording decreases in lymphocyte subsets and immunophenotyping in repeat-dose toxicity studies of longer duration would not have provided any extra information.

In the 39-week repeat-dose toxicity study in dogs, cysts in on the paws and inflammatory changes in interdigital skin were believed to be due to alterations in immune function related to the expected pharmacologic activity of upadacitinib. Increased white blood cell counts ranged from 37% up to 83% and from 21% up to 84% in upadacitinib-treated male and female dogs, respectively. Increased neutrophil counts ranged from 53% to 143% and 25% to 113% for affected males and females, respectively. These increases in white blood cells/neutrophils were considered to result of chronic swelling and inflammation in the paws and not a direct effect of upadacitinib administration. The exposure NOAEL at 1.5 mg/kg/day (the highest dose) provided a 2.2-fold safety margin to mean steady state plasma exposure in RA patients receiving 15 mg upadacitinib once daily. According to CPMP/SWP/1042/99 Rev 1 Corr* Guideline on repeated dose toxicity, a high dose should be selected to enable identification of target organ toxicity or other non-specific toxicity. Ideally, at the high dose level, the systemic exposure to the drug and/or principal metabolites in animal model should be a significant multiple of the anticipated clinical systemic exposure toxicity. The sufficiency of the selected highest dose for long-term toxicity assessment in dogs from the clinical point of view was discussed in the first round of the procedure. It was agreed that an adequate demonstration of toxicity was achieved in the 39-week toxicity study at the highest dose. Similar, but more severe immunosuppression-related findings were observed in 4-week GLP dog study resulting from a more extensive systemic exposure.

Absorption of upadacitinib in females was about two-fold higher compared to males in repeat-dose toxicity studies in rats. Although systemic exposures of upadacitinib in the 4-week and 26-week rat studies were approximately two-times higher in female rats than males across the dose groups, males tended to have an increased sensitivity to upadacitinib-related adverse effects, including mortality in four-week repeat-dose toxicity study in rats.

Due to the potent pharmacological effect of upadacitinib on lymphoid tissue and subsequent secondary effects, it is not unexpected that the margin of exposure for these effects is relatively low in relation to the therapeutic doses of upadacitinib to be used in patients with rheumatoid arthritis. However, reversible changes in hematological parameters associated with JAK inhibition generally occur earlier and at lower doses than the kidney and/or liver effects observed in the toxicological studies.

Upadacitinib had no effect on fertility in male or female rats at doses up to 50 mg/kg/day in males and 75 mg/kg/day in females in a fertility and early embryonic development study. Dose related increases in foetal resorptions associated with post-implantation losses at 25 and 75 mg/kg/day in this study in rats were attributed to the developmental/teratogenic effects of upadacitinib. Upadacitinib was teratogenic in both rats and rabbits. In a pre /postnatal development study in rats, there were no maternal effects, no effects on parturition, lactation or maternal behaviour and no effects on their offspring. JAK inhibitors are known to be teratogenic. Pregnant and breastfeeding women were excluded from the upadacitinib clinical trials. At the CHMP's request the Applicant agreed to add "pregnancy" as a contraindication for Rinvoq. SmPC sections 4.3 and 4.6 were updated accordingly. In addition, the SmPC recommends that women of childbearing potential should use effective contraception during treatment and for 4 weeks following the final dose of upadacitinib. The length of the period where contraception should be used after treatment is based on the half-life of upadacitinib, which is approximately 11 hours. Five half-lives is considered adequate to eliminate the drug from the

body, that is approximately 3 days. The 4 week period is also based on the duration of a woman's menstrual cycle.

Adequate risk minimization measures and pharmacovigilance activities are included in the RMP to address the risk of foetal malformation following exposure in utero (see RMP Section).

In rats, the milk/plasma ratio for upadacitinib was high. The milk Cmax:plasma Cmax concentration ratio was 19 (Tmax = 1 hr). The milk AUC0-t:plasma AUC0-t concentration ratio was 30.9. From 0.5 through 24 hours postdose, mean milk:plasma concentration ratios ranged from 7.96 to 70.4. It was however not determined how much of the dose that was actually absorbed by the offspring following ingestion of breast milk. Upadacitinib should not be used during breast-feeding; this is reflected in the SmPC.

Starting materials, raw materials, intermediates and potential manufacturing impurities were subjected to (Q)SAR analysis for potential mutagenicity concerns. A number of identified impurities were evaluated in the Ames test. Most of the impurities were subject to specification limits; however, limits for imidazole and citric acid were justified based on toxicology data available in the literature as they were either not detected or not tested for in lots of upadacitinib used in nonclinical toxicology studies. All studies on mutagenic potential of impurities complied with GLP regulations. Upadacitinib was not mutagenic or genotoxic based on the results of *in vitro* and *in vivo* tests for gene mutations and chromosomal aberrations.

Upadacitinib, at exposures (based on AUC) approximately 4 and 10 times the clinical dose of 15 mg in male and female Sprague-Dawley rats, respectively, was not carcinogenic in a 2 year carcinogenicity study in Sprague-Dawley rats. Upadacitinib was not carcinogenic in a 26 week carcinogenicity study in CByB6F1-Tg(HRAS)2Jic transgenic mice.

2.3.7. Conclusion on the non-clinical aspects

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.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology.

Studies in animals have shown reproductive toxicity. Upadacitinib was teratogenic in rats and rabbits with effects in bones in rat foetuses and in the heart in rabbit foetuses when exposed in utero. Upadacitinib is contraindicated during pregnancy. Women of childbearing potential should be advised to use effective contraception during treatment and for 4 weeks following the final dose of upadacitinib.

Upadacitinib should not be used during breast-feeding.

The CHMP considers the following measures necessary to address the non-clinical issues:

The applicant should provide the final report describing the n-octanol-buffer distribution coefficient according to OECD 107 and updated environmental risk assessment for upadacitinib by 31/03/2020.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2 Phase 1 clinical pharmacology studies of upadacitinib.

Study	Description
Single and Multiple Dose Studies	
M13-401 – Substudy 1	Single-ascending dose in healthy subjects
M13-845	Multiple-ascending dose in healthy subjects and multiple dose in subjects with RA
M14-680	Single- and multiple-dose assessment of upadacitinib ER formulation compared to the IR formulation
ADME Study	
M13-548	Radiolabeled upadacitinib ADME study
Intrinsic Factor Studies	
M13-543	Single- and multiple-dose study in healthy Asian subjects
M15-558	Multiple-dose study in healthy Chinese subjects
M13-539	Hepatic impairment study
M13-551	Renal impairment study
Extrinsic Factor Studies	
M13-401 – Substudy 2	Effect of multiple doses of ketoconazole on upadacitinib pharmacokinetics (and effect of high-fat meal on the IR formulation)
M13-540	Effect of single and multiple doses of rifampin on upadacitinib pharmacokinetics
M14-624	Effect of multiple doses of upadacitinib on the pharmacokinetics of sensitive substrates of different cytochrome P450 enzymes (Cocktail Drug Interaction Study)
M14-625	Effect of multiple doses of upadacitinib on the pharmacokinetics of ethinylestradiol and levonorgestrel
M13-541	Effect of multiple doses of upadacitinib on the pharmacokinetics of

	rosuvastatin and atorvastatin
M17-221	Effect of multiple doses of upadacitinib on the pharmacokinetics of bupropion
M14-680 – Part 2	Effect of high-fat meal on upadacitinib Phase 3 formulation (and bioavailability evaluation of the ER relative to the IR formulation)
M15-878	Effect of high-fat meal on upadacitinib market-image formulation (and bioequivalence evaluation of the Phase 3 and market-image formulations)

Table 3: Overview of Upadacitinib Clinical Development Program for RA – Supportive Studies

	M13-537 (Dose-Ranging)	M13-550 (Dose-Ranging)	M13-538 (OLE)	M14-663 (Japan Only Study)
Phase	2	2	2	2b/3
Population	MTX-IR	anti-TNF-IR	From M13-537 and M13-550	Japanese subjects who are csDMARD-IR
Background	MTX	MTX	MTX	csDMARD
Comparator	PBO	PBO	None	PBO
Upadacitinib Dose	3, 6, 12, and 18 mg BID 24 mg QD	3, 6, 12, and 18 mg BID	6 and 12 mg BID 15 and 30 mg QD[a]	7.5, 15, and 30 mg QD
Upadacitinib formulation	Immediate-release	Immediate-release	Immediate-release Extended-release[a]	Extended-release
Duration	12 weeks	12 weeks	Up to 264 weeks	P1: 12 weeks P2: Up to the regulatory approval of RA indication in Japan
Study Blind	Double-blind	Double-blind	N/A	Double-blind through Period 1. Sponsor was unblinded after Period 1 database lock (Week 12). Sites and subjects remain blinded in Period 2.
Number of subjects enrolled	300	276	494	197
Number of subjects exposed to at least 1 dose of study drug	299	276	493	197
Primary Efficacy Endpoint	ACR20 response at Week 12	ACR20 response at Week 12	N/A (primary objective is safety)	ACR20 response at Week 12

	M13-537 (Dose-Ranging)	M13-550 (Dose-Ranging)	M13-538 (OLE)	M14-663 (Japan Only Study)
Key secondary endpoints	• ACR50/70 response at Week 12 • LDA or CR based on DAS28 (CRP) and CDAI at Week 12 • CR based on DAS28 (CRP) and CDAI at Week 12	• ACR50/70 response at Week 12 • LDA or CR based on DAS28 (CRP) at Week 12 • CR based on DAS28 (CRP) at Week 12	• ACR20/50/70 response over time • Change from baseline in ACR components over time • LDA or CR based on DAS28 (CRP) and CDAI over time • Change from baseline in DAS28 (CRP), CDAI, FACIT-F, RA-WIS, and EQ-5D over time	• Change from baseline at Week 12 in DAS28 (CRP), HAQ-DI, SF-36 PCS, FACIT-F, RA-WIS, and morning stiffness severity • ACR50/70 response at Week 12 • ACR20 response at Week 1 • LDA based on DAS28 (CRP) at Week 12 • CR based on DAS28 (CRP) at Week 12
Status	Completed	Completed	Ongoing[b]	Ongoing[b]

ACR = American College of Rheumatology; ACR20/50/70 = American College of Rheumatology 20, 50, 70 response; BID = twice daily; CDAI = Clinical Disease Activity Index; CR = clinical remission; CRP = C-reactive protein; csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; DAS28 = disease activity score 28 joints; EQ-5D = EuroQoL-5-Dimensions-5-Levels; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI = Health Assessment Questionnaire - Disability Index; IR = inadequate response; LDA = low disease activity; MTX = methotrexate; N/A = not applicable; OLE = open-label extension; PBO = placebo; QD = once daily; RA = rheumatoid arthritis; RA-WIS = Rheumatoid Arthritis Work Instability Scale; SF-36 PCS = Short Form 36 Physical Component Score; TNF = tumor necrosis factor

a. From January 2017, all subjects who were at Week 72 or beyond received a once-daily tablet formulation. Subjects who were on 6 mg BID capsule dosing were transitioned to 15 mg QD tablet dosing. Subjects who were on 12 mg BID capsule dosing were transitioned to 30 mg QD tablet dosing.

b. Enrollment is complete and study is ongoing.

Table 4: Overview of Upadacitinib Clinical Development Program for RA – Pivotal Phase 3 Studies

	M13-545 (Select Early)	M13-549 (Select Next)	M14-465 (Select Compare)	M15-555 (Select Monotherapy)	M13-542 (Select Beyond)
Population	MTX-naïve	csDMARD-IR[a]	MTX-IR[a,b]	MTX-IR	bDMARD-IR
Background	None (monotherapy)	csDMARD	MTX	None (monotherapy)	csDMARD
Comparator	MTX	PBO	PBO; ADA	cMTX	PBO
Upadacitinib Dose (Extended-Release Formulation)	15 mg QD 30 mg QD 7.5 mg QD (subjects in Japan only)[c]	15 mg QD 30 mg QD	15 mg QD	15 mg QD 30 mg QD	15 mg QD 30 mg QD
Duration	Total duration up to 5 years; P1: 48 weeks (controlled period) P2: Long-term extension (MTX-controlled)	Total duration up to 5 years; P1: 12 weeks (controlled period) P2: Long-term extension	Total duration up to 5 years; P1: 48 weeks (26 weeks PBO-controlled and 48 weeks ADA-controlled period) P2: Long-term extension (ADA-controlled)	Total duration up to 5 years; P1: 14 weeks (controlled period) P2: Long-term extension	Total duration up to 5 years; P1: 24 weeks (12 weeks controlled period) P2: Long-term extension
Study Blind	Double-blind through P1. Sponsor was unblinded after Week 24 database lock. Sites and subjects remained blinded until last subject completed Week 48 in P1.	Double-blind through P1. Sponsor was unblinded after P1 database lock (Week 12). Sites and subjects remain blinded in P2.	Double-blind through P1. Sponsor was unblinded after Week 26 database lock. Sites and subjects remained blinded until last subject completed Week 48 in P1.	Double-blind through P1. Sponsor was unblinded after Period 1 database lock (Week 14). Sites and subjects remain blinded in P2.	Double-blind through P1. Sponsor was unblinded after P1 database lock (Week 24). Sites and subjects remain blinded in P2.
Number of subjects randomized/exposed to at least 1 dose of study drug	947[c]/945[c]	661/661	1629/1629	648/648	499/498

	M13-545 (Select Early)	M13-549 (Select Next)	M14-465 (Select Compare)	M15-555 (Select Monotherapy)	M13-542 (Select Beyond)
Number of subjects randomized to each treatment group	Upadacitinib 15 mg QD: N = 317 Upadacitinib 30 mg QD: N = 315 MTX: N = 315	Upadacitinib 15 mg QD: N = 221 Upadacitinib 30 mg QD: N = 219 Placebo: N = 221	Upadacitinib 15 mg QD: N = 651 Adalimumab (40 mg eow): N = 327 Placebo: N = 651	Upadacitinib 15 mg QD: N = 217 Upadacitinib 30 mg QD: N = 215 cMTX: N = 216	Upadacitinib 15 mg QD: N = 165 Upadacitinib 30 mg QD: N = 165 Placebo: N = 169
Primary Efficacy Endpoint (US FDA)[d]	ACR50 response at Week 12	ACR20 response at Week 12	ACR20 response at Week 12	ACR20 response at Week 14	ACR20 response at Week 12
Primary Efficacy Endpoint (EMA)[e]	CR based on DAS28 (CRP) at Week 24	LDA based on DAS28 (CRP) at Week 12	CR based on DAS28 (CRP) at Week 12	LDA based on DAS28 (CRP) at Week 14	LDA based on DAS28 (CRP) at Week 12
Primary Efficacy Endpoint (Japan PMDA)	ACR20 response at Week 12 and ΔmTSS at Week 24	--	--	--	--
Status	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing

Δ = change from baseline; ACR20/50 = American College of Rheumatology 20/50 response; ADA = adalimumab; bDMARD = biologic disease-modifying anti-rheumatic drug; cMTX = continuing MTX; CR = clinical remission; CRP = C-reactive protein; csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; DAS28 = disease activity score 28; EMA = European Medicines Agency; eow = every other week; FDA = Food and Drug Administration; HAQ-DI = Health Assessment Questionnaire – Disability Index; hsCRP = high-sensitivity C-reactive protein; IR = inadequate response; LDA = low disease activity; mTSS = modified Total Sharp Score; MTX = methotrexate; P1 = Period 1; P2 = Period 2; PBO = placebo; PMDA = Pharmaceutical and Medical Devices Agency; PhGA = Physician's Global Assessment of Disease Activity; PtGA = Patient's Global Assessment of Disease Activity; QD = once daily; RA = rheumatoid arthritis; US = United States; VAS = Visual Analog Scale

a. Subjects with prior exposure to at most one bDMARD for RA could be enrolled in the study (up to 20% of study total number of subjects) after the required washout period was satisfied and if they had a) limited bDMARD exposure (< 3 months), OR b) responded to a bDMARD but had to discontinue that bDMARD due to intolerability (regardless of treatment duration).

b. Prior exposure to adalimumab was not permitted.

c. The upadacitinib 7.5 mg QD group (subjects in Japan only) is excluded from this summary (n = 55). Total number of subjects randomized/received at least 1 dose of study drug: 1002/1000.

2.4.2. Pharmacokinetics

Pharmacokinetic data are available from 22 Phase 1 studies, 2 supportive dose ranging Phase 2 studies, 1 supportive Phase 2b/3 dose ranging study in Japanese subjects, and 5 pivotal Phase 3 studies. The exposure-efficacy and exposure-safety relationships were evaluated by PKPD-modelling.

During the development, an immediate release (IR) tablet was used in several of the Phase 1 studies and in early Phase 2 studies. To enhance patients' compliance, a QD extended release (ER) tablet formulation was developed and further evaluated in Phase 3 trials in subjects with RA. To improve manufacturability a modified ER tablet was developed which is the planned commercial formulation.

Upadacitinib concentrations in plasma was analysed using validated LC/MS/MS methods.

Absorption

Upadacitinib has a high solubility according to the Biopharmaceutical Classification System (BCS). A study in MDCK cells indicate that permeability may be high. Upadacitinib was a substrate for P-gp and BCRP in vitro.

Following oral administration of upadacitinib prolonged-release formulation, upadacitinib is absorbed with a median Tmax of 2 to 4 hours . An absolute bioavailability study has not been conducted. The bioavailability of the ER tablet formulation was estimated to be 76% relative to the IR capsule. Bioequivalence has been demonstrated between the proposed commercial formulation and the Phase 3 formulation.

The effect of food on upadacitinib bioavailability was evaluated in several studies during formulation development. In studies with the upadacitinib IR capsule formulation, the effect of a high-fat, high-calorie meal resulted in no effect on AUC and a 23-30% decrease in Cmax compared to fasting conditions. For different ER formulations, there was a small to moderate effect of food on both AUC and Cmax. The effect of a high-fat meal appears to be somewhat higher for the proposed commercial formulation than for the Phase 3 formulation. For the commercial formulation, upadacitinib Cmax and AUC increased 40% and 30% respectively, relative to the fasting conditions while Cmax and AUC increased by 20% and 17% respectively for the Phase 3 formulation. Upadacitinib was administered without regards to food in in the Phase 3 studies.

There was no indication of dose dumping of upadacitinib ER formulation when administered with a high-fat meal. Furthermore, results from in vitro dissolution experiments in ethanol, indicate that no dose dumping is expected in vivo.

A level A numerical IVIVC was established using the *in vivo* pharmacokinetic results from Study M15-868 and in vitro dissolution data at pH 6.8 condition.

Distribution

Based on the popPK analysis, upadacitinib volume of distribution at steady state is estimated to be 294 L following administration of the extended-release formulation. Plasma protein binding of upadacitinib was determined by equilibrium dialysis. The mean unbound fraction (fu) in human plasma was 0.48.

Upadacitinib partitions similarly between plasma and blood cellular components, as indicated by the blood to plasma ratio of 1.0.

Elimination

Upadacitinib is eliminated both by the renal and the hepatic route. Approximately 24% and 31% of total upadacitinib radioactive dose were recovered as parent drug in urine and faeces, respectively, in a single-dose study with radiolabeled upadacitinib. This fraction may originate either from absorbed and biliary secreted upadacitinib or of unabsorbed drug. Upadacitinib was a substrate of P-gp and BCRP in vitro. Hence, it is possible that there is either intestinal and/or biliary efflux in vivo. An absolute bioavailability study would have been helpful to further elucidate the absorption/elimination of

upadacitinib. However, considering all available data, a significant part of the fraction excreted unchanged in faeces has likely been absorbed:

- Upadacitinib has high solubility and possibly high permeability.

- Results from the SAD and MAD studies do not indicate that the absorption is saturated at higher doses.

- There was no effect of food on upadacitinib exposure for oral IR formulations.

- About 60% of the parent drug was recovered in the late faecal fractions (>48 h) which likely originate from absorbed upadacitinib.

Thus, if the fraction absorbed is high (i.e. close to 1), the results from the mass-balance study support that 24% is excreted by the renal route, and that metabolism and biliary excretion would account for 31% each. Considering also a worst-case scenario, assuming that the unchanged fraction in faeces constitutes of unabsorbed upadacitinib, then the absolute bioavailability would only be 0.6. In that case, the fraction excreted unchanged in urine would be approximately 40% and metabolism would account for 60% of the total elimination. The true bioavailability is like somewhere in between 0.6 and 1 but there are indications of a relatively high extent of absorption for IR formulations of upadacitinib.

Renal CL was approximately 120 ml/min being higher than fu x GFR implying active secretion of upadacitinib. Based on in vitro data, upadacitinib is a substrate of P-gp but involvement of other renal transporters in the excretion of upadacitinib has not been evaluated. Based on the in vitro data, the CYP 3A4 enzyme is main metabolising enzyme of upadacitinib, the CYP 2D6 playing minor role.

The pharmacologic activity of upadacitinib is attributed to the parent molecule and there are no known active metabolites.

Based on the popPK analysis, upadacitinib CL/F is estimated to be 40.5 L/h for the extended release formulation in the RA patient population.

Upadacitinib mean terminal elimination t1/2 ranged from 9 to 14 hours following administration of the extended-release formulation.

Dose proportionality and time dependencies

Upadacitinib Cmax and AUC were approximately dose-proportional over all evaluated single and multiple immediate- and extended-release dose ranges. This encompassed a) single doses ranging from 1 to 48 mg using the immediate-release formulation, b) multiple BID doses ranging from 3 mg BID to 24 mg BID using the immediate-release formulation, c) single doses ranging from 7.5 to 45 mg using the extended-release formulation, and d) multiple QD doses from 15 mg to 30 mg using the extended-release formulation.

Steady-state was reached after approximately four days of administration of upadacitinib ER. There was no significant accumulation at steady-state, with AUC accumulation ratio (Rac) close to 1. There were no indications of time-dependency in upadacitinib pharmacokinetics.

Special populations

A study in subjects with renal impairment has been performed (n=6 mild renal impairment; n=6 moderate renal impairment; n=6 severe renal impairment; n=6 normal renal function). Upadacitinib exposure (AUCinf) were 18%, 33% and 44% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function.

In a study with subjects with mild hepatic impairment (Child-Pugh [CP]-A, N = 6), moderate hepatic impairment (CP-B, N = 6), and with normal hepatic function (N = 6), upadacitinib AUC was 28% and 24% higher in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function. Upadacitinib was not studied in subjects with severe hepatic impairment.

The covariates gender, race, body weight, and age (≥18 years of age) are not expected to have a clinically relevant effect on upadacitinib pharmacokinetics.

Table 5 Ages of Subjects in the Pharmacokinetic Studies

Studies with Pharmacokinetics Assessments	**Age 65-74 (number of subjects with age of 65-74/total number of evaluated subjects)**	**Age 75-84 (number of subjects with age of 75-84/total number of evaluated subjects)**	**Age 85+ (number of subjects with age of 85+/total number of evaluated subjects)**
Summary in Subjects with RA			
M13-537	43/242	15/242	0/242
M13-542	103/470	18/470	1/470
M13-545	115/669	25/669	1/669
M13-549	84/437	13/437	0/437
M13-550	46/214	16/214	1/214
M14-465	228/1383	36/1383	1/1383
M14-663	31/147	5/147	0/147
M15-555	73/420	10/420	0/420
M13-845 Substudy 2	3/10	0/10	0/10
Total across subjects with RA	726/3992	138/3992	4/3992
Summary in Phase 1 Studies in non-RA patients			
M13-539	2/18	0/18	0/18
M13-551	11/24	1/24	0/24

Pharmacokinetic interaction studies

Upadacitinib as a victim drug

In vitro, upadacitinib was a substrate for CYP3A4, CYP2D6, P-pg and BCRP. Upadacitinib was not a substrate for CYP1A2, 2B6, 2C8, 2C9, 2C18, 2C19, 2J2, FMO1, FMO3, OATP1B1, OATP1B3 or OCT1 in vitro.

In vivo, the effect of the strong CYP3A/P-gp inhibitor ketoconazole, 400 mg QD, on upadacitinib administered as the IR formulation was weak to moderate; upadacitinib AUC and Cmax increased 1.8-

and 1.7-fold respectively, compared to administration of upadacitinib alone. Following multiple doses of rifampicin, a strong CYP3A/P-gp inducer, 600 mg QD for 8 days, upadacitinib AUC and Cmax decreased by 60% and 50% respectively.

Given the comparability of upadacitinib CL/F between subjects with extensive and poor metabolizer phenotypes for CYP2D6, concomitant medications that are strong inhibitors of CYP2D6 are expected to have no effect on upadacitinib plasma exposures.

There is no expected effect of pH modifying medications on upadacitinib pharmacokinetics.

There was no effect on upadacitinib exposure following co-administration with methotrexate.

Upadacitinib as a perpetrator drug

There was no in vivo relevant inhibition by upadacitinib on any of the enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4) or transporters evaluated in vitro (P-gp, BCRP, BSEP, OATP1B1, OATB1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K). Upadacitinib was an inducer of CYP3A4 and CYP2B6 in vitro while the results for CYP1A2 were borderline with only a minor concentration dependence.

The effect of repeated doses of 30 mg upadacitinib on the pharmacokinetics of specific substrates of different CYP enzymes (CYP1A2, 3A, 2D6, 2C9 and 2C19) was evaluated in an in vivo cocktail study. The exposure of oral midazolam was decreased by 26%, indicating that upadacitinib is a weak inducer of CYP3A4. There was no relevant effect on the plasma exposure of CYP1A2, 2D6, 2C9 and 2C19. In a study with bupropion, there was no relevant effect on bupropion AUC or Cmax and hence, no indication of upadacitinib being an inducer of CYP2B6 *in vivo*.

Upadacitinib 30 mg QD decreased rosuvastatin AUC by 33% and atorvastatin AUC by 23% while its metabolite ortho-hydroxyatorvastatin AUC remained unchanged.

The effect of multiple doses of upadacitinib ER 30 mg did not change the exposure of ethinylestradiol and levonorgestrel.

Population pharmacokinetics

A population approach was used to characterize the PK of upadacitinib in target population and healthy subjects, characterize the between-patient variability, assess intrinsic and extrinsic factors that could significantly influence upadacitinib, and estimate individual patient exposure for exposure-response analyses. The population analyses were performed in two steps, first based on phase 1-2 data in support of dose selection for phase 3. Upon the availability of the phase 3 data, the population PK model was reassessed with phase 1-3 data.

A two-compartment model with first-order absorption for the immediate-release formulation, mixed zero and first order absorption with lag time for the extended-release formulation, and linear elimination adequately described upadacitinib pharmacokinetics. Statistically significant covariates were patient population (RA versus healthy), creatinine clearance, and baseline bodyweight on CL/F; and body weight on Vc/F. For a typical RA patient and reference body weight of 74 kg and CrCL of 109 mL/min, upadacitinib CL/F is estimated to be 40.5 L/h and the volume of distribution at steady state is estimated to be 294 L following administration of the extended-release formulation. The inter-subject variability for upadacitinib CL/F and Vc/F were estimated to be 21%, 24%, respectively, in the Phase 1 studies, and 37% and 53%, respectively, in the Phase 2/3 studies. The oral bioavailability of the extended-release formulation relative to immediate-release formulation was estimated to be 76%.

Summary of upadacitinib model-estimated plasma exposures at steady-state in subjects with RA who received the extended-release formulation regimens 15 mg or 30 mg QD are summarized in the table below (based on the empirical Bayesian individual pharmacokinetic parameter estimates).

Table 6 Summary of C_{max}, C_{avg}, and C_{trough} from 15 mg and 30 mg QD Regimens Using the Extended-Release Formulation in Subjects with RA Based on the Individual Pharmacokinetic Parameter Estimates from the Population Pharmacokinetic Model

Treatment	C_{max} (ng/mL) [mean; median (5^{th} – 95^{th} Percentiles)]	C_{avg} (ng/mL) [mean; median (5^{th} – 95^{th} Percentiles)]	C_{trough} (ng/mL) [mean; median (5^{th} – 95^{th} Percentiles)]
15 mg QD	41.3; 41.1 (28.2 – 56.0)	16.5; 15.1 (8.96 – 32.7)	5.67; 3.82 (1.28 – 21.3)
30 mg QD	83.4; 82.0 (57.7 – 117)	32.5; 30.0 (18.1 – 63.8)	10.7; 7.74 (2.49 – 40.5)

2.4.3. Pharmacodynamics

Mechanism of action

Janus Kinases (JAKs) are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, haematopoiesis and immune surveillance. The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and TYK2 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.

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. In healthy volunteers, the administration of upadacitinib (immediate release formulation) resulted in a dose-, and concentration-dependent inhibition of IL-6 (JAK1/JAK2) - induced STAT3 and IL-7 (JAK1/JAK3)-induced STAT5 phosphorylation in whole blood. The maximal inhibition was observed 1 hour after dosing which returned to near baseline by the end of dosing interval.

Primary and Secondary pharmacology

Upadacitinib doses evaluated in the two Phase 2 dose-ranging studies were selected based on exposure-response analyses for the effects of upadacitinib on interleukin (IL)-6 and IL-7 signalling pathways evaluated in ex-vivo assays compared to tofacitinib 5 mg BID in early Phase 1 studies. The applicant carried out exposure response analysis from Phase 2 studies and Phase 3 studies that supported the selection of 15 mg QD for the sought RA indication.

Exposure-QT

To evaluate the risk of the QT interval prolongation and pro-arrhythmic potential of upadacitinib, a linear mixed-effects exposure-response analysis was conducted. The effect of food on the QT interval corrected for heart rate by Fridericia's formula (QTcF) in subjects who received placebo under non-fasting conditions in the multiple ascending dose (MAD) study versus those who received placebo under fasting conditions in the upadacitinib single ascending dose study was used to evaluate ECG assay sensitivity. Bias analysis which explored the relationship between the means and differences of the semi-automated and fully-automated QT measurements was conducted to ensure lack of bias in the QT intervals corrected by the over-reader and protect against false negatives. The analyses

demonstrated that there was no relationship between upadacitinib plasma concentrations and QT interval prolongation at therapeutic or supra-therapeutic plasma exposures.

Exposure-efficacy

Exposure-response analyses characterized the relationships between upadacitinib exposures and efficacy (assessed as the percentage of subjects achieving ACR20/50/70) using data from the two dose-ranging Phase 2 studies and supported, along with the analyses of safety, the selection of doses for Phase 3. The results of the analyses indicated that upadacitinib plasma exposures associated with 6 mg BID to 12 mg BID using the immediate-release formulation were predicted to maximize efficacy in patients with moderate to severely active RA who are on background treatment of MTX. Upadacitinib doses of 15 mg QD and 30 mg QD using the ER formulation were predicted to have similar efficacy to 6 mg BID and 12 mg BID using the immediate-release formulation. Upadacitinib dose of 3 mg BID using the immediate-release formulation (7.5 mg using the ER formulation) was predicted to provide sub-optimal efficacy compared to higher doses, especially in the more refractory anti-TNF-IR population.

Based on exposure-response analyses of efficacy and effects on laboratory parameters in Phase 2 studies, upadacitinib 15 mg and 30 mg QD doses using the ER formulation were predicted to provide the optimal balance of benefit-risk in subjects with moderately to severely active RA and were selected to be evaluated in Phase 3.

Exposure-response analyses based on both phase 2 and phase 3 data, demonstrated that plasma exposures associated with upadacitinib 15 mg QD dose maximize upadacitinib efficacy and the 30 mg QD dose provides only a small incremental benefit in subjects with RA (≤ 5% increase in ACR20, ACR50, ACR70, LDA based on disease activity score 28 joint count based on C-reactive protein [DAS28 (CRP)] or CR based on DAS28 (CRP) from 15 mg QD to 30 mg QD).

Exposure-safety

The relationship between upadacitinib C_{avg} and the probability of experiencing specific changes in hemoglobin, natural killer (NK) cells, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), creatine phosphokinase (CPK), and neutrophils at Week 12 in Phase 2b studies (Studies M13-537 and M13-550) were characterized. The analyses demonstrated that upadacitinib doses higher than 12 mg BID using the immediate-release formulation (30 mg QD using the ER formulation) were predicted to result in greater effects on hemoglobin, NK cells and CPK compared to 12 mg BID. Decreases in hemoglobin were observed mostly at exposures associated with doses of ≥ 12 mg BID immediate-release (30 mg QD ER formulation) or higher.

Exposure-response relationships were evaluated for the different safety measures using a pooled dataset across Phase 2 and 3 studies. No trends for exposure-response relationships were observed for pneumonia, herpes zoster infection, changes in platelet count (platelets ≥ 600 × 10^9/L with baseline ≤ 400 × 10^9/L, platelets > 400 × 10^9/L with baseline ≤ 400 × 10^9/L), lymphopenia (Grade 4 or higher), and neutropenia (Grade 3 or higher) at Week 12/14 or Week 24/26.

Increased upadacitinib exposures were statistically associated with higher incidence of hemoglobin decrease from baseline (> 1 g/dL and > 2 g/dL) at Week 12/14 and at Week 24/26; decreases in hemoglobin were observed mostly at exposures associated with 30 mg QD or higher. Upadacitinib exposures were associated with higher incidence of lymphopenia Grade 3 or higher at Week 12/14, but was not statistically significant at Week 24/26. Upadacitinib exposures were associated with slight increase in the incidence of serious infections at Week 24/26, but not at Week 12/14. Upadacitinib plasma AUC was comparable between subjects who experienced venous thromboembolic event or

major adverse cardiovascular event and subjects who did not experience these events based on long-term safety data across the Phase 3 studies.

Based on the established exposure-safety relationships, scenarios for increases in exposures by 25% to 75% were simulated which cover the effects of all evaluated intrinsic and extrinsic factors. A summary of the simulated effects is in the table below.

Table 7 Model-Simulated Percentage of Subjects Experiencing Safety Outcomes with Increased Upadacitinib Cmax or Cavg Relative to 15 mg QD Dose.

	Simulated Percentage of Subjects Based on C_{avg} Modeling		Simulated Percentage of Subjects Based on C_{max} Modeling	
Scenario	**Median**	**90% Confidence Interval**	**Median**	**90% Confidence Interval**
Percentage of Subjects with > 2 g/dL Decrease from Baseline in Hemoglobin at Week 12				
Reference (15 mg QD)	1.4	0.0, 3.6	1.4	0.0, 3.6
25% Higher Upadacitinib Exposure	1.4	0.0, 4.3	2.1	0.7, 3.6
50% Higher Upadacitinib Exposure	2.1	0.7, 5.0	2.1	0.7, 5.0
75% Higher Upadacitinib Exposure	3.6	0.7, 5.7	2.8	1.4, 5.7
Percentage of Subjects with Lymphopenia Grade 3 or Higher at Week 12				
Reference (15 mg QD)	5.3	3.0, 8.3	6.2	3.0, 9.0
25% Higher Upadacitinib Exposure	6.0	3.0, 8.3	6.8	3.7, 9.8
50% Higher Upadacitinib Exposure	6.0	3.0, 9.0	6.8	4.5, 10.5
75% Higher Upadacitinib Exposure	6.8	3.8, 9.8	7.5	4.5, 11.3
Percentage of Subjects with Serious Infections at Week 24				
Reference (15 mg QD)	1.7	0.6, 3.4	1.7	0.6, 3.4
25% Higher Upadacitinib Exposure	1.7	0.6, 3.9	1.7	0.6, 3.9
50% Higher Upadacitinib Exposure	2.2	0.6, 3.9	1.7	0.6, 3.9
75% Higher Upadacitinib Exposure	2.2	0.6, 3.9	2.2	0.6, 3.9

2.4.4. Discussion on clinical pharmacology

Bioanalytical methods

The bioanalytical method was in general well validated.

Absorption

Overall the clinical pharmacokinetics of upadacitinib in healthy subjects has been extensively evaluated. There are uncertainties in the bioavailability and absorption of upadacitinib because the absolute bioavailability has not been studied. However, this was considered acceptable to CHMP.

Following oral administration of upadacitinib prolonged-release formulation, upadacitinib is absorbed with a median Tmax of 2 to 4 hours.

The 25-30% lower bioavailability of the extended-release tablet relative to immediate-release formulations may be the result of lower permeability of upadacitinib in the distal part of the intestine/colon. The effect of a high-fat meal appears to be somewhat higher for the proposed commercial formulation than for the Phase 3 formulation. For the commercial formulation,

upadacitinib Cmax and AUC increased 39% and 29% respectively, relative to the fasting conditions while Cmax and AUC increased by 20% and 17% respectively for the Phase 3 formulation. The food-effect is not considered to be clinically relevant and the CHMP agreed that upadacitinib may be administered with or without food. In clinical trials, upadacitinib was administered without regard to meals.

In vitro, upadacitinib is a substrate for the efflux transporters P-gp and BCRP.

Distribution

Upadacitinib has a relatively large volume of distribution. Plasma protein binding is moderate (52%).

Elimination

Following single dose administration of [14C]-upadacitinib immediate-release solution, upadacitinib was eliminated predominantly as the unchanged parent substance in urine (24%) and faeces (31%).

Renal CL indicates some involvement of renal transporters in the excretion. Renal secretion is however not estimated to contribute to more than 25% of the elimination.

In vitro, upadacitinib was mainly metabolised by CYP3A4 and to a lesser extent by CYP2D6. Involvement of CYP3A4 was confirmed in an *in vivo* interaction study with ketoconazole where a 1.75-fold increase in upadacitinib exposure was observed. The contribution of CYP2D6 is expected to be minor given the comparability of upadacitinib CL/F in extensive and poor metabolisers in the Phase 1 and Phase 2 population (popPK analysis).

Approximately 34% of upadacitinib dose was excreted as metabolites.

Upadacitinib mean terminal elimination half-life ranged from 9 to 14 hours.

Special populations

The effect of different intrinsic factors has been evaluated in dedicated PK studies in renal and hepatic impairment and in Asian subjects, and by population pharmacokinetic analysis from the phase 2/3 studies.

Upadacitinib AUC was 18%, 33% and 44% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. This is consistent with an approximately 25% contribution of the renal route to upadacitinib elimination. Based on the exposure-response analyses, no dose adjustment is necessary in patients with renal impairment. However, as stated in the SmPC, upadacitinib should be used with caution in patients with severe renal impairment. The use of upadacitinib has not been studied in subjects with end stage renal disease.

The effect of mild and moderate hepatic impairment on upadacitinib pharmacokinetics was modest. AUC increased by 28 and 24% in subjects with mild and moderate hepatic impairment respectively compared to normal subjects. No dose adjustment is proposed in these patients. Data for severe hepatic impairment is missing. Based on clinical considerations, upadacitinib is contraindicated in severe hepatic impairment patients.

The population pharmacokinetic analysis indicated no relevant effects of gender, race, age or weight on upadacitinib pharmacokinetic parameters. As stated in the SmPC, there are limited data in patients aged 75 years and older and there is no pharmacokinetic data in children and adolescents.

Interactions

The drug interaction potential with methotrexate has been addressed adequately and no clinically significant drug interaction was observed.

Upadacitinib as victim drug

Based on the elimination mechanisms (CYP3A4 metabolism, transport via Pgp and BCRP), the relevant in vivo interaction studies have been performed, i.e. with ketoconazole (CYP3A4/Pgp inhibitor) and rifampicin (PXR inducer). A study with a BCRP inhibitor was not performed, but this is acceptable as, at present, there are few or no specific BCRP inhibitors used clinically.

The strong CYP3A4/P-gp inhibitor ketoconazole increased upadacitinib AUC and Cmax 1.75 and 1.7-fold. There was no effect on half-life indicating an effect mainly on pre-systemic metabolism or P-gp. Multiple doses of rifampicin, a strong PXR inducer, decreased upadacitinib AUC by 60%. An appropriate wording for concomitant administration with 3A4 inhibitors and inducers is included in the SmPC. The effect of moderate CYP3A4/P-gp inhibitors on upadacitinib exposure is not expected to be clinically relevant.

Upadacitinib as a perpetrator drug:

The potential of upadacitinib to act as perpetrator in drug-drug interactions was thoroughly investigated in vitro in accordance with the EMA interaction guideline. There was no in vivo relevant inhibition by upadacitinib on any of the enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4) or transporters evaluated in vitro (P-gp, BCRP, BSEP, OATP1B1, OATB1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K). Upadacitinib was identified as an inducer of CYP3A4 (PXR) and CYP2B6 (CAR) in vitro, while the results for CYP1A2 (Ah-receptor) were borderline with only a minor concentration dependence.

In vivo, the exposure of oral midazolam, a sensitive CYP3A4 substrate, was decreased by 26%, indicating that upadacitinib (30 mg dose) is a weak inducer of the PXR-mediated metabolism by CYP3A4. The effect is expected to be lower with the clinical dose 15 mg. There was no inducing effect of upadacitinib on ethinylestradiol/levonorgestrel following multiple-doses of upadacitinib ER 30 mg. There was no relevant effect on the plasma exposure of other PXR regulated enzymes (CYP2C9 and 2C19) or enzymes regulated by the Ah-receptor (CYP1A2). In a study with bupropion, there was no relevant effect on bupropion AUC or Cmax and hence, no indication of upadacitinib being an inducer of CAR (CYP2B6).

Upadacitinib 30 mg QD decreased rosuvastatin AUC by 33% and atorvastatin AUC by 23% while its metabolite ortho-hydroxyatorvastatin AUC remained unchanged.

Population PK

Standard population analysis methodology for model development and evaluation has been used. Parameter uncertainty values, goodness-of-fit plots, and visual predictive checks all indicate that the final PopPK model provides an adequate description of upadacitinib PK.

Shrinkage for empirical Bayes estimates of CL and V2 in RA patients are 19% and 50%, respectively. These values indicate that predicted individual average concentrations are considered adequate for exposure-response analyses, since CL is the most influential parameter for average concentration. The CHMP noted that predicted individual C_{max} concentrations are expected to be shrunk towards the population mean; hence, exposure-response model results using C_{max} as the exposure metric should be interpreted with some caution.

Pharmacodynamics

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

Exposure-QTc

Data from MAD and SAD studies with an exposure range well exceeding therapeutic exposure rage were used for the exposure-QTc analysis. Furthermore, the concentration and the ECG measurements were time-matched. Overall, the data used for the exposure-QTc analysis is considered adequate.

The analysis methodology follows the ICH E14 Q&A and is considered acceptable. The upper bound of the 2-sided 90% confidence interval of the predicted ΔΔQTcF was below 3.33 msec for the highest exposure level (442 ng/mL) which is well below the upper cut-off of 10 msec. Subsequently it is concluded that upadacitinib has no clinically relevant effect on the QT interval.

Exposure-efficacy

The exposure-efficacy analyses for both ACR and LDA/CR response variables display that the efficacy of upadacitinib is (dose)-exposure-dependent.

The applicant carried out exposure response analysis from Phase 2 studies and Phase 3 studies that supported the selection of 15 mg QD for the sought RA indication.

Exposure-safety

Logistic regression models were used to describe the effect of upadacitinib on safety endpoints at week 12/14 and week 24/26. Separate models have been developed for week 12/14 and 24/26 data and consequently no time-effect has been evaluated. However, standard logistic regression models have been developed and evaluated, and the model-based analysis methodology is considered adequate. Furthermore, the exposure-safety models are considered appropriate to use to support the dose justification for upadacitinib.

Exposure-dependent changes were observed for decreases in hemoglobin and Grade 3 or higher lymphopenia, as well as for severe infection. As reflected in the SmPC, treatment should not be initiated in patients with an absolute lymphocyte count (ALC) that is < 500 cells/mm3, an absolute neutrophil count (ANC) that is < 1,000 cells/mm3 or who have haemoglobin (Hb) levels that are < 8 g/dL In addition, treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

The analyses demonstrated that there was no relationship between upadacitinib plasma concentrations and QT interval prolongation at therapeutic or supra therapeutic plasma exposures.

Graphical analysis for exposure versus MACE and VTE events have been provided. No trend with increasing exposure and MACE or VTE event could be detected.

2.4.5. Conclusions on clinical pharmacology

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.

The pharmacokinetics and the interaction potential of upadacitinib have been thoroughly investigated.

Population PK analyses are in general well described. The exposure-response analyses describe the relationship between upadacitinib plasma concentrations and efficacy and safety sufficiently well to support the recommended upadacitinib dose of 15mg once daily.

Treatment with upadacitinib should not be initiated in patients with an absolute lymphocyte count (ALC) that is < 500 cells/mm3, an absolute neutrophil count (ANC) that is < 1,000 cells/mm3 or who have haemoglobin (Hb) levels that are < 8 g/dL In addition, treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

2.5. Clinical efficacy

Considering the indication sought by the applicant, study M13-545 (1st line) could be considered supportive rather than pivotal. However, it does include important data for the sought indication; hence, it will be described among the pivotal studies.

2.5.1. Dose response studies

2.5.1.1. Study M13-537

Methods

Phase 2, randomized, double-blind, parallel-group, placebo-controlled multicenter study comparing the safety and efficacy of multiple doses of ABT-494 versus placebo administered for 12 weeks in subjects with moderately to severely active RA who had shown inadequate response to MTX and were naïve to biologic therapy. Subjects who met eligibility criteria were randomized to placebo twice daily (BID) or ABT-494 3 mg BID, 6 mg BID, 12 mg BID, 18 mg BID, or 24 mg once daily (QD) (immediate-release capsules). The primary endpoint was ACR20 response rate at Week 12.

Results

The outcome of the primary endpoint is displayed in the table below.

Table 8: ACR20 Response Rates at Week 12 (mITT Population; LOCF) in study M13-537

		ABT-494				
Variable at Week 12	Placebo	3 mg BID	6 mg BID	12 mg BID	18 mg BID	24 mg QD
ACR20 response rate						
N	46	48	49	49	47	49
Responder, n (%)	23 (50.0)	31 (64.6)	36 (73.5)	40 (81.6)	36 (76.6)	40 (81.6)
P value[a]	-	n.s.	0.018	0.001	0.008	0.001

n.s. = not statistically significant ($P > 0.05$)

a. *P* value for comparison between ACR20 response rate for treatment group and placebo group was calculated using a chi-square test or Fisher's exact test (if ≥ 20% of the cells had expected counts less than 5).

Note: The primary analysis was performed using LOCF missing data imputation but with the as-observed approach for joints not assessed and replaced (i.e., not imputed).

The outcomes of the secondary endpoints are displayed in the table below.

Table 9: ACR50/70 Responses and Proportion of Subjects Achieving LDA at Week 12 (mITT Population; LOCF) in study M13-537

Variable at Week 12	Placebo	ABT-494				
		3 mg BID	6 mg BID	12 mg BID	18 mg BID	24 mg QD
ACR50 response rate						
N	46	48	49	50	47	48
Responder, n (%)	9 (19.6)	19 (39.6)	24 (49.0)	25 (50.0)	21 (44.7)	21 (43.8)
P value[a]		0.034	0.003	0.002	0.010	0.012
ACR70 response rate						
N	46	47	49	50	47	48
Responder, n (%)	3 (6.5)	11 (23.4)	15 (30.6)	8 (16.0)	13 (27.7)	12 (25.0)
P value[a]		0.023	0.003	n.s.	0.007	0.014
LDA (DAS28 [CRP]) < 3.2[b])						
N	47	49	49	50	49	49
Responder, n (%)	10 (21.3)	24 (49.0)	28 (57.1)	23 (46.0)	25 (51.0)	21 (42.9)
P value[a]		0.005	< 0.001	0.010	0.002	0.024
LDA (CDAI ≤ 10[b])						
N	47	49	49	50	49	49
Responder, n (%)	10 (21.3)	20 (40.8)	20 (40.8)	20 (40.0)	24 (49.0)	18 (36.7)
P value[a]		0.039	0.039	0.046	0.005	n.s.
Clinical remission (DAS28 [CRP]) < 2.6])						
N	47	49	49	50	49	49
Responder, n (%)	7 (14.9)	18 (36.7)	19 (38.8)	17 (34.0)	21 (42.9)	11 (22.4)
P value[a]		0.015	0.008	0.029	0.003	n.s.
Clinical remission (CDAI ≤ 2.8)						
N	47	49	49	50	49	49
Responder, n (%)	2 (4.3)	6 (12.2)	7 (14.3)	3 (6.0)	7 (14.3)	3 (6.1)
P value[a]		n.s.	n.s.	n.s.	n.s.	n.s.

n.s. = not statistically significant ($P > 0.05$)

a. *P* value for comparison between treatment group and placebo group was calculated using a chi-square test or Fisher's exact test (if ≥ 20% of the cells had expected counts less than 5).

b. Subjects who achieved clinical remission are included in LDA criteria cited.

The outcome of PK-analysis and safety-analyses are discussed in separate sections of this AR. In brief, the proportion of subjects with any AE was in the placebo, 3 mg BID, 6 mg BID, 12 mg BID, 18 mg BID and 24 mg QD groups: 26.0, 40.0, 46.0, 58.0, 50.0 and 34.7%. The proportion of subjects with any SAE was the placebo, 3 mg BID, 6 mg BID, 12 mg BID, 18 mg BID and 24 mg QD groups: 0, 0, 4.0, 2.0, 6.0 and 4.1%. There were no AEs leading to death in any of the groups during the conduct of the study. However, one death from lung neoplasm malignant occurred 14 weeks after study completion, this patient belonged to the 6 mg BID group.

2.5.1.2. Study M13-550

Methods

Phase 2, randomized, double-blind, parallel-group, placebo-controlled multicenter study comparing the safety and efficacy of multiple doses of ABT-494 versus placebo administered for 12 weeks in subjects with moderately to severely active RA who had an inadequate response or intolerance to anti-TNF biologic therapy. Subjects were randomized to placebo twice daily (BID) or ABT-494 3 mg BID, 6 mg BID, 12 mg BID, or 18 mg BID (immediate release capsules). The primary endpoint was ACR20 response rate at Week 12.

Results

The outcome of the primary endpoint and the secondary endpoints are presented in the respective below tables.

Table 10: ACR20 Response Rates at Week 12 (mITT Population; LOCF) in study M13-550

Variable at Week 12	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID	ABT-494 12 mg BID	ABT-494 18 mg BID
ACR20 response rate					
N	54	54	52	55	55
Responder, n (%)	19 (35.2)	30 (55.6)	33 (63.5)	40 (72.7)	39 (70.9)
P value[a]	--	0.033	0.004	< 0.001	< 0.001

a. Comparison between ACR20 response rate for treatment group and placebo group using a chi-square test or Fisher's exact test (if 20% of the cells had expected counts less than 5).

Note: The primary analysis was performed using LOCF missing data imputation but with the as observed approach for joints not assessed and replaced (i.e., not imputed).

Table 11: ACR50/70 Responses and Proportion of Subject Achieving LDA and Clinical Remission at Week 12 (mITT Population; LOCF) in study M13-550

Variable at Week 12	Placebo	ABT-494 3 mg BID	ABT-494 6 mg BID	ABT-494 12 mg BID	ABT-494 18 mg BID
ACR50 response rate					
N	53	54	52	55	55
Responder, n (%)	9 (17.0)	13 (24.1)	20 (38.5)	24 (43.6)	22 (40.0)
P value[a]	--	n.s.	0.014	0.003	0.008
ACR70 response rate					
N	55	54	52	55	55
Responder, n (%)	2 (3.6)	7 (13.0)	14 (26.9)	12 (21.8)	12 (21.8)
P value[a]	--	n.s.	< 0.001	0.004	0.004
LDA (DAS28 [CRP]) < 3.2[b])					
N	55	54	53	55	55
Responder, n (%)	14 (25.5)	18 (33.3)	20 (37.7)	29 (52.7)	25 (45.5)
P value[a]	--	n.s.	n.s.	0.003	0.028
Clinical remission (DAS28[CRP])					
N	55	54	53	55	55
Responder, n (%)	7 (12.7)	13 (24.1)	14 (26.4)	18 (32.7)	17 (30.9)
P value[a]	--	n.s.	n.s.	0.012	0.021

The outcome of PK-analysis and safety-analyses are discussed in separate sections of this AR. In brief, the proportion of subjects with any AE was in the placebo, 3 mg BID, 6 mg BID, 12 mg BID and 18 mg BID: 44.6, 47.3, 56.4, 67.3 and 70.9%. The proportion of subjects with any SAE was in the placebo, 3 mg BID, 6 mg BID, 12 mg BID and 18 mg BID: 1.8, 3.6, 3.6, 0 and 1.8%. There were no AES leading to deaths in any of the treatment groups.

2.5.1.3. Study M14-663

Methods

This was a Phase 2b/3 multicenter study that included two periods. Period 1 was a 12-week, randomized, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 7.5 mg QD, 15 mg QD, and 30 mg QD (extended-release tablets) versus placebo for the treatment of signs and symptoms of Japanese subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs. The primary endpoint was ACR 20 response at week 12.

Results

The outcomes of the primary and secondary efficacy endpoints are displayed in the tables below.

Table 12: Summary of ACR20 Response Rate at Week 12 with Cochran-Armitage Test (NRI; FAS) in Study M14-663

Treatment	N	Responder n (%)	Responder Rate (95% CI)[a]	Response Rate Difference (Upadacitinib – Placebo)			
				Point Estimate	95% CI[b]	P-value[c]	P-value[d]
Placebo	49	21 (42.9)	42.9 (29.0, 56.7)				
Upadacitinib 7.5 mg QD	49	37 (75.5)	75.5 (63.5, 87.6)	32.7	(14.3, 51.0)	< 0.001***	< 0.001***
Upadacitinib 15 mg QD	49	41 (83.7)	83.7 (73.3, 94.0)	40.8	(23.5, 58.1)	< 0.001***	
Upadacitinib 30 mg QD	50	40 (80.0)	80.0 (68.9, 91.1)	37.1	(19.4, 54.9)	< 0.001***	

a. 95% confidence intervals (CIs) for response rate were calculated based on normal approximation to the binominal distribution.

b. 95% CIs for response rate difference were calculated based on normal approximation using Proc Freq.

c. Nominal p-value was constructed using Cochran-Mantel-Haenszel test adjusted for stratification factor prior bDMARD use.

d. P-value was constructed using Cochran-Armitage trend test for dose-response.

***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively.

Table 13: Summary of Secondary Endpoint Results at Week 12 (FAS) in study M14-663

Endpoint[a] Treatment	N	Within Group Point Estimate (95% CI)	Between Group Difference (Upadacitinib - Placebo) Point Estimate (95% CI)	P-Value
DAS28 (CRP) change from baseline				
Placebo	49	–0.79 (–1.158, –0.426)		
Upadacitinib 7.5 mg QD	49	–2.08 (–2.430, –1.727)	–1.29 (–1.693, –0.880)	< 0.001***
Upadacitinib 15 mg QD	49	–2.39 (–2.735, –2.043)	–1.60 (–2.005, –1.190)	< 0.001***
Upadacitinib 30 mg QD	50	–2.41 (–2.776, –2.050)	–1.62 (–2.027, –1.216)	< 0.001***
HAQ-DI change from baseline				
Placebo	49	–0.10 (–0.245, 0.043)		
Upadacitinib 7.5 mg QD	49	–0.41 (–0.545, –0.267)	–0.30 (–0.465, –0.144)	< 0.001***
Upadacitinib 15 mg QD	49	–0.45 (–0.583, –0.309)	–0.34 (–0.505, –0.184)	< 0.001***
Upadacitinib 30 mg QD	50	–0.49 (–0.636, –0.347)	–0.39 (–0.550, –0.229)	< 0.001***
ACR50 response rate				
Placebo	49	16.3 (6.0, 26.7)		
Upadacitinib 7.5 mg QD	49	40.8 (27.1, 54.6)	24.5 (7.3, 41.7)	0.007**
Upadacitinib 15 mg QD	49	65.3 (52.0, 78.6)	49.0 (32.1, 65.9)	< 0.001***
Upadacitinib 30 mg QD	50	58.0 (44.3, 71.7)	41.7 (24.5, 58.8)	< 0.001***
ACR70 response rate				
Placebo	49	2.0 (0.0, 6.0)		
Upadacitinib 7.5 mg QD	49	20.4 (9.1, 31.7)	18.4 (6.4, 30.3)	0.004**
Upadacitinib 15 mg QD	49	34.7 (21.4, 48.0)	32.7 (18.7, 46.6)	< 0.001***
Upadacitinib 30 mg QD	50	28.0 (15.6, 40.4)	26.0 (12.9, 39.0)	< 0.001***
SF–36 PCS change from baseline				
Placebo	47	2.88 (1.03, 4.72)		
Upadacitinib 7.5 mg QD	49	7.21 (5.43, 8.99)	4.33 (2.10, 6.57)	< 0.001***
Upadacitinib 15 mg QD	48	6.38 (4.60, 8.15)	3.50 (1.25, 5.75)	0.002**
Upadacitinib 30 mg QD	44	8.81 (6.93, 10.68)	5.93 (3.64, 8.22)	< 0.001***
LDA based on DAS28 (CRP)				
Placebo	49	18.4 (7.5, 29.2)		
Upadacitinib 7.5 mg QD	49	53.1 (39.1, 67.0)	34.7 (17.0, 52.4)	< 0.001***
Upadacitinib 15 mg QD	49	69.4 (56.5, 82.3)	51.0 (34.2, 67.9)	< 0.001***
Upadacitinib 30 mg QD	50	72.0 (59.6, 84.4)	53.6 (37.1, 70.1)	< 0.001***

Endpoint[a] Treatment	N	Within Group Point Estimate (95% CI)	Between Group Difference (Upadacitinib - Placebo) Point Estimate (95% CI)	P-Value
Clinical remission based on DAS28 (CRP)				
Placebo	49	6.1 (0.0, 12.8)		
Upadacitinib 7.5 mg QD	49	36.7 (23.2, 50.2)	30.6 (15.5, 45.7)	< 0.001***
Upadacitinib 15 mg QD	49	57.1 (43.3, 71.0)	51.0 (35.6, 66.4)	< 0.001***
Upadacitinib 30 mg	50	50.0 (36.1, 63.9)	43.9 (28.5, 59.3)	< 0.001***
ACR20 response rate at Week 1				
Placebo	49	8.2 (0.5, 15.8)		
Upadacitinib 7.5 mg QD	49	30.6 (17.7, 43.5)	22.4 (7.4, 37.5)	0.006**
Upadacitinib 15 mg QD	49	24.5 (12.4, 36.5)	16.3 (2.1, 30.6)	0.026*
Upadacitinib 30 mg QD	50	34.0 (20.9, 47.1)	25.8 (10.6, 41.0)	0.002**
FACIT-F change from baseline				
Placebo	47	1.81 (–0.35, 3.97)		
Upadacitinib 7.5 mg QD	49	4.47 (2.38, 6.55)	2.66 (0.12, 5.20)	0.040*
Upadacitinib 15 mg QD	48	3.60 (1.53, 5.68)	1.79 (–0.77, 4.35)	0.169
Upadacitinib 30 mg QD	44	2.66 (0.48, 4.85)	0.85 (–1.73, 3.43)	0.516
RA-WIS change from baseline				
Placebo	34	–0.69 (–2.58, 1.21)		
Upadacitinib 7.5 mg QD	31	–3.22 (–5.09, –1.36)	–2.54 (–4.68, –0.39)	0.021*
Upadacitinib 15 mg QD	24	–2.74 (–4.75, –0.74)	–2.06 (–4.36, 0.25)	0.080
Upadacitinib 30 mg QD	18	–2.24 (–4.40, –0.09)	–1.56 (–4.06, 0.94)	0.220
Morning stiffness (severity) change from baseline				
Placebo	47	–1.02 (–1.65, –0.39)		
Upadacitinib 7.5 mg QD	49	–2.83 (–3.44, –2.22)	–1.81 (–2.57, –1.04)	< 0.001***
Upadacitinib 15 mg QD	48	–2.84 (–3.45, –2.23)	–1.82 (–2.59, –1.05)	< 0.001***
Upadacitinib 30 mg QD	44	–2.98 (–3.62, –2.34)	–1.96 (–2.73, –1.18)	< 0.001***

a. Results for binary endpoints were based on NRI. Results for DAS28 (CRP) and HAQ-DI were based on analysis of covariance with multiple imputation (MI) for missing data handling. Results for other continuous endpoints were based on Mixed Effect Model Repeat Measurement (MMRM) model.

