26 April 2018
EMA/CHMP/197115/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xeljanz

International non-proprietary name: tofacitinib

Procedure No. EMEA/H/C/004214/II/0006

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

ACR	American College of Rheumatology
ACR20	American College of Rheumatology criteria ≥20% improvement
ACR50	American College of Rheumatology criteria ≥50% improvement
ACR70	American College of Rheumatology criteria ≥70% improvement
ADA	Adalimumab
ADRs	Adverse drug reactions
AE	Adverse event
AEDC	Adverse event leading to discontinuation
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
ARTIS	Antirheumatic Therapies In Sweden
AS	Ankylosing Spondylitis
AUC	Steady-state area under the plasma concentration curve
AUC24	Area under the concentration-time curve over 24 hours
BCC	Basal cell carcinoma
bDMARD	Biologic disease-modifying anti-rheumatic drug
BA	Bioavailability
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BE	Bioequivalence
BID	Twice daily
BMI	Body mass index
BSA	Body surface area
CASPAR	ClASsification criteria for Psoriatic ARthritis
Cavg	Steady-state average concentration
Cmax	Maximum plasma concentration
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CK	Creatine kinase
COPD	Chronic obstructive pulmonary disease
CORRONA	Consortium of Rheumatology Researchers of North America
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
CSR	Clinical study report
CV	Cardiovascular
%CV	% coefficient of variation

CYP	Cytochrome P450
Δ	Change from Baseline
DMARD	Disease-modifying anti-rheumatic drug
DSS	Dactylitis Severity Score
Emax	Maximum estimated efficacy
EC51	Exposure at which 51% of maximum drug effect (Emax) is observed
EC68	Exposure at which 68% of maximum drug effect (Emax) is observed
EMA	European Medicines Agency
E-R	Exposure-response
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACS	fluorescence-activated cell sorting
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDA	DDDP Food and Drug Administration Division of Dermatology and Dental Products
GCP	Guidelines for Good Clinical Practice
GI	Gastrointestinal
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire – Disability Index
Hgb	Haemoglobin
HDL	High density lipoprotein
HRQL	Health-related quality of life
HZ	Herpes zoster
ICH	International Committee on Harmonisation
IFN	Interferon
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
IL	Interleukins
ILD	Interstitial Lung Disease
IR	Inadequate Responder
JAK	Janus kinase
LDL	Low density lipoprotein
LEF	Leflunomide
LEI	Leeds Enthesitis Index
LS	Least squares
LTE	Long-term extension
JSN	Joint space narrowing

MA	Marketing authorisation
MAA	Marketing Authorisation Application
MACE	Major Adverse Cardiovascular Events
MAH	Marketing Authorisation Holder
MCID	Minimal clinically important difference
MCS	Mental component summary
MDA	Minimum Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MI-JTR	Multiple imputation jump-to-reference
mL	Millilitre
MNAR	Missing not at random
MMRM	Mixed model for repeated measures
MOA	Mechanism of action
MR=NR	Missing Response = Non-Response
MRI	Magnetic resonance imaging
mTSS	van der Heijde-modified Total Sharp Score
MTX	Methotrexate
NA	Not applicable
Ng	Nanogram
NMSC	Non-melanoma skin cancer
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York heart Association
OI	Opportunistic infection
OMERACT	Outcome Measures in Rheumatology
P123LTE	Phase 123 Long Term Extension
P3	Phase 3
PAAP	Patient’ s Assessment of Arthritis Pain
PASDAS	Psoriasis Area and Severity Disease Activity Score
PASI	Psoriasis Area and Severity Index
PASI75	PASI 75% improvement from Baseline
PBRER	Periodic Benefit-Risk Evaluation Report format
PCS	Physical component summary
PDE4	Phosphodiesterase 4
PF	Physical Functioning domain
PGA	Physician’s Global Assessment
PK	Pharmacokinetic
PsA	Psoriatic arthritis
PsAQOL	Psoriatic Arthritis Quality of Life

PGA-PsO	Physician's Global Assessment of Psoriasis
PRO	Patient-reported outcome
PsO	Psoriasis
PT	Preferred Term
PTE	Probability of achieving a clinically meaningful target effect
PYs	Patient-years
q2w	Every 2 weeks
QD	Once daily
RA	Rheumatoid arthritis
RMP	Risk management plan
RCT	randomised controlled trial
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAWP	Scientific Advice Working Party
SC	Subcutaneous
SCC	Squamous cell carcinoma
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SE	Standard error
SF-36v2	Short-Form-36 Health Survey version 2
SI	Serious infection
SmPC	Summary of Product Characteristics
sNDA	Supplemental New Drug Application
SOC	System Organ Class
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine
TB	Tuberculosis
TEAE	Treatment emergent adverse event
Th17	T-helper phenotype
THIN	The Health Improvement Network
TNF-α	Tumour necrosis factor-alpha
TNFi	Tumour necrosis factor inhibitor
TNF-IR	Inadequate response to TNFi
Tofa	Tofacitinib
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drug
TyK2	Tyrosine kinase 2
UK	United Kingdom

US	United States
VAS	Visual Analog Scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 23 August 2017 an application for a variation.

The following variation was requested:

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

Extension of Indication to include treatment of adult patients with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy, based on data from studies A3921091, A3921092, A3921125. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the Annex II with minor editorial changes. The RMP version 3.0 has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0054/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0054/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant 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: Robert James Hemmings Co-Rapporteur: Daniela Melchiorri

Timetable	Actual dates
Submission date	23 August 2017
Start of procedure:	16 September 2017
CHMP Rapporteur Assessment Report	10 November 2017
CHMP Co-Rapporteur Assessment Report	10 November 2017
PRAC Rapporteur Assessment Report	15 November 2017
PRAC members comments	22 November 2017
PRAC Outcome	30 November 2017
CHMP members comments	
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 December 2017
Request for supplementary information (RSI)	14 December 2017
MAH submission	14 February 2018
Restart of procedure:	26 February 2018
(Co)Rapporteur's joint preliminary assessment report on the MAH's responses circulated on:	26 March 2018
PRAC Rapporteur preliminary assessment report on the MAH's responses	28 March 2018
PRAC members comments	4 April 2018
Updated PRAC Rapporteur Assessment Report	n/a
PRAC RMP advice and assessment overview adopted by PRAC	12 April 2018
CHMP members comments	16 April 2018
Updated CHMP Rapporteur Assessment Report	23 April 2018
CHMP Opinion	26 April 2018

2. Scientific discussion

2.1. Introduction

This procedure concerns an extension of indication to include treatment of adult patients with active psoriatic arthritis for Xeljanz (tofacitinib).

Tofacitinib is a selective reversible inhibitor of the Janus kinase (JAK) family. Tofacitinib inhibits JAK1, JAK2, JAK3 and to a lesser extent tyrosine kinase 2 (TyK2). In a cellular setting where JAKs signal in combinations, tofacitinib preferentially inhibits cytokines which use JAK1 and/or JAK3 to signal. The cytokines inhibited at clinical doses are known to have a role in multiple inflammatory diseases such as Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), ulcerative colitis (UC), ankylosing spondylitis, and

psoriasis (PsO). Many of the cytokines that are associated specifically with the pathogenesis of PsA (e.g. IL-2, IFN-γ, IL-12, IL-23) are modulated directly by JAK inhibition with tofacitinib.

PsA is a chronic progressive inflammatory arthritis associated with psoriasis, which may result in permanent joint damage and disability[1,2]. Peak onset is between the ages of 30 and 60, and it affects men and women equally[1]. Prevalence estimates in Europe range from 0.05% to 0.21%[2].

Except for the distal interphalangeal joints, there are no predictable joints for involvement in PsA and the signs of inflammation are often non-symmetrical. In addition to peripheral joint arthritis and irreversible progressive articular damage, patients may have concurrent psoriasis, enthesitis, dactylitis, and spondylitis. The inflammation of PsA is characterised by infiltration of dendritic cells, B cells, T cells, and macrophages into the peripheral or axial joints, entheses, and tenosynovial sheaths. This infiltration is driven by inflammatory cytokines including IL-1β, IL-2, IL-10, interferon gamma (IFN-γ), and tumour necrosis factor-alpha (TNF-α)[3,4].

For most patients, skin manifestations predate the arthritis. Prognosis of PsA may range widely from a mild monoarthritic form with good prognosis to an erosive and destructive polyarticular form, comparable with that in patients with RA. Axial forms may also range from mild to severe and disabling. Flares and remissions usually characterise the course of PsA.

Mild PsA is generally treated with NSAIDs. When only few joints are involved, local injections of steroids might be effective. For more extensive or severe PsA, disease-modifying anti-rheumatic drugs (DMARDs) are recommended. Conventional synthetic DMARDs (csCMARDs) such as methotrexate, sulfasalazine and leflunomide, are standard therapies. For patients in whom csDMARDs are not effective, biological DMARDs (bDMARDs) or targeted DMARDs are recommended by guidelines such as EULAR[5]. These include tumour necrosis factor inhibitors (TNFi) (e.g. etanercept, infliximab, adalimumab, golimumab, certolizumab pegol), bDMARDs with novel mechanisms of action such as ustekinumab (IL-12/23 antagonist) and secukinumab (IL-17A antagonist), and the PDE4 inhibitor apremilast.

Evidence of medical need for improvement of today's PsA treatment has been published in a study of real-life data from 141 PsA outpatients fulfilling the CASPAR criteria and examined between January 2013 and May 2014. Musculoskeletal inflammatory involvement was more prominent than psoriatic skin involvement in these patients. The study showed that although the treatment options in PsA have been revolutionized in the last decade with the introduction of TNFi, there are still a substantial proportion of patients who do not achieve satisfactory results. There is a need for new treatments with new MOAs in PsA patients who are not responding to currently available treatment options for PsA[6].

The claimed indication was:

XELJANZ in combination with a conventional synthetic disease-modifying antirheumatic drug (csDMARD) is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy (see section 5.1).

[1] Gladman DD, Antoni C, Mease P, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis 2005;64 (Suppl II):ii14-7.
[2] Ogdie A, Weiss P. The epidemiology of psoriatic arthritis. Rheum Dis Clin N Am 2015 (41):545- 68
[3] FitzGerald O, Winchester R. Psoriatic arthritis: from pathogenesis to therapy. Arthritis Res Ther 2009;11(1):214.
[4] Shamji MF, Bafaquh M, Tsai ET. The pathogenesis of ankylosing spondylitis. Neurosurg Focus 2008;24(1):E3
[5] European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Gossec L.,et al. Ann Rhem Dis 2016 75:499-510
[6] Michelsen B, Diamantopoulos AP, Kilander Høiberg H, et al. Need for improvement in current treatment of psoriatic arthritis: Study of an Outpatient Clinic Population. J Rheumatol 2017;44(4);431-6.

The approved indication is:

XELJANZ in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy (see section 5.1).

The proposed dose is 5 mg twice daily, the same as for rheumatoid arthritis (RA).

2.2. Non-clinical aspects

2.2.1. Introduction

No new non-clinical studies have been performed in the context of this variation.

The nonclinical assessment for psoriatic arthritis (PsA) has been supported by the nonclinical overview for rheumatoid arthritis (RA), based on similarity of pharmacokinetic (PK) parameters between RA and PsA patients as measured by Cmax and AUC24. The exposure margins to assess nonclinical safety in PsA are assumed to be the same as those in RA patients using the geometric mean Cmax and AUC24 estimates in RA patients.
Also, literature references have been provided in order to complement the information, already submitted for Rheumatoid Arthritis at the time of the initial MA, on non-clinical pharmacology.

2.2.2. Pharmacology

Although there are limited animal models of PsA, tofacitinib is efficacious in models of RA and psoriasis which have been used to characterize agents such as antibodies to TNF in RA and IL-17 and IL-23 in psoriasis respectively, which are also efficacious in various domains of PsA. Tofacitinib has been shown to be efficacious in rodent models of arthritis as assessed by clinical and histological measures of disease progression in the mouse collagen induced arthritis (CIA) and rat adjuvant induced arthritis (AIA). At efficacious doses, significant reduction in inflammatory proteins and gene sets were also observed.

Tofacitinib is efficacious in mouse models of skin inflammation induced by imiquimod application and IL-23 injection as assessed by clinical, histological and gene expression measures in the mouse ear. Tofacitinib is also efficacious in a CD4+CD45RBhighCD25- T-cell transfer model that mimics aspects of psoriasis pathology and in a xenograft model where human psoriatic skin from psoriasis patients was transplanted onto SCID mice.

In a publication resulting from an IIR, selective deletion of A20 in myeloid cells of mice (A20myelko mice) results in spontaneous development of inflammation of the synovioentheseal complex (region of the Achilles tendon and proximal tarsal region). STAT1 expression is elevated in the A20myelko mouse macrophages resulting in enhanced production of STAT1-dependent gene expression in response to IFNα and IL-6. Treatment of A20myelko mice with tofacitinib (50 mg/kg BID) attenuated inflammation in the synovio-entheseal complex and reduced STAT1 gene expression (De Wilde et al, 2016). PsA is characterized by altered bone remodeling with both bone formation and erosion (Barnas & Ritchlin, 2015). In unpublished work from an IIR, tofacitinib did not have an effect on mesenchymal stem cell proliferation or osteogenic or chondrogenic differentiation (report on file from Prof. McGonagle, Leeds Institute of Rheumatic and Musculoskeletal Medicine).

2.2.3. Pharmacokinetics

No new data has been submitted. This was considered acceptable by CHMP.

2.2.4. Toxicology

No new data has been submitted. This was considered acceptable by CHMP.

2.2.5. Ecotoxicity / environmental risk assessment

The MAH has submitted an ERA (dated May 2017) as part of the application for a MA for Xeljanz for treatment of adult patients with active psoriatic arthritis (PsA). The recommended dose of tofacitinib is 5 mg administered twice daily in combination with a conventional synthetic disease-modifying anti-rheumatic drug (csDMARD).

For the purposes of this assessment, tofacitinib is considered the primary entity released into the environment following patient use and is therefore considered a valid model for assessing environmental fate and effects resulting from use. Tofacitinib has a log D value < 4.5 at all environmentally relevant pHs, therefore screening for persistence, bioaccumulation and toxicity (PBT) is not required. However, the PECsw value is greater than the 0.01 µg/L action limit. Based on the PEC value, a Phase II environmental fate and effects analysis for tofacitinib is required.

Environmental Fate Summary

Biodegradation studies conducted in sludge indicate tofacitinib may undergo moderate degradation during the wastewater treatment process via mineralization and primary biodegradation. Based on a sludge sorption coefficient (Kd) of 37, a minimal amount (0.6%) may be removed through sorption to sludge during the wastewater treatment process. Therefore exposure to the terrestrial compartment as a result of sludge application to land is not a concern. Upon release of wastewater effluents into the aquatic environment, tofacitinib residues will reside in the water and sediment compartments. Based on an aqueous dissipation half-life of 6.3 –19 days under aerobic conditions, tofacitinib is expected to quickly dissipate from the water to the sediment and continue to degrade once in the environment (primary degradation half-life total system of 26.3 to 52.8 days). Multiple degradation products, all present at < 10%, were observed in the sediment compartment sampled throughout the study, indicating that tofacitinib is expected to undergo primary degradation under the aerobic conditions present in the water-sediment system; it is not expected to persist. Tofacitinib is not volatile and therefore will not enter the air compartment.

Aquatic Effects Summary

The chronic aquatic effects of tofacitinib were assessed in green algae, fish and daphnia. Based on these data, the fathead minnow was determined to be the most sensitive species tested. Therefore, the PNECsurfacewater will be calculated using the NOEC for this species. The fathead minnow NOEC, based on sub-lethal effects related to observations of crocked tails was more conservative than the NOEC established for population relevant of survival. As per guidance, the chronic NOEC for *Daphnia magna was* used to calculate the PNECgroundwater and the NOEC for sludge was used to calculate the PNECmicro-organisms.

Aquatic Sediment Organism Effects

Based on a PEC/PNECsurfacewater < 1, it may be concluded that tofacitinib is unlikely to represent a risk to the aquatic environment. No further testing is required.

Based on a PEC/PNECgroundwater < 1, it may be concluded that tofacitinib is unlikely to represent a risk to the aquatic environment. No further testing is required.

Based on a PEC/PNEC < 0.1, it may be concluded that tofacitinib is unlikely to represent a risk to wastewater microorganisms. No further testing is required.

Based on a PEC/PNECsediment < 1, it may be concluded that tofacitinib is unlikely to represent a risk to sediment dwelling organisms. No further testing is required.

Results of Phase II Tier A

Following a single oral administration of tofacitinib to healthy humans, 30% of the dose is excreted as unchanged drug in urine and faeces, with 21.2 % excreted as a hydroxylated metabolite. Tofacitinib is considered the primary entity released into the environment following patient use. The presence of tofacitinib in the sewage treatment plant (STP) following excretion will not impact the performance of the microorganisms. Tofacitinib is biodegradable and based on the outcome of the sludge die away study, is expected to undergo degradation in the STP. With a primary biodegradation half-life of 23.8 hours, tofacitinib is expected to be moderately removed during the wastewater treatment process. Based on a sludge sorption coefficient (Kd) of 37, a minimal amount (0.6%) may be removed through sorption to sludge during the wastewater treatment process. Therefore, exposure to the terrestrial compartment, as a result of sludge application to land, is not a concern.

Following wastewater treatment and discharge of effluents, tofacitinib and its residues are expected to reside in the water compartment and subsequently dissipate into the sediment compartment (aqueous dissipation half-life of 6.3 - 19.0 days). Once in the sediment compartment, it will continue to degrade with a primary degradation half-life of 26.3 - 52.8 days. Based on wastewater and water-sediment biodegradation, tofacitinib is unlikely to persist in the environment.

Based on log D values < 4.5 at environmentally relevant pHs (4-9) tofacitinib is unlikely to bioaccumulate. 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 (1.7×10^{-4}), groundwater (2.6×10^{-5}), micro-organisms (5.0×10^{-7}) and sediment dwelling organisms (1.7×10^{-2}), are all significantly below the respective action limits.

