EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 May 2022
EMA/CHMP/623552/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xeljanz

International non-proprietary name: tofacitinib

Procedure No. EMEA/H/C/004214/II/0039

Note

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

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Table of contents

List of abbreviations

%CV	percent coefficient of variation
ACR	American College of Rheumatology
AE(s)	adverse event(s)
AS	ankylosing spondylitis
ASAS	Assessment of Spondylo Arthritis International Society
ASAS20	≥20% increase from Baseline and ≥1 unit increase in at least 3 domains on a scale of 0 to 10, and no worsening of ≥20% and ≥1 unit in the remaining domain
ASAS40	≥40% increase from Baseline and ≥2 units in at least 3 domains on a scale of 0 to 10 and no worsening at all in the remaining domain
ASDAS(CRP)	Ankylosing Spondylitis Disease Activity Score using C-Reactive Protein
ASQoL	Ankylosing Spondylitis Quality of Life
ATE	arterial thromboembolism
AUC	area under the plasma concentration-time curve over a dosing interval
AUC_{24}	area under the plasma concentration-time curve over a 24-hour period
BA	bioavailability
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
bDMARD	biological disease-modifying antirheumatic drug
BE	bioequivalence
BID	twice-daily
C_{avg}	average plasma concentration
CHMP	Committee for Medicinal Products for Human Use
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CO	Clinical Overview
CRP	C-reactive protein
C_{trough}	predose plasma concentration
CV	cardiovascular
CYP	cytochrome P450
DDI	drug-drug interaction
DMARD	disease-modifying antirheumatic drug
DVT	deep vein thrombosis
ECS	Extrudable Core System
EMA	European Medicines Agency
EPITT	European Pharmacovigilance Issues Tracking Tool
E-R	exposure-response
ESI	Emerging Safety Issue
EU	European Union
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
GI	gastrointestinal
hsCRP	high-sensitivity C-reactive protein
HV(s)	healthy volunteer(s)
HZ	herpes zoster
IC50	concentration producing 50% of maximum inhibition
IL	interleukin
ILD	Interstitial Lung Disease
IR	immediate release
IVIVC	in vitro in vivo correlation
JAK	Janus Kinase
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MACE	major adverse cardiovascular events
MAH	Marketing Authorisation Holder
mCIA	muramyl dipeptide/collagen induced arthritis
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NMSC	non-melanoma skin cancer
non-IR	non-inadequate response/responder
NSAID-IR	non-steroidal anti-inflammatory drug inadequate responder

PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PCS	Physical Component Summary
PD	pharmacodynamics
PE	pulmonary embolism
PGA	Patient Global Assessment
PK	pharmacokinetics
PL	patient leaflet
PMR	Post-Marketing Requirement
PR	prolonged release
PsA	psoriatic arthritis
PsO	psoriasis
PY	Patient-Years
QD	once daily
RA	rheumatoid arthritis
RMP	Risk Management Plan
SAE(s)	serious adverse event(s)
SAWP	Scientific Advice Working Party
SBP	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SF-36v2	Short Form - 36 Health Survey Version 2
SmPC	Summary of Product Characteristics
sNDA	supplemental New Drug Application
STAT	signal transducer and activator of transcription
TB	tuberculosis
TEAE(s)	treatment-emergent adverse event(s)
TNF-α/γ	tumor necrosis factor alpha/gamma
TNFi	TNF inhibitor
TNFi-IR	TNFi-inadequate response/responder
UC	ulcerative colitis
US	United States
VTE	venous thromboembolism

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 2 April 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of active ankylosing spondylitis for Xeljanz prolonged release; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 18.1 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0227/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0227/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Armando Genazzani Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	2 April 2021
Start of procedure:	18 September 2021
CHMP Rapporteur Assessment Report	12 November 2021
PRAC Rapporteur Assessment Report	18 November 2021
PRAC Outcome	2 December 2021
CHMP members comments	6 December 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 December 2021
Request for supplementary information (RSI)	16 December 2021
CHMP Rapporteur Assessment Report	19 April 2022
PRAC members comments	26 April 2022
PRAC Outcome	5 May 2022
CHMP members comments	10 May 2022
Updated CHMP Rapporteur Assessment Report	12 May 2022
CHMP Opinion	19 May 2022

2. Scientific discussion

2.1. Introduction

This Type II variation seeks approval of tofacitinib 11 mg prolonged-release tablets (dosed QD) for treatment of adult patients with active AS, as an alternative to the proposed posology of the tofacitinib 5 mg IR tablet (dosed BID). The 11 mg PR formulation is an ECS osmotic delivery tablet and is currently approved for QD dosing in RA and PsA.

The registration of Xeljanz prolonged-release tablets for RA was supported by an understanding of the exposure-response (E-R) relationships from the IR development programme which established the AUC or Cavg as the relevant parameter for clinical response. Biopharmaceutic studies demonstrated equivalence between tofacitinib PR 11 mg QD and tofacitinib IR 5 mg BID in terms of Cmax and AUC. These data formed the basis to bridge efficacy and safety from 5 mg IR BID to 11 mg PR QD.

A similar bridging approach is herein utilised to support the use of 11 mg PR QD for the treatment of AS.

In adult patients with active AS, the safety and efficacy of Xeljanz have been established using the IR formulation, dosed at 5 mg BID. Efficacy and safety data principally included 1 completed Phase 2 dose-ranging double-blind, placebo-controlled efficacy and safety trial (Study A3921119) and pivotal Phase 3, double-blind, placebo-controlled efficacy and safety trial (Study A3921120). The recommended dose of the tofacitinib IR tablet for the treatment of AS is 5 mg BID (approved with variation II/35), the same tofacitinib dose as approved for the treatment of RA and PsA.

2.1.1. Problem statement

Disease or condition

Ankylosing Spondylitis (AS) is a chronic inflammatory rheumatic disease primarily affecting the sacroiliac joints and spine and is part of the family of related SpA disorders, which also includes PsA. AS or radiographic axial SpA is defined by the presence of definitive radiographic sacroiliitis based upon 1984 Modified New York classification criteria. AS causes chronic inflammation at the insertion of ligaments and tendons in the axial skeleton (entheses) and may progress from inflammation in the sacroiliac joints to sacroiliac and spine ankylosis over time. AS is also associated with peripheral arthritis, and enthesitis, and extra-articular manifestations such as anterior uveitis, psoriasis, and IBD. Osteoporosis is a common AS comorbidity. AS is often present for many years before it is diagnosed and typically presents in people between 20 and 40 years of age, with a higher prevalence in males, leading to back pain, stiffness, fatigue, progressive disability and adverse effects on health-related quality of life

State the claimed the therapeutic indication

The proposed indication of Tofacitinib 11 mg PR once daily is for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

Epidemiology and risk factors, screening tools/prevention

The incidence and prevalence of AS for a range of countries and geographical regions are provided in the following table:

Table 1. Incidence and Prevalence of Ankylosing Spondylitis by Region

	Incidence per 100,000 PY	Prevalence (%)	Reference(s)
Region			
Overall	0.44-15	0.01 – 1.8	16-37
Northern Europe and North America	3-15	0.1-1.8	16,19,21-28
Iceland	0.44	-	17,18
Asia	0.48	0.01-0.54	16,17,20,29,30
Eastern Europe	-	0.07-0.12	31-33
Southern Europe	-	0.06-1.6	16,34,35
Middle East	-	0.12-0.49	16
Sub-Saharan Africa	-	0.02	36
Mexico	-	0.1	37

The highest incidence rates have been reported in Northern Europe and North America, while the lowest have been reported in Asia and Iceland (Table 1). The reported prevalence across geographic regions follows a similar trend to the reported incidence. Mortality rates among patients with AS are 1.5 times higher than the general population, due to respiratory complications, and consequences from spinal fractures and other fractures.

Studies consistently report that AS occurs more frequently among men than women. One study in the United States reported a four-fold higher incidence in men than women and a similar difference in incidence rates between men and women was reported in the Czech Republic. The prevalence reported among men is also similarly higher than the prevalence reported among women. Studies report a male to female

ratio ranging from 1.2-9 to 1.

AS usually starts in the second or third decade of life, with peak incidence occurring in the 20 to 34 age group. Studies report that the average age at onset of symptoms is between 20.9 and 32.5 years, while

the average age of diagnosis is later, between 24.2 and 39.8 years.

Biologic features, Aetiology and pathogenesis

Overall, the pathogenesis of AS is not well characterised but seems to include both genetic and environmental components, which combine to elicit a chronic inflammatory response involving the innate and adaptive immune systems. A genetic link was noted in that 90 - 95% of white Western European people with AS are positive for the HLA-B27 allele, and risk increases with HLA-B27-positive relatives. Environmental factors, such as infections and mechanical stress at the entheses, have been postulated as being potential triggers of AS in genetically susceptible individuals. In AS, these entheseal stresses might activate downstream events that lead to inflammation, bone erosion and spur formation.
Key aspects of the pathology and pathogenesis of AS are listed below:

- In the earlier stages of the disease, AS primarily involves inflammation of the entheses (enthesitis) in the axial skeleton (mainly the sacroiliac joints) and bone erosion in the vertebral bodies;
- In the later stages of the disease, syndesmophyte (spur) formation and then fusion of adjacent vertebral bodies and syndesmophytes occur. These processes appear to be uncoupled from inflammation;
- The development of AS is associated with specific genes; the most important is HLAB27; additional genes associated with AS include ERAP1, IL-23R, ANTXR2, and IL- R2;
- Key innate and adaptive immune cells involved in the initiation, progression, and modulation of inflammation in AS are reported to include dendritic cells, macrophages, NK cells, Th1 cells, Th2 cells, Th17 cells, Th22 cells, Treg cells, and T CD8+ cells. There may be a limited role for B cells.
- These innate and adaptive immune cells secrete a number of pro-inflammatory cytokines implicated in the pathogenesis of AS including IL-1, IL-6, IL-7, IL-12, IL-15, IL-17 IL- 22, IL-23, IFNγ and TNFalpha.

Confirmation that TNFaplha (secreted by Th1 and T CD8+ cells) and IL-17 (secreted by Th17 and T CD8+ cells) contribute to the pathogenesis of AS has been provided by the efficacy of interventions such as TNFi and anti-IL-17 mAb. These biologic therapies directly inhibit the effect of 1 cytokine pathway. Tofacitinib, a small molecule inhibitor of JAK, interferes directly (eg, IL-23) or indirectly (eg, TNFalpha, IL-17) with the
signalling of multiple AS-associated cytokines.
Tofacitinib therapy therefore has the potential to suppress the articular, as well as the extraarticular manifestations of AS, without the drug-induced immunogenicity and antidrug neutralising antibody formation seen with long-term monoclonal antibody use.

Clinical presentation, diagnosis and stage/prognosis

There are no specific diagnostic tests or biomarkers for the diagnosis of AS. For the purpose of clinical trials, consistent with the EMA clinical guideline on Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis, the classification criteria based on the 1984 Modified New York Criteria for Ankylosing Spondylitis is used to define AS if the radiological criterion (pelvic radiograph) is associated with at least 1 clinical criterion. In the Phase 2 dose-ranging Study A3921119 and the Phase 3 pivotal Study A3921120, in addition to the above Modified New York criteria, a patient must have had active AS defined as a BASDAI score of ≥4 and a back pain score (BASDAI Question 2) of ≥4 at both screening and baseline in order to be included.

Management

For many decades, the mainstay of treatment of AS has been NSAIDs and structured exercise programs including physical therapy with the aim of relieving clinical symptoms. However, gastrointestinal and other adverse effects limit the tolerability of NSAIDs including some COX-2 selective inhibitors. In addition, AS patients report insufficient control with NSAIDs alone. Treatment with csDMARDs that have shown efficacy in RA have not shown similar efficacy in AS. Sulfasalazine may provide some benefits for peripheral arthritis but does not impact axial disease. Locally administered parenteral glucocorticoids are also a treatment option for patients with active enthesitis, sacroiliitis or peripheral arthritis that have not responded fully to NSAID therapy. However, although local corticosteroid injections are widely used in clinical practice to good effect in AS patients, no clinical trials exist to support this use. TNFα antagonists or inhibitors, also known as TNFi, have demonstrated efficacy and are approved for the reduction of clinical signs and symptoms, in patients with AS. A recent ASAS recommendation stated that TNFi therapy is indicated for those patients with persistently high disease activity despite conventional treatment. Additional bDMARDs that inhibit IL-17, secukinumab and ixekizumab, have been subsequently approved in the US and EU. However, there is a substantial proportion of patients who have an inadequate response to each of these bDMARDs and as such therapy options are administered parenterally, this may act as an additional barrier to their use. Moreover, the long-term efficacy of some TNFi and IL-17i mAb may be limited by immunogenicity. Moreover, recently, also another JAK inhibitor (Upadacitinib) has been authorized in EU for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

Current updates to the ASAS-EULAR axial SpA management recommendations provide initial therapy recommendations based upon an individual's disease activity, the patient characteristics including comorbidities and psychosocial factors. Based on the current evidence and the considerations of ASAS and EULAR, NSAIDs and TNFi remain the primary classes of medications for the treatment of axial SpA (including AS). Sulfasalazine is considered only for the treatment of peripheral arthritis. IL-17i are recommended for patients with active disease in whom TNFi are contraindicated, and in primary nonresponders to TNFi. The use of IL-17i should be avoided in patients with active IBD, as TNFi monoclonal antibodies are better options.

Treatments are available to control and delay the progression of symptoms of AS. However, additional therapy options are still needed as up to 50% of patients with AS continue to have active disease despite treatment with NSAIDs or biological agents.

The use of NSAIDs is limited by gastrointestinal and other adverse events. Other effective agents for the treatment of active AS are bDMARDs, which require parenteral administration and may be limited by loss of efficacy, often due to immunogenicity. Of note, in a recent survey of patients receiving injectable bDMARDs to treat PsA, a condition related to AS, 54% found the therapy to be burdensome, with fear of injections and inconvenience amongst the most commonly reported reasons. Accordingly, there is a need for an oral tsDMARD with similar efficacy to bDMARDs for the treatment of AS.

As a number of genes and cytokines have been implicated in the pathogenesis of AS, it is likely that the etiology of AS is complex and has a plethora of underlying contributory factors. This implies that additional treatment options with mechanisms of action distinct from those currently available, such as tofacitinib, are needed as options for different AS patients.

In summary, despite the advances that have been made in the last decade in the treatment of AS, a significant number of patients with AS still have active disease and remain refractory to currently available pharmacotherapies. Unmet medical need therefore remains for a new effective oral DMARD with a new MOA that provides a favourable benefit-risk profile and broadens the treatment options for adult patients with AS to achieve and sustain clinical benefit.

2.1.2. About the product

Mode of action.

Tofacitinib is a selective JAK inhibitor, with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TYK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signalling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2.

Pharmacological classification.

Tofacitinib belongs to the therapeutic group of Immunosuppressants (L04) and its therapeutic subgroup is L04AA29

Previously approved indications

Xeljanz was approved in the EU at a dose of 5 mg BID (IR film-coated tablets approved on 22 Mar 2017; RA MAA procedure EMEA/H/C/004214/0000) as monotherapy or in combination with MTX in adult patients with moderate to severe active RA, who have had an inadequate response or intolerance to 1 or more DMARDs.

On 25 Jun 2018, tofacitinib was approved in the EU at a dose of 5 mg BID in combination with MTX, in adult patients with active PsA, who have had an inadequate response or intolerance to a previous DMARD treatment (procedure EMEA/H/C/004214/II/0006). Furthermore, tofacitinib was approved in the EU at a dose of 5 mg and 10 mg IR BID (26 Jul 2018; procedure EMEA/H/C/004214/X/0005/G) for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

An extension application to introduce a new pharmaceutical form (prolonged-release tablet) associated with a new strength (11 mg), was approved for RA patients on 16/12/2019 (EMEA/H/C/004214/X/0012). The same PR pharmaceutical form (11 mg) has been approved for PsA patients on 23/07/2021 (EMEA/H/C/004214/II/0027). An extension of indication in patients with AS using the 5 mg BID IR dosage (EMEA/H/C/004214/II/0035) was approved on 14 October 2021.

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

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

2.1.4. General comments on compliance with GLP, GCP

Not applicable. This application is based on modelling approach. No new non-clinical and clinical studies have been submitted.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

This Environmental Risk Assessment (ERA) was submitted by the MAH as part of II/35 variation seeking approval for a new indication (treatment of ankylosing spondylitis (AS) in adult patients).

The submitted ERA referred to the treatment of AS, in which the maximum recommended dosage of Xeljanz is 5 mg twice daily (IR tablet) or 11 mg once daily (MR tablet).

Tofacitinib has a log D value <4.5 at all environmentally relevant pHs. Screening for Persistence, Bioaccumulation and Toxicity (PBT) is not required.

Calculation of the Predicted Environmental Concentration in Surface Water (PECsw) Annual consumption of tofacitinib in the EU member states over the 12-month period from 1Q2019 through 4Q2019 was obtained from the IQVIA™ [formerly the Intercontinental Marketing Services (IMS)], the Health Management Integrity and Data Assessment System (MIDAS) database. Based on these data, total annual consumption in the EU is 117.4 kg and includes patient use of tofacitinib for treatment of the approved indications, RA, PsA and UC. The highest consumption per inhabitant was found in Luxembourg, therefore the data from Luxembourg will be used to determine the most conservative consumption based Fpen. As per the ERA Guideline, the Fpen based on consumption is determined as follows:

$$Fpen = \frac{Consumption\ (mg \cdot yr^{-1})}{DDD \times inhabitants \times 365\ (d \cdot yr^{-1})}$$

F*pen*	Market penetration factor	
Consumption	mg per year (2019)	545,900 mg·yr^{-1}
DDD	Defined daily dose*	10 mg·inh^{-1}·d^{-1}
Inhabitants	Luxembourg population, 2019 (Worldbank)	619,896
*Lowest recommended daily dose = 10 mg/day		

$$Fpen = \frac{545{,}900\ mg \cdot yr^{-1}}{10\ mg \cdot inh^{-1} \cdot d^{-1} \times\ 619{,}896\ inh\ \times 365\ d \cdot yr^{-1}}$$

F*pen* = 0.00024

Determination of PECsw, approved indications:

$$PECsw\ [mg/L] = \frac{DOSEai \times Fpen}{WASTEWinhab \times Dilution}$$

PEC_{SW}	Predicted environmental concentration in surface water	-- mg/L
DOSE*ai*	Maximum daily dose applied per inhabitant*	22 mg·inh^{-1}·d^{-1}
Fpen	Market penetration	0.00024 [Refined]
WASTEW*inhab*	Amount of wastewater per inhabitant per day	200 L·inh^{-1}·d^{-1} [Default]
DILUTION	Dilution factor	10 [Default]
*Maximum recommended daily dose = 22 mg/day (UC indication)		

$$PECsw = \frac{22\ mg \cdot inh^{-1} \cdot d^{-1}) \times 0.00024}{200\ L/(inh \cdot d) \times 10}$$

$$PECsw = 2.6 \times 10^{-6}\ mg/L = 0.0026\ \mu g/L$$

PECsw = 0.0026 µg/L based on consumption attributed to RA, PsA and UC.

Determination of PECsw, new indication (AS)

$$PECsw\,[mg/L] = \frac{DOSEai \times Fpen}{WASTEWinhab \times Dilution}$$

PEC_{SW}	Predicted environmental concentration in surface water	-- mg/L
DOSE*ai*	Maximum daily dose applied per inhabitant	11 $mg \cdot inh^{-1} \cdot d^{-1}$
Fpen	Market penetration	0.01 [Default]
WASTEW*inhab*	Amount of wastewater per inhabitant per day	200 $L \cdot inh^{-1} \cdot d^{-1}$ [Default]
DILUTION	Dilution factor	10 [Default]

$$PECsw = \frac{11\,mg \cdot inh^{-1} \cdot d^{-1}) \times 0.01}{200\,L/(inh \cdot d) \times 10}$$

$$PECsw = 5.5 \times 10^{-5}\,mg/L = 0.055\,\mu g/L$$

Total PECsw all indications (RA, PsA, UC, and AS):

PECsw = 0.0026 ug/L + 0.055 ug/L = 0.058 ug/L

The PECsw value is greater than the 0.01 µg/L action limit. Based on the PECsw value, a Phase II environmental fate and effects analysis for tofacitinib is required.

PHASE II – TIER A: PHYSICAL-CHEMICAL PROPERTIES, ENVIRONMENTALFATE AND EFFECTS ANALYSIS

The PECsurfacewater was not refined for human metabolism and excretion, for removal during wastewater treatment or for biodegradation in the water-sediment environment. In this conservative estimate, the PEC is more than 4 orders of magnitude less than the lowest chronic NOEC obtained with fish. In addition, the PEC/PNEC values for surface water (2 x 10-4), groundwater (3.1 x 10-5), micro-organisms (5.8 x 10-6) and sediment dwelling organisms (1.9 x 10-2), are all significantly below the respective action limits, therefore it may be concluded that tofacitinib will not present an environmental risk following patient use. No environmental concerns are apparent.

2.2.2. Discussion on non-clinical aspects

PECsw calculation was made by the MAH by summing up the PECsw of all indications, Fpen refinement was made by taking into consideration the annual consumption for the already approved indications (RA, PsA and UC). This is made for renewal applications, as per ERA guideline.
In case of a type II variation, specifically the addition of a new indication, the Fpen should be refined by submitting European disease prevalence data for the sought indication. Such data should be published by a reliable and independent source, as per ERA Q&A.

Moreover, a PECsw of all indications was made by summing up the already approved and the new one. Also here, the PECsw of the sought indications only have to be summed to reach the PECsurface water that will be used in the ERA, as per ERA Q&A.

In light of these considerations, as the present submission was dealing with a type II variation, the MAH was asked to recalculate the PECsw for the new indication (SA) only, and to refine the Fpen by submitting EU prevalence data, as per ERA Q&A. For the new indication, AS, the default Fpen value of 0.01 was used to calculate the PECsw of 0.055 µg/L, as per ERA guideline and Q&A documents. Fpen from Luxembourg was used for the previosly approved ones. Therefore, the Fpen from this member state was used for PECsw of 0.0026 µg/L. As this application is dealing with a line extension, a total PECsw can be calculated and the ERA based on the total PECsw of 0.058 µg/L, representing contributions from newly sought and from approved indications, as originally submitted by the MAH, is appropriate for this line extension application.

2.2.3. Conclusion on the non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

No new clinical data have been submitted for this application. The majority of AR presents data submitted and assessed for the procedure II/35.

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

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

- Tabular overview of clinical studies

Table 2. Tabular overview of clinical studies

Listing of All Studies

Protocol No. (Countries)	Study Design and Objectives	Treatment Groups	No. of Subjects (by Treatment Group)[a]	Demographics (sex, age, race) (No. of Subjects)	Duration of Treatment	Study Status	Study Synopsis
Efficacy and Safety Studies							
A3921119 (Canada, Czech Republic, Germany[b], Hungary, Poland, Russia, Spain, Republic of Korea, Taiwan, United States)	A phase 2 multicenter, randomized, DB, PC dose-ranging, parallel group efficacy and safety study designed to characterize the dose-response of tofacitinib in subjects with active AS. Study consisted of 12 weeks of tofacitinib treatment followed by 4 weeks off treatment. Primary objective: To compare the efficacy of tofacitinib, at doses of 2 mg BID, 5 mg BID, 10 mg BID versus placebo on the ASAS20 response rate at Week 12 in subjects with active AS that had an inadequate response to previous treatment. The primary analysis was by Emax modelling.	Tofacitinib 2 mg BID Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo	52 52 52 51	Sex: 143 M/64 F Mean/Median Age (min/max): 41.6/39.0 (22/75) years Race: W/A/O: 168/39/0	12 weeks DB	Completed	CSR Module 5.3.5.4 A3921119
A3921120 (Australia, Bulgaria, Canada, China, Czech Republic, France, Hungary, Poland, Russia, Republic of Korea, Turkey, Ukraine, United States)	A phase 3, randomized, DB, PC, study of the efficacy and safety of tofacitinib in subjects with active AS. Eligible subjects were randomized in a 1:1 ratio to tofacitinib 5 mg BID or matching placebo BID for a total of 16 weeks of blinded treatment. At the Week 16 visit all subjects were assigned to receive OL tofacitinib 5 mg BID until Week 48. Primary objective: To compare the efficacy of tofacitinib 5 mg BID versus placebo on the ASAS20 response rate at Week 16 in subjects with active AS that had an inadequate response to previous treatment.	Tofacitinib 5 mg BID Placebo (16 weeks) → Tofacitinib 5 mg BID (32 weeks)	133 136	Sex: 224 M/45 F Mean/Median Age (min/max): 41.1/40.0 (20/70) years Race: W/A/O: 213/55/1	16 weeks DB 32 weeks OL	Completed	CSR Module 5.3.5.1 A3921120
A3921092 LTE (Australia, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Germany, Hungary, Mexico, Poland, Russia, Slovakia, Spain, Taiwan, United Kingdom, United States)	An OL, LTE Study of tofacitinib for the treatment of PsA. Primary objective: To evaluate the long-term safety and tolerability of treatment with tofacitinib (5 mg BID and 10 mg BID) in adult subjects with PsA.	Tofacitinib (5 or 10 mg BID)	686	Sex: 316 M/370 F Mean/Median Age (min/max): 48.8/50.0 (18/78) years Race: W/A/B/O: 646/21/2/17	Approximately 3 years[c]	Completed	CSR Module 5.3.5.2 A3921092 LTE
A3921092 Substudy (Australia, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Germany, Hungary, Mexico, Poland, Russia, Slovakia, Spain, Taiwan, United Kingdom, United States)	A Randomized, DB Parallel Group MTX withdrawal A3921092 sub-study of tofacitinib for the treatment of PsA. Primary objective: To assess the efficacy of tofacitinib 5 mg BID monotherapy as compared to tofacitinib 5 mg BID with background MTX in subjects from Study A3921092 who had received prior treatment of tofacitinib in combination with MTX	Tofacitinib 5 mg BID + MTX Tofacitinib 5 mg BID + Placebo	89 90	Sex: 83 M/96 F Mean/Median Age (min/max): 52.4/54.0 (25/77) years Race: W/A/B/O: 170/3/0/6	12 months[d]	Completed	CSR Module 5.3.5.2 A3921092 Substudy

a. Number of subjects randomized and treated.
b. 4 active sites in Germany which terminated during the study; across the 4 sites there was 1 subject in the Screening phase
c. 36 standardized 4 week months; a month was defined as 4 weeks or 28 days.
d. 12 standardized 4-week months; a month was defined as 4 weeks or 28 days.

Note: A=Asian; AS = Ankylosing Spondylitis; ASDAS20= An improvement from Baseline ≥20% and ≥1 unit increase in at least 3 domains on a scale of 0 to 10, and no worsening of ≥20% and ≥1 unit in the remaining domain; B = Black; BID = Twice daily; CSR=Clinical Study Report; DB = Double-blind; F = Female; LTE= Long-term extension; M = Male; MTX = methotrexate; No = Number; O = Other; OL = Open-label; PC = Placebo-controlled; PsA = Psoriatic Arthritis; W = White.

2.3.2. Pharmacokinetics

No new pharmacology data was submitted in the current variation. The bridging of efficacy and safety of the IR formulation to the PR formulation in AS is based on the bridging strategy used in the previously approved RA PR submission EMEA/H/C/004214/X/0012.

Given that the efficacy of tofacitinib IR in AS has been demonstrated, the bridging of efficacy from tofacitinib IR to the PR formulation in AS, is supported by:

1. Previously provided Phase 1 studies that have demonstrated similarity of PK parameters between PR 11 mg QD and IR 5 mg BID (equivalent AUC and Cmax, and slightly lower Cmin).

2. Previously provided E-R analyses in RA that have demonstrated that a metric of overall exposure (Cav or AUC) is the relevant PK parameter to predict efficacy of tofacitinib (RA PR Module 2.7.2).

3. Longitudinal E-R analyses using efficacy data for the IR formulation in AS patients that have demonstrated that Cav is the exposure metric most closely associated with efficacy.

The time delay in the attainment of tofacitinib steady-state PK versus steady-state clinical response is consistent across multiple JAK-mediated inflammatory disorders including RA, PsA and AS supporting the conclusion that a measure of overall exposure (e.g., Cav or AUC) is the relevant parameter for efficacy, regardless of indication.

2.3.1. PK/PD modelling

Point 1 of the bridging strategy

Previously provided Phase 1 studies that have demonstrated similarity of PK parameters between PR 11 mg QD and IR 5 mg BID (equivalent AUC and Cmax, and slightly lower Cmin)

The supportive basis of this application includes previously submitted Phase I clinical studies conducted for Xeljanz IR application in RA and Xeljanz PR application in RA.
For tofacitinib RA IR application, results from the 25 Phase 1 studies were provided. These included 20 clinical pharmacology studies that evaluated single and/or multiple-dose PK, renal or hepatic impairment PK, drug-drug interactions, PD evaluations (ie, QT, mGFR) as well as 5 biopharmaceutics studies.
For tofacitinib PR application for RA 7 Phase 1 clinical pharmacology/biopharmaceutic studies were conducted. These included results from 4 BA studies (A3921113; A3921131; A3921132; A3921163), which evaluated PK of the pilot or initial commercial scale formulations, a food effect study (A3921180), and a single- and multiple-dose PK study with the proposed commercial formulation (A3921212) and an IVIVC study (A3921195), which investigated the relationship between in-vitro dissolution and in-vivo PK performance of the PR formulations. The conclusions from these studies are provided below for reference:

- Studies using prototype PR formulations of tofacitinib supported the choice of the osmotic tablet at a total daily dose of 11 mg to account for a 10% difference in BA compared to the IR formulation.
- Tofacitinib PR osmotic tablets at dose strength of 11 mg, administered QD, have equivalent AUC and Cmax compared to tofacitinib IR 5 mg tablets, administered BID.
- Cmin and Ctrough at steady-state were approximately 29% and 26% lower, respectively, for PR 11 mg QD compared to IR 5 mg BID.
- Based on the equivalence demonstrated for AUC and Cmax, and E-R relationships from the RA, PsA (and submitted now for AS) IR development programs indicating Cav (or AUC) as the relevant PK

parameter for efficacy, the slightly lower Cmin was not considered to have an impact on the efficacy of tofacitinib PR 11 mg QD.

- The tofacitinib PR 11 mg tablet can be administered with or without food.
- A single, Level A IVIVC model was established and validated for tofacitinib PR tablets (11 and 22 mg), confirming that in vitro dissolution is a reliable predictor of in vivo performance.

Point 2 of the bridging strategy

Previously provided E-R analyses in RA that have demonstrated that a metric of overall exposure (Cav or AUC) is the relevant PK parameter to predict efficacy of tofacitinib

The contextualisation of efficacy in RA clinical trials using the PR formulation (A3921215 and A3921192) to the E-R relationships based on the tofacitinib IR RA Phase 2 studies, as well as nonclinical E-R modelling using mCIA data from Nonclinical Dose Fractionation Study, to show efficacy between the PR 11 mg QD and IR 5 mg BID.

Cytokine signalling promotes disease through the recruitment and activation of effector cells at sites of pathologic inflammation, the pharmacological effect of tofacitinib on clinical endpoints resulting from inhibition of cytokine signalling is indirect in all diseases where efficacy has been shown. Therefore, it is expected that clinical endpoints in these diseases, like AS, would be dependent on the overall average tofacitinib exposure over time, such as, measured by AUC or Cav (where Cav = AUC/dosing interval), and would not be significantly influenced by short-term fluctuations in plasma concentrations within the dosing interval. This was observed in RA and further substantiated with evaluations that demonstrated that differences in the shape of the plasma-concentration profiles between IR and PR formulations were progressively less relevant for PD endpoints that were further downstream in the JAK-signalling cascade (i.e., with the 2 tofacitinib formulations, small differences were observed in the profiles of upstream biomarkers such as IP-10, whereas no differences were observed in the profiles of downstream biomarkers such as CRP and on the clinical endpoint of DAS-28). E-R analyses that supported bridging of efficacy in RA between the 2 formulations on this basis were previously provided (procedure EMEA/H/C/004214/X/0012).

In the tofacitinib RA PR assessment, a dose mapping study for QD and BID regimens of IR tofacitinib that was conducted using the mCIA (Murine collagen induced arthritis model) was discussed to delineate the predictive values of PK parameters. These results showed concordance of E-R curves and EC50 values using Cav (ratio of EC50 values [QD/BID] ~1.8) (ie, concordance when exposure was represented by average concentration over 24 hours [ie, Cav]), and divergence with either Cmax (~4.3) or Cmin (~84), supporting the relevance of Cav in predicting nonclinical anti-inflammatory activity (Study CP 690550_04Nov10_150736).

Results from this model could be informative of the E-R relationship in AS patients, given the similarity of disease pathogenesis and indirect mechanism of action of tofacitinib between AS and RA patients.

Point 3 of the bridging strategy

Longitudinal E-R analyses using efficacy data for the IR formulation in AS patients that have demonstrated that Cav is the exposure metric most closely associated with efficacy

The E-R evidence to support the bridging of efficacy from the IR formulation to the PR formulation in AS patients is described below.

An ordered categorical longitudinal E-R model was used to evaluate the relationship between ASAS20 and ASAS40 response rates and tofacitinib exposure (PK) using data from the 2 AS studies, A3921119 and A3921120.

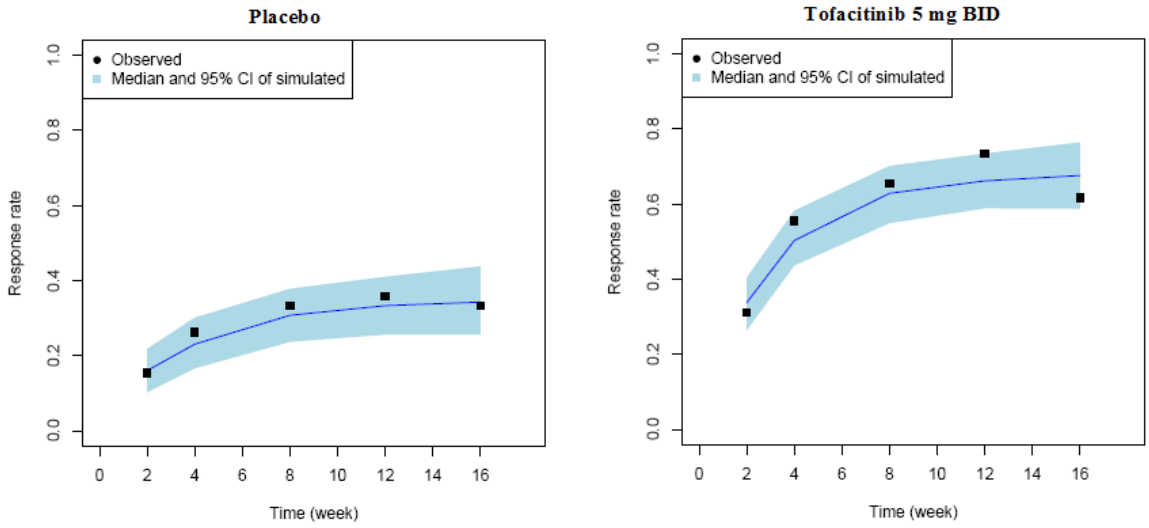
- The longitudinal E-R analysis evaluated the relationship between ASAS20 and ASAS40 response rates and tofacitinib exposure (Cav) in AS patients. Study A3921119 was a Phase 2, randomised, double-blind, placebo-controlled, dose-ranging study of the efficacy and safety of tofacitinib in patients with active AS, who have had an inadequate response to previous NSAID treatment and were naive to previous bDMARD therapy. Subjects received either placebo or tofacitinib 2 mg, 5 mg or 10 mg BID for 12 weeks. The pivotal study, A3921120 was a Phase 3, randomised, double-blinded, placebo-controlled efficacy and safety study in adult patients with active AS, who were stratified by prior treatment history of either i) bDMARD-naive (approximately 80%) or ii) TNFi-IR or bDMARD use (non-IR) (approximately 20%). Subjects received either placebo or tofacitinib 5 mg BID for 16 weeks (double-blind phase) and then continued in the open-label phase thereafter, where all subjects received tofacitinib 5 mg BID up to Week 48. Efficacy data in the double-blind phase (i.e., up to Week 16) was included in this analysis. In both studies, patients were allowed to be on background therapy of non-bDMARD (eg, methotrexate or sulfasalazine) as noted in the respective study protocols.

A longitudinal E-R model was formulated using ASAS20 and ASAS40 response rates and tofacitinib exposures after administration of tofacitinib IR doses of 2 mg, 5 mg or 10 mg BID, pooled across the 2 AS studies (dose-ranging and pivotal).

The model, which consisted of baseline, placebo (or non-drug) and drug effect components, used an Emax model to describe the drug effect component. The ASAS20 and ASAS40 responder criteria used in the modelling were assessed at Week 2, 4, 6, 8 and 12 in Study A3921119 and at Week 2, 4, 6, 8, 12 and 16 in Study A3921120. Cav was used as the exposure metric for these E-R evaluations in AS; the use of Cav is supported by prior knowledge from the RA program, which established Cav as the most relevant tofacitinib exposure metric for efficacy (PMAR-EQDD-A392a-sNDA-830). Estimates of Cav for this analysis were obtained from a population PK analysis using PK samples from the AS patients in A3921119 and A3921120 (PMAR-EQDD-A392k-sNDA-1064).

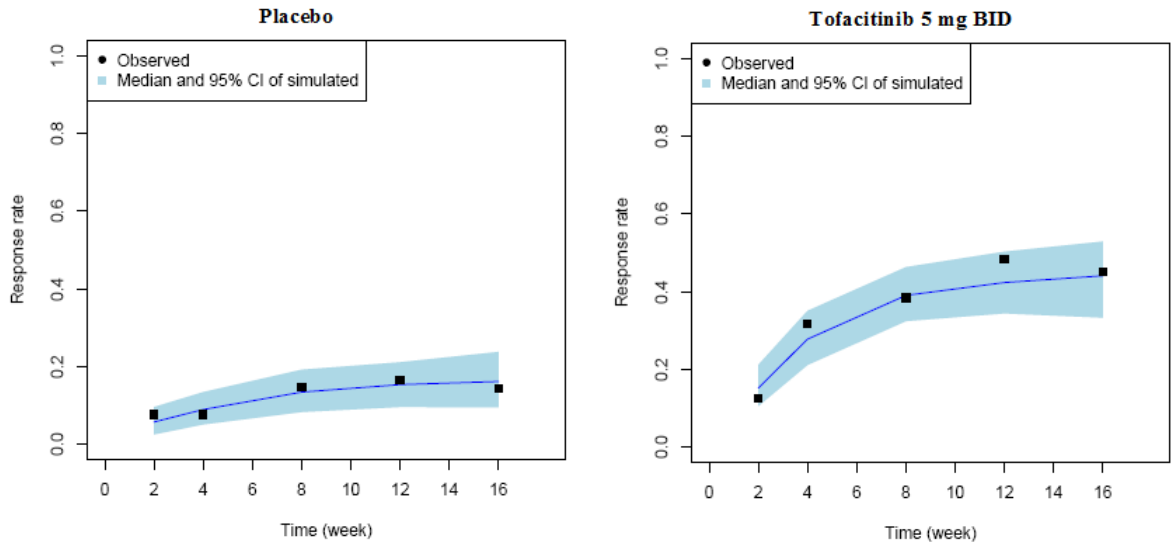
Plots of model-predicted ASAS20 and ASAS40 response rates compared to observed response rates for placebo and IR 5 mg BID, in adult AS patients who are bDMARD-naive, are shown in Figure 1 and Figure 2, respectively.

Figure 1. Longitudinal Model-Predicted ASAS20 Responses in bDMARD-naive AS Patients Pooled Across A3921119 and A3921120



Black solid squares correspond to observed ASAS20 response rates. Blue line and shaded area represent median and 95% CI of estimated response rates, respectively.
Source: AS IR Module 5.3.3.5 PMAR-EQDD-A392k-sNDA-1065, Figure 6.

Figure 2. Longitudinal Model-Predicted ASAS40 Responses in bDMARD-naive AS Patients Pooled Across A3921119 and A3921120



Black solid squares correspond to observed ASAS40 response rates. Blue line and shaded area represent median and 95% CI of estimated response rates, respectively.
Source: AS IR Module 5.3.3.5 PMAR-EQDD-A392k-sNDA-1065, Figure 6.

Following an early onset of efficacy by Week 2, the drug effect continues to increase up to Week 8. The estimate of the time of onset parameter (half-life of drug effect for efficacy responses) from the longitudinal model is 1.18 weeks, demonstrating a delay or time lag in attaining PD (clinical response) steady-state relative to PK. Placebo-corrected estimates of ASAS20 response rates after tofacitinib IR 5 mg BID were 18%, 28%, 31% and 32%, at Week 2, 4, 6 and 8, respectively, in AS patients who were bDMARD-naive, indicating that efficacy in these patients continued to increase beyond Week 4 and approached steady-state (plateau) after Week 8. These results, which are consistent with observed ASAS20 response rates demonstrate that the delay in the attainment of efficacy (PD) steady-state occurs over a substantially longer time period (in weeks) compared to the attainment of PK steady-state of tofacitinib (in 24–48 hours).

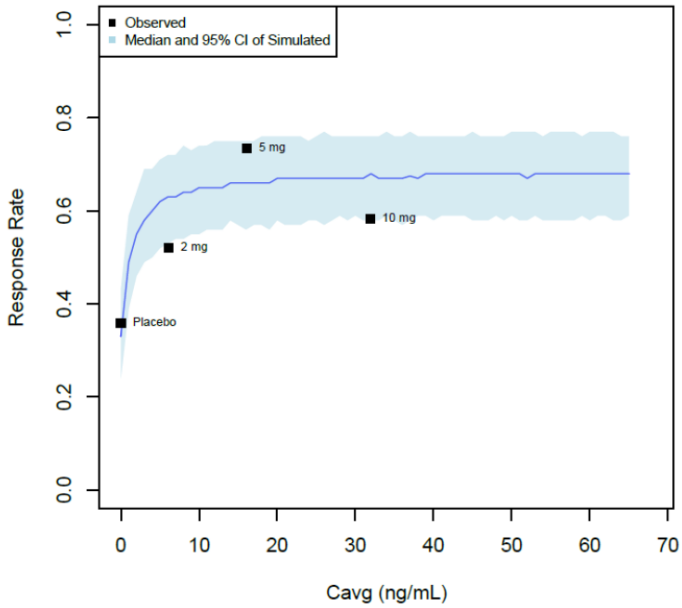
These data are consistent with the estimated onset half-life for clinical responses in RA and in PsA. The similar delay in attainment of PD steady-state as in RA and in PsA, suggests that within day fluctuations in PK profile of tofacitinib are unlikely to confer differential effectiveness in AS. The longitudinal E-R relationship in AS supports the conclusion that Cav is the relevant parameter for efficacy and that the 29% lower Cmin for the PR formulation is not relevant to efficacy in AS.

- The Cav-based E-R model adequately characterised the relationship between tofacitinib exposure and clinical efficacy in adult patients with active AS (the use of Cav is supported by prior knowledge from the RA program, which established Cav as the most relevant exposure metric for efficacy). Model-predicted estimates of ASAS20 and ASAS40 were 67% and 44%, respectively after tofacitinib 5 mg BID in bDMARD-naive AS patients at Week 16. The predicted placebo-corrected estimates were 32% and 28%, respectively

The predictive abilities of different tofacitinib exposure metrics were previously evaluated using data from RA patients. These evaluations identified Cav as the most relevant PK parameter in the characterisation of E-R relationships of clinical response despite the high correlation among Cav, Cmin and Cmax. Furthermore, it was seen that Cmin did not provide additive predictive value over and above that of Cav (PMAR-EQDD-A392a-sNDA-830).

Based on this prior knowledge from the RA program, a longitudinal ordered categorical E-R model was used to characterise the relationship between ASAS20 and ASAS40 responses in AS patients and tofacitinib exposures, using Cav estimates as the predictor variable (ASAS20 illustrated in Figure 3). This analysis showed that model-predicted ASAS20 and ASAS40 response rates in bDMARD-naive AS patients at Week 16 after tofacitinib 5 mg BID were 67% and 44%, respectively. Placebo-corrected estimates of ASAS20 and ASAS40 were 32% and 28%, respectively.

Figure 3. Exposure-Response Relationship Using ASAS20 Responders at Week 12 in bDMARD-Naive AS Patients Pooled Across A3921119 and A3921120



Blue line and shaded area are median and 95% CI of model-predicted ASAS20 response rates. Black squares are observed response rates at mean C_{av} values of each dose group. Simulations from final E-R model depicted at Week 12 as observed data across all dose groups were only available at this visit (unlike at Week 16).

Source: AS IR Module 5.3.5.3 PMAR-EQDD-A392k-sNDA-1065, Figure 7.

E-R models for ASAS20 and ASAS40 responses using Cav, Cmin or Cmax as the tofacitinib exposure metric were compared based on model diagnostics such as the OFV and AIC. Table below summarises the model evaluation for the different E-R models fitted.

Table 3. Comparison of E-R Models for ASAS20 and ASAS40 Response Rates

Run Number	Exposure Metric in E-R Model	OFV	AIC
4	C_{av}	3054.663	3072.663
9	C_{max}	3054.155	3072.155
10	C_{min}	3055.281	3073.281

Source: AS IR Module 5.3.5.3 PMAR-EQDD-A392k-sNDA-1065, Table 9

Comparison of models with Cav, Cmin or Cmax as the predictor (univariate analysis) did not show differences in model diagnostics (ΔOFV or ΔAIC were less than 3.84, the critical chi squared value) that would lead to the conclusion of any one parameter (or exposure metric) as being more relevant than another to clinical efficacy. This was not unexpected since these PK parameters are highly correlated, particularly Cavg and Cmin (correlation coefficient = 0.85, PMAR-EQDD-A392k-sNDA-1065), indicating that the exposure measures contain very similar information.

Although this comparative assessment did not show differences in model diagnostics that would identify any one exposure parameter (Cav, Cmin or Cmax) as more relevant than another for clinical efficacy, the results suggest that a measure of overall exposure (such as Cav) can adequately describe the observed efficacy responses, and metrics such as, Cmin and Cmax (plasma concentrations at discrete time points) do not provide greater predictive value compared to Cav. This is consistent with the indirect mechanism of action of tofacitinib as well as the demonstrated lag between the times to attain steady-state clinical response (PD) versus PK.

The Exposure-Response Evaluation of Tofacitinib for Efficacy (ASAS20/40) in Patients with Ankylosing Spondylitis (PMAR-EQDD-A392k-sNDA-1065) has been submitted by the MAH during the variation II/35 (eCTD 0113) in addition to efficacy data from studies A3921119 and A3921120, to describe the relationship between tofacitinib exposure and clinical efficacy in patients with active AS after the administration of placebo or tofacitinib doses of 2 mg, 5 mg or 10 mg BID up to Week 16.

For completeness of assessment, a summary of the aforementioned report is reported below.

The primary *objectives* in PMAR-EQDD-A392k-sNDA-1065 are:

• To characterize the relationship between tofacitinib exposure and ASAS response levels of 20% and 40% (ASAS20 and ASAS40, respectively) over time, in subjects with active AS using a longitudinal exposure response model.

• To compare predicted PK measures, including of steady state Cavg, Cmin and Cmax, in an E-R analysis of ASAS20 and ASAS40 responses in subjects with active AS.

The secondary *objectives* are:

• Investigate the effects of specified covariates (prior biologic therapy) on the E-R relationship for ASAS20 and ASAS40

A dose-response analysis (with a Bayesian Emax model) was conducted, using ASAS20 responder rates at Week 12 from the Phase 2 dose-ranging study, Study A3921119. This study had evaluated placebo and 3 tofacitinib doses (2 mg, 5 mg or 10 mg BID) for 12 weeks in bDMARD naïve patients with active AS. Placebo-corrected ASAS20 responder rates, along with 95%, 60% and 50% credible intervals were estimated using this Bayesian model.

This primary endpoint analysis using an Emax model, estimated that ASAS20 response rates were higher than placebo for all tofacitinib dose groups. However, although the tofacitinib 2 mg BID and tofacitinib 5 mg BID treatment groups showed an estimated difference from placebo of 15.8% and 22.9%, respectively, they both did not meet the pre-specified statistical decision rules for the primary endpoint of the ASAS20 response rate at Week 12. Only the tofacitinib 10 mg BID treatment group met pre-specified rules for the primary endpoint of the ASAS20 response rate at Week 12 with an estimated response rate of 67.4%, an estimated difference from placebo of 27.3%, a 20.3% difference from placebo for the lower bound of the 2-sided 60% credible interval (ie, 1-sided 80% lower bound), and a 33.0% difference for the upper bound of the 2-sided 50% credible interval (ie, 1-sided 75% upper bound).

The population E-R model was carried out using the nonlinear mixed effects modeling approach as implemented in the software package NONMEMR version 7.4.1 (ICON Development Solutions, Hanover, MD). Perl-speaks-NONMEM (PsN), version 4.8.0 was used as supporting software for the execution of NONMEM.

METHODS

The analysis was conducted based on the following strategy: Base Structural Model Development; Inclusion of Covariates; Assessment of Model Adequacy (Goodness of Fit); Assessment of Final Model Predictive Performance.

Base Model Description. The ASAS20 and ASAS40 responses were modelled simultaneously as an ordered categorical variable Y(t) taking on possible responses with **Y = 2 if achieving ASAS40, Y = 1 if achieving ASAS20 but not ASAS40 and Y = 0, if not achieving ASAS20**, at time t. Hence the probability of achieving Y = k, with **k = 1 or 2** to a predictor M(X;b) can be modelled using logistic regressions, such as:

$$h^{-1} prob[Y(t) \geq k] = \alpha_k + M(X, \beta), k = 1, 2 \qquad (1)$$

where α1 > α2 represents the intercepts of each ASAS cutpoint, X a matrix of covariates, β a vector of regression coefficients, and h^{-1} the inverse link function that restricts the probability between 0 and 1. In a logistic regression, this parameterization where M(X;β) is the same for all k corresponding to the proportional odds assumption.

Note that prob[Y(t) ≥ 0] = 1, so that in the model it is only necessary to estimate the cumulative probability for the score 1 and 2. The probability for each individual score can thereafter be calculated from the estimated cumulative probability using following equations.

$$prob[Y(t) = 0] = 1 - prob[Y(t) \geq 1] \qquad (2)$$

$$prob[Y(t) = k] = prob[Y(t) \geq k] - prob[Y(t) \geq k + 1] \qquad (3)$$

For a logistic regression, the link function and its inverse function can be defined such as:

$$h(x) = \frac{e^x}{1 + e^x} \qquad (4)$$

$$h^{-1}(x) = log[\frac{x}{1 - x}] \qquad (5)$$

For the E-R modeling, a general nonlinear mixed-effects model was constructed based on the combined ASAS20 and ASAS40 response:

$$h^{-1} prob[Y(t) \geq k] = \eta + \alpha_k + f_{drug}(t) + f_{placebo}(t) \qquad (6)$$

Where η is the inter-individual variance (IIV) which is assumed to be normally distributed with mean 0 and variance 1, fdrug(t) the drug effect function, and fplacebo(t) the placebo effect function. For the longitudinal analysis, the following exponential equation was used to investigate the time course and onset of drug effect and placebo effect:

$$f_{drug}(t) = D_{effect} \cdot (1 - exp[-\frac{ln2}{D_{Thalf}}t]) \quad (7)$$

$$f_{placebo}(t) = P_{effect} \cdot (1 - exp[-\frac{ln2}{P_{Thalf}}t]) \quad (8)$$

where Deffect and Peffect are the drug effect and placebo effect, respectively; DThalf and PThalf are the half-life of drug effect and placebo effect respectively; t stands for time with unit of week.

Drug effect was evaluated using individual Cavg values as the exposure metric, and investigated with linear, Emax, or exponential models (Equation 9).

$$D_{effect} = \begin{cases} D_{slp} \cdot C_{avg} & \text{linear model} \\ \frac{Emax \cdot C_{avg}}{EC50 + C_{avg}} & \text{Emax model} \\ Emax \cdot (1 - exp[-K \cdot C_{avg}]) & \text{exponential model} \end{cases} \quad (9)$$

where Dslp is the slope for the exposure-response relationship with Cavg. Emax is the maximum drug effect. EC50 is the concentration to reach 50% of Emax. K is shape parameter.

Inclusion of Covariates. The primary covariate of interest in this analysis was previous bDMARD use. Approximately 20% of subjects in Study A3921120 were stratified to be biologic-experienced (either TNF-inadequate responders or bDMARD-experienced). A covariate effect for previous bDMARD use was evaluated. This effect was assessed on the most appropriate model parameter (i.e., Peffect of the placebo effect, or Deffect of the drug effect) or function.

RESULTS

A total of 466 patients were included in the longitudinal analysis.

Table 4. Number of subjects by treatment group

Dose	A3921119	A3921120	Total
Placebo	51	136	187
2 mg BID	50	0	50
5 mg BID	49	132	181
10 mg BID	48	0	48

Table below summarizes prior bDMARD experience for the patients in this analysis dataset.

Table 5. Summary of prior bDMARD Experience

Prior bDMARD	A3921119	A3921120	Total
Naive	198 (100%)	207 (77.2%)	405 (86.9%)
Experienced	0 (0%)	61 (22.8%)	61 (13.1%)

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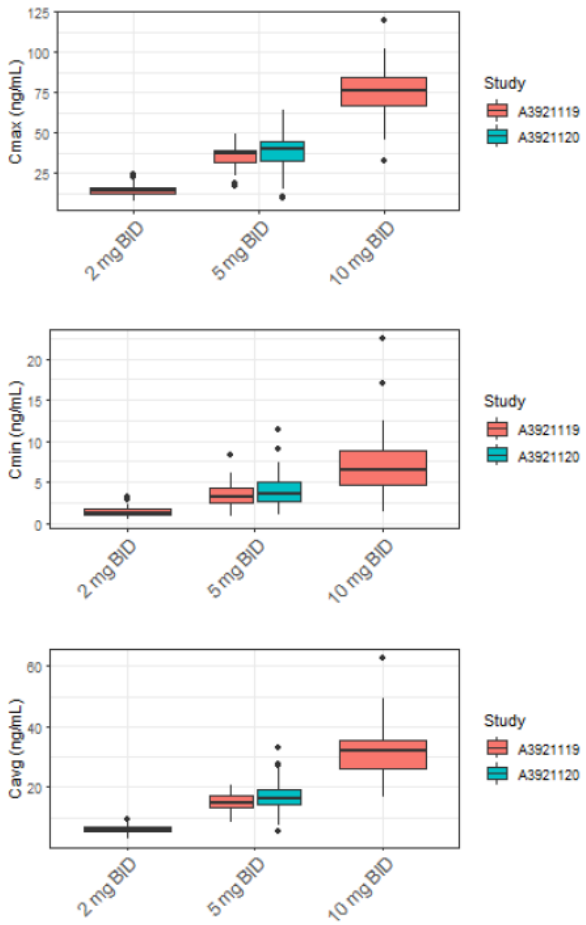
bDMARD=biologic disease-modifying antirheumatic drug

Individual exposure metrics from a post processing step based on the final tofacitinib population PK modeling were used. The distribution of Cmax, Cmin and Cavg grouping by treatment groups is shown in Figure 4 and summary statistics are listed in Table 6.

Figure 4. Tofacitinib exposure metrics by study and dose



Repository artifact ID FI-4118742.
C_{max}= maximum concentration; C_{min}= minimum concentration; C_{avg}=average concentration; BID=twice daily

Table 6. Summary of exposure metrics

Variable	Study	Treatment	Mean	Median	Min	Max
C_{min} (ng/mL)	1119	2 mg BID	1.4	1.3	0.4	3.2
		5 mg BID	3.5	3.2	0.8	8.2
		10 mg BID	7	6.5	1.3	22.4
	1120	5 mg BID	4	3.6	0.9	11.4
C_{max} (ng/mL)	1119	2 mg BID	14.5	14.1	7.8	24.3
		5 mg BID	35.7	37.1	17.2	49.3
		10 mg BID	75.6	76.6	32.5	119.7
	1120	5 mg BID	38.7	40	10	64
C_{avg} (ng/mL)	1119	2 mg BID	6.2	6	3.1	9.5
		5 mg BID	15.3	15	8.4	20.7
		10 mg BID	31.9	32.2	16.8	62.8
	1120	5 mg BID	16.7	16.3	5.4	33.1

Repository artifact ID FI-4118746.

C_{avg}=average concentration, C_{max}=maximum concentration, C_{min}=minimum concentration, BID=twice daily

A longitudinal ordered categorical model with exponential time-dependent onsets of placebo and drug effect was used to evaluate the relationship between tofacitinib exposure and ASAS20/40. Linear, exponential and Emax model forms using Cavg, an exposure metric that has been previously established as relevant for the efficacy of tofacitinib in diseases like RA and PsA, were evaluated to characterize the drug effect component. A summary of model evaluation metrics for the key runs are provided in Table 7.

Table 7. List of key model runs

Run	Improve ID	Model Description	OFV	Comments
1	ST-4099121	Emax/EC50 model with C_{avg}	3073.949	Base model
2	ST-4148540	Linear model with C_{avg}	3111.643	-
3	ST-4589958	Exponential model with C_{avg}	3073.569	-
4	ST-4245150	Run1 + prior bDMARDs experience as covariate on P_{effect}	3054.663	Final model
5	ST-4245170	Run4 + Study effect on baseline	3051.985	-
6	ST-4411916	Run4 + Study effect on P_{effect}	3054.658	-
7	ST-4411960	Run 1 with the same D_{Thalf} and P_{Thalf}	3077.242	-
8	ST-4157085	Emax/ED50 model with dose	3073.743	-

OFV= Objective Function Value; C_{avg}= average concentration at steady state.

Source: Improve analysis tree: AT-2109636

After careful evaluation of the various structural models, including a model that used tofacitinb BID dose, a model with exponential time-dependent onsets of placebo and drug effect, and the drug effect component described by an Emax model form (Run 1) was selected to describe the relationship between tofacitinib exposure and efficacy in AS.

Parameter estimates of the base model (Run 1) are presented in Table 8.

Table 8. Parameter estimates of the base model

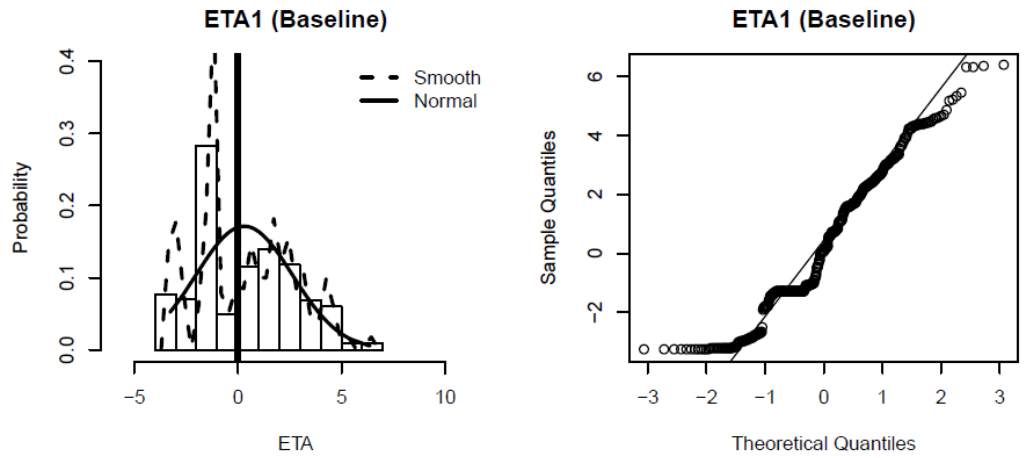
Parameter	Comment	Estimate	RSE (%)	Bootstrap 90% CI
$\alpha 1$	$logit(prob[Y(t) \geq 1])$ without drug or placebo effect	-5	16.5	(-6.52 to -3.99)
$\alpha 2$	$logit(prob[Y(t) \geq 1])$ - $logit(prob[Y(t) \geq 2])$	-2.06	5.88	(-2.28 to -1.87)
D_{Thalf} (week)	Half-life of drug effect	1.16	29	(0.735 to 2.02)
E_{max}	Maximum drug effect	3.13	40.5	(2.63 to 4.48)
EC50 (ng/mL)	Concentration at which half of E_{max} was reached	0.831	604	(0.2 to 6.24)
P_{Thalf} (week)	Half-life of placebo effect	2.55	37.7	(1.62 to 4.36)
P_{effect}	Maximum placebo effect	3.31	22.7	(2.45 to 4.64)
IIV	Inter-individual variability of $logit(prob[Y(t) \geq 1])$	8.8	13.3	(7.09 to 11.1)

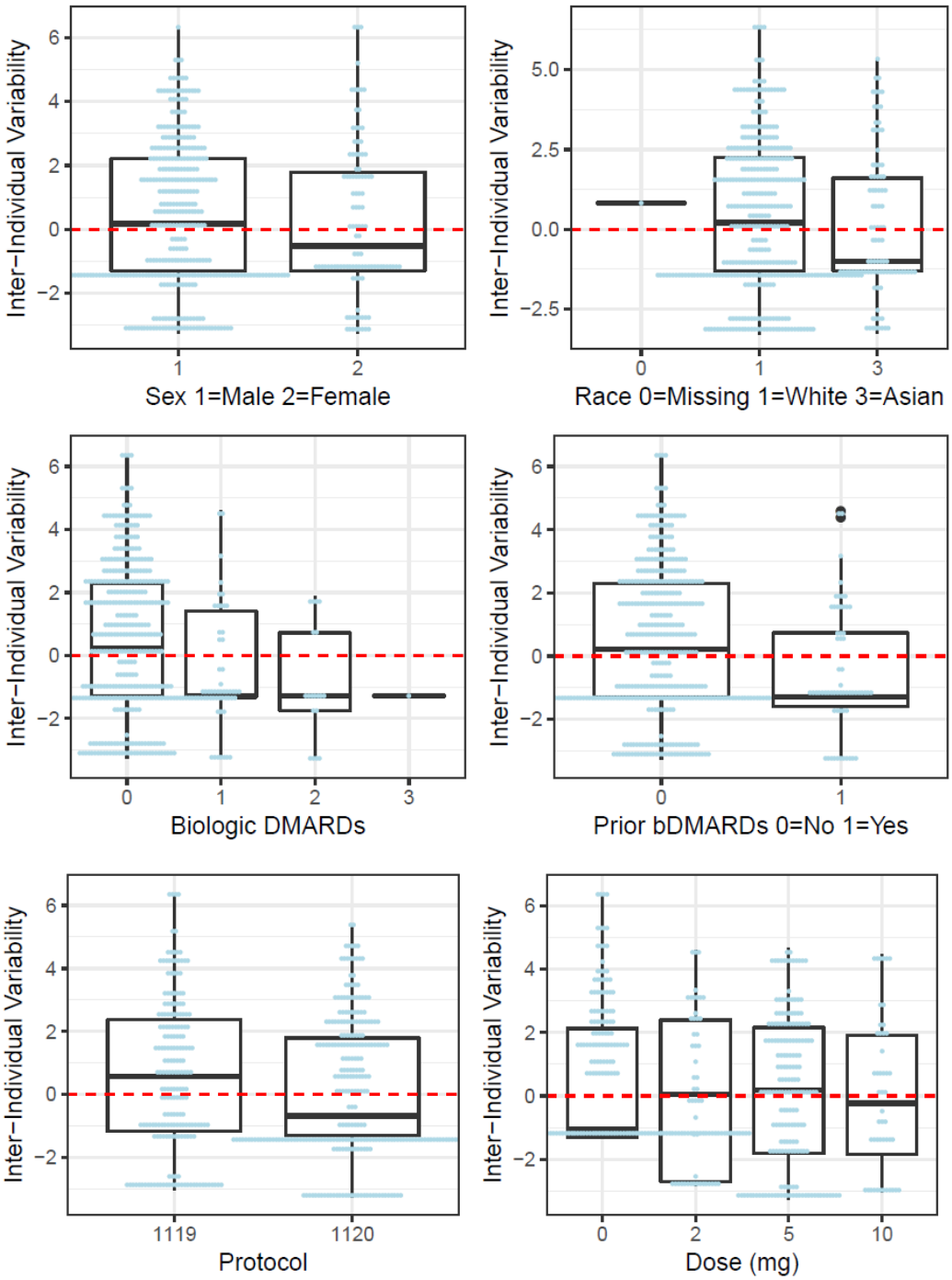
Repository artifact ID FI-4319783.
Bootstrap 90% CI was based on 645 successful runs out of 1000.
RSE: relative standard error, CI: confidence interval.

Inter Individual Variability (IIV) was applied to the logit value of cumulative probability (h^{-1} prob[Y(t) ≥ k]). The standard errors for the parameter estimates were small (30%), except for estimate of EC50 (RSE = 604%). h-shrinkage was 21.5%. There was absence of extreme pairwise correlations (r>0.95) of the parameters or high condition number of the correlation matrix of the parameter estimates (k>1000). 1000 non-parametric bootstrap were performed to generate the 90%CI of parameter estimates using the base model. Of these, 29 runs with miminisation terminated and 326 runs with estimates near a boundary (total 355) were excluded when calculating the bootstrap results.

Diagnostic plots for the base model are presented in Figure 5.

Figure 5. Diagnostic plots of the base model





As shown in the ETA (η) histograms and quantile-quantile plots, there is lack of normality in the η distribution. The sharp peak on the lower end of the distribution represents the inflated η values from non-responders (data not shown). The η values estimated for these patients were consistently low. However, this lack of normality in distribution did not impact the goodness of fit evaluated using simulation-based diagnostic plots, which are the primary diagnostic plots.

Final Model Results

Prior bDMARD experience (PMED) and study effect (PROT) were tested on baseline (h^{-1} prob[Y(t) ≥ 1]), placebo effect (Peffect), or drug effect (Deffect) in order to evaluate their effect on ASAS20/40 response rates. PMED has 2 levels including 0 and 1, which represents bDMARD naive (0) or experienced (1). PMED was identified as significant covariate on Peffect (Run 4). Patients with prior bDMARD treatment

experience showed a lower response to placebo in Study A3921120. However, study effect as a covariate did not provide a better fitting (Run 5 and 6), therefore, it was not included in the final model. Run 4 was considered the final model.

The parameter estimates for the final model are presented in Table 9.

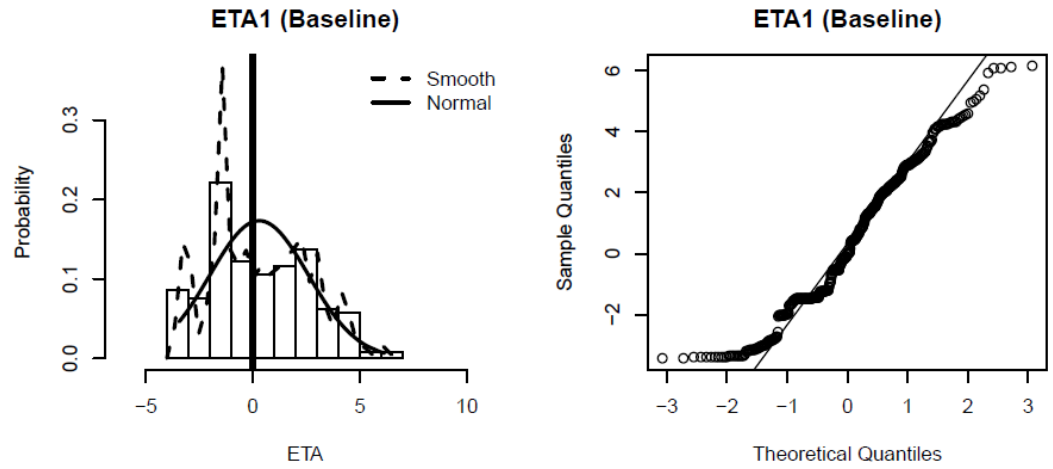
Table 9. Parameter estimates of the final model run (Run 4)

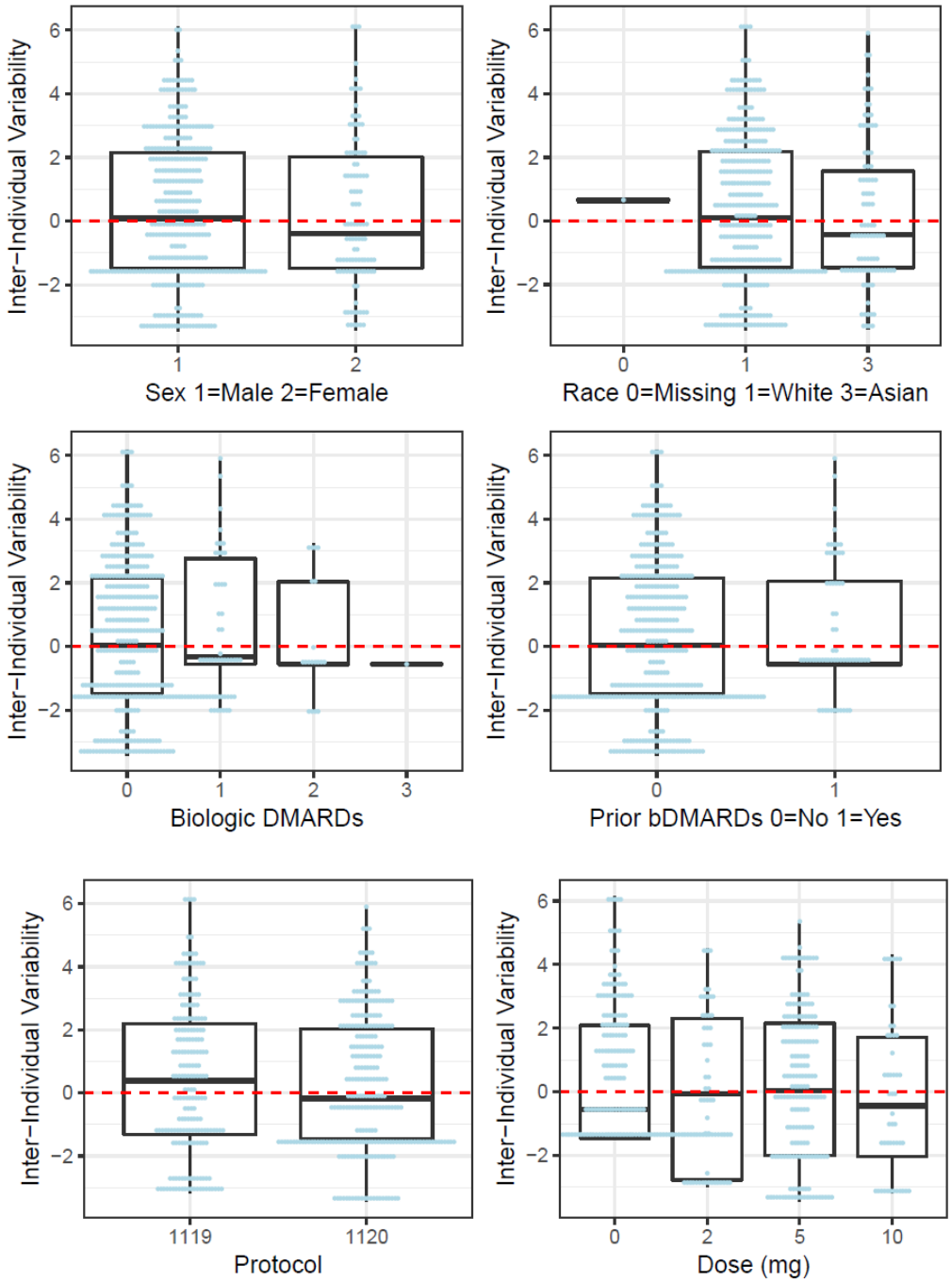
Parameter	Comment	Estimate	RSE (%)	Bootstrap 90% CI
$\alpha 1$	$logit(prob[Y(t) \geq 1])$ without drug or placebo effect	-4.93	14.9	(-6.3 to -3.96)
$\alpha 2$	$logit(prob[Y(t) \geq 1])$ - $logit(prob[Y(t) \geq 2])$	-2.07	5.73	(-2.3 to -1.9)
D_{Thalf} (week)	Half-life of drug effect	1.18	30.5	(0.742 to 2.14)
E_{max}	Maximum drug effect	3.11	17.1	(2.59 to 4.53)
EC50 (ng/mL)	Concentration at which half of E_{max} was reached	1.24	135	(0.181 to 6.75)
P_{Thalf} (week)	Half-life of placebo effect	2.55	26.4	(1.63 to 4.06)
P_{effect}	Placebo effect	3.6	18.7	(2.64 to 4.79)
PMED=1 on P_{effect}	Coefficient of PMED=1 on placebo effect	-2.18	26.1	(-3.16 to -1.24)
IIV	Inter-individual variability of $logit(prob[Y(t) \geq 1])$	8.61	12.4	(7.02 to 10.5)

Repository artifact ID FI-4312649.
Bootstrap 90% CI was based on 728 successful runs out of 1000.
RSE: relative standard error, CI: confidence interval, PMED: prior bDMARD experience

The standard errors for the parameter estimates were small (30%), except for the EC50 estimate with RSE of 135%. h-shrinkage was 21.6%. There was absence of extreme pairwise correlations (r>0.95) of the parameters or high condition number of the correlation matrix of the parameter estimates (k>1000). Diagnostic plots for goodness of fit are presented in the figure below:

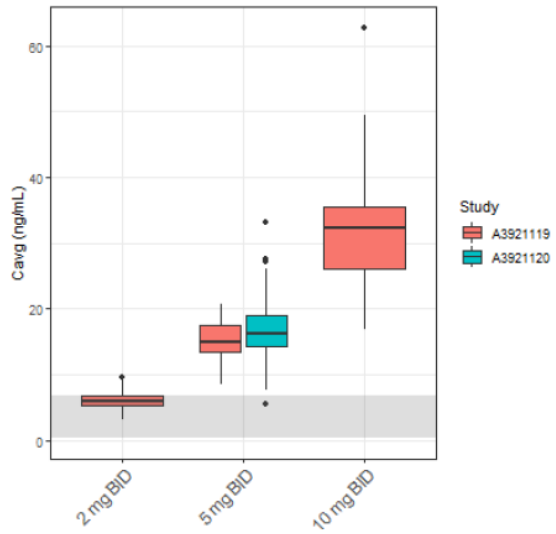
Figure 6. Diagnostic plots of the final model





As shown in the parameter estimates from both the base and final models, there is a high degree of uncertainty on the EC50 estimate (high RSE values), most likely due to the lack of data at the lower end of the concentration range (Figure 7). 1000 non-parametric bootstrap were performed to generate the 90%CI of parameter estimates using the final model. Of these, 27 runs for which miminisation terminated, and 245 runs with estimates near a boundary (total 272 runs) were excluded when calculating the bootstrap results. This may be due to the limited information in the data to precisely characterize the EC50. Placebo treatment reached half of the maximum effect in 2.55 weeks (90%CI [1.63, 4.06]). The half-life of drug onset was estimated to be 1.18 weeks for ASAS20/40 (90%CI [0.74, 2.14]).