***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively.

The proportion of subjects with any AE was in the placebo, upadacitinib 7.5 mg QD, 15 mg QD, 30 mg QD: 49.0, 59.2, 57.1 and 74.0. The proportion of subjects with any SAE was in the placebo, upadacitinib 7.5 mg QD, 15 mg QD, 30 mg QD: 0, 2.0, 2.0 and 10.0%. No deaths were reported through Week 12 (Period 1). After Week 12, 2 deaths were reported and both subjects were initially randomized to the upadacitinib 30 mg group.

2.5.2. Main studies

M13-545 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Once Daily Monotherapy to Methotrexate (MTX)

Monotherapy in MTX-Naïve Subjects with Moderately to Severely Active Rheumatoid Arthritis" (Select Early)

Methods

Study Participants

Inclusion criteria (summary of most notable)

- Duration of symptoms consistent with RA for ≥ 6 weeks and fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA
- Naïve to MTX or, if already on MTX, have received no more than 3 weekly MTX doses with requirement to complete a 4-week MTX washout before the first dose of study drug.
- Subjects with prior exposure to csDMARDs other than MTX may have been enrolled if completed the defined washout period or washout should have been at least five times the mean terminal elimination half-life of a drug.
- ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at screening and baseline visits and high-sensitivity C-reactive protein (hsCRP) ≥ 5 mg/L (central lab, upper limit of normal [ULN] 2.87 mg/L) at screening
- ≥ 1 bone erosion on x-ray (by local reading) or in the absence of documented bone erosion, both positive rheumatoid factor (RF) and positive anti-cyclic citrullinated peptide (anti-CCP) autoantibodies at screening

Exclusion criteria (summary of most notable)

- Intolerant to MTX
- Prior exposure to any JAK inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib) or any bDMARD(s);

There were also exclusion criteria related to abnormal laboratory values, active infections, history of malignancy/ gastrointestinal perforation/allergic reactions/ cardiovascular conditions and systemic use of known strong cytochrome P450 3A (CYP3A) inhibitors or strong CYP3A inducers.

Treatments

The study is a Phase 3 multicenter study that includes Period 1 (48 weeks) and Period 2 (up to 4 years) and a Japan sub-study, see figure below for treatment groups and overall design. An unblinded analysis was conducted when all subjects had completed Week 24 or otherwise prematurely discontinued. Subjects and sites remained blinded until after all subjects had completed Period 1. The interim week 24 report (CSR) for this study was included in the current submission.

Rescue therapy was defined for Weeks 12 through 24, Week 26, and Weeks 36 through 40. Rescue therapy for those subjects who meet the following criteria from Week 12 through Week 24 are as follows: Those who do not achieve ≥ 20% improvement in both TJC and SJC compared with baseline at two consecutive visits starting at Week 12 will continue on their blinded therapy and the Investigator should optimize background RA medications (NSAIDs, corticosteroids and/or low-potency analgesics). Subjects who meet the joint count rescue criteria at Week 16 or 20 were treated as non-responders at Week 24 for the primary analysis. Rescue possibilities at week 26, for patients that did not achieve CR

by CDAI, included either optimization of background RA medications or addition of the other drug (MTX or upadacitinib) depending on the degree of response registered, see figure below.

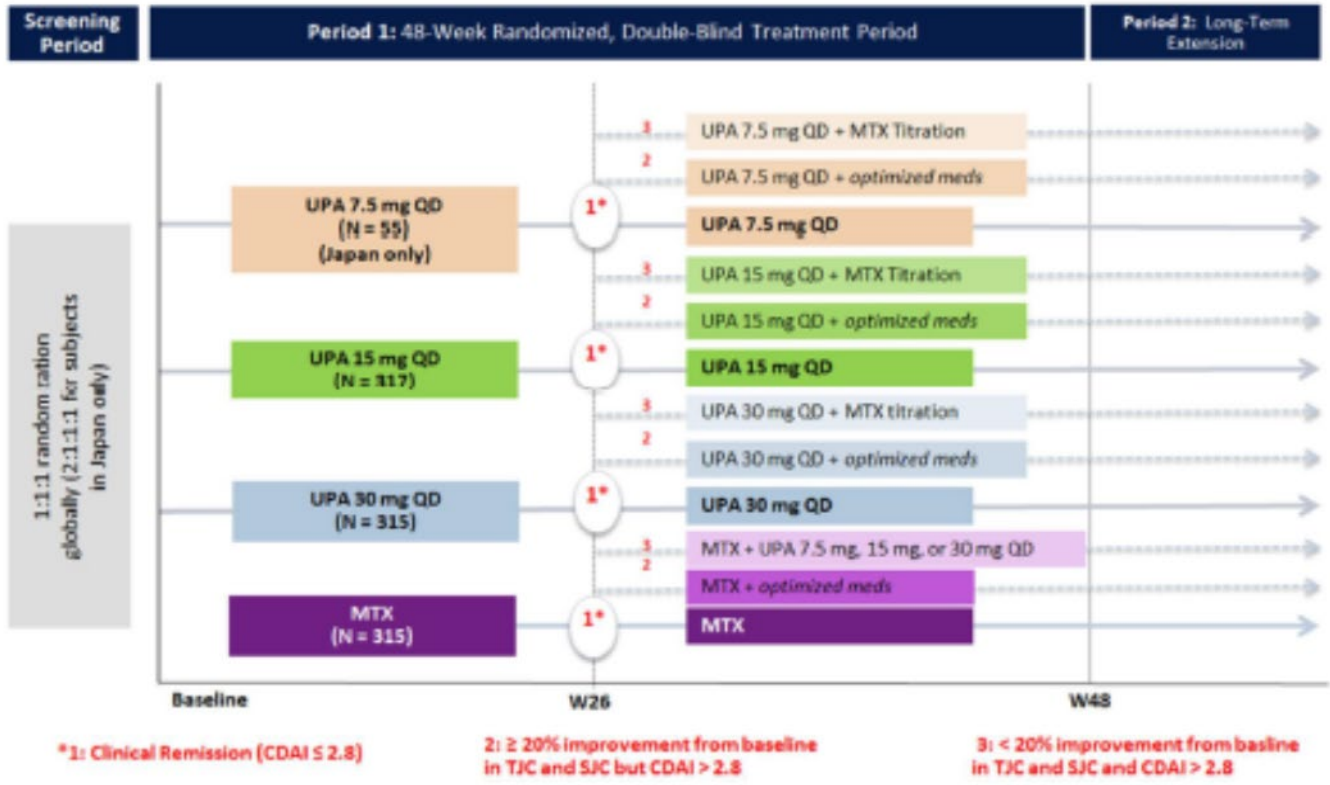


Figure 2: Study Design Schematic of M13-545 (Select Early)

Outcomes/endpoints

The primary endpoint was the proportion of subjects achieving CR (Clinical Remission) defined by Disease Activity Score 28 (DAS28) C-reactive protein (CRP) < 2.6, at Week 24.

Ranked key secondary endpoints at Week 24 were: 1) change from baseline in DAS28 (CRP); 2) change from baseline in HAQ-DI; 3) ACR50 response rate; 4) change from baseline in modified Total Sharp Score (mTSS); 5) proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2; 6) change from baseline in SF-36 PCS; 7) proportion of subjects with no radiographic progression (defined as change from baseline in mTSS ≤ 0) at Weeks 24.

Sample size, Randomisation, Blinding (masking)

Subjects were randomized in a 1:1:1 ratio to treatment Groups 2, 3, and 4 below, except for subjects from Japan, who were randomized in a 2:1:1:1 ratio to Groups 1, 2, 3, and 4:

- Group 1: Upadacitinib 7.5 mg QD monotherapy (subjects in Japan only; N = 75)
- Group 2: Upadacitinib 15 mg QD monotherapy (N = 300; includes 37 subjects from Japan)
- Group 3: Upadacitinib 30 mg QD monotherapy (N = 300; includes 37 subjects from Japan)
- Group 4: MTX monotherapy (N = 300; includes 37 subjects from Japan)

Randomization was stratified by geographic region.

Each subject was to be instructed to take 2 capsules once weekly (MTX and/or matching placebo) and 1 tablet QD (upadacitinib or matching placebo) to maintain blinding.

Study drug assignment remained blinded to sites and subjects until the last subject had completed Period 1 (Week 48); thereafter, open-label study drug was provided. The sponsor was unblinded after the Week 24 database lock. The blind was broken for the primary efficacy analysis when all subjects had completed the Week 24 visit.

Statistical methods

A global analysis was conducted for the comparisons of upadacitinib 15 mg QD and 30 mg QD treatment groups versus the MTX treatment group for all subjects (excluding the Japan specific upadacitinib 7.5 mg treatment group).

The analysis of the primary efficacy endpoint was conducted on the FAS based on treatment as randomized. Supportive analysis was also conducted on the Per Protocol Analysis Set. For the analysis of DAS28 CR response rate, ACR20 and ACR50, the comparisons were made between each upadacitinib dose and the MTX group using the Cochran-Mantel-Haenszel test adjusting for geographic region. Non-Responder Imputation (NRI) was used as the primary analysis. Point estimate, 95% CI and p-value for the treatment comparison were presented. Both nominal p-value constructed using the Cochran-Mantel-Haenszel test and adjusted p-value through the graphical multiplicity procedure are provided. Subjects who meet the joint count rescue criteria at Week 16 or 20 will be treated as non-responders at Week 24 for the primary analysis.

The overall significance level was maintained over the primary endpoint and ranked key secondary endpoints with the graphical procedure defined in the figure below.

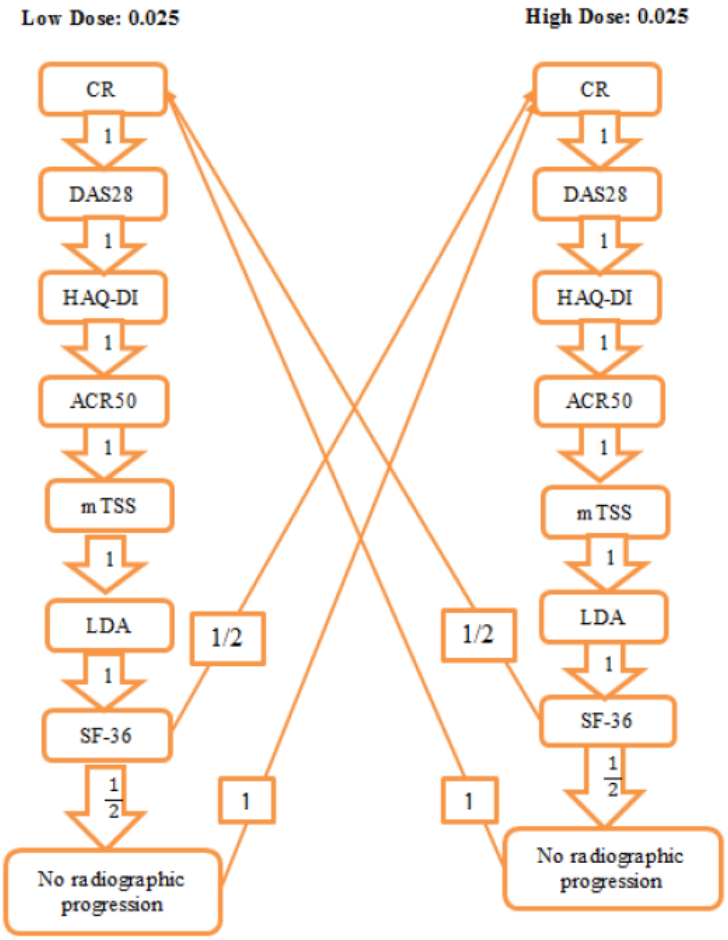


Figure 3 Graphical multiple testing procedure

The primary efficacy analyses were performed in demographic subgroups including age, gender, weight, body mass index, race, and geographical region to assess the consistency of the treatment effect. Additional subgroup analyses based on baseline disease characteristics and stratification factors were also conducted.

Analysis Sets

The Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of study drug. The FAS was used for all efficacy and baseline analyses.

The Per Protocol Analysis Set represented a subset of the FAS and consisted of all FAS subjects who did not meet any major protocol deviations through Week 24 of the study.

The Safety Analysis Set consisted of all subjects who received at least 1 dose of study drug. For the Safety Analysis Set, subjects were assigned to a treatment group based on the "as treated" treatment group, regardless of the treatment randomized. The "as treated" was determined by the treatment the subject received during the majority of the subject's drug exposure time in the analysis period. All subjects who received at least 1 dose of study drug received the treatment to which they were randomized and therefore, the Safety Analysis Set was the same as the FAS.

For all analysis sets, global analyses were performed on the treatment groups of upadacitinib 15 mg QD, upadacitinib 30 mg QD, and MTX and included all subjects enrolled under these three treatment groups.

Sensitivity Analysis of Primary Efficacy Variables

The analysis of ACR20 and ACR50 at Week 12 were repeated using Observed Cases and the analysis of CR at Week 24 were repeated using As Observed as a sensitivity analysis without any imputation.

Supportive NRI analysis for ACR20, ACR50 and CR and supportive linear extrapolation and AO analysis for change from baseline in mTSS were also conducted on the Per Protocol Analysis Set.

Tipping point analyses were conducted for the following endpoints as a sensitivity check to assess the impact of potential departures from the missing-at-random assumption: change from baseline in DAS28 (CRP), HAQ-DI, and SF-36 PCS at Week 12, ACR50 response rate at Week 12, and change from baseline in mTSS at Week 24. This analysis is classified as a post hoc analysis.

Results

Participant flow

The number of randomized subjects was 947 and the FAS included 945 subjects. The proportion of randomized patients that completed the week 24 study drug was 85.1% in the MTX group, 91.5% in the upadacitinib 15 mg group and 89.5% in the upadacitinib 30 mg group.

Recruitment

First Subject First Visit: 23 February 2016. Last Subject Last Visit (Week 24): 15 March 2018.

Conduct of the study

At the time of the data cut-off for this clinical study report (15 March 2018), the original protocol (01 October 2015, 00 subjects) had 5 global amendments. The SAP was, according to the applicant, finalized prior to the Week 24 unblinded analysis.

Baseline data

Mean age (± Standard Deviation [SD]) was in the MTX, UPA 15 mg and UPA 30 mg group: 53.3 (12.89), 51.9 (12.58) and 54.9 (12.58). The proportion of females was in the MTX, UPA 15 mg and UPA 30 mg group: 76.4%, 76.0% and 76.4%. The proportion of current tobacco/nicotine use was in the MTX, UPA 15 mg and UPA 30 mg group: 22.3%, 23.3% and 21.5%.

Proportion of aCCP-positive subjects was in the MTX, UPA 15 mg and UPA 30 mg group: 75.2%, 81.4% and 73.7%. Mean (SD) DAS28 was in the MTX, UPA 15 mg and UPA 30 mg group: 5.9 (0.97) 5.9 (0.97) 5.8 (1.02).

Outcomes and estimation

The outcomes of the primary and key secondary endpoints are provided in the table below.

Table 14: Summary of primary and key secondary endpoint results- for EU/EMA (FAS), Study M13-545

ENDPOINT [A] TREATMENT	N	WITHIN GROUP POINT ESTIMATE (95% CI)	BETWEEN GROUP DIFFERENCE (ABT-494 - MTX) POINT ESTIMATE (95% CI)	NOMINAL P-VALUE	ADJUSTED P-VALUE [B]
CLINICAL REMISSION BASED ON DAS28(CRP) AT WEEK 24$					
MTX	314	18.5 (14.2, 22.8)			
ABT-494 15 MG QD	317	48.3 (42.8, 53.8)	29.8 (22.8, 36.8)	<0.001***	<0.001***
ABT-494 30 MG QD	314	50.0 (44.5, 55.5)	31.5 (24.5, 38.5)	<0.001***	<0.001***
DAS28(CRP) CHANGE FROM BASELINE AT WEEK 24					
MTX	312	-2.15 (-2.31, -1.99)			
ABT-494 15 MG QD	317	-3.07 (-3.21, -2.92)	-0.92 (-1.12, -0.71)	<0.001***	<0.001***
ABT-494 30 MG QD	310	-3.34 (-3.49, -3.19)	-1.19 (-1.40, -0.99)	<0.001***	<0.001***
HAQ-DI CHANGE FROM BASELINE AT WEEK 24					
MTX	313	-0.60 (-0.67, -0.52)			
ABT-494 15 MG QD	317	-0.87 (-0.94, -0.80)	-0.27 (-0.37, -0.17)	<0.001***	<0.001***
ABT-494 30 MG QD	310	-0.91 (-0.98, -0.84)	-0.31 (-0.41, -0.21)	<0.001***	<0.001***
ACR50 RESPONSE RATE AT WEEK 24					
MTX	314	33.4 (28.2, 38.7)			
ABT-494 15 MG QD	317	60.3 (54.9, 65.6)	26.8 (19.3, 34.3)	<0.001***	<0.001***
ABT-494 30 MG QD	314	65.6 (60.4, 70.9)	32.2 (24.8, 39.6)	<0.001***	<0.001***
MODIFIED TOTAL SHARP SCORE (MTSS) CHANGE FROM BASELINE AT WEEK 24					
MTX	264	0.67 (0.43, 0.90)			
ABT-494 15 MG QD	279	0.14 (-0.09, 0.37)	-0.53 (-0.85, -0.20)	0.001**	0.001**
ABT-494 30 MG QD	270	0.07 (-0.16, 0.31)	-0.59 (-0.91, -0.27)	<0.001***	<0.001***
LOW DISEASE ACTIVITY BASED ON DAS28(CRP) AT WEEK 24					
MTX	314	32.2 (27.0, 37.3)			
ABT-494 15 MG QD	317	59.9 (54.5, 65.3)	27.8 (20.3, 35.2)	<0.001***	0.001**
ABT-494 30 MG QD	314	65.0 (59.7, 70.2)	32.8 (25.4, 40.2)	<0.001***	<0.001***
SF-36 PCS CHANGE FROM BASELINE AT WEEK 24					
MTX	313	6.97 (6.03, 7.91)			
ABT-494 15 MG QD	315	10.70 (9.76, 11.63)	3.72 (2.42, 5.03)	<0.001***	0.001**
ABT-494 30 MG QD	312	11.39 (10.42, 12.36)	4.42 (3.12, 5.72)	<0.001***	<0.001***
PROPORTION OF SUBJECTS WITH NO RADIOGRAPHIC PROGRESSION AT WEEK 24					
MTX	264	77.7 (72.6, 82.7)			
ABT-494 15 MG QD	279	87.5 (83.6, 91.3)	9.8 (3.5, 16.2)	0.002**	0.002**
ABT-494 30 MG QD	270	89.3 (85.6, 93.0)	11.6 (5.4, 17.8)	<0.001***	0.001**

[A]: RESULTS FOR BINARY ENDPOINTS ARE BASED ON NON-RESPONDER IMPUTATION WHICH IS ALSO THE RESCUE HANDLING APPROACH FOR SUBJECTS WHO MEET THE RESCUE CRITERIA AT WEEK 16 OR 20, WITH THE EXCEPTION OF PROPORTION OF SUBJECTS WITH NO RADIOGRAPHIC PROGRESSION. RESULTS FOR DAS28(CRP), SF-36 PCS AND HAQ-DI ARE BASED ON ANCOVA WITH MULTIPLE IMPUTATION FOR MISSING DATA HANDLING. RESULTS FOR MTSS AND NO RADIOGRAPHIC PROGRESSION ARE BASED ON LINEAR EXTRAPOLATION ANALYSIS. NO LINEAR EXTRAPOLATION WAS PERFORMED SINCE NO SUBJECT HAD APPLICABLE DATA FOR LINEAR EXTRAPOLATION.

[B]: ADJUSTED P-VALUES ARE OBTAINED VIA THE GRAPHICAL MULTIPLE TESTING PROCEDURE CONTROLLING THE OVERALL TYPE I ERROR RATE OF ALL PRIMARY AND RANKED KEY SECONDARY ENDPOINTS (FOR BOTH ABT-494 DOSE GROUPS) AT THE 0.05 LEVEL.

OTHER KEY SECONDARY ENDPOINTS FOR EU/EMA ARE ACR20 RESPONSE RATE AT WEEK 24 AND ACR70 RESPONSE RATE AT WEEK 24.

***, **, * STATISTICALLY SIGNIFICANT AT 0.001, 0.01, AND 0.05 LEVEL, RESPECTIVELY.

Ancillary analyses

According to the applicant, results of subgroup analysis for non-mTSS primary efficacy endpoints were generally consistent with the primary analysis. Forests plots of the primary endpoint CR at week 24 were provided for age, gender, weight, BMI, race, region, geographic region, RA duration, baseline DAS28 and serological status (not displayed here).

The applicant also presented the outcome of efficacy analysis at earlier timepoints on which an effect was reported to be apparent as early as week 2; an example was mean decreases in DAS28 (CRP) from baseline.

M13-549 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional

Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs" (Select Next)

Methods

Study participants

Inclusion criteria (summary of most notable)

- Diagnosis of RA for ≥ 3 months and fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA
- ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at screening and baseline visits, and high-sensitivity C-reactive protein ≥ 3 mg/L (central lab) at screening.
- Subjects must have been receiving csDMARD therapy ≥ 3 months and on a stable dose of csDMARD therapy (restricted to methotrexate [MTX], chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide) for ≥ 4 weeks prior to the first dose of study drug
- Subjects must have failed at least one of the following: MTX, sulfasalazine, or leflunomide. Subjects with inadequate response to hydroxychloroquine and/or chloroquine were to only be included if they also failed MTX, sulfasalazine, or leflunomide.

Exclusion criteria (summary of most notable)

- Prior exposure to any Janus kinase inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib)
- Considered inadequate responders to biological DMARD (bDMARD) therapy (subjects with prior exposure to at most one bDMARD were eligible to be enrolled in the study-up to 20% of total number of subjects-if they had either exposure<3 months or had to discontinue due to intolerability).

There were also exclusion criteria relating to abnormal laboratory values etc.

Treatments and overall design

This was a Phase 3 multi-center study that included Period 1 (12 weeks) and Period 2 (up to 5 years), see figure below for treatment groups and overall design. An unblinded analysis was to be conducted after all subjects had completed Period 1 (Week 12). Study sites and subjects were to remain blinded for the duration of the study (i.e. during Period 2). The submitted CSR covers Period 1.

At week 24, subjects that did not achieve LDA could adjust background RA medication as rescue. No rescue possibilities were reported for Period 1.

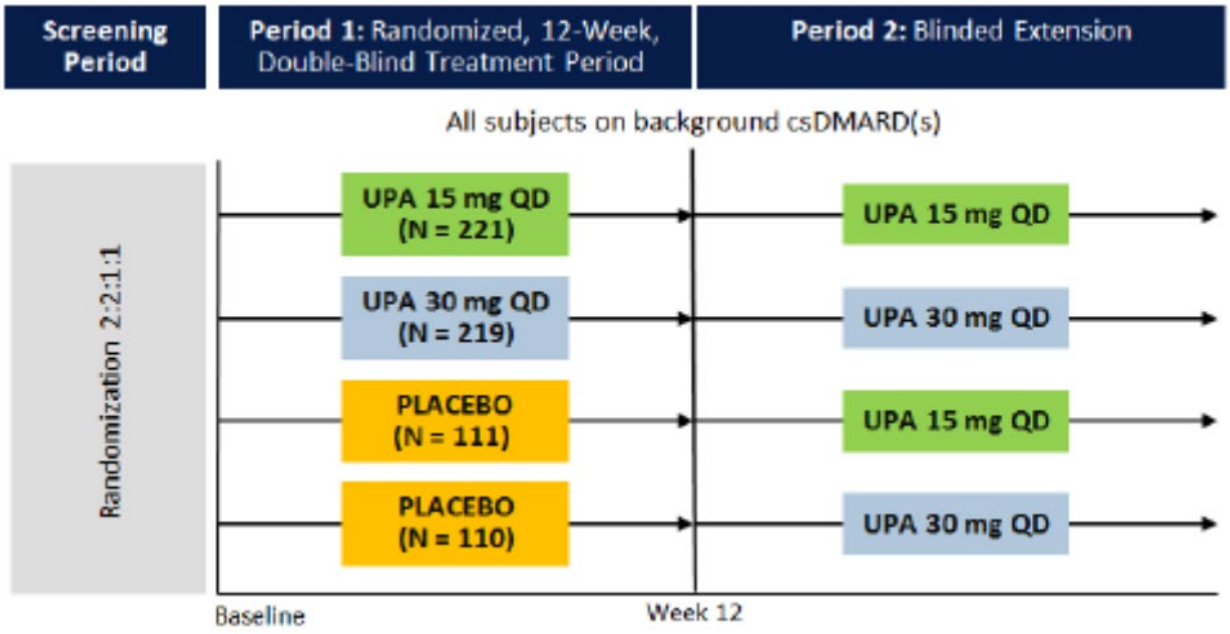


Figure 4 Study Design Study M13-549 (Select Next)

The primary endpoint is LDA (Low Disease Activity) based on DAS28 (CRP) ≤ 3.2 at Week 12.

Ranked key secondary endpoints (at Week 12): 1) change from baseline in DAS28 (CRP); 2) change from baseline in HAQ-DI; 3) ACR20 response rate; 4) change from baseline in SF-36 PCS; 5) proportion of subjects achieving CR based on DAS28 (CRP); 6) proportion of subjects achieving LDA based on CDAI ≤ 10; 7) change from baseline in morning stiffness (duration); and 8) change from baseline in FACIT-F.

Other key secondary endpoints (at Week 12, if not specified) included: 1) ACR 50% response (ACR50) rate; 2) ACR 70% response (ACR70) rate; 3) proportion of subjects achieving ACR20 response rate at Week 1.

Randomisation

Randomization was stratified by prior exposure to bDMARD (yes/no) and geographic region. Subjects who met eligibility criteria were to be randomized in a 2:2:1:1 ratio to one of four treatment groups:

- Group 1: upadacitinib 30 mg QD (N = 200) (Period 1) → upadacitinib 30 mg QD (Period 2)
- Group 2: upadacitinib 15 mg QD (N = 200) (Period 1) → upadacitinib 15 mg QD (Period 2)
- Group 3: Placebo (N = 100) (Period 1) → upadacitinib 30 mg QD (Period 2)
- Group 4: Placebo (N = 100) (Period 1) → upadacitinib 15 mg QD (Period 2)

Blinding

Each subject was instructed to take 1 tablet QD with the randomised treatment. The tablets were identical in appearance for all treatments to maintain blinding.

Study drug assignment remained blinded to subject, sites, and sponsor until the last subject had completed Period 1 (week 12), when an unblinded analysis was conducted by the sponsor. Subjects

and study sites remained blinded for the duration of the single-blinded 5-year (long-term) extension period.

Statistical Methods

The analysis of the primary efficacy endpoint was conducted on the FAS based on treatment as randomized. Supportive analysis was also conducted on the Per Protocol Analysis Set.

The null hypotheses stated that the efficacy of upadacitinib 30mg once daily (QD) and upadacitinib 15 mg QD versus the combined placebo groups for the treatment of signs and symptoms as measured by the primary endpoint (EMA) "LDA as measured by Disease Activity Score (DAS) 28 (CRP) at Week 12" and multiple ranked binary and continuous secondary endpoints is equal.

Binary endpoints were compared between groups using the Cochran-Mantel-Haenszel test adjusted for the stratification factor "prior bDMARD use". The point estimate, the 95% confidence interval using normal approximation and the p-value for the treatment comparison was presented. Missing values were imputed by non-responder imputation (NRI) (incl. the primary endpoint). In addition, exploratory tipping point efficacy analyses, including the primary endpoint (DAS28[CRP] at week 12), were performed. The overall significance level was maintained over the primary endpoint and key secondary endpoints with the graphical procedure defined in the figure below.

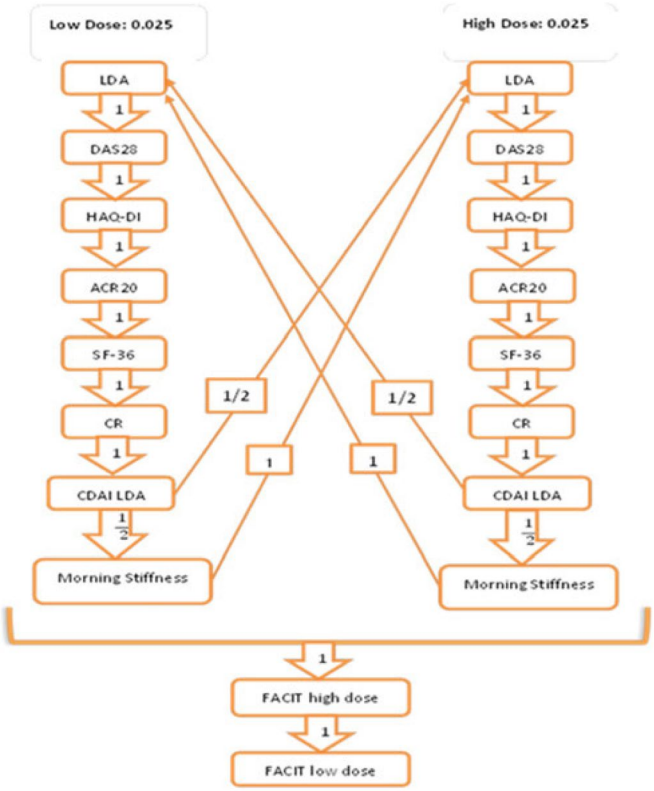


Figure 5 Graphical multiple testing procedure

Major continuous endpoints (DAS28, HAQ-DI) were compared between groups based on their change from baseline using an analysis of covariance (ANCOVA). The ANCOVA model included endpoint at baseline, stratification factor "prior DMARD use", and the treatment as fixed factors. Missing values were imputed by multiple imputation (MI).

Other continuous endpoints were compared between groups using a Mixed Model with Repeated Measurements (MMRM) with the stratification factor "prior bDMARD use", endpoint at baseline, visit, treatment, and visit x treatment interaction as fixed effect variables. An unstructured variance-covariance matrix was used. The parameter estimations used the method of Restricted Maximum Likelihood (REML) and were based on the assumption of data being missing-at-random.

For continuous endpoints, the LS mean and 95% confidence interval was reported for each randomized treatment group; the LS mean treatment difference and associated 95% confidence interval was reported comparing each upadacitinib dose group with the combined placebo group. The nominal p-value was adjusted using a graph-based multiple testing procedure.

The primary efficacy analyses were performed in demographic subgroups including age, sex, weight, BMI, race, geographic region, duration of RA diagnosis, baseline RF status, baseline anti-CCP antibody status, baseline both RF positive and anti-CCP positive, baseline both RF negative and anti-CCP negative, baseline DAS28 (CRP), and prior bDMARD use.

Safety analysis were performed in the Safety Analysis Set. Safety endpoints consisted of AE monitoring, physical examinations, vital sign measurements, electrocardiogram (ECG), and clinical laboratory testing (haematology, chemistry, and urinalysis) as a measure of safety and tolerability for the entire study duration.

Analysis sets

The Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of study drug. The FAS was used for all efficacy and baseline analyses.

The Per Protocol Analysis Set represented a subset of the FAS and consisted of all FAS subjects who did not meet any major protocol deviations during Period 1 of the study.

The Safety Analysis Set consisted of all subjects who received at least 1 dose of study drug. For the Safety Analysis Set, subjects were assigned to a treatment group based on the "as treated" treatment group, regardless of the treatment randomized. The "as treated" was determined by the treatment the subject received during the majority of the subject's drug exposure time in the analysis period. All subjects received the treatment they were randomized to in Period 1 and therefore, the Safety Analysis Set was the same as the FAS for Period 1.

Sensitivity Analysis of the Primary Efficacy Variables

The primary analysis for point estimate and CI was repeated using Observed Cases without any imputation as a sensitivity analysis. This was conducted on the FAS based on randomized treatment groups. Supportive NRI analysis was conducted on the Per Protocol Analysis Set.

Results

Participant flow

A total of 661 subjects were randomized; all 661 subjects received study drug i.e. were included in the FAS. In all treatment groups >90% of subjects completed study period 1 as well as study drug during period 1.

Recruitment

First Subject First Visit: 17 December 2015. Last Subject Last Visit: 21 April 2017 (Period 1).

Conduct of the study

The original protocol (30 September 2015, 4 subjects) had 3 global amendments during Period 1.

Baseline data

Mean age (+SD) was in the full analysis set in the Placebo, UPA 15 mg and UPA 30 mg groups: 56.0 (12.22), 55.3 (11.47) and 55.8 (11.29). The proportion of females was in the Placebo, UPA 15 mg and UPA 30 mg groups: 75.1%, 82.4% and 82.4%. The proportion of current tobacco use was in the Placebo, UPA 15 mg and UPA 30 mg groups: 19.0%, 17.6% and 15.5%.

Proportion of aCCP-positive subjects was in the Placebo, UPA 15 mg and UPA 30 mg groups: 75.9%, 79.1% and 70.8%. Mean (SD) DAS28 (CRP) was in the Placebo, UPA 15 mg and UPA 30 mg groups: 5.6 (0.84), 5.7 (0.97) and 5.7 (0.90).

The proportion of subjects with MTX as the only concomitant csDMARD at baseline as in the Placebo, UPA 15 mg and UPA 30 mg groups: 64.1%, 55.5% and 62.1%. The proportion of subjects with MTX and other csDMARD was in the Placebo, UPA 15 mg and UPA 30 mg groups: 22.3%, 21.4% and 17.8%. The proportion of subjects with csDMARD other than MTX was in the Placebo, UPA 15 mg and UPA 30 mg groups: 13.6%, 23.2% and 20.1%. The total number of subjects on concomitant Salazopyrin (FAS) was reported to be 98 (14.8%). The total number of subjects on concomitant Leflunomide was reported to be 62 (9.4%).

Outcomes and estimation

A summary of the outcome of the primary and key secondary endpoints (FAS) are presented in the table below.

Table 15 Summary of primary and key secondary endpoint results (FAS) in study M13-549 (Select Next)

ENDPOINT [A] TREATMENT	N	WITHIN GROUP POINT ESTIMATE (95% CI)	BETWEEN GROUP DIFFERENCE (ABT-494 - PBO) POINT ESTIMATE (95% CI)	NOMINAL P-VALUE	ADJUSTED P-VALUE [B]
LOW DISEASE ACTIVITY BASED ON DAS28(CRP) AT WEEK 12					
PLACEBO	221	17.2 (12.2 , 22.2)			
ABT-494 15 MG QD	221	48.4 (41.8 , 55.0)	31.2 (23.0 , 39.5)	<0.001***	<0.001***
ABT-494 30 MG QD	219	47.9 (41.3 , 54.6)	30.8 (22.5 , 39.0)	<0.001***	<0.001***
DAS28(CRP) CHANGE FROM BASELINE AT WEEK 12					
PLACEBO	220	-1.02 (-1.22, -0.82)			
ABT-494 15 MG QD	217	-2.20 (-2.40, -2.00)	-1.18 (-1.42, -0.94)	<0.001***	<0.001***
ABT-494 30 MG QD	219	-2.34 (-2.54, -2.14)	-1.32 (-1.56, -1.08)	<0.001***	<0.001***
HAQ-DI CHANGE FROM BASELINE AT WEEK 12					
PLACEBO	220	-0.25 (-0.34, -0.17)			
ABT-494 15 MG QD	216	-0.59 (-0.67, -0.51)	-0.33 (-0.43, -0.24)	<0.001***	<0.001***
ABT-494 30 MG QD	219	-0.54 (-0.62, -0.46)	-0.28 (-0.38, -0.18)	<0.001***	<0.001***
ACR20 RESPONSE RATE AT WEEK 12					
PLACEBO	221	35.7 (29.4 , 42.1)			
ABT-494 15 MG QD	221	63.8 (57.5 , 70.1)	28.1 (19.1 , 37.0)	<0.001***	<0.001***
ABT-494 30 MG QD	219	66.2 (59.9 , 72.5)	30.5 (21.6 , 39.4)	<0.001***	<0.001***
SF-36 PCS CHANGE FROM BASELINE AT WEEK 12					
PLACEBO	207	3.03 (1.88, 4.18)			
ABT-494 15 MG QD	209	7.58 (6.43, 8.74)	4.55 (3.13, 5.98)	<0.001***	<0.001***
ABT-494 30 MG QD	197	8.01 (6.84, 9.18)	4.98 (3.54, 6.42)	<0.001***	<0.001***
CLINICAL REMISSION BASED ON DAS28(CRP) AT WEEK 12					
PLACEBO	221	10.0 (6.0 , 13.9)			
ABT-494 15 MG QD	221	30.8 (24.7 , 36.9)	20.8 (13.6 , 28.1)	<0.001***	<0.001***
ABT-494 30 MG QD	219	28.3 (22.3 , 34.3)	18.4 (11.2 , 25.5)	<0.001***	<0.001***
LOW DISEASE ACTIVITY BASED ON CDAI AT WEEK 12					
PLACEBO	221	19.0 (13.8 , 24.2)			
ABT-494 15 MG QD	221	40.3 (33.8 , 46.7)	21.3 (13.0 , 29.5)	<0.001***	<0.001***
ABT-494 30 MG QD	219	42.0 (35.5 , 48.5)	23.0 (14.7 , 31.3)	<0.001***	<0.001***
MORNING STIFFNESS DURATION (MINUTES) CHANGE FROM BASELINE AT WEEK 12					
PLACEBO	202	-34.27 (-54.63, -13.91)			
ABT-494 15 MG QD	207	-85.28 (-105.61, -64.95)	-51.01 (-78.14, -23.87)	<0.001***	<0.001***
ABT-494 30 MG QD	197	-85.13 (-105.65, -64.62)	-50.86 (-78.19, -23.53)	<0.001***	<0.001***
PACIT-P CHANGE FROM BASELINE AT WEEK 12					
PLACEBO	207	2.96 (1.62, 4.30)			
ABT-494 15 MG QD	207	7.91 (6.56, 9.27)	4.95 (3.31, 6.60)	<0.001***	<0.001***
ABT-494 30 MG QD	197	7.74 (6.38, 9.11)	4.78 (3.12, 6.44)	<0.001***	<0.001***
ACR50 RESPONSE RATE AT WEEK 12					
PLACEBO	221	14.9 (10.2 , 19.6)			
ABT-494 15 MG QD	221	38.0 (31.6 , 44.4)	23.1 (15.1 , 31.0)	<0.001***	
ABT-494 30 MG QD	219	43.4 (36.8 , 49.9)	28.4 (20.4 , 36.5)	<0.001***	
ACR70 RESPONSE RATE AT WEEK 12					
PLACEBO	221	5.9 (2.8 , 9.0)			
ABT-494 15 MG QD	221	20.8 (15.5 , 26.2)	14.9 (8.7 , 21.1)	<0.001***	
ABT-494 30 MG QD	219	26.5 (20.6 , 32.3)	20.6 (14.0 , 27.2)	<0.001***	
ACR20 RESPONSE RATE AT WEEK 1					
PLACEBO	221	8.6 (4.9 , 12.3)			
ABT-494 15 MG QD	221	22.2 (16.7 , 27.6)	13.6 (7.0 , 20.2)	<0.001***	
ABT-494 30 MG QD	219	28.3 (22.3 , 34.3)	19.7 (12.7 , 26.7)	<0.001***	

[A]: RESULTS FOR BINARY ENDPOINTS ARE BASED ON NON-RESPONDER IMPUTATION. RESULTS FOR DAS28(CRP) AND HAQ-DI ARE BASED ON ANCOVA WITH MULTIPLE IMPUTATION FOR MISSING DATA HANDLING. RESULTS FOR OTHER CONTINUOUS ENDPOINTS ARE BASED ON MMRM MODEL.
[B]: ADJUSTED P-VALUES ARE OBTAINED VIA THE GRAPHICAL MULTIPLE TESTING PROCEDURE CONTROLLING THE OVERALL TYPE I ERROR RATE OF ALL PRIMARY AND RANKED KEY SECONDARY ENDPOINTS (FOR BOTH ABT-494 DOSE GROUPS) AT THE 0.05 LEVEL.
***, **, * STATISTICALLY SIGNIFICANT AT 0.001, 0.01, AND 0.05 LEVEL, RESPECTIVELY.

Ancillary analyses

The primary efficacy endpoint was examined in the following subgroups: age, weight, BMI race, geographic region; duration of RA diagnosis; baseline RF status; baseline anti-CCP antibody status; baseline both RF positive and anti-CCP positive; baseline both RF negative and anti-CCP negative;

baseline DAS28 (CRP) and prior bDMARD use. In all examined subgroups, a difference with regards to the comparison with placebo was noted for both doses examined. No subgroup analysis according to concomitant DMARD could be found.

The outcomes of the subgroup analysis according to prior bDMARD use are displayed in the table below.

Table 16: Summary of the outcome of primary endpoint; LDA (DAS28 CRP) at week 12 by prior biologic DMARD use (FAS) in Study M13-549

SUBGROUP TREATMENT	N	RESPONDER n (%)	RESPONSE RATE (95% CI) [A]	--- RESPONSE RATE DIFF (ABT-494 - PBO) --- POINT ESTIMATE	 95% CI [B]
YES					
PLACEBO	29	3 (10.3)	10.3 (0.0, 21.4)		
ABT-494 15 MG QD	27	15 (55.6)	55.6 (36.8, 74.3)	45.2	(23.4, 67.0)
ABT-494 30 MG QD	28	13 (46.4)	46.4 (28.0, 64.9)	36.1	(14.5, 57.6)
NO					
PLACEBO	192	35 (18.2)	18.2 (12.8, 23.7)		
ABT-494 15 MG QD	194	92 (47.4)	47.4 (40.4, 54.4)	29.2	(20.3, 38.1)
ABT-494 30 MG QD	191	92 (48.2)	48.2 (41.1, 55.3)	29.9	(21.0, 38.9)

M14-465" A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR) (Select Compare)

Methods

Study participants

Inclusion criteria (summary of most notable)

- Diagnosis of RA for ≥ 3 months who also fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA who have had an inadequate response to MTX treatment. Local guidelines for MTX dosage may have applied.
- ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits, and high-sensitivity C-reactive protein level ≥ 5 mg/L (central lab, upper limit of normal [ULN] 2.87 mg/L) at Screening.
- Subjects were also to have had the following at Screening: ≥ 3 bone erosions on x-ray; or ≥ 1 bone erosion and a positive rheumatoid factor; or ≥ 1 bone erosion and a positive anti-cyclic citrullinated peptide autoantibody

Exclusion criteria (summary of the most notable)

- Prior exposure to any Janus kinase inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib) or adalimumab
- Had been treated with other biologic disease-modifying anti-rheumatic drug (bDMARD) therapy for ≥ 3 months who were considered inadequate responders (lack of efficacy) to bDMARD therapy as determined by the investigator (subjects with prior exposure to at most one bDMARD-up to 20% of total number of subjects-were eligible to be enrolled if they had either exposure<3 months or had to discontinue the bDMARD due to intolerability but subjects with prior exposure to adalimumab were excluded).

There were also exclusion criteria relating to abnormal laboratory values etc.

Treatments and overall design

This is a Phase 3 multicenter study that included Period 1 (48 weeks) and Period 2 (up to 5 years), see figure below for treatment groups and overall design. An unblinded analysis was conducted after all subjects had completed their Week 26 visit or otherwise had prematurely discontinued. Subjects and sites were to remain blinded until after all subjects have completed Period 1 (and Period 1 database lock was complete). The interim week 26 report, CSR, was included in the current submission. The cut-off date for the CSR was 02 February 2018.

Starting at the Week 26 visit (after Week 26 assessments were performed) and thereafter, initiation of or change in background RA medication was allowed as per local label. Starting at Week 48 (and thereafter, initiation of or change in conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) was allowed as per local label.

Rescue therapy was to be offered to subjects who met the following criteria:

a) Placebo:

Subjects who did not achieve a ≥ 20% improvement in tender joint count (TJC) and swollen joint count (SJC) at Weeks 14, 18, or 22 compared to Baseline were to be switched to blinded upadacitinib treatment.

At Week 26, all remaining subjects were switched to blinded upadacitinib treatment regardless of clinical response.

b) Adalimumab:

Subjects who did not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to Baseline were to be switched to blinded upadacitinib treatment.

At Week 26, all remaining subjects who did not achieve low disease activity (LDA) according to Clinical Disease Activity Index (CDAI) (LDA defined as CDAI ≤ 10) at Week 26 were to be switched to blinded upadacitinib treatment.

c) Upadacitinib:

Subjects who did not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to Baseline were to be switched to blinded adalimumab treatment.

At Week 26, all remaining subjects who did not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 were to be switched to blinded adalimumab treatment.

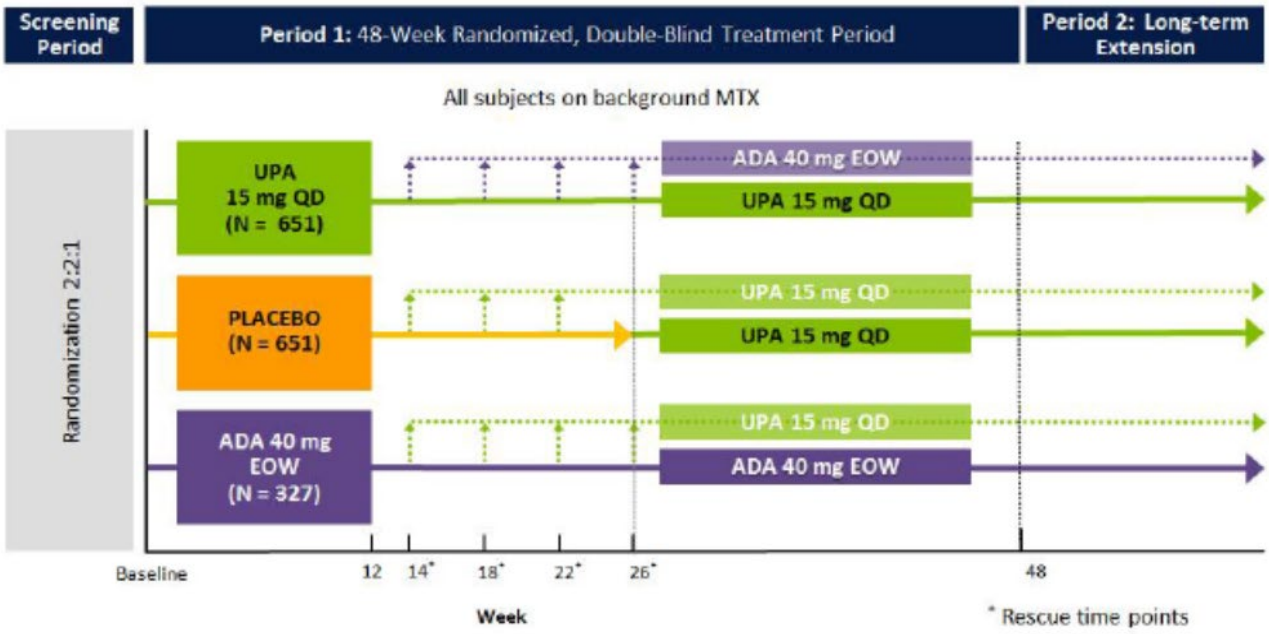


Figure 6 Study Design of M14-465 (Select Compare)

Outcomes/Endpoints

The primary endpoint is the proportion of subjects achieving CR (based on DAS28 CRP < 2.6) at Week 12.

Ranked key secondary endpoints (upadacitinib versus placebo if not otherwise specified) were: 1) change from Baseline in mTSS at Week 26; 2) proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12; 3) change from Baseline in DAS28 (CRP) at Week 12; 4) change from Baseline in HAQ-DI at Week 12; 5) ACR20 response rate at Week 12; 6) proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 (non-inferiority of upadacitinib versus adalimumab); 7) change from Baseline in SF-36 PCS at Week 12; 8) proportion of subjects achieving LDA based on CDAI at Week 12; 9) change from Baseline in morning stiffness (duration) at Week 12; 10) change from Baseline in FACIT-F at Week 12; and 11) proportion of subjects with no radiographic progression (defined as change from Baseline in mTSS ≤ 0) at Week 26.

Other key secondary endpoints (upadacitinib versus placebo) were: 1) ACR50 response rate at Week 12; and 2) ACR70 response rate at Week 12.

Randomisation

Subjects who met eligibility criteria were randomized in a 2:2:1 ratio to one of three treatment groups:

- Group 1: upadacitinib 15 mg QD (N = 600)
- Group 2: placebo (N = 600)
- Group 3: adalimumab (40 mg every other week [eow]) (N = 300)

Randomization is stratified by prior exposure to bDMARD (yes/no) and geographic region.

Blinding

To maintain the study blind, subjects received both oral study drug QD (either upadacitinib 15 mg or matching placebo) and subcutaneous study drug eow (either adalimumab 40 mg or matching placebo) until the study is unblinded.

An unblinded analysis was conducted when all subjects had completed their Week 26 visit. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects remained blinded for the duration of Period 1.

The long-term extension period is blinded until the last subject completes Period 1. When the last subject completes the last visit of Period 1 (Week 48), study drug assignment in both periods will be unblinded to the Sponsor and sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

Statistical methods

The Full Analysis Set (FAS) includes all randomized subjects who received at least one dose of study drug. The FAS will be used for all efficacy and baseline analyses.

The Per Protocol Analysis Set represents a subset of the FAS and consists of all FAS subjects who did not meet any major protocol violations during the study. Definitions of major protocol violations will be detailed in the SAP. Additional analysis may be conducted on the Per Protocol analysis set, in order to evaluate the impact of major protocol violations.

The Safety Analysis Set consists of all subjects who received at least one dose of study drug. For the Safety Analysis Set, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

Statistical tests are at two-sided significance level of 0.05 for efficacy analyses and all other analyses. A test will be deemed significant if the P value is less than or equal to 0.05 unless otherwise specified.

Analysis of the primary endpoint was conducted on the FAS based on treatment as randomized. For the ACR20 and CR comparison between the upadacitinib group and the placebo group, Cochran-Mantel-Haenszel test adjusting for main stratification factors was used. For the primary analysis of ACR20 and CR response at Week 12, Non-Responder Imputation (NRI) was used. In addition, sensitivity analysis was done using Observed Cases. Supportive analysis was conducted on the Per Protocol Analysis Set.

To preserve Type I error, a step-down approach was used to test the primary and ranked key secondary endpoints where statistical significance can be claimed for a lower ranked endpoint only if the previous endpoints in the sequence meet the requirements of significance.

Interim Analysis

An unblinded analysis was conducted after all subjects had completed Week 26. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects were remain blinded for the duration of Period 1. Additional unblinded analyses were conducted after the Week 26 unblinded analysis.

Tipping point analyses were conducted for the following endpoints as a sensitivity check to assess the impact of potential departures from the missing-at-random assumption: change from Baseline in DAS28 (CRP) and HAQ-DI at Week 12, ACR20 response rate at Week 12, and change from Baseline in mTSS at Week 26. These were defined after finalization of the SAP.

Results

Participant flow

The overall number of randomized patients was 1629, which was equal to the number included in the FAS. More than 90% in all treatment groups completed week 14 on study drug. Overall >90% completed week 26 on study drug. A higher proportion of subjects in the placebo group was rescued after the Week 14, 18 and 22 visits compared to the proportion of subjects rescued in the adalimumab and upadacitinib groups at those timepoints.

Recruitment

First Subject First Visit: 01 December 2015. Last Subject Last Visit: 02 February 2018 (Week 26).

Conduct of the study

According to the CSR, at the time of the data cut-off for the CSR (02 February 2018), the original protocol (30 September 2015, 9 subjects enrolled) had 5 global amendments. The third and fourth amendments concerned rescue criteria and concomitant medication modifications.

Baseline data

Mean age (+SD) was in the full analysis set in the placebo, Ada 40 mg and UPA 15 mg groups: 53.6 (12.24) 53.7 (11.70) and 54.2 (12.08) years. The proportion of females were in the placebo, Ada 40 mg and UPA 15 mg groups: 78.6, 79.2 and 80.0%. The proportion of subjects with current tobacco use was in the placebo, Ada 40 mg and UPA 15 mg groups: 18.6, 22.5 and 17.7%.

Proportion of aCCP-positive subjects was in the placebo, Ada 40 mg and UPA 15 mg groups: 81.5, 80.7 and 80.6%. Mean (SD) DAS28 (CRP) was in the placebo, Ada 40 mg and UPA 15 mg groups 5.8 (± 0.94), 5.9 (± 0.96) and 5.8 (± 0.97). Mean (SD) baseline mTSS was in the placebo, Ada 40 mg and UPA 15 mg groups: 35.9 (± 51.66) and 34.5 (± 47.06) 34.0 (± 50.08).

Outcomes and estimation

The outcomes of the primary and key secondary endpoints are displayed in the table below.