Substance (INN/Invented Name): Xeljanz (Tofacitinib)			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log *D* = 0.114 at pH 4 Log *D* = 1.19 at pH 7 Log *D* = 1.18 at pH 9	Screening for PBT not required
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater	0.05	µg/L	> 0.01 threshold Phase II ERA required
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**

Adsorption-Desorption	OECD 106	K_{oc} = 102 (activated sludge) 4266 (clay soil) 977 (sandy soil) 10000 (silty sediment) 4786 (sandy sediment) Kd= 37 (activated sludge) 189 (clay soil) 8.6 (sandy soil) 368 (silty sediment) 18 (sandy sediment)			Sludge, sediment and soil adsorption coefficients
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sludge Die Away- 28day sludge biodegradation	OECD 308, parent OECD 314B	DT50 water 6.3-19.0 days DT50 total system 26.3 and 52.8 days Elimination rate constant Ke 0.024hrs DT50water 28.9 hours Elimination rate constant Ke 0.024 hrs^{-1}			Aerobic transformation in aquatic sediment Sludge Die away
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Green Algae, *Pseudokirchneriella subcapitata*	OECD 201	NOEC	11 11	mg a.i./ L	96 hrs exposure Biomass Growth rate
Daphnids (*Daphnia magna)*	OECD 211	NOEC	4.8	mg a.i./ L	
Fish, Fathead Minnow *(Pimephales promelas)*	OECD 210	NOEC	2	µg/L	
Chiromomus riparius	OECD 218	NOEC	46	mg a.i./ kg	Aquatic sediment organism effects. Organic carbon content 2.2%
Activated Sludge Respiration inhibition		NOEC (EC_{10})	1000	mg a.i./L	Used to calculate PNEC microorganisms

2.2.6. Discussion on non-clinical aspects

The additional non-clinical information submitted as part of this variation does not affect the interpretation and assessment of the nonclinical data previously submitted for the RA MAA.

Concerning the ERA, based on the outcome of the Phase II assessment, tofacitinib will not present an environmental risk following the proposed therapeutic use.

2.2.7. Conclusion on the non-clinical aspects

The non-clinical data is considered by the CHMP to be acceptable to support this variation.

2.3. Clinical aspects

2.3.1. Introduction

The tofacitinib PsA development programme is based on 3 global studies, including 2 completed Phase 3 double-blind, placebo-controlled efficacy and safety studies investigating tofacitinib 5 mg BID and 10 mg BID (Studies A3921125 and A3921091, also referred to as pivotal studies) and one ongoing Phase 3 open-label, long-term extension (LTE) study (Study A3921092).

The clinical pharmacology of tofacitinib has been previously characterised. Cross reference is made to the data submitted at the time of the original MAA submission for Rheumatoid Arthritis. These clinical pharmacology data support the use of tofacitinib in PSA.

No new clinical pharmacology studies have been submitted in this application. However, data from the psoriatic arthritis (PsA) development programme focusing on population pharmacokinetics (PK), exposure-response (E-R) relationships for selected efficacy and safety outcomes, and PK data supporting the recommended dosing for PsA patients as well as dose modifications for special populations, such as PsA patients with renal and hepatic impairment, and drug-drug interactions (DDIs) are presented below.

GCP

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

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

- Tabular overview of clinical studies

Study Number / Study Population	Study Design / Primary Objective / Primary Endpoint / Duration	Treatment Groups	N
Phase 3 Global Studies (Completed)			
A3921091 Subjects with active PsA who had an inadequate response to at least one csDMARD and were TNFi-naïve Tofacitinib added to previous stable background csDMARD in all patients. No monotherapy treatment was allowed.	Randomised, multicentre, global, double-blind, double-dummy, placebo-controlled, active-controlled parallel-group study to evaluate the efficacy and safety of two doses of tofacitinib in adult subjects with active PsA. Primary Objectives: To compare the efficacy of tofacitinib at doses of 5 mg BID and 10 mg BID versus placebo for the treatment of rheumatological signs and symptoms, and function ability	Total Randomisation 2:2:2:1:1 for: Tofacitinib 5 mg BID Tofacitinib 10 mg BID Adalimumab 40 mg SC q2w Placebo to Month 3, then	Total=422 107 104 106

Study Number / Study Population	Study Design / Primary Objective / Primary Endpoint / Duration	Treatment Groups	N
	Primary Endpoints: - ACR20 response rates at Month 3; - ∆HAQ-DI at Month 3. Duration: 12 months	Tofacitinib 5 mg BID Placebo to Month 3, then Tofacitinib 10 mg BID	52 53
A3921125 Patients with active PsA who had an inadequate response to at least one TNFi Tofacitinib added to previous stable background csDMARD in all patients. No monotherapy treatment was allowed.	Randomised, multicentre, global, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of 2 doses of tofacitinib in adult subjects with active PsA. Primary Objectives: To compare the safety and tolerability of tofacitinib at doses of 5 mg BID and 10 mg BID versus placebo for treatment of rheumatological signs and symptoms, and function ability. Primary Endpoints: - ACR20 response rates at Month 3; - ∆HAQ-DI at Month 3. Duration: 6 months	Total Randomised in a 2:2:1:1 ratio for: Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo to Month 3, then Tofacitinib 5 mg BID Placebo to Month 3, then Tofacitinib 10 mg BID	394 131 132 66 65
Phase 3 Long-Term Extension Study (Ongoing)			
A3921092 Subjects with active PsA who have previously participated in randomised PsA pivotal clinical studies (A3921091 or A3921125) with tofacitinib	Long-term, open-label extension study Primary Objective: To evaluate the long-term safety and tolerability of tofacitinib in adult subjects with active PsA. Primary Endpoints: Safety and tolerability of tofacitinib (5 mg BID and 10 mg BID) as measured by a) Incidence and severity of AEs; b) Incidence of clinical abnormalities and change from Baseline (in this and/or prior	Tofacitinib 5 mg BID All LTE study subjects began the study on 5 mg BID of tofacitinib. The tofacitinib dose could be increased to 10 mg BID at later study visits if, based upon investigator's discretion, subjects receiving tofacitinib 5 mg BID would benefit from a higher dose and are not experiencing any tofacitinib-related AEs, including abnormalities in laboratory parameters that	686 enrolled

Study Number / Study Population	Study Design / Primary Objective / Primary Endpoint / Duration	Treatment Groups	N
	study) in clinical laboratory values during treatment. Duration: 3 years per subject	are judged to be related to tofacitinib. Tofacitinib dose could be decreased from 10 mg BID to 5 mg BID for safety reasons at any time during the study.	

2.3.2. Pharmacokinetics

Population Pharmacokinetics in Patients with PsA

The PK of tofacitinib in PsA patients is based upon pooled population PK analysis of 2 Phase 3 studies. The objectives of this analysis were: (a) to characterise the PK of tofacitinib in patients with active PsA, (b) to identify intrinsic factors (covariates) that impact the PK of tofacitinib in PsA patients, and (c) to obtain individual steady-state exposures for subsequent E-R analyses.

Table 1 – Overview of tofacitinib phase 3 studies in patients with PsA included in the population PK analysis

Study Identifier	Design Features	Treatment	Plasma Sampling
A3921091	Phase 3, 12-month, double-blind, parallel group, placebo-controlled, background csDMARD study with active comparator in csDMARD-inadequate responder and TNFi-naïve patients	5 mg BID 10 mg BID Placebo x 3 months → 5 mg BID Placebo x 3 months → 10 mg BID Adalimumab 40 mg Q2W	Pre-dose and 2 hrs post dose at Month 1 Pre-dose, 0.5, 2, and 3 hrs post dose at Month 4 or 6
A3921125	Phase 3, 6-month, double-blind, parallel group, placebo-controlled, background csDMARD study with active comparator in TNFi-inadequate responder patients	5 mg BID 10 mg BID Placebo x 3 months → 5 mg BID Placebo x 3 months → 10 mg BID	Pre-dose a and 2 hrs post dose at Month 1 Pre-dose, 0.5, 2, and 3 hrs post dose at Month 4 or 6

Abbreviations: BID = Twice daily; csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; Hrs = Hours; Q2W = once every 2 weeks; TNFi= Tumour necrosis factor inhibitor.

Data from 2 Phase 3 studies, A3921091, a 12-month study, in patients with active PsA who were conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) inadequate responders (IR) and TNFi-naïve, and A3921125, a second study, of 6-month duration, in patients who were TNFi IR, comprising of 3252 observations from 650 patients, were pooled and analysed using nonlinear mixed-effects modelling approaches. Two (2) tofacitinib doses of 5 mg and 10 mg BID were evaluated in both PsA Phase 3 studies. Both studies required patients to be on a background of stable csDMARDs during the trial. The study population in the population PK dataset consisted of 290 males and 360 females with ages ranging from 18 to 78 years and weights ranging from 38.1 to 159.7 kg. This included 93.9% White, 0.5% Black, 3.1% Asian, and 2.6% patients belonging to other races. Hispanic and non-Hispanic patients represented 10.6% and 89.4% of the study population, respectively.

The dose-normalized plasma concentration versus time after dose plots for the 2 studies suggests that the PK of tofacitinib is linear in psoriatic arthritis patients.

Population PK analysis was conducted using nonlinear mixed-effects modelling method with NONMEM, and Perl-speaks-NONMEM was used as a supporting software. The estimation method used was first-order conditional estimation with interaction (FOCEI). Model building was undertaken in the following steps: a) base structural model development, b) random effects model development, c) full model development, d) assessment of model adequacy and predictive performance.

A full covariate modelling approach was used, emphasising parameter estimation rather than stepwise hypothesis testing. Inferences regarding the clinical relevance of covariate effects were based on parameter estimates from the full model and measures of estimated precision. No model-reduction techniques were applied to the full model. Hence, the full model was considered to be the final model. Covariates evaluated in the population PK analysis included race (White, Black, Asian, Others), sex, ethnicity (Hispanic, non-Hispanic), and continuous covariates including baseline age, baseline body weight, creatinine clearance (CLcr) at baseline, and baseline C-reactive protein (CRP) as potential predictors of oral clearance (CL/F); and baseline age and baseline body weight as potential predictors of volume of distribution (V/F). Body weight and age were incorporated as power functions, normalised to the reference (approximate median) values of 83.3 kg and 50 years, respectively. To characterise the effects of CLcr on tofacitinib CL/F, a power function was incorporated to estimate effects. A disease related covariate, baseline CRP, was added as power function (as was done for body weight and age), normalised to the reference value of 0.49 mg/dL (median value in the dataset).

Base Model

A one compartment model parameterised in terms of CL/F and V/F with first-order absorption (Ka) and absorption lag time was chosen as the base model. Inter-individual variability (IIV) for CL/F and V/F was modelled using exponential variance models with a covariance term. Residual random effects were described with 2 proportional error models for observations collected before or after 5 hours and IIV was introduced into residual error.

The typical estimates of CL/F and V/F from the base model were 23.5 L/h and 113 L with relative standard errors of <2%. The absorption rate was estimated to be 13.7/hr with a relative standard error of 8.46%. IIV estimates (% CV) for CL/F and Ka were 35% and 199%, respectively. The scaling parameter to describe IIV of V/F on IIV of CL was 0.52. Residual variability for observations collected before or after 5 hours were 24% and 60%, respectively, with IIV estimated at 60%. Shrinkage estimates from the base model were 4.24% for IIV of CL/F, 35.0% for IIV of Ka and ~0% for IIV of residual error, respectively.

Full Model

The population PK parameters estimates (95% CI) for a reference (typical) individual (defined as White, Male, 83.3 kg, 50 years, baseline CLcr 120 ml/min, Hispanic, and baseline CRP 0.49 mg/dL) were 20.4 L/h (18.6, 21.8) for CL/F, 110 L (108, 113) for V/F, and 13.8/ h (12.1,16.6) for Ka. The inter-individual variability (% CV) estimates from final model were 32% for CL/F and 198% for Ka. Residual variability (% CV) for observations collected before or after 5 hours was 22.9% and 52.6%, respectively, with an IIV of 66%.

Table 2 – Parameter estimates from the population pharmacokinetic model

Parameter	Full model (Run 92)		Bootstrap*	
	Typical value (RSE %)	IIV (RSE %)	Median (IIV %)	95%CI (95%CI for IIV)
CL/F (L/hr)	20.4 (4.66)	32 (3.65)	20.2 (31.3)	18.6, 21.8 (28.2, 34.8)
V/F (L)	110 (1.20)	--	110	108, 113
Ka (hr^{-1})	13.8 (7.93)	198 (4.15)	14.0 (198)	12.1, 16.6 (180, 222)
Prop Error (TAD≤5hr, %)	22.9 (3.84)	66 (5.50)	22.8 (66.4)	21.0, 24.7 (57.2, 73.1)
Prop Error (TAD>5hr, %)	52.6 (4.72)	66 (5.50)	52.5 (66.4)	48.0, 57.3 (57.2, 73.1)
Lag (hr)	0.32 (0.79)	--	0.32	0.317, 0.328
Scale Parameter	0.46 (8.96)	--	0.47	0.368, 0.549

*: 760 in 1000 runs minimised successfully.
Abbreviations: %RSE = Relative standard error; CL/F = Apparent oral clearance; CI = Confidence interval (95% CI was calculated based on bootstrap method); F = Bioavailable fraction; IIV = Inter-individual variability; TAD=Time after dose; V/F = Apparent volume of distribution.

The covariate parameter estimates are summarised in table 3. Based on the covariate assessment:

- An 80-year-old patient was predicted to have a 9.0% lower CL/F compared to a 50-year-old (median value).
- Females were predicted to have a 5.4 % higher CL/F compared to males.
- Asian patients were predicted to have a 4.7% lower CL/F compared to White patients.
- Non-Hispanics were predicted to have a 12.3% higher CL/F compared to Hispanics.
- A patient with a CLcr of 50 mL/min was estimated to have 24.3 % lower CL/F compared to a patient with a CLcr of 120 mL/min (median value).
- A patient with baseline CRP of 3.0 mg/dL was predicted to have a 3.6% lower CL/F compared to a patient with baseline CRP of 0.49 mg/dL (median value).
- V/F estimates for patients weighing 61 or 109 kg (corresponding to the 10th and 90th percentiles of the weight distribution in the PK dataset) were approximately 19% lower or 20% higher, respectively, relative to a patient weighing 83.3 kg (median value).
- V/F was estimated to be 9.9% lower for an elderly patient, 80 years of age, compared to that of a 50-year-old patient (median).

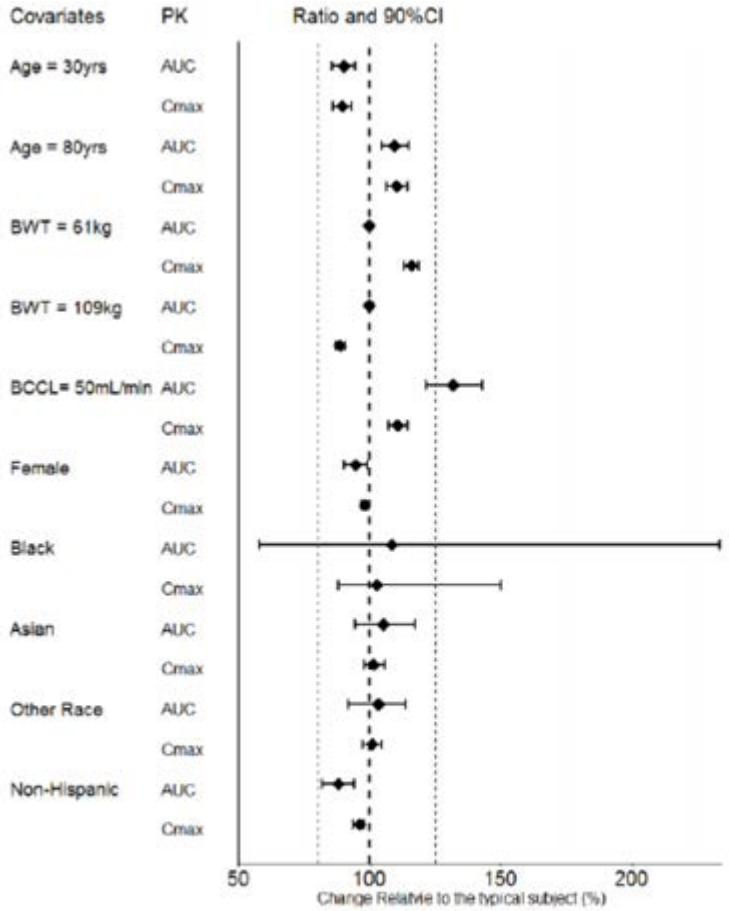
Table 3 – Covariate parameter estimates for the final population pharmacokinetic model

PK Parameter	Covariate	Estimate	%RSE	95% CI
CL/F	Age	-0.200	28.6	-0.313 , -0.084
CL/F	Body weight	0 (FIX)	NA	0 , 0 (FIX)
CL/F	Baseline CLcr	0.318	16.7	0.208 , 0.421
CL/F	Baseline CRP	-0.0203	46.0	-0.0405 , -0.0016
CL/F	Black	0.906	54.9	0.420 , 1.78
CL/F	Asian	0.953	6.07	0.829 , 1.08
CL/F	Other race	0.956	5.91	0.860 , 1.12
CL/F	Non-Hispanic	1.12	4.75	1.04 , 1.24
CL/F	Female	1.05	2.77	0.994 , 1.11
V/F	Age	-0.222	22.6	-0.320 , -0.133
V/F	Body weight	0.678	8.37	0.545 , 0.785

Abbreviations: %RSE = Relative standard error; CL/F = Apparent oral clearance; CI = Confidence interval (95% CI was calculated based on bootstrap method); CLcr = Creatinine clearance; CRP = C-reactive protein; V/F = Apparent volume of distribution.

The effects of the aforementioned intrinsic factors on AUC and Cmax are presented in figure 1. Data are presented as ratios (with 90% CI) for AUC and Cmax for each covariate of interest, relative to a reference patient (white male, Hispanic, body weight 83.3 kg, baseline CRP 0.49 mg/dL, baseline CLcr 120 mL/min, age 50 years). For continuous covariates, the 10th and 90th percentile values from the population PK dataset were used to calculate the expected magnitude of change at the tails of the distribution in this population.

Figure 1 – Impact of covariates on the pharmacokinetics of tofacitinib in PsA patients



Dotted line represents limits of a range from 80% to 125%. A typical (reference) patient is represented as: White Male, Hispanic, Body weight 83.3 kg, BCRP (baseline C-reactive protein) 0.488 mg/dL, BCCL (baseline creatinine clearance) 120 mL/min, Age 50 years. Weights of 61 and 109 kg are the 10th and 90th percentiles of body weight in this analysis dataset. BCCL of 50 mL/min with reference to the typical patient reported above (49 mL/min was the lowest BCCL in the analysis dataset). AUC = Area under the concentration-time curve over a dosing interval; C_{max} = Maximum concentration; CI = Confidence interval; kg = Kilogram; mg = Milligram; PK = Pharmacokinetics.
[1]: No dose adjustment for patients with mild or moderate renal impairment.