Figure 7. Overlay of EC50 Bootstrap 90% CI with Cavg distribution

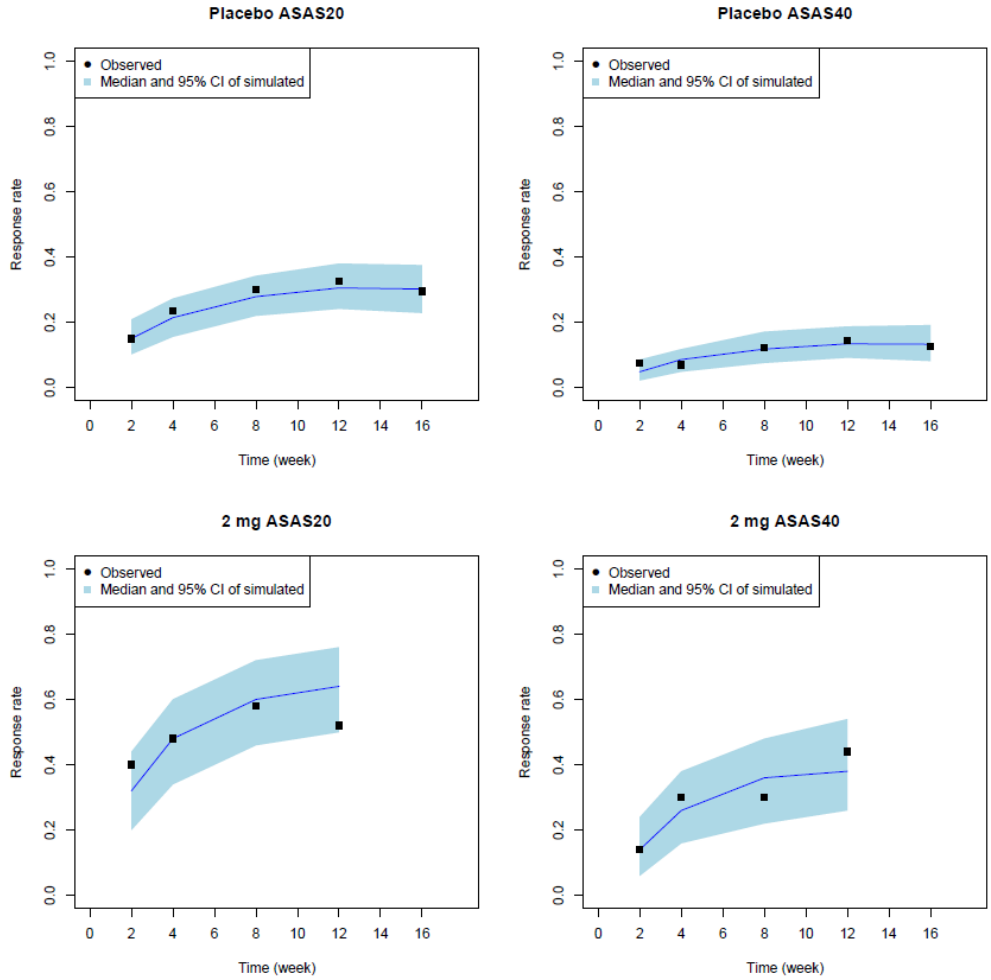


Repository artifact ID FI-4370385.
Shaded area represents the bootstrap 90% CI of EC50

Final Model Predictive Performance

VPC plots for the final model are presented in Figure 8 and Figure 9.

Figure 8. Visual predictive check for ASAS20 and ASAS40 response rates stratified by dose



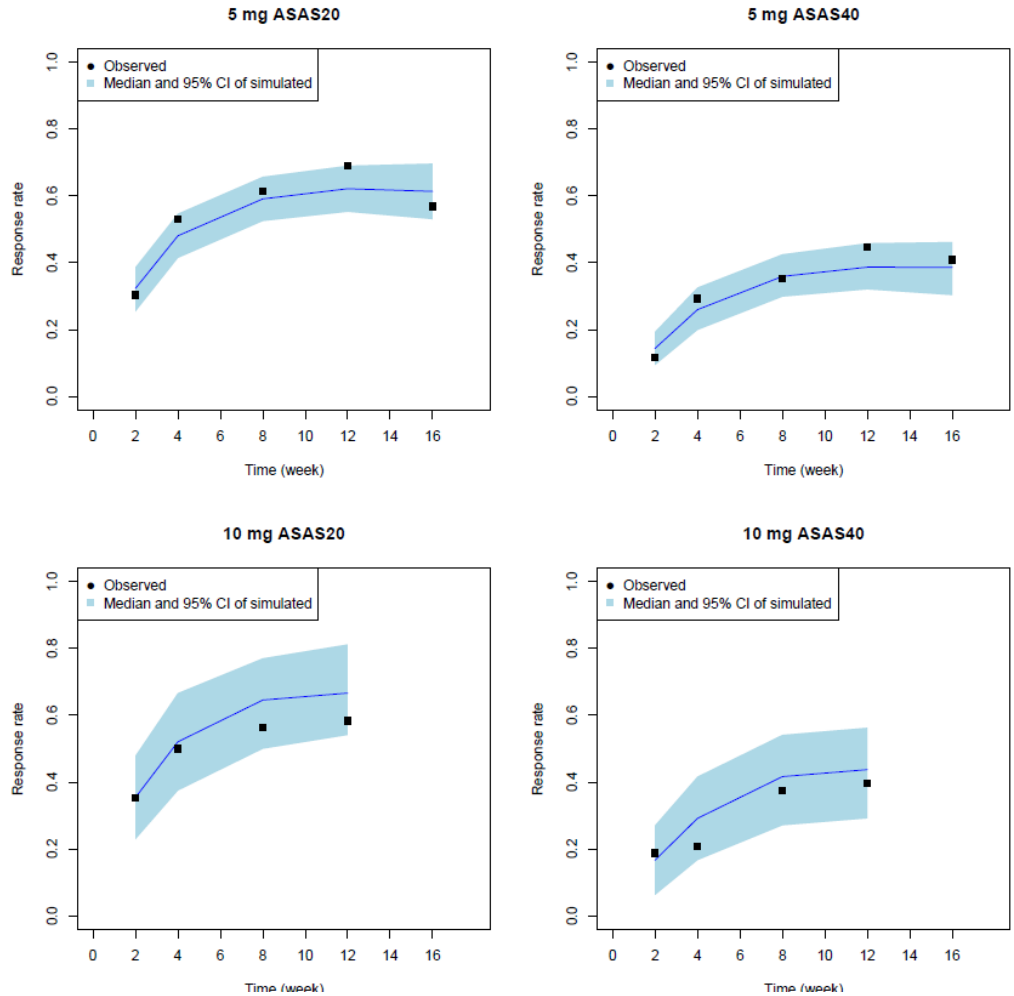
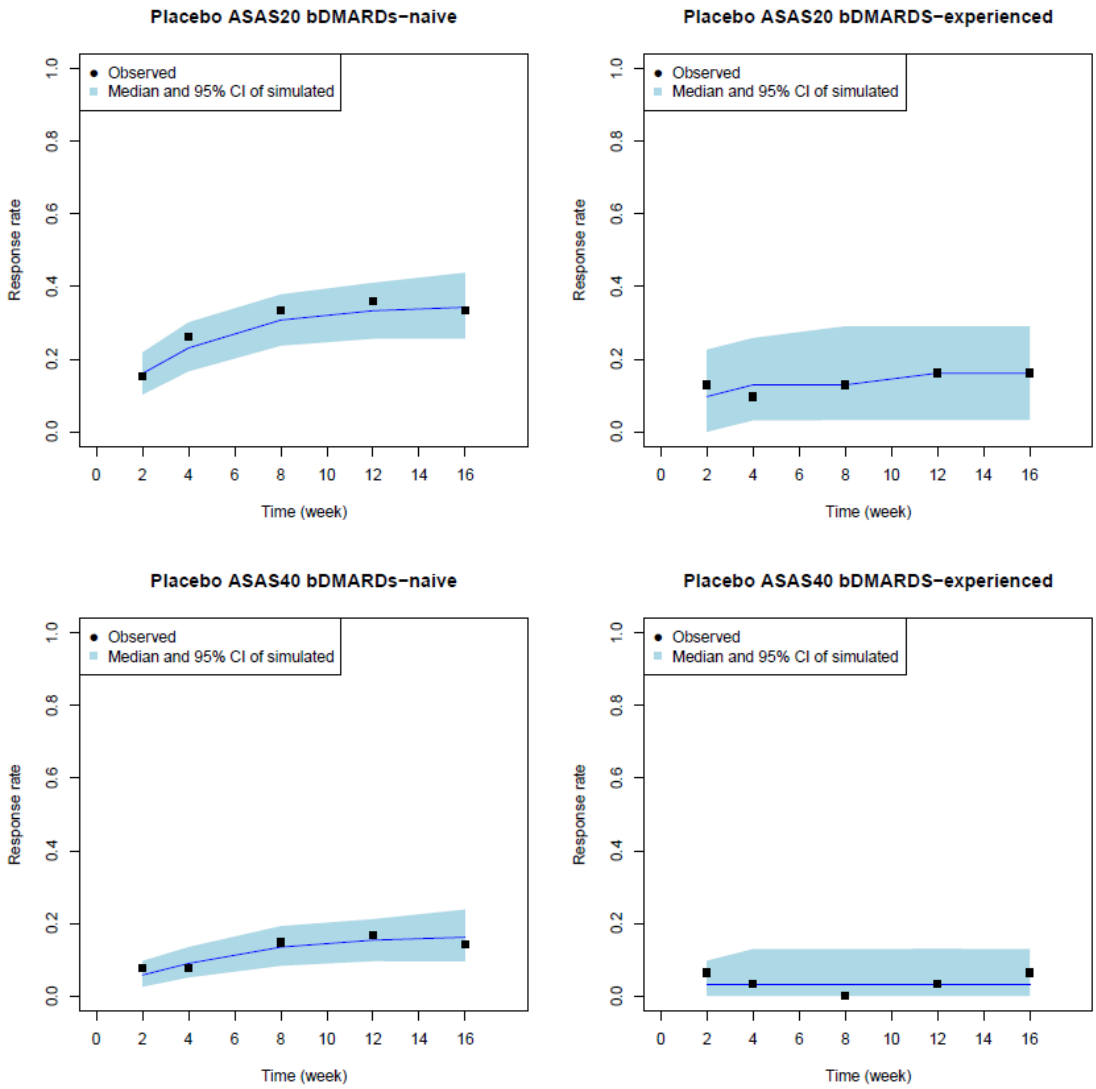
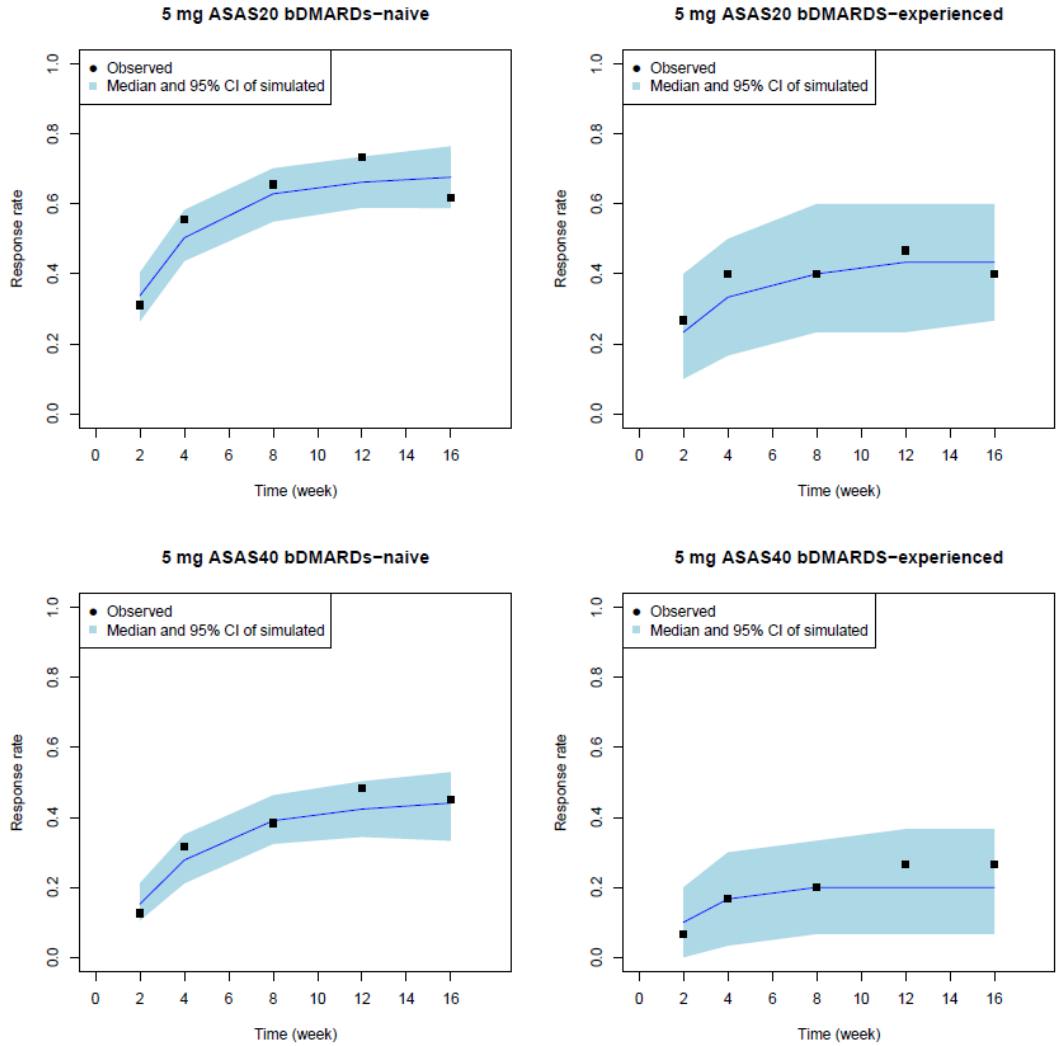

5 mg ASAS20
Observed
Median and 95% CI of simulated
Response rate
Time (week)
5 mg ASAS40
Observed
Median and 95% CI of simulated
Response rate
Time (week)
10 mg ASAS20
Observed
Median and 95% CI of simulated
Response rate
Time (week)
10 mg ASAS40
Observed
Median and 95% CI of simulated
Response rate
Time (week)

Figure 9. Visual predictive check for ASAS20 and ASAS40 response rates stratified by prior bDMARD experience





Model-Predicted ASAS20 and ASAS40 Responses based on Simulation

The model-predicted ASAS20 and ASAS40 response rates based on simulation are listed in Table 10. Model-predicted ASAS20 response rates after tofacitinib 2 mg, 5 mg and 10 mg BID were 64%, 67% and 68%, respectively and ASAS40 response rates were 40%, 44%, and 45% respectively, in bDMARD-naive AS patients at Week 16.

Placebo-corrected estimates of ASAS20 and ASAS40 response rates at Week 16 were 32% and 28% after 5 mg BID in AS patients who were bDMARD-naive. In the bDMARD-experienced group, placebo-corrected ASAS20 and ASAS40 response rates at Week 16, after 5 mg BID were estimated to be 27% and 16%, respectively.

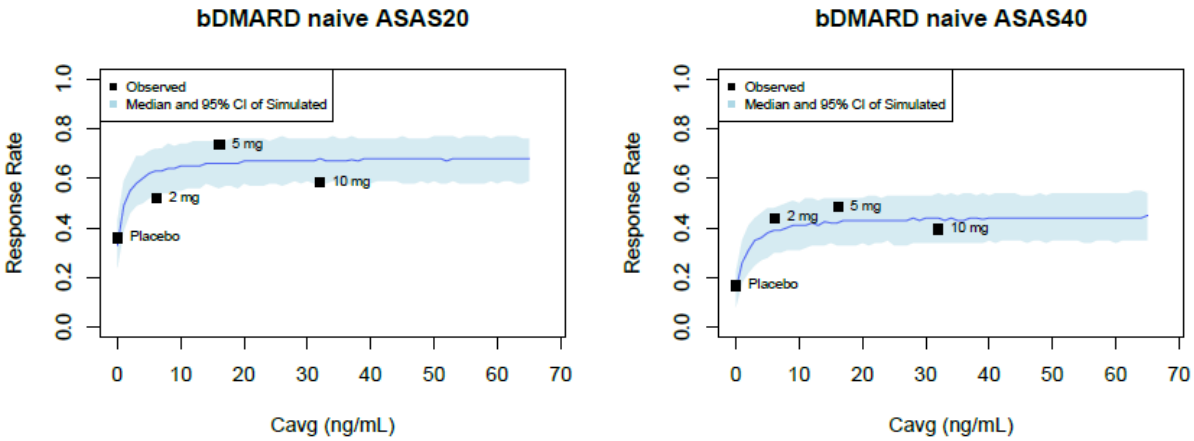
Table 10. Model-predicted ASAS20 and ASAS40 response rates at week 16 in bDMARD-naïve patients

Endpoint	Dose	Response rate (95%CI)	Placebo-corrected response rate (95%CI)
ASAS20	Placebo	0.34 (0.28 - 0.42)	-
ASAS20	2 mg BID	0.64 (0.56 - 0.7)	0.29 (0.2 - 0.38)
ASAS20	5 mg BID	0.67 (0.6 - 0.74)	0.32 (0.24 - 0.41)
ASAS20	10 mg BID	0.68 (0.62 - 0.75)	0.34 (0.25 - 0.43)
ASAS40	Placebo	0.16 (0.11 - 0.21)	-
ASAS40	2 mg BID	0.4 (0.33 - 0.46)	0.24 (0.15 - 0.32)
ASAS40	5 mg BID	0.44 (0.36 - 0.5)	0.28 (0.2 - 0.36)
ASAS40	10 mg BID	0.45 (0.38 - 0.52)	0.29 (0.2 - 0.38)

Repository artifact ID FI-4955677. Line 1 substituted.

Simulations to illustrate the exposure-response relationship were also performed, and plotted with observed response rates at Week 12 (Figure 10, Figure 11). Model predictions of placebo-corrected estimates after 2 mg BID (ASAS20 of 29% and ASAS40 of 24%) in bDMARD-naive AS patients at Week 16 were slightly lower compared to 5 mg BID.

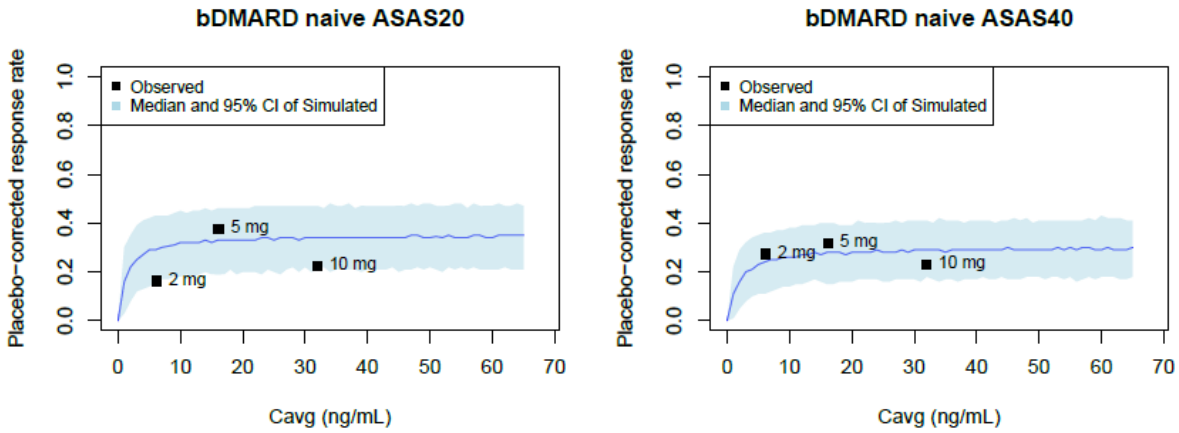
Figure 10. Exposure-Response relationship in bDMARD-naïve patients (Week 12)



Repository artifact ID FI-4320119.

bDMARD=biologic disease-modifying antirheumatic drug; C_{avg}=average concentration. The C_{avg} of the observation data points were the mean C_{avg} values for each dose group. Median predictions and CIs for ASAS20 and ASAS40 were based on 1000 simulations (at Cavg values ranging from 0 to 65 ng/ml) using the final model

Figure 11. Exposure-Response relationship in bDMARD-naïve patients (Week 12, PBO-corrected)



Repository artifact ID FI-4955670.
bDMARD=biologic disease-modifying antirheumatic drug; C_{avg}=average concentration. The C_{avg} of the observation data points were the mean C_{avg} values for each dose group. Median predictions and CIs for ASAS20 and ASAS40 were based on 1000 simulations (at Cavg values ranging from 0 to 65 ng/ml) using the final model

Comparison Between Tofacitinib Exposure Metrics

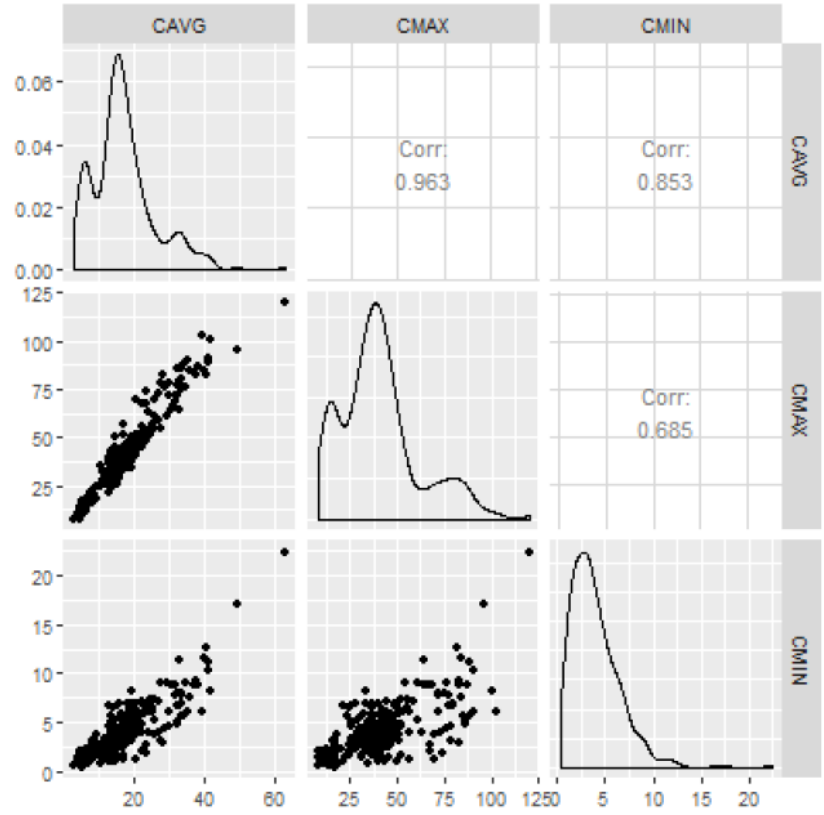
Table 11 summarizes the model evaluation for the different E-R models fitted using ASAS20 and ASAS40 response rates in AS patients. Models with Cavg, Cmin or Cmax as the predictor (univariate analysis) did not show differences in model diagnostics (OFV or AIC differences less than 3.84 units) that would support the conclusion of any one exposure parameter being more relevant to clinical efficacy compared to another. This was not unexpected since these PK parameters are highly correlated, particularly Cavg and Cmin (correlation coefficient=0.85) (Figure 12); the exposure measures contain very similar information.

Table 11. Runs to compare between tofacitinib exposure metrics

Run	Improve ID	Model Description	OFV	AIC
4	ST-4245150	Final model using C_{avg}	3054.663	3072.663
9	ST-4616071	Final model applied to C_{max}	3054.155	3072.155
10	ST-4616082	Final model structure applied to C_{min}	3055.281	3073.281

OFV= Objective Function Value; AIC= Akaike information criterion; C_{max}= maximum concentration; C_{min}= minimum concentration; C_{avg}=average concentration.

Figure 12. Frequency distribution and correlation between tofacitinib exposure metrics



Repository artifact ID FI-4370386.
Corr=correlation coefficient, CAVG=average concentration, CMAX=maximum concentration, CMIN=minimum concentration

Bridging Safety Data from Tofacitinib IR Formulation to PR Formulation in AS Patients (applicant's summary)

The data and strategy that supported the bridging of safety from tofacitinib IR (5 mg BID) to PR (11 mg QD) using similarity in PK, and supportive E-R analyses of expected on-target (possibly mechanism-based) safety endpoints in patients with RA, that have also indicated that Cav(or AUC) was the relevant predictor when an E-R relationship existed was previously discussed in the RA PR application (EMEA/H/C/004214/X/0012).

The overall similarity of PK parameters (equivalent AUC and Cmax and slightly lower Cmin at steady-state) between the 2 formulations in healthy volunteers, provides assurance that the safety profile of PR is likely to be similar of that of IR in patients with AS. Inter- and intra-subject variability was similar between tofacitinib IR and PR formulations for all PK parameters.

Negligible accumulation of systemic exposure (AUC accumulation ratio of 1.12) was seen following repeated dosing of tofacitinib PR. Similar to IR, more than 95% of PR is eliminated within 24 hours following discontinuation of treatment.

In addition, the expected duration of steady state plasma concentrations above the in vitro, whole blood IC50 for JAK 1/3 inhibition (17 ng/mL) is approximately 12-13 hours for both formulations over a 24-hour period. This suggests a similar level of target enzyme inhibition over the dosing interval. All these data suggest that the safety profile of the PR formulation in AS patients would be consistent with that of the IR formulation in AS.

Population PK analysis of tofacitinib in patients with active AS indicated that tofacitinib exposure, as measured by the steady-state AUC (over 24 hours) after 5 mg BID, was similar (differences between geometric means within 25%) among AS, PsA and RA patients. Geometric means of Cmax were also comparable between these 3 patient populations (AS IR PMAR-EQDD-A392k-sNDA-1064, PsA IR PMAR-EQDD-A392j-sNDA-601, RA IR PMAR- 00178). Furthermore, the similarities between the safety profile of tofacitinib 5 mg IR BID in AS subjects and the safety profile of tofacitinib 5 mg IR BID in RA and PsA support the conclusion that the safety profile of the PR formulation in AS would also be consistent with the PR formulation in RA.

Finally, the observed safety data with the PR formulation in RA patients from 2 clinical studies (A3921215 and A3921192), the Corrona registry and post-marketing pharmacovigilance activities demonstrated a consistent safety profile for the 2 formulations, adding substantially to the totality of evidence that supports the bridging of safety from the IR to the PR formulation.

2.3.2. Discussion on clinical pharmacology

No new pharmacology data was submitted in the current variation. The bridging of efficacy and safety of the IR formulation to the PR formulation in AS is based on the bridging strategy used in the previously approved RA PR submission (EMEA/H/C/004214/X/0012).

Given that the efficacy of tofacitinib IR in AS has been demonstrated (II/35), the bridging of efficacy from tofacitinib IR to the PR formulation in AS, is supported by: 1) previously provided Phase 1 studies that have demonstrated similarity of PK parameters between PR 11 mg QD and IR 5 mg BID (equivalent AUC and Cmax, and slightly lower Cmin); 2) Previously provided E-R analyses in RA that have demonstrated that a metric of overall exposure (Cav or AUC) is the relevant PK parameter to predict efficacy of tofacitinib; 3) Longitudinal E-R analyses using efficacy data for the IR formulation in AS patients that have demonstrated that Cav is the exposure metric most closely associated with efficacy.

Regarding the first point of the bridging strategy, no concern on the available information has been raised.

Regarding the second and third points, the comparison of models with Cav, Cmin or Cmax as the predictor (univariate analysis) did not show differences in model diagnostics, therefore it cannot be concluded that any one parameter (or exposure metric) as being more relevant than another to clinical efficacy. This conclusion is acknowledged by the MAH.

The MAH choose Cavg as PK parameter to predict efficacy in line with RA procedure also justifying by the indirect mechanism of action of tofacitinib indicated by the lag between the times to attain steady-state clinical response (PD) versus PK.

Therefore, Cavg has been used as exposure metric to select the model to describe the relationship between tofacitinib exposure and efficacy in AS, since it was previously established as relevant for tofacitinib efficacy in RA.

To note during the assessment of variation II/35 (extension of indication in AS with IR tablets), in which the E/R report was submitted for the first time, the following weaknesses on the aforementioned analysis were highlighted. For the E/R base model the standard error was high, not only for the estimate of EC50 (RSE = 604%), but also for the estimate of Emax (RSE=40.5%); in the final model the standard error for the parameter estimates continues to be high for the EC50 estimate with RSE of 135%. The high degree of uncertainty on the EC50 estimate was imputed (most likely) to the lack of data at the lower end of the concentration range contributing to the limitations of an E-R analysis.

In section Assessment of Model Adequacy (Goodness of Fit) it is reported that "ETA (h) histograms and quantile-quantile plots were used assessing the assumption of normality and the appropriateness of the selected parameter variability." However, in both models, the base and the final ones, ETA (η) histograms and quantile-quantile plots showed lack of normality in the η distribution. The MAH commented that this lack of normality in distribution did not impact the goodness of fit evaluated using simulation-based diagnostic plots, which are the primary diagnostic plots.

The simulated exposure-response relationship in AS appears to be flat, even flatter compared to observed data. In all the exposure-response plots, the 10 mg Cavg values are lower than the 5 mg, and, for the ASAS40 values (placebo-corrected), also lower than the 2 mg. The CHMP expressed concern that the E/R relationship was not properly captured by the E/R model (i.e. the 10 mg Cavg values being lower than the 5 mg, and, for the ASAS40 values also lower than the 2 mg) thus hampering its reliability.

In their response the MAH has provided a re-discussion of submitted data focusing on the demonstration of E/R model reliability in AS. Although the VPCs performed for the base and final models show concordance between observed and predicted data, the simulations to illustrate the exposure-response relationship plotted with observed response rates at Week 12 did not capture the unexpected lower observed response rate forASAS20 and ASAS40 using 10 mg IR BID that was expected to be higher than that observed for 5 mg BID. The MAH justified this unexpected behaviour as likely due to variability in the observed data and not as a measure of the reliability of the E-R model.

Probably, concomitant factors could have contributed to this outcome, including the variability in patient's response (in Study A3921119 the ASAS20 response rate at Week 12 for 5 mg is 63% analysed by Emax model and 80.7% by normal approximation method; in Study A3921120, ASAS20 response rate at Week 16 is 56.39%) and the limited data used to populate the model i.e. 2 mg (N=50) and 10 mg (N=48) as compared to 5 mg (N=181).

Although the above-mentioned reasons might be considered a plausible explanation of the observed outcome.

The E/R relationship *per se* is still considered not certain enough (due to plausible hypothesis of an artefact) to waive the clinical study as foreseen in the EMA Guideline on modified-release formulation (EMA/CHMP/EWP/280/96 Rev1); however, the totality of data available show the following:

i) the demonstrated BE between PR (11 mgx1) and IR formulations (5 mgx2) in terms of AUC and Cmax with only a difference in average Cmin (29% lower) not considered clinically relevant and having the Cavg as the primary PK parameter;

ii) the efficacy of PR formulation in RA and PsA;

iii) the same PK metrics are considered important for efficacy and safety in AS as in PsA;

The relevance of Cavg as the parameter for efficacy in AS was illustrated by the strong association between Cavg on one hand, and Cmin and Cmax on the other hand, in both PsA as well as in AS (r = 0.93 between Cavg and Cmin).

A comparison of models with Cavg, Cmin, and Cmax did not show great differences in model diagnostics in AS, and may support the acceptability of the Cmin and Ctrough levels in the treatment of AS.

iv) the similarities in disease between PsA and AS.

Finally, the absence of a clear exposure-response relationship was likely to be due to the smaller patient numbers in the 10 mg BID group (n = 48) compared to the 5 mg BID group (n = 181), as mentioned

above. However, although the observed response rates did not show a straight ER relationship at week 12, these rates were all within the 95% CI of the predicted response rates of the ASA20 and ASAS40, which supports the adequacy of the ER model.

Considering all the above and taking into account that the safety profile is not expected to be different with the use of PR formulation as compared to IR formulation, the absence of a clear E/R relationship in the presented model is not foreseen to affect the efficacy and safety of the 11 mg QD PR tablet in AS.

2.3.3. Conclusions on clinical pharmacology

Considering the totality of available data, and the fact that the safety profile is not expected to be different with the use of PR formulation as compared to IR formulation, the absence of a clear E/R relationship in the presented model is not foreseen to affect the efficacy and safety of the 11 mg QD PR tablet in AS.

2.4. Clinical efficacy

This application supports the efficacy of *tofacitinib PR tablets (11 mg QD)* for the treatment of adult patients with active AS.

Clinical studies of the tofacitinib PR formulation have not been conducted in patients with active AS.

Tofacitinib (Xeljanz) IR formulation is currently approved in the EU for treatment of RA, PsA, and UC. The tofacitinib IR formulation was approved in the EU at a dose of 5 mg BID (IR film-coated tablets approved on 22 Mar 2017; RA MAA procedure number EMEA/H/C/004214/0000) as monotherapy or in combination with MTX in adult patients with moderate to severe active RA, who have had an inadequate response or intolerance to 1 or more DMARDs. This formulation is also approved in the EU at a dose of 5 mg BID, in combination with MTX, for the treatment of active PsA in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy (25 June 2018; procedure EMEA/H/C/004214/II/0006). Recently tofacitinib IR at a dose of 5 mg BID obtained approval in the following indication: *"Tofacitinib is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy".*

The tofacitinib PR formulation, administered as 11 mg QD, for RA was approved by the EU Commission (16 Dec 2019, procedure EMEA/H/C/004214/X/0012).

The approval of the tofacitinib PR tablet (administered as 11 mg QD) for RA in the EU was based on E-R modelling and totality of evidence demonstrating similarity of efficacy and safety between the 11 mg PR QD and 5 mg IR BID, including:

- E-R analysis of RA patient data with the IR formulation to identify relevant exposure metrics for efficacy and safety (including characterisation of delay in the dynamics of clinical response in RA compared to the time to reach steady-state plasma drug concentrations or when considering within day fluctuations drug concentrations), along with Phase 1 PK studies to demonstrate similarity of relevant exposure metrics between the IR and PR formulations,
- Supportive evidence of similar clinical efficacy and safety between the IR and PR formulations in patients with RA from the clinical RA Studies A3921215 and A3921192, the observational US Corrona RA registry studies (A3921359 efficacy and A3921205 safety), and a real-world claims database adherence study (A3921349).

Similarity of efficacy was established by demonstration of AUC (Cavg) as the relevant PK parameter for efficacy in RA patients, and equivalence of AUC between tofacitinib 11 mg PR formulation administered QD and the 5 mg IR formulation administered BID. Additional supportive evidence for similar efficacy

was based on direct comparison of clinical efficacy between IR and PR in the Japan only clinical study A3921215, and global clinical study A3921192 (single-arm PR) where efficacy of the PR formulation was consistent with efficacy of the IR formulation in prior RA studies, the US Corrona RA registry effectiveness study (A3921359), and a real-world claims adherence and effectiveness study (A3921349). In addition, efficacy of the PR formulation in RA clinical studies A3921215 and A3921192 (single arm PR) were demonstrated to be consistent with efficacy of the IR formulation in prior RA studies, based on cross trial comparisons and E-R contextualisation.

The bridging approach to demonstrate therapeutic similarity (efficacy) between tofacitinib IR (dosed at 5 mg BID) and PR (dosed at 11 mg QD) in RA patients is proposed to be extrapolated to a similar immune-mediated inflammatory disease AS, to support the claim of therapeutic similarity of 11 mg PR QD and 5 mg IR BID in AS patients, given that the efficacy of tofacitinib IR (dosed at 5 mg BID) in AS has been established, and given that E-R relationships established in RA and in AS patients support Cavg (or AUC) as the relevant parameter for efficacy.

The tofacitinib IR AS development programme was designed to evaluate the efficacy of tofacitinib IR (5 mg BID) for the treatment of patients with active AS. The IR clinical programme included:

- **Study A3921120**, a pivotal Phase 3, randomised double blind, placebo-controlled that evaluated the efficacy and safety of tofacitinib in patients with active AS. The treatment duration was 48 weeks, which comprised an initial placebo-controlled treatment period of 16 weeks duration (primary efficacy analysis), followed by an open-label treatment period of 32 weeks duration.

- **Study A3921119**, a dose-ranging, Phase 2b, randomised, double-blind, placebo-controlled efficacy and safety study designed to characterise the dose-response of tofacitinib (2, 5, and 10 mg IR BID) versus placebo in patients with active AS. The treatment duration was 12 weeks.

The assessment of these studies is reported below.

2.4.1. Dose response study

A3921119 This was a Phase 2, multicenter, randomised, double-blind, placebo-controlled dose ranging, parallel group efficacy and safety study designed to characterise the dose response of tofacitinib in patients with active AS who had experienced an inadequate response to NSAIDs and were naïve to previous bDMARDs. This was a proof-of-concept as well as a dose-ranging study that evaluated the efficacy and safety of tofacitinib doses of 2 mg, 5 mg, and 10 mg IR BID versus placebo (randomised in 1:1:1:1 ratio) over a 12-week treatment period in adult patients with active AS who had an inadequate response to NSAIDs but were bDMARD-naïve. Given the results of Study A3921119, as well as taking into consideration the recommended BID posology for tofacitinib in other rheumatologic diseases, 5 mg IR BID of tofacitinib was selected to be evaluated in Study A3921120.

For complete study information please see section "Supportive study".

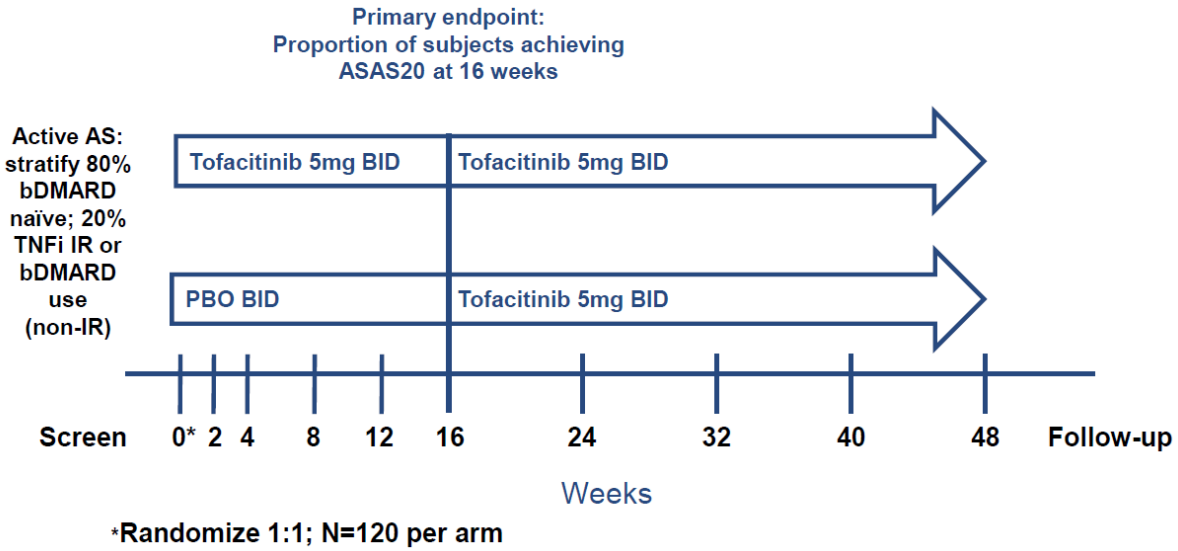
2.4.2. Main study

Study A3921120

Methods

The design of the pivotal A3921120 Study is presented in the **Figure 13**:

Figure 13. Pivotal Study A3921120 Schematic of Study Design



The study design includes a screening period of approximately 30 days, a 16-week double-blind treatment period, a 32-week open-label treatment period and a 28-day follow-up period (duration of participation for eligible subjects was approximately 56 weeks).

The primary efficacy analysis was at 16 weeks (data cutoff 19DEC2019, data snapshot 29JAN2020) and maintenance follow-up to 48 weeks.

In support of the sought indication the MAH is providing confirmatory evidence from one pivotal study only. As per the POINTS TO CONSIDER ON APPLICATION WITH 1. META-ANALYSES; 2. ONE PIVOTAL STUDY, CPMP/EWP/2330/99, this study will have to be exceptionally compelling, and in the regulatory evaluation special attention will be paid to key aspects including the internal/external validity; Clinical relevance, the estimated size of treatment benefit must be large enough to be clinically valuable; the degree of statistical significance, statistical evidence considerably stronger-internal consistency. Similar effects demonstrated in different pre-specified sub-populations. All-important endpoints showing similar findings.

The proposed study design is randomised, double-blind, placebo-controlled, parallel group comparing tofacitinib 5mg dosed twice daily to placebo in subjects with active AS, who had experienced an inadequate response to NSAIDs (NSAID-IR) and were additionally either naïve to previous bDMARDs, or TNFi-IR or experienced to previous bDMARDs but without inadequate response (bDMARD Use [Non-IR]). As per the EMA *guideline on the Clinical Investigation of Medicinal products for the treatment of Axial Spondyloarthritis (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1*)* the design could be acceptable however since tofacitinib belongs to a new therapeutic class for the AS indication and the study includes biological naïve patients a three-arm trial (including an accepted active comparator) would have been recommended, particularly for assessing a relative B/R balance. The Applicant has performed a meta-

analysis of approved treatments and also included the results of the tofacitinib trials (dose-finding and pivotal study) as supportive data.

The time point for the primary analysis (DB phase) is within the time period indicated by the above guideline; the maintenance period is in line with the guideline although a longer Open-Label (OL) period would have been recommended for assessing structural changes. Moreover, evaluation of dose reduction/stop and/or increased dose interval for subjects obtaining resolution of inflammation could have been useful to guide prescribers for long term treatment to avoid unnecessary toxicity.

The MAH clarified that dose reduction/changing dose interval in AS patients after resolution of inflammation following tofacitinib treatment has not been evaluated and that there are no data supporting changing dose interval. The same apply for other tofacitinib indications such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA). The MAH does not intend to seek therapeutic claims in this area and therefore any decision on modifying or stopping treatment should be at physician discretion. Moreover, the MAH has also specified that at present there is no plan to conduct a long-term extension study for tofacitinib in ankylosing spondylitis (AS) patients.

Study participants

Key Inclusion criteria:

1. Adults' subjects with a diagnosis of AS based on the Modified New York Criteria for Ankylosing Spondylitis (1984).
2. The subject must have a radiograph of the SI joints (AP Pelvis) documenting diagnosis of AS. Previous radiographs (up to 2 years old) can be used if they are accepted by the central reader. Otherwise, a new radiograph will be obtained during the screening period.
3. Subject has **active** AS Screening and Baseline (Day 1) visits defined as:
    - BASDAI score of ≥4; and
    - Back pain score (BASDAI Question 2) of ≥4.
4. Subject has active disease despite nonsteroidal anti-inflammatory drug (NSAID) therapy or is intolerant to NSAIDs as defined by:

    Subject must have had at least a total of 2 occurrences of an inadequate clinical response (minimum of 4 weeks trial) or intolerance to at least 2 different oral NSAIDs. An inadequate response to a previous NSAID or TNFi is defined as a lack of sufficient clinical response based on a clinical judgment or based on a related adverse event. Intolerance is defined as having discontinued NSAID treatment due to a related adverse event (e.g., allergic reaction, gastrointestinal symptoms or signs, hypertension, etc).
5. Subjects who are designated as TNFi-IR must have received at least 1, but not more than 2 approved TNFi that was administered in accordance with its labelling recommendations and was inadequately effective after the minimum treatment times listed below and/or not tolerated after one or more doses.
    - At least 3 months of adalimumab treatment;
    - At least 3 months of etanercept treatment;
    - At least 4 infusions of infliximab;
    - At least 3 injections of golimumab;

- At least 3 months of certolizumab treatment.

Intolerance is defined as having experienced a treatment-related AE. Subjects may be receiving the following csDMARDs at the time of the screening visit. These medications should be continued throughout the entire study and doses should remain unchanged. Any other Disease-Modifying Anti-Rheumatic Drugs (DMARDs) require discussion prior to enrolment with the sponsor for washout timeframe.

- Methotrexate (MTX): Maximum dose of 25 mg/week. Minimum duration of therapy 4 months and dose stable for 4 weeks prior to first dose of investigational product.
- Sulfasalazine (Azulfidine, Salazopyrin): Maximum dose of 3 gm/day. Minimum duration of therapy 2 months and dose stable for 4 weeks prior to first dose of investigational product.

6. Subjects who are already taking oral corticosteroids (not injectables) may participate in

   the study:

   - Oral corticosteroids: Subjects who are already receiving oral corticosteroids must be on a stable dose of ≤10 mg/day of prednisone or equivalent for 1 week prior to the first dose of investigational product.
   - Injected (e.g., intraarticular, intramuscular, epidural or intravenous) corticosteroids must be discontinued 4 weeks prior to the first dose of investigational product.
   - Topical and intra-rectal corticosteroids will be allowed during the study.

7. Subjects who are receiving any investigational or marketed treatment for AS, arthritis or back pain not mentioned elsewhere must have that treatment discontinued for 4 weeks or 5 half-lives, whichever is longer.
8. Subjects receiving non-prohibited concomitant medications for any reason must be willing to stay on a stable regimen (doses and frequency) as defined in the protocol.
9. No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by all of the following:

   - A negative QuantiFERON-TB Gold (QFT G) In Tube test performed at or within 3 months prior to the Screening visit. Subjects with a history of Bacille Calmette Guérin (BCG) vaccination will be tested with the QFT G test.
   - A chest radiograph taken at or within the 3 months prior to screening.
   - No history of either untreated or inadequately treated latent or active TB infection.

     Women of childbearing potential must test negative for pregnancy prior to enrolment in this study.

Female subjects of non-childbearing potential only according to strict criteria.

<u>Key Exclusion criteria:</u>

1. History of known or suspected complete ankylosis of the spine.
2. Subjects that have been exposed to or are currently receiving targeted synthetic DMARDS (including JAK inhibitors) or those currently on biological DMARDS (i.e., washout from any current bDMARD required per Section 5.8.1), thalidomide (including

previous use) and other prohibited concomitant medications noted in Appendix 4 of the bioanalytical report.

3. History of allergies, intolerance or hypersensitivity to lactose or tofacitinib (CP-690,550). This includes subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
4. Blood dyscrasias at screening or within 3 months prior to the first dose of investigational product including confirmed:
    - Hemoglobin <10 g/dL
    - Absolute white blood cell count (WBC) <3.0 x 10^9/L (<3000 mm^3)
    - Absolute neutrophil count (ANC) <1.5 x 10^9/L (<1500 mm^3)
    - Absolute lymphocyte count <1.0 x 10^9/L (<1000/mm^3)
    - Platelet count <100 x 10^9/L (<100,000/mm^3).
5. Estimated Creatinine Clearance <40 mL/min based on Cockcroft Gault equation at Screening visit.
6. Total bilirubin, AST or ALT more than 1.5 times the upper limit of normal (ULN) at screening visit.
7. History of any other autoimmune rheumatic disease.
8. History of an infected joint prosthesis at any time, with the prosthesis still in situ.
9. History of any lymphoproliferative disorder, such as Epstein Barr Virus related lymphoproliferative disease (EBV-LPD), history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.
10. History of recurrent (more than one episode) herpes zoster or disseminated/multi-dermatomal (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.
11. History of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 3 months prior to the first dose of investigational product. History of infection requiring antimicrobial therapy within 2 weeks prior to the first dose of investigational product.
12. Any prior treatment with non-B cell specific lymphocyte depleting agents/therapies (e.g., alemtuzamab, efalizumab), alkylating agents (e.g., cyclophosphamide or chlorambucil), or total lymphoid irradiation.
13. Any subject who has been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of investigational product or is to be vaccinated with these vaccines at any time during treatment or within 6 weeks after last dose of investigational product.
14. A subject with any condition possibly affecting oral drug absorption, e.g., gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding, that simply divide the stomach into separate chambers, are NOT exclusionary.
15. A subject that is considered at risk for GI perforation by the investigator or Sponsor.

16. Screening 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities which may affect subject safety (e.g., pattern of acute myocardial infarction, acute ischemia or serious arrhythmia) or interpretation of study results (e.g., continuously paced ventricular rhythm or complete left bundle branch block).
17. A subject with a known immunodeficiency disorder or a first degree relative with a hereditary immunodeficiency.
18. A subject with a malignancy or with a history of malignancy, with the exception of adequately treated or excised non metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
19. Significant trauma or surgery procedure within 1 month prior to first dose of study medication, or any planned elective surgery during the study period.
20. A subject known to be infected with human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus or any chronic infection.

Treatments

During the first 16-week treatment period, patients were randomised in a double-blind 1:1 ratio to tofacitinib 5 mg BID or matching placebo BID. At the Week 16 visit, all patients, including those who were randomised to placebo, received open label tofacitinib 5 mg BID for the remaining 32 weeks of the study period.

Prior and Concomitant Treatments

Patients continued their stable background AS therapy, which included NSAIDs including selective COX-2 inhibitors, MTX, sulfasalazine, and corticosteroids.

Methotrexate was allowed if it had been used for at least 4 months, on a stable dose (≤25mg/week) during the last 4 weeks. Sulfasalazine was allowed if used for at least 2 months, on a stable dose (≤ 3g/day) during the last 4 weeks. Patients who were already receiving oral corticosteroids must be on a stable dose of ≤10 mg/day of prednisone or equivalent for 1 week before baseline. Topical NSAIDs were allowed during the study.

Daily dosages of NSAIDs/COX-2 inhibitors, opioids, and paracetamol must be stable for 1 week prior to first study dose and must remain so during the study treatment period (Week 48) except if adjustment is needed to protect a subject's safety. The total daily dose of acetaminophen may not exceed 2.6 grams per day, and the total daily dose of opioid may not exceed the potency equivalent of 30 mg of orally administered morphine.

Rescue medications

The maximum dose of acetaminophen/paracetamol was 2.6 g/day for no more than 10 consecutive days. The maximum dose of opioids was the maximum potency equivalent of 30 mg/day of orally-administered morphine (with or without acetaminophen/paracetamol) for no more than 10 consecutive days (Table 12). Subjects who were not on stable, background opioid therapy, any of single opioid agents (e.g., hydrocodone, oxycodone or tramadol) could be given as rescue medication (with or without acetaminophen/paracetamol) for no more than 10 consecutive days. Subjects who required rescue medication for more than 10 consecutive days were discontinued from the investigational product. In addition, subjects were not dosed with rescue acetaminophen/paracetamol or opioids within 24 hours prior to a study visit.

Table 12. Rescue therapy for Study A3921119 and A3921120

Study	Rescue therapy
A3921119	Increases of acetaminophen/paracetamol and opioids were allowed as rescue medication for no more than 10 consecutive days. Acetaminophen/paracetamol were added or increased to a maximum of 2.6 gm/day. Opioids were added or increased to a maximum potency equivalent of 30 mg of orally-administered morphine. Subjects who required rescue for more than 10 consecutive days were discontinued from the study. There was no limit to the duration of nonconsecutive use of rescue medications. Subjects were not dosed with rescue medication during the 24 hours prior to a study visit. Baseline stable use acetaminophen/paracetamol or opioids were not discontinued in advance of study visits. Subjects were not dosed with rescue acetaminophen/paracetamol or opioids within 24 hours prior to a study visit. Baseline stable acetaminophen/paracetamol or opioids was not discontinued in advance of study visits.
A3921120	Increases of acetaminophen/paracetamol and opioids were allowed as rescue medication for no more than 10 consecutive days. Acetaminophen/paracetamol was added or increased to a maximum of 2.6 gm/day. Combination products such as over-the-counter "cold remedies" or pain medications were assessed for acetaminophen/paracetamol content so that the total dose will not exceed 2.6 gm/day. Opioids were added or increased to a maximum potency equivalent of 30 mg of orally-administered morphine. Subjects who required rescue for more than 10 consecutive days were discontinued from the investigational product and designated as discontinued from the investigational product for lack of efficacy. There was no limit to the duration of nonconsecutive use of rescue medications. Subjects were not dosed with rescue medication during the 24 hours prior to a study visit. In the judgement of the investigator, if rescue therapy had any effect on efficacy data collected during a study visit, this constituted a protocol deviation. Baseline stable use of acetaminophen/paracetamol or opioids was not discontinued in advance of study visits.

Source: S0113 Module 5.3.5.4 A3921119 Protocol Amendment 1 Section 5.6 and Appendix 6; S0113 Module 5.3.5.1 A3921120 Protocol Amendment 3 Section 5.8.3 and Appendix 6

Treatment compliance

At the study visits, sufficient investigational product was dispensed to complete dosing until the next scheduled visit and all study medication had to be returned at each visit. Compliance was assessed by pill count at each visit. If compliance was <80% the patient was offered counselling to improve compliance. If a patient was less than 80% compliant as assessed at two consecutive visits, the patient was withdrawn from investigational treatment.

Discontinuation Criteria from the Investigational Product:

- ✓ serious or significant opportunistic infections, other serious or severe AEs
- ✓ defined alterations of neutrophils, lymphocytes, Hb, PLT, AST/ALT +/- hepatic injury, creatinine, CK,
- ✓ pregnancy,
- ✓ rescue medication >10 consecutive days, interruption of IMP for more than 5 consecutive days (DB period) or 28 consecutive days (OL period) or <80% compliance

Objectives

Part I, double-blind, placebo-controlled (0-16 weeks): to evaluate the efficacy and safety of tofacitinib compared with placebo (superiority).

Part II, open label, tofacitinib 5mg (16-48 weeks): to evaluate the efficacy and safety of tofacitinib through up to 48 weeks of treatment in subjects who have completed Part I.

Outcomes/endpoints

Improvement criteria based upon ASAS response have been developed for clinical trials in AS which include the ASAS20, ASAS40, ASAS 5/6 assessments and partial remission.[1,2] These composite scores are derived from several of the PRO measures or disease activity assessments. The composite score was calculated by the Sponsor.

A summary of the efficacy endpoints evaluated in Study A3921120 are presented Table 13.

Table 13. Summary of the efficacy endpoints

Table 1. Study Objectives and Endpoints		
Type	**Objective**	**Endpoint**
Primary		
Efficacy	To compare the efficacy of tofacitinib 5 mg BID versus placebo on the ASAS20[1] response rate at Week 16 in subjects with active AS that have had an inadequate response to previous treatment.	• ASAS20 response* at Week 16.
Key Secondary		
Efficacy	To compare the efficacy of tofacitinib 5 mg BID versus placebo on the ASAS40[2] response rate at Week 16 in subjects with active AS that have had an inadequate response to previous treatment.	• ASAS40 response* at Week 16.
Other Secondary		
Safety	To compare the safety and tolerability of tofacitinib 5 mg BID versus placebo in subjects with active AS that have had an inadequate response to previous treatment.	• Incidence and severity of AEs. • Clinical laboratory tests, vital signs, physical examination and 12-lead ECG parameters.
Efficacy/HRQoL	To compare the efficacy (including health-related quality of life, function, pain, and fatigue) of tofacitinib 5 mg BID versus placebo at all time points in subjects with active AS that have had an inadequate response to previous treatment.	• ASAS20[1] response* at all other time points. • ASAS40[2] response* at all other time points. • Change from baseline in ASDAS(CRP)* at all time points. • Change from baseline in hsCRP* at all time points. • Change from baseline in ASQoL* at all time points collected.

Table 1. Study Objectives and Endpoints		
Type	**Objective**	**Endpoint**
		• Change from baseline in SF-36v2* at all time points collected. • Change from baseline in BASMI* including the 5 components (lateral spine flexion, tragus-to-wall distance, lumbar flexion, maximal intermalleolar distance and cervical rotation) at all time points. • Change from baseline in FACIT-F (3 endpoints: total score*, experience domain and impact domain scores) at all time points. • Change from baseline in PGA** at all time points collected. • Change from baseline in Patient's Assessment of Spinal Pain (Total Back Pain**, Nocturnal Spinal Pain) at all time points collected. • Change from baseline in BASFI** at all time points. • Change from baseline in inflammation** (mean of the answers to questions 5 and 6 of the BASDAI) at all time points collected. • ASAS 5/6 response at all time points. • ASAS partial remission criteria at all time points. • Change from baseline in BASDAI at all time points.

Table 1. Study Objectives and Endpoints		
Type	**Objective**	**Endpoint**
		• BASDAI50 response at all time points. • ASDAS clinically important improvement, ASDAS major improvement and ASDAS inactive disease at all time points. • Change from baseline in MASES at all time points collected. • Change from baseline in extra-articular Involvement (Specific Medical History and peripheral articular involvement [as assessed by change from baseline in swollen joint count]) at all time points collected. • Change from baseline in spinal mobility at all time points collected. • Change from baseline in EQ-5D-3L and EQ-VAS, at all time points collected. • Change from baseline in WPAI Questionnaire: Spondyloarthritis at all time points collected.
Tertiary/Exploratory		
PK	To describe the PK of tofacitinib in subjects with active AS.	• Oral clearance (CL/F) and other PK parameters calculated from plasma tofacitinib concentrations.
Safety	To evaluate the effect of tofacitinib 5 mg BID on lymphocyte subsets using FACS analysis.	• FACS analysis of lymphocyte subsets.

Table 1. Study Objectives and Endpoints		
Type	**Objective**	**Endpoint**
Medical Resource Utilization	To measure the effect of tofacitinib 5 mg BID on healthcare resource utilization at all collected time points.	• AS-HCRU at all time points collected.

[1]ASAS20 improvement is defined as ≥20% and ≥1 unit in at least 3 domains on a scale of 0-10 and no worsening of ≥20% and ≥1 unit in the remaining domain.
[2]ASAS40 improvement criteria are classified as ≥40% and ≥2 units in at least 3 domains on a scale of 0-10 and no worsening at all in the remaining domain.
*Global Type I error-controlled efficacy endpoints at Week 16 were tested in the following sequence: ASAS20, ASAS40, change from baseline in ASDAS(CRP), change from baseline in hsCRP, change from baseline in ASQoL, change from baseline in SF-36v2 Physical Component Summary, change from baseline in BASMI, and change from baseline in the FACIT-F Total score.
**Type I error-controlled secondary efficacy endpoints in the ASAS family at Week 16 were tested in the following sequence: change from baseline in PGA, change from baseline in total back pain, change from baseline in BASFI, and change from baseline in inflammation (average of questions 5 and 6 of the BASDAI). Type I error-control for ASAS20 at earlier timepoints tested in the following sequence: Weeks 16, 12, 8, 4 and 2. Type I error-control for ASAS40 at earlier timepoints tested in the following sequence: Weeks 16, 12, 8, 4 and 2.

The Table 14 summarises the description of the endpoints and the time points of the assessment.

Table 14. Summary and Description of all Efficacy Measures

Assessment Endpoint	Description	Measurement Timepoint(s) A3921120
Primary efficacy endpoint (subject to hierarchical testing procedure for global Type I error-control at Week 16)		
ASAS20 Response	ASAS20 assesses 4 domains: the Patient Global Assessment of Disease, Spinal Pain (total back pain), Function (BASFI) and Inflammation (average of questions 5 and 6 of BASDAI). ASAS20 response is defined as an improvement from Baseline ≥20% and ≥1 unit in at least 3 domains on a scale of 0 to 10 and no worsening of ≥20% and ≥1 unit in the remaining domain.	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48 At Week 16 was the Primary Efficacy Endpoint
Key secondary efficacy endpoint (subject to hierarchical testing procedure for global Type I error-control at Week 16)		
ASAS40 Response	ASAS40 assesses the 4 domains as specified above. ASAS40 response is defined as an improvement from Baseline ≥40% and ≥2 units in at least 3 domains on a scale of 0 to 10 and no worsening at all in the remaining domain	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48 At Week 16 was the Key Secondary Efficacy Endpoint
Secondary efficacy endpoints (subject to hierarchical testing procedure for global Type I error-control at Week 16)		
ΔASDAS(CRP)[a]	The ASDAS(CRP) endpoint is derived from several patient-reported outcomes (Back Pain, Duration of Morning Stiffness, Patient Global Assessment, and Peripheral Pain/Swelling) and hsCRP and was calculated by the Sponsor. The following formula was used to calculate the ASDAS(CRP): ASDAS(CRP) = 0.121 × Back Pain + 0.058 × Duration of Morning Stiffness + 0.110 × Patient Global + 0.073 × Peripheral Pain/Swelling + 0.579×Ln (hsCRP mg/L+1)	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
ΔhsCRP	Blood samples were analysed by a central laboratory.	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
ΔASQoL	The ASQoL is an 18-item patient-completed questionnaire assessing the amount of restriction the patient is experiencing in daily activities, level of pain and fatigue, and the impact on the patient's emotional state. Each item is scored as 0 (no impact) or 1 (yes - impact). A total score was calculated by summing the items. The total score ranges from 0 to 18, with higher values indicating more impaired health-related quality of life.	Weeks 16 and 48
ΔSF-36v2	The SF-36 (Acute) is a 36-item patient-completed generic health status measure. It measures 8 general health domains (norm-based scores were used in analysis): physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. These domains are also summarised as physical and mental component summary scores (PCS and MCS, respectively). Higher scores indicate better health outcomes. PCS was a Type I error-controlled endpoint.	Weeks 16 and 48

Assessment Endpoint	Description	Measurement Timepoint(s) A3921120
ΔBASMI Score – Linear Method	The BASMI was used to assess the axial status and mobility (cervical, dorsal and lumbar spine, hips and pelvic soft tissue). Five clinical measures comprise this scale and in this clinical study the linear function method was used. The combined index score was calculated by the Sponsor using the individual scores from the following measures: lateral spinal flexion, tragus to wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance, and cervical rotation.	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
ΔFACIT-F	The FACIT – Fatigue Scale is a patient completed questionnaire consisting of 13 items that assess fatigue. Instrument scoring yields a range from 0 to 52 for the total score, with higher scores representing better patient status (less fatigue). FACIT-F is also summarised as FACIT-F experience domain score (range 0-20) and FACIT-F impact domain (range 0-32) score. FACIT-F Total score was a Type I error-controlled endpoint.	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
Secondary efficacy endpoints (subject to hierarchical testing procedure for Type I error-control within the family of ASAS responses at Week 16)		
ΔPGA	Patients assessed their overall disease activity over the last week using a NRS between 0 (Not Active) and 10 (Very Active) to the question, "How active was your spondylitis on average during the last week?" PGA is 1 of the 4 ASAS20/ASAS40 components and the results of this assessment were used to calculate the ASAS improvement criteria.	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
ΔSpinal pain	Two NRS scales were used to assess the patient's spinal pain: level of nocturnal pain and total back pain on average during the last week. For each of these scales, patients marked their level of pain on a 0 to 10 NRS anchored by 0 for "No Pain" to 10 "Most Severe Pain." Results of total back pain were used to calculate the ASAS improvement criteria. The total back pain was a Type I error-controlled endpoint.	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
ΔInflammation (morning stiffness)	Inflammation is 1 of the 4 ASAS20/ASAS40 components, which is the average of the answers to questions 5 & 6 of BASDAI.	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
ΔBASFI	The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patients' ability to cope with everyday life. A 0-10 NRS is used to answer the questions with 0 being "Easy" and 10 being "Impossible." BASFI is the average of these 10 scores and it ranges from 0 to 10, with higher scores indicating greater functional limitation. BASFI is 1 of the 4 ASAS20/ASAS40 components.	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
Secondary efficacy endpoints (not controlled for Type I error)		
ASAS 5/6 response	ASAS 5/6 assesses 6 domains: the domains as noted in the ASAS20 and ASAS40, hsCRP and Spinal mobility, specifically lateral spinal flexion (from the BASMI). Response is defined as improvement ≥20% in at least 5 domains	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
ASAS partial remission	ASAS partial remission is based on the same 4 ASAS domains noted above. Partial remission is defined as a response if a score of 2 or less (on a scale of 0 to 10) for each of the 4 domains	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48

Assessment Endpoint	Description	Measurement Timepoint(s)
		A3921120
ΔSpinal mobility (Chest expansion)	The chest expansion (cm) was measured as the difference between maximal inspiration and expiration. Two attempts were performed and the better (ie, larger) of the 2 attempts was utilised for data analysis.	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
ΔBASDAI	The BASDAI is a validated patient-completed questionnaire that consists of 6 questions pertaining to the 5 major symptoms of AS: fatigue; spinal pain; peripheral arthritis; enthesitis, intensity of morning stiffness and duration of morning stiffness. Each question was rated using a NRS from 0 (none) to 10 (very severe). The BASDAI score was calculated by computing the mean of questions 5 and 6 and adding it to the sum of questions 1 to 4. This score was then divided by 5.	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
ASDAS Clinically Important Improvement, Major Improvement and Inactive Disease[a]	The ASDAS Clinically Important Improvement, Major Improvement and Inactive Disease were calculated from the ASDAS(CRP) data. Clinically important improvement and major improvement were defined as a decrease from Baseline in ASDAS(CRP) ≥1.1 units and ≥2.0 units, respectively. Inactive disease was defined as ASDAS(CRP) <1.3 unit.	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
ΔMASES	Enthesitis was evaluated by the qualified blinded assessor using the MASES. Thirteen sites (right and left) were assessed for tenderness: costochondral 1 (right and left), costochondral 7 (right and left), spina iliaca anterior superior (right and left), crista iliaca (right and left), spina iliaca posterior (right and left), processus spinosus at L5 and Achilles tendon proximal insertion (right and left). Scoring at each site will be 0 for no tenderness or 1 for tenderness.	At Weeks 4, 8, 12, 16, 24, 32, 40, and 48
ΔSwollen Joint Count	Forty-four (44) joints were assessed for swelling and included the following: sternoclaviculars, acromioclaviculars, shoulders, elbows, wrists, metacarpophalangeals (MCP I, II, III, IV, V), thumb interphalangeal (IP), proximal interphalangeals (PIP II, III, IV, V), knees, ankles, and metatarsophalangeals (MTP I, II, III, IV, V).	At Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
ΔEuroQoL EQ-5D-3L and EQ-VAS	The EuroQol 3 Levels EQ-5D-3L Health State Profile is a patient completed instrument designed to assess impact on health-related quality of life in 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with lower scores indicating better health outcomes. EQ-VAS (Your own health state today) records the patient's self-rated health, a score ranging from 0 to 100 mm is recorded, with higher scores representing better health state today	Weeks 16 and 48
ΔWPAI	The WPAI: Spondyloarthritis is a 6-item patient-completed questionnaire that is specific for spondyloarthritis which yields 4 types of scores: percent work time missed due to health problem; percent impairment while working due to health problem; percent overall work impairment due to health problem; percent inactivity due to health problem. WPAI outcomes are expressed as impairment percentages with higher numbers indicating greater impairment and less productivity.	Weeks 16 and 48

a. Per the method published by Machado et al3, for hsCRP values < 2 mg/L, it is set to 2 mg/L in the formula to derive ASDAS(CRP) and endpoints based on ASDAS(CRP).

Sample size

The primary efficacy analysis is to compare the ASAS20 response rate at week 16 of the tofacitinib 5 mg BID and placebo via the normal approximation for the difference in binomial proportions. Assuming a placebo response rate of 40% for ASAS20 response at week 16, a sample size of 120 per arm will yield about 89% power to detect a difference of at least 20% between tofacitinib 5 mg BID and placebo at a two-sided significance level of 5%. In the Phase 2 proof of concept trial A3921119, ASAS20 response rates at week 12 were 63% and 40% for tofacitinib 5 mg BID and placebo, respectively.

Sample size calculation for pivotal phase III study A3921120 was based on the response rate found in phase 2 dose-ranging, proof of concept trial. It is recognized as appropriate, although the primary efficacy endpoint was then analysed by the Cochran-Mantel-Haenszel (CMH) test stratified by the randomisation strata (prior treatment history).

Randomisation

By use of an automatic Interactive web-based Response system. Subjects were randomised at the Baseline visit in a 1:1 ratio to one of the following two parallel blinded treatment sequences for a total of 16 weeks of treatment. Randomization was stratified by prior treatment history: (1) bDMARD-naive and (2) TNFi-IR or bDMARD use (non-IR) as shown in Table 15. The clinical trial was designed to reflect the proportion of bDMARD-naïve and TNFi-IR or bDMARD use (non-IR) of approximately 80%/20%.

Table 15. Safety Analysis Set (Final Analysis)

Stratum	Number of bDMARDs with Inadequate Response	Tofacitinib 5 mg BID (N=133) n (%)	Placebo -> Tofacitinib 5 mg BID (N=136) n (%)	Total (N=269) n (%)
bDMARD-naive		102 (76.7)	105 (77.2)	207 (77.0)
TNFi-IR or bDMARD Use (Non-IR)		31 (23.3)	31 (22.8)	62 (23.0)
TNFi-IR	1 TNFi-IR	23 (79.3)	20 (66.7)	43 (72.9)
	2 TNFi-IR	6 (20.7)	10 (33.3)	16 (27.1)
bDMARD Use (Non-IR)	1 bDMARD Use (Non-IR)	2 (100.0)	1 (100.0)	3 (100.0)

WHO DDE v202003 coding dictionary applied.
Prior drug treatment was defined as a drug taken on or before Day -1.
Each subject was counted with the number of unique bDMARD-naive, TNFi-IR, or bDMARD Use (Non-IR) .
ie. If there was more than one record per drug for a subject, count as one medication.
The strata of bDMARD-naïve, TNFi-IR, and bDMARD Use (Non-IR) were derived from clinical database
Numbers of inadequate responses were summarized as number (%) of subjects in each category.
Safety Analysis Set (SAFETY) - All subjects who were randomized and received at least one dose of the investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 11SEP2020 (02:55) Source Data: adcm Table Generation: 26SEP2020 (21:12)
Output File: ./cdisc/A3921120_SCD/adcm_s005_i_a
Table 14.1.4.4.4.2A is for Pfizer internal use.

At the end of the 16 weeks double-blinded treatment period, all subjects were assigned to open-label tofacitinib 5 mg BID to Week 48. The investigators, subjects and sponsor study team remained blinded to the first 16 weeks of treatment assignment through the entire duration of the trial until database release.

Blinding (masking)

This study was subject-, investigator-, and sponsor-blinded. An IRT drug management system was used to dispense the bottles with medication at each visit from baseline to week 40, using unique container numbers. For the open-label treatment period, subjects, investigator and sponsor study team remained blinded to the double-blind treatment period study sequence. All subjects received tofacitinib 5 mg tablets supplied in containers labelled according to local regulatory requirements.

Statistical methods

Analysis of efficacy parameters

Full Analysis Set: The full analysis set (FAS) included all randomized subjects who received at least one dose of the randomised investigational product (i.e., tofacitinib or placebo).

Per Protocol Analysis Set: The Per-Protocol (PP) analysis set excluded all subjects who had a protocol deviation The PP analysis set was used as a supportive analysis for the primary endpoint of ASAS20 and the key secondary endpoint of ASAS40.

There were 2 planned analyses: Week 16 Analysis (data cut-off 19DEC2019, data snapshot 29JAN2020) and Week 48 Analysis following the final database release.

The Week 16 Analysis included all placebo-controlled efficacy data through Week 16. The Week 48 analysis results, which contained placebo-controlled results through Week 16 as well as open-label results post-Week 16, were secondary and supportive in nature.

All statistical tests were conducted on a 2 sided 5% significance level for comparing tofacitinib 5 mg BID to placebo. Type I error was controlled on a 2-sided 5%.

For the primary endpoint of ASAS20 response at Week 16, if the 2-sided p-value was $\leqslant$5%, the superiority of tofacitinib 5 mg BID to placebo was declared and the primary objective of the study was considered as being met.

Estimands for ASAS20 and ASAS40 at Week 16

Only discontinuation of the investigational product was considered as an intercurrent event to define the estimands for this study. There are three estimands for the primary endpoint of ASAS20 at Week 16.

Estimand 1:

The first estimand of ASAS20 at Week 16 is a composite estimand that accounts for both treatment adherence and response. A responder is defined as having a response without discontinuation of the investigational product prior to Week 16.

Estimand 2:

The second estimand of ASAS20 at Week 16 is supportive to Estimand 1 and is a treatment policy estimand. It estimates the effect regardless of treatment adherence.

Estimand 3:

The third estimand of ASAS20 at Week 16 is supportive to Estimand 1 and is a hypothetical estimand. It estimates the treatment effect as if the intercurrent event of discontinuation of investigational product prior to Week 16 has not occurred.

The main difference between Estimand 1 and 3 is that Estimand 3 assumes the intercurrent event of discontinuation of investigational product prior to Week 16 has not occurred, while Estimand 1 considers the response after discontinuation of investigational product as non-response via the composite strategy. Also, the population-level summary in Estimand 3 is an odds ratio instead of difference in response rates as in Estimand 1.

Similarly, the same three estimand are also applicable to ASAS40 at Week 16. Specifically, Estimand 1 for ASAS40 at Week 16 is called the Key Secondary Estimand, defined according to the key secondary objective. Estimand 1 was also used for other binary secondary endpoints.

Estimands for Continuous Secondary Endpoints

Only discontinuation of the investigational product was considered as an intercurrent event to define the estimands for this study. Estimand 4, a hypothetical estimand was used for other continuous secondary endpoints that estimates the treatment effect as if the intercurrent event of discontinuation of investigational product prior to Week 16 has not occurred

Estimand 5 was used only for the Type I error controlled continuous secondary endpoints as supportive analyses to Estimand 4 and is a treatment policy estimand.

Estimand 4: The difference between Estimand 5 and 4 is that Estimand 5 disregards treatment adherence and includes the additional data collected after the intercurrent event of discontinuation of the investigational product prior to Week 16, ie, On-Study data are used.

Primary analysis: For the primary analysis of the ASAS20 response at Week 16, the normal approximation for the difference in binomial proportions adjusting for the stratification factor (ie, prior treatment history: "bDMARD naïve" versus "TNFi IR or bDMARD Use [Non-IR]") at randomisation via the CMH approach was used to test the superiority of tofacitinib 5 mg BID to placebo and to generate a 95% CI for the difference on the FAS.

ASAS40 response at Week 16 was analysed using the same methods as those for the primary endpoint ASAS20 response, as well as other binary endpoints.

Continuous endpoints were analysed as change from baseline with a mixed model for repeated measures (MMRM).

When analysis included only a single post-baseline visit, these endpoints were analysed as change from baseline with an analysis of covariance (ANCOVA) model that included treatment group, stratification factor (i.e., prior treatment history), and baseline value.

For both MMRM and ANCOVA, if the Baseline was missing or if there were no post-baseline measurements, the patient was excluded from the analysis. In the final analysis, all data up to Week 48 were included in the analyses using another MMRM.

A tipping point analysis for the primary endpoint of ASAS20 and the key secondary endpoint of ASAS40 was conducted to address impact of missing values on the conclusions and to assess the robustness of the data; it was based on multiple imputation.

Analysis at week 48

At week 16 all subjects have been assigned to open-label tofacitinib until week 48. Both primary and secondary endpoints have been analysed by the same models used until week 16 but extending visits until week 48. As the primary endpoint (ASAS20), the key secondary endpoint (ASAS40), and the other Type I error controlled secondary endpoints were at week 16, there was no additional adjustment made for Type I error rate at the final analysis at week 48. The week 48 contains results for earlier visits and

serves as sensitivity analysis only to ensure there were no major changes to the definitive results for the primary and key secondary endpoints obtained at week 16.