Table 17: The Outcome of the primary and key secondary endpoints in Study M14-465 (Select Compare)

ENDPOINT [A] TREATMENT	N	WITHIN GROUP POINT ESTIMATE (95% CI)	---------- BETWEEN GROUP DIFFERENCE (ABT-494 - CONTROL) --------- POINT ESTIMATE (95% CI)	P-VALUE
CLINICAL REMISSION BASED ON DAS28(CRP) AT WEEK 12				
PLACEBO	651	6.1 (4.3 , 8.0)		
ABT-494 15 MG QD	651	28.7 (25.2 , 32.2)	22.6 (18.6 , 26.5)	<0.001***
MTSS CHANGE FROM BASELINE AT WEEK 26				
PLACEBO	599	0.92 (0.64, 1.20)		
ABT-494 15 MG QD	593	0.24 (-0.04, 0.53)	-0.67 (-0.97, -0.37)	<0.001***
LOW DISEASE ACTIVITY BASED ON DAS28(CRP) AT WEEK 12				
PLACEBO	651	13.8 (11.2 , 16.5)		
ABT-494 15 MG QD	651	45.0 (41.2 , 48.8)	31.2 (26.5 , 35.8)	<0.001***
DAS28(CRP) CHANGE FROM BASELINE AT WEEK 12				
PLACEBO	643	-1.15 (-1.28, -1.02)		
ABT-494 15 MG QD	634	-2.48 (-2.61, -2.35)	-1.33 (-1.47, -1.19)	<0.001***
HAQ-DI CHANGE FROM BASELINE AT WEEK 12				
PLACEBO	648	-0.28 (-0.34, -0.23)		
ABT-494 15 MG QD	644	-0.60 (-0.65, -0.54)	-0.31 (-0.37, -0.25)	<0.001***
ACR20 RESPONSE RATE AT WEEK 12				
PLACEBO	651	36.4 (32.7 , 40.1)		
ABT-494 15 MG QD	651	70.5 (67.0 , 74.0)	34.1 (29.0 , 39.2)	<0.001***
LOW DISEASE ACTIVITY BASED ON DAS28(CRP) AT WEEK 12 (NON-INFERIORITY VS ADALIMUMAB)				
ADALIMUMAB 40 MG EOW	327	28.7 (23.8 , 33.7)		
ABT-494 15 MG QD	651	45.0 (41.2 , 48.8)	16.3 (10.0 , 22.5)	NON-INFERIORITY MET [B]
SF-36 PCS CHANGE FROM BASELINE AT WEEK 12				
PLACEBO	616	3.56 (2.79, 4.33)		
ABT-494 15 MG QD	616	7.89 (7.11, 8.68)	4.33 (3.52, 5.15)	<0.001***
LOW DISEASE ACTIVITY BASED ON CDAI AT WEEK 12				
PLACEBO	651	16.3 (13.4 , 19.1)		
ABT-494 15 MG QD	651	40.4 (36.6 , 44.2)	24.1 (19.4 , 28.8)	<0.001***
MORNING STIFFNESS DURATION (MINUTES) CHANGE FROM BASELINE AT WEEK 12				
PLACEBO	619	-48.59 (-58.84, -38.34)		
ABT-494 15 MG QD	618	-92.63 (-103.03, -82.23)	-44.04 (-55.39, -32.69)	<0.001***
PACIT-F CHANGE FROM BASELINE AT WEEK 12				
PLACEBO	613	4.81 (3.85, 5.77)		
ABT-494 15 MG QD	612	8.95 (7.98, 9.93)	4.15 (3.13, 5.16)	<0.001***
ACR50 RESPONSE RATE AT WEEK 12				
PLACEBO	651	14.9 (12.2 , 17.6)		
ABT-494 15 MG QD	651	45.2 (41.3 , 49.0)	30.3 (25.6 , 35.0)	<0.001***
ACR70 RESPONSE RATE AT WEEK 12				
PLACEBO	651	4.9 (3.3 , 6.6)		
ABT-494 15 MG QD	651	24.9 (21.6 , 28.2)	20.0 (16.3 , 23.7)	<0.001***
PROPORTION OF SUBJECTS WITH NO RADIOGRAPHIC PROGRESSION AT WEEK 26				
PLACEBO	599	76.0 (72.5 , 79.4)		
ABT-494 15 MG QD	593	83.5 (80.5 , 86.5)	7.5 (3.0 , 12.1)	0.001**

[A]: RESULTS FOR BINARY ENDPOINTS ARE BASED ON NON-RESPONDER IMPUTATION, WITH THE EXCEPTION OF PROPORTION OF SUBJECTS WITH NO RADIOGRAPHIC PROGRESSION, WHICH IS BASED ON LINEAR EXTRAPOLATION. RESULTS FOR DAS28(CRP) AND HAQ-DI ARE BASED ON ANCOVA WITH MULTIPLE IMPUTATION FOR MISSING DATA HANDLING. RESULTS FOR MTSS ARE BASED ON ANCOVA WITH LINEAR EXTRAPOLATION FOR MISSING DATA AND RESCUE HANDLING. RESULTS FOR OTHER CONTINUOUS ENDPOINTS ARE BASED ON MMRM MODEL.
[B]: NON-INFERIORITY TEST OF ABT-494 VERSUS ADALIMUMAB IS EVALUATED USING LOWER BOUND OF 95% CONFIDENCE INTERVAL OF TREATMENT DIFFERENCE AGAINST A NON-INFERIORITY MARGIN OF 10%.
***, **, * STATISTICALLY SIGNIFICANT AT 0.001, 0.01, AND 0.05 LEVEL, RESPECTIVELY.

Ancillary analyses

Subgroups analysis of the primary endpoint included analysis according to prior bDMARD use, age, gender, weight, BMI, race, geographic region, duration of RA diagnosis, baseline serological status and

baseline DAS 28 CRP. In all the examined subgroups, a difference between upadacitinib and placebo was observed.

The outcome of the analysis of the primary endpoint by prior bDMARD use is presented in the table below.

Table 18: Summary of the outcome of the primary endpoint, clinical remission at week 12 (based on DAS28 CRP) by prior bDMARD use

SUBGROUP TREATMENT	N	RESPONDER n (%)	RESPONSE RATE (95% CI) [A]	------ RESPONSE RATE DIFF (ABT-494 - PBO) ----- POINT ESTIMATE	 95% CI [B]
YES					
PLACEBO	63	6 (9.5)	9.5 (2.3, 16.8)		
ADALIMUMAB 40 MG EOW	34	4 (11.8)	11.8 (0.9, 22.6)		
ABT-494 15 MG QD	54	17 (31.5)	31.5 (19.1, 43.9)	22.0	(7.6, 36.3)
NO					
PLACEBO	588	34 (5.8)	5.8 (3.9, 7.7)		
ADALIMUMAB 40 MG EOW	293	55 (18.8)	18.8 (14.3, 23.2)		
ABT-494 15 MG QD	597	170 (28.5)	28.5 (24.9, 32.1)	22.7	(18.6, 26.8)

Data in support of a rapid onset of effect (detected as early as week 2) was presented by the applicant.

M15-555 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Monotherapy to Methotrexate (MTX) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response to MTX" (Select Monotherapy)

Methods

Study participants

Inclusion criteria (summary of most notable)

- Diagnosis of RA for ≥ 3 months who also fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA who have had an inadequate response to MTX treatment but were able to tolerate ≥ 15 mg of weekly oral MTX or ≥ 10 mg/week in subjects who were intolerant of MTX at doses ≥ 12.5 mg/week. Local guidelines for MTX dosage may have applied (patients discontinued all csDMARD other than MTX at least 4 weeks)
- ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits, and high sensitivity C-reactive protein level ≥ 3 mg/L (central lab) at Screening.

Exclusion criteria (summary of most notable)

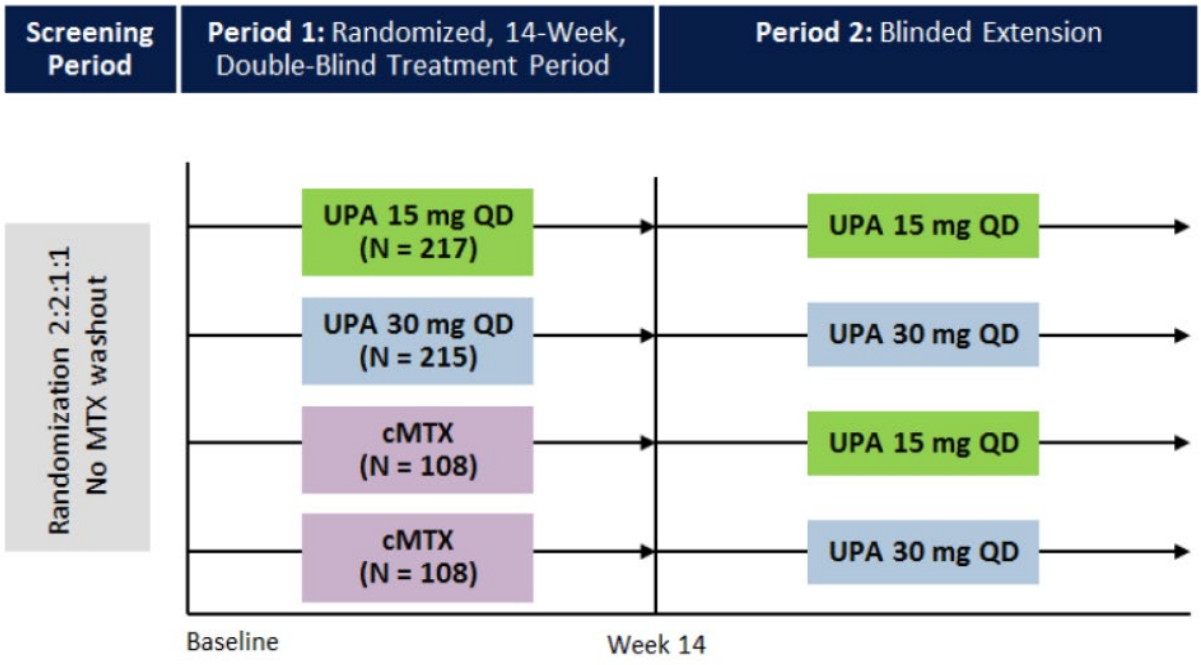
- Prior exposure to any Janus kinase inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib) or any biologic disease-modifying anti-rheumatic drug

There were also exclusion criteria relating to abnormal laboratory values etc.

Treatments

This is a Phase 3 multicenter study that included Period 1 (14 weeks) and Period 2 (226-week), see figure below for treatment groups and overall design. An unblinded analysis was conducted at the end of Period 1 (Week 14) i.e. after all subjects have completed Period 1. The subjects and sites are to remain blinded during Period 2. The current submission included the period 1 CSR.

In Period 2, subjects who do not achieve LDA as defined by CDAI ≤ 10 at Week 26 should have background medication(s) adjusted or initiated as rescue after assessments for Week 26 have been completed.



Note: cMTX= continuing MTX

Figure 7: Study Design of Study M15-555 (Select Monotherapy)

Outcomes/Endpoints

The primary endpoint was the proportion of subjects achieving LDA (based on DAS28 [CRP] ≤ 3.2) at Week 14.

Ranked key secondary endpoints (at Week 14) were: 1) change from Baseline in DAS28 (CRP); 2) change from Baseline in HAQ-DI; 3) ACR20 response rate; 4) change from Baseline in SF-36 PCS; 5) proportion of subjects achieving CR based on DAS28 (CRP); and 6) change from Baseline in morning stiffness (duration).

Other key secondary endpoints (at Week 14): 1) ACR 50% response (ACR50) rate and 2) ACR 70% response (ACR70) rate.

There were also additional efficacy analyses.

Randomisation

Randomization was stratified by geographic region. Subjects were randomized in a 2:2:1:1 ratio using interactive response technology (IRT) to receive double-blind study drug in one of the following treatment groups:

- Group 1: ABT-494 30 mg QD (N = 200) (Period 1) → ABT-494 30 mg QD (Period 2)
- Group 2: ABT-494 15 mg QD (N = 200) (Period 1) → ABT-494 15 mg QD (Period 2)
- Group 3: MTX (N = 100) (Period 1) → ABT-494 30 mg QD (Period 2)

- Group 4: MTX (N = 100) (Period 1) → ABT-494 15 mg QD (Period 2)

Blinding

Each subject was instructed to take 1 tablet QD with the randomised treatment. The tablets were identical in appearance for all treatments to maintain blinding.

Study drug assignment remained blinded to subjects, sites and the sponsor until the last subject had completed Period 1 (week 14), when an unblinded analysis was conducted by the sponsor. Subjects and study sites remained blinded for the duration of the single-blinded 226-week (long-term) extension study.

Statistical Methods

The analysis of the primary efficacy endpoint was conducted on the FAS based on treatment as randomized. Supportive analysis was also conducted on the Per Protocol Analysis Set.

The null hypotheses stated that the efficacy of upadacitinib 30mg once daily (QD) alone and upadacitinib 15 mg QD alone versus continuing MTX alone for the treatment of signs and symptoms as measured by the primary endpoint (EMA) "LDA as measured by Disease Activity Score 28 [DAS28] C-reactive protein [CRP] ≤ 3.2) at week14" and multiple ranked binary and continuous secondary endpoints is equal.

Binary endpoints were compared between groups using the Cochran-Mantel-Haenszel test adjusted for the stratification factor "geographic region". The point estimate, the 95% confidence interval using normal approximation and p-value for the treatment comparison was presented. Missing values were imputed by non-responder imputation (NRI) (incl. the primary endpoint). In addition, exploratory tipping point efficacy analyses, including the primary endpoint (DAS28[CRP] at week 14), were performed. The overall significance level was maintained over the primary endpoint and key secondary endpoints with the graphical procedure defined in the figure below.

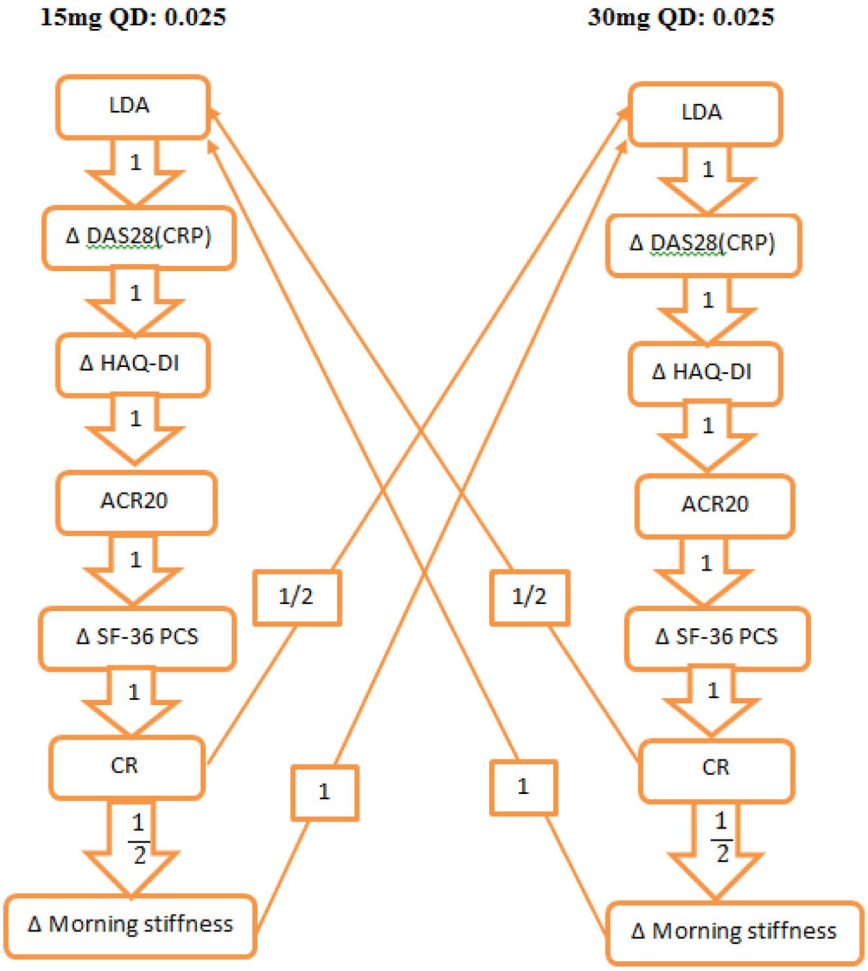


Figure 8 Graphical multiple testing procedure

Major continuous endpoints (DAS28, HAQ-DI) were compared between groups based on their change from baseline using an analysis of covariance (ANCOVA). The ANCOVA model included endpoint at baseline, stratification factor "geographic region", and treatment as fixed factors. Missing values were imputed by multiple imputation (MI).

Other continuous endpoints were compared between groups using a Mixed Model with Repeated Measurements (MMRM) with the stratification factor "geographic region", endpoint at baseline, visit, treatment, and visit x treatment interaction as fixed effect variables. An unstructured variance-covariance matrix was used. The parameter estimations used the method of Restricted Maximum Likelihood (REML) and were based on the assumption of data being missing-at-random.

For continuous endpoints, the LS mean and 95% confidence interval was reported for each randomized treatment group; the LS mean treatment difference and associated 95% confidence interval was reported comparing each upadacitinib dose group with the combined MTX group. The nominal p-value was adjusted using a graph-based multiple testing procedure.

The primary efficacy analyses were performed in demographic subgroups including age, sex, weight, BMI, race, geographic region, duration of RA disease diagnosis, Baseline RF status, Baseline anti-CCP antibody status, Baseline RF and anti-CCP, Baseline RF and anti-CCP, and Baseline DAS28 (hsCRP).

Safety analyses were performed in the Safety Analysis Set for period 1 and period 2. Safety endpoints consisted of AE monitoring, physical examinations, vital sign measurements, ECG, and clinical laboratory testing (haematology, chemistry, and urinalysis) as a measure of safety and tolerability for the entire study duration.

The Full Analysis Set (FAS) includes all randomized subjects who received at least one dose of study drug. The FAS will be used for all efficacy and baseline analyses.

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 during Period 1 of the study. Additional analysis of the primary efficacy endpoint will be conducted on the Per Protocol analysis set, in order to evaluate the impact of major protocol deviations. Major protocol deviations (ICH deviation and other clinically significant non-ICH deviation) will be identified prior to database lock.

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

Sensitivity Analysis of the Primary Efficacy Variables

The primary analysis for point estimate and CI will be repeated using Observed Cases without any imputation as a sensitivity analysis. This will be conducted on the FAS based on randomized treatment groups. Supportive NRI analysis will also be conducted on the Per Protocol Analysis Set.

Results

Participant flow

All 648 randomized subjects received study drug i.e. were included in the FAS. The proportion of subjects that completed Period 1 as well as the proportion of subjects that completed Period 1 study drug was >90% across all treatment groups.

Recruitment

First Subject First Visit: 23 March 2016. Last Subject Last Visit: 02 October 2017 (Period 1)

Conduct of the study

At the time of the data cut-off for this Period 1 clinical study report, the original protocol (01 October 2015, 0 subjects enrolled) had 3 global amendments.

Baseline data

Mean age (+SD) was in the FAS in the MTX, UPA 15 mg and UPA 30 mg groups 55.3 (11.12), 54.5 (12.20) 53.1 (12.72) years. The proportion of females were in the MTX, UPA 15 mg and UPA 30 mg groups 82.9, 80.2 and 79.1%. The proportion of subjects with current tobacco use was in the UPA 15 mg and UPA 30 mg groups 22.7, 20.4 and 15.3%.

The proportion of aCCP-positive subjects was in the MTX, UPA 15 mg and UPA 30 mg groups 70.8, 73.3 and 70.6%. Mean (SD) DAS28 (CRP) was in the MTX, UPA 15 mg and UPA 30 mg groups 5.6 (± 1.04) 5.6 (± 0.92) and 5.6 ± 1.06.

Outcomes and estimation

The outcomes of the primary and key secondary endpoints are presented in the table below.

Table 19: Summary of the outcome of the primary and key secondary endpoints in study M15-555 (Select Monotherapy)

ENDPOINT [A] / TREATMENT	N	WITHIN GROUP POINT ESTIMATE (95% CI)	BETWEEN GROUP DIFFERENCE (ABT-494 - MTX) POINT ESTIMATE (95% CI)	NOMINAL P-VALUE	ADJUSTED P-VALUE [B]
LOW DISEASE ACTIVITY BASED ON DAS28(CRP) AT WEEK 14					
MTX	216	19.4 (14.2 , 24.7)			
ABT-494 15 MG QD	217	44.7 (38.1 , 51.3)	25.3 (16.8 , 33.7)	<0.001***	<0.001***
ABT-494 30 MG QD	215	53.0 (46.4 , 59.7)	33.6 (25.1 , 42.1)	<0.001***	<0.001***
DAS28(CRP) CHANGE FROM BASELINE AT WEEK 14					
MTX	215	-1.20 (-1.39, -1.01)			
ABT-494 15 MG QD	215	-2.29 (-2.48, -2.10)	-1.08 (-1.32, -0.85)	<0.001***	<0.001***
ABT-494 30 MG QD	213	-2.61 (-2.80, -2.41)	-1.40 (-1.64, -1.17)	<0.001***	<0.001***
HAQ-DI CHANGE FROM BASELINE AT WEEK 14					
MTX	216	-0.32 (-0.41, -0.23)			
ABT-494 15 MG QD	216	-0.65 (-0.73, -0.56)	-0.33 (-0.43, -0.22)	<0.001***	<0.001***
ABT-494 30 MG QD	215	-0.73 (-0.82, -0.64)	-0.41 (-0.51, -0.30)	<0.001***	<0.001***
ACR20 RESPONSE RATE AT WEEK 14					
MTX	216	41.2 (34.6 , 47.8)			
ABT-494 15 MG QD	217	67.7 (61.5 , 74.0)	26.5 (17.5 , 35.6)	<0.001***	<0.001***
ABT-494 30 MG QD	215	71.2 (65.1 , 77.2)	30.0 (21.0 , 38.9)	<0.001***	<0.001***
SF-36 PCS CHANGE FROM BASELINE AT WEEK 14					
MTX	195	4.32 (3.19, 5.44)			
ABT-494 15 MG QD	200	8.28 (7.17, 9.40)	3.97 (2.52, 5.42)	<0.001***	<0.001***
ABT-494 30 MG QD	201	10.19 (9.07, 11.30)	5.87 (4.42, 7.32)	<0.001***	<0.001***
CLINICAL REMISSION BASED ON DAS28(CRP) AT WEEK 14					
MTX	216	8.3 (4.6 , 12.0)			
ABT-494 15 MG QD	217	28.1 (22.1 , 34.1)	19.8 (12.8 , 26.8)	<0.001***	<0.001***
ABT-494 30 MG QD	215	40.5 (33.9 , 47.0)	32.1 (24.6 , 39.7)	<0.001***	<0.001***
MORNING STIFFNESS DURATION (MINUTES) CHANGE FROM BASELINE AT WEEK 14					
MTX	196	-53.03 (-72.18, -33.88)			
ABT-494 15 MG QD	199	-94.56 (-113.57, -75.54)	-41.53 (-66.56, -16.50)	0.001**	0.001**
ABT-494 30 MG QD	202	-102.34 (-121.24, -83.45)	-49.31 (-74.23, -24.40)	<0.001***	<0.001***
ACR50 RESPONSE RATE AT WEEK 14					
MTX	216	15.3 (10.5 , 20.1)			
ABT-494 15 MG QD	217	41.9 (35.4 , 48.5)	26.7 (18.5 , 34.8)	<0.001***	
ABT-494 30 MG QD	215	52.1 (45.4 , 58.8)	36.8 (28.6 , 45.0)	<0.001***	
ACR70 RESPONSE RATE AT WEEK 14					
MTX	216	2.8 (0.6 , 5.0)			
ABT-494 15 MG QD	217	22.6 (17.0 , 28.1)	19.8 (13.8 , 25.8)	<0.001***	
ABT-494 30 MG QD	215	33.0 (26.7 , 39.3)	30.2 (23.6 , 36.9)	<0.001***	

Ancillary analyses

For the primary endpoint, subgroup analysis according to age, gender, weight, BMI, race, geographic region, duration of RA, baseline serological status and baseline DAS28 (CRP) were conducted. Generally, a (numerical) difference vs placebo (in favour of upadacitinib) was noted for both doses in the analysed subgroups.

CDAI was included among the analysis in this study. At all visits beginning at Week 2, improvement in disease activity with upadacitinib treatment, as shown by mean decreases in CDAI from Baseline, was greater (nominal $P < 0.001$) compared with the cMTX group for both the upadacitinib 15 mg and 30 mg groups.

Further, analysis of DAS28 at all visits revealed that at all visits beginning at Week 2, improvement in disease activity with upadacitinib treatment, as shown by mean decreases in DAS28 (CRP) and DAS28 (ESR) from baseline, was greater (nominal $P < 0.001$) compared with the cMTX group for both the upadacitinib 15 mg and 30 mg groups.

Study M13-542 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo on Stable Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response or Intolerance to Biologic DMARDs (bDMARDs) (Select Beyond)

Methods

Study participants

Inclusion criteria (summary of most notable)

- Diagnosis of RA for ≥ 3 months and fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA.
- ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at screening and baseline visits, and high sensitivity C-reactive protein ≥ 3 mg/L (central lab) at screening.
- Treated with bDMARD therapy for RA in the past and failed at least 1 bDMARD therapy prior to first dose of study drug as defined by either not showing an adequate response to at least 1 bDMARD after a treatment of ≥ 3 month or having had to discontinue at least 1 bDMARD due to intolerability or toxicity, irrespective of treatment duration.
- On csDMARD therapy ≥ 3 months and on a stable dose of csDMARD therapy (restricted to methotrexate, chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide) for ≥ 4 weeks prior to the first dose of study drug.

Exclusion criteria (summary of most notable)

- Prior exposure to any janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib)

There were also exclusion criteria relating to abnormal laboratory values etc.

Treatments and overall design

This was a Phase 3 multicenter study that included Period 1 (24 weeks) and Period 2 (216-week), see figure below for treatment groups and overall design. An unblinded analysis was conducted after all subjects had completed Period 1. Subjects and sites are to remain blinded during Period 2.

The current submission includes the Period 1 CSR. Subjects that did not achieve LDA (by CDAI) at week 24 were to adjust background RA medication as rescue.

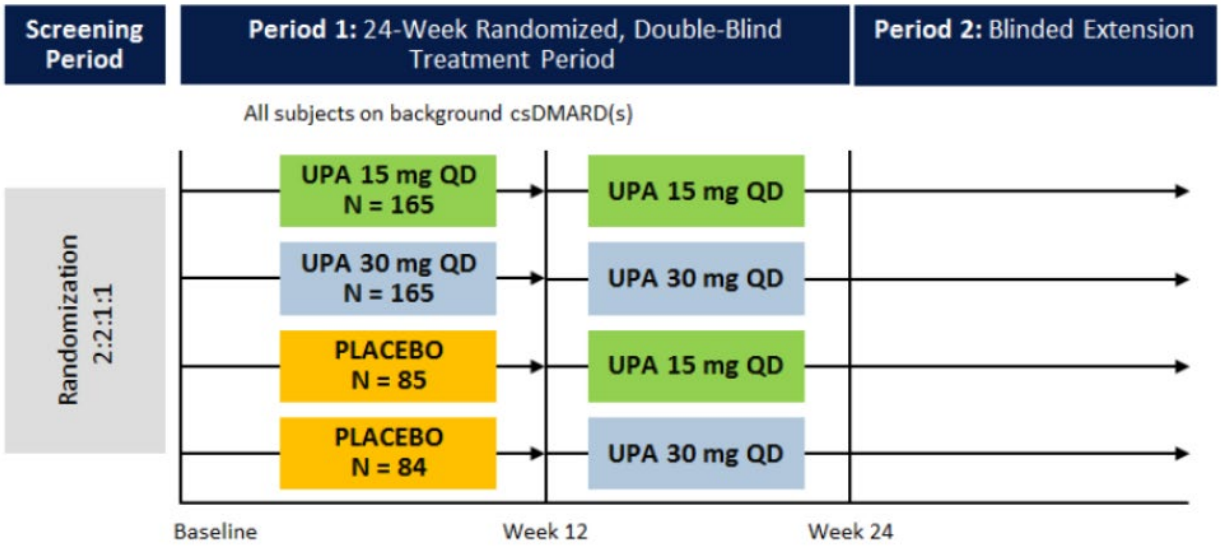


Figure 9 Design of Study of Study M13-542 (Select Beyond)

Outcomes/Endpoints

The primary endpoint was the proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12.

Ranked key secondary endpoints (at Week 12) were: 1) change from baseline in DAS28 (CRP); 2) ACR20 response rate; 3) change from baseline in HAQ-DI; 4) change from baseline in SF-36 PCS.

Other key secondary endpoints (at Week 12, if not specified) were: 1) proportion of subjects achieving ACR 50 response (ACR50) rate; 2) proportion of subjects achieving ACR 70 response (ACR70) rate; 3) proportion of subjects achieving ACR20 response at Week 1.

There were also additional efficacy analyses, these included assessment of clinical remission.

Randomisation

Subjects were randomized in a 2:2:1:1 ratio using interactive response technology (IRT) to receive double-blind study drug in one of the following treatment groups:

- Group 1: ABT-494 30 mg QD, N = 150 (Day 1 to Week 12) → ABT-494 30 mg QD (Week 12 and thereafter)
- Group 2: ABT-494 15 mg QD, N = 150 (Day 1 to Week 12) → ABT-494 15 mg QD (Week 12 and thereafter)
- Group 3: Placebo, N = 75 (Day 1 to Week 12) → ABT-494 30 mg QD (Week 12 and thereafter)
- Group 4: Placebo, N = 75 (Day 1 to Week 12) → ABT-494 15 mg QD (Week 12 and thereafter)

Randomization was stratified by number of prior bDMARD use (stratum 1: failed 1 or 2 biologics with the same mechanism of action; stratum 2: failed ≥ 3 biologics with the same mechanism of action and/or multiple mechanisms of action) and geographic region.

Once approximately 35% of the total subjects have been randomized in stratum 2, further screening of subjects who meet stratum 2 criteria may be suspended.

Blinding

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the Investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. In order to maintain the blind, the ABT-494 tablets and placebo tablets provided for the study will be identical in appearance.

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 24). Study sites and subjects will remain blinded for the duration of the study.

Statistical methods

The Full Analysis Set (FAS) includes all randomized subjects who received at least one dose of study drug based on treatment as randomized. The FAS will be used for all efficacy and baseline analyses.

The Per Protocol Analysis Set represents a subset of the FAS and consists of all FAS subjects who did not meet any major protocol violations during the study. Definitions of major protocol violations will be detailed in the SAP. Additional analysis may be conducted on the Per Protocol analysis set, in order to evaluate the impact of major protocol violations.

The Safety Analysis Set consists of all subjects who received at least one dose of study drug. For the Safety Analysis Set, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

For all efficacy analyses in Period 1, the two placebo groups (Groups 3 and 4) were combined and treated as one placebo group for analysis purposes. Each ABT-494 dose was compared with the combined placebo group.

Comparisons of the primary endpoint were made between each ABT-494 dose and the combined placebo group using the Cochran-Mantel-Haenszel test adjusting for main stratification factors. For the primary analysis, non-responder imputation (NRI) was used. The analysis was repeated using Observed Cases (OC) and LOCF imputation. Supportive analysis was also conducted on the Per Protocol Analysis Set.

For continuous endpoints between-group comparisons for each ABT-494 treatment group and the combined placebo groups were performed using the analysis of covariance model with treatment as the fixed factor, and the corresponding baseline value and the main stratification factors as the covariates.

The primary efficacy analyses were performed in demographic subgroups including age, gender, weight, body mass index, race, and geographical region to assess the consistency of the treatment effect. Additional subgroup analyses based on baseline disease characteristics and stratification factors will also be conducted.

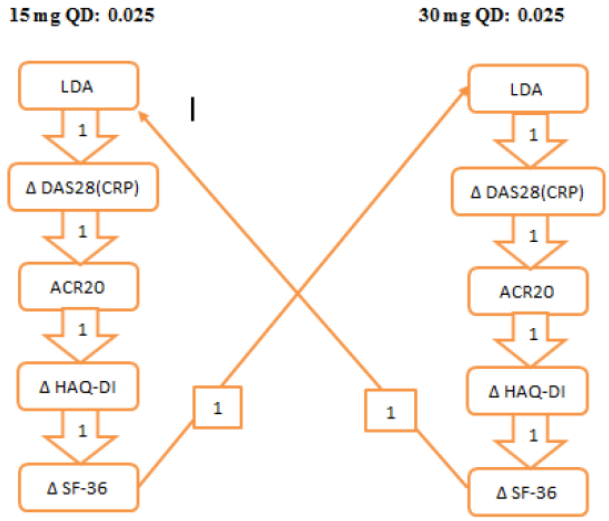


Figure 10 Graphical multiple testing procedure

Results

Participant flow

A total of 499 subjects were randomized. Of these subjects, 498 subjects received study drug i.e. were included in the FAS (that was used for all efficacy analysis). The proportion of subjects that completed week 12 study participation ranged from 88.2 to 95.7% across the treatment groups. The proportion of subjects that completed week 12 study drug ranged from 84.7% to 95.1% across treatment groups.

Recruitment

First Subject First Visit: 15 March 2016. Last Subject Last Visit: 27 June 2017 (Period 1).

Conduct of the study

At the time of the data cut-off for this Period 1 clinical study report, the original protocol (21 January 2016, 3 subjects enrolled) had 2 global amendments.

Baseline data

Mean age (+SD) was in the FAS in the placebo, UPA 15 mg and UPA 30 mg groups: 57.6 (± 11.39), 56.3 (± 11.34) and 57.3 (± 11.55) years. The proportion of females was in the placebo, UPA 15 mg and UPA 30 mg groups: 84.6, 83.5 and 83.6%. The proportion of subjects with current tobacco use was in the placebo, UPA 15 mg and UPA 30 mg groups: 13.0, 22.6 and 23.6%.

The proportion of aCCP-positive subjects was in the placebo, UPA 15 mg and UPA 30 mg groups: 69.2%, 72.6% and 72.7%. Mean (SD) DAS28 (CRP) was in the placebo, UPA 15 mg and UPA 30 mg groups: 5.8 (± 1.00) 5.9 (± 0.95) 5.8 (± 0.89).

The proportion of subjects that belonged to the stratum Prior failed bDMARDs; Stratum 1=1 Mechanism of Action and ≤ 2 prior bDMARDs, was in the placebo, UPA 15 mg and UPA 30 mg groups: 69.2%, 70.7% and 67.3%.

According to the CSR, 38 subjects (7.6%) of the FAS were treated with leflunomide, 2 (0.4%) with chloroquine, 63 (12.7%) on hydroxychloroquine and 39 subjects (7.8%) were treated with

sulfasalazine. These groups could include subjects that were also on MTX; according to the CSR, 412 (82.7%) were on concomitant treatment with MTX.

Outcomes and Estimation

The outcomes of the primary and key secondary endpoints are displayed in the table below.

Table 20: Outcomes of the primary and key secondary endpoints in study M13-542

ENDPOINT [A] / TREATMENT	N	WITHIN GROUP POINT ESTIMATE (95% CI)	BETWEEN GROUP DIFFERENCE (ABT-494 - PBO) POINT ESTIMATE (95% CI)	NOMINAL P-VALUE	ADJUSTED P-VALUE [B]
LOW DISEASE ACTIVITY BASED ON DAS28(CRP) AT WEEK 12					
PLACEBO	169	14.2 (8.9 , 19.5)			
ABT-494 15 MG QD	164	43.3 (35.7 , 50.9)	29.1 (19.9 , 38.3)	<0.001***	<0.001***
ABT-494 30 MG QD	165	42.4 (34.9 , 50.0)	28.2 (19.0 , 37.4)	<0.001***	<0.001***
DAS28(CRP) CHANGE FROM BASELINE AT WEEK 12					
PLACEBO	165	-1.02 (-1.23, -0.80)			
ABT-494 15 MG QD	163	-2.31 (-2.52, -2.10)	-1.29 (-1.57, -1.01)	<0.001***	<0.001***
ABT-494 30 MG QD	161	-2.29 (-2.50, -2.09)	-1.28 (-1.56, -0.99)	<0.001***	<0.001***
ACR20 RESPONSE RATE AT WEEK 12					
PLACEBO	169	28.4 (21.6 , 35.2)			
ABT-494 15 MG QD	164	64.6 (57.3 , 72.0)	36.2 (26.2 , 46.2)	<0.001***	<0.001***
ABT-494 30 MG QD	165	56.4 (48.8 , 63.9)	28.0 (17.8 , 38.1)	<0.001***	<0.001***
HAQ-DI CHANGE FROM BASELINE AT WEEK 12					
PLACEBO	165	-0.17 (-0.26, -0.08)			
ABT-494 15 MG QD	163	-0.39 (-0.48, -0.30)	-0.22 (-0.34, -0.10)	<0.001***	<0.001***
ABT-494 30 MG QD	160	-0.42 (-0.51, -0.33)	-0.25 (-0.38, -0.13)	<0.001***	<0.001***
SF-36 PCS CHANGE FROM BASELINE AT WEEK 12					
PLACEBO	145	2.39 (1.14, 3.64)			
ABT-494 15 MG QD	156	5.83 (4.60, 7.05)	3.44 (1.72, 5.15)	<0.001***	<0.001***
ABT-494 30 MG QD	147	7.02 (5.78, 8.25)	4.63 (2.89, 6.36)	<0.001***	<0.001***
ACR50 RESPONSE RATE AT WEEK 12					
PLACEBO	169	11.8 (7.0 , 16.7)			
ABT-494 15 MG QD	164	34.1 (26.9 , 41.4)	22.3 (13.6 , 31.1)	<0.001***	
ABT-494 30 MG QD	165	35.8 (28.4 , 43.1)	23.9 (15.1 , 32.7)	<0.001***	
ACR70 RESPONSE RATE AT WEEK 12					
PLACEBO	169	6.5 (2.8 , 10.2)			
ABT-494 15 MG QD	164	11.6 (6.7 , 16.5)	5.1 (-1.1 , 11.2)	0.110	
ABT-494 30 MG QD	165	23.0 (16.6 , 29.5)	16.5 (9.1 , 23.9)	<0.001***	
ACR20 RESPONSE RATE AT WEEK 1					
PLACEBO	169	10.7 (6.0 , 15.3)			
ABT-494 15 MG QD	164	27.4 (20.6 , 34.3)	16.8 (8.5 , 25.1)	<0.001***	
ABT-494 30 MG QD	165	24.8 (18.3 , 31.4)	14.2 (6.1 , 22.3)	<0.001***	

[A]: RESULTS FOR BINARY ENDPOINTS ARE BASED ON NON-RESPONDER IMPUTATION. RESULTS FOR DAS28(CRP) AND HAQ-DI ARE BASED ON ANCOVA WITH MULTIPLE IMPUTATION FOR MISSING DATA HANDLING. RESULTS FOR OTHER CONTINUOUS ENDPOINTS ARE BASED ON MMRM MODEL.
[B]: ADJUSTED P-VALUES ARE OBTAINED VIA THE GRAPHICAL MULTIPLE TESTING PROCEDURE CONTROLLING THE OVERALL TYPE I ERROR RATE OF ALL PRIMARY AND RANKED KEY SECONDARY ENDPOINTS (FOR BOTH ABT-494 DOSE GROUPS) AT THE 0.05 LEVEL.
***, **, * STATISTICALLY SIGNIFICANT AT 0.001, 0.01, AND 0.05 LEVEL, RESPECTIVELY.

Ancillary analyses

The primary endpoint, LDA at week 12, was analyzed according to subgroups based on age, gender, weight, BMI, race, geographic region, baseline serological status, duration of RA diagnosis, baseline DAS28 (CRP), prior failed bDMARD use, failed at least 1 prior biologic DMARD due to lack of efficacy and failed anti-IL6 due to lack of efficacy.

Overall, across the subgroups, upadacitinib performed (numerically) better than placebo.

The outcome of the subgroup analysis of the primary endpoint according to prior failed bDMARD is presented in the table below.

Table 21: Summary of primary endpoint, LDA at week 12 (based on DAS28 CRP) according to prior failed bDMARD in study M13-542

SUBGROUP TREATMENT	N	RESPONDER n (%)	RESPONSE RATE (95% CI) [A]	--- RESPONSE RATE DIFF (ABT-494 - PBO) --- POINT ESTIMATE	95% CI [B]
1 MOA AND <= 2 PRIOR BIOLOGIC DMARDS					
PLACEBO	117	19 (16.2)	16.2 (9.6, 22.9)		
ABT-494 15 MG QD	116	52 (44.8)	44.8 (35.8, 53.9)	28.6	(17.3, 39.8)
ABT-494 30 MG QD	111	50 (45.0)	45.0 (35.8, 54.3)	28.8	(17.4, 40.2)
OTHER					
PLACEBO	52	5 (9.6)	9.6 (1.6, 17.6)		
ABT-494 15 MG QD	48	19 (39.6)	39.6 (25.7, 53.4)	30.0	(14.0, 46.0)
ABT-494 30 MG QD	54	20 (37.0)	37.0 (24.2, 49.9)	27.4	(12.3, 42.6)

CDAI was analyzed as an additional efficacy analysis. At all visits beginning at Week 1 through Week 12, improvement in disease activity with upadacitinib treatment, as shown by mean decreases in CDAI from baseline, was greater for both the 15 mg and 30 mg groups compared with the placebo group (nominal $P < 0.001$).

Summary of main studies

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

Table 22: Tabulated summary of efficacy for trial M13-545

Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Once Daily Monotherapy to Methotrexate (MTX) Monotherapy in MTX-Naïve Subjects with Moderately to Severely Active Rheumatoid Arthritis" (Select Early)					
Study identifier	M13-545				
Design	Randomized, double-blind, parallel-group, active comparator controlled				
	Duration of main phase and extension phase:		Main phase 48 weeks (Period 1), Long-term extension 192 weeks (Period 2)		
Hypothesis	Superiority				
Treatments groups (monotherapy)	MTX		315 randomized		
	Upadacitinib 15 mg QD		317 randomized		
	Upadacitinib 30 mg QD		315 randomized		
Endpoints and definitions	Primary endpoint	CR week 24	Clinical Remission based on DAS28CRP<2.6		
	Secondary endpoints		Please refer to previous section of this AR.		
Database lock	***1 May 2018 (primary data base lock)***				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	The analysis was conducted on FAS (n=945) which included all randomized subjects (n=947) who received at least 1 dose of study drug, Non-responder imputation (NRI) was used <Intent to treat> <Per protocol> <other: specify> *{consider adding a brief description of the definition of the population}* <time point>				
Descriptive statistics and estimate variability	Treatment group	Control; MTX	Upadacitinib 15 mg QD	Upadacitinib 30 mg QD	
	Number of subject	314	317	314	
	Proportion with CR (%), point estimate	18.5	48.3	50.0	
	95% CI	14.2, 22.8	42.8, 53.8	44.5, 55.5	
Effect estimate per comparison	Primary endpoint	Comparison groups	Upadacitinib 15 mg QD-MTX		
		Between groups difference in the proportion of CR (%)(%week 24	29.8		
		95% CI	22.8, 36.8		
		P-value	<0.001		
Notes	The outcomes of the secondary analysis were generally in line with the outcome of the primary analysis, see table in previous section.				

Table 23: Tabulated summary of efficacy for trial M13-549

Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs" (Select Next)				
Study identifier	M13-549			
Design	Randomized, double-blind, parallel-group, placebo-controlled			
	Duration of main phase and extension phase		Main phase 12 weeks (Period 1), Long-term extension up to 5 years (Period 2)	
Hypothesis	Superiority			
Treatments groups (add on to csDMARD)	Placebo		221 randomized	
	Upadacitinib 15 mg QD		221 randomized	
	Upadacitinib 30 mg QD		219 randomized	
Endpoints and definitions	Primary endpoint	LDA at week 12	Low Disease Activity based on DAS28 CRP ≤ 3.2	
	Secondary endpoints		Please refer to previous section.	
Database lock	***4 May 2017 (primary data base lock)***			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	The analysis was conducted on FAS (n=661) which included all randomized subjects (n=661) who received at least 1 dose of study drug, non-responder imputation (NRI) was used.			
Descriptive statistics and estimate variability	Treatment group	Placebo	Upadacitinib 15 mg QD	Upadacitinib 30 mg QD
	Number of subject	221	221	119
	LDA (%)	17.2	48.4	47.9
	95% CI	12.2, 22.2	41.8, 55.0	41.3, 54.6
Effect estimate per comparison	Primary endpoint	Comparison groups	Upadacitinib 15 mg QD-placebo	
		Between groups difference in the proportion of LDA	31.3	
		95% CI	23.0, 39.5	
		P-value	<0.001	
Notes	The outcomes of the secondary analysis were generally in line with the outcome of the primary analysis, see table in previous section.			

Table 24: Tabulated summary of efficacy for trial M14-465

Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR) (Select Compare)

Study identifier	M14-465		
Design	Randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled design		
	Duration of main phase and extension phase		Main phase 48 weeks (Period 1), Long term extension up to 5 years (Period 2)
Hypothesis	Superiority (vs placebo), Non-inferiority (vs active comparator)		
Treatments groups (add-on to MTX)	Placebo		651 randomized
	Upadacitinib 15 mg QD		651 randomized
	Adalimumab 40 mg EOW		327 randomized
Endpoints and definitions	Primary endpoint	CR week 12	Clinical Remission based on DAS28 CRP<2.6
	Secondary endpoints	LDA week 12	LDA based on DAS28 (CRP) ≤ 3.2 (including non-inferiority of upadacitinib versus adalimumab) For other secondary endpoints, please refer to previous section.
Database lock	***22 Mar 2018 (primary database lock)***		

Results and Analysis

Analysis description	**Primary Analysis and Secondary Analysis**			
Analysis population and time point description	The analysis was conducted on FAS (n=1629) which included all randomized subjects (n=1629) who received at least 1 dose of study drug and non-responder imputation (NRI) was used.			
Descriptive statistics and estimate variability	Treatment group	Placebo	Upadacitinib 15 mg QD	Adalimumab 40 mg EOW
	Number of subject	651	651	327
	Primary endpoint; CR (%)	6.1	28.7	
	95% CI	4.3, 8.0	25.2, 32.2	
	Secondary endpoint; LDA (%)	13.8	45.0	28.7
	95% CI	11.2, 16.5	41.2, 48.8	23.8, 33.7

Effect estimate per comparison	Primary endpoint	Comparison groups	Upadacitinib 15 mg QD-placebo
		Between groups difference in the proportion of CR	22.6
		95% CI	18.6, 26.5
		P-value	<0.001
	Secondary endpoint	Comparison groups	Upadacitinib 15 mg QD-adalimumab 40 mg EOW
		Between groups difference in the proportion of LDA	16.3
		95% CI	10.0, 22.5

		P-value	Non-inferiority met
		P-value	NA
Notes	The outcomes of the secondary analysis were generally in line with the outcome of the primary analysis, see table in previous section.		

Table 25: Tabulated summary of efficacy for trial M15-555

Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Monotherapy to Methotrexate (MTX) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response to MTX" (Select Monotherapy)				
Study identifier	M15-555			
Design	Randomized, double-blind, parallel-group, controlled			
	Duration of main phase and extension phase		Main phase 14 weeks (Period 1), long term extension 226 weeks (Period 2)	
Hypothesis	Superiority			
Treatments groups (monotherapy)	cMTX (continue MTX)		216 randomized	
	Upadacitinib 15 mg QD		217 randomized	
	Upadacitinib 30 mg QD		215 randomized	
Endpoints and definitions	Primary endpoint	LDA week 14	Low Disease Activity based on DAS28 (CRP) ≤ 3.2	
	Secondary endpoints		Please refer to previous section.	
Database lock	***6 Dec 2017 (primary database lock)***			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	The analysis was conducted on FAS (n=648) which included all randomized subjects (n=648) who received at least 1 dose of study drug and non-responder imputation (NRI) was used.			
Descriptive statistics and estimate variability	Treatment group	cMTX	Upadacitinib 15 mg QD	Upadacitinib 30 mg QD
	Number of subject	216	217	215
	LDA (%)	19.4	44.7	53.0
	95% CI	14.2, 24.7	38.1, 51.3	46.4, 59.7
Effect estimate per comparison	Primary endpoint	Comparison groups	Upadacitinib 15 mg QD-cMTX	
		Between groups difference in the proportion of LDA	25.3	
		95% CI	16.8, 33.7	
		P-value	<0.001	
Notes	The outcomes of the secondary analysis were generally in line with the outcome of the primary analysis, see table in previous section.			

T*able 26: Tabulated summary of efficacy for trial M13-542*

Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo on Stable Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response or Intolerance to Biologic DMARDs (bDMARDs) (Select Beyond)	
Study identifier	M13-542
Design	Randomized, double-blind, parallel-group, placebo-controlled

	Duration of main phase and extension phase		Main phase 24 weeks (Period 1), long-term extension 216-weeks (Period 2)		
Hypothesis	Superiority				
Treatments groups (add-on to csDMARD)	Placebo		169 randomized		
	Upadacitinib 15 mg		165 randomized		
	Upadacitinib 30 mg		165 randomized		
Endpoints and definitions	Primary endpoint	LDA week 12	Low Disease Activity based on DAS28 (CRP) ≤ 3.2		
	Secondary endpoints		Please refer to previous section.		
Database lock	***14 Jul 2017***				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	The analysis was conducted on FAS (n=498) which included all randomized subjects (n=499) who received at least 1 dose of study drug and non-responder imputation (NRI) was used.				
Descriptive statistics and estimate variability	Treatment group	Placebo	Upadacitinib 15 mg QD	Upadacitinib 30 mg QD	
	Number of subject	169	164	165	
	LDA (%)	14.2	43.3	42.4	
	95% CI	8.9, 19.5	35.7, 50.9	34.9, 50.0	
Effect estimate per comparison	Primary endpoint	Comparison groups	Upadacitinib 15 mg QD-placebo		
		Between groups difference in the proportion of LDA	29.1		
		95% CI	19.9, 38.3		
		P-value	<0.001		
Notes	The outcomes of the secondary analysis were generally in line with the outcome of the primary analysis, see table in previous section.				

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

Short-term integrated efficacy analysis

Two integrated analysis sets of the Phase 3 studies were defined for the purpose of short-term integrated efficacy analyses (ISE SAP). In both integrated analysis sets, the randomization ratio between upadacitinib and control is the same across all the studies being integrated:

- Placebo-controlled upadacitinib 15 mg analysis set: The objective of this analysis set was to compare upadacitinib 15 mg QD versus placebo on top of background MTX and/or other csDMARDs. This analysis set integrated the placebo-controlled studies that included upadacitinib 15 mg QD as a treatment arm. Specifically, it included subjects from the following studies: Studies M13-549, M14-465, and M13-542. Subjects in the upadacitinib 15 mg QD and placebo groups were included in this analysis set.
- Placebo-controlled upadacitinib 15 mg and 30 mg analysis set: The objective of this analysis set was to compare upadacitinib 15 mg QD and 30 mg QD versus placebo on top of background csDMARDs. This analysis set integrated the placebo-controlled studies that included both upadacitinib 15 mg QD and upadacitinib 30 mg QD as treatment arms.

Specifically, it included subjects from the following studies: Studies M13-549 and M13-542. Subjects in the upadacitinib 15 mg QD, upadacitinib 30 mg QD, and placebo groups were included in this analysis set.

No discrepancies were found between the integrated data and study-specific data.

Comparison of Results in Subpopulations

To examine efficacy across subpopulations, subgroup analyses were conducted for ACR20 and LDA based on DAS28 (CRP) at Week 12 for the two integrated analysis sets (placebo-controlled upadacitinib 15 mg QD and placebo-controlled upadacitinib 15 mg and 30 mg QD analysis sets) for the following subgroups: age, gender, weight, BMI, race, geographic region, baseline rheumatoid factor status, baseline anti-CCP antibody status, and background csDMARD at baseline (only applicable to the placebo-controlled upadacitinib 15 mg and 30 mg analysis set), and prior bDMARD intolerance.

The figure below provides the LDA based on DAS28 (CRP) results on the pooled analysis set [placebo-controlled upadacitinib 15mg]. Similar results were obtained for ACR20 (data not shown here).

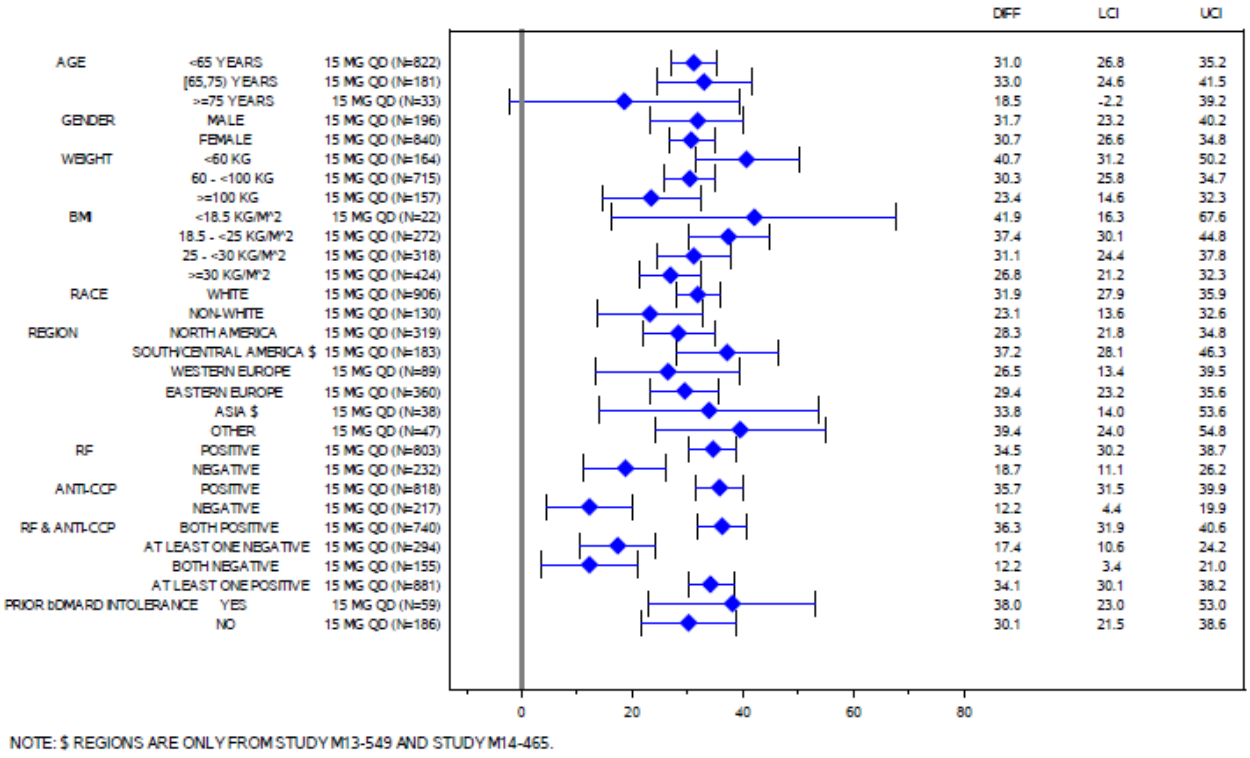


Figure 11 LDA based on DAS28 (CRP) results on the pooled analysis set [placebo-controlled upadacitinib 15mg]

Efficacy of Upadacitinib in bDMARD-Intolerant Subjects

The short-term efficacy of upadacitinib was assessed in bDMARD-intolerant subjects versus other bDMARD-exposed subjects (that discontinued bDMARD therapy due to lack of efficacy or other reasons). This analysis was based on CHMP Scientific Advice to support the use of upadacitinib in bDMARD-intolerant subjects. Subgroup analysis was performed for ACR20 and LDA based on DAS28 (CRP) at Week 12 in the two integrated analysis sets i.e. the placebo-controlled upadacitinib 15 mg and placebo-controlled upadacitinib 15 mg and 30 mg analysis sets (as described above). The outcomes of these two analyses in the placebo-controlled upadacitinib 15 mg are presented in the tables below.

Table 27: ACR20 Response Rate at Week 12 by Prior bDMARD Intolerance (Placebo-Controlled Upadacitinib 15 mg Analysis Set) (NRI)

Subgroup Treatment	N	Responder % (95% CI)[a]	Between Group Comparison Adjusted by Study[b] (Upadacitinib - Placebo) Response Rate Difference (95% CI)
Yes[c]			
Placebo	59	30.5 (18.8, 42.3)	
Upadacitinib 15 mg QD	59	62.7 (50.4, 75.1)	33.9 (17.2, 50.7)
No[d]			
Placebo	202	30.7 (24.3, 37.1)	
Upadacitinib 15 mg QD	186	65.6 (58.8, 72.4)	34.8 (25.5, 44.2)

ACR20 = American College of Rheumatology 20 response; bDMARD = biologic disease-modifying anti-rheumatic drug; CI = confidence interval; NRI = non-responder imputation; QD = once daily

a. 95% CI for response rate were calculated based on normal approximation to the binominal distribution.
b. Point estimate and 95% CI for between group difference were based on Mantel-Haenszel estimation (using proc stdrate) adjusting for study as a stratification factor.
c. "Prior bDMARD intolerant" is defined as subjects who discontinued at least one prior bDMARD due to safety/tolerability (regardless of length of exposure) and who have NOT discontinued any prior bDMARD due to lack of efficacy.
d. Subjects with prior bDMARD exposure who did not satisfy the above definition of "prior bDMARD intolerant" (discontinued bDMARD therapy due to lack of efficacy or other reasons).

Table 28: Low Disease Activity Based on DAS28 (CRP) at Week 12 by Prior bDMARD Intolerance (Placebo-Controlled Upadacitinib 15 mg Analysis Set) (NRI)

Subgroup Treatment	N	Responder % (95% CI)[a]	Between Group Comparison Adjusted by Study[b] (Upadacitinib - Placebo) Response Rate Difference (95% CI)
Yes[c]			
Placebo	59	11.9 (3.6, 20.1)	
Upadacitinib 15 mg QD	59	49.2 (36.4, 61.9)	38.0 (23.0, 53.0)
No[d]			
Placebo	202	13.9 (9.1, 18.6)	
Upadacitinib 15 mg QD	186	44.1 (37.0, 51.2)	30.1 (21.5, 38.6)

bDMARD = biologic disease-modifying anti-rheumatic drug; CI = confidence interval; CRP = C-reactive protein; DAS28 = disease activity score 28; NRI = non-responder imputation; QD = once daily

a. 95% CI for response rate were calculated based on normal approximation to the binominal distribution.
b. Point estimate and 95% CI for between group difference were based on Mantel-Haenszel estimation (using proc stdrate) adjusting for study as a stratification factor.
c. "Prior bDMARD intolerant" is defined as subjects who discontinued at least one prior bDMARD due to safety/tolerability (regardless of length of exposure) and who have NOT discontinued any prior bDMARD due to lack of efficacy.
d. Subjects with prior bDMARD exposure who did not satisfy the above definition of "prior bDMARD intolerant" (discontinued bDMARD therapy due to lack of efficacy or other reasons).

Efficacy of Upadacitinib in Combination with MTX Versus Other csDMARDs

To examine the short-term placebo-controlled efficacy of upadacitinib in combination with MTX versus other csDMARDs, a model-based analysis assessing the interaction between treatment effect and background csDMARD type was conducted for ACR20 and LDA based on DAS28 (CRP) at Week 12 within Studies M13-542 and M13-549, respectively, where csDMARDs other than MTX were permitted as background therapy per protocol. Note that subjects on a combination of MTX plus other csDMARDs were counted under MTX. Logistic regression was performed with treatment (upadacitinib 15 mg QD, upadacitinib 30 mg QD, and placebo) and background csDMARD type (MTX versus other), as well as the interaction term between treatment and background csDMARD type as the fixed factors.