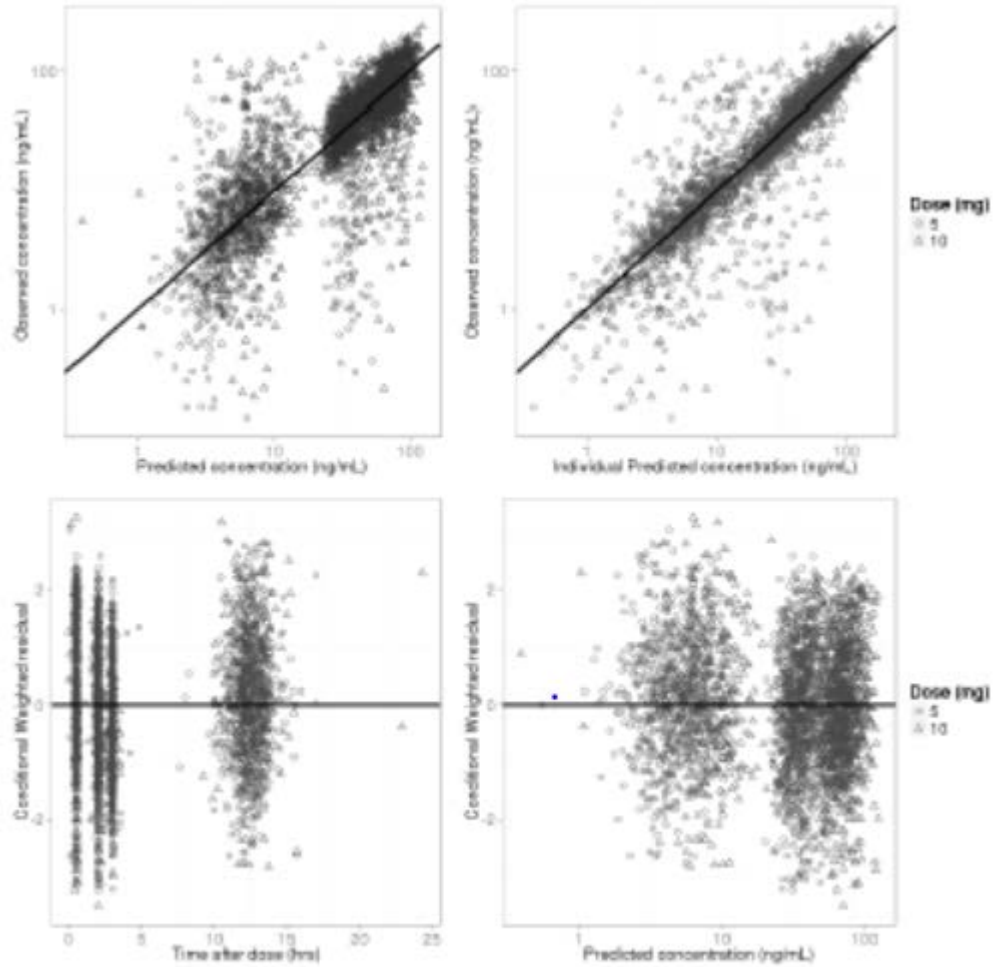
With the exception of baseline CLcr, point estimates of AUC and Cmax ratios ranged between 0.88 and 1.10, and between 0.89 and 1.16, respectively. For a patient with a CLcr of 50 mL/min, AUC was estimated to be 32% higher relative to a reference patient with baseline CLcr of 120 mL/min. However, as no patients with baseline CLcr values (estimated by CG equation) below 49 mL/min were included in the PsA population PK dataset, the need for dose adjustments in renal impairment was assessed using Phase 1 data from Studies A3921004 and A3921006.

The point estimates of the AUC and Cmax ratios and the associated 90% CI, excluded ≥19% difference (except patients of Black race), indicating no major differences in tofacitinib exposure over the range of ages and body weights studied as well as race, ethnicity and gender. Only 3 patients of Black race were in this dataset and therefore the CIs for the AUC and Cmax ratios for this covariate were large. Data from

the population PK evaluation in RA patients which included 19 Black patients, showed ≤ 5% difference (CIs excluded ≥ 25% difference) in AUC and Cmax relative to patients of White race.

Similar results were observed in Black psoriasis (PsO) patients. Taken together, the data suggests that no major differences in tofacitinib exposure are expected in PsA patients of Black race.

Figure 2 – Basic goodness of fit plots for the full model



Solid lines in top panel are the reference for identity. And the lines are y=0.

Figure 3 – Prediction corrected VPS's for the full model stratified by study (protocol)

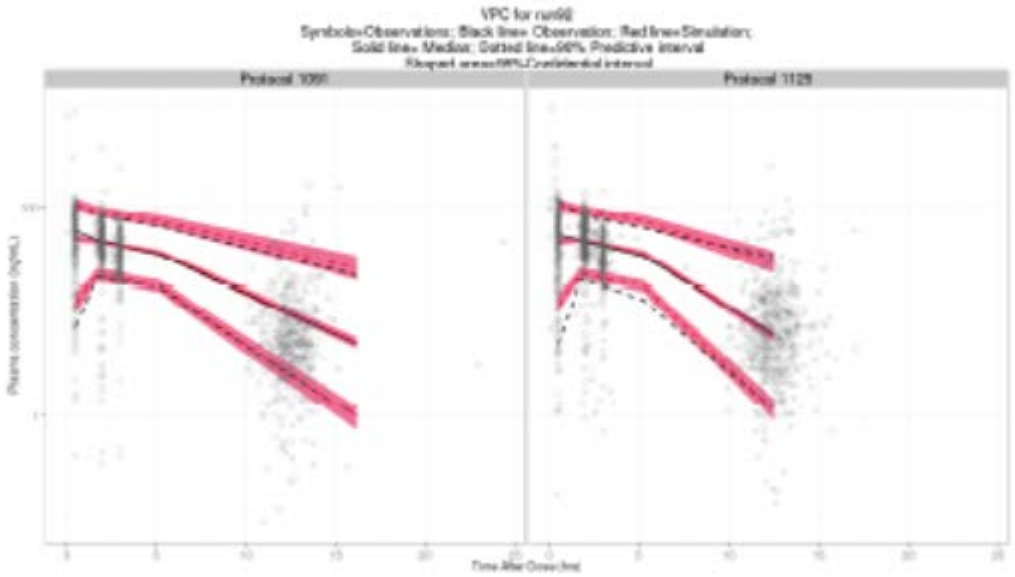
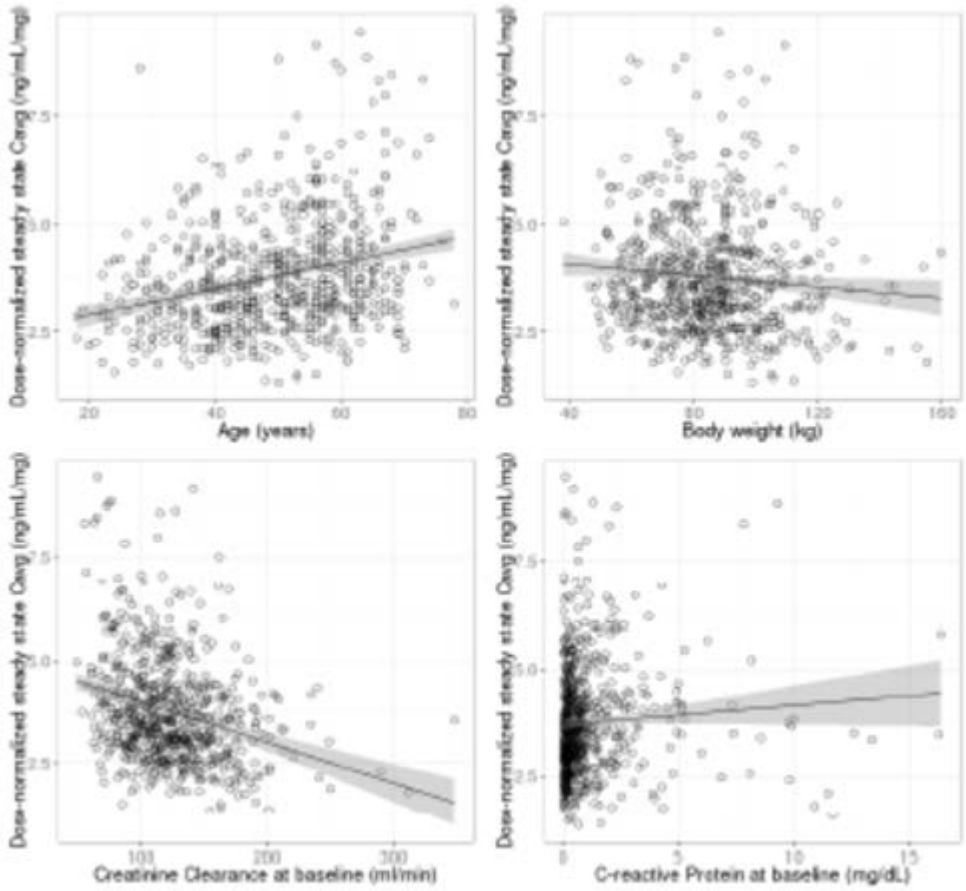


Figure 4 – Relationships between dose-nromalized Cavg at steady state and continuous covariate in psoriatic arhtritis patients



Black circles are C_{avg} vs. different covariates. Black lines are linear regression lines for reference. Shaded areas around black lines are 95% confidence intervals. ePharm artifact ID: RA12223502

Comparison of Systemic Exposures Among PsA, RA and PsO Patients

Population PK analysis results indicated that tofacitinib exposure, as measured by the steady-state AUC24 after 5 mg BID is similar (differences between geometric means within 20%) among PsA (419 ng•hr/mL), RA (507 ng•hr/mL) and PsO (404 ng•hr/mL) patients.

Evaluation of covariates across the PsA, RA and PsO patient populations showed consistent results in that none of these patient populations require dose modification or restrictions with respect to age, body weight, sex, race, or ethnicity.

While the time-dependence of oral clearance was not evaluated in the PsA population (inter-occasion variability could not be evaluated in the model, and also PK data collection in most patients was less than 4 months after start of tofacitinib treatment), these evaluations in the RA and PsO populations showed that tofacitinib clearance was not time-dependent.

Population PK analysis results indicated comparable inter-subject variability (%CV) in AUC across PsA, RA and PsO patients (32%, 27% and 28%, respectively). Across these patient populations, systemic exposures are increased relative to healthy patients (geometric means of steady-state AUC24 in healthy volunteers is 311 ng•hr/mL, which is significantly lower than exposures in the patient populations presented above. This may be related to the inflammation burden in the disease populations versus healthy patients as a consequence of down-regulation of CYP450s by inflammation stimuli (Schmitt et al, 2010).

2.3.3. Pharmacodynamics

No new Pharmacodynamics data has been submitted which is considered acceptable by CHMP.

2.3.4. PK/PD modelling

Rationale for Selection of Doses for PsA Phase 3 Studies

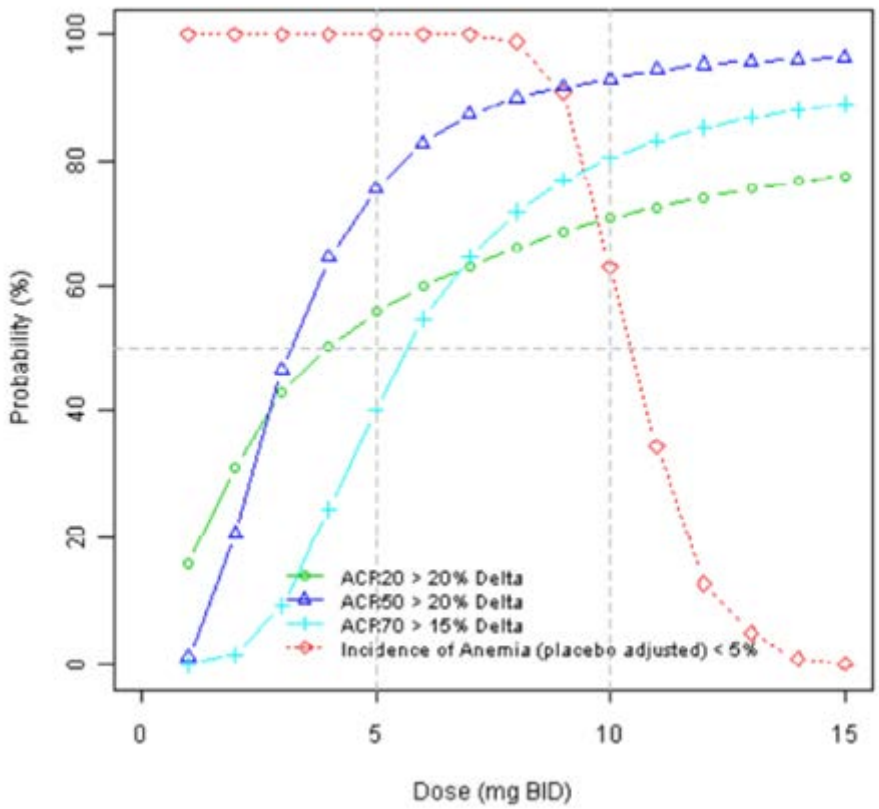
The PsA Phase 3 programme evaluated the efficacy and safety of tofacitinib 5 mg and 10 mg BID doses, which were the same as those studied in the RA and PsO Phase 3 development programmes. No Phase 2 dose-ranging studies were conducted with tofacitinib in the PsA programme.

Dose-selection in the RA and PsO tofacitinib programmes were based on modelling of Phase 2 dose-response data of those efficacy and safety outcomes that were identified to be key drivers for dose-selection. ACR responses for RA, and Psoriasis Area and Severity Index (PASI) 75 and Physician's Global Assessment (PGA) responses for PsO were identified as endpoints to evaluate for efficacy. E-R relationships for decreases in Hgb and associated risk of anaemia were useful to discriminate among doses in both RA and PsO programmes for safety. The probability of achieving a clinically meaningful target effect (PTE), where the target effect was defined in terms of a placebo-adjusted difference at a specific time point considered to be clinically meaningful (for example, 20% for ACR20), was utilised. Doses that were considered for Phase 3 evaluation were those that achieved a PTE of approximately 50% or higher on each endpoint. The tofacitinib 5 mg BID and 10 mg BID doses met the criteria (PTE of approximately 50% or higher on nearly all endpoints) for progression into Phase 3 for both indications.

The RA dose-selection was based primarily on longitudinal dose-response modelling of the ACR20, ACR50 and ACR70 responses for efficacy and change in Hgb (and associated anaemia incidence) for safety using data from Study A3921025 (which evaluated doses of 1 mg, 3 mg, 5 mg, 10 mg and 15 mg BID of tofacitinib and placebo for up to 24 weeks). The inclusion of tofacitinib 5 mg BID as the lowest dose for Phase 3 reflected the predicted increased PTE over, for example, the 3 mg BID dose on ACR50 (76% for

5 mg BID versus 47% for 3 mg BID) and ACR70 (40% for 5 mg BID versus 9% for 3 mg BID), without any loss in the PTE for anaemia (figure 5). The inclusion of tofacitinib 10 mg BID in the Phase 3 programme reflected the possibility of increased benefit over the 5 mg BID dose on ACR70, while still maintaining a sufficiently conservative safety profile. ACR20/50/70 results observed in the RA Phase 3 studies confirmed the selection of tofacitinib 5 mg BID dose in that population.

Figure 5 – Probability of achieving a target effect for efficacy (ACR20, ACR50 and ACR70 response rates) and change in haemoglobin (anaemia) based on dose-response modelling (AR3921025 in RA)



In PsO, the Phase 2 data was derived from Study A3921047, where doses of 2 mg, 5 mg and 15 mg BID of tofacitinib and placebo up to 12 weeks, were evaluated. Similar to RA, the selection of doses for PsO was based on modelling of efficacy responses (PASI75 and PGA) and changes in Hgb for safety. The tofacitinib 5 mg BID and 10 mg BID doses provided acceptable PTE for PASI75 responses (49% and 99%, respectively) and a high probability of observing a placebo-adjusted incidence rate of <5% for a Hgb decrease of >2 g/dL from baseline (100% and 87%, respectively), although 5 mg BID did not achieve the desired PTE for PGA response of clear or almost clear (23% ie, less than the target of 50%). However, the model predictions for the 5 mg BID suggested an adequate placebo-adjusted response rate for both PASI75 and PGA response (50% and 46%, respectively) at this dose level.

Thus, the inclusion of the tofacitinib 5 mg BID dose as the lowest dose for Phase 3 reflected the lowest dose that could achieve efficacy with the desired product profile. The inclusion of tofacitinib 10 mg BID in the Phase 3 studies reflected an increased benefit over the 5 mg BID dose on both PASI75 and PGA responses; predicted response rates were over 10% higher in the tofacitinib 10 mg BID dose group compared to the 5 mg BID group.

In summary, the 5 mg and 10 mg BID doses of tofacitinib were chosen based on the assumption that the dose/exposure-response relationships derived from the RA studies will be applicable to PsA patients.

Specifically, evaluation of a 30-fold dose range (1-30 mg BID) in RA patients over durations ranging from 6 weeks to 6 months across 5 Phase 2 studies, showed that the 5 mg BID dose provided clinically meaningful and comparable efficacy as compared to standard of care therapies such as TNFi. Doses lower than 5 mg BID did not consistently demonstrate clinically meaningful efficacy, particularly in the more stringent measures of efficacy, while doses greater than 10 mg BID did not provide meaningful improvements beyond those observed in the 5 to 10 mg BID dose range. Similar results were obtained in the PsO programme. Exposure-response relationships for changes in Hgb were also consistent in both RA and in PsO. The internal consistency of these results in both indications supported the selection of the same doses (5 mg and 10 mg BID) for the PsA programme.

Considering the collective model-based dose-selection rationale and experience from the RA and PsO programmes and the similarities that could be drawn between these 2 diseases and PsA, 5 mg BID and 10 mg BID were the 2 tofacitinib doses selected and subsequently evaluated in Phase 3 in PsA patients (Studies A3921091 and A3921125).

Following the completion of the PsA Phase 3 studies, E-R analyses were conducted and the results indicate that E-R relationships in PsA are consistent with those observed in RA and PsO. These E-R relationships for efficacy (ACR responses) and for changes in Hgb using data from the Phase 3 PsA studies (A3921091 and A3921125) are summarised below.

Exposure-Response Relationships for Efficacy and Change in Haemoglobin from PsA Phase 3 Studies

Efficacy

ACR responses from 2 Phase 3 studies in patients with active PsA, A3921091 and A3921125, were pooled to support a landmark exposure-response (E-R) analysis. An ordered categorical E-R model was developed to jointly model 20%, 50% and 70% ACR response levels (ACR20, ACR50 and ACR70) using data captured at Month 3 after administration of placebo, or tofacitinib doses of 5 mg or 10 mg BID.

