Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Upadacitinib

Proprietary Product Name: Rinvoq

Sponsor: AbbVie Pty Ltd

April 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACR	American College of Rheumatology
ACR20	20% improvement in American College of Rheumatology response criteria
ACR50	50% improvement in American College of Rheumatology response criteria
ACR70	70% improvement in American College of Rheumatology response criteria
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-CCP	Anti-cyclic citrullinated peptide
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific Annex
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve over the dosing interval
AST	Aspartate aminotransferase
BD	Twice daily, Latin: *bis in die*
bDMARD	Biological disease-modifying anti-rheumatic drug(s)
BRCP	Breast cancer resistance protein
CCP	Cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CHMP	Committee for Medicinal Products for Human Use (EU)
CPMP	Committee for Proprietary Medicinal Products (EU)
CI	Confidence interval

Abbreviation	Meaning
C_{max}	Maximum serum drug concentration
CMI	Consumer Medicines Information
CNS	Central nervous system
CPK	Creatine phosphokinase
CrCL	Creatinine clearance
CRP	C-reactive protein
CS	Corticosteroid(s)
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug(s)
CV	Coefficient of variation
CYP	Cytochrome P450
DAS	Disease Activity Score
DLP	Data lock point
DMARD	Disease modifying anti-rheumatic drug(s)
EAER	Exposure adjusted event rate
EAIR	Exposure adjusted incidence rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency (EU)
ER	Extended release
ES	Erosion score
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FAS	Full analysis set
FDA	Food and Drug Administration (US)
HAQ-DI	Health Assessment Questionnaire – Disability Index

Abbreviation	Meaning
HCP	Healthcare professional
HCQ	Hydroxychloroquine
HDL	High density lipoprotein
hsCRP	High sensitivity C-reactive protein
ICH	International Council for Harmonisation
IL	Interleukin(s)
IL-6	Interleukin 6
IL-7	Interleukin 7
Ig	Immunoglobulin
IR	Immediate release
JAK	Janus kinase
JAK1	Janus kinase 1
JSN	Joint space narrowing
LDL	Low density lipoprotein
LEF	Leflunomide
LS	Least squares
M4	Main human metabolite of upadacitinib
MACE	Major adverse cardiovascular events
mITT	Modified intention-to-treat
mTSS	Modified Total Sharp Score
MTX	Methotrexate
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drug(s)
OAT	Organic anion transporter
PBO	Placebo
PD	Pharmacodynamic(s)

Abbreviation	Meaning
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PO	Orally, Latin: *per os*
Pop PK	Population pharmacokinetic(s)
PJP	*Pneumocystis jiroveci* pneumonia
PP	Per protocol
pSTAT3	Phosphorylated signal transducer and activator of transcription 3
PT	Preferred Term
PY	Patient-years
QD	Once daily, Latin: *quaque die*
QR	Quick Response
QTc	Cardiac QT interval corrected for heart rate
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SDAI	Simplified Disease Activity Index
SOC	System Organ Class
SSZ	Sulfasalazine
STAT	Signal transducer and activator of transcription
STAT3	Signal transducer and activator of transcription 3
TB	Tuberculosis
$T_{1/2}$	Apparent terminal elimination; elimination half life

Abbreviation	Meaning
T_{max}	Time to maximum plasma concentration
TNF	Tumour necrosis factor
TYK2	Tyrosine kinase 2
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
USA	United States of America
VAS	Visual Analogue Scale
VTE	Venous thromboembolism
WPAI	Work productivity and activity impairment

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	17 January 2020
Date of entry onto ARTG:	17 January 2020
ARTG number:	312687
, *Black Triangle Scheme*	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Active ingredient:	Upadacitinib
Product name:	Rinvoq
Sponsor's name and address:	AbbVie Pty Ltd, 241 O'Riordan St, Mascot NSW 2020
Dose form:	Modified release tablet
Strength:	15 mg
Container:	Blister pack
Pack sizes:	7 tablets (starter pack) and 28 tablets (monthly pack)
Approved therapeutic use:	*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 disease-modifying anti-rheumatic drugs (csDMARDs).*
Route of administration:	Oral
Dosage:	Therapy with Rinvoq should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis. The recommended oral dose of Rinvoq is 15 mg once daily with or without food. Rinvoq should not be initiated in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm^3, an absolute neutrophil count (ANC) less than 1000 cells/mm^3 or who have haemoglobin levels less than 8 g/dL (see Product Information Sections 4.4 Special Warnings And Precautions For Use and

4.8 Adverse Effects).

Rinvoq may be used as monotherapy or in combination with methotrexate or other csDMARDs.

Combination with other janus kinase (JAK) inhibitors or potent immunosuppressants has not been studied and is not recommended.

For further information, refer to the Product Information.

Product background

This AusPAR describes the application by AbbVie Pty Ltd (the sponsor) to register a new chemical entity, upadacitinib (Rinvoq), for the treatment of adult patients with rheumatoid arthritis 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 or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).*

Upadacitinib is a selective and reversible inhibitor of Janus kinase 1 (JAK1).

Janus kinases (JAK) are important intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, haematopoiesis and immune surveillance. They are involved in various diseases including haematological malignancies and autoimmune diseases such as rheumatoid arthritis.

The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) that work in pairs to phosphorylate and activate signal transducers and activators of transcription (STAT). This phosphorylation, in turn, modulates gene expression and cellular function. JAK1 is important in inflammatory cytokine signals while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function.

Upadacitinib more potently inhibits JAK1 compared to JAK2 and JAK3. In cellular potency assays that correlated with the in vivo pharmacodynamic responses, upadacitinib demonstrated 33 to 197 fold greater selectivity for JAK1-associated signalling over JAK2-JAK2 signalling. In enzyme assays, upadacitinib had > 50 fold selectivity for JAK1 over JAK3.

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterised by polyarticular inflammation of predominately small to medium sized joints in a symmetric pattern. The condition affects approximately 1% of the Australian population and its prevalence increases with age. The primary lesion is synovitis whereby immune cells invade the normally acellular synovium leading to the formation of inflammatory pannus. This hyperplastic invasive tissue causes cartilage breakdown, bony erosion and ultimately loss of function of the affected joints. Systemic involvement may also occur, and there is an increased risk of atherosclerosis, infection and lymphoma over time, particularly if the condition is insufficiently controlled.

The treatment of RA emphasises the importance of achieving clinical remission, or at least low disease activity, and in addition to treating the signs and symptoms of RA, an impact on inhibiting the structural bone damage of the condition is highly desirable. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs; in particular, methotrexate

(MTX)), alone or in combination with each other, are the initial recommended treatments for RA. Biological disease-modifying anti-rheumatic drugs (bDMARDs) either as add-on or as single drug therapy is the next recommended line of therapy in active RA after csDMARD failure or intolerability. Inhibition of JAK mediated pathways is an established treatment approach for adult RA patients with two current JAK inhibitors (tofacitinib and baricitinib) approved in Australia for this indication. Upadacitinib is claimed to have greater affinity for the JAK1 isoform (*in vitro*) and less potency for the JAK2, JAK3 and TYK2 enzyme systems compared with less selective JAK inhibitors such as baricitinib and tofacitinib.

The currently approved rheumatoid arthritis indications for tofacitinib and baricitinib in Australia are as follows:

> *Tofacitinib*
>
> *Xeljanz is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. Xeljanz can be used alone or in combination with conventional synthetic disease-modifying antirheumatic drugs (DMARDs), including methotrexate.*
>
> *Baricitinib*
>
> *Olumiant is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately, or who are intolerant, to one or more DMARDs.*
>
> *Olumiant can be taken as monotherapy or in combination with cDMARDs, including methotrexate (methotrexate).*

The proposed dose of Rinvoq is 15 mg once daily with or without food and the sponsor has requested that upadacitinib may be used as monotherapy or in combination with methotrexate or other csDMARDs.

The submission is supported by five pivotal Phase III studies, including studies in methotrexate naïve subjects and subjects with prior treatment with csDMARDs and/or bDMARDs. Two of the studies examined radiological outcomes and two of the studies were monotherapy studies with methotrexate as a comparator. One long-term, Phase II, safety study was also included along with a number of supportive and pharmacology studies.

Regulatory status

Upadacitinib has not been previously registered or considered by the TGA.

At the time the submission was under consideration, upadacitinib was currently registered in the United States of America (USA) only (August 2019) and had received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP), formerly known as Committee for Proprietary Medicinal Products(CPMP) in the European Union (EU) (October 2019). The application is under evaluation in Canada, Switzerland and New Zealand. The approved indication in the USA and positive opinion in EU are as follows, below.

USA

> *Rinvoq (upadacitinib) is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.*

Limitation of Use: Use of Rinvoq in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended.

European Union (CHMP opinion)

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.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

The following table summarises the key steps and dates for this application.

Table 1: Timeline for Submission PM-2018-05603-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	31 January 2019
First round evaluation completed	1 August 2019
Sponsor provides responses on questions raised in first round evaluation	30 August 2019
Second round evaluation completed	18 October 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	31 October 2019
Sponsor's pre-Advisory Committee response	13 November 2019
Advisory Committee meeting	6 December 2019
Registration decision (Outcome)	17 January 2020
Completion of administrative activities and registration on the ARTG	17 January 2020
Number of working days from submission dossier acceptance to registration decision*	221

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

The following EU guideline adopted by the TGA is relevant to this submission, besides the general guidelines:

- CPMP/EWP/556/95 rev 1 Final: 'Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for the Treatment of Rheumatoid Arthritis' (effective 29 January 2007).