Demographic and baseline covariates were adjusted in the model. The p-value for the interaction term between treatment and background csDMARD type was reported. NRI was used for missing data imputation on the response variable.

The outcomes of these analyses are presented in the figures and tables below.

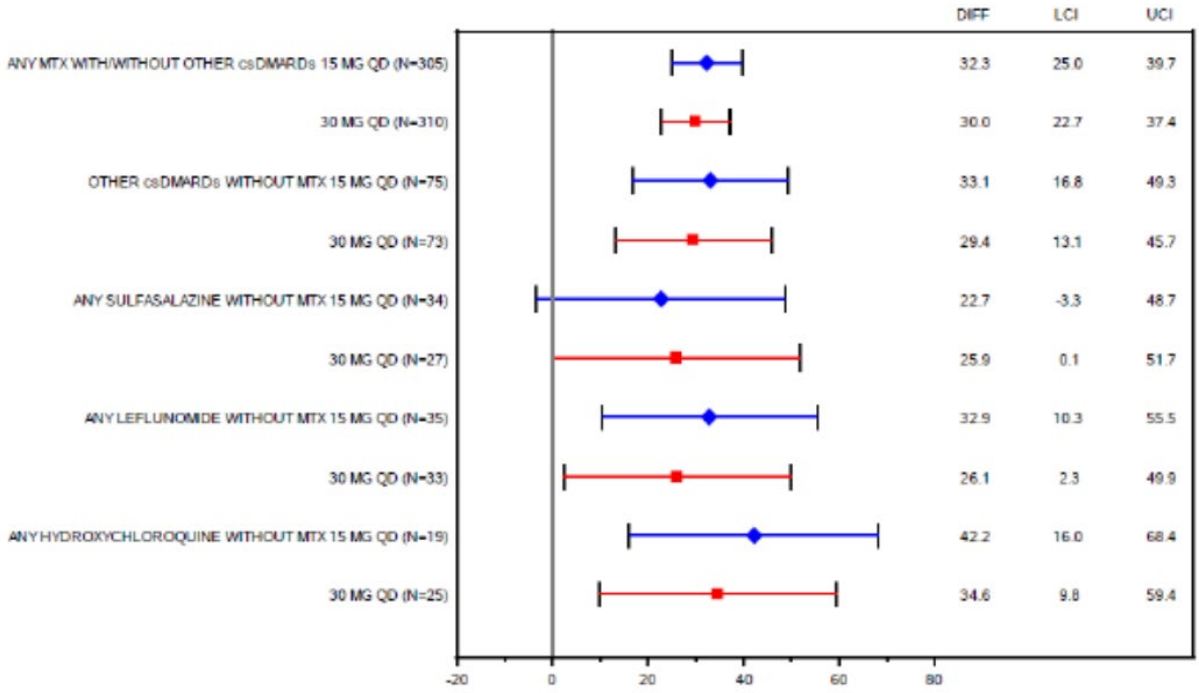


Figure 12: Forest Plot of Placebo-Subtracted ACR 20 Response Rate at Week 12 by Background csDMARD (NRI; Placebo-Controlled Upadacitinib 15 mg and 30 mg Analysis Set)

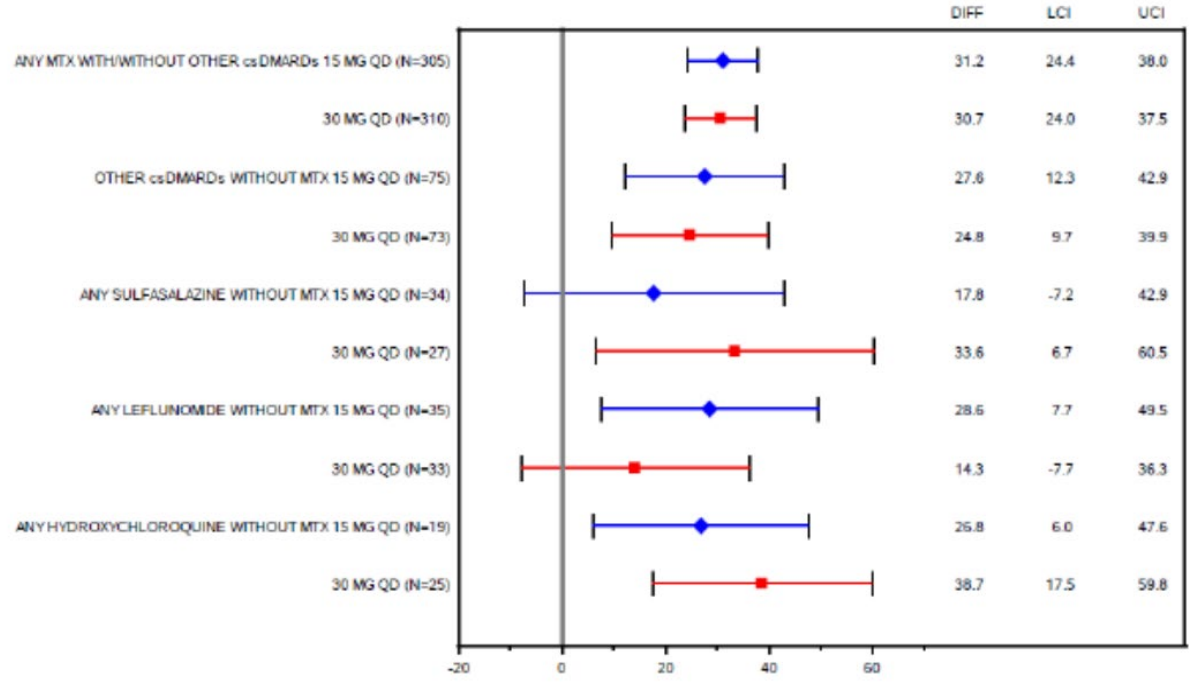


Figure 13: Forest Plot of Placebo-Subtracted Response Rate of LDA Based on DAS28 (CRP) at week 12 by Background csDMARD (NRI; Placebo-Controlled Upadacitinib 15 mg and 30 mg Analysis Set)

Table 29: Logistic Regression Analysis of Upadacitinib in Combination with MTX vs Other csDMARDs in ACR20 and LDA Based on DAS28 (CRP) at Week 12 in Study M13-549 (NRI; FAS)

Concomitant csDMARDs Treatment	N	Responder % (95% CI)[a]	Response Rate Difference (Upadacitinib – Placebo) Point Estimate (95% CI)[b]	Response Rate Difference (Upadacitinib – Placebo) Interaction P-value[c]
ACR20 response rate				
MTX				
Placebo	191	37.2 (30.3, 44.0)		
Upadacitinib 15 mg QD	169	65.1 (57.9, 72.3)	27.9 (18.0, 37.8)	
Upadacitinib 30 mg QD	175	67.4 (60.5, 74.4)	30.3 (20.5, 40.0)	
				0.990
Other csDMARDs				
Placebo	29	27.6 (11.3, 43.9)		
Upadacitinib 15 mg QD	51	58.8 (45.3, 72.3)	31.2 (10.1, 52.4)	
Upadacitinib 30 mg QD	44	61.4 (47.0, 75.8)	33.8 (12.1, 55.5)	
LDA based on DAS28 (CRP)				
MTX				
Placebo	191	16.8 (11.5, 22.1)		
Upadacitinib 15 mg QD	169	49.1 (41.6, 56.6)	32.4 (23.1, 41.6)	
Upadacitinib 30 mg QD	175	49.1 (41.7, 56.5)	32.4 (23.3, 41.5)	
				0.878
Other csDMARDs				
Placebo	29	20.7 (5.9, 35.4)		
Upadacitinib 15 mg QD	51	45.1 (31.4, 58.8)	24.4 (4.3, 44.5)	
Upadacitinib 30 mg QD	44	43.2 (28.5, 57.8)	22.5 (1.7, 43.3)	

ACR20 = American College of Rheumatology 20 response; CI = confidence interval; CRP = C-reactive protein; csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; DAS28 = disease activity score 28; FAS = full analysis set; LDA = low disease activity; MTX = methotrexate; NRI = non-responder imputation; QD = once daily; vs = versus

a. 95% CI for response rate were calculated based on normal approximation to the binominal distribution.

b. 95% CI for response rate difference were calculated based on normal approximation using Proc Freq.

c. P-value was for testing the interaction term between treatment and type of concomitant csDMARDs, based on a logistic regression model adjusting for demographic and baseline covariates.

Note: MTX includes subjects on MTX and a combination of MTX + other csDMARD. Other csDMARDs included subjects on csDMARDs other than MTX.

Table 30: Logistic Regression Analysis of Upadacitinib in Combination with MTX vs Other csDMARDs in ACR20 and LDA Based on DAS28 (CRP) at Week 12 in Study M13-542 (NRI; FAS)

Treatment	N	Responder % (95% CI)[a]	Response Rate Difference (Upadacitinib – Placebo) Point Estimate (95% CI)[b]	Interaction P-value[c]
ACR20 response rate				
MTX				
Placebo	139	27.3 (19.9, 34.7)		
Upadacitinib 15 mg QD	136	65.4 (57.4, 73.4)	38.1 (27.2, 49.0)	
Upadacitinib 30 mg QD	135	57.0 (48.7, 65.4)	29.7 (18.5, 40.9)	
				0.979
Other csDMARDs				
Placebo	29	31.0 (14.2, 47.9)		
Upadacitinib 15 mg QD	24	66.7 (47.8, 85.5)	35.6 (10.3, 60.9)	
Upadacitinib 30 mg QD	29	55.2 (37.1, 73.3)	24.1 (-0.6, 48.9)	
LDA based on DAS28 (CRP)				
MTX				
Placebo	139	13.7 (8.0, 19.4)		
Upadacitinib 15 mg QD	136	43.4 (35.1, 51.7)	29.7 (19.6, 39.8)	
Upadacitinib 30 mg QD	135	42.2 (33.9, 50.6)	28.6 (18.5, 38.7)	
				0.834
Other csDMARDs				
Placebo	29	13.8 (1.2, 26.3)		
Upadacitinib 15 mg QD	24	45.8 (25.9, 65.8)	32.0 (8.5, 55.6)	
Upadacitinib 30 mg QD	29	41.4 (23.5, 59.3)	27.6 (5.7, 49.5)	

ACR20 = American College of Rheumatology 20 response; CI = confidence interval; CRP = C-reactive protein; csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; DAS28 = disease activity score 28; FAS = full analysis set; LDA = low disease activity; MTX = methotrexate; NRI = non-responder imputation; QD = once daily; vs = versus

a. 95% CI for response rate were calculated based on normal approximation to the binominal distribution.

b. 95% CI for response rate difference were calculated based on normal approximation using Proc Freq.

c. P-value was for testing the interaction term between treatment and type of concomitant csDMARDs, based on a logistic regression model adjusting for demographic and baseline covariates.

Note: MTX includes subjects on MTX and a combination of MTX + other csDMARD. Other csDMARDs included subjects on csDMARDs other than MTX.

Cross-Study Indirect Comparison of Upadacitinib Monotherapy Versus Upadacitinib + MTX Combination Therapy

In accordance with recommendations received during CHMP Scientific Advice, a cross-study analysis was conducted to provide an indirect comparison of the efficacy of upadacitinib as monotherapy versus in combination with MTX in the MTX-IR population. This analysis was primarily conducted to support the use of upadacitinib monotherapy in a MTX-IR population. A model-based analysis was conducted on subjects from Studies M13-549 and M15-555, as these two studies had similar patient characteristics based on the inclusion and exclusion criteria. To be consistent with the MTX-IR population in the monotherapy Study M15-555, subjects in Study M13-549 who were MTX-IR with no prior exposure to bDMARD were included in this analysis. Analyses were conducted for ACR20 and LDA based on DAS28 (CRP) at Week 12 (Study M13-549)/Week 14 (Study M15-555).

Logistic regression was performed with treatment group as the fixed factor and adjusting for demographic and baseline covariates. The comparison between monotherapy and combination therapy (for upadacitinib 15 mg QD and 30 mg QD, respectively) was based on the contrast between the cMTX group-adjusted upadacitinib monotherapy treatment effect and placebo group-adjusted upadacitinib combination treatment effect (on the logit scale). The p-value for this comparison was reported. NRI was used for missing data imputation on the response variables.

Baseline variables including sex, age, race, serological status and disease activity were compared across the treatment groups included in the analysis; in all treatment groups the majority of subjects were female (ranged from 75.2% to 82.9% across groups), mean age was around 55 years (ranged from 53.1 to 56.2 across groups), a majority of subjects were aCCP-positive (ranged from 68.6% to 81.1% across groups) and had a high mean disease activity measured as DAS28 (ranged from 5.5-5.7 across groups).

The outcome of this analysis is presented in the table below.

Table 31: Logistic Regression Analysis of Cross-Study Comparison of Upadacitinib Monotherapy and Upadacitinib + MTX Combination Therapy in ACR20 and LDA Based on DAS28 (CRP) at Week 12/14 (NRI; Pooled Analysis Set from Studies M13-549 and M15-555)

			Response Rate Difference[b] (Upadacitinib – Control)	
Treatment	N	Responder % (95% CI)[a]	Point Estimate (95% CI)	Mono vs Combo P-value[c]
ACR20 response rate				
cMTX	216	41.2 (34.6, 47.8)		
Upadacitinib 15 mg QD Monotherapy	217	67.7 (61.5, 74.0)	26.5 (17.5, 35.6)	
Upadacitinib 30 mg QD Monotherapy	215	71.2 (65.1, 77.2)	30.0 (21.0, 38.9)	
Placebo + MTX	165	38.2 (30.8, 45.6)		
Upadacitinib 15 mg QD + MTX	148	66.2 (58.6, 73.8)	28.0 (17.4, 38.7)	0.962
Upadacitinib 30 mg QD + MTX	153	65.4 (57.8, 72.9)	27.2 (16.6, 37.8)	0.561
LDA based on DAS28 (CRP)				
cMTX	216	19.4 (14.2, 24.7)		
Upadacitinib 15 mg QD Monotherapy	217	44.7 (38.1, 51.3)	25.3 (16.8, 33.7)	
Upadacitinib 30 mg QD Monotherapy	215	53.5 (46.8, 60.2)	34.0 (25.5, 42.5)	
Placebo + MTX	165	18.2 (12.3, 24.1)		
Upadacitinib 15 mg QD + MTX	148	48.6 (40.6, 56.7)	30.5 (20.5, 40.4)	0.564
Upadacitinib 30 mg QD + MTX	153	49.7 (41.8, 57.6)	31.5 (21.6, 41.4)	0.878

ACR20 = American College of Rheumatology 20 response; CI = confidence interval; cMTX = continuing methotrexate; CRP = C-reactive protein; DAS28 = disease activity score (28 joints); LDA = low disease activity; MTX = methotrexate; NRI = non-responder imputation; QD = once daily; vs = versus

a. 95% CI for response rate were calculated based on normal approximation to the binominal distribution.

b. Response rate difference is between each upadacitinib monotherapy group vs cMTX and each upadacitinib combination group versus placebo combination. 95% CI for response rate difference were calculated based on normal approximation using Proc Freq.

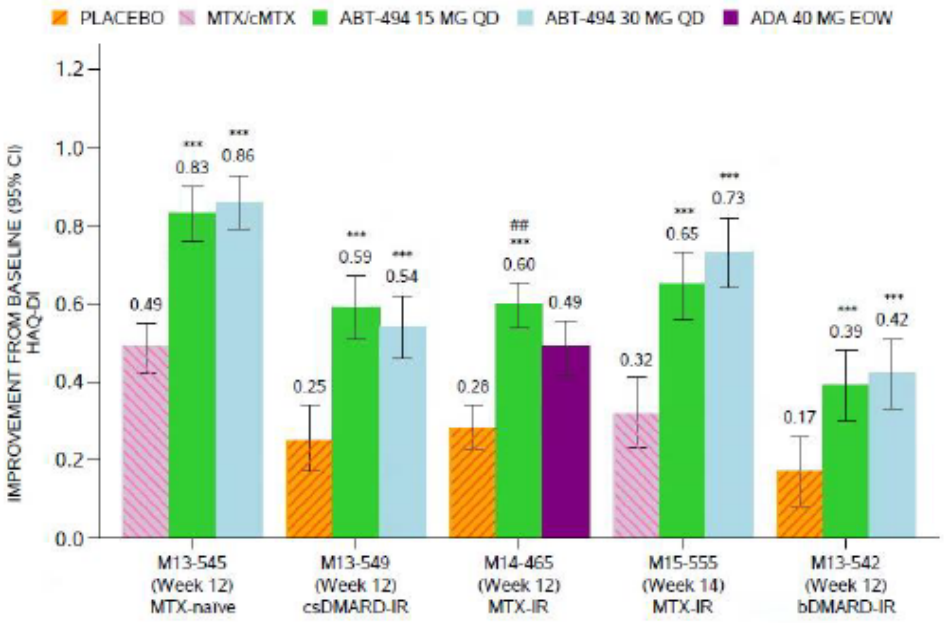
c. P-value for the comparison between monotherapy and combination therapy (for 15 mg and 30 mg, respectively) is based on the contrast between the cMTX group-adjusted upadacitinib monotherapy treatment effect and placebo group-adjusted upadacitinib combination treatment effect (on the logit scale) in a logistic regression model with treatment group as the fixed factor, and adjusting for various demographic and baseline covariates.

Patient reported outcomes (PROs)

As recommended in the Guideline on clinical investigation of medicinal products for the treatment of rheumatoid arthritis (CPMP/EWP/556/95 Rev. 2), the Phase 3 studies included several PROs as secondary outcome measures. Most of the PROs in the Ph3 trials were previously validated and widely used in clinical trials. These include the Health Assessment Questionnaire – Disability Index [HAQ-DI] for measuring physical function and disability, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) for the assessment of fatigue, and Short Form-36 (SF-36) and EuroQoL-5D-5L (EQ-5D-5L) as measures of general quality of life. Work Instability Scale for RA (RA-WIS) was used to measure work instability (WI) in patients with RA. It is applicable only to patients who are employed. Additionally visual analogue scale (VAS) was used for the patient's perception of disease activity (Patient Global Assessment of Disease Activity) and intensity of pain (Patient's Assessment of Pain VAS) and for measuring the study site's assessment of disease activity (Physician Global Assessment of Disease Activity VAS).

The applicant also created the measure on severity and duration of morning stiffness, a typical symptom of RA. This new measure has been validated by the Applicant.

As the results of different PROs were concordant, only the results of HAQ-DI are included here (see figure below).



***, **, * P-value ≤ 0.001, 0.01, and 0.05 level for upadacitinib versus placebo or MTX/cMTX comparison, respectively.

###, ##, # P-value ≤ 0.001, 0.01, and 0.05 level for upadacitinib versus adalimumab comparison, respectively.

Figure 14: Improvement from Baseline in HAQ-DI at the Primary Analysis Time Point (Month 3) For Pivotal Phase 3 Studies (MI; FAS)

Long-term efficacy analysis: Persistence of Efficacy and/or Tolerance Effects

Long-term efficacy analyses were conducted for each of the five Phase 3 studies separately. Efficacy data are presented through Week 60 for Studies M13-549 and M13-542 and through Week 48 for Studies M13-545, M14-465, and M15-555, with approximately 78%, 74%, 80%, 87%, and 84%,

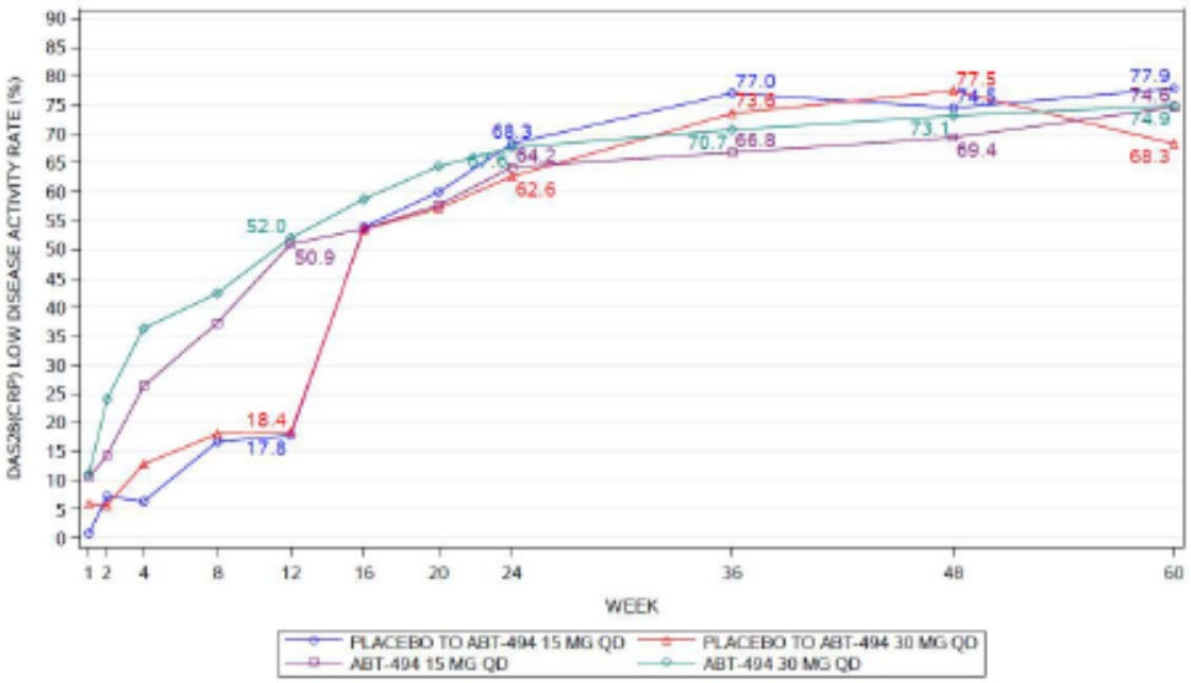
respectively, of subjects remaining in the study through the last summarized visit (by the data cut-off date). Descriptive statistics for long-term efficacy are reported by treatment sequence based on AO data. For Studies M13-545 and M14-465 (which have longer-term active comparator arms), additional analysis by randomized group were presented by the applicant with rescue handling using NRI for binary endpoints and using last observation carried forward (LOCF) for continuous endpoints (with the exception of rescue in Study M14-465 at Week 26 based on CDAI LDA, where LOCF was used for binary endpoints). These long-term comparisons were not among the ranked key secondary endpoints and therefore were not subject to multiplicity control. Nominal p-values were used as descriptive measures.

All analyses for long-term efficacy were to be performed on the Full Analysis Set (FAS) population that includes all randomized subjects who have received at least one dose of study drug.

The primary endpoint for study M13-545 and M14-465 was CR based on DAS28 CRP (at week 24 and week 12 respectively) while the primary endpoint in study M13-549, M15-555 and M13-542 was LDA based on DAS28 CRP (at week 12, 14 and 12 respectively). All these studies were reported to be on-going. The focus of the presentation of persistence of effect for the respective studies was on the outcomes of the primary endpoints.

Persistence of LDA: study M13-549, M15-555 and M13-542

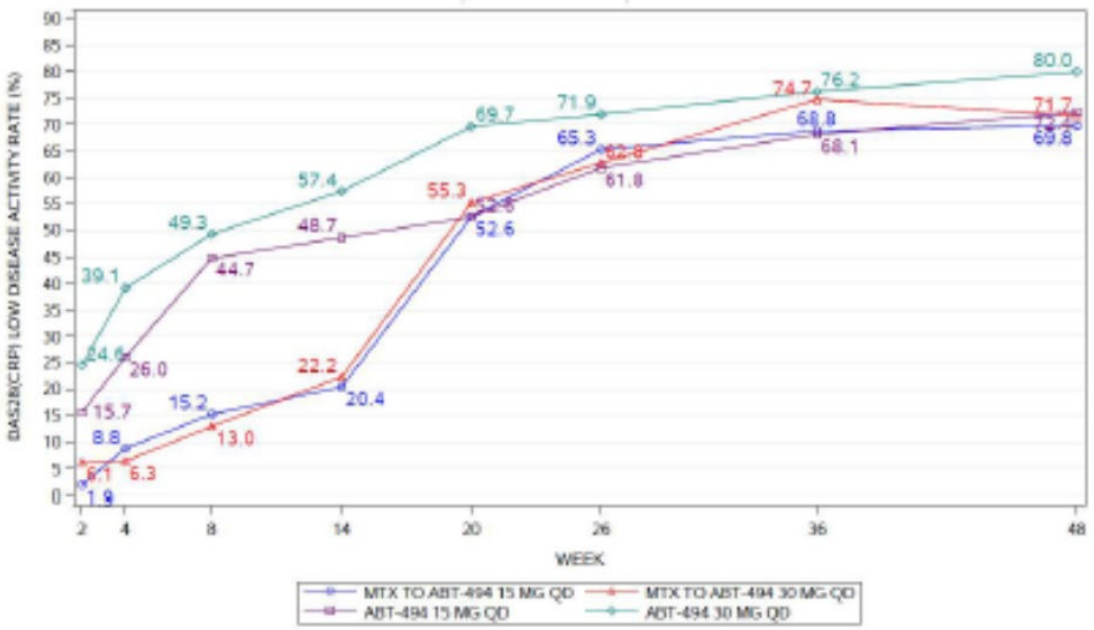
The following three figures display LDA over time in the three pivotal studies in which LDA was the primary endpoint. The added text below each respective figure indicate the number of subjects that were responders and number of subjects assessed in each group at different timepoints.



Treatment switch was at Week 12.

Figure 15: Study M13-549; LDA based on DAS28 CRP over time-Long Term Up to Week 60 (AO; FAS)

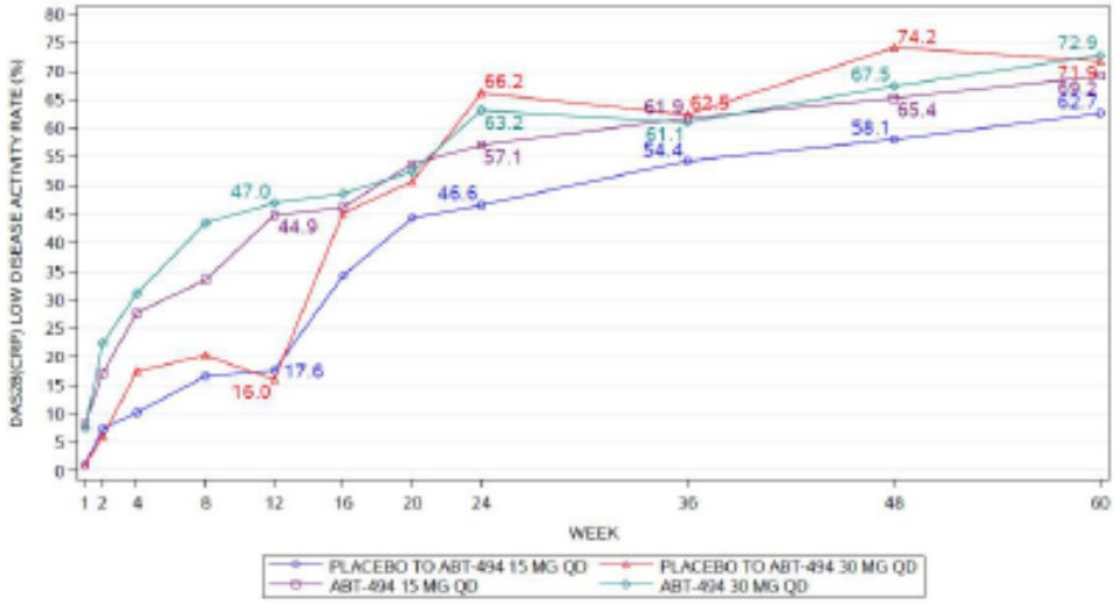
The fraction of responders in the placebo to UPA 15 mg group, placebo till UPA 30 mg group, UPA 15 mg group and UPA 30 mg group were: week 12 19/107, 19/103, 108/212 and 106/204; week 24 69/101, 62/99, 131/204 and 127/188, week 36: 77/100, 67/91, 127/190 and 130/184, week 48: 73/98, 69/89, 127/183 and 125/171, week 60: 74/95, 56/82, 129/173 and 125/167.



Treatment switch was at Week 14.

Figure 16: Study M15-555; LDA based on DAS28 (CRP) Over Time (AO; FAS)

The fraction of responders in the MTX to UPA 15mg, MTX to UPA 30 mg, UPA 15 mg and UPA 30 mg were: week 14 21/103, 22/99, 97/199 and 116/202, week 20: 50/95, 52/94, 102/194 and 131/188, week 26: 64/98, 59/94, 118/191 and 141/196, week 36: 66/96, 68/91, 126/185 and 144/189, week 48: 67/96, 66/92, 126/174 and 148/185.



Treatment switch was at Week 12.

Figure 17: Study M13-542: LDA Based on DAS28 (CRP) Over Time-Long Term Up to Week 60 (AO; FAS)

The fraction of responders in the placebo to UPA 15 mg, placebo to UPA 30 mg, UPA 15 mg and UPA 30 mg were: week 12 13/74, 12/75, 71/158 and 71/151, week 24 34/73, 49/74, 88/158 and 86/186,

week 36 37/68, 45/72, 91/147 and 77/126, week 48 36/62, 49/66, 89/136 and 81/120, week 60 37/59, 46/64, 92/133 and 86/118.

Persistence of CR: study M13-545 and M14-465

The following four figures display CR over time in the two pivotal studies in which CR was the primary endpoint. The first figures for each study present CR by treatment sequence (AO, FAS) and the added text below each respective figure indicate the fraction of subjects that was responders in each group at different timepoints. The second figure for each study presents CR by visit in Period 1 by randomized group (NRI, FAS).

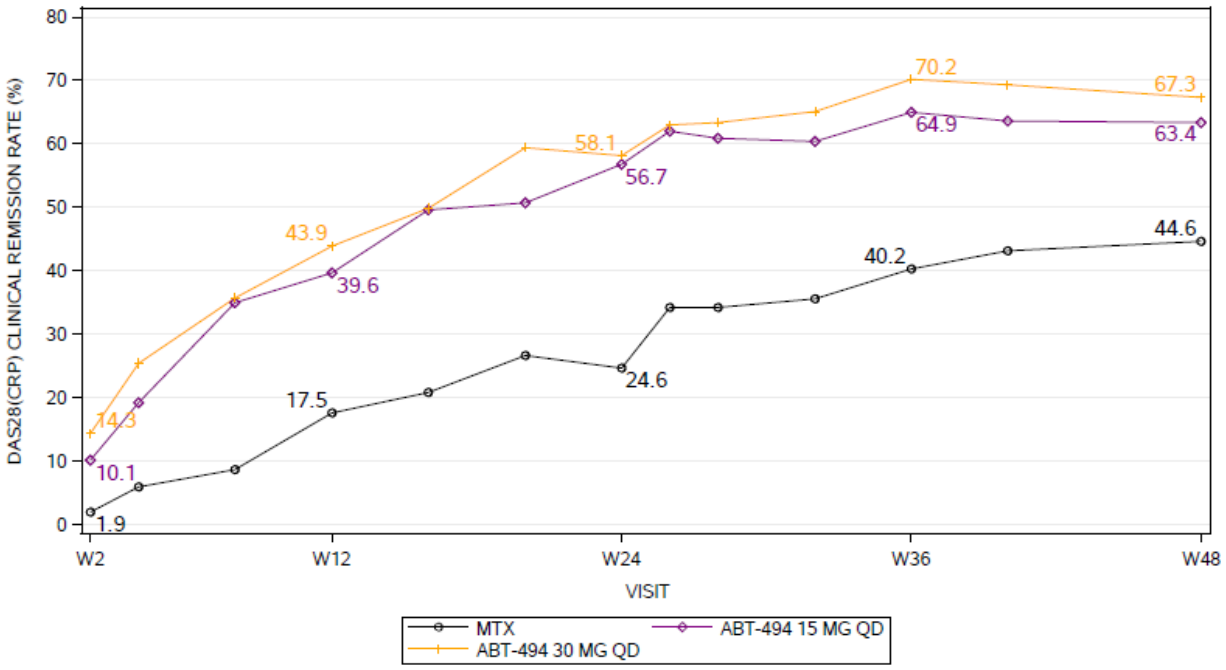
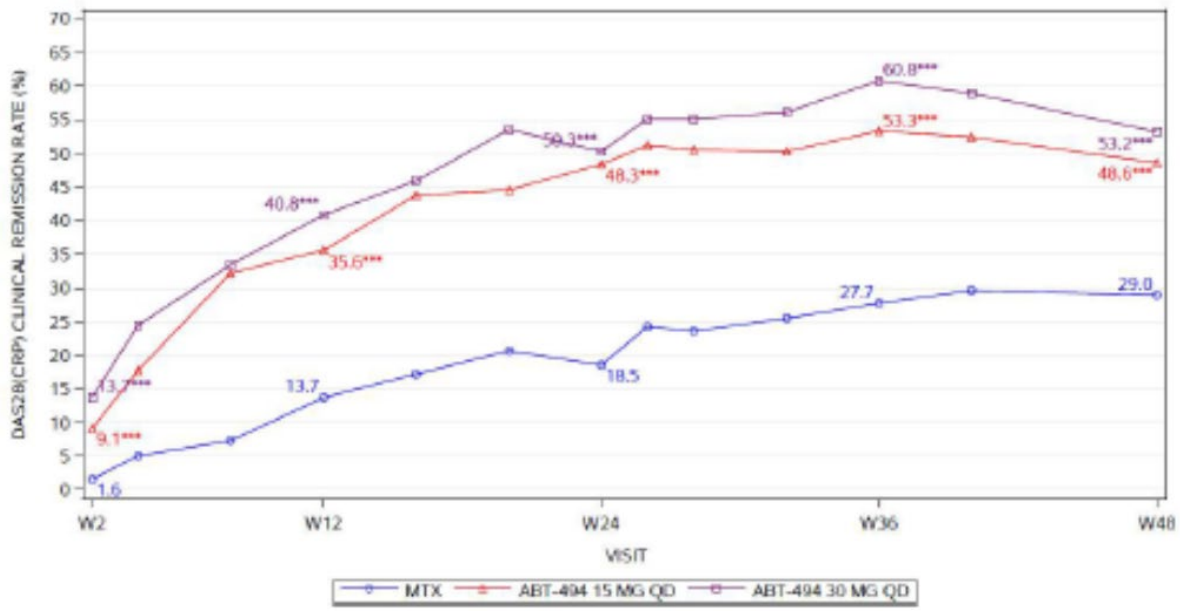


Figure 18: Study M13-545: CR based on DAS28 (CRP) over time by treatment sequence (AO; FAS)

At week 12, among the non-switchers 44/252 in the MTX-group, 112/283 in the UPA 15 mg group and 127/289 in the UPA 30 mg group were responders. At week 12 among the switchers, 0/18 in the MTX to MTX+UPA 15 mg group, 1/18 in the MTX to MTX+UPA 30 mg group, 1/19 in the UPA 15 mg to UPA 15 mg+MTX group and 2/9 in the UPA 30 mg to UPA 30 mg+MTX group were responders.

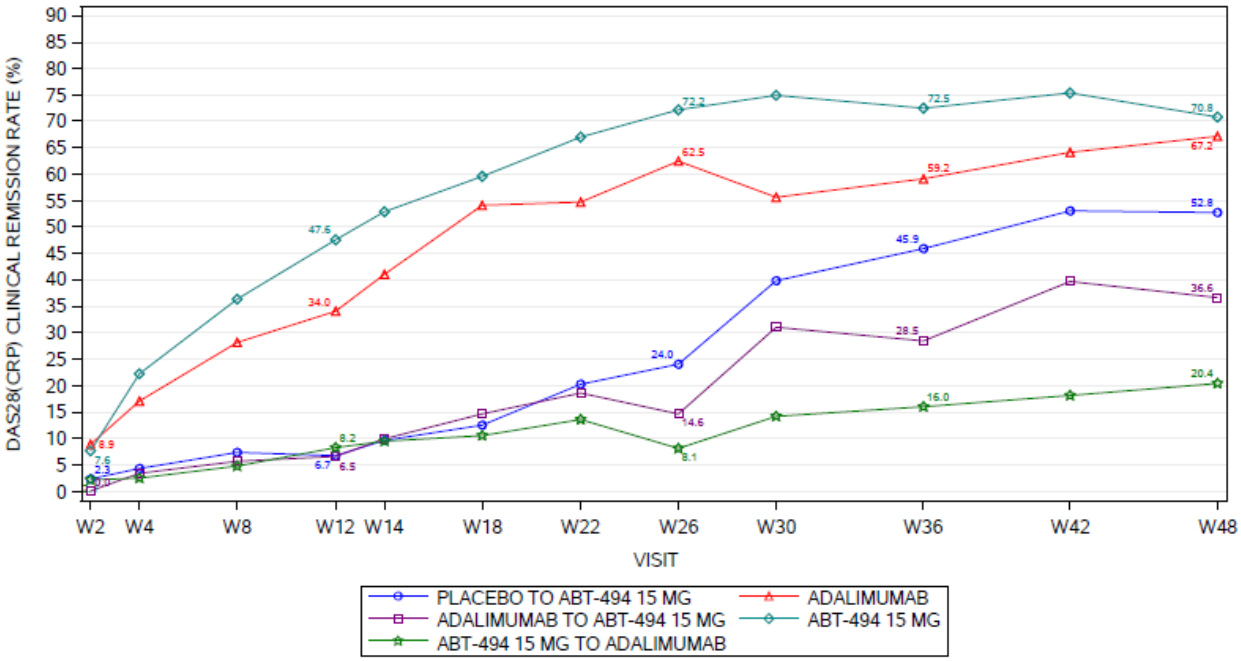
At week 48, among the non-switchers, 95/213 in the MTX group, 156/246 in the UPA 15 mg group, 169/251 in the UPA 30 mg group were responders. At week 48 among the switchers, 8/15 in the MTX to MTX+UPA 15 mg group, 10/18 in the MTX to MTX+UPA 30 mg group, 5/17 in the UPA 15 mg to UPA 15 mg+MTX group and 2/7 in the UPA 30 mg to UPA 30 mg+MTX group were responders.



Subjects who met the rescue criteria at Week 16, 20, or 24 or rescue switching criteria at Week 26 were treated as non-responders at visits after the first rescue visit.

***, **, * P-value ≤ 0.001, 0.01, and 0.05 level for upadacitinib versus MTX comparison, respectively.

Figure 19: Study M13-545: CR Based on DAS28 (CRP) Over Time by Randomized Group (NRI; FAS)

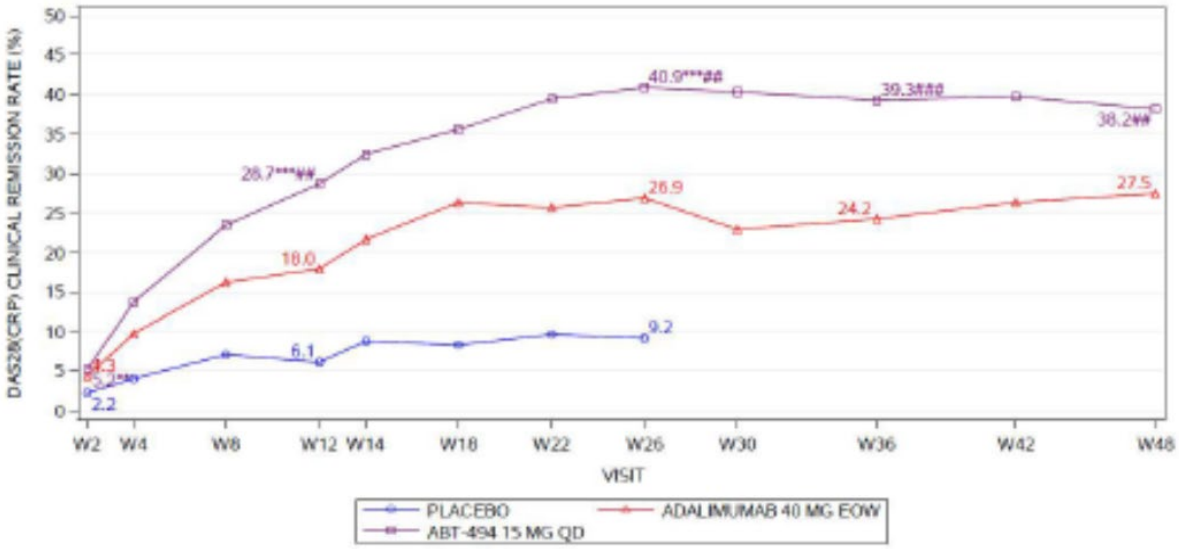


NOTE: ABT-494 15 MG = ABT-494 15 MG QD; ADALIMUMAB = ADALIMUMAB 40 MG EOW.

Figure 20: Study M14-465: CR based on DAS28 (CRP) over time by treatment sequence (AO; FAS)

At week 12, the fraction of responders was 40/594 in the placebo to upadacitinib 15 mg group, 49/144 in the adalimumab group, 10/153 in the adalimumab to upadacitinib 15 mg group, 169/355 in the upadacitinib 15 mg group and 19/233 in the upadacitinib 15 mg to adalimumab group.

At week 48, the fraction of responders was 304/576 in the placebo to upadacitinib 15 mg group, 90/134 in the adalimumab group, 53/145 in the adalimumab to upadacitinib 15 mg group, 245/346 in the upadacitinib 15 mg group and 48/235 in the upadacitinib 15 mg to adalimumab group.



Subjects who met the rescue criteria at Week 14, 18, or 22 were considered as non-responders at visits after rescue treatment switching. For subjects who met the rescue criteria at Week 26, data after rescue treatment switching were overwritten by the last response prior to rescue.

***, **, * P-value ≤ 0.001, 0.01, and 0.05 level for upadacitinib versus placebo comparison, respectively.

###, ##, # P-value ≤ 0.001, 0.01, and 0.05 level for upadacitinib versus adalimumab comparison, respectively.

Figure 21: Study M14-465; CR Based on DAS28 (CRP) Over Time by Randomized Group (NRI; FAS)

Structural Joint Damage

In study M13-545, radiographic assessment of structural joint damage was performed for up to Week 48. The radiographic data presented in the CSR for Study M13-545 were based on results from reading session 1, which included all available images from Baseline and Week 24 as of the data cut-off date of 15 March 2018. In contrast, the radiographic data for Study M13-545 presented in response to the Day 120 List of Questions are based on results from reading session 2, which included all available images from Baseline, Week 24, and Week 48 (1-year x-ray data) as of the data cut-off date of 21 February 2019. In reading session 2, images from Baseline and Week 24 were re-read, and images from Week 48 were read for the first time. Results from reading session 2, including the number of subjects with images for both linear extrapolation and as observed (AO) analyses, are presented in the table below.

Table 32: Summary of Change from Baseline in mTSS by Randomized Groups at Week 24 and Week 48 (Reading Session 2; FAS)

Measure Imputation Treatment	N	Within Group Least Square (LS) Mean (95% CI)[a]	Between Group Difference (Upadacitinib – MTX) Point Estimate (95% CI)[a]	 P-Value[b]
Week 24				
Linear extrapolation[a]				
MTX	264	0.66 (0.43, 0.89)		
Upadacitinib 15 mg QD	280	0.03 (–0.19, 0.25)	–0.63 (–0.94, –0.32)	< 0.001***
Upadacitinib 30 mg QD	273	0.10 (–0.12, 0.33)	–0.56 (–0.87, –0.24)	< 0.001***
AO				
MTX	268	0.65 (0.43, 0.88)		
Upadacitinib 15 mg QD	281	0.03 (–0.19, 0.25)	–0.62 (–0.93, –0.31)	< 0.001***
Upadacitinib 30 mg QD	275	0.10 (–0.12, 0.33)	–0.55 (–0.86, –0.24)	< 0.001***
Week 48				
Linear extrapolation[a]				
MTX	268	1.00 (0.68, 1.33)		
Upadacitinib 15 mg QD	287	0.03 (–0.28, 0.35)	–0.97 (–1.42, –0.53)	< 0.001***
Upadacitinib 30 mg QD	283	0.14 (–0.18, 0.46)	–0.87 (–1.31, –0.42)	< 0.001***
AO				
MTX	247	0.85 (0.53, 1.17)		
Upadacitinib 15 mg QD	265	0.07 (–0.24, 0.38)	–0.78 (–1.21, –0.35)	< 0.001***
Upadacitinib 30 mg QD	262	0.09 (–0.22, 0.40)	–0.76 (–1.19, –0.33)	< 0.001***

a. Results are based on linear extrapolation analysis

b. Within group LS mean and 95% CI, and between group LS mean, 95% CI and nominal p-value were based on analysis of covariance (ANCOVA) model analysis with geographic region (North America, South/Central America, Western Europe, Eastern Europe, Asia/other) as fixed factors and baseline value as covariate.

*** Statistically significant at 0.001 level.

The proportion of subjects with no radiographic progression (change from Baseline in mTSS ≤ 0) at week 48 by randomized groups (reading session 2; FAS) was 74.3% in the MTX group, 89.9% in the upadacitinib 15 mg group and 90.8% in the upadacitinib 30 mg group.

In study M14-465, radiographic assessment of structural joint damage was performed up to Week 48. The results presented in the tables below are based on reading session 2, which included all available images from baseline and Weeks 14, 26, and 48.

Table 33: Change from Baseline in mTSS by Randomized Groups at Week 26 and Week 48 in Study M14-465 (Reading Session 2; FAS)

Visit Imputation Randomized Treatment	N	Change from Baseline Within Group LS Mean (95% CI)[a]	Between Group Comparison (Upadacitinib – Control) LS Mean Diff (95% CI)[a]	P-Value[a]
Week 26				
Linear Extrapolation				
Placebo	601	0.94 (0.68, 1.21)		
Adalimumab 40 mg eow	297	0.19 (–0.15, 0.52)		
Upadacitinib 15 mg QD	596	0.16 (–0.11, 0.43)	–0.79 (–1.07, –0.51)	< 0.001 (vs placebo)
			–0.03 (–0.38, 0.32)	0.861 (vs adalimumab)
As Observed				
Placebo	588	0.67 (0.48, 0.87)		
Adalimumab 40 mg eow	291	0.14 (–0.10, 0.38)		
Upadacitinib 15 mg QD	584	0.16 (–0.04, 0.35)	–0.52 (–0.72, –0.31)	< 0.001 (vs placebo)
			0.01 (–0.24, 0.26)	0.920 (vs adalimumab)
Week 48				
Linear Extrapolation				
Placebo[b]	599	1.73 (1.25, 2.21)		
Adalimumab 40 mg eow	298	0.39 (–0.21, 1.00)		
Upadacitinib 15 mg QD	604	0.28 (–0.20, 0.77)	–1.44 (–1.95, –0.93)	< 0.001 (vs placebo)
			–0.11 (–0.74, 0.51)	0.730 (vs adalimumab)
As Observed				
Placebo (to Upadacitinib 15 mg QD)[b]	574	0.51 (0.25, 0.78)		
Adalimumab 40 mg eow	276	0.14 (–0.19, 0.48)		
Upadacitinib 15 mg QD	569	0.26 (–0.01, 0.52)	0.11 (–0.23, 0.46)	0.522 (vs adalimumab)

CI = confidence interval; eow = every other week; FAS = full analysis set; LS = least square; mTSS = modified Total Sharp Score; QD = once daily; vs = versus

a. Within group least squares mean and 95% CI, and between group least squares mean, 95% CI and p-value are based on ANCOVA model with treatment and prior bDMARD use as fixed factors and baseline value as covariate.

b. Per study design, all subjects in the placebo group were switched to receive upadacitinib 15 mg QD at Week 26 (if not already rescued to upadacitinib 15 mg QD at Week 14, 18, or 22).

Table 34: Proportion of Subjects with No Radiographic Progression (Change from Baseline in mTSS ⩽ 0) at Week 26 and Week 48 Results by Randomized Groups in Study M14-465 (FAS)

Visit Imputation Treatment	N	Responder % (95% CI)[a]	Response Rate Difference (Upadacitinib – Control) Point Estimate (95% CI)[b]	 P-value[c]
Week 26				
Linear Extrapolation				
Placebo	601	73.9 (70.4, 77.4)		
Adalimumab 40 mg eow	297	88.2 (84.5, 91.9)		
Upadacitinib 15 mg QD	596	87.4 (84.8, 90.1)	13.5 (9.1, 17.9) –0.8 (–5.3, 3.7)	< 0.001 (vs placebo) 0.716 (vs adalimumab)
As Observed				
Placebo	588	74.1 (70.6, 77.7)		
Adalimumab 40 mg eow	291	88.3 (84.6, 92.0)		
Upadacitinib 15 mg QD	584	86.6 (83.9, 89.4)	12.5 (8.0, 17.0) –1.7 (–6.3, 2.9)	< 0.001 (vs placebo) 0.469 (vs adalimumab)
Week 48				
Linear Extrapolation				
Placebo[d]	599	74.1 (70.6, 77.6)		
Adalimumab 40 mg eow	298	87.9 (84.2, 91.6)		
Upadacitinib 15 mg QD	604	86.4 (83.7, 89.2)	12.3 (7.9, 16.7) –1.5 (–6.1, 3.1)	< 0.001 (vs placebo) 0.517 (vs adalimumab)
As Observed				
Placebo (to Upadacitinib 15 mg QD)[d]	574	75.8 (72.3, 79.3)		
Adalimumab 40 mg eow	276	85.9 (81.8, 90.0)		
Upadacitinib 15 mg QD	569	84.7 (81.8, 87.7)	–1.2 (–6.2, 3.9)	0.642 (vs adalimumab)

CI = confidence interval; eow = every other week; FAS = full analysis set; mTSS = modified Total Sharp Score; QD = once daily; vs = versus

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

b. 95% confidence intervals for response rate difference are calculated based on normal approximation using proc freq.

c. Nominal P-value was constructed using CMH test adjusting for stratification factor prior bDMARD use.

d. Per study design, all subjects in the placebo group were switched to receive upadacitinib 15 mg QD at Week 26 (if not already rescued to upadacitinib 15 mg QD at Week 14, 18, or 22).

Other outcome measures over time

Other outcome measures, such as ACR 20, 50 and 70 as well as HAQ and CDAI-based LDA were also measured over time: the descriptive presentation of the results indicate that the improvements were largely maintained beyond the timepoint at which the primary efficacy analysis was conducted.

2.5.2.1. Clinical studies in special populations

No clinical studies targeting special age groups or patients with renal or hepatic impairment were performed. Patients with eGFR < 40 mL/min/1.73m2 were excluded from the Ph3 trials, so no data are available for subjects with severe renal impairment. In total 105 patients with eGFR 30-60 mL/min/1.73m2 had been treated with UPA 15mg in the Ph3 trials. This constitutes only about 5% or total patient number. There were 1013 patients with mild renal impairment (60-90 mL/min/1.73m2).

The number of older subjects in different age strata included in the 5 pivotal studies (n=4381) are presented in the table below. The applicant also provided data indicating that upadacitinib 15 mg was similarly efficacious in different age strata.

Table 35: Number of older subjects in different age strata included in the 5 pivotal studies (n=4381)

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials, phase III trials	***760***	***142***	***4***

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies (methods)

Design of the three dose-finding studies

Study M13-537 (n=299); the dose-ranging study in RA-patients failing MTX, investigated 5 different doses of upadacitinib ranging from 3 mg BID to 18 mg BID given as immediate-release capsules.

Study M13-550 (n=276); the dose-ranging study in RA-patients failing anti-TNF, investigated four different doses of upadacitinib ranging from 3 mg BID to 18 mg BID given as immediate-release capsules.

Study M14-663 (n=197) assessed dose-response for upadacitinib in three doses; 7.5 mg QD, 15 mg QD, and 30 mg QD given as extended-release tablets in a Japanese, csDMARD-IR population.

The primary endpoint in all the three dose-finding studies was ACR20 at week 12. This endpoint is, as stated in the relevant EMA guideline, appropriate for use in exploratory dose-finding trials. The time point for evaluation of the primary endpoint is also appropriate and consistent with the guideline. Further, the secondary endpoints assessed in these studies pertained to clinical efficacy and were adequate.

Design of the five main clinical studies

In all the 5 phase III-studies, for the analysis of the primary endpoint, non-responder imputation (NRI) was used.

Study M13-545 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Once Daily Monotherapy to Methotrexate (MTX) Monotherapy in MTX-Naïve Subjects with Moderately to Severely Active Rheumatoid Arthritis" (Select Early)" included subjects with active RA with negative prognostic factors. The proposed indication did not include the patients studied in M13-545. The inclusion/exclusion criteria are reasonable, and the study still confers data of importance for the overall assessment.

Study M13-545 compared upadacitinib 15 mg QD monotherapy, and 30 mg QD monotherapy versus MTX monotherapy. The design of the study is adequate and MTX is an appropriate comparator since it represents standard of care for this patient population. The primary endpoint was the proportion of subjects achieving CR defined by DAS28 [CRP] < 2.6 at Week 24 which is in line with relevant EMA guideline and previous CHMP Advice. The analysis was conducted on FAS (n=945) which included all randomized subjects (n=947) who received at least 1 dose of study drug. Subjects who meet joint count rescue criteria at Week 16 or 20 were treated as non-responders at Week 24 for the primary analysis, this is considered reasonable. The key secondary endpoints include HAQ-DI (function), ACR 50 response rate, LDA and mTSS (Structural joint damage as visualized by X–rays). This is in line with

current EMA guideline. Overall, the endpoints measure different aspects of the RA disease and are of clinical relevance.

The interim week 24 report (CSR) for Study M13-545 was submitted. A long-term extension of the study is on-going. An "Integrated Summary of Efficacy" (ISE) that contains long-term data for all individual studies (i.e., beyond the individual CSR cut-off dates) was submitted along with the CSRs in this application. This ISE includes week 48-data from study M13-545 (i.e. data spanning the complete double-blind period of the study). This approach was supported by the CHMP.

Study M13-549 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs (Select Next)" included subjects with active RA that had failed at least one of the following: MTX, sulfasalazine, or leflunomide. From the inclusion/exclusion criteria and the title of the study, "failure" seems to imply "inadequate response". Subjects that were "considered inadequate responders to biological DMARD (bDMARD) therapy" were excluded but subjects with prior exposure to at most one bDMARD were eligible to be enrolled in the study -up to 20% of total number of subjects- if they had either exposure<3 months or had to discontinue due to intolerability.

Study M13-549 compared upadacitinib 30 mg QD and 15 mg QD versus placebo as add-on to stable dose of csDMARDs. The study design is overall adequate. The primary endpoint was LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 which is in line with relevant EMA guideline and previous CHMP Advice. The analysis was conducted on FAS (n=661) which included all randomized subjects (n=661) who received at least 1 dose of study drug. The secondary endpoints include assessment of HAQ-DI, remission and ACR response; this is also in line with the EMA guideline and previous advice. Overall, the selected endpoints cover relevant aspects of the RA disease. In addition, the proportion of subjects achieving LDA based on CDAI ≤ 10 was included as a ranked key secondary endpoint. This is appropriate as this is a CRP-independent outcome measure.

Study M13-549 tested two sets of equality hypotheses in a Full Analysis Set (FAS) population using a pre-specified primary endpoint with two categories and other secondary endpoints at week 12. The statistical methods including statistical tests and models, imputation of missing values, and multiple testing procedures are considered appropriate and sufficiently conservative.

The first period of M13-549 was only 12 weeks and there seem to have been no rescue therapy during this period which is adequate. The current submission includes a CSR for Period 1. The ISE includes week 60-data. This approach was supported by the CHMP.

Study M14-465" A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR) (Select Compare)" included subjects with active RA who had negative prognostic factors. In the previous CHMP SA it was commented that positive aCCP or RF should be mandatory to ensure that patients are at high risk of progression. The applied inclusion criteria are not entirely consistent with this as subjects were to have either ≥ 3 bone erosions on x-ray at screening or ≥ 1 bone erosion with positive serology (aCCP or RF). However, the deviation from the given advice is considered acceptable given that patients that already have ≥ 3 bone erosions at screening are believed to have a sufficiently high risk of progression. The study included primarily MTX-inadequate responders defined in an acceptable way. Although subjects who were considered bDMARD inadequate responders were excluded, subjects with prior exposure to at most one bDMARD were eligible to be enrolled if they had either exposure <3 months or had to discontinue the bDMARD due to intolerability. Overall, the patient population is adequately selected and relevant in the view of the CHMP.

Study M14-465 compared upadacitinib 15 mg QD versus placebo, and versus adalimumab (per approved label) as add-on to MTX. The study design is overall adequate and adalimumab is appropriate as a comparator since it represents one of possible standard-of-care options for this population. The primary endpoint was the proportion of subjects achieving CR based on DAS28 CRP < 2.6 at Week 12. The analysis was conducted on FAS (n=1629) which included all randomized subjects (n=1629) who received at least 1 dose of study drug. The ranked secondary endpoints include: ACR20 response, structural damage, physical function, quality of life and fatigue. LDA based on CDAI was included among the ranked key secondary variables. These secondary endpoints were all also assessed at week 12, except for the radiological outcomes that were assessed at week 26. Overall, the selected endpoints were considered in line with EMA guideline and clinically relevant by the CHMP.

In study M14-465, at week 26 all subjects receiving placebo were to be switched to upadacitinib 15 mg QD regardless of response. Patients in all three groups could also be rescued and switch group at Weeks 14, 18, 22 or 26. For the radiological endpoints, linear extrapolation was used for missing data and treatment-switching handling. Analysis was also conducted based on AO data. This was considered acceptable by the CHMP considering that explicit demonstration of haltering radiological progression is not a prerequisite for approval of new RA-drugs.