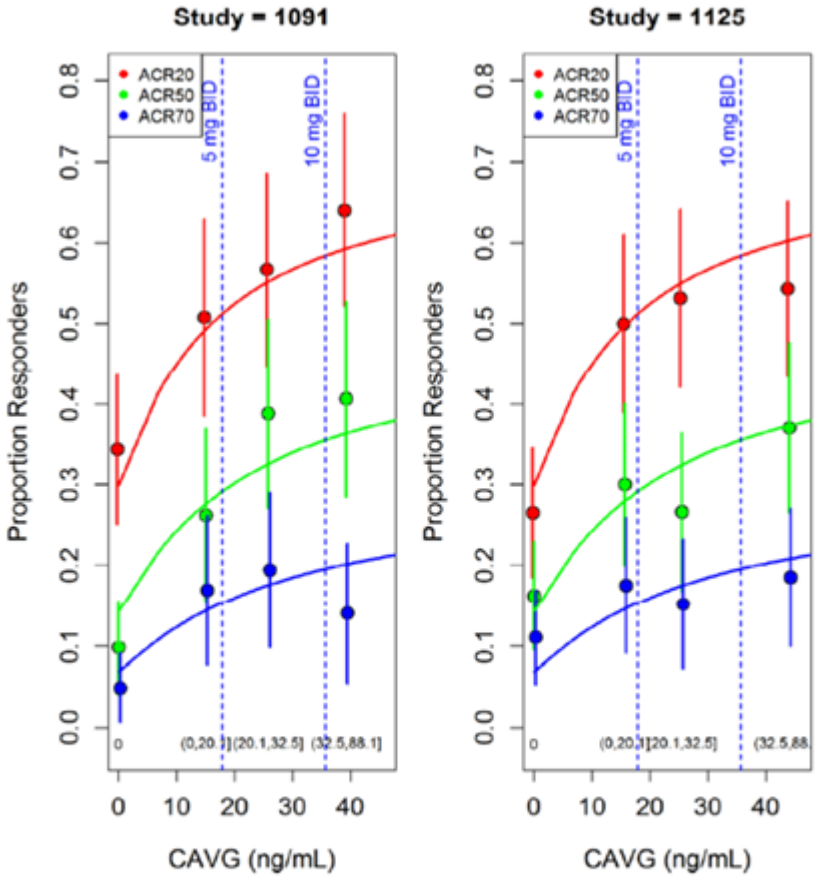
Figure 6 illustrates the exposure (Cavg)-response profiles for the proportion of ACR20, ACR50 and ACR70 responders, for Studies A3921091 and A3921125 at Month 3. For each endpoint, information with regard to the distribution of individual Cavg values as well as the prediction and CIs, are shown in Figure 7 (ACR20), Figure 8 (ACR50), and Figure 9 (ACR70), respectively.

The key findings from the E-R evaluation for efficacy are as follows:

- The E-R model (an ordered categorical model) for efficacy endpoints, ACR20, ACR50 and ACR70 adequately described the relationship between tofacitinib exposure and clinical response.
- As shown in Figure 6, there is evidence of an E-R relationship for ACR20, ACR50 and ACR70. The model-predicted proportion of ACR20 responders for exposures (median Cavg) corresponding to 5 mg and 10 mg BID at Month 3 were 51% and 58%, respectively, for ACR20; 29% and 36% for ACR50; and 15% and 20% for ACR70. The predicted proportion of responders for placebo was 30%, 14% and 7%, for ACR20, ACR50 and ACR70, respectively.
- Cavg values corresponding to 5 mg and 10 mg BID doses of tofacitinib were estimated to provide approximately 51% (EC51) and 68% (EC68) of the maximum drug effect (Emax) respectively. This is consistent with the E-R analysis in the RA programme, which showed that Cavg values corresponding to 5 mg and 10 mg BID doses provided approximately 62% (EC62) and 77% (EC77) of the Emax, from a similar model of ACR responses.
- The location of the 5 mg BID dose on the linear part of the E-R curve in PsA suggests that doses lower than 5 mg BID are likely to show reduced efficacy.

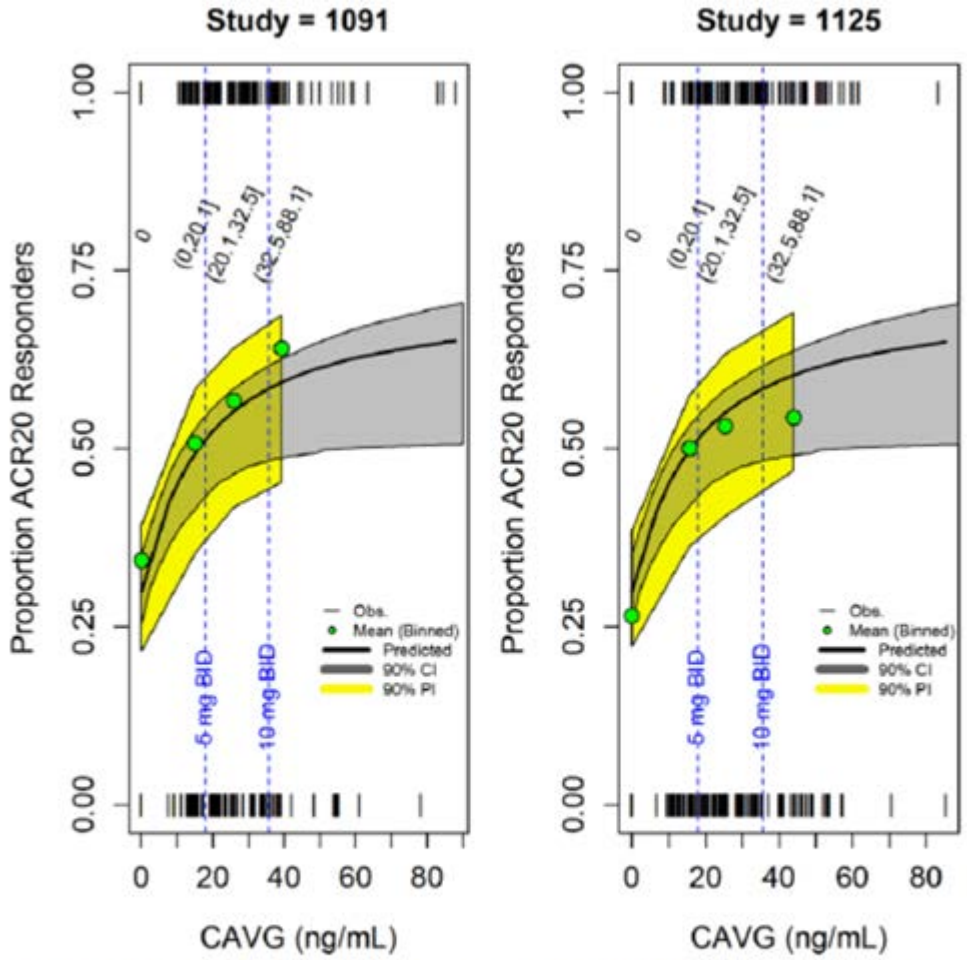
- Two specified covariates of interest, body weight (identified as an important covariate in PsO) and prior biologic use were evaluated. Neither covariate was found to influence the model parameters, Emax or EC50.
- Based on the E-R model, the relative benefits of tofacitinib 10 mg BID over 5 mg BID, expressed in terms of the ratio of the estimated proportion of responders, were 1.14, 1.22 and 1.27 for ACR20, ACR50 and ACR70, respectively. This is consistent with results from modelled ACR responses in RA, where the point estimates for the relative benefits of 10 mg over 5 mg BID across 4 dose-response studies ranged between 1.04-1.11 for ACR20, 1.17- 1.47 for ACR50, and 1.27-1.77 for ACR70.

Figure 6 – Exposure-Response relationship suing ACR responders in studies A3921091 and A3921125



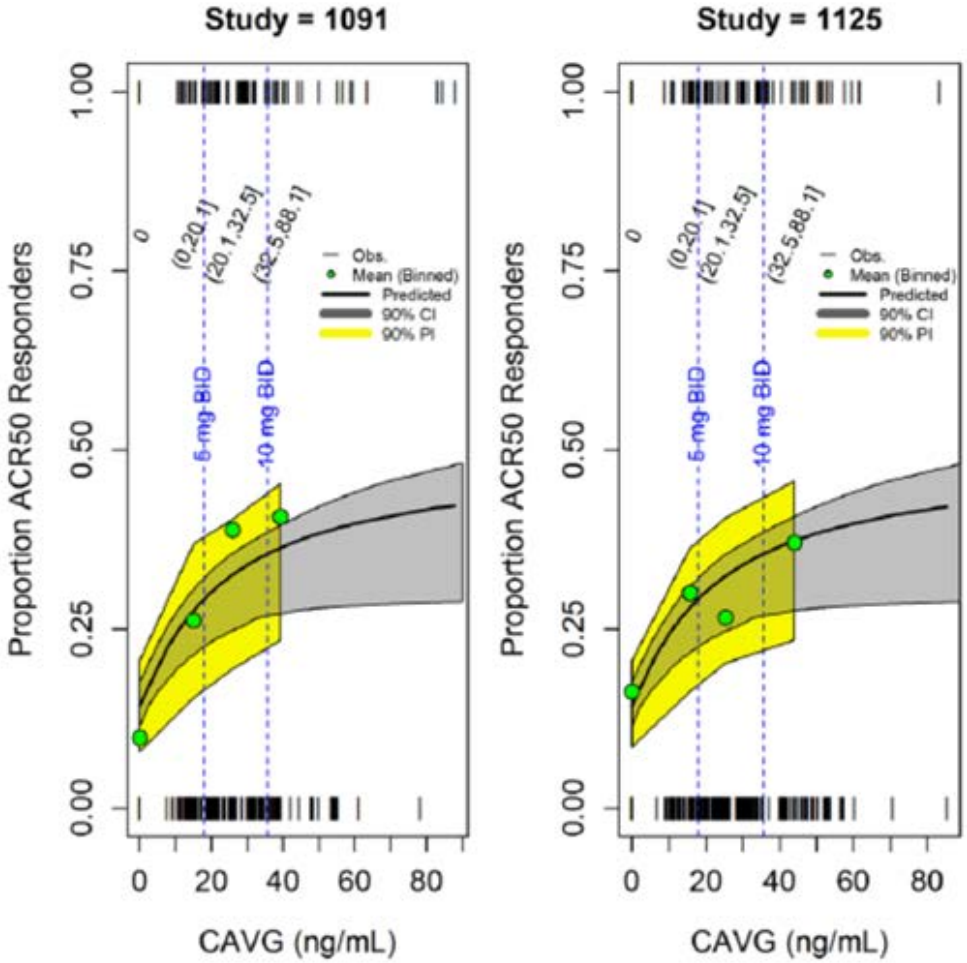
C_{avg} is the predicted tofacitinib average concentration at steady-state, binned by placebo treatment or tertile of distribution of C_{avg} for tofacitinib treatment (C_{avg} range for bin are in parentheses). The observed (filled symbols) and predicted (solid lines) proportions are displayed for ACR20 (red), ACR50 (green) and ACR70 (blue) and are plotted versus the medians of the C_{avg} bins. The error bars reflect 95% CIs of the observed responder rates. Vertical dotted blue lines represent dose standardised median of the C_{avg} values scaled to 5 mg or 10 mg BID. Note the range of the x-axis is based upon the C_{avg} values used for plotting the binned means. ACR = American College of Rheumatology; BID = twice daily; mL = millilitre; ng =nanograms.

Figure 7 – Exposure-response relationships using ACR20 responders in studies A3921091 and A3921125



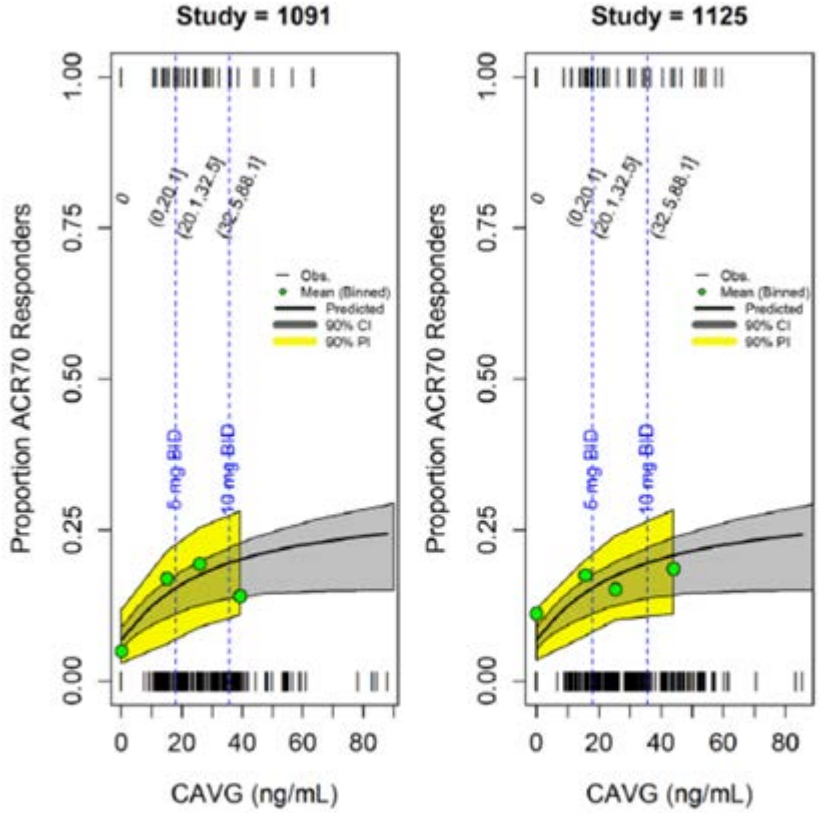
Numbers and intervals in black represent the C_{avg} intervals used for binning the observed responder rates (green circles). Vertical dotted blue lines represent dose standardised median of the C_{avg} values scaled to 5 mg or 10 mg BID. Note that the prediction intervals (yellow band) include sampling uncertainty of the mean responder rate and are for means (green circles) and thus the range is truncated relative to the x-axis; these were used to evaluate the quality of the model as per a visual predictive check. Obs. = Observed responder values (0 or 1, shown as vertical tick marks along the x-axis); CI = confidence interval; PI = prediction interval for binned means; C_{avg} = average concentrations at steady-state.

Figure 8 – Expsure-response relationships using ACR50 responders in studies A3921091 and A3921125



Numbers and intervals in black represent the C_{avg} intervals used for binning the observed responder rates (green circles). Vertical dotted blue lines represent dose standardised median of the C_{avg} values scaled to 5 mg or 10 mg BID. Note that the prediction intervals (yellow band) include sampling uncertainty of the mean responder rate and are for means (green circles) and thus the range is truncated relative to the x-axis; these were used to evaluate the quality of the model as per a visual predictive check. Obs. = Observed responder values (0 or 1, shown as vertical tick marks along the x-axis); CI = confidence interval; PI = prediction interval for binned means; C_{avg} = average concentrations at steady-state.

Figure 9 – Exposure-response relationships using ACR70 responders in studies A3921091 and A3921125



Numbers and intervals in black represent the C_{avg} intervals used for binning the observed responder rates (green circles). Vertical dotted blue lines represent dose standardised median of the C_{avg} values scaled to 5 mg or 10 mg BID. Note that the prediction intervals (yellow band) include sampling uncertainty of the mean responder rate and are for means (green circles) and thus the range is truncated relative to the x-axis; these were used to evaluate the quality of the model as per a visual predictive check. Obs. = Observed responder values (0 or 1, shown as vertical tick marks along the x-axis); CI = confidence interval; PI = prediction interval for binned means; C_{avg} = average concentrations at steady-state.

Change in Haemoglobin

The results of the E-R characterisation of Hgb change after tofacitinib treatment as well as the incidence of Hgb decrease from baseline of >2 g/dL are also summarised. Change in Hgb (a mechanistic marker of JAK2 inhibition by tofacitinib) was previously identified as a useful biomarker to discriminate among doses and support Phase 3 dose-selection in both RA and PsO programmes.

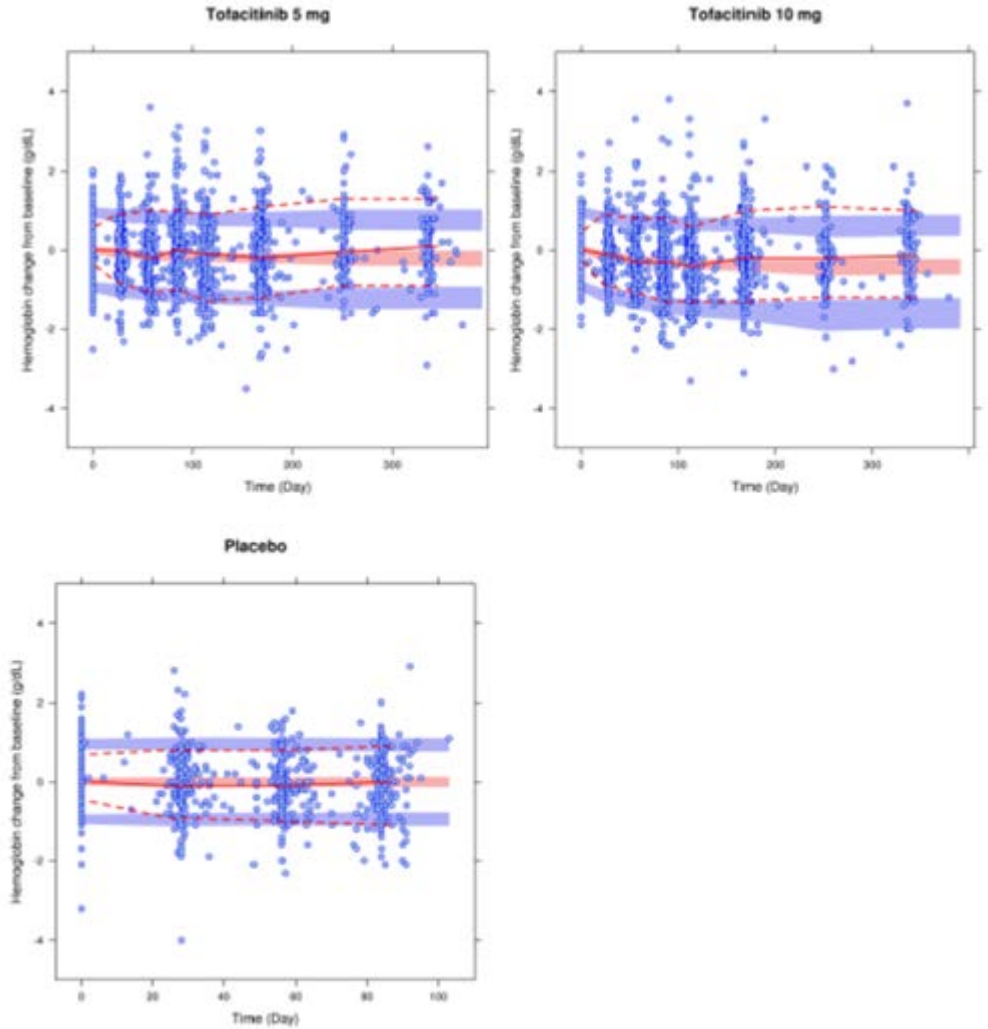
Hgb data from patients who received placebo, tofacitinib 5 mg or 10 mg BID from 2 Phase 3 studies A3921091 and A3921125 were pooled and used in this E-R analysis. For the placebo treated patients, data up to Month 3 was included in the analysis. For the 5 mg and 10 mg BID dose groups, data up to end of tofacitinib treatment (up to Month 12 for A3921091 and up to Month 6 for A3921125) were included. The dataset comprised of 685 patients, 309 of whom were males and 376 were females. The median weight, age and baseline Hgb levels of the patients were 83 kg, 50 years and 13.8 g/dL, respectively.

