14 October 2021
EMA/CHMP/743175/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xeljanz

International non-proprietary name: tofacitinib

Procedure No. EMEA/H/C/004214/II/0035

Note

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

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List of abbreviations

%CV % coefficient of variation

ACR American College of Rheumatology

AE(s) adverse event(s)

ALT alanine aminotransferase

ANCOVA analysis of covariance

ANOVA analysis of variance

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

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

ASAS 5/6 ASAS 5/6 assessed 6 domains: the domains as noted in the ASAS20 and 40, CRP and Spinal Mobility, specifically lateral spinal flexion (from the BASMI). Improvement was defined as ≥20% in at least 5 domains

ASDAS(CRP) Ankylosing Spondylitis Disease Activity Score using C-Reactive Protein

ASQoL Ankylosing Spondylitis Quality of Life

ASspiMRI Ankylosing Spondylitis Spine Magnetic Resonance Imaging

AST aspartate aminotransferase

ATC Anatomical Therapeutic Chemical

ATE arterial thromboembolism

AUC area under the plasma concentration-time curve

AUC24 area under the plasma concentration-time curve from time 0-24 hours

BA bioavailability

BASDAI Bath Ankylosing Spondylitis Disease Activity Index

BASFI Bath Ankylosing Spondylitis Functional Index

BASMI Bath Ankylosing Spondylitis Metrology Index

bDMARD biological disease-modifying antirheumatic drug

BE bioequivalence

BID twice-daily

BR benefit-risk

Cavg average plasma concentration

CI confidence interval

CK creatine kinase

Cmax maximum plasma concentration

CMH Cochran–Mantel–Haenszel

CPK creatine phosphokinase

CO Clinical Overview

COVID-19 Corona Virus Disease (identified 2019)

COX-2 cyclo-oxygenase subtype 2

csDMARD conventional synthetic disease-modifying antirheumatic drug

CSR clinical study report

CYP cytochrome P450

DMARD disease-modifying antirheumatic drug

DILI drug-induced liver injury

DVT deep vein thrombosis

Emax maximum drug effect

EQ-5D-3L EuroQol 5-dimension scale- 3 Levels

EQ-VAS EuroQol-visual analogue scale

E-R exposure-response

EULAR European League Against Rheumatism

FACIT-F Functional Assessment of Chronic Illness Therapy-Fatigue

FAS full analysis set

GI gastrointestinal

HAQ-DI Health Assessment Questionnaire – Disability Index

hsCRP high sensitivity C-reactive protein

HZ Herpes zoster

IBD Inflammatory Bowel Disease

iAP Integrated Analysis Plan

ILD Interstitial Lung Disease

IL interleukin

iPSP initial Pediatric Study Plan

IR immediate release

IV intravenous

JAK Janus kinase

JIA juvenile idiopathic arthritis

LOCF last observation carried forward

LSM least squares mean

LTE long-term extension

MA Marketing Application

mAb monoclonal antibody

MACE major adverse cardiovascular events

MedDRA Medical Dictionary for Regulatory Activities

MMRM Mixed Model for Repeated Measures

MOA mechanism of action

MR modified release

MRI magnetic resonance imaging

MTX methotrexate

N, n number of subjects

NA not applicable

NDA New Drug Application

NMSC non-melanoma skin cancer

Non-IR non inadequate responder/response

NRI nonresponder imputation

NSAID nonsteroidal anti-inflammatory drug

NSAID-IR NSAID inadequate response

OC Oracle Clinical

OI(s) opportunistic infection(s)

OPC oral powder for constitution

OTIS Organisation of Teratology Information Services

PBRER Periodic Benefit Risk Evaluation Report

PCS Physical Component Summary

PE pulmonary embolism

PGA Patient Global Assessment of Disease

PK pharmacokinetic(s)

PMAR Population Modelling Analysis Report

PsA psoriatic arthritis

PsO psoriasis

PT Preferred Term

PV pharmacovigilance

PY patient-years

QD once daily

RA rheumatoid arthritis

RCT randomised controlled trial

RMM risk minimisation measures

RMP Risk Management Plan

SAE(s) serious adverse event(s)

SAP Statistical Analysis Plan

SCE Summary of Clinical Efficacy

SCP Summary of Clinical Pharmacology

SCS Summary of Clinical Safety

SD standard deviation

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

SI sacroiliac

SJC Swollen Joint Count

sNDA Supplemental New Drug Application

SpA spondyloarthritis

SPARCC Spondyloarthritis Research Consortium of Canada

t½ half-life

TB tuberculosis

TEAE(s) treatment-emergent adverse event(s)

TNF tumor necrosis factor

TNFi(s) tumor necrosis factor inhibitor(s)

TNFi-IR tumor necrosis factor inhibitor inadequate responder/response

Tofa tofacitinib

tsDMARD targeted synthetic DMARD

UC ulcerative colitis

ULN upper limit of normal

US United States

VTE venous thromboembolism

WPAI Work Productivity and Activity

XR extended release

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 February 2021 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy for XELJANZ film-coated tablets; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 17.1 of the RMP has also been submitted.

The variation requested 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: Johann Lodewijk Hillege

Timetable	Actual dates
Submission date	2 February 2021
Start of procedure:	20 February 2021
CHMP Rapporteur Assessment Report	19 April 2021
CHMP Co-Rapporteur Assessment Report	21 April 2021
PRAC Rapporteur Assessment Report	21 April 2021
PRAC Outcome	6 May 2021
CHMP members comments	10 May 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 May 2021
Request for supplementary information (RSI)	20 May 2021
CHMP Rapporteur Assessment Report	14 September 2021
PRAC Rapporteur Assessment Report	20 September 2021
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	30 Sept 2021
CHMP members comments	04 Oct 2021
Updated CHMP Rapporteur Assessment Report	07 Oct 2021
Opinion	14 Oct 2021

2. Scientific discussion

2.1. Introduction

This Type II variation seeks approval for the treatment of active ankylosing spondylitis (AS) in adult patients. In total there are 2 studies in the Pfizer clinical development program for AS provided in this application: Study A3921119, a completed Phase 2, multicentre, randomized, double-blind, placebo-controlled dose-ranging, parallel group efficacy and safety study designed to characterize the dose-response of tofacitinib in patients with active AS; and Study A3921120, a Phase 3 randomized, placebo-controlled, and double-blind study in adult patients with active AS.

2.1.1. Problem statement

Disease or condition

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 for tofacitinib oral IR tablet 5 and 10 mg BID is for the treatment of active AS in adult patients 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 **Table 1:**

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 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. Accordingly, tofacitinib may result in modulation of the adaptive and innate immune response in IBD and may, therefore, be effective in interrupting the chronic cycle of GI inflammation.

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 (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 (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; 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 on 16/12/2019 (EMEA/H/C/004214/X/0012)

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

The clinical development program plans for the treatment of AS generally reflects the CHMP Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1). However, in certain instances the guideline has not been strictly adhered. For example, regarding the choice of **ASAS20 as primary endpont** the guideline states that "although the percentage of patients reaching an ASAS 20 response has been accepted as primary endpoint for a number of products, a higher magnitude of the clinical response are expected for biological medicinal products or products from a new therapeutic class. Thus, the ASAS 40 response criteria would be the preferred primary endpoint". The MAH reports to have used ASA20 as primary endpoint, with the EMA preferred ASAS40 endpoint as a key secondary endpoint, also based on interactions occurred with the FDA that informed the design of the Phase 3 program and content of the AS sNDA submission (the MAH has not sought scientific advice from the EMA or national member states in relation to the development of Xeljanz for the treatment of ankylosing spondylitis but has sought advice from the US FDA).

Summary of Meeting Correspondence with FDA:

Key interactions between Pfizer and the FDA for the ankylosing spondylitis (AS) program under IND 70903 have been provided (**Table 2**).

Table 2. FDA Interactions on Development of Tofacitinib for Ankylosing Spondylitis

Interaction	Date of Minutes/Correspondence
Type B End of Phase 2 Meeting	21 Feb 2018
FDA comments on protocol A3921120	17 May 2018
Type C Meeting, Written Response Only	01 Feb 2019
FDA comments on analysis plans	11 Feb 2019
FDA comments on A3921120 protocol amendment 2	30 May 2019
Type C meeting Written Response Only	29 Oct 2019
Type B pre-sNDA Meeting	06 Feb 2020

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) has been submitted by the MAH as part of this application for seeking approval for a new indication (treatment of ankylosing spondylitis (AS) in adult patients).

For the treatment of AS, the maximum recommended dosage of Xeljanz is 5 mg twice daily (IR tablet) or 10 mg once daily (IR).

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 (Appendix 1). 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 Guideline1 , 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 □g/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, 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 extension of indication, 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 extension of indication application.

2.2.3. Conclusion on the non-clinical aspect

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

Table 3 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	Tofacitinib 5 mg BID Placebo (16 weeks) → Tofacitinib 5 mg BID (32	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

	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.	weeks)					
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

The previously submitted clinical pharmacology and in vitro studies provided within the initial tofacitinib RA MAA included 25 Phase 1 studies comprising of 20 clinical pharmacology and 5 biopharmaceutic studies and 19 in vitro studies using biomaterials relevant to PK processes.

In addition, population PK reports in RA (S0000 PMAR-00178), PsA (S0014 PMAR-EQDD-A392j-sNDA-601) and PsO (S0002 PMAR-EQDD-A392g-DP3-112) were previously submitted.

Clinical pharmacology aspects that are included in this AS application are:

- Summary of population PK of tofacitinib in AS patients (PMAR-EQDD-A392k-sNDA-1064)
- E-R relationships for efficacy in AS patients
- Dose modifications based on PK data (ie, renal and hepatic impairment and DDIs)

No new Phase 1 clinical pharmacology studies or in vitro studies are included in this AS application.

Two studies are submitted within this application: Phase 2 dose-ranging Study A3921119 and Phase 3 Study A3921120. An overview of studies is presented in **Table 4.** Three tofacitinib doses of 2 mg, 5 mg and 10 mg BID were evaluated in both AS studies combined. Data from Studies A3921119 and A3921120 were pooled to characterise the PK of tofacitinib in adult patients with active AS and to identify intrinsic and extrinsic patient specific factors that may impact the PK of tofacitinib (pop PK: PMAR-EQDD-A392k-sNDA-1064). Population PK analysis was conducted using the nonlinear mixed effects modelling approach. Exposure metrics derived from the population PK model were used for the further development of the E-R relationships.

Table 4. Overview of Tofacitinib Studies in Patients With AS Included in the Population PK Analysis

Study Identifier	Design Features	Treatment Groups	PK Sampling Schedule/Period
A3921119 (Phase 2 Dose-Ranging Study)	Randomised, MC, DB, placebo-controlled, parallel group study to investigate the efficacy and safety of tofacitinib in patients with active AS in a bDMARD-naive population. Duration of blinded treatment: 12 weeks.	Tofacitinib 2 mg BID Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo BID	Week 4 Predose[a], 0.5, and 2 hours postdose Week 8 Predose[a], 0.5, 2, and 3 hours post dose Early termination sample, if done
A3921120 (Phase 3 Study)	Phase 3, randomised, DB, placebo-controlled study to evaluate the efficacy and safety of tofacitinib in patients with active AS in a bDMARD-naive (~80%) and bDMARD-experienced (~20%) population. Duration of blinded treatment: 16 weeks. (at the Week 16 visit, all patients assigned to open-label tofacitinib 5 mg BID until Week 48)[b]	Tofacitinib 5 mg BID Placebo BID	Week 4 Predose[a], 0.5 and 2 hours post dose Week 8 Predose[a], 0.5, 2, and 3 hours postdose

a. Predose sampling was planned to occur within 12 ± 2 hours of the previous dose of investigational product.
b. No PK samples were collected in the open-label portion of Study A3921120.
Source: Module 5.3.3.5 PMAR-EQDD-A392-k-sNDA-1064 Table 2.

Xeljanz immediate release (IR) formulation is currently approved in the EU as a BID treatment for RA, PsA and UC.

No new biopharmaceutic studies are included in this AS MAA IR dossier.

The biopharmaceutic data presented in that original submission for RA also support the use of tofacitinib in AS. Study A3921005 examined the BA of a tablet formulation used in the RA Phase 2A study relative to OPC, which was used in the single and multiple ascending dose studies (A3921002 and A3921003). Study A3921005 also estimated the effect of food on the pharmacokinetics of the tablet formulation. A pivotal BE study (A3921075) evaluated the BE between tofacitinib tablets used in Phase 2B and Phase 3 studies and commercial tablets. Study A3921076 estimated the effect of food on the commercial tablet. The absolute BA of tofacitinib was investigated in Study A3921077 using the commercial tablet versus an IV formulation. Study A3921135 was conducted to establish BE between tofacitinib 1 × 5 mg tablets and 5 × 1 mg tablets used in RA Phase 2B studies to support the registration in Japan for the treatment of RA.

Table 5 lists the formulations and dose strengths that were used in the AS studies. The commercial 5 mg tablet formulation was used in both AS trials, A3921119 and A3921120, while the 1 mg tablet formulation was used only in A3921119, a Phase 2 dose ranging study in AS patients.

Table 5 Formulations Used in Phase 2 and Phase 3 Studies in AS Patients

Dosage Form/Formulation	Strength	Protocol
Clinical Formulation[a]	1 mg	A3921119
Commercial Formulation - Plain/Clinical Image	5 mg	A3921119, A3921120

a. IND 70,903; Module 3; Section P.1 Description and Composition of the Drug Product (CP-690,550, Tablet).

The specific and sensitive bioanalytical methods using solid-phase extraction followed by the HPLC-MS/MS detection that were developed and validated for the measurement of tofacitinib concentrations in human plasma from AS patients are briefly described below.

A HPLC-MS/MS method (Pfizer Validation A3929023) was developed and validated at WuXi AppTec (Shanghai, China), with a quantitative range of 0.100 to 350 ng/mL with quadratic regression. The method was transferred to PPD (Richmond, VA and Middleton, WI) and validated (Pfizer Validation A3929032) with a truncated quantitative range from 0.100 to 100 ng/mL with linear regression.

Details of the specific methods, validation assessments and results can be found in the validation reports listed in the **Tables 6** as well as a summary of the bioanalytical assay performance during the sample analyses for clinical studies for the AS development program (**Table 7**).

Table 6 Summary of the Validated Analytical Method for Tofacitinib in Human Plasma

Pfizer/Vendor Validation No.	Matrix	Assay Laboratory	LLOQ (ng/mL)	Inter-assay Precision %CV[a]	Inter-assay Accuracy %RE[a]	Assay Range (ng/mL)	Comments on Validation	Clinical Study Protocol No.
A3929023 /11BAS0459	Sodium Heparin Plasma	WuXi AppTec, Shanghai, China	0.100	≤13.1%[b]	1.0% to 8.0%[b]	0.100 to 350	Full validation	A3921119
A3929023 Addendum 01 /12BAS0395	Lithium Heparin Plasma	WuXi AppTec, Shanghai, China	0.100	≤9.9%	−3.8% to 7.0%	0.100 to 350	Partial (cross) validation using lithium heparin as an anticoagulant	A3921119
A3929023 Addendum 02 /11BAS0459	Sodium Heparin Plasma	WuXi AppTec, Shanghai, China	0.100	≤15.0%	1.0% to 3.0%	0.100 to 350	Primary stock solution stability and frozen storage matrix stability	A3921119
A3929023 Addendum 03 /11BAS0459	Sodium Heparin Plasma	WuXi AppTec, Shanghai, China	0.100	≤9.3%	−0.5% to 5.3%	0.100 to 350	Matrix effect and whole blood stability	A3921119
A3929023 Addendum 04 /11BAS0459	Sodium Heparin Plasma	WuXi AppTec, Shanghai, China	0.100	≤7.3%	−3.3% to 2.0%	0.100 to 350	Ambient temperature matrix stability and frozen storage matrix stability	A3921119
A3929023 Addendum 05 /12BAS0395	Lithium Heparin Plasma	WuXi AppTec, Shanghai, China	0.100	≤10.0%	−2.3% to 12.0%	0.100 to 350	Frozen storage matrix stability	A3921119
A3929023 Addendum 06 /16BAS0584	Sodium Heparin Plasma	WuXi AppTec, Shanghai, China	0.100	≤5.5%	−0.7% to 4.1%	0.100 to 350	Cross validation between 2 laboratories	NA
A3929023 Amendment 01 /11BAS0459	Sodium Heparin Plasma	WuXi AppTec, Shanghai, China	0.100	NA[c]	NA[c]	NA	Update the freezer	A3921119

Pfizer/Vendor Validation No.	Matrix	Assay Laboratory	LLOQ (ng/mL)	Inter-assay Precision %CV[a]	Inter-assay Accuracy %RE[a]	Assay Range (ng/mL)	Comments on Validation	Clinical Study Protocol No.
A3929032 /RGTF2	Lithium Heparin Plasma	PPD, Richmond, VA	0.100	≤4.88%[b]	−2.04% to 1.31%[b]	0.100 to 100	Full validation	A3921120
A3929032 Addendum 01 /AKEX2	Lithium Heparin Plasma	PPD, Middleton, WI	0.100	NA[c]	NA[c]	0.100 to 100	Method transfer from PPD Richmond to PPD Middleton	A3921120
A3929032 Addendum 02 /RGTF3	Lithium Heparin Plasma	PPD, Richmond, VA	0.100	≤5.79%	−2.36% to −0.392%	0.100 to 100	Interference assessment, frozen storage matrix stability and primary stock solution stability	A3921120
A3929032 Addendum 03 /AKEX2	Lithium Heparin Plasma	PPD, Middleton, WI	0.100	NA[c]	NA[c]	0.100 to 100	Primary stock solution stability, IS stock and working solution stability and frozen storage matrix stability	A3921120

a. Statistics (%RE and %CV) based on mean assay performance of low-, mid- and high dilution (if applicable) QC samples from all analytical batches meeting acceptance criteria.
b. From accuracy and precision runs.
c. Inter-assay values were not available.

Table 7 Assay Performance of Tofacitinib in Human Plasma in Each Clinical Study

Clinical Study	Assay Laboratory	Pfizer Validation No.	Compound Analysed	Matrix	Inter-run Precision %CV[a]	Inter-run Accuracy %RE	ISR
A3921119	Wuxi AppTec, Shanghai, China	A3929023	Tofacitinib	Plasma	≤5.7%	0.0% to 1.4%	Yes
A3921120	PPD, Middleton, WI	A3929032	Tofacitinib	Plasma	≤5.64%	−1.56% to 8.59%	Yes

a. Statistics (%RE and %CV) based on mean assay performance of low, mid-low, mid-high, and high dilution (if applicable) QC samples from all analytical batches meeting acceptance criteria.

Tofacitinib plasma concentrations were measured through HPLC-MS/MS method developed and validated at Wuxi AppTec (Shangai, China – A3929023) and then transferred at PPD (Richmond and Middleton). Samples from Study A3921119 were analysed by Wuxi, whereas samples from Study A3921120 were analysed by PPD in Middleton. Furthermore, in study A3921119 sodium heparin plasma was used and in study A3921120 lithium heparin plasma. The table above reports the cross validation A3929023 addendum 6, however, as confirmed by the MAH and accepted by the CHMP this cross validation is not applicable to the current analysis since it is performed between Wuxi and PPD in Richmond

A method transfer was performed from PPD in Richmond to PPD in Middleton and an assay performance with respect to precision, accuracy, and specificity was conducted.

The Pfizer method A3929032 was transferred from PPD Richmond to PPD Middleton, and a method transfer was submitted as A3929032 addendum 1.

No cross-validation was performed between PPD Middleton and Wuxi, however the MAH is the opinion that since the method used at Richmond and that used at Middleton remained exactly the same, the cross validation between Wuxi and PPD Richmond supports the comparability of data analysis also between Wuxi and PPD Middleton. This is not exactly in line with EMA guideline on Bioanalytical methods reports that states *"Where data are obtained from different methods within and across studies or when data are obtained within a study from different laboratories, applying the same method, comparison of those data is needed, and a cross validation of the applied analytical methods should be carried out".* However, since the method transfer to PPD Middleton showed that selectivity, carryover, linearity, sensitivity, accuracy, precision, recovery, dilution, and stability were met, the method is considered valid for the extraction and analysis of human lithium heparin plasma. This issue was not therefore further pursued by the CHMP.

The MAH didn't resubmit the Bioanalytical report for the determination of tofacitinib samples collected in Study A3921119, this was acceptable as the study was already submitted and assessed by the CHMP in the context of extension of indication in psoriatic arthritis. In this Study, a total of 1011 samples were analysed by Wuxi (method A3929023); the maximum storage time at -20±5°C in sodium heparin was 309 days (validated LTS at 1274 day at -20±5°C). The ISR was performed on 104 samples and fulfilled the acceptance criteria.

The MAH has provided the bioanalytical report for study A3921120 and declared that all samples were analysed during the stability period. The number of samples received is 1848, however the samples analysed were 922. In the Appendix 4 of the bioanalytical report, the note 8 denotes samples not assayed at Sponsor's request and was reported for several samples, all in the treatment B. The MAH was requested to clarify what treatment the letter B refers to and the reason why the Sponsor requested to not analyse these samples.
The MAH clarified that, Appendix 4 of the Bioanalytical Report for Study A3921120, titled, "Concentration Data (ng/mL) for CP-690550 in Human Plasma Samples from Protocol A3921120" has a list of Comment Codes and Descriptions, of which samples with Code 8 or Note 8, identifies samples that were commented as, "Sample not assayed at Sponsor's request". The "Sponsor Instructions and Bioanalytical Notes" section of the bioanalytical plan (Module 5.3.5.1 CSR A3921120 Analytical Reports Section 8.7 Appendix 2) in the bioanalytical report provides the following instructional text: "Do not assay placebo samples". As per this bioanalytical plan, samples that were designated as treatment B in Study A3921120 were not assayed as they were placebo samples. The clarification provided by the MAH is endorsed by the CHMP.

Pharmacokinetic in target population

Study A3921120 - Week 16 Analysis - Tofacitinib plasma concentration data were summarized by time in the **Table 8**:

Table 8. Plasma Tofacitinib Concentration (ng/mL) versus Time Summary

		Tofacitinib 5 mg BID							
Visit	Planned Time Post Dose	N	NALQ	Mean	SD	CV(%)	Median	Min	Max
Week 4	0 H	132	127	5.4	9.11	169	3.3	0.0	78.6
	30 MIN*	131	130	44.7	24.52	55	46.3	0.0	98.4
	2 H	132	131	35.9	12.65	35	35.1	0.0	76.8
Week 8	0 H	131	129	5.7	7.50	131	3.7	0.0	62.4
	30 MIN	131	131	46.8	25.72	55	50.0	1.5	109.0
	2 H	132	132	36.1	13.03	36	34.9	1.6	86.4
	3 H	132	131	27.6	11.06	40	26.9	0.0	71.6

Study A3921119 plasma tofacitinib concentration data are reported in the **Table 9**, summarized by time and tofacitinib dose group, using the PK analysis set:

Table 9. Summary of PK concentration- safety Analysis Set

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CP-690,550 Protocol A3921119
Summary of PK Concentrations - Safety Analysis Set

Treatment Group	Visit	Planned Time	N	NALQ	Mean	SD	CV (%)	Median	Min	Max
Tofacitinib 2 mg BID	Week 4	Pre-dose	49	47	1.96	3.15	160.35	1.06	0.0	15.2
		0.5 hrs post-dose	49	48	15.90	9.83	61.84	16.40	0.0	36.7
		2 hrs post-dose	49	48	13.08	4.07	31.09	13.00	0.0	20.7
	Week 8	Pre-dose	48	45	1.76	2.33	132.49	1.13	0.0	14.4
		0.5 hrs post-dose	47	47	15.44	9.02	58.44	16.10	0.4	40.2
		2 hrs post-dose	48	48	12.48	4.09	32.75	11.85	1.2	20.7
		3 hrs post-dose	48	48	9.41	3.48	37.00	8.79	1.1	19.0
Tofacitinib 5 mg BID	Week 4	Pre-dose	48	48	4.23	9.53	225.55	2.67	0.2	67.5
		0.5 hrs post-dose	48	48	41.20	20.11	48.81	41.90	1.7	81.7
		2 hrs post-dose	48	48	29.02	7.86	27.08	29.80	2.5	46.5
	Week 8	Pre-dose	49	49	6.20	10.30	166.11	2.97	0.3	53.7
		0.5 hrs post-dose	49	49	37.69	21.63	57.38	40.70	1.3	82.7
		2 hrs post-dose	48	48	31.64	8.15	25.76	29.45	14.2	54.5
		3 hrs post-dose	48	48	22.86	6.66	29.12	22.05	12.8	42.5
Tofacitinib 10 mg BID	Week 4	Pre-dose	47	47	7.35	7.59	103.32	5.20	0.4	44.8
		0.5 hrs post-dose	46	46	88.64	45.70	51.56	95.70	4.0	198.0
		2 hrs post-dose	46	46	61.16	20.70	33.84	61.35	25.3	127.0
	Week 8	Pre-dose	44	42	9.64	10.26	106.42	7.01	0.0	48.8
		0.5 hrs post-dose	44	44	88.27	47.21	53.48	100.05	2.9	203.0
		2 hrs post-dose	44	44	67.97	23.08	33.96	66.05	29.4	130.0
		3 hrs post-dose	44	44	50.39	18.53	36.78	49.45	19.2	110.0

N = Number of subjects; hrs = hours. NALQ= number of observations above the lower limit of quantification
Summary statistics have been calculated by setting concentration values below the lower limit of quantification to zero.
The lower limit of quantification is 0.1 NG/ML.
PFIZER CONFIDENTIAL Source Data: Table 16.2.8.5 Date of Reporting Dataset Creation: 11AUG2015 Date of Table Generation: 07SEP2015 (12:23)

No statistical analysis has been performed in each study report for the two new studies because data have been included in the popPK, please refer to *Population PK in AS patients* section.

It is of note that a high variability is observed in PK parameters for all dosages and time points.

Population PK in AS patients: PMAR-EQDD-A392k-sNDA-1064

The population PK of tofacitinib has been previously characterized in RA patients by pooling data from 5 Phase 2 studies (A3921019, A3921025, A3921035, A3921039 and A3921040), and a long-term extension study A3921024, in PsO patients from one Phase 2 study(A3921047), 4 Phase 3 studies (A3921078, A3921079, A3921080, A3921111), in patients with active PsA from 2 Phase 3 studies, and in patients with UC from one Phase 2 study (A3921063) and 3 Phase 3 studies (A3921094, A3921095, A3920196).

A one compartment model parameterized in terms of apparent clearance (CL/F) and apparent volume of distribution (V/F), consistent with monophasic elimination, with either zero-order absorption or first absorption were previously utilized to describe the PK of tofacitinib in these patient populations.

The current PopPK includes data from studies A3921119 and A3921120 (**Table 10**). Study A3921229 was a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study of the efficacy and safety of tofacitinib in subjects with active ankylosing spondylitis with a duration of 12 weeks. Study A3921120 was Phase 3, randomized, double-blind, placebo-controlled, study of the efficacy and safety of tofacitinib in subjects with active ankylosing spondylitis; the duration was 16 weeks in double blind and 32 in open-label.

Table 10. PK Sampling Schedule in the Studies

PK Sampling Schedule in the Studies

Study	PK sampling schedule / Period	Treatment	Number of subjects in dataset
A3921119	Week 4 Pre-dose[a], 0.5 and 2 hrs post-dose Week 8 Pre-dose[a], 0.5, 2 and 3 hrs post-dose Early Termination sample, if done	2 mg BID 5 mg BID 10 mg BID	50 49 48
A3921120	Week 4 Pre-dose[a], 0.5 and 2 hrs post-dose Week 8 Pre-dose[a], 0.5, 2 and 3 hrs post-dose	5 mg BID	132

Abbreviation: BID = twice daily

[a] Pre-dose sampling was planned to occur within 12±2 hours of previous dose of investigational product.

The objectives of this analysis were:

• To characterize the PK of tofacitinib in patients with ankylosing spondylitis (AS)

• To identify intrinsic and extrinsic factors (covariates) that impact the PK of tofacitinib in these patients.

• To obtain individual steady state exposures and PK parameters for subsequent exposure-response analyses.

The population PK analysis was conducted using the nonlinear mixed-effects modeling approach. The software packages NONMEM version 7.4.3 (ICON plc., Gaithersburg, MD) and Perl-speaks-NONMEM (PsN) version 4.9.0 as supporting software for the execution of NONMEM was used. R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for data handling, exploratory data analysis and creation of graphs for presentations and reports. The estimation method was the first-order conditional estimation method with interaction (FOCEI).

The study population consisted of 222 males and 57 females with ages ranging from 20 to 75 years and weights ranging from 42.3 to 143 kg. The median values of age and body weights at baseline were 40 years and 78 kg. The median value of the Cockroft-Gault calculated creatinine clearance at baseline (BCCL) was 126 mL/min ranging from 48.1 mL/min to 244 mL/min. The distributions of age and BCCL were similar across studies. Baseline CRP (BCRP) had a median value of 0.851 mg/dL and ranged from 0.019 to 8.71 mg/dL. Distribution of race was: 79.9% White, and 19.7% Asian. Hispanic/Latino patients were only 1.4% in the dataset population.

Table 11. Number of Patients and Plasma Concentrations in the Analysis Dataset

Number of Patients and Plasma Concentrations in the Analysis Dataset

Study	2 mg BID	5 mg BID	10 mg BID	Total
Number of subjects				
A3921119	50	49	48	147
A3921120	0	132	0	132
All	50	181	48	279
Number of observed concentrations (number BLQ)				
A3921119	338 (7)	338 (0)	320 (3)	996 (10)
A3921120	0	921 (10)	0	921 (10)
All	338 (7)	1259 (10)	320 (3)	1917 (20)

Repository artifact ID FI-2108665.
Abbreviations: BLQ = below limit of quantification

Drug concentrations that were below the analytical lower limit of quantification, or any values that were otherwise missing, were labelled as such, and were excluded from the analyses. There were total of 20 (1.0%) data records below limit of quantification (BLQ) that were excluded. There were no missing observations in the final dataset, therefore no data imputations were performed. None of the covariates were missing data greater than 10%.

The analyses were conducted in the following steps: 1) Base Structural Model Development, 2) Random Effects Model Development, 3) Full Model Development, 4) Assessment of Model Adequacy and 5) Model Predictive Performance (Validation).

Base model. Given prior knowledge, a PK model based on the RA and PsA populations were used as a starting point for model development.

A one compartment disposition model parameterized in terms of apparent oral clearance (CL/F), apparent volume of distribution (V/F), and a first-order absorption rate constant (ka), was chosen as starting point.

Adding IIV to ka showed a decrease in OFV of 280. When an absorption lag time (tlag) was incorporated, the parameter value for ka was estimated to be very large (> 9 hr-1; absorption t1/2<5 minutes). According to the MAH, this may be due to the limited information describing the absorption in this sparsely sampled data set. Additionally, the distribution of the random effect on ka was still skewed in these models.

After evaluation of the different structural models, the one compartment model with first order absorption, IIV on CL/F and V/F with OMEGA block and no IIV on ka, different proportional residual error for observations with TAD<9 or ≥9 hours on residual error were chosen as the base model (**Run 1, table 12**).

Table 12. List of Key Runs for Based Model

List of Key Runs for Based Model

Run	Description	OFV	Comment
#1	1-compartment model with 1st-order absorption (OMEGA BLOCK for CL/F & V/F), RUV was divided by TAD=9 hr	619.251	**Base model**
#19	#1 + IIV of k_a (ω_{ka})	339.379	θ_{ka}=4.39, ω_{ka}=169%CV ($COV step was aborted, because ω_V^2 became less than ω_{CL-V}.)
#72	#19, replace ω_V to $\omega_{CL} \cdot \theta$(scaling factor) and remove covariance (ω_{CL-V}).	339.378	θ_{ka}=4.39 ω_{ka}=169%CV, (Distribution of individual ka estimate was skewed.)
#73	#72 + t_{lag} ($\theta_{t_{lag}}$)	263.083	θ_{ka}=9.85, ω_{ka}= 202%CV, $\theta_{t_{lag}}$=0.247 (Distribution of individual ka estimate was skewed.

Repository tree ID: AT-4367271.
Abbreviations: CV = coefficient of variation; IIV = inter-individual variance; OFV = objective function value; TAD = time after dose

The typical estimates of CL/F and V/F from the base model were 26.7 L/h and 124 L, respectively **(Table 13**), with relative standard errors of <3%. The ka was estimated to be 3.06 h−1 with an RSE of 10.1%. IIV estimates for CL/F and V/F were 30.5% and 39.2%, respectively. The correlation coefficient between CL/F and V/F was 0.735. Residual variability for observations with TAD <9 hours and TAD ⩾9 hours were 60.3% and 69.5%, respectively (**Table 13**). Shrinkage estimates from the base model were 21.5% for IIV of CL/F, 24.8% for IIV of V/F and 8.94% for IIV of residual error, respectively.