For study M14-465, the randomized, double blind first period of the study M14-465 lasted 48 weeks. The interim week 26 CSR was included in the current submission. The ISE includes week 48-data. This approach was supported by the CHMP.

Study M15-555 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Monotherapy to Methotrexate (MTX) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response to MTX (Select Monotherapy)" included subjects with active RA. The study population that will be captured by the inclusion and exclusion criteria was considered adequate. The definition of MTX-IR is considered acceptable.

Study M15-555 compared upadacitinib 30 mg QD alone and 15 mg QD alone versus continuing MTX alone in a randomized, double-blind, parallel-group design. In a previous Advice, the CHMP commented that little useful information is expected to be generated by the superiority comparison of the drug versus MTX as the MTX arm is being undertreated by definition. The CHMP stated that to support a monotherapy indication in second-line, at minimum an indirect comparison of efficacy and safety of monotherapy versus combination with MTX in the same second-line population (i.e. MTX-IR) should be conducted. To adhere to this, the applicant conducted cross-study comparisons. This approach was supported by the CHMP. The primary endpoint was the proportion of subjects achieving LDA (based on DAS28 [CRP] ≤ 3.2) at Week 14. The analysis was conducted on FAS (n=648) which included all randomized subjects (n=648) who received at least 1 dose of study drug. No rescue was allowed before the timepoint at which the primary endpoint was analysed. The ranked key secondary endpoints were also assessed at week 14 and included CR, ACR response and physical function. The selected endpoints are in line with EMA guideline and overall in line with the previous CHMP scientific advice given. CR was assessed at week 14 instead of at 6 months as recommended in the previous CHMP scientific advice given. However, that was considered acceptable to the CHMP considering that the study continued beyond the week 14 timepoint (=end of study period 1, which was included in the CSR and was the timepoint after which all patients received upadacitinib) and that efficacy data up to week 48 were presented in the current submission to support maintenance of effect.

The M15-555 study tested two sets of equality hypotheses in a Full Analysis Set (FAS) population using a pre-specified primary endpoint with two categories and other secondary endpoints at week 14. The statistical methods including statistical tests and models, imputation of missing values, and multiple testing procedures are considered appropriate and sufficiently conservative to support the claims.

Study M13-542 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo on Stable Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response or Intolerance to Biologic DMARDs (bDMARDs) (Select Beyond)" included subjects with active RA that failed at least one bDMARD either due to inadequate response or non-tolerability. The patient population was considered adequately selected.

Study M13-542 compared upadacitinib 30 mg QD and 15 mg QD versus placebo as add-on to a stable dose of csDMARDs in a randomized, double-blind, parallel-group design during the first 12 weeks of the study. This period included no rescue possibilities. As commented in the previous CHMP Scientific Advice, the design of this study is not optimal for studying the effect of upadacitinib in a third line population; "investigator's best choice" would have been a more appropriate comparator than placebo. At the CHMP's request, the Applicant discussed the effect. It was agreed that discontinuation of prior bDMARD therapy in the placebo arm did probably not have marked effect on the obtained efficacy results. In addition, some support for the third line indication also comes from other studies in the development programme. In relation to this, it is noted that study M14-465 and study M13-549 allowed inclusion of subjects that had discontinued bDMARD due to intolerability - although these two studies included subjects that had either documented evidence of intolerance or exposure <3 month which was not in complete agreement with previous CHMP scientific advice given - and one of the three treatment arms in M14-465 was adalimumab which could be considered as a possible standard-of-care in this third line population (subjects previously treated with adalimumab were excluded from this study). In conclusion, despite the design limitations in study M13-542, the data from the study together with data from other studies in the development programme could be supportive of a third line indication.

Study M13-542 had LDA based on DAS28 (CRP) ≤ 3.2 at week 12 as the primary endpoint. The analysis was conducted on FAS (n=498) which included all randomized subjects (n=499) who received at least 1 dose of study drug. The ranked key secondary endpoints included ACR response, physical function and quality of life assessment and were also assessed at week 12. The primary and key secondary endpoints are in line with the relevant EMA guideline and cover relevant aspects of the disease. CR was not included among the key secondary endpoints (which would have been adequate and in line with the previous CHMP Scientific Advice), but assessment of CR was at least included among the additional efficacy analysis. This is acceptable considering the totality of data (including data from the 4 other pivotal studies that include CR as a primary or key secondary endpoint) and as it is not explicitly stated in the EMA guideline that CR is mandatory as a key secondary endpoint in this third-line population. The current submission includes the Period 1 CSR (24 weeks). Week 60-data was included in the ISE.

In summary, the design of the design of the five main clinical trials are considered in line with current EMA guideline and sufficiently coherent with previously given CHMP Advice to be able to yield adequate and sufficient efficacy data for potential approval of upadacitinib in the proposed indication.

Some deviations from previously given CHMP advice have been noted such as CRP cut-off for active disease in the pivotal studies and definitions of bDMARD intolerance, but these were not considered crucial by the CHMP for the assessment of the effect size of upadacitinib vs the comparator. The number of subjects who had inadequate response to other csDMARDs than MTX is small. However, it is plausible that this new mode of action (JAK-inhibition) would have similar efficacy and safety after MTX or other csDMARDs.

Efficacy data and additional analyses (results)

Data from the three dose-finding studies

Based on the data from these three studies, the applicant chose 15 mg QD extended-release (equivalent to 6 mg BID immediate-release) and 30 mg QD extended-release (equivalent 12 mg BID immediate-release) as the doses to be tested in the phase 3 programme. The choice seems reasonable to the CHMP. The applicant explains that the extended-release formulation was developed to enable QD dosing and thus enhance patient compliance and provide more convenient dosing regimen. The recommended dose of upadacitinib is 15 mg once daily.

Data from five main clinical studies

M13-545

In M13-545, the proportion of randomized MTX-naïve subjects that completed week 24 study drug was 85.1% in the MTX group, 91.5% in the UPA 15 mg group and 89.5% in the UPA 30 mg group. Overall, the numbers of subjects rescued were low. There was no notable asymmetry between the treatment groups with regards to important baseline parameters.

In M13-545, the proportion of subjects (95% CI) that achieved the primary endpoint CR at week 24 was in the MTX monotherapy (n=314), UPA 15 mg monotherapy (n=317) and UPA 30 mg monotherapy (n=314): 18.5 (14.2, 22.8), 48.3 (42.8, 53.8) and 50.0 (44.5, 55.5) %, p 0.001 for both comparisons between MTX and upa. The difference between both the UPA groups relative to MTX are both statistically significant and highly clinically relevant. The outcomes of the key secondary endpoints, including the two radiological ranked key endpoints, are in line with the outcome of the primary endpoint. The proportion of subjects with no radiographic progression at week 24 was in the MTX, UPA 15 mg and UPA 30 mg group: 77.7%, 87.5% and 89.3% (nominal p-value 0.002 and <0.001 for the two respective comparisons with MTX).In M13-545, statistically significant improvements in the upadacitinib 15 mg QD and 30 mg QD groups compared with the MTX group were observed for all ranked key secondary endpoints using multiplicity adjustment. Overall, the 30mg dose seemed to perform only marginally better than the 15mg dose. It is noted that such a reduction compared to baseline was achieved by all three groups at week 12 but also that the difference in point estimate between the upadacitinib groups and the MTX group for this variable were >0.22.

In M13-545, no unexpected findings of significant importance were noted in the presented subgroup analysis. There are indications of a relatively rapid treatment response; an effect was reported as early as week 2 for some outcomes including mean decreases in DAS28 (CRP) from baseline.

In summary, Study M13-545 demonstrates that when upadacitinib 15 mg monotherapy is given as 1st line RA treatment, after 6 months, 48.3% of the patients achieve the very high hurdle endpoint clinical remission. The corresponding figure for MTX monotherapy (which represents standard of care first line RA treatment) is 18.5%. At this timepoint, the proportion of subjects with no radiographic progression is also higher in the upadacitinib 15 mg group than in the MTX group. The Applicant did not claim a 1st line RA indication. However, those data are indicative of favourable effects also in the proposed target population (2nd and 3rd line indication).

M13-549

In M13-549, in all treatment groups >90% of csDMARD-IR subjects completed study period 1 as well as study drug during period 1 and there were no rescue possibilities during this time period. The three treatment groups were overall fairly well balanced with regards to important baseline variables. The

proportion of subjects with csDMARD other than MTX was in the placebo, UPA 15 mg and UPA 30 mg groups: 13.6%, 23.2% and 20.1%.

In M13-549, the proportion of subjects (95% CI) that achieved the primary endpoint LDA at week 12, was in the Placebo, UPA 15 mg and UPA 30 mg groups: 17.2 (12.2, 22.2), 48.4 (41.8, 55.0) and 47.9 (41.3, 54.6) %, p <0.001 for both comparisons between the active treatment arms and placebo. The difference between placebo and upadacitinib are both clinical and statistically significant for both the tested doses. The same conclusion can be drawn for the outcome of the secondary endpoint analyses that included LDA based on CDAI, a CRP-independent outcome measure.

In M13-549, statistically significant improvement in both the upadacitinib 15 mg QD and 30 mg QD groups compared with the placebo group were observed for all ranked key secondary endpoints using multiplicity adjustment. The 30mg dose does not seem to perform substantially better than the 15-mg dose. Already at week 1, an effect on ACR 20 vs placebo was seen; ACR 20 response rate for UPA 15 mg was 22.2% compared to 8.6% in the placebo group, p<0.001 for the comparison.

M14-465

In M14-465, a higher proportion of subjects in the placebo group were rescued after the Week 14, 18 and 22 visits compared to the proportion of subjects rescued in the adalimumab and upadacitinib groups at those timepoints. The proportion of subjects that had discontinued study drug by week 14 was fairly similar and low in all treatment groups. Overall, a rather low number with similar magnitude in the different treatment groups, appear to have discontinued study drug between week 14 and 26. More than 90% completed week 26 on study drug which is of importance for the interpretation of the findings from the radiological analysis.

In M14-465, baseline characteristics of importance were overall balanced between the three treatment groups.

In study M14-465, the primary endpoint, CR at week 12, was achieved by 28.7% when upadacitinib 15 mg was added to MTX. For subjects that received placebo, the figure was 6.1%, p<0.001 for the comparison between the groups. The outcomes of the other key secondary endpoints, including the radiological endpoint and the CRP-independent outcome LDA based on CDAI, were consistent with the outcome of the primary endpoint; the differences vs placebo was both clinically and statistically convincing. Statistically significant improvement with upadacitinib 15 mg QD group compared with the placebo group were observed for all ranked key secondary endpoints using multiplicity adjustment. The proportion of subjects with no radiographic progression at week 26 was 76.0% in the placebo group and 83.5% in the upadacitinib 15 mg group, p=0.001 for the comparison.

In study M14-465, one of the key secondary endpoints involved a comparison vs the active comparator adalimumab; the proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 (non-inferiority comparison of upadacitinib versus adalimumab). This endpoint (95% CI) was achieved in 28.7 (23.8, 33.7) in the adalimumab group and 45.0 (41.2, 48.8) % in the upadacitinib group. The non-inferiority margin was 10% but the point estimate (95% CI) for between group difference was 16.3 (10.0, 22.5) % i.e. non-inferiority was met.

In study M14-465, in all the examined subgroups, a (numerical) difference vs placebo was observed. It is of interest that UPA 15 mg does not perform worse in the subgroup with previous bDMARD use compared to group with no previous bDMARD use. Thus, when upadacitinib 15 mg is added to MTX in a group of MTX-IR patients that also have previous bDMARD experience, 31.5% of the subjects achieve the high-hurdle endpoint clinical remission (based on DAS28) at week 12. It should however be noted that according to the eligibility criteria, only patients with <3 month exposure of bDMARD/who had

discontinued bDMARD due to intolerability could be included. The data supports of a rapid onset of effect (detected as early as week 2) of upadacitinib.

M15-555

In M15-555, a sufficiently high and equal proportion of the MTX-IR subjects in the three treatment groups completed Period 1 and completed study drug during this period i.e. stayed in the study long enough to be evaluated both for the primary and key secondary endpoints. Baseline characteristics of importance were overall sufficiently well balanced between the three treatment groups.

In study M15-555, the primary endpoint, LDA at week 14 was achieved by 19.4% in the MTX-group vs 44.7% in the UPA 15 mg monotherapy group and 53.0% in the UPA 30 mg monotherapy group, p<0.001 for both comparisons between MTX and upa. The results for the key secondary endpoints were in line with primary endpoint. Statistically significant improvement in both the upadacitinib 15 mg QD and 30 mg QD groups compared with the cMTX group were observed for all ranked key secondary endpoints using multiplicity adjustment. Although the superiority comparison between MTX and upadacitinib that was carried out in this study has its clear limitations (the MTX arm being undertreated by definition in a genuine MTX-IR population) almost half of patients that have active RA and are MTX-IR do achieve low disease activity with upadacitinib monotherapy in the proposed posology (15 mg once daily). LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 was achieved by 45.0% of the MTX-IR subjects in the Upadacitinib group 15 mg + MTX group in the M14-465 study which is similar to the outcome of Upadacitinib monotherapy in study M15-555. Further, clinical remission at week 12 based on DAS28 (CRP) was achieved by 28.7% of the MTX-IR RA-patients when upadacitinib was added to MTX in study M14-465 which is also similar to the outcome for this endpoint in the monotherapy study M15-555.

In M15-555, in general, a numerical difference vs placebo was noted for in the analysed subgroups. The treatment effect was seen early which indicates rapid onset of action. Analysis of DAS28 at all visits revealed that at all visits beginning at Week 2, improvement in disease activity with upadacitinib treatment, as shown by mean decreases in DAS28 (CRP) and DAS28 (ESR) from Baseline, was greater (nominal P < 0.001) compared with the cMTX group for both the upadacitinib 15 mg and 30 mg groups.

M13-542

In M13-542, a sufficiently high and equal number of subjects across treatment groups completed week 12 study participation and week 12 study drug i.e. were still in the study and on the study drug at the time point at which the primary efficacy endpoint and the key secondary endpoints were assessed. Baseline characteristics of importance were overall sufficiently well balanced between the three treatment groups.

In study M13-542, the primary endpoint, LDA at week 12, was achieved by 43.3% in the UPA 15 mg group, 42.4% in the UPA 30 mg group and 14.2% in the placebo group, p<0.001 for both comparisons between UPA and placebo. Although the limitations with regards to the comparison with placebo are acknowledged, it is still considered clearly clinically relevant that >40% of subjects in this difficult to treat population achieved LDA with 12-week treatment. The achieved difference between upadacitinib and placebo could probably not be explained only by the fact that prior bDMARDs were stopped without replacement in the placebo arms. The outcomes of the key secondary endpoints were overall in line with the outcome of the primary endpoint. Statistically significant improvement in both the upadacitinib 15 mg QD and 30 mg QD groups compared with the placebo group were observed for all ranked key secondary endpoints using multiplicity adjustment. Already at week 1, an effect on ACR response vs placebo was seen: 27.4% in the UPA 15 mg group vs 10.7% in the placebo group. In study M13-542, 30 mg upadacitinib did not perform consistently better than 15 mg upadacitinib.

In study M13-542, across the subgroups, upadacitinib performed better than placebo. No analysis according to concomitant csDMARD could be found. To support the proposed indication for use "*in combination with methotrexate or other conventional synthetic DMARDs (csDMARDs)*", it would have been of value to present a descriptive analysis of the outcome of the primary endpoint in subjects that were treated with concomitant leflunomide, chloroquine, hydroxychloroquine and sulfasalazine without also receiving MTX.

Data in special populations

No clinical studies targeting special age groups or patients with renal or hepatic impairment were performed. Patients with eGFR < 40 mL/min/1.73m2 were excluded from the Phase 3 trials, so no data are available for subjects with severe renal impairment. As stated in the SmPC, upadacitinib should be used with caution in patients with severe renal impairment and the use of upadacitinib has not been studied in subjects with end stage renal disease. In addition, upadacitinib is contraindicated in severe hepatic impairment patients. See clinical pharmacology discussions.

The data indicates that upadacitinib 15 mg was similarly efficacious in different age strata. There are limited data in patients aged 75 years and older.

Data from analysis performed across trials

Several integrated analyses across trial were conducted by the applicant. Two integrated analysis sets of the Phase 3 studies were defined for the purpose of short-term integrated efficacy analyses:

- Placebo-controlled upadacitinib 15 mg analysis set: The objective of this analysis set was to compare upadacitinib 15 mg QD versus placebo on top of background MTX and/or other csDMARDs. This analysis set integrated the placebo-controlled studies that included upadacitinib 15 mg QD as a treatment arm. Specifically, it included subjects from the following studies: Studies M13-549, M14-465, and M13-542. Subjects in the upadacitinib 15 mg QD and placebo groups were included in this analysis set.
- Placebo-controlled upadacitinib 15 mg and 30 mg analysis set: The objective of this analysis set was to compare upadacitinib 15 mg QD and 30 mg QD versus placebo on top of background csDMARDs. This analysis set integrated the placebo-controlled studies that included both upadacitinib 15 mg QD and upadacitinib 30 mg QD as treatment arms. Specifically, it included subjects from the following studies: Studies M13-549 and M13-542. Subjects in the upadacitinib 15 mg QD, upadacitinib 30 mg QD, and placebo groups were included in this analysis set.

Subgroup analysis

The integrated analyses yielded similar results that were obtained in the respective studies separately. The subgroup analyses were overall consistent with the primary analysis. Although UPA was overall efficacious, it seemed less efficacious in those patients with higher weight (in line with higher BMI): e.g. LDA response was 40.7 for those <60kg and 23.4 for those >100kg, with overlapping Cis. However, upadacitinib had a clinically relevant treatment effect across all weight groups. Furthermore, baseline weight did not affect safety (see Safety section). Hence, the CHMP was of the opinion that no guidance was needed regarding use of upadacitinib according to baseline weight. Also, pooled analysis and individual studies suggest that efficacy is better in those with poor prognostic factors (RF, anti-CCP). However, the therapeutic effect is positive across subgroups and several other factors than seropositivity are relevant for the choice of therapy. Hence, the CHMP was of the opinion that those subgroup results were not relevant for the treatment recommendations in the SmPC.

bDMARD-intolerant subjects

The short-term efficacy of upadacitinib was assessed in bDMARD-intolerant subjects versus other bDMARD-exposed subjects (that discontinued bDMARD therapy due to lack of efficacy or other reasons). Subgroup analysis was performed for ACR20 and LDA based on DAS28 (CRP) at Week 12 in the two integrated analysis sets i.e. the placebo-controlled upadacitinib 15 mg and placebo-controlled upadacitinib 15 mg and 30 mg analysis sets (as described above). The outcome of this analysis, in both analysis sets, indicate that bDMARD-intolerant subjects do equally well on Upadacitinib as subjects that discontinued bDMARD therapy due to other reasons.

Non-MTX csDMARDs

The short-term efficacy of upadacitinib in combination with MTX versus other non-MTX csDMARDs was analysed in order to support the use of upadacitinib in combination with csDMARDs (MTX and other csDMARDs). To examine the short-term placebo-controlled efficacy of upadacitinib in combination with MTX versus other csDMARDs, a model-based analysis assessing the interaction between treatment effect and background csDMARD type was conducted for ACR20 and LDA based on DAS28 (CRP) at Week 12 within Studies M13-542 and M13-549, respectively, where csDMARDs other than MTX were permitted as background therapy. It should be noted that subjects on a combination of MTX plus other csDMARDs were counted under MTX. The outcome of this analysis indicated that, with regards to the efficacy, subjects that received upadacitinib did well both when the drug was combined with MTX and when the drug was combined with other csDMARDs. There were some minor differences observed between the two groups. Thus, from an efficacy-point-of view, the Applicant's claim for an indication "in combination with other csDMARDs than MTX" could potentially be supported. However, there are difficulties associated with drawing solid conclusions on the subgroups that included a low number of subjects. In addition, this claim was not approvable from a safety perspective (see Safety Section).

Monotherapy

In line with the Scientific Advice, a cross-study analysis was conducted to provide an indirect comparison of the short-term efficacy of upadacitinib as monotherapy versus in combination with MTX in the MTX-IR population. A model-based analysis was conducted on subjects from Studies M13-549 and M15-555 as the populations in these studies was considered to have sufficiently similar baseline characteristics to enable the analysis. Analyses were conducted for ACR20 and LDA based on DAS28 (CRP) at Week 12 (Study M13-549)/Week 14 (Study M15-555). The outcome of these analysis indicate similar short-term efficacy is achieved by upadacitinib monotherapy compared to upadacitinib + MTX although slight numerical differences in the response rate difference based on LDA (25.3% for UPA 15mg monotherapy arm compared to 30.5% for the UPA + MTX arm) and on ACR20 (26.5% vs 28.0%) was noted. For the 30 mg dose, the outcomes are similar for the monotherapy vs the combination and with this dose, the slight numerical difference in response rate between the two treatment arms actually being in favour of monotherapy (34.0% for UPA 30 mg monotherapy and 31.5%% for UPA 30 mg + MTX for response rate difference based on LDA and 30.0% and 27.2% for response rate difference based on ACR20). The benefit of upadacitinib monotherapy vs the combination with MTX is not clear in terms of effect on radiological progression. Radiological progression was measured as a key secondary outcome in two studies; M13-545 and M14-465 in which one was indeed a monotherapy study (M13-545) and the other was not (M14-465 was designed as an add-on-to-MTX-study). However, a direct comparison between the outcome of these studies cannot be made since M14-465 included MTX-IR and M13-545 included MTX-naïve. In summary, the CHMP was of the opinion that both the combination therapy and monotherapy ≥ second line are considered supported by the data submitted.

PROs

The results of PROs were overall similar across all Phase 3 trials.

Maintenance of efficacy

According to the relevant EMA guideline, maintenance of efficacy should be demonstrated in a long-term randomized study where blinding and an active control is maintained for in total 12 months study duration. Descriptive statistics may suffice and no formal non-inferiority analyses are required. The applicant stated that long-term efficacy analyses were conducted for each of the five Phase 3 studies separately. Efficacy data are presented through Week 60 for Studies M13-549 and M13-542 and through Week 48 for Studies M13-545 (active control until week 48), M14-465 (active control until week 48), and M15-555, with approximately 78%, 74%, 80%, 87%, and 84%, respectively, of subjects remaining in the study through the last summarized visit (by the data cut-off date). It was for all studies stated that after the unblinded analysis for the pivotal efficacy endpoints had been conducted, subjects and sites remained blinded to the end of the so called "blinded periods" (Period 1 in Study M13-545, Period 2 in Study M13-549, Period 1 in Study M14-465, Period 2 in Study M15-555, Period 2 in study M13-542). Acknowledging the limitations of the presented descriptive as observed data, the treatment effect of upadacitinib, including the joint damage preventing effect measured in study M13-545 and M14-465 appears to be maintained up to and beyond one year. Thus, overall, the requirements of the guideline were considered fulfilled by the CHMP.

2.5.4. Conclusions on the clinical efficacy

The designs of the three dose-finding studies are adequate and the outcome supported the dose selection in the main clinical phase 3 studies. The design of the five main clinical studies was considered acceptable and overall in line with the EMA guideline. Although some deviations from previous CHMP Scientific Advice have been noted, the CHMP did not consider that these deviations significantly influence the ability to draw conclusions from the data yielded.

The data submitted support that upadacitinib, in the proposed posology 15 mg once daily, has a clinically relevant effect in inducing remission or low disease activity in patients with active RA both as second and third line treatment. Overall, a dose-increase to 30 mg seems to confer only marginal incremental effect. The CHMP was of the opinion that both the combination with MTX and monotherapy ≥ second line are considered supported by the data submitted. From an efficacy-point-of view, the proposed indication and the proposed posology (15 mg once daily) was considered supported by the CHMP. However, from a safety perspective, the combination of Upadacitinib and other csDMARDs was considered not appropriate to conclude on an indication in combination with other csDMARDs. Hence, the Applicant withdrew this claim from the indication during the assessment (see Safety section). The revised indication is as follows:

"*RINVOQ is indicated 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*".

Among the key secondary endpoints were measures of physical function (HAQ-DI), CRP-independent outcomes based on CDAI and radiological outcomes. An effect was demonstrated also for these endpoints although the relatively short follow-up time may have some impact on the achieved radiographic results, taking in account that a great majority of subjects had no radiographic progression. For many outcomes, an effect was seen as early as week 1-2, indicating rapid onset of

effect. The current application includes a direct comparison with adalimumab which indicates that upadacitinib is non-inferior to adalimumab on efficacy endpoints.

2.6. Clinical safety

An integrated approach to safety assessment was undertaken by the Applicant, and subject data from the Phase 2 and Phase 3 studies were combined into 6 primary analysis sets across clinical studies. Each integrated analysis set was designed to assess the safety profile in a particular population or subset of subjects. Dose changes (for lack of efficacy or safety concerns) were only allowed in the Phase 2 LTE, and integrated data from the Phase 3 studies thus represents safety information without dose changes from the originally assigned upadacitinib dose.

The integrated short-term controlled analysis sets, in which the exposure is generally limited to 12-14 weeks, were (the respective abbreviations used for each dataset are indicated in bold and are followed by the number of subjects in the respective groups within the analysis set):

- Placebo-Controlled Upadacitinib 15 mg (Studies M13-549, M14-465, M13-542); PBO-controlled UPA 15; N = 1,042 PBO, N = 1,035 UPA 15
- Placebo-Controlled Upadacitinib 15 mg and 30 mg (Studies M13-549, M13-542); PBO-controlled UPA 15/30; N = 390 PBO, N = 385 UPA 15, N = 384 UPA 30
- MTX-Controlled Upadacitinib 15 mg and 30 mg (Studies M13-545, M15-555); MTX-controlled UPA 15/30; N = 530 MTX/cMTX, N = 534 UPA 15, N = 529 UPA 30

The integrated long-term analysis sets were:

Any Phase 3 Upadacitinib 15 mg (all 5 Phase 3 studies); Any Ph3 UPA 15; N = 2,630 UPA 15

- Any Phase 3 Upadacitinib 15 mg and 30 mg (Studies M13-545, M13-549, M15-555, M13-542); Any Ph3 UPA 15/30; N = 1,213 UPA 15, N = 1,204 UPA 30
- Any RA Upadacitinib (global Phase 2 and Phase 3 studies combined); Any RA UPA; N = 4,443

Patient exposure

In the original submission, a total of 4,443 subjects received at least 1 dose of upadacitinib in the Phase 2 or Phase 3 studies, for a mean of 432.7 days. Of these subjects, 2,972 (66.9%) had exposure to upadacitinib for at least 48 weeks (Table 37).

In the updated safety data submitted with the responses to the D120 LoQ (cut-off date 14 November 2018), a total of 3,360 subjects had an exposure to upadacitinib for at least 48 weeks, giving a total exposure of 3,446 PY.

Table 36. Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (Any RA UPA Analysis Set)

	UPA 6 mg BID/ 15 mg QD (N = 2819) n (%)		UPA 12 mg BID/ 30 mg QD (N = 1309) n (%)		Any UPA (N = 4443) n (%)	
Duration						
≥ 4 weeks (28 days)	2776	(98.5)	1286	(98.2)	4373	(98.4)
≥ 12 weeks (84 days)	2673	(94.8)	1206	(92.1)	4205	(94.6)
≥ 24 weeks (168 days)	2415	(85.7)	1057	(80.7)	3852	(86.7)
≥ 36 weeks (252 days)	2032	(72.1)	1013	(77.4)	3413	(76.8)
≥ 48 weeks (336 days)	1710	(60.7)	908	(69.4)	2972	(66.9)
≥ 72 weeks (504 days)	680	(24.1)	382	(29.2)	1361	(30.6)
≥ 96 weeks (672 days)	188	(6.7)	60	(4.6)	520	(11.7)
Mean duration (days)	382.6		387.5		432.7	

Notes: UPA 6 mg BID/15 mg QD: Subjects who started on upadacitinib 6 mg BID and who changed dose from placebo to 6 mg BID in Phase 2 (censored by the time of first dose titration in Study M13-538), and subjects who received upadacitinib 15 mg QD in Phase 3.

UPA 12 mg BID/30 mg QD: Subjects who started on upadacitinib 12 mg BID in Phase 2 (up to the dose change to upadacitinib 6 mg BID in Phase 2 OLE), and subjects who received upadacitinib 30 mg QD in Phase 3.

Any UPA: All subjects who received at least one dose of upadacitinib, including doses other than 6 mg BID/15 mg QD and 12 mg BID/30 mg QD. Data was not censored when subjects switched between different upadacitinib doses.

Adverse events

Common adverse events

In both short-term and long-term datasets, adverse events were most frequently reported in the Infectious and Infestations SOC; in the short-term PBO-controlled UPA 15 analysis set, frequencies in the upadacitinib 15 mg group were as follows: Infections and infestations (27.2%), Gastrointestinal disorders (10.9%), and Investigations (10.0%), while the most frequently affected SOCs in the placebo group were Infections and infestations (20.6%), Musculoskeletal and connective tissue disorders (10.4%), and Gastrointestinal disorders (10.2%). Table 38 displays the most frequently reported short-term adverse events. In the long-term Any Ph 3 UPA 15 analysis set, the most common AEs (≥ 10 E/100 PY) were upper respiratory tract infection (13.4 E/100 PY), nasopharyngitis (10.7 E/100 PY), and urinary tract infection (10.1 E/100 PY). Similar to the short-term analyses, the most frequently affected SOCs were infections and infestations (91.6 E/100 PY), investigations (33.0 E/100 PY), and gastrointestinal disorders (26.1 E/100 PY).

Table 37. TEAEs Reported in ⩾ 2% of Subjects in Any Group by Decreasing Frequency in the UPA 15 mg Group (PBO-Controlled UPA 15 Analysis Set)

MedDRA 19.1 Preferred Term	PBO (N = 1042) n (%)		UPA 15 mg QD (N = 1035) n (%)	
Upper respiratory tract infection	38	(3.6)	53	(5.1)
Nasopharyngitis	33	(3.2)	46	(4.4)
Urinary tract infection	34	(3.3)	42	(4.1)
Nausea	23	(2.2)	36	(3.5)
Headache	38	(3.6)	33	(3.2)
Bronchitis	21	(2.0)	32	(3.1)
Diarrhoea	26	(2.5)	30	(2.9)
ALT increased	27	(2.6)	28	(2.7)
Blood CPK increased	9	(0.9)	26	(2.5)
Hypertension	22	(2.1)	24	(2.3)
Cough	10	(1.0)	23	(2.2)
AST increased	21	(2.0)	21	(2.0)
Back pain	14	(1.3)	21	(2.0)
Rheumatoid arthritis	36	(3.5)	11	(1.1)

In MTX- and adalimumab-controlled analyses, the adverse event profiles between upadacitinib 15 mg and the respective comparators, the profile of common adverse events was generally similar, with infectious disorders dominating the safety profile for all groups.

Adverse drug reactions for labelling

The applicant performed an integrated analysis of the safety datasets to identify adverse events that should be considered adverse drug reactions for labelling purposes. Adverse events identified as adverse drug reactions based on the totality of evidence, together with their respective frequencies, are displayed in Table 39 together with their respective frequencies in the PBO-controlled UPA 15 analysis set.

Table 38. Adverse Events Identified as Adverse Drug Reactions by the Applicant, with Frequencies in the UPA 15 mg and PBO Groups (PBO-Controlled UPA 15 Analysis Set)

Adverse Reactions	PBO (N = 1042) n (%)	UPA 15 mg QD (N = 1035) n (%)
Upper respiratory tract infection (URTI)[a]	99 (9.5)	140 (13.5)
Nausea	23 (2.2)	36 (3.5)
Blood CPK increased	9 (0.9)	26 (2.5)
Cough	10 (1.0)	23 (2.2)
Neutropenia	2 (0.2)	19 (1.8)
Pyrexia	0	12 (1.2)
Hypercholesterolemia	2 (0.2)	11 (1.1)
Herpes zoster	2 (0.2)	7 (0.7)
Pneumonia	3 (0.3)	5 (0.5)
Herpes simplex[b]	5 (0.5)	8 (0.8)
Oral candidiasis	1 (< 0.1)	4 (0.4)

a. URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection.

b. Herpes simplex includes oral herpes.

Adverse events of special interest

AESIs were identified for upadacitinib based on safety concerns reported for other JAK inhibitor products, as well as upadacitinib data from preclinical and Phase 2 RA studies, and customary regulatory concerns for novel small molecule drugs. The AESIs were:

- serious infection;
- opportunistic infection;
- herpes zoster;
- active/latent tuberculosis (TB);
- major adverse cardiovascular events (MACE, defined as cardiovascular (CV) death, non-fatal myocardial infarction (MI) and non-fatal stroke);
- thromboembolic events (including venous thromboembolic events [VTE] defined as pulmonary embolism [PE] and deep vein thrombosis [DVT])
- malignancy (including all possible malignancies, malignant tumors, non-melanoma skin cancer [NMSC], and malignant tumors excluding NMSC);
- hepatic disorders;
- gastrointestinal (GI) perforation;
- anemia;
- neutropenia;
- lymphopenia;
- renal dysfunction;

- CPK elevation.

Serious infections

Serious infections in the PBO-controlled UPA 15 mg analysis set (Studies M13-549, M14-465, M13-542) are shown in Table 40.

Table 39. Number and Percentage of Subjects with Treatment-Emergent Serious Infections – Controlled Short-Term Period Prior to Treatment Switching (PBO-Controlled UPA 15 mg Analysis Set; Studies M13-549, M14-465, M13-542)

System Organ Class MedDRA 19.1 Preferred Term	PBO (N = 1042) n (%)		UPA 15 mg QD (N = 1035) n (%)		Treatment Comparison (95% CI) UPA 15 mg QD – PBO
Any serious infection	6	(0.6)	12	(1.2)	0.6 (–0.2, 1.4)
Infections and infestations					
Appendicitis	0		2	(0.2)	
Bronchiolitis	0		1	(< 0.1)	
Bronchitis bacterial	1	(< 0.1)	0		
Enterocolitis infectious	0		1	(< 0.1)	
Fallopian tube abscess	0		1	(< 0.1)	
Gastroenteritis	3	(0.3)	2	(0.2)	
Influenza	0		1	(< 0.1)	
Kidney infection	0		1	(< 0.1)	
Lower respiratory tract infection	0		1	(< 0.1)	
Lung infection	0		1	(< 0.1)	
Peritonitis	0		1	(< 0.1)	
Pneumocystis jirovecii pneumonia	2	(0.2)	0		
Pneumonia	1	(< 0.1)	0		
Sepsis	1	(< 0.1)	0		
Urosepsis	0		1	(< 0.1)	
Viral infection	0		2	(0.2)	

In the MTX-controlled analysis set (Studies M13-545, M15-555) with exposure up to 3 months, the percentages of subjects with serious infection is presented in Table 41.

Table 40. Number and Percentage of Subjects with Treatment-Emergent Serious Infections – 3 Months (MTX-Controlled Analysis Set; Studies M13-545, M15-555)

	MTX/cMTX (N = 530) n (%)	UPA 15 mg QD (N = 534) n (%)	UPA 30 mg QD (N = 529) n (%)	Treatment Comparison (95% CI)	
				UPA 15 mg QD – MTX	UPA 30 mg QD – MTX
Any serious infection	2 (0.4)	3 (0.6)	8 (1.5)	0.2 (–0.6, 1.0)	1.1 (–0.0, 2.3)

The results from long-term analysis in study M14-465, where upadacitinib is directly compared to adalimumab, is shown below.

Table 41. Treatment-Emergent Serious Infections EAER Per 100 PY – All Study Drug Exposure (week 48, Study M14-465 Safety Analysis Set)

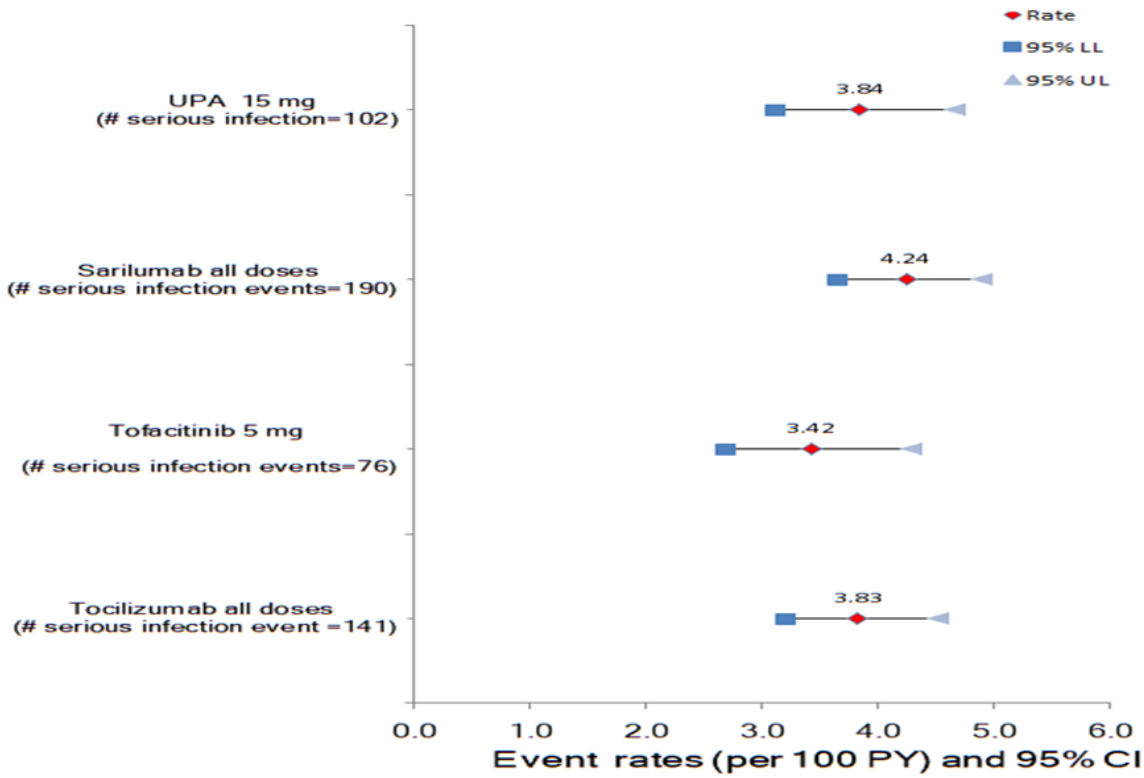
	Any ADA 40 mg EOW (N = 579) (PY = 467.8) E (E/100 PY)		**Any UPA 15 mg QD (N = 1417) (PY = 1243.3) E (E/100 PY)**		**UPA vs Control (95% CI) UPA – ADA**
Any serious infection	20	(4.3)	51	(4.1)	–0.2 (–2.4, 2.0)

Treatment-Emergent Serious Infections in the long-term Any Ph 3 UPA 15 and 30 mg analysis set (Studies M13-549, M13-542, M13-545, M15-555) are shown in Table 43. The EAER of discontinuation from study drug due to serious infections was 1.1 E/100 PY and 2.0 E/100 PY in the upadacitinib 15 mg and 30 groups, respectively.

Table 42. Treatment-Emergent Serious Infection EAERs ≥ 0.1 E/100 PY (In Either Dose Group) – Long-Term All Exposure (Any Ph 3 UPA 15 mg and 30 mg Analysis Set; Studies M13-545, M13-549, M15-555, M13-542)

System Organ Class MedDRA 19.1 Preferred Term	**UPA 15 mg QD (N = 1213) (PY = 1410.6) E (E/100 PY)**		**UPA 30 mg QD (N = 1204) (PY = 1365.0) E (E/100 PY)**	
Any serious infection	51	(3.6)	85	(6.2)
Infections and infestations				
Bartholin's abscess	2	(0.1)	0	
Bronchitis	4	(0.3)	5	(0.4)
Cellulitis	3	(0.2)	4	(0.3)
Diverticulitis	1	(< 0.1)	3	(0.2)
Gastroenteritis	0		3	(0.2)
Herpes zoster	0		5	(0.4)
Influenza	2	(0.1)	5	(0.4)
Pneumonia	13	(0.9)	23	(1.7)
Pyelonephritis	1	(< 0.1)	2	(0.1)
Sepsis	1	(< 0.1)	7	(0.5)
Upper respiratory tract infection	0		2	(0.1)
Urinary tract infection	2	(0.1)	4	(0.3)
Wound infection staphylococcal	0		4	(0.3)

The EAERs of serious infection for the upadacitinib 15 mg group and the clinical development programs of other immunomodulatory therapies for RA are shown in the figure below.



Notes: The upadacitinib 15 mg QD rate is from Any Ph 3 UPA 15 mg analysis set. Tofacitinib 5 mg = Tofacitinib 5 mg BID.EAERs with long-term treatment in RA clinical trials are presented above (Tofacitinib 5 mg = Tofacitinib 5 mg BID). Although there may be considerable variation in the demographics and other characteristics of the trial populations, the data shown serve as a benchmark for the rates in trials of moderately to severely active RA populations.

Figure 22. Event Rate of Serious Infection in RA Phase 3 Clinical Programs (Long-Term Exposure Adjusted)

Opportunistic infections

Opportunistic infections, including nonserious and serious events of oral candidiasis and disseminated herpes zoster in the PBO-controlled UPA 15 mg analysis set (Studies M13-549, M14-465, M13-542) are shown in Table 44.

Table 43. Number and Percentage of Subjects with Treatment-Emergent Opportunistic Infections - Controlled Short-Term Period Prior to Treatment Switching (PBO-Controlled UPA 15 mg Analysis Set; Studies M13-549, M14-465, M13-542)

System Organ Class MedDRA 19.1 Preferred Term	PBO (N = 1042) n (%)		UPA 15 mg QD (N = 1035) n (%)		Treatment Comparison (95% CI) UPA 15 mg QD – PBO
Any opportunistic infection	3	(0.3)	5	(0.5)	0.2 (–0.3, 0.7)
Infections and infestations					
Oesophageal candidiasis	0		1	(< 0.1)	
Oral candidiasis	1	(< 0.1)	4	(0.4)	
Pneumocystis jirovecii pneumonia	2	(0.2)	0		

Opportunistic infections in the MTX-controlled analysis set (Studies M13-545, M15-555) with exposure up to 3 months and 6 months is shown in Table 45.

Table 44. Number and Percentage of Subjects with Treatment-Emergent Opportunistic Infection – 3 Months (MTX-Controlled Analysis Set; Studies M13-545, M15-555)

	MTX/cMTX (N = 530) n (%)	UPA 15 mg QD (N = 534) n (%)	UPA 30 mg QD (N = 529) n (%)	Treatment Comparison (95% CI) UPA 15 mg QD – MTX	 UPA 30 mg QD – MTX
Any opportunistic infection	1 (0.2)	0	4 (0.8)	–0.2 (–0.6, 0.2)	0.6 (–0.3, 1.4)

The frequency of opportunistic infections by dose and during long term exposure is shown in Table 46.

Table 45. Treatment-Emergent Opportunistic Infections EAER Per 100 PY – Long-Term All Exposure (Any Ph 3 UPA 15 mg and 30 mg Analysis Set; Studies M13-545, M13-549, M15-555, M13-542)

System Organ Class MedDRA 19.1 Preferred Term	UPA 15 mg QD (N = 1213) (PY = 1410.6) E (E/100 PY)		UPA 30 mg QD (N = 1204) (PY = 1365.0) E (E/100 PY)	
Any opportunistic infection	8	(0.6)	24	(1.8)
Infections and infestations				
Cryptococcosis	0		1	(< 0.1)
Herpes zoster disseminated	0		1	(< 0.1)
Oesophageal candidiasis	1	(< 0.1)	1	(< 0.1)
Oral candidiasis	5	(0.4)	12	(0.9)
Oropharyngeal candidiasis	1	(< 0.1)	2	(0.1)
Pneumonia cryptococcal	1	(< 0.1)	1	(< 0.1)
Varicella zoster pneumonia	0		1	(< 0.1)
Investigations				
Cytomegalovirus test positive	0		5	(0.4)

Active/Latent TB

Subjects were screened for TB infection at study entry in the upadacitinib RA studies and subjects with latent TB were allowed to enrol in the study after documented initiation or prior completion of prophylactic treatment. Across the upadacitinib RA clinical studies, 6 cases of active TB were reported, of which 5 subjects were receiving upadacitinib (3 on upadacitinib 15 mg and 2 on upadacitinib 30 mg) and 1 subject was receiving adalimumab. All but 1 subject was receiving concomitant csDMARDs and/or corticosteroids. Of the 5 cases in subjects receiving upadacitinib, 3 were diagnosed with latent TB at screening and 2 manifested signs and symptoms of extra-pulmonary TB.

In the Any RA UPA analysis set, which includes all global Phase 2 and Phase 3 studies, the EAER of active/latent TB for all upadacitinib doses was 1.8 E/100 PY; 8 events (0.2 E/100 PY) of active/latent TB led to study discontinuation.

Most of the events identified by the CMQ search were cases of latent TB diagnosed at the annual TB re-testing in subjects with a negative TB test result at screening or most recent evaluation. There were 6 cases of active TB; 5 subjects were receiving upadacitinib and 1 subject was receiving adalimumab. Of the 5 subjects receiving upadacitinib, 3 subjects were receiving 15 mg and 2 subjects were receiving 30 mg at the time of the event. Of the 5 cases of active TB reported in subjects receiving upadacitinib, 3 had positive TB testing results at screening. Of these 3 subjects with latent TB diagnosed at screening, 1 had isoniazid (INH) therapy for ≥ 6 months, and 2 subjects had INH therapy for < 6 months (including 1 subject that was treated for 1 month).

Herpes Zoster

An increased risk of herpes zoster is observed in patients with underlying autoimmune diseases, such as RA, particularly due to the use of immunosuppressive therapies such as glucocorticoids, non-biologic disease-modifying anti-rheumatic drugs, and TNF-alpha inhibitors. Furthermore, JAK inhibition has been associated with an increased risk of herpes zoster

In the PBO-controlled UPA 15 mg short term analysis set (Studies M13-549, M13-542, M14-465), herpes zoster was reported in a higher percentage of subjects in the upadacitinib 15 mg group compared with the placebo group (Table 47).

Table 46. Number and Percentage of Subjects with Treatment-Emergent Herpes Zoster – Controlled Short-Term Period Prior to Treatment Switching (PBO-Controlled UPA 15 mg Analysis Set; Studies M13-549, M14-465, M13-542)

System Organ Class MedDRA 19.1 Preferred Term	PBO (N = 1042) n (%)		UPA 15 mg QD (N = 1035) n (%)		Treatment Comparison (95% CI) UPA 15 mg QD – PBO
Any herpes zoster	3	(0.3)	7	(0.7)	0.4 (–0.2, 1.0)
Infections and infestations					
Herpes zoster	2	(0.2)	7	(0.7)	
Varicella	1	(< 0.1)	0		

The frequency of herpes zoster in the MTX-controlled analysis set (Studies M13-545, M15-555) is shown in Table 48.

Table 47. Number and Percentage of Subjects with Treatment-Emergent Herpes Zoster – 3-Months (MTX-Controlled Analysis Set; Studies M13-545, M15-555)

	MTX/cMTX (N = 530) n (%)	UPA 15 mg QD (N = 534) n (%)	UPA 30 mg QD (N = 529) n (%)	Treatment Comparison (95%) UPA 15 mg QD – MTX (95% CI)	Treatment Comparison (95%) UPA 30 mg QD – MTX (95% CI)
Any herpes zoster	2 (0.4)	6 (1.1)	8 (1.5)	0.7 (–0.3, 1.8)	1.1 (–0.0, 2.3)

In the long-term studies, the IR was lower for UPA 15 mg than for UPA 30 mg (Table 49).

Table 48. Treatment-Emergent Herpes Zoster EAER Per 100 PY – Long-Term All Exposure (Any Ph 3 UPA 15 mg and 30 mg Analysis Set; Studies M13-545, M13-549, M15-555, M13-542)

System Organ Class MedDRA 19.1 Preferred Term	UPA 15 mg QD (N = 1213) (PY = 1410.6) E (E/100 PY)		UPA 30 mg QD (N = 1204) (PY = 1365.0) E (E/100 PY)	
Any herpes zoster	61	(4.3)	96	(7.0)
Infections and infestations				
Herpes zoster	57	(4.0)	86	(6.3)
Herpes zoster disseminated	0		1	(< 0.1)
Ophthalmic herpes zoster	1	(< 0.1)	1	(< 0.1)
Varicella	1	(< 0.1)	1	(< 0.1)
Varicella zoster pneumonia	0		1	(< 0.1)
Nervous system disorders				
Post herpetic neuralgia	2	(0.1)	6	(0.4)

Malignancy

In the upadacitinib global Phase 3 RA studies, subjects with a history of any malignancy except for successfully treated NMSC or localized carcinoma in situ of the cervix were excluded. Subjects who developed any malignancy, with the exception of localized NMSC or carcinoma in-situ of the cervix during the study conduct were discontinued from study drug.

In the long-term studies, the IR was higher for UPA 30 mg than for UPA 15 mg (Table 50).

Table 49. Treatment-Emergent Malignancies EAER Per 100 PY by SOC and PT – Long-Term All Exposure (Any Ph 3 UPA 15 mg and 30 mg Analysis Set; Studies M13-545, M13-549, M15-555, M13-542)

System Organ Class MedDRA 19.1 Preferred Term	UPA 15 mg QD (N = 1213) (PY = 1410.6) E (E/100 PY)		UPA 30 mg QD (N = 1204) (PY = 1365.0) E (E/100 PY)	
Any malignancy	23	(1.6)	34	(2.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Adenocarcinoma	0		1	(< 0.1)
Adenocarcinoma of colon	0		2	(0.1)
Anal cancer	0		1	(< 0.1)
B-cell small lymphocytic lymphoma	0		1	(< 0.1)
Basal cell carcinoma	3	(0.2)	6	(0.4)
Bladder cancer	1	(< 0.1)	0	
Bowen's disease	0		1	(< 0.1)
Breast cancer	1	(< 0.1)	1	(< 0.1)
Cervix carcinoma stage 0	0		1	(< 0.1)
Chronic lymphocytic leukaemia	0		1	(< 0.1)
Colon cancer	1	(< 0.1)	0	
Invasive breast carcinoma	0		1	(< 0.1)
Invasive ductal breast carcinoma	3	(0.2)	1	(< 0.1)
Lymphangiosis carcinomatosa	0		1	(< 0.1)
Malignant melanoma	0		2	(0.1)
Malignant melanoma in situ	1	(< 0.1)	0	
Malignant neoplasm progression	1	(< 0.1)	0	
Metastases to spine	0		1	(< 0.1)
Metastatic malignant melanoma	1	(< 0.1)	0	
Non-hodgkin's lymphoma	1	(< 0.1)	0	
Non-small cell lung cancer metastatic	1	(< 0.1)	0	
Pancreatic carcinoma stage IV	1	(< 0.1)	0	
Papillary thyroid cancer	1	(< 0.1)	0	
Prostate cancer	0		2	(0.1)
Prostate cancer stage II	0		1	(< 0.1)

Table 50. Treatment-Emergent Malignancies EAER Per 100 PY by SOC and PT – Long-Term All Exposure (Any Ph 3 UPA 15 mg and 30 mg Analysis Set; Studies M13-545, M13-549, M15-555, M13-542) (Continued)

System Organ Class MedDRA 19.1 Preferred Term	UPA 15 mg QD (N = 1213) (PY = 1410.6) E (E/100 PY)		UPA 30 mg QD (N = 1204) (PY = 1365.0) E (E/100 PY)	
Rectal adenocarcinoma	1	(< 0.1)	0	
Rectal cancer metastatic	0		1	(< 0.1)
Renal cancer stage I	1	(< 0.1)	0	
Squamous cell carcinoma of lung	1	(< 0.1)	0	
Squamous cell carcinoma of skin	2	(0.1)	8	(0.6)
Tongue neoplasm malignant stage unspecified	1	(< 0.1)	0	
Uterine cancer	0		1	(< 0.1)
Uterine carcinoma in situ	1	(< 0.1)	0	

The risk of subjects experiencing a NMSC when receiving upadacitinib 15 mg and 30 mg in the Phase 3 studies did not appear to increase over time (Figure 23).

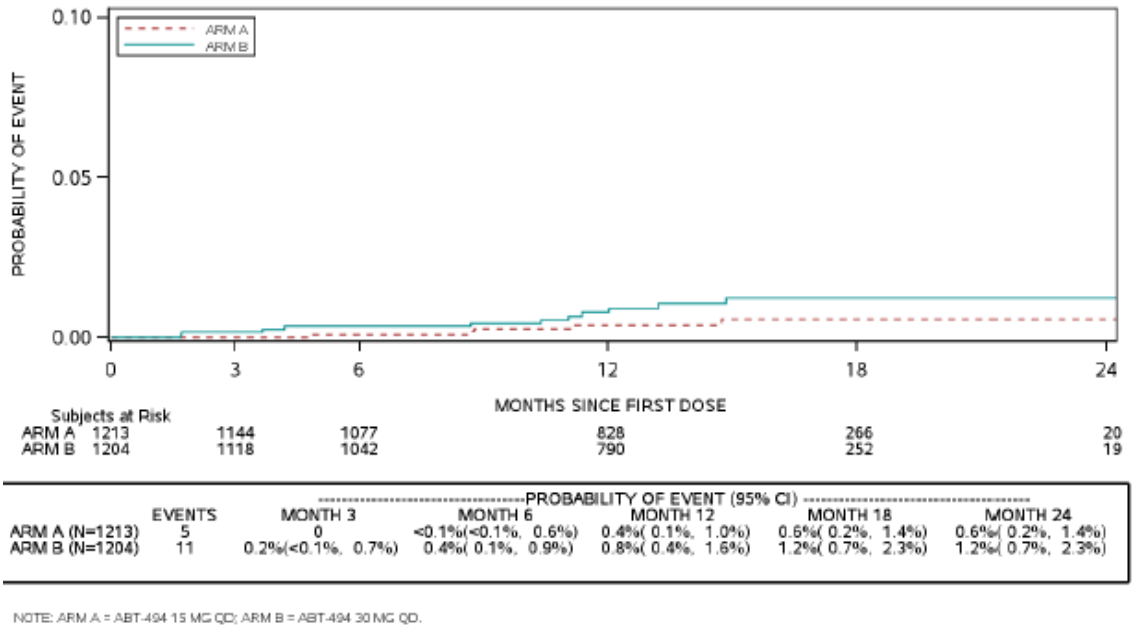
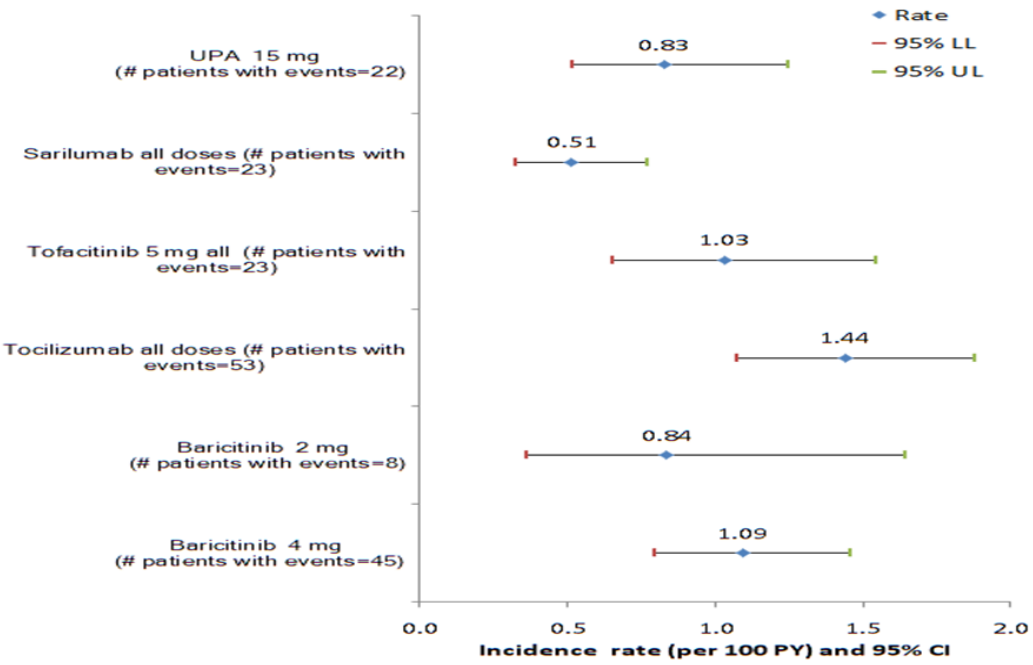


Figure 22. Kaplan-Meier Curve for Treatment-Emergent NMSC – Long-Term All Exposure (Any Ph 3 UPA 15 mg and 30 mg Analysis Set; Studies M13-545, M13-549, M15-555, M13-542)
Arm A=UPA 15 mg, Arm B=UPA 30 mg

The IR for malignancies excluding NMSC in relation to other RA products is shown in Figure 24.



Notes: The upadacitinib 15 mg QD rate is from Any Ph 3 UPA 15 mg analysis set.

EAIRs with long-term treatment in RA clinical trials are presented above (Tofacitinib 5 mg = Tofacitinib 5 mg BID. Baricitinib 2 mg or 4 mg = Baricitinib 2 mg QD or 4 mg QD). Although there may be considerable variation in the demographics and other characteristics of the trial populations, the data shown serve as a benchmark for the rates in trials of moderately to severely active RA populations.