The key findings for each outcome are summarised below:

- The longitudinal E-R model used, which was an indirect response model, described the Hgb time-course in PsA patients receiving placebo, tofacitinib 5 mg and 10 mg BID (Figure 10).

- The model-predicted median (95% CI) Hgb change from baseline, at Month 3 is - 0.2 (-0.3, 0.0) g/dL and -0.3 (-0.4, -0.2) g/dL for 5 mg and 10 mg BID tofacitinib doses respectively, compared to 0.0 (-0.1, 0.1) for placebo.

Figure 10 – Observed and model-predicted time-course of change in haemoglobin from baseline in PsA phase 3 studies



Note: For each panel, the red (red dashed) lines represent observed median (10^{th}, 90^{th} percentiles) Hgb change from baseline (CFB)-time-course. The red (blue) areas represent model-predicted 95% CIs of 50^{th} (10^{th} or 90^{th}) percentiles of the time-course. The closed circles indicate observed individual Hgb CFB. Tofacitinib 5 mg = tofacitinib 5 mg twice daily (BID), Tofacitinib 10 mg = tofacitinib 10 mg BID, Placebo = placebo arms up to Month 3, CI = confidence interval.

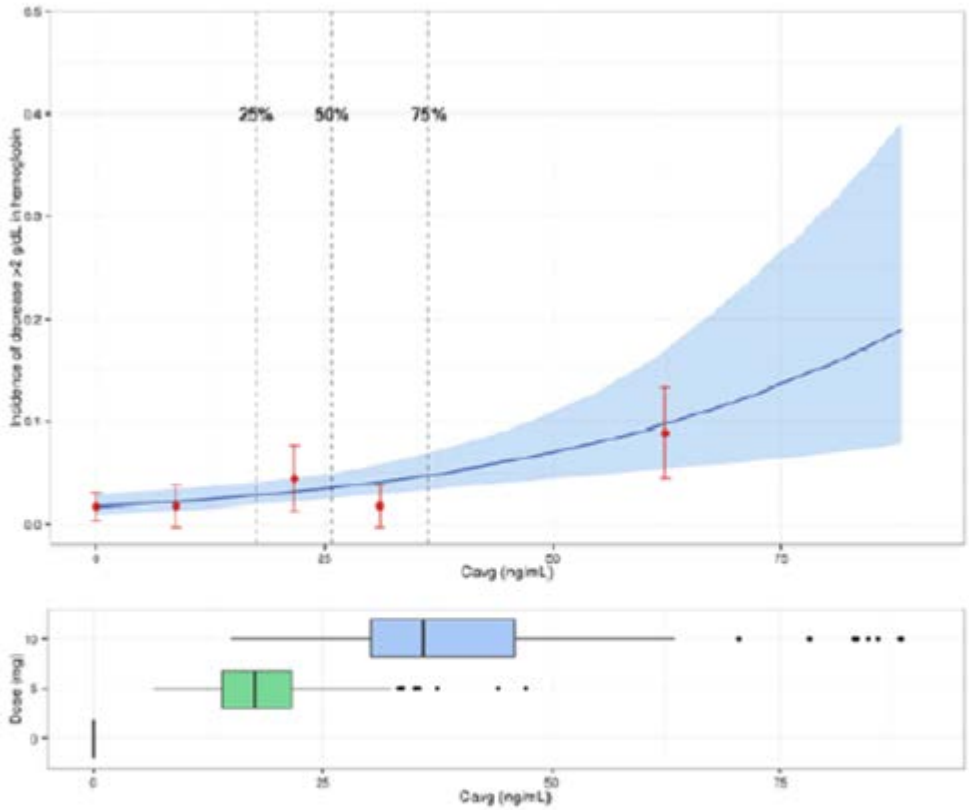
Based on a logistic regression analysis of Cavg versus the occurrence of a >2 g/dL decrease (from baseline) in Hgb, placebo-adjusted incidences (90% CI) were predicted to be 1.08% (0.61, 1.64) and 3.02% (1.48, 4.93) at median Cavg values of 17.6 ng/mL and 36.1 ng/mL respectively, corresponding to tofacitinib 5 mg BID and 10 mg BID (Figure 11).

Individual Cavg exposures in the upper quartile of the 10 mg BID dose group showed an increase in the proportion of patients experiencing a decrease in Hgb of >2 g/dL. For example, at the 90th percentile Cavg (54.8 ng/mL) in the 10 mg BID group, the estimated incidence was ~8%.

The proportion of patients experiencing a decrease in Hgb of >2 g/dL is similar (point estimates within 1.1%) between placebo and tofacitinib 5 mg BID dose. Based on the upper limit of the 90% CI for the

difference between 5 mg BID and placebo, a greater than 2% increase in incidence can be excluded at the 5 mg BID dose in comparison to placebo.

Figure 11 – Model-predicted incidence of Hgb decrease of>2g/dL vs C_{avg}.



Note: The red circles (error bars) represent observed incidence (90%CI) at each bin of C_{avg}. Blue line (area) represents incidence (90%CI) predicted from a logistic regression model M2. The dashed lines represent quartiles for C_{avg}. Dose = tofacitinib 0 mg (placebo), 5 mg or 10 mg BID. Vertical dashed lines (25%, 50% and 75%) indicate 25th, 50th, and 75th percentiles for C_{avg}. BID = twice daily; C_{avg} = average concentrations at steady-state; CI = confidence interval

The results are consistent with RA and with PsO that showed that a trend toward higher concentrations (Cavg) was associated with decreases in Hgb. Moreover, similar to RA and PsO, the results suggest that the 5 mg BID dose of tofacitinib is associated with similar levels of clinically important decrease (>2g/dL) in Hgb as those occurring with placebo in PsA patients.

2.3.5. Discussion on clinical pharmacology

Data from the 2 PsA Phase 3 studies suggest that the PK of tofacitinib is linear also in PsA patients.

The population modelling is considered to be well developed. Data is sparse from the clinical studies however data from the previous model in RA patients is used to inform the model and the fit of the data and estimation of parameters is acceptable. Inter-individual variability (IIV) for CL/F and V/F was modelled using exponential variance models with a covariance term.

VPCs demonstrated that the simulated distributions matched the observed concentrations which indicated the full model described the concentrations at 2 dose levels adequately except a bit over-predicted 5 mg at early phase.

The model is considered suitable to simulate exposure in special populations and for exposure response modelling. The recommended dose of tofacitinib 5 mg BID in PsA patients is the same that is currently approved for RA patients.

The evaluation of population pharmacokinetics of tofacitinib in PsA patients based on the popPK modelling, showed that, consistent with RA, no dosing modifications are needed for the covariates evaluated, including age, body weight, race, ethnicity and gender.

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

As such, the recommended total daily dose of tofacitinib is also reduced by half (i.e. reduced from 5 mg BID to 5 mg once daily [QD]) for PsA patients with:

- Severe renal impairment
- Moderate hepatic impairment
- Patients receiving potent inhibitors of CYP3A4 (for example, ketoconazole)
- Patients receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (for eg, fluconazole)

Tofacitinib is not recommended in PsA patients with severe hepatic impairment.

Co-administration of tofacitinib and potent inducers of CYP3A4, such as rifampicin, to PsA patients may result in loss of or reduced clinical response.

2.3.6. Conclusions on clinical pharmacology

Sparse sampling data from the phase 3 studies were used in a population PK analysis. The results of this analysis show similar exposure and variability to that seen in other patient groups e.g. RA and PsO patients. The exploration of covariates is also in agreement and suggests the same dose adjustments are appropriate in PsA patients. This is reflected in section 5.2 of the SmPC, where is stated that *Results from population PK analysis in patients with active PsA were consistent with those in patients with RA.*

Analyzing the results of the E-R analysis a relative higher benefit for tofacitinib 10 mg BID over 5 mg BID can be observed for data from study A3921091; instead the E-R relationship for ACR20, ACR50 and ACR70 is less evident for study A3921125. Logistic regression analysis of Cavg versus the occurrence of a >2 g/dL decrease in Hgb predicted higher incidences with 10 mg BID tofacitinib dose compared to 5 mg BID. The proportion of patients experiencing a decrease in Hgb of >2 g/dL is similar between placebo and tofacitinib 5 mg BID dose. The proposed dose of 5 mg BID has been justified based on safety considerations, in particular the dose dependency of serious infections, opportunistic infections and laboratory parameters.

2.4. Clinical efficacy

2.4.1. Dose response studies

No dose response studies have been performed. This was considered acceptable by CHMP since the dose is expected to be the same as for RA, based on experience with conventional DMARDs and TNF inhibitors.

2.4.2. Main studies

Study A3921091: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of 2 Doses of Tofacitinib (CP-690,550) or Adalimumab in Subjects With Active Psoriatic Arthritis

Methods

Study participants

The inclusion criteria included the following:

- Signs and symptoms consistent with the diagnosis of PsA for at least 6 months and fulfilled ClASsification Criteria for Psoriatic ARthritis (CASPAR)[7] criteria at screening.
- Evidence of active arthritis based upon both ≥3 tender/painful joints on motion (out of 68 joints assessed) and ≥3 swollen joints (out of 66 joints assessed).
- The subject must have had active plaque psoriasis which had been diagnosed or confirmed by a dermatologist or a Sponsor-approved rheumatologist at screening.
- Subjects must have received a permitted background csDMARD (e.g. methotrexate, sulfasalazine, leflunomide) dosed in accordance with the local regulatory label. Subjects remained on a stable dose of that csDMARD throughout the course of the study.
- Subjects had an inadequate response to at least one csDMARD due to lack of efficacy or toxicity/lack of toleration and must not have received any previous TNFi treatment.
- Subjects who were already receiving oral corticosteroids must have been on a stable dose of ≤10 mg/day of prednisone or equivalent for 4 weeks prior to first dose of study drug. Injected corticosteroids had to be discontinued 4 weeks prior to the first dose of study drug.
- Subjects who were already taking nonsteroidal anti-inflammatory drugs (NSAIDs)/cyclo-oxygenase 2 (COX-2) inhibitors may have participated in the study if the dose was stable for 1 week prior to first dose of study drug.
- Subjects discontinued active psoriasis treatment 2 weeks prior to being enrolled in the study (minimum of 6 months for biologics)
- Did not meet the New York Heart Association Class III and Class IV Congestive Heart Failure
- At least 18 years old at screening

[7] Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum Aug 2006;54(8):2665-73.

- No evidence of active or latent or inadequately treated infection with mycobacterium tuberculosis (TB)

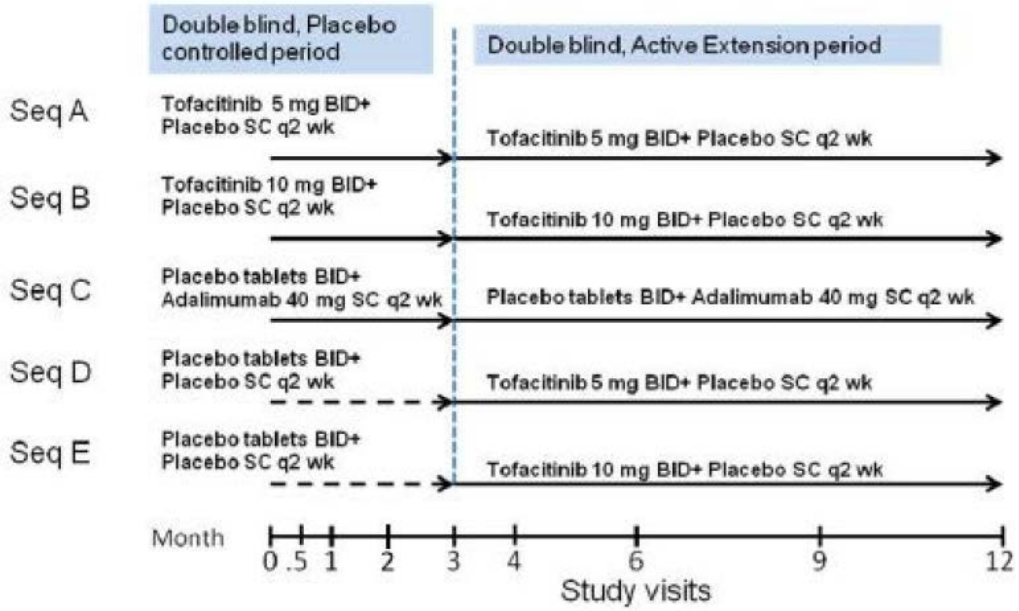
Exclusion criteria included:

- Currently had non-plaque forms of psoriasis, e.g., erythrodermic, guttate or pustular, except for nail psoriasis.
- Functional Class IV as defined by the ACR classification of functional status for RA, i.e., limited in ability to perform usual self-care, vocational and avocational activities.
- Pregnant females, breastfeeding females, females of childbearing potential not using highly effective contraception
- Criteria related to severe, progressive or uncontrolled organ dysfunction, blood dyscrasias (within 3 months prior to first dose of study drug), immunodeficiency
- Subjects with history of any autoimmune rheumatic disease other than PsA (including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis) or known diagnosis of fibromyalgia, without approval by Sponsor. Prior history of, or current, rheumatic inflammatory disease other than PsA (e.g., gout, reactive arthritis, chronic Lyme disease) without approval by Sponsor.
- History of any lymphoproliferative disorder, such as Epstein-Barr Virus-related lymphoproliferative disorder, history of lymphoma, leukaemia, or signs and symptoms suggestive of current lymphatic disease.
- History of recurrent (more than 1 episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.
- Recent history of active infection, vaccination with live or attenuated vaccines.
- A subject with evidence of skin conditions (e.g., eczema) at the time of the screening or baseline visit that would have interfered with evaluation of psoriasis.
- A subject that was considered at increased risk for gastrointestinal perforation (e.g., subjects with diverticulitis) by the Investigator or Sponsor.

Treatments

Subjects were randomised in a 2:2:2:1:1 ratio to one of the following 5 parallel treatment groups:

Figure 12 - Overview of Study Design



BID = twice daily; SC = subcutaneous; q = every; wk = week. At the Month 3 visit, subjects in Treatment Sequence D and E advanced to the second predetermined treatment in a blinded fashion for the remainder of the study.

The placebo controlled period was 3 months. At Month 3 (primary time point), all subjects randomised to placebo were advanced to tofacitinib 5 mg BID or 10 mg BID in a blinded manner for the remainder of the study.

- Tofacitinib 5 mg BID (n = 107)
- Tofacitinib 10 mg BID (n = 104)
- Adalimumab 40 mg SC q2w (n = 106)

The active control study medication, adalimumab, was administered at 40 mg subcutaneously (SC) once every 2 weeks (q2w) per PsA dosage. Adalimumab and matching placebo were provided by the Sponsor as prefilled syringes with instructions for self-injection.

Subjects continued a stable dose of their background csDMARD (e.g. methotrexate, sulfasalazine, leflunomide) dosed in accordance with the local regulatory label, for the duration of the study (see inclusion criteria). Subjects on methotrexate must have received folate supplementation per local methotrexate label guidelines and standard of care. Subjects were also permitted to remain on a stable dose of NSAIDs/COX-2 inhibitor, corticosteroid, opioids (up to potency equivalent of 30 mg oral morphine) and acetaminophen/paracetamol (up to 2.6 g daily) from 1 week prior to first study dose. The only exception was adjustment for safety reasons.

Certain medications were permitted for rescue. Increases of acetaminophen/paracetamol and opioids were allowable as rescue medication. Subjects who required rescue for more than 10 consecutive days were discontinued from the study. Intra-articular corticosteroids or hyaluronate sodium could be administered at or after the Month 3 visit (after study assessments) in no more than 2 joints. Injected joints were considered as having their pre-injection status (tender/painful and swollen joint count) and were not counted for the remainder of the study.

Objectives

The primary study objectives were:

- To compare the efficacy of tofacitinib at doses of 5 mg BID and 10 mg BID versus placebo for the treatment of rheumatological signs and symptoms of PsA, in subjects with active PsA who have had an inadequate response to a conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD)
- To compare physical function status of subjects with active PsA who have had an inadequate response to a csDMARD after administration of tofacitinib at doses of 5 mg BID and 10 mg BID versus placebo
- To compare the safety and tolerability of 2 doses (5 mg BID and 10 mg BID) of tofacitinib versus placebo in subjects with active PsA who have had an inadequate response to a csDMARD

Secondary objectives were, relating to efficacy for health outcome measures, dermatological signs and symptoms, and durability of treatment responses, as well as comparisons with adalimumab and pharmacokinetic (PK) characterisation.

Outcomes / endpoints

Primary efficacy evaluation

There were two primary efficacy endpoints: ACR20 responder rates at Month 3, and change from baseline in Health Assessment Quality-Disability Index (ΔHAQ-DI) at Month 3.

ACR20 was calculated as a ≥20% improvement in tender/painful and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. The specific components of the ACR assessments used in this study were: Tender/Painful Joint count (68); Swollen Joint Count (66); Patient's Assessment of Arthritis Pain (Visual Analog Scale [VAS]); Patient's Global Assessment of Arthritis (VAS); Physician's Global Assessment of Arthritis (VAS); CRP; HAQ-DI.

Secondary efficacy evaluation

Radiographs were taken at baseline and Month 12. For subjects with early termination, radiographs were obtained at the Early Termination visit. Radiographic changes scored by modified Total Sharp Score (ΔmTSS) at Month 12 and progressor rates (defined as ΔmTSS >0.5) at Month 12 were evaluated by 2 independent central, blinded assessors.

Signs and symptoms were evaluated by:

- ACR50 and ACR70 responder rates at all time points
- ACR20 responder rates at all time points other than Month 3
- ACR response criteria components (except HAQ-DI) at Month 3
- Psoriatic Arthritis Response Criteria (PsARC) at all time points
- Physician's Global Assessment of Psoriasis (PGA-PsO) response at Months 1, 3, 6, 9, and 12;
- Psoriasis Area and Severity Index 75 (PASI75) response at Months 1, 3, 6, 9, and 12
- Dactylitis Severity Score (DSS) at Months 1, 3, 6, 9, and 12

- Enthesitis (Leeds Enthesitis Index [LEI] and Spondyloarthritis Research Consortium of Canada [SPARCC] Enthesitis Index) at Months 1, 3, 6, 9, and 12

Secondary Patient-Reported Outcomes (PROs) of Physical Function and Health Outcome Measures (assessed at Months 1, 3, 6, 9, and 12):

- 36-Item Short-Form Health Survey (SF-36) Version 2, Acute (components and domains)
- EuroQol-5 Dimension health state profile (EQ-5D) and patient's self-rated health on a vertical VAS recorded on the EQ-5D questionnaire (EQ-VAS)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (3 endpoints: total score, experience domain score and impact domain score)
- Evaluation of spondylitis using Bath Anklyosing Spondylitis Disease Activity Index (BASDAI)

Sample size

The sample size and power analyses for all primary endpoints were based on subjects randomised in a 2:2:2:1:1 ratio to the 5 treatment sequences, effectively resulting in a 1:1:1:1 randomisation for the primary analysis at 3 months. All hypotheses were tested at the nominal alpha level of 2.5% (5% 2-sided).