Table 13. Parameter Estimates for the Base Population Pharmacokinetic Model (Run 1)

Parameter Estimates for the Base Population Pharmacokinetic Model (Run 1)

Parameter	Estimate	RSE (%)	IIV% (RSE%)
CL/F (L/hr)	26.7	2.17	30.5 (1.01)
V/F (L)	124	2.78	39.2 (2.01)
ka (/hr)	3.06	10.1	–
Prop. Error CV for $TAD < 9\ hr$(%)	60.3	4.41	–
Prop. Error CV for $TAD \geq 9\ hr$(%)	69.5	6.71	–
Covariance (CL/F & V/F)	0.0877	30.2	–

Source:FI-4390654
Abbreviations: ; CL/F = apparent clearance; CV = coefficient of variation; IIV = inter-individual variance; k_a = first-order absorption rate constant; RSE = relative standard error; TAD = time after dose;

Random Effects Model Development. Inter-individual variance (IIV) was included on the PK parameters using multiplicative exponential random effects. Inter-occasion variance (IOV) terms were investigated for F or CL/F. The individual parameter value (θi) is a function of the typical individual parameter value (θ) and an individual deviation represented by ηi and an occasion-specific deviation represented by ki j, expressed as: $\theta_i = \theta \bullet \exp(\eta_i + k_{i\,j})$.

Residual variability was modeled as additive on log-transformed scale or approximate additive + proportional on log-transformed scale error model: $\ln(Yijk) = \ln(Fi\,jk) + \varepsilon i\,jk$ where Yijk denotes the observed concentration for the ith individual at occasion jth, and time kth, Fijk denotes the corresponding predicted

concentration based on the PK model, and εijk is the proportional error (additive in log scale) on the log-transformed domain assumed to have zero mean and variance σ2.

ETA-shrinkage was monitored throughout model development.

Inclusion of Covariates and Full Model Development. The parameter-covariate combinations for included in the final full model are listed in **Table 14**.

Table 14. Covariates to be evaluated during PK modeling

Covariates evaluated during PK modeling

PK Parameter	Covariate
CL/F	Race [categorical], Sex [categorical], Ethnicity [categorical], Age, Body weight, Baseline renal function (CCL), and Baseline CRP
V/F	Body Weight, Age

Abbreviations: CL/F = apparent clearance, V/F = apparent volume of distribution, CCL = creatinine clearance, CRP = C-reactive protein

Continuous covariates (eg. body weight) were included in the model as follows:

$$\theta_i = \theta_{TV} \cdot \left(\frac{cov_i}{cov_{median}} \right)^{\theta_x}$$

where θi is the value of the parameter for the ith individual, θTV is the typical value of the parameter in the population, covi is the value of the covariate for the individual, covmedian is the median value of the covariate in the study population and θx is the effect of the covariate on the parameter.

Categorical covariates were introduced in the model as follows:

$$\begin{aligned} \theta_i &= \theta_{TV} \cdot (1 + \theta_{x,cov=X_y}) \quad if\ cov_i = X_y \\ \theta_i &= \theta_{TV} \quad if\ cov_i = X_0 \\ (\theta_{x,cov=X_y} &\geq -1) \end{aligned}$$

where θx,cov=Xy is the effect of the covariate belonging to category y, where y goes from 0 (reference category) to m (the number of categories-1).

Continuous covariates were incorporated as power functions, normalized to the reference (approximate median) values. Each category of categorical covariates (gender, and race) entered the model as one coefficient. The equations of the full model are listed below included for the final full model.

$$\begin{aligned} CL/F_i &= \theta_{CL/F} \cdot \left(\frac{AGE_i(years)}{40(years)} \right)^{\theta_6} \cdot \left(\frac{BWT_i(kg)}{78(kg)} \right)^{\theta_7} \cdot \left(\frac{BCCL_i(mL/min)}{126(mL/min)} \right)^{\theta_8} \\ &\cdot \left(\frac{BCRP_i(mg/dL)}{0.851(mg/dL)} \right)^{\theta_9} \cdot (1 + \theta_{10}^{Female}) \cdot (1 + \theta_{11}^{Asian}) \cdot e^{\eta_{CL/F_i}} \\ V/F_i &= \theta_{V/F} \cdot \left(\frac{AGE_i(years)}{40(years)} \right)^{\theta_{12}} \cdot \left(\frac{BWT_i(kg)}{78(kg)} \right)^{\theta_{13}} \cdot e^{\eta_{V/F_i}} \\ ka_i &= \theta_{ka} \end{aligned}$$

BWT and ethnicity (Hispanic or non-Hispanic) were also predefined as potential predictors of CL/F. However, for avoiding collinearity in predictors, BWT effect on CL/F was not employed in the final full model as BWT was correlated with BCCL (correlation coefficient>0.5).

As BCCL was calculated using Cockcroft-Gault equation based on subjects' serum creatinine level as well as age, sex and body weight at baseline, the impact of including both BWT and BCCL on CL/F in the full model was investigated by testing the models including BCCL or BWT on CL/F. Compared to Run 65 (full model with BCCL only), the model with both BWT and BCCL (Run 2) or with BWT only (Run 90) on CL/F led to change slightly in OFV of -0.066 and +6.301, respectively, indicating that the impact of BWT on CL/F was negligible.

Also, as most patients in the dataset were non-Hispanic/Latino (97.8%), ethnicity was not included.

The parameter estimates for the final full model and bootstrap results are presented in the **Tables 15, 16.**

Table 15. Parameter Estimates for the Final Full Model (Run 65)

Parameter Estimates for the Final Full Model (Run 65)

Parameter	Estimate (RSE%)	IIV% (RSE%)	Median[a] (IIV%)	95% CI[a] (95% CI for IIV)
CL/F (L/hr)	27.1 (2.41)	28.2 (0.923)	27.1 (27.6)	[25.8, 28.5] (21.4, 34.4)
V/F (L)	126 (2.81)	36.6 (1.90)	126 (36.0)	[120, 134] (25.6, 47.0)
ka (1/hr)	3.07 (10.2)	– –	3.08 –	[2.56, 3.74] –
Prop. Error CV for $TAD < 9\ hr$(%)	60.2 (4.42)	– –	60.1 –	[54.8, 65.3] –
Prop. Error CV for $TAD \geq 9\ hr$(%)	69.6 (6.73)	– –	69.3 –	[60.4, 78.3] –
Covariance (CL/F-V/F)	0.0760 (33.0)	– –	0.0728 –	[0.0348, 0.131] –

Repository artifact ID FI-4399871

[a]: Calculated by bootstrap method (All 1000 runs minimized successfully).

Abbreviations: CI = confidence interval; CL/F = apparent clearance; CV = coefficient of variation; IIV = inter-individual variance; k_a = first-order absorption rate constant; RSE = relative standard error; TAD = time after dose; V/F = apparent volume of distribution

The point estimates (95% bootstrap CI) of CL/F, V/F, and ka are 27.1 (25.8, 28.5) L/hr, 126 (120, 134) L and 3.07 (2.56, 3.74) hr-1, respectively, for the typical reference individual (white, male, 78 kg, 40 year old, BCCL 126 mL/min, and BCRP 0.851 mg/dL).

The 95% CIs for BCRP and SEX(Female) effects on CL/F contained the null value. The effects of Age, BCCL, and RACE(Asian) on CL/F were significant (CIs excluded null). Baseline body weight and age also impacted V/F (CIs excluding null).

Table 16. - Covariate Parameter Estimates for the Final Full Model (Run 65)

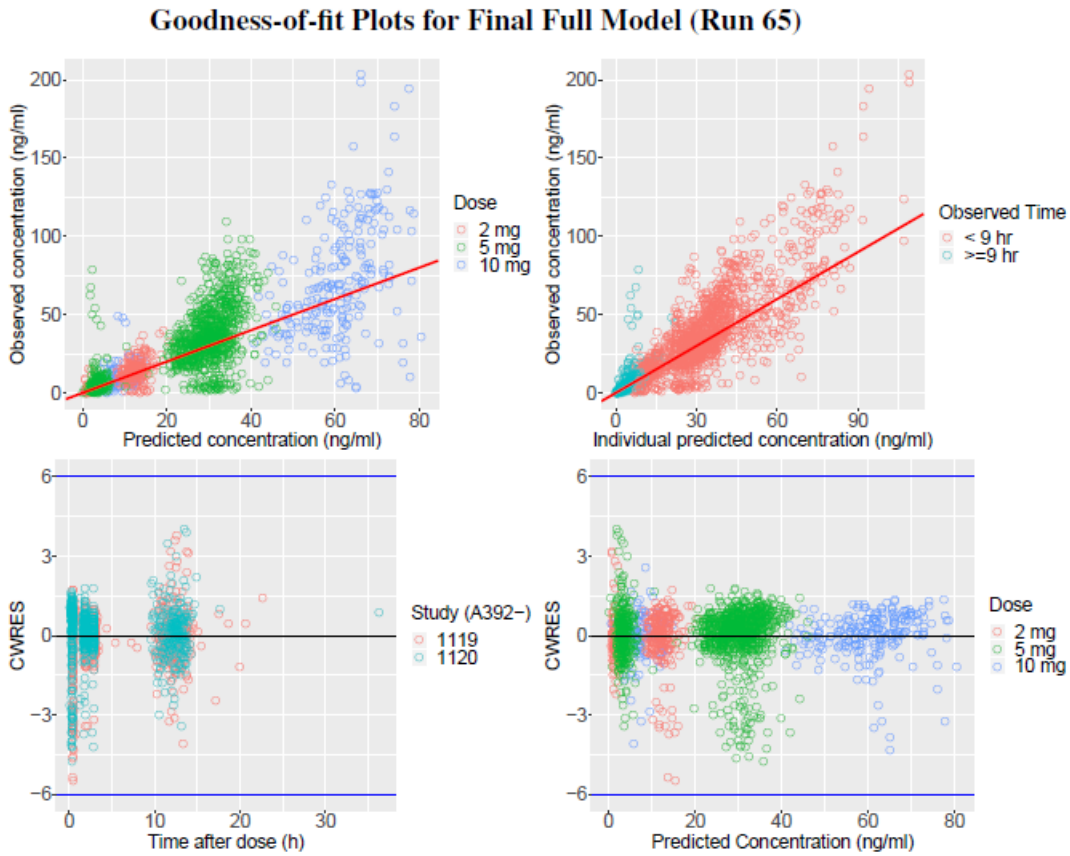
Covariate Parameter Estimates for the Final Full Model (Run 65)

Parameter	Covariate	Estimate	RSE%	95% CI[a]
CL/F	AGE	-0.244	33.7	[-0.419, -0.0989]
	BCCL	0.233	34.5	[0.0688, 0.377]
	BCRP	-0.0185	75.7	[-0.0447, 0.00881]
	SEX (Female)	0.0237	177	[-0.0598, 0.107]
	RACE (Asian)	-0.103	31.7	[-0.164, -0.0385]
V/F	AGE	-0.230	42.3	[-0.421, -0.0449]
	BWT	0.574	23.1	[0.306, 0.835]

Repository artifact ID FI-4399871
[a]: Calculated by bootstrap method (All 1000 runs minimized successfully).
Abbreviations: BCCL = creatinine clearance at baseline; BCRP = C-reactive protein at baseline; BWT = body weight at baseline; CI = confidence interval; CL/F = apparent clearance; RSE = relative standard error; V/F = apparent volume of distribution

Assessment of model adequacy. Goodness of fit (GOF) of different models to the data was evaluated using the following criteria: change in objective function value (OFV), visual inspection of various diagnostic plots (**Figure 1**), precision of the parameter estimates.

Figure 1. Goodness-of-fit Plots for Final Full Model (Run 65)



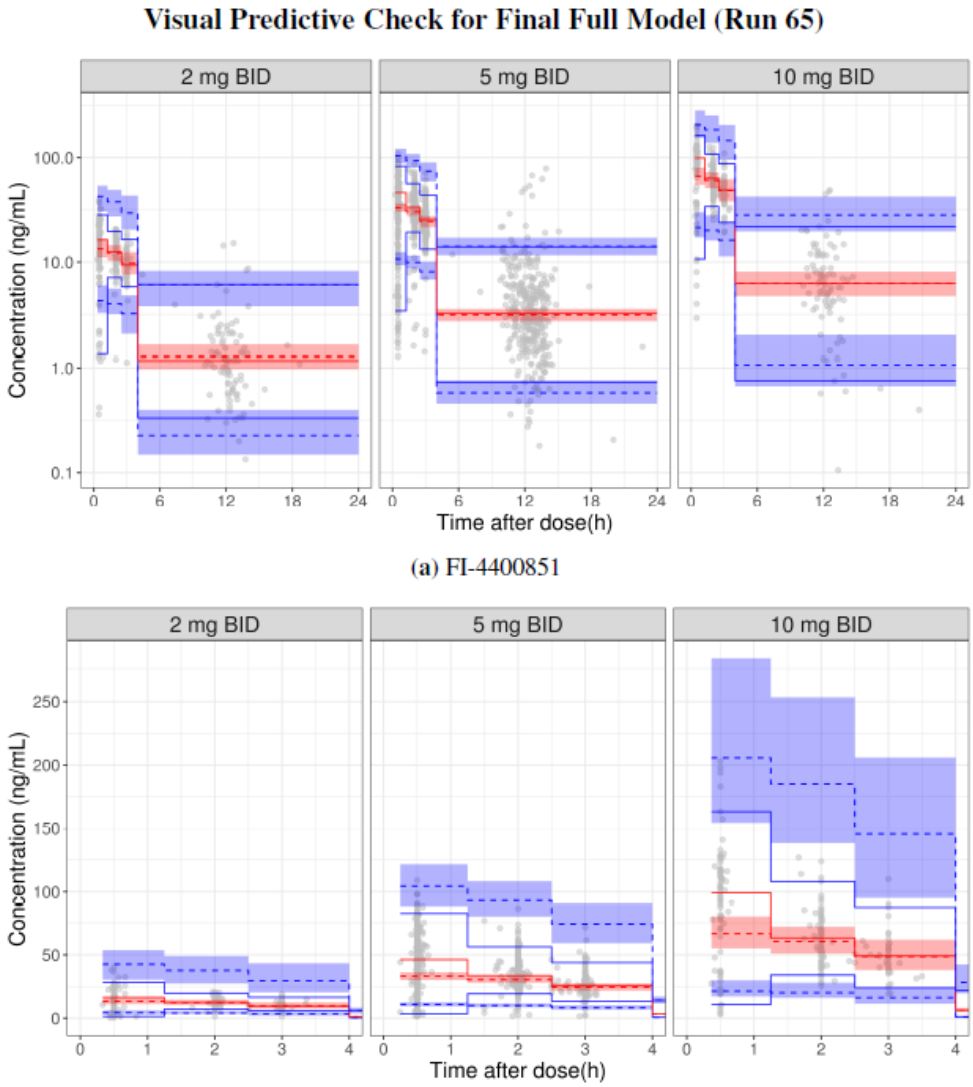
Repository artifact ID FI-4369226.

Red line is the reference line of identity. Blue line is the threshold for identifying outliers.

Model Predictive Performance (Validation). Visual predictive check (VPC) **Figure 2** were performed for the final base and full PK models.

VPCs of the full model demonstrated that the simulated distributions matched the observed concentrations except samples at 0.5 hours (immediately after dosing), which indicated the full model slightly under-predicted the absorption phase.

Figure 2. Visual Predictive Check for Final Full Model (Run 65)



Repository artifact IDs are shown in subfigure labels.
For each panel, the red solid line (blue solid lines) represents 50 percentile (5 and 95 percentiles) of observed concentration versus time profile. The red dashed line (blue dashed lines) represents 5 and 95 percentiles for concentration versus time profile. The red area (blue areas) represents 95% CIs of 50 percentile (2.5 and 97.5 percentiles) for concentration versus time profile. The closed circles indicate individual observed concentration time data. Upper and lower VPCs were same data source. Lower is focus on up to 4 hours after dose with normal scale y-axis.

Results

Some inferences could be made using the parameters from the full model:

• An elderly patient (64 years of age, 95th percentile of age) was estimated to have 10.9% lower CL/F compared to the CL/F a 40-year-old patient.

• Female patients were estimated to have 2.4% higher CL/F compared to males.

• Asian patients were estimated to have 10.3% lower CL/F compared to non-Asian patients.

• A patient with a BCCL of 50 mL/min, CL/F was estimated have a 19.4% lower CL/F relative to a patient with BCCL 126 mL/min (median value in the analysis dataset).

• A patient with BCRP of 8 mg/dL was predicted to have a 4.1% lower CL/F compared to a patient with BCRP of 0.851 mg/dL.

• V/F estimates of an elderly patient (64 years of age, 95th percentile of age) was estimated to be 10.2% lower compared to the V/F of a 40-year-old patient.

• V/F estimates for patients weighing 54 or 107 kg (5th and 95th percentile of body weight) were approximately 19% lower or 20% higher compared to patients with body weight 78 kg, respectively.

Secondary exposure metrics for exposure-response analyses were calculated using the individual parameter estimates obtained from the full model (**Table 17**).

Table 17. Summary of Secondary Pharmacokinetic Parameter Predictions Based on the Final Full Model (Run 65)

Summary of Secondary Pharmacokinetic Parameter Predictions Based on the Final Full Model (Run 65)

		Geometric					
Parameter	Dose	Mean	SD	%CV	Min	Median	Max
Cmax (ng/mL)	2 mg BID	14.0	1.27	24.7	7.83	14.1	24.3
	5 mg BID	36.7	1.32	28.0	10	37.9	64
	10 mg BID	73.9	1.25	22.5	32.5	76.6	120
Cavg (ng/mL)	2 mg BID	6.02	1.24	21.8	3.11	5.99	9.49
	5 mg BID	15.9	1.28	25.4	5.38	15.8	33.1
	10 mg BID	31.0	1.28	24.7	16.8	32.2	62.8
Cmin (ng/mL)	2 mg BID	1.28	1.51	43.4	0.4	1.29	3.17
	5 mg BID	3.46	1.60	49.7	0.825	3.46	11.4
	10 mg BID	6.19	1.70	57.4	1.31	6.53	22.4
AUC (ng.hr/mL)	2 mg BID	72.2	1.24	21.8	37.3	71.9	114
	5 mg BID	190.5	1.28	25.4	64.6	190	397
	10 mg BID	372.0	1.28	24.7	201	386	754

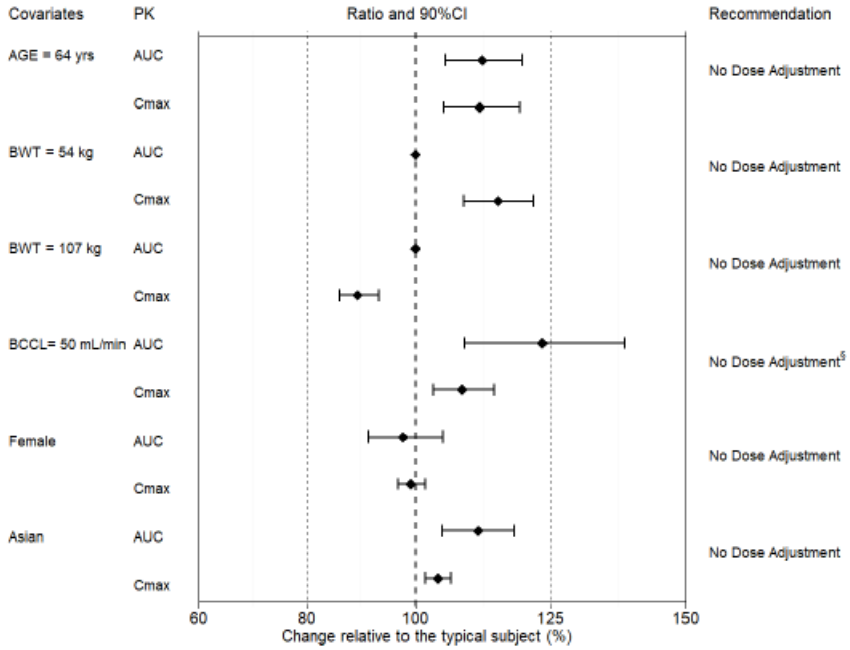
Repository artifact ID FI-4369223. Line 1 substituted. Columns [1 2 8 9 10 6 5 7] out of 10.

Abbreviations: AUC = area under the concentration-time curve over a dosing interval; BID = twice daily; C_{avg} = average steady-state tofacitinib concentration over the dosing interval; C_{max} = maximum steady-state tofacitinib concentration over the dosing interval; C_{min} = tofacitinib concentration at steady-state at the end of the nominal 12 hours dosing interval; CV = coefficient of variation; Max = maximum; Min = minimum; SD = standard deviation

The impact of covariate effects on tofacitinib secondary parameters (AUC and Cmax) is evaluated and demonstrated in Figure 3. With the exception of BCCL, point estimates of AUC and Cmax change relative to typical subject ranged between 98% and 112%, and between 89% and 115%, respectively. For a patient with a BCCL of 50 mL/min (lowest value in the analysis dataset was 48 mL/min), AUC was estimated to be 24% higher relative to a reference patient with baseline creatinine clearance of 126 mL/min. As subjects with baseline creatinine clearance values (estimated by Cockcroft-Gault equation) below 50 mL/min was very limited in the analysis dataset, the need for dose adjustment in renal impairment is primarily assessed using Phase 1 data from Studies A3921004 and A3921006. The point estimates of the AUC and Cmax ratios and the associated 90% CI indicated no major differences in tofacitinib exposure over the range of ages and body weights studied as well as race, and gender.

Figure 3. Impact of Covariates on the Pharmacokinetics of Tofacitinib in AS Patients

Impact of Covariates on the Exposure of Tofacitinib in AS Patients



Repository artifact ID FI-11546118.
Abbreviations: AUC = area under the concentration-time curve over a dosing interval; BCCL = creatinine clearance at baseline; C_{max} = maximum steady-state tofacitinib concentration over the dosing interval ; PK = pharmacokinetic; CI = confidence interval.
Dotted line represents limits of a range from 80% to 125%. A typical (reference) patient is represented as: White male with body weight 78 kg, C-reactive protein at baseline (BCRP) 0.851 mg/dL, creatinine clearance at baseline (BCCL) 126 mL/min, 40 year old. The impact of covariates were assessed at age of 64 year old (95th percentile) and body weights of 54 and 107 kg (5th and 95th percentiles, respectively), female, in Asian subjects with reference to the typical patient reported above. In addition. the impact of BCCL of 50 mL/min with respect to reference patient was also assessed. Dose adjustment recommendation for BCCL 50 mL/min is based on other data (Phase 1 renal impairment trials), as subjects with BCCL below 50 mL/min in this analysis dataset are limited (48.1 mL/min was the lowest BCCL in the analysis dataset). Magnitude of change is presented in reference to a typical patient. §: No dose adjustment for patients with mild or moderate renal impairment.

The population PK of tofacitinib in patients with active ankylosing spondylitis was adequately described by a one-compartment model with first order absorption.

Between-subject variability (%CV) in tofacitinib CL/F was estimated to be 28%.

Tofacitinib does not require dose modification or restrictions for age, body weight, gender, or race in the adult ankylosing spondylitis population based on the <20% differences in AUC and Cmax ratios across these patient factors relative to a reference AS patient.

The relationship between tofacitinib CL/F and creatinine clearance is consistent with the known contribution of renal excretion to the total clearance of tofacitinib.

Population PK analysis results in AS indicated that tofacitinib exposure, as measured by the steady state AUC24 after 5 mg BID is similar (differences between geometric means within 25%) among AS (382 ng•h/mL), PsA (419 ng•h/mL), RA (507 ng•h/mL) and PsO (404 ng•h/mL) patients.

Population PK analysis results indicated comparable inter-subject variability (%CV) in AUC across AS, RA, PsA and PsO patients (all ranged between 27% and 32%).

Based on the demonstrated similarity in the tofacitinib PK profile between AS and RA (and PsA) patients, it is proposed that dosing modifications derived for RA patients, primarily based on Phase 1 clinical pharmacology studies, are also applicable for patients with AS.

Consistent with dose adjustment recommendations in the current SmPC for RA and PsA patients, the recommended total daily dose of tofacitinib will be reduced by half, from 5 mg BID to 5 mg QD (of the IR formulation) for AS patients with severe renal impairment, moderate hepatic impairment, patients receiving potent inhibitors of CYP3A4 (for example, itraconazole), patients receiving 1 or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (for example, fluconazole), moreover tofacitinib is not recommended in AS patients with severe hepatic impairment and the coadministration of tofacitinib and potent inducers of CYP3A4, such as rifampin, to AS patients may result in loss of or reduced clinical response.

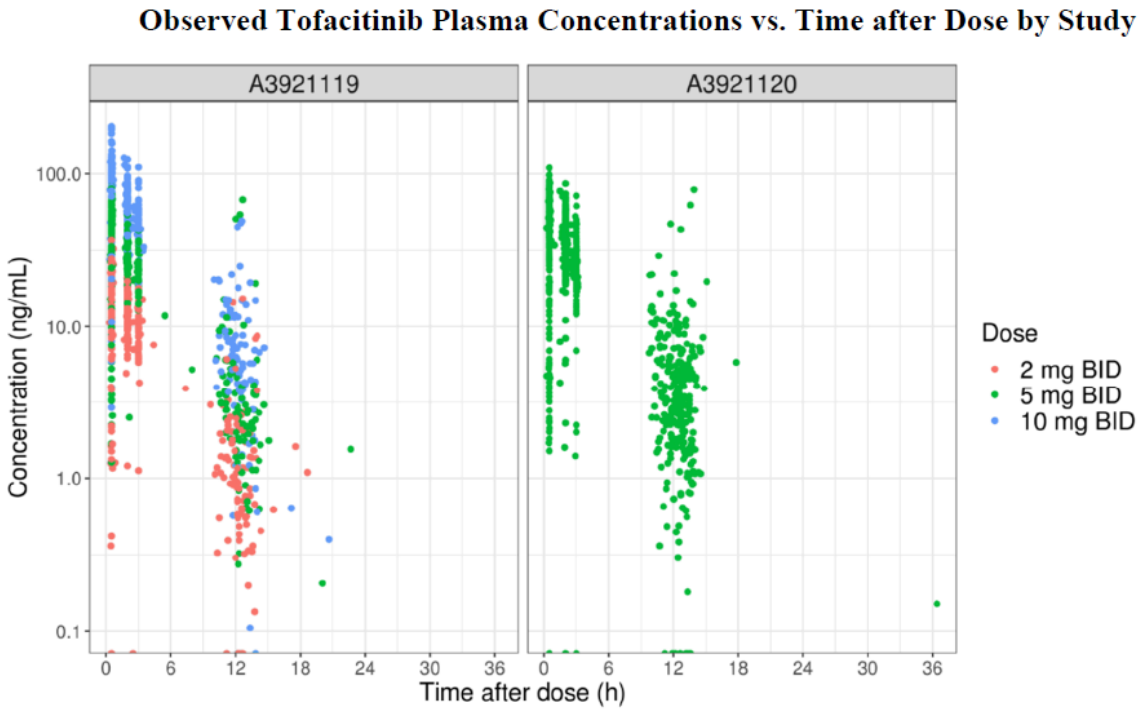
The starting point for the popPk in AS patients was based on models previously used in RA and PsA population. A one compartmental model with first order absorption and IIV on CL/F and V/F with OMEGA block was chosen. IIV on Ka reduced the OFV, moreover the inclusion of tlag determines an increase of Ka estimation with a very quickly absorption phase. The MAH justify this result, and then the exclusion of IIV on Ka, with the sparse sampling data limiting the information on the absorption phase. Although this justification is sharable, the exclusion of IIV on ka did not permit to evaluate the variability in the absorption phase that, in general is of interest for the investigation of the PK profile, thus even for a PopPK model. The residual error for observations with TAD <9 hours and TAD $\geqslant$9 hours was evaluated in the model.

The population (PK) analysis in AS patients was performed using pooled sparse samples collected in Studies A3921119 and A3921120, based on the PK sampling schema (i.e., pre-dose, 0.5, 2, and 3 hours after dose), as designated in the respective study protocols (S0113 Module 5.3.3.5 PMAR-EQDD-A392k-sNDA-1064).

In this population PK analysis in AS patients, residual random effects were described with 2 proportional error models for non-trough samples defined as time after dose (TAD) <9 hours, and trough samples (TAD ≥9 hours), respectively. Trough samples can be noisier than nontrough samples and tend to have a higher variability.

Figure 4 shows the distribution of observed tofacitinib plasma concentrations vs. time after dose by study. As mentioned above, the PK samples were collected based on a sparse sampling schema. It can be observed from Figure 4 that the trough samples (primarily from pre-dose sampling) were mostly collected beyond 9 hours post-dose, with very few to almost no samples between 5- and 9-hours TAD. Given this collection profile, 9 hours was used as the TAD cut-off value to differentially estimate residual errors for trough and non-trough plasma concentrations. Base on the provided justification, the choice of 9 hours as the TAD cut-off value is considered reasonable.

Figure 4. Observed Tofacitinib Plasma Concentrations vs. Time after Dose by Study



Abbreviations: BID = twice daily
Trough concentration was plotted as 12-hour observation instead of pre-dose.

In the initial MAA, the Applicant submitted a nonlinear mixed effects analysis of Cmax and AUC (derived using noncompartmental methods) from 16 Phase 1 studies concluding that Cmax is approximately dose proportional at least up to 10 times the proposed dose of 5 mg.

Study A3921002, a randomized, parallel-group, placebo-controlled, single-dose escalation study was also submitted in the initial MAA in which 95 subjects were randomized in different dose group to receive a single doses of 0.1 to 100 mg tofacitinib, (0.1 mg, 0.3 mg, 1 mg, 3 mg, 10 mg, 30 mg, 60 mg, 100 mg) administered as oral power for constitution (OPC). Systemic exposures (Cmax and AUC∞) of tofacitinib increased in a dose-proportional manner, indicating linear pharmacokinetics across the dose interval evaluated (0,1 and 100 mg dose, **Table 18).** There are only small changes from linearity mostly for Cmax values from 1 mg dose.

Table 18. Mean (SD) PK Parameters Following Single Oral Doses in Healthy Subjects (A3921002)

Dose group (mg)	N	C_{max} (ng/mL)	AUC_{last} (ng*hr/mL)	AUC_{∞} (ng*hr/mL)	T_{max}† (hr)	$t_{1/2}$ (hr)
0.1	5	1.27 (0.08)	0.16 (0.01)	NC	0.5 (0.5 – 0.5)	NC
0.3	8	2.65 (0.62)	3.91 (2.07)	NC	0.5 (0.5 – 1)	NC
1	8	10.5 (2.28)	19.2 (6.54)	NC	0.5 (0.5 – 1)	NC
3	8	21.8 (3.04)	69.5 (13.4)	75.5 (14)	0.5 (0.5 – 1)	2.31 (0.35)
10	8	88 (10.2)	283 (80.3)	289 (81.5)	0.5 (0.3 – 1)	2.61 (0.63)
30	9	240 (44.5)	933 (176)	938 (175)	0.5 (0.3 – 2)	2.72 (0.58)
60	8	408 (97.7)	1710 (435)	1720 (438)	1 (0.5 – 1)	2.68 (0.56)
100	7	638 (118)	2980 (709)	2990 (716)	0.5 (0.5 – 2)	3.07 (0.57)

†Median and Range are reported for Tmax
N = Number of subjects; NC = Not Calculated
Source: CSR A3921002, Tables 5.2.1 to 5.2.8

The MAH has provided the predicted PK parameters for 2 mg, 5 mg and 10 mg derived from PopPK in AS patients. Although, as previously highlighted, the results of the PopPK should be interpreted with caution, it seems that a dose proportionality exists between 2 mg and 5 mg.

The covariates included in the model are race, sex, ethnicity, age, BW, BCCL and BCRP on CL/F and BW and age on V/F. No stepwise testing was performed, whereas the full covariate approach was used. The correlation between covariates was assessed. BW was not included in the final model due to the high correlation with BCLL and also ethnicity was not included due to high prevalence of non-Hispanic/Latino. The inclusion of covariates in the model improved the parameter estimation with decrease in IIV. The bootstrap confidence intervals (95% CI) for the parameters were generated from 1000 non-parametric bootstrap. The median value of CL/F and V/F calculated by the bootstrap was similar to that estimated in the full model. Overall, the GoF showed that the model adequately fits the observed concentrations, however it is noted that a greater number of observations are above the line of identity. Moreover, the CWRES vs time showed that, in particular at earlier time points, a number of observations are outside the -/+ 2 CWRES. This is in line with the fact that the model is not able to catch the variability in the absorption phase. Some outliers are also showed in the graphs of CWRES vs predicted concentrations.

The VPC showed that the concentrations in the early phase of absorption were underpredicted by the model, in particular the lower concentrations (5^{th} percentile), whereas the concentrations in the 95^{th} percentile were overpredicted. Y axis of VPC plot reports "concentration.

The MAH was requested to better specify which PK parameter was reported and to provide the VPC plotting the Cmin, Cmax and Cavg as dependent variable. The response provided by the MAH is considered sufficient. However, a certain degree of variability has been observed. Although a sparse sampling has been applied to PK parameters, the number of observed values appear to be sufficient to conclude that high variability is observed after the administration of tofacitinib and that the model predictions (5 and 95 percentile) are even larger that observed concentrations. This reduce the reliability and the precision of the model. Therefore, all the analysis based on predicted plasma concentrations derived from the present model should be interpreted with caution.

The PopPK model was also used to calculate the secondary exposure parameters Cmax, Cavg, Cmin, AUC over the dosing interval and to evaluate the impact of covariates on AUC and Cmax. Except for BCLL, impacted by the renal elimination of tofacitinib, all covariates have a marginal effect on PK parameters.