Quality

The quality evaluator has recommended approval with respect to chemistry and manufacturing control. The starting materials and synthetic process are adequately controlled. Upadacitinib is a synthetic substance with many impurities identified, some of which are mutagenic. In the final specifications, non-mutagenic impurities are controlled as per the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use guidelines;[1,2] and other mutagenic impurities are below the threshold of toxicological concern.

The drug substance specifications include appropriate tests and acceptable limits for appearance.

The finished product is controlled using the finished product specifications. The specifications include appropriate tests and acceptable limits for appearance, identity, assay, uniformity of content and water content. Data was provided to support a shelf life of 24 months when stored below 30ºC.

A bioequivalence study demonstrated acceptable bioequivalence for the 15 mg tablet proposed for marketing and that used in the Phase III clinical studies. A high fat meal increased bioavailability of a 30 mg tablet by 30% (area under the drug concentration versus time curve (AUC)) however; the sponsor is requesting administration with or without food (as approved in the USA).

Hypromellose is used to provide the extended release properties of the dosage form with bioavailability of the extended release formulation being about 76% of the immediate release formulation. An immediate release formulation was used in the Phase II studies. Upadacitinib showed no accumulation in plasma with multiple once a day (QD) dosing using the extended release formulation.

There was some concern about the majority of the clinical batches not complying with the proposed dissolution limits; however, this has subsequently been resolved.

The carton labels are acceptable and include a Quick Response (QR) code that links to the PI, Consumer Medicine Information (CMI) and a voluntary non-promotional enrolment page for a patient support program. This program provides access to medication management, health coaches for exercise, psychologists, counsellors, dietitians, or exercise physiologists. The sponsor has full control over the content of the web address of the QR code, which is Australian owned. The website complies with the Therapeutic Goods Advertising Code or other legislative advertising requirements/restrictions.

[1] ICH Q3A (R6): International Council on Harmonisation, Harmonised Guideline; Impurities: guideline for residual solvents. Adopted on 20 October 2016.
[2] ICH M7 (R1): International Council on Harmonisation, Harmonised Guideline; Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. Current Step 4 version dated 31 March 2017.

Nonclinical

The nonclinical evaluator has no objections on nonclinical grounds to the registration of upadacitinib for the proposed indication. No major deficiencies were identified in the submission.

The pharmacology studies support the proposed monotherapy indication and proposed clinical dose. No nonclinical pharmacology studies to support the proposed combination therapy with other csDMARDs were submitted. Upadacitinib displayed greater potency at JAK1 and its associated signalling pathways than other JAKs.

No off-target effects were identified in adequately conducted secondary pharmacodynamics (PD) studies.

Some effects associated with inhibition of JAK2 signalling (such as effects on red blood cell parameters) may be seen during clinical use. Inhibitors/inducers of cytochrome P450 (CYP) isozyme 3A4, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) may alter upadacitinib exposures. Overall, the pharmacokinetic (PK) profile in animals was qualitatively similar to that of humans. Tissue distribution of upadacitinib was wide but penetration into brain and spinal cord was very limited. Retention in melanin-containing tissues was high in pigmented rats, but upadacitinib was not phototoxic. Upadacitinib was by far the dominant circulating species in humans and laboratory animals. The main human metabolite (M4) is of low toxicological concern. No adverse effects on QTc;[3] interval or respiratory or central nervous system (CNS) function are predicted during clinical use.

The safety studies indicate the following as potentially clinically relevant: mild effects on blood pressure (decrease) and heart rate (increase), decreases in lymphocytes and immunosuppression with a consequent higher risk of infection and malignancies may be seen in patients, mild anaemia and teratogenicity if used during pregnancy (Category D in pregnancy).[4]

Fertility was unaffected in rats and upadacitinib and/or its metabolites crossed the placenta in rats and could be detected in fetal tissues. However, an increased incidence of resorptions, post implantation loss with reduced litter size and fewer viable embryos were observed in the fertility study at ≥ 25 mg/kg/day orally (PO). An increased incidence of preimplantation loss was seen at ≥ 5 mg/kg/day PO. Breast-fed infants are likely to be exposed to drug-related material following maternal exposure and breastfeeding is not recommended during treatment. Upadacitinib was not mutagenic in the bacterial mutation assay or clastogenic *in vitro* (in human lymphocytes) or *in vivo* (in the rat micronucleus test). While exposures were low, there was no evidence of carcinogenic potential in the combined set of studies.

[3]The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

[4] Pregnancy category D: Have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Clinical

The clinical evaluator has recommended approval. The clinical dossier included:

- 22 clinical pharmacology studies, includingpharmacokinetic (PK) data from 8 Phase II and Phase III studies,
- 2 combined population pharmacokinetic (PopPK) analyses,
- 3 exposure response analyses,
- 5 pivotal Phase III studies,
- 2 supporting dose-ranging Phase II studies, one ongoing long term Phase II extension study and one Phase IIb/III study in Japanese patients.

The following information is derived from the clinical evaluation report.

Pharmacology

The pharmacology studies included 16 key studies (using immediate release (IR) and extended release (ER) formulations) and other studies that characterised the bioavailability of different upadacitinib formulations. The clinical studies also contributed PK data. Upadacitinib was administered as an IR capsule formulation in early Phase I and RA Phase II studies, and as an ER once daily tablet formulation in the later studies and in the pivotal Phase III studies. The pharmacology studies included healthy volunteers, patients with renal and hepatic impairment and six drug-drug interaction studies. Some of the key PK conclusions are:

- Orally administered upadacitinib is rapidly absorbed with median time to peak plasma concentration (T_{max}) of approximately 1 hour and 2 hours under fasting and non-fasting conditions (IR formulation), respectively.
- No absolute bioavailability has been conducted with upadacitinib, but the relative bioavailability of the ER formulation investigated in the Phase III studies versus oral solution is 70%.
- The relative bioavailability of the ER tablet formulation used in the Phase III studies compared to the IR capsule formulation of upadacitinib assessed in the Phase II trials is 76%. In Study M15-878, the proposed commercial formulation of upadacitinib (ER18) achieved PK similarity margins with the ER tablets used in the pivotal Phase III clinical trials.
- Ingestion of upadacitinib following a high fat, high calorie meal compared to drug administration under fasted conditions, results in an increase in upadacitinib maximum serum drug concentration (C_{max}) of 39% and an increase in AUC of 29%. The sponsor asserts that the administration of upadacitinib with meals is not associated with a clinically relevant effect on drug exposure and during the Phase II and Phase III studies upadacitinib was taken without regard to meals.
- Steady state is reached after the fourth dose of upadacitinib with minimal drug accumulation after multiple drug ingestion. Hence, multi-dose PK for upadacitinib is largely predictable with single dose data.
- Regarding dose proportionality, exposure to upadacitinib increases in a proportional manner over all evaluated immediate- and extended-release dose ranges. This encompassed the daily dose ranges of 1 to 48 mg using the IR formulation, and 7.5 to 45 mg using the ER formulation.

- Mean apparent volume of distribution at steady state after oral dosing with upadacitinib 15 mg and 30 mg ER formulation was 294 L (PopPK data). Upadacitinib is a substrate *in vitro* for P-gp and BRCP. Efflux transporters such as P-gp and BRCP, and their inhibitors are not anticipated to have clinically relevant effects on upadacitinib absorption or disposition.
- Upadacitinib is approximately 52% bound to human plasma proteins.
- From the human radioactively labelled (^{14}C) Study M13-548, 43% of upadacitinib is excreted in the urine (mainly as parent drug) and 53% is excreted in faeces. There are no biologically active metabolites.
- The mean apparent terminal elimination (elimination half life; $T_{1/2}$) of upadacitinib in the plasma ranges from 6 to 15 hours with a biphasic pattern of decline after reaching C_{max}.
- Upadacitinib metabolism is mediated by CYP3A4 with a potential minor contribution from CYP isozyme 2D6.
- Subjects with mild and moderate hepatic impairment compared to healthy volunteers with normal hepatic function have point estimates for upadacitinib AUC central values that are 28% and 24% higher, respectively, than subjects with normal hepatic function (Study M13-539).
- Subjects with mild renal impairment (creatinine clearance (CrCL) of 60 to 90 mL/min) have only small insignificant increases in AUC compared to those with normal renal function (Study M13-551). The PI notes the increase in AUC is 18%, 33% and 44% in subjects with mild, moderate and severe renal impairment compared with subjects with normal renal function. The PK of upadacitinib does not appear to be substantially affected by age, gender, ethnicity or body weight.
- The PK characteristics of upadacitinib in relation to C_{max} and AUC demonstrate low to moderate degrees of intra-subject and inter-subject variability across the tested dose range.
- A total of six *in vivo* drug-drug interaction studies in humans have been performed. The results indicate that upadacitinib did not appear to have clinically relevant effects on some concomitant medications or probe substrates although there were some PK changes (see Tables 3 and 4 from US Prescribing Information).[5] Ketoconazole increases exposure to upadacitinib AUC by approximately 75% and rifampicin decreases upadacitinib AUC by 61%. No specific study has been conducted examining the concomitant ingestion of a drug that increases gastric pH (such as omeprazole) and its effect on the absorption kinetics of upadacitinib.