Table 16. Numerical Characteristics of Select Continuous Efficacy Endpoints

Endpoint	Unit	Theoretical Range of Values	Direction of Improvement from Baseline
Patient Global Assessment of Disease	None	0-10	Decrease from Baseline
Patient Assessment of Spinal Pain (Total Back Pain, Nocturnal Spinal Pain)	None	All: 0-10	Decrease from Baseline
BASFI	None	0-10	Decrease from Baseline
BASDAI	None	0-10	Decrease from Baseline
Inflammation Score (ie, Average of Q5 and Q6 of BASDAI)	None	0-10	Decrease from Baseline
hsCRP	mg/L	≥0	Decrease from Baseline
BASMI score and its 5 component scores (A, S) (A is the unmapped component score, S is the mapped component score [range 0-10] via linear method	BASMI, 5 components (S): None Lateral flexion, Tragus-to-wall distance, lumbar flexion, and intermalleolar distance (A): cm Cervical rotation angle (A): degree (°)	BASMI, 5 components (S): 0-10 5 components (A): ≥0	BASMI, 5 components (S), Tragus-to-wall distance (A): Decrease from Baseline Lateral flexion, lumbar flexion, intermalleolar distance, and cervical rotation (A): Increase from Baseline.
Spinal Mobility – Chest Expansion	cm	≥0	Increase from Baseline (ie, higher score represents more spinal mobility)
$ASDAS_{CRP}$	None	≥0	Decrease from Baseline
MASES	None	0-13	Decrease from Baseline
Swollen Joint Count (44)	None	0-44	Decrease from Baseline
SF-36v2, 8 domain scale (ie, norm-based), PCS, and MCS scores	None	All: Real values (Mean=50, SD=10)	Increase from Baseline
EQ-5D-3L, 5 dimension scores	None	All: 1, 2, 3	Decrease from Baseline

EQ-VAS	mm	0-100	Increase from Baseline
EQ-5D-3L, Utility Score (UK)	None	-0.594 - 1	Increase from Baseline
FACIT-F (Total, Impact domain, Experience domain scores)	None	Total: 0-52 Impact domain: 0-32 Experience domain: 0-20	Increase from Baseline (ie, higher score represents less fatigue)
ASQoL	None	0-18	Decrease from Baseline
WPAI 4 subscale scores	%	All: 0-100	Decrease from Baseline
AS-HCRU Self-Rating of Job Performance	None	0-10	Decrease from Baseline
Abbreviations: % = percent; $ASDAS_{CRP}$ = Ankylosing Spondylitis Disease Activity Score using C-Reactive Protein; AS-HCRU = Ankylosing Spondylitis – HealthCare Resource Utilization Questionnaire; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; cm = centimeter; EQ-5D-3L = EuroQol Health State Profile – 5 Dimensions – 3 Levels; EQ-VAS = EuroQol Your own health state today-Visual Analog Scale; FACIT-F = Functional Assessment of Chronic Illness Therapy - Fatigue; hsCRP = high sensitivity C-Reactive Protein; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MCS = mental component summary; mg/L = milligrams per liter; PCS = physical component summary; SD = standard deviation; SF-36v2 = 36-Item Short Form Survey Version 2 Acute; UK = United Kingdom; WPAI = Work Productivity & Activity Impairment.			

For the Phase III study, all statistical tests were conducted at the 2-sided 5% significance level for comparing tofacitinib 5 mg BID to placebo. The family-wise Type I error rate has been controlled at the 2-sided 5% significance level using a step-down.

In Study A3921120, 5 estimands were defined for the efficacy endpoints. The discontinuation of the investigational product was considered as an intercurrent event for the respective definitions. There were 3 estimands for the primary endpoint of ASAS20 response at Week 16 and the key secondary endpoint of ASAS40 response at Week 16. Estimand 1 included only on-drug data and was the main estimand; Estimand 2 included on-study data; Estimand 3 assumed the intercurrent event had not occurred and included only on-drug data. Both Estimands 2 and 3 were supportive estimands. Two additional estimands, Estimand 4 (main) and Estimand 5 (supportive) were used for continuous secondary endpoints.

Results

Participant flow

Five hundred and fifty-six AS patients were screened globally. A total of 270 eligible patients were randomised in a 1:1 ratio to 1 of the following 2 parallel treatment groups

- Tofacitinib 5 mg BID (n = 134)
- Placebo (n = 136)

Of the 270 randomised patients, 1 patient was randomised to tofacitinib 5 mg BID in error by the site but did not receive study drug, thus was excluded from all analyses. There were 269 patients included in the FAS. Overall, 9 (3.3%) patients discontinued from the study drug; 4 (3.0%) from tofacitinib 5 mg BID and 5 (3.7%) in the placebo treatment group up to Week 16. Subject disposition Up to Week 16 and 48 is presented in Figures 14 and 15 respectively.

Figure 14. Subject Disposition Up to Week 16

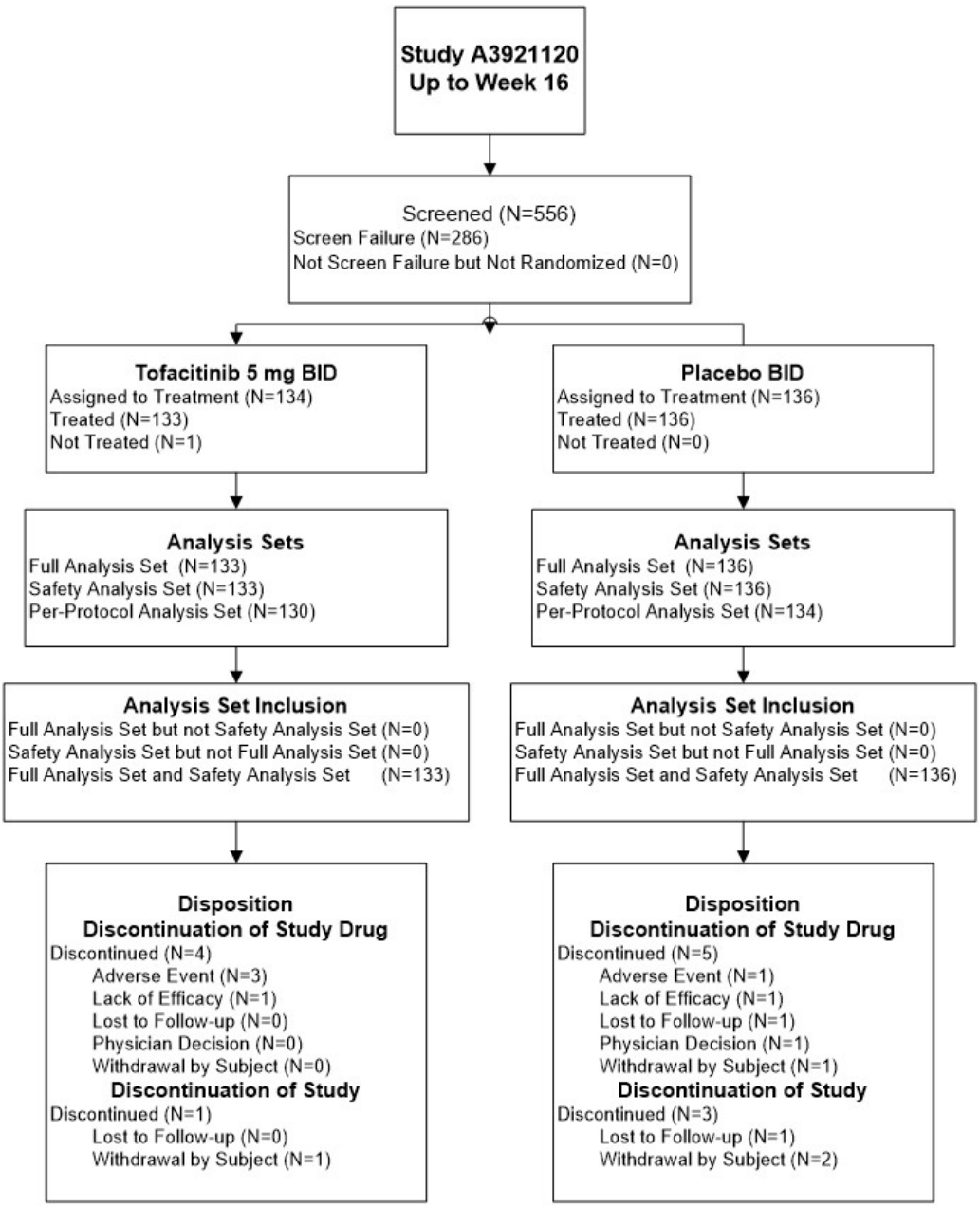


Figure 15. Subject Disposition Up to Week 48

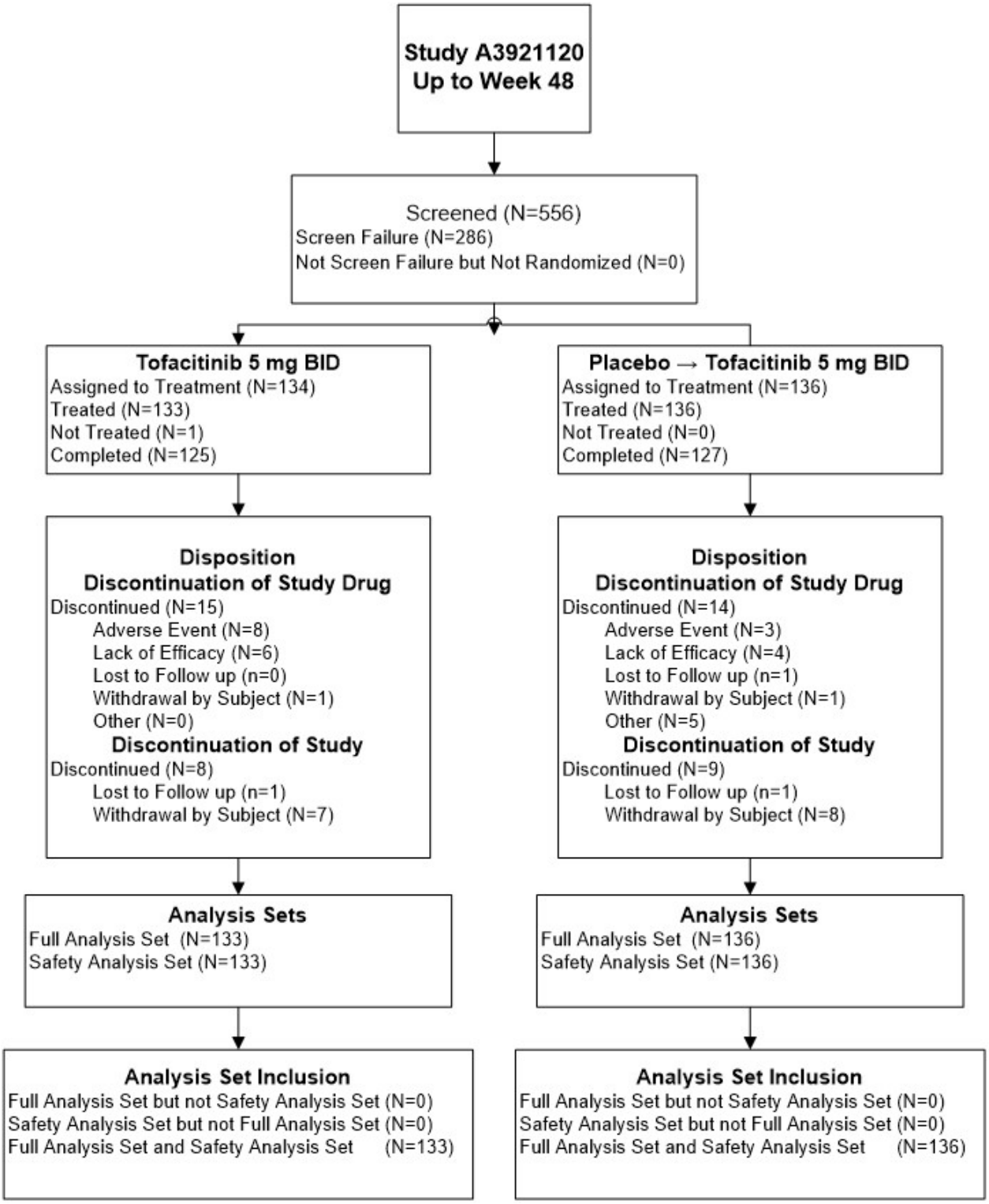


Table 17 summarises patient disposition for Study A3921120 up to Week 16 and Week 48, respectively.

Table 17. Patient Disposition

	Up to Week 16		Up to Week 48	
	Tofacitinib 5 mg BID	**Placebo**	**Tofacitinib 5 mg BID**	**Placebo->Tofacitinib 5 mg BID**
Randomised	134	136	134	136
Treated	133 (99.3)	136 (100.0)	133 (99.3)	136 (100.0)
Not treated	1 (0.7)	0	1 (0.7)	0
Discontinued	4 (3.0)	5 (3.7)	15 (11.3)	14 (10.3)
Discontinuations due to AE	3 (2.3)	1 (0.7)	8 (6.0)	3 (2.2)
Discontinuations due to Insufficient Clinical Response	1 (0.8)	2 (1.5)	6 (4.5)	4 (2.9)
Analysed for Efficacy				
Per-protocol analysis set	130 (97.7)	134 (98.5)	-	-
Full analysis set	133 (100.0)	136 (100.0)	133 (100.0)	136 (100.0)

Percentages for the 'Not treated' and 'Treated' rows are calculated using the number of patients assigned to treatment (randomised) as the denominator. Other percentages are calculated using the number of 'Treated' patients as the denominator.
Discontinuations due to AE and discontinuations due to insufficient clinical response refer to discontinuation of study drug and not discontinuation of study participation.
Based on the Week 48 Analysis data.

A total of 269 patients in the A3921120 were treated and included in the FAS and 133 received tofacitinib 5 mg BID as shown in Table 17.

Five hundred and fifty-six AS patients were screened and a total of 270 eligible patients were randomised (Tofacitinib 5 mg BID n = 134 and Placebo n = 136).

Patient's disposition was balanced across the study. The great majority completed the DIB 16 weeks phase (only 4 and 5 subjects discontinued study drug in the Tofa and PLB arm, respectively). A higher but similar number of subjects discontinued study drug up to 48 weeks: 15 in the Tofa-Tofa and 14 in the PLB-Tofa arm; the main reasons of discontinuation being the same safety and lack of efficacy although a higher number is registered in the Tofa-Tofa (8 and 6, respectively) as compared to PLB-Tofa (3 and 4) group.

Recruitment

Study Centres: A total of 57 sites randomised subjects from the following countries: Australia (3), Bulgaria (2), Canada (2), China (5), Czech Republic (3), France (1), Hungary (2), Republic of Korea (3), Poland (9), Russian Federation (6), Turkey (4), Ukraine (5), United States (12).

Conduct of the study

Amendments

Amendment 1, 06 September 2018 main changes:

1. Clarified the role of ASAS40 response at 16 weeks as a key secondary endpoint. Replaced ΔSF-36v2 Physical Functioning domain by ΔSF-36v2 PCS as a Type I error-controlled endpoint. Added ΔASQoL as an additional Type I error-controlled endpoint. Moved AS-HCRU from a secondary to tertiary endpoint.
2. Added Inflammation, Patients Assessment of Spinal Pain and PGA to the secondary endpoints. Clarified the BASMI secondary endpoint includes the 5 components. Realigned secondary endpoints to be consistent with the statistical testing (ie, Type I error control).

3. Updated sections based upon FDA feedback for subject discontinuation of investigational product and withdrawal from study.
4. Inclusion criteria #7 updated the definition of inadequate response and clarified the definition of intolerance.
5. Updated inclusion criteria #9 (Subject must be on a stable dose of corticosteroids for 1 week prior to first dose of investigational product).
6. Updated exclusion criteria #5 to exclude targeted synthetic DMARDs (including tofacitinib) and subjects that have been previously exposed to conventional synthetic, targeted synthetic, or biological DMARDs

Amendment 2 10 April 2019 main changes:

1. Changed to not exclude subjects with prior bDMARD use (non-IR) based on the available population to improve the recruitment in the study.
2. Moved the ASQol in sequence for global type 1 error control before the SF-36v2 PCS. Added the FACIT-F Total score to the global type I error control scheme.

Amendment 3 03 April 2020 main changes:

This global amendment incorporates venous thromboembolism (VTE) risk factor checks. Pfizer has determined that VTE is identified as an important identified risk/dose dependent adverse drug reaction for tofacitinib.

A summary of important protocol deviations is presented in Table 18:

- There was a similar proportion of subjects with protocol deviations in both treatment groups.
- The majority of the protocol deviations occurred in the category of procedures/tests and concomitant medications with the most common being efficacy assessment/procedure not performed at appropriate visits.

Table 18. Summary of important Protocol Deviations – Randomised Subjects (Final Analysis)

Category for Protocol Deviation Subcategory for Protocol Deviation	Tofacitinib 5 mg BID (N=134) n (%)	Placebo -> Tofacitinib 5 mg BID (N=136) n (%)	Total (N=270) n (%)
Number (%) of Subjects With Any Important Protocol Deviation	37 (27.6)	32 (23.5)	69 (25.6)
CCMEDS	10 (7.5)	12 (8.8)	22 (8.1)
Did not remain on stable dose of permitted Concomitant Medication as specified per Protocol	4 (3.0)	7 (5.1)	11 (4.1)
Subject took moderate or potent CYP3A4 inhibitors and/or moderate or potent CY3A4 inducers with concomitant use of study drug > 7 days	0	1 (0.7)	1 (0.4)
Took prohibited Concomitant Medication / Vaccine	6 (4.5)	5 (3.7)	11 (4.1)
INCLUSION/EXCLUSION	6 (4.5)	4 (2.9)	10 (3.7)
Did not meet inclusion criterion- Subject has active AS screening and baseline visits defined as- BASDAI score of >=4 and Back pain score >=4	3 (2.2)	1 (0.7)	4 (1.5)
Did not meet inclusion criterion- Subject has discontinued any investigational or marketed therapy for AS, back pain, arthritis, for 4 weeks or 5 half-lives	0	1 (0.7)	1 (0.4)
Did not meet inclusion criterion- Subject has inadequate clinical response of at least 2 NSAIDs (at least 4 weeks) or intolerance to at least 2 oral NSAIDs	2 (1.5)	2 (1.5)	4 (1.5)
Did not meet inclusion criterion- subject taking methotrexate or sulfasalazine should be taking it at appropriate dose and for minimum duration with a stable dose 4 weeks prior to first dose of study drug	1 (0.7)	0	1 (0.4)
Did not meet inclusion criterion- subjects designated as TNFi-IR must have an inadequate response or intolerance of 1or not more than 2 TNFi agents	2 (1.5)	1 (0.7)	3 (1.1)
Did not meet inclusion criterion- subjects taking injectable corticosteroid discontinued 4 weeks prior to first dose	1 (0.7)	0	1 (0.4)
INVESTIGATIONAL PRODUCT	3 (2.2)	0	3 (1.1)
Dosing / Administration Error- Compliance with study drug less than 80% for 2 consecutive visits after week 16 visit	3 (2.2)	0	3 (1.1)
LAB	8 (6.0)	5 (3.7)	13 (4.8)
Specimen could not be analyzed	7 (5.2)	5 (3.7)	12 (4.4)
Subject is a women of childbearing potential and pregnancy testing or FSH was not performed or negative test result was not documented prior to dosing	1 (0.7)	0	1 (0.4)
OTHER	6 (4.5)	1 (0.7)	7 (2.6)
Study personnel exposed to unblinded sensitive clinical data.	6 (4.5)	1 (0.7)	7 (2.6)
PROCEDURES/TESTS	13 (9.7)	21 (15.4)	34 (12.6)
Efficacy assessments/procedures not performed at appropriate visits	11 (8.2)	16 (11.8)	27 (10.0)
Patient reported outcome questionnaries not performed at appropriate visits	2 (1.5)	2 (1.5)	4 (1.5)
Procedure not performed by a medically qualified individual or by incorrect personnel	0	1 (0.7)	1 (0.4)
Procedure/Test not performed as specified in the protocol	0	3 (2.2)	3 (1.1)
RANDOMIZATION	2 (1.5)	0	2 (0.7)
Randomized under wrong stratification (ie- TNFi naive vs TNFi-IR)	1 (0.7)	0	1 (0.4)
Subject was randomized in error (received a randomization number however didn't qualify)	1 (0.7)	0	1 (0.4)
SAFETY REPORTING	1 (0.7)	0	1 (0.4)
Maternal or Paternal exposure in utero was not reported or was not reported in the required timeframe specified in the protocol	1 (0.7)	0	1 (0.4)

N: Number of randomized subjects; n (%): Number of subjects in each analysis category (Percentages were based on N).
PFIZER CONFIDENTIAL SDTM Creation: 13SEP2020 (09:08) Source Data: dv Table Generation: 26SEP2020 (21:11)
Output File: ./cdisc/A3921120_SCD/addv_s001_i_a
Table 14.1.5.1A is for Pfizer internal use.

Impact of COVID-19

In response to the COVID-19 pandemic, a PACL was approved on 30 March 2020 that outlined the administrative changes that were implemented to clarify study procedures during the pandemic.

The COVID-19 pandemic impact of protocol changes due to the deviations on the data quality, data analysis or conclusion was minimal as the majority of patients had completed study participation prior to start of the COVID-19 pandemic.

Amendments have been done basically to refine the endpoints and their hierarchy; another important point was the inclusion of bDMARD non-IR subjects. No impact on study results is foreseen.

Baseline data

Table 19 presents baseline demographic characteristics for the tofacitinib 5 mg BID and placebo groups for Study A3921120.

Table 19. Demographics and Baseline Characteristics by Treatment Group - Safety Analysis Set (Final Analysis)

	Tofacitinib 5 mg BID (N = 133)	**Placebo->Tofacitinib 5 mg BID (N = 136)**	**Total (N=269)**
Age years, n (%) [a]			
18-44	83 (62.4%)	86 (63.2%)	169 (62.8%)
45-64	44 (33.1%)	50 (36.8%)	94 (34.9%)
65-74	6 (4.5)	0	6 (2.2%)
75-84	0	0	0
≥85	0	0	0
N1	133	136	269
Mean (SD)	42.2 (11.85%)	40.0 (11.06%)	41.1 (11.49%)
Range	20, 70	20, 62	20, 70
Gender, n (%)			
Male	116 (87.2%)	108 (79.4%)	224 (83.3%)
Female	17 (12.8%)	28 (20.6%)	45 (16.7%)
Race, n (%)			
White	107 (80.5%)	106 (77.9%)	213 (79.2%)
Asian	25 (18.8%)	30 (22.1%)	55 (20.4%)
Not reported	1 (0.8%)	0	1 (0.4%)
Ethnicity, n (%)			

	Tofacitinib 5 mg BID (N = 133)	Placebo->Tofacitinib 5 mg BID (N = 136)	Total (N=269)
Hispanic/Latino	2 (1.5%)	2 (1.5%)	4 (1.5%)
Not Hispanic/Latino	129 (97.0%)	133 (97.8%)	262 (97.4%)
Not reported	2 (1.5%)	1 (0.7%)	3 (1.1%)
BMI (kg/m^2)			
N1	132	136	268
Mean (SD)	26.7 (5.6)	26.3 (5.77)	26.5 (5.70)
Range	16.0, 50.6	15.9, 48.9	15.9, 50.6
Weight (kg),n (%)			
<60	18 (13.5%)	16 (11.8%)	34 (12.6%)
>=60 to <=100	97 (72.9%)	110 (80.9%)	207 (77.0%)
>100	18 (13.5%)	10 (7.4%)	28 (10.4%)
Geographic Region [b], n (%)			
United States/Canada	16 (12.0%)	11 (8.1%)	27 (10.0%)
European Union	51 (38.3%)	55 (40.4%)	106 (39.4%)
Asia [b]	23 (17.3%)	30 (22.1%)	53 (19.7%)
ROW [c]	43 (32.3%)	40 (29.4%)	83 (30.9%)
Smoking Status, n (%)			
Never smoked	75 (56.4%)	72 (52.9%)	147 (54.6%)
Current smoker	34 (25.6%)	45 (33.1%)	79 (29.4%)
Ex-smoker	24 (18.0%)	19 (14.0%)	43 (16.0%)

a. Age at screening.
N = number of patients included in the safety analysis set
N1 = number of patients included in the analysis
The data for Study A3921120 was based on the Week 48 Analysis data

Table 20. Baseline Disease Characteristics by Treatment Group- Safety Analysis Set (Final Analysis)

Parameter	Summary Statistics	Tofacitinib 5 mg BID (N=133)	Placebo -> Tofacitinib 5 mg BID (N=136)	Total (N=269)
Prior Treatment History Derived from Clinical Database, n (%)	bDMARD-naive	102 (76.7%)	105 (77.2%)	207 (77.0%)
	TNFi-IR or bDMARD Use (Non-IR)	31 (23.3%)	31 (22.8%)	62 (23.0%)
	TNFi-IR	29 (21.8%)	30 (22.1%)	59 (21.9%)
	bDMARD Use (Non-IR)	2 (1.5%)	1 (0.7%)	3 (1.1%)
Ankylosing Spondylitis Disease Symptom Duration (Years), n (%)	<5	23 (17.3%)	35 (25.7%)	58 (21.6%)
	>=5	110 (82.7%)	101 (74.3%)	211 (78.4%)
	N1	133	136	269
	Mean	14.2	12.9	13.5
	Std. Dev.	9.80	9.47	9.64
	Median	11.3	10.3	10.7
	Range(min,max)	(0.3, 46.8)	(0.7, 49.4)	(0.3, 49.4)
Ankylosing Spondylitis Duration (Years) since Diagnosis, n (%)	<5	63 (47.4%)	74 (54.4%)	137 (50.9%)
	>=5	70 (52.6%)	62 (45.6%)	132 (49.1%)
	N1	133	136	269
	Mean	8.9	6.8	7.8
	Std. Dev.	9.06	6.94	8.11
	Median	5.8	4.8	4.9
	Range(min,max)	(0.1, 42.8)	(0.1, 34.9)	(0.1, 42.8)
History of Uveitis, n (%)	Yes	22 (16.5%)	20 (14.7%)	42 (15.6%)
	No	94 (70.7%)	94 (69.1%)	188 (69.9%)
	Missing	17 (12.8%)	22 (16.2%)	39 (14.5%)
Current Diagnosis of Uveitis for Subjects with History of Uveitis, n (%)	Yes	6 (27.3%)	5 (25.0%)	11 (26.2%)
	No	16 (72.7%)	15 (75.0%)	31 (73.8%)
History of Psoriasis, n (%)	Yes	5 (3.8%)	3 (2.2%)	8 (3.0%)
	No	95 (71.4%)	95 (69.9%)	190 (70.6%)
	Missing	33 (24.8%)	38 (27.9%)	71 (26.4%)
Current Diagnosis of Psoriasis for Subjects with History of Psoriasis, n (%)	Yes	2 (40.0%)	2 (66.7%)	4 (50.0%)
	No	3 (60.0%)	1 (33.3%)	4 (50.0%)
History of Inflammatory Bowel Disease (IBD), n (%)	Yes	1 (0.8%)	2 (1.5%)	3 (1.1%)
	No	95 (71.4%)	94 (69.1%)	189 (70.3%)

Parameter	Summary Statistics	Tofacitinib 5 mg BID (N=133)	Placebo -> Tofacitinib 5 mg BID (N=136)	Total (N=269)
	Missing	37 (27.8%)	40 (29.4%)	77 (28.6%)
Current Diagnosis of IBD for Subjects with History of IBD, n (%)	Yes	1 (100.0%)	1 (50.0%)	2 (66.7%)
	No	0	1 (50.0%)	1 (33.3%)
History of Peripheral Arthritis, n (%)	Yes	21 (15.8%)	25 (18.4%)	46 (17.1%)
	No	96 (72.2%)	94 (69.1%)	190 (70.6%)
	Missing	16 (12.0%)	17 (12.5%)	33 (12.3%)
Current Diagnosis of Peripheral Arthritis for Subjects with History of Peripheral Arthritis, n (%)	Yes	18 (85.7%)	22 (88.0%)	40 (87.0%)
	No	3 (14.3%)	3 (12.0%)	6 (13.0%)
HLA-B27, n (%)	Negative	12 (9.0%)	14 (10.3%)	26 (9.7%)
	Positive	117 (88.0%)	118 (86.8%)	235 (87.4%)
	Missing	4 (3.0%)	4 (2.9%)	8 (3.0%)
Baseline hsCRP (mg/L), n (%)	<=2.87	23 (17.3%)	20 (14.7%)	43 (16.0%)
	>2.87	110 (82.7%)	116 (85.3%)	226 (84.0%)
	<=5	41 (30.8%)	33 (24.3%)	74 (27.5%)
	>5	92 (69.2%)	103 (75.7%)	195 (72.5%)
	N1	133	136	269
	Mean	16.36	18.02	17.20
	Std. Dev.	17.255	19.685	18.508
	Median	9.12	13.55	11.60
	Range(min,max)	(0.23, 87.10)	(0.20, 173.00)	(0.20, 173.00)
Baseline PGA (NRS)	N1	133	136	269
	Mean	6.9	7.0	6.9
	Std. Dev.	1.76	1.66	1.71
	Median	7.0	7.0	7.0
	Range(min,max)	(1, 10)	(2, 10)	(1, 10)
Baseline Patient Assessment of Pain - Total Back Pain (NRS)	N1	133	136	269
	Mean	6.9	6.9	6.9
	Std. Dev.	1.52	1.61	1.57
	Median	7.0	7.0	7.0
	Range(min,max)	(1, 10)	(2, 10)	(1, 10)
Baseline Patient Assessment of Pain - Nocturnal Spinal Pain (NRS)	N1	133	136	269
	Mean	6.8	6.8	6.8
	Std. Dev.	1.92	1.86	1.89
	Median	7.0	7.0	7.0

Parameter	Summary Statistics	Tofacitinib 5 mg BID (N=133)	Placebo -> Tofacitinib 5 mg BID (N=136)	Total (N=269)
	Range(min,max)	(0, 10)	(1, 10)	(0, 10)
Baseline BASFI	N1	133	136	269
	Mean	5.8	5.9	5.9
	Std. Dev.	2.31	2.07	2.19
	Median	6.3	6.2	6.2
	Range(min,max)	(0.0, 10.0)	(0.3, 9.6)	(0.0, 10.0)
Baseline BASDAI Score	N1	133	136	269
	Mean	6.4	6.5	6.5
	Std. Dev.	1.48	1.44	1.46
	Median	6.5	6.7	6.5
	Range(min,max)	(1.5, 10.0)	(3.3, 10.0)	(1.5, 10.0)
Baseline Inflammation	N1	133	136	269
	Mean	6.6	6.8	6.7
	Std. Dev.	1.86	1.91	1.88
	Median	6.5	6.5	6.5
	Range(min,max)	(0.0, 10.0)	(1.5, 10.0)	(0.0, 10.0)
Baseline BASMI - Linear Method	N1	133	136	269
	Mean	4.5	4.4	4.4
	Std. Dev.	1.73	1.78	1.75
	Median	4.6	4.5	4.6
	Range(min,max)	(1.1, 7.8)	(0.6, 8.4)	(0.6, 8.4)
Baseline Spinal Mobility - Chest Expansion (cm)	N1	133	136	269
	Mean	3.0	3.3	3.2
	Std. Dev.	1.63	1.55	1.59
	Median	2.5	3.0	3.0
	Range(min,max)	(0.1, 9.0)	(0.0, 7.3)	(0.0, 9.0)
Baseline ASDAS(CRP), n (%)	<1.3 [inactive disease]	0	0	0
	>=1.3 to <2.1 [low disease activity]	2 (1.5%)	0	2 (0.7%)
	>=2.1 to <=3.5 [high disease activity]	48 (36.1%)	40 (29.4%)	88 (32.7%)
	>3.5 [very high disease activity]	83 (62.4%)	96 (70.6%)	179 (66.5%)
	N1	133	136	269
	Mean	3.8	3.9	3.9
	Std. Dev.	0.82	0.79	0.81
	Median	3.7	3.9	3.9
	Range(min,max)	(1.4, 5.6)	(2.1, 5.9)	(1.4, 5.9)

Parameter	Summary Statistics	Tofacitinib 5 mg BID (N=133)	Placebo -> Tofacitinib 5 mg BID (N=136)	Total (N=269)
Baseline Presence of Enthesitis Based on MASES , n (%)[a]	Yes	71 (53.4%)	81 (59.6%)	152 (56.5%)
	No	62 (46.6%)	55 (40.4%)	117 (43.5%)
Baseline MASES for Subjects with Baseline MASES > 0	N1	71	81	152
	Mean	3.7	3.6	3.7
	Std. Dev.	2.49	2.40	2.44
	Median	3.0	3.0	3.0
	Range(min,max)	(1, 11)	(1, 13)	(1, 13)
Baseline Presence of Swollen Joints, n (%)[b]	Yes	33 (24.8%)	38 (27.9%)	71 (26.4%)
	No	100 (75.2%)	98 (72.1%)	198 (73.6%)
Baseline SJC(44) for Subjects with Baseline SJC(44) > 0	N1	33	38	71
	Mean	3.4	4.1	3.8
	Std. Dev.	2.97	5.22	4.31
	Median	2.0	2.0	2.0
	Range(min,max)	(1, 11)	(1, 24)	(1, 24)
Baseline SF-36v2 Physical Component Summary (PCS) Score	N1	133	135	268
	Mean	33.5	33.1	33.3
	Std. Dev.	7.25	6.98	7.11
	Median	33.6	33.5	33.6
	Range(min,max)	(17.9, 57.3)	(14.7, 53.7)	(14.7, 57.3)
Baseline SF-36v2 Mental Component Summary (MCS) Score	N1	133	135	268
	Mean	39.4	39.8	39.6
	Std. Dev.	11.09	12.69	11.90
	Median	38.1	40.8	39.1
	Range(min,max)	(14.1, 65.3)	(8.0, 64.7)	(8.0, 65.3)
Baseline FACIT-F Total Score	N1	133	136	269
	Mean	27.2	27.4	27.3
	Std. Dev.	10.71	9.32	10.01
	Median	27.0	27.0	27.0
	Range(min,max)	(4, 52)	(1, 46)	(1, 52)
Baseline ASQoL Total Score	N1	133	136	269
	Mean	11.6	11.3	11.5
	Std. Dev.	4.67	4.20	4.43
	Median	12.0	12.0	12.0
	Range(min,max)	(0, 18)	(0, 18)	(0, 18)

Parameter	Summary Statistics	Tofacitinib 5 mg BID (N=133)	Placebo -> Tofacitinib 5 mg BID (N=136)	Total (N=269)

N: Number of subjects included in the Safety Analysis Set; N1: Number of subjects included in the analysis; n (%): Number of subjects in each analysis category (Percentages were
based on N). Percentages for current symptom of Uveitis, Psoriasis, IBD, Peripheral Arthritis were based on number of subjects with history of Uveitis, Psoriasis, IBD, Peripheral
Arthritis, respectively. For hsCRP values < 2 mg/L, it is set to 2 mg/L in the formula to derive ASDAS(CRP).
Inflammation baseline was the average of questions 5 and 6 of BASDAI.
Baseline was defined as last non-missing assessment on or before day 1 and prior to first dose of investigational product.
[a] Yes was defined for those subjects with baseline Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) > 0.
[b] Yes was defined for those subjects with baseline Swollen Joint Count (44) > 0.
For HLA-B27, if baseline results were not available, results after baseline were also included in the summary.
Safety Analysis Set (SAFETY) - All subjects who were randomized and received at least one dose of the investigational

Prior Treatments

NSAIDS

Most (99.6%) subjects received prior NSAIDs such as diclofenac, celecoxib and meloxicam and a minor rate of patients received corticosteroids (16%), the most of which were oral corticosteroids (13%). However, it was noted that a higher number of subjects was treated with corticosteroids in tofacitinib 5 mg (19.5%) compared to placebo group (12.5%) both with oral and intrarticular administration, suggesting possible more severe manifestations. Moreover, this imbalance was mainly observed in highly treated patients (TNFi-IR and bDMARD use), in which a higher percentage of subjects in the tofacitinib 5 mg BID group (19.4%) compared to placebo (6.5%) had prior use of oral corticosteroids and this is expected likely due to a more difficult to treat disease. No important differences were reported in previous csDMARDs use that was similar between tofacitinib and placebo group (57.1% vs 59.6%). The majority of patients were bDMARDs naïve (77%) with a similar distribution between the two groups. A minor number of patients (31 subjects in each arm, 23%) were bDMARDs experienced (bDMARDs use or TNFi-IR), 2 subjects were bDMARDs use non-IR.; 1 subject did not take NSAIDs due to prior medical history.

Table 21. Prior Drug Treatments by Medication Type (Corticosteroids, NSAIDs, DMARDs) and Treatment Group - Safety Analysis Set (Week 16 Analysis) (Data Cutoff 19Dec2019, Data Snapshot 29Jan2020)

Medication Type	Route/Subcategory	Tofacitinib 5 mg BID (N=133) n (%)	Placebo -> Tofacitinib 5 mg BID (N=136) n (%)	Total (N=269) n (%)
Corticosteroids	Overall	26 (19.5)	17 (12.5)	43 (16.0)
	Intra-articular	4 (3.0)	0	4 (1.5)
	Oral	19 (14.3)	16 (11.8)	35 (13.0)
	Topical	5 (3.8)	2 (1.5)	7 (2.6)
	Missing	0	2 (1.5)	2 (0.7)
DMARD	CS-DMARD	76 (57.1)	81 (59.6)	157 (58.4)
	B-DMARD	31 (23.3)	31 (22.8)	62 (23.0)
	TNFi B-DMARD	31 (23.3)	31 (22.8)	62 (23.0)
NSAID	Overall	133 (100.0)	135 (99.3)	268 (99.6)

Medication Type	Route/Subcategory	Tofacitinib 5 mg BID (N=133) n (%)	Placebo -> Tofacitinib 5 mg BID (N=136) n (%)	Total (N=269) n (%)

WHO DDE v201903 coding dictionary applied.
Prior drug treatment was defined as a drug taken on or before Day -1.
Safety Analysis Set (SAFETY) - All subjects who were randomized and received at least one dose of the investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2020 (23:27) Source Data: adcm Output File: ./unblind_1120/A3921120/adcm_s002_b_i Date of Generation: 17APR2020 (10:14)
Table 14.1.4.4.4.1 is for Pfizer internal use.

Table 22. Prior Treatment History of Stratification Factor (bDMARD-naive, TNFi-IR or bDMARD Use (Non-IR)) by Treatment Group - Safety Analysis Set (Week 16 Analysis) (Data Cutoff 19Dec2019, Data Snapshot 29Jan2020)

Stratum	Number of Inadequate Responses	Tofacitinib 5 mg BID (N=133) n (%)	Placebo -> Tofacitinib 5 mg BID (N=136) n (%)	Total (N=269) n (%)
bDMARD-naive		102 (76.7)	105 (77.2)	207 (77.0)
TNFi-IR or bDMARD Use (Non-IR)		31 (23.3)	31 (22.8)	62 (23.0)
TNFi-IR	1 TNFi-IR	23 (79.3)	20 (66.7)	43 (72.9)
	2 TNFi-IR	6 (20.7)	10 (33.3)	16 (27.1)
bDMARD Use (Non-IR)	1 bDMARD Use (Non-IR)	2 (100.0)	1 (100.0)	3 (100.0)

WHO DDE v201903 coding dictionary applied.
Prior drug treatment was defined as a drug taken on or before Day -1.
Each subject was counted with the number of unique bDMARD-naive, TNFi-IR, or bDMARD Use (Non-IR).
ie. if there was more than one record per drug for a subject, count as one medication.
The strata of bDMARD-naive, TNFi-IR, and bDMARD Use (Non-IR) were derived from clinical database.
Numbers of inadequate responses were summarized as number (%) of subjects in each category.
Safety Analysis Set (SAFETY) - All subjects who were randomized and received at least one dose of the investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2020 (22:27) Source Data: adcm Output File: ./unblind_1120/A3921120/adcm_s005_i Date of Generation: 25FEB2020 (08:47)
Table 14.1.4.4.4.2 is for Pfizer internal use.

Corticosteroid

Prior corticosteroid use for the bDMARD naïve strata was similar, 12.7% in the tofacitinib 5 mg BID group compared with 13.3% in the placebo group.

In the TNFi-IR and bDMARD (non-IR) strata, a higher percentage of subjects in the tofacitinib 5 mg BID group (19.4%) compared to placebo (6.5%) had prior use of oral corticosteroids.

DMARDs

A similar proportion of subjects received prior DMARDs in both treatment groups. The most frequently received prior csDMARD (approximately 50% in each treatment group) was sulfasalazine (Table 23).

Table 23 shows the most frequently received prior csDMARD (approximately 50% in each treatment group) was sulfasalazine.

Table 23. Most frequently received prior csDMARD

Subcategory	Preferred Term	Tofacitinib 5 mg BID (N=133) n (%)	Placebo -> Tofacitinib 5 mg BID (N=136) n (%)	Total (N=269) n (%)
CS-DMARD	Number (%) of Subjects with Any Prior Medication	76 (57.1)	81 (59.6)	157 (58.4)
	LEFLUNOMIDE	3 (2.3)	4 (2.9)	7 (2.6)
	METHOTREXATE	22 (16.5)	20 (14.7)	42 (15.6)
	METHOTREXATE SODIUM	2 (1.5)	1 (0.7)	3 (1.1)
	SULFASALAZINE	66 (49.6)	69 (50.7)	135 (50.2)

bDMARDs

The percentage of bDMARD naïve or TNFi-IR or bDMARD use (non-IR) subjects were similar between treatment groups. The most frequently received prior bDMARDs (approximately 10% in each treatment group) were etanercept and adalimumab (Table 24).

Table 24. Most frequently received prior bDMARDs

B-DMARD	Number (%) of Subjects with Any Prior Medication	31 (23.3)	31 (22.8)	62 (23.0)
	ADALIMUMAB	13 (9.8)	13 (9.6)	26 (9.7)
	CERTOLIZUMAB	3 (2.3)	1 (0.7)	4 (1.5)
	CERTOLIZUMAB PEGOL	0	3 (2.2)	3 (1.1)
	ETANERCEPT	14 (10.5)	13 (9.6)	27 (10.0)
	GOLIMUMAB	2 (1.5)	6 (4.4)	8 (3.0)
	INFLIXIMAB	7 (5.3)	7 (5.1)	14 (5.2)
	TUMOR NECROSIS FACTOR RECEPTOR - IGG1	0	1 (0.7)	1 (0.4)
INFi B-DMARD	Number (%) of Subjects with Any Prior Medication	31 (23.3)	31 (22.8)	62 (23.0)

- All subjects had received bDMARDs included in the category of TNFi. There were 43 (72.9%) subjects with 1 prior TNFi-IR and 16 (27.1%) subjects 2 prior TNFi-IR
- The most frequently received prior bDMARDs (approximately 10% in each treatment group) were etanercept and adalimumab. The most common reason for discontinuation in the majority of bDMARDs was lack of efficacy.
- There were 2 subjects in the tofacitinib 5 mg BID treatment group and 1 subject in the placebo group with prior use of 1 bDMARD (non-IR). These subjects had bDMARD use with the discontinuation reason of other, not due to either AE or lack of efficacy.

Concomitant Rescue Medications

- The most common rescue medication in either treatment group Day 1 up to Week 16 and Day 1 up to Week 48 was paracetamol (2.2% and 2.6% of subjects, respectively)
- The most common NSAIDs used throughout the study were celecoxib and meloxicam, approximately 16% and 18% of all subjects, respectively
- The most common concomitant corticosteroids taken at baseline (Day 1 only) and Day 1 up to Week 16 were methylprednisolone (3.7% of subjects for both) and prednisone (1.5% and 1.9% of subjects, respectively)
- The most common concomitant corticosteroids taken Day 1 up to Week 48 were dexamethasone (2.2% of subjects), methylprednisolone (4.1% of subjects), and prednisone (1.9% of subjects)
- The most common concomitant csDMARD in both treatment groups (approximately 20% of subjects) throughout the study was sulfasalazine

Concomitant rescue medications, NSAIDs, oral corticosteroids, intra-articular corticosteroids, and csDMARDs were taken by a similar proportion of subjects between treatment groups at baseline up to Week 48. A higher percentage of subjects with any csDMARDs was observed in placebo group than in tofacitinib group (33% vs 22%) probably reflecting a higher number of patients with a history of

peripheral arthritis (18.4% vs 15.8%). The most common rescue medication in either treatment group Day 1 up to Week 16 and Day 1 up to Week 48 was paracetamol (2.2% and 2.6% of subjects, respectively).

Table 25. Concomitant Medications (Rescue, NSAIDs, Oral Corticosteroids, Intra-Articular Corticosteroids, csDMARD, and Pain Management/Analgesics) by Treatment Group – Safety Analysis Set (Week 16 Analysis) Date Cutoff 19 Dec 2019) Data snapshot 29 Jan 2020

	Up to Week 16			Up to Week 48		
Medication Type	Tofacitinib 5 mg BID (N=133) n (%)	Placebo (N=136) n (%)	Total (N=269) n (%)	Tofacitinib 5 mg BID (N=133) n (%)	Placebo -> Tofacitinib 5 mg BID (N=136) n (%)	Total (N=269) n (%)
Number (%) of Subjects with Any Rescue Concomitant Medication	3 (2.3)	5 (3.7)	8 (3.0)	5 (3.8)	5 (3.7)	10 (3.7)
Number (%) of Subjects with Any Concomitant NSAID	105 (78.9)	109 (80.1)	214 (79.6)	107 (80.5)	109 (80.1)	216 (80.3)
Number (%) of Subjects with Any Oral Corticosteroid	13 (9.8)	10 (7.4)	23 (8.6)	13 (9.8)	10 (7.4)	23 (8.6)
Number (%) of Subjects with Any Intra-Articular Corticosteroid	1 (0.8)	0	1 (0.4)	2 (1.5)	0	2 (0.7)
Number (%) of Subjects with Any csDMARD	29 (21.8)	45 (33.1)	74 (27.5)	29 (21.8)	45 (33.1)	74 (27.5)
Number (%) of Subjects with Any Pain Management/Analgesics	16 (12.0)	19 (14.0)	35 (13.0)	22 (16.5)	20 (14.7)	42 (15.6)

WHO DDE v201903 coding dictionary applied.
Subjects were only counted once per treatment for each row.
Safety Analysis Set (SAFETY) – All subjects who were randomized and received at least one dose of the investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2020 (22:27) Source Data: adcm Output File: ./unblind_1120/A3921120/adcm_s001_bi Date of Generation: 19FEB2020 (12:55)
Table 14.4.2.7.11 is for Pfizer internal use.

Numbers analysed

Full Analysis Set: subjects 133 in the Tofa and 136 in the PLB arm.

Per Protocol Analysis Set: which excluded 3 subjects in the tofacitinib 5 mg BID group and 2 subjects in the placebo group from the FAS.

Outcomes and estimation

Primary Endpoint Result – ASAS20 Response Rate at Week 16

The study met the primary endpoint, tofacitinib 5 mg BID demonstrated superiority over placebo in ASAS20 response at Week 16 (p <0.0001) (as shown in Table 26). ASAS20 response was a global Type I error-controlled endpoint.

Table 26. ASAS20 Response Rate at week 16, Treatment Comparison -Estimand 1, FAS, On-Drug Date, MR=NR- Primary Anslysis (Week 16 Analysis)

							Treatment Comparison [a]			
Visit	Treatment	N	N1	n	Response Rate (%)	SE	Diff	SE	95% CI (Lower, Upper)	p-Value
Week 16	Tofacitinib 5 mg BID	133	129	75	56.39	4.30	27.08	5.71	(15.89, 38.28)	<.0001
	Placebo	136	131	40	29.41	3.91				

N: Number of subjects in FAS. N1: Number of subjects with observation at visit. n: Number of responses (Percentages were based on N).
MR=NR: Missing response as non-response.
Full Analysis Set (FAS) - All subjects who were randomized to the study and received at least one dose of the randomized investigational product.
[a] Normal approximation adjusting for the stratification factor (prior treatment history: bDMARD-naive vs TNFi-IR or bDMARD Use [Non-IR]) derived from clinical database via CMH approach was used.
ASAS20 response was defined as >=20% and >=1 unit improvement in at least 3 domains on a scale of 0-10 and no worsening of >=20% and >=1 unit in the remaining domain.
Diff, SE and 95% CI were represented as percent in the report.
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2020 (22:20) Source Data: adas Output File: ./unblind_1120/A3921120/adas_s003_i Date of Generation: 19FEB2020 (12:05)
Table 14.2.1.2.1.3 is for Pfizer internal use.

The results from pre-specified supportive analyses for ASAS20 response at Week 16 i.e. tipping analysis for different scenarios of missing responses in both arms were consistent with the primary analysis.

A summary of subjects was produced based on on-drug data for those who completed the Week 16 visit by their ASAS20 response status at Week 16 and those who discontinued from the investigational product prior to the Week 16 visit by their reason of discontinuation (estimand 1) are provided below (Table 27). The summary for the on-study data (Estimand 2 as shown in Table 27) was consistent with the on-drug data.

Table 27. ASAS20 Response Rate at week 16, Treatment Comparison -Estimand 2

Status - n (%)	Tofacitinib 5 mg BID (N=133) n (%)	Placebo (N=136) n (%)
ASAS20 Responders	75 (56.39)	40 (29.41)
ASAS20 Non-Responders	58 (43.61)	96 (70.59)
ASAS20 Non-Responders Who Completed the Week 16 Visit with Observed On-Drug Data	54 (40.60)	91 (66.91)
ASAS20 Non-Responders Who Completed the Week 16 Visit with Missing On-Drug Data	0	0
ASAS20 Non-Responders Who Discontinued Investigational Product Prior to Week 16 Visit	4 (3.01)	5 (3.68)
Reasons for Discontinuation of Investigational Product		
Adverse Event	3 (2.26)	1 (0.74)
Lack of Efficacy	1 (0.75)	1 (0.74)
Lost to Follow-Up	0	1 (0.74)
Physician Decision	0	1 (0.74)
Withdrawal by Subject	0	1 (0.74)

N: Number of subjects in FAS. n (%): Number of subjects in each analysis category (Percentages were based on N).
MR=NR: Missing response as non-response.
ASAS20 response was defined as >=20% and >=1 unit improvement in at least 3 domains on a scale of 0-10 and no worsening of >=20% and >=1 unit in the remaining domain.
Full Analysis Set (FAS) - All subjects who were randomized to the study and received at least one dose of the randomized investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2020 (23:20) Source Data: adas Output File: ./unblind 1120/A3921120/adas s001 Date of Generation: 16APR2020 (22:48)
Table 14.2.1.1.1 is for Pfizer internal use.

Subgroup Analysis for the Primary Endpoint

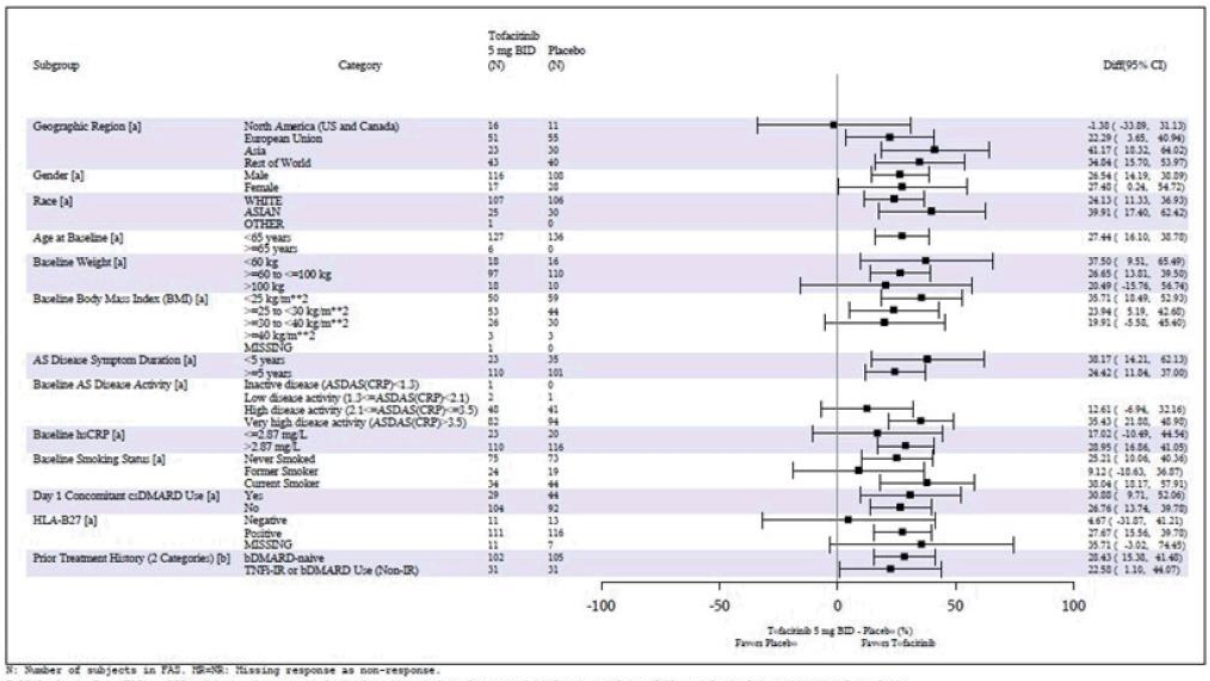
Subgroup comparisons for ASAS20 response at Week 16 were made on the FAS with missing values handled by MR=NR using the on-drug data corresponding to Estimand 1. Subgroup comparisons were not Type I error-controlled.

The efficacy of tofacitinib 5 mg BID versus placebo for ASAS20 responses at Week 16 was consistent across different subgroups examined with the exception of some which were smaller in size (Figure 16).

- For the subgroup of prior treatment history (bDMARD naïve and TNFi-IR or bDMARD use [Non-IR]), ASAS20 response rate of tofacitinib 5 mg BID was greater than that of placebo at Week 16 in both categories (Figure 16).

- The efficacy of tofacitinib 5 mg BID versus placebo for ASAS20 responses at Week 16 was consistent for the subgroup of baseline AS disease activity defined by the categorization of baseline ASDAS(CRP) derived using hsCRP 2 mg/L as minimum for values of hsCRP less than 2 mg/L.

Figure 16. Forest Plot of Subgroup Analysis of ASAS20 Response Rate at Week 16 (Estimand 1, FAS, On-Drug Data, MR=NR)



N: Number of subjects in FAS. MR=NR: Missing response as non-response.

Full Analysis Set (FAS) - All subjects who were randomized to the study and received at least one dose of the randomized investigational product.

[a] Normal approximation adjusting for the stratification factor (prior treatment history: bDMARD-naive vs TNFi-IR or bDMARD Use [Non-IR]) derived from clinical database via CMH approach was used for each category of a subgroup variable. [b] Normal approximation was used for each category of a subgroup variable.

ASAS20 response was defined as >=20% and >=1 unit improvement in at least 3 domains on a scale of 0-10 and no worsening of >=20% and >=1 unit in the remaining domain.

At a subgroup category, when one of the two treatment groups in comparison had 0 subject, no formal comparison was made. When response rate of 0% or 100% was observed in both treatment groups in comparison and in both strata, no formal comparison was performed. These included 'Other' for Race, '>= 65 years' for Age at Baseline, '>=40 kg/m**2' and 'Missing' for Baseline BMI, 'Inactive Disease' and 'Low Disease Activity' for Baseline AS Disease Activity.

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Table 28. Protocol A3921120 CMH Normal Approximation to ASAS20 Response Rate at Week 16 by Subgroup, Treatment Comparison - Estimand 1, FAS, On-Drug Data, MR=NR-Subgroup Analysis (Week 16 Analysis) (Data Cutoff 19Dec2019, Data Snapshot 29Jan2020)

									Treatment Comparison [a]		
Subgroup	Category	Visit	Treatment	N	N1	n	Response Rate (%)	SE	Diff	SE	95% CI (Lower, Upper)
	High disease activity (2.1<=ASDAS (CRP)<=3.5)	Week 16	Tofacitinib 5 mg BID	48	45	23	47.92	7.21	12.61	9.97	(-6.94, 32.16)
			Placebo	41	41	15	36.59	7.52			
	Very high disease activity (ASDAS (CRP)>3.5)	Week 16	Tofacitinib 5 mg BID	82	81	51	62.20	5.35	35.43	6.91	(21.88, 48.98)
			Placebo	94	89	25	26.60	4.56			
Baseline hsCRP	<=2.87 mg/L	Week 16	Tofacitinib 5 mg BID	23	22	11	47.83	10.42	17.02	14.04	(-10.49, 44.54)
			Placebo	20	20	6	30.00	10.25			
	>2.87 mg/L	Week 16	Tofacitinib 5 mg BID	110	107	64	58.18	4.70	28.95	6.17	(16.86, 41.05)
			Placebo	116	111	34	29.31	4.23			

Key Secondary Endpoint Result – ASAS40 Response Rate at Week 16

The study met the key secondary endpoint, tofacitinib 5 mg BID demonstrated superiority over placebo in ASAS40 response at Week 16 (p <0.0001) (Table 29). ASAS40 response was a global Type I error-controlled endpoint.

Table 29. ASAS40 Response Rate at Week 16

								Treatment Comparison [a]			
Visit	Treatment	N	N1	n	Response Rate (%)	SE	Diff	SE	95% CI (Lower, Upper)	p-Value
Week 16	Tofacitinib 5 mg BID	133	129	54	40.60	4.26	28.17	5.06	(18.26, 38.09)	<.0001
	Placebo	136	131	17	12.50	2.84				

N: Number of subjects in FAS. N1: Number of subjects with observation at visit. n: Number of responses (Percentages were based on N).
MR=NR: Missing response as non-response.
Full Analysis Set (FAS) – All subjects who were randomized to the study and received at least one dose of the randomized investigational product.
[a] Normal approximation adjusting for the stratification factor (prior treatment history: bDMARD-naive vs TNFi-IR or bDMARD Use [Non-IR]) derived from clinical database via CMH approach was used.
ASAS40 response was defined as >=40% and >=2 units improvement in at least 3 domains on a scale of 0-10 and no worsening at all in the remaining domain.
Diff, SE and 95% CI were represented as percent in the report.
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2020 (22:20) Source Data: adas Output File: ./unblind 1120/A3921120/adas s003 4 i Date of Generation: 19FEB2020 (11:47)
Table 14.2.2.2.1.3 is for Pfizer internal use.

Results from all the pre-specified supportive analyses for ASAS40 response at Week 16 (Table 30) were consistent with the key secondary analysis.

A summary of subjects was produced based on on-drug data for those who completed the Week 16 visit by their ASAS40 response status at Week 16 and those who discontinued from the investigational product

prior to the Week 16 visit by their reason of discontinuation (Table 30). The summary for the on-study data (Estimand 2) was consistent with the on-drug data.

Table 30. ASAS40 Response at Week 16 and Reasons for Study Drug Discontinuation prior to Week 16 – Estimand 1

Status - n (%)	Tofacitinib 5 mg BID (N=133) n (%)	Placebo (N=136) n (%)
ASAS40 Responders	54 (40.60)	17 (12.50)
ASAS40 Non-Responders	79 (59.40)	119 (87.50)
ASAS40 Non-Responders Who Completed the Week 16 Visit with Observed On-Drug Data	75 (56.39)	114 (83.82)
ASAS40 Non-Responders Who Completed the Week 16 Visit with Missing On-Drug Data	0	0
ASAS40 Non-Responders Who Discontinued Investigational Product Prior to Week 16 Visit	4 (3.01)	5 (3.68)
Reasons for Discontinuation of Investigational Product		
Adverse Event	3 (2.26)	1 (0.74)
Lack of Efficacy	1 (0.75)	1 (0.74)
Lost to Follow-Up	0	1 (0.74)
Physician Decision	0	1 (0.74)
Withdrawal by Subject	0	1 (0.74)

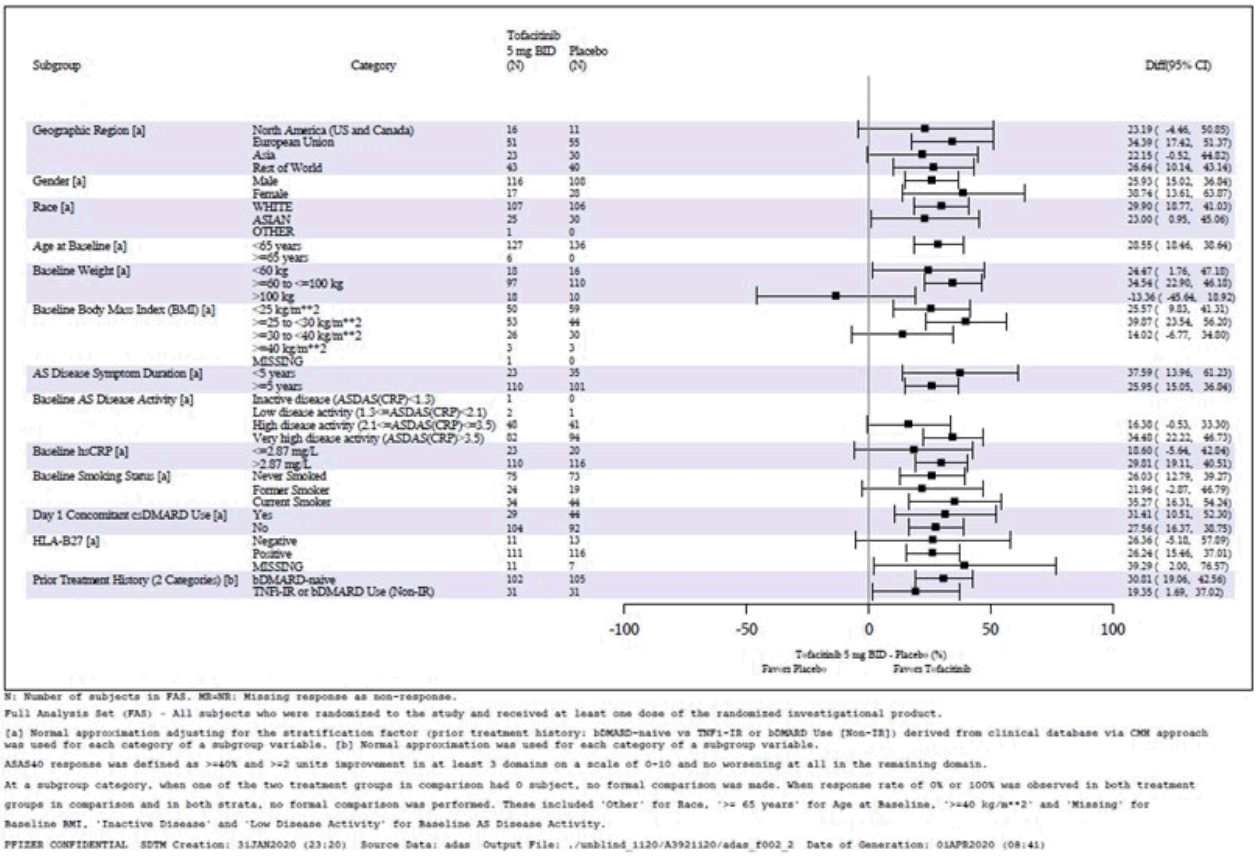
N: Number of subjects in FAS. n (%): Number of subjects in each analysis category (Percentages were based on N).
MR=NR: Missing response as non-response.
ASAS40 response was defined as >=40% and >=2 units improvement in at least 3 domains on a scale of 0-10 and no worsening at all in the remaining domain.
Full Analysis Set (FAS) - All subjects who were randomized to the study and received at least one dose of the randomized investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2020 (23:20) Source Data: adas Output File: ./unblind 1120/A3921120/adas s001 3 Date of Generation: 16APR2020 (22:57)
Table 14.2.2.1.1 is for Pfizer internal use.

Subgroup Analyses for the Key Secondary Endpoint

Subgroup comparisons for ASAS40 response at Week 16 were made on the FAS with missing values handled by MR=NR using the on-drug data corresponding to Estimand 1 (Figure 17). Subgroup comparisons were not Type Ierror-controlled.

- The efficacy of tofacitinib 5 mg BID versus placebo for ASAS40 responses at Week 16 was consistent across different subgroups examined except for baseline weight in the category of >100 kg, likely due to small sample size. The ASAS40 response rates for tofacitinib 5 mg BID were greater compared to placebo for the subgroups except for baseline weight in the category of >100 kg.
- For the subgroup of prior treatment history (bDMARD naïve and TNFi-IR or bDMARD use [Non-IR]), ASAS40 response rate of tofacitinib 5 mg BID was greater than that of placebo at Week 16 in both categories.
- The efficacy of tofacitinib 5 mg BID versus placebo for ASAS40 responses at Week 16 was consistent for the subgroup of baseline AS disease activity defined by the categorization of baseline ASDAS(CRP) derived using hsCRP 2 mg/L as minimum for values of hsCRP less than 2 mg/L.

Figure 17. Forest Plot of Subgroup Analysis of ASAS40 Response Rate at Week 16 (Estimand 1, FAS, On-Drug Data, MR=NR)



N: Number of subjects in FAS. MR=NR: Missing response as non-response.

Full Analysis Set (FAS) - All subjects who were randomized to the study and received at least one dose of the randomized investigational product.

[a] Normal approximation adjusting for the stratification factor (prior treatment history: bDMARD-naive vs TNFi-IR or bDMARD Use (Non-IR)) derived from clinical database via CMH approach was used for each category of a subgroup variable. [b] Normal approximation was used for each category of a subgroup variable.

ASAS40 response was defined as >=40% and >=2 units improvement in at least 3 domains on a scale of 0-10 and no worsening at all in the remaining domain.

At a subgroup category, when one of the two treatment groups in comparison had 0 subject, no formal comparison was made. When response rate of 0% or 100% was observed in both treatment groups in comparison and in both strata, no formal comparison was performed. These included 'Other' for Race, '>= 65 years' for Age at Baseline, '>=40 kg/m**2' and 'Missing' for Baseline BMI, 'Inactive Disease' and 'Low Disease Activity' for Baseline AS Disease Activity.

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Secondary Endpoints Results

Table 31 presents the results of primary endpoints and selected secondary endpoints of the study. Primary and key secondary endpoints are reported above in the AR.

Secondary efficacy endpoints supported the primary findings:

- Tofacitinib 5 mg BID demonstrated superiority to placebo in signs and symptoms as well as health-related outcomes, based on the mean changes from baseline in ASDAS(CRP), hsCRP, ASQoL, SF-36v2 PCS, BASMI Score (Linear Method), and FACIT-F Total Score at Week 16.

- Tofacitinib 5 mg BID demonstrated superiority to placebo in mean change from baseline in each of the 4 ASAS components: PGA, Total Back Pain, BASFI (physical function), and Inflammation at Week 16 (all $p<0.0001$; Table 31).

- Tofacitinib 5 mg BID also demonstrated superiority to placebo at all timepoints through Week16 for ASAS20 response rates. In addition, tofacitinib 5 mg BID demonstrated superiority to placebo at all timepoints through Week 16 except Week 2 for ASAS40 response rates (Figure 16).

- For most of the secondary efficacy endpoints not controlled for Type I error, including SF-36v2 Physical Functioning, Role-Physical, Bodily Pain, General Health, and Social Functioning domains, the tofacitinib 5 mg BID group showed greater numerical increases over placebo at Week 16 (Table 31).

- Tofacitinib 5 mg BID demonstrated sustained efficacy in ASAS20 and ASAS40 response rates and other secondary endpoints (ASDAS(CRP), hsCRP, ASQoL, SF-36v2 [PCS, Physical Functioning, Role-Physical, Bodily Pain, General Health, and Social Functioning domains], BASMI Score (Linear Method), FACIT-F Total Score, PGA, total back pain, BASFI, and inflammation) over time up to Week 48.