Figure 23. Incidence Rate of Malignancy Excluding NMSC in RA Phase 3 Clinical Programs (Long-Term Exposure-Adjusted)

In the long-term Any Ph 3 UPA 15 analysis set, there were 8 subjects with NMSC (EAER = 0.3 E/100 PY). In the long-term Any Ph 3 UPA 15/30 analysis set, the EAIR's of NMSC were 0.4 n/100 PY (5 subjects with NMSC) for upadacitinib 15 mg and 0.8 n/100 PY (11 subjects with NMSC) for 30 mg. When examined at 6 month periods from starting treatment, the incidence rates were consistently higher for 30 mg (Figure 25). In adalimumab-controlled analyses, the incidence rates of NMSC were comparable between upadacitinib 15 mg and adalimumab.

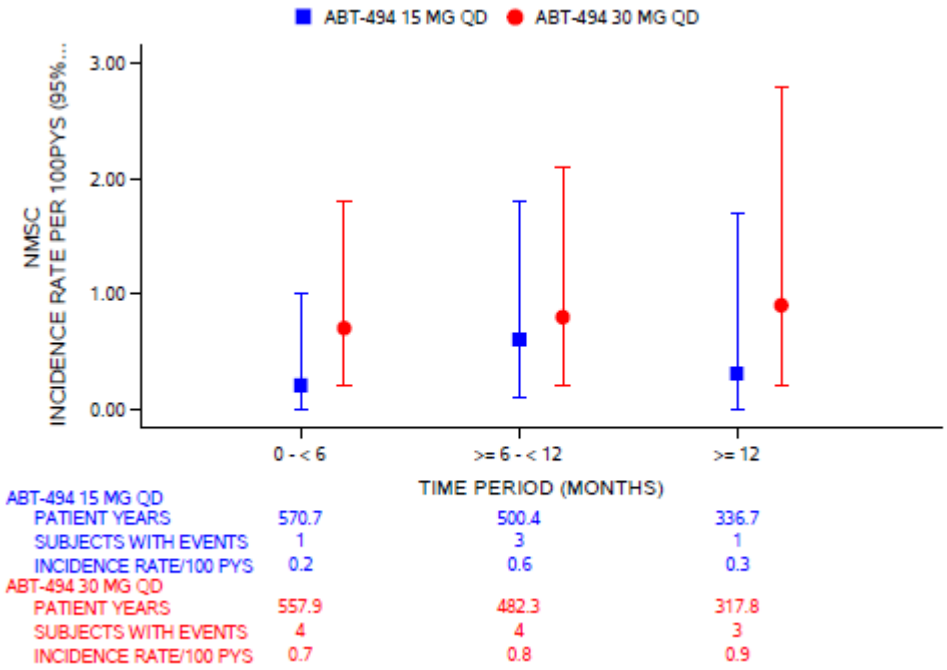


Figure 24. Treatment-Emergent NMSC Incidence Rate Per 100 PY by Onset of AE in 6 Month Interval – Long-Term All Exposure (Any Ph 3 UPA 15/30 Analysis Set)

Although the numbers are small, a dose-related increase in the frequency of NMSC from upadacitinib 15 mg to 30 mg cannot be excluded. Considering that the 30mg strength isn't proposed in the posology, no information is included in the SmPC.

Lymphoma is of special interest for the RA population which has a two-fold risk of lymphoma relative to the general population, with large RA cohort studies reporting standardized incidence rates between 0.6 – 0.9/100 PY. Across the global Upadacitinib Phase 2 and Phase 3 studies, 4 subjects (< 0.1 n/100 PY) with lymphoproliferative disorders were reported. Additionally, there were 2 subjects in the Japan Study M14-663 reported with a lymphoproliferative disease (one subject with Hodgkin's Lymphoma and one subject with acute lymphocytic leukemia). The types of lymphoma that were reported are, according to the applicant, consistent with lymphomas described in the RA population. The applicant concludes that the overall incidence rate of lymphoma in the upadacitinib development program for RA was within the range expected for a population of patients with RA.

Hepatic disorder

Transaminase elevations have been reported with JAK inhibitors approved for the treatment of RA, including baricitinib and tofacitinib. Upadacitinib 15 mg was associated with a small (about 5 U/L) increase in mean ALT and AST levels in short-term analyses, and ALT increases of 5*ULN or greater were seen in about 1.5% of subjects compared to less than 0.5% of subjects on placebo. This small increase persisted on long-term treatment. Two subjects in the long-term Any Ph 3 UPA 15 analysis set met biochemical criteria for Hy's Law, but both subjects had alternative aetiologies (malignant melanoma, and concomitant use of INH). In the long-term Any Ph 3 UPA 15 analysis set, the EAER of treatment-emergent hepatic disorders was 14.4 E/100 PY, most events being transaminase elevations. Elevations were usually asymptomatic and transient even in the setting of continued treatment; the EAER of hepatic disorders leading to study drug discontinuation was 0.8 E/100 PY.

There was no evidence of a dose-related effect on hepatic enzymes. The increase was generally larger on upadacitinib than with either of the active comparators (adalimumab or MTX), but event rates of treatment-emergent hepatic disorders were generally comparable between the treatment groups.

GI perforation

GI perforations are a rare but serious event observed in patients with RA. Anti-IL-6 receptor therapy has been associated with an increased risk of GI perforation. In the Phase 3 upadacitinib RA studies, 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.

In the Any RA UPA analysis set, 9 subjects experienced a total of 9 events (0.2 E/100 PY) identified by the GI Perforations SMQ search: 5 subjects continuously treated with upadacitinib 6 mg BID/15 mg QD and 4 subjects continuously treated with upadacitinib 12 mg BID/30 mg QD. There were no events of GI perforation identified in subjects receiving placebo, MTX, or adalimumab in the other analysis sets.

Based on sponsor medical review of the 5 events reported on upadacitinib 15 mg, 2 events were judged to represent GI perforation, both were serious; 1 event was a perforated appendix which occurred in the context of appendicitis and the other event was an anal fistula requiring surgical repair. The GI perforation EAER in the upadacitinib 15 mg group based on 2 events in 2655.1 PY (exposure in the Any Ph3 15 mg analysis set) was 0.075 E/100 PY. The applicant states that the EAER of GI perforation in the upadacitinib 15 mg group (0.075 E/100 PY) is within the range reported for other RA therapies.

Based on sponsor medical review, all 4 reported events on upadacitinib 30 mg were judged to represent a GI perforation. The subject with an event of intestinal perforation had vertebral fracture from a suspected neoplastic lesion in the dorsolumbar spine and developed paralytic ileus. One subject with large intestine perforation had a prior history of diverticulosis and the event occurred during an episode of diverticulitis. The other subject with an event of large intestine perforation had no relevant prior medical history but was receiving concomitant csDMARD therapy; the event was reported in the setting of acute kidney injury, haematemesis, ventricular tachycardia, and sepsis (no further event details available). The event of peritonitis was judged likely due to a gastric ulcer perforation in a subject with a history of bleeding gastric ulcer. All of these events were serious.

Anaemia

Anaemia is common in patients with active RA due to chronic inflammation. The resolution of inflammation has been associated with increases in haemoglobin values in patients receiving effective RA therapy. As stated by the applicant, the impact of JAK inhibition on anaemia is complex, due to potential beneficial effects of reducing inflammation and countering effects of reducing EPO signalling through JAK2/homodimers. Selective JAK1 inhibition was hypothesized to provide the potential to have an equivalent or greater impact on inflammation with a lesser impact on EPO signalling due to higher selectivity for JAK1 compared to JAK2 isoforms.

The number and percentage of subjects meeting criteria for potentially clinically significant values for Haemoglobin in the PBO-controlled UPA 15 mg analysis set (Studies M13-549, M14-465, M13-542) are shown in Table 51.

Table 50. Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Values for Haemoglobin (PBO-Controlled UPA 15 mg Analysis Set; Studies M13-549, M14-465, M13-542)

Haemoglobin (G/L)	PBO (N = 1042) n/N_OBS (%)		UPA 15 mg QD (N = 1035) n/N_OBS (%)	
Grade 2 (Decreased 15 – < 21)	85/1036	(8.2)	88/1034	(8.5)
Grade 3 (70 – < 80 or decreased 21 – < 30)	23/1036	(2.2)	30/1034	(2.9)
Grade 4 (< 70 or decreased ≥ 30)	8/1036	(0.8)	4/1034	(0.4)

The applicant concludes that consistent with the JAK1 selectivity of upadacitinib, there was no meaningful difference in haemoglobin changes or TEAEs of anaemia in subjects receiving upadacitinib 15 mg compared to placebo, adalimumab or MTX. Haemoglobin decreases and TEAEs of anaemia were higher in the upadacitinib 30 mg group compared to the upadacitinib 15 mg group. Overall across all upadacitinib groups, the rates of SAEs of anaemia and subjects discontinuing upadacitinib due to anaemia were low.

Neutropenia

According to the applicant, most cases of neutropenia in patients with RA are related to medications including MTX and other immunosuppressants. Neutrophil decreases have been reported with JAK inhibitors. In particular, Grade 4 neutropenia (< 500 cells/mm^3) is considered a concern in clinical practice due to an increased risk for infections.

The number and percentage of subjects meeting criteria for potentially clinically significant neutrophil values in the PBO-controlled UPA 15 mg analysis set (Studies M13-549, M14-465, M13-542) are shown in Table 52.

Table 51. Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Neutrophil Values (PBO-Controlled UPA 15 mg Analysis Set; Studies M13-549, M14-465, M13-542)

Neutrophils (10^9/L)	PBO (N = 1042) n/N_OBS (%)		UPA 15 mg QD (N = 1035) n/N_OBS (%)	
Grade 2 (1.0 – < 1.5)	6/1036	(0.6)	41/1034	(4.0)
Grade 3 (0.5 – < 1.0)	1/1036	(< 0.1)	6/1034	(0.6)
Grade 4 (< 0.5)	0/1036		5/1034	(0.5)

For the long-term Any RA UPA analysis set, please see Table 53.

Table 52. Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Values For Neutrophils – Long-Term All Exposure (Any RA UPA Analysis Set)

Neutrophils (10^9/L)	UPA 6 mg BID/15 mg QD (N = 2819) n/N_OBS (%)		UPA 12 mg BID/30 mg QD (N = 1309) n/N_OBS (%)		Any UPA (N = 4443) n/N_OBS (%)	
Grade 3 (0.5 – < 1.0)	23/2756	(0.8)	31/1297	(2.4)	78/4415	(1.8)
Grade 4 (< 0.5)	7/2756	(0.3)	3/1297	(0.2)	13/4415	(0.3)

The mean neutrophil count over time is shown in Figure 26.

Notes: Arm A = UPA 15 mg QD; Arm B = UPA 15 mg QD no ADA crossover.
Mean change from baseline over time by group with 95% CI.
LS means from ANCOVA model adjusting for baseline are used.

Figure 25. Plot of Mean Change from Baseline in Neutrophil Count Over Time –Long-Term All Exposure (Any Ph 3 UPA 15 mg Analysis Set; All5 Ph 3 Studies)

The applicant concludes that decreases in neutrophil count are an identified ADR for upadacitinib. Neutrophil levels need to be considered for initiation, interruption and restarting of upadacitinib treatment. According to the applicant, no clear evidence of an association of serious infections, opportunistic infections or herpes zoster with a low neutrophil count was observed.

Lymphopenia

According to the applicant, lymphopenia is not uncommon in autoimmune diseases including RA. Genetic JAK deficiency is associated with lymphocyte count changes due to inhibition of the various cytokine signalling pathways and lymphocyte count decreases have been observed with clinical use of tofacitinib and baricitinib in RA patients.

The number and percentage of subjects meeting criteria for potentially clinically significant values for lymphocytes in the PBO-controlled UPA 15 mg analysis set (Studies M13-549, M14-465, M13-542) are shown in Table 54 and Table 55.

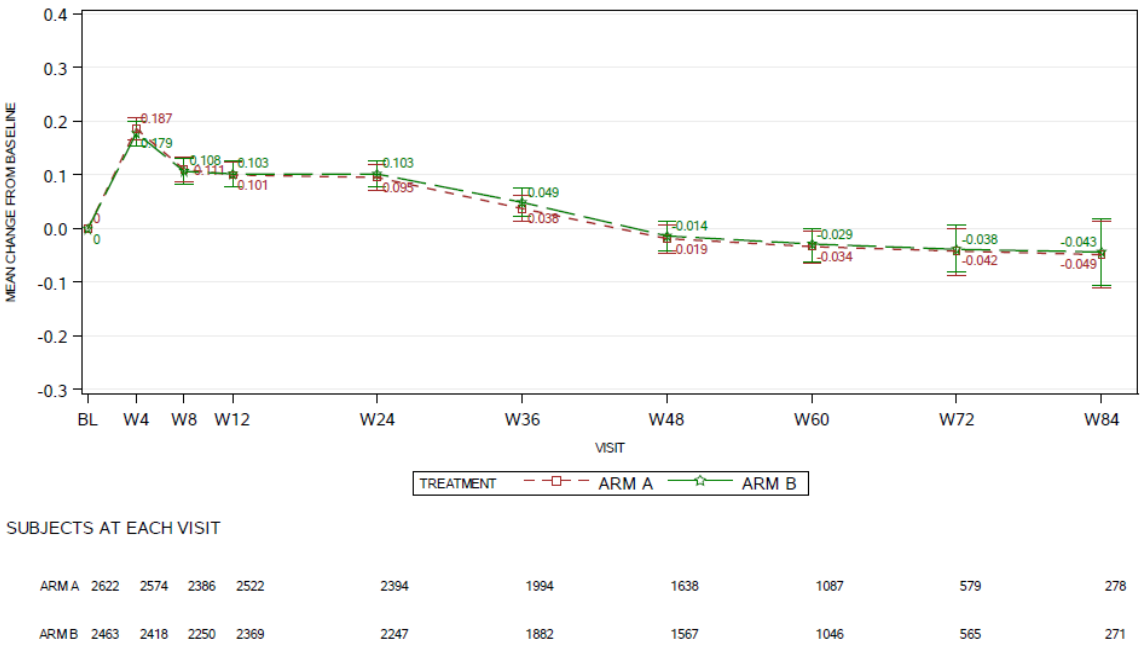
Table 53. Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Values for Lymphocytes (PBO-Controlled UPA 15 mg and 30 mg Analysis Set; Studies M13-549, M13-542)

Lymphocytes (10^9/L)	PBO (N = 390) n/N_OBS (%)	UPA 15 mg QD (N = 385) n/N_OBS (%)	UPA 30 mg QD (N = 384) n/N_OBS (%)
Grade 2 (1.0 – < 1.5)	73/386 (18.9)	71/384 (18.5)	71/381 (18.6)
Grade 3 (0.5 – < 1.0)	39/386 (10.1)	48/384 (12.5)	53/381 (13.9)
Grade 4 (< 0.5)	2/386 (0.5)	2/384 (0.5)	9/381 (2.4)

Table 54. Number and Percentage of Subjects with Treatment-Emergent Lymphopenia – Controlled Short-Term Period Prior to Treatment Switching (PBO-Controlled UPA 15 mg Analysis Set; Studies M13-549, M14-465, M13-542)

System Organ Class MedDRA 19.1 Preferred Term	PBO (N = 1042) n (%)		UPA 15 mg QD (N = 1035) n (%)		Treatment Comparison (95% CI) UPA 15 mg QD – PBO
Any lymphopenia	11	(1.1)	14	(1.4)	0.3 (–0.6, 1.2)
Blood and lymphatic system disorders					
Lymphopenia	11	(1.1)	13	(1.3)	
Lymphocyte count decreased	0		1	(< 0.1)	

According to the applicant, there was no SAE of lymphopenia in either upadacitinib group across the global Phase 2 and 3 studies. In Study M14-663 (Week 60 analysis set), 1 subject had a TEAE of lymphopenia that was considered serious, and developed pneumocystic jirovecii pneumonia 5 days later.



SUBJECTS AT EACH VISIT

ARM A	2622	2574	2386	2522	2394	1994	1638	1087	579	278
ARM B	2463	2418	2250	2369	2247	1882	1567	1046	565	271

Notes: Arm A = UPA 15 mg QD; Arm B = UPA 15 mg QD no ADA crossover.
Mean change from baseline over time by group with 95% CI.
LS means from ANCOVA model adjusting for baseline are used.

Figure 26. Plot of Mean Change from Baseline in Lymphocytes Over Time – Long-Term All Exposure (Any Ph 3 UPA 15 mg Analysis Set; All 5 Ph 3 Studies)

CPK elevation

According to the applicant, increases in CPK levels, mostly mild in severity, have been observed with other JAK inhibitors (tofacitinib and baricitinib). In the PBO-controlled UPA 15 mg analysis set (Studies M13-549, M14-465, M13-542), a greater mean increase in CPK levels from baseline to Week 12 and a higher percentage of subjects with Grade ≥ 2 CPK increases was observed for subjects receiving upadacitinib 15 mg compared with placebo.

Renal dysfynction

In the short-term PBO-controlled UPA 15 analysis set, upadacitinib 15 mg was associated with a 6 - 8% (3 - 4 umol/L) increase in serum creatinine concentration, but Grade 2 or higher increases (i.e. > 1.5 * ULN) were rare and occurred on both placebo and upadacitinib. TEAEs of renal dysfunction were reported in 1 subject (< 0.1%) in the upadacitinib 15 mg group and 2 subjects (0.2%) in the placebo group. In the long-term Any Ph 3 UPA 15 analysis set, the initial increase was observed to plateau after the first 4-8 weeks of treatment. Through long-term exposure, 1 subject had Grade 3 (> 3 * ULN) and 2 subjects had Grade 4 (> 6 * ULN) creatinine increases; the Grade 4 creatinine increases occurred at a single time point and normalised at following visits for both subjects. The EAER of renal dysfunction TEAEs was 0.4 E/100 PY, with a TEAE reported in 11 subjects. A small further increase in mean serum creatinine was seen with 30 mg vs. 15 mg, and mean increases on 15 mg were greater than on either adalimumab or MTX.

In the long-term Any RA UPA analysis set, 3 subjects in the upadacitinib 6 mg BID/15 mg QD group, and 1 subject in the 12 mg BID/30 mg QD group had a Grade 3-4 increase in serum creatinine. The EAIR of a renal dysfunction TEAE was 0.4 n/100 PY for upadacitinib 6 mg BID/15 mg QD and

1.0 n/100 PY for 12 mg BID/30 mg QD. There were a total of 9 subjects with a renal dysfunction SAE; these occurred in the context of acute infections.

MACE and Other Cardiovascular Events

Baseline CV risk factors such as hypertension, diabetes, and dyslipidemia that were present in the Any RA UPA analysis set of the phase 3 studies are shown in Table 56.

Table 55. Cardiovascular Categorical Variables at Baseline (Any RA UPA Analysis Set)

Variable	UPA 6 mg BID/ 15 mg QD (N = 2819) n (%)	UPA 12 mg BID/ 30 mg QD (N = 1309) n (%)	Any UPA (N = 4443) n (%)
History of CV events			
Yes	67 (2.4)	30 (2.3)	105 (2.4)
No	2733 (96.9)	1270 (97.0)	4279 (96.3)
Unknown[a]	19 (0.7)	9 (0.7)	59 (1.3)
CV risk factors at baseline			
Baseline medical history of hypertension			
Yes	1114 (39.5)	515 (39.3)	1742 (39.2)
No	1686 (59.8)	785 (60.0)	2642 (59.5)
Unknown[a]	19 (0.7)	9 (0.7)	59 (1.3)
Diabetes			
Yes	382 (13.6)	186 (14.2)	800 (18.0)
No	2418 (85.8)	1114 (85.1)	3584 (80.7)
Unknown[a]	19 (0.7)	9 (0.7)	59 (1.3)
History of tobacco/nicotine use			
Current	555 (19.7)	248 (18.9)	867 (19.5)
Former	522 (18.5)	306 (23.4)	903 (20.3)
Never	1740 (61.7)	753 (57.5)	2669 (60.1)
Unknown	2 (< 0.1)	2 (0.2)	4 (< 0.1)
Elevated LDL-C			
Yes (≥ 3.36 mmol/L)	788 (28.0)	364 (27.9)	1276 (28.8)
No (< 3.36 mmol/L)	2027 (72.0)	941 (72.1)	3159 (71.2)
Depressed HDL-C			
Yes (≤ 1.55 mmol/L)	1623 (57.6)	769 (58.7)	2569 (57.8)
No (> 1.55 mmol/L)	1196 (42.4)	540 (41.3)	1874 (42.2)
Statin use at baseline			
Yes	330 (11.7)	181 (13.8)	554 (12.5)
No	2489 (88.3)	1128 (86.2)	3889 (87.5)

a. Unknown category includes subjects enrolled in Studies M13-537 and M13-550 but not M13-538, since medical history data was not MedDRA coded.

The number of treatment-emergent MACE in the PBO-controlled UPA 15 mg analysis set up to 3 months (Studies M13-549, M14-465, M13-542), is shown in Table 57.

Table 56. Treatment-Emergent Adjudicated MACE EAIR Per 100 PY – Controlled Short-Term Period Prior to Treatment Switching (Global Ph 3 Safety Analysis Set)

	PBO (N = 1042) n/PY (n/100 PY)	MTX[a] (N = 530) n/PY (n/100 PY)	ADA 40 mg EOW (N = 327) n/PY (n/100 PY)	UPA 15 mg QD (N = 1569) n/PY (n/100 PY)	UPA 30 mg QD (N = 913) n/PY (n/100 PY)
Any adjudicated MACE[b]	3/256.8 (1.2)	1/121.7 (0.8)	1/86.0 (1.2)	3/386.1 (0.8)	4/211.6 (1.9)

a. Includes both Studies M13-545 and M15-555.

b. MACE: major adverse cardiovascular events, defined as CV death, non-fatal MI and non-fatal stroke.

In long-term analysis, the rate of MACE is shown in Table 58.

Table 57. Treatment-Emergent Adjudicated MACE EAIR Per 100 PY –Long-Term All Exposure (week 48 and beyond, Global Ph 3 Safety Analysis)

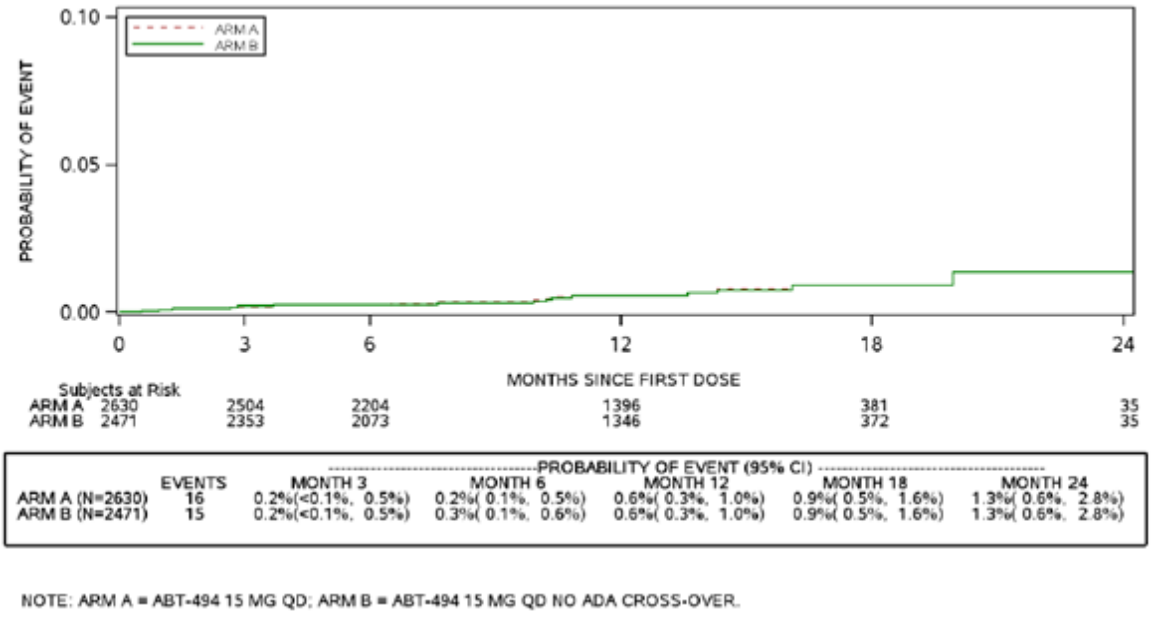
	MTX[a] (N = 314) n/PY (n/100 PY)	ADA 40 mg EOW (N = 579) n/PY (n/100 PY)	UPA 15 mg QD N = 2630 n/PY (n/100 PY)	UPA 30 mg QD N = 1204 n/PY (n/100 PY)
Any adjudicated MACE[b]	2/314.0 (0.6)	2/467.8 (0.4)	16/2651.0 (0.6)	13/1361.5 (1.0)

a. Includes Study M13-545 only which has the long-term MTX exposure.

b. MACE: major adverse cardiovascular events, defined as CV death, non-fatal MI and non-fatal stroke.

A Kaplan-Meier curve for MACE is shown in Figure 27.

Figure 27. Kaplan-Meier Curve for Treatment-Emergent Adjudicated MACE – Long-Term All Exposure (Any Ph 3 UPA 15 mg Analysis Set; All 5 Ph 3 Studies)



In study M14-465, which includes a direct comparison between upadacitinib and adalimumab, the results are as follows up to 26 weeks and during all exposure:

Table 58. Treatment-Emergent Adjudicated MACE EAIR Per 100 PY – Up to Week 26 Censored at Treatment Switching (Study M14-465 Safety Analysis Set)

	PBO (N = 652) n/PY (n/100 PY)	ADA 40 mg EOW (N = 327) n/PY (n/100 PY)	UPA 15 mg QD (N = 650) n/PY (n/100 PY)	UPA vs Control (95% CI)	
				UPA - PBO	UPA - ADA
Any adjudicated MACE[a]	3/250.0 (1.2)	2/137.6 (1.5)	0/289.6	–1.2 (–2.6, 0.2)	–1.5 (–3.5, 0.6)

a. MACE: major adverse cardiovascular events, defined as CV death, non-fatal MI and non-fatal stroke.

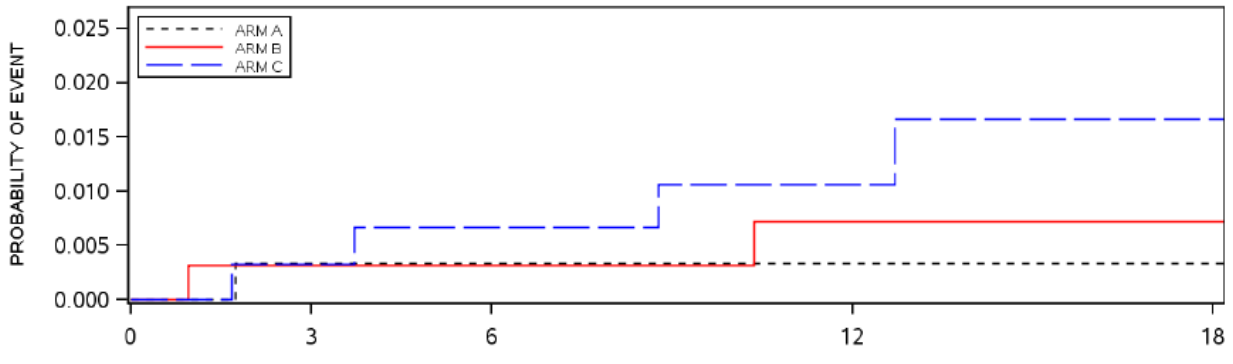
Table 59. Treatment-Emergent Adjudicated MACE EAIR Per 100 PY – All Study Drug Exposure (Study M14-465 Safety Analysis Set), week 48 and beyond

	Any ADA 40 mg EOW (N = 579) n/ PY (n/100 PY)		Any UPA 15 mg QD (N = 1417) n/ PY (n/100 PY)		UPA vs Control (95% CI) UPA – ADA
Any adjudicated MACE[a]	2/467.8	(0.4)	5/1242.0	(0.4)	–0.0 (–0.7, 0.7)

a. MACE: major adverse cardiovascular events, defined as CV death, non-fatal MI and non-fatal stroke.

Kaplan-Meier curves for treatment-emergent MACE in studies M13-545 and M14-654 (the studies that includes long -term data for a comparator) are shown in

FIGURE 2.4__9.2.1.7
KAPLAN-MEIER CURVE FOR TREATMENT-EMERGENT ADJUDICATED MACE - LONG TERM ALL EXPOSURE
(STUDY M13-545 - SAFETY ANALYSIS SET)



	EVENTS	PROBABILITY OF EVENT (95% CI) MONTH 3	MONTH 6	MONTH 12	MONTH 18
ARM A (N=314)	2	0.3%(0%, 2.4%)	0.3%(0%, 2.4%)	0.3%(0%, 2.4%)	0.3%(0%, 2.4%)
ARM B (N=317)	2	0.3%(0%, 2.3%)	0.3%(0%, 2.3%)	0.7%(0.2%, 2.9%)	0.7%(0.2%, 2.9%)
ARM C (N=314)	4	0.3%(0%, 2.3%)	0.7%(0.2%, 2.7%)	1.1%(0.3%, 3.3%)	1.7%(0.6%, 4.5%)

NOTE: ARM A = MTX MONO; ARM B = ABT-494 15 MG QD MONO; ARM C =ABT-494 30 MG QD MONO.
NOTE: ONLY EVENTS UP TO 18 MONTHS WERE COUNTED IN THIS FIGURE

Figure 29 and

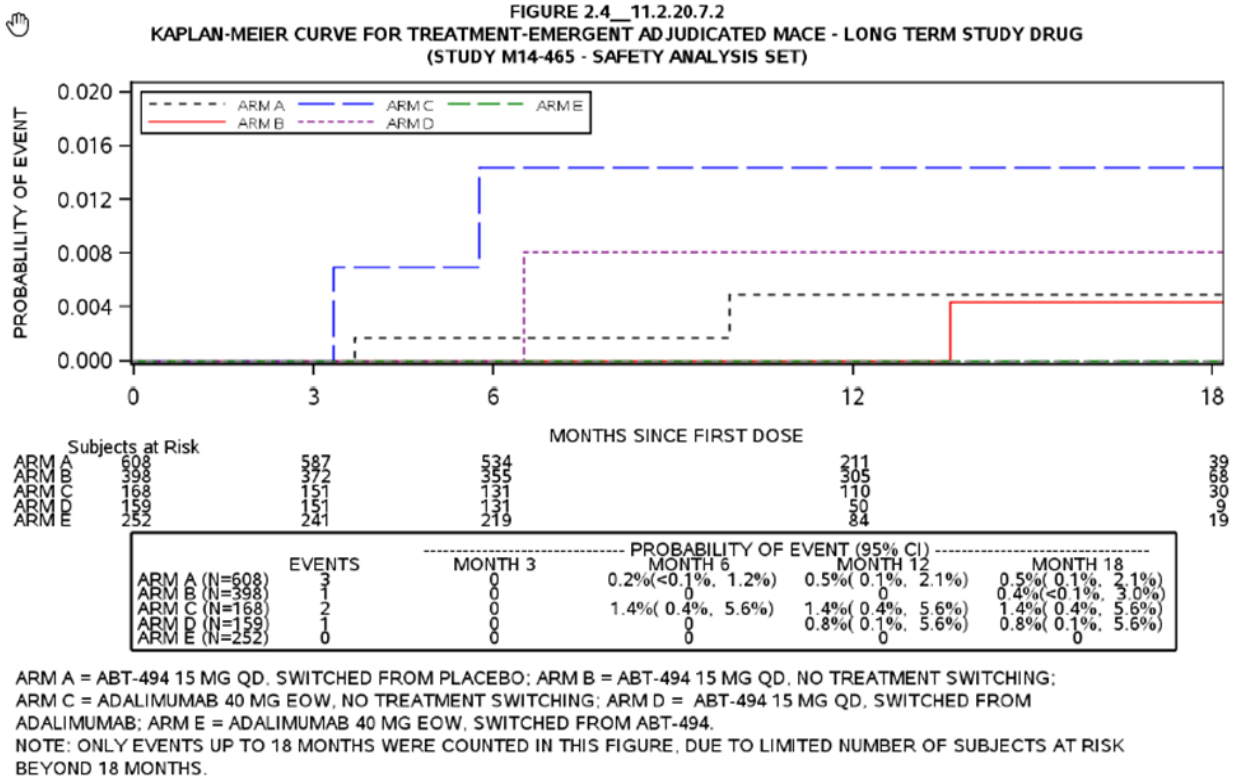


Figure 30.

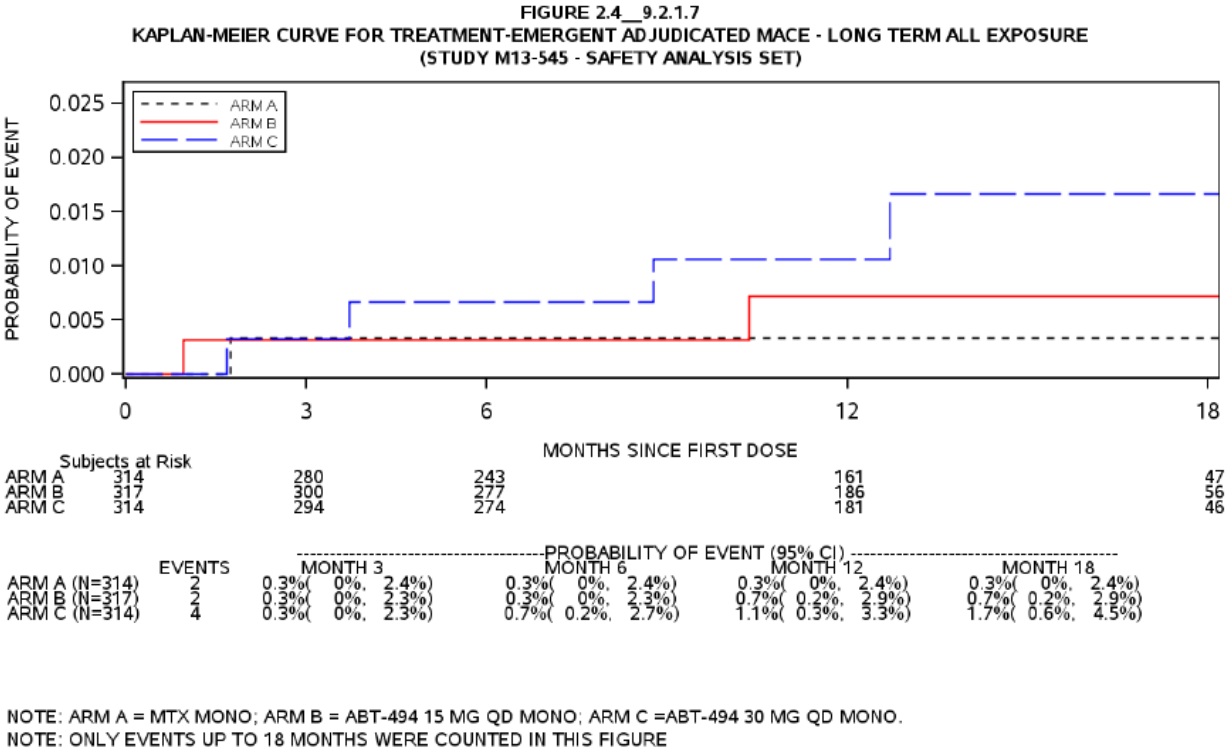


Figure 28. Kaplan-Meier curve for MACE in study M13-545.

Arm A: MTX, arm B: UPA 15 mg monotherapy, arm C: UPA 30 mg monotherapy.

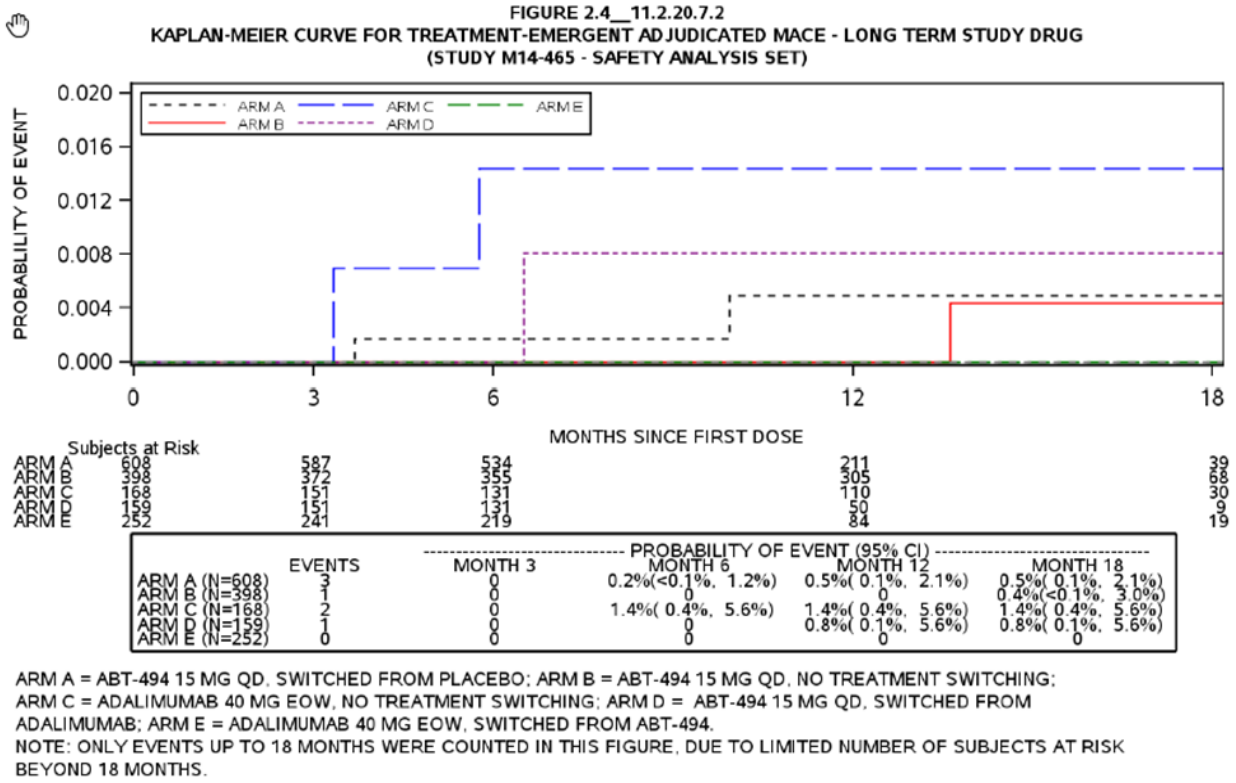


Figure 29. Kaplan-Meier curve for MACE in study M14-465.

Arm A: UPA 15 mg, switched from placebo, arm B: UPA 15 mg without switch, arm C: adalimumab without switch, arm D: UPA 15 mg switched from adalimumab, arm E: adalimumab switched from UPA. All subjects received background MTX.

A breakdown of all treatment-emergent MACE reported in the global Phase 2 and Phase 3 clinical RA trials by dose received at the time of the MACE is provided in Table 61.

Table 60. Number of Subjects with Treatment-Emergent Adjudicated MACE (Global Phase 2 and Phase 3 Studies)

Event Category Adjudicated Term	PBO (N = 1042)	ADA (N = 579)	MTX (N = 314)	UPA 6 mg BID/ 15 mg QD (N = 3143)	UPA 12 mg BID/ 30 mg QD (N = 1452)	Any UPA (N = 4443)
MACE	3	2	2	21	17	38
CV death	1	1	1	7	6	13
Non-fatal MI	2	0	0	9	7	16
Non-fatal stroke	0	1	1	6	4	10

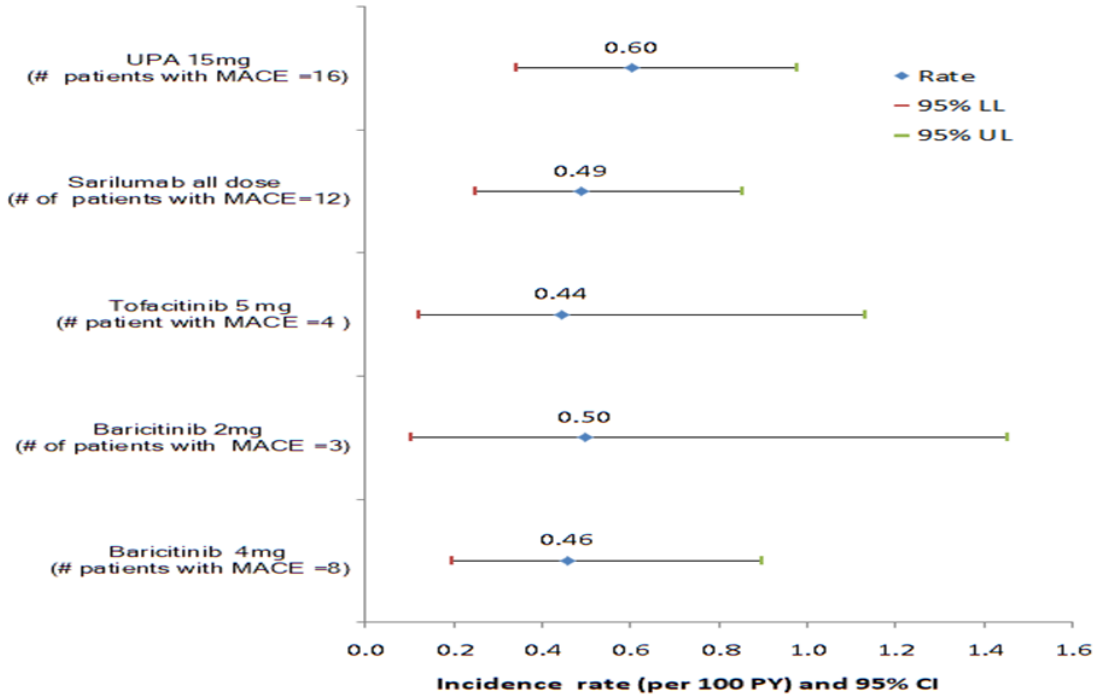
Notes: MACE events from Study M14-663 and from the placebo group in the Phase 2 studies are not included in this table.
Events are presented by treatment at the time of the event.

Of the 38 subjects (23 female and 15 male) on upadacitinib who experienced treatment-emergent MACE, the age range of the subjects was 42 to 83 years and 63% of them aged 60 years or older at study entry. Time to event onset ranged from 16 to 1181 days on upadacitinib therapy. All subjects had at least 1 CV risk factor in addition to the underlying RA.

Thirteen of the 38 subjects on upadacitinib (7 in the upadacitinib 6 mg BID/15 mg QD group and 6 in the upadacitinib 12 mg BID/30 QD mg group) experienced CV death. Eleven of the 13 deaths occurred during the study period (treatment-emergent); 2 subjects experienced treatment-emergent MACE and died after the study as a consequence to the previous MACE event.

Of the 13 subjects in the upadacitinib groups who died of MACE, 9 were aged ≥ 60 years and the other 4 subjects aged 54 years or older. Multiple CV risk factors were present in all 13 subjects, including a history of hypertension, hyperlipidemia, diabetes, obesity, smoking, MI, and other CV disorders, in addition to the existing medical condition of RA.

The incidence rate for MACE for upadacitinib compared to other agent is provided in Figure 31.



Note: EAIRs with long-term treatment in RA clinical trials that reported MACE are presented above. The upadacitinib 15 mg QD EAIR is the treatment-emergent incidence rate from the Any Ph 3 UPA 15 mg analysis set. Tofacitinib 5 mg data were based on all Phase 3 pooled 12 months exposure-adjusted data (cumulative long-term data was not available). Although there may be considerable variation in the demographics and other characteristics of the trial populations, the data shown serve as a benchmark for the rates in trials of moderately to severely active RA populations.

Figure 30. Incidence Rates of MACE in RA Phase 3 Clinical Programs (Long-Term Exposure-Adjusted)

At the CHMP's request, the applicant presented updated comparative MACE data with cut-off date Nov 2018 (Table 62).

Table 61 Treatment-emergent adjudicated MACE EAIR per 100 PY – Long-term all Exposure (Global Ph3 safety analysis)

	CSS				SUR			
	MTX[a] (N = 314) n/PY (n/100 PY)	ADA 40 mg EOW (N = 579) n/PY (n/100 PY)	UPA 15 mg QD (N = 2630) n/PY (n/100 PY)	UPA 30 mg QD (N = 1204) n/PY (n/100 PY)	MTX[a] (N = 314) n/PY (n/100 PY)	ADA 40 mg EOW (N = 579) n/PY (n/100 PY)	UPA 15 mg QD (N = 2630) n/PY (n/100 PY)	UPA 30 mg QD (N = 1203) n/PY (n/100 PY)
Any adjudicated MACE[b]	2/314.0 (0.6)	2/467.8 (0.4)	16/2651.0 (0.6)	13/1361.5 (1.0)	2/362.3 (0.6)	3/580.4 (0.5)	16/3439.3 (0.5)	15/1778.8 (0.8)

a. Includes Study M13-545 only, which has the long-term MTX exposure.

b. MACE: major adverse cardiovascular events, defined as CV death, non-fatal MI and non-fatal stroke.

Venous thromboembolism (VTE)

Data pooled across the global Phase 3 studies for TEAEs of VTE with short-term and long-term study drug treatment are presented in Table 63 and Table 64, respectively.

Table 62. Treatment-Emergent Adjudicated VTE EAIR Per 100 PY – Controlled Short-Term Period Prior To Treatment Switching (Global Ph 3 Safety Analysis Set)

	PBO (N = 1042) n/PY (n/100 PY)	MTX[a] (N = 530) n/PY (n/100 PY)	ADA 40 mg EOW (N = 327) n/PY (n/100 PY)	UPA 15 mg QD (N = 1569) n/PY (n/100 PY)	UPA 30 mg QD (N = 913) n/PY (n/100 PY)
Any adjudicated VTE	1/256.8 (0.4)	0/121.7	3/85.9 (3.5)	3/385.9 (0.8)	1/211.7 (0.5)

a. Includes both Studies M13-545 and M15-555.

Table 63. Treatment-Emergent Adjudicated VTE EAIR Per 100 PY – Long-Term All Exposure (Global Ph 3 Safety Analysis)

	MTX[a] (N = 314) n/PY (n/100 PY)	ADA 40 mg EOW (N = 579) n/PY (n/100 PY)	UPA 15 mg (N = 2630) n/PY (n/100 PY)	UPA 30 mg (N = 1204) n/PY (n/100 PY)
Any adjudicated VTE	2/314.3 (0.6)	5/467.5 (1.1)	16/2653.0 (0.6)	4/1362.3 (0.3)

a Includes Study M13-545 only which has the long-term MTX exposure.

A breakdown of the treatment-emergent VTE events reported in the global Phase 2 and Phase 3 RA studies by dose at the time of event is provided in Table 65 below for the 30 subjects on upadacitinib and 8 events on a comparator.

Table 64. Treatment-Emergent Adjudicated VTE (Global Phase 2 and 3 RA Studies)

Event Category Adjudicated Term	PBO (N = 1042)	ADA (N = 579)	MTX (N = 314)	UPA 6 mg BID/ 15 mg QD (N = 3143)	UPA 12 mg BID/ 30 mg QD (N = 1452)	Other UPA Dose (N = 315)	UPA Any Dose (N = 4443)
VTE[a]	1	5	2	21	8	1	30
DVT	0	1	1	12	5	0	17
PE	1	4	2	13	4	1	18
DVT/PE	0	0	1	5	2	0	7

a. Includes fatal and nonfatal VTE.

Notes: Subjects with concurrent DVT/PE are also counted under both the DVT and the PE rows.

MACE events from Study M14-663 and from the placebo group in the Phase 2 studies are not included in this table.

There were 2 fatal adjudicated VTEs, both pulmonary embolism:

- One subject in Study M13-542; upadacitinib 15 mg: experienced a PE on Day 436. The subject had a history of obesity, diabetes and hypertension and the PE occurred after prolonged driving.
- One subject in study M13-538; upadacitinib 12 mg BID: had a cardiac arrest on Day 897. The CAC adjudicated this event as a VTE event of PE.

Based on patients with RA having an increased risk for VTE and concerns raised for another JAK inhibitor product, the Applicant proposed that VTE is an important potential risk for upadacitinib.

Vital signs and ECG

In the PBO-controlled UPA 15 analysis set, mean changes in blood pressure were minimal in both groups, and the percentages of subjects meeting criteria for potentially clinically significant increases in systolic blood pressure (≥ 160 mmHg and ≥ 20 mmHg increase) and diastolic blood pressure (≥ 105 mmHg and ≥ 15 mmHg increase) were comparable between the upadacitinib group (3.6%, 0.8%) and the placebo group (2.8%, 0.7%). In the long-term any Ph 3 UPA 15 analysis set, the percentage of subjects with potentially clinically significant increases was 5.4% for systolic blood pressure and 1.6% for diastolic blood pressure. The percentages of subjects who experienced potentially clinically significant increases in systolic and diastolic blood pressure were similar between the upadacitinib 15 mg and other comparators (MTX, adalimumab) across the various analysis data sets for both short-term treatment and long-term exposure.

Based on an analysis of Phase 1 ECG data presented by the Applicant, the CHMP agreed in Scientific Advice that a thorough QT study would not be warranted; however the Applicant was advised to collect ECG safety data in the phase 3 development program. During the Phase 3 studies, ECG's were performed at 48 week intervals and as clinically indicated.

Overall, there were 34 adverse events captured with the broad Torsade de pointes/QT prolongation MedDRA SMQ. Of these, the majority of terms were "loss of consciousness" (4 events) and "syncope" (17 events). There were 4 nonserious events of "electrocardiogram QT prolonged" reported in 2 subjects (1 in the upadacitinib 15 mg group and 1 in the upadacitinib 30 mg group). At baseline, ECG was reported as abnormal but there was no description of QTc prolongation in the 2 subjects. None of the events resulted in study drug discontinuation and no QT prolongation was reported in subsequent ECG measurements. In addition, the SMQ captured 3 reports of "cardiac arrest", 2 reports of "ventricular tachycardia", 1 event each of "cardiac death" and "sudden cardiac death", and 2 events of "sudden cardiac death".

A total of 5 subjects were recorded with ECG QTcF prolongation in eCRFs based on the criteria (QT/QTc ≥ 450 msec for female and ≥ 430 msec for male). All subjects had QTcF interval < 500 msec recorded during the course of study.

Serious adverse event/deaths/other significant events

Deaths

Deaths in the respective phase 3 studies

Deaths in study M13-545 up to week 24 are shown in Table 66.

Table 65. Overview of Treatment-Emergent Adverse Events (EAER per 100 PY) – Up to Week 24 in Period 1 in study M13-545 (Safety Analysis Set)

	MTX (N = 314) (PYS = 131.6) Events (E/100PY)		Upadacitinib 15 mg QD (N = 317) (PYS = 139.4) Events (E/100PY)		Upadacitinib 30 mg QD (N = 314) (PYS = 136.9) Events (E/100PY)		Difference (95% CI)[c]	
							15 mg QD - MTX	30 mg QD - MTX
Any AE	532	(404.3)	596	(427.5)	642	(469.0)	23.3 (–25.3, 71.9)	64.7 (14.7,114.7)
Any SAE	18	(13.7)	19	(13.6)	28	(20.5)	–0.0 (–8.9, 8.8)	6.8 (–3.1, 16.6)
Any AE leading to discontinuation of study drug	18	(13.7)	19	(13.6)	20	(14.6)	–0.0 (–8.9, 8.8)	0.9 (–8.1, 9.9)
Any severe AE	28	(21.3)	14	(10.0)	35	(25.6)	–11.2 (–20.7, –1.8)	4.3 (–7.3, 15.9)
Any AE with reasonable possibility of being related to study drug[a]	237	(180.1)	275	(197.3)	293	(214.0)	17.2 (–15.5, 49.9)	33.9 (0.4, 67.5)
Any AE leading to death	1	(0.8)	4	(2.9)	4	(2.9)	2.1 (–1.1, 5.3)	2.2 (–1.1, 5.4)
Deaths[b]	1	(0.8)	2	(1.4)	3	(2.2)	0.7 (–1.8, 3.2)	1.4 (–1.5, 4.3)

E/100py = events per 100 PYs

a. As assessed by investigator.

b. Includes non treatment-emergent deaths.

c. The point estimate and 95% CI were using Poisson assumption and normal approximation.

Note: A TEAE was defined as any AE with an onset date on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date in Period 1 or up to 30 days after the last dose of study drug, if subject discontinued study drug prematurely before Week 24 dosing in Period 1 of the study. Events with unknown or life threatening toxicity grade was counted as severe. Events with unknown relationship to study drug was counted as having a reasonable possibility of being study drug-related.

In study M13-549, there were no deaths up to week 12.

Deaths in study M14-465, up to week 26, are shown in the table below.

Table 66. Overview of Treatment-Emergent Adverse Events (EAER per 100 PY) in study M14-465 – Up to Week 26 Censored at Treatment Switching in Period 1 (Safety Analysis Set)

	Placebo (N = 652) (PY = 250.3) E (E/100PY)	Adalimumab 40 mg EOW (N = 327) (PY = 137.6) E (E/100PY)	Upadacitinib 15 mg QD (N = 650) (PY = 289.6) E (E/100PY)	Between Group Difference Upadacitinib vs Control (Point Estimate [95% CI])[a]	
				Upadacitinib – Placebo	Upadacitinib – Adalimumab
Any AE	839 (335.2)	531 (385.9)	1123 (387.8)	52.6 (20.5, 84.7)	1.9 (–38.0, 41.8)
Any SAE	24 (9.6)	26 (18.9)	34 (11.7)	2.2 (–3.4, 7.7)	–7.2 (–15.4, 1.1)
Any AE leading to discontinuation of study drug	30 (12.0)	27 (19.6)	37 (12.8)	0.8 (–5.2, 6.7)	–6.8 (–15.3, 1.6)
Any severe AE[b]	39 (15.6)	29 (21.1)	40 (13.8)	–1.8 (–8.3, 4.7)	–7.3 (–16.0, 1.5)
Any AE with reasonable possibility of being related to study drug[c]	231 (92.3)	184 (133.7)	415 (143.3)	51.0 (32.8, 69.2)	9.6 (–14.2, 33.3)
Any AE leading to death	2 (0.8)	2 (1.5)	0	–0.8 (–1.9, 0.3)	–1.5 (–3.5, 0.6)
Deaths[d]	2 (0.8)	2 (1.5)	0	–0.8 (–1.9, 0.3)	–1.5 (–3.5, 0.6)

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

b. Severe AEs were defined as events with Grade 3 or above based on the Rheumatology CTC for AEs.

c. As assessed by investigator.

d. Any death including non-treatment-emergent deaths.

Note: A TEAE was defined as any AE with an onset date on or after the first dose of study drug in Period 1 and prior to the Week 26 dose date or up to 30 days after the last dose of placebo or upadacitinib, and 70 days for adalimumab, if subjects discontinued study drug prematurely before Week 26 dosing in the study.

Note: For subjects who were rescued to a different study drug prior to Week 26, data were censored at the time of treatment switching; i.e., events that occurred on or after the first dose of rescue study drug were excluded.

Through the data cut-off date for Study M14-465 (48 weeks and beyond), the EAER of death (including both treatment-emergent and nontreatment-emergent) in the upadacitinib 15 mg and adalimumab groups was 0.4 E/100 PY and 0.9 E/100 PY, respectively (Table 68). Among the subjects receiving upadacitinib 15 mg and adalimumab with no treatment switching during the study, the EAER of death was 0.9 E/100 PY and 1.1 E/100 PY, respectively (Table 69). The EAER of deaths while receiving upadacitinib 15 mg after switching from placebo and adalimumab was 0 E/100 PY and 0.7 E/100 PY, respectively.

Table 67. Death EAER Per 100 PY – All Study Drug Exposure (Study M14-465 Safety Analysis Set)

	Any ADA 40 mg EOW (N = 579) (PY = 467.8) E (E/100 PY)		Any UPA 15 mg QD (N = 1417) (PY = 1243.3) E (E/100 PY)		UPA vs Control (95% CI) UPA – ADA
Deaths[a]	4	(0.9)	5	(0.4)	−0.5 (−1.4, 0.5)

a. Includes nontreatment-emergent deaths.

Table 68. TEAEs by switching groups in study M14-465, 48-week data

	ABT-494 15 MG, SWITCHED FROM PLACEBO (N=608) (PYS=540.1) EVENTS (E/100PYS)		ABT-494 15 MG, NO TREATMENT SWITCHING (N=398) (PYS=465.3) EVENTS (E/100PYS)		ADALIMUMAB, NO TREATMENT SWITCHING (N=168) (PYS=181.8) EVENTS (E/100PYS)		ABT-494 15 MG, SWITCHED FROM ADALIMUMAB (N=159) (PYS=135.9) EVENTS (E/100PYS)		ADALIMUMAB, SWITCHED FROM ABT-494 15 MG (N=252) (PYS=222.6) EVENTS (E/100PYS)	
ANY ADVERSE EVENT (AE)	1276	(236.3)	1285	(276.2)	529	(291.0)	310	(228.1)	645	(289.8)
ANY SERIOUS AE (SAE)	65	(12.0)	53	(11.4)	38	(20.9)	32	(23.5)	32	(14.4)
ANY AE LEADING TO DISCONTINUATION OF STUDY DRUG	30	(5.6)	49	(10.5)	30	(16.5)	12	(8.8)	22	(9.9)
ANY SEVERE AE	82	(15.2)	62	(13.3)	35	(19.3)	28	(20.6)	28	(12.6)
ANY AE WITH REASONABLE POSSIBILITY OF BEING RELATED TO STUDY DRUG$	426	(78.9)	482	(103.6)	151	(83.1)	111	(81.7)	217	(97.5)
ANY AE LEADING TO DEATH	1	(0.2)	6	(1.3)	2	(1.1)	1	(0.7)	2	(0.9)
DEATHS#	0		4	(0.9)	2	(1.1)	1	(0.7)	2	(0.9)

ABT-494 15 MG = ABT-494 15 MG QD; ADALIMUMAB = ADALIMUMAB 40 MG EOW.
NOTE: TREATMENT-EMERGENT ADVERSE EVENT IS DEFINED AS ANY ADVERSE EVENT WITH AN ONSET DATE ON OR AFTER THE FIRST DOSE OF STUDY DRUG AND UP TO 30 DAYS AFTER THE LAST DOSE OF PLACEBO OR ABT-494 AND 70 DAYS FOR ADALIMUMAB, IF SUBJECTS DISCONTINUED PREMATURELY FROM THE STUDY.
SEVERE ADVERSE EVENTS ARE DEFINED AS EVENTS WITH GRADE 3 OR ABOVE BASED ON THE RHEUMATOLOGY COMMON TOXICITY CRITERIA FOR ADVERSE EVENTS. E/100PYS = EVENTS PER 100 PATIENT-YEARS.
$ AS ASSESSED BY INVESTIGATOR.
# INCLUDES NON TREATMENT-EMERGENT DEATHS.
[A]: THE POINT ESTIMATE AND 95% CI ARE USING POISSON ASSUMPTION AND NORMAL APPROXIMATION.