Studies contributing pharmacodynamic (PD) data include primary pharmacology for the effect on phosphorylated STAT formation, effect on QT interval;[6] effect on haematological parameters and population PD and PK-PD analyses. Some of the key conclusions on pharmacodynamics are:

- Inhibition of the JAK-STAT pathway by upadacitinib is reversible in nature. The decrease in the interleukin 6 (IL-6) stimulated phosphorylated signal transducer and activator of transcription 3 (pSTAT3) formation in response to single and multiple doses of upadacitinib therapy was measured in two clinical pharmacology studies (Studies M13-401 and M13-845) as the primary PD marker for JAK1 activity. The PD

[5] United States Prescribing Information for Rinvoq (upadacitinib), extended-release tablets, first approved 16 August 2019.
[6] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

data from these two studies were consistent and showed a dose dependent inhibition of pSTAT3 formation in response to cytokine stimulation in the single dose range of 1 to 48 mg (Study M13-401), and with multiple twice daily doses of 3 to 24 mg for up to14 days (Study M13-845). The clinical evaluator comments there is no evidence for a cumulative effect on cytokine stimulated pSTAT3 formation with repeated dosing of upadacitinib.

- The Phase I studies also examined the effect of upadacitinib upon interleukin 7 (IL-7) induced STAT5 phosphorylation as a marker for JAK1/JAK3 activity. In Study M13-845, the 3 mg dose of upadacitinib (IR formulation) provided a similar mean maximal inhibition (at 1 hour) of IL-6-induced STAT3 phosphorylation to 5 mg of tofacitinib, while a higher upadacitinib dose (12 mg) provided similar IL-7-induced phosphorylation to 5 mg dose of tofacitinib.
- Although changes in pSTAT levels mirror the PK profile of upadacitinib, the PK/PD relationship is not direct for the clinical efficacy endpoints such as American College of Rheumatology (ACR) response criteria;[7] and Disease Activity Score 28 joints (DAS28) response;[8] where there is a delay in any observable change. Therefore, the PK half-life does not translate into the efficacy PD half-life, and efficacy is more likely to relate to the daily average exposure (or AUC) to upadacitinib.
- Plasma exposure to upadacitinib in Japanese and Chinese subjects were 20% to 30% higher compared to Western subjects. A 25% increase in plasma exposure with upadacitinib 15 mg once daily therapy is predicted to have similar probability of decreases in haemoglobin, lymphopaenia (Grade 3 or higher) and/or serious infections to inter-subject variability with 15 mg once daily exposure.
- Upadacitinib in IR daily doses up to 48 mg does not cause any significant effects on cardiac repolarisation such as prolongation of the QT interval in normal healthy subjects. A thorough QT study was not required by the FDA or the European Medicines Agency (EMA).

Efficacy

Upadacitinib was investigated in the Phase II program between 3 mg twice daily to 18 mg twice daily or 24 mg once daily (using an IR tablet formulation). These trials supported the choice of the two daily upadacitinib dose regimens (15 mg and 30 mg extended release formulation) for evaluation in the Phase III program. The totality of data supported the once daily administration of upadacitinib 15 mg (ER formulation) as the recommended dose. Additionally, upadacitinib 7.5 mg dose in Japanese patients was on the plateau of the exposure response curve indicating that the 7.5 mg dose will be effective in some patients. Upadacitinib could be given orally with or without food in the pivotal Phase III studies.

[7] The ACR response criteria score is a composite measure of improvement in the number of tender and number of swollen joints, and an improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure, visual analog pain scale, and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).It was developed and validated by the American College of Rheumatology. The ACR score is reported as percentage improvement, comparing rheumatoid arthritis disease activity at two discrete time points (usually Baseline and a specified post-Baseline time point comparison). A ACR20/ACR50/ACR70 response is ≥ 20%/50%/70% improvement respectively, with ACR50 responders also being ACR20 responders, and ACR70 responders also being both ACR20 and ACR50 responders.

[8] The DAS28 (Disease Activity Score 28) is a system developed and validated by the EULAR (European League Against Rheumatism) to measure the progress and improvement of rheumatoid arthritis. Calculation of a DAS28 score involves the combination of an examination of 28 specified joints for tenderness upon touching and swelling, the erythrocyte sedimentation rate (ESR) via blood sample, and the patient's subjective assessment of disease activity during the preceding 7 days on a scale between 0 ('no activity')and 100 ('highest activity possible'. DAS28 is often used in clinical trials for the development of RA. DAS28 values range from 2.0 to 10.0; higher values mean a higher disease activity.

Pivotal studies

The 5 Phase III studies were designed to investigate the efficacy and safety of upadacitinib in different populations (methotrexate naive, csDMARD inadequate responders, and bDMARD inadequate responders) at 2 different dose levels (15 mg and 30 mg once daily). Studies compared upadacitinib to 2 active comparators (oral methotrexate and 40 mg adalimumab given fortnightly by subcutaneous (SC) injection) or placebo. Three of the Phase III studies were conducted in the csDMARD inadequate responder population, of which one study required patients to receive concomitant methotrexate as background therapy. The Phase III studies are supported for efficacy by two completed Phase II studies and one supportive study in Japanese patients.

A summary of the design of the Phase III studies is provided below in Table 2.

Table 2: Summary of the design of the Phase III 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.

All five of the pivotal Phase III studies in this submission were multicentre, multinational, randomised, double blind, active and/or placebo controlled trials conducted in adult subjects (in the outpatient or ambulatory care setting) with moderately to severely active

RA at baseline. All studies have a randomised controlled period and an ongoing long-term extension period, for a total study duration of 5 years each. Subjects had a diagnosis of RA based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 Criteria for Classification of RA and had at least 6 tender and swollen joints (of 68/66 joints examined) plus a high-sensitivity C-reactive protein (hsCRP) measurement ≥ 3 mg/L (central laboratory) at screening (or qualifying C-reactive protein (CRP) ≥ 5 mg/L for X-ray based Studies M13-545 and M14-465). In addition, to be eligible for inclusion in Study M13-545, patients needed to have at least 1 RA related bone erosion (by local reading), or in the absence of a documented bone erosion be positive for both rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) autoantibodies at screening. In order to be eligible for inclusion in Study M14-465 patients needed to have at least 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 at screening. In all studies, subjects were allowed concomitant oral corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) provided the doses were stable.

The studies assessed signs and symptoms of RA, physical functioning and disability, health-related quality of life and progression of structural joint damage as assessed by X-rays. The primary efficacy endpoints were either ACR (ACR20 or ACR50);[7] for the US or complete remission or low disease activity for the EU. The primary and ranked secondary efficacy endpoints are summarised by the sponsor in Table 3.

Table 3: Summary of the primary and ranked secondary efficacy endpoints

	Study M13-545			Study M13-549		Study M14-465		Study M15-555		Study M13-542	
	FDA	EMA	PMDA	FDA	EMA	FDA	EMA	FDA	EMA	FDA	EMA
Primary Efficacy Endpoint											
	ACR50	CR based on DAS28 (CRP)[b]	ACR20 and ΔmTSS[b]	ACR20	LDA based on DAS28 (CRP)	ACR20	CR based on DAS28 (CRP)	ACR20[a]	LDA based on DAS28 (CRP)[a]	ACR20	LDA based on DAS28 (CRP)
Ranked Key Secondary Efficacy Endpoints											
Ranking	US FDA	EMA	Japan PMDA	US FDA	EMA	US FDA	EMA	US FDA	EMA	US FDA	EMA
1	ΔDAS28 (CRP)	ΔDAS28 (CRP)[c]	ΔDAS28 (CRP)	ΔDAS28 (CRP)	ΔDAS28 (CRP)	ΔDAS28 (CRP)	ΔmTSS[d]	ΔDAS28 (CRP)[b]	ΔDAS28 (CRP)[b]	ΔDAS28 (CRP)	ΔDAS28 (CRP)
2	ΔHAQ-DI	ΔHAQ-DI[c]	ΔHAQ-DI	ΔHAQ-DI	ΔHAQ-DI	ΔmTSS[d]	LDA based on DAS28 (CRP)	ΔHAQ-DI[b]	ΔHAQ-DI[b]	ACR50	ACR20
3	ΔmTSS[c]	ACR50[c]	LDA based on DAS28 (CRP)	ΔSF-36 PCS	ACR20	ΔHAQ-DI	ΔDAS28 (CRP)	ΔSF-36 PCS[b]	ACR20[b]	ΔHAQ-DI	ACR50
4	LDA based on DAS28 (CRP)	ΔmTSS[c]	CR based on DAS28 (CRP)[c]	LDA based on DAS28 (CRP)	ΔSF-36 PCS	ACR50 NI upadacitinib versus adalimumab	ΔHAQ-DI	LDA based on DAS28 (CRP)[b]	ΔSF-36 PCS[b]	LDA based on DAS28 (CRP)	ΔHAQ-DI
5	CR based on DAS28 (CRP)[c]	LDA based on DAS28 (CRP)[c]	ΔSF-36 PCS	CR based on DAS28 (CRP)	CR based on DAS28 (CRP)	ΔSF-36 PCS	ACR20	CR based on DAS28 (CRP)[b]	CR based on DAS28 (CRP)[b]	ACR70	ACR70
6	ΔSF-36 PCS	ΔSF-36 PCS[c]		LDA based on CDAI	LDA based on CDAI	LDA based on DAS28 (CRP)	LDA based on DAS28 (CRP) NI upadacitinib versus adalimumab	ΔMorning stiffness duration[b]	ΔMorning stiffness duration[b]	ΔSF-36 PCS	ΔSF-36 PCS
7		No radiographic progression (ΔmTSS ≤ 0)[c]		ΔMorning stiffness duration	ΔMorning stiffness duration	CR based on DAS28 (CRP)	ΔSF-36 PCS			ACR20[a]	ACR20[a]
8				ΔFACIT-F	ΔFACIT-F	LDA based on CDAI	LDA based on CDAI				
9						ΔMorning stiffness duration	ΔMorning stiffness duration				
10						ΔFACIT-F	ΔFACIT-F				
11						ACR50 superiority of upadacitinib versus ADA	No radiographic progression (ΔmTSS ≤ 0)[d]				
12						ΔPatient's Assessment of Pain superiority of upadacitinib versus ADA					

Δ = change from baseline; ACR20/50 = American College of Rheumatology 20/50 response; ADA = adalimumab; CDAI = Clinical Disease Activity Index; CR = clinical remission; CRP = C-reactive protein; DAS28 = disease activity score 28 joints; EMA = European Medicines Agency; FACIT-F = Functional Assessment of Chronic Illness Therapy - Fatigue; FDA = Food and Drug Administration; HAQ-DI = Health Assessment Questionnaire – Disability Index; LDA = low disease activity; mTSS=modified total Sharp score; NI = non-inferiority; PCS = physical component summary; PMDA = Pharmaceutical and Medical Devices Agency; SF-36=Short Form-36; US = United States

All endpoints were assessed at Week 12, if not indicated otherwise:

a. Assessment at Week 1.
b. Assessment at Week 14.
c. Assessment at Week 24.
d. Assessment at Week 26.