The tofacitinib exposure showed in the PopPK for AS is superimposable to that observed in the other populations of patients (PsA, RA, PsO) in terms of AUC24 after 5 mg BID dose. The AUC24 considered were the following: AS (382 ng•h/mL), PsA (419 ng•h/mL), RA (507 ng•h/mL) and PsO (404 ng•h/mL).

In order to further compare the PK profile of tofacitinib throughout the different diseases, a summary of model-predicted exposure parameters based on the population PK analyses across indications is provided in the **Table 19**. The results shows that tofacitinib exposure for AS is superimposable to that observed in the other populations of patients (PsA, RA, PsO) in terms of AUC24, as well as in terms of Cavg, Cmax and Cmin after 5 mg BID dose. However, the submission of observed exposure parameters would have been more correct in order to compare them and their variability among different indications. However, the AS effect on PK profile is not expected to be clinically relevant if any.

Table 19. Comparison of estimated Exposer parameters (for 5 mg BID) based on Population PK

Comparison of estimated Exposure parameters (for 5 mg BID) based on Population PK analysis in AS, PsA, RA and UC Patients

	Geometric Mean (%CV*)			
Parameter	**AS**	**PsA**	**RA§**	**UC**
C_{avg} (ng/mL)	15.9 (25.4)	17.5 (34.1)	21.1 (18.5)	17.6 (22.6)
C_{max} (ng/mL)	36.7 (28)	42.4 (31.6)	58 (29.3)	46.9 (19.4)
C_{min} (ng/mL)	3.46 (49.7)	4.23 (70.8)	4.37 (82.8)	3.59 (47.4)
AUC_{24} (ng.h/mL)	382 (25.4)	419 (34.1)	507 (22)	423 (22.6)

* %CV of Geometric mean; §Derived for 5 mg BID

Sources: S0113 Module 5.3.3.5 PMAR-EQDD-A392k-sNDA-1064, S0014 Module 5.3.3.5 PMAR-EQDD-A392j-sNDA-601, S0000 Module 5.3.3.5 PMAR-00178, S0012 Module 5.3.3.5 PMAR-EQDD-A392i-sNDA-513

Abbreviations: AUC_{24} = area under the concentration-time curve over 24 hours; BID = twice daily; C_{avg} = average steady-state tofacitinib concentration over the dosing interval; C_{max} = maximum steady-state tofacitinib concentration over the dosing interval; C_{min} = tofacitinib concentration at steady-state at the end of the nominal 12 hours dosing interval; CV = coefficient of variation.

2.3.3. Pharmacodynamics

Exposure-Response Evaluation of Tofacitinib for Efficacy (ASAS20/40) in Patients with Ankylosing Spondylitis

The following studies were included in the analysis: A3921119 and A3921120. A brief overview of these studies is presented in **Table 20**.

Table 20. Tofacitinib Phase 2 and Phase 3 Studies in AS Population Included in the Analyses

Study	Design	Duration and Visits	Treatment Arm (Planned Number)
A3921119	Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study of the efficacy and safety of tofacitinib in subjects with active AS	12 weeks Visits on week 2, 4, 8 and 12	Placebo twice daily (BID) (n=50) 2 mg BID (n=50) 5 mg BID (n=50) 10 mg BID (n=50)
A3921120	Phase 3, randomized, double-blind, placebo-controlled, study of the efficacy and safety of tofacitinib in subjects with active AS	16 weeks double-blind phase followed by 32 weeks open-label phase Visits during double-blind phase on week 2, 4, 8, 12 and 16	5 mg BID 0-48 weeks (n=120) Placebo for 16 weeks then transfer to tofacitinib 5 mg BID 16-48 weeks (n=120)

Source: study protocols for A3921119 [5] and A3921120 [6]

The primary objectives 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.

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 modeled 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 modeled 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:

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

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

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 21**

Table 21. Number of Subjects by Treatment Groups

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

Table 22. Summary of Prior bDMARD Experience

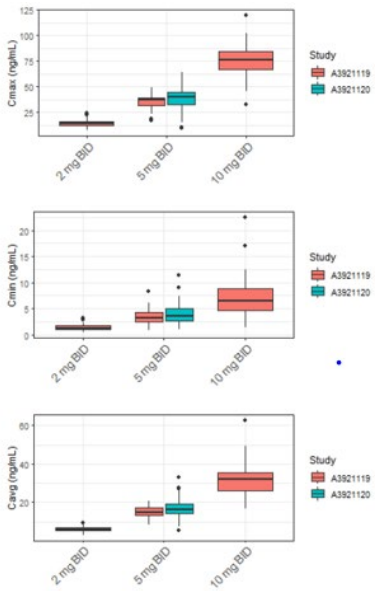
Prior bDMARD	A3921119	A3921120	Total
Naive	198 (100%)	207 (77.2%)	405 (86.9%)
Experienced	0 (0%)	61 (22.8%)	61 (13.1%)

Repository artifact ID FI-4370388. Line 1 substituted.

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 5** and summary statistics are listed in **Table 23**.

Figure 5. 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 23. 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 24.**

Table 24. 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 25.**

Table 25. 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.

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 immunization 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 6** and **7**.

Figure 6. Diagnostic Plots of the Base Model (1of 2)

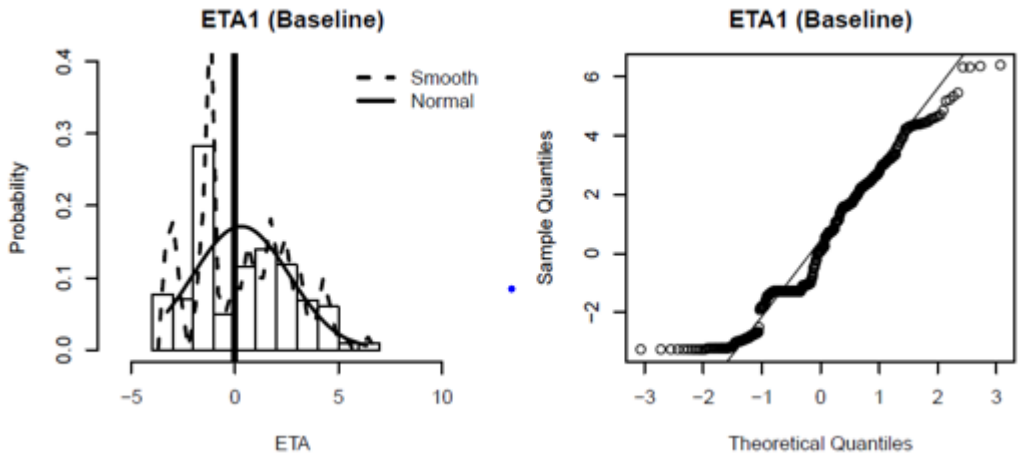
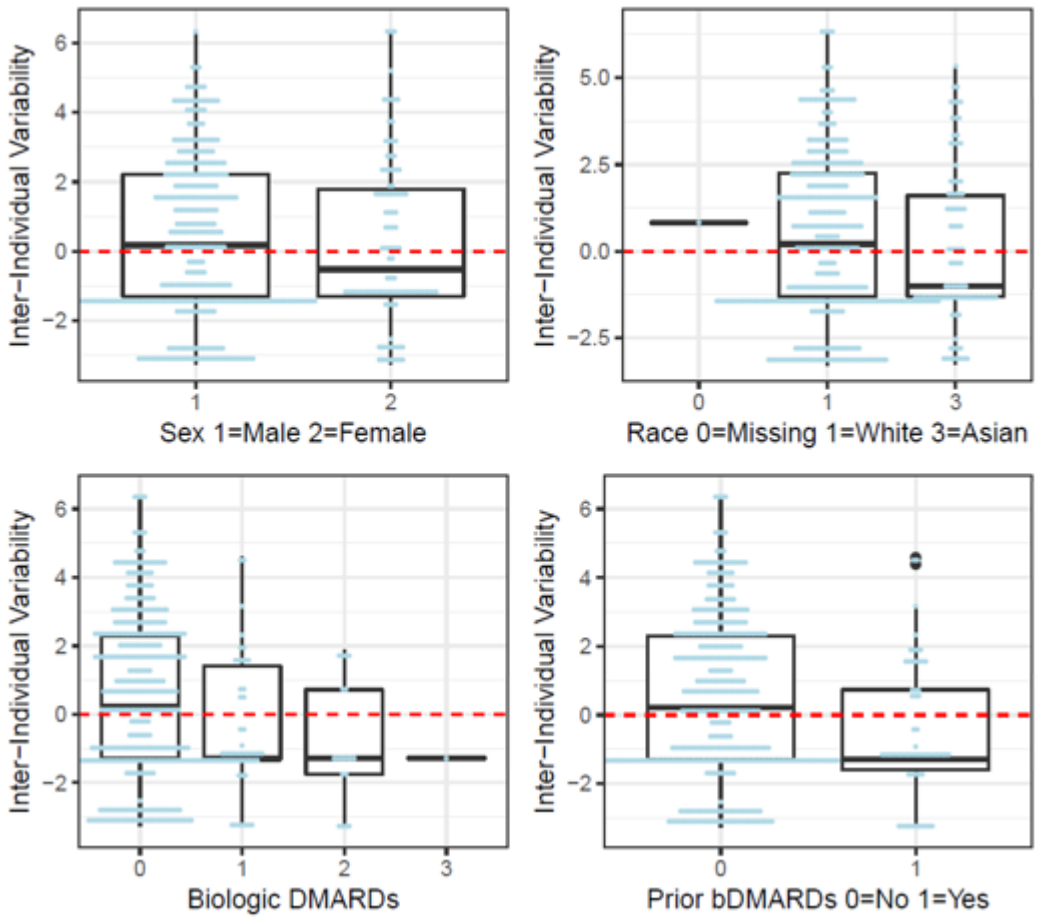
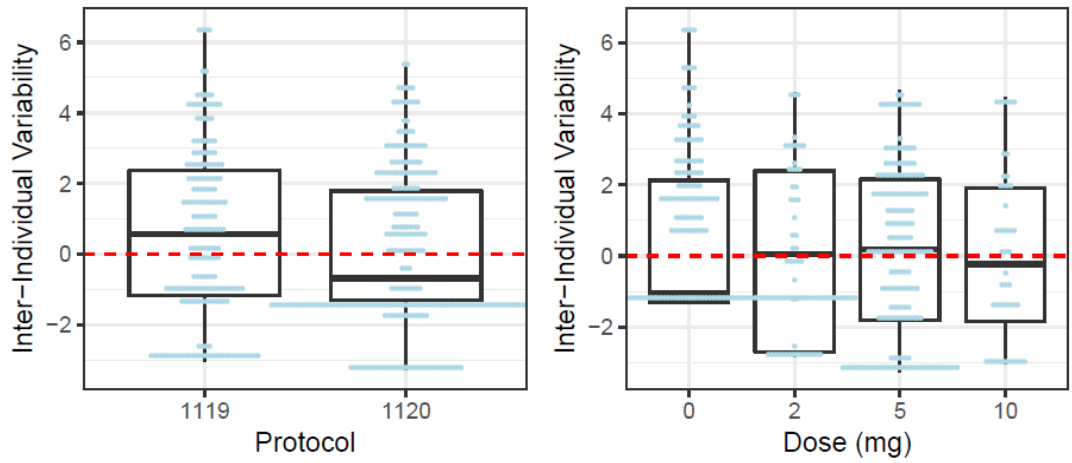


Figure 7. Diagnostic Plots of the Base Model (2 of 2)





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 26**.

Table 26. Parameter Estimates of the Final Model (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**s **8 and 9.**

Figure 8. Diagnostic Plots of the Final Model (1of 2)

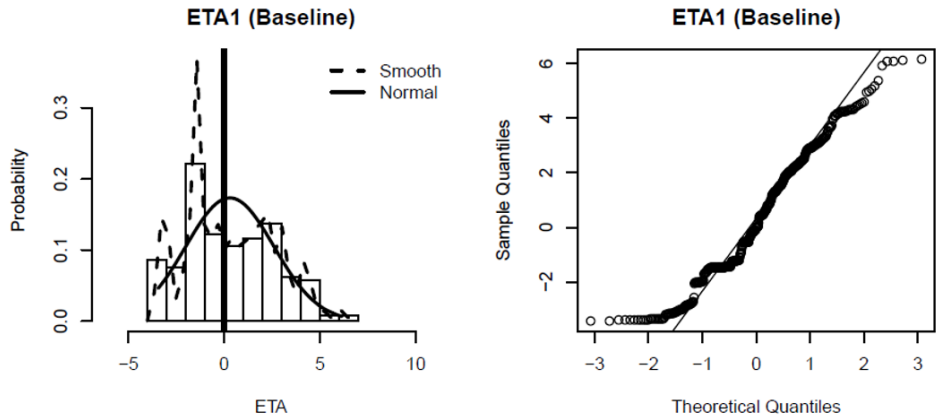
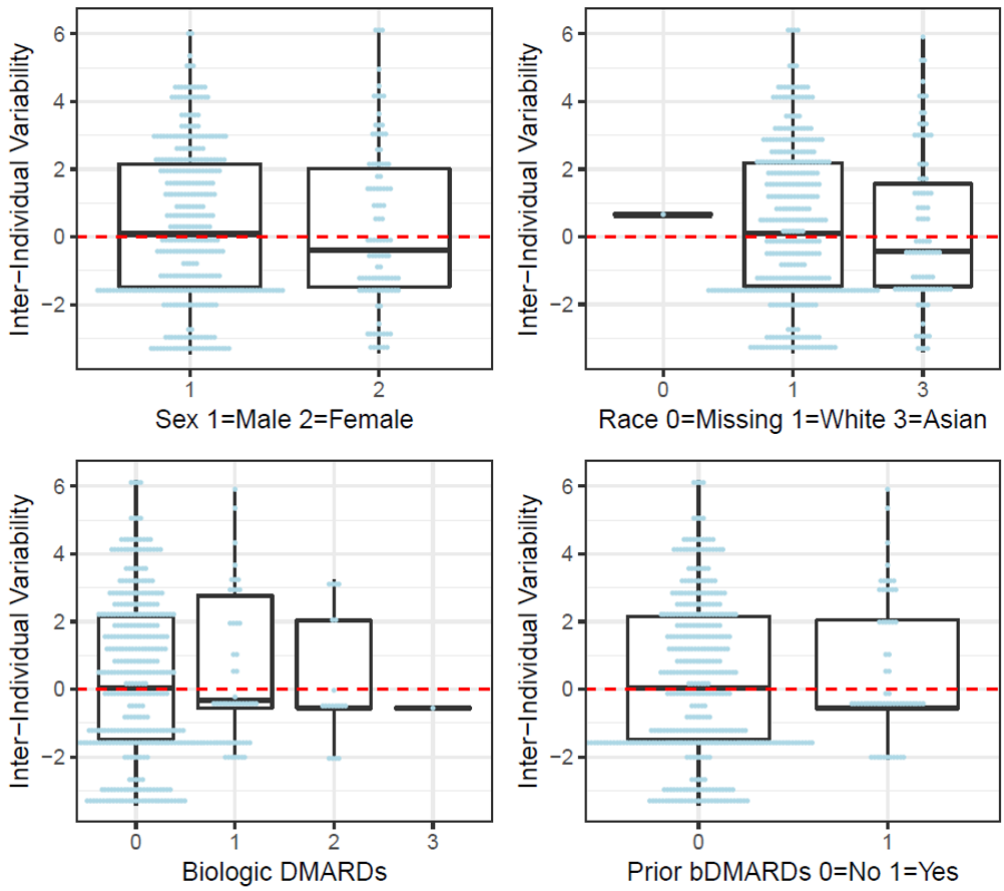
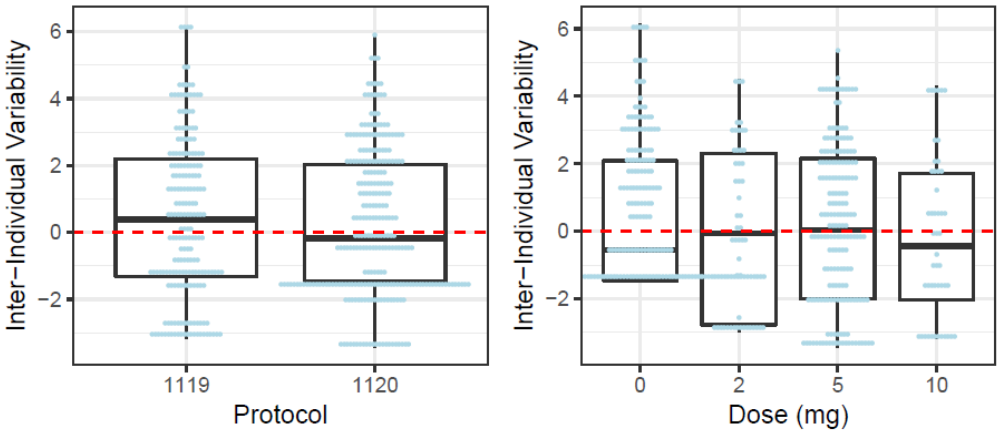


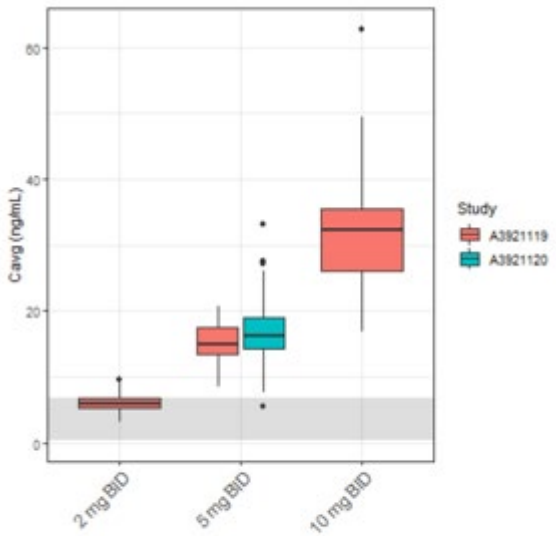
Figure 9. Diagnostic Plots of the Final Model (2 of 2





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 10). 1000 non-parametric bootstrap were performed to generate the 90%CI of parameter estimates using the final model. Of these, 27 runs for which miminization 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 10. 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 **Figures 11**, **12, 13, and 14**.

Figure 11. Visual Predictive Check for ASAS20 and ASAS40 Response Rates Stratified by Dose (1 of 2)

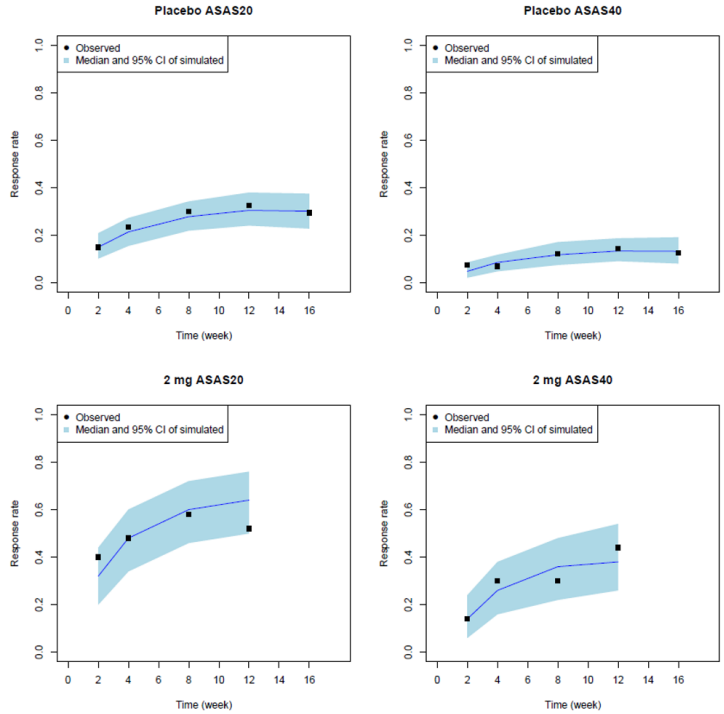


Figure 12. Visual Predictive Check for ASAS20 and ASAS40 Response Rates Stratified by Dose (2 of 2)

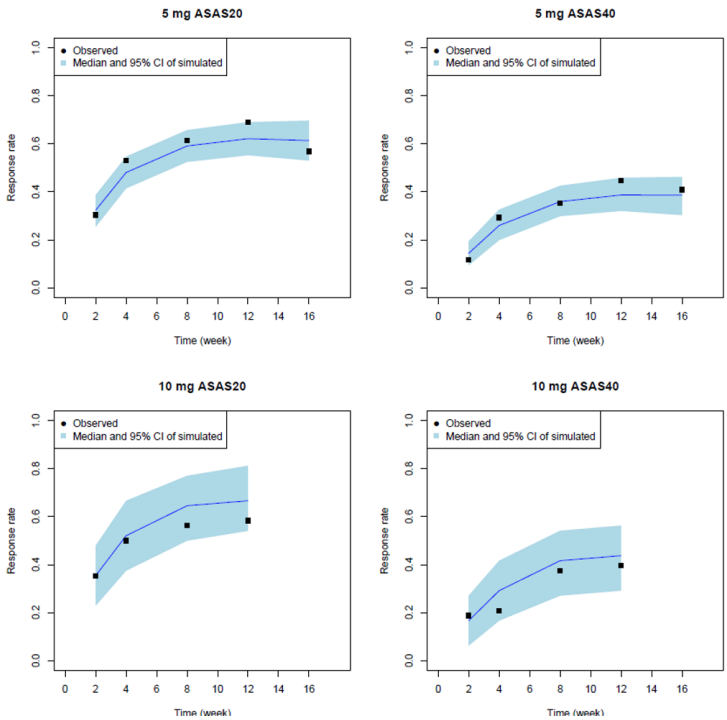


Figure 13. Visual Predictive Check for ASAS20 and ASAS40 Response Rates Stratified by Prior bDMARD Experience (1 of 2)

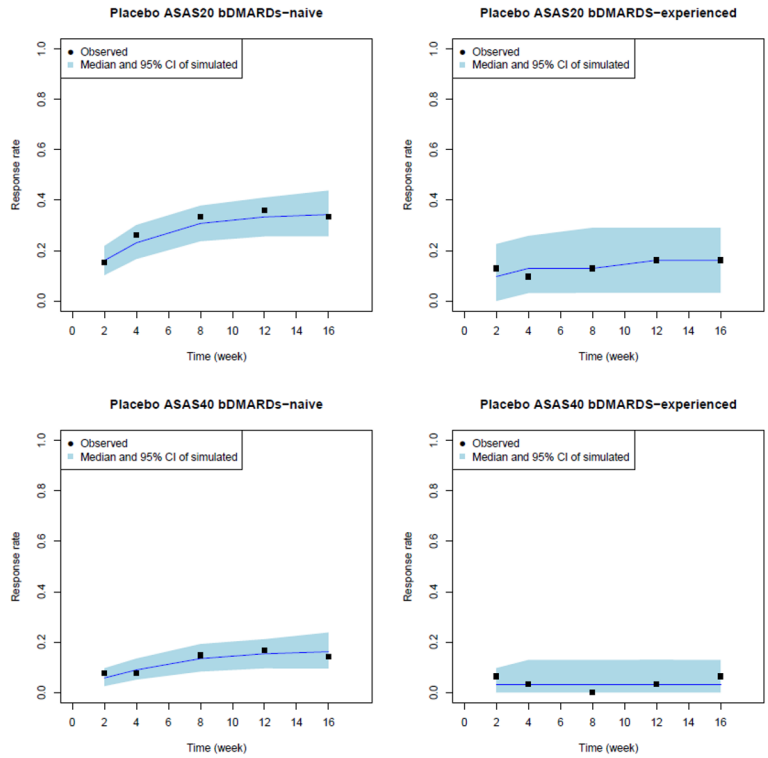
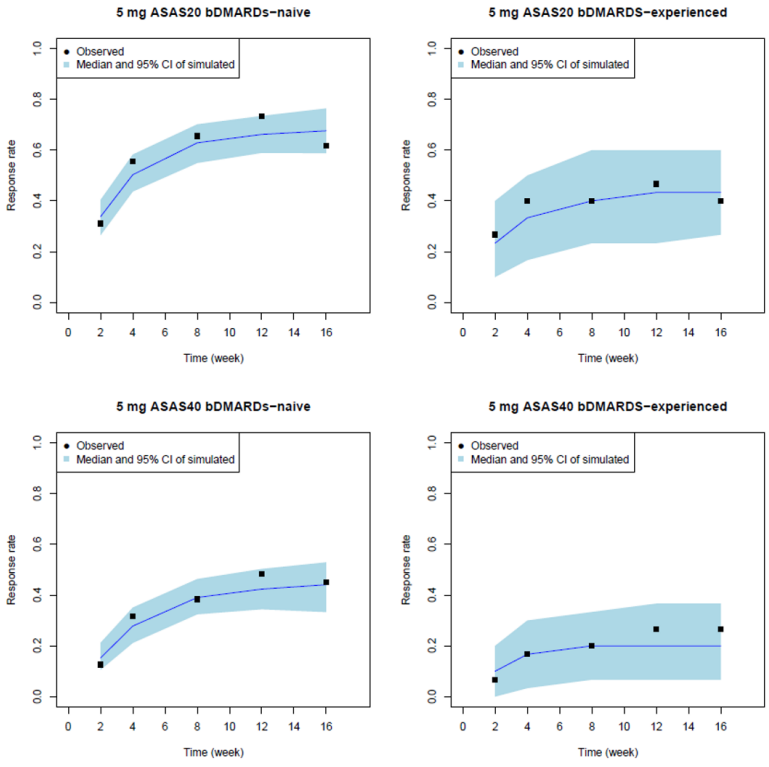


Figure 14. Visual Predictive Check for ASAS20 and ASAS40 Response Rates Stratified by Prior bDMARD Experience (2 of 2)



Model Predicted ASAS20 and ASAS40 Responses based on Simulation

The model predicted ASAS20 and ASAS40 response rates based on simulation are listed in **Table 27.** 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.

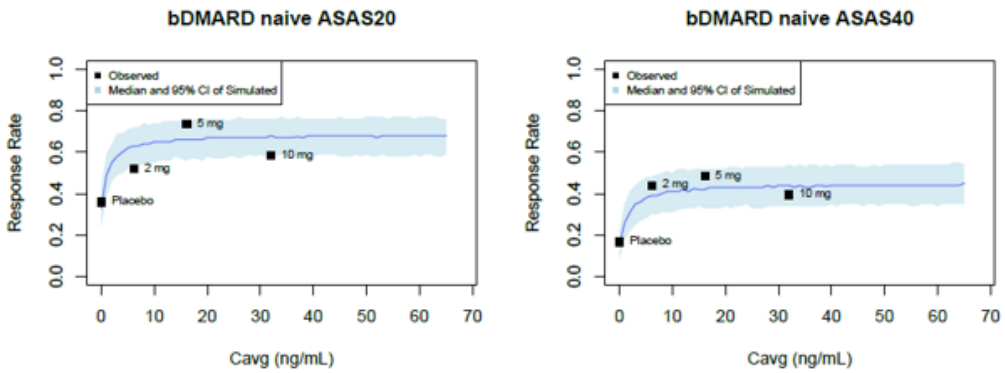
Table 27. Model- Predicted ASAS20 and ASAS40 Response Rates at Week 16 in bDMARD-Naïve Patients

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 15, Figure 16**). 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.

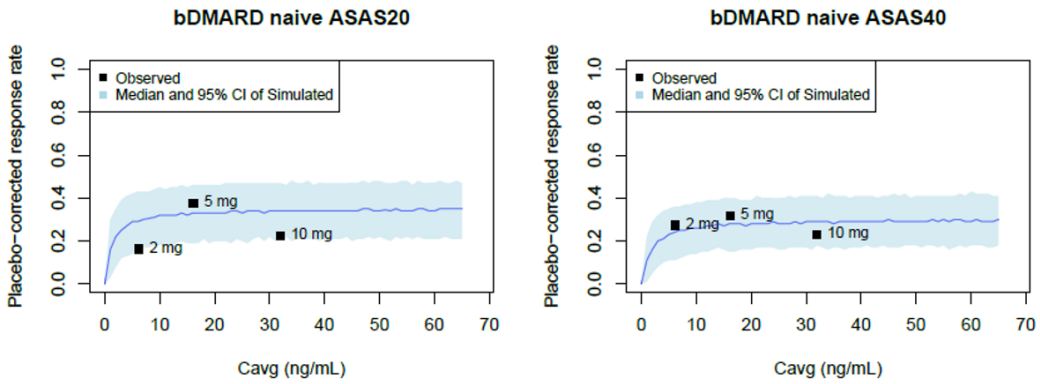
Figure 15. Exposure-Response Relationship in bDMARD-Naive Patients (Week 12)



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 16. Exposure-Response Relationship in bDMARD-Naive Patients Week 12 (Placebo-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

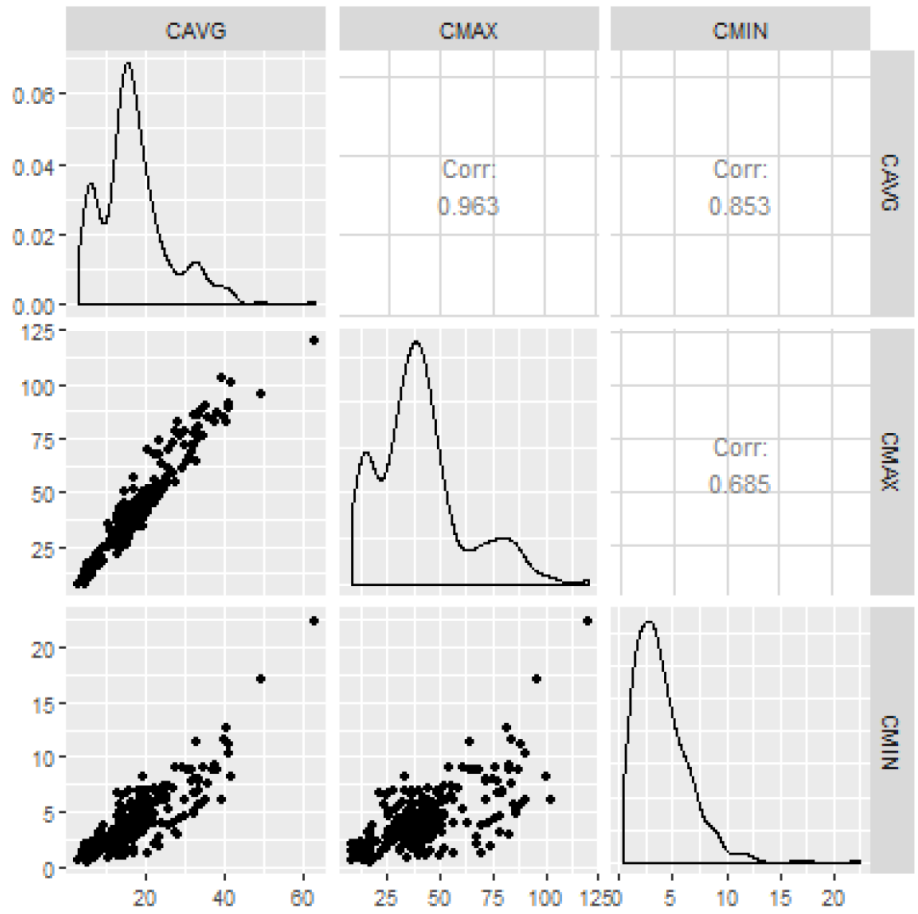
Table 28 summarizes the model evaluation for the different E-R models fitted using ASAS20 and ASAS40 response rates in AS patients. Models with Cavg, Cmin or Cmax as the predictor (univariate analysis) did not show differences in model diagnostics (OFV or AIC differences less than 3.84 units) that would 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 17**); the exposure measures contain very similar information.

Table 28. 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 17. 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

Ten (10) mg ASAS20 and ASAS40 VPC final model plots showed a slight overprediction; for 2 mg and 5 mg ASAS 20 and ASAS 40 they seem to look better.

Placebo-corrected estimates of ASAS20 response rates in bDMARD-naive patients after the 5 mg BID dose, were 18% by Week 2, and reached 28% by Week 4. 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.

For the 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, in any case, for an E-R analysis, this represents a limitation.

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." Howbeit 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, however this represents another limitation.

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), this would support the conclusion that none exposure parameter is more relevant to clinical efficacy compared to another. However, Cavg has been chosen as exposure metric to select the model to describe the relationship between tofacitinib exposure and efficacy in AS, since it was previously established as the most relevant parameter for tofacitinib efficacy in RA. Although there are similarities between RA and AS diseases, the profiles of the two pathologies are not perfectly superimposable, therefore the MAH was requested to discuss, in general, the potential of disease effect affecting PK profile, and, more in details, that Cavg is the most suitable exposure metric, in terms of close association with efficacy, also for AS. which was provided by the MAH and the issue considered resolved by the CHMP.

According to the MAH, the half-life of drug onset was estimated to be 1.18 weeks for ASAS20/40 (90%CI [0.74, 2.14]), which is applicable across all dose groups.