Table 31. Selected Efficacy Endpoints at Week 16 and Week 48 (FAS, On-Drug Data) – Study A3921120

	Week 16			Week 48	
	Tofacitinib 5 mg BID (N = 133)	Placebo (N = 136)	Difference From Placebo	Tofacitinib 5 mg BID (N = 133)	Placebo ->Tofacitinib 5 mg BID (N = 136)
Primary efficacy endpoint (subject to hierarchical testing procedure for global Type I error-control)					
ASAS20 response, n (%)	75 (56.39)	40 (29.41)	27.08***	87 (65.41)	82 (60.29)
[N1] or [95% CI] [a]	[129]	[131]	[15.89, 38.28]	[112]	[112]
Key secondary efficacy endpoint (subject to hierarchical testing procedure for global Type I error-control)					
ASAS40 response, n (%)	54 (40.60)	17 (12.50)	28.17***	67 (50.38)	61 (44.85)
[N1] or [95% CI] [a]	[129]	[131]	[18.26, 38.09]	[112]	[112]
Secondary efficacy endpoints (subject to hierarchical testing procedure for global Type I error-control)					
ΔASDAS(CRP), LSM (SE)	-1.36 (0.073)	-0.39 (0.073)	-0.98***	-1.70 (0.087)	-1.50 (0.086)
[N1] or [95% CI] [b]	[129]	[131]	[-1.16, -0.79]	[100]	[103]
ΔhsCRP (mg/dL), LSM (SE)	-1.05 (0.096)	-0.09 (0.096)	-0.96***	-1.17 (0.081)	-1.11 (0.080)
[N1] or [95% CI] [b]	[129]	[131]	[-1.20, -0.72]	[100]	[103]
ΔASQoL, LSM (SE)	-4.03 (0.404)	-2.01 (0.405)	-2.02**	-5.97 (0.454)	-4.70 (0.451)
[N1] or [95% CI] [c]	[129]	[130]	[-3.03, -1.01]	[112]	[112]
ΔSF-36v2 PCS, LSM (SE)	6.69 (0.588)	3.14 (0.590)	3.55***	8.81 (0.720)	7.39 (0.714)
[N1] or [95% CI] [c]	[129]	[130]	[2.09, 5.02]	[112]	[111]
ΔBASMI Score (Linear Method), LSM (SE)	-0.63 (0.060)	-0.11 (0.060)	-0.52***	-0.69 (0.074)	-0.54 (0.073)
[N1] or [95% CI] [b]	[129]	[131]	[-0.67, -0.37]	[100]	[103]
ΔFACIT-F Total score, LSM (SE)	6.54 (0.795)	3.12 (0.794)	3.43**	9.54 (0.897)	7.35 (0.891)
[N1] or [95% CI] [b]	[129]	[131]	[1.44, 5.42]	[112]	[111]
Secondary efficacy endpoints (subject to hierarchical testing procedure for Type I error-control within the family of ASAS responses)					
ΔPGA, LSM (SE)	-2.47 (0.204)	-0.91 (0.204)	-1.56***	-3.47 (0.225)	-2.94 (0.223)
[N1] or [95% CI] [b]	[129]	[131]	[-2.07, -1.05]	[112]	[112]
ΔTotal back Pain, LSM (SE)	-2.57 (0.191)	-0.96 (0.191)	-1.62***	-3.57 (0.220)	-2.87 (0.218)
[N1] or [95% CI] [b]	[129]	[131]	[-2.10, -1.14]	[113]	[112]
ΔBASFI, LSM (SE)	-2.05 (0.170)	-0.82 (0.169)	-1.23***	-2.61 (0.196)	-2.32 (0.195)
[N1] or [95% CI] [b]	[129]	[131]	[-1.66, -0.80]	[113]	[113]
ΔInflammation, LSM (SE)	-2.69 (0.185)	-0.97 (0.185)	-1.72***	-3.46 (0.214)	-2.90 (0.213)
[N1] or [95% CI] [b]	[129]	[131]	[-2.18, -1.25]	[113]	[113]

	Week 16			Week 48	
	Tofacitinib 5 mg BID (N = 133)	Placebo (N = 136)	Difference From Placebo	Tofacitinib 5 mg BID (N = 133)	Placebo ->Tofacitinib 5 mg BID (N = 136)
ASAS20 Response Rate Time Points (subject to hierarchical testing procedure for Type I error-control within the ASAS20 response rate time course)					
Week 12, n (%)	85 (63.91)	40 (29.41)	34.61***	NA	NA
[N1] or [95% CI] [a]	[132]	[132]	[23.63, 45.58]		
Week 8, n (%)	76 (57.14)	34 (25.00)	32.24***	NA	NA
[N1] or [95% CI] [a]	[132]	[133]	[21.32, 43.17]		
Week 4, n (%)	68 (51.13)	27 (19.85)	31.35***	NA	NA
[N1] or [95% CI] [a]	[132]	[132]	[20.64, 42.06]		
Week 2, n (%)	38 (28.57)	14 (10.29)	18.28**	NA	NA
[N1] or [95% CI] [a]	[132]	[133]	[9.06, 27.50]		
ASAS40 Response Rates Time Points (subject to hierarchical testing procedure for Type I error-control within the ASAS40 response rate time course)					
Week 12, n (%)	57 (42.86)	16 (11.76)	31.18***	NA	NA
[N1] or [95% CI] [a]	[132]	[132]	[21.34, 41.02]		
Week 8, n (%)	46 (34.59)	8 (5.88)	28.56***	NA	NA
[N1] or [95% CI] [a]	[132]	[133]	[19.66, 37.47]		
Week 4, n (%)	36 (27.07)	5 (3.68)	23.43***	NA	NA
[N1] or [95% CI] [a]	[132]	[132]	[15.30, 31.56]		
Week 2, n (%)	14 (10.53)	6 (4.41)	6.12	NA	NA
[N1] or [95% CI] [a]	[132]	[133]	[-0.13, 12.37]		

	Week 16			Week 48	
	Tofacitinib 5 mg BID (N = 133)	Placebo (N = 136)	Difference From Placebo	Tofacitinib 5 mg BID (N = 133)	Placebo ->Tofacitinib 5 mg BID (N = 136)
Secondary efficacy endpoints (not controlled for Type I error)					
ASAS 5/6, n (%)	58 (43.61)	10 (7.35)	36.34***	58 (43.61)	61 (44.85)
[N1] or [95% CI] [a]	[129]	[131]	[27.05, 45.63]	[100]	[103]
ASAS Partial Remission, n (%)	20 (15.04)	4 (2.94)	12.05**	31 (23.31)	24 (17.65)
[N1] or [95% CI] [a]	[129]	[131]	[5.29, 18.80]	[112]	[112]
ΔSpinal mobility (Chest expansion), LSM (SE)	0.59 (0.128)	0.38 (0.127)	0.21	0.50 (0.127)	0.47 (0.125)
[N1] or [95% CI] [b]	[129]	[131]	[-0.11, 0.53]	[100]	[103]
ΔBASDAI, LSM (SE)	-2.55 (0.175)	-1.11 (0.174)	-1.44***	-3.30 (0.199)	-2.80 (0.197)
[N1] or [95% CI] [b]	[129]	[131]	[-1.88, -1.00]	[113]	[113]
ASDAS Clinically Important Improvement, n (%)	81 (61.36)	26 (19.12)	42.30***	77 (58.33)	72 (52.94)
[N1] or [95% CI] [a]	[128]	[131]	[31.73, 52.88]	[100]	[103]
ASDAS Major Improvement, n (%)	37 (30.08)	6 (4.65)	25.28***	41 (33.33)	37 (28.68)
[N1] or [95% CI] [a]	[119]	[124]	[16.47, 34.10]	[94]	[100]
ASDAS Inactive Disease, n (%)	9 (6.77)	0 (0.00)	6.69*	20 (15.04)	18 (13.24)
[N1] or [95% CI] [a]	[129]	[131]	[2.05, 11.33]	[100]	[103]
ΔMASES, LSM (SE)	-1.94 (0.288)	-1.41 (0.272)	-0.53	-2.87 (0.225)	-2.56 (0.222)
[N1] or [95% CI] [b]	[70]	[76]	[-1.22, 0.16]	[60]	[59]
ΔSwollen Joint Count, LSM (SE)	-3.35 (0.475)	-2.79 (0.465)	-0.57	-3.31 (0.176)	-3.82 (0.174)
[N1] or [95% CI] [b]	[33]	[36]	[-1.78, 0.65]	[23]	[27]
ΔSF-36v2, LSM (SE)					
[N1] or [95% CI] [c]					
Physical Functioning	5.52 (0.665)	3.29 (0.665)	2.22*	7.80 (0.775)	6.94 (0.766)
	[129]	[130]	[0.56, 3.88]	[112]	[111]
Role Physical	6.13 (0.744)	3.13 (0.745)	3.00*	8.66 (0.870)	7.29 (0.862)
	[129]	[130]	[1.15, 4.85]	[112]	[111]
Bodily Pain	7.93 (0.710)	3.47 (0.713)	4.46***	11.67 (0.920)	9.55 (0.912)
	[129]	[130]	[2.69, 6.23]	[112]	[111]
General Health	5.00 (0.617)	1.76 (0.618)	3.24***	6.31 (0.777)	5.10 (0.770)
	[129]	[130]	[1.70, 4.78]	[112]	[111]

	Week 16			Week 48	
	Tofacitinib 5 mg BID (N = 133)	Placebo (N = 136)	Difference From Placebo	Tofacitinib 5 mg BID (N = 133)	Placebo ->Tofacitinib 5 mg BID (N = 136)
Vitality	5.34 (0.864)	3.56 (0.869)	1.78	9.83 (0.997)	9.28 (0.992)
	[129]	[130]	[-0.38, 3.94]	[112]	[111]
Social Functioning	5.45 (0.835)	2.49 (0.837)	2.96*	8.16 (0.923)	6.77 (0.915)
	[129]	[130]	[0.88, 5.05]	[112]	[111]
Role-Emotional	4.13 (1.020)	2.05 (1.017)	2.08	7.17 (1.004)	6.32 (0.989)
	[129]	[130]	[-0.46, 4.61]	[112]	[111]
Mental Health	3.57 (0.886)	2.49 (0.888)	1.08	7.10 (0.960)	6.45 (0.954)
	[129]	[130]	[-1.13, 3.29]	[112]	[111]
Mental Component Summary	3.45 (0.914)	2.13 (0.915)	1.33	7.07 (0.926)	6.35 (0.920)
	[129]	[130]	[-0.95, 3.61]	[112]	[111]
ΔEQ-VAS (mm), LSM (SE)	13.00 (1.840)	2.89 (1.840)	10.11***	20.64 (1.879)	18.00 (1.862)
[N1] or [95% CI] [c]	[128]	[130]	[5.52, 14.70]	[112]	[111]
ΔEuroQoL EQ-5D-3L, LSM (SE)					
[N1] [c]					
Mobility	-0.23 (0.044)	-0.06 (0.044)	-0.17*	-0.32 (0.051)	-0.26 (0.050)
	[129]	[131]	[-0.28, -0.06]	[112]	[112]
Self-care	-0.21 (0.043)	-0.20 (0.043)	-0.01	-0.33 (0.048)	-0.33 (0.047)
	[129]	[131]	[-0.11, 0.10]	[112]	[112]
Usual activities	-0.18 (0.046)	-0.09 (0.046)	-0.09	-0.32 (0.053)	-0.34 (0.053)
	[129]	[131]	[-0.20, 0.03]	[112]	[112]
Pain/discomfort	-0.30 (0.036)	-0.12 (0.036)	-0.18***	-0.37 (0.047)	-0.36 (0.047)
	[129]	[131]	[-0.27, -0.09]	[112]	[112]
Anxiety/depression	-0.11 (0.048)	-0.10 (0.048)	-0.01	-0.17 (0.054)	-0.21 (0.053)
	[129]	[131]	[-0.13, 0.11]	[112]	[112]
Δ WPAI, LSM (SE)					
[N1] or [95% CI] [c]					
Percent work time missed due to health problem	-3.65 (2.659)	0.88 (2.622)	-4.53	-8.10 (2.136)	-5.79 (2.047)
	[74]	[81]	[-11.15, 2.09]	[61]	[70]
Percent impairment while working due to health problem	-19.83 (2.274)	-6.94 (2.303)	-12.89***	-25.35 (2.769)	-23.00 (2.656)
	[71]	[77]	[-18.59, -7.19]	[58]	[70]
Percent overall work impairment due to health problem	-21.49 (2.508)	-7.64 (2.559)	-13.85***	-27.63 (3.005)	-23.22 (2.890)
	[71]	[76]	[-20.18, -7.52]	[58]	[69]

	Week 16			Week 48	
	Tofacitinib 5 mg BID (N = 133)	Placebo (N = 136)	Difference From Placebo	Tofacitinib 5 mg BID (N = 133)	Placebo ->Tofacitinib 5 mg BID (N = 136)
Percent activity impairment due to health problem	-19.03 (1.969) [129]	-5.63 (1.968) [131]	-13.40*** [-18.30, -8.50]	-27.37 (2.339) [112]	-19.77 (2.310) [112]

Nominal *p≤0.05; **p<0.001; ***p<0.0001
N = Number of patients in FAS. N1 = Number of patients with observation at visit. n: Number of responses (Percentages were based on N).
a. Normal approximation adjusting for the stratification factor (prior treatment history: bDMARD-naive versus TNFi-IR or bDMARD Use [Non-IR]) derived from clinical database via CMH approach was used. Missing response was considered as non-response.
b. MMRM included fixed effect of treatment group, visit, and treatment-group by visit interaction, stratification factor derived from clinical database, stratification-factor by visit interaction, baseline value, and baseline-value by visit interaction; an unstructured covariance matrix was used. Missing value was not imputed. Results at Week 16 were from 1 MMRM model fitted using data up to Week 16 for the 2 treatments: tofacitinib 5 mg BID and placebo (Week 16 Analysis). Results at Week 48 were from another MMRM model fitted using data up to Week 48 for the 2 treatments: tofacitinib 5 mg BID and placebo -> tofacitinib 5 mg BID (Week 48 Final Analysis).
c. ANCOVA model that included fixed effects of treatment group, stratification factor derived from clinical database, and baseline value, was fitted using data at Week 16 for the 2 treatments: tofacitinib 5 mg BID and placebo for Week 16 Analysis only. Missing value was not imputed. Results at Week 16 were from this ANCOVA model. Results at Week 48 were from another MMRM model fitted using data up to Week 48 for the 2 treatments: tofacitinib 5 mg BID and placebo -> tofacitinib 5 mg BID (Week 48 Final Analysis).
Results at Week 16 were based on the Week 16 Analysis data: data cutoff 19DEC2019, data snapshot 29JAN2020. Results at Week 48 were based on Week 48 Final Analysis.
Source: Module 5.3.5.1 A3921120 Week 16 Amended Study Report Table 14.2.1.2.1.1; Table 14.2.2.2.1.1; Table 394a.14.2.6.1.3; Table 14.2.7.1.3; Table 14.2.12.1.3; Table 14.2.11.1.3; Table 14.2.12.1.3.1; Table 14.2.10.1.3; Table 14.2.3.1.3; Table 14.2.4.2; Table 14.2.5.2; Table 14.2.19.3; Table 14.2.8.3.1; Table 14.2.3.1.3; Table 394a.14.2.6.3.2; 394a.Table 14.2.6.4.2; Table 394a.14.2.6.5.2; Table 14.2.17.4; Table 14.2.18.4; Table 14.2.12.1.6; Table 14.2.13.1.3; Table 14.2.14.1.3. Module 5.3.5.1 A3921120 Week 48 Study Report Table 14.2.1.2.1.1A; Table 14.2.2.2.1.1A; Table 14.2.6.1.3A; Table 14.2.7.1.3A; Table 14.2.11.1.3A; Table 14.2.12.1.3A; Table 14.2.16.1.3A; Table 14.2.10.1.3A; Table 14.2.3.1.3A; Table 14.2.4.2A; Table 14.2.5.2A; Table 14.2.19.3A; Table 14.2.8.3.1A; Table 14.2.6.3.2A; Table 14.2.6.4.2A; Table 14.2.6.5.2A; Table 14.2.17.4A; Table 14.2.18.4A; Table 14.2.13.1.3A; Table 14.2.14.1.3A.

The efficacy for the ASAS20 and ASAS40 response rates were increased at Week 24 (first post-placebo assessment) for tofacitinib 5 mg BID in patients who started placebo and advanced to tofacitinib at Week 16 (Figure 18 and Figure 19). This was maintained over time up to Week 48 in these patients (Figure 18 and Figure 19).

Figure 18. Line Graph of ASAS20 Response Rate (± SE) by Visit up to Week 48 - Estimand 1, FAS, On-Drug Data, MR=NR, Study A3921120

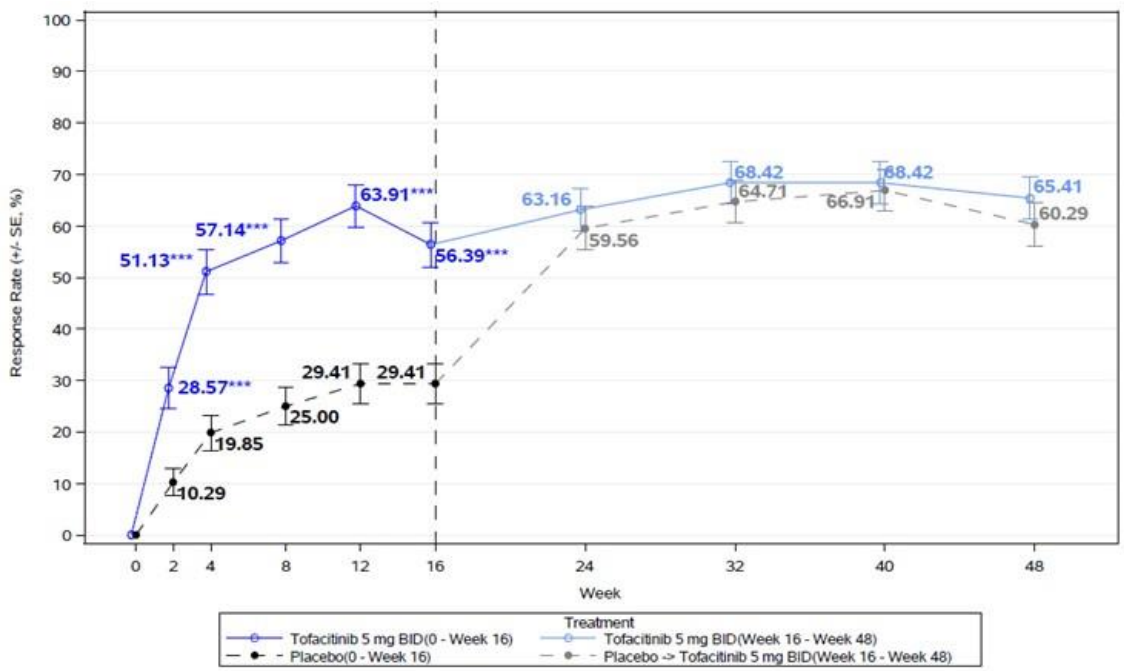
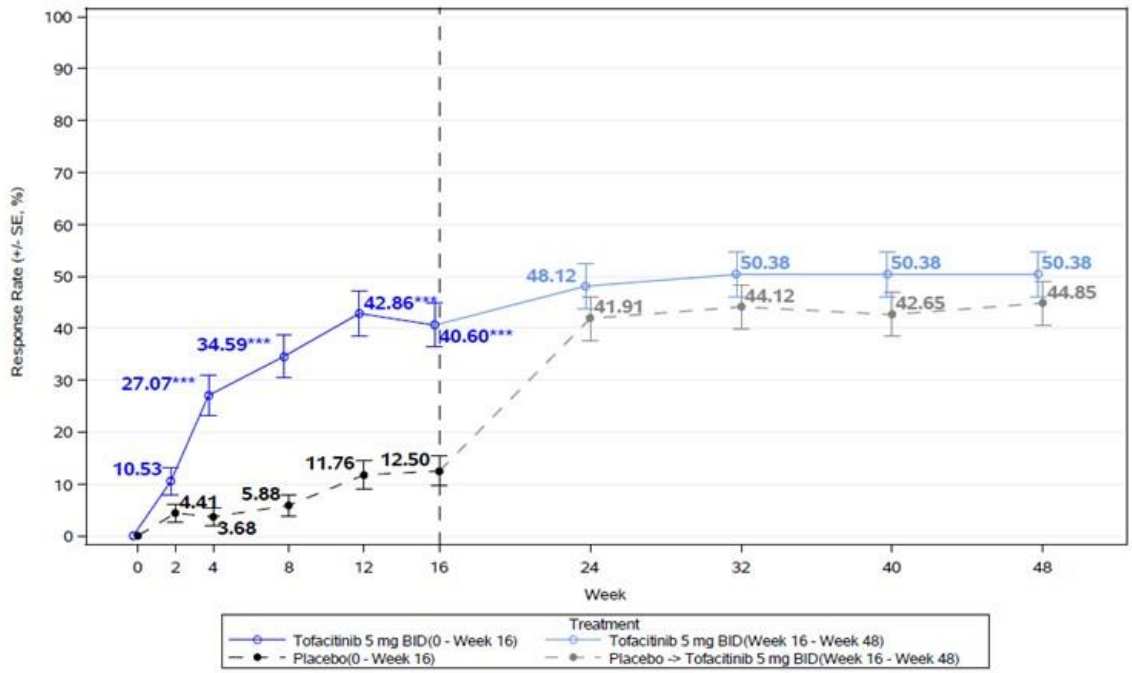


Figure 19. Line Graph of ASAS40 Response Rate (± SE) by Visit up to Week 48 - Estimand 1, FAS, On-Drug Data, MR=NR, Study A3921120



Ankylosing Spondylitis Disease Activity Score using C-Reactive Protein Change from Baseline

Change from baseline in ASDAS(CRP) at Week 16 was a global Type I error-controlled endpoint.

- The LS mean change from baseline in ASDAS(CRP) showed a statistically significant decrease for tofacitinib 5 mg BID compared to placebo at Week 16 ($p < 0.0001$) based on the MMRM analysis (Estimand 4).

- The LS means decrease from baseline in ASDAS(CRP) for tofacitinib 5 mg BID were greater than those of placebo at all other time points (2-sided 95% CI excluded 0).

- Results of the supportive analysis (MMRM, Estimand 5, FAS, on-study data, no imputation) were consistent with the on-drug data.

- Results were consistent for ASDAS(CRP) derived using hsCRP 2 mg/L as minimum for values of hsCRP less than 2 mg/L.

High Sensitivity C-Reactive Protein (hsCRP) Change from Baseline

Change from baseline in hsCRP at Week 16 was a global Type I error-controlled endpoint.

- The LS mean change from baseline in hsCRP showed statistically significant decreases for tofacitinib 5 mg BID compared to placebo at Week 16 ($p < 0.0001$) based on the MMRM analysis (Estimand 4).

- The LS means decrease from baseline in hsCRP for tofacitinib 5 mg BID were greater than those of placebo at all other time points (2-sided 95% CI excluded 0).

- Results of the supportive analysis (MMRM, Estimand 5, FAS, on-study data, no imputation) were consistent with the on-drug data.

Many secondary endpoints (21, 1 key) controlled for multiplicity (step-down testing procedure with a fixed alpha level for each comparison at the 2-sided 5%) were selected by the MAH.

Key secondary endpoint

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

ASDAS (CRP) the LS mean change from baseline in ASDAS(CRP) showed a statistically significant decrease for tofacitinib 5 mg BID compared to placebo at Week 16 (-1.36 in the tofa arm and -0.39 in the PLB arm at week 16, delta of -0.98, p <0.0001, FAS on drug data estimand 4), the achieved difference was clinically relevant. Consistent results were shown by the supportive analysis (MMRM, Estimand 5, FAS, on-study data, no imputation) were consistent with the on-drug data.

At week 48 improvement of ASDAS(CRP) from baseline is still seen in both arms similarly -1.70 and -1.50 for the TOFA-TOFA and PLB-TOFA, respectively.

Secondary endpoints type I controlled:

In the hierarchical order as second endpoint the MAH selected the Change from baseline of an inflammatory marker i.e., hsCRP at Week 16 showing statistically significant decreases for tofacitinib 5 mg BID compared to placebo at Week 16 (-1.05 versus -0.09, p <0.0001) based on the MMRM analysis (Estimand 4). Importantly this endpoint is not considered key for demonstration of tofacitinib clinical benefit but only regarded as supportive for effect on inflammation since no data support this biomarker as useful surrogate to assess efficacy in axial SpA.

Secondary endpoints but not controlled for type I error:

-ASDAS clinically important improvement (61.3 versus 19.1 delta 42.3), ASDAS major improvement (30 versus 4.6 delta 25.3) ASDAS inactive disease (6.7 versus 0 delta 6.7) at week 16 overall showing a greater response in the Tofa arm which is maintained at week 48 and with an effect size of clinical significance for endpoint measuring improvement. Low disease activity or partial remission endpoints: ASDAS inactive disease (6.7 versus 0 delta 6.7, p 0<0.05) at week 16 and ASAS partial remission (a value of =2 (on a 0 to 10 scale) present in each domain, 15 versus 3, p 0<0.001) showing very/limited effect size.

-ASAS 5/6 results are consistent with those of the primary and key secondary endpoint showing a statistical and clinical relevant improvement (44% responders, delta of 36 at week 16 and maintained at week 48).

As measure of improvement of enthesitis the MAH had included the change in MASES index (total score ranging 0 – 13) at week 16 as not controlled secondary endpoint showing an improvement of -2 versus -1.41, delta of -0.53 slightly increasing at week 48.

Other measures of symptoms and physical function recommended which has been included within secondary endpoints not controlled for multiplicity is the change of BASDAI at week 16 (showing an improvement of -2.55 at week 16 delta of -1.44), however i) this is a widely used measure of disease activity and its changes with treatment should be assessed as secondary endpoint; ii) the percentage of patients with clinical response as measured by an improvement of at least a 50% from the baseline score in BASDAI is considered useful to judge the clinical benefit of a treatment and was not included by the MAH.

Ancillary analyses

Combination With csDMARDs Versus Monotherapy

In Study A3921120, the efficacy of tofacitinib 5 mg BID versus placebo for ASAS20 response rate at Week 16 was consistent between patients who were receiving tofacitinib 5 mg BID as monotherapy and

those receiving tofacitinib 5 mg BID with concomitant csDMARDs However, the magnitude of the ASAS20 response rate was greater with concomitant csDMARD use. The efficacy of tofacitinib 5 mg BID versus placebo for ASAS40 response rate at Week 16 was consistent between patients who were receiving tofacitinib 5 mg BID as monotherapy and those receiving tofacitinib 5 mg BID with concomitant csDMARDs and again the magnitude of the response rate was greater with Day 1 concomitant csDMARD use (Table 32).

Table 32. CMH Normal Approximation to ASAS20 Response Rate at Week 16 by Subgroup, Treatment Comparison - Estimand 1, FAS, On-Drug Data, MR=NR -Subgroup Analysis (Week 16 Analysis)

-

									Treatment Comparison [a]		
Subgroup	Category	Visit	Treatment	N	N1	n	Response Rate (%)	SE	Diff	SE	95% CI (Lower, Upper)
Day 1 Concomitant csDMARD Use	Yes	Week 16	Tofacitinib 5 mg BID	29	29	20	68.97	8.59	30.88	10.80	(9.71, 52.06)
			Placebo	44	44	16	36.36	7.25			
	No	Week 16	Tofacitinib 5 mg BID	104	100	55	52.88	4.89	26.76	6.64	(13.74, 39.78)
			Placebo	92	87	24	26.09	4.58			

Table 33. CMH Normal Approximation to ASAS40 Response Rate at Week 16 by Subgroup, Treatment Comparison - Estimand 1, FAS, On-Drug Data, MR=NR- Subgroup Analysis (Week 16 Analysis)

									Treatment Comparison [a]		
Subgroup	Category	Visit	Treatment	N	N1	n	Response Rate (%)	SE	Diff	SE	95% CI (Lower, Upper)
	Current Smoker	Week 16	Tofacitinib 5 mg BID	34	33	16	47.06	8.56	35.27	9.68	(16.31, 54.24)
			Placebo	44	41	5	11.36	4.78			
Day 1 Concomitant csDMARD Use	Yes	Week 16	Tofacitinib 5 mg BID	29	29	14	48.28	9.28	31.41	10.66	(10.51, 52.30)
			Placebo	44	44	7	15.91	5.51			
	No	Week 16	Tofacitinib 5 mg BID	104	100	40	38.46	4.77	27.56	5.71	(16.37, 38.75)
			Placebo	92	87	10	10.87	3.25			

The ASAS20 and ASAS40 respones are higher in tofacitinib 5 mg BID compared to placebo group both in patients with concomitant csDMARDs use that in those with not (as shown in Tables 32 and 33). It is noted that the magnitude of the effect of tofacitnib is slightly greater when using concomitant csDMARDs compared to monotherapy (diff. of 30.88 vs 26.76 for ASAS20 and 31.41 vs 27.56 for ASAS 40 response), even though the number of patients with concomitant csDMARDs treatment (tofa: 29, PLB: 44) is limited compared to that of patients in monotherapy (tofa: 104, PLB: 92).

Efficacy in the Pivotal Study A3921120 Beyond Week 16

The efficacy of the tofacitinib IR for AS is based on the Week 16 data analysis and supplemented by the Week 48 data analysis from Study A3921120. As previously described, all patients in this study received active treatment of tofacitinib 5 mg BID after Week 16. Therefore, no placebo data are available after this time point.

The efficacy of tofacitinib 5 mg BID as measured by ASAS20 and ASAS40 responses are shown over the full 48-week treatment period in the study (Figure 5 and Figure 6 above). The ASAS20 and ASAS40 response rates were sustained for tofacitinib 5 mg BID after Week 16 to the end of the study (Week 48).

In addition, as measured by type-I error-controlled secondary endpoints (ASDAS(CRP), hsCRP, ASQoL, SF-36v2 PCS, BASMI Score (Linear Method), FACIT-F Total Score, PGA, total back pain, BASFI, and inflammation) efficacy was sustained or improved for tofacitinib 5 mg BID after Week 16 to the end of the study.

Summary of main study

Table 34 summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 34. Summary of Efficacy

Title: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY OF THE EFFICACY AND SAFETY OF TOFACITINIB IN SUBJECTS WITH ACTIVE ANKYLOSING SPONDYLITIS (AS)			
Study identifier	A3921120		
Design	Multicenter, Randomized, Double-Blind, Placebo-Controlled Study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		16 weeks not applicable 32 weeks
Hypothesis	Superiority to placebo		
Treatments groups	tofacitinib 5 mg		tofacitinib 5 mg po BID, N=134
	Placebo		Placebo po BID, N=136
Endpoints and definitions	Primary endpoint	ASAS20 response at week 16	Improvement of ⩾20% and ⩾1 unit on a scale of 0 to 10 in at least three of the four ASAS scale main domains and no worsening of ⩾ 20% and ⩾1 unit in the remaining domain, at week 16
	Secondary endpoint	ASAS40 response at week 16	Improvement of ⩾40% and ⩾2 units on a scale of 0 to 10 in at least three of the four ASAS scale main domains and no worsening at all in the remaining domain, at week 16
	Secondary endpoint	Change from baseline in ASDAS-CRP at week 16	Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) based on CRP at week 16
	Secondary endpoint	Change from baseline in hsCRP at week 16	Change from baseline in high-sensitivity C-Reactive protein at week 16
	Secondary endpoint	Change from baseline in ASQoL at week 16	Change from baseline in ankylosing spondylitis quality of life (ASQoL) at week 16
	Secondary endpoint	Change from baseline in SF-36v2 PCS at week 16	Change from baseline in Short-Form-36 Health Survey Version 2 (SF-36v2) Physical Component Summary (PCS) score at week 16

	Secondary endpoint	Change from baseline in BASMIlin at week 16	Change from baseline in linear Bath Ankylosing Spondylitis Metrology Index – linear method (BASMIlin) at week 16
	Secondary endpoint	Change from baseline in FACIT-F at week 16	Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale at week 16
Database lock	Data cutoff 19 Dec 2019; data snapshot 29 Jan 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis set (randomised, received at least one dose of study drug) Week 16		
Descriptive statistics and estimate variability	Treatment group	tofacitinib BID 5 mg	Placebo
	Number of subjects	133	136
	ASAS20 response %	56.39 %	29.41 %
	Number of subjects	129	131
	ASAS40 response %	40.60 %	12.50 %
	Number of subjects	129	131
	Change from baseline in ASDAS-CRP	-1.36	-0.39
	Number of subjects	129	131
	Change from baseline in hsCRP	-1.05	-0.09
	Number of subjects	129	131
	Change from baseline in ASQoL units	-4.03	-2.01
	Number of subjects	129	130
	Change from baseline in SF-36v2 PCS	6.69	3.14
	Number of subjects	129	130
	Change from baseline in BASMIlin units	-0.63	-0.11
	Number of subjects	129	131
	Change from baseline in FACIT-F	6.54	3.12
	Number of subjects	129	131
Effect estimates per comparison	Primary endpoint ASAS20 response	Comparison groups	tofacitinib BID 5 mg vs Placebo
		% difference in response rate	27.08
		95% CI	15.89, 38.28
		P-value	<0.0001
	Secondary endpoint ASAS40 response	Comparison groups	tofacitinib BID 5 mg vs Placebo
		% difference in response rate	28.17
		95% CI	18.26, 38.09
		P-value	<0.0001

	Secondary endpoint Change from baseline in ASDAS-CRP	Comparison groups	tofacitinib BID 5 mg vs Placebo
		LS Mean Diff	-0.98
		95% CI	-1.16, -0.79
		P-value	<0.0001
	Secondary endpoint Change from baseline in hsCRP	Comparison groups	tofacitinib BID 5 mg vs Placebo
		LS Mean Diff	-0.96
		95% CI	-1.20, -0.72
		P-value	<0.0001
	Secondary endpoint Change from baseline in ASQoL	Comparison groups	tofacitinib BID 5 mg vs Placebo
		LS Mean Diff	-2.02
		95% CI	-3.03, -1.01
		P-value	<0.001
	Secondary endpoint Change from baseline in SF-36v2 PCS	Comparison groups	tofacitinib BID 5 mg vs Placebo
		LS Mean Diff	3.55
		95% CI	2.09, 5.02
		P-value	<0.0001
	Secondary endpoint Change from baseline in BASMIlin units	Comparison groups	tofacitinib BID 5 mg vs Placebo
		LS Mean Diff	-0.52
		95% CI	-0.67, -0.37
		P-value	<0.0001
	Secondary endpoint Change from baseline in FACIT-F	Comparison groups	tofacitinib BID 5 mg vs Placebo
		LS Mean Diff	3.43
		95% CI	1.44, 5.42
		P-value	<0.001

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

The Applicant has submitted a report concerning a systematic review and meta-analysis of placebo-controlled trials of EMA-approved biological DMARDs, including ASAS20/40 at week 12-16, in patients with AS with or without previous experience with biological DMARDs.

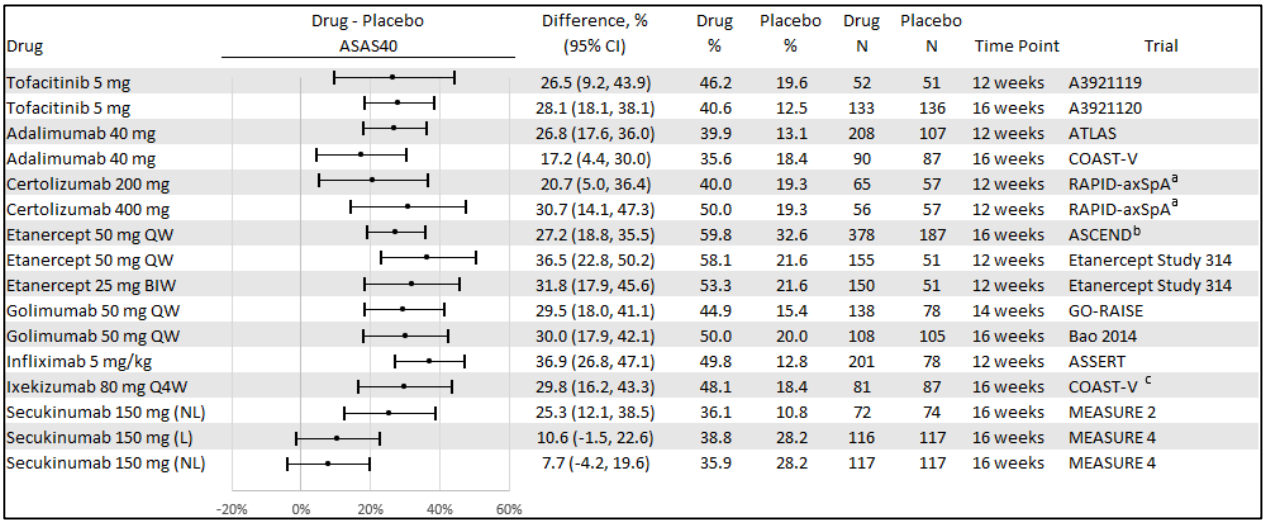
Placebo-controlled RCTs of biological DMARDs approved for AS by the EMA were included if they reported ASAS20 or ASAS40 at 12-16 weeks and included patients with prior nonsteroidal anti-inflammatory drug (NSAID) failure. Only multicenter studies were included and studies conducted in single countries were excluded. The initial search was conducted up to August 2019 and was recently refreshed up to August 2020. The studies concerning tofacitinib were studies A3921119 and A3921120 discussed in this report.

ASAS20 and ASAS40 response rates were extracted from the study reports, and from the AS subgroup in trials conducted in the SpA population. The mean differences and 95% confidence intervals (CI) for ASAS20 and ASAS40 responses between intervention arms and placebo were calculated, using ITT data. The results were depicted using forest plots, for all trials separately.

According to the results, ASAS20 and ASAS40 responses (Figure 20) for tofacitinib 5 mg BID across Studies A3921119 and A3921120, were similar compared with adalimumab, certolizumab, etanercept, golimumab, infliximab, ixekizumab and secukinumab. The treatment effects on ASAS40 were 26% and

28% in the two tofacitinib trials (Figure 20), while the majority of treatment effects of the other biological DMARDs ranged from 17% (adalimumab, COAST V) to 37% (infliximab, ASSERT). One of the secukinumab trials with a loading and a non-loading treatment arm versus placebo, had lower treatment effects (MEASURE 4).

Figure 20. ASAS40 Responses in placebo-controlled clinical trials: tofacitinib and approved AS therapies



Drug	Difference, % (95% CI)	Drug %	Placebo %	Drug N	Placebo N	Time Point	Trial
Tofacitinib 5 mg	26.5 (9.2, 43.9)	46.2	19.6	52	51	12 weeks	A3921119
Tofacitinib 5 mg	28.1 (18.1, 38.1)	40.6	12.5	133	136	16 weeks	A3921120
Adalimumab 40 mg	26.8 (17.6, 36.0)	39.9	13.1	208	107	12 weeks	ATLAS
Adalimumab 40 mg	17.2 (4.4, 30.0)	35.6	18.4	90	87	16 weeks	COAST-V
Certolizumab 200 mg	20.7 (5.0, 36.4)	40.0	19.3	65	57	12 weeks	RAPID-axSpA[a]
Certolizumab 400 mg	30.7 (14.1, 47.3)	50.0	19.3	56	57	12 weeks	RAPID-axSpA[a]
Etanercept 50 mg QW	27.2 (18.8, 35.5)	59.8	32.6	378	187	16 weeks	ASCEND[b]
Etanercept 50 mg QW	36.5 (22.8, 50.2)	58.1	21.6	155	51	12 weeks	Etanercept Study 314
Etanercept 25 mg BIW	31.8 (17.9, 45.6)	53.3	21.6	150	51	12 weeks	Etanercept Study 314
Golimumab 50 mg QW	29.5 (18.0, 41.1)	44.9	15.4	138	78	14 weeks	GO-RAISE
Golimumab 50 mg QW	30.0 (17.9, 42.1)	50.0	20.0	108	105	16 weeks	Bao 2014
Infliximab 5 mg/kg	36.9 (26.8, 47.1)	49.8	12.8	201	78	12 weeks	ASSERT
Ixekizumab 80 mg Q4W	29.8 (16.2, 43.3)	48.1	18.4	81	87	16 weeks	COAST-V [c]
Secukinumab 150 mg (NL)	25.3 (12.1, 38.5)	36.1	10.8	72	74	16 weeks	MEASURE 2
Secukinumab 150 mg (L)	10.6 (-1.5, 22.6)	38.8	28.2	116	117	16 weeks	MEASURE 4
Secukinumab 150 mg (NL)	7.7 (-4.2, 19.6)	35.9	28.2	117	117	16 weeks	MEASURE 4

Key: L = loading dose; NL = no loading dose.
a. Results from the RAPID-axSpA study were taken from the subgroup of patients with AS. The full analysis set included both patients with AS and non-radiographic axial spondyloarthritis.
b. The sulfasalazine arm of the ASCEND study was treated as placebo in this analysis.
c. The COAST-V study included ixekizumab 80 mg Q2W and Q4W. Results from ixekizumab Q4W are shown here.
Source: Module 5.3.5.3 Contextualization of Efficacy Endpoints for Tofacitinib Versus Currently Approved Treatments for AS Figure 3.

Clinical studies in special populations

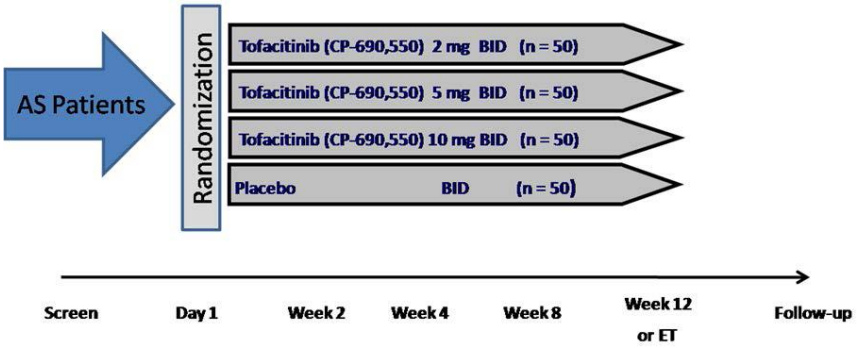
No data are available on special populations. No specific data on elderly are reported for axSA subjects. In the SmPC dose adjustments are included for renal and hepatic impairment based on initial submission.

Supportive studies

A3921119

This was Phase 2, multicentre, randomised, double-blind, placebo-controlled dose-ranging, parallel group efficacy and safety study designed to characterise the dose-response of tofacitinib in patients with active AS who had experienced an inadequate response to NSAIDs and were naïve to previous bDMARDs (Figure 21) for design schematic.

Figure 21. Study A3921119 Schematic of Study Design



Methods

Study participants

The clinical programme was designed to evaluate the efficacy of tofacitinib in adult patients with active AS who had experienced an inadequate clinical response or were intolerant to NSAID therapy. A diagnosis of AS was based on the Modified New York Criteria for AS (1984). Active disease was also defined as: BASDAI score of ≥4 and back pain score (BASDAI Question 2) of ≥4 despite treatment with NSAIDs at both screening and baseline. Patients met the definition of NSAID-IR if they had either an inadequate clinical response, intolerance to at least 2 different oral NSAIDs, or ongoing NSAID treatment but with active AS.

Patients continued their stable background AS therapy, which included NSAIDs including selective COX-2 inhibitors, MTX, sulfasalazine, and corticosteroids (≤10 mg/day of prednisone or equivalent). In Study A3921119, background therapies were to be stable for 4 weeks except NSAIDs (1 week) prior to the first dose of investigational product.

Selected key enrolment criteria for Study A3921119 are the same of the pivotal phase study with the exception of exclusion of subjects exposed to bDMARDs.

Treatments

A twice daily dosing regimen (3 doses of tofacitinib 2 mg, 5 mg, 10 mg, or placebo) was evaluated in the dose-ranging Phase 2 Study A3921119. During the 12-week treatment period, patients were randomised in a 1:1:1:1 ratio to receive 1 of the 4 blinded treatments. The assignment occurred according to a randomisation schedule and to which the patient, site personnel, and the Sponsor's personnel directly involved in the study conduct were blinded through the entire duration of the study.

The duration of participation for eligible patients was approximately 150 days. This included a screening period of approximately 28 days, a 12-week double-blind treatment period, and a 28-day follow-up period.

Of 445 subjects screened for entry into the study, 208 subjects were randomized in a 1:1:1:1 ratio to double-blind treatment; 52 subjects to each treatment group (tofacitinib 2 mg BID, tofacitinib 5 mg BID, tofacitinib 10 mg BID, and placebo).

The efficacy of Tofacitinib 5 mg BID dose was supported by the outcomes of the Phase 2 dose-ranging Study A3921119. The study design is considered appropriate and in line with the EMA guideline (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1*) recommendation for placebo controlled parallel group studies. Similar eligibility criteria were applied across the two key studies. Inclusion and exclusion criteria are

overall appropriate reflecting subjects with AS who have responded inadequately to conventional therapy. However, differently to Study A3921120, only patients naïve to previous bDMARDs were allowed to be included in Study A3921119, excluding patients bDMARDs experienced. Therefore, the phase 2 study could be of support of tofacitinib treatment only in a bDMARD naïve patient population. The activity of disease required for entry into this study was defined as for the pivotal on: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 and back pain score (BASDAI Question 2) of ≥4 despite treatment with NSAIDs (or intolerance to NSAIDs). Regarding the different doses, the MAH states that similar to the RA and psoriasis Phase 2 studies, where inclusion of doses <5 mg BID provided lower efficacy thereby allowing a complete characterization of the dose-response curve, a 2 mg BID dose was included in the study.

Objectives

1. To compare the efficacy of tofacitinib, in doses of 2 mg twice daily (BID), 5 mg BID, 10 mg BID versus placebo on the ASAS20 response rate at Week 12 in subjects with active AS that had an inadequate response to previous treatment.

2. To estimate the placebo-corrected dose-response for the ASAS20 at Week 12 in subjects with active AS that had an inadequate response to previous treatment.

3. To compare the safety of tofacitinib at all doses versus placebo in all study subjects.

Outcomes/endpoints

The primary efficacy endpoint was ASAS20 response rate at 12 weeks of treatment.

The secondary efficacy endpoints were:

- A validated endpoint such as Spondyloarthritis Research Consortium of Canada (SPARCC) MRI index of disease activity score and/or modified Berlin Ankylosing Spondylitis Spine Magnetic Resonance Imaging (ASspiMRI) Activity Score of the SI joints and spine at Week 12.
- ASAS20 response at all other time points (2,4 and 8 weeks).
- ASAS40 response at all time points (2,4,8 and 12 weeks).
- ASAS 5/6 response at all time points (2,4,8 and 12 weeks).
- ASAS partial remission criteria at all time points (2,4,8 and 12 weeks).
- Ankylosing Spondylitis Disease Activity Score (ASDAS) using C-Reactive Protein

  (ASDASCRP) at all time points (2,4,8 and 12 weeks).
- ASDAS clinically important improvement, ASDAS major improvement and ASDAS inactive disease at all time points (2,4,8 and 12 weeks).
- BASDAI at all time points (2,4,8 and 12 weeks).
- 50% improvement from Baseline in the BASDAI (BASDAI50) response at all time points (2,4,8 and 12 weeks).
- BASFI at all time points (2,4,8 and 12 weeks).
- BASMI at all time points (2,4,8 and 12 weeks).
- Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at all time points collected (4,8 and 12 weeks)

- Extra-articular involvement (specific medical history and peripheral articular involvement [as assessed by swollen joint count]) at all time points collected (2,4,8 and 12 weeks).

Other evaluations included QoL endpoints: Ankylosing Spondylitis Quality of Life (ASQoL), Short-Form-36 Health Survey (SF-36) Version 2, EuroQol Health State Profile – 5 Domains (EQ-5D), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Work Productivity and Activity Impairment (WPAI) Questionnaire: Spondyloarthritis, AS HealthCare Resource Utilization Questionnaire (AS-HCRU).

The efficacy of tofacitinib in active AS in phase 2 Study was evaluated using a core set of validated measures similar to those used in the pivotal Study and this is agreed. However, the primary endpoint (ASAS20) was assessed at week 12 instead of at week 16 as in Study A3921120 not allowing for a pooling of efficacy results. As reported in the above comment for Study A3921120, ASAS 20 is not the preferred primary endpoint according to EMA guideline (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1*) that recommends to use the more stringent endpoint ASAS40 as primary. However, due to the reasons explained above and considering this as a supportive study, ASAS20 is deemed an acceptable endpoint. Moreover, ASAS40 response is one of the secondary end-point together with other validated endpoints such as ASAS 5/6, ASAS partial remission, ASDAS (CRP), BASDAI improvement, BASDAI 50. It is also noted that a radiological endpoint is also included (SPARCC) and this is agreed according to EMA GL.

Eligible subjects were randomized in a 1:1:1:1 ratio to one of the 4 blinded treatments (tofacitinib 2 mg BID, tofacitinib 5 mg BID, tofacitinib 10 mg BID, or placebo BID as shown in Table 35). Tofacitinib was provided as 1 mg or 5 mg tablets with corresponding matching placebo. A total of 8 tablets per day encompassed the total daily dose taken by the subject:

Table 35. Treatment Allocation

Sequence	Treatment Description	Planned Number of Randomized Subjects
1	**Tofacitinib 2 mg BID** *Two 1 mg tablets and two 5 mg matching placebo tablets in AM and PM*	50
2	**Tofacitinib 5 mg BID** *One 5 mg tablet, one 5 mg matching placebo tablet and two 1 mg matching placebo tablets in AM and PM*	50
3	**Tofacitinib 10 mg BID** *Two 5 mg tablets and two 1 mg matching placebo tablets in AM and PM*	50
4	**Placebo BID** *Two 1 mg matching placebo tablets and two 5 mg matching placebo tablets in AM and PM*	50

Source: Final Protocol, Amendment 1, Section 16.1.1
Abbreviations: AM = ante meridiem, BID = twice daily, PM = post meridiem

Selection of Doses in the Study

The 5 and 10 mg BID doses were demonstrated to be efficacious in RA subjects and in subjects with psoriasis. Since 10 mg BID provided increased efficacy over 5 mg BID in RA and psoriasis while maintaining an acceptable safety profile, and doses >10 mg BID did not provide substantially improved efficacy, 10 mg BID was selected as the highest dose for the current study. Similar to the RA and psoriasis Phase 2 studies, where inclusion of doses <5 mg BID provided lower efficacy thereby allowing a complete characterization of the dose-response curve, a 2 mg BID dose was included in the study.

Rescue medications:

The maximum dose of acetaminophen/paracetamol was 2.6 g/day for no more than 10 consecutive days. The maximum dose of opioids was the maximum potency equivalent of 30 mg/day of orally-administered morphine.

Sample size

Sample size was assessed using clinical trial simulations in which a dose-response model (the 3-parameter maximal effect [Emax] model) determined the true percentage of ASAS20 responders at week 12. Simulations under several plausible truths were conducted assuming 50 subjects per treatment group to evaluate the operational characteristics of this same model when used for the analysis. If the true placebo-corrected ASAS20 response in the range of 1 to 10 mg BID was between 20 to 40%, then it was projected based on simulations that the estimated placebo-corrected effect for that dose ±10%, would capture the true placebo-corrected response at least 83% of the time. Under the same assumption about the true effect, it was projected that the estimated placebo-controlled effect ±5% would capture the true value at least approximately 50% of the time.

Emax model to the primary endpoint was used for the dose–response study A3921119. It is recognised to find the optimal dose and investigate the relationship between dose and efficacy relative to control.

Randomisation

A total of 208 patients were randomised in a 1:1:1:1 ratio to receive tofacitinib 2 mg BID, tofacitinib 5 mg BID, tofacitinib 10 mg BID, or placebo.

Blinding (masking)

The Study was conducted in a double-blind, placebo-controlled manner. The randomization scheme is considered adequate.

Statistical methods:

A 3-parameter Emax model to estimate the ASAS20 dose-response at Week 12, the primary efficacy endpoint, with missing response considered as non-response. As a supportive analysis, the normal approximation for estimating the difference in binomial proportions was used to compare each of the dose groups of tofacitinib to placebo at Week 12 with missing response considered as non-response. All analyses of the efficacy endpoints were based on the FAS. Evaluation of secondary efficacy endpoints was either by:

The normal approximation for the difference in binomial proportions (both testing and confidence interval) was applied to the following endpoints:

- ASAS20 response at all other time points.
- ASAS40 response at all time points.
- ASAS 5/6 response at all time points.
- ASAS partial remission criteria at all time points.
- ASDAS clinically important improvement, ASDAS major improvement and ASDAS inactive disease at all time points.
- BASDAI50 response at all time points.

Missing values due to dropout were set to non-responsive and mixed LOCF was used for missing data that may have existed in components of the above endpoints.

A repeated measures model was used to analyze change from Baseline for the endpoints listed below. The marginal repeated measure model included fixed effects of treatment group, visit, and treatment-group by visit interaction, and Baseline value. An unstructured variance covariance matrix was used. Pairwise comparisons of each tofacitinib dose to placebo (providing both 2-sided p-values and 95% confidence interval) at each post-Baseline time point was generated from contrast statements using this model.

- ASDASCRP at all time points.
- BASDAI at all time points.
- BASFI at all time points.
- BASMI (linear method) at all time points.
- MASES at all time points collected.
- Extra-articular involvement (specific medical history and peripheral articular involvement [as assessed by swollen joint count]) at all time points collected.
- Spinal mobility at all time points collected
- Total score on the FACIT-F at all time points.

An analysis of covariance (ANCOVA) model was used to analyze change from Baseline for the endpoints listed below. The ANCOVA model included a fixed effect for treatment group and Baseline value as a covariate. Pairwise comparisons of each tofacitinib dose to placebo (providing both 2-sided p-values and 95% confidence interval) were generated from contrast statements using this model.

- Total score on the ASQoL at Week 12.
- Summary components and domains of the SF-36 Version 2, Acute at Week 12.
- Domains and utility index from the EQ-5D at Week 12.
- WPAI Questionnaire: spondyloarthritis at Week 12.
- A validated endpoint such as SPARCC MRI index of disease activity score and/or modified Berlin ASspiMRI Activity Score of the SI joints and spine at Week 12.

The Early Termination visit value was used as the Week 12 value if the Week 12 value for a subject was missing.

The use of the Emax model as primary analysis to estimate the ASAS20 dose-response at Week 12, and the use of the normal approximation as supportive analysis for estimating the difference in binomial proportions to compare each of the dose groups of tofacitinib to placebo at Week 12 are acknowledged.

Participant flow

The duration of participation for eligible patients was approximately 150 days. This included a screening period of approximately 28 days, a 12-week double-blind treatment period, and a 28-day follow-up period. Table 36 summaries patient dispositions for Studies A3921119 up to week 12.

Of 445 subjects screened for entry into the study, 208 subjects were randomized in a 1:1:1:1 ratio to double-blind treatment; 52 subjects to each treatment group (tofacitinib 2 mg BID, tofacitinib 5 mg BID, tofacitinib 10 mg BID, and placebo).

Table 36. Patient Disposition - Studies A3921119 (up to Week 12)

	Number (%) of Patients			
	Tofacitinib 2 mg BID	**Tofacitinib 5 mg BID**	**Tofacitinib 10 mg BID**	**Placebo**
Study A3921119				
Randomised	52	52	52	52
Treated	52	52	52	51
Completed	51 (98.1)	51 (98.1)	47 (90.4)	47 (90.4)

Table 36. Patient Disposition - Studies A3921119 (up to Week 12)

	Number (%) of Patients			
	Tofacitinib 2 mg BID	**Tofacitinib 5 mg BID**	**Tofacitinib 10 mg BID**	**Placebo**
Discontinued	1 (1.9)	1 (1.9)	5 (9.6)	4 (7.7)
Discontinuations due to treatment related Adverse Event	0	1 (1.9)	1 (1.9)	2 (3.9)
Analysed for Efficacy				
Per-protocol analysis set	49 (94.2)	49 (94.2)	50 (96.2)	49 (94.2)
Full analysis set	52 (100.0)	52 (100.0)	52 (100.0)	51 (98.1)

Percentages for the 'Not treated' and 'Treated' rows are calculated using the number of patients assigned to treatment (randomised) as the denominator. Other percentages are calculated using the number of 'Treated' patients as the denominator.

Of the 208 randomised patients, 1 patient was randomised to placebo but did not receive study drug thus was excluded from analyses. There were 207 patients included in the FAS; all 207 patients in the FAS were analysed for AEs and 205 patients were analysed for laboratory data. Overall, 196 patients completed the study; approximately 98% of patients in the lower dose treatment groups (tofacitinib 2 mg and 5 mg BID) compared to approximately 90% in the tofacitinib 10 mg BID and placebo treatment groups.

Recruitment

Study A3921119

Study initiation date: 17 April 2013

Completion date: 18 March 2015

Conduct of the study: One amendment to the study A3921119 protocol was planned; the implemented changes seem do not impact study results, and no significant concern has been identified.

Baseline data

Patient baseline demographics and disease characteristics were similar across all treatment groups. The overall mean age was 41.6 years. The majority (82.7%) of patients in the study were White and 3.8% of patients were of Hispanic/Latino ethnicity. Patients were from the EU (61.8%), Asia (18.8%), North America (13.5%), and the ROW (5.8%). Patients were balanced across treatment groups in their corticosteroid (3.8% to 17.3%) and DMARD (34.6% to 55.8%) use at baseline. The mean (median) duration since diagnosis of AS for the 5 mg BID treatment group was 6.3 (3.5 [range: 0.0-24.4]) years and was similar across treatment groups.

Medical history

Table 37. Medical History Related to Primary Diagnosis – Safety Analysis Set

	Tofacitinib 2 mg BID			Tofacitinib 5 mg BID		
Number of subjects	**52**			**52**		
No significant history related to primary diagnosis	**32**			**34**		
	Yes n (%)	**No n (%)**	**Unknown n (%)**	**Yes n (%)**	**No n (%)**	**Unknown n (%)**
Eye disorders	13 (25.0)	12 (23.1)	0	12 (23.1)	14 (26.9)	0
Uveitis	13 (25.0)	12 (23.1)	0	12 (23.1)	14 (26.9)	0
Gastrointestinal disorders	0	25 (48.1)	0	3 (5.8)	23 (44.2)	0
Inflammatory bowel disease	0	25 (48.1)	0	3 (5.8)	23 (44.2)	0
Skin and subcutaneous tissue disorders	1 (1.9)	24 (46.2)	0	2 (3.8)	24 (46.2)	0
Psoriasis	1 (1.9)	24 (46.2)	0	2 (3.8)	24 (46.2)	0
Uncoded	11 (21.2)	14 (26.9)	0	6 (11.5)	20 (38.5)	0
Peripheral articular involvement	11 (21.2)	14 (26.9)	0	6 (11.5)	20 (38.5)	0
	Tofacitinib 10 mg BID			**Placebo**		
Number of subjects	**52**			**51**		
No significant history related to primary diagnosis	**36**			**36**		
	Yes n (%)	**No n (%)**	**Unknown n (%)**	**Yes n (%)**	**No n (%)**	**Unknown n (%)**
Eye disorders	6 (11.5)	14 (26.9)	0	7 (13.7)	14 (27.5)	0
Uveitis	6 (11.5)	14 (26.9)	0	7 (13.7)	14 (27.5)	0
Gastrointestinal disorders	0	20 (38.5)	0	1 (2.0)	20 (39.2)	0
Inflammatory bowel disease	0	20 (38.5)	0	1 (2.0)	20 (39.2)	0
Skin and subcutaneous tissue disorders	1 (1.9)	19 (36.5)	0	2 (3.9)	19 (37.3)	0
Psoriasis	1 (1.9)	19 (36.5)	0	2 (3.9)	19 (37.3)	0
Uncoded	9 (17.3)	10 (19.2)	1 (1.9)	6 (11.8)	15 (29.4)	0
Peripheral articular involvement	9 (17.3)	10 (19.2)	1 (1.9)	6 (11.8)	15 (29.4)	0

Source: Table 14.1.3.2
Subjects are counted only once for specific disease/syndrome in the table body.
MedDRA (v18.0) coding dictionary applied.
Abbreviations: BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities, n = number of subjects with data.

Few patients (7 treated and 4 placebo) discontinued the Study A3921119, of which the majority in tofacitinib 10 mg BID arm, and 94-96% of subjects were included in the Per-protocol analysis set.

Overall, demographic characteristics were quite balanced across groups and similar to those of phase 3 study. The majority of subjects in all treatment groups were white males HLA-B27 positive; the proportion of subjects positive for HLA-B27 was greatest in the tofacitinib 10 mg BID treatment group. The baseline disease characteristics were compatible with the diagnosis of active AS disease indicated by a median value of 6.2 in tofa 5 mg BID and 6.6 in placebo group for BASDAI and of 3.7 and 3.5, respectively in ASDAS (CRP). A slightly higher median baseline hsPCR value was observed in tofa 5 mg BID group (8.74) compared to placebo group (6.91). A higher number of patients in tofa 5 mg BID group compared to placebo group had a history of IBD, psoriasis and peripheral articular involvement.

Results

Results of the primary and secondary efficacy endpoints at Week 12 were as follows:

- The primary analysis of the ASAS20 response rate at Week 12 was conducted on the FAS using an Emax model with MR=NR (as shown in Table 38). The estimated response rates were 40.1% for placebo and 56.0%, 63.0%, 67.4% for tofacitinib 2, 5, and 10 mg BID, respectively, demonstrating that the response rates for tofacitinib were higher than for placebo.

Table 38. Analysis of ASAS20 Response Rate at Week 12 Using Emax Model, Comparison to Placebo – Full Analysis Set

			Difference from Placebo (Active – Placebo)						
				95% CI		60% CI		50% CI	
Treatment	N	Estimated Response Rate	Estimate	Lower	Upper	Lower	Upper	Lower	Upper
Tofacitinib 2 mg BID	52	56.0	15.8	5.0	30.3	10.2	21.2	11.1	19.9
Tofacitinib 5 mg BID	52	63.0	22.9	8.4	37.7	16.5	29.3	17.8	28.0
Tofacitinib 10 mg BID	52	67.4	27.3	10.7	43.4	20.3	34.4	21.8	33.0
Placebo	51	40.1							

Source: Table 14.2.1.1.1

Missing values due to a subject dropping from the study for any reason (eg, lack of efficacy or adverse event) are handled by setting the ASAS20 value to non-responsive. If components of the ASAS20 are missing at Week 12, LOCF mixed components are applied.

ASAS20 response is defined as ≥20% and ≥1 unit in at least 3 domains on a scale of 0-10 and no worsening of ≥20% and ≥1 unit in the remaining domain. The 4 ASAS domains are the 'Patient Global Assessment of Disease' (from the CRF labeled: 'NUMERICAL RATING SCALE - Patient Global Assessment of AS'), Spinal Pain (from the 'NUMERICAL RATING SCALE - Total Back Pain'), Function (average of the 10 questions from the BASFI CRF) and Inflammation (from the BASDAI ie. the average of question 5 and 6 from the BASDAI CRF).

Abbreviations: AS = ankylosing spondylitis, ASAS = Assessment of SpondyloArthritis international Society, ASAS20 = ≥20% increase from Baseline and ≥1 unit increase in at least 3 domains on a scale of 0 to 10, and no worsening of ≥20% and ≥1 unit in the remaining domain, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BID = twice a day, CI = credible interval, CRF = Case Report Form, LOCF = last observation carried forward, N = number of subjects with available data or data imputed using the non-responder/LOCF method.

The ASAS20 response rate at Week 12 with missing response as non-response was 41.2% for placebo and 51.9%, 80.8%, 55.8% for tofacitinib 2 mg, 5 mg, and 10 mg BID, respectively (as shown in Table 39); the difference in response rates by normal approximation method between tofacitinib 5 mg BID and placebo was statistically significant (p<0.001, without multiple comparison adjustment).

Table 39. Normal Approximation to ASAS20 Response at Week 12, Comparison to Placebo – Full Analysis Set NRL/LOCF

					Difference from Placebo[a] (Active – Placebo)				
							95% CI		
Treatment	N	n	Response Rate (%)	SE	Diff	SE	Lower	Upper	p-Value
Tofacitinib 2 mg BID	52	27	51.92	6.93	10.75	9.77	-8.41	29.90	0.271
Tofacitinib 5 mg BID	52	42	80.77	5.47	39.59	8.80	22.35	56.83	<.001
Tofacitinib 10 mg BID	52	29	55.77	6.89	14.59	9.74	-4.50	33.69	0.134
Placebo	51	21	41.18	6.89					

Source: Table 14.2.1.2.1

ASAS20 response is defined as ≥20% and ≥1 unit in at least 3 domains on a scale of 0-10 and no worsening of ≥20% and ≥1 unit in the remaining domain. The 4 ASAS domains are the 'Patient Global Assessment of Disease' (from the CRF labeled: 'NUMERICAL RATING SCALE - Patient Global Assessment of AS'), Spinal Pain (from the 'NUMERICAL RATING SCALE - Total Back Pain'), Function (average of the 10 questions from the BASFI CRF) and Inflammation (from the BASDAI ie. the average of question 5 and 6 from the BASDAI CRF).

Abbreviations: ASAS = Assessment of SpondyloArthritis international Society, ASAS20 = ≥20% increase from Baseline and ≥1 unit increase in at least 3 domains on a scale of 0 to 10, and no worsening of ≥20% and ≥1 unit in the remaining domain, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BID = twice daily, CI = confidence interval, CRF = Case Report Form, Diff = difference, LOCF = last observation carried forward, N = number of subjects with available data or data imputed using the non-responder/LOCF method; n = number of responders, NRI = non-responder imputation, SE = standard error.

a. Normal approximation.

The ASAS20 response rate in tofacitinib 5 mg BID was higher than placebo at Week 4 (55.8% versus 33.3%; p≤0.05 without multiple comparison adjustment).

- At Week 12, there was a statistically significant higher ASAS40 response rate for tofacitinib 5 mg BID compared with placebo: 21.6% for placebo and 42.3% (p=0.020), 46.2% (p=0.006), and 38.5% (p=0.057) for tofacitinib 2, 5, and 10 mg BID, respectively (without multiple comparison adjustment).

- At Week 12, all ASAS family components showed greater mean reductions from baseline for tofacitinib 5 mg BID versus placebo (2-sided 95% CI for the difference between tofacitinib 5 mg BID and placebo excluded 0).

- At Week 12, there was a statistically significant greater improvement from Baseline for the LS mean SPARCC MRI index of disease activity score of the SI joints and the spine and for the LS mean modified Berlin ASspiMRI Activity Score compared to placebo for the tofacitinib 5 mg BID (Table 40).

Table 40. Selected Efficacy Endpoints at Week 12 (FAS) – Study A3921119

	Tofacitinib 5 mg BID (N = 52)	**Placebo (N = 51)**
Primary efficacy endpoint		
ASAS20 response rate (Emax model) (%) [a]	63.0	40.1
Normal approximation to ASAS20 response rate, n (%) [N1] [a]	42 (80.8)** [52]	21 (41.2) [51]
Secondary efficacy endpoints		
Normal approximation to ASAS40 response rate, n (%) [N1] [a]	24 (46.2)* [52]	11 (21.6) [51]
ΔASDAS(CRP), LSM (SE) [N1]	-1.41 (0.119)** [50]	-0.68 (0.123) [45]
ΔhsCRP (mg/L), LSM (SE) [N1]	-7.00 (1.174)** [50]	-1.00 (1.221) [45]
ΔASQoL, LSM (SE) [N1] [b]	-4.79 (0.615)* [52]	-2.53 (0.627) [51]
ΔSF-36v2, LSM (SE) [N1][b]		
PCS	6.49 (0.914)** [52]	2.69 (0.932) [51]
MCS	4.15 (1.294) [52]	2.41 (1.318) [51]
ΔBASMI Score (Linear Method), LSM (SE) [N1] [c]	-0.39 (0.108) [50]	-0.15 (0.111) [46]
ΔFACIT-F Total Score, LSM (SE) [N1] [c]	7.03 (1.145)* [50]	3.08 (1.178) [46]
□PGA, mean (SD) [N1]	-2.8 (2.18) [50]	-1.7 (2.54) [46]
ΔTotal Back Pain, mean (SD) [N1]	-3.2 (2.19) [49]	-2.0 (2.40) [46]
ΔInflammation, mean (SD) [N1]	-3.17 (2.147) [50]	-1.78 (2.260) [46]
ΔBASFI, LSM (SE) [N1] [c]	-2.39 (0.260)* [50]	-1.43 (0.266) [46]
ASAS 5/6, n (%) [N1] [a]	36 (69.23)** [52]	12 (23.53) [51]
ASAS Partial Remission, n (%) [N1] [a]	10 (19.23) [52]	6 (11.76) [51]
ΔSpinal mobility (Chest expansion, cm), LSM (SE) [N1] [c]	0.49 (0.187) [50]	0.31 (0.193) [46]
BASDAI, LSM (SE) [N1] [c]	-2.88 (0.276)* [50]	-1.85 (0.283) [46]
ASDAS Clinically Important Improvement, n (%) [N1] [a,d]	33 (63.46)** [52]	14 (27.45) [51]

Table 40. Selected Efficacy Endpoints at Week 12 (FAS) – Study A3921119

	Tofacitinib 5 mg BID (N = 52)	Placebo (N = 51)
ASDAS Major Improvement, n (%) [N1] [a,e]	12 (23.08) [52]	6 (11.76) [51]
ASDAS Inactive Disease, n (%) [N1] [a,f]	7 (13.46) [52]	4 (7.84) [51]
ΔMASES, LSM (SE) [N1] [c]	-1.37 (0.259)* [50]	-0.34 (0.265) [46]
ΔSwollen Joint Count, LSM (SE) [N1] [c]	-0.79 (0.362) [50]	-0.99 (0.373) [46]
ΔEuroQoL EQ-5D-3L, LSM (SE) [N1] [b]		
Mobility	-0.29 (0.063) [52]	-0.11 (0.064) [51]
Self-care	-0.14 (0.055) [52]	-0.19 (0.056) [51]
Usual activities	-0.29 (0.071) [52]	-0.15 (0.073) [51]
Pain/discomfort	-0.30 (0.067) [52]	-0.22 (0.068) [51]
Anxiety/depression	-0.17 (0.070) [52]	-0.03 (0.071) [51]
ΔWPAI, LSM (SE) [N1] [b]		
Percent work time missed due to health problem	-5.19 (1.488) [35]	-1.40 (1.642) [29]
Percent impairment while working due to health problem	-20.91 (3.394)* [36]	-6.09 (3.780) [29]
Percent overall work impairment due to health problem	-21.67 (3.570)* [35]	-5.39 (3.916) [29]
Percent inactivity due to health problem	-19.46 (3.131)** [50]	-11.22 (3.270) [46]
ΔSPARCC MRI spine, LSM (SE) [N1] [b,g]	-5.51 (1.063)** [52]	-0.09 (1.085) [51]
ΔSPARCC MRI SI Joint, LSM (SE) [N1] [b]	-3.15 (0.788)* [52]	-0.81 (0.806) [51]
ΔASspiMRI, LSM (SE) [N1] [b]	-2.22 (0.364)** [52]	-0.41 (0.372) [51]

Nominal *p≤0.05; **p<0.001 tofacitinib 5 mg BID versus placebo at Week 12
N1 = number of patients evaluable at Week 12
a. NRI/LOCF Mixed Components
b. ANCOVA model includes fixed effects for treatment group and baseline value as a covariate with LOCF for imputing missing values.
c. The fixed effects of treatment group, visit, and treatment-group by-visit interaction and baseline value were included, an unstructured covariance matrix was used.
d. ASDAS clinically important improvement is defined as change (decrease) from baseline of ≥1.1 units.
e. ASDAS major improvement is defined as change (decrease) from baseline of ≥2.0 units.
f. ASDAS inactive disease is defined as ASDAS <1.3 units

Table 40. Selected Efficacy Endpoints at Week 12 (FAS) – Study A3921119

	Tofacitinib 5 mg BID (N = 52)	Placebo (N = 51)

g. Index of disease activity score of the spine at Week 12

Figure 22. Line Graph of ASAS20 Response Rate (+/- SE) (Normal Approximation) by Visit Up to Week 12 – FAS, NRI/LOCF Mixed Components - Study A3921119

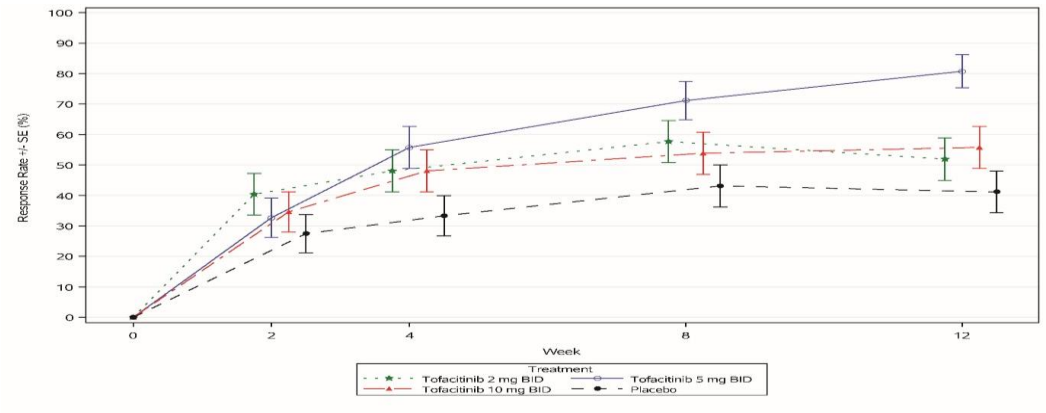
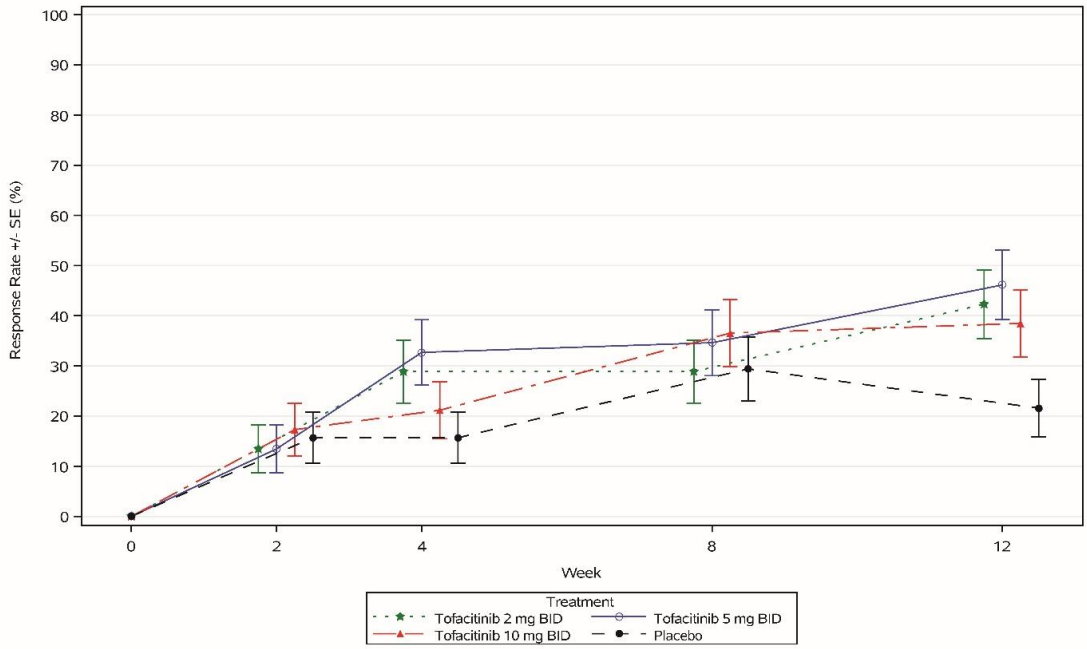


Figure 23. Line Graph of ASAS40 Response Rate (+/- SE) (Normal Approximation) by Visit Up to Week 12 – FAS, NRI/LOCF Mixed Components - Study A3921119



In the Phase 2 dose-ranging Study A3921119, at Week 12 patients with active AS receiving tofacitinib 2 mg, 5 mg, or 10 mg IR BID had a respective estimated ASAS20 response rate of 56.0%, 63.0%, or 67.4% compared to an estimated placebo response rate of 40.1% (primary analysis using an Emax model). Therefore, only the tofacitinib 10 mg BID treatment group met pre-specified statistical decision rules for the primary endpoint of the ASAS20, with an estimated difference from placebo of 27.3%, a 20.3% difference for the lower bound of the 2-sided 60% credible interval, and a 33.0% difference for the upper bound of the 2-sided 50% credible interval. Results from supportive analysis using the normal

approximation method showed the ASAS20 response rate of 51.9%, 80.8%, 55.8% for tofacitinib 2 mg, 5 mg, and 10 mg BID, respectively, and 41.2% for placebo. Only the difference between tofacitinib 5 mg BID and placebo was statistically significant ($p<0.001$). Across most of the secondary endpoint pertaining to disease activity and physical functions, health related outcomes and radiological progression, tofacitinib 5 mg showed to be more effective than placebo, supporting results from phase 3 pivotal study. Regarding spinal mobility, which is an important efficacy parameter to support ASAS as primary endpoint (see also comment above on pivotal study), a major change in Linear BASMI Score at week 12 was observed in tofacitinib 5 mg BID group (-0.39) compared to placebo group (-0.15) which however did not reach the statistical significance, as well as the other spinal mobility score used to evaluate chest expansion (0.49 vs 0.31). Moreover, for other more stringent endpoint at week 12 such as ASAS partial remission, ASDAS major improvement and ASDAS inactive disease for tofacitinib 5 mg BID there were no statistically significant differences from placebo, although a slightly greater response rate was observed.

Efficacy of Tofacitinib PR 11 mg QD in RA

The tofacitinib PR formulation was evaluated in the RA clinical programme. Brief summaries of the efficacy results are reported below.

Study A3921215 was a completed Phase 3 Japan-specific study comparing head-to-head the tofacitinib tablet formulations of PR (11 mg QD) to IR (5 mg BID). Although, this study did not meet the non-inferiority margin based on the stringent criteria (0.6 for the treatment difference of tofacitinib PR 11 mg QD versus IR 5 mg BID) requested by the Japanese Pharmaceutical and Medical Devices Agency, the point estimate of the difference in efficacy between the PR and IR formulations, based on the primary endpoint of DAS28, was within the pre-specified margin. While the data from this study are not sufficient to conclude statistical similarity, they also do not allow conclusion of a clinically relevant difference between the formulations. The results from this study support the following:

- Both IR and PR formulations have meaningful efficacy consistent with the similarity in PK parameters between the formulations and previously established E-R relationships in patients with RA.
- The observed PR efficacy results were well aligned with the model predicted dose-response profile from Phase 2 studies with the IR formulation in Japanese patients who have RA. Comparable and clinically meaningful responses at Week 12 were observed for both treatment arms. Whilst there were increased responses for some endpoints for IR versus PR, these differences were not clinically relevant when considering an EU population. As noted in the RA PR CHMP assessment report (EMA/H/C/004214/X/0012 CHMP Assessment Report Section 2.5.3), it is possible that efficacy responses (JAK1 inhibition) are also increased in Japanese patients. Based on the limited comparison of baseline characteristics with EU patients from an international collaboration of RA registers, there is evidence that the A3921215 study population is not that generalisable to an EU RA population. In addition, the double-dummy design meant that patients on PR who were non-adherent were more likely to miss their entire daily dose than they would be in the real world (when they are not taking a dummy tablet). Therefore, there is uncertainty when extrapolating the observed treatment differences to an un-blinded EU population.

Study A3921192 was a global Phase 3b/4 study with a substantial number (N=355) of European patients that provided a global perspective on the efficacy and safety of PR formulation in patients with moderate to severe RA who were inadequate responders to MTX. This was a MTX withdraw study which included an open label run-in phase with all patients (N=694) treated with PR 11 mg QD + MTX; and a double-blind phase during which patients that achieved LDA (low disease activity) were randomised (N=533) to

either continue MTX and tofacitinib PR 11 mg QD or withdraw MTX and receive MTX placebo and tofacitinib 11 mg PR QD. The efficacy responses from both the open-label phase, and those from the double-blind phase, were consistent with the 5 mg IR BID data from previous comparable studies conducted with the IR formulation. The final data for Study A3921192 and the final CSR A3921192 were submitted during the RA PR procedure.

Clinical Real-World Data for Patients with RA

Corrona Effectiveness Report on Real World Data from US Corrona RA Registry

The US Corrona RA Registry provided tofacitinib PR data in the real world setting to supplement the clinical findings in the PR RA EU procedure. The US Corrona RA Registry comparative effectiveness study (A3921359) provided robust evidence from propensity-score based analyses, that in a real-world clinical population treated with tofacitinib, which included relatively more patients in a population considered more difficult to treat (TNFi experienced) than in RCTs, the PR and IR formulations behaved similarly with respect to effectiveness. The US Corrona RA Registry Study is now complete. The final analysis did not include additional efficacy analyses to compare PR to IR formulations because the number of patients did not substantially increase since the analysis for the previous submission.

Observational Adherence Study A3921349

Study A3921349 was an observational adherence and effectiveness study conducted in an RA patient cohort within a US claims database that demonstrated greater patient adherence to tofacitinib 11 mg PR QD than patients initiating tofacitinib 5 mg IR BID, as well as comparable or higher effectiveness between 11 mg PR QD than 5 mg IR BID. These data were provided during the PR RA procedure

Bridging Efficacy From Tofacitinib IR Formulation to PR Formulation for AS

Given the similarity of efficacy between the IR and PR formulations in RA, the demonstrated efficacy of the IR formulation in patients with AS, the similarity of PK parameters (equivalent AUC and Cmax, and slightly lower Cmin [29%]) between the IR and PR formulations, the Applicant believes that E-R analyses of efficacy data in AS patients that demonstrate the relevance of AUC for efficacy would provide an adequate basis for bridging IR to PR.