Note for Table 3: The sponsor has advised of errors in the above table: Study M13-542 should not include ACR50 and ACR70 and ACR20 at Week 1 as ranked secondary endpoints, footnote 'b' for PMDA should be footnote 'c', Study M14-465 should include an additional last ranked secondary endpoint at Week 12 for FDA of change in Health Assessment Questionnaire without Disability Index (HAQ-DI) superiority of upadacitinib versus adalimumab, Study M15-555 should change footnote 'a' to 'b'.

For each Phase III study, the primary and ranked key secondary endpoints were multiplicity-adjusted for statistical testing, with strong control of the overall type I error rate at the 0.05 (2-sided) level using the graphical multiple testing procedure where 2 doses of upadacitinib were tested (Studies M13-545, M13-549, M15-555 and M13-542) or the sequential testing approach where only upadacitinib 15 mg once daily was examined (Study M14-465). A full analysis set and per-protocol population was defined for primary and key secondary efficacy endpoints. Study drug completion ranged from 85.1% to 95.2% in any treatment group at the visit for the primary analysis. The treatment

groups across the five studies were generally balanced regarding demographic features and baseline disease characteristics.

Study M13-545

This is a monotherapy study in methotrexate naïve patients comparing 15 mg and 30 mg upadacitinib with methotrexate 20 mg maximum/week for 48 controlled weeks in 947 patients. The study report to Week 24 only was submitted. From Week 26 onwards, subjects could receive rescue medication. This study included a lower dose of 7.5 mg for Japan.

The mean duration of rheumatoid arthritis was 2.7 years reflecting a cohort with recent onset disease and overall patients were consistent with severely active disease. The primary efficacy endpoint for the US was ACR50;[7] at Week 12 which showed 52.1% for 15 mg, 56.4% for 30 mg and 28.3% for methotrexate ($p < 0.001$ for both upadacitinib groups versus methotrexate). The primary efficacy endpoint for the EU was complete remission (DAS28-CRP < 2.6);[8] at Week 24 which showed 48.3% for 15 mg, 50.0% for 30 mg and 18.5% for methotrexate ($p < 0.001$ for both upadacitinib groups versus methotrexate). This study also examined radiological progression at Week 24, which showed subjects treated with upadacitinib 15 mg and 30 mg had a statistically significantly smaller mean increase in modified Total Sharp Score (mTSS) from Baseline compared with the methotrexate group. Both upadacitinib dose groups showed statistically significant improvement compared with methotrexate for all ranked key secondary endpoints at Week 12 or 24.

Study M13-549

This is a study in csDMARD inadequate responders on a background of csDMARDs comparing 15 mg and 30 mg upadacitinib with placebo for 12 controlled weeks in 661 patients. The mean duration of rheumatoid arthritis was 7.3 years reflecting established disease and overall patients were consistent with moderately to severely active disease. At Baseline, 60.5% were taking methotrexate alone, 20.5% were taking methotrexate and another csDMARD and 19% were taking a csDMARD other than methotrexate. The mean weekly dose of methotrexate was 16.7 mg. The primary efficacy endpoint for the US was ACR20;[7] at Week 12 which showed 63.8% for 15 mg, 66.2% for 30 mg versus 35.7% for placebo ($p < 0.001$ for both upadacitinib groups versus placebo). The primary efficacy endpoint for the EU was low disease activity (DAS28-CRP ≤ 3.2);[8] at Week 12 which showed 48.4% for 15 mg, 47.9% for 30 mg and 17.2% for placebo ($p < 0.001$ for both upadacitinib groups versus placebo). Both upadacitinib dose groups showed statistically significant improvement compared with control therapy for all ranked key secondary endpoints at Week 12.

Study M14-465

This is a study in methotrexate inadequate responders on a background of methotrexate (mean baseline weekly dose of 17 mg) comparing 15 mg upadacitinib with placebo and adalimumab 40 mg every other week for 26 weeks placebo controlled period and 48 weeks adalimumab controlled period in 1629 patients. At Week 26, all subjects receiving placebo were switched to upadacitinib 15 mg once daily regardless of response. The study report to Week 26 was submitted. The mean duration of rheumatoid arthritis was 8.2 years reflecting established disease and overall patients were consistent with severely active disease. The primary efficacy endpoint for the US was ACR20;[7] at Week 12 which showed 70.5% for 15 mg versus 36.4% for placebo ($p < 0.001$). The primary efficacy endpoint for the EU was complete remission (DAS28-CRP < 2.6);[8] at Week 12 which showed 28.7% for 15 mg and 6.1% for placebo. For all ranked key secondary endpoints that compared upadacitinib to placebo at Week 12, a statistically significant improvement with upadacitinib treatment was observed. For all radiographic endpoints, the upadacitinib group had statistically significantly less X-ray progression compared to

the placebo arm at Week 26. At Week 12, a numerically greater percentage of subjects treated with upadacitinib achieved ACR50 response (45.2%) compared with adalimumab (29.1%) with the treatment related difference being 16.1% (95% confidence interval (CI) 9.9, 22.3), meeting the non-inferiority and superiority requirements.

Study M15-555

This is a monotherapy study in methotrexate inadequate responders comparing 15 mg and 30 mg upadacitinib with continuing methotrexate (mean weekly dose of 16.7 mg) for 14 controlled weeks in 648 patients. The mean duration of rheumatoid arthritis was 6.6 years reflecting established disease and overall patients were consistent with severely active disease. The primary efficacy endpoint for the US was ACR20;[7] at Week 14 which showed 67.7% for 15 mg and 71.2% for 30 mg versus 41.2% for continued methotrexate ($p < 0.001$ for both upadacitinib groups versus methotrexate). The primary efficacy endpoint for the EU was low disease activity (DAS28-CRP ≤ 3.2);[8] at Week 14 which showed 44.7% for 15 mg and 53.0% for 30 mg versus 19.4% for continued methotrexate ($p < 0.001$ for both upadacitinib groups versus methotrexate). Both upadacitinib dose groups showed statistically significant improvement compared with continued methotrexate therapy for all ranked key secondary endpoints at Week 14.

Study M13-542

This is a study in bDMARD inadequate responders on a background of csDMARDs comparing 15 mg and 30 mg upadacitinib with placebo for 12 controlled weeks in 499 patients. From Week 12, placebo patients were switched to either 15 mg or 30 mg upadacitinib. The mean duration of rheumatoid arthritis was 13.2 years reflecting established refractory disease and overall patients were consistent with severely active disease. At Baseline, 73.8% were taking methotrexate alone, 9.5% were taking methotrexate and another csDMARD and 16.6% were taking a csDMARD other than methotrexate. The mean weekly dose of methotrexate was 16.7 mg. The primary efficacy endpoint for the US was ACR20;[7] at Week 12 which showed 64.6% for 15 mg and 56.4% for 30 mg versus 28.4% for placebo ($p < 0.001$ for both upadacitinib groups versus placebo). The primary efficacy endpoint for the EU was low disease activity (DAS28-CRP ≤ 3.2);[8] at Week 12 which showed 43.3% for 15 mg and 42.4% for 30 mg versus 14.2% for placebo ($p < 0.001$ for both upadacitinib groups versus placebo). Both upadacitinib dose groups showed statistically significant improvement compared with control therapy for all ranked key secondary endpoints at Week 12, except for ACR70 response rate at Week 12, in the upadacitinib 15 mg group.

Other studies

Study M13-537

This is a multicentre, multinational, randomised, double blind, placebo controlled dose ranging Phase II study in 300 adult subjects for 12 weeks with moderately to severely active rheumatoid arthritis who had an inadequate response to methotrexate and who were naïve to biological therapy. After Week 12, subjects could enter an open label extension study. Subjects were randomly assigned in an equal ratio to 1 of 6 treatment arms: placebo tablets twice daily, or upadacitinib IR formulation tablets 3 mg twice daily, 6 mg twice daily, 12 mg twice daily, 18 mg twice daily or 24 mg once daily. Subjects were to be maintained on pre-existing stable doses of NSAIDs, methotrexate 7.5 to 25 mg/week and low dose corticosteroids (CS) during the study. At Baseline, all subjects were taking methotrexate. Some 91% of subjects completed the 12 week study. The primary efficacy endpoint was the proportion of patients in each treatment arm who achieved ACR20 response at Week 12, using the mITT population which showed 81.6% in the upadacitinib 12 mg twice daily and 24 mg once daily groups, 76.6% in the upadacitinib 18 mg twice daily arm, 73.5% in the upadacitinib 6 mg twice daily group and 64.6% in the upadacitinib 3 mg twice daily arm compared with 50.0% in the control group. The pairwise comparison

of each upadacitinib dose group versus placebo for ACR20 response at Week 12 was statistically significant ($p < 0.05$) for all upadacitinib dose groups except 3 mg twice daily.