The simulated exposure-response relationship appears to be flat, even flatter compared to observed data. In all the exposure-response plots, the 10 mg Cavg median values are always overpredicted; moreover, the 10 mg Cavg values are lower than the 5 mg, and, for the ASAS40 values (placebo-corrected), also lower than the 2 mg. Considering the above, it can be concluded that the exposure-response curve does not properly capture the shape of the relationship showed by the observed Cavg values, even if predicted values are within observed ICs values. Overall, the relationship between tofacitinib exposure (Cavg) and clinical response seems to be not well captured by the E-R model. In response the MAH clarified that the ASAS20 and ASAS40 response rates shown in the VPC plots as "*observed*" are observed proportions for each stratified group.

2.3.4. Discussion on clinical pharmacology

Two studies were submitted within this extension of indication in AS. The study A3921119 was a phase 2 study in which three doses (2 mg, 5 mg and 10 mg) were administered in bDMARD naïve population. The PK dataset included was 50, 49 and 48 patients for 2 mg, 5 mg and 10 mg dose cohort, respectively. The PK sampling was at pre-dose, 0.5 hr and 2 hours post dose at Week 4 and pre-dose, 0.5 hr and 3hr post dose at Week 8. The Study A3921120 was a phase 3 study in which only 5 mg dose was administered. Patients enrolled were bDMARD naïve (77.2%) and bDMARD experienced (22.8%). The study consists of two parts, the first one was the blinded phase and lasted 16 weeks, the second one was the open label phase lasted until Week 48. The plasma samples were collected at pre-dose, 0.5 hr and 2 hours post dose at Week 4 and pre-dose, 0.5 hr and 3hr post dose at Week 8. The PK dataset included 132 patients.

Tofacitinib plasma concentrations were measured through HPLC-MS/MS method developed and validated at Wuxi AppTec (Shangai, China – A3929023) and then transferred at PPD (Richmond and Middleton). A method transfer was performed from PPD in Richmond to PPD in Middleton and an assay performance with respect to precision, accuracy, and specificity was conducted.

Samples from Study A3921119 were analysed by Wuxi, whereas samples from Study A3921120 were analysed by PPD in Middleton.

The cross validation A3929023 addendum 6 is not applicable to the current analysis since it is performed between Wuxi (method A3929023), Basi (A3929011) and PPD in Richmond (method A3929032). A further cross validation A3929023 Amendment 2 was performed between Wuxi and PPD Richmond.

No cross-validation was performed between PPD Middleton and Wuxi, however the MAH is of the opinion that since the method used at Richmond and Middleton remained exactly the same, the cross validation between Wuxi and PPD Richmond supports the comparability of data analysis also between Wuxi and PPD Middleton.

This is not exactly in line with EMA guideline, however since the method transfer to PPD Middleton showed that selectivity, carryover, linearity, sensitivity, accuracy, precision, recovery, dilution, and stability were met, the method is considered valid for the extraction and analysis of human lithium heparin plasma.

The CSR A3921119 mentions a Section 16.2.5.10 containing the bioanalytical report; however, this section/appendix was initially missing. The MAH clarified that Study A3921119 was already submitted as supportive study in the contest of extension indication in psoriatic arthritis. The bioanalytical report was attached to that eCTD sequence and not re-submitted for the current variation. Which is considered acceptable by the CHMP.

A total of 1011 samples were analysed by Wuxi (method A3929023); the maximum storage time at -20±5°C in sodium heparin was 309 days (validated LTS at 1274 day at -20±5°C). The ISR was performed on 104 samples and fulfilled the acceptance criteria.
The MAH provided the bioanalytical report for study A3921120 and declared that all samples were analysed during the stability period. The number of samples received is 1848, however the samples analysed were 922. In the Appendix 4 of the bioanalytical report for study A3921120, the note 8 denotes samples not assayed at Sponsor's request and was reported for several samples, all in the treatment B. The MAH clarified that these samples were not assayed as they were placebo samples.

The PK data were analysed in the PopPK model in which both studies were included. A one compartment model with first order absorption, IIV on CL/F and V/F with OMEGA block and no IIV on ka, different proportional residual error for observations with TAD<9 or ≥9 hours on residual error was chosen as the base model. The effect of covariates was evaluated through the full covariate approach.

IIV on Ka reduced the OFV, moreover the inclusion of tlag determines an increase of Ka estimation with a very quickly absorption phase. The MAH justify this result, and then the exclusion of IIV on Ka, with the sparse sampling data limiting the information on the absorption phase. Although this justification is sharable, the exclusion of IIV on ka did not permit to evaluate the variability in the absorption that, in general, is a significant part of PopPK model. The residual error for observations with TAD <9 hours and TAD ⩾9 hours was evaluated in the model, since the trough samples (primarily from pre-dose sampling) were mostly collected beyond 9 hours post-dose, with very few to almost no samples between 5- and 9-hours TAD. Given this collection profile, 9 hours was used as the TAD cut-off value to differentially estimate residual errors for trough and non-trough plasma concentrations.

In the initial MAA, dose proportionality was concluded over a dose range of 5 to 50 mg. The Applicant included plasma concentrations of patients with treated with 2 mg, 5 mg and 10 mg into the PopPK model. However, no information was provided on the dose-proportionately over the dose range of 2 to 5 mg in the current variation. In the initial MAA, the MAH submitted a nonlinear mixed effects analysis of Cmax and AUC (derived using noncompartmental methods) from 16 Phase 1 studies concluding that Cmax is approximately dose proportional at least up to 10 times the proposed dose of 5 mg.

Study A3921002, a randomized, parallel-group, placebo-controlled, single-dose escalation study was also submitted in the initial MAA in which 95 subjects were randomized in different dose group to receive a single doses of 0.1 to 100 mg tofacitinib, (0.1 mg, 0.3 mg, 1 mg, 3 mg, 10 mg, 30 mg, 60 mg, 100 mg) administered as oral power for constitution (OPC). Systemic exposures (Cmax and AUC∞) of tofacitinib increased in a dose-proportional manner, indicating linear pharmacokinetics across the dose interval evaluated (0,1 and 100 mg dose). There are only small changes from linearity mostly for Cmax values from 1 mg dose.

In the contest of this response, the MAH also provided the predicted PK parameters for 2 mg, 5 mg and 10 mg derived from PopPK in AS patients. Although, the results of the PopPK should be interpreted with caution, it seems that a dose proportionality exists between 2 mg and 5 mg.

The covariates included in the model are race, sex, ethnicity, age, BW, BCCL and BCRP on CL/F and BW and age on V/F. The correlation between covariates was assessed. BW was not included in the final model due to the high correlation with BCLL and also ethnicity was not included due to high prevalence of non-Hispanic/Latino. The inclusion of covariates in the model improved the parameter estimation with decrease in IIV% (RSE%). The bootstrap confidence intervals (95% CI) for the parameters were generated from 1000 non-parametric bootstrap. The median value of CL/F and V/F calculated by the bootstrap was similar to that estimated in the full model.

Overall, the GoF showed that the model adequately fits the observed concentrations, however it is noted that a greater number of observations are above the line of identity. Moreover, the CWRES vs time showed that, in particular at earlier time points, a number of observations are outside the -/+ 2 CWRES. This is in line with the fact that the model is not able to catch the variability in the absorption phase. Some outliers are also showed in the graphs of CWRES vs predicted concentrations.

The VPC, describing tofacitinib plasma concentration over time, showed that the concentrations in the early phase of absorption were underpredicted by the model, in particular the lower concentrations (5^{th} percentile), whereas the concentrations in the 95^{th} percentile were overpredicted. A certain degree of variability has been observed. Although a sparse sampling has been applied to PK parameters, the number of observed values appear to be sufficient to conclude that high variability is observed after the administration of tofacitinib and that the model prediction (5 and 95 percentile) are even larger that observed concentrations. This reduces the reliability and the precision of the model. Therefore, all the analysis based on predicted plasma concentrations derived from the present model should be interpreted with caution.

The PopPK model was also used to calculate the secondary exposure parameters Cmax, Cavg, Cmin, AUC over the dosing interval and to evaluate the impact of covariates on AUC and Cmax. Except for BCLL, impacted by the renal elimination of tofacitinib, all covariates have a marginal effect on PK parameters.

The tofacitinib exposure showed in the PopPK for AS is superimposable to that observed in the other populations of patients (PsA, RA, PsO) in terms of AUC24 after 5 mg BID dose. The AUC24 considered were the following: AS (382 ng•h/mL), PsA (419 ng•h/mL), RA (507 ng•h/mL) and PsO (404 ng•h/mL).

In order to further compare the PK profile of tofacitinib throughout the different diseases, the MAH was asked to provide a comparison of all the main exposure parameters, e.g. Cavg, Cmin, Cmax. The MAH submitted a summary of model-predicted exposure parameters based on PopPK analyses across indications for Cavg, Cmax, Cmin and AUC24, showing that tofacitinib exposure for AS is superimposable to that observed in the other populations of patients (PsA, RA, PsO) after 5 mg BID dose. However, also giving the comment above on the model reliability in AS, the submission of observed exposure parameters would have been more correct to compare them and their variability among different indications. However, the AS effect on PK profile is not expected to be clinically relevant if any.

ASAS20 and ASAS40 responses from 2 studies in patients with active AS, A3921119 and A3921120 were pooled to support E-R analyses. A longitudinal ordered categorical model was developed to jointly model ASAS20 and ASAS40 responses 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 (up to Week 12 for 2 mg and 10 mg BID dose groups). For the base model the standard error was high, not only 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%. 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, even if the assumption of normality was not met.

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.

Model evaluation with Cavg, Cmin or Cmax as the predictor (univariate analysis) for the different E-R models fitted using ASAS20 and ASAS40 response rates in AS patients, 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. PK parameters are highly correlated, particularly Cavg and Cmin (correlation coefficient=0.85).
Overall, as in RA, C_{avg} can be considered as parameter for efficacy in AS.
The simulated exposure-response relationship 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. Considering the above, it can be concluded that the predicted Cavg values do not properly capture the shape of the relationship showed by the observed Cavg values, even if predicted values are within observed ICs values. Overall, the relationship between tofacitinib exposure (Cavg) and clinical response seems to be not well captured by the E-R model. All the above considered, no reliable conclusion can be drown using the present analysis. In response the MAH clarified that the ASAS20 and ASAS40 response rates shown in the VPC plots as "*observed*" are observed proportions for each stratified group.

2.3.5. Conclusions on clinical pharmacology

The VPC in the PopPK model showed a high variability in the observed values and the model predictions (5^{th} and 95^{th} percentile) are even larger that the observed concentrations, reducing the reliability and precision of the model. On this basis, the PK comparison between the different indications should be interpreted with caution. However, the AS effect on PK profile is not expected to be clinically relevant if any. Given all the limitations of the Exposure-Response analysis, any conclusion should be taken with caution. However, the clinical pharmacology properties are still considered sufficiently characterised.

2.4. Clinical efficacy

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

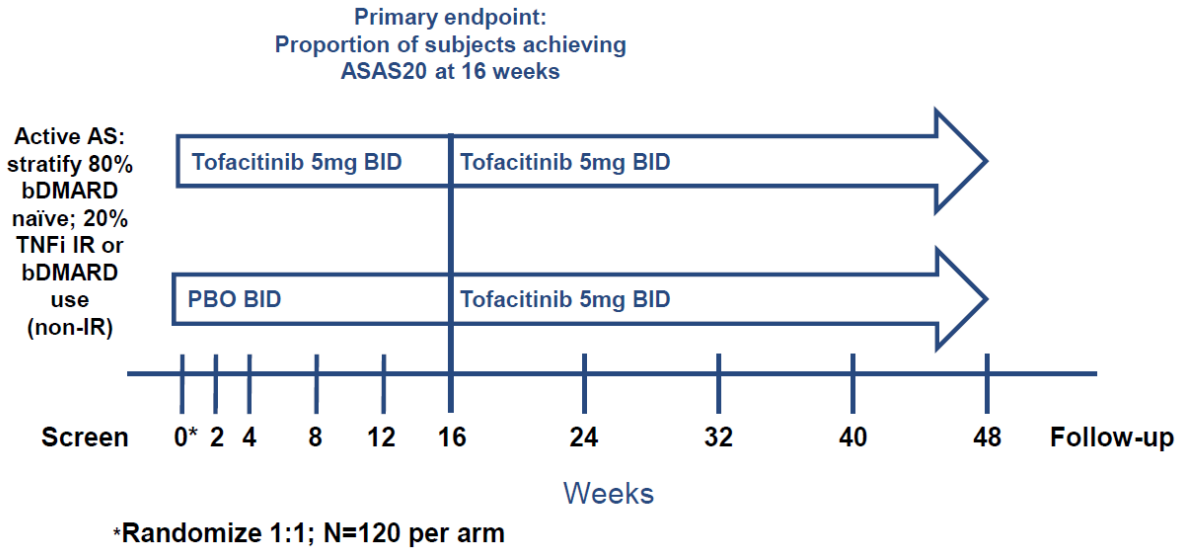
A3921120

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled efficacy and safety study designed to compare 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, TNFi-IR, or experienced to previous bDMARDs but without inadequate response (bDMARD Use [Non-IR]).

Methods

The design of the pivotal A3921120 Study is presented in the **Figure 18**:

Figure 18. 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 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 TNFì-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. This is endorsed.

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.

Key Exclusion criteria:

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) $<3.0 \times 10^9$/L (<3000 mm^3)
    - Absolute neutrophil count (ANC) $<1.5 \times 10^9$/L (<1500 mm^3)
    - Absolute lymphocyte count $<1.0 \times 10^9$/L (<1000/mm^3)
    - Platelet count $<100 \times 10^9$/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 29**). 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 29. 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 30**.

Table 30. 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 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 31** summarises the description of the endpoints and the time points of the assessment.

Table 31. 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 randomization strata (prior treatment history).

Randomisation

By use of an automatic Interactive web-based Response system. Subjects were randomized 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 32**. 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 32. 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.

The randomisation scheme is considered adequate.

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 randomized 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 thatestimates 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 33. 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.
The method is not very rigorous, since the alpha level for each comparison is fixed at the 2-sided 5%.

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 19 and 20** respectively.

Figure 19. Subject Disposition Up to Week 16port

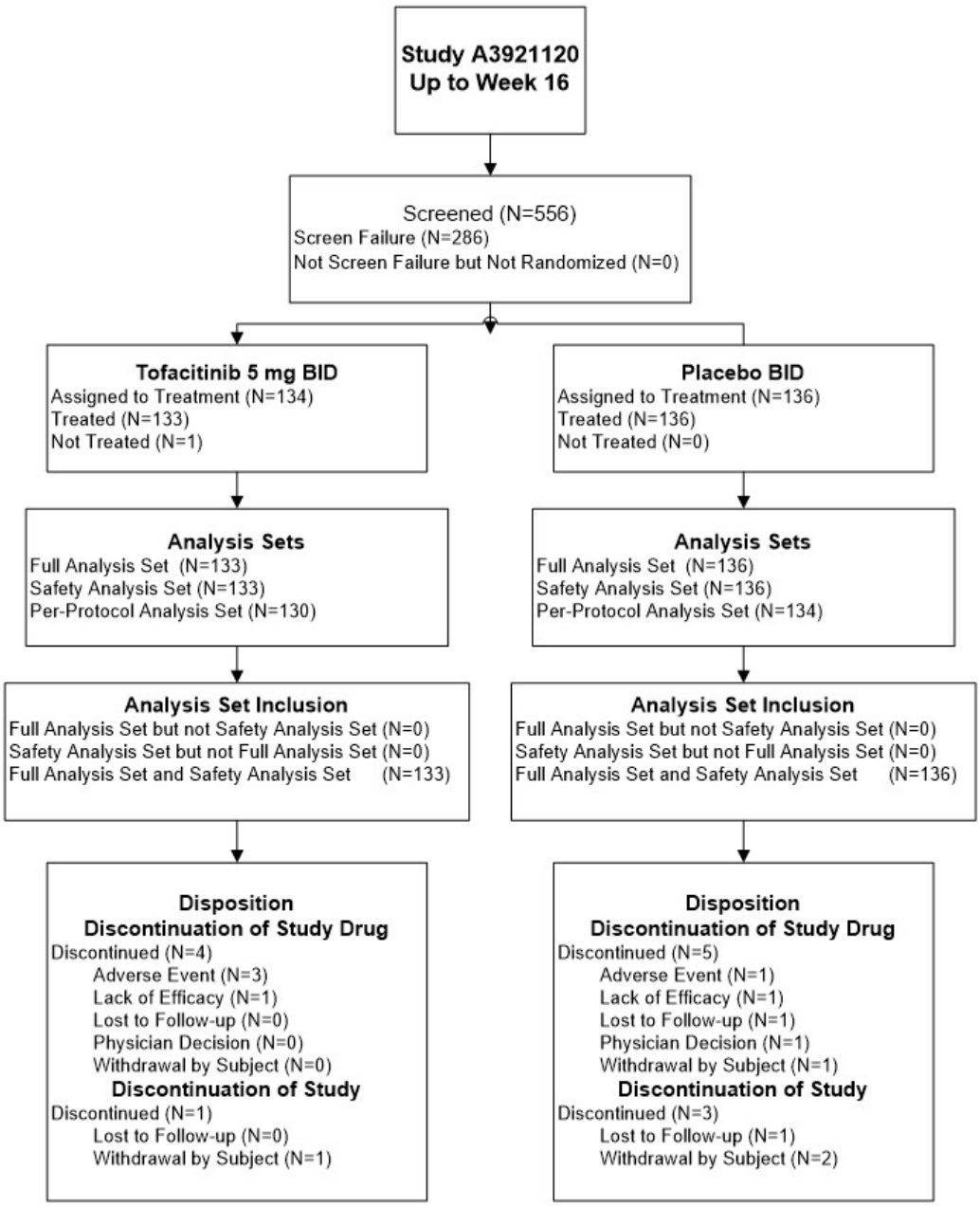


Figure 20. Subject Disposition Up to Week 48

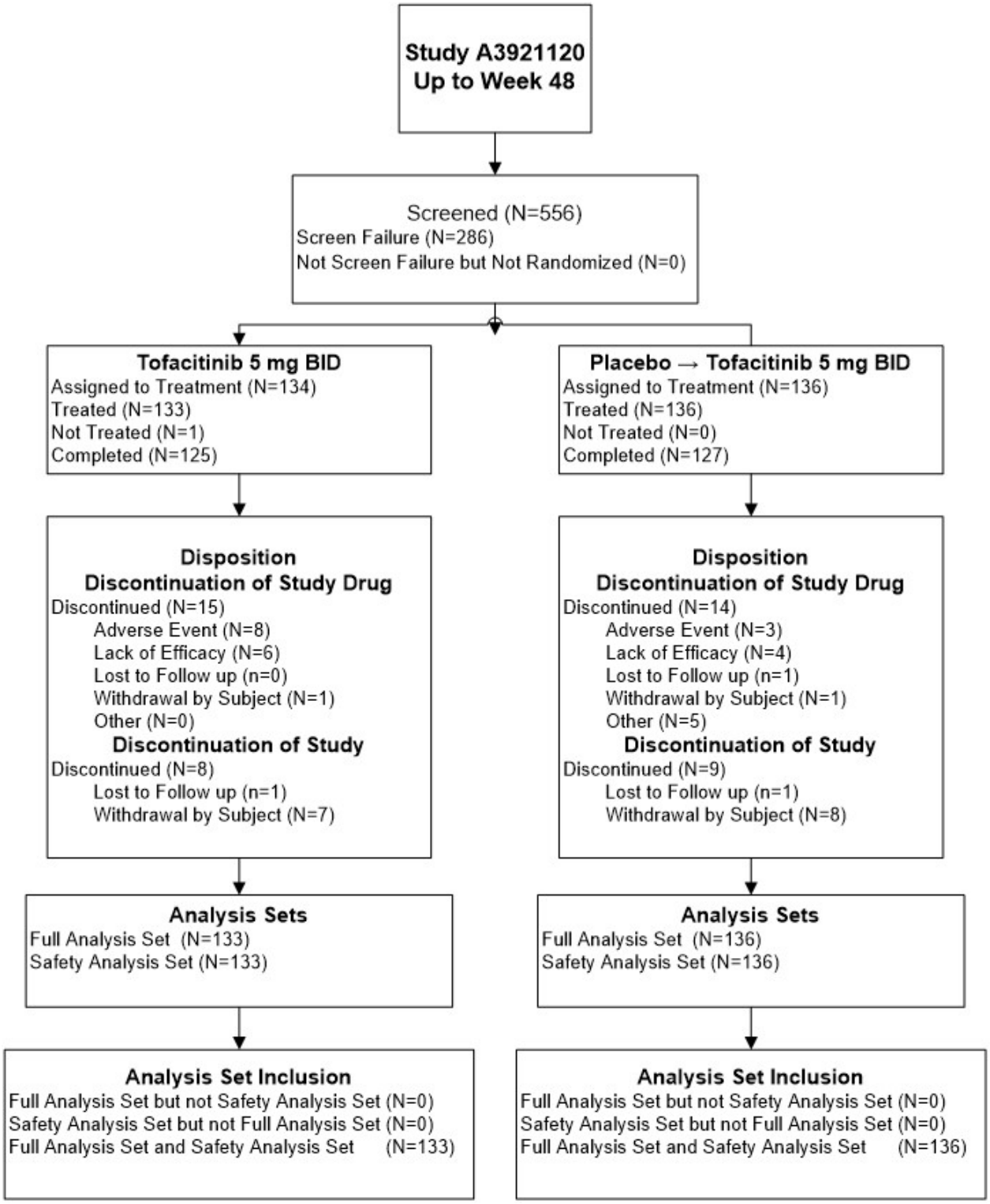


Table 34 summarises patient disposition for Study A3921120 up to Week 16 and Week 48, respectively.

Table 34. 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 34.**

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 Centers: A total of 57 sites randomized 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 35**:

- 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 35. Summary of important Protocol Deviations – Randomized 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 36 presents baseline demographic characteristics for the tofacitinib 5 mg BID and placebo groups for Study A3921120.

Table 16. 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 (%)			
Hispanic/Latino	2 (1.5%)	2 (1.5%)	4 (1.5%)

	Tofacitinib 5 mg BID (N = 133)	Placebo->Tofacitinib 5 mg BID (N = 136)	Total (N=269)
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 37. 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 38. 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 39. 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 40).

Table 40 shows the most frequently received prior **csDMARD** (approximately 50% in each treatment group) was sulfasalazine.

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 41**).

Table 41.

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)
TNFi 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%). (see related OC) 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 42. 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 43**). ASAS20 response was a global Type I error-controlled endpoint.

Table 43. ASAS20 Response Rate at week 16, Treatment Comparison -Estimand 1, FAS, On-Drug Date, MR=NR- Primary Anslysis (Week 16 Analysis)

Visit	Treatment	N	N1	n	Response Rate (%)	SE	Treatment Comparison [a] 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 44**). The summary for the on-study data (Estimand 2 as shown in **Table 44**) was consistent with the on-drug data.

Table 44. 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

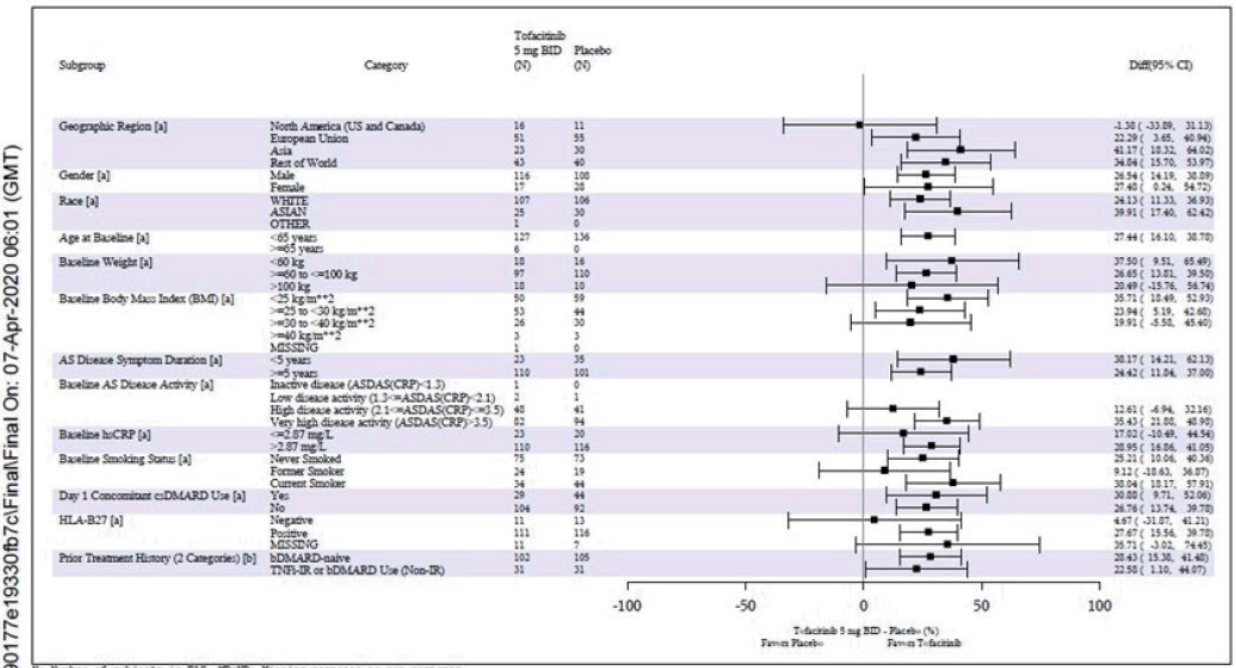
Subgroup comparisons for ASAS20 response at Week 16 were made on the FAS with missing values handled by MR=NR using the on-drug data corresponding to Estimand 1. Subgroup comparisons were not Type I error-controlled.

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 21)**.

- 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 21**.

- 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 21. 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.

PFIZER CONFIDENTIAL SDTM Creation: 31JAN2020 (23:20) Source Data: adas Output File: ./unblind_1120/A3921120/adas_f002 Date of Generation: 01APR2020 (08:38)

Table 45. 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 46**). ASAS40 response was a global Type I error-controlled endpoint.

Table 46. 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 47**) 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 47**). The summary for the on-study data (Estimand 2) was consistent with the on-drug data.

Table 47. 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)

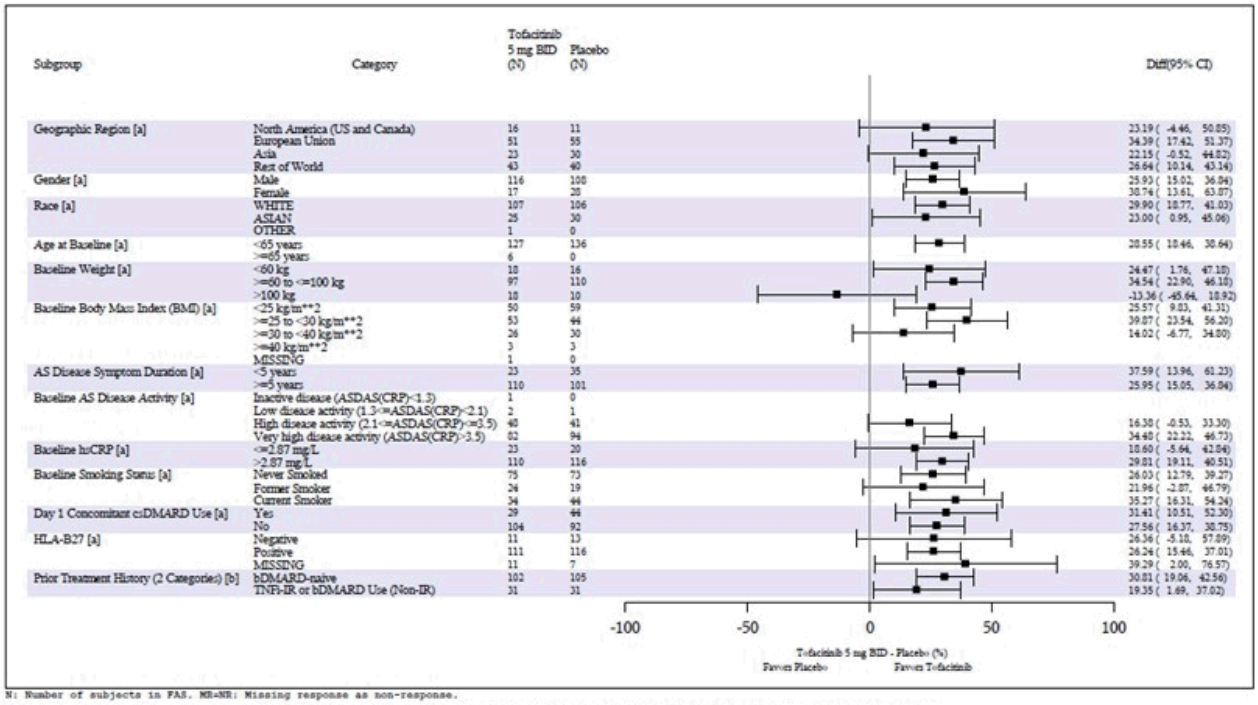
N: Number of subjects in FAS. n (%): Number of subjects in each analysis category (Percentages were based on N).
MR=NR: Missing response as non-response.
ASAS40 response was defined as >=40% and >=2 units improvement in at least 3 domains on a scale of 0-10 and no worsening at all in the remaining domain.
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 22**). 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 22. 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.

PFIZER CONFIDENTIAL SDTM Creation: 31JAN2020 (23:20) Source Data: adas Output File: ./unblind_1120/A3921120/adas_f002_2 Date of Generation: 01APR2020 (08:41)

Despite the limited sample size, the MAH was requested to include results according to bDMARDs naïve orTNF-IR subjects/bDMARD use subgroups in section 5.1 of the SmPC, in order to guide prescribers. The issue resolved and section 5.1 of the SmPC were updated accordingly.

Secondary Endpoints Results

Table 48 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 48**).

- Tofacitinib 5 mg BID also demonstrated superiority to placebo at all timepoints through Week16 for ASAS20 response rates (Figure 5). In addition, tofacitinib 5 mg BID demonstrated superiority to placebo at all timepoints through Week 16 except Week 2 for ASAS40 response rates (**Figure 21**).

- 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 48**).

- Tofacitinib 5 mg BID demonstrated sustained efficacy in ASAS20 and ASAS40 response rates (Figure 5, Figure 6, and Table 7) 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 7).

Table 48. 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 23** and **Figure 24**). This was maintained over time up to Week 48 in these patients (**Figure 23** and **Figure 24**).