The normal approximation to the binomial was used to calculate the power of the test statistic for the ACR20. Assuming a placebo response rate of about 15%, a sample size of 100 per arm would yield approximately 92% power for a difference between a tofacitinib dose and placebo of at least 20%.

For the analysis of the ΔHAQ-DI, the sample size of 100 per arm results in over 94% power for differences of 0.3 or greater between a tofacitinib dose and placebo, assuming a SD of 0.6.

Randomisation

Randomisation was conducted using an Interactive Voice Response System (IVRS). The randomisation was not stratified.

Blinding (masking)

This was a double-dummy design where all patients received either tofacitinib 5 mg tablets or a matching placebo. Similarly, patients received either an adalimumab injection or injection with a matching placebo.

The Sponsor provided tofacitinib as 5 mg tablets with corresponding matching placebo tablets. The blinded assignment consisted of 1 active 5 mg tablet and 1 placebo tablet for the 5 mg dose sequence or 2 active 5 mg tablets for the 10 mg dose sequence or 2 placebo tablets for the placebo sequences. Active control study drug was provided by the Sponsor as prefilled syringes with corresponding matching placebo.

All rheumatological and dermatological assessments including the physician's global efficacy assessments were performed by qualified assessors who were blinded to study drug treatment, laboratory values (including CRP), subject safety and prior efficacy data. The same qualified assessor was requested to score all evaluations for a particular assessment for a given subject throughout the study. Laboratory samples were analysed by a central laboratory. Radiographic images were evaluated by 2 independent central, blinded assessors.

Statistical methods

General Considerations

The primary efficacy analysis was conducted on data collected during the first 3 months where inferential comparisons to placebo entailed combining treatment sequences D and E to form 1 placebo group. The primary comparisons were between each tofacitinib dose and placebo at Month 3.

All statistical tests for efficacy endpoints were 2-sided at a significance level of 0.05.

In order to control the Type I error, a step-wise testing procedure was used. This implied that a given endpoint for a given dose can only achieve significance (i.e., conclude superiority) if the prior endpoint was significant. The order or fixed sequence for testing against placebo was as follows: tofacitinib 10 mg ACR20 response rate at Month 3, tofacitinib 5 mg ACR20 response rate at Month 3, tofacitinib 10 mg ΔHAQ-DI at Month 3 and tofacitinib 5 mg ΔHAQ-DI at Month 3.

A step-down approach was also applied to certain secondary efficacy endpoints. Key secondary efficacy variables were as follows: PASI75, ΔLEI, ΔDSS, ΔPhysical Functioning Domain of SF-36 and FACIT-F (3 endpoints in order of testing priority: ΔFACIT-F total score, ΔFACIT-F experience domain score and ΔFACIT-F impact domain score) at Month 3. In order to strongly protect the study-wise Type I error rate at the 0.05 (2-sided) level with respect to these key secondary endpoints and the primary endpoints, these endpoints were tested only if all endpoints/doses for the primary endpoints were statistically significant. The order of testing was as listed above; for each endpoint, tofacitinib 10 mg was tested versus placebo first, followed by tofacitinib 5 mg versus placebo. Testing stopped at the first instance in which statistical significance was not achieved.

Analysis sets

The Full Analysis Set (FAS): All subjects who were randomized to the study and received at least 1 dose of the randomized study drug (tofacitinib, adalimumab, or placebo). The FAS was used for all analyses of all efficacy and PRO endpoints, and was the primary dataset for the primary endpoints.

The Per-Protocol (PP) Analysis Set: The PP Analysis Set excluded all subjects who had a protocol deviation thought to have a material impact on the primary efficacy analysis The PP Analysis Set was used in a sensitivity analysis for each of the 2 primary endpoints.

Endpoint Specific Analysis Sets: Subjects were excluded from FAS for a specific endpoint if certain conditions were met for the endpoints based upon baseline criteria. These criteria were used to ensure that only patients with the condition present or severe enough to allow room for response were included in analyses for endpoints where presence of that condition was not an inclusion criterion.

Analysis of the primary endpoints

The normal approximation for the difference in binomial proportions was used to test the superiority of each dose of tofacitinib to placebo for ACR20 response at Month 3 on the FAS with missing value considered as non-response.

As a supportive analysis, a generalized marginal linear model for correlated data (due to repeated measures; also known as, GMMRM) was used. This model included fixed effects for treatment, visit (discrete, up to Month 3) and treatment by visit interaction; the dependent variable was logit of the probability of “response.” A common first-order autoregressive (AR(1)) variance-covariance matrix for all treatment groups was used to model the variability among observations within a subject.

The ΔHAQ-DI data from baseline through Month 3 on the FAS was analysed using a MMRM that included the fixed effects of treatment, visit (discrete, up to Month 3), treatment by visit interaction, geographic

location and baseline value. A common unstructured variance-covariance matrix was used for all treatment groups. There was no imputation for missing data. This analysis was referred to as MMRM1.

As a supportive analysis for ΔHAQ-DI through Month 3, a missing not at random (MNAR) multiple imputation (MI) approach was used. The specific MI that was implemented applies the "jump to reference" (JTR) imputation approach to the active dose groups but missing at random imputation approach to the combined placebo group. An analysis of covariance (ANCOVA) model, that included treatment and geographical location as fixed effects, and baseline value as a covariate was used to analyse the data after imputation. This analysis was referred to as MI-JTR.

Additional analyses of the HAQ-DI included a responder analysis at Month 3 where subjects with a change (i.e., decrease) of ≥ 0.30 were considered responders. Another responder analysis was conducted using a change (i.e., decrease) of ≥ 0.35 as the cut-point for response. The normal approximation for the difference in binomial proportions was used for these responder analyses.

For both primary endpoints sensitivity analyses were done using the PP analysis set, and using the FAS with 1 subject excluded whose data were not fully source verified.

Interim analyses

No interim analyses were conducted for this study.

Results

Participant flow

Of the 611 subjects screened, 422 were randomised as shown below.

Table 4 - Subject Evaluation Groups by Treatment Sequence, Month 12

Number (%) of Subjects	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Adalimumab 40 mg SC q 2 Weeks	Placebo → Tofacitinib 5 mg BID	Placebo → Tofacitinib 10 mg BID	Total
Screened - 611						
Assigned to study drug	107	104	106	52	53	422
Treated	107 (100.0)	104 (100.0)	106 (100.0)	52 (100.0)	53 (100.0)	422 (100.0)
Completed	96 (89.7)	96 (92.3)	94 (88.7)	44 (84.6)	43 (81.1)	373 (88.4)
Discontinued	11 (10.3)	8 (7.7)	12 (11.3)	8 (15.4)	10 (18.9)	49 (11.6)
Analyzed for efficacy						
FAS	107 (100.0)	104 (100.0)	106 (100.0)	52 (100.0)	53 (100.0)	422 (100.0)
PP Analysis Set	104 (97.2)	102 (98.1)	106 (100.0)	52 (100.0)	52 (98.1)	416 (98.6)
Analyzed for safety						
AEs	107 (100.0)	104 (100.0)	106 (100.0)	52 (100.0)	53 (100.0)	422 (100.0)
Laboratory data	107 (100.0)	104 (100.0)	106 (100.0)	52 (100.0)	52 (98.1)	421 (99.8)
Safety Analysis Set	107 (100.0)	104 (100.0)	106 (100.0)	52 (100.0)	53 (100.0)	422 (100.0)

Source: Table 14.1.1.1.1

FAS – All subjects who were randomized to the study and received at least 1 dose of the randomized study drug (tofacitinib, adalimumab or placebo).

PP Analysis Set – All FAS subjects who did not have a protocol deviation thought to have a material impact on the primary efficacy analysis.

Safety Analysis Set (Safety) – All subjects who received at least 1 dose of the study drug (tofacitinib, adalimumab or placebo).

Percentages for the 'treated' row were calculated using the number of randomized subjects as the denominator.

Other percentages were calculated using the number of treated subjects as the denominator.

Abbreviations: AE = adverse event; BID = twice daily; FAS = Full Analysis Set; PP = Per-Protocol; q = every; SC = subcutaneous.

Table 5 - Subject Discontinuation by Treatment Group and Treatment Sequence, Month 3 and Month 12 (Safety Analysis Set)

Number (%) of Subjects	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Adalimumab 40 mg SC q 2 Weeks	Placebo	Total
Discontinuations – Month 3					
Relation to study drug not defined[a]	3 (2.8)	1 (1.0)	2 (1.9)	4 (3.8)	10 (2.4)
Did not meet entrance criteria	1 (0.9)	0	1 (0.9)	0	2 (0.5)
No longer willing to participate in study	1 (0.9)	0	1 (0.9)	2 (1.9)	4 (0.9)
Other	1 (0.9)	0	0	0	1 (0.2)
Protocol violation	0	1 (1.0)	0	2 (1.9)	3 (0.7)
Related to study drug[b]	0	0	1 (0.9)	1 (1.0)	2 (0.5)
Adverse event	0	0	1 (0.9)	1 (1.0)	2 (0.5)
Not related to study drug[b]	3 (2.8)	0	1 (0.9)	0	4 (0.9)
Adverse event	3 (2.8)	0	1 (0.9)	0	4 (0.9)
Total	6 (5.6)	1 (1.0)	4 (3.8)	5 (4.8)	16 (3.8)

Number (%) of Subjects	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Adalimumab 40 mg SC q 2 Weeks	Placebo → Tofacitinib 5 mg BID	Placebo → Tofacitinib 10 mg BID	Total
Discontinuations – Month 12						
Subject died	0	0	0	1 (1.9)	0	1 (0.2)
Relation to study drug not defined[a]	5 (4.7)	5 (4.8)	8 (7.5)	5 (9.6)	8 (15.1)	31 (7.3)
Did not meet entrance criteria	1 (0.9)	0	1 (0.9)	0	0	2 (0.5)
Insufficient clinical response	0	1 (1.0)	2 (1.9)	2 (3.8)	0	5 (1.2)
Lost to follow-up	0	2 (1.9)	1 (0.9)	0	0	3 (0.7)
No longer willing to participate in study	2 (1.9)	0	3 (2.8)	2 (3.8)	2 (3.8)	9 (2.1)
Other	1 (0.9)	1 (1.0)	1 (0.9)	1 (1.9)	3 (5.7)	7 (1.7)
Protocol violation	1 (0.9)	1 (1.0)	0	0	3 (5.7)	5 (1.2)
Related to study drug[b]	2 (1.9)	2 (1.9)	2 (1.9)	2 (3.8)	1 (1.9)	9 (2.1)
Adverse event	2 (1.9)	2 (1.9)	2 (1.9)	2 (3.8)	1 (1.9)	9 (2.1)
Not related to study drug[b]	4 (3.7)	1 (1.0)	2 (1.9)	0	1 (1.9)	8 (1.9)
Adverse event	4 (3.7)	1 (1.0)	2 (1.9)	0	1 (1.9)	8 (1.9)
Total	11 (10.3)	8 (7.7)	12 (11.3)	8 (15.4)	10 (18.9)	49 (11.6)

Source: Table 14.1.1.2.1 and Table 14.1.1.2.2
Discontinued status was determined from the subject summary page at the end of study.
Abbreviations: AE = adverse event; BID = twice daily; CRF = Case Report Form; q = every; SC = subcutaneous.
a. All assessments where the relation to study drug was not defined.
b. Relationship was determined by Investigator's assessment of relationship to study treatment on the AE CRF page.

Recruitment

This global study was conducted in 94 centres in Australia, Canada, Mexico, Russian Federation, Taiwan, US and EU.

The study dates were 20/01/2014 (first subject first visit) to 18/12/2015 (last subject last visit).

Conduct of the study

There were 3 amendments to the final protocol (dated 21/12/2012). Amendments 1 and 2 were made prior to the first subject first visit and mainly included minor changes to the eligibility criteria following agency feedback. Amendment 3 (dated 09/01/2015) specified that subjects in Canada who were women of childbearing potential, and sexually active, were required to use 2 methods of contraception.

The SAP was amended 3 times after the original version (dated 17 May 2013). All updates were made prior to the treatment code unblinding and study database release.

The most common key protocol deviations were related to procedures/tests (16[3.8%]), inclusion/exclusion criteria (16[3.8%]) and study drug (14[3.3%]). Six subjects were excluded from the PP Analysis Set.

Three subjects were withdrawn due to under-compliance (1 subject each in tofacitinib 5 mg, tofacitinib 10 mg and adalimumab groups).

Baseline data

Demographic and baseline characteristics

Table 6 - Demographic and Baseline Characteristics by Treatment Group, Safety Analysis Set

	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Adalimumab 40 mg SC q 2 Weeks			Placebo			Overall		
Number (%) of Subjects	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
	50	**57**	**107**	**42**	**62**	**104**	**56**	**50**	**106**	**49**	**56**	**105**	**197**	**225**	**422**
Age (years)[a]															
Mean	49.5	49.3	49.4	44.6	48.5	46.9	46.7	48.2	47.4	46.6	48.7	47.7	46.9	48.7	47.9
SD	12.5	12.9	12.6	12.1	12.3	12.4	10.8	11.9	11.3	12.0	12.5	12.3	11.9	12.3	12.1
Range	20-70	23-72	20-72	18-74	22-68	18-74	27-81	23-73	23-81	23-70	19-74	19-74	18-81	19-74	18-81
18-44	17	19	36	21	21	42	23	19	42	23	21	44	84	80	164
	(34.0)	(33.3)	(33.6)	(50.0)	(33.9)	(40.4)	(41.1)	(38.0)	(39.6)	(46.9)	(37.5)	(41.9)	(42.6)	(35.6)	(38.9)
45-64	28	31	59	18	36	54	30	27	57	21	29	50	97	123	220
	(56.0)	(54.4)	(55.1)	(42.9)	(58.1)	(51.9)	(53.6)	(54.0)	(53.8)	(42.9)	(51.8)	(47.6)	(49.2)	(54.7)	(52.1)
65-74	5	7	12	3	5	8	2	4	6	5	6	11	15	22	37
	(10.0)	(12.3)	(11.2)	(7.1)	(8.1)	(7.7)	(3.6)	(8.0)	(5.7)	(10.2)	(10.7)	(10.5)	(7.6)	(9.8)	(8.8)
75-84	0	0	0	0	0	0	1	0	1	0	0	0	1	0	1
							(1.8)		(0.9)				(0.5)		(0.2)
≥85	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Race, n (%)															
White	49	56	105	38	59	97	54	49	103	49	55	104	190	219	409
	(98.0)	(98.2)	(98.1)	(90.5)	(95.2)	(93.3)	(96.4)	(98.0)	(97.2)	(100.0)	(98.2)	(99.0)	(96.4)	(97.3)	(96.9)
Black	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	4	3	7	1	1	2	0	1	1	5	5	10
				(9.5)	(4.8)	(6.7)	(1.8)	(2.0)	(1.9)		(1.8)	(1.0)	(2.5)	(2.2)	(2.4)
Other	1	1	2	0	0	0	1	0	1	0	0	0	2	1	3
	(2.0)	(1.8)	(1.9)				(1.8)		(0.9)				(1.0)	(0.4)	(0.7)
Ethnicity, n (%)															
Hispanic/	5	5	10	1	2	3	3	2	5	4	3	7	13	12	25
Latino	(10.0)	(8.8)	(9.3)	(2.4)	(3.2)	(2.9)	(5.4)	(4.0)	(4.7)	(8.2)	(5.4)	(6.7)	(6.6)	(5.3)	(5.9)
Not	45	52	97	41	60	101	53	48	101	45	53	98	184	213	397
Hispanic/	(90.0)	(91.2)	(90.7)	(97.6)	(96.8)	(97.1)	(94.6)	(96.0)	(95.3)	(91.8)	(94.6)	(93.3)	(93.4)	(94.7)	(94.1)
Latino															
Weight (kg)															
Mean	89.7	78.5	83.7	91.1	76.8	82.6	90.5	74.9	83.2	90.1	75.1	82.1	90.3	76.4	82.9
SD	12.6	17.9	16.6	17.4	16.1	18.0	15.3	16.8	17.8	15.2	17.6	18.1	15.0	17.1	17.6

	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Adalimumab 40 mg SC q 2 Weeks			Placebo			Overall		
Number (%) of Subjects	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
	50	**57**	**107**	**42**	**62**	**104**	**56**	**50**	**106**	**49**	**56**	**105**	**197**	**225**	**422**
Range	62.6-131.0	49.3-129.0	49.3-131.0	57.5-130.0	50.0-143.0	50.0-143.0	61.0-128.0	43.2-109.9	43.2-128.0	60.0-126.0	50.0-117.5	50.0-126.0	57.5-131.0	43.2-143.0	43.2-143.0
<60	0	8	8	3	6	9	0	9	9	0	8	8	3	31	34
		(14.0)	(7.5)	(7.1)	(9.7)	(8.7)		(18.0)	(8.5)		(14.3)	(7.6)	(1.5)	(13.8)	(8.1)
≥60 to ≤100	39	44	83	26	52	78	43	36	79	36	43	79	144	175	319
	(78.0)	(77.2)	(77.6)	(61.9)	(83.9)	(75.0)	(76.8)	(72.0)	(74.5)	(73.5)	(76.8)	(75.2)	(73.1)	(77.8)	(75.6)
>100	11	5	16	13	4	17	13	5	18	13	5	18	50	19	69
	(22.0)	(8.8)	(15.0)	(31.0)	(6.5)	(16.3)	(23.2)	(10.0)	(17.0)	(26.5)	(8.9)	(17.1)	(25.4)	(8.4)	(16.4)
BMI (kg/m^2)															
Mean	28.7	29.2	29.0	29.3	29.2	29.3	29.3	28.3	28.8	29.6	28.1	28.8	29.2	28.7	29.0
SD	3.7	6.3	5.2	5.7	5.5	5.5	4.6	6.0	5.3	4.9	6.5	5.8	4.7	6.1	5.5
Range	18.8-37.0	17.8-47.9	17.8-47.9	18.6-42.8	20.4-45.3	18.6-45.3	20.6-41.5	18.5-40.3	18.5-41.5	20.1-40.8	17.0-43.9	17.0-43.9	18.6-42.8	17.0-47.9	17.0-47.9
<18.5	0	2	2	0	0	0	0	1	1	0	1	1	0	4	4
		(3.5)	(1.9)					(2.0)	(0.9)		(1.8)	(1.0)		(1.8)	(0.9)
18.5 to <25	7	13	20	9	14	23	7	15	22	8	20	28	31	62	93
	(14.0)	(22.8)	(18.7)	(21.4)	(22.6)	(22.1)	(12.5)	(30.0)	(20.8)	(16.3)	(35.7)	(26.7)	(15.7)	(27.6)	(22.0)
25 to <30	26	20	46	17	23	40	31	16	47	16	17	33	90	76	166
	(52.0)	(35.1)	(43.0)	(40.5)	(37.1)	(38.5)	(55.4)	(32.0)	(44.3)	(32.7)	(30.4)	(31.4)	(45.7)	(33.8)	(39.3)
30 to <40	17	20	37	15	23	38	15	17	32	24	14	38	71	74	145
	(34.0)	(35.1)	(34.6)	(35.7)	(37.1)	(36.5)	(26.8)	(34.0)	(30.2)	(49.0)	(25.0)	(36.2)	(36.0)	(32.9)	(34.4)
≥40	0	2	2	1	2	3	3	1	4	1	4	5	5	9	14
		(3.5)	(1.9)	(2.4)	(3.2)	(2.9)	(5.4)	(2.0)	(3.8)	(2.0)	(7.1)	(4.8)	(2.5)	(4.0)	(3.3)

Source: Table 14.1.2.1.1.1

Weight and height are from the last assessments prior to the first dose of study drug. Other includes Mestizo, Native Canadian. Categories of parameters were analyzed as number (%) of subjects in each category. There were no subjects <18 years old in the study.