Study M13-550

This is a multicentre, multinational, randomised, double-blind, placebo-controlled, dose ranging, parallel group Phase II trial in 276 adult subjects for 12 weeks with moderately to severely active RA who had an inadequate response to or who were intolerant of anti-TNF therapy. After Week 12, subjects could enter an open label extension period. Subjects were randomly assigned in an equal ratio to 1 of 5 treatment arms: placebo tablets twice daily, or upadacitinib immediate release formulation tablets 3 mg twice daily, 6 mg twice daily, 12 mg twice daily or 18 mg twice daily. Subjects were to be maintained on pre-existing stable doses of NSAIDs, methotrexate 7.5 to 25 mg/week and low dose CS during the study. Some 88% completed the 12 week study. The primary efficacy endpoint was the proportion of patients in each treatment arm who achieved ACR20 response at Week 12 using the mITT population which showed 70.9% in the upadacitinib 18 mg twice daily group, 72.7% in the upadacitinib 12 mg twice daily arm, 63.5% in the upadacitinib 6 mg twice daily group and 55.6% in the upadacitinib 3 mg twice daily arm compared with 35.2% in the control group. The pairwise comparison of each upadacitinib dose group versus placebo for ACR20 response at Week 12 was statistically significant ($p < 0.05$) for all upadacitinib dose groups except 3 mg twice daily.

Study MI3-663

This is a Phase IIb/III randomised, double blind, placebo-controlled, dose response, parallel group trial in 197 Japanese subjects with moderately to severely active RA who were receiving a stable dose of csDMARDs and had an inadequate response to that therapy. The study consisted of a 12 week controlled period (Period 1) followed by a blinded long-term extension phase until regulatory approval in Japan. The submission contained efficacy data to Week 60 in 156 subjects. Subjects were randomly assigned in a 3:3:3:1:1:1 ratio to 1 of 6 treatment arms: upadacitinib 7.5 mg once daily, 15 mg once daily or 30 mg once daily for Period 1 (and to receive the same treatment in Period 2), or placebo in Period 1 followed by upadacitinib 7.5 mg once daily, 15 mg once daily or 30 mg once daily in Period 2 (that is, upadacitinib therapy in Period 2 was assigned according to pre-specified randomisation at Baseline). Subjects were to be maintained on pre-existing stable doses (for at least 4 weeks) of csDMARDs, NSAIDs, methotrexate 4 to 16 mg/week, leflunomide (LEF) 10 to 20 mg/day, sulfasalazine (SSZ) up to 3 g daily, hydroxychloroquine (HCQ) and low dose CS during the study (initial 24 weeks). At Baseline, 60.4% of all enrolled subjects were taking methotrexate alone and another 23.4% were taking methotrexate with other csDMARDs. 94.9% completed Period 1.

16.6% have discontinued treatment in Period 2 at a higher incidence in the upadacitinib 30 mg once daily group (25.0%) compared to the upadacitinib 7.5 mg once daily arm (12.3%) and the upadacitinib 15 mg once daily group (12.9%). The most common reason for discontinuation in Period 2 is adverse events.

The primary efficacy endpoint of ACR20 response at Week 12 was 75.5% in the upadacitinib 7.5 mg once daily group, 83.7% in the upadacitinib 15 mg once daily arm, 80.0% in the upadacitinib 30 mg once daily group compared with 42.9% in the control group. The pairwise comparison of each upadacitinib dose group versus placebo for ACR20 response at Week 12 was statistically significant ($p < 0.001$) for all upadacitinib dose groups. For subjects who continued on upadacitinib through to Week 60, the rates of ACR20/50/70 response showed improvement, which was most marked up until Week 24 and then plateaued somewhat between Weeks 24 and 60. For example, the rates of ACR50 response at Week 60 ranged from 66.7% to 86.0% in the continuous upadacitinib dose groups (versus 41.7% to 66.7% at Week 12; and 60.0% to 76.1% at Week 24).

Safety

Studies M13-545, M14-465 and M15-555 have collected safety data up to Week 48 and through cut-off date, while Studies M13-549 and M13-542 have presented safety information obtained up to Week 60 and through cut-off date. In addition to the above studies and Phase II studies, Study M13-538 was submitted, which included open label extension data from subjects who completed the Phase II dose ranging Studies M13-550 and M13-537. Subjects were also switched at Week 72 or later in this study to either 15 mg or 30 mg once daily from their original 6 mg twice a day (BD) IR or 12 mg BD IR formulations receptively. Safety data from this study was up to Week 144 and through cut-off date. Safety data from the Japanese extension study to Week 60 and through cut-off date was also provided.

As of the data cut-off date for this submission, a total of 4443 subjects have received at least one dose of upadacitinib in the Phase II or III studies, for a mean 432.7 days. For subjects with RA, enrolled in the pivotal Phase III studies, a total of 2630 patients have received at least one dose of upadacitinib 15 mg once daily for a mean of 368.7 days. Of these subjects, 1607 (61.1%) received upadacitinib 15 mg once daily treatment for at least 48 weeks.

Compared to placebo, a numerically higher incidence of overall adverse events (AEs) (15 mg: 56% versus 48.4% placebo controlled period), treatment related AEs (15 mg: 26.6% versus 20.2% placebo controlled period) and AEs resulting in permanent treatment discontinuation were observed with upadacitinib treatment. Some of the AE types (mainly, various laboratory abnormalities including increased serum creatine phosphokinase (CPK) and neutropaenia) occurred with a higher incidence in the higher dose upadacitinib treatment cohort (30 mg once daily versus 15 mg once daily). Infections were the most common AEs recognised with upadacitinib and these occurred at a higher frequency with upadacitinib treatment (both dose regimens) versus control therapy during the true placebo-controlled treatment periods (first 12 to 24 weeks for the pivotal Phase III trials), for example, Infections and infestations: 27.2% 15 mg versus 20.6% placebo. The majority of infections were mild in severity, self-limiting, and were predominately either upper respiratory tract infection (URTI), urinary tract infection or nasopharyngitis. The use of concurrent methotrexate did not appear to increase the overall risk of AEs as well as infection related AEs. Nausea (often in the absence of other gastrointestinal symptoms) was more commonly reported with upadacitinib 15 mg/day therapy versus placebo, and approximately half of all cases occurred within 4 weeks of commencing treatment.

The most common AEs that occurred in ≥ 2% of subjects in any treatment group in the placebo controlled analysis set (Studies M13-549, M14-465 and M13-542) are described in the table below.

Table 4: Most common adverse events that occurred in ≥ 2% of subjects in any treatment group in the placebo controlled analysis set (Studies M13-549, M14-465 and M13-542)

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)

The treatment related AEs most frequently associated with upadacitinib 15 mg therapy in the placebo controlled set (≥ 1% frequency) were leukopenia, neutropaenia, diarrhoea, nausea, bronchitis, nasopharyngitis, URTI, urinary tract infection, raised aspartate aminotransferase (AST) and alanine aminotransferase (ALT), increased serum CPK level and headache.

In the methotrexate controlled set up to 3 months, the most common types of AEs by Preferred Term (PT) (≥ 3% of subjects) reported with upadacitinib 15 mg/day monotherapy were urinary tract infection (4.3%), URTI (3.2%) and nausea (3.2%). In the upadacitinib 30 mg monotherapy arm, the most common AEs reported were increased blood CPK levels (4.9%), urinary tract infection (4.2%), URTI (3.6%) and headache (3.2%). In the methotrexate group, the most common AEs reported were URTI (4.3%), worsening of RA (3.4%) and urinary tract infection (3.2%). The most common types of AEs were generally comparable between upadacitinib and methotrexate with the exception of increased blood CPK level.

In the long-term any Phase III upadacitinib 15 mg analysis set, the most common AEs considered related to study drug (≥ 1.0 per 100 patient years (PY)) were similar to those in the placebo controlled dataset (events/100 PY): anaemia (1.7), leukopenia (2.5), lymphopaenia (1.3), neutropaenia (2.3), nausea (2.0), bronchitis (2.5), herpes zoster infection (2.8), influenza (1.1), latent tuberculosis (TB) (1.0), nasopharyngitis (3.5), oral herpes (1.1), pneumonia (1.5), sinusitis (1.6), URTI (5.3), urinary tract infection (4.4), ALT increased (4.6), AST increased (3.4), increased blood CPK level (4.6), and elevated serum lipid levels (4.4%).

The types of AEs observed in the long-term Any RA upadacitinib exposure dataset are consistent with that recorded in the Phase III upadacitinib analysis set. Infections were the most common types of AEs in the long-term treatment analysis and generally occurred at a higher frequency in the higher upadacitinib dose group. Herpetic infection was also more common with higher dose upadacitinib therapy: zoster affected 3.9 events/100 PY of 15 mg treated subjects versus 6.5 events/100 PY of 30 mg patients, and oral herpes infection affected 1.7 events/100 PY of 15 mg treated subjects versus 3.0 events /100 PY of 30 mg

patients. However, cases of latent TB were of similar incidence with both upadacitinib regimens.

In the placebo controlled analysis set, *permanent discontinuation* from treatment due to AEs occurred at a higher frequency with upadacitinib 15 mg/day (exposure adjusted event rate (EAER) of 16.2 per 100 PY) versus placebo (EAER of 10.9 per 100 PY). Compared to methotrexate and placebo, there was no specific type of AE for more patients ceasing upadacitinib 15 mg/day. Treatment cessation rates were higher with upadacitinib 30 mg/day versus 15 mg/day, mainly due to a higher occurrence of severe infection with the higher dose upadacitinib regimen. The rate of treatment discontinuation with long term exposure to upadacitinib was comparable to methotrexate (EAER of 8.9 per 100 PY) and slightly lower than that observed with adalimumab. In the long term any RA upadacitinib set, the EAERs of AEs leading to drug discontinuation were lower in the upadacitinib 6 mg twice daily/15 mg once daily cohort (8.2 per 100 PY) compared to the higher dose group of 12 mg twice daily/30 mg once daily (13.3 per 100 PY).