Figure 23. Line Graph of ASAS20 Response Rate (± SE) by Visit up to Week 48 -Estimand 1, FAS, On-Drug Data, MR=NR, Study A3921120

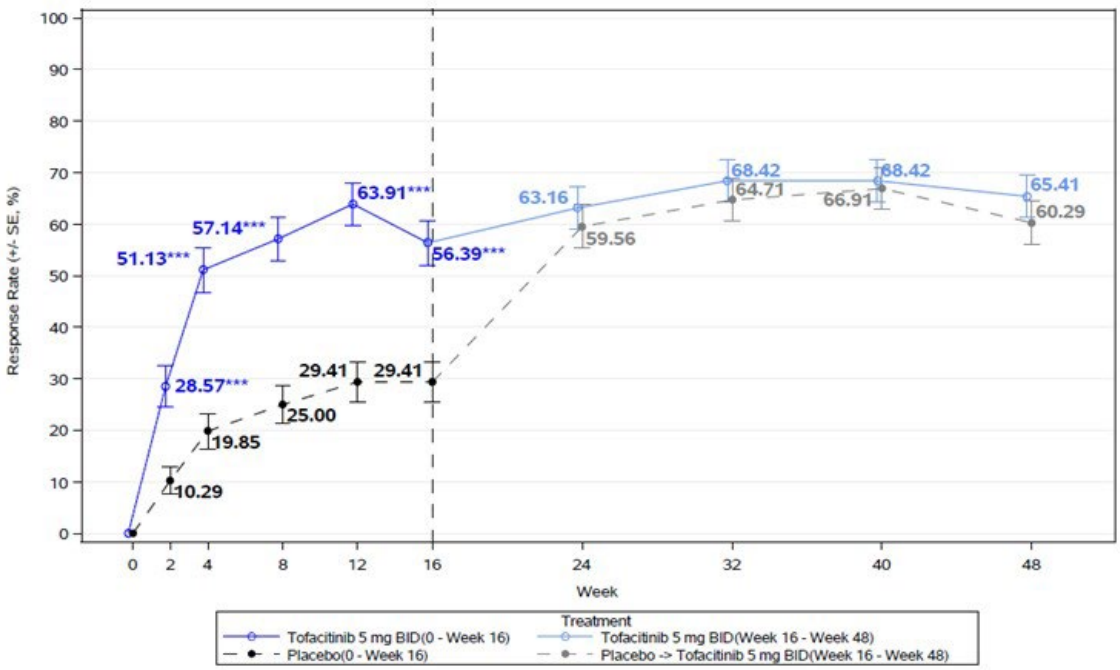
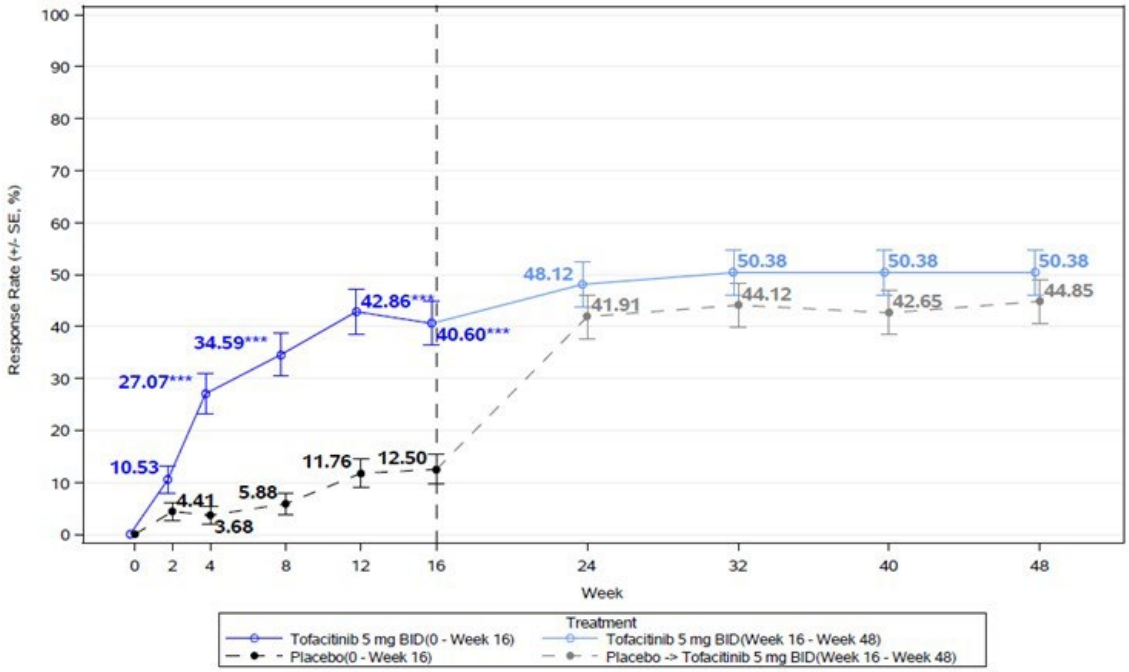


Figure 24. Line Graph of ASAS40 Response Rate (± SE) by Visit up to Week 48 - Estimand 1, FAS, On-Drug Data, MR=NR, Study A3921120



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 49).**

Table 49. 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 50 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 49 and 50**). 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 51 summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 51. 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)

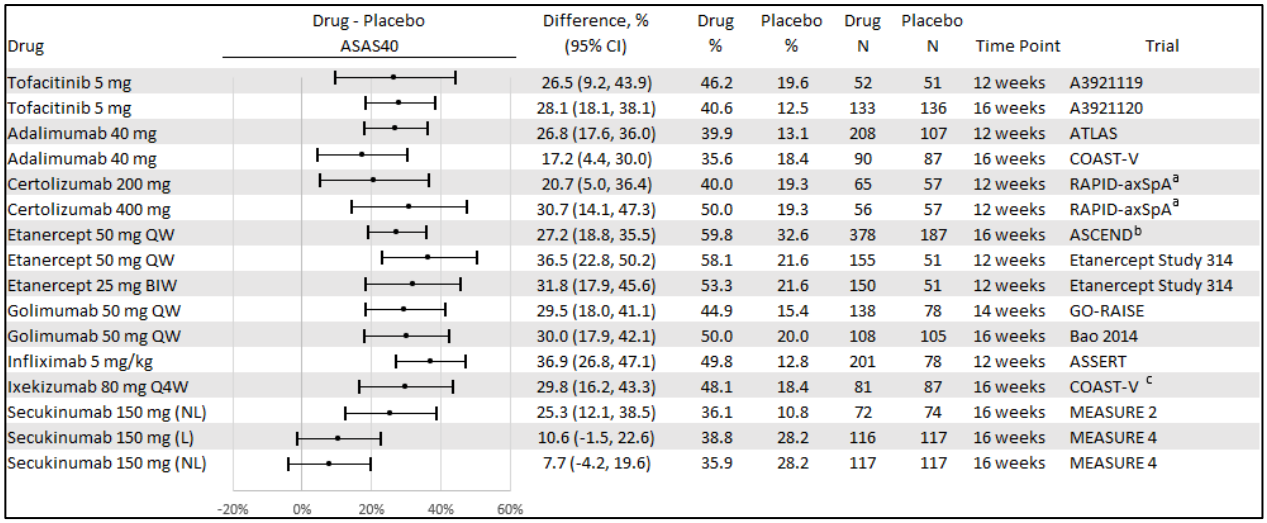
The Applicant has submitted a report concerning a systematic review and meta-analysis of placebo-controlled trials of EMA-approved biological DMARDs, including ASAS20/40 at week 12-16, in patients with AS with or without previous experience with biological DMARDs.

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 (**Figure25**) 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 25**), 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 25 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

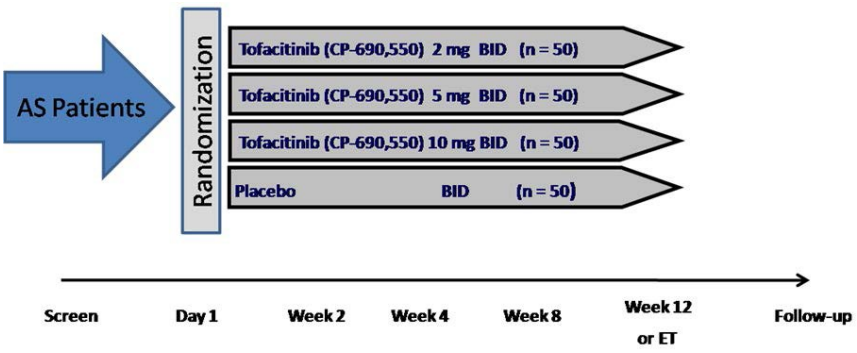
No data are available on special populations. No specific data on elderly are reported for axSA subjects. In the SmPC dose adjustments are included for renal and hepatic impairment based on initial submission.

Supportive studies

A3921119

This was Phase 2, 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 (**Figure 26**)for design schematic).

Figure 26. 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 52**). 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 52. 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 53** 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 53. 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)
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 54. Medical History Related to Primary Diagnosis – Safety Analysis Set

Table 10. 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	**No**	**Unknown**	**Yes**	**No**	**Unknown**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**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	**No**	**Unknown**	**Yes**	**No**	**Unknown**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**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 55**). 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 55. 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 56**); 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 56. 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 57**).

Table 27. 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]

Table 27. Selected Efficacy Endpoints at Week 12 (FAS) – Study A3921119

	Tofacitinib 5 mg BID (N = 52)	**Placebo (N = 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]
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]

Table 27. Selected Efficacy Endpoints at Week 12 (FAS) – Study A3921119

	Tofacitinib 5 mg BID (N = 52)	Placebo (N = 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
g. Index of disease activity score of the spine at Week 12

Figure 17. Line Graph of ASAS20 Response Rate (+/- SE) (Normal Approximation) by Visit Up to Week 12 – FAS, NRI/LOCF Mixed Components - Study A3921119

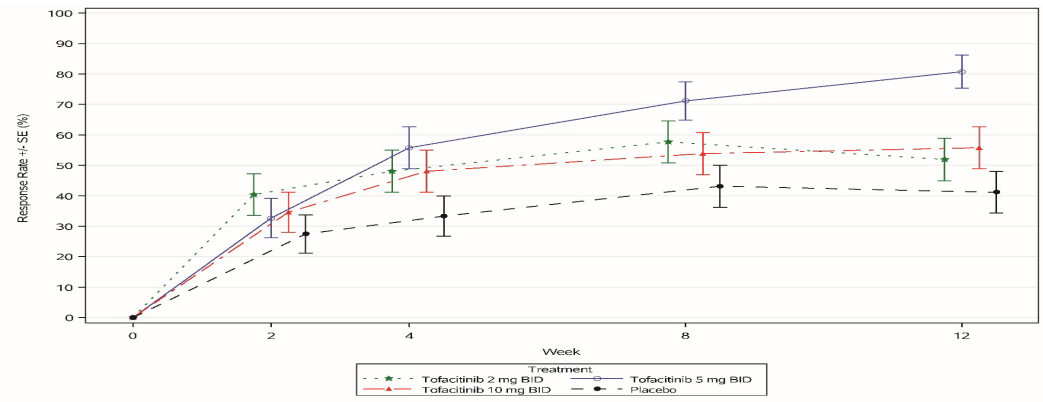
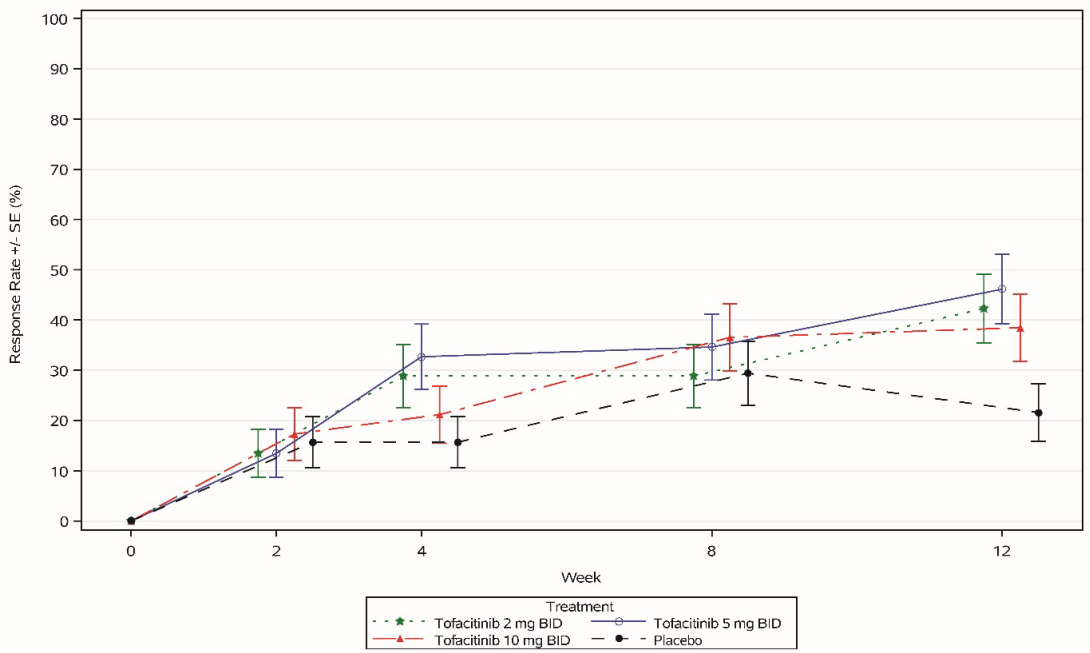


Figure 28. Line Graph of ASAS40 Response Rate (+/- SE) (Normal Approximation) by Visit Up to Week 12 – FAS, NRI/LOCF Mixed Components - Study A3921119



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.

Additional supportive studies

The Applicant has submitted a report summarising the existing scientific evidence on the development and psychometric properties of three patient reported outcomes: ASQoL, SF-36v2, FACIT-F (**Table 55**). These three outcomes were included in the set of secondary outcomes subjected to the hierarchical testing procedure for control of global type-I error in the pivotal study A 391120 (Table 58) The concept and psychometric properties of the ASQoL and of the FACIT-F for use in AS is presented below. Similar results supporting the reliability, validity and sensitivity to change of the SF-36 in AS were also prepared by the MAH but are not reproduced in this section.

Table 58 Patient reported efficacy outcomes in study A3921120.

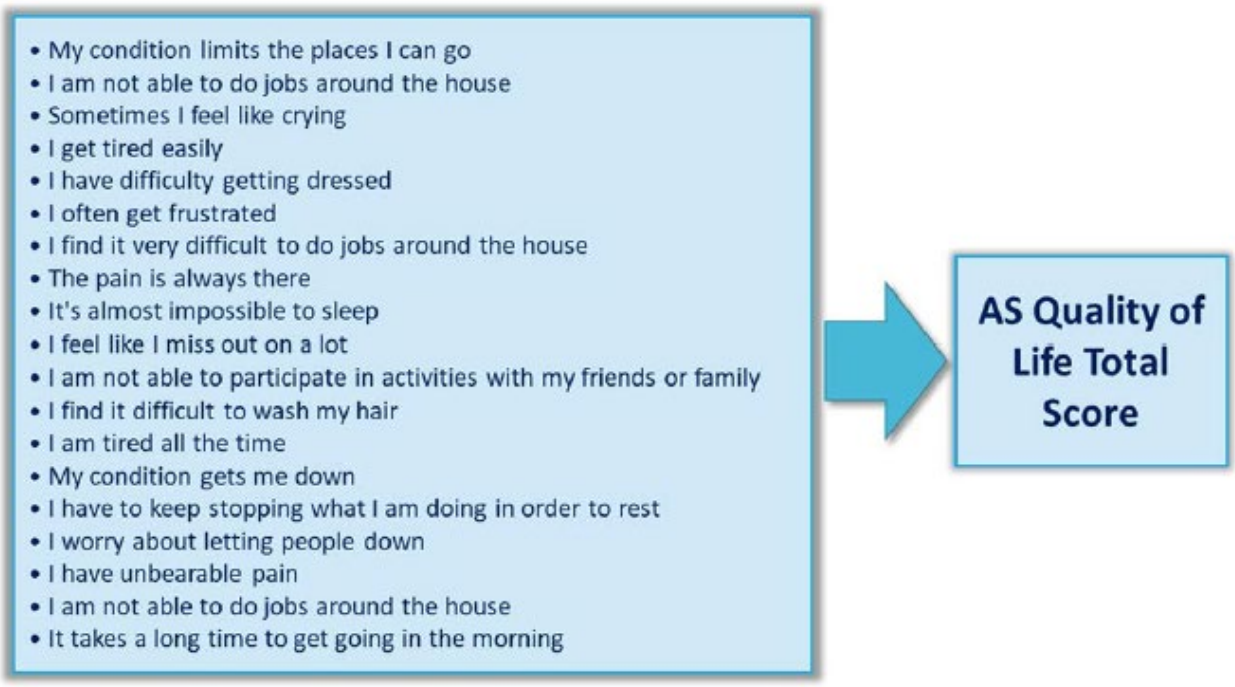
Concept/Outcome	Measurement Tool	Endpoint
Disease-specific HRQoL	ASQoL	Δ in ASQoL at Week 16 and Week 48
Functional Health Status	SF-36v2	Δ in SF-36v2 Acute (10 endpoints: eight norm-based domain scores [PF, RP, BP, GH, VT, SF, RE, and MH] as well as PCS and MCS scores) at Week 16 and Week 48.
Fatigue	FACIT-F	Δ in FACIT-F (three endpoints: total score, experience domain, and impact domain scores) at all timepoints collected up to Week 48

Abbreviations: Δ = change from baseline; ASQoL = Ankylosing Spondylitis Quality of Life; BP = bodily pain; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; GH = General Health; HRQoL = Health-related Quality of Life; MCS = Mental Component Summary; MH = Mental Health; PCS = Physical Component Summary; PF = Physical Functioning; RE = Role-Emotional; RP = Role-Physical; SF-36v2 = Short Form 36 Version 2; SF = Social Functioning; VT = Vitality

ASQoL

The ASQoL is an 18-item PRO questionnaire to assess QoL impacts specific to AS (**Figure 29**). It was originally developed in the United Kingdom through qualitative, unstructured interviews and focus groups with patients to ensure that the content was relevant and covered issues of importance to AS patients.

Figure 29 Overview of the ASQoL items



The ASQoL leads to a single total score. Each ASQoL statement is given a score of 1 = Yes or 0 = No, with an answer of 'Yes' indicating adverse QoL. All item scores are summed to give a total score ranging from 0 (good QoL) to 18 (poor QoL). For respondents with one to three missing responses (no more than 20% missing), a total score can still be calculated, based on the nonmissing items. The ASQoLhas been fitted to the Rasch Measurement Model to allow for parametric statistical analyses (the

Rasch model was not applied in the analyses for study A3921120). The ASQoL is completed previous to the clinical visit, on paper with a pen/pencil, and generally takes less than 10 minutes for respondent to complete.

The **internal consistency** or item-scale correlation of the ASQoL is good with high values for Cronbach's α in several studies **(Table 59**).

Table 59 Internal consistency of the ASQoL

Reference	Instrument	Population	Timepoint / Instrument Version	Internal Consistency
ASQoL User Manual – Galen Research 2019[4]	ASQoL	N/A	N/A	α=0.94
Doward et al. 2003[5]	ASQoL	129 AS patients	UK time 1	α=0.91
			UK time 2	α=0.92
		119 AS patients	NL time 1	α=0.89
			NL time 2	α=0.90
Duruöz et al. 2013[6]	ASQoL (Turkish version)	277 AS patients		α=0.89
Fallahi et al. 2014[7]	ASQoL (Iranian version)	163 AS patients		α=0.91
Graham et al. 2015[8]	ASQoL (Greek version)	92 AS patients		α=0.92
Leung et al. 2017[9]	ASQoL (Singapore Chinese version)	183 axSpA patients	English version	α=0.86
			Singapore Chinese version	α=0.93

Abbreviations: AS = ankylosing spondylitis; ASQoL = Ankylosing Spondylitis Quality of Life; axSpA = axial spondyloarthritis; UK = United Kingdom; N/A = Not Available; NL = Netherlands; α = Cronbach's alpha coefficient

The **test-retest reliability**, preferably analysed using intraclass correlation coefficients (ICC) is high in several studies-and-languages/cultures (**Table 60**).

Table 60 Test-retest reliability of the ASQoL

Reference	Instrument	Population	Timepoint / Instrument Version	Correlation Coefficient
ASQoL User Manual – Galen Research 2019[4]	ASQoL	N/A	N/A	0.94†
Doward et al. 2003[5]	ASQoL	129 AS patients	UK two weeks apart	ρ=0.92*
		119 AS patients	NL two weeks apart	ρ=0.91*
Duruöz et al. 2013[6]	ASQoL (Turkish version)	277 AS patients	One week apart	ICC=0.96
Fallahi et al. 2014[7]	ASQoL (Iranian version)	163 AS patients	Two visits for 54 patients within a 48-hour interval	ICC=0.97**
Graham et al. 2015[8]	ASQoL (Greek version)	92 AS patients	87 patients at two timepoints	ρ=0.98
Leung et al. 2017[9]	ASQoL (Singapore Chinese version)	42 axSpA patients	19 completed the Singapore Chinese, and 23 completed the English version at timepoints two weeks apart	ρ=0.81

Abbreviations: AS = ankylosing spondylitis; ASQoL = Ankylosing spondylitis Quality of Life; axSpA = axial spondyloarthritis; ICC = intraclass correlation coefficient; UK = United Kingdom; N/A = Not Available; NL = Netherlands; ρ = Spearman's rank correlation coefficient

*Spearman rank correlation coefficient and ICCs were identical; **$p < 0.001$; †correlation coefficient used not specified

The **construct validity** of the ASQoL (**Table 61**) was assessed by relating scores to the Nottingham Health Profile (NHP) and self-perceived severity of illness. Moderately high Spearman rank correlation coefficients were seen between the ASQoL and NHP section scores: energy levels (0.80), pain (0.77), emotional reactions (0.66), sleep disturbance (0.59), social isolation (0.62), and physical mobility (0.87).

Table 61 Construct validity of the ASQoL

Reference	Trial Description	Sample Size (treatment)	Domain	Criterion Measure	Correlation
Deodhar et al. 2019[26]	A five-year, Phase III, randomised control trial in Austria, Canada, Czech Republic, Finland, Germany, Italy, Netherlands, Russia, Singapore, Spain, Switzerland, UK, and US	72 (secukinumab 150 mg) 74 placebo	ASQoL Item 5 Response (sleep)	VAS spinal pain at Week 16	r= -0.46*
				VAS nocturnal pain at Week 16	r= -0.43*
				VAS spinal pain at Week 52	r= -0.31*
				VAS nocturnal pain at Week 52	r= -0.34*
Doward et al. 2003[5]	Development of the ASQoL in parallel in the UK and NL involving patient interviews, field testing, and postal surveys	129 UK AS patients	ASQoL	NHP physical mobility	ρ=0.78
				NHP energy	ρ=0.74
				NHP pain	ρ=0.81
				NHP emotional reactions	ρ=0.72
				BASFI	ρ=0.72
		119 NL AS patients		NHP physical mobility	ρ=0.79
				NHP energy	ρ=0.73
				NHP pain	ρ=0.79
				NHP emotional reactions	ρ=0.73
				BASFI	ρ=0.75
Revicki et al. 2011[10]	Psychometric analyses of PRO data collected from two Phase III, randomised, double-blind, placebo-controlled clinical trials that assessed the safety and clinical efficacy of adalimumab in Canada, Europe, and US	397 AS patients (adalimumab 40 mg)	ASQoL	FACIT-F at Week 12	r= -0.81**
				SF-36 PF at Week 12	r= -0.70**
				SF-36 PF at Week 12	r= -0.73**
				SF-36 RP at Week 12	r= -0.73**
				SF-36 BP at Week 12	r= -0.76**
				SF-36 VT at Week 12	r= -0.72**
				SF-36 SF at Week 12	r= -0.77**

Abbreviations: AS = ankylosing spondylitis; ASQoL = ankylosing spondylitis quality of life; ASAS = Assessment of Spondyloarthritis International Society; BASFI = Bath Ankylosing Spondylitis Functional Index; BP = bodily pain; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; GH = general health; NL = Netherlands; NHP = Nottingham Health Profile; PCS = physical component summary; PF = physical function; RP = role-physical; SF = social function; SF-36 = Short Form 36; UK = United Kingdom; US = United States; VAS = visual analogue scale; VT = vitality; r = Pearson correlation coefficient; ρ = Spearman's rank correlation coefficient

*p<0.05; **p < 0.0001

Evidence of **sensitivity to change** is found in several clinical trials. In a clinical trial for adalimumab (van der Heijde 2015) the MID was defined as a decrease of ≥1.8 points on the ASQoL. This definition was also used in a clinical trial for certolizumab pegol (Sieper 2015). The ASQoL has since been used in Food and Drug Administration (FDA) and EMA labelling claims for adalimumab and certolizumab pegol. Thus, although the MID has not been explicitly mentioned in the labels, this change provides a precedent, a threshold, which should be expected for an efficacious drug endpoint, and can support interpretation of the ASQoL instrument in a clinical trial for AS.

Additional data on the ability of the ASQoL to detect change between groups in placebo-controlled trials with FDA and EMA-approved drugs are: secukinumab (Deodhar 2016), certolizumab pegol (Sieper 2015), tofacitinib and adalimumab (Strand 2019).

FACIT-F

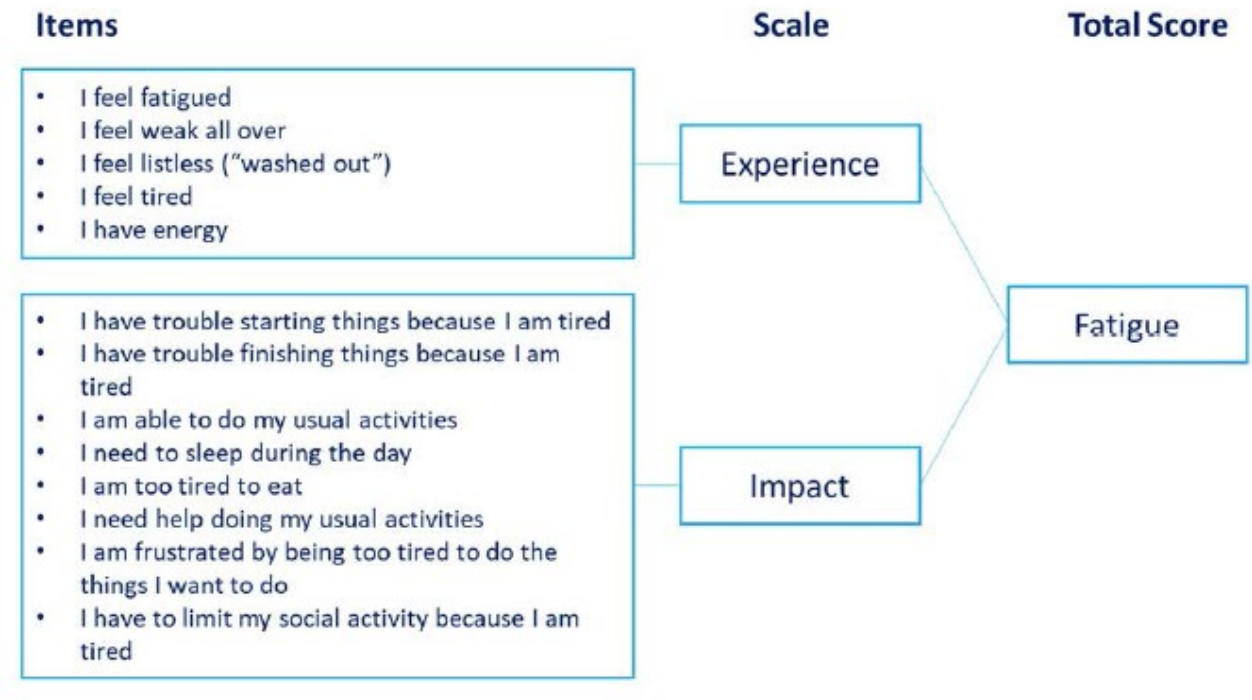
The FACIT-F is a 13-item questionnaire to asses self-reported fatigue and its impact upon daily activities and function. It is a subset of items from the larger 47-item Functional Assessment of Cancer Therapy Anaemia (FACT-An) that is comprised of the 27-item Functional Assessment of Cancer Therapy General (FACT-G) and a 20-item anaemia subscale. The FACT-An, from which the FACIT-F is derived, was developed in 1994 to 1995 for cancer-related anaemia over a series of four phases: item generation involving

interviews with patients and medical experts; item review and selection, involving additional interviews with medical experts; scale construction; and psychometric evaluation (Cella 2012; FACIT.org).

The FACIT-F uses a five-point Likert scale for all items (where 0=Not at all, 1=A little bit, 2=Somewhat, 3=Quite a bit, and 4=Very Much) and has a recall period of "the past 7 days." Thus, each FACIT-F item is scored from 0 to 4; higher scores indicate lower fatigue.

Three endpoints can be derived from the FACIT-F: the FACIT-F total score, the FACIT-F experience domain score, and the FACIT-F impact domain score (**Figure 30**). The FACIT-F total score is calculated by summing the 13 items and ranges from 0 to 52. If there are missing items and more than 50% of the items were answered (i.e., at least seven of 13 for the FACIT-F total score, at least three of five for FACIT-F experience domain score, and at least five of eight for the FACIT-F impact domain score), then the score can be considered valid.

Figure 30 FACIT-F overview of items, subscales and total score



The FACIT-F was originally developed to assess fatigue in cancer patients that resulted from chemotherapy regimens or a corresponding anaemia. Regarding **content validity**, the development process ensured that the fatigue subscale items covered concepts relevant to fatigue in general. The development process included item generation with patients and medical experts, item selection, psychometric testing and item reduction and validation.

Up to now, the FACIT-F was used in one EMA labelling claim for secukinumab in AS. In the initial study for FACIT-F development, convergent and divergent validity of the FACIT-F in testing to differentiate patients by haemoglobin level and patient-rated performance status was demonstrated (Cella 2012; FACIT.org). Data regarding the psychometric properties of the FACIT-F in AS is found in several studies (tables below).

The **internal consistency**, or item-scale correlation, of the FACIT-F, as shown in the tofacitinib studies in this application and three other studies in patients with Psoriatic Arthritis is good, with high levels of Cronbach's α (**Table 62**).

Table 62 Internal consistency of the FACIT-F

Reference	Instrument	Population	Domain / Timepoint	Internal Consistency
Appendix 5. FACIT-F Validation in AS	FACIT-F	204 AS patients	Study 1119 total score baseline	α=0.94
		194 AS patients	Study 1119 total score Week 12	α=0.95
		204 AS patients	Study 1119 experience domain baseline	α=0.89
		194 AS patients	Study 1119 experience domain Week 12	α=0.93
		204 AS patients	Study 1119 impact domain baseline	α=0.90
		194 AS patients	Study 1119 impact domain Week 12	α=0.92
		268 AS patients	Study 1120 total score baseline	α=0.93
		264 AS patients	Study 1120 total score Week 16	α=0.94
		268 AS patients	Study 1120 experience domain baseline	α=0.88
		265 AS patients	Study 1120 experience domain week 16	α=0.92
		269 AS patients	Study 1120 impact domain baseline	α=0.88
		264 AS patients	Study 1120 impact domain Week 16	α=0.90
Cella 2013[36] Yellen et al. 1997[11]	FACIT-F	49 anaemic patients	Initial	α=0.93
			Retest	α=0.95
Cella et al. 2019[12]	FACIT-F	760 PsA patients	Total score	α=0.95
		763 PsA patients	Experience domain	α=0.93
		762 PsA patients	Impact domain	α=0.91
		766 PsA patients	Total score	α=0.94
		768 PsA patients	Experience domain	α=0.91
			Impact domain	α=0.90
Revicki et al. 2011[10]	FACIT-F	82 AS patients	Baseline	α=0.82
			Week 12	α=0.86

Abbreviations: AS = ankylosing spondylitis; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; PsA = psoriatic arthritis; α = Cronbach's alpha coefficient

The **test-retest reliability** of the FACIT-F was assessed in the current tofactitinib trials using the baseline and week 2 data, and in some other trials in patients with anaemia and in patients with Psoriatic Arthritis. The intraclass correlation coefficients point to good test-retest reliability **(Table 63).**

Table 63 Test-retest reliability of the FACIT-F

Reference	Instrument	Population	Domain	Correlation Coefficient
Appendix 5. FACIT-F Validation in AS	FACIT-F	AS patients	Total score	ICC=0.86-0.89
			Experience domain	ICC=0.75-0.86
			Impact domain	ICC=0.84-0.87
Cella 2013[36]	FACIT-F	49 anaemic patients		r=0.90
Yellen et al. 1997[11]				
Cella et al. 2019[12]	FACIT-F	760 PsA patients	Total score	ICC=0.79
			Experience domain	ICC=0.78
			Impact domain	ICC=0.78
		766 PsA patients	Total score	ICC=0.87
			Experience domain	ICC=0.81
			Impact domain	ICC=0.87

Abbreviations: AS = ankylosing spondylitis; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; ICC = intraclass correlation coefficient; PsA = psoriatic arthritis; r = Pearson correlation coefficient

The **construct validity** in patients with AS has been assessed in the two current trials with tofacitinib and in two other trials in AS. Medium to high-sized correlation coefficients were found for relations with other patient assessed questionnaires assessing related outcomes: ASQoL, SF-36, ASAS20, VAS pain, PGA **(Table 64**).