At the CHMP request, the applicant presented updated safety data (cut-off date November 2018) as presented below.

Table 69. Overview of treatment-emergent adverse events per 100 patient-years (PYs) - long term study drug (study M14-465 - safety analysis set)

	ABT-494 15 MG, SWITCHED FROM PLACEBO (N=608) (PYS=728.1) EVENTS (E/100PYS)		ABT-494 15 MG, NO TREATMENT SWITCHING (N=398) (PYS=582.5) EVENTS (E/100PYS)		ADALIMUMAB, NO TREATMENT SWITCHING (N=168) (PYS=226.0) EVENTS (E/100PYS)		ABT-494 15 MG, SWITCHED FROM ADALIMUMAB (N=159) (PYS=183.2) EVENTS (E/100PYS)		ADALIMUMAB, SWITCHED FROM ABT-494 15 MG (N=252) (PYS=291.2) EVENTS (E/100PYS)	
ANY ADVERSE EVENT (AE)	1587	(218.0)	1460	(250.6)	591	(261.5)	372	(203.1)	757	(260.0)
ANY SERIOUS AE (SAE)	82	(11.3)	60	(10.3)	45	(19.9)	37	(20.2)	44	(15.1)
ANY AE LEADING TO DISCONTINUATION OF STUDY DRUG	39	(5.4)	51	(8.8)	38	(16.8)	12	(6.6)	22	(7.6)
ANY SEVERE AE	99	(13.6)	71	(12.2)	39	(17.3)	32	(17.5)	34	(11.7)
ANY AE WITH REASONABLE POSSIBILITY OF BEING RELATED TO STUDY DRUG$	525	(72.1)	534	(91.7)	161	(71.2)	125	(68.2)	253	(86.9)
ANY AE LEADING TO DEATH	5	(0.7)	7	(1.2)	6	(2.7)	1	(0.5)	2	(0.7)
DEATHS#	3	(0.4)	5	(0.9)	3	(1.3)	1	(0.5)	2	(0.7)

Table 70. Overview of TEAEs EAERs Per 100 PY – All Study Drug Exposure (Study M14-465 Safety Analysis Set)

	CSS		SUR	
	Any ADA 40 mg Every Other Week (EOW) (N = 579) (PY = 467.8) E (E/100 PY)	**Any UPA 15 mg QD (N = 1417) (PY = 1243.3) E (E/100 PY)**	**Any ADA 40 mg EOW (N = 579) (PY = 580.7) E (E/100 PY)**	**Any UPA 15 mg QD (N = 1417) (PY = 1595.7) E (E/100 PY)**
Any AE	1379 (294.8)	3312 (266.4)	1554 (267.6)	3859 (241.8)
Any SAE	73 (15.6)	161 (12.9)	92 (15.8)	190 (11.9)
Any AE leading to discontinuation of study drug	52 (11.1)	92 (7.4)	60 (10.3)	103 (6.5)
Any severe AE	69 (14.7)	189 (15.2)	79 (13.6)	219 (13.7)
Any AE with reasonable possibility of being related to study drug	448 (95.8)	1169 (94.0)	495 (85.2)	1332 (83.5)
Any AE leading to death	4 (0.9)	8 (0.6)	8 (1.4)	13 (0.8)
Deaths[a]	4 (0.9)	5 (0.4)	5 (0.9)	9 (0.6)

a. Includes nontreatment-emergent deaths. In total, there was 1 nontreatment-emergent death on ADA and no nontreatment-emergent death on UPA 15 mg in the CSS, and 2 nontreatment-emergent deaths on ADA and 1 nontreatment-emergent death on UPA 15 mg cumulatively through the data cutoff for this SUR.

CSS: Clinical Summary of Safety. SUR: Safety Update Report.

In study M15-555 up week 14, there was one case of death in the upadacitinib 15 mg group (0.5%) vs no case in the MTX group.

In study M13-542, there was one death among upadacitinib 15 mg-treated subjects up to week 24 (IR1.1), compared to 0 cases in the placebo group.

Pooled data

Across the global Phase 2 and Phase 3 RA studies, a total of 40 deaths (31 treatment-emergent and 9 non treatment-emergent deaths) have been reported across all groups.

- 33 deaths (25 of which were treatment-emergent) in the upadacitinib groups
    - 14 deaths (11 treatment-emergent and 3 nontreatment-emergent) in subjects receiving upadacitinib 15 mg
    - 14 deaths (11 treatment-emergent and 3 nontreatment-emergent) in subjects receiving upadacitinib 30 mg
    - 4 deaths (2 treatment-emergent and 2 nontreatment-emergent) in subjects receiving upadacitinib 6 mg BID
    - 1 treatment-emergent death in subjects receiving upadacitinib 12 mg BID
- 4 deaths in the adalimumab group (3 treatment-emergent and 1 nontreatment-emergent)
- 2 treatment-emergent deaths in the placebo group
- 1 treatment-emergent death in the MTX group

All deaths among upadacitinib 15 mg-treated subjects (treatment-emergent and non treatment-emergent) are summarised below.

Table 71. Treatment-emergent and non-treatment-emergent deaths among upadacitinib 15 mg-treated subjects

Study Number Subject Number Age/Sex Race	Treatment at Event Occurrence	Onset Day[a]/ Days Since Last Dose	Treatment Sequence	Days Since First Dose on Study	Cause of Death Preferred Term (Adjudicated Term)	Comments
UPA 6 mg BID/15 mg QD						
M13-538 2604 69/F/White	UPA 6 mg BID	932/18	UPA 18 mg/ UPA 6 mg BID	932	Acute respiratory distress syndrome (Non cardiovascular death)	Subject presented with hypotension, dyspnea, cough, chest pain. Diagnosed with acute respiratory distress syndrome (ARDS). Study drug was discontinued, and subject died post-treatment Day 18. No further information was reported. Risk factors: Ischemic cardiomyopathy, stents, infarction, pulmonary fibrosis, smoker (51 years, 1 pack/day).
M13-538 5203 69/M/White	UPA 6 mg BID	189/1	UPA 18 mg/ UPA 6 mg BID	189	Death	Site tried to contact subject, however was unsuccessful. Neighbor reported that the subject had died (Day 189). Cause of death was unknown, no further information was available. Risk factors: Hypertension, diabetes, abdominal aortic aneurysm.
M13-542 543509 55/F/White	UPA 15 mg QD	436/8	UPA 15 mg QD	436	Pulmonary embolism (Cardiovascular death - death due to other cardiovascular causes)	Subject developed DVT of lower extremities and PE associated with prolonged sitting while driving. Risk factors: Obesity, diabetes, hypertension, hyperlipidemia.
M13-542 560507 (CSR narrative) 80/F/Black or African American	UPA 15 mg QD	163/1	UPA 15 mg QD	163	Cardiac arrest (Undetermined/unk cause of death)	Subject died at home; death was not witnessed by anyone. Risk Factors: Hypertension, diabetes, hyperlipidemia.
M13-545 582303 (CSR narrative) 67/M/White	UPA 15 mg QD	315/1	UPA 15 mg QD	315	Myocardial infarction (Cardiovascular death - sudden cardiac death)	Subject died at home after experiencing an MI. No autopsy or death certificate was reported. Risk factors: Hypertension, diabetes, hyperlipidemia, first-degree atrioventricular block.
M13-545 808337 37/F/White	UPA 15 mg QD	183	UPA 15 mg QD	183	Death (Non cardiovascular death) Hepatic enzyme increased (Non cardiovascular death)	Subject had experienced bronchitis 10 days earlier and was treated with amoxicillin/clavulanate. On Day 183, she had come for a scheduled site visit and was seen by the investigator who reported no signs or symptoms of liver disease. On her way home subject felt unwell with shortness of breath and visited a rural health clinic, where physical exam was unremarkable and subject was sent home. She died in the car on her way home. No autopsy was performed. Central labs obtained at the site visit showed severe transaminase elevations. Cause of death was reported as unknown. No relevant risk factors reported.
M14-465 168102 60/F/White	UPA 15 mg QD	238/1	UPA 15 mg QD	238	Arteriosclerosis coronary artery (Undetermined/unk cause of death) Hypertensive heart disease (Undetermined/unk cause of death) Myocardial infarction (Undetermined/unk cause of death)	Subject experienced an MI and died. No autopsy was performed. Risk factors: Obesity, insulin resistance, ex-smoker.
M14-465 264106 79/F/White	UPA 15 mg QD	419/8	UPA 15 mg QD	419	Cardiac failure (Non cardiovascular death)	Subject experienced a worsening of hypertension followed by cardiac failure. Subject died with cause of death reported as cardiac failure. Risk factors: Hypertension, ischemic heart disease.
M14-465 315125 77/M/White	UPA 15 mg QD	414/1	UPA 15 mg QD	414	Sudden death (Cardiovascular death - sudden cardiac death)	The subject experienced sudden severe abdominal pain and died suddenly at home. No autopsy was performed. Risk factors: Hypertension, ex-smoker.
M14-465 524103 60/M/White	UPA 15 mg QD	314	ADA 40 mg EOW/UPA 15 mg QD	496	Death (Undetermined/unk cause of death)	Subject was found dead at home. No autopsy was performed. Risk factors: Asthma, obesity, ex-smoker.
M14-465 549111 66/M/Black or African American	UPA 15 mg QD	195/15	UPA 15 mg QD	195	Death (Undetermined/unk cause of death)	The subject died at home. No autopsy was performed and no further details provided by the family regarding the subject's death. Risk factors: Hypertension, coronary artery disease, atherosclerosis, current smoker.
M15-555 172401 (CSR narrative) 68/F/White	UPA 15 mg QD	39	UPA 15 mg QD	39	Haemorrhagic stroke (Cardiovascular death - fatal stroke)	Subject experienced headache, vomiting and hypertensive crisis and subsequent coma. A brain scan revealed an extensive hemorrhagic lesion secondary to a ruptured aneurysm. Risk factors: Hypertension, obesity, ex-smoker.
M15-555 387404 66/F/White	UPA 15 mg QD	81	MTX/UPA 15 mg QD	179	Sudden cardiac death (Cardiovascular death - sudden cardiac death)	Subject was found dead in bed by relatives, no autopsy report or death certificate were reported. Risk factors: Hypertension, hypercholesterolemia, MI (2005).

M13-537 27601 79/M/White	UPA 6 mg BID	196/112	UPA 6 mg BID	196	Lung adenocarcinoma Stage II	Subject died 3 months after completing Study M13-537. Risk factors: 40 year smoking history, Age > 65 years, family history of lung cancer.
M13-538 27802 74/M/White	UPA 6 mg BID	513/177	UPA 12 mg/ UPA 6 mg BID	513	Hodgkin's disease (Non cardiovascular death)	Subject presented with complaints of fever (6 days), dehydration, night sweats and shortness of breath. He was hospitalized and diagnostic workup including a lymph node biopsy confirmed the diagnosis of Hodgkin's disease. He died approximately 6 months post-treatment. Risk factors: Age ≥ 65 years, ex-smoker (40 years, 1 pack/day), and chronic RA.
M13-545 267301 66/M/White	UPA 15 mg QD	142/31	UPA 15 mg QD	142	Malignant neoplasm progression (Non cardiovascular death) Metastatic malignant melanoma (Non cardiovascular death)	Subject presented with fatigue, abdominal pain and distension, and elevated liver enzymes. He was diagnosed with multiple metastases with a primary cancer of melanoma. Per autopsy report there were extensive metastases to liver, lung, heart and lymph nodes. Risk factors: Age ≥ 65 years, white, melanoma removal from left upper arm (1993).
M13-545 348301 (CSR narrative) 69/M/White	UPA 15 mg QD	112/84	UPA 15 mg QD	112	Hypoxic-ischaemic encephalopathy (Cardiovascular death - death due to other cardiovascular causes) Myocardial infarction (Cardiovascular death - death due to other cardiovascular causes)	Subject experienced an MI with cardiac arrest of indeterminate time requiring resuscitation with subsequent hypoxic-ischemic encephalopathy. He underwent cardiac catheterization and was placed in hypothermia and deep sedation. He died 84 days post-treatment. Risk factor: Current smoker (30 years, 1 pack/day).
M15-555 599401 55/M/Black or African American	UPA 15 mg QD	487/167	MTX/ UPA 15 mg QD	585	Congestive cardiomyopathy (Cardiovascular death - sudden cardiac death)	Subject had 2 episodes of mild chest pain and an abnormal ECG and was diagnosed with dilated cardiomyopathy. Study drug was discontinued and he died on post-treatment Day 167. Risk factors: Hypertension, diabetes, hyperlipidemia, ex-smoker (20 years, 1 pack/day).

Study Number Subject Number Age/Sex Race	Treatment at Event Occurrence	Onset Day*/ Days Since Last Dose	Treatment Sequence	Days Since First Dose on Study	Cause of Death Preferred Term (Adjudicated Term)	Comments
UPA 6 mg BID/15 mg QD						
M13-538	UPA 6 mg BID	932/18	UPA 18 mg/ UPA 6 mg BID	932	Acute respiratory distress syndrome (Non cardiovascular death)	Subject presented with hypotension, dyspnea, cough, chest pain. Diagnosed with acute respiratory distress syndrome (ARDS). Study drug was discontinued, and subject died post-treatment Day 18. No further information was reported. Risk factors: Ischemic cardiomyopathy, stents, infarction, pulmonary fibrosis, smoker (51 years, 1 pack/day).
M13-538	UPA 6 mg BID	189/1	UPA 18 mg/ UPA 6 mg BID	189	Death	Site tried to contact subject, however was unsuccessful. Neighbor reported that the subject had died (Day 189). Cause of death was unknown, no further information was available. Risk factors: Hypertension, diabetes, abdominal aortic aneurysm.
M13-542	UPA 15 mg QD	436/8	UPA 15 mg QD	436	Pulmonary embolism (Cardiovascular death - death due to other cardiovascular causes)	Subject developed DVT of lower extremities and PE associated with prolonged sitting while driving. Risk factors: Obesity, diabetes, hypertension, hyperlipidemia.
M13-542	UPA 15 mg QD	163/1	UPA 15 mg QD	163	Cardiac arrest (Undetermined/unk cause of death)	Subject died at home; death was not witnessed by anyone. Risk Factors: Hypertension, diabetes, hyperlipidemia.
M13-545	UPA 15 mg QD	315/1	UPA 15 mg QD	315	Myocardial infarction (Cardiovascular death - sudden cardiac death)	Subject died at home after experiencing an MI. No autopsy or death certificate was reported. Risk factors: Hypertension, diabetes, hyperlipidemia, first-degree atrioventricular block.
M13-545	UPA 15 mg QD	183	UPA 15 mg QD	183	Death (Non cardiovascular death) Hepatic enzyme increased (Non cardiovascular death)	Subject had experienced bronchitis 10 days earlier and was treated with amoxicillin/clavulanate. On Day 183, she had come for a scheduled site visit and was seen by the investigator who reported no signs or symptoms of liver disease. On her way home subject felt unwell with shortness of breath and visited a rural health clinic, where physical exam was unremarkable and subject was sent home. She died in the car on her way home. No autopsy was performed. Central labs obtained at the site visit showed severe transaminase elevations. Cause of death was reported as unknown. No relevant risk factors reported.
M14-465	UPA 15 mg QD	238/1	UPA 15 mg QD	238	Arteriosclerosis coronary artery (Undetermined/unk cause of death) Hypertensive heart disease (Undetermined/unk cause of death) Myocardial infarction (Undetermined/unk cause of death)	Subject experienced an MI and died. No autopsy was performed. Risk factors: Obesity, insulin resistance, ex-smoker.
M14-465	UPA 15 mg QD	419/8	UPA 15 mg QD	419	Cardiac failure (Non cardiovascular death)	Subject experienced a worsening of hypertension followed by cardiac failure. Subject died with cause of death reported as cardiac failure. Risk factors: Hypertension, ischemic heart disease.
M14-465	UPA 15 mg QD	414/1	UPA 15 mg QD	414	Sudden death (Cardiovascular death - sudden cardiac death)	The subject experienced sudden severe abdominal pain and died suddenly at home. No autopsy was performed. Risk factors: Hypertension, ex-smoker.
M14-465	UPA 15 mg QD	314	ADA 40 mg EOW/UPA 15 mg QD	496	Death (Undetermined/unk cause of death)	Subject was found dead at home. No autopsy was performed. Risk factors: Asthma, obesity, ex-smoker.
M14-465	UPA 15 mg QD	195/15	UPA 15 mg QD	195	Death (Undetermined/unk cause of death)	The subject died at home. No autopsy was performed and no further details provided by the family regarding the subject's death. Risk factors: Hypertension, coronary artery disease, atherosclerosis, current smoker.
M15-555	UPA 15 mg QD	39	UPA 15 mg QD	39	Haemorrhagic stroke (Cardiovascular death - fatal stroke)	Subject experienced headache, vomiting and hypertensive crisis and subsequent coma. A brain scan revealed an extensive hemorrhagic lesion secondary to a ruptured aneurysm. Risk factors: Hypertension, obesity, ex-smoker.
M15-555	UPA 15 mg QD	81	MTX/UPA 15 mg QD	179	Sudden cardiac death (Cardiovascular death - sudden cardiac death)	Subject was found dead in bed by relatives, no autopsy report or death certificate were reported. Risk factors: Hypertension, hypercholesterolemia, MI (2005).

M13-537	UPA 6 mg BID	196/112	UPA 6 mg BID	196	Lung adenocarcinoma Stage II	Subject died 3 months after completing Study M13-537. Risk factors: 40 year smoking history, Age > 65 years, family history of lung cancer.
M13-538	UPA 6 mg BID	513/177	UPA 12 mg/ UPA 6 mg BID	513	Hodgkin's disease (Non cardiovascular death)	Subject presented with complaints of fever (6 days), dehydration, night sweats and shortness of breath. He was hospitalized and diagnostic workup including a lymph node biopsy confirmed the diagnosis of Hodgkin's disease. He died approximately 6 months post-treatment. Risk factors: Age ≥ 65 years, ex-smoker (40 years, 1 pack/day), and chronic RA.
M13-545	UPA 15 mg QD	142/31	UPA 15 mg QD	142	Malignant neoplasm progression (Non cardiovascular death) Metastatic malignant melanoma (Non cardiovascular death)	Subject presented with fatigue, abdominal pain and distension, and elevated liver enzymes. He was diagnosed with multiple metastases with a primary cancer of melanoma. Per autopsy report there were extensive metastases to liver, lung, heart and lymph nodes. Risk factors: Age ≥ 65 years, white, melanoma removal from left upper arm (1993).
M13-545	UPA 15 mg QD	112/84	UPA 15 mg QD	112	Hypoxic-ischaemic encephalopathy (Cardiovascular death - death due to other cardiovascular causes) Myocardial infarction (Cardiovascular death - death due to other cardiovascular causes)	Subject experienced an MI with cardiac arrest of indeterminate time requiring resuscitation with subsequent hypoxic-ischemic encephalopathy. He underwent cardiac catheterization and was placed in hypothermia and deep sedation. He died 84 days post-treatment. Risk factor: Current smoker (30 years, 1 pack/day).
M15-555	UPA 15 mg QD	487/167	MTX/ UPA 15 mg QD	585	Congestive cardiomyopathy (Cardiovascular death - sudden cardiac death)	Subject had 2 episodes of mild chest pain and an abnormal ECG and was diagnosed with dilated cardiomyopathy. Study drug was discontinued and he died on post-treatment Day 167. Risk factors: Hypertension, diabetes, hyperlipidemia, ex-smoker (20 years, 1 pack/day).

Data pooled across the global Phase 3 studies for deaths (both treatment-emergent and non

M13-537	UPA 6 mg BID	196/112	UPA 6 mg BID	196	Lung adenocarcinoma Stage II	Subject died 3 months after completing Study M13-537. Risk factors: 40 year smoking history, Age > 65 years, family history of lung cancer.
M13-538	UPA 6 mg BID	513/177	UPA 12 mg/ UPA 6 mg BID	513	Hodgkin's disease (Non cardiovascular death)	Subject presented with complaints of fever (6 days), dehydration, night sweats and shortness of breath. He was hospitalized and diagnostic workup including a lymph node biopsy confirmed the diagnosis of Hodgkin's disease. He died approximately 6 months post-treatment. Risk factors: Age ≥ 65 years, ex-smoker (40 years, 1 pack/day), and chronic RA.
M13-545	UPA 15 mg QD	142/31	UPA 15 mg QD	142	Malignant neoplasm progression (Non cardiovascular death) Metastatic malignant melanoma (Non cardiovascular death)	Subject presented with fatigue, abdominal pain and distension, and elevated liver enzymes. He was diagnosed with multiple metastases with a primary cancer of melanoma. Per autopsy report there were extensive metastases to liver, lung, heart and lymph nodes. Risk factors: Age ≥ 65 years, white, melanoma removal from left upper arm (1993).
M13-545	UPA 15 mg QD	112/84	UPA 15 mg QD	112	Hypoxic-ischaemic encephalopathy (Cardiovascular death - death due to other cardiovascular causes) Myocardial infarction (Cardiovascular death - death due to other cardiovascular causes)	Subject experienced an MI with cardiac arrest of indeterminate time requiring resuscitation with subsequent hypoxic-ischemic encephalopathy. He underwent cardiac catheterization and was placed in hypothermia and deep sedation. He died 84 days post-treatment. Risk factor: Current smoker (30 years, 1 pack/day).
M15-555	UPA 15 mg QD	487/167	MTX/ UPA 15 mg QD	585	Congestive cardiomyopathy (Cardiovascular death - sudden cardiac death)	Subject had 2 episodes of mild chest pain and an abnormal ECG and was diagnosed with dilated cardiomyopathy. Study drug was discontinued and he died on post-treatment Day 167. Risk factors: Hypertension, diabetes, hyperlipidemia, ex-smoker (20 years, 1 pack/day).

treatment-emergent) with short-term and long-term study drug treatment are presented in Table 73 and Table 74, respectively.

Table 72. Death EAER Per 100 PY – Controlled Short-Term Period (3 months) Prior To Treatment Switching (Global Ph 3 Safety Analysis Set=M13-545, M13-549, M14-465, M15-555, M13-542))

	PBO (N = 1042) (PY = 256.8) E (E/100 PY)	MTX[a] (N = 530) (PY = 121.7) E (E/100 PY)	ADA 40 mg EOW (N = 327) (PY = 86.0) E (E/100 PY)	UPA 15 mg QD (N = 1569) (PY = 386.1) E (E/100 PY)	UPA 30 mg QD (N = 913) (PY = 211.7) E (E/100 PY)
Deaths[b]	2 (0.8)	1 (0.8)	1 (1.2)	1 (0.3)	4 (1.9)

a. Includes both Studies M13-545 and M15-555.

b. Includes nontreatment-emergent deaths.

Table 73. Death EAER Per 100 PY – Long-Term All Exposure (Global Ph 3 Safety Analysis Set, 48-week data)

	MTX[a] (N = 314) (PY = 314.4) E (E/100 PY)	ADA (N = 579) (PY = 467.8) E (E/100 PY)	UPA 15 mg (N = 2630) (PY = 2925.0) E (E/100 PY)	UPA 30 mg (N = 1204) (PY = 1410.3) E (E/100 PY)
Deaths[b]	1 (0.3)	4 (0.9)	14 (0.5)	14 (1.0)

a Includes Study M13-545 only which has the long-term MTX exposure.

b. Includes nontreatment-emergent deaths.

Updated safety data from the responses to day 120 LoQ (cut-off date Nov 2018) is presented below.

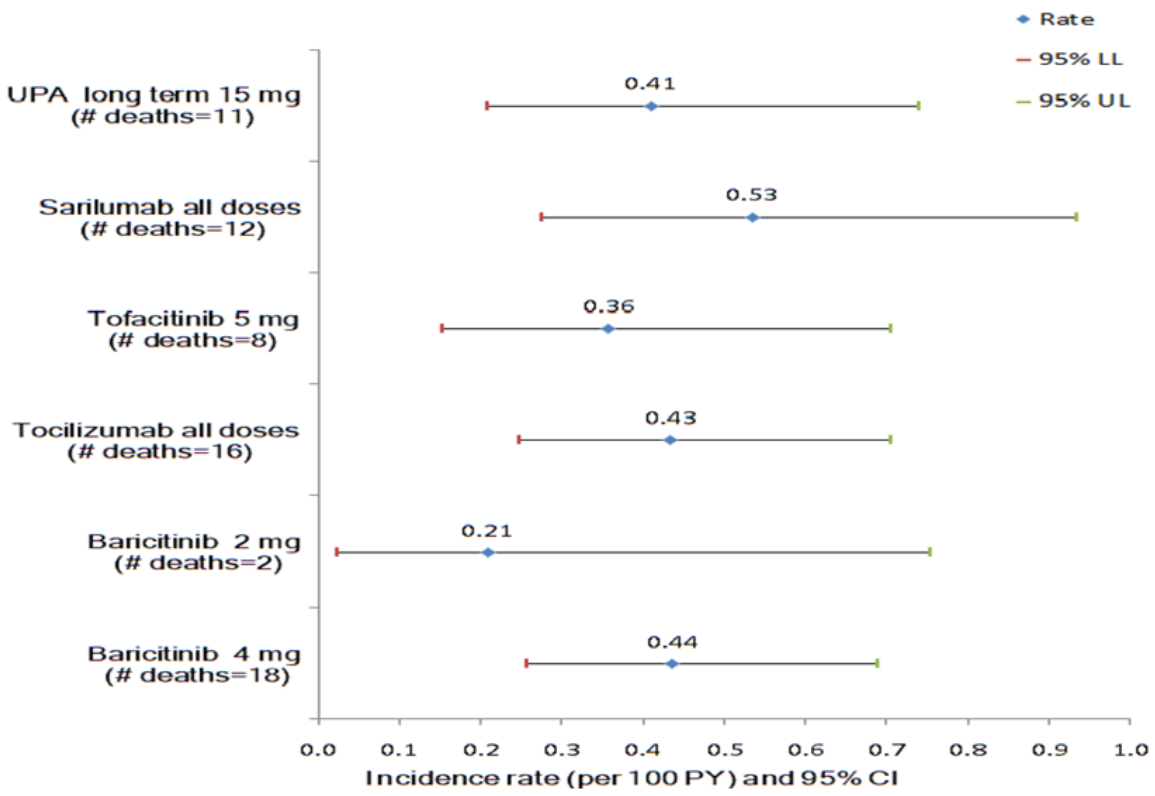
Table 74. Death EAER per 100 PY – Long-term all exposure (across global phase 3 studies)

	CSS				SUR			
	MTX[a] (N = 314) (PY = 314.4) E (E/100 PY)	ADA (N = 579) (PY = 467.8) E (E/100 PY)	UPA 15 mg (N = 2630) (PY = 2925.0) E (E/100 PY)	UPA 30 mg (N = 1204) (PY = 1410.3) E (E/100 PY)	MTX[a] (N = 314) (PY = 362.9) E (E/100 PY)	ADA (N = 579) (PY = 580.7) E (E/100 PY)	UPA 15 mg (N = 2630) (PY = 3737.7) E (E/100 PY)	UPA 30 mg (N = 1203) (PY = 1815.8) E (E/100 PY)
Deaths[b]	1 (0.3)	4 (0.9)	14 (0.5)	14 (1.0)	1 (0.3)	5 (0.9)	20 (0.5)	18 (1.0)

a. Includes Study M13-545 only, which has the long-term MTX exposure.

b. Includes nontreatment-emergent deaths.

The EAERs of treatment-emergent deaths for upadacitinib 15 mg and for clinical development programs of other immunomodulatory therapies for RA, as provided by the applicant based on EPAR data, are shown in Figure 32.



Notes: The upadacitinib 15 mg QD rate is from Any Ph 3 UPA 15 mg analysis set.

For the event of death, the EAER and the EAIR are the same. Incidence rates of death from various RA clinical trials are presented in the above graphics (Tofacitinib 5 mg = Tofacitinib 5 mg BID. Baricitinib 2 mg or 4 mg = Baricitinib 2 mg QD or 4 mg QD). All death rates are based on exposure adjusted long term data. Although there may be considerable variation in the composition of trial population with regard to demographic and other characteristics that may have an impact on incidence rates, this is a benchmark of mortality rates from trials of moderately to severely RA population.

Figure 31. Incidence Rate of Death in RA Clinical Trial Programs (Long-Term Exposure-Adjusted)

Serious adverse events

In the PBO-controlled UPA 15 mg short term analysis set (Studies M13-549, M14-465, M13-542), the percentage of subjects with SAEs was higher in the upadacitinib 15 mg group (3.4%) compared with the placebo group (1.8%). The majority of SAEs were reported in 1 subject each in any group, except for appendicitis, gastroenteritis, viral infection, and wrist fracture which were each reported in 2 subjects in the upadacitinib 15 mg group; pneumocystis jirovecii pneumonia and gastroenteritis that were reported in 2 subjects and 3 subjects in the placebo group, respectively.

In the integrated PBO-controlled UPA 15 mg and 30 mg short term analysis set (Studies M13-549, M13-542), the percentages of subjects with SAEs were in the upadacitinib 15 mg and 30 mg groups 4.7% and 4.9%, respectively, both of which were higher than the placebo group; 1.3%. The majority of SAEs were reported in 1 subject each in the groups, except for wrist fracture (2 subjects in the 15 mg group) and pneumonia and prostate cancer (each reported in 2 subjects in the upadacitinib 30 mg group).

In the long-term Any Ph 3 UPA 15 and 30 mg analysis set (Studies M13-545, M13-549, M15-555, M13-542), the EAERs of SAEs were 16.9 E/100 PY and 21.3 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 (0.9 E/100 PY and 1.7 E/100 PY, respectively).

Laboratory findings

Lipids

In the upadacitinib development program, approximately 29% of subjects had elevated LDL cholesterol (LDL-C) (≥ 3.36 mmol/L) and 58% had lower HDL cholesterol (HDL-C) (≤ 1.55 mmol/L) at baseline.

In the short-term PBO-controlled UPA 15 analysis set, upadacitinib induced a rapid and persistent increase in lipids; mean increases from baseline to Week 12 were approximately 13% for total cholesterol (TC), HDL-C and LDL-C, and approximately 10% for triglycerides, whereas the levels remained quite stable in the placebo group. Shift analyses for TC demonstrated 10.4% of subjects on upadacitinib 15 mg vs. 2.0% of subjects on placebo shifting from a baseline value of < 5.17 mmol/L (desirable) to a maximum value ≥ 6.21 mmol/L (high); similarly, for LDL-C, 8.5% of subjects on upadacitinib 15 mg and 1.7% of subjects on placebo shifted from a baseline LDL-C value of < 3.36 mmol/L (optimal or near optimal) to a maximum value of ≥ 4.14 mmol/L (high or very high). With all lipids being similarly affected, there was no detrimental net effect on LDL-C/HDL-C ratio.

The elevated levels of HDL-C and LDL-C were persistent on long-term treatment; with all lipids being similarly affected, the TC/HDL-C and LDL-C/HDL-C ratios only increased by less than 5% on long term exposure.

In the PBO-controlled UPA 15/30 analysis set, there was a small incremental increase in lipids from upadacitinib 15 mg to 30 mg. Mean changes in lipid parameters from baseline to Week 12 for placebo, upadacitinib 15 mg and 30 groups were: TC: -0.036, 0.652, 0.765 mmol/L; HDL-C: 0.010, 0.252, 0.233 mmol/L; LDL-C: -0.035, 0.353, 0.444 mmol/L; and triglycerides: -0.020, 0.127, 0.163 mmol/L. Corresponding mean changes from baseline to Week 12 in lipid ratios for placebo, upadacitinib 15 mg and 30 mg groups were: TC/HDL-C: -0.046, -0.078, 0.040; LDL-C/HDL-C: -0.040, -0.078, 0.037. The same overall pattern, i.e. a small incremental effect with upadacitinib 30 mg over 15 mg, prevailed on long term exposure.

An alternative "atherogenic index", the apolipoprotein ApoB/ApoA1 ratio, was also evaluated in Studies M13-549 and M13-542; ApoB is considered an atherogenic indicator and ApoA1 an anti-atherogenic indicator. Compared to placebo, small increases in both ApoB and ApoA1 were seen with both upadacitinib 15 mg and 30 mg. However, the ApoB/ApoA1 ratio slightly decreased from baseline to Week 12 in all groups.

In adalimumab-controlled analyses, the increases in lipids were consistently greater with upadacitinib 15 mg than placebo or adalimumab; from baseline to Week 12, mean lipid changes in the placebo, adalimumab and upadacitinib 15 mg groups were: TC: -0.037, 0.160, 0.666 mmol/L; HDL-C: 0.017, 0.032, 0.187 mmol/L; LDL-C: –0.025, 0.079, 0.400 mmol/L; and triglycerides: -0.061, 0.106, 0.168 mmol/L. At Week 12, the mean ratios of LDL-C/HDL-C were 2.049, 1.986 and 2.043 for placebo, adalimumab and upadacitinib 15 mg, respectively.

Similarly, in MTX-controlled analyses, the increases in lipids were consistently greater with both upadacitinib 15 mg and 30 mg compared to MTX; from baseline to Week 12/14, mean lipid changes for the MTX, upadacitinib 15 mg, and upadacitinib 30 mg groups were: TC: 0.054, 0.729, 0.894 mmol/L; HDL-C: 0.021, 0.264, 0.270 mmol/L; LDL-C: 0.029, 0.403, 0.507 mmol/L; and triglycerides: –0.015, 0.149, 0.268 mmol/L. The LDL-C/HDL-C ratios remained comparable at 2.063, 1.986 and 2.073 for MTX, upadacitinib 15 mg and upadacitinib 30 mg, respectively.

Approximately 11% of subjects in the Any Ph 3 UPA 15 analysis set reported statin use at baseline. According to the Applicant, subjects with statin use showed a trend toward smaller mean increases in TC and LDL-C while having no discernible change in HDL cholesterol. Comparing subjects with statin

use versus without statin use at baseline, the mean changes from baseline to Week 12 for the upadacitinib 15 mg group were: TC: 0.537 vs 0.681 mmol/L; HDL-C: 0.176 vs 0.207 mmol/L; LDL-C: 0.286 vs 0.398 mmol/L.

In addition, during placebo-controlled periods in the Phase 3 studies, 9 subjects initiated statin treatment post-baseline in the upadacitinib 15 mg group and 5 in the placebo group. Although the data are based on a small sample size, after statin treatment there was a trend for reduction in LDL-C returning to its baseline levels.

Safety in special populations

Age

According to the applicant, in all short-term analysis sets, the percentages of subjects with TEAEs, SAEs, severe TEAEs, and AEs leading to discontinuation were generally comparable across age groups. In the long-term analysis sets, subjects ≥ 75 years of age in the upadacitinib 30 mg groups experienced increased rates of overall infections compared to subjects < 75 years of age.

Pregnancy

In the upadacitinib clinical development program, lactating and pregnant females were excluded from the studies and all female subjects of childbearing potential were required to use protocol-specified pregnancy avoidance measures. Study drug was immediately discontinued in any female subject found to be pregnant during the clinical trials.

The pregnancy outcomes of the 16 subjects exposed to upadacitinib during pregnancy are as follows: 4 live births without congenital anomaly, 2 elective terminations (no foetal defects or unknown), 6 spontaneous abortions, 3 ongoing pregnancies and 1 lost to follow-up. All 6 subjects of spontaneous abortion were either taking MTX concomitantly or used MTX within 1 month prior to conception. All subjects were exposed to upadacitinib at the time of conception and during the first trimester of pregnancy. All 4 live births were without congenital anomalies; 3 subjects gave birth to full term infants without complications and 1 subject gave birth to a 28 week premature infant without reported complications. In the 4 pregnancies resulting in live births, the women were exposed to upadacitinib through approximately 4 – 8 weeks gestation. According to the applicant, no relevant maternal medical problems or complications during pregnancy, delivery or postpartum period were reported.

Four paternal exposure pregnancies have been reported in the partner of a male study subject in the upadacitinib clinical development program (1 in a RA study and 3 in a CD study). The two cases with known outcome resulted in live birth without congenital anomaly and spontaneous abortion.

Concomitant DMARDs

The drug interaction potential of upadacitinib with MTX was evaluated in a Phase 1 study which, according to the applicant, demonstrated that concomitant administration of upadacitinib and MTX had no effect on either upadacitinib or MTX plasma exposures.

A subgroup analysis of subjects in the placebo-controlled upadacitinib 15 mg QD and 30 mg QD analysis set who were on background MTX and those who were on background csDMARDs other than MTX was performed. The number and percentage of subjects with TEAEs was summarized by csDMARD use (any MTX [with/without other csDMARD], other csDMARD without MTX, any sulfasalazine without MTX, any hydroxychloroquine without MTX, and any leflunomide without MTX) for the PBO-controlled UPA 15 mg and 30 mg analysis set (Studies M13-549, M13-542).

According to the applicant, there was no clear pattern with respect to csDMARD use for any category of TEAE, including overall TEAEs, SAEs, severe TEAEs, and TEAEs leading to discontinuation (Table 76), as well as the types of TEAEs by csDMARD use (Table 77).

Table 75. Overview of number and percentage of subjects with treatment-emergent adverse events by csDMARDs - controlled short term period prior to treatment switching (pbo-controlled upadacitinib 15 mg and 30 mg analysis set)

	ANY MTX (WITH/WITHOUT OTHER CSDMARD)						OTHER CSDMARD(S), WITHOUT MTX					
			ABT-494						ABT-494			
	PLACEBO (N=330) n (%)		15 MG QD (N=305) n (%)		30 MG QD (N=310) n (%)		PLACEBO (N=58) n (%)		15 MG QD (N=75) n (%)		30 MG QD (N=73) n (%)	
ANY ADVERSE EVENT (AE)	169	(51.2)	173	(56.7)	189	(61.0)	33	(56.9)	40	(53.3)	40	(54.8)
ANY SERIOUS AE	3	(0.9)	12	(3.9)	18	(5.8)	2	(3.4)	5	(6.7)	1	(1.4)
ANY AE LEADING TO DISCONTINUATION OF STUDY DRUG	16	(4.8)	8	(2.6)	23	(7.4)	0		2	(2.7)	5	(6.8)
ANY SEVERE AE	9	(2.7)	11	(3.6)	15	(4.8)	0		4	(5.3)	2	(2.7)
ANY AE WITH REASONABLE POSSIBILITY OF BEING RELATED TO STUDY DRUG$	72	(21.8)	70	(23.0)	84	(27.1)	14	(24.1)	19	(25.3)	22	(30.1)
ANY AE LEADING TO DEATH	0		0		1	(0.3)	0		0		0	
DEATHS	0		0		1	(0.3)	0		0		0	

Table 76. Overview of number and percentage of subjects with treatment-emergent adverse events of special interest by csDMARDs - controlled short term period prior to treatment switching (PBO-controlled upadacitinib 15 mg and 30 mg analysis set)

	ANY MTX (WITH/WITHOUT OTHER CSDMARD)						OTHER CSDMARD(S), WITHOUT MTX					
			ABT-494						ABT-494			
	PLACEBO (N=330) n (%)		15 MG QD (N=305) n (%)		30 MG QD (N=310) n (%)		PLACEBO (N=58) n (%)		15 MG QD (N=75) n (%)		30 MG QD (N=73) n (%)	
ANY INFECTION	76	(23.0)	91	(29.8)	103	(33.2)	22	(37.9)	23	(30.7)	23	(31.5)
ANY SERIOUS INFECTION	1	(0.3)	0		7	(2.3)	0		2	(2.7)	0	
ANY OPPORTUNISTIC INFECTION	0		2	(0.7)	5	(1.6)	1	(1.7)	0		1	(1.4)
ANY POSSIBLE MALIGNANCY	1	(0.3)	0		4	(1.3)	0		0		1	(1.4)
ANY MALIGNANCY	0		0		4	(1.3)	0		0		1	(1.4)
ANY NON-MELANOMA SKIN CANCER (NMSC)	0		0		2	(0.6)	0		0		0	
ANY MALIGNANCY OTHER THAN NMSC	0		0		2	(0.6)	0		0		1	(1.4)
ANY LYMPHOMA	0		0		1	(0.3)	0		0		0	
ANY HEPATIC DISORDER	9	(2.7)	4	(1.3)	7	(2.3)	0		1	(1.3)	2	(2.7)
ANY GASTROINTESTINAL PERFORATION	0		0		0		0		0		0	
ANY ANEMIA	1	(0.3)	0		4	(1.3)	1	(1.7)	1	(1.3)	0	
ANY NEUTROPENIA	0		7	(2.3)	9	(2.9)	0		3	(4.0)	3	(4.1)
ANY LYMPHOPENIA	2	(0.6)	3	(1.0)	6	(1.9)	1	(1.7)	0		1	(1.4)
ANY HERPES ZOSTER	1	(0.3)	2	(0.7)	5	(1.6)	1	(1.7)	0		1	(1.4)
ANY CREATINE PHOSPHOKINASE (CPK) ELEVATION	0		4	(1.3)	6	(1.9)	0		3	(4.0)	3	(4.1)
ANY RENAL DYSFUNCTION	2	(0.6)	0		0		0		0		0	
ANY ACTIVE/LATENT TUBERCULOSIS	0		0		0		0		0		0	
ANY ADJUDICATED MACE#	0		1	(0.3)	1	(0.3)	0		0		0	
ANY ADJUDICATED VTE##	0		1	(0.3)	0		0		0		0	

At the CHMP's request, the applicant submitted updated data. Across the five Phase 3 RA studies, 122 subjects received upadacitinib 15 mg QD dose in combination with non-MTX-csDMARDs and 1854 subjects received upadacitinib 15 mg QD dose in combination with MTX alone. The safety data for these subjects are presented in Table 78 and Table 79.

Table 77. Overview of TEAE EAERs per 100 PY – Long-Term Exposure

	UPA 15 mg QD in Combination with non-MTX-csDMARDs (N=122) (PYs=139.3)		**UPA 15 mg QD in Combination with MTX Alone (N=1854) (PYs=1748.4)**	
	Events	E/100 PYs	Events	E/100 PYs
Any AE	520	373.3	4646	265.7
Any SAE	33	23.7	216	12.4
Any AE leading to discontinuation of study drug	18	12.9	116	6.6
Any severe AE	27	19.4	243	13.9
Any AE with reasonable possibility of being related to study drug	155	111.3	1551	88.7
Any AE leading to death	0	0	10	0.6
Deaths	0	0	7	0.4

Table 78. Overview of Treatment-Emergent AESIs Event Rate per 100 PY – Long-Term Exposure

	UPA 15 mg QD in Combination with non-MTX-csDMARDs (N=122) (PYs=139.3)		**UPA 15 mg QD in Combination with MTX alone (N=1854) (PYs=1748.4)**	
	Events	**E/100 PYs**	**Events**	**E/100 PYs**
Serious infection	10	7.2	58	3.3
OpportunisticOpportunistic infection	0	0	12	0.7
Any herpes zoster	5	3.6	54	3.1
Any active/latent TB	1	0.7	38	2.2
MalignancyMalignancy	3	2.2	14	0.8
Any non-melanoma skin cancer (NMSC)	1	0.7	6	0.3
Any malignancy other than NMSC	2	1.4	8	0.5
Any lymphoma	0	0	0	0
Any hepatic disorder	13	9.3	264	15.1
Any GI perforation[a]	0	0	3	0.2
Any anemia	10	7.2	66	3.8
Any neutropenia	5	3.6	51	2.9
Any lymphopenia	6	4.3	35	2.0
Any CPK elevation	14	10.1	84	4.8
Any renal dysfunction	2	1.4	5	0.3
Any adjudicated MACE	1	0.7	10	0.6
Any adjudicated VTE	2	1.4	8	0.5

Age

Table 79. Frequencies of MedDRA terms per (older) age category

	Events (E/100 PY)		
AESI (selected AESI where a difference was observed)	**< 65 years UPA 15 mg QD (N=2112, PY=2140.1)**	**≥65 and <75 years UPA 15 mg QD (N=440, PY=437.2)**	**≥ 75 years UPA 15 mg QD (N=78, PY=77.7)**
Any Adverse Event (AE)	6199 (289.7)	1381 (315.9)	272 (350.1)
Any serious AE	265 (12.4)	95 (21.7)	39 (50.2)
Any AE leading to Discontinuation of Study Drug	138 (6.4)	63 (14.4)	23 (29.6)
Any severe AE	283 (13.2)	82 (18.8)	32 (41.2)
Any AE with reasonable Possibility of being related to Study Drug[a]	2145 (100.2)	455 (104.1)	76 (97.8)
Any AE leading to Death[b]	9 (0.4)	8 (1.8)	3 (3.9)
Any Infection	2012 (94.0)	398 (91.0)	77 (99.1)
Any Serious Infection	80 (3.7)	15 (3.4)	7 (9.0)
Any Opportunistic Infection	9 (0.4)	6 (1.4)	2 (2.6)
Any active/latent Tuberculosis	49 (2.3)	7 (1.6)	2 (2.6)
Any Herpes Zoster	72 (3.4)	21 (4.8)	6 (7.7)
Any Malignancy	18 (0.8)	13 (3.0)	0
Any Hepatic Disorder	316 (14.8)	59 (13.5)	7 (9.0)
Any Gastrointestinal Perforation	5 (0.2)	0	0
Any Anemia	84 (3.9)	34 (7.8)	3 (3.9)
Any Neutropenia	58 (2.7)	22 (5.0)	2 (2.6)
Any Lymphopenia	42 (2.0)	7 (1.6)	1 (1.3)
An CPK Elevation	132 (6.2)	26 (5.9)	5 (6.4)
Any Renal Dysfunction	3 (0.1)	7 (1.6)	1 (1.3)
Any Adjudicated MACE	7 (0.3)	7 (1.6)	3 (3.9)
Any Adjudicated VTE	8 (0.4)	7 (1.6)	1 (1.3)

Safety related to drug-drug interactions and other interactions

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

At the CHMP's request, the applicant confirmed that no observations of potential interactions have been reported in the clinical program.

Discontinuation due to adverse events

In the PBO-controlled UPA 15 mg analysis set (Studies M13-549, M14-465, M13-542), the percentage of subjects with TEAEs leading to discontinuation of study drug was 2.8% in upadacitinib 15 mg and 2.0% in the placebo group. The majority of TEAEs leading to discontinuation of study drug were reported in 1 subject each in any group, except for anemia, vertigo, bronchitis, ALT increased, blood creatinine increased, and headache each reported in 2 subjects, and AST increased reported in 3 subjects in the upadacitinib 15 mg group; PJP and worsening rheumatoid arthritis were reported in 2 subjects each in the placebo group.

In the integrated MTX-controlled analysis set (Studies M13-545, M15-555) at 3 months, the percentage of subjects with TEAEs leading to discontinuation of study drug was as follows: upadacitinib 30 mg (2.6%), upadacitinib 15 mg (3.4%) and MTX (2.6%). The majority of TEAEs leading to discontinuation were reported in 1 subject each in the groups, except for ALT increased reported in 2 subjects each in all groups, and worsening rheumatoid arthritis reported in 2 subjects in the MTX group.

When compared to adalimumab, the percentage of subjects with TEAEs leading to discontinuation of study drug was 4.9% in the adalimumab group and 2.8% in the upadacitinib 15 mg group after 14 weeks.

In the long-term Any Phase 3 UPA 15 mg and 30 mg analysis set (Studies M13-549, M13-542, M13-545, M15-555), the EAERs of TEAEs leading to discontinuation of study drug were 9.4 E/100 PY and 13.3 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 in the upadacitinib 15 mg and 30 groups was pneumonia (0.5 E/100 PY and 0.9 E/100 PY, respectively).

Post marketing experience

Upadacitinib has not yet been approved for marketing in any country.

2.6.1. Discussion on clinical safety

Summary of the data

Known risks with JAK inhibitors are neutropenia, infections (especially herpes zoster), lipid disorders, hepatotoxicity, gastrointestinal symptoms and perforation and elevated muscle enzymes. There has been concern on an increased risk for malignancies and cardiovascular events, and long-term studies are ongoing. In addition, an Article 20 referral is currently on-going for Xeljanz (tofacitinib) assessing the risk of thrombotic events, in particular PE and VTE, on the benefit / risk profile of the medicine.

In the upadacitinib phase 2 and 3 studies, a total of 4,443 subjects received at least 1 dose of upadacitinib for a mean of 432.7 days. Of these subjects, 2,972 (66.9%) had exposure to upadacitinib for at least 48 weeks. Five pivotal phase 3 studies have been performed; two in which upadacitinib has been studied in monotherapy and compared against MTX (M13-545 [MTX-naïve subjects] - and M15-555 [MTX-failures], pooled into "MTX-controlled" dataset), and three in which upadacitinib has been studied as add-on to MTX or other csDMARDs and compared against monotherapy with MTX or other csDMARDs (M13-549, M14-465 and M13-542, pooled into "placebo-controlled"). It should be noted that "placebo" refers to background therapy with MTX or other csDMARDs, and that no true placebo

arm exists. Study M14-465 included both an arm with MTX in monotherapy and an arm with active comparator, adalimumab (also on top of MTX). Two doses were, 15 mg and 30 mg.

Infectious disorders were the most commonly reported adverse events. Most infections were upper respiratory tract infections and non-serious in nature; however, susceptibility to serious infections was also increased. Typical laboratory observations included increases in CPK, cholesterol, creatinine and hepatic enzymes, and a decrease in neutrophil count. With the recommended 15 mg QD dosage, there was little effect on haemoglobin. These observed changes in laboratory parameters have been evaluated in parallel with clinical events that could potentially be associated with the corresponding changes.

The overall size of the safety database (4,443 subjects exposed in the Any RA UPA analysis set, with 3,360 subjects exposed for 48 weeks or more) was considered sufficient to the CHMP to enable appropriate characterisation of the general safety profile.

The cut-off for data provided for original assessment has occurred at various times in early to mid-2018. At the CHMP's request, updated data up to Nov 2018 were presented in which no new significant safety signals arose. Long term safety is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

The applicant has summarised the safety data into a number of datasets:

- For monotherapy, the following analysis set is relevant: "MTX-controlled Upadacitinib 15 mg and 30 mg" (studies M13-545 and M15-555). Study M13-545 included MTX-naïve subjects, whereas M15-555 included subjects previously treated with MTX.
- For combination therapy, the following analysis set is relevant: Placebo-controlled Upadacitinib 15 mg (studies M13-542, M13-549, M14-465).

In general, the integrated approach to safety analysis that the Applicant has used is considered relevant. At the CHMP's request, the Applicant submitted summaries of overall adverse event rates as well as rates of events of special interest for subpopulations at different stages of the disease. The CHMP concluded that the overall safety profile of upadacitinib is quite consistent across the subpopulations at different stages of the disease.

Placebo (which in MTX-failures equals to continuing MTX) is not an alternative treatment in this population with an active disease, and thus the risk must be compared to the other alternative treatments. Subjects eligible for upadacitinib are csDMARD-experienced and for these subjects the alternative to treatment with upadacitinib is other JAK inhibitors or biologics. Therefore, the comparison to adalimumab is of high relevance. Study M14-465 includes a direct comparison to adalimumab.

In summary, the frequency of adverse events during the first 3 months was 49.6% when upadacitinib was given in monotherapy (compared to 48.3% for MTX), and 56% when upadacitinib was given in combination with other csDMARDs (vs 48.4% for placebo+csDMARD, and 48.3% for adalimumab+MTX). The frequency of SAEs was 3.0 % for upadacitinib in monotherapy (vs 2.3% for MTX) and 3.4% when upadacitinib was given in combination with other csDMARDs (vs 1.8 % for placebo+csDMARDs and 2.4% for adalimumab+MTX). These data support the use of upadacitinib as second-line treatment, after failing on MTX.

A dose-dependent relationship was seen when comparing 15 and 30 mg upadacitinib, supporting the use of the lower dose of 15 mg.

When upadacitinib 15 mg was compared to adalimumab (both in combination with MTX), most adverse events (for example serious infections, hepatic disorder, neutropenia, lymphopenia, herpes zoster, CPK elevation) occurred more frequently for upadacitinib than for adalimumab, although the differences are small. The frequencies of SAEs and severe AEs were comparable between the arms. Although the lack of long-term safety studies for upadacitinib is acknowledged, those data support the proposed second line indication.

In CHMP Scientific Advice, the applicant was advised to document the reversibility of any adverse effects to manage risks. For most of the assessed laboratory parameters, reversibility is seen regardless of continuation or discontinuation of upadacitinib treatment, the only exception being haemoglobin, for which there is no data on reversibility upon continued treatment (this could be due to protocol-mandated interruption of study drug in subjects with decreased haemoglobin). There is no evidence of progressive deterioration in the laboratory parameters assessed. The guidance for monitoring and treatment interruption/discontinuation is adequately reflected in the SmPC.

Deaths

A summary of the respective phase 3 studies is provided below and followed by the pooled data.

In study M13-545 (first line, monotherapy) up to week 24, there were 2 cases of deaths (0.6%) in the upadacitinib 15 mg group compared to 1 (0.3%) in the placebo group. The first death in the UPA 15 mg group had a prior history of malignant melanoma and died due to metastatic malignant melanoma and tumor infiltration of the hepatic vein, after a treatment period of 111 days. An association with upadacitinib is possible. The other case was a subject who died from a myocardial infarction on day 29 of treatment.

In the upadacitinib 30 mg group, the following causes of death were noted: pneumonia/sepsis, sudden death and peritonitis. In the MTX-group, a subject with type 2 DM and hypertension died due to acute myocardial infarction.

In long-term all study drug exposure analysis (to week 48 and beyond) in the same study, EAERs of death (including treatment-emergent and nontreatment-emergent) for the upadacitinib 15 mg monotherapy, upadacitinib 30 mg monotherapy, and MTX monotherapy groups were 1.2 E/100 PY, 2.1 E/100 PY, and 0.3 E/100 PY, respectively. The mortality rate is numerically higher for UPA 15 mg monotherapy in study M13-545 including MTX-naïve subjects (IR 1.2E/100PY) than in the pooled data (IR 0.5E/100PY). At the CHMP's request, the applicant presented comparative data through week 48 (i.e. up to the end of the active controlled study period) on the number of deaths that occurred in the upadacitinib 15 mg arm and the MTX arm respectively. The CHMP concluded that no specific pattern could be observed and the difference observed is likely due to the small sample size.

In study M13-549 (≥ second line, csDMARD add-on), there were no deaths up to week 12. Data beyond week 12 was not included in the CSR, but is summarised in the pooled data below.

In study M14-465 (≥ second line, MTX add-on), there were no deaths in the upadacitinib 15 mg group compared to 2 deaths in the adalimumab group and 2 deaths in the placebo (=MTX) group up to week 26. In the long-term extension (week 48 and beyond), there were 4 TEAEs leading to death in the upadacitinib 15 mg group (1.1 E/100PY) compared to 2 cases in the adalimumab group (1.5E/100PY). Also in the updated safety data presented in response to the day 120 LoQ, the mortality was lower for upadacitinib 15 mg (9 deaths or 0.6 E/100PY for upadacitinib vs 5 deaths or 0.9 E/100PY for adalimumab, this includes also non treatment-emergent deaths).

Taken together, data up to 48 weeks from the clinically highly relevant study M14-465 (including a direct comparison with adalimumab) comparative data do not indicate an increased mortality for upadacitinib compared to adalimumab.

In study M15-555 (second line, monotherapy) up week 14, there was one case of death in the upadacitinib 15 mg group (0.5%) vs no case in the MTX group. This was a subject who was a former smoker and with concurrent hypertension, who died on day 39 from a ruptured aneurysm leading to a haemorrhagic stroke. No controlled, long term data were available for this study.

In study M13-542 (third line, csDMARD add-on), there was one death among upadacitinib 15 mg-treated subjects up to week 24 (IR1.1), compared to 0 cases in the placebo (=csDMARDs) group. This was a subject with a history of type 2 diabetes, hyperlipidaemia and hypertension who died from a cardiac arrest at day 163. The subject had multiple risk factors, and causality with upadacitinib cannot be considered established. No controlled, long term data were available for this study.