Abbreviations: BID = twice daily; BMI = body mass index; DOB = date of birth; n = number; q = every; SC = subcutaneous; SD = standard deviation.

a. Age at screening. Age was calculated as screening date year – birth year. If the screening date month was less than the DOB month, or the screening date month = DOB month and the screening date day was less than the DOB day, then age = (screening date year – DOB year) – 1.

Table 7 - Additional Demographic and Baseline Characteristics by Treatment Group

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 107)	Tofacitinib 10 mg BID (N = 104)	Adalimumab 40 mg SC q 2 Weeks (N = 106)	Placebo (N = 105)	Overall (N = 422)
Geographic Region[a]					
United States and Canada	20 (18.7)	14 (13.5)	11 (10.4)	7 (6.7)	52 (12.3)
Australia and Western Europe	16 (15.0)	20 (19.2)	17 (16.0)	8 (7.6)	61 (14.5)
Russia and Eastern Europe	65 (60.7)	64 (61.5)	72 (67.9)	87 (82.9)	288 (68.2)
Rest of World	6 (5.6)	6 (5.8)	6 (5.7)	3 (2.9)	21 (5.0)
Smoking classification					
Never smoked	64 (59.8)	64 (61.5)	66 (62.3)	72 (68.6)	266 (63.0)
Current smoker	16 (15.0)	25 (24.0)	23 (21.7)	21 (20.0)	85 (20.1)
Ex-smoker	27 (25.2)	15 (14.4)	17 (16.0)	12 (11.4)	71 (16.8)
Alcohol use					
Yes	36 (33.6)	39 (37.5)	35 (33.0)	28 (26.7)	138 (32.7)
No	71 (66.4)	65 (62.5)	71 (67.0)	77 (73.3)	284 (67.3)

Source: Table 14.1.2.1.1.3
Categories of parameters were analyzed as number (%) of subjects in each category.
Abbreviations: BID = twice daily; N = number of subjects in Safety Analysis Set; q = every; SC = subcutaneous; UK = United Kingdom.
a. Western Europe includes Belgium, France, Germany, Spain, and UK. Eastern Europe includes Bulgaria, Czech Republic, Hungary, Poland, and Slovakia. Rest of world includes Mexico and Taiwan.

Table 8 - Baseline disease characteristics by treatment group

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 107)	Tofacitinib 10 mg BID (N = 104)	Adalimumab 40 mg SC q 2 Weeks (N = 106)	Placebo (N = 105)	Total (N = 422)
Psoriatic arthritis duration (years) since first diagnosed					
<2	32 (29.9)	41 (39.4)	34 (32.1)	27 (25.7)	134 (31.8)
≥2	75 (70.1)	63 (60.6)	72 (67.9)	78 (74.3)	288 (68.2)
N	107	104	106	105	422
Mean (SD)	7.27 (8.169)	5.37 (5.764)	5.26 (5.310)	6.44 (6.416)	6.09 (6.544)
Median	4.00	2.75	3.00	4.58	3.75
Min, max	0.5-39.0	0.3-25.0	0.5-29.0	0.5-37.1	0.3-39.0
Baseline PsA subtype					
<5 joints	0	2 (1.9)	1 (0.9)	1 (1.0)	4 (0.9)
≥5 joints	107 (100.0)	102 (98.1)	105 (99.1)	104 (99.0)	418 (99.1)
Baseline PASDAS					
≤3.2	1 (0.9)	1 (1.0)	4 (3.8)	2 (1.9)	8 (1.9)
>3.2 to <5.4	26 (24.3)	27 (26.0)	28 (26.4)	26 (24.8)	107 (25.4)
≥5.4	78 (72.9)	74 (71.2)	74 (69.8)	75 (71.4)	301 (71.3)
Missing	2 (1.9)	2 (1.9)	0	2 (1.9)	6 (1.4)
N	105	102	106	103	416
Mean (SD)	6.03 (1.149)	6.01 (1.055)	5.92 (1.250)	6.03 (1.154)	6.00 (1.152)
Median	6.12	6.09	5.95	6.12	6.06
Min, max	3.1-8.7	2.5-8.1	2.8-8.9	3.2-8.7	2.5-8.9
Baseline CPDAI for subjects with baseline BSA ≥3%					
n[a]	83	70	78	82	313
≤4	1 (1.2)	2 (2.9)	4 (5.1)	0	7 (2.2)
>4 to <8	11 (13.3)	11 (15.7)	12 (15.4)	16 (19.5)	50 (16.0)
≥8	69 (83.1)	55 (78.6)	61 (78.2)	65 (79.3)	250 (79.9)
Missing	2 (2.4)	2 (2.9)	1 (1.3)	1 (1.2)	6 (1.9)
n[a]	81	68	77	81	307
N	81	68	77	81	307
Mean (SD)	9.9 (2.39)	10.0 (2.76)	9.7 (2.84)	9.9 (2.65)	9.9 (2.65)
Median	10.0	10.0	9.0	10.0	10.0
Min, max	4-15	4-15	3-15	5-15	3-15
Baseline swollen joint count (66)					
N	107	104	106	105	422

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 107)	Tofacitinib 10 mg BID (N = 104)	Adalimumab 40 mg SC q 2 Weeks (N = 106)	Placebo (N = 105)	Total (N = 422)
Mean (SD)	12.9 (9.89)	11.7 (7.67)	9.8 (7.88)	11.5 (8.75)	11.5 (8.64)
Median	11.0	10.0	8.0	9.0	9.0
Min, max	3-59	3-49	3-66	3-57	3-66
Baseline tender/painful joint count (68)					
N	107	104	106	105	422
Mean (SD)	20.5 (12.58)	20.3 (12.86)	17.1 (11.20)	20.6 (14.37)	19.6 (12.83)
Median	18.0	16.5	13.0	15.0	16.0
Min, max	3-62	3-58	4-64	4-65	3-65
Baseline HAQ-DI					
N	107	104	106	105	422
Mean (SD)	1.1636 (0.60933)	1.0817 (0.60358)	1.0959 (0.62385)	1.1107 (0.59427)	1.1132 (0.60654)
Median	1.2500	1.1250	1.1250	1.1250	1.1250
Min, max	0.000-2.500	0.000-2.625	0.000-2.875	0.000-2.625	0.000-2.875
Screening presence of distal interphalangeal joints involvement					
Yes	64 (59.8)	59 (56.7)	63 (59.4)	62 (59.0)	248 (58.8)
No	43 (40.2)	45 (43.3)	43 (40.6)	43 (41.0)	174 (41.2)
Screening presence of arthritis mutilans					
Yes	9 (8.4)	7 (6.7)	9 (8.5)	8 (7.6)	33 (7.8)
No	98 (91.6)	97 (93.3)	97 (91.5)	97 (92.4)	389 (92.2)
Baseline presence of enthesitis measured by SPARCC Enthesitis Index or LEI (SPARCC >0 or LEI >0)					
Yes	89 (83.2)	83 (79.8)	85 (80.2)	80 (76.2)	337 (79.9)
No	17 (15.9)	20 (19.2)	21 (19.8)	25 (23.8)	83 (19.7)
Missing	1 (0.9)	1 (1.0)	0	0	2 (0.5)
Baseline presence of enthesitis measured by SPARCC Enthesitis Index >0					
Yes	81 (75.7)	81 (77.9)	82 (77.4)	79 (75.2)	323 (76.5)
No	22 (20.6)	21 (20.2)	24 (22.6)	26 (24.8)	93 (22.0)
Missing	4 (3.7)	2 (1.9)	0	0	6 (1.4)
Baseline presence of enthesitis measured by LEI >0					
Yes	75 (70.1)	64 (61.5)	76 (71.7)	65 (61.9)	280 (66.4)
No	32 (29.9)	40 (38.5)	30 (28.3)	39 (37.1)	141 (33.4)
Missing	0	0	0	1 (1.0)	1 (0.2)
Baseline Enthesitis index measured by SPARCC Enthesitis Index (continuous) for those subjects with SPARCC Enthesitis Index >0 at baseline					
N	81	81	82	79	323
Mean (SD)	5.0 (3.30)	4.9 (3.32)	4.5 (2.83)	5.3 (3.83)	4.9 (3.33)
Median	4.0	4.0	4.0	4.0	4.0
Min, max	1-15	1-16	1-14	1-16	1-16
Baseline Enthesitis Index measured by LEI (continuous) for those with LEI >0 at baseline					
N	75	64	76	65	280
Mean (SD)	2.5 (1.42)	3.0 (1.58)	2.3 (1.20)	2.8 (1.47)	2.6 (1.44)
Median	2.0	3.0	2.0	2.0	2.0
Min, max	1-6	1-6	1-6	1-6	1-6
Baseline presence of dactylitis (DSS >0)					
Yes	61 (57.0)	60 (57.7)	58 (54.7)	58 (55.2)	237 (56.2)
No	45 (42.1)	43 (41.3)	48 (45.3)	46 (43.8)	182 (43.1)
Missing	1 (0.9)	1 (1.0)	0	1 (1.0)	3 (0.7)
Baseline DSS (continuous) for those subjects with DSS >0 at baseline					
N	61	60	58	58	237
Mean (SD)	9.1 (8.01)	8.5 (8.24)	8.0 (7.40)	9.9 (8.36)	8.9 (7.99)
Median	6.0	6.0	6.0	7.5	6.0
Min, max	1-36	1-40	1-36	1-31	1-40
Baseline presence of spondylitis (defined as presence of spondylitis at screening and baseline BASDAI >0)					
Yes	24 (22.4)	21 (20.2)	10 (9.4)	22 (21.0)	77 (18.2)
No	83 (77.6)	83 (79.8)	96 (90.6)	83 (79.0)	345 (81.8)
Baseline BASDAI for subjects with presence of spondylitis at screening					
n[b]	24	21	10	22	77

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 107)	Tofacitinib 10 mg BID (N = 104)	Adalimumab 40 mg SC q 2 Weeks (N = 106)	Placebo (N = 105)	Total (N = 422)
0	0	0	0	0	0
>0 to <4	6 (25.0)	5 (23.8)	2 (20.0)	4 (18.2)	17 (22.1)
≥4	18 (75.0)	16 (76.2)	8 (80.0)	18 (81.8)	60 (77.9)
Baseline BASDAI (continuous) for those subjects with presence of spondylitis at screening and BASDAI >0 at baseline					
N	24	21	10	22	77
Mean (SD)	5.60 (2.283)	5.83 (2.657)	5.79 (2.333)	6.17 (2.119)	5.85 (2.317)
Median	5.90	5.58	6.33	7.03	5.98
Min, max	1.2-9.2	1.4-9.4	1.3-8.7	1.2-8.9	1.2-9.4
Baseline total psoriatic BSA (%)					
0	1 (0.9)	3 (2.9)	1 (0.9)	1 (1.0)	6 (1.4)
>0 to <3	22 (20.6)	31 (29.8)	26 (24.5)	22 (21.0)	101 (23.9)
≥3	82 (76.6)	70 (67.3)	78 (73.6)	82 (78.1)	312 (73.9)
Missing	2 (1.9)	0	1 (0.9)	0	3 (0.7)
Baseline total psoriatic BSA (continuous) for those subjects with BSA >0% at baseline					
N	104	101	104	104	413
Mean (SD)	10.31 (15.070)	9.06 (11.266)	12.25 (16.501)	12.85 (17.297)	11.14 (15.255)
Median	5.00	5.00	5.00	5.00	5.00
Min, max	0.1-98.0	0.1-55.0	0.1-77.0	0.1-81.0	0.1-98.0
Baseline PASI					
0	0	0	0	0	0
>0 to ≤20	75 (70.1)	63 (60.6)	68 (64.2)	74 (70.5)	280 (66.4)
>20	7 (6.5)	7 (6.7)	9 (8.5)	8 (7.6)	31 (7.3)
Missing	1 (0.9)	0	1 (0.9)	0	2 (0.5)
Not assessed[c]	24 (22.4)	34 (32.7)	28 (26.4)	23 (21.9)	109 (25.8)
Baseline PASI (continuous) for those subjects with BSA ≥3% and PASI >0 at baseline					
N	82	70	77	82	311
Mean (SD)	8.28 (8.269)	8.97 (6.381)	10.05 (8.706)	9.42 (8.814)	9.18 (8.139)
Median	5.55	7.75	7.00	6.55	6.50
Min, max	0.4-46.0	0.3-24.3	2.0-47.1	0.8-41.4	0.3-47.1

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 107)	Tofacitinib 10 mg BID (N = 104)	Adalimumab 40 mg SC q 2 Weeks (N = 106)	Placebo (N = 105)	Total (N = 422)
Baseline PGA-PsO					
0	4 (3.7)	6 (5.8)	3 (2.8)	3 (2.9)	16 (3.8)
1	31 (29.0)	27 (26.0)	35 (33.0)	27 (25.7)	120 (28.4)
2	46 (43.0)	42 (40.4)	43 (40.6)	51 (48.6)	182 (43.1)
3	23 (21.5)	27 (26.0)	22 (20.8)	20 (19.0)	92 (21.8)
4	2 (1.9)	2 (1.9)	2 (1.9)	3 (2.9)	9 (2.1)
Missing	1 (0.9)	0	1 (0.9)	1 (1.0)	3 (0.7)
Baseline PGA-PsO (continuous) for those subjects with PGA-PsO >0 at baseline					
N	102	98	102	101	403
Mean (SD)	2.0 (0.78)	2.0 (0.80)	1.9 (0.80)	2.0 (0.77)	2.0 (0.79)
Median	2.0	2.0	2.0	2.0	2.0
Min, max	1-4	1-4	1-4	1-4	1-4
Baseline PGA-PsO ≥3, PASI ≥12, and BSA ≥10%					
Yes	12 (11.2)	13 (12.5)	12 (11.3)	11 (10.5)	48 (11.4)
No	69 (64.5)	57 (54.8)	65 (61.3)	71 (67.6)	262 (62.1)
Missing	2 (1.9)	0	1 (0.9)	0)	3 (0.7)
Not assessed for PASI	24 (22.4)	34 (32.7)	28 (26.4)	23 (21.9)	109 (25.8)
Baseline SF-36 Physical Functioning Domain					
N	107	104	106	105	422
Mean (SD)	34.45 (10.009)	36.73 (9.531)	36.55 (9.798)	36.53 (9.090)	36.06 (9.627)
Median	32.55	36.65	36.65	36.65	36.65
Min, max	16.2-57.1	16.2-57.1	16.2-55.1	16.2-55.1	16.2-57.1
Baseline SF-36 Physical Component Score					
N	107	104	106	105	422
Mean (SD)	35.35 (7.874)	36.37 (7.581)	35.94 (8.573)	36.01 (7.427)	35.91 (7.859)
Median	36.54	35.72	36.33	35.49	35.97
Min, max	8.9-52.2	20.3-62.1	13.2-55.8	18.5-52.8	8.9-62.1

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 107)	Tofacitinib 10 mg BID (N = 104)	Adalimumab 40 mg SC q 2 Weeks (N = 106)	Placebo (N = 105)	Total (N = 422)
Baseline SF-36 Mental Component Score					
N	107	104	106	105	422
Mean (SD)	40.78 (10.697)	40.38 (11.971)	42.80 (11.440)	39.54 (10.553)	40.88 (11.201)
Median	39.76	39.83	42.59	38.80	40.14
Min, max	13.8-68.7	10.5-62.1	15.8-63.3	10.0-64.1	10.0-68.7
Baseline FACIT-F total score					
N	107	104	106	105	422
Mean (SD)	28.0 (10.46)	28.2 (10.63)	30.0 (11.23)	28.5 (9.52)	28.7 (10.47)
Median	29.0	28.0	30.0	28.0	29.0
Min, max	6-50	5-51	8-52	5-49	5-52
Baseline FACIT-F experience domain score					
N	107	104	106	105	422
Mean (SD)	8.9 (4.27)	8.7 (4.42)	9.7 (4.64)	9.3 (3.98)	9.1 (4.34)
Median	8.0	8.0	9.5	9.0	9.0
Min, max	1-19	0-19	1-20	1-19	0-20
Baseline FACIT-F impact domain score					
N	107	104	106	105	422
Mean (SD)	19.1 (6.66)	19.5 (6.71)	20.3 (6.96)	19.3 (5.94)	19.6 (6.57)
Median	20.0	19.5	20.5	19.0	20.0
Min, max	4-32	4-32	5-32	4-30	4-32
Baseline DLQI					
<5	40 (37.4)	37 (35.6)	45 (42.5)	38 (36.2)	160 (37.9)
≥5	67 (62.6)	67 (64.4)	61 (57.5)	67 (63.8)	262 (62.1)
N	107	104	106	105	422
Mean (SD)	8.8 (7.27)	9.0 (7.66)	7.7 (7.10)	9.4 (7.64)	8.8 (7.42)
Median	7.0	7.0	5.0	8.0	7.0
Min, max	0-27	0-30	0-28	0-30	0-30