In the integrated safety dataset populations, there was an increased incidence of *serious infection* with upadacitinib versus placebo and methotrexate. The risk of serious infection with upadacitinib 15 mg once daily compared to adalimumab is similar. In the placebo controlled periods of the Phase III studies, the proportion of subjects experiencing *opportunistic infection* were EAERs of 1.2 per 100 PY placebo and 2.3 per 100 PY upadacitinib 15 mg, but higher in subjects receiving upadacitinib 30 mg once daily (EAER of 7.1 per 100 PY). In the long-term datasets, the same trend continued, driven mainly by a higher rate of mucosal candida infections on 30 mg. In the 6 month and long-term controlled analysis sets, the rate of opportunistic infection was similar between methotrexate, adalimumab and upadacitinib 15 mg once daily (EAERs of ≥ 1.8 per 100 PY). In the long-term safety population, cases of PJP[9] and subjects experienced disseminated cutaneous or ophthalmic herpes zoster infection.

During extended follow-up, 5 upadacitinib treated patients recorded *TB* infection (< 0.1 events/100 PY) in the upadacitinib clinical study program along with one subject treated with adalimumab. All observed TB cases occurred in countries where TB is prevalent, and the sponsor has included a warning about the risk of TB and screening pre-treatment in the proposed PI. However, there was an increased risk of *herpes zoster and oral herpes* viral infections with upadacitinib versus placebo. The EAER of herpes zoster (serious and non-serious) in the upadacitinib 15 mg once daily group was 3.7 per 100 PY in the Phase III studies. In the 5 Phase III trials, a total of 90 upadacitinib 15 mg treated subjects (3.7% of 2630) experienced 99 herpes zoster AEs. An upadacitinib dose effect was observed for the risk of herpes zoster infection. The majority of herpetic infections were rated as mild or moderate in severity, and responded to standard treatment.

A total of 40 *deaths* (33 in upadacitinib treated subjects) have been reported in the Phase II/III studies as of the data cut-off date, including 11 major adverse cardiovascular events (MACE) and 7 cancer related deaths in upadacitinib treated subjects. Mortality rates and the causes of death were similar between upadacitinib and placebo, or comparator therapies (methotrexate and adalimumab) in relatively short-term treatment follow-up (up to 2 years).

A total of 79 subjects across all groups recorded treatment-emergent malignancy including 71 subjects treated with upadacitinib, 3 patients receiving adalimumab, 3 subjects in the methotrexate alone cohort and 2 placebo treated subjects. A total of 4 subjects (EAIR of < 0.1 per 100 PY) developed lymphoproliferative malignancy (excluding the 2 additional cases in the Japanese Study M14-663).

[9] Two cases reported in subjects with TE opportunistic infections excluding oral and oropharyngeal candidiasis (Summary of Clinical Safety Table 134).

- In the placebo controlled set, there were two deaths on placebo, none on 15 mg and one on 30 mg. *Malignancies* were reported in 6 subjects ; 2 subjects (0.2%) in the placebo group, 1 patient (0.1%) in the upadacitinib 15 mg cohort and in 3 subjects (0.8%) in the 30 mg group. For malignancies other than non-melanoma skin cancers, the short term exposure-adjusted incidence rates (EAIRs) were 0.4 per 100 PY, 1.2 per 100 PY for upadacitinib 15 mg and 3.5 per 100 PY for upadacitinib 30 mg. The percentage of subjects experiencing serious adverse events (SAEs) was higher in the upadacitinib 15 mg group (3.4%) compared with placebo group (1.8%).
- In the methotrexate controlled set, up to 3 months, a total of 5 deaths were reported; 3 subjects (0.6%) in the upadacitinib 30 mg group (1 sudden death and 2 serious infection), and 1 each in the other 2 treatment arms (0.2% for upadacitinib 15 mg and the methotrexate group). The deaths in the methotrexate and upadacitinib 15 mg groups were a consequence of myocardial infarction. A total of 5 malignancies were reported; 3 subjects (0.6%) in the upadacitinib 15 mg group, none in the upadacitinib 30 mg arm and 2 subjects (0.4%) in the methotrexate group. The percentage of subjects with SAEs was comparable among the groups; 3.0% in the upadacitinib 15 mg group, 3.6% in the upadacitinib 30 mg arm and 2.3% in the methotrexate group.
- In the long-term Any RA upadacitinib set, the EAIR of treatment emergent death was 0.4 per 100 PY in the upadacitinib 15 mg once daily group and 0.8 per 100 PY in the upadacitinib 30 mg once daily cohort. There were also 4 deaths in patients treated with adalimumab (3 were treatment emergent), 2 treatment emergent deaths in the placebo cohort and 1 treatment emergent mortality in a methotrexate treated subject. Of the 25 treatment emergent deaths reported in upadacitinib treated subjects across the global Phase II/III studies, 11 (44%) were MACE (as per central adjudication). All fatal MACE episodes occurred in subjects with underlying or known pre-existing atherosclerotic disease risk factors. The EAERs of SAEs were 14.4 per 100 PY (14.4%) in the upadacitinib 6 mg twice daily/15 mg once daily cohort, and higher at 21.0 per 100 PY in the upadacitinib 12 mg twice daily/30 mg once daily group. The types of SAEs observed in the long-term Any RA upadacitinib exposure dataset are consistent with that recorded in the Phase III upadacitinib analysis set.

In the combined Phase III Study dataset, the EAIR of *MACE* for upadacitinib 15 mg once daily therapy was 0.6 per 100 PY. The clinical evaluator commented that the rate of MACE in the RA dataset is within expectations for the treatment population and the types of MACE observed did not identify any specific safety signals with upadacitinib. The long-term EAIR of MACE in the upadacitinib 15 mg group was similar to the adalimumab and methotrexate groups.

Data pooled across the global Phase III studies, showed that upadacitinib therapy did not appear to be associated with an increased EAIR for *venous thromboembolism* compared with comparators long term but there is some variability short term (see Table 5 below).

Table 5: Adjudicated VTE with short term exposure in Phase III study dataset

	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 6: Adjudicated VTE with long term exposure in Phase III study dataset

	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.

In the any RA upadacitinib analysis set, 9 subjects (0.2 per 100 PY) experienced *gastrointestinal perforation* including 5 subjects continuously treated with upadacitinib 6 mg twice daily/15 mg once daily and 4 subjects continuously treated with upadacitinib 12 mg twice daily/30 mg once daily.[10]There were no gastrointestinal perforation AEs identified in subjects who received placebo, methotrexate or adalimumab.

In the placebo controlled analysis set, the incidence of *hepatic* AEs (two thirds of which were asymptomatic serum transaminase elevations) was comparable between the upadacitinib 15 mg group (4.4%) and placebo arm (3.6%). Some patients developed markedly abnormal liver function test results (≥ 5 x upper limit of normal (ULN) in AST/ALT and/or serum bilirubin ≥ 2 x ULN), but none of these events were consistent with upadacitinib induced liver injury. As expected, hepatic AEs were slightly more frequent in the methotrexate treatment population versus upadacitinib 15 mg once daily, but less frequent in those receiving adalimumab. In the long-term Any RA upadacitinib set, 1.8% were identified as experiencing ALT (50 subjects) or AST elevations (31 subjects) ≥ 5 × ULN or total bilirubin elevations ≥ 2 × ULN (20 subjects) during treatment with upadacitinib. There did not appear to be a dose-relationship or discernible pattern in time to peak transaminase values. Most transaminase elevations resolved or were resolving regardless of whether upadacitinib was continued. Of the 78 subjects, most were concomitantly taking methotrexate, NSAIDs or isoniazid at the time of the transaminase or bilirubin elevation. Three cases met biochemical criteria for Hy's Law,[11] but the clinical evaluator considered none were consistent with probable drug induced liver injury attributable to upadacitinib.

Small mean increases in serum *creatinine* values were also observed with upadacitinib therapy, but Grade 2 or higher elevations in serum creatinine were rarely observed. The rates of renal dysfunction AEs were low and similar in upadacitinib 15 mg once daily, placebo, methotrexate and adalimumab groups. In the long-term analysis sets, there were three SAEs of renal dysfunction and none of the SAEs was attributed to upadacitinib.

In the placebo controlled period of the Phase III studies, small mean changes in *haemoglobin* values were similarly observed with upadacitinib 15 mg once daily and placebo therapy. This change remained stable through to Week 12. In the placebo controlled period of the Phase III studies, Grade 2, Grade 3 and Grade 4 decreases in *neutrophil* count were observed more frequently in the upadacitinib 15 mg and 30 mg therapy as compared to placebo. In addition, two subjects treated with upadacitinib 15 mg developed Grade 4 neutropaenia. Across the Phase II and III RA studies, 0.3% of upadacitinib treated subjects discontinued due to anaemia. In the long-term analyses, the EAIR of neutropaenia was lower in the upadacitinib 15 mg group (3.1 per 100 PY) than in the 30 mg cohort (6.8 per 100 PY). Among all subjects who received upadacitinib in the

[10] Sponsor comment: Based on a comprehensive medical review of the 9 events identified, 6 events were considered treatment emergent adverse events of GI perforation (0.1 events/100 PY, 6 events per 5263.5 PY). Of the 6 events, 3 subjects were on concomitant csDMARDs and 2 were on concomitant steroids.
[11] Hy's Law: Evidence of hepatocellular injury with a rise in ALT and/or AST > 3 x ULN and total bilirubin > 2 x ULN, and no other reason to explain rise in aminotransferases and total bilirubin. Hy's law is a rule of thumb that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury with jaundice.