Therefore, the bridging of efficacy from tofacitinib IR 5 mg BID to tofacitinib PR 11 mg QD in AS patients is based upon E-R analyses of data from the 2 AS studies with the tofacitinib IR formulation supplemented by i) the 7 clinical pharmacology and biopharmaceutic studies previously provided as a part of the approved tofacitinib RA PR Application, ii) the demonstrated E-R relationships in RA patients to bridge clinical efficacy data from the IR to the PR formulation and iii) the nonclinical E-R relationships previously demonstrated using the murine Collagen-Induced Arthritis (mCIA) inflammation model.

Briefly, as also described in the clinical pharmacology section, the application and subsequent approval for the use of tofacitinib PR 11 mg QD in RA patients, was supported by the following clinical pharmacology and E-R evidence:

- Clinical pharmacology and biopharmaceutic studies in healthy patients demonstrated equivalent AUC and Cmax for the 11 mg PR formulation administered QD compared to the 5 mg IR formulation administered BID.

- E-R relationships from the tofacitinib IR RA Phase 2 studies, the contextualisation of efficacy in RA clinical trials using the PR formulation (A3921215 and A3921192) to the predicted E-R relationships based on the tofacitinib IR Phase 2 studies as well as nonclinical E-R modelling using mCIA data, also supported the conclusion of consistent efficacy between the 11 mg PR QD and 5 mg IR BID.

Evaluations of the relationship between clinical efficacy and tofacitinib exposure (PK) from the 2 AS studies, A3921119 and A3921120, demonstrated that, as previously shown in RA and PsA patients, measures reflective of overall exposure (i.e., Cavg or AUC) are the exposure metrics most closely associated with efficacy. Evidence includes:

- A delay (or time lag) in the attainment of steady-state clinical response in AS (just as the delay previously demonstrated for RA) relative to PK steady state.

- Characterisation of the relationship between tofacitinib exposure and clinical efficacy in adult patients with active AS using a Cavg-based E-R model.

- A similar prediction of efficacy using Cavg, Cmin, or Cmax as the exposure metric in the E-R model, indicating that a measure of overall exposure (such as Cavg) can adequately describe the observed efficacy responses, and metrics such as Cmin and Cmax (plasma concentrations at discrete time points) do not provide greater predictive value compared to Cavg.

The E-R evidence supporting the bridging of efficacy of the IR formulation (5 mg BID) to the PR formulation (11 mg QD) in patients with AS, is further described below.

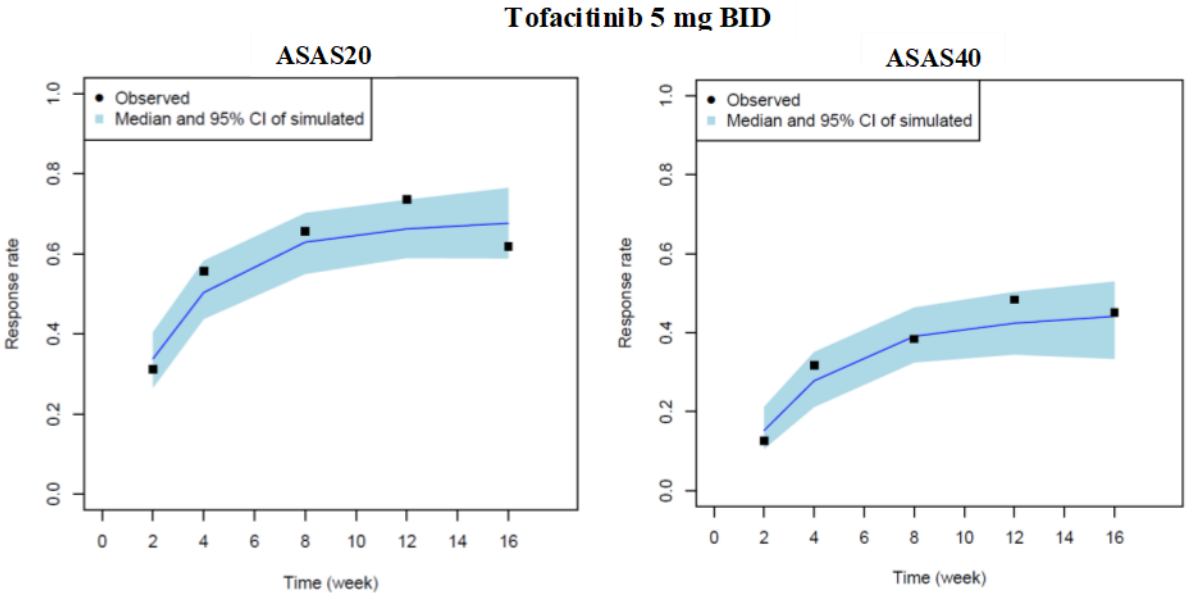
E-R of Efficacy in AS Patients using Cavg as the Relevant Parameter

As cytokine signalling promotes disease through the recruitment and activation of effector cells at sites of pathologic inflammation, the pharmacological effect of tofacitinib on clinical endpoints resulting from inhibition of cytokine signalling is indirect in all diseases where efficacy has been shown. Therefore, it is expected that clinical endpoints in these diseases, including AS, would be dependent on the overall average tofacitinib exposure over time, as measured by AUC or Cavg (where Cavg = AUC/dosing interval), and would not be significantly influenced by short-term fluctuations in plasma concentrations within the dosing interval. This was observed in RA and was supported by the E-R analyses provided in that population. This hypothesis is also supported in AS, as demonstrated by the E-R evidence using clinical data from the IR AS development programme as detailed below.

Characterisation of Delay in Time Course of Efficacy Response in AS Patients

A longitudinal E-R analysis that evaluated the relationship between ASAS20 and ASAS40 response rates and tofacitinib exposure (Cavg) in AS patients after administration of tofacitinib IR doses of 2 mg, 5 mg or 10 mg BID using pooled data across 2 studies, A3921119 and A3921120, demonstrated a similar delay or time-lag in the attainment of steady-state clinical response as previously demonstrated for RA, compared to the attainment of PK steady state (24-48 hours)

Figure 24. Longitudinal Model-Predicted ASAS20 and ASAS40 Responses in bDMARD-naive AS Patients Pooled Across Studies A3921119 and A3921120



Source: Module 2.7.2, Figure 1.

Black solid squares correspond to observed ASAS20 or ASAS40 response rates, respectively. Blue line and shaded area represent median and 95% CI of estimated ASAS20 or ASAS40 response rates, respectively.

The time of onset parameter from the longitudinal model was estimated to be 1.18 weeks demonstrating that following an early onset of efficacy by Week 2, the drug effect continues to increase up to Week 8. Placebo-corrected estimates of ASAS20 response rates after tofacitinib 5 mg IR BID were 28%, 31%, and 32%, at Week 4, 6, and 8, respectively, in AS patients who were bDMARD-naive, indicating that efficacy continued to increase beyond Week 4 and approached steady state (plateau) after Week 8. In the applicant's view this delay in the attainment of efficacy (PD) steady state, compared to PK steady state, indicates that within-day fluctuations in the PK profile of tofacitinib and differences in the plasma concentration-time course between 5 mg IR BID and 11 mg PR QD are unlikely to confer differential effectiveness in AS. These data are consistent with the estimated onset half-life for clinical responses in RA and in PsA. The longitudinal E-R relationship in AS supports the conclusion that Cavg is the relevant parameter for efficacy and that the 29% lower Cmin for the PR formulation is not relevant to efficacy in AS.

Assessment of the E-R of Efficacy Using Different PK Parameters in AS Patients

The predictive abilities of different tofacitinib exposure metrics were previously evaluated using data from RA patients. These evaluations identified Cavg as the most relevant PK parameter in the characterisation of E-R relationships of clinical response despite the high correlation among Cavg, Cmin, and Cmax. Furthermore, it was seen that Cmin did not provide additive predictive value over and above that of Cavg.

Based on this prior knowledge from the RA programme, a longitudinal ordered categorical E-R model was used to characterise the relationship between ASAS20 and ASAS40 responses in AS patients and tofacitinib exposures, using Cavg estimates as the predictor variable. Model-predicted estimates of ASAS20 and ASAS40 were 67% and 44%, respectively after tofacitinib 5 mg BID in bDMARD-naive AS patients at Week 16. The predicted placebo-corrected estimates were 32% and 28%, respectively.

Additionally, in order to compare exposure metrics, E-R models using Cavg, Cmin, or Cmax as the predictor (univariate analysis) were assessed within the AS E-R dataset. Although this assessment did not show differences in model diagnostics that would identify any 1 exposure parameter (Cavg, Cmin, or Cmax) as more relevant than another for clinical efficacy due to the high correlation between the PK parameters (i.e., correlation coefficient = 0.85 between Cavg and Cmin), in applicant's view the results suggest that a measure of overall exposure (such as Cavg) can adequately describe the observed efficacy responses, and metrics such as Cmin and Cmax (plasma concentrations at discrete time points) do not provide greater predictive value compared to Cavg in AS. This is consistent with the indirect mechanism of action of tofacitinib as well as the demonstrated lag between the time to attain steady-state clinical response (PD) versus PK.

Nonclinical Dose Fractionation Study

The non-clinical mCIA experiment which had previously demonstrated the superiority of Cavg over other PK parameters in predicting anti-inflammatory effect, is considered applicable to AS, as it is to RA in applicant's view. The dose-fractionation technique employed in this experiment was successfully used in other therapeutic areas to delineate the relative effect of various PK parameters on response. Results from this model could be informative of the E-R relationship in AS patients, given some level of similarity of disease pathogenesis and mechanism of action of tofacitinib between AS and RA.

Summary of Efficacy Bridging

In conclusion, given that the efficacy of tofacitinib IR in AS has been demonstrated, the bridging of efficacy from tofacitinib IR (5 mg BID) to the PR formulation (11 mg QD) in AS patients, is supported in applicant's view by the following totality of E-R evidence:

- Previously provided results from Phase 1 studies that have demonstrated similarity of PK parameters between 11 mg PR QD and 5 mg IR BID (equivalent AUC and Cmax and slightly lower Cmin).

- Previously provided E-R analyses in RA have demonstrated that a metric of overall exposure (Cavg or AUC) is the relevant PK parameter to predict efficacy of tofacitinib.

- E-R analyses using efficacy data for the IR formulation in AS patients (ASAS20 and ASAS40 response rates) demonstrated that measurements reflective of Cavg are the exposure metrics most closely associated with efficacy.

- The time delay in the attainment of tofacitinib clinical response steady state versus PK steady state are consistent across multiple JAK-mediated inflammatory disorders including RA, PsA, and in AS supporting the conclusion that a measure of overall exposure (eg, AUC or Cavg) is the relevant parameter for efficacy, regardless of indication.

2.4.3. Discussion on clinical efficacy

No comparative clinical efficacy data with tofacitinib 11 mg PR formulation in SA patients have been provided within this application in order to demonstrate that the new modified release formulation is as effective as the existing IR formulation. However, given that the efficacy of tofacitinib IR formulation (5 mg BID) in AS has been demonstrated within the previous application (II/35), the MAH has proposed a bridging of the efficacy of tofacitinib IR formulation (5 mg BID) in AS to the PR formulation.

The efficacy of IR 5 mg in AS bid has been demonstrated based on two studies (one phase 3 and one phase 2 study), as reported below. Similarly, the tofacitinib 11 mg PR QD formulation was assessed during the RA clinical programme and approved on the basis of the studies reported below.

Design and conduct of clinical studies

Tofacitinib IR 5 mg BID in AS

In support of tofacitinib IR 5 mg BID in the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy, the MAH provided: i) supportive data from Study A3921119 a phase 2, multicenter, randomised, double-blind, placebo-controlled dose ranging, parallel group efficacy and safety study designed to characterize the dose response of tofacitinib 2 mg BID, 5 mg BID and 10 mg BID in patients with active AS who had experienced an inadequate response to NSAIDs and were naïve to previous bDMARDs; dose of 5mg BID was selected; ii) confirmatory evidence from one pivotal study A3921120, a phase 3, randomized, double-blind, placebo-controlled, parallel group comparing tofacitinib 5mg dosed twice daily to placebo in subjects with active AS, who had experienced an inadequate response to NSAIDs (NSAID-IR) and were additionally either naïve to previous bDMARDs, or TNFi-IR or experienced to previous bDMARDs but without inadequate response (bDMARD Use [Non-IR]). The study design included a 16-week double-blind treatment period, a 32-week open-label treatment period (all subjects were assigned to open-label tofacitinib 5 mg BID to Week 48) and a 28-day follow-up period (duration of participation for eligible subjects was approximately 56 weeks).
The design of the pivotal study could be acceptable, however since tofacitinib belongs to a new therapeutic class for the AS indication and the study includes biological naïve patients a three-arm trial (including an accepted active comparator) would have been recommended as per the EMA *guideline on the Clinical Investigation of Medicinal products for the treatment of Axial Spondyloarthritis (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1*)*, particularly for assessing a relative B/R balance. However, the MAH has performed a meta-analysis of approved treatments and also included the results of the tofacitinib trials (dose-finding and pivotal study) as supportive data.
The duration of the maintenance period is in line with the guideline although a longer OL period would have been recommended for assessing structural changes. Dose reduction/changing dose interval in ankylosing spondylitis (AS) patients after resolution of inflammation following tofacitinib treatment has not been evaluated and there are no data supporting changing dose interval, which has been acceptable.
The study included subjects with active AS defined as: Modified New York Criteria for Ankylosing Spondylitis (1984), BASDAI score of ≥4 and back pain score (BASDAI Question 2) of ≥4 at both screening and baseline and that have had an inadequate response to at least 2 different NSAIDs. Additionally, bDMARD naïve, TNFi-IR, or bDMARD (non-IR) exposed were enrolled in this study.
Overall inclusion and exclusion criteria are adequate for selecting an active AS population and also for taking into account the safety profile of the drug.

The proportion of bDMARD-naïve and TNFi-IR or bDMARD use (non-IR i.e., discontinued the bDMARD due to other reasons than lack of efficacy or intolerance) was of approximately 80%/20%. Randomisation was stratified by prior treatment history: (1) bDMARD-naive and (2) TNFi-IR or bDMARD use (non-IR).
From the Clinical Overview and from what can be derived from clinicaltrials.gov, it appears that no studies with tofacitinib in patients with non-radiographic axial spondyloarthritis are being performed. Upon request the MAH specified that at present there are no plans to conduct tofacitinib studies for patients with non-radiographic axial spondyloarthritis and therefore will not be applying for this sub-indication/therapeutic claim. Moreover, criteria for defining previous or concomitant allowed, or prohibited therapies and stable doses are considered acceptable. The MAH specified the criteria for using rescue therapy in both studies. The agents allowed (acetaminophen/paracetamol, opioid agents) were

used primarily to relieve pain conditions and it seems to be unlikely that they could have affected the clinical course or the outcome of the disease, also considering that subjects were not dosed with rescue medication during the 24 hours prior to a study visit and that a small number of subjects used rescue therapy.
The study evaluates 1 primary endpoint, 1 key secondary endpoint, and other 20 secondary endpoints; moreover, the statistical analysis includes 3 estimands for binary endpoint, and 2 estimands for continuous secondary endpoints. This choice is considered suboptimal. A statistical planning more focussed on the relevant estimations by using more robust approaches would have been preferable.
The primary endpoint of the study was ASAS20 response at week 16. This is not in line with the current *Guideline on the Clinical Investigation of Medicinal products for the treatment of Axial Spondyloarthritis (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1*)* stating that the ASAS 40 response is preferred primary endpoint for biological medicinal products or products from a new therapeutic class, as a higher magnitude of the clinical response are expected. It is disappointing that the MAH did not seek advice to EMA on this choice nor considered a separate statistical analysis plans (SAPs), each using the endpoint preferred by the approving regulatory agency. ASAS40 was therefore defined as key secondary endpoint.

The use of the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata (bDMARD-naïve, TNFi-IR or bDMARD use) for the analysis of the primary efficacy endpoint (ASAS20) is acknowledged.

Numerous secondary endpoints have been proposed. However, the established hierarchy and the absence of some important endpoint assessing the clinical benefit of the drug as also clearly recommended in the EMA GL is not completely understood. Analyses of key secondary endpoints using MMRM or ANCOVA models are recognized as adequate.

It should be noted that no endpoint that could monitor structural changes, as highly recommended in the EMA GL was included.
The MAH justified the lack of endpoints monitoring structural changes in Study A3921120 stating that the study design for Study A3921120 was not considered of sufficient duration to provide evidence of structural changes relative to placebo using radiography (modified Stoke Ankylosing Spondylitis Spinal Score [mSASS]) given that the placebo period was only of 16 weeks duration and the entire treatment duration was 48 weeks.

Sample size calculation for pivotal phase III study A3921120 was based on the response rate found in phase 2 dose-ranging, proof of concept trial. It is recognized as appropriate, although the primary efficacy endpoint was then analysed by the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata (prior treatment history).
A total of 269 patients in the A3921120 were treated and included in the FAS and 133 received tofacitinib 5 mg bid. Patient's disposition was balanced across the study. The great majority completed the DB 16 weeks phase. A higher but similar number of subjects discontinued study drug up to 48 weeks: 15 in the Tofa-Tofa and 14 in the PLB-Tofa arm; the main reasons of discontinuation being the same safety and lack of efficacy although a higher number is registered in the Tofa-Tofa (8 and 6, respectively) as compared to PLB-Tofa (3 and 4) group.
Demographic and baseline characteristics were quite balanced between the two arms and representative of the target population i.e., active AS. The majority of patients were white males with a mean age of 41 years. Patients from Europe were adequately represented being about 40% although enrolment was exclusively done in few countries.
Enrolled subjects had an active disease status as well indicated by a median value of 6.5 in BASDAI, of 3.9 in ASDAS (CRP) and a Patient's Assessment of Total Back Pain (NRS) and nocturnal spinal pain of 7.

An involvement of the spine as shown by the spinal mobility index BASMI (mean 4.5, range 0-10) and chest expansion (mean 3, range 0-12, enthesis involvement in roughly 50% of subjects and swollen joints in slightly less than 30% and impaired quality of life i.e., ASQoL (mean 11-11.5, range 0-18).
Considering ASDAS (CRP) score, the majority of patients (66.5%) had a very high disease activity [ASDAS (CRP) >3.5] with an imbalance between tofacitinib and placebo group with a slightly higher number of patients (70.6%) with very high disease activity as compared to tofacitinib group (62.4%). According to the more recent EULAR management recommendations for axial spondyloarthritis (2016), ASDAS is considered a relevant measure to assess disease activity (it correlates far better with both patients' and physicians' level of disease activity) and an elevated ASDAS index is considered more predictive of a good response than an elevated BASDAI. Therefore, the higher representativeness of subjects with very high disease activity according to ASDAS(CRP) in the placebo arm could impact the response.
Patients were generally balanced across treatment groups in their csDMARD (57.1% for tofacitinib 5 mg BID group to 60.3% for placebo group), oral corticosteroid (14.3% to 11.0%), and NSAID (100.0% to 99.3%) use at baseline. The majority of patients were positive for HLA-B27 (87.4% of subjects) and the median AS diagnosis duration was of 4.9 years (range: 0.1, 42.8).
A minority of patients had extra-articular manifestations at baseline. Regarding peripheral arthritis, the number of patients with current symptoms in tofacitinib and placebo groups were respectively 19 and 26 corresponding to 86.4% and 89.7% of subjects with history of peripheral arthritis. Moreover, a higher percentage of subjects with any csDMARDs was observed in placebo group than in tofacitinib group (33% vs 22%) probably reflecting a higher number of patients with a history of peripheral arthritis (18.4% vs 15.8%). However, no meaningful differences were noted between patients with and without concomitant csDMARDs with regard to ASAS40 and ASDAS(CRP) endpoints as well as with and without swollen joints. A slightly higher response in ASAS20 endpoint, a less stringent endpoint, was observed in tofacitinib group with concomitant csDMARDs (diff from plb: 30.88) compared to those without concomitant csDMARDs (diff from plb: 26.76), with the trend in favour of tofacitinib.
Almost all patients (99.6%) received prior NSAIDs, and a minor rate of patients received corticosteroids (16%). However, it was noted that a higher number of subjects was treated with corticosteroids in tofacitinib 5 mg (19.5%) compared to placebo group (12.5%) both with oral and intrarticular administration, suggesting possible more severe manifestations. Moreover, this imbalance was mainly observed in highly treated patients (TNFi-IR and bDMARD use [non-IR]), in which a higher percentage of subjects in the tofacitinib 5 mg BID group (19.4%) compared to placebo (6.5%) had prior use of oral corticosteroids and this is expected likely due to a more difficult to treat disease. No important differences were reported in previous csDMARDs use. The majority of patients were bDMARDs naïve (77%) with a similar distribution between the two groups. A minor number of patients (31 subjects in each arm, 23%) were bDMARDs experienced (bDMARDs use or TNFi-IR), 2 subjects were bDMARDs use non-IR.
Concomitant rescue medications, NSAIDs, oral corticosteroids, intra-articular corticosteroids, and csDMARDs were taken by a similar proportion of subjects between treatment groups at baseline up to Week 48.

Tofacitinib 11 mg PR QD in RA

Clinical efficacy data in the tofacitinib 11 mg PR QD formulation was provided from the phase 3 study A3921215 (a phase 3, 12-week, randomised, double-blind, parallel group, multicentre study to demonstrate non-inferiority for the efficacy of tofacitinib MR 11 mg QD compared to IR 5 mg BID in adult Japanese patients with RA on stable background MTX). In addition, the applicant has also provided single arm efficacy data from a US/EU study (study A3921192), observational comparative efficacy data from a US registry (CORRONA), and adherence data from a US insurance database retrospective cohort study (study A3921349) (data assessed in EMEA/H/C/004214/X/0012).

Efficacy data and additional analyses

Tofacitinib IR 5 mg BID in AS

Primary endpoint: a statistically significant higher proportion of patients in the tofacitinib 5 mg BID group reached ASAS20 at week 16 in comparison to the placebo group (56.4% vs 29.4%, p<0.0001), with a treatment difference of 27.08 (95% CI: 15.89, 38.28), which is in line with the 20% difference expected in the sample size calculation. Moreover, the primary analysis is supported by results from all the pre-specified supportive analyses.
ASAS20 is a weaker endpoint compared to the more stringent ASAS40, which is preferred by the EMA guidelines. The choice of ASAS20 has been discussed and agreed with FDA and not with EMA. ASAS40 has been used as the key secondary endpoint and this was also met from a statistical perspective with a higher response rate of subjects in tofacitinib 5 mg BID group (40.6%) compared to placebo group (12.5%) at week 16 (difference of 28.17, 95% CI: 18.26, 38.09 p< 0.0001). The effect size being very similar to that observed for ASAS20. A post-hoc analysis for ASAS20 at week 16 has been provided for the main subgroups showing no important differences except for geographic region of North America in which a smaller difference between tofacitinib 5 mg and placebo is seen (however, the small sample size of this subgroup hampers any firm conclusion) and body weight. In the subgroup with a body weight >100 kg the estimate of the treatment effect based on ASAS40 was -13% in favour of placebo. The MAH considers that the trend of ASAS40 at Week 16 in the Study A3921120 participants with a body weight >100 kg is most likely explained by the small sample size (10 and 18 patients, respectively in placebo and tofacitinib groups). This was not seen in the subgroup analysis of body weight and ASAS20, where the treatment effect was 20% in patients >100kg, 27% in patients 60-100kg and 38% in patients <60kg. The treatment effect in the highest BMI classes was in line with the other results, for ASAS20 as well as ASAS40.

Moreover, no major differences in tofacitinib exposure over the range of body weights studied were reported and no clinically significant decrease in efficacy of tofacitinib has been observed in >100 kg RA patients and according to SmPC section 5.2, systemic exposure (AUC) of tofacitinib in the extremes of body weight (40 kg, 140 kg) were similar (within 5%) to that of a 70 kg patient. Therefore, changes in the SmPC are not warranted at present.

A higher efficacy of tofacitinib 5 mg compared to placebo was observed in the subgroups with very high disease activity (ASDAS (CRP)>3.5) (Δ 35.43 vs 12.61 of patients with high disease activity) and higher baseline hsCRP (>2.87 mg/L) (Δ 28.95 vs 17.02 of patients with lower baseline hsCRP), suggesting that tofacitinib could perform better in this target population. The same figure was also observed for ASAS40 endpoint.

For both ASAS20 and ASAS40 a better response rate between study drug and placebo is reported in bDMARDs naïve compared to TNF-IR subjects or bDMARD use [non-IR] (difference form placebo 28 versus 22.5 and 28.4 versus 23 for ASAS20 and 40, respectively; in the TNF-IR or bDMARD use due to the limited sample size wide CI are seen); the better performance of the active drug is clinically expected in bDMARD naïve patients. Results according to bDMARDs naïve or TNF-IR subjects/bDMARD use [non-IR] subgroups have been included in 5.1 section of the SmPC, in order to guide prescribers.
Many secondary endpoints (21, 1 key) controlled for multiplicity (step-down testing procedure with a fixed alpha level for each comparison at the 2-sided 5%) were selected by the MAH.
Secondary endpoint: ASDAS (CRP) is a validated and accepted method to assess disease activity and physical function considered a very important disease activity score a clinically important improvement of ≥1.1 is required to define a response. The LS mean change from baseline in ASDAS(CRP) showed a statistically significant decrease for tofacitinib 5 mg BID compared to placebo at Week 16 (-1.36 in the tofa arm and -0.39 in the PLB arm at week 16, delta of -0.98, p <0.0001, FAS on drug data estimand

4), the achieved difference was clinically relevant. Consistent results were shown by the supportive analysis (MMRM, Estimand 5, FAS, on-study data, no imputation) were consistent with the on-drug data. At week 48 improvement of ASDAS(CRP) from baseline is still seen in both arms similarly -1.70 and -1.50 for the TOFA-TOFA and PLB-TOFA, respectively.
However, as per EMA GL, to facilitate interpretation of the clinical relevance of the observed effect, responder analyses are preferable over mean absolute changes. The MAH has provided these analyses for secondary endpoints not controlled for type I error so results are only descriptive/supportive including ASDAS clinically important improvement (61.3 versus 19.1 delta 42.3), ASDAS major improvement (30 versus 4.6 delta 25.3), ASDAS inactive disease (6.7 versus 0 delta 6.7) at week 16 overall showing a greater response in the Tofa arm which is maintained at week 48 and with an effect size of clinical significance for endpoint measuring improvement. In view of available treatments for ax SpA, disease remission is increasingly regarded as an appropriate therapeutic goal, no validate definition still exists. Therefore, endpoints aimed at assessing low disease activity or partial remission are considered of key importance for establishing the clinical benefit of a drug meant for axial SpA treatment as highlighted by EMA GL. ASDAS inactive disease (6.7 versus 0 delta 6.7, p 0<0.05) at week 16 and ASAS partial remission (a value of =2 (on a 0 to 10 scale) present in each domain, 15 versus 3, p 0<0.001) were assessed only as part of secondary not controlled endpoints showing very/limited effect size when inactive disease/partial remission was the goal, of interest is an increase of responders at week 48 (roughly 13-15% for ASDAS inactive and 18-23% for ASAS partial remission.
In the hierarchical order as second endpoint the MAH selected the Change from baseline of an inflammatory marker i.e., hsCRP at Week 16 showing statistically significant decreases for tofacitinib 5 mg BID compared to placebo at Week 16 (-1.05 versus -0.09, p <0.0001) based on the MMRM analysis (Estimand 4). Importantly this endpoint is not considered key for demonstration of tofacitinib clinical benefit but only regarded as supportive for effect on inflammation since no data support this biomarker as useful surrogate to assess efficacy in axial SpA.

Patient reported outcomes

Descending in the established order there is the change in Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire (total scores range from 0 to 18, with higher scores representing worse QoL) at week 16 showing an improvement at week 16 (tofa -4 versus PLB -2 and increasing at -6 and -5 at week 48). The ASQoL is an AS specific QoL measure and improvement of this disease domain is within treatment objectives and as such patient reported outcomes and quality of life evaluation may also be considered as secondary endpoints as per EMA GL. The MAH gave priority to these QOL endpoints (3 out of 6 of type I controlled endpoints) over other endpoints. To support the validity of these three outcomes, the MAH has provided a study report summarising the psychometric properties of these QoL measures. These are used in SA and considered useful for the assessment of QoL, and overall results support clinically meaningful changes.
The inclusion among secondary endpoints (type I controlled) of a measure of spinal mobility i.e., BASMI: Linear BASMI (BASMI lin) composite score change at week 16, is supported being a relevant efficacy parameter in axial SpA. In particular, when ASAS is used as primary endpoint, as in this case, since this index does not include the assessment of the spine mobility should be supplemented with the assessment of spinal mobility as a secondary endpoint. Results showed a change at week 16 of -0.63 versus -0.11 for Tofa and PLB, respectively; similar change (-0.6-0.7) at week 48 in both arms showing a statistical significance p 0.001 but not a clinically relevant difference for which improvement of > 1 point is expected. Another endpoint assessing spinal mobility i.e., change of spinal mobility (chest expansion, score 0-12) at week 16 was included with secondary endpoints not controlled for type I error showing a change of 0.59 versus 0.21 in the Tofa and PLB arm, not significant. Overall results on spinal mobility, which is an important domain of axSpA are not robust as those evaluating tofacitinib efficacy on sign and symptoms/inflammation of the disease.

The individual components of the ASAS responses have been included within secondary endpoints (type I controlled) in general showing a consistent and similar (delta of -1.5-1.7 at week 16) improvement slightly higher at week 48 for all the components.
ASAS20 and 40 responses over time: the onset of efficacy for tofacitinib 5 mg BID was seen early in the ASAS20 and ASAS40 response rates. Tofacitinib 5 mg BID become superior to placebo at Week 2 for ASAS20 response rate and at Week 4 for ASAS40 response rate and was sustained after Week 16 to the end of the study (Week 48). However, a slightly decrease was noted at week 16 as compared to week 12, -7.5% for ASAS20 (from 63.91% at week 12 to 56.39 at week 16) and -2.3% for ASAS40, although subsequently increased again at week 24 reaching a plateau thereafter. The reduction observed at week 16 has been clarified by the MAH by given a plausible response assuming that the observed trend was due to a random variability, since ASAS20 comprises subjective (patient-reported) components. However, it should be noted that a "real" decrease may have occurred. Moreover, considering the ASAS20 response rate, the same trend was observed with both Estimand 1 (on-drug data) and Estimand 2 (on-study data), with only 4/133 (3%) subjects discontinuing the investigational product; therefore, the intercurrent event of discontinuation which classifies the subject as non-responder for the visit of interest shouldn't have impacted the response rate at week 16. The issue was not further pursued.

According to the ASAS40 and all other secondary outcomes over time, the effect was maintained. In the group that was originally allocated to tofacitinib, the ASAS40 response at week 16 was 41%, which increased to 50% at week 48. In the patient group that was on placebo at week 16 and switched to tofacitinib, the proportion of patients with an ASAS40 response increased over time to 45% at week 48. Nevertheless, the increasing response after week 16, the Applicant was asked to analyse the new occurrences of response over time, and to discuss the inclusion of a statement in the SmPC about when to stop tofacitinib if no response occurred. An update of the 4.2 section of the SmPC suggesting to carefully reconsidering to continue therapy in patients exhibiting no clinical improvement within 16 weeks was added.

The EMA GL recommends using as secondary endpoints if not selected as primary endpoints, measures of disease activity such as the ASAS 5/6 as well as the peripheral tender joints and swollen joint count which were included by the MAH only as secondary (not controlled type I error) endpoints. ASAS 5/6 results are consistent with those of the primary and key secondary endpoint showing a statistical and clinically relevant improvement (44% responders, delta of 36 at week 16 and maintained at week 48).
As measure of improvement of enthesitis the MAH had included the change in MASES index (total score ranging 0 – 13) at week 16 as not controlled secondary endpoint showing an improvement of -2 versus -1.41, delta of -0.53 slightly increasing at week 48. Therefore, no significant statistical difference has been shown for this domain of the disease.
Other measures of symptoms and physical function recommended which has been included within secondary endpoints not controlled for multiplicity is the change of BASDAI at week 16 (showing an improvement of -2.55 at week 16 delta of -1.44). However, this is a widely used measure of disease activity and its changes with treatment should be assessed as secondary endpoint. Moreover, the percentage of patients with clinical response as measured by an improvement of at least a 50% from the baseline score in BASDAI is considered useful to judge the clinical benefit of a treatment but was not included by the MAH.
Overall, results from Study A3921119 were supportive of the phase 3 study with regard to different endpoints pertaining to disease activity and physical functions, health related outcomes, spinal mobility.

Indirect comparison with active treatments

The placebo-controlled trial did not include an active comparator. To indirectly compare the treatment effects of tofacitinib 5 mg BID with other treatments for AS, the MAH performed a systematic review and

meta-analysis of placebo-controlled trials of EMA-approved biological DMARDs, including ASAS20/40 at week 12-16, in patients with AS with or without previous experience with biological DMARDs.

According to the results, ASAS20 and ASAS40 responses for tofacitinib 5 mg BID across Studies A3921119 and A3921120, were similar compared with adalimumab, certolizumab, etanercept, golimumab, infliximab, ixekizumab and secukinumab. The treatment effects on ASAS40 were 26% and 28% in the two tofacitinib trials, while the majority of treatment effects of the other biological DMARDs ranged from 17% (adalimumab, COAST V) to 37% (infliximab, ASSERT). The MEASURE 4 trial in secukinumab showed lower treatment effects than the other trials including MEASURE 2. MEASURE 1 and 3 were not included in the meta-analysis, because of the iv loading dose that was used in those trials, which is not in the approved posology of secukinumab.

Tofacitinib 11 mg PR QD in RA

For Study A3921215, non-inferiority of the MR formulation to the IR formulation was not demonstrated according to the pre-specified margin of 0.60 with regard to the primary endpoint of change from baseline in DAS28-4(CRP) at week 12. Moreover, although ACR20 and ACR50 response rates were comparable between the two formulations, the more stringent enspoints rates of remission (DAS28-4[CRP] or DAS28-4[ESR] < 2.6) and ACR70 showed a statistically significant difference in favour of IR formulation. However, due to the possible increased efficacy responses (JAK1 inhibition) in Japanese patients and the limited comparison of baseline characteristics with EU patients from an international collaboration of RA registers, there were uncertainties when extrapolating the observed treatment differences to an un-blinded EU population. Supportive studies were: a) Study A3921192 based on cross-trial comparisons with blinded RCTs, 11 mg MR QD which compared favourably with 5 mg IR BID, particularly at week 24, across a range of endpoints, including remission and ACR70. However, bias may remain due to differences in unknown factors between trials; b) CORRONA registry (updated analysis): an updated comprehensive sensitivity analysis (including data up to 31st August 2019) of the previously reported outcomes (30th September 2018) was performed and explore the effects of extending the window of the 6-month visit. The proportions achieving the primary outcome of MCID improvement in CDAI from initiation to 6 months were 27.6% and 22.1% in the 11mg MR and 5 mg IR groups respectively (propensity score matched population). The adjusted odds ratio (95% CI) for improvement in the 11 mg MR group compared to the 5 mg BID group was 1.38 (0.81, 2.34). The results of supportive analyses were consistent with those in the propensity score matched population. The applicant has also provided analyses of change from baseline in CDAI. In the cohort with recent follow-up and a visit at 6 months ±3 months (cohort B), the mean (± SD) change in CDAI was -2.83 ± 13.93 and -2.71 ± 12.68 for MR and IR, respectively. The difference was 0.02 (95% CI: -2.31, 2.35). Supportive analyses in alternative matched and unmatched cohorts suggest close similarity between MR and IR; The MAH states that the US Corrona RA Registry Study is now complete, but the final analysis did not include additional efficacy analyses to compare PR to IR formulations because the number of patients did not substantially increase since the analysis for the previous submission c) Study A3921349 whose results suggested that after 12 months, adherence to 11mg MR QD was increased compared to 5 mg IR BID, using two measures of adherence.

The CHMP concluded that the RCT conducted in Japan suggested at less beneficial outcomes of the MR formulation to the IR formulation, particularly for the more stringent endpoints, but to an acceptable extent. However, due to higher variability of RA clinical endpoints compared to PK endpoints, the pivotal clinical study for this application was considered the comparative bioavailability study A3921212, whilst the clinical efficacy data were considered supportive. Therefore, comparable efficacy of the MR and IR formulations was expected based on the equivalent AUC at steady state and the observational registry data, retrospective adherence data, and single arm US/EU efficacy data were compatible with the assumption of similar efficacy based on PK.

No new efficacy data have been submitted within the current application. For discussion on the bridging strategy used in support of efficacy extrapolation in AS please refer to the section on clinical pharmacology.

2.4.4. Conclusions on the clinical efficacy

No comparative clinical efficacy and safety data with tofacitinib 11 mg PR formulation in SA patients have been provided within this application in order to demonstrate that the new modified release formulation is as safe and effective as the existing IR formulation. The MAH is supporting the extension of indication applying a bridging strategy of the efficacy of tofacitinib IR formulation (5 mg BID) in AS, which has been demonstrated (II/35), to the PR formulation relying on a well-defined E/R as considered in the EMA guideline on "the pharmacokinetic and clinical evaluation of modified release dosage forms".

Conclusion from tofacitinib IR 5 mg AS: a clinically relevant effect as measured by ASAS20/ASA40 has been demonstrated for tofacitinib IR 5 mg BD in the target population of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy. Most of the secondary endpoints measuring mainly signs and symptoms, inflammation and QoL endpoints provide supportive results. For other disease domains such as spinal mobility and enthesitis only limited or only a trend in effect was seen.

Conclusion from the 11 mg PR QD in RA population: the RCT conducted in Japan suggested at less beneficial outcomes of the MR formulation to the IR formulation, particularly for the more stringent endpoints, the pivotal clinical study was considered the comparative bioavailability study A3921212, whilst the clinical efficacy data were considered supportive. Overall, comparable efficacy of the MR and IR formulations was expected based on the equivalent AUC at steady state and the observational registry data (CORRONA), retrospective adherence data (Study A3921349), and single arm US/EU efficacy data were compatible with the assumption of similar efficacy based on PK.

For conclusions on the bridging strategy used in support of efficacy extrapolation in AS please refer to the section on clinical pharmacology.

2.5. Clinical safety

Introduction

No clinical studies with the PR formulation have been conducted in patients with AS.

As mentioned earlier, tofacitinib was approved in the EU at a dose of 5 mg IR BID on 22 Mar 2017 (MAA procedure EMEA/H/C/004214/0000) and at a dose of 11 mg PR QD on 16 Dec 2019 (MAA procedure EMEA/H/C/004214/X/0012) for the treatment of active moderate to severe RA in adult patients who have had an inadequate response or intolerance to MTX. The PR tablet formulation of tofacitinib was developed for patient's convenience by enabling QD dosing as another oral treatment option for patients with AS.

The CHMP opinion was that the overall benefit/risk of tofacitinib 11 mg PR QD for patients with RA is favourable and that the efficacy and safety of the PR formulation in that population are expected to be comparable to that of the IR formulation based on totality of evidence (MAA procedure EMEA/H/C/004214/X/0012).

As described earlier, the approval of the PR formulation for RA was primarily based on a bridging strategy that demonstrated PK similarity between the PR and IR formulations as well as demonstrating the E-R relationships in RA patients, using the IR formulation.

The MAH utilises the following totality of evidence approach to support the safety profile of tofacitinib 11 mg PR QD in patients with active AS:

- The previously established similar safety profile of tofacitinib 5 mg IR BID to 11 mg PR QD in patients with RA.
- The established safety profile of tofacitinib 5 mg IR BID in AS patients.
- The comparison of incidence rates of select AEs from the final integrated safety data for AS versus RA and PsA clinical development safety data demonstrated the overall safety profile of tofacitinib in AS is consistent with RA and PsA.
- Similar safety profile of PR in AS patients to the IR formulation is inferred as all exposure metrics for a QD regimen of the 11 mg PR formulation (e.g. Cmax, AUC, Cmin) are equivalent or slightly lower than those for a BID regimen using the 5 mg IR formulation.

Furthermore, the MAH monitors post-marketing data across the different indications and for both formulations. The MAH notes that four new important potential risks have been determined for tofacitinib based on final data from Study A3921133: MACE, myocardial infarction, lymphoma, lung cancer. Study A3921133 was a Phase 3b/4 randomised, parallel-arm, open-label, safety endpoint study evaluating the safety of tofacitinib at 2 doses (5 mg BID and 10 mg BID) versus TNFi.

Of note, at the time of conclusion of this extension application the impact of the study A3921133 findings on tofacitinib safety and efficacy profile is being assessed in the parallel EMEA/H-A20/1517/C/004214/0048 procedure.

In summary, in applicant's view the safety profile of the PR formulation characterised in RA patients is similar to that of the IR formulation and the PK and safety profile of tofacitinib 5 mg IR BID has shown to be consistent between indications (i.e., RA, PsA, and AS); therefore, the safety profile of tofacitinib 11 mg PR QD in patients with AS is expected to be similar to that of tofacitinib 5 mg IR BID in patients with AS. This is without prejudice to the outcome of the ongoing EMEA/H-A20/1517/C/004214/0048 procedure.

Patient exposure

No AS patients have been exposed to tofacitinib PR formulations.

The next table provides an overview of the non-AS clinical trial populations used to determine the safety profile of tofacitinib 11 mg PR.

Table 41. Overview of safety populations in Non-AS clinical trials for PR and IR tablets

Healthy volunteer PR Population		**RA PR Population**		**RA P2P3 IR Population**	
Consists of 7 Phase 1 PK studies		**Consists of 1 completed Phase 3 study and 1 completed Phase 3b/4 study**		**Consists of completed Phase 2 and 3 IR studies**	
Study Numbers	**N (PY)**	**Study Numbers**	**N (PY)**	**Study Numbers**	**N (PY)**
A3921113 A3921131 A3921132	172 (NA)	A3921215 (11 mg PR QD arm)	104 (NA)	RA P2P3 Studies (5 mg BID) described	2664 (2476.66)

Healthy volunteer PR Population	RA PR Population	RA P2P3 IR Population
A3921163 A3921180 A3921195 A3921212	A3921192 694 (539.29) 11 mg PR QD	in **Error! Reference source not found.**.

Sources: RA PR Module 5.3.1.2 CSRs A3921113, A3921131, A3921132, A3921163, A3921212; RA PR Module 5.3.1.1 CSR A3921180; RA PR Module 5.3.1.3 CSR A3921195; UC PR Module 5.3.5.1 CSR A3921215 Table 14.1.2.1; Module 5.3.5.1 CSR A3921192 Table 14.1.1.1.1; Module 5.3.5.3 RA P2P3 Table 1571.2.1; Module 5.3.5.3 A3921192 Adhoc Analysis Table 1613.3.
RA P2P3: 01 Feb 2017 (final data)
RA P2P3 includes completed studies: A392-1019, -1025, -1032, -1035, -1039, -1040, -1044 (2 year data), -1045, -1046, -1064, -1068, -1069 (2 year data), -1073, -1129, -1187 and -1237.

Adverse events

Adverse events for (5 mg IR BID in AS)

The clinical safety profile of tofacitinib 5 mg IR BID in AS has been evaluated in the Phase 2 (A3921119) and Phase 3 (A3921120) clinical studies conducted in patients with AS.

The integrated safety analysis for AS IR is summarised in this document and, according to the MAH, is consistent with that for the RA and PsA clinical programmes with no new tofacitinib-related safety signals identified in AS patients.

There were no deaths in the AS programme and the incidence rates of SAEs and events of special interest in the AS programme, according to the MAH, were low and consistent with the rates seen in the RA and PsA safety datasets.

Therefore, most of the data presented from this point on, from the IR formulation, has been already included in the procedure for the IR formulation in AS patients (EMEA/H/C/004214/II/0035).

An overall summary of Treatment-Emergent Adverse Events in the AS Placebo-Controlled Cohort, for the IR formulation, is shown in the next table (Table 42).

Table 42. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Treatment-Emergent Adverse Events (All Causalities) - Treatment Policy Estimand, AS Placebo-Controlled Cohort

Number (%) of Subjects	Tofa 5 mg BID n (%)	Placebo n (%)
Subjects evaluable for adverse events	185	187
Number of adverse events	205	205
Subjects with adverse events	101 (54.6)	92 (49.2)
Subjects with serious adverse events	3 (1.6)	2 (1.1)
Subjects with severe adverse events	3 (1.6)	3 (1.6)
Subjects discontinued from study due to adverse events (a)	1 (0.5)	3 (1.6)
Subjects discontinued study drug due to adverse events (b)	4 (2.2)	4 (2.1)
Subjects with dose reduced or temporary discontinuation due to adverse events	12 (6.5)	6 (3.2)

Table 42. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Treatment-Emergent Adverse Events (All Causalities) - Treatment Policy Estimand, AS Placebo-Controlled Cohort

Number (%) of Subjects	Tofa 5 mg BID n (%)	Placebo n (%)

The table is based on the data from OC AE only.
Except for the Number of Adverse Events subjects are counted only once per analysis group in each row.
(a) Subjects who have an AE record that indicates that the AE causes the subject to be discontinued from the study.
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment is Drug Withdrawn.
TEAE in A3921119 is defined as those on-treatment events which are new or worsened in severity relative to the pre-treatment period prior to Day 1.
TEAE in A3921120 is defined as those on-treatment events which start during the effective duration of treatment.
Percentages are calculated using number of subjects evaluable for adverse events as the denominator.
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adae Table Generation: 11NOV2020 (23:37)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCSPC_EU/adae_s010
Table C1.3.1.2.1-E is for Pfizer internal use.

The following table (Table 43) shows an overall summary in the AS All Tofa Cohort.

Table 43. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Treatment-Emergent Adverse Events (All Causalities) - Treatment Policy Estimand, AS All Tofa Cohort

Number (%) of Subjects	All Tofa 5 mg BID n (%)	All Tofa n (%)
Subjects evaluable for adverse events	316	420
Number of adverse events	507	617
Subjects with adverse events	201 (63.6)	251 (59.8)
Subjects with serious adverse events	10 (3.2)	11 (2.6)
Subjects with severe adverse events	7 (2.2)	8 (1.9)
Subjects discontinued from study due to adverse events (a)	2 (0.6)	3 (0.7)
Subjects discontinued study drug due to adverse events (b)	11 (3.5)	12 (2.9)
Subjects with dose reduced or temporary discontinuation due to adverse events	30 (9.5)	32 (7.6)

The table is based on the data from OC AE only.
Except for the Number of Adverse Events subjects are counted only once per analysis group in each row.
(a) Subjects who have an AE record that indicates that the AE causes the subject to be discontinued from the study.
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment is Drug Withdrawn.
TEAE in A3921119 is defined as those on-treatment events which are new or worsened in severity relative to the pre-treatment period prior to Day 1.
TEAE in A3921120 is defined as those on-treatment events which start during the effective duration of treatment.
Percentages are calculated using number of subjects evaluable for adverse events as the denominator.
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adae Table Generation: 12NOV2020 (02:05)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCS_EU/adae_s010
Table C2.3.1.2.1-E is for Pfizer internal use.

Most Common AEs

The most frequently reported TEAEs in the Placebo-controlled cohort, by SOC and PT (≥2% of patients), are documented in the table 44 (all causalities).

Table 44. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence and Severity of Treatment-Emergent Adverse Events in >=2% of Subjects in Any Analysis Group by System Organ Class and Preferred Term (All Causalities) - Treatment Policy Estimand, AS Placebo-Controlled Cohort

Number of Subjects Evaluable for AEs	Tofa 5 mg BID (N=185)				Placebo (N=187)			
Severity(a)	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (1.1)	0	0	2 (1.1)	4 (2.1)	0	0	4 (2.1)
EYE DISORDERS	3 (1.6)	0	1 (0.5)	4 (2.2)	4 (2.1)	0	0	4 (2.1)
GASTROINTESTINAL DISORDERS	20 (10.8)	4 (2.2)	0	24 (13.0)	25 (13.4)	3 (1.6)	0	28 (15.0)
Abdominal pain upper	0	0	0	0	5 (2.7)	0	0	5 (2.7)
Diarrhoea	7 (3.8)	0	0	7 (3.8)	4 (2.1)	2 (1.1)	0	6 (3.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (4.3)	2 (1.1)	0	10 (5.4)	6 (3.2)	1 (0.5)	0	7 (3.7)
Fatigue	3 (1.6)	1 (0.5)	0	4 (2.2)	1 (0.5)	0	0	1 (0.5)
INFECTIONS AND INFESTATIONS	38 (20.5)	13 (7.0)	0	51 (27.6)	33 (17.6)	10 (5.3)	0	43 (23.0)
Influenza	5 (2.7)	1 (0.5)	0	6 (3.2)	1 (0.5)	0	0	1 (0.5)
Nasopharyngitis	12 (6.5)	1 (0.5)	0	13 (7.0)	12 (6.4)	1 (0.5)	0	13 (7.0)
Respiratory tract infection viral	3 (1.6)	1 (0.5)	0	4 (2.2)	0	0	0	0
Upper respiratory tract infection	13 (7.0)	1 (0.5)	0	14 (7.6)	9 (4.8)	2 (1.1)	0	11 (5.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (2.2)	1 (0.5)	0	5 (2.7)	6 (3.2)	2 (1.1)	0	8 (4.3)
INVESTIGATIONS	17 (9.2)	3 (1.6)	1 (0.5)	21 (11.4)	8 (4.3)	0	0	8 (4.3)
Alanine aminotransferase increased	5 (2.7)	0	1 (0.5)	6 (3.2)	1 (0.5)	0	0	1 (0.5)
Aspartate aminotransferase increased	3 (1.6)	0	1 (0.5)	4 (2.2)	0	0	0	0
Protein urine present	4 (2.2)	1 (0.5)	0	5 (2.7)	2 (1.1)	0	0	2 (1.1)
METABOLISM AND NUTRITION DISORDERS	4 (2.2)	0	0	4 (2.2)	6 (3.2)	0	0	6 (3.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7 (3.8)	8 (4.3)	0	15 (8.1)	13 (7.0)	7 (3.7)	1 (0.5)	21 (11.2)
Arthralgia	1 (0.5)	2 (1.1)	0	3 (1.6)	5 (2.7)	3 (1.6)	0	8 (4.3)
Arthritis	2 (1.1)	2 (1.1)	0	4 (2.2)	1 (0.5)	0	0	1 (0.5)
Spinal pain	0	1 (0.5)	0	1 (0.5)	2 (1.1)	1 (0.5)	1 (0.5)	4 (2.1)
NERVOUS SYSTEM DISORDERS	7 (3.8)	1 (0.5)	0	8 (4.3)	9 (4.8)	1 (0.5)	0	10 (5.3)
Dizziness	1 (0.5)	0	0	1 (0.5)	4 (2.1)	0	0	4 (2.1)
Headache	3 (1.6)	1 (0.5)	0	4 (2.2)	4 (2.1)	0	0	4 (2.1)

Table 44. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence and Severity of Treatment-Emergent Adverse Events in >=2% of Subjects in Any Analysis Group by System Organ Class and Preferred Term (All Causalities) - Treatment Policy Estimand, AS Placebo-Controlled Cohort

Number of Subjects Evaluable for AEs	Tofa 5 mg BID (N=185)				Placebo (N=187)			
Severity(a)	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
PSYCHIATRIC DISORDERS	1 (0.5)	0	0	1 (0.5)	4 (2.1)	0	0	4 (2.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	9 (4.9)	1 (0.5)	0	10 (5.4)	9 (4.8)	1 (0.5)	0	10 (5.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5 (2.7)	0	0	5 (2.7)	6 (3.2)	1 (0.5)	0	7 (3.7)

(a) If the same subject in a given treatment has more than one occurrence in the same preferred term event category, only the most severe occurrence is counted.
Subjects are counted only once per treatment per event. For the TESS algorithm any missing severities have been imputed as severe unless the subject experiences another occurrence of the same event in a given treatment for which severity is recorded. In this case, the reported severity is summarized.
Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
TEAE in A3921119 is defined as those on-treatment events which are new or worsened in severity relative to the pre-treatment period prior to Day 1.
TEAE in A3921120 is defined as those on-treatment events which start during the effective duration of treatment.
N: Number of subjects included in the Safety Analysis Set; n (%): Number of subjects with the events (Percentages are based on N).
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
Each SOC row counts all the events. Each SOC or PT row shows AE in >=2% of subjects in any treatment group (Total column).
PFIZER CONFIDENTIAL Source Data: adae Table Generation: 17NOV2020 (10:41)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCSPC_EU/adae_s160
Table C1.3.1.2.3.2-E is for Pfizer internal use.

The most frequent TEAEs by SOC in the Placebo-controlled Cohort were as follows:

- Infections and infestations (Tofa 5 mg BID: 27.6%, Placebo: 23.0%)
- GI disorders (Tofa 5 mg BID: 13.0%, Placebo: 15.0%)
- Investigations (Tofa 5 mg BID: 11.4%, Placebo: 4.3%)
- Musculoskeletal and connective tissue disorders (Tofa 5 mg BID: 8.1%, Placebo: 11.2%)

TEAE frequencies by PT that were higher (>1% difference between treatment groups) in the Tofa 5 mg BID group compared to the Placebo group included:

- Fatigue, influenza, respiratory tract infection viral, upper respiratory tract infection, ALT increased, AST increased, protein urine present, and arthritis.

In contrast, the following PTs were higher (>1% difference between treatment groups) for the Placebo group compared to the Tofa 5 mg BID group:

- Abdominal pain upper, arthralgia, spinal pain, and dizziness.

The most frequently reported TEAEs in the All Tofa cohort, by SOC and PT (≥2% of patients), are documented in table 45.

Table 45. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence and Severity of Treatment-Emergent Adverse Events in >=2% of Subjects in Any Analysis Group by System Organ Class and Preferred Term (All Causalities) - Treatment Policy Estimand, AS All Tofa Cohort

Number of Subjects Evaluable for AEs	All Tofa 5 mg BID (N=316)				All Tofa (N=420)			
Severity(a)	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
EYE DISORDERS	6 (1.9)	4 (1.3)	1 (0.3)	11 (3.5)	7 (1.7)	5 (1.2)	2 (0.5)	14 (3.3)
GASTROINTESTINAL DISORDERS	41 (13.0)	11 (3.5)	0	52 (16.5)	53 (12.6)	15 (3.6)	0	68 (16.2)
Abdominal pain upper	5 (1.6)	0	0	5 (1.6)	9 (2.1)	1 (0.2)	0	10 (2.4)
Diarrhoea	14 (4.4)	0	0	14 (4.4)	15 (3.6)	1 (0.2)	0	16 (3.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	14 (4.4)	3 (0.9)	0	17 (5.4)	17 (4.0)	3 (0.7)	0	20 (4.8)
Fatigue	7 (2.2)	2 (0.6)	0	9 (2.8)	8 (1.9)	2 (0.5)	0	10 (2.4)
HEPATOBILIARY DISORDERS	10 (3.2)	4 (1.3)	0	14 (4.4)	13 (3.1)	4 (1.0)	0	17 (4.0)
Hepatic function abnormal	6 (1.9)	2 (0.6)	0	8 (2.5)	7 (1.7)	2 (0.5)	0	9 (2.1)
INFECTIONS AND INFESTATIONS	79 (25.0)	35 (11.1)	0	114 (36.1)	93 (22.1)	42 (10.0)	0	135 (32.1)
Influenza	7 (2.2)	2 (0.6)	0	9 (2.8)	7 (1.7)	2 (0.5)	0	9 (2.1)
Nasopharyngitis	23 (7.3)	2 (0.6)	0	25 (7.9)	28 (6.7)	3 (0.7)	0	31 (7.4)
Upper respiratory tract infection	27 (8.5)	5 (1.6)	0	32 (10.1)	33 (7.9)	6 (1.4)	0	39 (9.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	7 (2.2)	5 (1.6)	0	12 (3.8)	13 (3.1)	6 (1.4)	0	19 (4.5)
INVESTIGATIONS	45 (14.2)	7 (2.2)	1 (0.3)	53 (16.8)	50 (11.9)	8 (1.9)	1 (0.2)	59 (14.0)
Alanine aminotransferase increased	7 (2.2)	3 (0.9)	1 (0.3)	11 (3.5)	8 (1.9)	3 (0.7)	1 (0.2)	12 (2.9)
Aspartate aminotransferase increased	3 (0.9)	3 (0.9)	1 (0.3)	7 (2.2)	3 (0.7)	3 (0.7)	1 (0.2)	7 (1.7)
Blood creatine phosphokinase increased	7 (2.2)	1 (0.3)	0	8 (2.5)	8 (1.9)	1 (0.2)	0	9 (2.1)
Protein urine present	10 (3.2)	1 (0.3)	0	11 (3.5)	10 (2.4)	1 (0.2)	0	11 (2.6)
Weight increased	9 (2.8)	1 (0.3)	0	10 (3.2)	9 (2.1)	1 (0.2)	0	10 (2.4)
METABOLISM AND NUTRITION DISORDERS	8 (2.5)	1 (0.3)	0	9 (2.8)	11 (2.6)	1 (0.2)	0	12 (2.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	18 (5.7)	15 (4.7)	3 (0.9)	36 (11.4)	23 (5.5)	18 (4.3)	3 (0.7)	44 (10.5)
Arthralgia	4 (1.3)	3 (0.9)	0	7 (2.2)	4 (1.0)	4 (1.0)	0	8 (1.9)
NERVOUS SYSTEM DISORDERS	14 (4.4)	3 (0.9)	0	17 (5.4)	21 (5.0)	3 (0.7)	0	24 (5.7)
Headache	9 (2.8)	2 (0.6)	0	11 (3.5)	13 (3.1)	2 (0.5)	0	15 (3.6)
RENAL AND URINARY DISORDERS	7 (2.2)	1 (0.3)	0	8 (2.5)	10 (2.4)	1 (0.2)	0	11 (2.6)

Table 45. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence and Severity of Treatment-Emergent Adverse Events in >=2% of Subjects in Any Analysis Group by System Organ Class and Preferred Term (All Causalities) - Treatment Policy Estimand, AS All Tofa Cohort

Number of Subjects Evaluable for AEs	All Tofa 5 mg BID (N=316)				All Tofa (N=420)			
Severity(a)	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	18 (5.7)	4 (1.3)	1 (0.3)	23 (7.3)	23 (5.5)	4 (1.0)	1 (0.2)	28 (6.7)
Cough	4 (1.3)	3 (0.9)	0	7 (2.2)	6 (1.4)	3 (0.7)	0	9 (2.1)
Oropharyngeal pain	8 (2.5)	0	0	8 (2.5)	9 (2.1)	0	0	9 (2.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	9 (2.8)	2 (0.6)	0	11 (3.5)	10 (2.4)	2 (0.5)	0	12 (2.9)

(a) If the same subject in a given treatment has more than one occurrence in the same preferred term event category, only the most severe occurrence is counted.
Subjects are counted only once per treatment per event. For the TESS algorithm any missing severities have been imputed as severe unless the subject experiences another occurrence of the same event in a given treatment for which severity is recorded. In this case, the reported severity is summarized.
Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
TEAE in A3921119 is defined as those on-treatment events which are new or worsened in severity relative to the pre-treatment period prior to Day 1.
TEAE in A3921120 is defined as those on-treatment events which start during the effective duration of treatment.
N: Number of subjects included in the Safety Analysis Set; n (%): Number of subjects with the events (Percentages are based on N).
Each SOC row counts all the events. Each SOC or PT row shows AE in >=2% of subjects in any treatment group (Total column).
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adae Table Generation: 17NOV2020 (10:52)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCS_EU/adae_s161
Table C2.3.1.2.3.2-E is for Pfizer internal use.

Table 46 shows incidence and severity of Treatment Related TEAEs in >=2% of Subjects in Any Analysis Group by System Organ Class and Preferred Term - Treatment Policy Estimand, AS Placebo-Controlled Cohort.

Table 46. Incidence and Severity of Treatment Related TEAEs

Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis)
Incidence and Severity of Treatment-Emergent Adverse Events in >=2% of Subjects in Any Analysis Group by System Organ Class and Preferred Term (Treatment Related) - Treatment Policy Estimand, AS Placebo-Controlled Cohort

Number of Subjects Evaluable for AEs	Tofa 5 mg BID (N=185)				Placebo (N=187)			
Severity(a)	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
GASTROINTESTINAL DISORDERS	4 (2.2)	1 (0.5)	0	5 (2.7)	12 (6.4)	0	0	12 (6.4)
INFECTIONS AND INFESTATIONS	10 (5.4)	3 (1.6)	0	13 (7.0)	11 (5.9)	2 (1.1)	0	13 (7.0)
Upper respiratory tract infection	7 (3.8)	1 (0.5)	0	8 (4.3)	5 (2.7)	0	0	5 (2.7)
INVESTIGATIONS	10 (5.4)	1 (0.5)	1 (0.5)	12 (6.5)	5 (2.7)	0	0	5 (2.7)
NERVOUS SYSTEM DISORDERS	3 (1.6)	1 (0.5)	0	4 (2.2)	2 (1.1)	0	0	2 (1.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (2.2)	1 (0.5)	0	5 (2.7)	4 (2.1)	0	0	4 (2.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.5)	0	0	1 (0.5)	4 (2.1)	1 (0.5)	0	5 (2.7)

(a) If the same subject in a given treatment has more than one occurrence in the same preferred term event category, only the most severe occurrence is counted. Subjects are counted only once per treatment per event. For the TESS algorithm any missing severities have been imputed as severe unless the subject experiences another occurrence of the same event in a given treatment for which severity is recorded. In this case, the reported severity is summarized.
Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
TEAE in A3921119 is defined as those on-treatment events which are new or worsened in severity relative to the pre-treatment period prior to Day 1.
TEAE in A3921120 is defined as those on-treatment events which start during the effective duration of treatment.
N: Number of subjects included in the Safety Analysis Set; n (%): Number of subjects with the events (Percentages are based on N).
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
Each SOC row counts all the events. Each SOC or PT row shows AE in >=2% of subjects in any treatment group (Total column).
PFIZER CONFIDENTIAL Source Data: adae Table Generation: 21NOV2020 (07:54)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCSPC_EU/adae_s183_1

Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis)
Incidence and Severity of Treatment-Emergent Adverse Events in >=2% of Subjects in Any Analysis Group by System Organ Class and Preferred Term (Treatment Related) - Treatment Policy Estimand, AS All Tofa Cohort

Number of Subjects Evaluable for AEs	All Tofa 5 mg BID (N=316)				All Tofa (N=420)			
Severity(a)	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
GASTROINTESTINAL DISORDERS	12 (3.8)	1 (0.3)	0	13 (4.1)	19 (4.5)	3 (0.7)	0	22 (5.2)
HEPATOBILIARY DISORDERS	6 (1.9)	1 (0.3)	0	7 (2.2)	8 (1.9)	1 (0.2)	0	9 (2.1)
INFECTIONS AND INFESTATIONS	28 (8.9)	8 (2.5)	0	36 (11.4)	35 (8.3)	11 (2.6)	0	46 (11.0)
Upper respiratory tract infection	13 (4.1)	1 (0.3)	0	14 (4.4)	16 (3.8)	1 (0.2)	0	17 (4.0)
INVESTIGATIONS	31 (9.8)	3 (0.9)	1 (0.3)	35 (11.1)	34 (8.1)	4 (1.0)	1 (0.2)	39 (9.3)
Protein urine present	7 (2.2)	0	0	7 (2.2)	7 (1.7)	0	0	7 (1.7)
Weight increased	7 (2.2)	0	0	7 (2.2)	7 (1.7)	0	0	7 (1.7)
NERVOUS SYSTEM DISORDERS	6 (1.9)	2 (0.6)	0	8 (2.5)	9 (2.1)	2 (0.5)	0	11 (2.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	8 (2.5)	1 (0.3)	0	9 (2.8)	9 (2.1)	1 (0.2)	0	10 (2.4)

(a) If the same subject in a given treatment has more than one occurrence in the same preferred term event category, only the most severe occurrence is counted. Subjects are counted only once per treatment per event. For the TESS algorithm any missing severities have been imputed as severe unless the subject experiences another occurrence of the same event in a given treatment for which severity is recorded. In this case, the reported severity is summarized.
Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
TEAE in A3921119 is defined as those on-treatment events which are new or worsened in severity relative to the pre-treatment period prior to Day 1.
TEAE in A3921120 is defined as those on-treatment events which start during the effective duration of treatment.
N: Number of subjects included in the Safety Analysis Set; n (%): Number of subjects with the events (Percentages are based on N).
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
Each SOC row counts all the events. Each SOC or PT row shows AE in >=2% of subjects in any treatment group (Total column).
PFIZER CONFIDENTIAL Source Data: adae Table Generation: 21NOV2020 (07:57)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCS_EU/adae_s040_1

AEs of special interest

Summaries on selected signals of interest for tofacitinib are presented below from the AS pooled safety analysis. These signals of interest were derived from clinical experience with tofacitinib in RA and PsA patients and were as follows:

- Infection including serious infections, adjudicated OIs, all HZ, and TB.
- Malignancy excluding NMSC.
- NMSC.
- Cardiovascular safety including adjudicated CV events and events of DVT, PE, ATE and VTE.
- GI perforation.
- EBV-related events.
- ILD.
- Hepatic function.
- Renal function.

- Rhabdomyolysis.
- Lipids.
- Haematological.
- Vital signs.

Incidence rates, incidence proportion and hazard ratio for selected adverse events in the Tofa 5 mg BID and Placebo groups of the Placebo-controlled Cohort are summarised in table 47.

Table 47. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Numbers of Subjects with Events, Incidence Proportions, Incidence Rates (Number of Subjects with Event per 100 PY) by Analysis Group, Hazard Ratio and Incidence Proportions (Estimand 4) for Selected Adverse Events - While on Treatment Estimand, AS Placebo-Controlled Cohort

	Tofa 5 mg BID N = 185 Exposure = 52.77 Patient-Years				Placebo N = 187 Exposure = 53.07 Patient-Years				Comparison (Tofa 5 mg BID - Placebo)
Adverse Events	**n (%)**	**n1 (%)**	**PY**	**IR (95% CI) per 100 PY**	**n (%)**	**n1 (%)**	**PY**	**IR (95% CI) per 100 PY**	**HR (95% CI)**
General									
TEAEs	101 (54.59)	0	37.74	267.61 (215.42, 319.81)	91 (48.66)	1 (0.53)	38.41	237.37 (188.59, 286.14)	1.12 (0.85, 1.49)
Serious AEs	3 (1.62)	0	56.76	5.28 (0.00, 11.25)	2 (1.07)	1 (0.53)	56.59	3.56 (0.00, 8.49)	1.47 (0.25, 8.80)
Severe AEs	3 (1.62)	0	56.82	5.27 (0.00, 11.24)	3 (1.60)	0	56.68	5.41 (0.00, 11.98)	0.96 (0.19, 4.78)
Discontinuation of study	2 (1.08)	0	57.06	3.49 (0.00, 8.33)	7 (3.74)	0	57.02	12.35 (3.20, 21.50)	0.28 (0.06, 1.36)
Discontinuation of study treatment	5 (2.70)	0	56.79	8.82 (1.09, 16.55)	9 (4.81)	0	56.80	15.90 (5.51, 26.29)	0.55 (0.18, 1.65)
Discontinuation due to AEs	4 (2.16)	0	56.85	7.04 (0.14, 13.94)	4 (2.14)	0	56.95	7.10 (0.14, 14.05)	0.97 (0.24, 3.90)
Death (Mortality)	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Infections									
Serious Infections	1 (0.54)	0	56.98	1.77 (0.00, 5.89)	0	0	57.02	0.00 (0.00, 3.31)	NC (0.00, Inf.)
Opportunistic Infections*	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Pneumonia	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Serious Pneumonia	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Herpes Zoster	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Serious Herpes Zoster	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Urinary Tract Infection	2 (1.08)	0	56.96	3.53 (0.00, 8.92)	2 (1.07)	0	56.86	3.50 (0.00, 8.87)	1.00 (0.14, 7.07)
Cellulitis	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Tuberculosis*	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)

Table 47. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Numbers of Subjects with Events, Incidence Proportions, Incidence Rates (Number of Subjects with Event per 100 PY) by Analysis Group, Hazard Ratio and Incidence Proportions (Estimand 4) for Selected Adverse Events - While on Treatment Estimand, AS Placebo-Controlled Cohort

	Tofa 5 mg BID N = 185 Exposure = 52.77 Patient-Years				Placebo N = 187 Exposure = 53.07 Patient-Years				Comparison (Tofa 5 mg BID - Placebo)
Adverse Events	**n (%)**	**n1 (%)**	**PY**	**IR (95% CI) per 100 PY**	**n (%)**	**n1 (%)**	**PY**	**IR (95% CI) per 100 PY**	**HR (95% CI)**
Candidiasis*	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Pneumocystis Jirovecii Pneumonia*	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Malignancy									
Malignancy excluding NMSC*	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
NMSC*	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
GI									
GI Perforation*	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Cardiovascular Events									
Total MACE*	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Deep vein thrombosis*	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Pulmonary embolism*	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Arterial thromboembolism*	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Venous thromboembolism[a] *	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Thromboembolism[b] *	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Additional Adverse Events									
Epstein-Barr Virus (EBV)-Related Events	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Interstitial Lung Disease (ILD)*	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Rhabdomyolysis									
Rhabdomyolysis	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Creatine Kinase (CK) Elevation	3 (1.62)	0	56.64	5.26 (0.00, 11.20)	2 (1.07)	0	56.65	3.55 (0.00, 8.46)	1.50 (0.25, 9.00)
Renal									
Acute Renal Failure	5 (2.70)	0	56.50	8.92 (0.78, 17.05)	2 (1.07)	0	56.93	3.49 (0.00, 8.85)	2.57 (0.50, 13.27)
Serum Creatinine Elevations	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Hepatic									

Table 47. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Numbers of Subjects with Events, Incidence Proportions, Incidence Rates (Number of Subjects with Event per 100 PY) by Analysis Group, Hazard Ratio and Incidence Proportions (Estimand 4) for Selected Adverse Events - While on Treatment Estimand, AS Placebo-Controlled Cohort

	Tofa 5 mg BID N = 185 Exposure = 52.77 Patient-Years				Placebo N = 187 Exposure = 53.07 Patient-Years				Comparison (Tofa 5 mg BID - Placebo)
Adverse Events	**n (%)**	**n1 (%)**	**PY**	**IR (95% CI) per 100 PY**	**n (%)**	**n1 (%)**	**PY**	**IR (95% CI) per 100 PY**	**HR (95% CI)**
Hepatic Steatosis	2 (1.08)	0	56.84	3.54 (0.00, 8.94)	0	0	57.02	0.00 (0.00, 3.31)	NC (0.00, Inf.)
Transaminase Elevations	8 (4.32)	0	56.11	14.27 (4.38, 24.16)	2 (1.07)	0	56.73	3.55 (0.00, 8.47)	4.03 (0.86, 18.97)
Hematologic									
Lymphopenia	1 (0.54)	0	56.98	1.73 (0.00, 5.88)	0	0	57.02	0.00 (0.00, 3.31)	NC (0.00, Inf.)
Neutropenia	0	0	57.06	0.00 (0.00, 3.28)	0	0	57.02	0.00 (0.00, 3.31)	NE (-, -)
Thrombocytopenia	1 (0.54)	0	56.83	1.77 (0.00, 5.91)	0	0	57.02	0.00 (0.00, 3.31)	NC (0.00, Inf.)
Anemia	1 (0.54)	0	56.98	1.76 (0.00, 5.89)	2 (1.07)	0	56.88	3.50 (0.00, 8.87)	0.51 (0.05, 5.57)
Vital Signs									
Hypertension	4 (2.16)	0	56.35	7.14 (0.00, 14.51)	2 (1.07)	0	56.51	3.52 (0.00, 8.92)	2.05 (0.37, 11.17)
Weight Increase	2 (1.08)	0	56.75	3.55 (0.00, 8.97)	1 (0.53)	0	56.90	1.79 (0.00, 6.03)	2.00 (0.18, 22.10)
Lipids									
Hyperlipidemia	4 (2.16)	0	56.29	7.11 (0.14, 14.08)	2 (1.07)	0	56.51	3.56 (0.00, 8.50)	2.01 (0.37, 10.95)

Exposure is the sum of treatment exposures of all the subjects in the group. * Adjudicated events in all studies. a. Venous thromboembolism includes deep vein
thrombosis and/or pulmonary embolism. b. Thromboembolism includes deep vein thrombosis, pulmonary embolism and/or arterial thromboembolism.
The Ankylosing Spondylitis Placebo-Controlled Cohort includes safety data from the double-blind placebo-controlled periods of the two studies, completed A3921119
(Up to Week 12) and completed A3921120 (Up to Week 16). Under While on Treatment Estimand, PY (ie, denominator for IR) is the sum of the times to the first event for
subjects with an event or the risk periods for subjects without an event within the 28-Day While on Treatment Risk Period.
n is the number of subjects with an event within the 28-Day While on Treatment Risk Period. n1 is the number of subjects with an event beyond the 28-Day While on
Treatment Risk Period which are not included in the IR estimation. Incidence proportions, PYs, IRs, and HRs are estimated based on n under this estimand/risk period.
IRs (95% CI) by analysis group are estimated using Cochran-Mantel-Haenszel weighting method adjusting to study.
HR and its associated CI are estimated from a Cox regression model including fixed effects of treatment and study. MedDRA v23.0 coding dictionary applied.
NC: not calculated, 0 events in one analysis group of the comparison. NE: not estimable, 0 events in both analysis groups of the comparison.
PFIZER CONFIDENTIAL Source Data: adae & adsaec & adaj & adds Table Generation: 24NOV2020 (05:07)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCSPC_EU/adae_ir_combine_3
Table C1.5.15.2.3-E is for Pfizer internal use.

Serious infections

In the Placebo-controlled Cohort:

- 1 patient in the Tofa 5 mg BID group experienced a serious infection, meningitis aseptic, representing an incidence rate (While on Treatment Estimand) of 1.77 patients with events per 100 PY. This serious infection was not considered to be opportunistic by the independent adjudication committee.
- No serious infections were reported in the Placebo group.

Overall, 1 serious infection of meningitis aseptic was reported for the All Tofa Cohort representing an incidence rate (While on Treatment Estimand) of 0.43 patients with events per 100 PY for the All Tofa 5 mg BID group.

No cases of tuberculosis were reported in the AS Programme.

Herpes Zoster

There were 7 patients with HZ reported in the All Tofa Cohort as follows:

- All Tofa 5 mg BID group: 5 patients reported HZ, which represented an incidence rate (While on Treatment Estimand) of 2.18 patients with events per 100 PY.

- All Tofa group: In addition to the 5 patients who reported HZ in the All Tofa 5 mg BID group, there were 2 additional patients (1 received tofacitinib 2 mg BID and the other received tofacitinib 10 mg BID) reporting HZ representing an incidence rate (While on Treatment Estimand) of 2.68 patients with events per 100 PY.

None of the events were serious.

- 1 event occurred in a patient who received tofacitinib 2 mg BID.
- 5 events occurred in patients who received tofacitinib 5 mg BID.
- 1 event occurred in a patient who received tofacitinib 10 mg BID.