Table 64. Construct validity of the FACIT-F

Reference	Trial Description	Sample Size (Treatment)	Domain	Criterion Measure	Correlation/ Effect Size
Appendix 5. FACIT-F Validation in AS	FACIT-F validation analyses in two AS trials for tofacitinib	Study 1119	Total score	ASQoL at Week 12	r= -0.82
				SF-36v2 PF at Week 12	r=0.66
				SF-36v2 RP at Week 12	r=0.75
				SF-36v2 BP at Week 12	r=0.66
				SF-36v2 GH at Week 12	r=0.59
				SF-36v2 VT at Week 12	r=0.82
				SF-36v2 SF at Week 12	r=0.76
				SF-36v2 RE at Week 12	r=0.71
				SF-36v2 MH at Week 12	r=0.74
				SF-36v2 PCS at Week 12	r=0.65
				SF-36v2 MCS at Week 12	r=0.78
		Study 1119	Experience domain	ASQoL at Week 12	r= -0.75
				SF-36v2 PF at Week 12	r=0.57
				SF-36v2 RP at Week 12	r=0.68
				SF-36v2 BP at Week 12	r=0.62
				SF-36v2 GH at Week 12	r=0.59
				SF-36v2 VT at Week 12	r=0.85
				SF-36v2 SF at Week 12	r=0.69
				SF-36v2 RE at Week 12	r=0.62
				SF-36v2 MH at Week 12	r=0.71
				SF-36v2 PCS at Week 12	r=0.60
				SF-36v2 MCS at Week 12	r=0.74
		Study 1119	Impact domain	ASQoL at Week 12	r= -0.82
				SF-36v2 PF at Week 12	r=0.67
				SF-36v2 RP at Week 12	r=0.75
				SF-36v2 BP at Week 12	r=0.64
				SF-36v2 GH at Week 12	r=0.55
				SF-36v2 VT at Week 12	r=0.75
				SF-36v2 SF at Week 12	r=0.76
				SF-36v2 RE at Week 12	r=0.73
				SF-36v2 MH at Week 12	r=0.71
				SF-36v2 PCS at Week 12	r=0.64
				SF-36v2 MCS at Week 12	r=0.75
		Study 1120	Total score	ASQoL at Week 16	r= -0.80
				SF-36v2 PF at Week 16	r=0.65
				SF-36v2 RP at Week 16	r=0.74
				SF-36v2 BP at Week 16	r=0.72
				SF-36v2 GH at Week 16	r=0.60

Reference	Trial Description	Sample Size (Treatment)	Domain	Criterion Measure	Correlation/ Effect Size
				SF-36v2 VT at Week 16	r=0.80
				SF-36v2 SF at Week 16	r=0.76
				SF-36v2 RE at Week 16	r=0.69
				SF-36v2 MH at Week 16	r=0.74
				SF-36v2 PCS at Week 16	r=0.65
				SF-36v2 MCS at Week 16	r=0.77
		Study 1120	Experience domain	ASQoL at Week 16	r= -0.74
				SF-36v2 PF at Week 16	r=0.60
				SF-36v2 RP at Week 16	r=0.70
				SF-36v2 BP at Week 16	r=0.69
				SF-36v2 GH at Week 16	r=0.63
				SF-36v2 VT at Week 16	r=0.85
				SF-36v2 SF at Week 16	r=0.72
				SF-36v2 RE at Week 16	r=0.66
				SF-36v2 MH at Week 16	r=0.72
				SF-36v2 PCS at Week 16	r=0.62
				SF-36v2 MCS at Week 16	r=0.76
		Study 1120	Impact domain	ASQoL at Week 16	r= -0.78
				SF-36v2 PF at Week 16	r=0.64
				SF-36v2 RP at Week 16	r=0.71
				SF-36v2 BP at Week 16	r=0.68
				SF-36v2 GH at Week 16	r=0.53
				SF-36v2 VT at Week 16	r=0.71
				SF-36v2 SF at Week 16	r=0.74
				SF-36v2 RE at Week 16	r=0.66
				SF-36v2 MH at Week 16	r=0.70
				SF-36v2 PCS at Week 16	r=0.61
				SF-36v2 MCS at Week 16	r=0.72
		Study 1119	Total score	PGA at Week 12	r= -0.39**
		Study 1120	Total score	PGA at Week 12	r= -0.53**
		Study 1120	Total score	PGA at Week 16	r= -0.46**
		Study 1119	Experience domain	PGA at Week 12	r= -0.34**
		Study 1120	Experience domain	PGA at Week 12	r= -0.50**
		Study 1120	Experience domain	PGA at Week 16	r= -0.45**
		Study 1119	Impact domain	PGA at Week 12	r= -0.38**
		Study 1120	Impact domain	PGA at Week 12	r= -0.49**
		Study 1120	Impact domain	PGA at Week 16	r= -0.42**
		Study 1119	Total score	PGA "not active disease" and "very active disease" at post-baseline visits up to Week 12	ES=1.38**
			Experience domain		ES=1.63**
			Impact domain		ES=1.17**
		Study 1120	Total score	PGA "not active disease" and "very active disease" at post-baseline visits up to Week 16	ES=1.40**
			Experience domain		ES=1.61**
			Impact domain		ES=1.23**
Deodhar, 2019[26]	A five-year, phase III, randomised control trial in Austria, Canada, Czech Republic,	72 (secukinumab 150 mg) 74 (placebo)	FACIT-F score	VAS spinal pain at Week 16	r= -0.49*
				VAS nocturnal pain at Week 16	r= -0.48*

Reference	Trial Description	Sample Size (Treatment)	Domain	Criterion Measure	Correlation/ Effect Size
	Finland, Germany, Italy, Netherlands, Russia, Singapore, Spain, Switzerland, UK, and US			VAS spinal pain at Week 104	r= -0.58*
				VAS nocturnal pain at Week 104	r= -0.50*
			FACIT-F response	VAS spinal pain at Week 16	r= -0.48*
				VAS nocturnal pain at Week 16	r= -0.51*
				VAS spinal pain at Week 104	r= -0.68*
				VAS nocturnal pain at Week 104	r= -0.58*
Revicki, 2011[10]	Psychometric analyses of PRO data collected from two phase III, randomised, double-blind, placebo-controlled clinical trials that assessed the safety and clinical efficacy of adalimumab in Canada, Europe, and US	397 AS patients (adalimumab 40 mg)	FACIT-F total score	ASQoL at Week 12	r= -0.81**
				SF-36 MCS at Week 12	r=0.71**
				SF-36 BP at Week 12	r=0.75**
				SF-36 VT at Week 12	r=0.82**
				SF-36 SF at Week 12	r=0.73**
				ASAS20	ES=0.92† (n=12)

Abbreviations: AS = ankylosing spondylitis; ASAS = Assessment of Spondyloarthritis International Society; ASQoL = ankylosing spondylitis quality of life; BP = bodily pain; ES = effect size; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; GH = general health; MCS = mental component summary; MH = mental health; PCS = physical component summary; PGA = Patient Global Assessment of Disease; PF = physical functioning; RE = role emotional; RP = role physical; SF = social functioning; SF-36 = Short Form 36; VAS = visual analogue scale; VT = vitality; r = Pearson correlation coefficient

*$p < 0.05$; **$p < 0.0001$; †Effect sizes reported for ≥ 0.70, $p < 0.0001$

The **sensitivity to change** of the FACIT-F was confirmed in several recent placebo-controlled trials in AS (secukinumab, Deodhar 2016), and in PsA (tofacitinib, Strand 2019a, Strand 2019b, Gladman 2017; golimumab, Krüger 2018).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

With this submission, the MAH seeks a new indication for Tofacitinib for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy. The recommended dose of tofacitinib is 5 mg administered twice daily.
In support of the sought indication the MAH is providing 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 that 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%. Randomization was stratified by prior treatment history: (1) bDMARD-naive and (2) TNFi-IR or bDMARD use (non-IR). Overall inclusion and exclusion criteria were adequate for selecting an active AS population and also for taking into account the safety profile of the drug. 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.

Efficacy data and additional analyses

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.

2.4.4. Conclusions on the clinical efficacy

A clinically relevant effect as measured by ASAS20/ASA40 has been demonstrated for tofacitinib 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.

2.5. Clinical safety

Introduction

Tofacitinib Clinical Programmes in RA and PsA

Tofacitinib has previously been evaluated in other clinical programmes such as RA and PsA.

The RA and PsA programmes comprise a larger number of patients over a longer duration compared to the current AS programme. Safety data from these non-AS indications have been included for contextualisation of the safety data observed in the AS clinical programme.

The RA and PsA databases integrated within each programme enable the following evaluations:

- To compare the incidence rates for AEs of special interest to determine whether there are similarities.

- To compare the rates of certain AEs, especially those with long latency periods (e.g., malignancies), to determine whether there is an increase following exposures to tofacitinib for longer periods than in AS studies.

The integrated datasets from the 23 RA studies and the 3 PsA studies were used to compare key safety endpoints to further contextualise the safety profile in AS. Details on the safety populations from the RA and PsA studies used for contextualisation are shown in **Table 65.**

Table 35. 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
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

Known Safety Profile

Tofacitinib, in the already approved indications, has shown a safety profile mainly characterised by the following considerations (from the current SmPC section 4.4):

- Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT), have been observed in patients taking tofacitinib. A dose dependent increased risk for VTE was observed in a clinical study with tofacitinib compared to TNF inhibitors.
- Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving tofacitinib. The risk of opportunistic infections is higher in Asian geographic regions.
- Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with tofacitinib. In patients treated with tofacitinib, the incidence of herpes zoster appears to be increased in: Japanese or Korean patients, Patients with an ALC less than 1,000 cells/mm3, Patients with long standing RA who have previously received two or more biological disease- modifying antirheumatic drugs (DMARDs), Patients treated with 10 mg twice daily.
- Lymphomas have been observed in patients treated with tofacitinib. Other malignancies were observed in clinical studies and the post-marketing setting, including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer. The effect of tofacitinib on the development and course of malignancies is not known.
- NMSCs have been reported in patients treated with tofacitinib.
- Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with tofacitinib in RA clinical trials and in the post-marketing setting although the role of Janus kinase (JAK) inhibition in these events is not known.
- Events of gastrointestinal perforation have been reported in clinical trials although the role of JAK inhibition in these events is not known.
- Treatment with tofacitinib was associated with an increased incidence of liver enzyme elevation in some patients.

Furthermore, 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 for the co-primary endpoints in Study A3921133, specifically including the increased incidence of adjudicated **MACE** and adjudicated **malignancies** (excluding NMSC). Interim results of the study have been assessed as part of a signal procedure (EPITT ref. No. 19382). Consequently, sections 4.4, 4.8 and 5.1 of the SmPC and correspondent sections of the Package Leaflet were updated to appropriately reflect the information. The RMP was also updated with additional risk minimisation measures and a DHPC for tofacitinib was also endorsed. The final study report of Study A3921133 is currently under evaluation (EMEA/H/C/004212/II/0044) and the assessment will follow.

Source of Safety Data

The studies included in the present analysis are:

- **1 completed Phase 2**, 12-week long randomised double-blind, placebo-controlled, dose-ranging Study A3921**119** in patients with AS. Tofacitinib IR was evaluated at doses of 2, 5 and 10 mg BID.
- **1 completed pivotal** Study A3921**120** in patients with AS. This was a 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.

Note that for **Study A3921120**, the treatment duration was 48 weeks which comprised an initial placebo-controlled treatment period of 16 weeks duration followed by an open-label treatment period of 32 weeks duration. All patients, investigators, and the study team remained blinded to the double-blinded treatment until Week 48 when the final database was released.

The studies in the AS development programme are described in **Table 66**.

Table 66. Completed Studies in the Tofacitinib Clinical Programme for AS

Protocol	Title/Study Population	Treatment	Safety Population
Phase 3 Study			
A3921120	A phase 3, randomised, double-blind, placebo-controlled, study of the efficacy and safety of tofacitinib in patients with active AS. The study enrolled patients with an inadequate response to NSAIDs who were either: bDMARD naïve (~80%) or TNFi inadequate responders or had prior bDMARD use (non-inadequate responder) (~20%).	Double-blind Placebo→Tofacitinib 5 mg IR BID Double-blind: Placebo 0-16 weeks Open-label[b]: Tofacitinib 5 mg IR BID 16-48 weeks Tofacitinib 5 mg IR BID → Tofacitinib 5 mg IR BID Double-blind: Tofacitinib 5 mg IR BID 0-16 weeks Open-label: Tofacitinib 5 mg IR BID 16-48 weeks	Total = 269[a] n = 136 n = 133[c]
Phase 2 Dose-ranging 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 in patients with active AS. Duration of blinded treatment was 12 Weeks. The study enrolled bDMARD naïve patients with an inadequate response to NSAIDs.	Double-blind Tofacitinib 2 mg BID 0-12 weeks Tofacitinib 5 mg IR BID 0-12 weeks Tofacitinib 10 mg BID 0-12 weeks Placebo 0-12 weeks	Total[d] = 207 n = 52 n = 52 n = 52 n = 51[e]

Source: Module 5.3.5.1 A3921120 Week 48 Study Report Table 14.1.1.1.1A; Module 5.3.5.4 A3921119 Amended Study Report Table 14.1.1.1

a. 270 patients were randomised but 269 patients received study treatment and were included in the analysis.
b. Patients switched to open-label treatment at Week 16 visit until Week 48.
c. 134 patients were randomised to Tofacitinib 5 mg IR BID→Tofacitinib 5 mg IR BID but 133 patients received study treatment and were included in the analysis.
d. 208 patients were randomised, but 207 patients received study treatment and were included in the analysis.
e. 52 patients were randomised to Placebo, but 51 patients received study treatment and were included in the analysis.

The **integrated analysis of safety** included pooling of Studies A3921119 and A3921120 (**Table 67**) to assess:

- Short-term (0-16 weeks) safety of tofacitinib 5 mg IR BID in comparison to placebo in the combined trials (the 'Placebo-controlled Cohort'; table below).

- Longer-term (0-48 weeks) safety of tofacitinib in the combined trials' exposure to the study drug (the 'All Tofa Cohort'; next table). The All Tofa Cohort has 2 analysis groups: All Tofa 5 mg BID

(tofacitinib 5 mg IR BID in the combined trials) and All Tofa (tofacitinib 2 mg, 5 mg, and 10 mg BID in the combined trials).

Table 67. Safety Populations in Integrated Analysis

Integrated Study Cohorts	Studies Included and Pooling Strategies
16 Week Placebo-controlled Cohort	• A3921119 (0 - 12 Weeks), A3921120 (0 - 16 Weeks) • This cohort includes patients who were randomised and received tofacitinib 5 mg IR BID or placebo from the double-blinded placebo-controlled periods of the studies. • Analysis groups of the cohort: (1) Tofa 5 mg BID, (2) Placebo. • Comparison: Tofa 5 mg BID versus Placebo.
48 Week All Tofa Cohort	• A3921119 (0 - 12 Weeks), A3921120 (0 – 48 Weeks) • This cohort includes all randomised patients and treated with at least 1 dose of tofacitinib (2 mg, 5 mg, and 10 mg BID) from the tofacitinib-exposed periods, therefore excluding placebo-exposed period for patients randomised to placebo → tofacitinib 5 mg IR BID group[a] in Study A3921120. • Analysis groups of the cohort: (1) All Tofa 5 mg BID, (2) All Tofa. The All Tofa 5 mg BID group differs from All Tofa analysis group because the All Tofa 5 mg BID group includes only the patients who received 5 mg BID, while the All Tofa analysis group includes additional data from the Tofa 2 mg BID and 10 mg BID groups from Study A3921119. • Comparison: None.

Source: Module 5.3.5.3 SCS iAP Table 3

a. In Study A3921120, patients randomised to the placebo → tofacitinib 5 mg IR BID group received placebo during the double-blind period (0 - 16 Weeks) and switched to open-label tofacitinib 5 mg IR BID at Week 16 in a blinded fashion. All patients, investigators, and the Pfizer study team remained blinded to the double-blinded treatment until Week 48 when the final database was released.

Safety data come from 2 studies, one Phase 2 (A3921**119**) and one pivotal Phase 3 (A3921**120**). The Study 119 was double-blind and different tofacitinib doses were tested (2, 5, and 10 mg BID) and included a placebo arm, for a duration of 12 weeks. The Study 120 (phase 3) was double-blind placebo-controlled for the first 16 weeks and after that continued as open-label with all subjects receiving tofacitinib, until 32 weeks (total 48 weeks).

Patient exposure

The number of patients included in the Placebo-controlled Cohort and the All Tofa Cohort, including those exposed to tofacitinib 5 mg IR BID, are presented in **Table 68.**

Table 68. Tofacitinib summary of Clinical Safety (Ankylosing Spondylitis) Number of Subjects and Tofacitinib Exposure- AS Placebo-Controlled Cohort and All Tofa Cohort

Exposure Duration (Standardization Exposure Duration)	AS Placebo-Controlled Cohort				All Tofa Cohort			
	Tofa 5 mg BID		Placebo		All Tofa 5 mg BID		All Tofa	
	N	PY	N	PY	N	PY	N	PY
At least one dose (>0.00 subject-year)	185	52.77	187	53.07	316	208.90	420	232.98
>=1 month (>=0.08 subject-year)	183	52.71	186	53.01	314	208.84	416	232.91
>=3 months (>=0.23 subject-year)	170	49.81	169	49.74	297	205.22	375	224.24
>=6 months (>=0.46 subject-year)	NA	NA	NA	NA	253	193.83	253	193.83
>=12 months (>=0.92 subject-year)	NA	NA	NA	NA	108	100.46	108	100.46

N: Number of subjects included in the analysis. NA: Not Applicable. One month is equivalent to 28 days.
PY (Patient-Year in subject-year) is calculated as sum of duration of investigational product exposure.
Both N and PY are cumulative.
Exposure duration in days = date of last dose - date of first dose +1. Any missed doses between subject's first dose and last dose are counted as dosed.
The durations of exposure are standardized to subject-years by dividing the sum of exposure times in days by 365.25.
For subjects randomized to Placebo -> Tofa 5 mg BID in All Tofa cohort, the date of first dose refers to the date of first dose of tofacitinib treatment.
Included Protocols: A3921119, A3921120 (Final Data).
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 24NOV2020 (07:35)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCSPC_EU/adsl_s102
Table C12.4.2-E is for Pfizer internal use.

In the Placebo-controlled Cohort, the mean age was 41.9 years in the Tofa 5 mg BID group and 40.5 years in the Placebo group, <5% (n=13 in All Tofa) of patients were ≥65, there was a predominance of males (83.8% in the Tofa 5 mg BID group and 74.9% in the Placebo group) and the majority of patients were White (81.1% in the Tofa 5 mg BID group and 79.7% in the Placebo group). Geographic distribution in the Tofa 5 mg BID group was as follows: North America (14.6%), European Union (43.8%), Asia (17.3%) and Rest of World (24.3%).

Prior Medication Use

Prior medication use in the AS programme is summarised below:

- 96.5% of patients had an inadequate response to 2 or more NSAIDs
- 83.3% of the patients were bDMARD naïve
- 11.0% of patients had prior use of oral CS

Concomitant Medication Use

Concomitant medications to treat AS on Day 1 are summarised below:

- 27.7% of patients were on csDMARDs on Day 1. There were more patients in the Placebo arm (31.0%) on concomitant csDMARDs than the Tofa 5 mg BID arm (24.3%).

83.3% of patients were on concomitant NSAIDs and 9.7% were on other pain management/analgesics.

- 8.1% of patients were on CS on Day 1. There were more patients in the Tofa 5 mg BID arm (9.7%) on concomitant CS than the Placebo arm (6.4%).

For the All Tofa Cohort, demographic and baseline characteristics are presented in **Table 69.** The characteristics in the All Tofa 5 mg BID were comparable to those in the Tofa 5 mg BID group in the Placebo-controlled Cohort, according to the MAH.

Table 69. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Demographic and Baseline Characteristics - AS Placebo-Controlled Cohort and All Tofa Cohort

	Placebo-Controlled Cohort		All Tofa Cohort	
	Tofa 5 mg BID (N=185)	Placebo (N=187)	All Tofa 5 mg BID (N=316)	All Tofa (N=420)
Age (Years), n (%)				
<18	0	0	0	0
>=18 to <=44	115 (62.2%)	120 (64.2%)	199 (63.0%)	263 (62.6%)
>=45 to <=64	63 (34.1%)	63 (33.7%)	110 (34.8%)	144 (34.3%)
>=45 to <=49	23 (12.4%)	25 (13.4%)	42 (13.3%)	55 (13.1%)
>=50 to <=59	28 (15.1%)	28 (15.0%)	50 (15.8%)	66 (15.7%)
>=60 to <=64	12 (6.5%)	10 (5.3%)	18 (5.7%)	23 (5.5%)
>=65	7 (3.8%)	4 (2.1%)	7 (2.2%)	13 (3.1%)
>=65 to <=74	7 (3.8%)	4 (2.1%)	7 (2.2%)	12 (2.9%)
>=75 to <=84	0	0	0	1 (0.2%)
>=85	0	0	0	0
<50	138 (74.6%)	145 (77.5%)	241 (76.3%)	318 (75.7%)
>=50	47 (25.4%)	42 (22.5%)	75 (23.7%)	102 (24.3%)
<60	166 (89.7%)	173 (92.5%)	291 (92.1%)	384 (91.4%)
>=60	19 (10.3%)	14 (7.5%)	25 (7.9%)	36 (8.6%)
N1	185	187	316	420
Mean (Std.Dev.)	41.9 (11.43)	40.5 (11.60)	41.0 (11.29)	41.1 (11.51)
Median (Min, Max)	41.0 (20, 70)	39.0 (20, 70)	40.0 (20, 70)	40.0 (20, 75)
Q1, Q3	33.0, 50.0	32.0, 48.0	33.0, 49.0	33.0, 49.0
Gender, n (%)				
Male	155 (83.8%)	140 (74.9%)	261 (82.6%)	333 (79.3%)
Female	30 (16.2%)	47 (25.1%)	55 (17.4%)	87 (20.7%)
Race, n (%) [a]				
White	150 (81.1%)	149 (79.7%)	252 (79.7%)	334 (79.5%)
Asian	34 (18.4%)	38 (20.3%)	63 (19.9%)	85 (20.2%)
Black	0	0	0	0
Other	1 (0.5%)	0	1 (0.3%)	1 (0.2%)
Ethnicity, n (%)				
Hispanic or Latino	4 (2.2%)	2 (1.1%)	6 (1.9%)	6 (1.4%)
Not Hispanic or Latino	179 (96.8%)	184 (98.4%)	308 (97.5%)	412 (98.1%)
Not Reported	2 (1.1%)	1 (0.5%)	2 (0.6%)	2 (0.5%)
Height (cm)				
N1	184	186	315	419

Table 69. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Demographic and Baseline Characteristics - AS Placebo-Controlled Cohort and All Tofa Cohort

	Placebo-Controlled Cohort		All Tofa Cohort	
	Tofa 5 mg BID (N=185)	Placebo (N=187)	All Tofa 5 mg BID (N=316)	All Tofa (N=420)
Mean (Std.Dev.)	172.8 (9.09)	171.2 (9.02)	172.4 (8.82)	171.9 (8.86)
Median (Min, Max)	173.0 (146.0, 194.9)	171.3 (140.0, 196.0)	172.0 (145.5, 196.0)	172.0 (145.5, 196.0)
Q1, Q3	167.8, 179.0	165.0, 177.0	167.0, 178.0	166.8, 178.0
Weight (kg), n (%)				
<60	26 (14.1%)	25 (13.4%)	42 (13.3%)	63 (15.0%)
>=60 to <=100	136 (73.5%)	146 (78.1%)	242 (76.6%)	318 (75.7%)
>100	23 (12.4%)	16 (8.6%)	32 (10.1%)	39 (9.3%)
N1	185	187	316	420
Mean (Std.Dev.)	79.3 (18.15)	78.0 (18.03)	78.5 (17.76)	78.0 (17.41)
Median (Min, Max)	78.2 (45.0, 142.9)	77.9 (34.5, 148.0)	78.0 (34.5, 148.0)	78.0 (34.5, 148.0)
Q1, Q3	65.2, 88.0	65.5, 88.5	65.1, 88.0	65.0, 88.0
Body Mass Index (kg/m**2), n (%)				
<18.5	5 (2.7%)	12 (6.4%)	15 (4.7%)	19 (4.5%)
>=18.5 to <25	69 (37.3%)	67 (35.8%)	117 (37.0%)	157 (37.4%)
>=25 to <30	69 (37.3%)	62 (33.2%)	112 (35.4%)	148 (35.2%)
>=30 to <40	37 (20.0%)	41 (21.9%)	65 (20.6%)	88 (21.0%)
>=40	4 (2.2%)	4 (2.1%)	6 (1.9%)	7 (1.7%)
Missing	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.2%)
<30	143 (77.3%)	141 (75.4%)	244 (77.2%)	324 (77.1%)
>=30	41 (22.2%)	45 (24.1%)	71 (22.5%)	95 (22.6%)
Missing	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.2%)
<35	174 (94.1%)	173 (92.5%)	299 (94.6%)	398 (94.8%)
>=35	10 (5.4%)	13 (7.0%)	16 (5.1%)	21 (5.0%)
Missing	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.2%)
N1	184	186	315	419
Mean (Std.Dev.)	26.6 (5.45)	26.5 (5.82)	26.4 (5.42)	26.4 (5.28)
Median (Min, Max)	26.1 (16.0, 50.6)	26.2 (15.9, 48.9)	26.0 (15.9, 50.6)	26.1 (15.9, 50.6)
Q1, Q3	22.7, 29.5	22.0, 29.9	22.4, 29.6	22.6, 29.7
Geographic Region, n (%) [b]				
North America (US and Canada)	27 (14.6%)	15 (8.0%)	38 (12.0%)	51 (12.1%)
European Union	81 (43.8%)	89 (47.6%)	136 (43.0%)	200 (47.6%)

Table 69. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Demographic and Baseline Characteristics - AS Placebo-Controlled Cohort and All Tofa Cohort

	Placebo-Controlled Cohort		All Tofa Cohort	
	Tofa 5 mg BID (N=185)	Placebo (N=187)	All Tofa 5 mg BID (N=316)	All Tofa (N=420)
Asia	32 (17.3%)	38 (20.3%)	61 (19.3%)	83 (19.8%)
Rest of World	45 (24.3%)	45 (24.1%)	81 (25.6%)	86 (20.5%)
Smoking Status, n (%)				
Never Smoked	95 (51.4%)	99 (52.9%)	165 (52.2%)	217 (51.7%)
Former Smoker	32 (17.3%)	24 (12.8%)	51 (16.1%)	67 (16.0%)
Current Smoker	58 (31.4%)	64 (34.2%)	100 (31.6%)	136 (32.4%)
Duration of Smoking Started (Years) for Current Smoker or Former Smoker				
N1	88	87	149	200
Mean (Std.Dev.)	21.9 (12.11)	22.4 (11.65)	22.0 (11.72)	21.6 (11.67)
Median (Min, Max)	20.1 (1.3, 49.8)	19.8 (2.7, 55.0)	20.0 (1.3, 50.0)	19.8 (1.3, 50.0)
Q1, Q3	12.9, 30.0	14.4, 30.0	13.7, 30.0	12.8, 30.0
Duration of Smoking Stopped (Years) for Former Smoker				
N1	32	24	51	67
Mean (Std.Dev.)	10.9 (9.72)	10.2 (9.91)	10.2 (8.63)	10.1 (8.44)
Median (Min, Max)	7.8 (0.3, 37.0)	8.1 (0.8, 46.0)	7.8 (0.3, 37.0)	7.7 (0.3, 37.0)
Q1, Q3	3.5, 16.1	3.4, 13.8	3.7, 13.8	4.0, 13.8
Current Alcohol Use, n (%) [c]				
Yes	68 (36.8%)	70 (37.4%)	115 (36.4%)	152 (36.2%)
No	117 (63.2%)	117 (62.6%)	201 (63.6%)	268 (63.8%)
Amount of Alcohol Use (Units/Week) for Current Alcohol User				
N1	67	70	114	151
Mean (Std.Dev.)	3.7 (4.84)	3.1 (3.25)	3.4 (4.26)	3.0 (3.88)
Median (Min, Max)	2.0 (0.3, 35.0)	2.0 (0.5, 15.0)	2.0 (0.3, 35.0)	2.0 (0.3, 35.0)
Q1, Q3	1.0, 5.0	1.0, 4.0	1.0, 4.0	1.0, 4.0

Table 69. Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis) Demographic and Baseline Characteristics - AS Placebo-Controlled Cohort and All Tofa Cohort

	Placebo-Controlled Cohort		All Tofa Cohort	
	Tofa 5 mg BID (N=185)	Placebo (N=187)	All Tofa 5 mg BID (N=316)	All Tofa (N=420)

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 are based on N).
[a] Race used for subgroup analysis, 'Other' here stands for other than White, Asian and Black. [b] North America (US and Canada) includes United States and Canada. European Union includes Bulgaria,
Czech Republic, France, Hungary, Poland and Spain. Asia includes China, South Korea and Taiwan. Rest of World includes Ukraine, Russia, Australia and Turkey. [c] Yes is defined for subjects who have
current alcohol use at baseline, else No.
Body Mass Index (kg/m**2) = weight (kg) / [height (cm)*0.01]**2. Height is at Screening and weight is at baseline for both studies.
For Placebo-Controlled Cohort: Baseline is defined as last non-missing assessment prior to first dose of investigational product (including Placebo).
For All Tofa Cohort: Baseline is defined as last non-missing assessment prior to first dose of the study.
Included Protocols: A3921119, A3921120 (Final Data).
PFIZER CONFIDENTIAL Source Data: adsl and adsc Table Generation: 12NOV2020 (01:46)
(Final Data: 10Sep2020) Output File: ./unblind_1120/A392_SCSPC_EU/adsl_s001_pboat
Table C12.1.2.1-E is for Pfizer internal use.

Exposure in the RA and PsA Integrated Dataset

Exposure to tofacitinib 5 mg IR BID in the RA and PsA databases is larger than the exposure to tofacitinib in the AS integrated safety dataset (All Tofa Cohort).

The Tofacitinib 5 mg IR BID RA P2P3 and All Tofa 5 mg BID PsA Cohort 2a have been compared to the AS All Tofa 5 mg BID group. The maximum exposure for these groups is as follows:

- Tofacitinib 5 mg IR BID RA P2P3: 2664 patients representing 2476.66 PY of exposure
- All Tofa 5 mg BID PsA Cohort 2a: 347 patients representing 196.2 PY of exposure.

The RA P123LTE All Tofa group and PsA Cohort 3 All Tofa group have been compared to the AS All Tofa group. Exposure data are provided in **Table 70**

Table 70. Number of Patients and Tofacitinib Exposure in the RA P123LTE and PsA Cohort 3 Integrated Datasets

	All Tofa RA P123LTE		All Tofa PsA Cohort 3	
Duration	N	PY	N	PY
At least 1 dose	7964	23496.73	783	2037.97
≥1 month	7792	23489.51	771	2037.47
≥3 months	7115	23370.21	748	2034.41
≥6 months	6622	23178.14	713	2023.62
≥12 months	5028	21821.56	636	1973.80
≥18 months	4504	21215.76	579	1910.80
≥24 months	4168	20636.96	538	1845.47
≥30 months	3816	19880.70	508	1784.31

Source: RA IR Module 5.3.5.3 RA P123LTE Table 1582.10.4 Final data date for RA dataset 18 Jan 2019; PsA IR Module 5.3.5.3 PsA Cohort 3 Table 00118.C3.3.13.3 Final data date for PsA dataset 31 Jul 2019

Adverse events

An overall summary of Treatment-Emergent Adverse Events (All Causalities) in the AS Placebo-Controlled Cohort is shown in **Table 71.**

Table 71. 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)

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.

Table 72 shows an overall summary in the AS All Tofa Cohort.

Table 72. 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)

Table 72. 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 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 **Table 73** (all causalities).

Table 73. 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)

Table 73. 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 (%)
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)
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)

Table 73. 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 (%)

(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 74**.

Table 74 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)

Table 74 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 (%)
RENAL AND URINARY DISORDERS	7 (2.2)	1 (0.3)	0	8 (2.5)	10 (2.4)	1 (0.2)	0	11 (2.6)
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 75 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 75. Incidence and Severity of Treatment Related TEAEs

Table C1.3.1.3.3.2-E **Page 1 of 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 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

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.
- Hematological.
- 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 76**.

Table 76. 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 (-, -)
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									
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.

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 **Table 77.**

Table77. 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

Table77. 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
3 Cohort	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

Table 78 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 78. 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)

Adverse Events	Ankylosing Spondylitis (All Tofa Cohort) All Tofa 5 mg BID[a] N = 316 Exposure (patient-years) = 208.90				Psoriatic Arthritis (Cohort 2a) All Tofa 5 mg BID[a] N = 347 Exposure (patient-years) =196.2				Rheumatoid Arthritis (Cohort P2P3) Tofa 5 mg BID[b] N = 2664[c] Exposure (patient-years) = 2476.66			
	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	8	2.53	229.39	3.49 (1.51, 6.87)	15	4.3	198.14	7.57 (4.24, 12.49)	242	9.1	2487.66	9.73 (8.54, 11.03)
Serious infections	1	0.32	231.28	0.43 (0.01, 2.41)	4	1.2	200.74	1.99 (0.54, 5.10)	67	2.5	2570.31	2.61 (2.02,3.31)
OI[d,e]	0	0	231.35	0.00 (0.00, 1.59)	1	0.3	200.84	0.50 (0.01, 2.77)	9	0.3	2582.80	0.35 (0.16,0.66)
TB[d]	0	0	231.35	0.00 (0.00, 1.59)	0	0	201.10	0.00 (0.00, 1.83)	2	0.1	2584.24	0.08 (0.01,0.28)
HZ	5	1.58	229.74	2.18 (0.71, 5.08)	3	0.9	199.58	1.50 (0.31, 4.39)	74	2.8	2535.74	2.92 (2.29,3.66)
Malignancies excluding NMSC[d]	0	0	231.35	0.00 (0.00, 1.59)	3	0.9	200.76	1.49 (0.31, 4.37)	9	0.3	2583.73	0.35 (0.16,0.66)
Lymphoma[d]	0	0	231.35	0.00 (0.00, 1.59)	0	0	201.10	0.00 (0.00, 1.83)	0	0	2584.41	0.00 (0.00,0.14)
NMSC[d]	0	0	231.35	0.00 (0.00, 1.59)	0	0	201.10	0.00 (0.00, 1.83)	11	0.4	2578.26	0.43 (0.21,0.76)
MACE[d]	0	0	231.35	0.00 (0.00, 1.59)	1	0.3	201.10	0.50 (0.01, 2.77)	7	0.3	2500.08	0.28 (0.11,0.58)
DVT[f]	0	0	231.35	0.00 (0.00, 1.59)	0	0	201.10	0.00 (0.00, 1.83)	4	0.2	2581.36	0.15 (0.04,0.40)
PE[f]	0	0	231.35	0.00 (0.00, 1.59)	0	0	201.10	0.00 (0.00, 1.83)	3	0.1	2583.34	0.12 (0.02,0.34)
ATE[f]	0	0	231.35	0.00 (0.00, 1.59)	1	0.3	200.76	0.50 (0.01, 2.78)	6	0.2	2582.94	0.23 (0.09, 0.51)
VTE[f,g]	0	0	231.35	0.00 (0.00, 1.59)	0	0	201.10	0.00 (0.00, 1.83)	7	0.3	2580.29	0.27 (0.11,0.56)
Thrombosis[f,h]	0	0	231.35	0.00 (0.00, 1.59)	1	0.3	200.76	0.50 (0.01, 2.78)	13	0.5	2578.82	0.50 (0.27,0.86)
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)

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.