Phase II and III RA studies, < 0.1% discontinued upadacitinib due to neutropaenia and the percentage of subjects with Grade 4 (< 0.5 x 10^9/L) neutropaenia was 0.3% in the upadacitinib 15 mg group.

Increases in serum *CPK* values were observed with upadacitinib in the RA treatment studies. In the placebo controlled analysis set, a greater mean increase in serum CPK levels from baseline to Week 12 was observed for subjects receiving upadacitinib 15 mg compared with placebo (59.7 U/L versus 1.9 U/L). The mean increases in serum CPK peaked at 2 to 4 weeks of treatment, then plateaued and remained stable until Week 12. The proportion of subjects with Grade 2 (2.8% with upadacitinib versus 0.6% with placebo) and Grade 3 CPK increases (0.8% with upadacitinib versus 0.3% with placebo) was higher in the upadacitinib 15 mg group than the placebo arm. For subjects receiving upadacitinib 15 mg, 2 (0.2%) subjects had asymptomatic Grade 4 increases in serum CPK levels compared with no subjects in the placebo arm. In the long-term Phase III trial analysis set, mean increases from Baseline to Week 84 in serum CPK values were higher in the upadacitinib 30 mg group (133.1 U/L) compared with the upadacitinib 15 mg arm (101.7 U/L).

In the placebo controlled period, upadacitinib 15 mg once daily treatment resulted in a small mean increase in total serum *cholesterol*, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and serum triglycerides. The mean changes from Baseline in LDL and HDL cholesterol levels peaked by Week 8 of therapy, and then plateaued through to Week 84. Upadacitinib 30 mg therapy showed a dose related increase in lipids. The long-term clinical consequences of altered lipid profiles associated with upadacitinib remains unknown.

In the Phase III upadacitinib analysis set, the percentage of subjects with *weight* increase and weight decrease was 22.4% and 6.3%, respectively. The percentages of subjects who experienced increases in systolic and diastolic *blood pressure* were similar between upadacitinib 15 mg therapy and comparator treatments (methotrexate and adalimumab) across the various analysis data sets for both short-term treatment and long-term exposure.

Risk management plan

- The sponsor submitted core risk management plan (RMP) version 1.0 (dated December 2018; data lock point (DLP) 13 September 2018) and Australian specific Annex (ASA) version 1.0 (dated December 2018) in support of this application at the first round evaluation. In its response to the TGA's request for further information, the sponsor has provided updated core RMP version 1.1 (dated July 2019; DLP 13 September 2018) and ASA version 1.1 (dated August 2019).
- The sponsor has also provided EU-RMP version 1.6 (dated October 2019; DLP 13 September 2018) and ASA version 1.3 (dated November 2019) along with Australian adapted additional risk minimisation materials (HealthCare Professional (HCP) Educational Brochure and Patient Alert Card) for review.
- In its response to the recommendations made by the TGA, the sponsor has updated the HCP educational brochure and Patient Alert Card (PAC) and submitted these as part of ASA version 1.4 (dated November 2019).

- The sponsor has proposed the following summary of safety concerns and their associated risk monitoring and mitigation strategies, as summarised below in Table 7.[12]

Table 7: Sponsor's summary of ongoing safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	Serious and opportunistic infections including TB	ü[1]	ü[2, 3, 4]	ü	ü[5, 6]
	Herpes zoster	ü[1]	ü[2, 3, 4]	ü	ü[5, 6]
Important potential risks	Malignancies	ü[1]	ü[2, 3]	ü	–
	Major adverse cardiovascular event (MACE)	ü[1]	ü[2, 3, 4]	ü	ü[5, 6]
	VTEs (deep venous thrombosis and pulmonary embolus)	ü[1]	ü[2, 3, 4]	ü	ü[5, 6]
	Gastrointestinal perforation	ü	ü[2, 3]	ü	–
	Drug-induced liver injury (DILI)	ü	ü[2, 3]	ü	–
	Foetal malformation following exposure in utero	ü[1]	ü[3,4]	ü	ü[5,6]
Missing information	Use in very elderly (≥ 75 years of age)	ü	ü[2]	ü	–
	Effect on vaccination efficacy	ü	ü[7]	ü	–
	Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C	ü	ü[2]	ü	–
	Use in patients with severe hepatic impairment	ü	ü[2]	ü	–
	Long term safety	ü	ü[2,3]	ü	–

[12] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Use in patients with severe renal impairment	ü	ü[2]	ü	–

[1] Specific adverse reaction follow-up questionnaire.[2] Long-term cohort studies. [3] Long-term extensions of Phase III clinical trials. [4]Evaluate effectiveness of the aRMMs in improving the awareness and education of physicians. [5] Healthcare professional education. [6] Patient alert card. [7]Vaccination substudy

The proposed pharmacovigilance plan through routine and additional pharmacovigilance activities is considered acceptable. The proposed risk minimisation plan through routine and additional risk minimisation measures is generally acceptable. The sponsor will supply a patient alert card to prescribers and make it available as a printable version on its website.

All recommendations made in the second round evaluation report have been resolved with the RMP section and there are no outstanding RMP recommendations.

However, the RMP evaluator had concerns about the lack of information on MACE in the PI. The sponsor is proposing to use additional risk minimisation activity for education on MACE for HCPs but is not including this information in the proposed PI. The evaluator comments that the sponsor states that there will be further evaluation of MACE through long-term safety studies and that the Australian PI will be updated if MACE is confirmed as a risk. The RMP evaluator considered this acceptable at this point as MACE is still being evaluated with post-market monitoring to provide evidence, and the sponsor has committed to updating the PI if required.

Risk-benefit analysis

Delegate's considerations

Benefit/risk

Upadacitinib is the third JAK inhibitor for rheumatoid arthritis. The sponsor has submitted a development program that includes monotherapy and combination therapy with csDMARDs in the setting of inadequate control with csDMARDs (mainly methotrexate), inadequate control with biological therapies and methotrexate naïve patients. Upadacitinib was also compared with methotrexate and adalimumab. The doses of concomitant background treatment with csDMARD therapy (predominately methotrexate) were mostly consistent with contemporary clinical practice in Australia, however, this may reflect sub-optimal practice. The sponsor has requested the indication include use as monotherapy or with other csDMARDs including methotrexate, which is supported by the submitted studies. Overall, the submission appears to generally adhere to the adopted EU guideline on rheumatoid arthritis. There are some caveats to the generalisability of the treatment population, for example, all the studies excluded patients who were at a significant risk of infection or malignancy, or who had various abnormal laboratory results at baseline (for example, abnormal haematology or liver function tests).

Data from the five pivotal Phase III studies that are ongoing have demonstrated statistically significant efficacy for upadacitinib in adults with moderately to severely active rheumatoid arthritis across the short-medium term (12 to 24 weeks). The clinical study report for study 663 from Japan included efficacy data to Week 60 in 156 patients demonstrating a maintenance of effect in patients responding and tolerating the medicine. The evaluator also comments that the clinical efficacy data available up to 60 weeks in

Studies M13-549 and M13-542 indicate that the majority of responding patients appear to maintain their treatment related benefit with continued upadacitinib.[13] However, the sponsor is requested to clarify this longer-term data and provide an update from these ongoing studies.

The current submission for upadacitinib contains X-ray data up until 48 weeks of therapy. Radiographic data from two studies were supportive but unclear as to their clinical relevance at this stage given the limited duration of the data and not meeting the minimum two years expected. Upadacitinib had statistically significantly less X-ray progression compared to placebo and methotrexate treatment at Weeks 24-26 and radiographic benefit with upadacitinib therapy was similar to that observed with adalimumab.

Both ER doses of upadacitinib are similarly efficacious and an integrated analysis of the Phase III studies showed that 30 mg once daily does not consistently offer a meaningful improvement over 15 mg once daily.

The safety data indicate that upadacitinib has an acceptable overall safety profile in the short-medium term for the treatment of adult patients with moderately to severely active RA. The risk profile of upadacitinib is based on a total of 4443 upadacitinib-treated patients with RA involved in the clinical study program, of which 2972 patients were exposed to upadacitinib for at least 1 year. All five of the Phase III studies are ongoing with up to 5-year data expected upon completion. However, there are limited long-term safety data in the current submission to assess the risk of some types of AEs such as malignancy and MACE. From the assessment of the safety dataset, there are some significant safety concerns with upadacitinib therapy including the risk of infection, opportunistic infection (such as oral herpes zoster infection and TB), increased serum CPK values, anaemia, neutropaenia, lymphopaenia, abnormal liver function tests (raised serum transaminases) and dyslipidaemia. Gastrointestinal perforations and thromboses were also observed. The clinical evaluator comments that malignancy represents a risk but there is no clear evidence that upadacitinib confers an increased risk for certain types of malignancies such as non-melanoma skin cancer and lymphoma in the current dataset. Nevertheless, significant pharmacovigilance will be required for serious and opportunistic infections, MACE and malignancy (particularly, non-melanoma skin cancers and lymphoma). Upadacitinib is a Category D;[4] drug in pregnancy. Clinically relevant drug interactions have been observed with ketoconazole and rifampicin.