Hypertension

There were 6 patients with hypertension in the Placebo-controlled Cohort and are described as follows:

- Tofa 5 mg BID group: 4 (2.16%) patients had events of hypertension representing an incidence rate (While on Treatment Estimand) of 7.14 patients with events per 100 PY.

- Placebo group: 2 (1.07%) patients had events of hypertension representing an incidence rate (While on Treatment Estimand) of 3.52 patients with events per 100 PY.

Overall, there were 11 patients with hypertension in the All Tofa Cohort and are described as follows:

- All Tofa 5 mg BID group: 9 (2.85%) patients had events of hypertension representing an incidence rate (While on Treatment Estimand) of 3.97 (95% CI: 1.81, 7.53) patients with events per 100 PY.

- All Tofa group: 11 (2.62%) patients had events of hypertension representing an incidence rate (While on Treatment Estimand) of 4.26 (95% CI: 2.13, 7.62) patients with events per 100 PY.

Hepatic AEs

Treatment with tofacitinib is associated with an increased incidence of liver enzyme elevations compared to placebo. As part of the evaluation of hepatic safety within the AS Programme, a SMQ search was performed to identify hepatic-related adverse events, specifically events of hepatic steatosis and

transaminase elevations, which were then summarised for the Placebo-controlled Cohort and the All Tofa Cohort.

Adverse events of transaminase elevations in the Placebo-controlled Cohort are described as follows:

- Tofa 5 mg BID Group: 8 (4.32%) patients had transaminase elevations representing an incidence rate (While on Treatment Estimand) of 14.27 patients with events per 100 PY.
- Placebo Group: 2 (1.07%) patients had transamainase elevations representing an incidence rate (While on Treatment Estimand) of 3.55 patients with events per 100 PY.

Hepatic steatosis events in the Placebo-controlled Cohort are described as follows:

- Tofa 5 mg BID group: 2 (1.08%) patients had events of hepatic steatosis representing an incidence rate (While on Treatment Estimand) of 3.54 patients with events per 100 PY.
- Placebo group: No events.

A total of 3 patients in the Tofa 5 mg BID group had adverse events that met criteria for adjudication by the hepatic adjudication committee. None of these events met Hy's Law criteria, according to the MAH.

Adverse events of transaminase elevations in the All Tofa Cohort were as follows:

- All Tofa 5 mg BID group: 24 (7.59%) patients had transaminase elevations representing an incidence rate (While on Treatment Estimand) of 10.92 (95% CI: 7.00, 16.25) patients with events per 100 PY.
- All Tofa group: 28 (6.67%) patients had transaminase elevations representing an incidence rate (While on Treatment Estimand) of 11.18 (95% CI: 7.43, 16.15) patients with events per 100 PY.

Hepatic steatosis events in the All Tofa Cohort were as follows:

- All Tofa 5 mg BID group: 4 (1.27%) patients had events of hepatic steatosis representing an incidence rate (While on Treatment Estimand) of 1.74 (95% CI: 0.47, 4.45) patients with events per 100 PY.
- All Tofa group: 5 (1.19%) patients had events of hepatic steatosis representing an incidence rate (While on Treatment Estimand) of 1.91 (95% CI: 0.62, 4.46) patients with events per 100 PY.

In addition to the events described above for the Placebo-controlled Cohort, 2 additional patients in the All Tofa Cohort (All Tofa 5 mg BID group) had adverse events that met criteria for adjudication by the hepatic adjudication committee. Neither event met Hy's Law criteria.

Renal Function

No AEs of serum creatinine elevations were observed in the Placebo-controlled Cohort.

There were 7 patients with AEs coding to PTs in the acute renal failure SMQ in the Placebo-controlled Cohort described as follows:

- Tofa 5 mg BID group: 5 (2.70%) patients had events of protein urine present representing an incidence rate (While on Treatment Estimand) of 8.92 patients with events per 100 PY.
- Placebo group: 2 (1.07%) patients had events of protein urine present representing an incidence rate (While on Treatment Estimand) of 3.49 patients with events per 100 PY.

Serum creatinine elevations in the All Tofa Cohort were as follows:

- All tofa 5 mg BID group: 1 (0.32%) patient representing an incidence rate rate (While on Treatment Estimand) of 0.43 patients with events per 100 PY.
- All Tofa group: 1 (0.24%) patient representing an incidence rate rate (While on Treatment Estimand) of 0.38 patients with events per 100 PY.

There were 12 patients with AEs coding to PTs in the acute renal failure SMQ in the All Tofa Cohort described as follows:

- All Tofa 5 mg BID group: 12 (3.80%) patients had events of acute renal failure representing an incidence rate (While on Treatment Estimand) of 5.36 (95% CI: 2.77, 9.36) patients with events per 100 PY. Of these 11 patients had events of protein urine present and 1 patient had an event of blood creatinine increased.
- All Tofa group: 12 (2.86%) patients had events of acute renal failure representing an incidence rate (While on Treatment Estimand) of 4.70 (95% CI: 2.43, 8.21) patients with events per 100 PY. Of these 11 patients had events of protein urine present and 1 patient had an event of blood creatinine increased.

Haematology

There were no patients with events of neutropenia in the Placebo-controlled Cohort.

AEs of lymphopenia reported in the Placebo-controlled Cohort were as follows:

- Tofa 5 mg BID group: 1 (0.54%) patient had an event of lymphopenia representing an incidence rate (While on Treatment Estimand) of 1.73 patients with events per 100 PY.
- Placebo group: No patients had events of lymphopenia.

AEs of thrombocytopenia reported in the Placebo-controlled Cohort were as follows:

- Tofa 5 mg BID group: 1 (0.54%) patient had an event of thrombocytopenia representing an incidence rate (While on Treatment Estimand) of 1.77 patients with events per 100 PY.
- Placebo group: No patients had events of thrombocytopenia.

AEs of anaemia reported in the Placebo-controlled Cohort were as follows:

- Tofa 5 mg BID group: 1 (0.54%) patient had an event of anaemia representing an incidence rate (While on Treatment Estimand) of 1.76 patients with events per 100 PY.
- Placebo group: 2 (1.07%) patients had events of anaemia representing an incidence rate (While on Treatment Estimand) of 3.50 patients with events per 100 PY.

AEs of lymphopenia reported in the All Tofa Cohort were as follows:

- All Tofa 5 mg BID group: 1 (0.32%) patient had an event of lymphopenia representing an incidence rate (While on Treatment Estimand) of 0.43 (95% CI: 0.01, 2.41) patients with events per 100 PY.
- All Tofa group: 2 (0.48%) patients had events of lymphopenia representing an incidence rate (While on Treatment Estimand) of 0.76 (95% CI: 0.09, 2.75) patients with events per 100 PY.

AEs of neutropenia reported in the All Tofa Cohort were as follows:

- All Tofa 5 mg BID group: No patients had events of neutropenia.
- All Tofa group: 1 (0.24%) patient had an event of neutropenia representing an incidence rate (While on Treatment Estimand) of 0.38 (95% CI: 0.01, 2.12) patients with events per 100 PY.

AEs of anaemia reported in the All Tofa Cohort were as follows:

- All Tofa 5 mg BID group: 3 (0.95%) patients had events of anaemia representing an incidence rate (While on Treatment Estimand) of 1.30 (95% CI: 0.27, 3.81) patients with events per 100 PY.
- All Tofa group: 3 (0.71%) patients had events of anaemia representing an incidence rate (While on Treatment Estimand) of 1.15 (95% CI: 0.24, 3.35) patients with events per 100 PY.

Thrombocytopenia

AEs of thrombocytopenia reported in the All Tofa Cohort were as follows:

- All Tofa 5 mg BID group: 1 (0.32%) patient had an event of thrombocytopenia representing an incidence rate (While on Treatment Estimand) of 0.43 (95% CI: 0.01, 2.42) patients with events per 100 PY.
- All Tofa group: 1 (0.24%) patient had an event of thrombocytopenia representing an incidence rate (While on Treatment Estimand) of 0.38 (95% CI: 0.01, 2.13) patients with events per 100 PY.

See then section on platelets in the Laboratory Findings section.

In the AS programme were not observed cases of: Malignancies, NMSC, CV events of MACE or thrombosis (ATE, PE, and DVT), GI Perforation, Rhabdomyolysis.

Safety of Tofacitinib in the RA and PsA development programmes

The safety databases from the RA and PsA programmes provide insight on the incidence rates and range of AEs reported with tofacitinib treatment in the AS programme, whilst recognising the differences regarding the design of the RA (separate monotherapy and background csDMARD) and PsA (background csDMARD only) programmes.

A description of the RA P2P3, RA P123LTE, PsA Cohort 2a, and PsA Cohort 3 safety populations is in table 48.

Table 48. RA and PsA Safety Populations and Completed Studies Contributing to Safety Assessment for the AS Programme

Analysis Set	Brief Description	Safety Analysis	Phase / Studies
RA Safety Populations (for contextualisation)			
RA P2P3	All patients randomised to tofacitinib 5 mg IR BID during the full randomised periods of the completed Phase 2 and 3 studies in the RA clinical programme.	The Tofa 5 mg BID group of the RA P2P3 Cohort will provide RA contextualisation for the All Tofa 5 mg BID group of the AS All Tofa Cohort.	Phase 3 A3921045; A3921046; A3921064; A3921032, A3921044; A3921069; A3921187; A3921237 Phase 2 A3921019; A3921025; A3921035; A3921039; A3921040; A3921073; A3921129; A3921068

Table 48. RA and PsA Safety Populations and Completed Studies Contributing to Safety Assessment for the AS Programme

Analysis Set	Brief Description	Safety Analysis	Phase / Studies
RA P123LTE	All patients exposed to at least 1 dose of tofacitinib from the completed Phase 1, 2, 3 and LTE studies	The All Tofa group of the Cohort RA P123LTE will provide RA contextualisation for the All Tofa group of the AS All Tofa Cohort.	P2P3 Studies listed above Phase 1 A3921130; A3921152 Phase 2 A3921109 Phase 3 A3921192; A3921215 (Japan specific); LTE A3921024; A3921041 (Japan specific)
PsA Safety Populations (for contextualisation)			
Cohort 2a	All patients randomised to tofacitinib 5 mg IR BID or placebo→ tofacitinib 5 mg IR BID sequences and received at least 1 dose of tofacitinib 5 mg IR BID during the full randomised periods of the completed Phase 3 Studies A3921125 (up to 6 months) and A3921091 (up to 12 months).	The All Tofa 5 mg BID group of PsA Cohort 2a will provide PsA contextualisation for the All Tofa 5 mg BID group of the AS All Tofa Cohort	Phase 3 A3921125; A3921091
Cohort 3	All patients who received at least 1 dose of tofacitinib (tofacitinib 5 or 10 mg BID) from the completed Phase 3 Studies A3921091, A3921125 and the long-term extension (LTE) Study A3921092.	The All Tofa group of the PsA Cohort 3 will provide PsA contextualisation for the All Tofa group of the AS All Tofa Cohort	Phase 3 and LTE A3921125; A3921091; A3921092

Comparison of incidence rates of select AEs from the final integrated safety data for AS versus RA and PsA clinical development safety data

The next table summarises the incidence rate (While on Treatment Estimand) per 100 PY (with 95% CIs) for the AEs of special interest in all patients treated with tofacitinib 5 mg IR BID comparing the AS All Tofa 5 mg BID group in the All Tofa Cohort to the PsA Cohort 2a All Tofa 5 mg BID group and the RA P2P3 Tofa 5 mg BID group.

Table 49. Incidence Rates (Number of Patients with Event per 100 PYs) of SAEs and Adverse Events of Special Interest in Patients Treated with Tofacitinib 5 mg IR BID in AS (Randomised Phase 2 and 3 Studies), PsA (Randomised Phase 3 Studies) and RA (Randomised Phase 2 and 3 Studies) Programmes (While on Treatment Estimand)

Source: Module 5.3.5.3 SCS Tables C2.6.1.1-E, C2.5.1.2.1-E, C2.5.2.2.1-E, C2.5.4.2.1-E, C2.5.10.2.1-E, C2.5.11.2.1-E, C2.3.3.3.1-E, C2.3.3.3.2-E, C2.3.1.3.6-E, C2.5.1.2.1.1-E; PsA IR Module 5.3.5.3 PsA Cohort 2a Tables 00118.C2a.2.19.1, 295a.1.2a., C2a.10.2.1, C2a.2.1.1, C2a.2.2.1, C2a.2.5.1, C2a.3.11.1, C2a.2.8.1, C2a.2.10.1, C2a.10.1.2.3; RA IR Module 5.3.5.3 RA P2P3 Tables 1571.2.1, 1571.10.1.1.1, 1571.8.1.1.1, 1571.11.1.1.1, 1571.5.1.1.1, 1571.6.1.1.1, 1571.7.1.1, 1571.9.1.1.1, 1571.9.1.2.1, 1571.12.1.1

a. Includes the data from subjects who were randomised to tofacitinib 5 mg IR BID and the tofacitinib-treated period for the subjects who were randomised to the placebo → tofacitinib 5 mg IR BID.
b. Includes the data from subjects who were randomised to tofacitinib 5 mg IR BID.
c. N value for MACE is 2401
d. Adjudicated events in all studies.
e. Opportunistic infections exclude Tuberculosis.
f. Adjudicated events in AS studies only.
g. VTE includes DVT and/or PE.
h. Thrombosis includes DVT, PE and/or ATE.
i. Adjudicated events by a Pfizer Internal Review Committee.
j. The numerator counts all the events occurred either on- or off-treatment, while PY (the denominator) is calculated to subject's Treatment Policy Risk Period in AS and subject's last dose + 28 days in RA.
Exposure is the sum of treatment exposures of all the subjects in the group. Risk period is to subject's last dose + 28 days or to the end of the cohort. Events are counted within the risk period. PY (in patient-year) is the sum of the times to the first event for subjects with event or to the end of the risk period for subjects without event and is the denominator for the incidence rate calculation.
Incidence rate is a naïve estimate without adjusting for study. Exact Poisson (adjusted for PY) 95% CI is provided for the Incidence rate.
AS All Tofa Cohort All Tofa 5 mg BID group includes completed randomised Phase 2 Study A3921119 and Phase 3 Study A3921120.
PsA Cohort 2a All Tofa 5 mg BID group includes completed randomised Phase 3 Studies A3921091 and A3921125.
RA Cohort P2P3 Tofa 5 mg BID group includes completed randomised Phase 2 and 3 Studies A392-1019, 1025, 1032, 1035, 1039, 1040, 1044 (2 years), 1045, 1046, 1064, 1068, 1069 (2 years), 1073, 1129, 1187 and 1237.

GI perforation[d]	0	0	231.35	0.00 (0.00, 1.59)	1	0.3	201.02	0.50 (0.01, 2.77)	0	0	2584.41	0.00 (0.00,0.14)
ILD[i]	0	0	231.35	0.00 (0.00, 1.59)	0	0.0	201.10	0.00 (0.00, 1.83)	3	0.1	2583.22	0.12 (0.02,0.34)
All-cause mortality	0	0	231.35	0.00 (0.00, 1.59)	1	0.3	201.10	0.50 (0.01, 2.77)	8	0.3	2584.41	0.31 (0.13,0.61)
All-cause mortality (all Event Last Dose Algorithm)[j]	0	0	261.97	0.00 (0.00, 1.41)	NA	NA	NA	NA	15	0.6	2584.41	0.58 (0.32,0.96)

Table 50 summarises the incidence rate (While on Treatment Estimand) per 100 PY (with 95% CIs) for the AEs of special interest in All Tofa doses comparing the AS All Tofa group in the All Tofa Cohort to the PsA Cohort 3 All Tofa group and the RA P123LTE All Tofa group.

Table 50. Incidence rate (While on Treatment Estimand) per 100 PY (with 95% CIs) for the AEs of special interest in All Tofa doses comparing the AS All Tofa group in the All Tofa Cohort to the PsA Cohort 3 All Tofa group and the RA P123LTE All Tofa group

Adverse Events	Ankylosing Spondylitis (All Tofa Cohort) All Tofa N = 420 Exposure (patient-years) = 232.98				Psoriatic Arthritis (Cohort 3) All Tofa N = 783 Exposure (patient-years) = 2037.97				Rheumatoid Arthritis (Cohort RA P123LTE) All Tofa N = 7964 Exposure (patient-years) =23496.73			
	n	%	PY	Incidence rate (95% CI) Per 100 PY	n	%	PY	Incidence rate (95% CI) Per 100 PY	n	%	PY	Incidence rate (95% CI) Per 100 PY
SAEs	9	2.14	260.64	3.45 (1.58, 6.55)	135	17.2	1938.22	6.97 (5.84, 8.24)	1913	24.0	21361.14	8.96 (8.56, 9.37)
Serious infections	1	0.24	262.75	0.38 (0.01, 2.12)	24	3.1	2091.93	1.15 (0.74, 1.71)	592	7.4	23883.77	2.48 (2.28, 2.69)
OI[a,b]	0	0	262.82	0.00 (0.00, 1.40)	7	0.9	2089.54	0.34 (0.13, 0.69)	133	1.7	24054.65	0.55 (0.46, 0.66)
TB[a]	0	0	262.82	0.00 (0.00, 1.40)	0	0.0	2099.94	0.00 (0.00, 0.18)	38	0.5	24134.75	0.16 (0.11, 0.22)
HZ	7	1.67	260.89	2.68 (1.08, 5.53)	36	4.6	2045.98	1.76 (1.23, 2.44)	795	10.0	22198.96	3.58 (3.34, 3.84)
Malignancies excluding NMSC[a]	0	0	262.82	0.00 (0.00, 1.40)	15	1.9	2098.40	0.71 (0.40, 1.18)	179	2.2	24108.42	0.74 (0.64, 0.86)
Lymphoma[a]	0	0	262.82	0.00 (0.00, 1.40)	1	0.1	2099.86	0.05 (0.00, 0.27)	12	0.2	24137.17	0.05 (0.03, 0.09)
NMSC[a]	0	0	262.82	0.00 (0.00, 1.40)	16	2.0	2076.76	0.77 (0.44, 1.25)	133	1.7	23860.11	0.56 (0.47, 0.66)
MACE[a]	0	0	262.82	0.00 (0.00, 1.40)	6	0.8	2095.81	0.29 (0.11, 0.62)	85	1.2	22966.82	0.37 (0.30, 0.46)
DVT[c]	0	0	262.82	0.00 (0.00, 1.40)	1	0.1	2099.86	0.05 (0.00, 0.27)	37	0.5	24083.96	0.15 (0.11, 0.21)
PE[c]	0	0	262.82	0.00 (0.00, 1.40)	1	0.1	2098.46	0.05 (0.00, 0.27)	31	0.4	24107.10	0.13 (0.09, 0.18)
ATE[c]	0	0	262.82	0.00 (0.00, 1.40)	7	0.9	2086.35	0.34 (0.13, 0.69)	85	1.1	23957.05	0.35 (0.28, 0.44)
VTE[c,d]	0	0	262.82	0.00 (0.00, 1.40)	2	0.3	2098.38	0.10 (0.01, 0.34)	61	0.8	24064.63	0.25 (0.19, 0.33)
Thrombosis[c,e]	0	0	262.82	0.00 (0.00, 1.40)	9	1.1	2084.79	0.43 (0.20, 0.82)	145	1.8	23887.58	0.61 (0.51, 0.71)
GI perforation[a]	0	0	262.82	0.00 (0.00, 1.40)	1	0.1	2099.86	0.05 (0.00, 0.27)	27	0.3	24135.92	0.11 (0.07, 0.16)
ILD[f]	0	0	262.82	0.00 (0.00, 1.40)	1	0.1	2099.59	0.05 (0.00, 0.27)	45	0.6	24084.98	0.19 (0.14, 0.25)
All-cause mortality	0	0	262.82	0.00 (0.00, 1.40)	2	0.3	2099.94	0.10 (0.01, 0.34)	59	0.7	24139.28	0.24 (0.19, 0.32)
All-cause mortality (all Event Last Dose Algorithm)[g]	0	0	297.13	0.00 (0.00, 1.24)	7	0.9	2037.38	0.34 (0.14, 0.71)	121	1.5	24139.28	0.50 (0.42, 0.60)

Source: Module 5.3.5.3 SCS Tables C2.3.3.3.2-E, C2.6.1.1-E, C2.5.1.2.1-E, C2.5.2.2.1-E, C2.5.4.2.1-E, C2.5.10.2.1-E, C2.5.11.2.1-E, C2.3.3.3.1-E, C2.3.1.3.6-E; PsA IR Module 5.3.5.3 PsA Cohort 3 Tables 00118.C3.10.1.2.3, 00118.C3.10.2.1.a, 00118.C3.10.2.1, 00118.C3.2.10.1, 00118.C3.2.8.1, 00118.C3.2.19.1, 00118.C3.2.5.1, 00118.C3.2.1.1, 00118.C3.3.13.3, 00118.C3.2.2.1; RA IR Module 5.3.5.3 RA P123LTE Tables 1571.6.2.1.1, 1571.5.2.1.1, 1582.1.1.1, 1582.3.1.1, 1582.2.1.1, 1582.11.1.1, 1582.4.1.1, 1582.10.4, 1571.10.2.1.1, 1571.11.2.1.1, 1571.12.2.1.

a. Adjudicated events in all studies.
b. Opportunistic infections exclude Tuberculosis.
c. Adjudicated events in AS studies only.
d. VTE includes DVT and/or PE.
e. Thrombosis includes DVT, PE and/or ATE.
f. Adjudicated events by a Pfizer Internal Review Committee.
g. The numerator counts all the events occurred either on- or off-treatment, while PY (the denominator) is calculated to subject's Treatment Policy Risk Period in AS, subject's last dose in PsA and subject's last dose + 28 days in RA.
Exposure is the sum of treatment exposures of all the subjects. Risk period is to subject's last dose + 28 days or to the end of the cohort except for all-cause mortality (all event last dose algorithm) noted above. Events are counted within the risk period.
PY (in patient-year) is the sum of the times to the first event for subjects with event or to the end of the risk period for subjects without event and is the denominator for the incidence rate calculation.
Incidence rate was a naïve estimate without adjusting for study. Exact Poisson (adjusted for PY) 95% CI is provided for the incidence rate.
AS All Tofa Cohort All Tofa group includes completed randomised Phase 2 Study A3921119 and Phase 3 Study A3921120.
PsA Cohort 3 All Tofa group includes completed randomised Phase 3 Studies A3921091, A3921125 and LTE Study A3921092.
RA Cohort RA P123LTE All Tofa group includes completed randomised Phase 2, 3 and LTE Studies A392-1019, 1024 (LTE), 1025, 1032, 1035, 1039, 1040, 1041 (LTE), 1044 (2 years), 1045, 1046, 1064, 1068, 1069 (2 years), 1073, 1109, 1129, 1130, 1152, 1187, 1192, 1215, and 1237.

Serious adverse event/deaths/other significant events

Ankylosing Spondylitis

Deaths

No deaths were reported in the AS IR clinical programme.

SAEs

The proportion of patients reporting SAEs for each treatment group and the associated incidence rates (While on Treatment Estimand) are as follows:

- Tofa 5 mg BID group: 3 (1.62%) patients representing an incidence rate of 5.28 patients with events per 100 PY.
- Placebo group: 2 (1.07%) patients representing an incidence rate of 3.56 patients with events per 100 PY. There was an additional patient who experienced 3 SAEs (Foetal death, Vaginal haemorrhage, and Uterine spasm) outside the 28-Day While on Treatment Risk Period; these events were not included in the incidence rate calculation.

SAEs in the Placebo-controlled Cohort are reported in table 51.

Table 51. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Summary of Serious Adverse Events by System Organ Class and Preferred Term (All Adverse Events) - Treatment Policy Estimand, AS Placebo-Controlled Cohort

Number of Subjects Evaluable for Adverse Events	Tofa 5 mg BID (N=185)	Placebo (N=187)
Number (%) of Subjects with Serious Adverse Events (a): by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**
EAR AND LABYRINTH DISORDERS	1 (0.5)	1 (0.5)
Hypoacusis	1 (0.5)	0
Vertigo	0	1 (0.5)
EYE DISORDERS	1 (0.5)	0
Iridocyclitis	1 (0.5)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.5)	1 (0.5)
Condition aggravated	1 (0.5)	1 (0.5)
INFECTIONS AND INFESTATIONS	1 (0.5)	0
Meningitis aseptic	1 (0.5)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (0.5)
Thoracic vertebral fracture	0	1 (0.5)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	1 (0.5)
Foetal death	0	1 (0.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	1 (0.5)
Uterine spasm	0	1 (0.5)
Vaginal haemorrhage	0	1 (0.5)
Total preferred term events (b)	4	6
Total Number of Cases (c)	3	4
Total Number of Subjects with Serious Adverse Events (d)	3	3
Total Number of Subjects with Serious Adverse Events (e): 6		

(a) SAEs are counted at MedDRA preferred term/analysis group with each individual SAE counted only once per subject per analysis group.
(b) Total number of events per subject per analysis group. (c) Number of cases that started in the analysis group.
(d) Total number of subjects having an event that started in the analysis group. (e) Overall count of subjects that had a Serious adverse Event in any analysis group.
A case is a single event or a series of related events not separated in time occurring in a single subject.
Source of Analysis Group is OC(Oracle Clinical). Source of SAE is SDW(Safety Data Warehouse).
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v.23.0J coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adsaec Table Generation: 11NOV2020 (20:46)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCSPC_EU/adsae_s001
Table C1.3.3.2-E is for Pfizer internal use.

SAEs reported in the All Tofa Cohort are summarised in table 52.

Table 52. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Summary of Serious Adverse Events by System Organ Class and Preferred Term (All Adverse Events) - Treatment Policy Estimand, AS All Tofa Cohort

Number of Subjects Evaluable for Adverse Events	All Tofa 5 mg BID (N=316)	All Tofa (N=420)
Number (%) of Subjects with Serious Adverse Events (a): by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**
EAR AND LABYRINTH DISORDERS	1 (0.3)	1 (0.2)
Hypoacusis	1 (0.3)	1 (0.2)
EYE DISORDERS	1 (0.3)	1 (0.2)
Iridocyclitis	1 (0.3)	1 (0.2)
GASTROINTESTINAL DISORDERS	1 (0.3)	1 (0.2)
Abdominal adhesions	1 (0.3)	1 (0.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.3)	1 (0.2)
Condition aggravated	1 (0.3)	1 (0.2)
HEPATOBILIARY DISORDERS	1 (0.3)	1 (0.2)
Hyperplastic cholecystopathy	1 (0.3)	1 (0.2)
INFECTIONS AND INFESTATIONS	1 (0.3)	1 (0.2)
Meningitis aseptic	1 (0.3)	1 (0.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.3)	2 (0.5)
Rib fracture	1 (0.3)	1 (0.2)
Tendon injury	0	1 (0.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.3)	1 (0.2)
Spinal osteoarthritis	1 (0.3)	1 (0.2)
NERVOUS SYSTEM DISORDERS	1 (0.3)	1 (0.2)
Migraine	1 (0.3)	1 (0.2)
RENAL AND URINARY DISORDERS	1 (0.3)	1 (0.2)
Ureterolithiasis	1 (0.3)	1 (0.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.3)	1 (0.2)
Pneumothorax	1 (0.3)	1 (0.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.3)	1 (0.2)
Subcutaneous emphysema	1 (0.3)	1 (0.2)
Total preferred term events (b)	12	13
Total Number of Cases (c)	9	10
Total Number of Subjects with Serious Adverse Events (d)	9	10
Total Number of Subjects with Serious Adverse Events (e): 10		

Table 52. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Summary of Serious Adverse Events by System Organ Class and Preferred Term (All Adverse Events) - Treatment Policy Estimand, AS All Tofa Cohort

Number of Subjects Evaluable for Adverse Events	All Tofa 5 mg BID (N=316)	All Tofa (N=420)
Number (%) of Subjects with Serious Adverse Events (a): by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**

(a) SAEs are counted at MedDRA preferred term/analysis group with each individual SAE counted only once per subject per analysis group.
(b) Total number of events per subject per analysis group. (c) Number of cases that started in the analysis group.
(d) Total number of subjects having an event that started in the analysis group.
(e) Overall count of subjects that had a Serious adverse Event in any analysis group.
A case is a single event or a series of related events not separated in time occurring in a single subject.
Source of Analysis Group is OC(Oracle Clinical). Source of SAE is SDW(Safety Data Warehouse). Included Protocols: A3921119, A3921120 (Final Data).
MedDRA v.23.0J coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adsaec Table Generation: 11NOV2020 (22:32)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCS_EU/adsae_s001
Table C2.3.3.2-E is for Pfizer internal use.

The proportion of patients reporting SAEs for the All Tofa 5 mg BID group and the associated incidence rate (While on Treatment Estimand) are: All Tofa 5 mg BID group: 8 (2.53%) patients representing an incidence rate of 3.49 (95% CI: 1.51, 6.87) patients with events per 100 PY.

Laboratory findings

The pooled safety population has been used to evaluate changes from baseline in laboratory parameters of AS patients. For the Placebo-controlled Cohort, data for both A3921119 and A3921120 were pooled through Week 16. For the A3921119 study, the last dose of study medication was at the Week 12 visit. The Week 16 visit was a follow up visit 4 weeks after the last dose of study medication and was also included in the pooled safety population datasets.

Incidence of laboratory abnormalities are shown in table 53, without regard to baseline abnormality for the Placebo-controlled Cohort.

Table 53. Tofacitinib Summary of Clinical Safety

Table C1.3.4.1.1-E
Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis)
Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) - Treatment Policy Estimand, AS Placebo-Controlled Cohort

Laboratory Abnormalities: Number of Subjects Evaluable for Laboratory Abnormalities: Number (%) of Subjects with Laboratory Abnormalities:			Tofa 5 mg BID 184 76 (41.3%)		Placebo 184 89 (48.4%)	
Group	Parameter (Units)	Primary Criteria	N	n (%)	N	n (%)
HEMATOLOGY	Hemoglobin (g/dL)	<0.8x LLN	184	0	184	1 (0.5)
	Erythrocytes (10^6/mm^3)	<0.8x LLN	184	0	184	1 (0.5)
	Reticulocytes (10^3/mm^3)	>1.5x ULN	184	0	184	1 (0.5)
	Ery. Mean Corpuscular Volume (10^-15L)	<0.9x LLN	132	3 (2.3)	134	3 (2.2)
		>1.1x ULN	132	2 (1.5)	134	1 (0.7)
	Reticulocytes/Erythrocytes (%)	>1.5x ULN	184	1 (0.5)	184	1 (0.5)
	Leukocytes (10^3/mm^3)	>1.5x ULN	184	0	184	2 (1.1)
	Lymphocytes (10^3/mm^3)	<0.8x LLN	184	1 (0.5)	184	1 (0.5)
		>1.2x ULN	184	0	184	1 (0.5)
	Lymphocytes/Leukocytes (%)	<0.8x LLN	184	7 (3.8)	184	5 (2.7)
		>1.2x ULN	184	1 (0.5)	184	0
	Neutrophils (10^3/mm^3)	<0.8x LLN	184	3 (1.6)	184	1 (0.5)
		>1.2x ULN	184	6 (3.3)	184	14 (7.6)
	Neutrophils/Leukocytes (%)	<0.8x LLN	184	0	184	1 (0.5)
	Basophils (10^3/mm^3)	>1.2x ULN	184	0	184	2 (1.1)
	Basophils/Leukocytes (%)	>1.2x ULN	184	5 (2.7)	184	6 (3.3)
	Eosinophils (10^3/mm^3)	>1.2x ULN	184	1 (0.5)	184	4 (2.2)
	Eosinophils/Leukocytes (%)	>1.2x ULN	184	2 (1.1)	184	6 (3.3)
	Monocytes (10^3/mm^3)	>1.2x ULN	184	1 (0.5)	184	1 (0.5)
	Monocytes/Leukocytes (%)	>1.2x ULN	184	5 (2.7)	184	1 (0.5)
CLINICAL CHEMISTRY	Total Bilirubin (mg/dL)	>1.5x ULN	184	1 (0.5)	184	0
	Aspartate Aminotransferase (U/L)	>3.0x ULN	184	4 (2.2)	184	1 (0.5)
	Alanine Aminotransferase (U/L)	>3.0x ULN	184	5 (2.7)	184	1 (0.5)
	Gamma Glutamyl Transferase (U/L)	>3.0x ULN	184	1 (0.5)	184	2 (1.1)
	Blood Urea Nitrogen (mg/dL)	>1.3x ULN	54	1 (1.9)	50	0
	Urea (mg/dL)	>1.3x ULN	132	2 (1.5)	134	0
	Creatinine (mg/dL)	>1.3x ULN	184	1 (0.5)	184	0

Laboratory Abnormalities: Number of Subjects Evaluable for Laboratory Abnormalities: Number (%) of Subjects with Laboratory Abnormalities:			Tofa 5 mg BID 184 76 (41.3%)		Placebo 184 89 (48.4%)	
Group	Parameter (Units)	Primary Criteria	N	n (%)	N	n (%)
	URINE Leukocytes (/HPF)	>=20	74	4 (5.4)	79	3 (3.8)
	Hyaline Casts (/LPF)	>1	4	3 (75.0)	8	6 (75.0)

NOTE: N = total number of subjects in the Safety Analysis Set with at least one observation of the given laboratory test while on study treatment or during lag time.
n = number of subjects with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.
Percentages are displayed for the laboratory tests having a category with greater or equal to 1 evaluable subjects.
Included Protocols: A3921119, A3921120 (Final Data).

Patients who had abnormalities for selected laboratory evaluations of interest for tofacitinib were required to promptly retest a laboratory parameter or discontinue study medication due to the laboratory abnormalities. The number of patients who met the criteria for retesting a laboratory parameter of interest, or had to discontinue study medication due to laboratory abnormalities are presented in the table below for the Placebo-controlled Cohort.

Table 54. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence of Laboratory Values Meeting Protocol Criteria for Monitoring and Discontinuation of Study Drug - Treatment Policy Estimand, AS Placebo-Controlled Cohort

	Tofa 5 mg BID (N=185) n (%)	Placebo (N=187) n (%)
Category: Monitoring Criteria		
Met any monitoring criteria	4 (2.2)	9 (4.8)
Any single hemoglobin drops >2 g/dL below baseline	0	4 (2.1)
Absolute neutrophil count <1.2 x 10**9/L	1 (0.5)	0
Absolute lymphocyte count <0.5 x 10**9/L	1 (0.5)	0
Platelet count <100 x 10**9/L	0	1 (0.5)
Serum creatinine increase >50% or increase >0.5 mg/dL over the average of screening and baseline values	0	1 (0.5)
Any creatine kinase (CK) >5x ULN	2 (1.1)	3 (1.6)
Category: Discontinuation Criteria		
Met any discontinuation criteria	1 (0.5)	1 (0.5)
Two sequential absolute neutrophil counts <1.0 x 10**9/L	0	0
Two sequential absolute lymphocyte counts <500 lymphocytes/mm**3	0	0
Two sequential hemoglobin <8.0 g/dL or decreases of >30% from baseline value	0	0
Two sequential platelet counts <75 x 10**9/L	0	0
Two sequential AST or ALT elevations >=3x ULN with at least one total bilirubin >= 2x ULN	0	0
Two sequential AST or ALT elevations >=3x ULN accompanied by hepatic injury (eg, new onset elevated PT/INR)	0	0
Two sequential AST or ALT elevations >5x ULN	1 (0.5)	0
Two sequential serum creatinine increase >50% and increase >0.5 mg/dL over the average of screening and baseline values	0	0
Two sequential creatine kinase (CK) elevations >10x ULN	0	0
A confirmed positive urine pregnancy test in a woman of childbearing potential	0	1 (0.5)

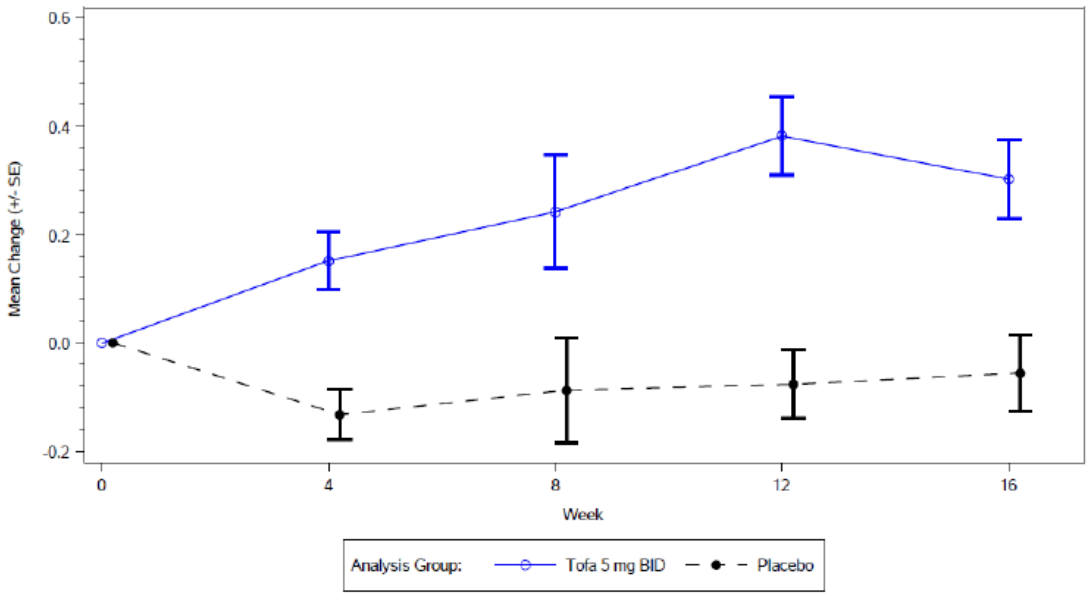
A subject may have met multiple criteria. Each subject is counted only once for each row.
Baseline is defined as last non-missing assessment prior to first dose of investigational product (including Placebo).
N: Number of subjects included in the Safety Analysis Set; n (%): Number of subjects who meet the criteria (Percentages are based on N).
Included Protocols: A3921119, A3921120 (Final Data).
PFIZER CONFIDENTIAL Source Data: adlb Table Generation: 11NOV2020 (08:37)
(Final Data: 10Sep2020) Output File: ./unblind 1120/A392 SCSPC EU/adlb s401
Table C1.3.4.4-E is for Pfizer internal use.

Haemoglobin

Tofacitinib is associated with increased incidence of anaemia. Therefore, patient selection based on threshold Hb values was an exclusion criterion. Patients were required to have Hb levels ≥10 g/dL at the study enrollment visit to enroll in the AS studies.

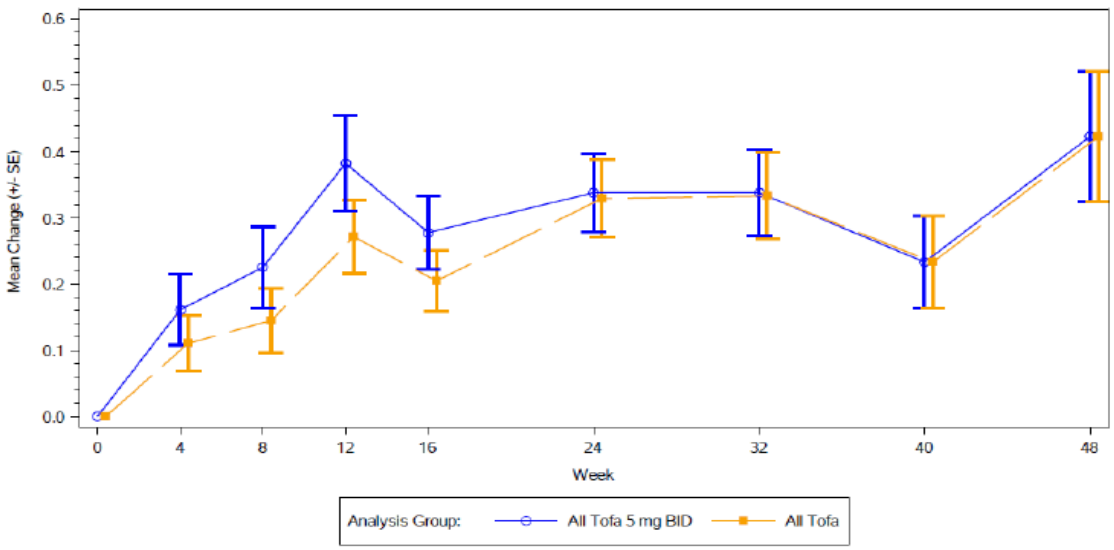
Hb changes over time are presented for the Placebo-controlled Cohort in the figure below and All Tofa Cohort in the following figure. There were no patient discontinuations due to decreases in Hb.

Figure 25. Tofacitinib Summary of Clinical Safety - Mean (± SE) Change from Baseline in Haemoglobin (g/dL) – AS Placebo-controlled Cohort



Source: Module 5.3.5.3 SCS Figure C1.3.4.3.4.4-E

Figure 26. Tofacitinib Summary of Clinical Safety – Mean (± SE) Change from Baseline in Haemoglobin (g/dL) – AS All Tofa Cohort

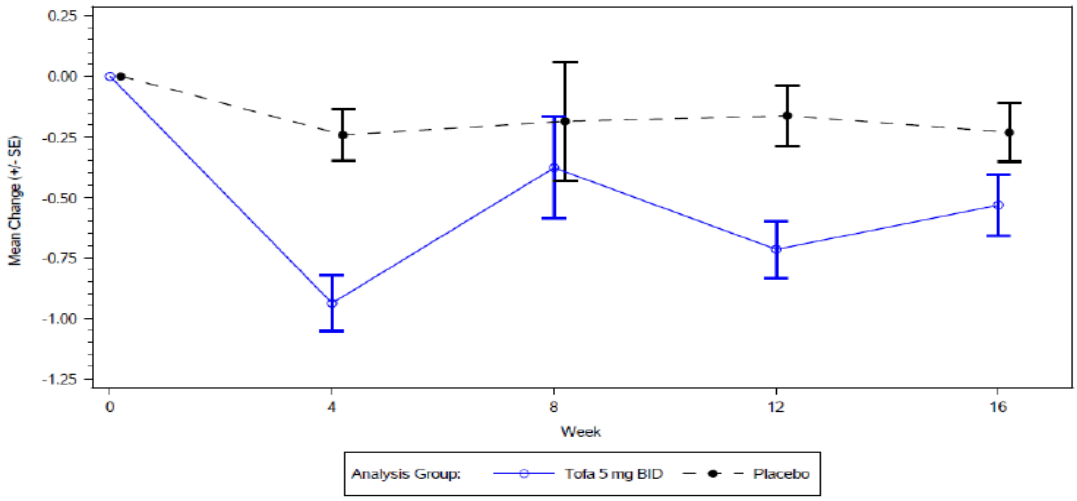


Source: Module 5.3.5.3 SCS Figure C2.3.4.3.4.4-E

Neutrophils

Tofacitinib has been associated with an increased incidence of neutropenia, therefore patient selection based on threshold ANC values was an exclusion criterion. The mean (± SE) Change from Baseline in Absolute Neutrophil Count is reported in the next table.

Figure 27. Tofacitinib Summary of Clinical Safety - Mean (± SE) Change from Baseline in Absolute Neutrophil Count ($10^3/mm^3$) – AS Placebo-controlled Cohort



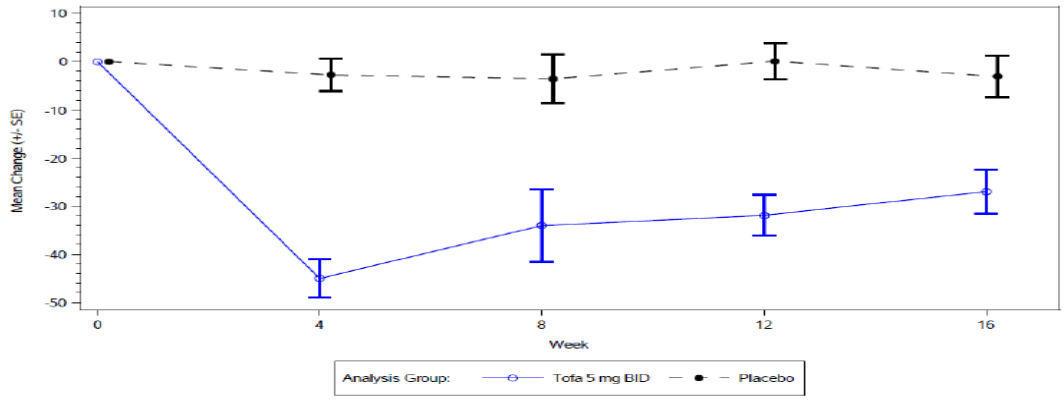
Source: Module 5.3.5.3 SCS Figure C1.3.4.3.4.4-E

Platelets

Patient selection based on threshold platelet counts was implemented as exclusion criteria in clinical trials. To enrol in the AS programme, patients were required to have a platelet count ≥100,000 platelets/mm3 at the study enrolment visit. Platelet count changes over time are presented for the Placebo-controlled Cohort in the Figure below. In the Placebo-controlled Cohort, there was a mean decrease from baseline to Week 4 for the Tofacitinib 5 mg IR BID group. Platelet counts decreased around 40,000 averagely from baseline during the first 4 weeks. Afterwards, the platelet counts increased slightly until 16 weeks but remained averagely 30,000 under the baseline average count. Platelet change in the placebo arm was not considerable and remained almost unchanged compared to the baseline. In the placebo-controlled phase, there were no patients that had to discontinue because of 2 sequential platelet counts <75 x 10**9/L.

The mean platelet counts were lower in the Tofacitinib 5 mg IR BID group compared to the Placebo group up to Week 16. The mean and median platelet counts remained within the normal range for all visits.

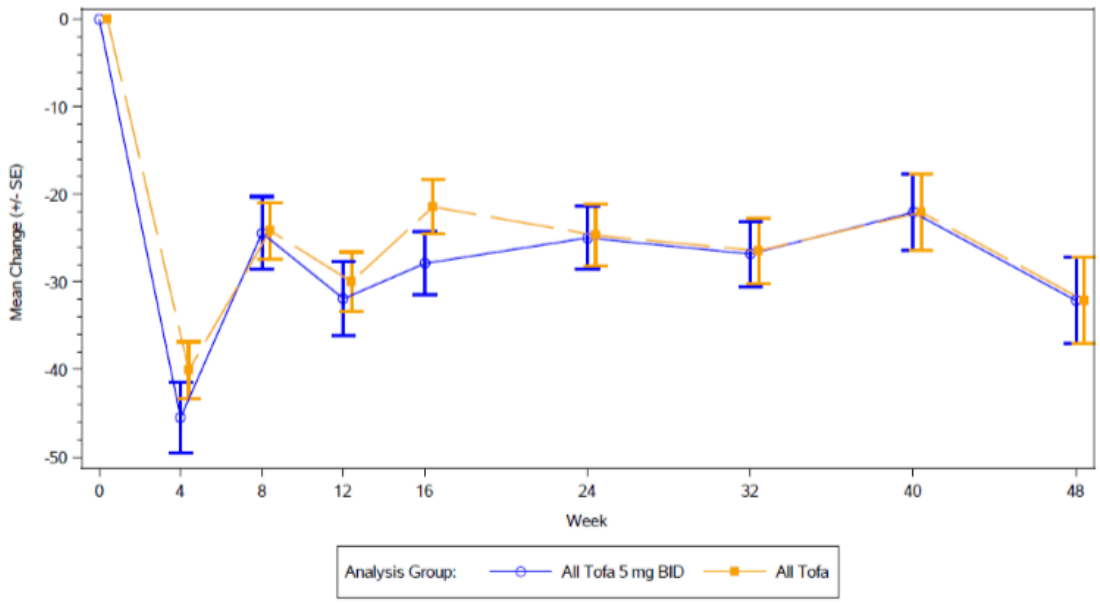
Figure 28. Tofacitinib Summary of Clinical Safety - Mean (± SE) Change from Baseline in Platelets ($10^3/mm^3$) – AS Placebo-controlled Cohort



Source: Module 5.3.5.3 SCS Figure C1.3.4.3.4.4-E

Platelet counts decreased during the first 4 weeks of tofacitinib treatment significantly (mean of approximately -45,000 in tofacitinib 5mg BID group). After 4th week the platelet counts increased slightly but still remained significantly lower than the baseline (mean decrease of –30,000 until week 48).

Figure 29. Tofacitinib Summary of Clinical Safety–Mean (±SE) Change from Baseline in Platelets (103/mm3)–AS All Tofa Cohort



Tables 55 show a comparison of platelet counts in AS vs RA/PsA clinical programs.

Table 55. Platelet Count ($10^3/mm^3$) by Visit for AS Placebo-controlled Cohort versus RA and PsA – 3-month data

		AS Placebo-controlled cohort		RA All Phase 3 Tofa 5 mg BID		PsA Cohort 1	
Visit	**Summary Statistics**						
		Tofa 5 mg BID	**Placebo**	**Tofa 5 mg BID**	**Placebo**	**Tofa 5 mg BID**	**Placebo**
Baseline	N1	185	187	1183	666	238	236
	Mean (SD)	296.60 (81.705)	307.26 (84.463)	328.21 (95.81)	325.16 (93.87)	280.24 (86.30)	283.99 (88.04)
	Median (min, max)	285.00 (138.00, 666.00)	298.00 (156.00, 593.00)	314.0 (81.0, 849.0)	311.0 (38.0, 833.0)	271.00 (153.00, 703.00)	268.50 (125.00, 703.00)
Week 4	N1	183	179	1150	630	233	226
	Mean (SD)	251.04 (61.375)	304.13 (82.488)	295.57 (82.28)	327.23 (97.47)	257.67 (72.07)	280.24 (81.70)
	Median (min, max)	247.00 (109.00, 412.00)	294.00 (151.00, 584.00)	286.0 (67.0,746.0)	309.0 (125.0, 834.0)	248.00 (117.00, 540.00)	274.00 (105.00, 678.00)
	Mean Change from Baseline (SD)	-45.03 (54.579)	-2.78 (44.965)	-33.08 (58.40)	-0.26 (51.43)	-22.79 (51.11)	-1.70 (47.19)
Week 8	N1	52	51	-	-	227	222
	Mean (SD)	260.27 (62.552)	291.25 (74.371)	-	-	262.87 (67.36)	275.50 (78.16)
	Median (min, max)	250.00 (165.00, 452.00)	279.00 (160.00, 537.00)	-	-	257.00 (138.00, 547.00)	265.00 (94.00, 594.00)
	Mean Change from Baseline (SD)	-34.04 (54.349)	-3.57 (36.120)	-	-	-17.90 (52.83)	-5.44 (49.79)
Week 12	N1	178	168	1105	606	225	216
	Mean (SD)	264.25 (57.953)	304.09 (82.642)	298.42 (82.69)	326.22 (97.79)	264.97 (73.14)	276.53 (90.24)
	Median (min, max)	261.50 (119.00, 418.00)	293.00 (86.00, 548.00)	289.0 (48.0,833.0)	312.0 (112.0, 833.0)	259.00 (108.00, 647.00)	262.00 (76.00, 759.00)
	Mean Change from Baseline (SD)	-31.92 (56.558)	0.08 (48.507)	-29.17 (65.69)	0.52 (60.12)	-16.23 (53.19)	-4.19 (54.04)
Week 16*	N1	179	175	-	-	237	234
	Mean (SD)	270.58 (61.094)	304.48 (89.657)	-	-	264.57 (73.25)	278.32 (92.01)
	Median (min, max)	274.00 (124.00, 440.00)	293.00 (160.00, 604.00)	-	-	259.00 (108.00, 647.00)	262.50 (76.00, 759.00)
	Mean Change from	-26.98 (61.020)	-3.10 (56.815)	-	-	-15.52 (52.95)	-4.91 (56.60)

	Baseline (SD)						

Source: S0113 Module 5.3.5.3 SCS Tables C1.3.4.3.4.1-E and C1.3.4.3.4.3-E; S0000 Module 5.3.5.3 All Phase 3 Tables 14.2.2 and 14.2.3; S0014 Module 5.3.5.3 PsA Cohort 1 Tables C1.6.1.1 and C1.6.1.2

Abbreviation: AS = ankylosing spondylitis; BID = twice a day; max = maximum; min = minimum; N1= number of participants; PsA = psoriatic arthritis; RA= rheumatoid arthritis; SD = standard deviation; Tofa = tofacitinib.

Baseline is the latest pre-study treatment (Tofacitinib or placebo) dose measurement.

Includes subjects with a Baseline measurement and at least one post Baseline measurement.

AS Placebo-Controlled Cohort: Includes Protocols A3921119 and A3921120.

RA All Phase 3: Includes Protocols A3921032, A3921044(1 year), A3921045, A3921046 and A3921064.

PsA Cohort 1: Includes Protocols A3921091 and A3921125.

*PsA Cohort 1 last observation

Table 56. Platelet Count ($10^3/mm^3$) by Visit in AS for All Tofa Cohort versus RA and PsA – 1-year data

		AS All Tofa Cohort All Tofa 5 mg BID	RA All Phase 3 Tofa 5 mg BID	PsA All PsA Average Tofa 5 mg BID
Visit	**Summary Statistics**			
Baseline	N1	316	1183	445
	Mean (SD)	302.26 (84.419)	328.21 (95.81)	274.48 (80.18)
	Median (Min, Max)	292.50 (138.00, 666.00)	314.0 (81.0, 849.0)	262.00 (76.0, 703.0)
Week 4	N1	185	1150	442
	Mean (SD)	251.87 (61.586)	295.57 (82.28)	254.46 (69.27)
	Median (Min, Max)	247.00 (109.00, 412.00)	286.0 (67.0,746.0)	245.50 (105.0, 658.0)
	Mean Change from	-45.50 (54.922)	-33.08 (58.40)	-20.08 (53.22)
Week 8	N1	181	-	-
	Mean (SD)	281.24 (75.193)	-	-
	Median (Min, Max)	268.00 (121.00, 556.00)	-	-
	Mean Change from	-24.41 (55.588)	-	-
Week 12	N1	178	1105	437
	Mean (SD)	264.25 (57.953)	298.42 (82.69)	264.90 (70.14)
	Median (Min, Max)	261.50 (119.00, 418.00)	289.0 (48.0,833.0)	259.00 (108.0, 647.0)
	Mean Change from	-31.92 (56.558)	-29.17 (65.69)	-10.04 (55.12)
Week 16	N1	305	-	-
	Mean (SD)	274.40 (65.597)	-	-
	Median (Min, Max)	276.00 (124.00, 612.00)	-	-
	Mean Change from	-27.90 (63.231)	-	-
Week 24	N1	256	1252	412
	Mean (SD)	278.95 (72.070)	294.05 (84.79)	263.04 (64.91)
	Median (Min, Max)	270.00 (122.00, 577.00)	287.0 (95.0, 694.0)	254.00 (105.0, 514.0)
	Mean Change from	-24.97 (57.480)	-36.12 (67.57)	-12.28 (58.56)

Week 32	N1	247	-	-
	Mean (SD)	278.57 (74.249)	-	-
	Median (Min, Max)	271.00 (118.00, 552.00)	-	-
	Mean Change from	-26.81 (58.408)	-	-
Week 36	N1	-	871	396
	Mean (SD)	-	282.57 (81.88)	262.64 (68.38)
	Median (Min, Max)	-	275.0 (88.0, 694.0)	251.50 (119.0, 602.0)
	Mean Change from	-	-41.39 (67.81)	-12.32 (62.11)
Week 40	N1	214	-	-
	Mean (SD)	282.83 (76.655)	-	-
	Median (Min, Max)	270.50 (115.00, 569.00)	-	-
	Mean Change from	-22.06 (63.704)	-	-
Week 48	N1	124	-	-
	Mean (SD)	264.94 (58.191)	-	-
	Median (Min, Max)	257.50 (117.00, 459.00)	-	-
	Mean Change from	-32.13 (55.047)	-	-
Week 52	N1	-	820	383
	Mean (SD)	-	288.42 (80.06)	262.52 (67.87)
	Median (Min, Max)	-	282.0 (98.0, 910.0)	253.00 (107.0, 583.0)
	Mean Change from	-	-35.38 (64.14)	-13.34 (62.53)

Source: S0113 Module 5.3.5.3 SCS Tables C2.3.4.3.4.1-E and C2.3.4.3.4.3-E; S0000 Module 5.3.5.3 All Phase 3 Table 14.2.2 and 14.2.3; S0014 Module 5.3.5.3 PsA Cohort 3 Tables 00118.C3.6.1.1 and 00118.C3.6.1.2

Abbreviation: AS = ankylosing spondylitis; BID = twice a day; max = maximum; min = minimum; N1= number of participants; PsA = psoriatic arthritis; RA= rheumatoid arthritis; SD = standard deviation; Tofa = tofacitinib.

Baseline is the latest pre-Tofacitinib dose measurement.

Includes subjects with a Baseline measurement and at least one post Baseline measurement.

AS All Tofa Cohort: Includes Protocols A3921119 and A3921120.

RA All Phase 3: Includes Protocols A3921032, A3921044(1 year), A3921045, A3921046 and A3921064.

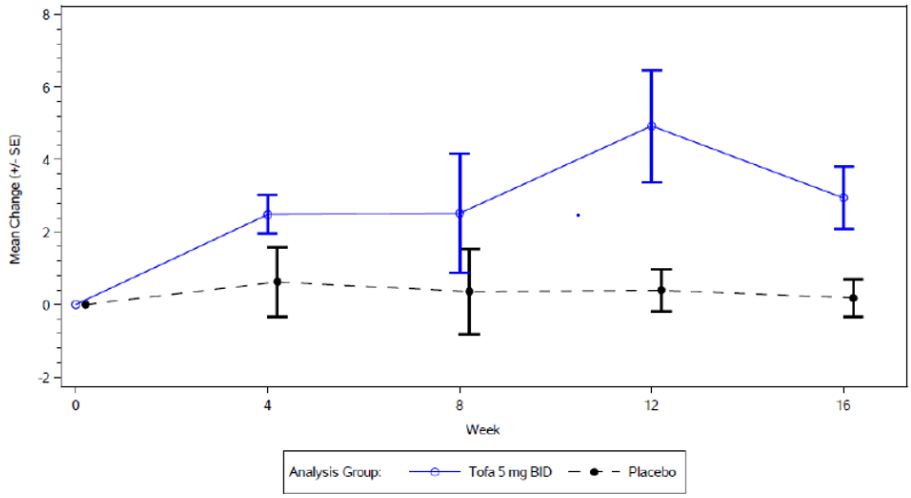
PsA Average Tofa 5 mg : Subjects with an average total daily dose of <15 mg from Day 1 on Tofa. Includes Protocols A3921091,

Liver Parameters

Tofacitinib has been associated with increases in liver test values compared to placebo. Most of these abnormalities have occurred in studies with background DMARD (primarily MTX) therapy.

Changes in AST in the placebo-controlled period are shown in the next figure.

Figure 30. Tofacitinib Summary of Clinical Safety–Mean (±SE) Change from Baseline in AST (U/L) – AS Placebo-controlled Cohort

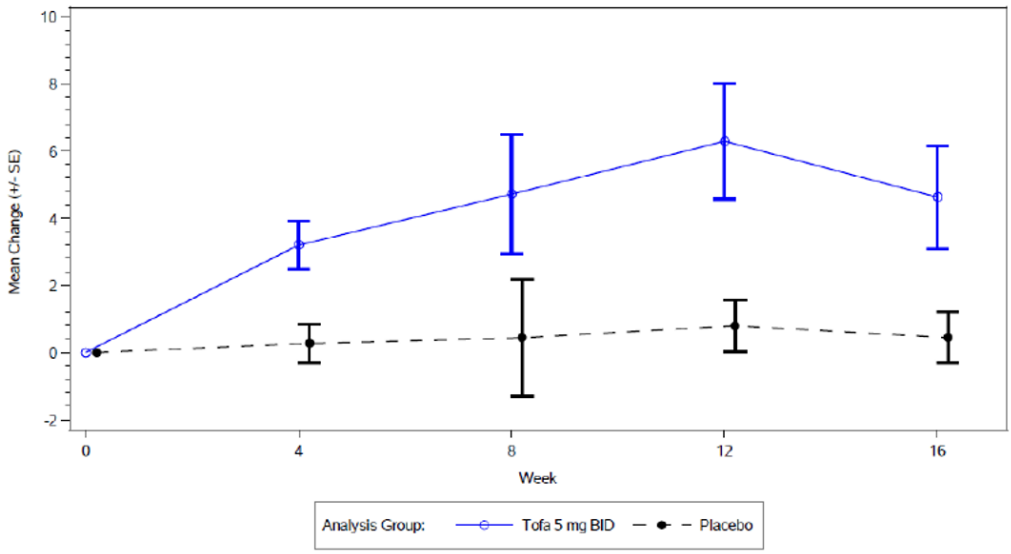


Module 5.3.5.3 SCS Figure C1.3.4.3.1.4-E

The change of AST (U/L) levels at 16 week from baseline was: mean (SD) 2.94 (11.588) in tofacitinib 5 mg vs 0.18 (6.903) in placebo.

Changes in ALT in the placebo-controlled period are shown in the next figure.

Figure 31. Tofacitinib Summary of Clinical Safety – Mean (± SE) Change from Baseline in ALT (U/L) – AS Placebo-controlled Cohort



Module 5.3.5.3 SCS Figure C1.3.4.3.1.4-E

The change of AST (U/L) levels at 16 week from baseline was: mean (SD) 4.62 (20.662) in tofacitinib 5 mg vs 0.44 (10.134) in placebo.

An analysis of the proportion of patients who experienced confirmed liver test values (2 consecutive elevations) at multiples of the ULN is presented for the Placebo-controlled Cohort is shown in the following table (Table 57).

Table 57. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Number (%) of Subjects With Confirmed Liver Test Values as Multiples of Upper Limit of Normal (Without Regard to Baseline Abnormality) - Treatment Policy Estimand, AS Placebo-Controlled Cohort

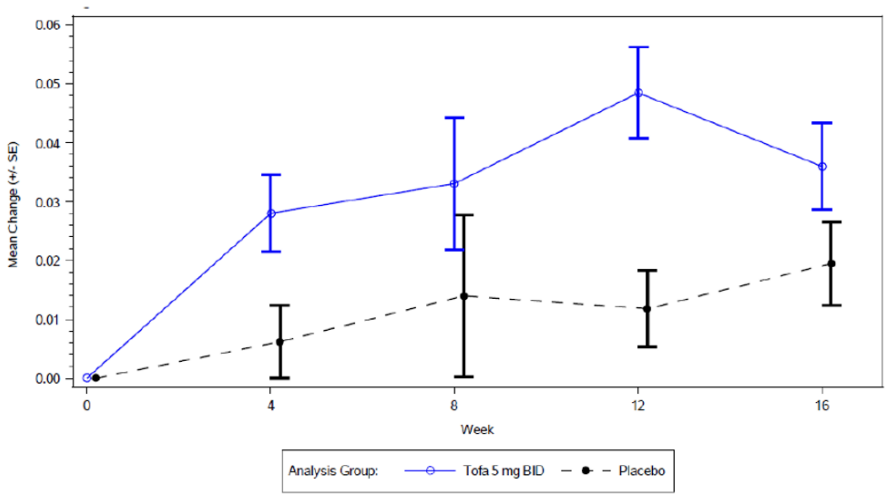
	Tofa 5 mg BID (N=184) n (%)	Placebo (N=184) n (%)
ALT		
>=2 x ULN	4 (2.2)	1 (0.5)
>=3 x ULN	1 (0.5)	0
>=5 x ULN	1 (0.5)	0
>=10 x ULN	0	0
AST		
>=2 x ULN	3 (1.6)	0
>=3 x ULN	1 (0.5)	0
>=5 x ULN	0	0
>=10 x ULN	0	0
Total Bilirubin		
>=2 x ULN	0	0
>=3 x ULN	0	0

Confirmed=at least 2 consecutive measurements with the subject.
N: Number of subjects who have a post-baseline observation for AST, ALT or total bilirubin; n (%): Number of subjects with the events (percentage based on N).
Included Protocols: A3921119, A3921120 (Final Data).
PFIZER CONFIDENTIAL Source Data: adlb Table Generation: 09NOV2020 (21:09)
(Final Data: 10Sep2020) Output File: ./unblind 1120/A392 SCSPC EU/adlb s003 4
Table C1.3.4.3.4.8-E is for Pfizer internal use.

Renal Function Testing

Studies in RA patients treated with tofacitinib have demonstrated small mean increases in serum creatinine, which remained within the normal reference range. The mean change from baseline for creatinine is shown in the following figure (Fig. 32) for the Placebo-controlled Cohort.

Figure 32. Tofacitinib Summary of Clinical Safety - Mean (± SE) Change from Baseline in creatinine (mg/dL) – AS Placebo-controlled Cohort



Module 5.3.5.3 SCS Figure C1.3.4.3.2.4-E

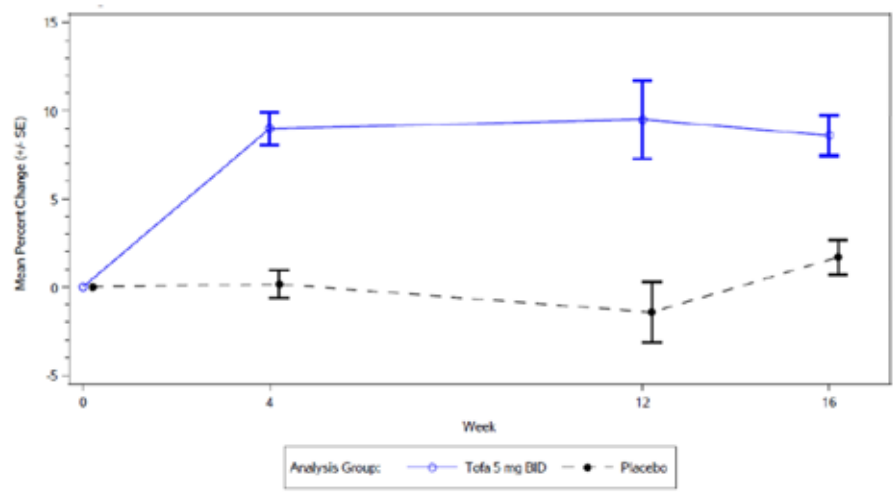
The changes of serum creatine at week 16 from baseline was: Mean (SD) 0.04 (0.100) in tofacitinib 5 mg vs 0.02 (0.095) in placebo.

Lipid Parameters

Treatment with tofacitinib has been associated with dose-dependent increases in lipid parameters including total cholesterol, LDL cholesterol and HDL cholesterol. Maximum effects have generally been observed within 6 weeks.

The mean change from baseline for cholesterol is shown in the following figure (Fig. 33) for the Placebo-controlled Cohort.

Figure 33. Tofacitinib Summary of Clinical Safety - Mean (± SE) Percent Change from Baseline in Cholesterol (mg/dL) – AS Placebo-controlled Cohort

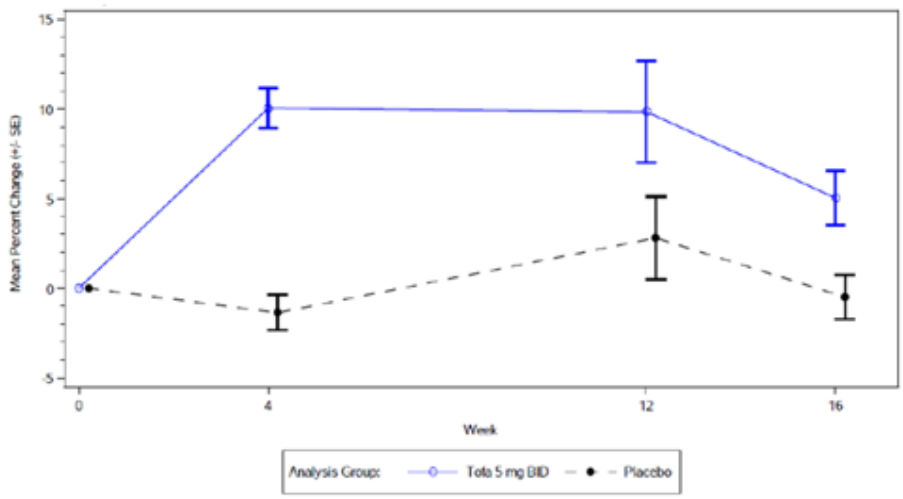


Module 5.3.5.3 SCS Figure C1.3.4.3.3.4-E

The changes from baseline for cholesterol were: mean (SD) 8.60 (15.164) in tofacitinib 5 mg vs 1.69 (13.083) in placebo.

The mean changes from baseline for HDL cholesterol are shown in the following figure (Fig. 34) for the Placebo-controlled Cohort.

Figure 34. Tofacitinib Summary of Clinical Safety – Mean (± SE) Percent Change from Baseline in HDL Cholesterol (mg/dL) – AS Placebo-controlled Cohort

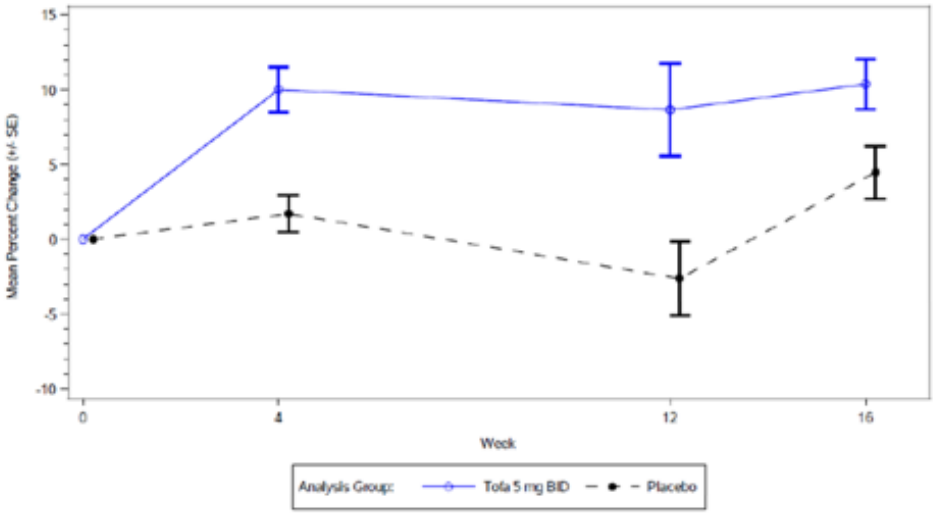


Module 5.3.5.3 SCS Figure C1.3.4.3.3.4-E

The changes at week 16 from baseline for HDL (mg/dL) cholesterol were: mean (SD) 5.04 (19.951) in tofacitinib 5 mg vs -0.49 (16.540) in placebo.

The mean changes from baseline for LDL cholesterol are shown in Figure 35 for the Placebo-controlled Cohort.

Figure 35. Tofacitinib Summary of Clinical Safety - Mean (± SE) Percent Change from Baseline in LDL Cholesterol (mg/dL) – AS Placebo-controlled Cohort

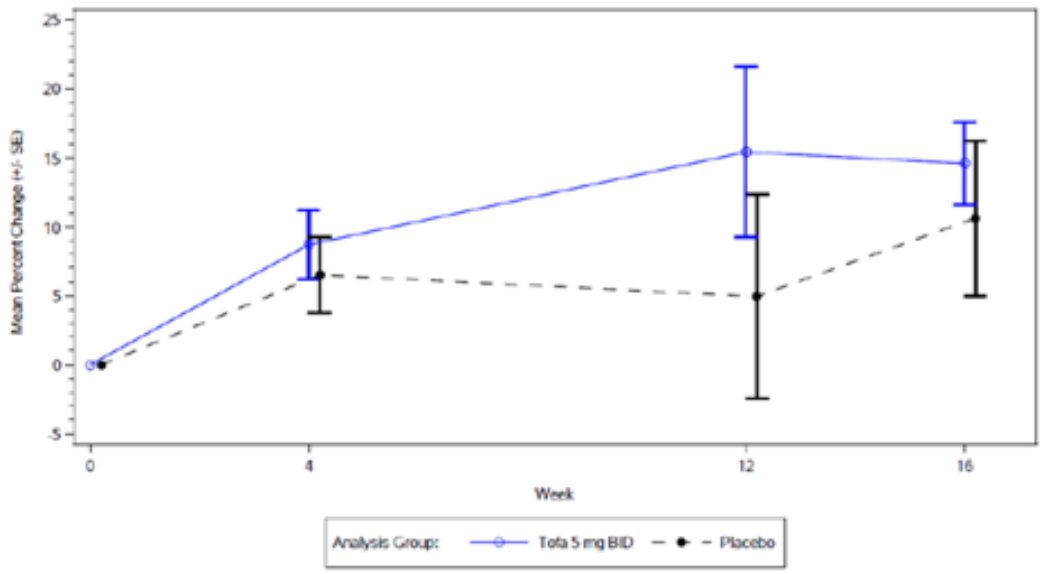


Module 5.3.5.3 SCS Figure C1.3.4.3.3.4-E

The changes at week 16 from baseline for LDL (mg/dL) cholesterol were: mean (SD) 10.37 (21.387) in tofacitinib 5 mg vs 4.46 (23.451) in placebo.

The mean changes from baseline for Triglycerides are shown in the following figure for the Placebo-controlled Cohort.

Figure 36. Tofacitinib Summary of Clinical Safety - Mean (± SE) Percent Change from Baseline in Triglycerides (mg/dL) – AS Placebo-controlled Cohort



Module 5.3.5.3 SCS Figure C1.3.4.3.3.4-E

The changes at week 16 from baseline for Triglycerides (mg/dL) were: mean (SD) 14.58 (39.489) in tofacitinib 5 mg vs 10.62 (74.379) in placebo.

Blood pressure

Changes at week 16 from baseline for systolic blood pressure (mmHg) were, mean (SD): -0.1 (10.91) in tofacitinib 5 mg vs -0.2 (10.73) in placebo.

Changes at week 48 from baseline for systolic blood pressure (mmHg) were, mean (SD): -0.4 (11.20) in tofacitinib 5 mg BID and All tofa doses.

Changes at week 16 from baseline for diastolic blood pressure (mmHg) were, mean (SD): -0.1 (7.05) in tofacitinib 5 mg vs -0.5 (8.73) in placebo.

The next table shows the categorisation of changes in blood pressure parameters.