Table 79 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.

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.

Overall, in the AS placebo-controlled cohort (with exposure up to 16 weeks, thus short-term), the proportion of subject with AEs was similar or slightly higher in tofacitinib than in placebo: 101 (54.6%) vs 92 (49.2%). However, when the AS All Tofa cohort is considered (with longer duration of exposure), a higher incidence of AEs is found. In particular, subjects with AEs were 201 (63.6%) in tofacitinib 5 mg BID vs 251 (59.8%) in All tofacitinib (for a rough comparison, the number in the short-term placebo arm was 92, 49.2%).

Subjects with **dose reduced or temporary discontinuation** due to adverse events were 30 (9.5%) in tofacitinib 5 mg BID vs 32 (7.6%) in All tofacitinib (for a rough comparison, the number in the short-term placebo arm was 6, 3.2%).

Among the most **common AEs**, those with more marked difference vs placebo are reported (during the 16 weeks of the placebo-controlled period): infections and infestations were 114 (36.1%) in tofacitinib 5mg BID vs 135 (32.1%) in All tofacitinib vs 43 (23.0%) in placebo. Investigations AEs were reported in 53 (16.8%) in tofacitinib 5 mg BID vs 59 (14.0%) in all tofacitinib cohort vs 8 (4.3%) in the placebo. Most of these investigation AE cases were related to increased liver transaminases. The type of observed AEs is in line with the safety profile of tofacitinib kwon so far.

In the placebo-controlled cohort (with a limited exposure up to 16 weeks), more AEs considered **related** to the IMP, were moderate in intensity in the tofacitinib arm compared to the placebo (8/185, 4% vs 3/187, 1%).

Due to the limited number of patients studied (185 in tofacitinib 5mg 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.

Acute renal failure was observed in more cases in tofacitinib than in placebo, 5 (2.70%) vs 2 (1.07%). Increased creatinine is currently reported at the 4.8 tabular listing of ADRs and it is also observed in this submission (see below at lab findings). Even if the absolute numbers are small, the MAH was asked to elaborate more on the risk of acute renal failure (e.g. possible unbalanced risk factors, medication use, etc). With the exception of 1 participant with an AE coded to as "serum creatinine increased", all events listed under the SMQ of "acute renal failure" were coded as "protein urine present". 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 (WNL) at all visits. Therefore, it seems that the severity of the AEs observed was mild on average. The issues was solved.

Hepatic AEs (including: Hepatic Steatosis, Transaminase Elevations) were overall observed more frequently in tofacitinib than in placebo, 10 (5.40%) vs 2 (1.07%) (manually calculated adding the two PTs above) and this is consistent with the known impact of tofacitinib on liver enzymes.

There was a case of serious infection in the tofacitinib 5mg during the placebo-controlled period (meningitis aseptic) not considered as an opportunistic infection (and thus considered not related to the immunosuppressant effects of tofacitinib).

Haematological alterations were few in absolute numbers and difficult to assess.

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 limited exposure.

When the incidence rate for AEs of special interest in patients treated with tofacitinib 5 mg IR BID 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 most probably due to the low exposure in the AS program compared to the other two conditions. The same is observed when the comparison is among the All tofacitinib cohort, that is among patients who received any tofacitinib dosage (and not only the 5 mg BID); in this case an exception is only observed for herpes zoster incidence that is higher in AS patients, incidence per 100 PY (95% CI) 2.68 (1.08, 5.53), compared to PsA, 1.76 (1.23, 2.44), but lower compared to RA, 3.58 (3.34, 3.84).

Serious adverse event/deaths/other significant events

Deaths

No deaths were reported in the AS 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 80**

Table 80. 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 81.**

Table 81. 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 81. 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.

Severity of SAEs is shown in **Table 82**

Table 82. Incidence and Severity od Treatment-Emergent Adverse Events

Table C2.3.1.3.3.2-E **Page 1 of 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

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.

Regarding the **SAEs**, incidence rate was 5.28/100 PY in the tofacitinib 5mg BID in the placebo-controlled cohort, vs 3.56/100 PY of the placebo arm; the total number of cases were (tofacitinib 5 mg vs placebo) 3 vs 2. In All tofacitinib doses the incidence rate was 3.49/100 PY, that is similar to the placebo arm of the controlled cohort (but with different length of exposure); the total number of cases in the All tofacitinib cohort were (tofacitinib 5 mg BID vs All tofacitinib doses) 9 vs 10. However, it is important to keep in mind the limited number of subjects studied. 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 in both 5mg and all dosses for tofacitinib during the 48-week period of the study.

In the placebo group a patient experienced "foetal death". Since "pregnancy" was an exclusion criterion, the MAH clarified that the patient's pregnancy was a result of a contraceptive failure (condom and spermicide) but she was negative at the start of the study.

The MAH provided data of comparison between patients treated with tofacitinib in the AS program vs those in the RA/PsA programs for SAEs and AEs of Special Interest. Basically, except for herpes zoster in patients taking tofacitinib 5mg BID, all the SAEs and other AEs of special interest were apparently less frequent in the AS program compared to the RA and PsA programs. This was most probably due to the very low exposure in the AS program (PYR=232.98 for tofacitinib 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).

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 83**, without regard to baseline abnormality for the Placebo-controlled Cohort.

Table 83. Tofacitinib Summary of Clinical Safety (AS)

Table C1.3.4.1.1-E Pa
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

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 (%)
	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 (%)
	LDL Cholesterol (mg/dL)	>1.2x ULN	181	4 (2.2)	184	3 (1.6)
	Triglycerides (mg/dL)	>1.3x ULN	184	7 (3.8)	184	3 (1.6)
	Sodium (mEq/L)	<0.95x LLN	184	0	184	1 (0.5)
	Potassium (mEq/L)	>1.1x ULN	184	2 (1.1)	184	0
	Glucose (mg/dL)	>1.5x ULN	184	6 (3.3)	184	4 (2.2)
	Creatine Kinase (U/L)	>2.0x ULN	184	8 (4.3)	184	9 (4.9)
	Cholesterol (mg/dL)	>1.3x ULN	184	0	184	1 (0.5)
URINALYSIS	Specific Gravity (Scalar)	>1.035	183	2 (1.1)	183	6 (3.3)
	pH (Scalar)	>8	183	1 (0.5)	183	0
	URINE Glucose	>=1	183	2 (1.1)	183	1 (0.5)
	Ketones	>=1	183	5 (2.7)	183	7 (3.8)
	URINE Protein	>=1	183	3 (1.6)	183	0
	URINE Hemoglobin	>=1	183	27 (14.8)	183	35 (19.1)
	URINE Erythrocytes (/HPF)	>=20	72	2 (2.8)	73	5 (6.8)
	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 **Table 84** for the Placebo-controlled Cohort.

Table 84. 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)

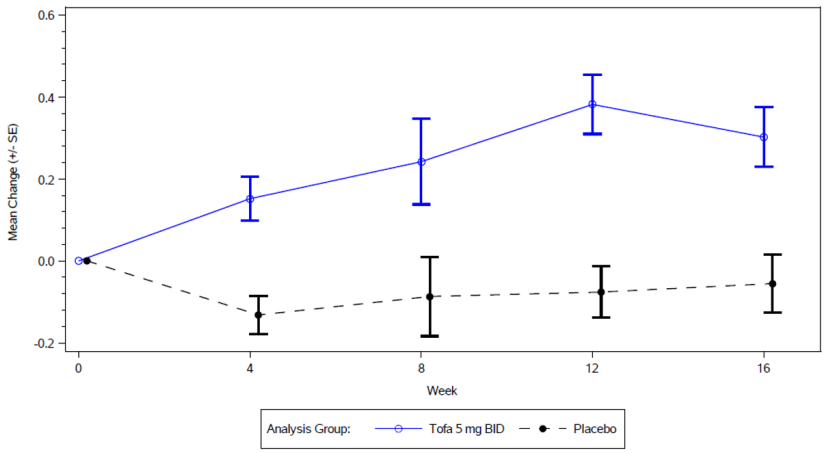
A subject may have met multiple criteria. Each subject is counted only once for each row.
Baseline is defined as last non-missing assessment prior to first dose of investigational product (including Placebo).
N: Number of subjects included in the Safety Analysis Set; n (%): Number of subjects who meet 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.

Hemoglobin

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

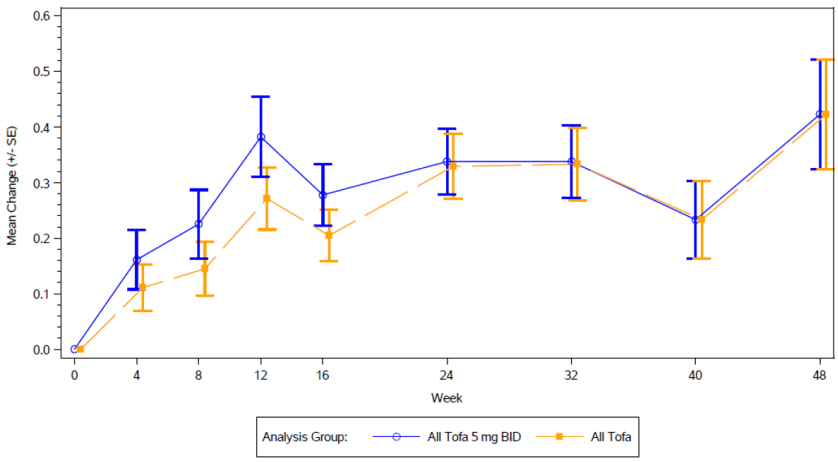
Hb changes over time are presented for the Placebo-controlled Cohort in **Figure 31** and All Tofa Cohort in **Figure 32**. There were no patient discontinuations due to decreases in Hb.

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



Source: Module 5.3.5.3 SCS Figure C1.3.4.3.4.4-E

Figure 32. Tofacitinib Summary of Clinical Safety – Mean (± SE) Change from Baseline in Hemoglobin (g/dL) – AS All Tofa Cohort

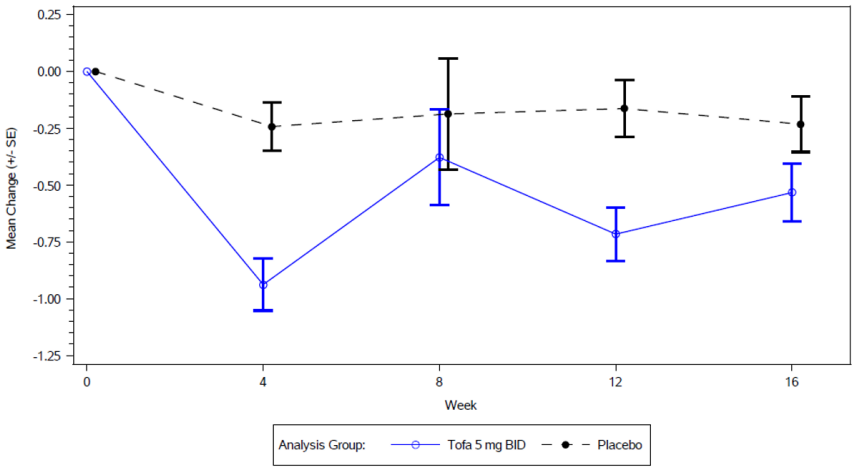


Source: Module 5.3.5.3 SCS Figure C2.3.4.3.4.4-E

Neutrophils

Tofacitinib has been associated with an increased incidence of neutropenia, therefore patient selection based on threshold ANC values was an exclusion criteria. The mean (± SE) Change from Baseline in Absolute Neutrophil Count is reported in **Figure 33.**

Figure 33. Tofacitinib Summary of Clinical Safety - Mean (± SE) Change from Baseline in Absolute Neutrophil Count ($10^3/mm^3$) – AS Placebo-controlled Cohort



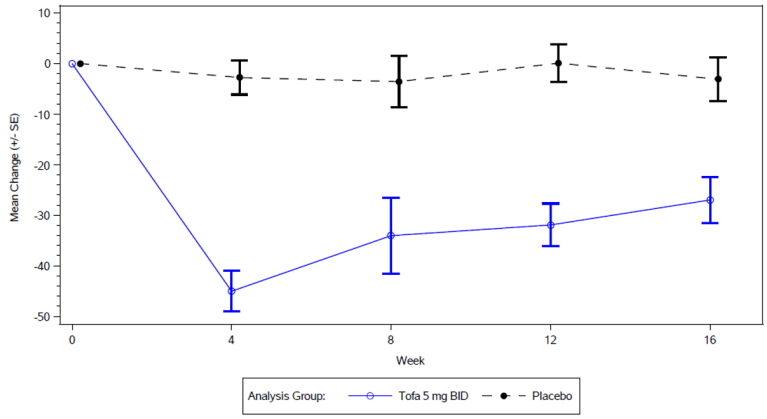
Source: Module 5.3.5.3 SCS Figure C1.3.4.3.4.4-E

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 (**Figure 34)** and All Tofa Cohort (**Figure 35).** 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 34. 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 (**Table 85)** 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 35 Tofacitinib Summary of Clinical Safety–Mean (±SE) Change from Baseline in Platelets (103/mm3)–AS All Tofa Cohort

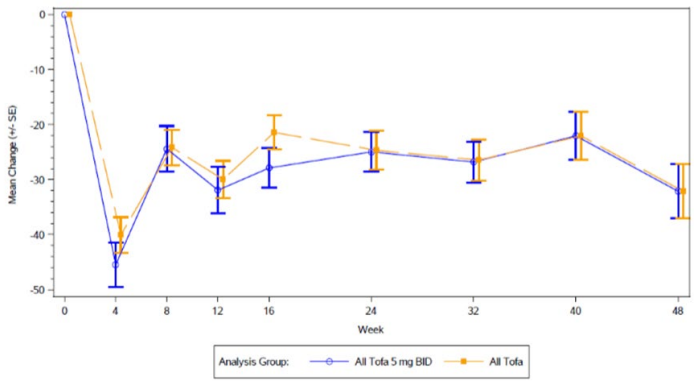


Table 85 show a comparison of platelet counts in AS vs RA/PsA clinical programs.

Table 85. 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 Baseline (SD)	-26.98 (61.020)	-3.10 (56.815)	-	-	-15.52 (52.95)	-4.91 (56.60)

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 86. 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.

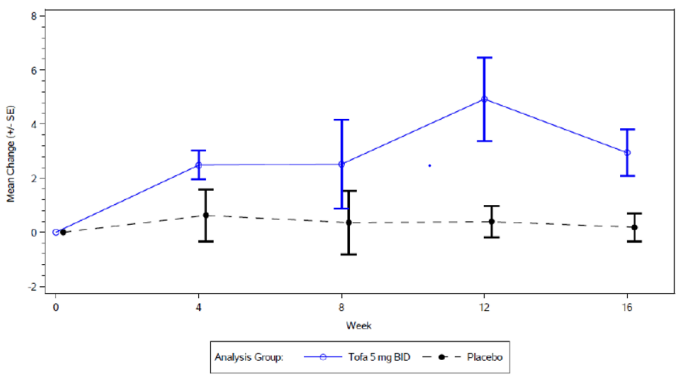
PsA Average Tofa 5 mg : Subjects with an average total daily dose of <15 mg from Day 1 on Tofa. Includes Protocols A3921091,

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 **Figure 36.**

Figure 36. Tofacitinib Summary of Clinical Safety–Mean (±SE) Change from Baseline in AST (U/L) – AS Placebo-controlled Cohort

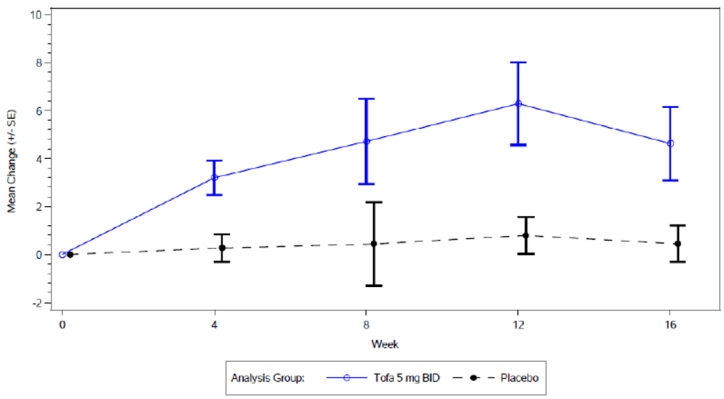


Module 5.3.5.3 SCS Figure C1.3.4.3.1.4-E

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 **Figure 37.**

Figure 37. 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 **Table 87.**

Table 87. 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

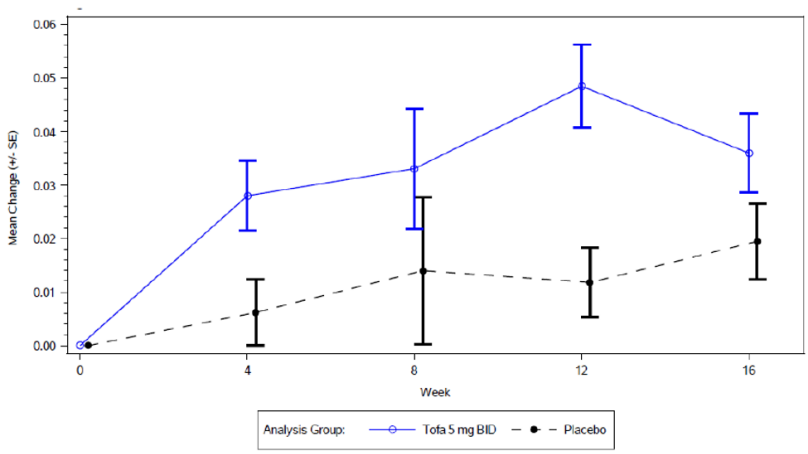
	Tofa 5 mg BID (N=184) n (%)	Placebo (N=184) n (%)
ALT		
>=2 x ULN	4 (2.2)	1 (0.5)
>=3 x ULN	1 (0.5)	0
>=5 x ULN	1 (0.5)	0
>=10 x ULN	0	0
AST		
>=2 x ULN	3 (1.6)	0
>=3 x ULN	1 (0.5)	0
>=5 x ULN	0	0
>=10 x ULN	0	0
Total Bilirubin		
>=2 x ULN	0	0
>=3 x ULN	0	0

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 (**Figure 38**). The mean change from baseline for creatinine is shown in the following figure for the Placebo-controlled Cohort.

Figure 38. 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

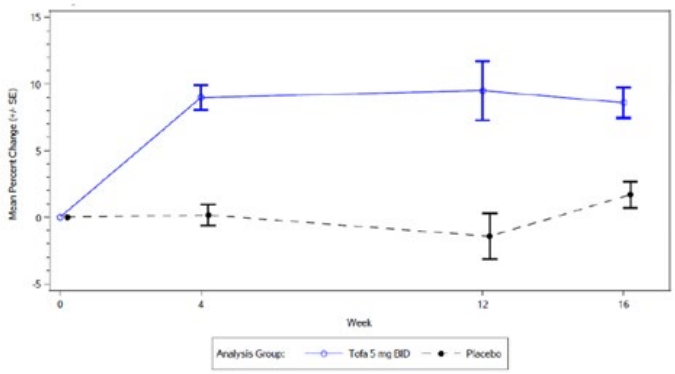
The changes of serum creatine at week 16 from baseline was: Mean (SD) 0.04 (0.100) in tofacitinib 5 mg vs 0.02 (0.095) in placebo.

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 **Figure 39** for the Placebo-controlled Cohort.

Figure 39. Tofacitinib Summary of Clinical Safety - Mean (± SE) Percent Change from Baseline in Cholesterol (mg/dL) – AS Placebo-controlled Cohort

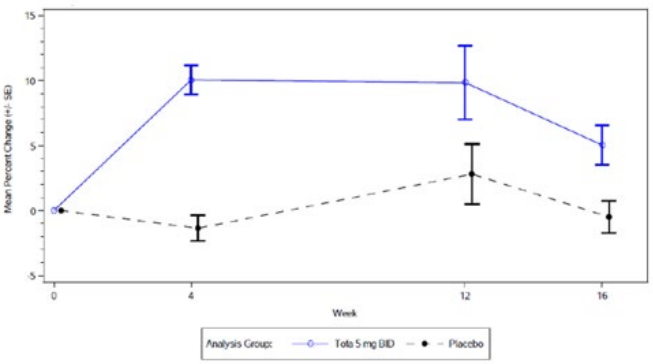


Module 5.3.5.3 SCS Figure C1.3.4.3.3.4-E

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 **Figure 40** for the Placebo-controlled Cohort.

Figure 40. Tofacitinib Summary of Clinical Safety – Mean (± SE) Percent Change from Baseline in HDL Cholesterol (mg/dL) – AS Placebo-controlled Cohort

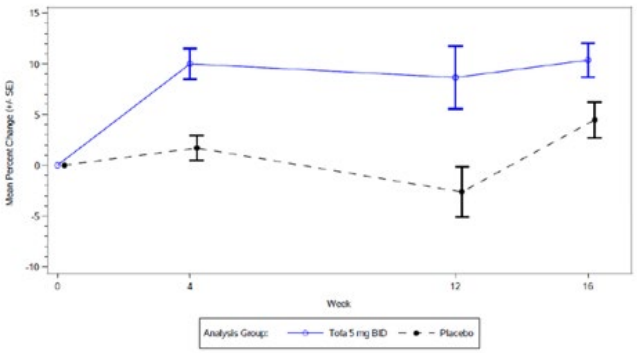


Module 5.3.5.3 SCS Figure C1.3.4.3.3.4-E

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 41** for the Placebo-controlled Cohort.

Figure 41. Tofacitinib Summary of Clinical Safety - Mean (± SE) Percent Change from Baseline in LDL Cholesterol (mg/dL) – AS Placebo-controlled Cohort

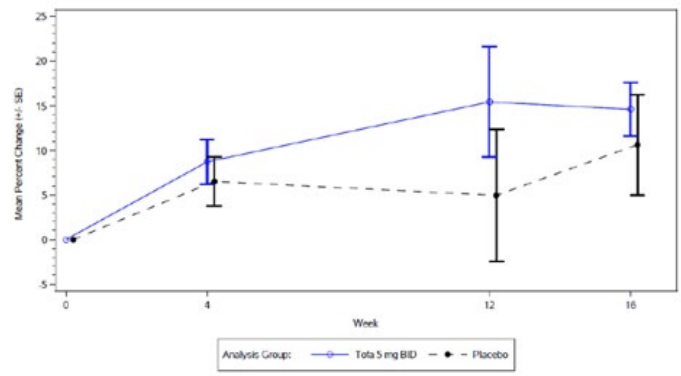


Module 5.3.5.3 SCS Figure C1.3.4.3.3.4-E

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 **Figure 42**. for the Placebo-controlled Cohort.

Figure 42. 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.

Table 87 shows the categorization of changes in blood pressure parameters

Table 87. Tofacitinib Summary of Clinical Safety (AS) – Categorization of Vital Signs Data

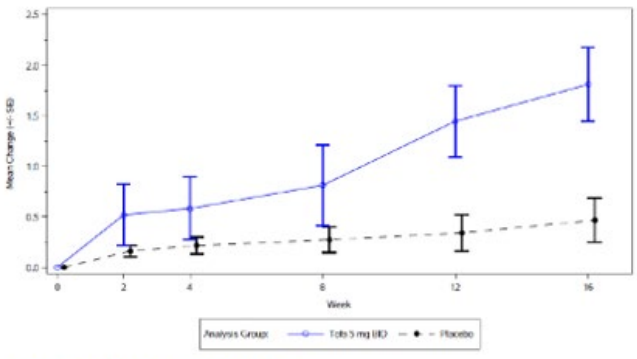
Table C2.3.5.2-E
Tofacitinib Summary of Clinical Safety (Ankylosing Spondylitis)
Categorization of Vital Signs Data - Treatment Policy Estimand, AS All Tofa Cohort

		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 43**).

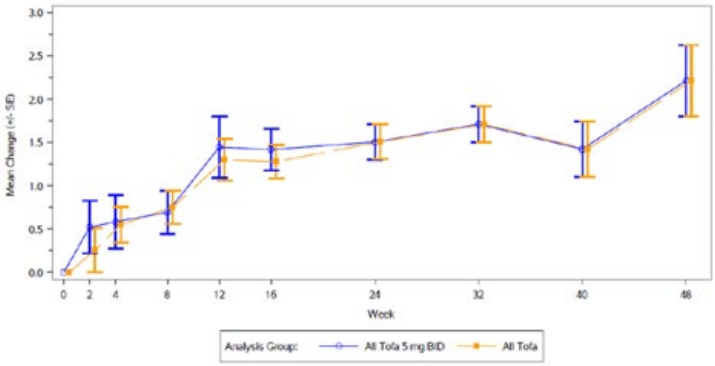
Figure 43. Tofacitinib Summary of Clinical Safety - Mean (± SE) Change from Baseline Weight (Kg) – AS Placebo-controlled Cohort



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 **Figure 44.**

Figure 44. 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).

Table 88 shows the shift in BMI categories.

Table 88 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

Table 89 shows the ECG parameters categorization for the placebo-controlled cohort.

Table 89. Tofacitinib Summary of Clinical Safety (AS) – Categorization 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)
	480<=Value<500	183	0	180	0
	Value>=500	183	1 (0.5)	180	0
	30<=Chg<60	183	7 (3.8)	180	6 (3.3)
	Chg>=60	183	1 (0.5)	180	0

In the comparison between tofacitinib 5 mg BID and placebo (with exposure up to 16 weeks) there seem to be no particular signals of safety issues from laboratory findings, except for a slight higher proportion of subjects that had increased **liver** transaminases in tofacitinib compared to placebo. In particular, subjects with AST >3.0x ULN were 4 (2.2%) in tofacitinib vs 1 (0.5%) in placebo; ALT >3.0x ULN were 5 (2.7%) vs 1 (0.5%). Also Triglycerides (mg/dL) >1.3x ULN were increased in 7 (3.8%) patients taking tofacitinib vs 3 (1.6%) in placebo. This confirms the known increase in the liver function tests.

No reduction in **haemoglobin** levels was observed in the AS program, despite the tendency of tofacitinib to induce anemia. Again, the plausible explanation is the limited exposure.

During the placebo-controlled period, a slight decrease in the **neutrophil** count was observed in the tofacitinib 5 mg BID compared to placebo. The reduction occurred already after few weeks of treatment. At week 16 (last visit of the placebo-controlled period), Neutrophils (10^3/mm^3) were: mean (SD) 4.66 (1.673) in tofacitinib 5mg vs 4.97 (1.831) in placebo.

There was a slight reduction in **platelets** count at week 16 in tofacitinib 5 mg vs placebo, mean (SD) (10^3/mm^3): 270.58 (61.094) vs 304.48 (89.657). However, the values remained in the normal range for all the visits.

Lipids were influenced by tofacitinib treatment, in particular a mild increase in total cholesterol, LDL, HDL and triglycerides was observed.

No clinically significant changes were observed in **blood pressure** during the up to 16 weeks of the placebo-controlled period in patients taking tofacitinib, and also at the end of the 48 weeks in the uncontrolled period.

An increase in **weight** was observed among tofacitinib patients: at week 16 the change from baseline was (kg) mean (SD): 1.8 (4.96) in tofacitinib 5mg vs 0.5 (2.93) in placebo. In the All tofacitinib cohort the increase was 2.2 (4.59) at 48 weeks in both arms (tofacitinib 5mg and All tofacitinib doses). The MAH has specified that the overall magnitude of the weight increase in the AS clinical program was considered

to be mild in severity, with a mean increase of 2.2 kg at Week 48 in the All Tofa Cohort. Similar increases were observed in the rheumatoid arthritis (RA) and psoriatic arthritis (PsA) clinical programs.

The percentage of participants that switched from the <25 kg/m2 category to ≥25 - <35 kg/m2 category was 14.3% and from the ≥25 to <35 kg/m2 category to ≥35 kg/m2 category was 4.4% for the tofacitinib 5 mg BID treatment group at Week 48.

Since weight increase is already present in the tabular list at the 4.8 of the SmPC, this is considered sufficient in relation to the magnitude of observed effect.

No alterations in the ECG parameters were observed during the placebo-controlled phase.

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 **Table 90.**

Table 90. 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)

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 **Table 91.**

Table 91. 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 **Table 92.**

Table 92. 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
		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)
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)

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 93.**

Table 93. 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)

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 **Table 94.**

Table 94. 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 **Table 95.**

Table 95. 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)

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.

Effects by **age** are very difficult to estimate since the limited number of subjects >65 years (n=13) vs <65 years (n=407) and thus no conclusions can be drawn.

As to the **gender**, in almost all the categories for the 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. Therefore, firm conclusions are difficult to be drawn.

Regarding the **race** most patients in the tofacitinib 5 mg BID group were White (n=252) and few were Asian (n=63). In general, Asian patients in the tofacitinib 5 mg group experienced more AEs, n=49 (77.78%), IR per 100PY (95% CI): 302.22 (223.58, 399.55) compared to White, n=149 (59.13%), IR per 100PY (95% CI): 136.90 (115.80, 160.73), and experienced more Infections, Asian: n=33 (52.38%), IR per 100PY (95% CI): 111.78 (76.94, 156.98) vs White: n=78 (30.95%), IR per 100PY (95% CI):

53.80 (42.53, 67.14). A similar trend was observed for the All tofacitinib doses. However, again the limited number of Asian patients makes difficult to draw any firm conclusion.

Some differences were observed in the distribution of AEs by **geographical** region. However, the number of patients for each regions does not allow a fully reliable evaluation. Overall, general events for European region were in line, or less frequent, than for the other regions, and data about Asia confirm the increased AEs incidence rate for Asian sub-population.

When analysed by **previous treatment**, patients were divided in two categories: bDMARD-naive (approximately 80%) and TNF inhibitor-inadequate responder or bDMARD use (without inadequate response) (approximately 20%). Therefore, the number of subjects with previous bDMARD use was small (n=58, all treated with tofacitinib 5 mg BID) compared to those bDMARD-naïve (n=362 with all tofacitinib doses). 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 n=42 (72.41%), IR per 100 PY (95% CI): 201.32 (145.09, 272.12) in previous treated vs n=156 (60.47%), IR per 100 PY (95% CI): 148.31 (125.95, 173.49) in naïve patients. The highest difference was observed for Discontinuation of study treatment, which involved n=13 (22.41%) subjects, IR per 100 PY (95% CI): 30.02 (15.98, 51.33) in previous treated, vs n=12 (4.65%), IR per 100 PY (95% CI): 6.44 (3.33, 11.25) in naïve patients. The number of patients in the previous 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.

When analysed by **concomitant csDMARD** therapy, a trend of higher incidence was observed in many categories of general events in patients **not** taking concomitant csDMARD compared to those taking csDMARD (TEAEs 64.3% vs 58.4%, SAEs 3.1% vs 1.1%, Discontinuation of study treatment 8.8% vs 5.6%, Discontinuation due to AEs 4.0% vs 2.3%, All Infections 37.0% vs 30.3%; in tofacitinib 5 mg BID of the All tofacitinib odes cohort). Again the number of patients enrolled in the two groups was not high, 227 vs 89 in the "not taking concomitant csDMARD" vs "taking concomitant csDMARD" respectively, and was unbalanced with a very small group of patients taking concomitant csDMARD. Therefore, any difference observed is difficult to evaluate. Furthermore, there doesn't seem to be a biological rationale, since the contrary was expected.

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 96**):

- 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 96. 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)

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 **Table 97**. 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:

- 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 97. 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)
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

Table 97. 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 (%)

(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.

The incidence rate of AEs leading to drug discontinuation was similar between tofacitinib 5mg BID and placebo, during the placebo-controlled periods (which was up to 16 weeks): 7.04/100 PY in tofacitinib vs 7.10/100 PY in placebo. The number of subjects with any AE leading to discontinuation was 4 (2.2%) in tofacitinib 5mg BID vs 4 (2.1%) in placebo (placebo-controlled cohort) and there was no single AE that was more common than others (due to the limited exposure). In the tofacitinib 5mg BID of the All tofa cohort (up to 48 weeks), the incidence rate was 4.77/100 PY. In this cohort, the number of subjects with any AE leading to discontinuation was 11 (3.5%) in the tofacitinib 5mg BID and 12 (2.9%) in All tofacitinib.

Post marketing experience

In the EU, Xeljanz was granted a marketing authorisation on 21 March 2017, for the treatment of RA. In June 2018, it was approved for treatment of psoriatic arthritis (PsA), and in July 2018, it was also approved for the treatment of ulcerative colitis (UC).

The MAH monitors post-marketing data across the different approved indications (RA, PsA, and UC), which reflects the safety profile of tofacitinib since marketing approval. The updated post-marketing surveillance data and US Corrona RA Registry Study A3921205 subset analysis, provided in this SCS, supplements the clinical data and provides evidence of the long-term safety of tofacitinib 5 mg IR BID in the real-world setting. An additional 4 EU based ongoing registries (ARTIS, RABBIT, BIOBADASER and BSRBR) in RA patients are monitored and provide further evidence of the long-term safety of tofacitinib 5 mg IR BID in the real-world setting.

The MAH has provided a literature search of published clinical trials and observational studies to identify relevant safety data relating to AEs of special interest in patients treated with biologic DMARDs for AS. Incidence rates from external published clinical trials and observational studies were compared to rates from the tofacitinib AS programme.