The clinical evaluator noted that higher rates of AEs of special interest were recorded in subjects treated with versus without concomitant corticosteroids in the upadacitinib 15 mg arm for serious infection, anaemia, lymphopaenia and herpes zoster. With long-term exposure, the rates of AEs of special interest were; lymphopenia, active/latent TB, adjudicated MACE (0.9% versus 0.4%) and adjudicated venous thromboembolism (VTE) (0.8% versus 0.4%), which had higher rates in subjects receiving concomitant CS. The evaluator commented that evaluation of the safety data for subjects receiving methotrexate or adalimumab, with or without concomitant CS showed a similar trend as upadacitinib 15 mg once daily therapy.

A total of 40 deaths (33 in upadacitinib treated subjects) have been reported in the Phase II/III studies as of the data cut-off date. The clinical evaluator commented that mortality rates and the causes of death were similar between upadacitinib and placebo, or comparator therapies in relatively short-term treatment follow-up. In the long term any

[13] The submitted clinical study reports for the pivotal Phase III studies included data up to Week 26 for efficacy, however the sponsor's clinical overview and integrated summary of efficacy refers to data up to Weeks 48 to60. For Study M13-545, the results to week 60 note: 'Through data cut-off date of 16 August 2018 and data are subject to change when all subjects have completed Week 48 or otherwise prematurely discontinued study.' The sponsor is requested to clarify this information.

RA upadacitinib set, the EAIR of treatment emergent death was 0.4 per 100 PY in the upadacitinib 15 mg once daily group but higher at 0.8 per 100 PY in the upadacitinib 30 mg once daily group.

The RMP and ASA have been accepted by the RMP evaluator, and the outstanding issues are now considered resolved. The sponsor has agreed to include information on thromboses in both the PI and CMI, however this should be expanded. The RMP evaluator has accepted the sponsor's response that further evaluation of MACE will occur through long-term safety studies and the PI will then be updated if MACE is confirmed as a risk. The sponsor has included it as an important potential risk in the RMP.

The US Prescribing Information includes a Boxed Warning about serious infections, malignancy and thrombosis however, the Australian PI does not. The Australian PIs for tofacitinib and baricitinib also do not include Boxed Warnings on these issues. Given the other two JAK inhibitors approved for rheumatoid arthritis do not include a Boxed Warning then it appears reasonable to not require one for upadacitinib, however the sponsor should ensure that all of the content of the US Boxed Warning is included in the Warnings and Precautions section of the PI.

The clinical evaluator considered Study M13-545 (recent disease onset, DMARD naïve population) to have an unclear benefit-risk balance with upadacitinib (that is, better clinical efficacy but at the cost of increased side effects compared to methotrexate). The clinical evaluator commented that the choice of comparator is sub-optimal and has limited external validity since patients at high risk of disease progression should be treated with higher doses of methotrexate (20 to 25 mg/week), often in combination with other csDMARD therapies if insufficient clinical response cannot be achieved with methotrexate monotherapy. In response to the clinical evaluation report, the sponsor has updated the indication to reflect second line treatment in patients who have responded inadequately to, or who are intolerant to one or more DMARDs. This is acceptable given the data and consistent with other JAK inhibitors currently registered in Australia for rheumatoid arthritis.

The clinical evaluator has requested that upadacitinib should only be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis, which the sponsor has agreed and included a statement in the PI.

The sponsor has included a QR code that includes a link to a patient support program. This should comply with the Code of Conduct requirements.

Data deficiencies and outstanding issues

Upadacitinib has not been studied in patients with severe hepatic impairment (use is not recommended in the PI), end stage renal disease, < 18 years of age, significant organ dysfunction, those at risk of reactivated TB, pregnant/lactating women and concurrent administration with other biological DMARDs. Based on the mechanism of action of JAK inhibition, co-administration of upadacitinib with other biological DMARD therapy or other JAK inhibitors is not recommended. There were no studies examining live vaccines.

Further data are required to confirm the risk benefit in DMARD naive patients with early disease and longer-term safety data are required to characterise the risk of some adverse events such as malignancy and major adverse cardiovascular events.

The clinical evaluator raised concerns that the RMP did not adequately cover various blood test abnormalities such as anaemia, neutropaenia and lymphopaenia or increases in serum CPK levels. The sponsor commented that many of the above laboratory AEs are of limited impact and that there is no evidence of a clear link between many of the laboratory test abnormalities and adverse clinical sequelae (for example, neutropaenia and lymphopenia with infections). The sponsor also commented that the CHMP has agreed to

include lymphopenia, decreased haemoglobin and neutropaenia as risks not considered important. However, these are all identified in the PI as adverse events with upadacitinib treatment and that there are specific dose interruptions recommended for patients with low neutrophil counts, low lymphocyte counts and low haemoglobin. Given these three are known risks that require dose interruptions then further consideration should be given to including them in the RMP.

Summary of issues

The primary issues with this submission are as follows:

1. Upadacitinib studies have identified significant safety concerns including serious infections, herpes zoster and oral herpes, opportunistic infections, haematological abnormalities, dyslipidaemia, raised CPK, raised transaminases and gastrointestinal perforations. There is also limited long-term safety data to characterise the potential for some risks such as malignancy and MACE.
2. Thromboses have occurred in patients with JAK inhibitors including upadacitinib. The submitted data do not appear to demonstrate a clear increased risk long term but this less clear short term compared with placebo and methotrexate.
3. Gastrointestinal perforations were reported in patients on upadacitinib compared with none in subjects on placebo, methotrexate or adalimumab. The US Prescribing Information includes a warning on gastrointestinal perforation but the proposed Australian PI does not.
4. The US Prescribing Information includes a Boxed Warning on the risks of serious infections, malignancies and thromboses however, a similar Boxed Warning is not proposed for the Australian PI. Neither the tofacitinib nor baricitinib PIs include a Boxed Warning in Australia although they do describe these potential risks in their Warnings and Precautions sections of their PIs.

Proposed action

Pending advice from the Advisory Committee on Medicines (ACM) and the sponsor's Pre-ACM Response, the Delegate considers the benefit/risk profile to be positive and recommends approval for the 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 disease-modifying anti-rheumatic drugs (csDMARDs).*

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. What are ACMs comments on the safety profile of upadacitinib and have these been adequately described in the PI? Is information required on the potential for MACE at this stage?
2. What are ACMs comments on the potential risk of thromboses and is the proposed information in the PI adequate?
3. What are ACMs comments on the potential risk of gastrointestinal perforations and should the PI include a warning similar to the US Prescribing Information?

4. What are ACMs comments on the need for a Boxed Warning given the other JAK inhibitors do not include a Boxed Warning in Australia?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory Committee Considerations[14]

The ACM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Rinvoq film-coated modified release tablets, containing 15 mg of upadacitinib.

The ACM considered this product to have an overall positive benefit-risk profile for the proposed 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 disease-modifying anti-rheumatic drugs (csDMARDs).'*

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice:

1. *What are ACM's comments on the safety profile of upadacitinib and have these been adequately described in the PI? Is information required on the potential for MACE at this stage?*

The ACM was of the view that the safety profile of upadacitinib was similar to that of other products within the same class, and was adequately characterised within the product information document. The ACM agreed that the occurrence of MACE would need to be monitored vigilantly, but was of the view that no evidence was currently present to suggest that upadacitinib contributed to or caused an early increased risk of MACE. The ACM was satisfied that these risks were effectively addressed in the proposed risk management plan.

2. *What are ACM's comments on the potential risk of thromboses and is the proposed information in the PI adequate?*

The ACM advised that current evidence does not indicate a significant safety risk in relation to thromboses and that therefore the information in the proposed product information regarding VTE is appropriate. The ACM noted recent concerns relating to an increased risk of VTE in relation to another drug in the same class, and agreed that the

[14] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

incidence of VTE should be carefully monitored as proposed in the risk management plan, without need for additional measures or warnings at this stage.[15]

3. *What are ACM's comments on the potential risk of gastrointestinal perforations and should the PI include a warning similar to the US Prescribing InformationI?*

The ACM was of the view that as the incidence of gastrointestinal ulceration and perforation was low, the most appropriate course of action would be to monitor cautiously. A specific warning in the product information is not required at present. The ACM considered the suggestion of a causal relationship between upadacitinib use and ulceration or perforation, but was of the view that this was unlikely, and may have been confounded by concomitant use of non steroidal anti inflammatory drugs, which are a common treatment modality for inflammatory and/or arthritic conditions.

4. *What are ACMs comments on the need for a Boxed Warning given the other JAK inhibitors do not include a Boxed Warning in Australia?*

The ACM advised that as neither of the previous JAK inhibitors contain a Boxed Warning and current evidence suggests a similar safety profile for upadacitinib, then a Boxed Warning for upadacitinib is not required at the present time.

5. *The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application*

   Nil.

General advice

Nil.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Rinvoq upadacitinib 15 mg modified release tablet for oral administration, indicated for:

> *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 disease-modifying anti-rheumatic drugs (csDMARDs).*

Specific conditions of registration applying to these goods

- Rinvoq (upadacitinib) is to be included in the Black Triangle Scheme. The Product Information (PI) and Consumer Medicines Information (CMI) for Rinvoq must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Rinvoq European Union-Risk Management Plan (EU-RMP) (version 1.6, dated October 2019, data lock point 13 September 2018), with Australian Specific Annex (version 1.4, dated November 2019), included with submission PM-2018-05603-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

[15] Sponsor clarification: VTE should be carefully monitored as proposed in the risk management plan EU-RMP v1.6), including needs for additional measures, but no warnings at this stage.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- The final study reports for the following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as Category 1 submission(s):
  - MI3-545
  - MI3-549
  - MI4-465
  - MI5-555
  - MI3-542

Attachment 1. Product Information

The PI for Rinvoq approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au