Table 58. Tofacitinib Summary of Clinical Safety (AS) – Categorisation of Vital Signs Data

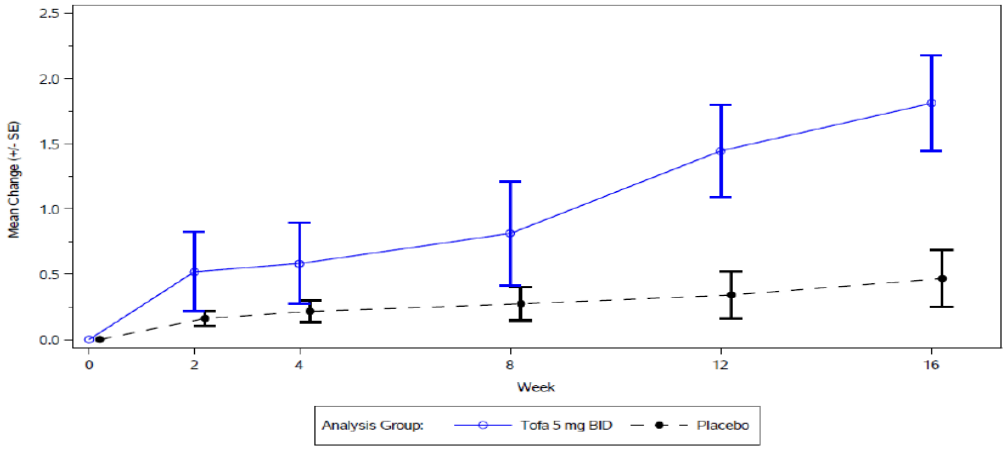
Table C2.3.5.2-E
Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis)
Categorization of Vital Signs Data - Treatment Policy Estimand, AS All Tofa Cohort

		All Tofa 5 mg BID (N=316)		All Tofa (N=420)	
Parameter (units)	**Criteria**	**N1**	**n (%)**	**N1**	**n (%)**
SITTING SYSTOLIC BLOOD PRESSURE (MMHG)	Value <90mmHg	314	1 (0.3)	415	1 (0.2)
	Chg >= 30mmHg increase	314	11 (3.5)	415	12 (2.9)
	Chg >= 30mmHg decrease	314	8 (2.5)	415	11 (2.7)
SITTING DIASTOLIC BLOOD PRESSURE (MMHG)	Value <50 mmHg	314	0	415	2 (0.5)
	Chg >= 20mmHg increase	314	16 (5.1)	415	19 (4.6)
	Chg >= 20mmHg decrease	314	16 (5.1)	415	23 (5.5)
SITTING PULSE RATE (BPM)	Value <40 bpm	314	0	415	0
	Value >120 bpm	314	1 (0.3)	415	1 (0.2)

Body weight

Changes at week 16 from baseline for weight (kg) were, mean (SD): 1.8 (4.96) in tofacitinib 5 mg vs 0.5 (2.93) in placebo (see figure below).

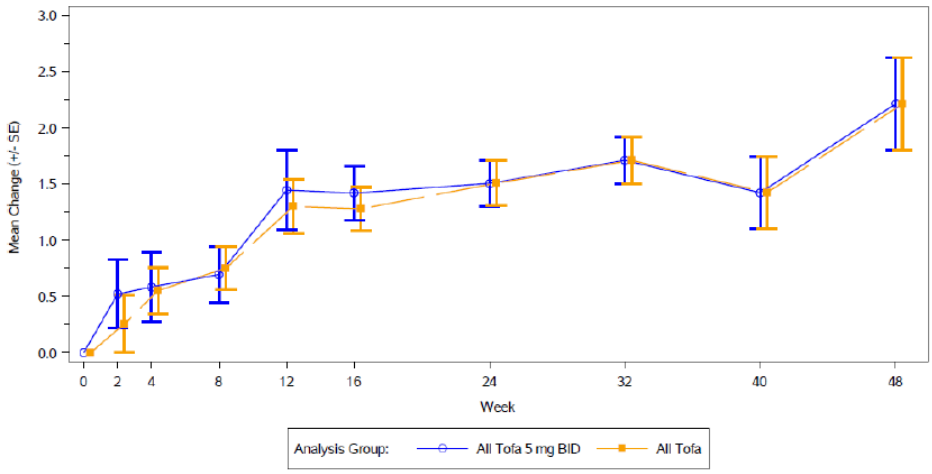
Figure 37. Tofacitinib Summary of Clinical Safety - Mean (± SE) Change from Baseline Weight (Kg) – AS Placebo-controlled Cohort



Module 5.3.5.3 SCS Figure C1.3.5.1.3-E

The changes of the weight from baseline among the All tofacitinib patients is shown in the following figure (Fig. 38).

Figure 38. Tofacitinib Summary of Clinical Safety - Mean (± SE) Change from Baseline in Weight (Kg) – AS All Tofa Cohort



Module 5.3.5.3 SCS Figure C2.3.5.1.3-E

At 48 weeks the change from baseline of the weight (kg) was, mean (SD) 2.2 (4.59) in the tofacitinib cohort in both arms (tofacitinib 5 mg and all tofacitinib doses).

The next table (Table 59) shows the shift in BMI categories.

Table 59. Shift Table of BMI Categories Relative to Baseline by Visit (Safety Analysis Set) (Final Analysis) - A3921120

		BMI Category at Visit (kg/m^2)									
		Tofacitinib 5 mg BID (N=133)					Placebo → Tofacitinib 5 mg BID (N=136)				
Visit	**BMI Category at Baseline (kg/m^2)**	**N**	**N1**	**<25 n (%)**	**≥25 to <35 n (%)**	**≥35 n (%)**	**N**	**N1**	**<25 (%)**	**≥25 to <35 n (%)**	**≥35 n (%)**
Week 16	<25	50	50	46 (92.0)	4 (8.0)	0	59	58	52 (89.7)	6 (10.3)	0
	≥25 to <35	74	73	2 (2.7)	67 (91.8)	4 (5.5)	69	68	3 (4.4)	65 (95.6)	0
	≥35	8	8	0	0	8 (100.0)	8	7	0	0	7 (100.0)
Week 48	<25	50	49	42 (85.7)	7 (14.3)	0	59	54	46 (85.2)	8 (14.8)	0
	≥25 to <35	74	68	1 (1.5)	64 (94.1)	3 (4.4)	69	66	1 (1.5)	63 (95.5)	2 (3.0)
	≥35	8	7	0	0	7 (100.0)	8	5	0	0	5 (100.0)

Source: S0113 Module 5.3.5.1 A3921120 Table 420a.1.4
Abbreviations: BID= twice a day; BMI= body mass index; N = number of subjects in the Safety Analysis Set; N1 = number of subjects with observations at baseline and at post-baseline visits.
Baseline was defined as last non-missing assessment on or before day 1 and prior to first dose of investigational product.
One subject in tofacitinib 5 mg BID has missing baseline BMI.
Percentages of BMI categories at post-baseline visit is calculated using N1 as denominator, conditioned on BMI category at baseline.
BMI at Week 16 and Week 48 are calculated using Height at Screening and Weight at Week 16 and Week 48 respectively.

ECG

The following table shows the ECG parameters categorisation for the placebo-controlled cohort.

Table 60. Tofacitinib Summary of Clinical Safety (AS) – Categorisation of ECG Data

Table C1.3.6.2-E
Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis)
Categorization of ECG Data - Treatment Policy Estimand, AS Placebo-Controlled Cohort

		Tofa 5 mg BID (N=185)		Placebo (N=187)	
Parameter (units)	**Criteria**	**N1**	**n (%)**	**N1**	**n (%)**
PR INTERVAL, SINGLE BEAT (MSEC)	Value>=300	183	0	180	0
	%Chg>=25/50%	183	2 (1.1)	180	1 (0.6)
QRS DURATION, SINGLE BEAT (MSEC)	Value>=140	183	1 (0.5)	180	2 (1.1)
	%Chg>=50%	183	0	180	1 (0.6)
QT INTERVAL, SINGLE BEAT (MSEC)	Value>=500	183	1 (0.5)	180	0
QTCB INTERVAL, SINGLE BEAT (MSEC)	450<=Value<480	183	4 (2.2)	180	10 (5.6)
	480<=Value<500	183	0	180	2 (1.1)
	Value>=500	183	1 (0.5)	180	0
	30<=Chg<60	183	11 (6.0)	180	10 (5.6)
	Chg>=60	183	1 (0.5)	180	0
QTCF INTERVAL, SINGLE BEAT (MSEC)	450<=Value<480	183	4 (2.2)	180	6 (3.3)
	Chg>=60	183	1 (0.5)	180	0

N: Number of subjects included in the Safety Analysis Set; N1: Number of subjects evaluated against criteria; n: Number of subjects that meet criteria (Percentages are based on N1).
Included Protocols: A3921119, A3921120 (Final Data).

Safety in special populations

Age

The incidence proportions and incidence rates (While on Treatment Estimand) for TEAEs by Age Group for the AS All Tofa Cohort are presented in the next table.

Table 61. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence Proportions and Incidence Rates for General Events and Infections by Age Group - While on Treatment Estimand, AS All Tofa Cohort

Events Category	Age (Years)	Analysis Group	N	n (%)	n1 (%)	PY	IR (95% CI) per 100 PY
TEAEs	<65	All Tofa 5 mg BID	309	193 (62.46)	3 (0.97)	122.63	157.39 (135.97, 181.23)
		All Tofa	407	241 (59.21)	3 (0.74)	142.60	169.01 (148.34, 191.75)
	>=65	All Tofa 5 mg BID	7	5 (71.43)	0	3.43	145.98 (47.40, 340.68)
		All Tofa	13	7 (53.85)	0	4.87	143.88 (57.85, 296.45)
SAEs	<65	All Tofa 5 mg BID	309	8 (2.59)	1 (0.32)	223.73	3.58 (1.54, 7.05)
		All Tofa	407	8 (1.97)	1 (0.25)	253.30	3.16 (1.36, 6.22)
	>=65	All Tofa 5 mg BID	7	0	0	5.66	0.00 (0.00, 65.18)
		All Tofa	13	1 (7.69)	0	7.35	13.61 (0.34, 75.82)
Severe AEs	<65	All Tofa 5 mg BID	309	7 (2.27)	0	223.86	3.13 (1.26, 6.44)
		All Tofa	407	8 (1.97)	0	253.30	3.16 (1.36, 6.22)
	>=65	All Tofa 5 mg BID	7	0	0	5.66	0.00 (0.00, 65.18)
		All Tofa	13	0	0	7.56	0.00 (0.00, 48.80)
Discontinuation of study	<65	All Tofa 5 mg BID	309	9 (2.91)	5 (1.62)	225.69	3.99 (1.82, 7.57)
		All Tofa	407	14 (3.44)	6 (1.47)	255.26	5.48 (3.00, 9.20)
	>=65	All Tofa 5 mg BID	7	1 (14.29)	0	5.66	17.67 (0.45, 98.45)
		All Tofa	13	1 (7.69)	0	7.56	13.23 (0.33, 73.71)
Discontinuation of study treatment	<65	All Tofa 5 mg BID	309	24 (7.77)	0	224.03	10.71 (6.86, 15.94)
		All Tofa	407	30 (7.37)	0	253.46	11.84 (7.99, 16.90)
	>=65	All Tofa 5 mg BID	7	1 (14.29)	0	5.66	17.68 (0.45, 98.50)
		All Tofa	13	1 (7.69)	0	7.56	13.23 (0.34, 73.73)
Discontinuation due to AEs	<65	All Tofa 5 mg BID	309	10 (3.24)	0	224.86	4.45 (2.13, 8.18)
		All Tofa	407	11 (2.70)	0	254.43	4.32 (2.16, 7.74)
	>=65	All Tofa 5 mg BID	7	1 (14.29)	0	5.66	17.68 (0.45, 98.50)
		All Tofa	13	1 (7.69)	0	7.56	13.23 (0.34, 73.73)
All Infections	<65	All Tofa 5 mg BID	309	108 (34.95)	3 (0.97)	170.95	63.18 (51.82, 76.27)
		All Tofa	407	129 (31.70)	3 (0.74)	196.48	65.66 (54.82, 78.01)
	>=65	All Tofa 5 mg BID	7	3 (42.86)	0	4.55	65.89 (13.59, 192.56)
		All Tofa	13	3 (23.08)	0	6.45	46.49 (9.59, 135.86)
Serious Infections	<65	All Tofa 5 mg BID	309	1 (0.32)	0	225.62	0.44 (0.01, 2.47)
		All Tofa	407	1 (0.25)	0	255.19	0.39 (0.01, 2.18)
	>=65	All Tofa 5 mg BID	7	0	0	5.66	0.00 (0.00, 65.18)
		All Tofa	13	0	0	7.56	0.00 (0.00, 48.80)
Herpes Zoster	<65	All Tofa 5 mg BID	309	5 (1.62)	0	224.08	2.23 (0.72, 5.21)
		All Tofa	407	7 (1.72)	0	253.33	2.76 (1.11, 5.69)
	>=65	All Tofa 5 mg BID	7	0	0	5.66	0.00 (0.00, 65.18)
		All Tofa	13	0	0	7.56	0.00 (0.00, 48.80)

28-Day (While on Treatment) Risk Period is defined as the smallest of [time (in days) to last dose + 28 days], [time to discontinuation from study], [time to last observation], and [time to death]. Under While on Treatment Estimand, PY (denominator for IR) is the sum of the times to the first event for subjects with an event or the risk periods for subjects without an event within the 28-Day (While on Treatment) Risk Period. N: Number of subjects included in the Safety Analysis Set; n: Number of subjects with an event within the 28-Day (While on Treatment) Risk Period; n1: Number of subjects with an event beyond the 28-Day (While on Treatment) Risk Period which are not included in the IR estimation. Incidence proportions, PYs and IRs are estimated based on n under this estimand.
95% CI for IR is based on Exact Poisson Distribution without adjustment to study. For subjects randomized to Placebo -> Tofa 5 mg BID, the date of first dose refers to the date of first dose of tofacitinib treatment. Discontinuation due to AEs is a mixture of discontinuation of study (in study A3921119) and discontinuation of study treatment (in study A3921120) due to adverse events.
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adae & adsaec & adds Table Generation: 10NOV2020 (03:41)
(Final Data: 10Sep2020) Output File: ./unblind 1120/A392 SCS EU/adae spe s401 tof e2 s
Table C2.3.3.4.1-E is for Pfizer internal use.

Gender

The incidence proportions and incidence rates (While on Treatment Estimand) for TEAEs SAEs, and discontinuations due to AEs by Gender for the AS All Tofa Cohort are presented in the next table (Table 62).

Table 62. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence Proportions and Incidence Rates for General Events and Infections by Gender - While on Treatment Estimand, AS All Tofa Cohort

Events Category	Gender	Analysis Group	N	n (%)	n1 (%)	PY	IR (95% CI) per 100 PY
TEAEs	Male	All Tofa 5 mg BID	261	160 (61.30)	3 (1.15)	107.68	148.59 (126.46, 173.48)
		All Tofa	333	189 (56.76)	3 (0.90)	123.81	152.65 (131.66, 176.03)
	Female	All Tofa 5 mg BID	55	38 (69.09)	0	18.37	206.85 (146.38, 283.92)
		All Tofa	87	59 (67.82)	0	23.65	249.48 (189.91, 321.81)
SAEs	Male	All Tofa 5 mg BID	261	6 (2.30)	1 (0.38)	193.78	3.10 (1.14, 6.74)
		All Tofa	333	7 (2.10)	1 (0.30)	215.52	3.25 (1.31, 6.69)
	Female	All Tofa 5 mg BID	55	2 (3.64)	0	35.61	5.62 (0.68, 20.29)
		All Tofa	87	2 (2.30)	0	45.12	4.43 (0.54, 16.01)
Severe AEs	Male	All Tofa 5 mg BID	261	6 (2.30)	0	193.33	3.10 (1.14, 6.76)
		All Tofa	333	6 (1.80)	0	215.28	2.79 (1.02, 6.07)
	Female	All Tofa 5 mg BID	55	1 (1.82)	0	36.20	2.76 (0.07, 15.39)
		All Tofa	87	2 (2.30)	0	45.57	4.39 (0.53, 15.85)
Discontinuation of study	Male	All Tofa 5 mg BID	261	8 (3.07)	4 (1.53)	195.10	4.10 (1.77, 8.08)
		All Tofa	333	12 (3.60)	4 (1.20)	217.05	5.53 (2.86, 9.66)
	Female	All Tofa 5 mg BID	55	2 (3.64)	1 (1.82)	36.25	5.52 (0.67, 19.93)
		All Tofa	87	3 (3.45)	2 (2.30)	45.77	6.56 (1.35, 19.16)
Discontinuation of study treatment	Male	All Tofa 5 mg BID	261	19 (7.28)	0	193.78	9.81 (5.90, 15.31)
		All Tofa	333	23 (6.91)	0	215.72	10.66 (6.76, 16.00)
	Female	All Tofa 5 mg BID	55	6 (10.91)	0	35.91	16.71 (6.13, 36.36)
		All Tofa	87	8 (9.20)	0	45.30	17.66 (7.63, 34.80)
Discontinuation due to AEs	Male	All Tofa 5 mg BID	261	8 (3.07)	0	194.42	4.11 (1.78, 8.11)
		All Tofa	333	9 (2.70)	0	216.38	4.16 (1.90, 7.90)
	Female	All Tofa 5 mg BID	55	3 (5.45)	0	36.10	8.31 (1.71, 24.29)
		All Tofa	87	3 (3.45)	0	45.61	6.58 (1.36, 19.22)
All Infections	Male	All Tofa 5 mg BID	261	89 (34.10)	3 (1.15)	148.76	59.83 (48.05, 73.63)
		All Tofa	333	99 (29.73)	3 (0.90)	168.86	58.63 (47.65, 71.38)
	Female	All Tofa 5 mg BID	55	22 (40.00)	0	26.75	82.25 (51.54, 124.52)
		All Tofa	87	33 (37.93)	0	34.07	96.86 (66.67, 136.03)
Serious Infections	Male	All Tofa 5 mg BID	261	1 (0.38)	0	195.03	0.51 (0.01, 2.86)
		All Tofa	333	1 (0.30)	0	216.98	0.46 (0.01, 2.57)
	Female	All Tofa 5 mg BID	55	0	0	36.25	0.00 (0.00, 10.18)
		All Tofa	87	0	0	45.77	0.00 (0.00, 8.06)
Herpes Zoster	Male	All Tofa 5 mg BID	261	2 (0.77)	0	194.60	1.03 (0.12, 3.71)
		All Tofa	333	3 (0.90)	0	216.48	1.39 (0.29, 4.05)
	Female	All Tofa 5 mg BID	55	3 (5.45)	0	35.13	8.54 (1.76, 24.95)
		All Tofa	87	4 (4.60)	0	44.41	9.01 (2.45, 23.06)

28-Day (While on Treatment) Risk Period is defined as the smallest of [time (in days) to last dose + 28 days], [time to discontinuation from study], [time to last observation], and [time to death]. Under While on Treatment Estimand, PY (denominator for IR) is the sum of the times to the first event for subjects with an event or the risk periods for subjects without an event within the 28-Day (While on Treatment) Risk Period. N: Number of subjects included in the Safety Analysis Set; n: Number of subjects with an event within the 28-Day (While on Treatment) Risk Period; n1: Number of subjects with an event beyond the 28-Day (While on Treatment) Risk Period which are not included in the IR estimation. Incidence proportions, PYs and IRs are estimated based on n under this estimand.
95% CI for IR is based on Exact Poisson Distribution without adjustment to study. For subjects randomized to Placebo -> Tofa 5 mg BID, the date of first dose refers to the date of first dose of tofacitinib treatment. Discontinuation due to AEs is a mixture of discontinuation of study (in study A3921119) and discontinuation of study treatment (in study A3921120) due to adverse events.
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adae & adsaec & adds Table Generation: 10NOV2020 (03:42)
(Final Data: 10Sep2020) Output File: ./unblind 1120/A392 SCS EU/adae spe s402 tof e2 s
Table C2.3.3.4.2-E is for Pfizer internal use.

Race

The incidence proportions and incidence rates (While on Treatment Estimand) for TEAEs SAEs, and discontinuations due to AEs by race for the AS All Tofa Cohort presented in the next table (Table 63).

Table 63. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence Proportions and Incidence Rates for General Events and Infections by Race - While on Treatment Estimand, AS All Tofa Cohort

Events Category	Race	Analysis Group	N	n (%)	n1 (%)	PY	IR (95% CI) per 100 PY
TEAEs	White	All Tofa 5 mg BID	252	149 (59.13)	3 (1.19)	108.84	136.90 (115.80, 160.73)
		All Tofa	334	183 (54.79)	3 (0.90)	126.79	144.33 (124.18, 166.82)
	Asian	All Tofa 5 mg BID	63	49 (77.78)	0	16.21	302.22 (223.58, 399.55)
		All Tofa	85	65 (76.47)	0	19.67	330.47 (255.05, 421.22)
	Other	All Tofa 5 mg BID	1	0	0	1.00	0.00 (0.00, 369.14)
		All Tofa	1	0	0	1.00	0.00 (0.00, 369.14)
SAEs	White	All Tofa 5 mg BID	252	6 (2.38)	0	182.74	3.28 (1.20, 7.15)
		All Tofa	334	7 (2.10)	0	207.02	3.38 (1.36, 6.97)
	Asian	All Tofa 5 mg BID	63	2 (3.17)	1 (1.59)	45.64	4.38 (0.53, 15.83)
		All Tofa	85	2 (2.35)	1 (1.18)	52.62	3.80 (0.46, 13.73)
	Other	All Tofa 5 mg BID	1	0	0	1.00	0.00 (0.00, 369.14)
		All Tofa	1	0	0	1.00	0.00 (0.00, 369.14)
Severe AEs	White	All Tofa 5 mg BID	252	7 (2.78)	0	182.43	3.84 (1.54, 7.91)
		All Tofa	334	8 (2.40)	0	206.78	3.87 (1.67, 7.62)
	Asian	All Tofa 5 mg BID	63	0	0	46.09	0.00 (0.00, 8.00)
		All Tofa	85	0	0	53.08	0.00 (0.00, 6.95)
	Other	All Tofa 5 mg BID	1	0	0	1.00	0.00 (0.00, 369.14)
		All Tofa	1	0	0	1.00	0.00 (0.00, 369.14)
Discontinuation of study	White	All Tofa 5 mg BID	252	8 (3.17)	3 (1.19)	184.26	4.34 (1.87, 8.55)
		All Tofa	334	13 (3.89)	4 (1.20)	208.74	6.23 (3.32, 10.65)
	Asian	All Tofa 5 mg BID	63	2 (3.17)	2 (3.17)	46.09	4.34 (0.53, 15.67)
		All Tofa	85	2 (2.35)	2 (2.35)	53.08	3.77 (0.46, 13.61)
	Other	All Tofa 5 mg BID	1	0	0	1.00	0.00 (0.00, 369.14)

Events Category	Race	Analysis Group	N	n (%)	n1 (%)	PY	IR (95% CI) per 100 PY
		All Tofa	1	0	0	1.00	0.00 (0.00, 369.14)
Discontinuation of study treatment	White	All Tofa 5 mg BID	252	19 (7.54)	0	183.16	10.37 (6.25, 16.20)
		All Tofa	334	25 (7.49)	0	207.51	12.05 (7.80, 17.78)
	Asian	All Tofa 5 mg BID	63	6 (9.52)	0	45.53	13.18 (4.84, 28.68)
		All Tofa	85	6 (7.06)	0	52.51	11.43 (4.19, 24.87)
	Other	All Tofa 5 mg BID	1	0	0	1.00	0.00 (0.00, 369.14)
		All Tofa	1	0	0	1.00	0.00 (0.00, 369.14)
Discontinuation due to AEs	White	All Tofa 5 mg BID	252	10 (3.97)	0	183.50	5.45 (2.61, 10.02)
		All Tofa	334	11 (3.29)	0	207.99	5.29 (2.64, 9.46)
	Asian	All Tofa 5 mg BID	63	1 (1.59)	0	46.02	2.17 (0.06, 12.11)
		All Tofa	85	1 (1.18)	0	53.00	1.89 (0.05, 10.51)
	Other	All Tofa 5 mg BID	1	0	0	1.00	0.00 (0.00, 369.14)
		All Tofa	1	0	0	1.00	0.00 (0.00, 369.14)
All Infections	White	All Tofa 5 mg BID	252	78 (30.95)	3 (1.19)	144.98	53.80 (42.53, 67.14)
		All Tofa	334	93 (27.84)	3 (0.90)	166.80	55.76 (45.00, 68.30)
	Asian	All Tofa 5 mg BID	63	33 (52.38)	0	29.52	111.78 (76.94, 156.98)
		All Tofa	85	39 (45.88)	0	35.13	111.01 (78.94, 151.75)
	Other	All Tofa 5 mg BID	1	0	0	1.00	0.00 (0.00, 369.14)
		All Tofa	1	0	0	1.00	0.00 (0.00, 369.14)
Serious Infections	White	All Tofa 5 mg BID	252	1 (0.40)	0	184.18	0.54 (0.01, 3.03)
		All Tofa	334	1 (0.30)	0	208.67	0.48 (0.01, 2.67)
	Asian	All Tofa 5 mg BID	63	0	0	46.09	0.00 (0.00, 8.00)
		All Tofa	85	0	0	53.08	0.00 (0.00, 6.95)
	Other	All Tofa 5 mg BID	1	0	0	1.00	0.00 (0.00, 369.14)
		All Tofa	1	0	0	1.00	0.00 (0.00, 369.14)

Events Category	Race	Analysis Group	N	n (%)	n1 (%)	PY	IR (95% CI) per 100 PY
Herpes Zoster	White	All Tofa 5 mg BID	252	5 (1.98)	0	182.64	2.74 (0.89, 6.39)
		All Tofa	334	6 (1.80)	0	207.05	2.90 (1.06, 6.31)
	Asian	All Tofa 5 mg BID	63	0	0	46.09	0.00 (0.00, 8.00)
		All Tofa	85	1 (1.18)	0	52.84	1.89 (0.05, 10.54)
	Other	All Tofa 5 mg BID	1	0	0	1.00	0.00 (0.00, 369.14)
		All Tofa	1	0	0	1.00	0.00 (0.00, 369.14)

28-Day (While on Treatment) Risk Period is defined as the smallest of [time (in days) to last dose + 28 days], [time to discontinuation from study], [time to last observation], and [time to death]. Under While on Treatment Estimand, PY (denominator for IR) is the sum of the times to the first event for subjects with an event or the risk periods for subjects without an event within the 28-Day (While on Treatment) Risk Period. N: Number of subjects included in the Safety Analysis Set; n: Number of subjects with an event within the 28-Day (While on Treatment) Risk Period; n1: Number of subjects with an event beyond the 28-Day (While on Treatment) Risk Period which are not included in the IR estimation. Incidence proportions, PYs and IRs are estimated based on n under this estimand.
95% CI for IR is based on Exact Poisson Distribution without adjustment to study. For subjects randomized to Placebo -> Tofa 5 mg BID, the date of first dose refers to the date of first dose of tofacitinib treatment. Discontinuation due to AEs is a mixture of discontinuation of study (in study A3921119) and discontinuation of study treatment (in study A3921120) due to adverse events.
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adae & adsaec & adds Table Generation: 10NOV2020 (03:44)
(Final Data: 10Sep2020) Output File: ./unblind 1120/A392 SCS EU/adae spe s404 tof e2 s
Table C2.3.3.4.4-E is for Pfizer internal use.

Geographical region

The incidence proportions and incidence rates (While on Treatment Estimand) for TEAEs SAEs, and discontinuations due to AEs by geographic region for the AS All Tofa Cohort are presented in Table 64.

Table 64. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence Proportions and Incidence Rates for General Events and Infections by Geographic Region - While on Treatment Estimand, AS All Tofa Cohort

Events Category	Geographic Region	Analysis Group	N	n (%)	n1 (%)	PY	IR (95% CI) per 100 PY
TEAEs	North America (US and Canada)	All Tofa 5 mg BID	38	33 (86.84)	0	8.94	369.17 (254.12, 518.45)
		All Tofa	51	39 (76.47)	0	11.37	343.08 (243.96, 469.00)
	European Union	All Tofa 5 mg BID	136	75 (55.15)	1 (0.74)	59.88	125.25 (98.52, 157.00)
		All Tofa	200	103 (51.50)	1 (0.50)	73.85	139.47 (113.84, 169.14)
	Asia	All Tofa 5 mg BID	61	47 (77.05)	0	15.19	309.42 (227.35, 411.47)
		All Tofa	83	63 (75.90)	0	18.64	337.90 (259.65, 432.32)
	Rest of World	All Tofa 5 mg BID	81	43 (53.09)	2 (2.47)	42.04	102.28 (74.02, 137.77)
		All Tofa	86	43 (50.00)	2 (2.33)	43.59	98.64 (71.38, 132.86)
SAEs	North America (US and Canada)	All Tofa 5 mg BID	38	0	0	24.47	0.00 (0.00, 15.07)
		All Tofa	51	0	0	28.05	0.00 (0.00, 13.15)
	European Union	All Tofa 5 mg BID	136	3 (2.21)	0	95.82	3.13 (0.65, 9.15)
		All Tofa	200	4 (2.00)	0	114.96	3.48 (0.95, 8.91)
	Asia	All Tofa 5 mg BID	61	2 (3.28)	1 (1.64)	43.60	4.59 (0.56, 16.57)
		All Tofa	83	2 (2.41)	1 (1.20)	50.58	3.95 (0.48, 14.28)
	Rest of World	All Tofa 5 mg BID	81	3 (3.70)	0	65.49	4.58 (0.94, 13.39)
		All Tofa	86	3 (3.49)	0	67.04	4.47 (0.92, 13.08)
Severe AEs	North America (US and Canada)	All Tofa 5 mg BID	38	1 (2.63)	0	24.30	4.12 (0.10, 22.93)
		All Tofa	51	1 (1.96)	0	27.88	3.59 (0.09, 19.99)
	European Union	All Tofa 5 mg BID	136	2 (1.47)	0	95.67	2.09 (0.25, 7.55)
		All Tofa	200	3 (1.50)	0	114.89	2.61 (0.54, 7.63)
	Asia	All Tofa 5 mg BID	61	0	0	44.05	0.00 (0.00, 8.37)
		All Tofa	83	0	0	51.04	0.00 (0.00, 7.23)
	Rest of World	All Tofa 5 mg BID	81	4 (4.94)	0	65.50	6.11 (1.66, 15.64)

Events Category	Geographic Region	Analysis Group	N	n (%)	n1 (%)	PY	IR (95% CI) per 100 PY
All Infections	North America (US and Canada)	All Tofa 5 mg BID	38	19 (50.00)	0	16.78	113.23 (68.17, 176.82)
		All Tofa	51	20 (39.22)	0	20.07	99.65 (60.87, 153.89)
	European Union	All Tofa 5 mg BID	136	43 (31.62)	0	74.92	57.40 (41.54, 77.31)
		All Tofa	200	57 (28.50)	0	91.89	62.03 (46.98, 80.37)
	Asia	All Tofa 5 mg BID	61	31 (50.82)	0	28.44	109.02 (74.07, 154.74)
		All Tofa	83	37 (44.58)	0	34.05	108.68 (76.52, 149.80)
	Rest of World	All Tofa 5 mg BID	81	18 (22.22)	3 (3.70)	55.37	32.51 (19.27, 51.38)
		All Tofa	86	18 (20.93)	3 (3.49)	56.92	31.62 (18.74, 49.98)
Serious Infections	North America (US and Canada)	All Tofa 5 mg BID	38	0	0	24.47	0.00 (0.00, 15.07)
		All Tofa	51	0	0	28.05	0.00 (0.00, 13.15)
	European Union	All Tofa 5 mg BID	136	0	0	97.00	0.00 (0.00, 3.80)
		All Tofa	200	0	0	116.36	0.00 (0.00, 3.17)
	Asia	All Tofa 5 mg BID	61	0	0	44.05	0.00 (0.00, 8.37)
		All Tofa	83	0	0	51.04	0.00 (0.00, 7.23)
	Rest of World	All Tofa 5 mg BID	81	1 (1.23)	0	65.74	1.52 (0.04, 8.47)
		All Tofa	86	1 (1.16)	0	67.30	1.49 (0.04, 8.28)
Herpes Zoster	North America (US and Canada)	All Tofa 5 mg BID	38	2 (5.26)	0	23.53	8.50 (1.03, 30.71)
		All Tofa	51	2 (3.92)	0	27.11	7.38 (0.89, 26.65)
	European Union	All Tofa 5 mg BID	136	3 (2.21)	0	96.33	3.11 (0.64, 9.10)
		All Tofa	200	4 (2.00)	0	115.61	3.46 (0.94, 8.86)
	Asia	All Tofa 5 mg BID	61	0	0	44.05	0.00 (0.00, 8.37)
		All Tofa	83	1 (1.20)	0	50.80	1.97 (0.05, 10.97)
	Rest of World	All Tofa 5 mg BID	81	0	0	65.82	0.00 (0.00, 5.60)
		All Tofa	86	0	0	67.37	0.00 (0.00, 5.48)

Events Category	Geographic Region	Analysis Group	N	n (%)	n1 (%)	PY	IR (95% CI) per 100 PY
All Infections	North America (US and Canada)	All Tofa 5 mg BID	38	19 (50.00)	0	16.78	113.23 (68.17, 176.82)
		All Tofa	51	20 (39.22)	0	20.07	99.65 (60.87, 153.89)
	European Union	All Tofa 5 mg BID	136	43 (31.62)	0	74.92	57.40 (41.54, 77.31)
		All Tofa	200	57 (28.50)	0	91.89	62.03 (46.98, 80.37)
	Asia	All Tofa 5 mg BID	61	31 (50.82)	0	28.44	109.02 (74.07, 154.74)
		All Tofa	83	37 (44.58)	0	34.05	108.68 (76.52, 149.80)
	Rest of World	All Tofa 5 mg BID	81	18 (22.22)	3 (3.70)	55.37	32.51 (19.27, 51.38)
		All Tofa	86	18 (20.93)	3 (3.49)	56.92	31.62 (18.74, 49.98)
Serious Infections	North America (US and Canada)	All Tofa 5 mg BID	38	0	0	24.47	0.00 (0.00, 15.07)
		All Tofa	51	0	0	28.05	0.00 (0.00, 13.15)
	European Union	All Tofa 5 mg BID	136	0	0	97.00	0.00 (0.00, 3.80)
		All Tofa	200	0	0	116.36	0.00 (0.00, 3.17)
	Asia	All Tofa 5 mg BID	61	0	0	44.05	0.00 (0.00, 8.37)
		All Tofa	83	0	0	51.04	0.00 (0.00, 7.23)
	Rest of World	All Tofa 5 mg BID	81	1 (1.23)	0	65.74	1.52 (0.04, 8.47)
		All Tofa	86	1 (1.16)	0	67.30	1.49 (0.04, 8.28)
Herpes Zoster	North America (US and Canada)	All Tofa 5 mg BID	38	2 (5.26)	0	23.53	8.50 (1.03, 30.71)
		All Tofa	51	2 (3.92)	0	27.11	7.38 (0.89, 26.65)
	European Union	All Tofa 5 mg BID	136	3 (2.21)	0	96.33	3.11 (0.64, 9.10)
		All Tofa	200	4 (2.00)	0	115.61	3.46 (0.94, 8.86)
	Asia	All Tofa 5 mg BID	61	0	0	44.05	0.00 (0.00, 8.37)
		All Tofa	83	1 (1.20)	0	50.80	1.97 (0.05, 10.97)
	Rest of World	All Tofa 5 mg BID	81	0	0	65.82	0.00 (0.00, 5.60)
		All Tofa	86	0	0	67.37	0.00 (0.00, 5.48)

Events Category	Geographic Region	Analysis Group	N	n (%)	n1 (%)	PY	IR (95% CI) per 100 PY
		All Tofa	86	4 (4.65)	0	67.05	5.97 (1.63, 15.27)
Discontinuation of study	North America (US and Canada)	All Tofa 5 mg BID	38	4 (10.53)	1 (2.63)	24.47	16.34 (4.45, 41.85)
		All Tofa	51	5 (9.80)	2 (3.92)	28.05	17.82 (5.79, 41.60)
	European Union	All Tofa 5 mg BID	136	2 (1.47)	2 (1.47)	97.00	2.06 (0.25, 7.45)
		All Tofa	200	6 (3.00)	2 (1.00)	116.36	5.16 (1.89, 11.22)
	Asia	All Tofa 5 mg BID	61	2 (3.28)	2 (3.28)	44.05	4.54 (0.55, 16.40)
		All Tofa	83	2 (2.41)	2 (2.41)	51.04	3.92 (0.47, 14.16)
	Rest of World	All Tofa 5 mg BID	81	2 (2.47)	0	65.82	3.04 (0.37, 10.98)
		All Tofa	86	2 (2.33)	0	67.37	2.97 (0.36, 10.72)
Discontinuation of study treatment	North America (US and Canada)	All Tofa 5 mg BID	38	8 (21.05)	0	24.07	33.23 (14.35, 65.49)
		All Tofa	51	10 (19.61)	0	27.52	36.34 (17.43, 66.83)
	European Union	All Tofa 5 mg BID	136	6 (4.41)	0	96.59	6.21 (2.28, 13.52)
		All Tofa	200	10 (5.00)	0	115.93	8.63 (4.14, 15.86)
	Asia	All Tofa 5 mg BID	61	6 (9.84)	0	43.49	13.80 (5.06, 30.03)
		All Tofa	83	6 (7.23)	0	50.47	11.89 (4.36, 25.87)
	Rest of World	All Tofa 5 mg BID	81	5 (6.17)	0	65.54	7.63 (2.48, 17.80)
		All Tofa	86	5 (5.81)	0	67.09	7.45 (2.42, 17.39)
Discontinuation due to AEs	North America (US and Canada)	All Tofa 5 mg BID	38	3 (7.89)	0	24.29	12.35 (2.55, 36.10)
		All Tofa	51	3 (5.88)	0	27.87	10.77 (2.22, 31.46)
	European Union	All Tofa 5 mg BID	136	4 (2.94)	0	96.66	4.14 (1.13, 10.60)
		All Tofa	200	5 (2.50)	0	116.02	4.31 (1.40, 10.06)
	Asia	All Tofa 5 mg BID	61	1 (1.64)	0	43.98	2.27 (0.06, 12.67)
		All Tofa	83	1 (1.20)	0	50.96	1.96 (0.05, 10.93)
	Rest of World	All Tofa 5 mg BID	81	3 (3.70)	0	65.59	4.57 (0.94, 13.37)
		All Tofa	86	3 (3.49)	0	67.14	4.47 (0.92, 13.06)

28-Day (While on Treatment) Risk Period is defined as the smallest of [time (in days) to last dose + 28 days], [time to discontinuation from study], [time to last observation], and [time to death]. Under While on Treatment Estimand, PY (denominator for IR) is the sum of the times to the first event for subjects with an event or the risk periods for subjects without an event within the 28-Day (While on Treatment) Risk Period. N: Number of subjects included in the Safety Analysis Set; n: Number of subjects with an event within the 28-Day (While on Treatment) Risk Period; n1: Number of subjects with an event beyond the 28-Day (While on Treatment) Risk Period which are not included in the IR estimation. Incidence proportions, PYs and IRs are estimated based on n under this estimand.
95% CI for IR is based on Exact Poisson Distribution without adjustment to study. For subjects randomized to Placebo -> Tofa 5 mg BID, the date of first dose refers to the date of first dose of tofacitinib treatment. Discontinuation due to AEs is a mixture of discontinuation of study (in study A3921119) and discontinuation of study treatment (in study A3921120) due to adverse events.
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adae & adsaec & adds Table Generation: 10NOV2020 (03:43)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCS_EU/adae_spe_s403_tof_e2_s
Table C2.3.3.4.3-E is for Pfizer internal use.

Concomitant and Prior Medications for AS

The impact of prior bDMARD medication use and csDMARD use at baseline on safety was assessed in the overall pooled safety population. In both Study A3921119 and Study A3921120, patients were prohibited from receiving bDMARDs during the study. In A3921119, patients with prior use of bDMARDs were excluded. In Study A3921120, patients with prior use of bDMARDS were permitted to be enrolled; however, approximately 80% were required to be bDMARD naïve. Patients were stratified by prior treatment history: (1) bDMARD-naive (approximately 80%) and (2) Tumor Necrosis Factor inhibitor-inadequate responder or bDMARD use (without inadequate response) (approximately 20%).

The majority of patients with AS in the clinical programme were naive to bDMARDs, with 81.6% in the All Tofa 5 mg BID group in the All Tofa Cohort having no previous experience with bDMARDs.

The incidence and proportions and incidence rates for general events and infections by prior treatment history are presented in the next table (Table 65).

Table 65. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence Proportions and Incidence Rates for General Events and Infections by Prior Treatment History - While on Treatment Estimand, AS All Tofa Cohort

Events Category	Prior Treatment History	Analysis Group	N	n (%)	n1 (%)	PY	IR (95% CI) per 100 PY
TEAEs	bDMARD-naive	All Tofa 5 mg BID	258	156 (60.47)	3 (1.16)	105.19	148.31 (125.95, 173.49)
		All Tofa	362	206 (56.91)	3 (0.83)	126.60	162.72 (141.26, 186.52)
	TNFi-IR or bDMARD Use (Non-IR)	All Tofa 5 mg BID	58	42 (72.41)	0	20.86	201.32 (145.09, 272.12)
		All Tofa	58	42 (72.41)	0	20.86	201.32 (145.09, 272.12)
SAEs	bDMARD-naive	All Tofa 5 mg BID	258	6 (2.33)	1 (0.39)	185.47	3.23 (1.19, 7.04)
		All Tofa	362	7 (1.93)	1 (0.28)	216.73	3.23 (1.30, 6.65)
	TNFi-IR or bDMARD Use (Non-IR)	All Tofa 5 mg BID	58	2 (3.45)	0	43.91	4.55 (0.55, 16.45)
		All Tofa	58	2 (3.45)	0	43.91	4.55 (0.55, 16.45)
Severe AEs	bDMARD-naive	All Tofa 5 mg BID	258	4 (1.55)	0	185.80	2.15 (0.59, 5.51)
		All Tofa	362	5 (1.38)	0	217.13	2.30 (0.75, 5.37)
	TNFi-IR or bDMARD Use (Non-IR)	All Tofa 5 mg BID	58	3 (5.17)	0	43.72	6.86 (1.41, 20.05)
		All Tofa	58	3 (5.17)	0	43.72	6.86 (1.41, 20.05)
Discontinuation of study	bDMARD-naive	All Tofa 5 mg BID	258	4 (1.55)	4 (1.55)	187.26	2.14 (0.58, 5.47)
		All Tofa	362	9 (2.49)	5 (1.38)	218.73	4.11 (1.88, 7.81)
	TNFi-IR or bDMARD Use (Non-IR)	All Tofa 5 mg BID	58	6 (10.34)	1 (1.72)	44.09	13.61 (4.99, 29.62)
		All Tofa	58	6 (10.34)	1 (1.72)	44.09	13.61 (4.99, 29.62)
Discontinuation of study treatment	bDMARD-naive	All Tofa 5 mg BID	258	12 (4.65)	0	186.38	6.44 (3.33, 11.25)
		All Tofa	362	18 (4.97)	0	217.71	8.27 (4.90, 13.07)
	TNFi-IR or bDMARD Use (Non-IR)	All Tofa 5 mg BID	58	13 (22.41)	0	43.31	30.02 (15.98, 51.33)
		All Tofa	58	13 (22.41)	0	43.31	30.02 (15.98, 51.33)
Discontinuation due to AEs	bDMARD-naive	All Tofa 5 mg BID	258	5 (1.94)	0	186.84	2.68 (0.87, 6.25)
		All Tofa	362	6 (1.66)	0	218.31	2.75 (1.01, 5.98)
	TNFi-IR or bDMARD Use (Non-IR)	All Tofa 5 mg BID	58	6 (10.34)	0	43.67	13.74 (5.04, 29.90)
		All Tofa	58	6 (10.34)	0	43.67	13.74 (5.04, 29.90)
All Infections	bDMARD-naive	All Tofa 5 mg BID	258	86 (33.33)	3 (1.16)	143.93	59.75 (47.79, 73.79)
		All Tofa	362	107 (29.56)	3 (0.83)	171.36	62.44 (51.17, 75.46)
	TNFi-IR or bDMARD Use (Non-IR)	All Tofa 5 mg BID	58	25 (43.10)	0	31.58	79.17 (51.24, 116.88)
		All Tofa	58	25 (43.10)	0	31.58	79.17 (51.24, 116.88)
Serious Infections	bDMARD-naive	All Tofa 5 mg BID	258	1 (0.39)	0	187.18	0.53 (0.01, 2.98)
		All Tofa	362	1 (0.28)	0	218.65	0.46 (0.01, 2.55)
	TNFi-IR or bDMARD Use (Non-IR)	All Tofa 5 mg BID	58	0	0	44.09	0.00 (0.00, 8.37)
		All Tofa	58	0	0	44.09	0.00 (0.00, 8.37)
Herpes Zoster	bDMARD-naive	All Tofa 5 mg BID	258	3 (1.16)	0	186.59	1.61 (0.33, 4.70)
		All Tofa	362	5 (1.38)	0	217.74	2.30 (0.75, 5.36)
	TNFi-IR or bDMARD Use (Non-IR)	All Tofa 5 mg BID	58	2 (3.45)	0	43.15	4.64 (0.56, 16.74)
		All Tofa	58	2 (3.45)	0	43.15	4.64 (0.56, 16.74)

28-Day (While on Treatment) Risk Period is defined as the smallest of [time (in days) to last dose + 28 days], [time to discontinuation from study], [time to last observation], and [time to death]. Under While on Treatment Estimand, PY (denominator for IR) is the sum of the times to the first event for subjects with an event or the risk periods for subjects without an event within the 28-Day (While on Treatment) Risk Period. N: Number of subjects included in the Safety Analysis Set;
n: Number of subjects with an event within the 28-Day (While on Treatment) Risk Period; n1: Number of subjects with an event beyond the 28-Day (While on Treatment) Risk Period which are not included in the IR estimation. Incidence proportions, PYs and IRs are estimated based on n under this estimand.
95% CI for IR is based on Exact Poisson Distribution without adjustment to study. For subjects randomized to Placebo -> Tofa 5 mg BID, the date of first dose refers to the date of first dose of tofacitinib treatment. Discontinuation due to AEs is a mixture of discontinuation of study (in study A3921119) and discontinuation of study treatment (in study A3921120) due to adverse events.
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adae & adsaec & adds Table Generation: 10NOV2020 (03:44)
(Final Data: 10Sep2020) Output File: ./unblind 1120/A392 SCS EU/adae spe s405 tof e2 s
Table C2.3.3.4.5-E is for Pfizer internal use.

Concomitant csDMARDs

The majority (71.8%) of patients in the AS clinical programme were not taking concomitant csDMARDs (Day 1). The incidence and proportions and incidence rates for general events and infections by Day 1 concomitant csDMARD use are presented in the next table (Table 66).

Table 66. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence Proportions and Incidence Rates for General Events and Infections by Day 1 Concomitant csDMARD Use - While on Treatment Estimand, AS All Tofa Cohort

Events Category	Day 1 Concomitant csDMARD Use	Analysis Group	N	n (%)	n1 (%)	PY	IR (95% CI) per 100 PY
TEAEs	Yes	All Tofa 5 mg BID	89	52 (58.43)	1 (1.12)	35.84	145.11 (108.37, 190.29)
		All Tofa	128	74 (57.81)	1 (0.78)	43.59	169.76 (133.29, 213.11)
	No	All Tofa 5 mg BID	227	146 (64.32)	2 (0.88)	90.21	161.84 (136.65, 190.32)
		All Tofa	292	174 (59.59)	2 (0.68)	103.87	167.52 (143.55, 194.34)
SAEs	Yes	All Tofa 5 mg BID	89	1 (1.12)	1 (1.12)	62.81	1.59 (0.04, 8.87)
		All Tofa	128	2 (1.56)	1 (0.78)	74.70	2.68 (0.32, 9.67)
	No	All Tofa 5 mg BID	227	7 (3.08)	0	166.57	4.20 (1.69, 8.66)
		All Tofa	292	7 (2.40)	0	185.95	3.76 (1.51, 7.76)
Severe AEs	Yes	All Tofa 5 mg BID	89	2 (2.25)	0	62.02	3.22 (0.39, 11.65)
		All Tofa	128	2 (1.56)	0	74.12	2.70 (0.33, 9.75)
	No	All Tofa 5 mg BID	227	5 (2.20)	0	167.50	2.99 (0.97, 6.97)
		All Tofa	292	6 (2.05)	0	186.74	3.21 (1.18, 6.99)
Discontinuation of study	Yes	All Tofa 5 mg BID	89	2 (2.25)	1 (1.12)	62.89	3.18 (0.39, 11.49)
		All Tofa	128	3 (2.34)	1 (0.78)	74.98	4.00 (0.83, 11.69)
	No	All Tofa 5 mg BID	227	8 (3.52)	4 (1.76)	168.47	4.75 (2.05, 9.36)
		All Tofa	292	12 (4.11)	5 (1.71)	187.84	6.39 (3.30, 11.16)
Discontinuation of study treatment	Yes	All Tofa 5 mg BID	89	5 (5.62)	0	62.56	7.99 (2.59, 18.65)
		All Tofa	128	6 (4.69)	0	74.65	8.04 (2.95, 17.49)
	No	All Tofa 5 mg BID	227	20 (8.81)	0	167.13	11.97 (7.31, 18.48)
		All Tofa	292	25 (8.56)	0	186.37	13.41 (8.68, 19.80)
Discontinuation due to AEs	Yes	All Tofa 5 mg BID	89	2 (2.25)	0	62.81	3.18 (0.39, 11.50)
		All Tofa	128	2 (1.56)	0	74.90	2.67 (0.32, 9.65)
	No	All Tofa 5 mg BID	227	9 (3.96)	0	167.71	5.37 (2.45, 10.19)
		All Tofa	292	10 (3.42)	0	187.08	5.35 (2.56, 9.83)
All Infections	Yes	All Tofa 5 mg BID	89	27 (30.34)	1 (1.12)	49.00	55.10 (36.31, 80.17)
		All Tofa	128	36 (28.13)	1 (0.78)	59.53	60.47 (42.35, 83.71)
	No	All Tofa 5 mg BID	227	84 (37.00)	2 (0.88)	126.50	66.40 (52.96, 82.21)
		All Tofa	292	96 (32.88)	2 (0.68)	143.40	66.95 (54.23, 81.75)
Serious Infections	Yes	All Tofa 5 mg BID	89	0	0	62.89	0.00 (0.00, 5.87)
		All Tofa	128	0	0	74.98	0.00 (0.00, 4.92)
	No	All Tofa 5 mg BID	227	1 (0.44)	0	168.39	0.59 (0.02, 3.31)
		All Tofa	292	1 (0.34)	0	187.77	0.53 (0.01, 2.97)
Herpes Zoster	Yes	All Tofa 5 mg BID	89	0	0	62.89	0.00 (0.00, 5.87)
		All Tofa	128	0	0	74.98	0.00 (0.00, 4.92)
	No	All Tofa 5 mg BID	227	5 (2.20)	0	166.85	3.00 (0.97, 6.99)
		All Tofa	292	7 (2.40)	0	185.91	3.77 (1.51, 7.76)

28-Day (While on Treatment) Risk Period is defined as the smallest of [time (in days) to last dose + 28 days], [time to discontinuation from study], [time to last observation], and [time to death]. Under While on Treatment Estimand, PY (denominator for IR) is the sum of the times to the first event for subjects with an event or the risk periods for subjects without an event within the 28-Day (While on Treatment) Risk Period. N: Number of subjects included in the Safety Analysis Set; n: Number of subjects with an event within the 28-Day (While on Treatment) Risk Period; n1: Number of subjects with an event beyond the 28-Day (While on Treatment) Risk Period which are not included in the IR estimation. Incidence proportions, PYs and IRs are estimated based on n under this estimand.
95% CI for IR is based on Exact Poisson Distribution without adjustment to study. For subjects randomized to Placebo -> Tofa 5 mg BID, the date of first dose refers to the date of first dose of tofacitinib treatment. Discontinuation due to AEs is a mixture of discontinuation of study (in study A3921119) and discontinuation of study treatment (in study A3921120) due to adverse events.
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adae & adsaec & adds Table Generation: 10NOV2020 (03:45)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCS_EU/adae_spe_s406_tof_e2_s
Table C2.3.3.4.6-E is for Pfizer internal use.

Discontinuation due to adverse events

AEs leading to discontinuation of study drug in the Placebo-controlled Cohort, described in the next table, were infrequent in both treatment groups (<3%). The proportion of patients reporting discontinuations of study drug due to AEs for each treatment group and the associated incidence rates (While on Treatment Estimand) are as follows (Table 67):

- Tofa 5 mg BID group: 4 (2.16%) patients representing an incidence rate of 7.04 patients with events per 100 PY.
- Placebo group: 4 (2.14%) patients representing an incidence rate of 7.10 patients with events per 100 PY.

Table 67. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence of Adverse Events leading to Discontinuation by System Organ Class and Preferred Term - Treatment Policy Estimand, AS Placebo-Controlled Cohort

Number of Subjects Evaluable for AEs	Tofa 5 mg BID (N=185)	Placebo (N=187)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**
With Any Adverse Event	4 (2.2)	4 (2.1)
EAR AND LABYRINTH DISORDERS	1 (0.5)	0
Hypoacusis	1 (0.5)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.5)	0
Peripheral swelling	1 (0.5)	0
HEPATOBILIARY DISORDERS	0	1 (0.5)
Hypertransaminasaemia	0	1 (0.5)
INFECTIONS AND INFESTATIONS	1 (0.5)	0
Meningitis	1 (0.5)	0
INVESTIGATIONS	1 (0.5)	0
Alanine aminotransferase increased	1 (0.5)	0
Aspartate aminotransferase increased	1 (0.5)	0
Gamma-glutamyltransferase increased	1 (0.5)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (0.5)
Spinal pain	0	1 (0.5)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	1 (0.5)
Pregnancy	0	1 (0.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.5)
Psoriasis	0	1 (0.5)

Table 67. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence of Adverse Events leading to Discontinuation by System Organ Class and Preferred Term - Treatment Policy Estimand, AS Placebo-Controlled Cohort

Number of Subjects Evaluable for AEs	Tofa 5 mg BID (N=185)	Placebo (N=187)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**

Subjects are only counted once per treatment per event.
Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events
within the higher level category. The table is based on the data from OC AE only.
N: Number of subjects included in the Safety Analysis Set. n (%): Number of subjects with the event (Percentages are based on N).
Included Protocols: A3921119, A3921120 (Final Data). MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adae Table Generation: 10NOV2020 (03:04)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCSPC_EU/adae_s181_1
Table C1.3.1.1-E is for Pfizer internal use.

AEs leading to discontinuation of study drug in the All Tofa Cohort are described in the next table. In the All Tofa Cohort, the proportion of patients who discontinued study drug due to AEs for the All Tofa 5 mg BID group and the associated incidence rate (While on Treatment Estimand), which was similar to the All Tofa group is presented below (Table 68).

- All Tofa 5 mg BID group: 11 (3.48%) patients representing an incidence rate of 4.77 (95% CI: 2.38, 8.54) patients with events per 100 PY.

Table 68. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence and Severity of Treatment-Emergent Adverse Events leading to Discontinuation by System Organ Class and Preferred Term - Treatment Policy Estimand, AS All Tofa Cohort

Number of Subjects Evaluable for AEs	All Tofa 5 mg BID (N=316)				All Tofa (N=420)			
Severity(a)	**Mild**	**Mod.**	**Sev.**	**Total**	**Mild**	**Mod.**	**Sev.**	**Total**
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
With Any Adverse Event	1 (0.3)	9 (2.8)	1 (0.3)	11 (3.5)	1 (0.2)	10 (2.4)	1 (0.2)	12 (2.9)
CARDIAC DISORDERS	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Tachycardia	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
EAR AND LABYRINTH DISORDERS	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Hypoacusis	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
GASTROINTESTINAL DISORDERS	1 (0.3)	1 (0.3)	0	2 (0.6)	1 (0.2)	1 (0.2)	0	2 (0.5)
Abdominal adhesions	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Abdominal pain	1 (0.3)	0	0	1 (0.3)	1 (0.2)	0	0	1 (0.2)

Table 68. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Incidence and Severity of Treatment-Emergent Adverse Events leading to Discontinuation by System Organ Class and Preferred Term - Treatment Policy Estimand, AS All Tofa Cohort

Number of Subjects Evaluable for AEs	All Tofa 5 mg BID (N=316)				All Tofa (N=420)			
Severity(a)	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Peripheral swelling	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
HEPATOBILIARY DISORDERS	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Hepatic function abnormal	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
INFECTIONS AND INFESTATIONS	0	3 (0.9)	0	3 (0.9)	0	4 (1.0)	0	4 (1.0)
Herpes zoster	0	1 (0.3)	0	1 (0.3)	0	2 (0.5)	0	2 (0.5)
Meningitis	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Pharyngitis streptococcal	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
INVESTIGATIONS	0	1 (0.3)	1 (0.3)	2 (0.6)	0	1 (0.2)	1 (0.2)	2 (0.5)
Alanine aminotransferase increased	0	1 (0.3)	1 (0.3)	2 (0.6)	0	1 (0.2)	1 (0.2)	2 (0.5)
Aspartate aminotransferase increased	0	1 (0.3)	1 (0.3)	2 (0.6)	0	1 (0.2)	1 (0.2)	2 (0.5)
Blood alkaline phosphatase increased	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Gamma-glutamyltransferase increased	0	1 (0.3)	1 (0.3)	2 (0.6)	0	1 (0.2)	1 (0.2)	2 (0.5)
NERVOUS SYSTEM DISORDERS	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Dizziness	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
VASCULAR DISORDERS	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Hypertension	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Total preferred term events	1	14	3	18	1	15	3	19

(a) If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is counted. Subjects are counted only once per treatment
per event. For the TESS algorithm any missing severities have been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was
recorded. In this case, the reported severity is summarized.
Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
TEAE in A3921119 is defined as those on-treatment events which are new or worsened in severity relative to the pre-treatment period prior to Day 1.
TEAE in A3921120 is defined as those on-treatment events which start during the effective duration of treatment.
N: Number of subjects included in the Safety Analysis Set; n: Number of subjects with the events (Percentages are based on N).
Included Protocols: A3921119, A3921120 (Final Data). The table is based on the data from OC AE only.
MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: adae Table Generation: 10NOV2020 (07:26)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCS_EU/adae_s040_tof
Table C2.1.1.3.3-E is for Pfizer internal use.

Post marketing experience

Tofacitinib received its first regulatory approval on 06 Nov 2012 for the IR formulation in the US and 22 Mar 2017 in the EU. The tofacitinib 11 mg PR formulation was subsequently approved on 23 Feb 2016 in the US and 16 Dec 2019 in the EU.

The clinical rationale for developing a PR formulation of tofacitinib is to enable QD dosing to enhance patient convenience. A QD dosing regimen provides a lower frequency of administration and thereby is likely to improve patient compliance in patients who can adhere better to a once daily regimen compared to the 5 mg IR BID dosing regimen.

The Sponsor monitors post-marketing data across the different indications and for both formulations, which reflect the safety profile of tofacitinib since marketing approval. Four new important potential risks have been determined for tofacitinib based on final data from Study A3921133: MACE, myocardial infarction, lymphoma, lung cancer. Study A3921133 was a Phase 3b/4 randomised, parallel-arm, open-label, safety endpoint study evaluating the safety of tofacitinib at 2 doses (5 mg BID and 10 mg BID) versus TNFi. As mentioned before the impact of the study results on tofacitinib safety and efficacy is being currently assessed in the EMEA/H-A20/1517/C/004214/0048 referral.

According to the MAH, updated post-marketing data provide evidence that the long-term safety of 11 mg PR QD in RA and PsA patients in the real-world setting is consistent with the safety profile of tofacitinib 5 mg IR BID in AS patients observed in the clinical trial programme.

The cumulative worldwide exposure to tofacitinib in all indications and both formulations since product approval is estimated at 391,640 PY based on marketing experience as of data lock point 05 Nov 2020.

The next table presents exposure data by tofacitinib dosing regimen (5 mg IR BID and 11 mg PR QD) for the updated US Corrona RA Registry Study A3921205 subset analysis and post-marketing surveillance reports.

Table 69. Overview of Populations in Post-marketing Safety Data

US Corrona RA Registry Study A3921205		Post-Marketing Surveillance Reports for RA[a]	
Subset analysis of incidence rates of select AEs of interest for patients taking tofacitinib 11 mg PR QD and 5 mg IR BID		Consists of post-marketing spontaneous reports, non-interventional solicited reports, and non-study literature case reports	
Treatment Group	**N (total follow-up PY)[b]**	**Treatment Group**	**Approximate Exposure (PY)*[c]**
Corrona Registry 5 mg IR BID	937 (2409.75)	Tofacitinib 5 mg IR BID	220,492[d]
Corrona Registry 11 mg PR QD	603 (647.67)	Tofacitinib 11 mg PR QD	112,495[d]

Source: PsA PR Module 5.3.6 Corrona Safety Analysis; Module 5.3.6 November 2020 PSUR Table 3.
* Estimation of patient-years (PY) of exposure is based on estimated worldwide sales data
a. RA indication includes a combination of patients diagnosed with both seropositive RA and Other RA
b. US Corrona RA Registry Study A3921205 subset analysis dated 31 Jul 2020 (using final data 31 Jan 2019).
c. Total exposure across all indications from post-marketing surveillance as of 05 Nov 2020 is estimated at 391,640 PY
d. Dose split obtained from RX share calculations from IQVIA Health Prescriber Insights

Data from US Corrona RA Registry

The US Corrona RA Registry is a prospective, multicentre, observational, disease-based registry; established in 2000, is an ongoing longitudinal clinical registry that has enrolled >45,000 patients with RA and accumulated >155,000 patient years of data.

The US Corrona RA Registry Study A3921205, a non-interventional post-authorisation safety study (PASS), was completed in March 2020 using a 31 Jan 2019 data cut. The aim was to describe the rates of safety events in tofacitinib initiators compared with bDMARD initiators in real-world clinical use using data from the Corrona RA registry.

This section presents results from a post hoc subset analysis (report dated 31 Jul 2020) of the US Corrona RA Registry Study A3921205 (final data 31 Jan 2019) conducted to further characterise the post approval safety of tofacitinib 5 mg IR BID and 11 mg PR QD via the evaluation of incidence rates of select AEs of interest. This post hoc subset analysis is an update to previously submitted data that reflects events for the entire study period.

Demographic baseline characteristics of Tofacitinib Initiators by Dose (5 mg IR BID and 11 mg PR QD) are shown below:

Table 70. Patient Demographic and Clinical Characteristics of Tofacitinib Initiators by Dose (5 mg IR BID and 11 mg PR QD) - US Corrona RA Registry Study A3921205 (31 Jul 2020 subset analysis of final data 31 Jan 2019)

At time of Tofacitinib initiation	Tofacitinib 5 mg IR BID	Tofacitinib 11 mg PR QD	P-value
	N=937	N=603	
Female: n (%)	751 (80.15)	474 (78.61)	0.464
Age (yrs)			
Mean ± SD	59.19 ± 12.02	59.91 ± 12.2	0.256
Median (IQR)	59 (52, 68)	60 (52, 68)	
Age Categories n (%)			
18-<45	99 (10.57)	68 (11.28)	0.661
45-<50	84 (8.96)	44 (7.30)	0.247
50-<55	126 (13.45)	67 (11.11)	0.177
55-<60	162 (17.29)	112 (18.57)	0.520
60-<65	153 (16.33)	85 (14.10)	0.237
65-<70	126 (13.45)	100 (16.58)	0.089
70-<75	99 (10.57)	63 (10.45)	0.941
≥75	88 (9.39)	64 (10.61)	0.433
Duration of RA (yrs): Mean ± SD	13.72 ± 9.63	13.42 ± 10.98	0.576
Race: n (%)			
White	848 (90.5)	545 (90.38)	0.938
Black/African American	36 (3.84)	27 (4.48)	0.539
Asian	11 (1.17)	9 (1.49)	0.590
Other	42 (4.48)	22 (3.65)	0.424
Weight (lbs): Mean ± SD	182.74 ± 51.21	183.35 ± 45.93	0.814
BMI Category: n (%)			
Normal/Under weight	231 (24.79)	149 (25.04)	0.910
Overweight	262 (28.11)	182 (30.59)	0.299
Obese	439 (47.1)	264 (44.37)	0.296
Smoking Status: n (%)			
Never	445 (47.75)	288 (48.16)	0.874
Prior	291 (31.22)	179 (29.93)	0.594
Current	196 (21.03)	131 (21.91)	0.683
Drinking Status: n (%)			
Not at All	524 (58.29)	330 (57.19)	0.678
Occasionally	158 (17.58)	110 (19.06)	0.469
1-3 Per Week	159 (17.69)	99 (17.16)	0.794
1-2 Per Day	55 (6.12)	36 (6.24)	0.925
3 or More Daily	3 (0.33)	2 (0.35)	0.967

Table 70. Patient Demographic and Clinical Characteristics of Tofacitinib Initiators by Dose (5 mg IR BID and 11 mg PR QD) - US Corrona RA Registry Study A3921205 (31 Jul 2020 subset analysis of final data 31 Jan 2019)

At time of Tofacitinib initiation	Tofacitinib 5 mg IR BID	Tofacitinib 11 mg PR QD	P-value
Comorbid Conditions: n (%)			
Hx of Hypertension	306 (32.66)	229 (37.98)	0.032
Hx of Diabetes	106 (11.31)	69 (11.44)	0.937
Hx of Malignancy	73 (7.79)	48 (7.96)	0.904
Hx of CV disease	399 (42.58)	300 (49.75)	0.006
Hx of Serious Infections	141 (15.05)	84 (13.93)	0.545
Hx of COPD	28 (2.99)	25 (4.15)	0.224
Medication History: n (%)			
Prior number of cDMARD (including current cDMARD) Mean ± SD	2.31 ± 1.26	2.09 ± 1.07	<0.001
Prior TNFi Use n (%)			
0 prior TNFi	124 (13.23)	115 (19.07)	0.002
1 prior TNFi	261 (27.85)	172 (28.52)	0.776
2+ prior TNFi	552 (58.91)	316 (52.4)	0.012
Prior non-TNFi Use n (%)			
0 prior non-TNFi	413 (44.08)	369 (61.19)	<0.001
1 prior non-TNFi	288 (30.74)	135 (22.39)	<0.001
2+ prior non-TNFi	236 (25.19)	99 (16.42)	<0.001
Prior Biologic Use n (%)			
0 prior biologic	88 (9.39)	90 (14.93)	0.001
1 prior biologic	171 (18.25)	141 (23.38)	0.014
2 prior biologic	213 (22.73)	155 (25.7)	0.182
3+ biologics	465 (49.63)	217 (35.99)	<0.001
Current Concomitant Medication n (%)			
Monotherapy	421 (44.93)	236 (39.14)	0.025
Combination Therapy			
MTX Alone	257 (27.43)	202 (33.5)	0.011
MTX + other cDMARD	73 (7.79)	38 (6.3)	0.270
Other cDMARD	186 (19.85)	127 (21.06)	0.565
Prednisone Use n (%)	303 (32.34)	170 (28.19)	0.085
Prednisone dose among users			
Dose ≤10 mg	255 (88.54)	151 (92.07)	0.233
Dose >10 mg	33 (11.46)	13 (7.93)	0.233
Current Statin Use: n (%)	212 (22.63)	128 (21.23)	0.519
Disease Activity: Mean ± SD			
Tender Joint Count (28)	6.31 ± 6.91	6.55 ± 6.88	0.561
Swollen Joint Count (28)	4.55 ± 5.13	4.4 ± 5	0.639
Physician Global Assessment (0-100)	31.38 ± 21.79	32.93 ± 21.53	0.230
Patient Global Assessment (0-100)	46.64 ± 26.99	46.49 ± 26.87	0.922
CDAI	18.67 ± 13.15	18.89 ± 13.37	0.782
Patient Pain (0-100)	50.18 ± 28.6	49.94 ± 28.42	0.889
Patient reported fatigue (0-100)	51.17 ± 29.96	50.09 ± 30.73	0.552
EQ5D (0-1)	0.97 ± 0.07	0.97 ± 0.07	0.113
mDAS	4.29 ± 1.41	4.34 ± 1.41	0.569
DAS28 (CRP)	3.69 ± 1.39	3.61 ± 1.4	0.380
DAS28 (ESR)	4.28 ± 1.47	4.15 ± 1.59	0.301
Line of Therapy* n (%)			
1st	4 (0.43)	5 (0.83)	0.312
2nd	84 (8.96)	85 (14.1)	0.002
3rd	171 (18.25)	141 (23.38)	0.014
4th +	678 (72.36)	372 (61.69)	<0.001

Source: PsA PR Module 5.3.6 Corrona Safety Analysis Table 1.
Body Mass Index (BMI) is calculated as weight/(height*0.01)*2.

Table 70. Patient Demographic and Clinical Characteristics of Tofacitinib Initiators by Dose (5 mg IR BID and 11 mg PR QD) - US Corrona RA Registry Study A3921205 (31 Jul 2020 subset analysis of final data 31 Jan 2019)

At time of Tofacitinib initiation	Tofacitinib 5 mg IR BID	Tofacitinib 11 mg PR QD	P-value

*Line of therapy definitions are consistent with previous reports: 1st line: Naïve to conventional synthetic DMARD-IR (csDMARDs) and all Biologic DMARD; 2nd line: csDMARDs, but biologic naïve; third line: Biologic DMARD-IR;fourth plus line: ≥2 Biologic DMARD-IR.)

Table 71. Crude Incidence Rates (per 100 PY) for Tofacitinib by Dose (5 mg IR BID versus 11 mg PR QD) of US Corrona RA Registry Study A3921205 (31 Jul 2020 subset analysis of final data 31 Jan 2019)

Event of Interest	Tofacitinib 5 mg IR BID					Tofacitinib 11 mg PR QD				
	N	PYR	Rate	95% CI		N	PYR	Rate	95% CI	
Total CVD*	45	1709.13	2.63	1.92	3.52	19	554.67	3.43	2.06	5.35
MACE†	15	1746.58	0.86	0.48	1.42	3	563.57	0.53	0.11	1.56
Total Serious Infections	49	1701.19	2.88	2.13	3.81	26	548.83	4.74	3.09	6.94
Total Herpes Zoster	33	1720.84	1.92	1.32	2.69	7	561.23	1.25	0.50	2.57
Serious Herpes Zoster	0	1758.05	0.00	0.00	0.21	0	564.02	0.00	0.00	0.65
Non-serious Herpes Zoster	33	1720.84	1.92	1.32	2.69	7	561.23	1.25	0.50	2.57
GI Perforations	1	1757.97	0.06	0.00	0.32	0	564.02	0.00	0.00	0.65
DVT or PE	6	1752.49	0.34	0.13	0.75	2	562.63	0.36	0.04	1.28
Total Cancer	63	2330.67	2.70	2.08	3.46	13	638.04	2.04	1.08	3.48
Cancer excluding NMSC	29	2389.28	1.21	0.81	1.74	7	642.25	1.09	0.44	2.25
Death	23	2419.98	0.95	0.60	1.43	4	647.67	0.62	0.17	1.58

Source: PsA PR Module 5.3.6 Corrona Safety Analysis Table 2.
Important Statistical Note about Results: due to the small number of events observed, only rates and 95% CIs are presented. At this time, any comparisons between tofacitinib 5 mg IR BID group and tofacitinib 11 mg PR QD group would be underpowered. Caution is recommended when drawing any conclusions based on these analyses.
*Total CVD is defined as hypertension requiring hospitalisation, cardiac revascularisation procedure (CABG, stent, angioplasty), ventricular arrhythmia, cardiac arrest, myocardial Infarction, acute coronary syndrome, unstable angina, CHF requiring hospitalisation, stroke, transient ischemic attack, other cardiovascular event ***(***specify***),*** deep vein thrombosis, peripheral arterial thromboembolic event, urgent peripheral arterial revascularisation, peripheral ischemia or gangrene (necrosis) and pulmonary embolism.
†MACE is defined as MI, stroke, TIA and CV death.

Age and gender standardised incidence rates for **serious infections** are as follows:

- PR group: 26 patients representing an incidence rate of 4.23 (95% CI: 2.71, 6.31) patients with events per 100 PY.
- IR group: 49 patients representing an incidence rate of 2.88 (95% CI: 2.13, 3.81) patients with events per 100 PY.

Age and gender standardised incidence rates for **Total HZ** are as follows:

- PR group: 7 patients representing an incidence rate of 1.38 (95% CI: 0.55, 2.83) patients with events per 100 PY.
- IR group: 33 patients representing an incidence rate of 1.92 (95% CI: 1.32, 2.69) patients with events per 100 PY.

When considering events stratified by line of therapy for RA, the CIs for the crude point estimates in the tofacitinib 5 mg IR BID group overlap with those in the 11 mg PR QD group with the exception of serious infections rates among patients taking tofacitinib as fourth plus line of therapy, which are presented below:

- PR group: 24 patients representing a crude incidence rate of 7.21 (95% CI: 4.62, 10.72) patients with events per 100 PY.
- IR group: 36 patients representing a crude incidence rate of 2.94 (95% CI: 2.06, 4.06) patients with events per 100 PY.

According to the MAH, the numerically higher incidence rate observed for serious infections within the tofacitinib 11 mg PR QD group relative to the 5 mg IR BID group in the fourth plus line of therapy stratum is inconsistent both with the totality of tofacitinib safety data showing similarity between IR and PR formulations (similar PK parameters and E-R data between IR to PR in RA PR), and with other results from this subset analysis of the US Corrona RA Registry Study.

According to the MAH, the differences in the serious infection rates could be due to the difference in market authorisation timing and post tofacitinib initiation follow-up time between the tofacitinib PR and IR dosing regimens in RA. Due to the market authorisation timing, patients in the overall tofacitinib IR group had longer follow-up time (on average 2.57 years), while the average follow-up time was 1.07 years in the overall PR group. To address this point, the MAH presented a Kaplan-Meier curve to summarise incidence rates of serious infections at time intervals following tofacitinib initiation for all patients (next figure).

Maximum follow-up time in the US Corrona RA Registry Study A3921205 for tofacitinib PR was 36 months. Maximum follow-up time for tofacitinib IR was ~72 months; during the 36 to 72-month follow-up timeframe, 7 serious infection events were reported for the IR formulation.

Figure 39. Kaplan-Meier Curve of All Patients without Serious Infections Among Tofacitinib Initiators by Dose (5 mg IR BID versus 11 mg PR QD)

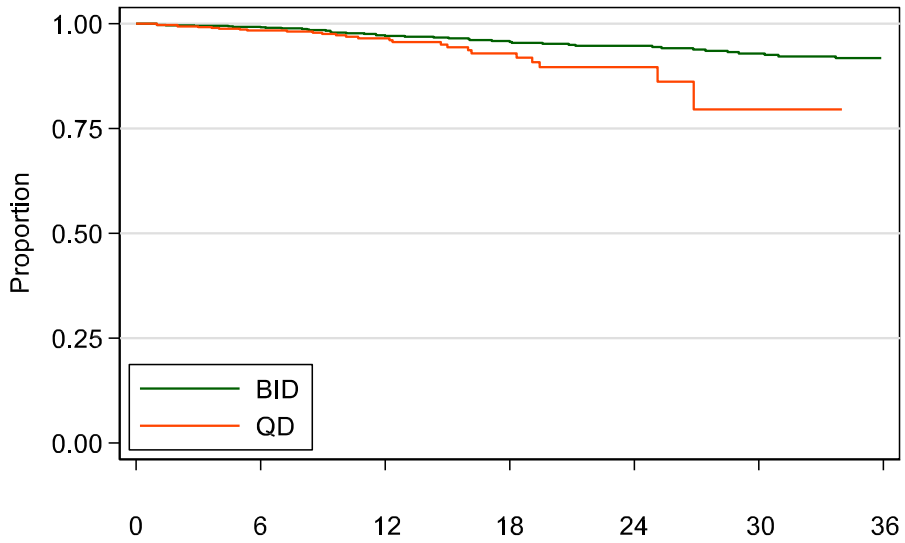


Table 72. Number of Patients with Serious Infection Events (5 mg IR BID versus 11 mg PR QD)

Time (Months)

Number at risk							
5 mg IR BID	937	817	572	429	349	277	196
11 mg PR QD	603	454	217	95	35	5	0

Time Frame (Months)	Number of Patients with Serious Infection Events	
	5 mg IR BID	11 mg PR QD
[0, 6]	8	9
[6, 12]	14	6
[12, 18]	7	6
[18, 24]	4	3
[24, 30]	6	2
[30, 36]	3	0

Source: PsA PR Module 5.3.6 Corrona Safety Analysis Appendix A Figure 1

Data from Post-Marketing Surveillance Reports

The RMP includes post-marketing data (data cut off 05 Nov 2019). Information from the post marketing setting is also included in the PSUR submitted to the EMA at 1 year intervals. Findings from post-marketing data have been consistent with the safety profile for tofacitinib.