In the pooled data from all phase 3 studies (M13-545, M13-549, M14-465, M15-555, M13-542) up to 3 months , the IR for death appeared comparable for the upadacitinib 15 mg, MTX (from M13-545 and M15-555 where MTX was the comparator), placebo (= MTX or csDMARDs, from the studies where all subjects received background treatment) and adalimumab. The CHMP noted that the lowest figure was actually seen for upadacitinib 15 mg although the comparison is hampered by the small exposure and low number of absolute events in the different arms.

In the pooled long-term data from all phase 3 studies (48 weeks and beyond), there were 14 deaths in upadacitinib 15 mg treated subjects. Among these cases, the majority were cardiovascular deaths. The CHMP considered that 9 of the 14 cases were cardiovascular. It is noted that there were no deaths due to infections among upadacitinib-treated subjects.

Also in the long-term analysis set, the calculated mortality rates appear similar for upadacitinib and the comparators. The rate for upadacitinib 15 mg was numerically higher than for MTX but lower than for adalimumab but the comparison is hampered by relatively low exposure and absolute number of events (in the comparator arms).

The CHMP concluded based on the pooled data that the mortality rates did not substantially differ according to the treatments received in this population with active, potentially debilitating inflammatory disease in which underlying risk factors for both CV death and infections are expected to be frequent.

The applicant provided mortality-figures for the two other approved JAK-inhibitors based on EPAR data. Fully acknowledging the limitations of inter-study comparisons, the CHMP considered that the observed numbers of deaths (tofacitinib IR=0.36, baricitinib IR=0.44 and upadacitinib 15 mg IR 0.5E/100PY) were roughly comparable between the three drugs.

Among all upadacitinib-treated subjects (both 15 and 30 mg), the following causes of death were noted: Acute respiratory distress syndrome, pulmonary embolism, cardiac arrest, myocardial infarction, cardiac failure, haemorrhagic stroke, sudden cardiac death, metastatic rectal cancer, infections (including meningitis), peritonitis, lung adenocarcinoma, Hodgkin's disease, metastatic malignant melanoma (removed several years ago), adenocarcinoma of colon, and congestive cardiomyopathy. Thus, in many cases, the causes of death were cardiovascular, in some cases the reasons were infections or malignancies.

Serious infections

In short-term analysis (3 months), the frequency of serious infections was 0.6% for upadacitinib 15 mg in monotherapy (vs 0.4% for MTX), 1.2% for upadacitinib in combination with other csDMARDs (vs

0.6% for placebo+csDMARDs and 1.2% for adalimumab+MTX). When compared to adalimumab during long-term exposure, the risk for serious infections was numerically lower for upadacitinib (IR 4.1) than for adalimumab (IR 4.3).

During long-term exposure (48 weeks), the incidence rate of serious infections was numerically lower for UPA 15 mg than for UPA 30 mg. The risk of serious infection clearly seems to be dose-related, as evidenced by consistently higher event rates with the 30 mg dose.

Fully acknowledging the limitations of inter-study comparisons, the incidence rate is slightly higher for upadacitinib 15 mg (IR 3.84) than for the JAK-inhibitors Olumiant (from EPAR: overall serious infection IR 3.2/100 PY) and Xeljanz (from EPAR: 2.71/100PY for 5 mg BID in RCTs).

Serious infections are included in section 4.4 of the SmPC, and a list of infections are summarised in 4.8 of the SmPC. At the CHMP's request the applicant has also included specific information on tuberculosis and meningitis in the Section 4.4 of the SmPC. In addition, Upadacitinib is contraindicated in patients with active severe infections. Serious infections including TB is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Opportunistic infections

There were no reported opportunistic infections for upadacitinib in monotherapy (up to 3 months). When upadacitinib was given in combination with other csDMARDs, the frequency of opportunistic infections was 0.5% for upadacitinib vs 0.3% for placebo+csDMARDs. The IR for UPA 15 mg is comparable to the IR for adalimumab (IR for upadacitinib = 1.4, IR for adalimumab=1.5 in study M14-465). The most common opportunistic infection for both doses of upadacitinib was oral candidiasis. For more severe opportunistic infections such as pneumocystis jirovecii pneumonia, there were 4 cases in the Japanese study M14-663, but no cases among upadacitinib-treated subjects in the global studies. There were no deaths due to an opportunistic infection in subjects receiving upadacitinib in the RA clinical development program. A detailed description of opportunistic infections is included in the SmPC section 4.8. Opportunistic infections is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Herpes zoster

The frequency of herpes zoster was over 2 times higher in subjects receiving upadacitinib compared to placebo, and event rates were increased as compared to either MTX or adalimumab. The finding is consistent with the EPAR of other JAK inhibitors and thus clearly indicative of a class effect. The majority of events involved a single dermatome; development of post-herpetic neuralgia was reported in about 5% of cases. The applicant stated that a prior history of herpes zoster was identified as a significant risk factor for developing a herpes zoster event; furthermore, herpes zoster was more frequent in Asia than elsewhere.

The SmPC includes recommendations for precautionary measures, including prophylactic zoster vaccination, and the risk of herpes zoster is described in Sections 4.4 and 4.8 of the SmPC. Herpes zoster is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Tuberculosis

There were 5 cases of active TB infection among upadacitinib-treated subjects. Of these, 3 had a latent TB at screening whereof 1 received isoniazid therapy for ≥ 6 months. This case is important, implying a residual risk for active TB although screening is performed and prophylactic treatment is given.

The IR of 1.8 E/100 PY seems rather high when compared to the other JAK inhibitors (tofacitinib all doses 0.19E/100 PY, baricitinib 4 mg 0.2E/100PY according to the respective EPARs). As recommended in Section 4.4 of the SmPC, patients should be screened for latent TB before starting upadacitinib treatment. In addition, Upadacitinib is contraindicated in patients with active TB infections. Serious infections including TB is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Malignancy

Subjects with a history of any malignancy except for successfully treated NMSC or localized carcinoma in situ of the cervix were excluded from the phase 3 studies. The long-term exposure for upadacitinib is currently limited; 520 subjects have been exposed for at least 96 weeks. The cancers observed during the current observation period are dominated by skin and breast cancer. The risk will have to be carefully followed post-approval. At the CHMP's request, an adequate warning has been included in Section 4.4 of the SmPC. Malignancy is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Hepatic disorder

In short-term analysis up to 3 months, liver transaminase elevations were more common when upadacitinib was given in combination with other csDMARDs (proportion of subjects with ALT ≥ 3 × ULN: 2.1% in the upadacitinib group compared to 1.5% for placebo) than in monotherapy (1.7%), which is expected since most csDMARDs can affects the liver function. Transaminase elevations were less frequent for upadacitinib in monotherapy (1.7%) than for MTX (3.6%). This ADR is described in Section 4.8 of the SmPC at the CHMP's request.

However, most events were asymptomatic and transient even in the setting of continued use of upadacitinib and there is currently no evidence of actual hepatotoxicity.

Patients with severe hepatic impairment (Child Pugh C) were excluded from the phase 3 studies. As severe hepatic impairment is expected to lead to an increased exposure of upadacitinib, and considering the less favourable safety profile observed with the 30 mg dose, the CHMP requested upadacitinib to be contraindicated in patients with Child-Pugh C.

Use in patients with moderate hepatic impairment, DILI, use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C are listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

GI perforation

The observed frequency of gastrointestinal perforations was not higher among upadacitinib-treated subjects than frequency observed in a background population.

GI perforation is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Anemia

Overall, there was very little effect on mean haemoglobin with the 15 mg dosage of upadacitinib, and according to the Applicant, Grade 3 and even Grade 4 decreases were in most cases transient and recovered without study drug discontinuation. However, the 30 mg dosage did induce a more observable decrease in haemoglobin, and Grade 3 and 4 decreases were more common on 30 mg than 15 mg.

Monitoring guidelines and instructions on potential treatment interruptions in case of haematological abnormalities are provided in Sections 4.2 and 4.4 of the SmPC.

Neutropenia

During the first 3 months, the frequency of neutropenia (<1.5x109/L) was 4% in the upadacitinib 15 mg group vs 0.6% in the csDMARD group. Upadacitinib is associated with a consistent and persistent decrease, averaging about 15% with 15 mg, in neutrophil counts. Whereas the temporal association of decreased neutrophil counts with the increased propensity is not straight-forward and the overall numbers are not sufficient for any robust association analysis, the fundamental concern of neutropenia being associated with an increased susceptibility to infections cannot be excluded.

There was a higher proportion of subjects in the UPA 15 and 30 mg groups experiencing neutropenia than in the placebo group.

Neutropenia is therefore listed in section 4.8 of the SmPC. Dosing recommendations in case of neutropenia are also provided in Section 4.2 of the SmPC.

Lymphopenia

There were no differences in lymphocyte count between UPA 15 mg and placebo during the short-term placebo-controlled period of the studies. Administration of upadacitinib was associated with an increase in mean ALC over the first 36 weeks of starting treatment, followed by slight decreases afterwards. No clinically relevant decrease from baseline was observed.

Although there were no SAEs of lymphopenia in the global studies, in the Japanese study M14-663 there was 1 subject with a TEAE of lymphopenia who developed pneumocystic jirovecii pneumonia 5 days later.

Monitoring guidelines and instructions on potential treatment interruptions are included in sections 4.2 and 4.4 of the SmPC.

CPK elevation

CPK elevations were observed for a higher proportion of UPA15- and UPA30mg-treated subjects than for subjects treated with placebo (the majority with a mild increase of >2.5-5 x ULN). There seemed to be a dose-dependency. This ADR is described in Section 4.8 of the SmPC.

Renal dysfunction

Upadacitinib was associated with a consistent increase in serum creatinine, averaging about 10% at the 15 mg dose. The rate of serious adverse events, severe adverse events and adverse events leading to discontinuation is increased in patients with mild renal impairment compared to patients with normal renal function, and the rates are increased even further in patients with moderate renal impairment. Increased rates are also seen in corresponding placebo groups. While exposure-response analyses may not suggest an increased risk of serious infections, a substantially higher risk of serious infections in

subjects on upadacitinib 30 mg than 15 mg was clinically observed. Further safety information from the moderate renal impairment group is required post approval.

At CHMP's request, Section 4.2 of the SmPC includes precautionary message regarding severely renal impaired patients. Use in patients with severe renal impairment is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Lipids

Upadacitinib induced rapidly developing and persistent increases averaging 10-15% across all lipid classes. However, the effect being equal across total cholesterol, LDL and HDL cholesterol, atherogenic indices based on cholesterol (TC/HDL-C; LDL-C/HDL-C) and major apolipoproteins (i.e. ApoB/ApoA1) remained essentially unchanged. The increases did not seem to be associated with adverse clinical consequences (e.g. MACE).

The very limited available evidence supports the notion of these increases being statin-responsive. Sections 4.2, 4.4 and 4.8 of the SmPC adequately reflect the risks and provide monitoring guidance. MACE is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Effect on body weight

Long-term treatment with upadacitinib was frequently associated with an increase in body weight, but weight changes have only been characterised with a single threshold of >7% change from baseline. While weight increase may be a sign of improved disease control, a large proportion of subjects had a high body mass index already at baseline (>30% of subjects had a BMI exceeding 30 kg/m^2 in the Any Ph 3 UPA 15 analysis set), and a further increase body weight could have adverse consequences in such patients. Weight increased is listed as an ADR in Section 4.8 of the SmPC.

Age, BMI, other intrinsic factors

Analysis by age group is limited by the small number of patients > 75 years of age in the program (N = 78 in the Any Ph 3 UPA 15 analysis set). There was an increased frequency of adverse event in the elderly group notably infections. At the CHMP's request, the Section 4.4 of the SmPC was updated to include a precautionary statement for this population. Use in very elderly (≥ 75 years of age) is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

A high baseline body weight or BMI was associated with an increased frequency of serious and severe adverse events as well as events leading to discontinuation. This likely reflects the underlying characteristics of this patient group, but should be considered in the context of a potential weight increase being associated with upadacitinib. See paragraph above.

MACE and Other Cardiovascular Events

There were 13 cases of cardiovascular death among upadacitinib-treated subjects; 7 on upadacitinib 15 mg and 6 on upadacitinib 30 mg. All of these cases had cardiovascular risk factors (such as hypertension, diabetes mellitus, smoking, hyperlipidaemia or obesity).

In the long-term exposure analysis of all phase 3 studies (data up to week 48 and beyond), the estimate for the exposure-adjusted IR for MACE is similar for MTX (2 events/314 PY, IR=0.6) and upadacitinib 15 mg (16 events/2651 PY, IR=0.6) but numerically lower for adalimumab (2 events/468

PY, IR=0.4). This analysis did not include the comparison with placebo, the reasoning probably being that there is limited phase 3 study placebo exposure beyond 14 weeks, only study M14-465 included 26 weeks placebo exposure but this study included opportunities for switch to upadacitinib at week 14,18 and 22 for subjects with poor improvement (see efficacy section of this AR for details) and a final switch to upadacitinib at week 26 for all placebo subjects regardless of response, which complicates the interpretation of data. However, two phase 3 studies included active controlled safety data up to week 48; study M13-545 that included a 48 week-comparison with MTX and study M14-465 that included a week 48-comparison with adalimumab. Placebo is not a realistic alternative treatment option in the proposed target population with an active and potentially debilitating disease, not responding to first line RA treatment. Consequently, the direct comparison with adalimumab in study M14-465, is considered to be of most relevance although the direct comparison with MTX in study M13-545 is also of interest to further characterize the magnitude of risk for MACE.

When looking specifically at study M14-465, up to week 26 (Censored at Treatment Switching), there were 3 cases in the PBO arm (1.2/100 PY, 2 cases in the adalimumab arm (1.5/100 PY) and no cases in the upadacitinib 15 mg arm). At long-term exposure (48 weeks and beyond), the IR for MACE was 0.4 for both upadacitinib and adalimumab. In the updated data with a cut-off date of Nov 2018, the IR for MACE was lower for upadacitinib (5 events or 0.3E/100PY) than for adalimumab (3 events or 0.5 E/100PYs). The applicant presented a Kaplan-Meier curve for study M14-465 through 48 weeks (the time point up to which there is a direct comparison with the active comparator adalimumab), where no increased risk for MACE for upadacitinib compared to the active comparator adalimumab is indicated. Based on the totality of data above, there does not seem to be an increased risk for MACE in subjects treated with upadacitinib, compared to subjects treated with adalimumab (clinically relevant comparator).

Subjects with a history of any of the following cardiovascular conditions were excluded from the pivotal studies: Moderate to severe congestive heart failure (New York Heart Association class III or IV), Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting; Uncontrolled hypertension as defined by a persistent, confirmed systolic blood pressure (BP) > 160 mmHg or diastolic BP > 100 mmHg or Clinically relevant or significant ECG abnormalities.

At the CHMP request, the applicant has included a warning regarding the CV risk in section 4.4 of the SmPC. The risk for MACE is planned to be continuously followed post-approval. MACE is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Venous thromboembolism (VTE)

The frequency of VTE was numerically higher for UPA15 mg than for placebo (in short-term analysis up to 3 months), but similar to the risk for MTX and lower than the risk for adalimumab at long-term analysis (48 weeks).

Based on investigator-reported adverse event data, the majority of VTE events were observed in patients with impaired renal function.

A warning on the risk of VTE is included in Section 4.4 of the SmPC. At the CHMP's request, the SmPC has been modified to mention that if clinical features of DVT/PE occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment. VTE is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Pregnancy

Since the initial submission of this application, two additional live births without congenital anomalies have been reported for mothers exposed to upadacitinib during pregnancy. However, experience remains very limited, and there is evidence of potential teratogenicity in non-clinical studies. As discussed in the Non Clinical section, Upadacitinib is contraindicated during and should not be used during breast-feeding.

Foetal malformation following exposure in utero is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Section 4.4 of the SmPC will include language that no data are available on the response to vaccination with live or inactivated vaccines in patients receiving upadacitinib and that use with live, attenuated vaccines during, or immediately prior to, upadacitinib therapy is not recommended. Finally, the SmPC Section 4.4 states that prior to initiating upadacitinib, it is recommended that patients be brought up to date with all immunisations in agreement with current immunisation guidelines. Effect on vaccination efficacy is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The proposed dose to be marketed (15 mg) is clearly preferable from a safety perspective than the higher dose of 30 mg.

Safety data on upadacitinib in combination with other csDMARDs than MTX are limited since only 122 subjects were exposed for any non-MTX-csDMARD in combination with the dose of upadacitinib proposed to be marketed (15 mg). Also, the results for these subjects on non-MTX-csDMARDs are somewhat worrisome, since the safety profile in less favourable than for the combination with MTX. There were numerically more AEs, SAEs, serious infections and haematologic disturbances in the non-MTX-csDMARD group than in the MTX group. Hence, the applicant withdrew this claim from the indication during the assessment (see Efficacy section). The revised indication was as follows:

"*RINVOQ is indicated 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 most commonly reported adverse drug reactions are upper respiratory tract infections (13.5%), nausea (3.5%), blood creatine phosphokinase (CPK) increased (2.5%) and cough (2.2%). The most common serious adverse reactions were serious infections.

Important observed adverse events are infections, haematological disturbances, elevated liver enzymes and CPK elevations. The risk for malignancy and cardiovascular disorder needs to be further addressed in post-authorization studies. Based on the data submitted in this application, the risk for MACE and overall death does not appear higher for upadacitinib than for the comparator adalimumab. However, at the CHMP request, the applicant has included a warning regarding the CV risk in section 4.4 of the SmPC.

While exposure-response analyses may not suggest an increased risk of serious infections, a substantially higher risk of serious infections in subjects on upadacitinib 30 mg than 15 mg is clinically

observed. This raised a concern for subjects with impaired renal function. At CHMP's request, Section 4.2 of the SmPC includes precautionary message regarding patients with severely renal impaired patients. Use in patients with severe renal impairment is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Upadacitinib is contraindicated in active tuberculosis (TB) or active serious infections, severe hepatic impairment and pregnancy. Upadacitinib should not be used during breast-feeding.

2.7. Risk Management Plan

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious and opportunistic infections including TB	Routine risk minimization measures: • SmPC Section 4.4 will summarize the risk and provides guidance on ways to reduce the risk. • The PL will warn 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 will advise that patients do not take Rinvoq if they have active TB and will warn 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 will outline lymphocyte and neutrophil counts and when not to initiate upadacitinib dosing. • SmPC Section 4.2 will outline interruption guidelines based on ALC and ANC. • SmPC Section 4.3 will indicate that upadacitinib is contraindicated in patients with active TB or active serious infections. • SmPC Section 4.4 will state 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 will advise to consider the risks and	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)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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 will describe the risk of viral reactivation such as herpes zoster. • SmPC Section 4.8 will describe findings from upadacitinib clinical trials. • The PL will warn 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 will warn 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 will advise 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)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Malignancies	Routine risk minimization measures: • SmPC Section 4.4 will describe the risk in patients with RA and indicate that upadacitinib clinical data are currently limited and long-term studies are ongoing. • The PL will warn 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 will advise 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)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
MACE	Routine risk minimization measures: • SmPC Section 4.4 will describe the effect of upadacitinib on lipids and describes that impact on CV morbidity and mortality has not been determined. • SmPC Section 4.4 will contain 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 will describe monitoring of lipid parameters following initiation of upadacitinib. • The PL will warn 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)

VTEs (deep venous thrombosis and pulmonary embolus)	Routine risk minimization measures: • SmPC Section 4.4 will indicate that events of deep vein thrombosis and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib. • The PL will warn 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 will advise that patients tell their doctor if they get a painful swollen leg, chest pain, or shortness of breath. • SmPC Section 4.4 will advise 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 will advise that if clinical features of deep vein thrombosis/pulmonary embolism occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment. Additional risk minimization measures: • HCP educational brochure • PAC	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)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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)
DILI	Routine risk minimization measures: • SmPC Section 4.4 will describe the effect of upadacitinib on transaminases. • SmPC Section 4.4 will recommend prompt investigation of the cause of liver enzyme elevation to identify potential cases of DILI. • SmPC Section 4.4 will advise 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)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Foetal malformation following exposure in utero	Routine risk minimization measures: • SmPC Section 4.6 will describe the teratogenic effects observed in animals receiving upadacitinib and state that there are no or limited data from use of upadacitinib in pregnant women. • The PL will advise 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 will indicate that upadacitinib is contraindicated during pregnancy. • SmPC Section 4.6 and PL will advise on use of effective contraception. 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 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)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in very elderly (≥ 75 years of age)	Routine risk minimization measures: • SmPC Section 4.2 will state that there are limited data in patients aged 75 years and older. • SmPC Section 4.8 will state that there was a higher rate of serious infections in patients ≥ 75 years of age, although data are limited. • SmPC Section 4.4 will state 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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Effect on vaccination efficacy	Routine risk minimization measures: • SmPC Section 4.4 will include language that no data are available on the response to vaccination with live or inactivated vaccines in patients receiving upadacitinib. • SmPC Section 4.4 will state that use with live, attenuated vaccines during, or immediately prior to, upadacitinib therapy is not recommended. • SmPC Section 4.4 will include 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 will describe the risk of viral reactivation. • The PL will warn 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 will describe 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 will describe use in patients with hepatic impairment. • SmPC Section 4.2 will state that upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment. • SmPC Section 4.3 will indicate that upadacitinib is contraindicated for use in patients with severe hepatic impairment. • The PL will advise that patients do not take Rinvoq if they have severe liver problems and will warn 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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with severe renal impairment	Routine risk minimization measures: • SmPC Section 4.2 will describe use in patients with renal impairment. • SmPC Section 4.2 will state 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
Long-term safety	Routine risk minimization measures: SmPC Section 4.4 will indicate 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)

The CHMP and PRAC considered that the risk management plan version 1.6 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 16.08.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of upadacitinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers upadacitinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of providing statutory information (see below) on the medicinal product has been submitted by the applicant and has been found acceptable.

The following elements (statutory information) have been agreed to be provided through a QR code:

- Package leaflet
- Educational material for patients as outlined in the Risk Management Plan

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rinvoq (upadacitinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant applied for the following indication:

"*RINVOQ is indicated 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 or other conventional synthetic DMARDs (csDMARDs)*."

Patients with active RA have persistent synovitis with systemic inflammation leading to destruction of articular cartilage and bone, which ultimately interfere with function of the joint. Left untreated, or

inadequately treated, progressive functional impairment can ultimately lead to significant disability. Treatment of RA should be aimed at reaching a target of sustained low disease activity (or even remission); thus reducing the symptoms of active joint inflammation such as pain, stiffness and reduced joint function as well as preventing structural joint damage (long-term goal).

3.1.2. Available therapies and unmet medical need

According to EULAR recommendations (EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update), treatment should be initiated as soon as the RA diagnosis is made. Methotrexate (MTX) should be the first treatment strategy. In patients with contraindications to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as the (first) line treatment strategy. If there is no improvement by at most 3 months after start of treatment or the target has not been reached by 6 months, therapy should be adjusted. Depending on whether poor prognostic factors are present or not, other csDMARD or addition of a bDMARD (biologic DMARD) or tsDMARD (targeted synthetic DMARD) could then be considered. JAK-inhibitors are tsDMARD. There are two other already approved JAK-inhibitors in EU; tofacitinib and baricitinib.

Despite the recent advances in this therapeutic field, there all still patients who either cannot tolerate or do not respond to the available treatment options.

3.1.3. Main clinical studies

The clinical development programme included efficacy data from 8 controlled studies: 3 supportive/dose-ranging studies: M13-537, M13-550 and M14-663 as well as 5 pivotal randomized, double-blind, Phase 3 studies: M13-545 (1st line RA treatment), M13-549, M14-465 and M15-555 (≥2nd line), and M13-542 (3rd line).

Based on the data from the 3 supportive/dose-ranging studies, the applicant chose 15 mg QD extended-release (equivalent to 6 mg BID immediate-release) and 30 mg QD extended-release (equivalent 12 mg BID immediate-release) as the doses to be tested in the phase 3 programme.

In all the 5 phase III-studies, the analysis of the primary endpoint was conducted on FAS which included all randomized subjects who received at least 1 dose of study drug and non-responder imputation (NRI) was used.

Study M13-545 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Once Daily Monotherapy to Methotrexate (MTX) Monotherapy in MTX-Naïve Subjects with Moderately to Severely Active Rheumatoid Arthritis (Select Early)" included subjects with negative prognostic factors. The study compared upadacitinib 15 mg QD monotherapy, and 30 mg QD monotherapy versus MTX monotherapy. The primary endpoint was the proportion of subjects achieving CR defined by DAS28 [CRP] < 2.6 at Week 24. Subjects who meet joint count rescue criteria at Week 16 or 20 were treated as non-responders for the primary analysis. Structural joint damage (mTSS) was included among the key secondary endpoints.

Study M13-549 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs (Select Next)" included subjects that had failed at least one of the following: MTX, sulfasalazine, or leflunomide. Subjects with prior exposure to at most one bDMARD were eligible to be enrolled in the study if they had either exposure<3 months or had to discontinue due to intolerability. The study compared upadacitinib 30 mg QD and 15 mg QD versus placebo as

add-on to stable dose of csDMARDs. The primary endpoint for was LDA based on DAS28 (CRP) ≤ 3.2 at Week 12. There seem to have been no rescue possibilities before assessment of the primary endpoint.

Study M14-465 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR) (Select Compare)" included subjects with negative prognostic factors. Subjects with prior exposure to at most one bDMARD were eligible to be enrolled if they had either exposure<3 months or had to discontinue the bDMARD due to intolerability. The study compared upadacitinib 15 mg QD versus placebo, and versus adalimumab (per approved label) as add-on to MTX. The primary endpoint was the proportion of subjects achieving CR based on DAS28 CRP < 2.6 at Week 12. The ranked secondary endpoints included structural damage (at week 26). Patients could be rescued and switch group at Weeks 14, 18, 22 or 26.

Study M15-555 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Monotherapy to Methotrexate (MTX) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response to MTX" (Select Monotherapy)" compared upadacitinib 30 mg QD alone and 15 mg QD alone versus continuing MTX. The primary endpoint was the proportion of subjects achieving LDA (based on DAS28 [CRP] ≤ 3.2) at Week 14. No rescue was allowed before the timepoint at which the primary endpoint was analysed.

Study M13-542 "A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo on Stable Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response or Intolerance to Biologic DMARDs (bDMARDs) (Select Beyond)" compared upadacitinib 30 mg QD and 15 mg QD versus placebo as add-on to a stable dose of csDMARDs in a randomized, double-blind, parallel-group design during the first 12 weeks of the study. This period included no rescue-possibilities. Study M13-542 had LDA based on DAS28 (CRP) ≤ 3.2 at week 12 as the primary endpoint.

The design of the five main clinical trials is considered broadly in line with current EMA guidelines and previous CHMP Scientific Advice.

3.2. Favourable effects

Data from the five pivotal trials

In M13-545 (1st line, monotherapy), the proportion of subjects (95% CI) that achieved the primary endpoint CR at week 24 was in the MTX monotherapy (n=314), UPA 15 mg monotherapy (n=317) and UPA 30 mg monotherapy (n=314): 18.5 (14.2, 22.8), 48.3 (42.8, 53.8) and 50.0 (44.5, 55.5) %, p 0.001 for both comparisons between MTX and Upa. Statistically significant improvements in the upadacitinib 15 mg QD and 30 mg QD groups compared with the MTX group were observed for all ranked key secondary endpoints using multiplicity adjustment. The proportion of subjects with no radiographic progression at week 24 was in the MTX, UPA 15 mg and UPA 30 mg group: 77.7%, 87.5% and 89.3% (nominal p-value 0.002 and <0.001 for the two respective comparisons with MTX).

In M13-549 (≥ 2nd line, csDMARD add-on), the proportion of subjects (95% CI) that achieved the primary endpoint LDA at week 12, was a in the Placebo (n=221), UPA 15 mg (n=221) and UPA 30 mg group (n=119): 17.2 (12.2, 22.2), 48.4 (41.8, 55.0) and 47.9 (41.3, 54.6) %, p <0.001 for both comparisons between the active treatment arms and placebo. Statistically significant improvement in

both the upadacitinib 15 mg QD and 30 mg QD groups compared with the placebo group were observed for all ranked key secondary endpoints using multiplicity adjustment.

In M14-465 (≥ 2nd line, MTX add-on), the proportion of subjects (95% CI) that achieved the primary endpoint CR at week 12 was 28.7(25.2, 32.2) % when upadacitinib 15 mg (n=651) was added to MTX. For subjects that received placebo (n=651), the corresponding figure was 6.1% (4.3, 8.0), p<0.001 for the comparison between the groups. Statistically significant improvement with upadacitinib 15 mg QD group compared with the placebo group were observed for all ranked key secondary endpoints using multiplicity adjustment. The proportion of subjects with no radiographic progression at week 26 was 76.0% in the placebo group and 83.5% in the upadacitinib 15 mg group, p=0.001 for the comparison. One of the key secondary endpoints involved a comparison vs the active comparator adalimumab; the proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 (non-inferiority comparison of upadacitinib versus adalimumab). This endpoint (95% CI) was achieved in 28.7 (23.8, 33.7) in the adalimumab group and 45.0 (41.2, 48.8) % in the upadacitinib group. The non-inferiority margin was 10% but the point estimate (95% CI) for between group difference was 16.3% (10.0, 22.5) i.e. non-inferiority was met.

In M15-555 (2nd line, monotherapy), the proportion of subjects (95% CI) that achieved the primary endpoint LDA at week 14 was 19.4 (14.2, 24.7) % in the cMTX-group (n=216) vs 44.7 (38.1, 51.3) % in the UPA 15 mg monotherapy group (n=217) and 53.0 (46.4, 59.7) % in the UPA 30 mg monotherapy group (n=215), p<0.001 for both comparisons between cMTX and upadacitinib. Statistically significant improvement in both the upadacitinib 15 mg QD and 30 mg QD groups compared with the cMTX group were observed for all ranked key secondary endpoints using multiplicity adjustment.

In M13-542 (3rd line, csDMARD add-on), the proportion of subjects (95% CI) that achieved the primary endpoint, LDA at week 12, was 43.3 (35.7, 50.9) % in the UPA 15 mg group (n=164), 42.4 (34.9, 50.0) % in the UPA 30 mg group (n= 165) and 14.2 (8.9, 19.5) % in the placebo group(n=169), p<0.001 for both comparisons between upadacitinib and placebo. Statistically significant improvement in both the upadacitinib 15 mg QD and 30 mg QD groups compared with the placebo group were observed for all ranked key secondary endpoints using multiplicity adjustment.

Across the five pivotal studies, the 30mg dose performed only marginally better than the 15mg dose. The results were generally consistent across relevant subgroups and a rapid onset of effect (as early as week 1-2) was noted.

Data from analysis performed across trials

Several integrated analyses across trial were conducted by the applicant. Two integrated analysis sets of the Phase 3 studies (M13-549, M14-465, and M13-542) were defined for the purpose of short-term integrated efficacy analyses.

The short-term efficacy of upadacitinib was assessed in bDMARD-intolerant subjects versus other bDMARD-exposed subjects (that discontinued bDMARD therapy due to lack of efficacy or other reasons). Subgroup analysis was performed for ACR20 and LDA based on DAS28 (CRP) at Week 12 in the two integrated analysis sets. For bDMARD-intolerant subjects in the Placebo-Controlled upadacitinib 15 mg Analysis Set (NRI), the proportion that achieved ACR20 at week 12 was 30.5% in the placebo group vs 62.7% in the upadacitinib 15 mg group. The corresponding figures for other bDMARD-exposed subjects in this set was 30.7% in the placebo group vs 65.6% in the upadacitinib 15 mg QD-group. The finding in the other analysis-set was consistent with the finding in the first analysis set. For bDMARD-intolerant subjects in the Placebo-Controlled upadacitinib 15 mg Analysis Set (NRI), the proportion that achieved LDA at week 12 was 11.9% in the placebo group vs 49.2% in the

upadacitinib group. The corresponding figures for other bDMARD-exposed subjects in this set was 13.9% vs 44.1%. The finding in the other analysis-set was consistent with the finding in the first analysis set.

The short-term efficacy of upadacitinib in combination with MTX versus other non-MTX csDMARDs was examined. To examine the short-term placebo-controlled efficacy of upadacitinib in combination with MTX versus other csDMARDs, a model-based analysis assessing the interaction between treatment effect and background csDMARD type was conducted for ACR20 and LDA based on DAS28 (CRP) at Week 12 within Studies M13-542 and M13-549, respectively. In study M13-549, for subjects treated with concomitant MTX (FAS, NRI), the proportion that achieved LDA at week 12 was 16.8% in the placebo group vs 49.1% in the upadacitinib 15 mg QD group. The corresponding figures for subjects treated with other csDMARDs were 20.7% in the placebo group and 45.1% in the upadacitinib 15 mg QD group. In study M13-542, for subjects treated with concomitant MTX (FAS, NRI), the proportion that achieved LDA at week 12 was 13.7% in the placebo group and 43.4% in the upadacitinib 15 mg QD group. The corresponding figures for subjects with other csDMARDs were 13.8% in the placebo group and 45.8% in the upadacitinib 15 mg QD group.

A cross-study analysis was conducted to provide an indirect comparison of the short-term efficacy of upadacitinib as monotherapy versus in combination with MTX in the MTX-IR population. A model-based analysis was conducted on subjects from Studies M13-549 and M15-555. Analyses were conducted for ACR20 and LDA based on DAS28 (CRP) at Week 12 (Study M13-549)/Week 14 (Study M15-555). According to this analysis (pooled analysis set; M13-549 and M15-555, NRI) the proportion of subjects that achieved LDA (at week 12/14) on upadacitinib 15 mg QD monotherapy was 44.7% and on upadacitinib 15 mg QD+MTX 48.6%.

Maintenance of efficacy should be demonstrated in a long-term randomized study where blinding and an active control is maintained for in total 12 months study duration; descriptive statistics may suffice. The applicant presented efficacy data through Week 60 for Studies M13-549 and M13-542 and through Week 48 for Studies M13-545 (active control until week 48), M14-465 (active control until week 48), and M15-555, with approximately 78%, 74%, 80%, 87%, and 84%, respectively, of subjects remaining in the study through the last summarized visit (by the data cut-off date). According to the presented descriptive AO data, the treatment effect of upadacitinib, including the joint damage preventing effect, appears to be maintained up to and beyond one year.

In conclusion, data from the primary efficacy analyses of the four pivotal Phase 3 clinical studies and the supportive phase 3 study in MTX-naïve patients, as well as the phase 2 dose-finding studies demonstrated efficacy of upadacitinib. Both doses of upadacitinib met all primary and ranked key secondary endpoints across all Phase 3 studies, including prevention of structural progression in two studies. Compared to adalimumab, higher rates of low disease activity were achieved at week 12 in one of the studies that included adalimumab as an active comparator.

Across studies, around half of the patients could attain a low disease activity state during the controlled periods of the studies (ranging from 12 to 26 weeks), and about one third of subjects achieved clinical remission. The long-term extensions of the studies are still ongoing, but interim data up to 60 weeks demonstrate that the treatment response to upadacitinib is preserved over time. The results were consistent across the different efficacy and patient-reported outcomes and in various subgroups.

3.3. Uncertainties and limitations about favourable effects

Similar short-term efficacy appears to be achieved by upadacitinib monotherapy compared to upadacitinib + MTX although a noteworthy limitation of the data is that direct head-to-head

comparisons between monotherapy and combination therapy are not available. However, little is known about the benefit of upadacitinib monotherapy vs the combination with MTX in terms of radiological progression and long-term outcome. For upadacitinib, radiological progression was measured as key secondary outcome in two studies; M13-545 and M14-465 in which one was indeed a monotherapy study (M13-545) and the other was not (M14-465). However, since M14-465 included MTX-IR and M13-545 included MTX-naïve subjects, a direct comparison between the outcome of these studies cannot be made.

3.4. Unfavourable effects

Adverse events

The frequency of adverse events in short-term analysis (3 months) was 49.6% when upadacitinib was given in monotherapy (compared to 48.3% for MTX), and 56% when upadacitinib was given in combination with other csDMARDs (vs 48.4% for placebo+csDMARD, and 48.3% for adalimumab+MTX). The frequency of SAEs was 3.0 % for upadacitinib in monotherapy (vs 2.3% for MTX) and 3.4% when upadacitinib was given in combination with other csDMARDs (vs 1.8 % for placebo+csDMARDs and 2.4% for adalimumab+MTX). A dose-dependent relationship was seen when comparing 15 and 30 mg upadacitinib.

Deaths

There were 20 cases of death among patients treated with upadacitinib 15 mg in the phase 3 studies. Cardiovascular disease was the most frequent cause of death. The exposure-adjusted IR of deaths was 0.5/100PY for upadacitinib 15 mg, 0.8 for MTX and 1.2 for adalimumab in the short-term analysis (3 month, based on data from all five phase III studies). The exposure-adjusted IR of deaths was 0.5 for upadacitinib, 0.3 for MTX and 0.9 for adalimumab in updated pooled long-term analysis to week 48 (based on all five phase III studies).

Serious infections

In short-term analysis (3 months), the frequency of serious infections was 0.6% for upadacitinib 15 mg in monotherapy (vs 0.4% for MTX), 1.2% for upadacitinib in combination with other csDMARDs (vs 0.6% for placebo+csDMARDs and 1.2% for adalimumab+MTX). During long-term exposure in study M14-465 with a direct comparison with adalimumab, the IR of serious infections was 4.1/100PY for upadacitinib 15 mg vs 4.3/100PY for adalimumab.

During long-term exposure (up to 1 year), the incidence rate of serious infections was lower for UPA 15 mg than for UPA 30 mg in pooled data.

Opportunistic Infections

In short-term analysis up to 3 months, opportunistic infections occurred in 0.5% of upadacitinib-treated subjects and 0.3% in placebo-treated subjects (both in combination with csDMARDs). In monotherapy up to 3 months, there were no opportunistic infections in the upadacitinib 15 mg group.

Herpes zoster

Episodes of herpes zoster were reported at an increased rate with upadacitinib compared to both placebo as well as either of the active controls, and reporting rates were higher with 30 mg than with 15 mg. In the Any Ph 3 UPA 15 analysis set (N = 2,630), the long-term EAER for herpes zoster with upadacitinib 15 mg was 3.7 E/100 PY. 75% of the events involved a single dermatome; there were

2 events of ophthalmic herpes zoster, 1 event of disseminated herpes zoster, and 5 events of postherpetic neuralgia. Risk factors for herpes zoster, as identified by the Applicant, were prior herpes zoster history, older age, as well as geographic region (with the reporting rate being higher in Asia). The observation of increased rates of herpes zoster is common across the class of JAK inhibitors.

Tuberculosis

There were 5 cases of active TB infection among upadacitinib-treated subjects. Upadacitinib is contraindicated in patients with active TB infections. In addition, as stated in Section 4.4 of the SmPC patients should be screened for latent TB before starting upadacitinib treatment.

Hepatic disorder

In short-term analysis up to 3 months, the proportion of subjects with ALT ≥ 3 × ULN was 2.1% in the upadacitinib group compared to 1.5% for placebo when upadacitinib was combined with csDMARDs, and 1.7% when upadacitinib was given in monotherapy (compared to 3.6% for MTX). Transaminase elevations is described in Section 4.8 of the SmPC at the CHMP's request.

Patients with severe hepatic impairment (Child Pugh C) were excluded from the phase 3 studies. As severe hepatic impairment is expected to lead to an increased exposure of upadacitinib, and considering the less favourable safety profile observed with the 30 mg dose, the CHMP requested upadacitinib to be contraindicated in patients with Child-Pugh C.

VTE

The IR of VTE was 0.8/100PY for UPA15 mg vs 0.4/100PY for placebo. During long-term exposure, the IR was 0.6/100 PY for upadacitinib 15 mg and MTX, vs 1.1/100PY for adalimumab. A warning is proposed in 4.4, which is considered acceptable.

A warning on the risk of VTE is included in Section 4.4 of the SmPC. At the CHMP's request, the SmPC has been modified to mention that if clinical features of DVT/PE occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

Gastrointestinal perforations

In the phase 2 and phase 3 studies, 5 subjects in the upadacitinib 15 mg group experienced GI perforations. There were no events of GI perforation identified in subjects receiving MTX/other csDMARDs, or adalimumab.

The observed frequency of gastrointestinal perforations was not higher among upadacitinib-treated subjects than frequency observed in a background population.

Neutropenia

There was a higher proportion of subjects in the UPA 15 and 30 mg groups experiencing neutropenia than in the placebo group. The fundamental concern of neutropenia being associated with an increased susceptibility to infections cannot be excluded.

Neutropenia is therefore considered an important unfavourable effect and is listed in section 4.8 of the SmPC. Dosing recommendations in case of neutropenia are also provided in Section 4.2 of the SmPC.

CPK elevations

CPK elevations were observed in 2.8 % of upadacitinib 15 mg-treated patients, vs in 0.6% of placebo-treated patients (both in combination with csDMARDs) during the first 3 months. The majority had a mild increase of >2.5-5 x ULN. This ADR is described in Section 4.8 of the SmPC.

MACE

There were 13 cases of cardiovascular death among upadacitinib-treated subjects; 7 on upadacitinib 15 mg and 6 on upadacitinib 30 mg. All of these cases had cardiovascular risk factors (such as hypertension, diabetes mellitus, smoking, hyperlipidaemia or obesity).

In the updated long-term exposure analysis of all phase 3 studies (data to week 48 and beyond), the exposure-adjusted IR for MACE was very similar for MTX (2/314 events/100PY, IR=0.6), upadacitinib 15 mg (16/2630 events/100PY, IR=0.5), and adalimumab (3/579 events/100PY, IR=0.5).

At the CHMP request, the Applicant has included a warning regarding the CV risk in section 4.4 of the SmPC. The risk for MACE is planned to be continuously followed post-approval.

Lipids

Upadacitinib 15 mg treatment was associated with increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by week 8 and remained stable thereafter. Up to 12/14 weeks, the following changes were noted for upadacitinib 15 mg:

- Mean LDL cholesterol increased by 0.38 mmol/L.
- Mean HDL cholesterol increased by 0.21 mmol/L.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 0.15 mmol/L.

Sections 4.2, 4.4 and 4.8 of the SmPC adequately reflect the risks and provide monitoring guidance for the prescribers.

3.5. Uncertainties and limitations about unfavourable effects

Important uncertainties relate to unfavourable effects of long latency and low frequency on one hand, and effects on multiple laboratory parameters with uncertain clinical correlates on the other hand. The long-latency low-frequency events of primary interest, for which long-term follow-up data will be required for a robust characterisation of any risk increase, are:

Malignancies

In data reported to date, the overall incidence of malignancies (0.8 n/100 PY in the Any PH 3 UPA 15 analysis set) was within the range reported for comparable programs, and the types of malignancies reported were variable and seem to reflect overall incidences of different malignancies in an RA population. However, a dose-dependent risk on NMSC cannot be excluded, but the observation is based on small numbers. At the CHMP's request, an adequate warning has been included in Section 4.4 of the SmPC. The risk of malignancy will be followed post approval.

Major adverse cardiovascular events

The overall incidence rate of adjudicated MACE of 0.5 n/100 PY for upadacitinib 15 mg reported in the program falls within the range reported in other programs, and in comparative analyses, the 95% CI for treatment comparisons against both adalimumab and MTX spanned 0. Upadacitinib-induced increases in cholesterol levels were not observed to correlate with the risk of MACE, and E/R analyses did not demonstrate exposure dependency in MACE events. At the CHMP request, the applicant has included a warning regarding the CV risk in section 4.4 of the SmPC. The risk for MACE will be followed post approval.

Venous thromboembolic events

The calculated overall EAIR of adjudicated VTE events (0.6 n/100 PY) for upadacitinib 15 mg was within the background incidence of 0.3 - 0.8 n/100 PY quoted by the Applicant for the general RA population. It was also lower than that observed for intra-program comparators (MTX and adalimumab). There is however a concern regarding an increased risk of VTE associated with other JAK inhibitors. A warning on the risk of VTE is included in Section 4.4 of the SmPC. At the CHMP's request, the SmPC has been modified to mention that if clinical features of DVT/PE occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment. The risk for VTE will be followed post approval.

The laboratory parameters of interest in terms of risk assessment are:

- **Hepatic enzyme elevations**

Upadacitinib was associated with a small (< 10 U/L) mean increase in hepatic enzymes that persisted on long-term treatment. However, most events were asymptomatic and transient even in the setting of continued use of upadacitinib and there is currently no evidence of actual hepatotoxicity.

Transaminase elevations is described in Section 4.8 of the SmPC at the CHMP's request.

- **Lymphocyte counts**

Upadacitinib, on one hand, induces an increase in mean lymphocyte counts that reverts to baseline over the course of several months. On the other hand, decreased counts were frequently observed in individual patients. With this mixed pattern, and currently no actual observation of an association of decreased lymphocyte counts being associated with increased infections, the finding is considered a limitation (in contrast to the consistent decrease in neutrophils being considered an actual unfavourable effect). Hence, monitoring guidelines and instructions on potential treatment interruptions are included in sections 4.2 and 4.4 of the SmPC.

- **Lipids**

Upadacitinib induces a rapid and persistent increase of 10-15% across all lipid classes. The clinical consequences, if any, remain to be determined. Sections 4.2, 4.4 and 4.8 of the SmPC adequately reflect the risks and provide monitoring guidance.

Deaths

Although the mortality does not seem to be increased in subjects treated with upadacitinib compared to adalimumab, mortality will be carefully evaluated post-approval.

Pregnancy and lactation

Studies in animals have shown reproductive toxicity. Upadacitinib was teratogenic in rats and rabbits with effects in bones in rat foetuses and in the heart in rabbit foetuses when exposed in utero. Pregnant and breastfeeding women were excluded from the upadacitinib clinical trials. Upadacitinib is contraindicated during pregnancy. Women of childbearing potential should be advised to use effective contraception during treatment and for 4 weeks following the final dose of upadacitinib.

Upadacitinib should not be used during breast-feeding.

Adequate risk minimization measures and pharmacovigilance activities are included in the RMP to address the risk of foetal malformation following exposure in utero.

Severe renal impairment

Upadacitinib was associated with a consistent increase in serum creatinine, averaging about 10% at the 15 mg dose. The rate of serious adverse events, severe adverse events and adverse events leading to discontinuation is increased in patients with mild renal impairment compared to patients with normal renal function, and the rates are increased even further in patients with moderate renal impairment. Increased rates are also seen in corresponding placebo groups. While exposure-response analyses may not suggest an increased risk of serious infections, a substantially higher risk of serious infections in subjects on upadacitinib 30 mg than 15 mg was clinically observed. Further safety information from the moderate renal impairment group is required post approval.

At CHMP's request, Section 4.2 of the SmPC includes precautionary message regarding patients with severely renal impaired patients. Use in patients with severe renal impairment is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Severe hepatic impairment

Patients with severe hepatic impairment (Child Pugh C) were excluded from the phase 3 studies. As severe hepatic impairment is expected to lead to an increased exposure of upadacitinib, and considering the less favourable safety profile observed with the 30 mg dose, the CHMP requested upadacitinib to be contraindicated in patients with Child-Pugh C.

Use in patients with moderate hepatic impairment is listed as a safety concern in the RMP and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP (see Section 2.7).

Combination with csDMARDs other than MTX

The majority of the patients on concomitant csDMARDs were on MTX. Due to paucity of data, the use of upadacitinib together with csDMARDs other than MTX is not considered to be sufficiently characterised. In fact, the safety profile in subjects treated with csDMARDs other than MTX seem to be less favourable than the safety profile in subjects treated with MTX. Hence, the Applicant withdrew this claim for use "with other csDMARDs" from the indication during the assessment.

3.6. Effects Table

Table 80: Effects Table for upadacitinib 15 mg QD

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
CR week 24, first line	Monotherapy; upadacitinib 15 mg QD vs MTX	% (95% CI)	48.3 (42.8, 53.8)	18.5 (14.2, 22.8)	Data does not pertain to the proposed target population but still provides some support through extrapolation	M13-545
LDA week 12, ⩾second line	add-on to csDMARD; upadacitinib 15 mg QD vs placebo	% (95% CI)	48.4 (41.8, 55.0)	17.2 (12.2, 22.2)		M13-549
CR week 12, ⩾second line	add-on to MTX; upadacitinib 15 mg QD vs placebo	% (95% CI)	28.7 (25.2, 32.2)	6.1 (4.3, 8.0)		M14-465
LDA week 12, ⩾second line	add-on to MTX; upadacitinib 15 mg QD vs adalimumab EOW/placebo	% (95% CI)	45.0 (41.2, 48.8)	28.7 (23.8-33.7) adalimumab 13.8 (11.2, 16.5) placebo		M14-465
LDA week 14, second line	monotherapy; upadacitinib 15 mg QD vs MTX	% (95% CI)	44.7 (38.1, 51.3)	19.4 (14.2, 24.7)	The value of the direct comparison between MTX and upadacitinib is limited due to the MTX arm being undertreated by definition but the outcome in monotherapy treatment arm can be compared to outcome in the treatment arm in add-on studies	M15-555
LDA week 12, third line	add-on to csDMARD; upadacitinib 15 mg QD vs placebo	% (95% CI)	43.3 (35.7, 50.9)	14.2 (8.9, 19.5)		M13-542
No radiographic progression, first line	Monotherapy; upadacitinib 15 mg QD vs MTX	% (95% CI)	87.5 (83.6, 91.3)	77.7 (72.6, 82.7)	Data does not pertain to the proposed target population but still provides some support through extrapolation	M13-545
No radiographic progression, ⩾second line	add-on to MTX; upadacitinib 15 mg QD vs placebo	% (95% CI)	83.5 (80.5, 86.5)	76.0 (72.5, 79.4)		M14-465
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
AEs	Monotherapy, 3 months	N (%)	265/534 (49.6)	MTX: 256/530 (48.3)		M13-545, M15-555
AEs	Monotherapy, 48 weeks	N (E/ 100PY)	1185 (345.4)	MTX: 953 (303.1)		M13-545
AEs	Combination with csDMARDs, 3months	N (%)	580/1035 (56.0) 348/650 (53.5)	Placebo + csDMARD:504/1042 (48.4) ADA: 158/327 (48.3)		M13-549, M14-465, M13-542 M14-465
AEs	Combination with MTX, 48 weeks	N (E/ 100PY)	3312 (266.4)	ADA: 1379 (294.8)		M14-465
SAEs	Monotherapy, 3 months	N (%)	16/534 (3.0)	MTX: 12/530 (2.3)		M13-545, M15-555
SAEs	Combination with csDMARDs, 3months	N (%)	35/1035 (3.4) 18/650 (2.8)	Placebo + csDMARD:19/1042 (1.8) ADA: 8/327 (2.4)		M13-549, M14-465, M13-542 M14-465
Serious infections	Monotherapy, 3 months	N (%)	3/534 (0.6)	MTX: 2/530 (0.4)		M13-545, M15-555
Serious infections	Combination with csDMARDs, 3months	N (%)	12/1035 (1.2)	Placebo + csDMARD:6/1042 (0.6)		M13-549, M14-465, M13-542
Serious infections	Combination with MXT, 48w	N (E/ 100PY)	51 (4.1)	ADA: 20 (4.3)		M14-465
Deaths	48 w, pooled data from all phase 3 studies	N (E/ 100PY)	20 (0.5)	MTX: 1 (0.3) ADA: 5 (0.9)		All phase 3 studies
MACE	48 w, pooled data from all phase 3 studies	N (E/ 100PY)	16 (0.5)	MTX: 2 (0.6) ADA: 3 (0.5)		All phase 3 studies

Abbreviations: CR= Clinical Remission (based on DAS28CRP<2.6). LDA=Low Disease Activity (based on DAS28 CRP≤3.2). QD=every day/daily. MTX=Methotrexate. CI=Confidence Interval. EOW= Every Other Week, ADA=adalimumab, PY= patient year.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

Study M13-545 demonstrates favourable effects that can to some extent be extrapolated to the proposed target population (2nd and 3rd line indication).

Study M13-549 indicates that when upadacitinib 15 mg is given as ≥2nd line RA treatment as add-on to csDMARD, after 3 months, the treatment goal low disease activity is achieved by almost half of the patients. This effect is clearly clinically relevant and of importance for the overall assessment of benefit in the proposed target population.

Study M14-465 showed that when upadacitinib 15 mg is given as ≥2nd line RA treatment as add-on to MTX, after 3 months, 28.7% of the patients achieve the very high hurdle endpoint clinical remission. The corresponding figure for placebo was 6.1%. After 26 weeks a difference between the two groups with regards to the proportion of subjects with no radiographic progression was noted. One of the key secondary endpoints involved a non-inferiority comparison vs the active comparator adalimumab. The CHMP considered that the comparator was relevant as it represents one of the standards of care choices in second line treatment. The proportion of subjects achieving low disease activity at Week 12 was compared and non-inferiority was met.

It is also of interest that in M14-465, upadacitinib 15 mg does not perform worse in the subgroup with previous bDMARD use compared to group with no previous bDMARD use (patients with <3 month exposure of bDMARD/who had discontinued bDMARD due to intolerability could be included in the study). Thus, when upadacitinib is added to MTX in a group of MTX-IR patients that also have previous bDMARD experience (i.e. would correspond more to the 3rd line situation), almost a third achieve the high-hurdle endpoint clinical remission.

Study M15-555 shows that when upadacitinib 15 mg is given as monotherapy 2nd line, after 14 weeks, 44.7% of the subjects achieve the treatment goal low disease activity. Although the superiority comparison between MTX and upadacitinib that was carried out within this study has its clear limitations (the MTX arm being undertreated by definition, as pointed out in previous SA), cross-study comparisons that include the comparison between upadacitinib 15 mg monotherapy and upadacitinib 15 mg + MTX (an acceptable approach according to previous CHMP SA) indicate that at least short term, these two treatment regimens confer similar beneficial effects. Thus, taken together, the CHMP consider the data clinically relevant to support the proposed monotherapy indication second line.

Study M13-542 indicates that also when upadacitinib 15 mg is given 3rd line as add-on to csDMARD, >40% of the patients achieve the treatment goal low disease activity. Although the limitations with regards to the comparison with placebo are acknowledged (as pointed out in previous SA), the results are considered clinically relevant.

The treatment effect of upadacitinib, including the joint damage preventing effect, appears to be maintained up to and beyond one year.

Across studies, a rapid onset of effect has been noted which is favourable for patients suffering from acute symptoms of arthritis.

Another favourable effect is the oral mode of administration, which is convenient for patients.

Importance of unfavourable effects

Safety problems with upadacitinib include infections, neutropenia, cardiovascular events, thrombosis, elevated liver enzymes and elevated CPK. These risks are considered possible to handle through adequate information in the SmPC. Long-term effects with regards to malignancy are currently unclear and will be closely monitored post approval (see RMP section).

The risk of increased infectious liability is inherent for any immunomodulatory therapy and is also clearly present with upadacitinib. In this respect, the CHMP considers that this risk can be managed with continued vigilance and educational efforts, as described in the RMP. The same holds true for herpes zoster; prescribers and patients considering upadacitinib therapy will need to accept an increased susceptibility to an episode of herpes zoster, and the risk will be greatest for patients with a previous history of zoster.

Regarding mortality, in the short-term analysis set (3 months) based on the phase III studies (M13-545, M13-549, M14-465, M15-555, M13-542), the IR for death appeared comparable for the upadacitinib 15 mg, MTX, placebo and adalimumab. It is noted that the lowest figure was actually seen for upadacitinib 15 mg although the comparison is hampered by the small exposure and low number of absolute events in the different arms. Also in the long-term analysis set (48 weeks) based on the phase 3 studies (M13-545, M13-549, M14-465, M15-555, M13-542), the calculated mortality rates appear similar. The rate for upadacitinib 15 mg was numerically higher than for MTX but lower than for adalimumab but again the comparison is hampered by relatively low exposure and absolute number of events (in the comparator arms). The mortality rates did not substantially differ according to treatment received in this population with active, potentially debilitating inflammatory disease in which underlying risk factors for both CV death and infections are expected to be frequent. Again, at the CHMP's request, those risks are adequately described in the SmPC and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP.

3.7.2. Balance of benefits and risks

The data submitted support that upadacitinib, in the proposed posology 15 mg once daily (taken orally), has a clinically relevant effect with regards to in inducing remission or low disease activity in patients with active RA both as 2nd and 3rd line treatment. Both upadacitinib monotherapy and upadacitinib in combination with different csDMARDs, including methotrexate, are able to induce remission and low disease activity. The magnitude of effect of upadacitinib was non-inferior to adalimumab (direct comparison). For many of the analysed outcomes, an effect was seen as early as week 1-2. A favourable effect with regards to haltering radiological progression has been demonstrated.

Unfavourable effects include infections, neutropenia, elevated liver enzymes, elevated lipid levels, and CPK elevation. The reported study mortality was comparable to that of the active comparator adalimumab. Unfavourable effects are adequately described in the SmPC and adequate risk minimisation measures / additional pharmacovigilance activities are in included in the RMP.

From an efficacy-point-of view, the combination of upadacitinib and other csDMARDs could have been considered supported by the CHMP. However, from a safety perspective, the CHMP considered that it was not appropriate to conclude positively on an indication in combination with other csDMARDs. Indeed, the observed safety profile was less favourable with the combination of upadacitinib and other csDMARDs. Hence, the Applicant withdrew this claim from the indication during the assessment (see Safety section). The revised indication is as follows:

"*RINVOQ is indicated 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 CHMP considered that the favourable effects in this revised indication outweigh the unfavourable effects.

3.8. Conclusions

The overall benefits/risks of Rinvoq is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rinvoq is favourable in the following indication:

RINVOQ is indicated 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 CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

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

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 RA patients and the need to consider typical CV risk factors (e.g., hypertension, hyperlipidaemia) when treating RA 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that upadacitinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.