Post-authorisation study A3921133

Post-authorisation study A3921133 has been designed to evaluate the safety of tofacitinib 5 mg BID and tofacitinib 10 mg BID compared to a tumour necrosis factor inhibitor (etanercept or adalimumab) in patients with RA. The available data shows that tofacitinib increases the risk of venous thromboembolism (DVT and pulmonary embolism (PE)) in patients with RA and PsA, especially in patients treated with tofacitinib 10 mg BID, and patients with risk factors for venous thromboembolism, as well as risk factors for cardiovascular events. On 12 February 2019 the MAH informed EMA that an increased risk of PE and overall mortality had been reported in Study A3921133. In this clinical trial, the overall incidence of PE was 5.96-fold higher in tofacitinib 10 mg twice daily arm of the study compared with the TNF inhibitor arm, and approximately 3-fold higher than tofacitinib in other studies across the tofacitinib development programme.

On 12 February 2019, the MAH informed EMA that an increased risk of pulmonary embolism (PE) and overall mortality had been reported in Study A3921133. In this clinical trial, the overall incidence of PE was 5.96-fold higher in tofacitinib 10 mg twice daily arm of the study compared with the TNF inhibitor arm, and approximately 3-fold higher than tofacitinib in other studies across the tofacitinib development programme. The data safety monitoring board (DSMB) recommended to modify Study A3921133 to discontinue treatment with tofacitinib 10 mg BID. Of note, the FDA subjected the continuation of the trial to the condition that subjects assigned to the 10 mg BID dose were switched to the lower 5 mg BID dose.

Post-Marketing Surveillance Reports

The RMP (Module 5.3.6 RMP Report) includes the current post-marketing data (data cut off 05 Nov 2019). Information from the post-marketing setting is also included in the PSUR submitted to the EMEA at 1-year intervals (Module 5.3.6 November 2020 PSUR). Findings from post-marketing data have been consistent with the safety profile for tofacitinib.

US Corrona RA Registry Study A3921205 Safety 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 study of the safety of tofacitinib in exposed RA patients was based on data collected within the US Corrona RA Registry. The report of Corrona RA registry has not been found in the dossier.

Safety from the ARTIS real-world dataset

The ARTIS register study (A3921391) comprised a cohort of 10,603 Swedish patients who were comparable to patients in the Phase 3 AS clinical trial programme (A3921120). The crude incidence rates for safety events in the ARTIS database for AS patients overall and for all bDMARD initiators (bDMARD experienced or bDMARD naïve as of the index date 01 Jul 2006) are presented in **Table 98.**

Table 98. Crude Incidence Rates (per 100 PYs) of Safety Events Among Ankylosing Spondylitis Patients in the ARTIS Register, With Censoring at 48 Weeks

	Overall AS (N = 10603)			bDMARD-naïve[b] (N = 9756)			bDMARD-experienced[c] (N = 3463)		
	NE	PYs	CIR	NE	PYs	CIR	NE	PYs	CIR
Serious infections[d]	217	6755	3.21 (2.80, 3.65)	201	6009	3.34 (2.90, 3.82)	34	2271	1.50 (1.04, 2.04)
OI[e]	3	6755	0.04 (0.01, 0.11)	3	6009	0.05 (0.01, 0.12)	1	2271	0.04 (0.00, 0.16)
TB[f]	1	6755	0.01 (0.00, 0.05)	1	6009	0.02 (0.00, 0.06)	0	2271	0.00 (0.00, 0.00)
Pneumonia[f]	84	6755	1.24 (0.99, 1.52)	78	6009	1.30 (1.03, 1.60)	7	2271	0.31 (0.12, 0.58)
Hospitalised HZ[f]	0	6755	0.00 (0.00, 0.00)	0	6009	0.00 (0.00, 0.00)	0	2271	0.00 (0.00, 0.00)
All malignancies[g]	45	6587	0.68 (0.50, 0.90)	44	5924	0.74 (0.54, 0.98)	10	2025	0.49 (0.24, 0.84)
NMSC[h]	19	6582	0.29 (0.17, 0.43)	18	5919	0.30 (0.18, 0.46)	3	2024	0.15 (0.03, 0.36)
MACE[i]	211	6726	3.14 (2.73, 3.57)	205	5982	3.43 (2.97, 3.91)	11	2270	0.48 (0.24, 0.81)
DVT[j]	15	6747	0.22 (0.12, 0.35)	15	6002	0.25 (0.14, 0.39)	1	2270	0.04 (0.00, 0.16)
Hospitalised PE[k]	26	6747	0.39 (0.25, 0.55)	24	6003	0.40 (0.26, 0.57)	1	2270	0.04 (0.00, 0.16)
VTE[l]	39	6740	0.58 (0.41, 0.77)	37	5996	0.62 (0.43, 0.83)	2	2269	0.09 (0.01, 0.25)
ATE[m]	2	6755	0.03 (0.00, 0.08)	2	6009	0.03 (0.00, 0.09)	0	2271	0.00 (0.00, 0.00)
Hypertension[n]	56	6734	0.83 (0.63, 1.06)	53	5990	0.88 (0.66, 1.14)	5	2269	0.22 (0.07, 0.45)
GI perforations[n]	5	6753	0.07 (0.02, 0.15)	5	6009	0.08 (0.03, 0.17)	1	2270	0.04 (0.00, 0.16)
ILD[o]	0	6755	0.00 (0.00, 0.00)	0	6009	0.00 (0.00, 0.00)	0	2271	0.00 (0.00, 0.00)
All-cause mortality[o]	54	6755	0.80 (0.60, 1.03)	54	6009	0.90 (0.68, 1.15)	3	2271	0.13 (0.03, 0.32)

Incidence rates for all events, except hospitalized HZ and ILD, were higher among bDMARD-naïve compared with the bDMARD-experienced group.

Safety "Trial-Like Subcohort" from the US Truven MarketScan Analysis

The Truven MarketScan study consisted of 2 patient cohorts. Cohort A comprised adults (≥18 years of age) with active AS within the United States Truven MarketScan database between 01 Jan 2010 and 31 Dec 2017. Cohort B was a subset of Cohort A, but more closely reflected patients within Study A3921120 via the application of trial-like exclusion criteria. A total of 5,196 AS patients were identified with 6,506 eligible biologic treatment episodes in Cohort A; 2,253 patients with 2,662 treatment episodes included in the Cohort B analysis. AEs of special interest in "Trial-like" Sub-Cohort (Cohort B) is presented in **tables 99, 100, 101, 102 and 103, 104**.

Table 99 "Trial-like" Sub-Cohort (Cohort B) –Serious Infections

	Time	All bDMARD initiators (N=2,253)		bDMARD naive initiators (N=1,362)		bDMARD experienced initiators (N=891)	
		n	Weighted Incidence Rate (95% CI) per 100 PY	n	Weighted Incidence Rate (95% CI) per 100 PY	n	Weighted Incidence Rate (95% CI) per 100 PY
Serious Infection[a]	16 weeks	24	3.24 (2.00, 4.98)	10	2.12 (0.94, 4.10)	14	5.03 (2.58, 8.82)
	48 weeks	47	3.59 (2.57, 4.87)	25	2.78 (1.76, 4.18)	22	5.16 (3.08, 8.10)

Table 100 "Trial-like" Sub-Cohort (Cohort B) –Other Infections

	Time	All bDMARD initiators (N=2,253)	
		n	Weighted Incidence Rate (95% CI) per 100 PY
OI	16 weeks	2	0.24 (0.03, 0.91)
	48 weeks	3	0.17 (0.03, 0.51)
HZ	16 weeks	5	0.53 (0.17, 1.26)
	48 weeks	12	0.74 (0.37, 1.34)

Table 101 "Trial-like" Sub-Cohort (Cohort B) -Malignancies

	Time	All bDMARD initiators (N=2,253)	
		n	Weighted Incidence Rate (95% CI) per 100 PY
Malignancies excluding NMSC	16 weeks	0	0.00 (0.00, 0.57)
	48 weeks	3	0.15 (0.03, 0.43)
Lymphoma	16 weeks	0	0.00 (0.00, 0.57)
	48 weeks	1	0.05 (0.00, 0.30)
NMSC	16 weeks	3	0.32 (0.06, 0.95)
	48 weeks	6	0.29 (0.10, 0.64)
Breast Cancer (females only; N=874)	16 weeks	0	0.00 (0.00, 1.49)
	48 weeks	1	0.04 (0.00, 2.79)
Prostate Cancer (males only; N=1.379)	16 weeks	0	0.00 (0.00, 0.93)
	48 weeks	1	0.05 (0.00, 0.45)

Table 102 "Trial-like" Sub-Cohort (Cohort B) -Cardiovascular Events

	Time	All bDMARD initiators (N=2,253)	
		n	Weighted Incidence Rate (95% CI) per 100 PY
MI	16 weeks	1	0.14 (0.00, 0.78)
	48 weeks	4	0.28 (0.07, 0.77)
Stroke	16 weeks	2	0.23 (0.03, 0.86)
	48 weeks	4	0.23 (0.06, 0.58)
MI or Stroke	16 weeks	3	0.37 (0.07, 1.11)
	48 weeks	8	0.51 (0.21, 1.04)
MACE	16 weeks	5	0.60 (0.19, 1.43)
	48 weeks	10	0.61 (0.28, 1.16)

Table 103 "Trial-like" Sub-Cohort (Cohort B) -Thromboembolic Events

	Time	All bDMARD initiators (N=2,253)	
		n	Weighted Incidence Rate (95% CI) per 100 PY
DVT	16 weeks	4	0.80 (0.20, 2.15)
	48 weeks	5	0.39 (0.11, 0.96)
PE	16 weeks	1	0.23 (0.01, 1.29)
	48 weeks	2	0.22 (0.03, 0.80)
VTE	16 weeks	5	1.04 (0.32, 2.49)
	48 weeks	7	0.62 (0.23, 1.33)

Table 104"Trial-like" Sub-Cohort (Cohort B) -ILD

	Time	All bDMARD initiators (N=2,253)	
		n	Weighted Incidence Rate (95% CI) per 100 PY
ILD	16 weeks	0	0.00 (0.00, 0.57)
	48 weeks	2	0.10 (0.01, 0.37)

2.5.1. Discussion on clinical safety

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 for co-primary endpoints in Study A3921133, specifically including the increased incidence of adjudicated **MACE** and adjudicated **malignancies** (excluding NMSC). Interim results of the study have been assessed as part of a signal procedure (EPITT ref. No. 19382). Consequently, sections 4.4, 4.8 and 5.1 of the SmPC and correspondent sections of the Package Leaflet were updated to appropriately reflect the information. The RMP was also updated with additional risk minimisation measures and a DHPC for tofacitinib was also endorsed. The final study report of Study A3921133 is currently under evaluation (EMEA/H/C/004212/II/0044) and the assessment will follow.

Source of data Two studies are included in the present analysis: 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 BID (tofacitinib 5 mg IR BID in the combined trials) and All Tofa (tofacitinib 2 mg, 5 mg, and 10 mg BID in the combined trials).

Exposure 253 patients were exposed to tofacitinib 5 mg BID (the intended dosage for the current application) 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. 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 (≥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 than in placebo (54.6% vs 49.2%).

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%). 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 BID.

Due to the limited number of patients studied in the placebo-controlled trial (185 in tofacitinib 5mg 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 table 6 of current 4.8.

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 BID. Almost all the events listed under the SMQ of "acute renal failure" were coded as "protein urine present". 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 ADR 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 limited exposure.

When the incidence rate for AEs of special interest in patients treated with tofacitinib 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 5mg 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 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).

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 than in placebo (5.28 vs 3.56) but the total number of cases was small (3 vs 2). In All tofacitinib 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 (BID) group: platelets decreased of about 30.000/mm^3 at Week 16, wehereas in the placebo group there was no substantial change compared to baseline (up to 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. 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 No participants had platelet counts meeting the criteria of moderate or severe laboratory abnormalities. Therefore, the data presented by the MAH indicates that the risk of platelet reduction is not specific to AS but it seems to be present in the other indications, too. 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 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.

An increase in **weight** was observed among tofacitinib patients compared to placebo groups at 16 weeks (mean change from baseline: 1.8 vs 0.5 kg). In the All tofacitinib cohort at 48 weeks the increase was 2.2 kg (tofacitinib users). The percentage of participants that switched from the <25 kg/m2 category to ≥25 - <35 kg/m2 category was 14.3% and from the ≥25 - <35 kg/m2 category to ≥35 kg/m2 category was 4.4% for the tofacitinib 5 mg BID treatment group at Week 48. Weight increase is already present in the AEs tabular list at the 4.8 of the SmPC.

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 5mg 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 section 4.4. No new concerns are raised due to discontinuation after infection.

Post-marketing experience

US Corrona RA Registry Study A3921205 report has not been provided in the submitted dossier. However, the results of this study are assessed separately by PRAC (EMEA/H/C/004214/II/0023). Indirect comparison between the ARTIS register safety results and the All Tofa AS cohort shows a higher incidence rate for HZ (0 vs 2.8, respectively) in treatment with tofacitinib. The weighted incidence rate for HZ is also higher in All Tofa AS cohort compared to this rate in the Truven analysis (2.8 and 0.74, respectively). Therefore, it can be concluded that the risk of HZ is higher if patients with AS would be treated with tofacitinib compared to bDMARDs or general AS population. This is reflected in SmPC, 4.4 and 4.8 (see assessor's discussion on "adverse events of special interest").

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. This is reflected adequately in the RMP.

2.5.2. Conclusions on clinical safety

In conclusion, patient's exposure in the sought indication is limited. However, from the data available do not emerge new important signals of safety, and tofacitinib is already used in similar conditions (RA and PsA). The MAH considers that the safety profile of tofacitinib in the intended population can be extrapolated from the long-term safety data available for the RA and PsA population and does not plan to conduct any other clinical trial to gather these data from the AS population. This is acceptable.

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 17.1 with this application. The (main) proposed RMP changes include information for the new therapeutic indication ankylosing spondylitis (AS). This includes information regarding:

- The epidemiology of AS (Part II, Module SI)
- AS clinical trial exposure and description of AS clinical dataset (Part II, Module SIII)
- AS inclusion criteria and AS exposure of special populations from the AS development programme (Part II, Module SIV)
- A summary of the AS clinical datasets presented for the safety concerns, as well as inclusion of AS clinical data for all safety concerns (Part II, Module SVII)

In addition, the MAH included some changes regarding updated post-authorisation exposure (Part II Module SV, and Module SVII), a clarification regarding the age of juvenile rats and juvenile

monkeys under juvenile toxicity (Part II, Module SII), and explanatory notes regarding studies in the pharmacovigilance plan (Part III, Part V, Part VI).

The CHMP endorsed the Risk Management Plan version 17.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Venous thromboembolic events (DVT/PE)
	Serious and other important infections
	HZ reactivation
	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	Malignancy
	Cardiovascular risk
	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
	Off-label use including in children with JIA or IBD[a]
	Higher incidence and severity of AEs in the elderly

Summary of safety concerns	
Missing information[b]	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 elevated transaminases
	Use in patients with malignancy

[a]In the previously submitted RMP version 12.2 for pcJIA, this safety concern was proposed to be removed as an important potential risk.
[b]In the previously submitted RMP version 12.2 for pcJIA, "Long-term safety in pcJIA patients" was added as a missing information.
AE = adverse event; CYP = cytochrome P450; DILI = drug-induced liver injury; DVT = deep vein thrombosis; GI = gastrointestinal; Hgb = haemoglobin; HZ = herpes zoster; IBD = inflammatory bowel disease; ILD = interstitial lung disease; JIA = juvenile idiopathic arthritis; MTX = methotrexate; NMSC = non-melanoma skin cancer; pcJIA = polyarticular course juvenile idiopathic arthritis; PE = pulmonary embolism; PML = progressive multifocal leukoencephalopathy; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RMP = risk management plan

Pharmacovigilance plan

Table Part III.3.1: 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				
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 2 safety concerns that have a long latency period (ie, adjudicated MACE and adjudicated malignancies excluding NMSC of tofacitinib in patients with RA	- adjudicated MACEs (suspected PE cases are being adjudicated as part of the secondary endpoint of CV events other than adjudicated MACE - adjudicated malignancies excluding NMSC - adjudicated opportunistic OI events including TB - adjudicated hepatic events - all-cause mortality (adjudicated)	Study start Study finish Final report	14/03/2014 05/10/2020 31/10/2021
Biospecimen Testing Study (Study Number Pending) On-going	To explore potential biomarkers from the A3921133 study to a) assess the biological basis for the observed excess risk of VTE in subjects receiving tofacitinib (10 mg BID) and/or b) to identify patients at higher risk for PE or VTE events.	- venous thromboembolism	Study start Study finish Final report	30/09/2019 31/03/2020 30/09/2020 (please note this study has completed and included in the previous EU RMP version 14.1, which is currently under PRAC review)
Prescribers' survey A3921334 (RA, PsA, UC) Planned	An EU-based survey for prescribers of tofacitinib for RA, PsA, and UC. (aRMM effectiveness assessment)	- venous thromboembolism (DVT/PE) - serious and other important infections - HZ reactivation - malignancies - NMSC	Study start Study finish Final report	31/01/2021 31/07/2021 30/06/2022

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
		- 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 populations with severe hepatic impairment		
Drug utilisation study A3921321 Planned	An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment)	- the extent to which patient screening and laboratory monitoring recommendations and recommendations regarding limitations of use, including off label use of 10 mg BID among RA and PsA patients, minimisation of use of 10 mg BID maintenance therapy among UC patients at high risk for venous thromboembolism and among UC patients without high risk for venous thromboembolism who have not been treated with alternative treatment options (and concurrent conditions, such as pregnancy, hepatic impairment, or concomitant use of bDMARDs) are followed - off label use	Study start Study finish Final report	31/12/2019 30/06/2022 30/06/2023

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
A US-based drug utilisation study using either electronic health care records (EHR) or administrative claims database (A3921348) Planned	To assess prescription trends over time, as well as evaluate compliance with RMMs	- Extent to which patient screening and laboratory monitoring recommendations and recommendations regarding limitations of use, including avoidance of 10 mg maintenance therapy among UC patients at high risk for venous thromboembolism (and concurrent conditions, such as pregnancy, hepatic impairment, or concomitant use of biologics) are followed - off-label use.	Study start Study finish Final report	30/06/2020 30/06/2025 30/06/2026 (please note this study has merged into study A3921347 and addressed in EU RMP version 16.1, currently under PRAC review)
Prospective, non-interventional active surveillance study embedded within the ARTIS registry (A3921314) On-going	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting	- venous thromboembolism (DVT/PE) - serious infections - HZ reactivation - NMSC - malignancy - CV risk[a] - 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	Study start Study finish Final report	30/09/2018 30/09/2025 30/09/2026
Prospective, non-interventional active surveillance study embedded within the BSRBR registry (A3921312) On-going	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting	- venous thromboembolism (DVT/PE) - serious infections - HZ reactivation - NMSC - malignancy - CV risk[a] - 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	Study start Study finish Final report	30/09/2018 30/09/2025 30/09/2026
Prospective, non-interventional active surveillance study embedded within the RABBIT registry (A3921317) On-going	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting	- venous thromboembolism (DVT/PE) - serious infections - HZ reactivation - NMSC - malignancy - CV risk[a] - GI perforation - PML - all-cause mortality	Study start Study finish Final report	30/09/2018 30/09/2025 30/09/2026

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
		- 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		
Prospective, non-interventional active surveillance study embedded within the BIOBADASER registry (A3921316) On-going	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting	- venous thromboembolism (DVT/PE) - serious infections - HZ reactivation - NMSC - malignancy - CV risk[a] - 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	Study start Study finish Final report	30/09/2018 30/09/2025 30/09/2026
Prospective, non-interventional active surveillance pregnancy study embedded within the US OTIS registry (A3921203) On-going	To estimate the risk of birth defects and other adverse pregnancy outcomes occurring in offspring of patients exposed to tofacitinib during pregnancy, and to detect any increase in the prevalence or pattern of these outcomes among exposed pregnancies as compared with internally generated disease-matched and non-diseased control group.	- birth defects and other adverse pregnancy outcomes	Study start Study finish Final report	RA: 30/04/2014 PsA: 30/06/2019 UC: 30/06/2019 AS: TBD RA: 30/09/2023 PsA: 30/09/2023 UC: 30/09/2023 AS: TBD RA: 30/09/2024 PsA: 30/09/2024 UC: 30/09/2024 AS: TBD

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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.	- venous thromboembolism (DVT/PE) - serious infections - HZ reactivation - malignancies - NMSC - MACE - PML - GI perforation - all-cause mortality - higher incidence and severity of AEs in elderly patients (≥65 years) including infections- safety outcomes with 10 mg BID dose during maintenance (in a separate sub-analysis)	UC Study start Study finish Final report	 30/06/2019 30/06/2027 31/12/2027
Prospective, non-interventional active surveillance study (SWIBREG) A3921344 Planned	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting.	- venous thromboembolism (DVT/PE) - serious infections - HZ reactivation - NMSC - malignancy - MACE - 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 (in a separate sub-analysis)	Study start Study finish Final report	30/06/2020 31/10/2025 31/10/2026
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.	- venous thromboembolism (DVT/PE) - serious infections - HZ reactivation - NMSC - malignancy - MACE - GI perforation - PML - all-cause mortality - higher incidence and severity of adverse events in elderly patients (≥65 years) including infections	Study start Study finish Final report	30/06/2020 31/10/2025 30/09/2026

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Prospective, non-interventional active surveillance study examining tofacitinib safety in UC A3921347 On-going	To quantify the incidence of key safety events of interest in moderate-to-severe UC patients treated with tofacitinib and other systemic therapies in the clinical practice (real world) setting	- venous thromboembolism (DVT/PE) - mortality[b] - malignancies - opportunistic and serious infections - HZ - major adverse cardiovascular endpoints - GI perforation- safety outcomes with 10 mg BID dose during maintenance (in a separate sub-analysis)	Study start Study finish Final report	30/06/2020 30/06/2025 30/06/2026 (please note study A3921348 has been merged into A3921347 and milestones updated, which are included in EU RMP version 16.1, currently under PRAC review)
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

a. Specifically, MACE
b. Due to limitations related to the claims database, only in-hospital mortality can be assessed
Please note, for Study A3921133, on 19 February 2019, the 10 mg dose was discontinued.
AE = Adverse Event; ARTIS = Anti-rheumatic Therapies In Sweden; BIOBADASER = Registro Español De Acontecimientos Adversos De Terapias Biológicas En Enfermedades Reumáticas; BSRBR = British Society For Rheumatology Biologics Register; CV = cardiovascular; DLP = data lock point; ENEIDA = Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales; EU = European Union; GI = gastrointestinal; MACE = major adverse cardiac event; MTX = methotrexate; NMSC = non-melanoma Skin Cancer; OI = opportunistic infection; OTIS = Organisation Of Teratology Information Specialists; 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; SWIBREG = Swedish National Quality Registry for Inflammatory Bowel Disease, TB = tuberculosis; TBD = to be determined; TNF = tumour necrosis factor; UC = ulcerative colitis; US = United States

Risk minimisation measures

No new routine risk minimisation measures have been proposed by the applicant.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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: •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) •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •A3921348: A US-based drug utilisation study using electronic health care records (aRMM effectiveness assessment): please note A3921348 was merged into A3921347 in the EU RMP version 16.1, which is currently under PRAC review. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: Prospective non-interventional active surveillance study in the US (UC): please note A3921348 was merged into A3921347 in the EU RMP version 16.1, which is currently under PRAC review. •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. •Biospecimen Testing Study (Study Number Pending): please note this study has completed and included in the previous EU RMP version 14.1, which is currently under PRAC review.
Serious and other important infections	Routine risk minimisation measures: 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	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

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	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).	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 (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: Prospective non-interventional active surveillance study in the US (UC): please note A3921348 was merged into A3921347 in the EU RMP version 16.1, which is currently under PRAC review.
HZ reactivation	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 Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •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: Prospective non-interventional active surveillance study in the US (UC): please note A3921348 was merged into A3921347 in the EU RMP version 16.1, which is currently under PRAC review.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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 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 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	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).	•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.
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.
Important Potential Risks		
Malignancy	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: •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.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•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: Prospective non-interventional active surveillance study in the US (UC): please note A3921348 was merged into A3921347 in the EU RMP version 16.1, which is currently under PRAC review.
Cardiovascular risk	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: •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. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: Prospective non-interventional active surveillance study in the US (UC): please note A3921348 was merged into A3921347 in the EU RMP version 16.1, which is currently under PRAC review.
GI perforation	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: •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

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		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: Prospective non-interventional active surveillance study in the US (UC): please note A3921348 was merged into A3921347 in the EU RMP version 16.1, which is currently under PRAC review.
ILD	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: None
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: •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. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.
All-cause mortality	Routine risk minimisation measures: SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•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. •A3921347 (UC): Prospective non-interventional active surveillance study in the US (in-hospital mortality): please note A3921348 was merged into A3921347 in the EU RMP version 16.1, which is currently under PRAC review.
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 MTX in RA or PsA patients	<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 Prescriber Brochure).	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •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)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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
Off-label use including children with JIA or IBD	Routine risk minimisation measures: SmPC Section 4.1 Therapeutic indication SmPC Section 4.2 Posology and method of administration Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Protocol A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment)
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 SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •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 t 5 years.
Missing Information		

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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) •A3921321: An EU-based drug utilisation study using electronic health care records (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)
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	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None proposed	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: 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

AE = adverse event; ARTIS = Anti-rheumatic Therapies In Sweden; BIOBADASER = Registro Español De Acontecimientos Adversos De Terapias Biológicas En Enfermedades Reumáticas; BSRBR = British Society For Rheumatology Biologics Register; DILI = drug-induced liver injury; DVT = deep vein thrombosis; EU = European Union; GI = gastrointestinal; Hgb = haemoglobin; HZ = herpes zoster; IBD = inflammatory bowel disease; ILD = interstitial lung disease; JIA = juvenile idiopathic arthritis; MACE = major adverse cardiac event; MTX = methotrexate; NMSC = non-melanoma skin cancer; OI = opportunistic infection; PASS = post-authorisation safety study; PE = pulmonary embolism; PML = progressive multifocal leukoencephalopathy; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RABBIT = Rheumatoide Arthritis–Beobachtung Der Biologika-Therapie; RMM = risk minimisation measure; SmPC = Summary of Product Characteristics; SWIBREG = Swedish National Quality Registry for Inflammatory Bowel Disease, TNF = tumour necrosis factor; UC = ulcerative colitis

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xeljanz 5mg/10 mg/ 11 mg PR. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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 (eg, IL-23) or indirectly (eg, 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 a new indication for Tofacitinib for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy. The recommended dose of tofacitinib is 5 mg administered twice daily.

In support of the sought indication, the MAH is providing:

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 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).
The study included subjects with active AS defined as: Modified New York Criteria for Ankylosing Spondylitis (1984), BASDAI score of $\geqslant$4 and back pain score (BASDAI Question 2) of $\geqslant$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. 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%.
Randomization was stratified by prior treatment history: (1) bDMARD-naive and (2) TNFi-IR or bDMARD use (non-IR).
Overall inclusion and exclusion criteria were adequate for selecting an active AS population and also for taking into account the safety profile of the drug. Moreover, criteria for defining previous or concomitant allowed, or prohibited therapies and stable doses are considered acceptable.

3.2. Favourable effects

Tofacitinib dose selected for the phase 3 pivotal A3921120 study comes from the phase 2 study.

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 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.

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.

According to 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: ASAS40 responses for tofacitinib 5 mg BID across Studies A3921119 and A3921120, were similar compared with adalimumab, certolizumab, etanercept, golimumab, infliximab, ixekizumab and secukinumab.

3.3. Uncertainties and limitations about favourable effects

Dose selection comes from the phase 2 study A3921119 (2 mg, 5 mg and 10 mg doses) in order to derive the optimal dose for the phase 3 study A3921120. The relationship between tofacitinib exposure (Cavg) and clinical response was not adequately captured by the E-R model. The MAH clarified that the ASAS20 and ASAS40 response rates shown in the VPC plots as "*observed*" are observed proportions for each stratified group.

Although the design of the phase 3 pivotal Study A3921120 could be acceptable, the lack of an active comparator arm hampers assessing the relative B/R balance. As an alternative, the Applicant has performed a meta-analysis of approved treatments and included the results of the tofacitinib trials (dose-finding and pivotal study) as supportive data. Accordingly, the treatment effects of tofacitinib 5 mg BID versus placebo were within the range of EMA approved treatments, which indirectly supports the clinical relevance of treatment effects. Moreover, no information was provided on evaluation of dose reduction/stop and/or increased dose interval for subjects obtaining resolution of inflammation to avoid unnecessary toxicity.

The choice of the primary endpoint (ASAS20 response at week 16) is not in line with the current EMA Guideline indicating that ASAS40 response is preferred primary endpoint since is more stringent. However, the clinical development program plans for the treatment of AS generally reflects the CHMP Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1).

Efficacy of tofacitinib 5 mg BID was maintained up to week 48 in the patients on tofacitinib, while patients switching from placebo to tofacitinib at week 16 'catched up' and approached the effect of the group already on tofacitinib from baseline. It is remarkable that the group originally on placebo did not completely reach the effect of the group remaining on tofacitinib in ASAS response and secondary outcomes. However, as this is a randomised trial, as baseline variables were on average similar between the two treatment groups, and attrition was low, it is not expected that this observation can be meaningfully explained (not pursued). It also is possible that the open-label phase may have contributed to the observation of an increase in efficacy from week 16 to week 48, which however cannot be fully evaluated due to a lack of blinding and lack of comparator (not pursued).
In the subgroup of AS patients with a body weight >100 kg, the estimate of the treatment effect in ASAS40 was -13% in favour of placebo. This was not seen in the subgroup analysis of body weight and ASAS20, and bodyweight does not appear to influence exposure up to 140 kg (SmPC section 5.2). According to the MAH the trend of ASAS40 at Week 16 in the Study A3921120 participants with a body weight >100 kg could be explained by the small sample size. 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. Therefore, all together these observations do not allow to draw firm conclusion on a lower efficacy in patients with >100 kg body weight.
Although consistent results were shown by subgroup analyses for both ASAS20 and ASAS40 response rates, these were higher in the subgroups of subjects identified by very high disease activity or in those with higher baseline hsCRP (>2.87 mg/L) suggesting that tofacitinib could perform better in this target population however numbers are limited.
A minority of patients had extra-articular manifestations at baseline to perform a subgroup analysis. In view of the potential differences in response in this subgroup of subject's uncertainty remains on it. In order to get reassurance on the efficacy of tofacitinib in subjects with peripheral arthritis a separate analysis for ASAS20, ASAS40, delta ASDAS(CRP) has been required for this subgroup.

Among secondary endpoint, no endpoint that could monitor structural changes, has been included thus no data could be derived on this disease domain.
Measures of low disease activity or partial remission were also supportive of a better effect of tofacitinib but were assessed only as part of secondary not controlled endpoints and showed very/limited effect size when inactive disease/partial remission was the goal therefore these could not be regarded as conclusive. Some questionnaire used to evaluate Quality of Life endpoints is not disease specific and broadly used thus results could be seen only as indicative.

3.4. Unfavourable effects

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 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 doses' 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 mmmg 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.

ALT and bilirubin increased in the tofacitinib arm but were steady in the placebo arm.

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

The limited exposure 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.

Inclusion criteria for AS trials only allowed inclusion of patients with a platelet count ≥100,000 platelets/mm3. 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/mm3 after 48 weeks in the All Tofa cohort. However, only one patient had an

AE of thromocitopenya (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 /mm3.

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. This is considered acceptable by the CHMP.

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 1. Effects Table for tofacitinib 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 response at Week 16	%	56.39%	29.41%	Difference in response 27.08 (p<0.0001)	Study A3921120
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	Change from baseline in SF-36v2 PCS		6.69	3.14	p<0.0001 for comparison vs placebo	Study A3921120

Effect	Short description	Unit	Tofacitinib 5mg BID	Placebo	Uncertainties / Strength of evidence	References
at week 16						
BASMIlin 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

A clinically relevant effect as measured by ASAS20/ASA40 has been demonstrated for tofacitinib 5 mg BD in the target population of adult patients with 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.

Infections were the only reported AE of Special Interest in the AS studies; 7 cases of HZ (all non-serious) were reported. Platelet decrease has been observed during the AS trials (mean change from baseline until 48 weeks of −30,000). There are concerns regarding the risk of bleeding for patients with low platelet counts (<100,000/mm3), since a reduction in platelets is observed with tofacitinib also in the other indications.

In general, from the available safety data no new important safety concerns emerge, the safety profile seems overlapping with what already known from other approved indications. However, patient's exposure is limited, and the sought indication is a chronic disease, requiring long-term therapy. 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. This is considered acceptable by the CHMP.

3.7.2. Balance of benefits and risks

The benefits of using tofacitinib for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy are considered to outweigh the risks.

3.8. Conclusions

The overall B/R of Xeljanz is positive in the following indication:

Ankylosing spondylitis

Tofacitinib is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy for XELJANZ film-coated tablets; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 17.1 of the RMP has been accepted.

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

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being

received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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-4214-II-35

Attachments

1. SmPC, Package Leaflet (changes highlighted) as a relevant example with changes highlighted as adopted by the CHMP on 14 October 2021.