At the time of the November 2020 data cut, the cumulative worldwide exposure to tofacitinib since product approval is estimated to be 391,640 PY. The data were extrapolated for the third quarter of

2020 by taking the average of previous 4 quarters and pro-rated to the end of the current reporting period.

There are limitations to the interpretation of the post-marketing data: under-reporting of AEs and incomplete clinical information, unknown number of patients taking the drug, no placebo control, causality is uncertain. Therefore, the data presented should be interpreted with caution.

Summary of Spontaneous Cases

There has been a total of 69,758 spontaneous case reports received. A cumulative summary of all cases and AEs, regardless of indication or dose, has been provided in the Annual PSUR with DLP 05 Nov 2019.

An overview of cases for tofacitinib by dosing regimen (11 mg PR QD, 5 mg IR BID) and indication for PsA and RA are presented in Table 73.

Table 73. Case Summary for Tofacitinib PR and IR in PsA and PR and IR in RA (Post-marketing Surveillance Spontaneous Reports) (DLP: 05 Nov 2019)

	PsA[a]		RA[a]	
	Tofacitinib 11 mg PR QD[b]	**Tofacitinib 5 mg IR BID[c]**	**Tofacitinib 11 mg PR QD[b]**	**Tofacitinib 5 mg IR BID[c]**
Total Number of Cases, n	677	890	10566	29845
Number of AEs, n	1705	2518	31776	99807
Gender, n (%)				
Male	197 (29.1)	231 (26.0)	1738 (16.4)	4961 (16.6)
Female	472 (69.7)	642 (72.1)	8766 (83.0)	24437 (81.9)
No Data	8 (1.2)	17 (1.9)	62 (0.6)	447 (1.5)
Age (yr)				
Mean	56.4	55.6	60.1	60.3
Median	58.0	56.0	61.0	61.0
Case Seriousness, n (%)				
Serious	105 (15.5)	175 (19.7)	2609 (24.7)	8679 (29.1)
Nonserious	572 (84.5)	715 (80.3)	7957 (75.3)	21166 (70.9)
Case Outcome, n (%)				
Fatal	3 (0.4)	4 (0.4)	117 (1.1)	513 (1.7)
Non-fatal[d]	674 (99.6)	886 (99.6)	10449 (98.9)	29332 (98.3)

Source: Data on file.

a. Patients included are those where the administered dose and indication were provided in the case report.

b. Tofacitinib 11 mg PR QD or total daily dose is 11 mg.

c. Tofacitinib 5 mg IR BID or total daily dose is 10 mg. Post-marketing cases for IR formulation included a very limited number of cases for which the total daily dose may be indicative of use of 10 mg tablet strength and a posology of 10 mg BID.

d. Non-fatal includes not recovered/not resolved, recovered/resolved, recovered/resolved with sequel, recovering/resolving, unknown.

A total of 25,902 cases (which included 69,672 AEs) and 43,856 cases (which included 131,691 AEs) were reported for tofacitinib PR and IR (includes data for all approved indications as well as off-label use), respectively. The majority of the cases were non-serious (79.9% for PR and 74.9% for IR). There were 5,197 and 11,011 SAEs reported for PR and IR respectively. The proportion of serious cases and the proportion of fatal cases was similar for the PR and IR formulations, for both PsA and RA.

Table 74 presents the most frequently reported AEs by SOC and PT for tofacitinib PR and IR divided by indications of PsA and RA when the indication and dose were known for the case. The distribution of AEs by SOC and PT was similar for both IR and PR formulations and for both indications. These updated data provide support that the long-term safety of 11 mg PR QD in the real-world setting is consistent with the established safety profile of tofacitinib 5 mg IR BID.

A comparison of post-marketing AEs for RA tofacitinib 11 mg PR QD to RA tofacitinib 5 mg IR BID demonstrated an identical rank order for the 10 SOCs within which AEs were most frequently reported (SOCs in rank order starting with highest reported proportions). In RA patients, the % of AEs within SOCs for which the % was ≥ 2% in either formulation were similar.

Table 74. Distribution of Post-Marketing Surveillance Adverse Events by SOC (all) and Preferred Term (≥2%) for PsA or RA (DLP: 05 Nov 2019)

	PsA[a]		RA[a]	
MedDRA SOC n (%) Preferred Term n (%)	**Tofacitinib 11 mg PR QD[c]**	**Tofacitinib 5 mg IR BID[d]**	**Tofacitinib 11 mg PR QD[c]**	**Tofacitinib 5 mg IR BID[d]**
Blood and lymphatic Disorders[b]	7 (1.0)	11 (1.2)	136 (1.3)	523 (1.8)
Cardiac disorders[b]	13 (1.9)	20 (2.2)	229 (2.2)	798 (2.7)
Congenital familial and genetic disorders[b]	0	1 (0.1)	11 (0.1)	24 (0.1)
Ear and labyrinth disorders[b]	11 (1.6)	5 (0.6)	162 (1.5)	496 (1.7)
Endocrine disorders[b]	2 (0.3)	3 (0.3)	32 (0.3)	102 (0.3)
Eye disorders[b]	13 (1.9)	23 (2.6)	424 (4.0)	1114 (3.7)
Gastrointestinal disorders	163 (24.1)	288 (32.4)	2958 (28.0)	10355 (34.7)
Abdominal discomfort	16 (2.4)	31 (3.5)	191 (1.8)	893 (3.0)
Abdominal pain upper	12 (1.8)	18 (2.0)	258 (2.4)	741 (2.5)
Diarrhoea	32 (4.7)	51 (5.7)	497 (4.7)	1734 (5.8)
Nausea	27 (4.0)	54 (6.1)	413 (3.9)	1715 (5.8)
Vomiting	9 (1.3)	14 (1.6)	175 (1.7)	597 (2.0)
General disorders and administration site conditions	419 (61.9)	690 (77.5)	7952 (75.3)	25721 (86.2)
Condition aggravated	38 (5.6)	59 (6.6)	1028 (9.7)	2881 (9.7)
Drug ineffective	120 (17.7)	170 (19.1)	1768 (16.7)	5666 (19.0)
Fatigue	32 (4.7)	68 (7.6)	588 (5.6)	2000(6.7)
Gait disturbance	12 (1.8)	11 (1.2)	202 (1.9)	656 (2.2)
Malaise	29 (4.3)	62(7.0)	692 (6.6)	1848 (6.2)
Pain	49 (7.2)	40 (4.5)	908 (8.6)	2276 (7.6)
Peripheral swelling	18 (2.7)	15 (1.7)	380 (3.6)	1104 (3.7)
Pyrexia	12 (1.8)	15 (1.7)	189 (1.8)	745 (2.5)
Therapeutic product effect incomplete	19 (2.8)	76 (8.5)	356 (3.4)	2258 (7.6)
Hepatobiliary disorders[b]	7 (1.0)	9 (1.0)	109 (1.0)	418 (1.4)
Immune system disorders[b]	20 (3.0)	28 (3.1)	355 (3.4)	754 (2.5)
Infections and infestations	175 (25.8)	286 (32.1)	3929 (37.2)	12002 (40.2)
Bronchitis	10 (1.5)	19 (2.1)	234 (2.2)	592 (2.0)
Herpes Zoster	11 (1.6)	13 (1.5)	236 (2.2)	922 (3.1)
Infection	7 (1.0)	16 (1.8)	221 (2.1)	647 (2.2)
Influenza	15 (2.2)	23 (2.6)	301 (2.9)	1017 (3.4)
Nasopharyngitis	18 (2.7)	40 (4.5)	548 (5.2)	1571 (5.3)
Pneumonia	7 (1.0)	8 (0.9)	288 (2.7)	969 (3.2)
Sinusitis	17 (2.5)	15 (1.7)	338 (3.2)	697(2.3)
Upper respiratory tract infection	14 (2.1)	7 (0.8)	187 (1.8)	331 (1.1)
Urinary tract infection	15 (2.2)	17 (1.9)	289 (2.7)	782 (2.6)
Injury, poisoning and procedural complications	270 (39.9)	293 (32.9)	2416 (22.9)	7300 (24.5)
Fall	10 (1.5)	5 (0.6)	211 (2.0)	707 (2.4)
Off label use	29 (4.3)	46 (5.2)	116 (1.1)	493 (1.7)
Product dose omission	29 (4.3)	21 (2.4)	547 (5.2)	1131 (3.8)

Table 74. Distribution of Post-Marketing Surveillance Adverse Events by SOC (all) and Preferred Term (≥2%) for PsA or RA (DLP: 05 Nov 2019)

	PsA[a]		RA[a]	
MedDRA SOC n (%) Preferred Term n (%)	**Tofacitinib 11 mg PR QD[c]**	**Tofacitinib 5 mg IR BID[d]**	**Tofacitinib 11 mg PR QD[c]**	**Tofacitinib 5 mg IR BID[d]**
Product use in unapproved indication	131 (19.4)	117 (13.1)	52 (0.5)	109 (0.4)
Product use issue	11 (1.6)	33 (3.7)	173 (1.6)	708 (2.4)
Investigations	90 (13.3)	95 (10.7)	1767 (16.7)	5002 (16.8)
Weight increased	11 (1.6)	27 (3.0)	294 (2.8)	733 (2.5)
Metabolism and nutrition disorders[b]	16 (2.4)	22 (2.5)	277 (2.6)	910 (3.0)
Musculoskeletal and connective tissue disorders	109 (16.1)	164 (18.4)	3636 (34.4)	11638 (39.0)
Arthralgia	19 (2.8)	21 (2.4)	646 (6.1)	1846 (6.2)
Back pain	9 (1.3)	14 (1.6)	210 (2.0)	694 (2.3)
Joint swelling	4 (0.6)	10 (1.1)	297 (2.8)	903 (3.0)
Musculoskeletal stiffness	6 (0.9)	3 (0.3)	265 (2.5)	621 (2.1)
Pain in extremity	21 (3.1)	26 (2.9)	482 (4.6)	1542 (5.2)
Rheumatoid arthritis	2 (0.3)	5 (0.6)	86 (0.8)	912 (3.1)
Neoplasms benign, malignant and unspecified (includes cysts and polyps)[b]	7 (1.0)	8 (0.9)	238 (2.3)	807 (2.7)
Nervous system disorders	116 (17.1)	198 (22.2)	2123 (20.1)	7072 (23.7)
Dizziness	7 (1.0)	26 (2.9)	205 (1.9)	928 (3.1)
Headache	43 (6.4)	107 (12.0)	763 (7.2)	2704 (9.1)
Pregnancy, puerperium and perinatal conditions[b]	0	0	2 (0.0)	19 (0.1)
Product issues[b]	2 (0.3)	0	32 (0.3)	68 (0.2)
Psychiatric disorders[b]	34 (5.0)	60 (6.7)	676 (6.4)	2347 (7.9)
Renal and urinary disorders[b]	13 (1.9)	19 (2.1)	303 (2.9)	971 (3.3)
Reproductive system and breast disorders[b]	4 (0.6)	1 (0.1)	92 (0.9)	293 (1.0)
Respiratory, thoracic and mediastinal disorders	86 (12.7)	122 (13.7)	2051 (19.4)	5677 (19)
Cough	10 (1.5)	22 (2.5)	368 (3.5)	1119 (3.8)
Dyspnoea	13 (1.9)	21 (2.4)	200 (1.9)	695 (2.3)
Oropharyngeal pain	6 (0.9)	14 (1.6)	244 (2.3)	626 (2.1)
Skin and subcutaneous tissue disorders	100 (14.8)	137 (15.4)	1381 (13.1)	3777 (12.7)
Psoriasis	13 (1.9)	21 (2.4)	30 (0.3)	42 (0.1)
Rash	15 (2.2)	20 (2.3)	255 (2.4)	636 (2.1)
Social circumstances[b]	8 (1.2)	5 (0.6)	143 (1.4)	466 (1.6)
Surgical and medical procedures[b]	0	0	6 (0.1)	16 (0.1)
Vascular disorders[b]	20 (3.0)	30 (3.4)	336 (3.2)	1136 (3.8)

Table 74. Distribution of Post-Marketing Surveillance Adverse Events by SOC (all) and Preferred Term (≥2%) for PsA or RA (DLP: 05 Nov 2019)

	PsA[a]		RA[a]	
MedDRA SOC n (%) Preferred Term n (%)	**Tofacitinib 11 mg PR QD[c]**	**Tofacitinib 5 mg IR BID[d]**	**Tofacitinib 11 mg PR QD[c]**	**Tofacitinib 5 mg IR BID[d]**

Source: Data on file.
*Most frequently occurring events are listed here
a. Patients included are those where the administered dose and indication were provided in the case report.
b. SOC had no events ≥2%
c. Tofacitinib 11 mg PR QD or total daily dose is 11 mg.
d. Tofacitinib 5 mg IR BID or total daily dose is 10 mg. Post-marketing cases for IR formulation included a very limited number of cases for which the total daily dose may be indicative of use of 10 mg tablet strength and a posology of 10 mg BID.

The most frequent AEs by SOC for RA were as follows:

- General disorders and administration site condition
- Infections and infestations
- Musculoskeletal and connective tissue disorders.

A comparison of post-marketing AEs for PsA tofacitinib 11 mg PR QD to PsA tofacitinib 5 mg IR BID demonstrated the 10 SOCs within which AEs were most frequently reported were the same for the 2 formulations, with a few differences in rank order.

The most frequent AEs by SOC for PsA were as follows:

- General disorders and administration site condition
- Injury, poisoning and procedural complications
- Infections and infestations.

2.5.1. Discussion on clinical safety

No AS patient has been exposed to tofacitinib 11 mg PR formulation, since the MAH maintains that the safety profile of the PR formulation is expected to be similar to that of the IR formulation in the specific setting (i.e. AS), and to that of the PR formulation in the other indications where the PR formulation has been already tested/used (i.e. RA and PsA). This bridging approach is considered acceptable.

Known Safety Profile: Tofacitinib, in the already approved indications, has shown a safety profile mainly characterised by the following: serious venous thromboembolism (VTE) events including pulmonary embolism (PE), some of which fatal, and deep vein thrombosis (DVT); serious and sometimes fatal infections; viral reactivation and cases of herpes virus reactivation; lymphomas have been observed; non-melanoma skin cancers (NMSC) have been reported; gastrointestinal perforation.

Moreover, on 18 January 2021 the MAH informed the EMA about an Emerging Safety Issue (ESI) notification for tofacitinib pertaining to two signals identified from review of the final study data in Study A3921133, specifically including the increased incidence of adjudicated MACE and adjudicated malignancies (excluding NMSC). As mentioned before the impact of the study results on tofacitinib safety and efficacy is being currently assessed in the EMEA/H-A20/1517/C/004214/0048 referral.

Source of data: Two studies have tested the IR formulation in the AS indication: 1) one completed Phase 2, 12-week long randomised double-blind, placebo-controlled, dose-ranging Study A3921119 in patients with AS (tofacitinib IR was evaluated at doses of 2, 5 and 10 mg BID); 2) one completed pivotal Study A3921120, 48-week long phase 3, randomised, double-blind, placebo-controlled (first 16 weeks) study

of the efficacy and safety of tofacitinib in patients with active AS (tofacitinib IR was evaluated at a dose of 5 mg BID).

The integrated analysis of safety included pooling of the two studies to assess: 1) short-term (0-16 weeks) safety of tofacitinib 5 mg IR BID in comparison to placebo in the combined trials (the 'Placebo-controlled Cohort'); 2) longer-term (0-48 weeks) safety of tofacitinib in the combined trials' (the 'All Tofa Cohort'). The All Tofa Cohort has 2 analysis groups: All Tofa 5 mg IR BID (tofacitinib 5 mg IR BID in the combined trials) and All Tofa (tofacitinib IR 2 mg, 5 mg, and 10 mg BID in the combined trials).

Exposure: 253 patients were exposed to tofacitinib 5 mg IR BID (the intended dosage in AS) for at least 6 months (patients-year (PY)=194), and 108 patients for at least 1 year (PY=100). There were 108 patients with AS with an exposure longer than 12 months. The number of patients exposed to a long-term treatment (e.g. 12 months) is limited, considering that the sought indication is a chronic disease requiring long-term therapy and also considering some safety concerns of the drug emerging with long term use. No patients were exposed to the PR formulation. In accordance with EMA guidelines, which consider appropriate to have data from periods longer than 12-month in this specific context, the MAH was asked to update the safety data and analysis for those subjects who experienced an exposure longer than 1 year. However, the MAH responded that during the AS program, no additional risks specific to AS emerged, and that the overall safety profile, including long-term safety, of the AS population is consistent with rheumatoid arthritis (RA) and psoriatic arthritis (PsA). Since RA and PsA are also chronic diseases requiring long-term therapy, the MAH, thus, considers the long-term safety data ($\geq$1 year) for tofacitinib gathered from RA and PsA patients to be applicable to the AS population. Therefore, the MAH does not foresee to conduct a specific study to gather long-term data in the AS population. This is acceptable.

Adverse events: Overall, in the AS placebo-controlled cohort (short-term exposure, up to 16 weeks), the proportion of subject with AEs was slightly higher in tofacitinib IR than in placebo (54.6% vs 49.2%).

The most frequently reported TEAEs in the tofacitinib IR arm of the Placebo-controlled Cohort were within the Infections and infestations (27.6%), Gastrointestinal disorders (13%), Musculoskeletal and connective tissue disorders SOCs (8.1%), and ALT/AST increase (3.2% and 2.2%). This was slightly lower in the placebo arm (23%, 15%, 11.2%, 0.5% and 0%, respectively). Similarly, the most frequently reported TEAEs in the All Tofa Cohort were within the Infections and infestations (32.1%), Gastrointestinal disorders (16.2%), Musculoskeletal and connective tissue disorders (10.5%) SOCs.

However, when the All Tofa cohort is considered, a higher incidence of AEs is found (as expected since the longer exposure): subjects with AEs were 63.6% in tofacitinib 5 mg IR BID.

Due to the limited number of patients studied in the placebo-controlled trial (185 in tofacitinib 5 mg IR BID) and the short duration of the placebo-controlled period (up to 16 weeks), it is very difficult to evaluate the observed difference in the incidence of AEs; furthermore, many AEs that are typically associated to tofacitinib treatment (such as herpes zoster), are not observed in the placebo-controlled period.

For the following AEs Hazard Ratios are higher in tofacitinib arm versus placebo: acute renal failure (HR=2.57), hypertension (2.05), weight increase (2), hyperlipidaemia (2.01) and transaminase elevations (4.03). Hypertension, weight increase, hyperlipidaemia and transaminase elevation are mentioned in SmPC 4.8. Seven cases of HZ (all non-serious) were reported in the AS clinical programme. The incidence rate per 100 PY was higher than in the PsA dataset and comparable to RA dataset (2.7, 1.7 and 3.6, respectively). Herpes zoster is already reported as a common AE in the table of the 4.8 section of the SmPC.

Acute renal failure was observed in more cases in tofacitinib than in placebo, 5 (2.70%) vs 2 (1.07%). It was 3.8% in All Tofa cohort, all treated with tofacitinib 5mg IR BID. Almost all the events listed under the SMQ of "acute renal failure" were coded as "protein urine present". Upon request, the MAH specified that in most of the cases the severity of the alteration was classified as "trace" or "+1", only one patient had "+2" as severity of the finding and none had "+3" or "+4". Moreover, all participants with AEs of "protein urine present" had creatinine levels within normal limits at all visits. Therefore, it seems that the severity of the AEs observed was mild on average. The risk of creatinine increase is already recognized at the 4.8 tabular listing of ADRs in the SmPC.

Hepatic AEs (including: Hepatic Steatosis, Transaminase Elevations) were overall observed more frequently in tofacitinib than in placebo (5.40% vs 1.07%) and this is consistent with the known impact of tofacitinib on liver safety.

In the AS program were not observed cases of: Malignancies, NMSC, CV events of MACE or thrombosis (ATE, PE, and DVT), GI Perforation, Rhabdomyolysis. To interpret correctly these data, it must be taken into account the small number of patients and the short duration of the exposure.

When the incidence rate for AEs of special interest in patients treated with tofacitinib IR in the AS development program is compared to those observed in the PsA and RA programs, the incidences in the AS are lower, this is almost certainly due to the low exposure in the AS program compared to the other two conditions. An exception is observed for herpes zoster incidence that is higher in AS patients (2.68/100 PY) compared to PsA (1.76/100 PY) but lower compared to RA (3.58/100 PY).

When compared to the RA/PsA programs, except for herpes zoster in patients taking tofacitinib 5 mg IR BID, all the SAEs were apparently less frequent in the AS program. This was most probably due to the very low exposure in the AS program (PYR=232.98 for tofacitinib IR all doses) compared to PsA in which exposure was about 10 times higher (2037.97) and RA in which it was 100 times higher (23496.73). Therefore, no conclusions can be drawn from these data and the need of having further safety information (even if only from a post-marketing setting) from a higher exposure in AS subjects is therefore foreseen.

SAEs and deaths: No deaths were reported in the AS clinical program. Incidence rate of SAEs (per 100 PY) was slightly higher in tofacitinib 5 mg IR than in placebo (5.28 vs 3.56) but the total number of cases was small (3 vs 2). In All tofacitinib IR doses the incidence rate was 3.49, that is similar to the placebo arm of the controlled cohort. There were 13 SAEs in 10 patients occurred under all tofa cohort (n=1 for each PT): Hypoacusis, Iridocyclitis, Abdominal adhesions, Condition aggravated, Hyperplastic cholecystopathy, Meningitis aseptic, Rib fracture, Tendon injury, Spinal osteoarthritis, Migraine, Ureterolithiasis, Pneumothorax and Subcutaneous emphysema. The rate of SAEs is comparable in the tofacitinib arm as compared to placebo. Since the small numbers, it is difficult to identify the most common SAEs, because virtually all the observed SAEs occurred each in a single subject. Most of the SAEs were mild in severity and many were managed by drug withdrawal.

Laboratory findings

Inclusion criteria for AS trials only allowed patients with a platelet count ≥100,000 platelets/mm^3. Platelet counts showed a mean decrease of almost 30,000/mm^3 after 48 weeks in the All Tofa cohort. In the AS clinical program, a decrease in mean platelet counts was observed from baseline to Week 4 in the Tofacitinib 5 mg IR twice a day group: platelets decreased of about 30.000/mm3 at Week 16, whereas in the placebo group there was no substantial change compared to baseline (data through Week 16). Furthermore, the reduction observed in the tofacitinib group persisted with the same magnitude (i.e. at least 30.000/mm^3) through Week 48. The MAH states that platelet profile changes over time similar to those in AS program were also seen in the rheumatoid arthritis (RA) and psoriatic arthritis (PsA) clinical programs. Pooled data were not used "due to the differences in patient populations and

study designs", according to the MAH. It is agreed that, from the data provided, a reduction in platelet count is also observed in RA and PsA patients, and the magnitude of this reduction is somehow comparable to what observed in SA. The lowest platelet count for an individual participant was 109,000 cells/mm^3 and was mild in severity according to the Rheumatology Common Toxicity Criteria. No participants had platelet counts meeting the criteria of moderate or severe laboratory abnormalities. Therefore, it can be concluded that the data presented by the MAH do not seem to indicate an AS-specific risk of platelet reduction. The SmPC section 4.8. has been modified to reflect the fact that patients enrolled in the clinical program were required to have a platelet count >100,000 /mm^3.

AST, ALT and bilirubin increased in tofacitinib IR arm but were steady in the placebo arm (AST >3.0x ULN: 2.2% vs 0.5%; ALT >3.0x ULN: 2.7% vs 0.5%). This is mentioned adequately in 4.4 and 4.8 of the proposed SmPC.

Subjects with increased Triglycerides were also higher in tofacitinib than in placebo (>1.3x ULN: 3.8% vs 1.6%). In general, the whole lipid profile was influenced by tofacitinib, with mild increase in total cholesterol, LDL, HDL and triglycerides; these AEs are already acknowledged in the SmPC.

Other laboratory result changes were comparable between tofacitinib arm and placebo arm in placebo-controlled cohort.

Vital signs No clinically significant changes were observed in blood pressure during the 16 weeks of the placebo-controlled period in patients taking tofacitinib or at the end of the 48 weeks (in the uncontrolled period); no alterations in the ECG parameters were found.

Special populations Effects by age are very difficult to estimate since the limited number of subjects (exposed to all tofacitinib doses) >65 years (n=13) vs <65 years (n=407) and thus no conclusions can be drawn). Data from the RA indication has shown a higher risk for serious infections in patients older than 65 years. This is reflected in the SmPC (4.4).

As to the gender, in almost all the categories of general events (and also for herpes zoster) female patients had higher incidence rates compared to male. However, the cohort was unbalanced since there were 594 males and 142 females.

Regarding the race most patients in the tofacitinib 5 mg BID group were White (n=252) and few were Asian (n=63). In general, more Asian patients in the tofacitinib 5 mg group experienced AEs (77.78%) compared to White (59.13%); more Asian subjects experienced Infections (52.38%) than White patients (30.95%). This is reflected in the SmPC, section 4.4.

Limited data regarding treatment with tofacitinib during pregnancy is available. No additional concerns are raised from AS pivotal trials.

Concomitant medication

Recommendations regarding DDIs are extrapolated from RA and PsA studies. No additional DDI studies have been conducted for the AS indication. This is considered acceptable, because, considering the underlying pathophysiology of RA, PsA and AS (all auto-immune diseases) and treatment options, no additional interaction issues are expected for the AS indication.

Most patients (80%) were bDMARD-naïve, and only few (20%, n=58) had used TNF inhibitor or bDMARD (20%, n=58) prior to the start of the study. Overall, a consistent increase in general events (such as AEs, SAEs, discontinuations, etc) and infections was observed in patients with previous treatment with TNFi or bDMARD compared to those bDMARD-naïve: AEs were 72.41% vs 60.47%. The highest difference was observed for "Discontinuation of study treatment", which involved 22.41% vs 4.65% of patients. The number of patients in the "previously treated" group is small and thus any conclusion is difficult, but

such results could be expected, since it is biologically plausible that patients already exposed to previous treatments develop more AEs when subsequently treated with tofacitinib.

Discontinuation due to AEs

The rate of discontinuation due to AEs was low (n=11, 3.48%) in tofacitinib 5 mg IR BID arms. The most frequent SOC reported for discontinuation belongs to infections (n=3, 0.9%). Infection is a known risk of JAK-inhibitors and is adequately discussed in proposed text of tofacitinib SmPC. No new concerns are raised due to discontinuation after infection.

Post-marketing experience

From the Corrona RA Registry Study A3921205, **Total Serious Infections** had a higher crude incidence (per 100 PY) with the PR 11 mg formulation (4.74, 95%CI: 3.09, 6.94) compared to the 5 mg IR (2.88, 95%CI: 2.13, 3.81); however, the Herpes zoster was more frequent in the IR use vs the PR.

When used as 4th or more line of therapy, serious infections were markedly higher with the PR formulation (7.21, 95% CI: 4.62, 10.72) compared to the IR formulation (2.94, 95% CI: 2.06, 4.06) with non-overlapping CI limits.

This point was already discussed in the procedure of tofacitinib PR in PsA. Briefly, the MAH maintains that this result is inconsistent with data about 3rd line and with the overall safety data, and that it could be due to the different timing in the marketing of the two formulations (more recent for the PR). However, 3rd line data are from few patients. It is acknowledged that the trend of the herpes zoster is in the opposite direction (i.e. higher risk with IR formulation vs PR), but this is considered not sufficient to rule out an overall increased risk of tofacitinib PR formulation for infections in general. However, it is recognised that the current exposure to the PR formulation is still not enough for a thorough assessment, and that the CI limits are often overlapping. Also, the Kaplan-Meier curves (used to compensate for the different marketing times of the two formulations) do not allow to rule out convincingly the possibility of an increased risk.

From the Corrona Registry also emerges a possible higher risk for CVD with the PR formulation compared to the IR: (n=19, PYR=554.67), incidence rate: 3.43 (95%CI: 2.06, 5.35) with PR vs (n=45, PYR=1709.13), incidence rate: 2.63 (95% CI, 1.92, 3.52) with IR.

Post-marketing data from surveillance do not seem to suggest a greater risk of any AE with the PR formulation respect to the IR (with the limits of the source of data).

Bridging Safety Data from Tofacitinib IR Formulation to PR Formulation in AS Patients

The data and strategy that supported the bridging of safety from tofacitinib IR (5 mg BID) to PR (11 mg QD) using similarity in PK, and supportive E-R analyses of expected on-target (possibly mechanism-based) safety endpoints in patients with RA, that have indicated that Cav(or AUC) was the relevant predictor when an E-R relationship existed, is being proposed to justify the extrapolation of efficacy and safety data from 5 mg BI) to PR (11 mg QD) in AS.

The overall similarity of PK parameters (equivalent AUC and Cmax and slightly lower Cmin at steady-state) between the 2 formulations as demonstrated in healthy volunteers, provides assurance that the safety profile of PR is likely to be similar of that of IR in patients with AS. Inter- and intra-subject variability was similar between tofacitinib IR and PR formulations for all PK parameters.

Negligible accumulation of systemic exposure (AUC accumulation ratio of 1.12) was seen following repeated dosing of tofacitinib PR. Similar to IR, more than 95% of PR is eliminated within 24 hours following discontinuation of treatment.

In addition, the expected duration of steady state plasma concentrations above the in vitro, whole blood IC50 for JAK 1/3 inhibition (17 ng/mL) is approximately 12-13 hours for both formulations over a 24-hour period. This suggests a similar level of target enzyme inhibition over the dosing interval. All these data suggest that the safety profile of the PR formulation in AS patients would be consistent with that of the IR formulation in AS.

Population PK analysis of tofacitinib in patients with active AS indicated that tofacitinib exposure, as measured by the steady-state AUC (over 24 hours) after 5 mg BID, was similar (differences between geometric means within 25%) among AS, PsA and RA patients. Geometric means of Cmax were also comparable between these 3 patient populations (AS IR PMAR-EQDD-A392k-sNDA-1064, PsA IR Module PMAR-EQDD-A392j-sNDA-601, RA IR PMAR- 00178). Furthermore, the similarities between the safety profile of tofacitinib 5 mg IR BID in AS subjects and the safety profile of tofacitinib 5 mg IR BID in RA and PsA support the conclusion that the safety profile of the PR formulation in AS would also be consistent with the PR formulation in RA.

2.5.2. Conclusions on clinical safety

No AS patients have been exposed to tofacitinib 11 mg PR formulation. Given that the entirety of data suggest the safety profile of the PR is similar to that of the IR formulation in the same indications and to the safety profile of the PR formulation in the other indications where it has already been tested or used, it is acceptable. From the data presented about the PR formulation, mainly post-marketing/registry data, an increase of serious infections seems to emerge with the PR formulation, especially when it is used as 4th or more line of therapy, compared to the IR. Also, a slightly higher CV risk seems to have been observed with the PR formulation vs the IR one. However, the nature of the data and the different exposure do not allow a thorough assessment of these signals and therefore it is difficult to reach a firm conclusion. The information about serious infections with the PR formulation, and the caution about its interpretation, are already reflected in the SmPC. In addition, as mentioned before the impact of the Study A3921133 results on tofacitinib safety and efficacy is being currently assessed in the EMEA/H-A20/1517/C/004214/0048 referral.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application. The CHMP received the following PRAC Advice on the submitted Risk Management Plan: The PRAC considered that the risk management plan version 28.1 is acceptable.

The CHMP endorsed this advice without changes. The CHMP endorsed the Risk Management Plan version 28.1 with the following content:

Safety concerns

Table 75. Summary of Safety Concerns

Important identified risks	Venous thromboembolic events (DVT/PE)
	Serious and other important infections
	HZ reactivation
	Lung cancer
	Lymphoma
	Myocardial infarction
	Decrease in neutrophil counts and neutropenia
	Decrease in lymphocyte counts and lymphopenia
	Decrease in Hgb levels and anaemia
	Lipid elevations and hyperlipidaemia
	NMSC
	Transaminase elevation and potential for DILI
Important potential risks[a]	Malignancy
	Cardiovascular risk (excl MI)
	GI perforation
	ILD
	PML
	All-cause mortality
	Increased immunosuppression when used in combination with biologics and immunosuppressants including B-lymphocyte depleting agents
	Increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients
	Primary viral infection following live vaccination
	Increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors
	Higher incidence and severity of AEs in the elderly
Missing information	Effects on pregnancy and the foetus
	Use in breastfeeding
	Effect on vaccination efficacy and the use of live/attenuated vaccines
	Use in patients with mild, moderate, or severe hepatic impairment
	Use in patients with moderate or severe renal impairment
	Use in patients with evidence of hepatitis B or hepatitis C infection
	Use in patients with malignancy
	Long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances)

a. Fractures was added as an important potential risk in EU RMP version 21.1.
AE = adverse event; CYP = cytochrome P450; DILI = drug-induced liver injury; DVT = deep vein thrombosis; Excl = excluding; GI = gastrointestinal; Hgb = haemoglobin; HZ = herpes zoster; IBD = inflammatory bowel disease; ILD = interstitial lung disease; JIA = juvenile idiopathic arthritis; MI = myocardial infarction; MTX = methotrexate; NMSC = non-melanoma skin cancer; pJIA = polyarticular juvenile idiopathic arthritis; PE = pulmonary embolism; PML = progressive multifocal leukoencephalopathy; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RMP = risk management plan

Pharmacovigilance plan

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Study A3921133: Phase 3B/4 randomised safety endpoint study of 2 doses of tofacitinib in comparison to a TNF inhibitor in subjects with RA On-going	To continue to evaluate the long-term safety of tofacitinib in patients with RA. The safety of tofacitinib at 2 doses versus adalimumab (co-primary endpoints include adjudicated MACEs and adjudicated malignancies excluding NMSC, secondary endpoints will evaluate adjudicated opportunistic OI events including TB and adjudicated hepatic events). Suspected PE cases are being adjudicated as part of the secondary endpoint of CV events other than MACE (adjudicated). All-cause mortality (adjudicated) is also a secondary endpoint.	- venous thromboembolic events (DVT/PE) - cardiovascular risk (excl MI) - MI - malignancy - NMSC - serious and other important infections - PML - transaminase elevation and potential for DILI - all-cause mortality	Study start Study finish Final report	14/03/2014 31/12/2020[a] 31/10/2021 (Please note this study completed and was addressed in EU RMP version 21.1)
Prospective, non-interventional active surveillance studies embedded within the Corrona registry (A3921329 UC) On-going	To provide additional longitudinal safety data regarding the use of tofacitinib in the US for UC patients. This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, malignancies (including lymphoma and lung	- venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - malignancy - lymphoma - lung cancer - NMSC - cardiovascular risk (excl MI)[b] - MI - PML - GI perforation - all-cause mortality	UC Study start Study finish Final report	 30/06/2019 30/06/2027 31/12/2027

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	cancer), NMSC, cardiovascular risk (specifically MACE), MI, PML, GI perforation, all-cause mortality, higher incidence and severity of AEs in elderly patients (≥65 years) including infections. In the UC study, safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.	- higher incidence and severity of AEs in the elderly		
Prospective, non-interventional active surveillance study embedded within the ARTIS registry (A3921314) On-going	To describe safety outcomes among RA patients treated with Xeljanz and other new advanced targeted therapies in real-world clinical use in ARTIS (Sweden). This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk,[b] MI, GI perforation, PML, all-cause mortality, increased risk of AEs in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of AEs in elderly patients (≥65 years) including infections.	- venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - NMSC - malignancy - lymphoma - lung cancer - CV risk (excl MI)[b] - MI - GI perforation - PML - all-cause mortality - increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients - higher incidence and severity of AEs in the elderly	Study start Interim report Study finish Final report	30/09/2018 Year 2, 4, 6 30/09/2025 30/09/2026
Prospective, non-interventional active surveillance study	To describe safety outcomes among RA patients treated with Xeljanz versus	- venous thromboembolic events (DVT/PE)	Study start Interim report	30/09/2018 Year 2, 4, 6

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
embedded within the BSRBR registry (A3921312) On-going	other new advanced targeted therapies in real-world clinical use in BSRBR (UK). This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk,[b] MI, GI perforation, PML, all-cause mortality, increased risk of AEs in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of AEs in elderly patients (≥65 years) including infections.	- serious and other important infections - HZ reactivation - NMSC - malignancy - lymphoma - lung cancer - CV risk (excl MI)[b] - MI - GI perforation - PML - all-cause mortality - increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients - higher incidence and severity of AEs in the elderly	Study finish Final report	30/09/2025 30/09/2026
Prospective, non-interventional active surveillance study embedded within the RABBIT registry (A3921317) On-going	To describe safety outcomes among RA patients treated with Xeljanz versus other new advanced targeted therapies in real-world clinical use in RABBIT (Germany) This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk,[b] MI, GI perforation, PML, all-cause mortality, increased risk of AEs in patients treated with tofacitinib in combination use of	- venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - NMSC - malignancy - lymphoma - lung cancer - CV risk (excl MI)[b] - MI - GI perforation - PML - all-cause mortality - increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients - higher incidence and severity of AEs in the elderly	Study start Interim report Study finish Final report	30/09/2018 Year 2, 4, 6 30/09/2025 30/09/2026

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	MTX, higher incidence and severity of AEs in elderly patients (≥65 years) including infections.			
Prospective, non-interventional active surveillance study embedded within the BIOBADASER registry (A3921316) On-going	To describe safety outcomes among RA patients treated with Xeljanz versus other new advanced targeted therapies in real-world clinical use in BIOBADASER (Spain). This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk,[b] MI, GI perforation, PML, all-cause mortality, increased risk of AEs in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of AEs in elderly patients (≥65 years) including infections.	- venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - NMSC - malignancy - lymphoma - lung cancer - CV risk (excl MI)[b] - MI - GI perforation - PML - all-cause mortality - increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients - higher incidence and severity of AEs in the elderly	Study start Interim report Study finish Final report	30/09/2018 Year 2, 4, 6 30/09/2025 30/09/2026
Prospective, non-interventional active surveillance pregnancy study embedded within the US OTIS registry (A3921203) On-going	To evaluate over a minimum of 5-years the potential increase in risk of birth defects, specifically a pattern of anomalies, in tofacitinib exposed pregnancies relative to 2 comparator populations. This will address the concerns of birth defects and	- effects on pregnancy and the foetus	Study start	RA: 30/04/2014 PsA: 30/06/2019 UC: 30/06/2019 pJIA: TBD AS: TBD
			Study finish	RA: 30/09/2023 PsA: 30/09/2023 UC: 30/09/2023 pJIA: TBD AS: TBD

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	pregnancy outcomes.		Final report	RA: 30/09/2024 PsA: 30/09/2024 UC: 30/09/2024 pJIA: TBD AS: TBD
Prescribers' survey A3921334 (RA, PsA, UC) Planned	The research question is whether aRMMs implemented across Europe are effective in communicating the key risk messages associated with the use of tofacitinib to health care professionals. This study will address the concerns of venous thromboembolism (DVT/PE), serious and other important infections, HZ reactivation, malignancies (including NMSC), changes in laboratory parameters, GI perforation, liver injury, increased immunosuppression when tofacitinib is used with biologics, increased risk of adverse events in patients treated with tofacitinib in combination use of MTX, primary viral infection following live vaccination, higher incidence and severity of adverse events in elderly patients, effects on pregnancy and the foetus, use in breastfeeding, effects on vaccination efficacy, use in	- venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - malignancy - NMSC - GI perforation - transaminase elevation and potential for DILI - increased immunosuppression when used in combination with biologics and immunosuppressants including B-lymphocyte depleting agents - increased risk of adverse events when tofacitinib is administered in combination with MTX in RA or PsA patients - primary viral infection following live vaccination - higher incidence and severity of adverse events in the elderly - effects on pregnancy and the foetus - use in breastfeeding - effects on vaccination efficacy and the use of live/attenuated vaccines - use in populations with mild, moderate, or severe hepatic impairment	Start of data collection End of data collection Final report	01/11/2021[f] 18/04/2022[g] 18/04/2023[h]

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	populations with severe hepatic impairment.			
Drug utilisation study A3921321 Planned	The research question is: Is there evidence that prescribers in the EU are compliant with the recommendations and limitations for use described in the tofacitinib aRMM materials? The primary objectives are to: 1. Describe the characteristics of patients treated with tofacitinib, stratified by study country (i.e., Sweden and Hungary) and indication (i.e., RA, PsA, and UC; off-label indications), in terms of: • Demographics (e.g., age, sex); and • Comorbidities and prior and current medication use. 2. Evaluate prescribers' adherence to the tofacitinib aRMMs, specifically: • Compliance to the recommended posology per indication (average daily dose) and duration of use; • Compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment; and • Compliance to recommendations for limitations of use, including:	- venous thromboembolism (DVT/PE) - use in patients with mild, moderate, or severe hepatic impairment - increased immunosuppression when used in combination with biologics and immunosuppressants including B-lymphocyte depleting agents - MI - use in patients with malignancy	Start of data collection[j] End of data collection[j] Interim study report 1 Interim study report 2 Final study report	30/09/2022 31/10/2026 31/08/2023 31/08/2025 31/10/2027[k]

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	• Use in patients with VTE risk factors; • Use in patients aged 65 years and older; • Use in patients with CV risk factors; • Use in patients with malignancy risk factors; • Contraindicated use; and • Use with concomitant medications not compatible with tofacitinib. The secondary objectives are to: 1. Describe prescribing patterns over time; and 2. To describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use implemented after the Article 20 referral and the 2021 signal evaluation procedure, specifically: • Use in patients with VTE risk factors; • Use in the elderly (patients aged 65 years and older); • Use in patients with CV risk factors; and • Use in patients with malignancy risk factors.			

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Prospective, non-interventional active surveillance study (SWIBREG) A3921344 On-going	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting. Safety concerns addressed include venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), MACE, MI, GI perforation, PML, all-cause mortality, higher incidence and severity of adverse events in elderly patients (≥65 years) including infections. Safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.	- venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - NMSC - malignancy - lymphoma - lung cancer - cardiovascular risk (excl MI)[b] - MI - GI perforation - PML - all-cause mortality - higher incidence and severity of adverse events in the elderly	Study start Interim report Study finish Final report	31/03/2021[i] Years 2 and 4 31/03/2026 31/03/2027
Prospective, non-interventional active surveillance study (UR-CARE) A3921352 Planned	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting. Safety concerns addressed include venous thromboembolism (DVT/PE), serious infections, HZ reactivation, lymphoma, lung cancer, NMSC, malignancy, cardiovascular risk (specifically MACE), MI, GI perforation, PML, all-cause mortality, higher	- venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - NMSC - malignancy - lymphoma - lung cancer - cardiovascular risk (excl MI)[b] - MI - GI perforation - PML - all-cause mortality - higher incidence and severity of adverse events in the elderly	Study start Interim report Study finish Final report	30/06/2020 Years 2 and 4 31/10/2025 30/09/2026 (Please note, study start date and other milestone dates will be updated once protocol has been submitted and approved by PRAC through a PAM)

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	incidence and severity of adverse events in elderly patients (≥65 years) including infections. Safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.			
Drug utilisation and active surveillance, post-authorisation study examining utilisation patterns and tofacitinib safety in UC (US) A3921347 On-going	To understand the patterns of tofacitinib use in the US, as well as assess the risk of safety events of interest that may be associated with its use, a non-interventional, drug utilisation and active surveillance study will be conducted using data from an administrative healthcare claims database. This study will assess overall patterns of tofacitinib use, as well as potential off-label use among non-approved indications, use of 10 mg BID in patients without a recorded diagnosis of UC, and use of 10 mg maintenance therapy among UC patients at a high risk for thrombosis. Safety concerns include venous thromboembolism (DVT/PE), mortality,[e] malignancies (including lymphoma and lung	- venous thromboembolic events (DVT/PE) - all-cause mortality[c] - malignancy - lymphoma - lung cancer - serious and other important infections - HZ reactivation - cardiovascular risk (excl MI)[b] - MI - GI perforations	Start of data collection End of data collection Interim report 1 Interim report 2 Final report	30/06/2020[d] 30/06/2025 30/06/2022 30/06/2024 30/06/2026

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	cancer), opportunistic and serious infections, herpes zoster, MACE, MI, and GI perforations Safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.			
Shingrix study Planned	To determine the immune response from the new non-live zoster vaccine (Shingrix; Recombinant, adjuvanted zoster vaccine) vs placebo vaccine in UC and RA patients on background tofacitinib or TNF blocker.	- primary viral infection following live vaccination	Study start Study finish Final report	TBD TBD TBD
Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry Planned	To contextualise the rates of safety events observed among tofacitinib-treated polyarticular JIA and juvenile PsA patients	- venous thromboembolism (DVT/PE) - serious and other important infections - malignancies - lymphoma - lung cancer - MI - GI perforation - cardiovascular risk (excl MI)[b] - long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances) - PML - all-cause mortality - HZ reactivation - NMSC - ILD	Study start Study finish Final report	TBD TBD TBD
Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for	To contextualise the rates of safety events observed among tofacitinib-treated polyarticular JIA	- venous thromboembolic events (DVT/PE) - serious and other important infections - malignancies	Study start Study finish Final report	TBD TBD TBD

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry Planned	and juvenile PsA patients	- lung cancer - lymphoma - MI - GI perforation - cardiovascular risk (excl MI)[b] - long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances) - PML - all-cause mortality - HZ reactivation - NMSC - ILD		
Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register Planned	To contextualise the rates of safety events observed among tofacitinib-treated polyarticular JIA and juvenile PsA patients	- venous thromboembolic events (DVT/PE) - serious infections and other important infections - malignancies - lymphoma - lung cancer - MI - GI perforation - cardiovascular risk (excl MI)[b] - long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances) - PML - all-cause mortality - HZ reactivation - NMSC - ILD	Study start Study finish Final report	TBD TBD TBD
An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry Planned	To evaluate risks (malignancies, serious infections [including opportunistic infections], and thrombosis) in pJIA patients in the US	- malignancies - NMSC - lymphoma - lung cancer - MI - serious and other important infections - venous thromboembolic events (DVT/PE) - long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances)	Study start Study finish Final report	TBD TBD TBD

Table 76. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
A3921145 On-going	To determine the long-term safety and tolerability of tofacitinib for treatment of the signs and symptoms of JIA. To evaluate the persistence of efficacy of tofacitinib for treatment of the signs and symptoms of JIA.	- long-term safety in pJIA and juvenile PsA patients (e.g., growth or development disturbances)	Study start Study finish Final report	18/03/2013 TBD TBD

a. Database release
b. Specifically, MACE
c. Due to limitations related to the claims database, only in-hospital mortality can be assessed
d. This represents start of data collection for the active surveillance portion of the study. Start of data collection for the drug utilisation study will be 31 March 2021.
e. Due to limitations related to the claims database, only in-hospital mortality can be assessed.
f. The start of data collection will be contingent upon PRAC's endorsement of the protocol amendment/ modified questionnaire, completion of user testing of the translated questionnaire in study countries, and local submissions of the final study protocol. There is a potential for variability in start dates (e.g., related to submissions/approvals from local Health Authorities, Ethics Committees, and other privacy and/or disclosure organizations).
g. The survey will occur over a 12 week (3 month) period in each country. The time between the start and end of data collection is more than 12 weeks because data collection in Germany is not estimated to begin until 16 February 2022.
h. The final study report will contain the pooled results from all 8 survey countries. The date of the final study report submission will be dependent on the start of data collection for the last survey country. Survey initiation may be delayed due to submissions to local Health Authorities, Ethics Committees, and/or other competent authorities.
i. Study protocol approved on 01/03/2021. Study start date does not impact patient accrual as data can be obtained retrospectively.
j. Start and end of data collection refer to the start and end of data extraction, respectively, due to the approximate 2-year data lag associated with the databases. Interim study report 1 will cover data from 01 April 2016 through 31 December 2020. Interim study report 2 will cover data from 01 April 2016 through 31 December 2022. The final study report will cover data from 01 April 2016 through 31 December 2024.
k. If it is necessary to extend the study observation period for a country because the minimum number of tofacitinib patients (100 patients) per indication has not been met for all three indications by the end of the study observation period, the study observation period will be extended for those countries as the data are available and the MAH will submit the final study report later than 31 October 2027. For those countries that have met the minimum patient threshold of at least 100 tofacitinib patients per indication for all three indications at the end of the study observation period, a second interim study report will be submitted within 12 months after the planned end of data collection.
Please note, for Study A3921133, on 19 February 2019, the 10 mg dose was discontinued.
AE = Adverse Event; ARTIS = Anti-rheumatic Therapies In Sweden; AS = ankylosing spondylitis; bDMARD = biologic disease-modifying antirheumatic drug; BID = twice daily; BIKER = German Biologics in Pediatric Rheumatology Registry; BIOBADASER = Registro Español De Acontecimientos Adversos De Terapias Biológicas En Enfermedades Reumáticas; BSRBR = British Society For Rheumatology Biologics Register; CARRA = Childhood Arthritis and Rheumatology Research Alliance; CV = cardiovascular; EHR = electronic health care records; ENEIDA = Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales; EU = European Union; excl = excluding; GI = gastrointestinal; JuMBO = Juvenile Arthritis Methotrexate/Biologics long-term Observation; MACE = major adverse cardiac event; MI = myocardial infarction; MTX = methotrexate; NMSC = non-melanoma Skin Cancer; OI = opportunistic infection; OTIS = Organisation Of Teratology Information Specialists; PAM = Post-Authorisation Measure; pJIA = polyarticular juvenile idiopathic arthritis; PML = progressive multifocal leukoencephalopathy; PRAC = Pharmacovigilance Risk Assessment Committee; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RABBIT = Rheumatoide Arthritis–Beobachtung Der Biologika-Therapie; RMP = Risk Management Plan; SWIBREG = Swedish National Quality Registry for Inflammatory Bowel Disease, TB = tuberculosis; TBD = to be determined; TNF = tumour necrosis factor; UC = ulcerative colitis; UR-CARE = United Registries for Clinical Assessment and Research; US = United States; VTE = venous thromboembolism

Risk minimisation measures

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Venous thromboembolic events (DVT/PE)	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314],

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (Swedish National Quality Registry for Inflammatory Bowel Disease [SWIBREG] – A3921344, and the United Registries for Clinical Assessment and Research [UR-CARE] – A3921352), over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database. •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. (Please note this study completed and was addressed in EU RMP version 21.1)
Serious and other important infections	<u>Routine risk minimisation measures:</u> SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties <u>Additional risk minimisation measures:</u>	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •Post-Authorisation Active Safety Surveillance Program Among

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
HZ reactivation	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).	<u>reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Lung cancer	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
Lymphoma	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		(SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
Myocardial infarction	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		[A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database. •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. (Please note this study completed and was addressed in EU RMP version 21.1) •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment)
Decrease in neutrophil counts and neutropenia	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Decrease in lymphocyte counts and lymphopenia	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	
Decrease in Hgb levels and anaemia	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Lipid elevations and hyperlipidaemia	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
NMSC	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	prescribers (including Prescriber Brochure).	PsA within BIKER and within the JuMBO Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. (Please note this study completed and was addressed in EU RMP version 21.1) •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Transaminase elevation and potential for DILI	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. (Please note this study completed and was addressed in EU RMP version 21.1) • A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment)
Important Potential Risks		
Malignancy	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. (Please note this study completed and was addressed in EU RMP version 21.1) •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
Cardiovascular risk (excl MI)	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 Special warnings and precautions for use SmPC Section 5.1 Pharmacodynamic properties <u>Additional risk minimisation measures:</u> None proposed	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. (Please note this study completed and was addressed in EU RMP version 21.1) •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
GI perforation	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 Special warnings and precautions for use <u>Additional risk minimisation measures:</u>	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u>

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	•Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
ILD	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 Special warnings and precautions for use	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register
PML	Routine risk minimisation measures: Not applicable Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. (Please note this study completed and was addressed in EU RMP version 21.1) •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.
All-cause mortality	<u>Routine risk minimisation measures:</u> SmPC Section 5.1 Pharmacodynamic properties <u>Additional risk minimisation measures:</u> None proposed	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		PsA within the UK JIA Biologics Register •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. (Please note this study completed and was addressed in EU RMP version 21.1) •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (in-hospital mortality)
Increased immunosuppression when used in combination with biologics and immunosuppressants including B-lymphocyte depleting agents	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 Special warnings and precautions for use <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment)
Increased risk of AEs when tofacitinib is administered in combination with	<u>Routine risk minimisation measures:</u>	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u>

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
MTX in RA or PsA patients	SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).	None Additional pharmacovigilance activities: •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment)
Primary viral infection following live vaccination	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Shingrix study
Increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Higher incidence and severity of AEs in the elderly	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities:

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).	•A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.
Missing Information		
Effects on pregnancy and the foetus	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, pregnancy, and lactation Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Monitoring via an established pregnancy registry (US OTIS). •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment)
Use in breastfeeding	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, pregnancy, and lactation Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment)

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Effect on vaccination efficacy and the use of live/attenuated vaccines	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment)
Use in patients with mild, moderate, or severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 5.2 Pharmacokinetic properties Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment)
Use in patients with moderate or severe renal impairment	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 5.2 Pharmacokinetic properties Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with evidence of hepatitis B or C infection	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with malignancy	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse

Table 77. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None proposed	reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment)
Long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances)	Routine risk minimisation measures: None Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Study A3921145: A Long Term, Open Label Follow Up Study of Tofacitinib for Treatment of JIA

AE = adverse event; ARTIS = Anti-rheumatic Therapies In Sweden; BIKER = German Biologics in Pediatric Rheumatology Registry; BIOBADASER = Registro Español De Acontecimientos Adversos De Terapias Biológicas En Enfermedades Reumáticas; BSRBR = British Society For Rheumatology Biologics Register; CARRA = Childhood Arthritis and Rheumatology Research Alliance; CYP = cytochrome P450; DILI = drug-induced liver injury; DVT = deep vein thrombosis; EU = European Union; Excl = excluding; GI = gastrointestinal; Hgb = haemoglobin; HZ = herpes zoster; IBD = inflammatory bowel disease; ILD = interstitial lung disease; JIA = juvenile idiopathic arthritis; JuMBO = Juvenile Arthritis Methotrexate/Biologics long-term Observation;MI = myocardial infarction; MTX = methotrexate; NMSC = non-melanoma skin cancer; OTIS = Organisation of Teratology Information Specialists; PASS = post-authorisation safety study; PE = pulmonary embolism; pJIA = polyarticular juvenile idiopathic arthritis; PML = progressive multifocal leukoencephalopathy; PRAC = Pharmacovigilance Risk Assessment Committee; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RABBIT = Rheumatoide Arthritis–Beobachtung Der Biologika-Therapie; RMM = risk minimisation measure; RMP = Risk Management Plan; SmPC = Summary of Product Characteristics; SWIBREG = Swedish National Quality Registry for Inflammatory Bowel Disease, TNF = tumour necrosis factor; UC = ulcerative colitis; UR-CARE = United Registries for Clinical Assessment and Research; US = United States

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

The MAH will submit the results of a user consultation with target patient groups on the package leaflet that meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use following the conclusion of the ongoing variation and Art. 20 referral procedure.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication for tofacitinib oral PR tablet 11 mg once daily is for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

AS is a chronic inflammatory rheumatic disease primarily affecting the sacroiliac joints and spine and is part of the family of related SpA disorders, which also includes PsA. AS or radiographic axial SpA is defined by the presence of definitive radiographic sacroiliitis based upon 1984 Modified New York classification criteria. AS causes chronic inflammation at the insertion of ligaments and tendons in the axial skeleton (entheses) and may progress from inflammation in the sacroiliac joints to sacroiliac and spine ankylosis over time. AS is also associated with peripheral arthritis, and enthesitis, and extra-articular manifestations such as anterior uveitis, psoriasis, and IBD. Osteoporosis is a common AS comorbidity. AS is often present for many years before it is diagnosed and typically presents in people between 20 and 40 years of age, with a higher prevalence in males, leading to back pain, stiffness, fatigue, progressive disability and adverse effects on health.

Overall, the pathogenesis of AS is not well characterised but seems to include both genetic and environmental components, which combine to elicit a chronic inflammatory response involving the innate and adaptive immune systems. A genetic link was noted. 90 - 95% of white Western European people with AS are positive for the HLA-B27 allele, and risk increases with HLA-B27-positive relatives. -related

quality of life. Confirmation that TNFaplha (secreted by Th1 and T CD8+ cells) and IL-17 (secreted by Th17 and T CD8+ cells) contribute to the pathogenesis of AS has been provided by the efficacy of interventions such as TNFi and anti-IL-17 mAb. These biologic therapies directly inhibit the effect of 1 cytokine pathway. Tofacitinib, a small molecule inhibitor of JAK, interferes directly (e.g., IL-23) or indirectly (e.g., TNFalpha, IL-17) with the signalling of multiple AS-associated cytokines.

3.1.2. Available therapies and unmet medical need

Based on the current evidence and the considerations of ASAS and EULAR, NSAIDs and TNFi remain the primary classes of medications for the treatment of axial SpA (including AS). Sulfasalazine is considered only for the treatment of peripheral arthritis. IL-17i are recommended for patients with active disease in whom TNFi are contraindicated, and in primary nonresponders to TNFi. The use of IL-17i should be avoided in patients with active IBD, as TNFi monoclonal antibodies are better options. Moreover, recently, also another JAK inhibitor has been authorized in EU for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

Treatments are available to control and delay the progression of symptoms of AS. However, additional therapy options are still needed as up to 50% of patients with AS continue to have active disease despite treatment with NSAIDsor biological agents.

The use of NSAIDs is limited by gastrointestinal and other adverse events. Other effective agents for the treatment of active AS are bDMARDs, which require parenteral administration and may be limited by loss of efficacy, often due to immunogenicity.

As a number of genes and cytokines have been implicated in the pathogenesis of AS, it is likely that the etiology of AS is complex and has a plethora of underlying contributory factors. This implies that additional treatment options with mechanisms of action distinct from those currently available, are needed as options for different AS patients.

In summary, despite the advances that have been made in the last decade in the treatment of AS, a significant number of patients with AS still have active disease and remain refractory to currently available pharmacotherapies. Unmet medical need therefore remains for a new effective oral DMARD with a new MOA that provides a favourable benefit-risk profile and broadens the treatment options for adult patients with AS to achieve and sustain clinical benefit.

3.1.3. Main clinical studies

With this submission, the MAH seeks approval for tofacitinib PR tablets (11 mg QD) for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

No comparative clinical efficacy and safety data with tofacitinib 11 mg PR formulation in SA patients have been provided within this application in order to demonstrate that the new modified release formulation is as effective as the existing IR formulation. However, given that the efficacy of tofacitinib IR formulation (5 mg BID) in AS has been demonstrated within the previous application (II/35), the MAH proposed a bridging of the efficacy of tofacitinib IR formulation (5 mg BID) in AS to the PR formulation (approved in the RA and PsA indications) relying on E/R relationship.

In support of the IR formulation (5 mg BID) in AS indication the MAH provided:

i) supportive data from Study A3921119 a phase 2, multicentre, randomised, double-blind, placebo-controlled dose ranging, parallel group efficacy and safety study designed to characterise the dose

response of tofacitinib 2 mg BID, 5 mg BID and 10 mg BID in patients with active AS who had experienced an inadequate response to NSAIDs and were naïve to previous bDMARDs;

ii) confirmatory evidence from one pivotal study A3921120, a phase 3, randomized, double-blind, placebo-controlled, parallel group comparing tofacitinib 5mg dosed twice daily to placebo in subjects with active AS, who had experienced an inadequate response to NSAIDs (NSAID-IR) and were additionally either naïve to previous bDMARDs, or TNFi-IR or experienced to previous bDMARDs but without inadequate response (bDMARD Use [Non-IR]). The study design included a 16-week double-blind treatment period, a 32-week open-label treatment period (all subjects were assigned to open-label tofacitinib 5 mg BID to Week 48) and a 28-day follow-up period (duration of participation for eligible subjects was approximately 56 weeks).

3.2. Favourable effects

No efficacy data has been provided with the PR 11 mg QD formulation in AS.

The only possible and expected favourable effects of the 11 mg PR formulations in patients with AS is the greater adherence to treatment compared with their respective licensed IR formulations (5 mg BID) due to the one daily regimen.

The following aspects are referred to the IR 5mg formulation:

In the phase 3 pivotal A3921120 study in the IR 5 mg BID formulation in AS the primary endpoint showed a statistically significant higher proportion of patients in the tofacitinib 5 mg BID group reached ASAS20 at week 16 in comparison to the placebo group with a treatment difference of 27.08 (95% CI: 15.89, 38.28), which is in line with the 20% difference expected in the sample size calculation. Moreover, the primary analysis was supported by results from all the pre-specified supportive analyses.

The key secondary endpoint ASAS40 was also met from a statistical perspective with a higher response rate of subjects in tofacitinib 5 mg BID group (40.6%) compared to placebo group (12.5%) at week 16.

The effect size of ASAS40 being very similar to that observed for ASAS20 and of clinical relevance. Consistent results are shown by subgroup analyses. For both ASAS20 and ASAS40 a better response rate between study drug and placebo is reported in bDMARDs naïve compared to TNF-IR subjects or bDMARD [Non-IR].

The individual components of the ASAS responses (type I controlled) and ASAS 5/6 (not controlled) results were consistent with those of the primary and key secondary endpoint.

Numerous secondary endpoints controlled for multiplicity have been selected for assessing tofacitinib efficacy on different disease domains and this is supported, however limitations are foreseen.

Results from primary and key secondary endpoint were supported by an important secondary (type I controlled) endpoint ASDAS (CRP) which is a validated and accepted method to assess disease activity and physical function considered a very important disease activity. The LS mean change from baseline in ASDAS(CRP) showed a statistically significant decrease for tofacitinib 5 mg BID compared to placebo at Week 16 (-1.36 in the tofa arm and -0.39 in the PLB arm at week 16, delta of -0-98) showing a clinically relevant difference. At week 48 improvement of ASDAS(CRP) from baseline is still seen.

Other endpoint has been provided as secondary but not controlled for type I error supporting tofacitinib effect across important clinical measures i.e.: ASDAS clinically important improvement (61.3 versus 19.1 delta 42.3), ASDAS major improvement (30 versus 4.6 delta 25.3), ASDAS inactive disease (6.7 versus 0 delta 6.7) at week 16; a greater response in the Tofa arm which is maintained at week 48 and with an effect size of clinical significance for endpoints measuring improvement. Measure of partial remission

was also supportive [i.e., ASDAS partial remission: a value of =2 (on a 0 to 10 scale) present in each domain, 15 versus 3, p 0<0.001]

Supportive results were obtained from different Quality of Life endpoints (i.e., ASQoL).

Measures of spinal mobility, i.e., Linear BASMI (BASMI lin) composite score change at week 16, is a relevant efficacy parameter in axial SpA. Results were not robust as those evaluating tofacitinib efficacy on sign and symptoms/inflammation of the disease showing a change at week 16 (of -0.63 versus -0.11 for Tofa and PLB, respectively; similar change (-0.6-0.7) at week 48) statistically significant but not clinically relevant.

Results from Study A3921119 were supportive of the phase 3 study with regard to different endpoints mainly pertaining to disease activity and physical functions, health related outcomes.

3.3. Uncertainties and limitations about favourable effects

There are no dedicated clinical data with the 11 mg PR formulation in AS patients. This variation application is therefore based on a bridging strategy consisting of three points: two of them referring to previously submitted data/studies in RA patients and the third once refers to the E/R in AS using IR formulation. To predict the efficacy the Cavg has been chosen as the exposure metrics as previously done in RA and justified by the indirect mechanism of action of tofacitinib The simulated E/R relationship in AS appears to be flat, even flatter compared to observed data. It is worth mentioning that in all the E/R plots, the 10 mg Cavg values are even lower than the 5 mg, and, for the ASAS40 values (placebo-corrected), also lower than the 2 mg.

The E/R relationship per se is still considered not supportive (due to plausible hypothesis of an artefact) to waive the clinical study according to the EMA Guideline on modified-release formulation (EMA/CHMP/EWP/280/96 Rev1).

However, the totality of data available show the following: i) the demonstrated BE between PR (11 mgx1) and IR formulations (5 mgx2) in terms of AUC and Cmax with only a difference in average Cmin (29% lower) not considered clinically relevant and ii)the Cavg as the primary PK parameter; iii) the approval of PR formulation for RA and PsA; iv) the same PK metrics are considered important for efficacy and safety in AS as in PsA; v) the similarities in disease between PsA and AS.

Considering all the above and taking into account that the safety profile is not expected to be different with the use of PR formulation as compared to IR formulation, the lack of a clear E/R relationship can be overcome and not further pursued.

In the absence of clinical data, the effect of increased adherence to treatment with the PR formulations remains hypothetical.

3.4. Unfavourable effects

All the safety data come from the clinical program in which the immediate release (IR) formulation has been used and they are extrapolated to cover the safety of the PR formulation for the current application.

The safety profile of tofacitinib is mainly characterised by different types of AEs, included venous thromboembolism and pulmonary embolism, serious infections, cases of non-melanoma skin cancers (NMSC), gastrointestinal perforation. Moreover, a recent Emerging Safety Issue (ESI) has been notified pertaining cardiovascular events (MACE) and malignancies.

The proportion of subject with AEs (exposure up to 16 weeks) was slightly higher in tofacitinib IR than in placebo (54.6% vs 49.2%). However, when the All Tofa cohort is considered (longer exposure), a higher incidence of AEs is found: subjects with AEs were 63.6% in tofacitinib 5 mg BID.

The most frequently reported TEAEs in the tofacitinib arm of the Placebo-controlled Cohort were within the Infections and infestations (27.6%), Gastrointestinal disorders (13%), Musculoskeletal and connective tissue disorders SOCs (8.1%), and ALT/AST increase (3.2% and 2.2%). The most frequently reported TEAEs in the All Tofa Cohort were within the Infections and infestations (32.1%), Gastrointestinal disorders (16.2%), Musculoskeletal and connective tissue disorders (10.5%) SOCs.

Among the most common AEs, those more common in tofacitinib 5 mg BID, and with the highest differences vs placebo, were "infections and infestations" (36.1% vs 23.0%) and "investigations" AEs (16.8% vs 4.3%). Most of these investigation AEs were related to increased liver transaminases.

Acute renal failure was observed in more patients treated with tofacitinib than with placebo, 5 (2.70%) vs 2 (1.07%). The small number does not allow drawing any conclusion on this point, but most of the events were mild and creatine increase is already listed as AE in the SmPC.

Hepatic AEs were overall observed more frequently in tofacitinib than in placebo (5.40% vs 1.07%). Consistently with this, a higher proportion of subjects had increased liver transaminases in tofacitinib compared to placebo (AST >3.0x ULN: 2.2% vs 0.5%; ALT >3.0x ULN: 2.7% vs 0.5%).

Seven cases of HZ (all non-serious) were reported in the AS clinical programme. The incidence rate per 100 PY was higher than the incidence rate in the PsA dataset and comparable to the RA dataset (2.7, 1.7 and 3.6, respectively).

SAEs (per 100 PY) were higher in tofacitinib 5 mg than in placebo (5.28 vs 3.56) but occurred in a minority of subjects. Most SAEs were considered mild in severity, only one subject experienced a severe SAE in both tofacitinib 5 mg and tofacitinib all dose groups during the 48 weeks period.

The number of patients needing "dose reduced or temporary discontinuation" was 9.5% vs 3.2% in tofacitinib 5 mg BID versus placebo.

The whole lipid profile was influenced by tofacitinib, with mild increase in total cholesterol, LDL, HDL and triglycerides; an increase in weight was observed among tofacitinib patients compared to placebo groups at 16 weeks (mean change from baseline, kg: 1.8 vs 0.5; in the All tofacitinib cohort at 48 weeks the increase was 2.2 kg) both potentially negatively impacting the CV risk of these patients.

Platelet counts showed a mean decrease of almost –30,000/mm3 after 48 weeks in the All Tofa cohort. AST, ALT and bilirubin increased in the tofacitinib arm but were steady in the placebo arm. However, only one patient had an AE of thrombocytopenia (considered as mild).

Incidence rates for TEAEs, discontinuation of study treatment, discontinuations due to AEs, all infections and HZ were generally higher for females compared to males and for patients >= 65 years old compared to younger patients.

A worst safety profile was observed in patients with previous treatment with TNFi or bDMARD compared to those bDMARD-naïve: AEs were 72.41% vs 60.47%. The highest difference was observed for "Discontinuation of study treatment", which involved 22.41% vs 4.65% of patients.

3.5. Uncertainties and limitations about unfavourable effects

Even if the safety profile of PR formulation is not expected to be different as compared to IR formulation, still a degree of uncertainty is in place due to the absence of real data on PR formulation and to relying on an assumption.

From a safety perspective, the limited exposure to tofacitinib IR in the sought indication could not be sufficient to unveil possible adverse effects that could be specific to AS. The placebo-controlled period was limited to 16 weeks; due to this fact, and also to the limited number of patients studied, it is very difficult to evaluate the observed difference in the incidence of AEs; furthermore, many AEs that are typically associated to tofacitinib treatment (such as herpes zoster), are not observed in the placebo-controlled period. This uncertainty applies to PR formulation as well.

Inclusion criteria for AS trials only allowed inclusion of patients with a platelet count ≥100,000 platelets/mm^3. It is not clear whether patients with lower platelet counts should safely be allowed to be treated with tofacitinib, as a general decrease in platelet count has been observed over time, not only in the AS program but also in the other approved indications (RA and PsA). Platelet counts showed a mean decrease of almost 30,000/mm^3 after 48 weeks in the All Tofa cohort. However, only one patient had an AE of thrombocytopenia (considered as mild). The SmPC has been modified to reflect the fact that patients enrolled in the clinical program were required to have a platelet count >100,000 /mm^3.

Although the incidence rate for most AEs of special interest observed in the AS development program is lower compared to that observed in the PsA and RA programs and cases of AEs that are known components of the safety profile of tofacitinib in the other indications: Malignancies, NMSC, CV events of MACE or thrombosis (ATE, PE, and DVT), GI Perforation, Rhabdomyolysis could noy be excluded that these findings should be ascribed to the limited exposure.

Considering that the sought indication is a chronic disease requiring long-term therapy and also considering some safety concerns of the drug emerging with long-term use, an update of safety data and analyses coming from AS subjects exposed more than 1 year was deemed important to provide reassurance on this key uncertainty. However, the MAH considers the long-term safety profile of tofacitinib in the AS population as similar to what observed for RA and PsA patients and, thus, the MAH does not plan to conduct further studies to gather long-term safety data from the AS population. Of note, at the time of conclusion of this extension application the impact of the study A3921133 findings on tofacitinib safety and efficacy profile is being assessed in the parallel EMEA/H-A20/1517/C/004214/0048 procedure.

Effects by age are very difficult to estimate since the limited number of subjects >65 years (n=13) vs <65 years (n=407).

Overall, female patients had higher incidence rates of AEs compared to male, but the cohort was unbalanced since there were 594 males and 142 females.

Most patients in the tofacitinib 5 mg BID group were White and few were Asian (n=63). Higher incidence of AEs (including infections) was observed in Asian patients.

A higher incidence of venous thromboembolism has been observed in post-marketing RA study A3921133 compared to AS pivotal trials. Considering short follow up in AS pivotal trials, VTE events remain a concern for AS indication also.

3.6. Effects Table

Table 78. Effects Table for tofacitinib IR 5 mg in the AS indication

Effect	Short description	Unit	Tofacitinib 5mg BID	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
ASAS20 Wk 16	% patients achieving ASAS20	%	56.39%	29.41%	Difference in response 27.08 (p<0.0001)	Study A3921120

Effect	Short description	Unit	Tofacitinib 5mg BID	Placebo	Uncertainties / Strength of evidence	References
	response at Week 16					
ASAS40 Wk 16	% patients achieving ASAS40 response at Week 16	%	40.60 %	12.50 %	Difference in response 28.17 (p<0.0001)	Study A3921120
ASDAS-CRP change at week 16	Change from baseline in ASDAS-CRP at week 16		-1.36	-0.39	p<0.0001 for comparison vs placebo	Study A3921120
ASQoL change at week 16	Change from baseline in ASQoL units		-4.03	-2.01	p<0.001 for comparison vs placebo	Study A3921120
SF-36 v2 PCS change at week 16	Change from baseline in SF-36v2 PCS		6.69	3.14	p<0.0001 for comparison vs placebo	Study A3921120
BASMI lin change at week 16	Change from baseline in BASMIlin units		-0.63	-0.11	p<0.0001 for comparison vs placebo	Study A3921120
FACIT-F change at week 16	Change from baseline in FACIT-F		6.54	3.12	p<0.001 for comparison vs placebo	Study A3921120
Unfavourable Effects						
% of n with AE	proportion of subject with AEs	%	54.6	49.2		Studies A3921120/ 119
infections and infestations	proportion of subject with infections and infestations	%	36.1	23		Studies Studies A3921120/ 119
investigation	proportion of subject with investigation AEs	%	16.8	4.3		Studies A3921120/ 119
Hepatic AEs	proportion of subject with hepatic AEs	%	5.40	1.07		Studies A3921120/ 119
SAEs	proportion of subject with SAEs	%	5.28	3.56		Studies A3921120/ 119

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The favourable effects of the 11 mg PR formulations in patients with AS is the greater adherence to treatment compared with their respective licensed IR formulations (5 mg BID) due to the one daily regimen. However, in the absence of clinical data, the effect of increased adherence to treatment with the PR formulations remains hypothetical.

3.7.2. Balance of benefits and risks

The benefits of using tofacitinib 11 mg QD PR formulation for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy are expected to be similar from the AEs perspective to 5 mg BID IR formulation in the same indication.

3.7.3. Additional considerations on the benefit-risk balance

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

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

3.8. Conclusions

The overall B/R of Tofacitinib is positive provided all conditions of the marketing authorisation are fulfilled.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of active ankylosing spondylitis for Xeljanz prolonged release tablets; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. In

addition, editorial changes have been introduced throughout the PI. The Package Leaflet is updated in accordance. Version 28.1 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular, the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Xeljanz-H-C-004214-II-0039'

Attachments

1. SmPC, Package Leaflet (changes highlighted) as adopted by the CHMP on 19 May 2022.