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 107)	Tofacitinib 10 mg BID (N = 104)	Adalimumab 40 mg SC q 2 Weeks (N = 106)	Placebo (N = 105)	Total (N = 422)
Baseline CRP (mg/L)					
≤2.87	39 (36.4)	38 (36.5)	42 (39.6)	42 (40.0)	161 (38.2)
>2.87	68 (63.6)	66 (63.5)	64 (60.4)	63 (60.0)	261 (61.8)
N	107	104	106	105	422
Mean (SD)	10.4947 (18.43035)	8.1303 (11.21222)	14.2905 (24.70168)	10.3949 (16.71460)	10.8406 (18.50319)
Median	4.7800	5.0650	4.2700	4.9900	4.8900
Min, max	0.200-115.000	0.200-92.900	0.200-131.000	0.200-113.000	0.200-131.000
Baseline rheumatoid factor positive					
Yes	8 (7.5)	5 (4.8)	5 (4.7)	1 (1.0)	19 (4.5)
No	98 (91.6)	98 (94.2)	100 (94.3)	102 (97.1)	398 (94.3)
Missing	1 (0.9)	1 (1.0)	1 (0.9)	2 (1.9)	5 (1.2)
Baseline cyclic citrullinated peptide antibody positive					
Yes	8 (7.5)	4 (3.8)	4 (3.8)	3 (2.9)	19 (4.5)
No	98 (91.6)	99 (95.2)	101 (95.3)	100 (95.2)	398 (94.3)
Missing	1 (0.9)	1 (1.0)	1 (0.9)	2 (1.9)	5 (1.2)
Baseline mTSS					
0	11 (10.3)	7 (6.7)	7 (6.6)	8 (7.6)	33 (7.8)
>0	96 (89.7)	96 (92.3)	99 (93.4)	95 (90.5)	386 (91.5)
Missing	0	1 (1.0)	0	2 (1.9)	3 (0.7)
Baseline mTSS for subjects with baseline score >0					
N	96	96	99	95	386
Mean (SD)	17.08 (28.568)	10.42 (18.355)	14.42 (39.202)	17.58 (43.380)	14.87 (33.811)
Median	6.00	3.25	4.00	5.00	4.50
Min, max	0.5-160.5	0.5-109.0	0.5-352.5	0.5-310.0	0.5-352.5
Baseline erosion score					
0	11 (10.3)	7 (6.7)	7 (6.6)	8 (7.6)	33 (7.8)
>0	96 (89.7)	96 (92.3)	99 (93.4)	95 (90.5)	386 (91.5)
Missing	0	1 (1.0)	0	2 (1.9)	3 (0.7)

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 107)	Tofacitinib 10 mg BID (N = 104)	Adalimumab 40 mg SC q 2 Weeks (N = 106)	Placebo (N = 105)	Total (N = 422)
Baseline erosion score for subjects with baseline score >0					
N	96	96	99	95	386
Mean (SD)	10.82 (16.316)	6.93 (10.534)	9.16 (23.190)	10.67 (24.141)	9.39 (19.357)
Median	4.50	3.00	3.00	3.50	3.75
Min, max	0.5-103.5	0.5-62.0	0.5-214.5	0.5-184.5	0.5-214.5
Baseline joint space narrowing score					
0	56 (52.3)	64 (61.5)	68 (64.2)	55 (52.4)	243 (57.6)
>0	51 (47.7)	39 (37.5)	38 (35.8)	48 (45.7)	176 (41.7)
Missing	0	1 (1.0)	0	2 (1.9)	3 (0.7)
Baseline joint space narrowing score for subjects with baseline score >0					
N	51	39	38	48	176
Mean (SD)	11.78 (16.994)	8.59 (11.486)	13.70 (24.255)	13.68 (26.173)	12.01 (20.580)
Median	6.50	4.50	5.00	3.75	5.00
Min, max	0.5-91.5	0.5-47.0	0.5-138.0	0.5-125.5	0.5-138.0

Source: Table 14.1.2.2.1
Abbreviations: BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BID = twice daily; BSA = body surface area; CPDAI = Composite Psoriatic Disease Activity Index; CRP = C-reactive protein; DLQI = Dermatology Life Quality Index; DSS = Dactylitis Severity Score; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI = Health Assessment Questionnaire - Disability Index; LEI = Leeds Enthesitis Index; Max = maximum; Min = minimum; mTSS = modified Total Sharp Score; N = number of subjects in Safety Analysis Set; PASDAS = Psoriatic Arthritis Disease Activity Score; PASI = Psoriasis Area and Severity Index; PGA-PsO = Physician's Global Assessment of Psoriasis; PsA = psoriatic arthritis; q = every; SC = subcutaneous; SD = standard deviation; SF-36 = 36-Item Short-Form Health Survey; SPARCC = Spondyloarthritis Research Consortium of Canada.
a. n is the number of subjects with baseline BSA ≥3% and is used as the denominator for the percent calculation.
b. n is the number of subjects with presence of spondylitis at screening and is used as the denominator for the percent calculation.
c. PASI was not assessed if baseline BSA <3% per study protocol.

Prior drug treatment

All subjects were required have ongoing treatment with a stable dose of csDMARD at baseline. Therefore 100% of subjects had prior csDMARD treatment. In addition, 11 subjects (2.6%) had prior biological DMARD treatment. Prior treatment with TNFi was not permitted; however, one subject in the placebo arm had prior TNFi therapy.

Table 9 - Summary of prior drug treatment (including csDMARDs taken by more than 2% of subjects)

	Tofacitinib 5 mg BID (n=107) n (%)	Tofacitinib 10 mg BID (n=104) n (%)	Adalimumab 40 mg sc q 2 weeks (n=106) n (%)	Placebo (n=105) n (%)
Biologic DMARD	3 (2.8)	4 (3.8)	1 (0.9)	4 (3.8)
Oral steroids	31 (29.0)	18 (17.3)	25 (23.6)	23 (21.9)
Non-DMARDs*	75 (70.1)	64 (61.5)	74 (69.8)	68 (64.8)
NSAIDs	72 (67.3)	54 (51.9)	65 (61.3)	62 (59.0)
Joint injections	0	0	0	0
csDMARD	107 (100)	104 (100)	106 (100)	105 (100)
ciclosporin	6 (5.6)	5 (4.8)	10 (9.4)	12 (11.4)
leflunomide	14 (13.1)	10 (9.6)	17 (16.0)	9 (8.6)
methotrexate	103 (96.3)	99 (95.2)	101 (95.3)	97 (92.4)
sulfasalazine	27 (25.2)	27 (26.0)	33 (31.1)	25 (23.8)
Number of prior csDMARDs				

1 csDMARD	67 (62.6)	66 (63.5)	61 (57.5)	69 (65.7)
2 csDMARD	31 (29.0)	31 (29.8)	32 (30.2)	25 (23.8)
≥3 csDMARD	6 (5.6)	3 (2.9)	12 (11.3)	7 (6.7)

* drug treatments for psoriatic arthritis other than DMARDs

Concomitant drug treatment

Table 10 - Summary of baseline (day 1) drug treatment

	Tofacitinib 5 mg BID (n=107) n (%)	Tofacitinib 10 mg BID (n=104) n (%)	Adalimumab 40 mg sc q 2 weeks (n=106) n (%)	Placebo (n=105) n (%)
Biologic DMARD	0	0	0	0
Non-DMARDs*	75 (70.1)	67 (64.4)	70 (66.0)	67 (63.8)
NSAIDs	68 (63.6)	52 (50.0)	61 (57.5)	59 (56.2)
Oral steroids	29 (27.1)	11 (10.6)	21 (19.8)	18 (17.1)
Joint injections	0	0	0	0
csDMARDs	107 (100)	104 (100)	106 (100)	105 (100)
methotrexate	92 (86.0)	93 (89.4)	80 (75.5)	92 (87.6)
sulfasalazine	9 (8.4)	8 (7.7)	16 (15.1)	9 (8.6)
leflunomide	7 (6.5)	4 (3.8)	10 (9.4)	4 (3.8)
hydroxychloroquine	0	0	1 (0.9)	0

* drug treatments for psoriatic arthritis other than DMARDs

No biological DMARDs were used at baseline, in line with the protocol.

Table 11 - New concomitant medications (taken on or after day 2) up to month 12

	Tofacitinib 5 mg BID (n=107) n (%)	Tofacitinib 10 mg BID (n=104) n (%)	Adalimumab 40 mg sc q 2 weeks (n=106) n (%)	Placebo -> tofacitinib 5 mg BID (n=52) n (%)	Placebo -> tofacitinib 10 mg BID (n=53) n (%)
Biologic DMARD	0	0	0	0	0
Non-DMARDs*	4 (3.7)	3 (2.9)	6 (5.7)	1 (1.9)	0
Oral steroids	1 (0.9)	2 (1.9)	1 (0.9)	0	0
Joint injections	0	1 (1.0)	0	1 (1.9)	0
Rescue treatment	0	0	0	2 (3.8)	0
csDMARD					

methotrexate	1 (0.9)	0	0	0	0
sulfasalazine	0	1 (1.0)	0	0	0
leflunomide	0	0	0	0	0
hydroxychloroquine	0	0	0	0	0

* drug treatments for psoriatic arthritis other than DMARDs

Per protocol, concomitant treatment also included the csDMARD therapy at baseline, the commonest being methotrexate. No new csDMARDs were used during the first 3 months.

Numbers analysed

The primary analysis was conducted with the full analysis set, which included all patients randomised and treated.

Outcomes and estimation

Co-primary endpoint: ACR20 response rates at Month 3

Table 12 - Normal Approximation to ACR20 Response Rates at Month 3 (FAS, Missing Response = Non-Response) – Treatment Comparisons – Primary Analysis

Visit	Treatment Group	N	n	Response Rate (%)	SE (%)	Difference				
						Difference (%)	SE of Difference (%)	95% CI Lower (%)	95% CI Upper (%)	P-value
Month 3	Tofa 5	107	54	50.47	4.83					
	Tofa 10	104	63	60.58	4.79					
	ADA	106	55	51.89	4.85					
	PBO	105	35	33.33	4.60					
	Tofa 5 vs PBO					17.13	6.67	4.06	30.21	0.0102
	Tofa 10 vs PBO					27.24	6.64	14.22	40.26	<0.0001
	ADA vs PBO					18.55	6.69	5.45	31.66	0.0055

Source: Table 14.2.1.1.2.1

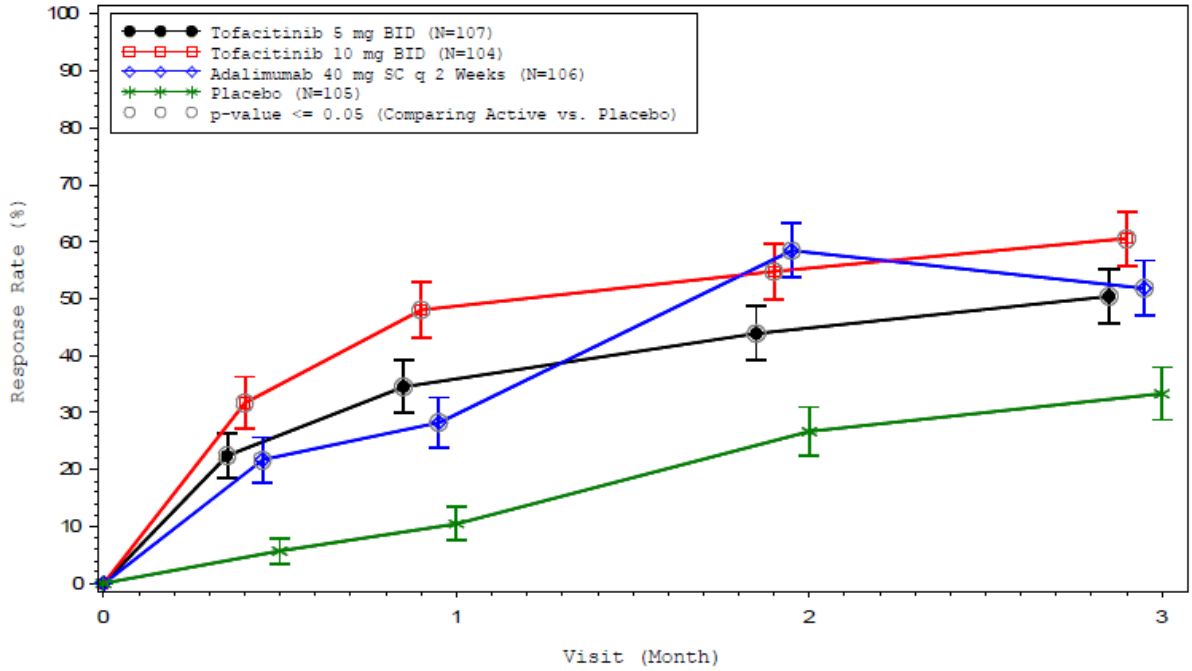
ACR20 was calculated as a ≥20% improvement from baseline in tender/painful and swollen joint counts and ≥20% improvement from baseline in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.

Two-sided 95% CIs and p-values were based on the normal approximation for the difference in binomial proportions.

P-values are nominal.

Abbreviations: ACR20 = American College of Rheumatology Response Criteria ≥20%; ADA = adalimumab 40 mg SC q 2 weeks; BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; N = number of subjects in FAS; n = number of responders; PBO = placebo; q = every; SC = subcutaneous; SE = standard error; Tofa = tofacitinib; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs=versus.

Figure 13 - Line Graph of ACR20 Response Rates (±SE) up to Month 3 (FAS, Missing Response = Non-Response) – Comparison to Placebo – Primary Analysis



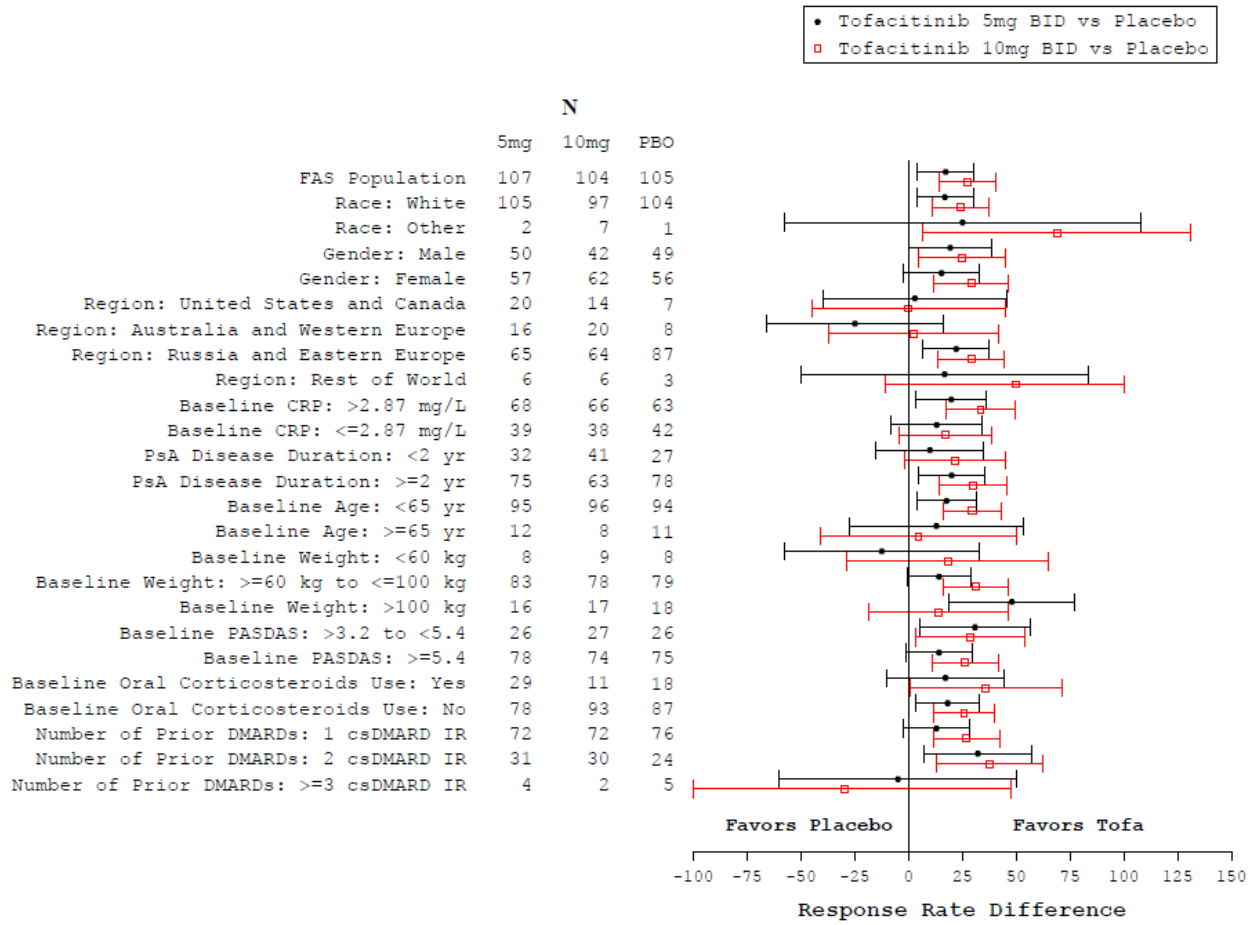
Source: Figure 14.2.1.1.2.1

ACR20 was calculated as a ≥20% improvement from baseline in tender/painful and swollen joint counts and ≥20% improvement from baseline in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.

Abbreviations: ACR20 = American College of Rheumatology Response Criteria ≥20%; BID = twice daily; FAS = Full Analysis Set; SC = subcutaneous; SE = standard error; q = every; vs=versus.

Subgroup analyses

Figure 14 - Forest Plot of Differences (95% CIs) in ACR20 Response Rates at Month 3 by Subgroup (FAS, Missing Response = Non-Response) – Comparisons to Placebo



Source: Figure 14.2.1.2.12.1, Tables 14.2.1.2.1 through 14.2.1.2.11, and Table 14.2.1.1.2.1
Western Europe includes Belgium, France, Germany, Spain, and UK. Eastern Europe includes Bulgaria, Czech Republic, Hungary, Poland, and Slovakia. Rest of world includes Mexico and Taiwan.
ACR20 was calculated as a ≥20% improvement from baseline in tender/painful and swollen joint counts and ≥20% improvement from baseline in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.
Two-sided 95% CIs were based on the normal approximation for the difference in binomial proportions. Difference was calculated as tofacitinib – placebo.
Due to low number of subjects in the categories, number of prior DMARDs: ≥1 bDMARDs IR and baseline PASDAS: ≤3.2, these categories were dropped from the analysis.
Abbreviations: ACR20 = American College of Rheumatology Response Criteria ≥20%; *b*DMARDs IR = biologic DMARDs that resulted in inadequate response; BID = twice daily; CI = confidence interval; CRP = C-reactive protein; csDMARDs IR = conventional synthetic DMARDs that resulted in inadequate response; DMARDs = disease-modifying anti-rheumatic drugs; FAS = Full Analysis Set; N = number of patient in FAS Population; PASDAS = Psoriatic Arthritis Disease Activity Score; UK = United Kingdom; vs = versus.

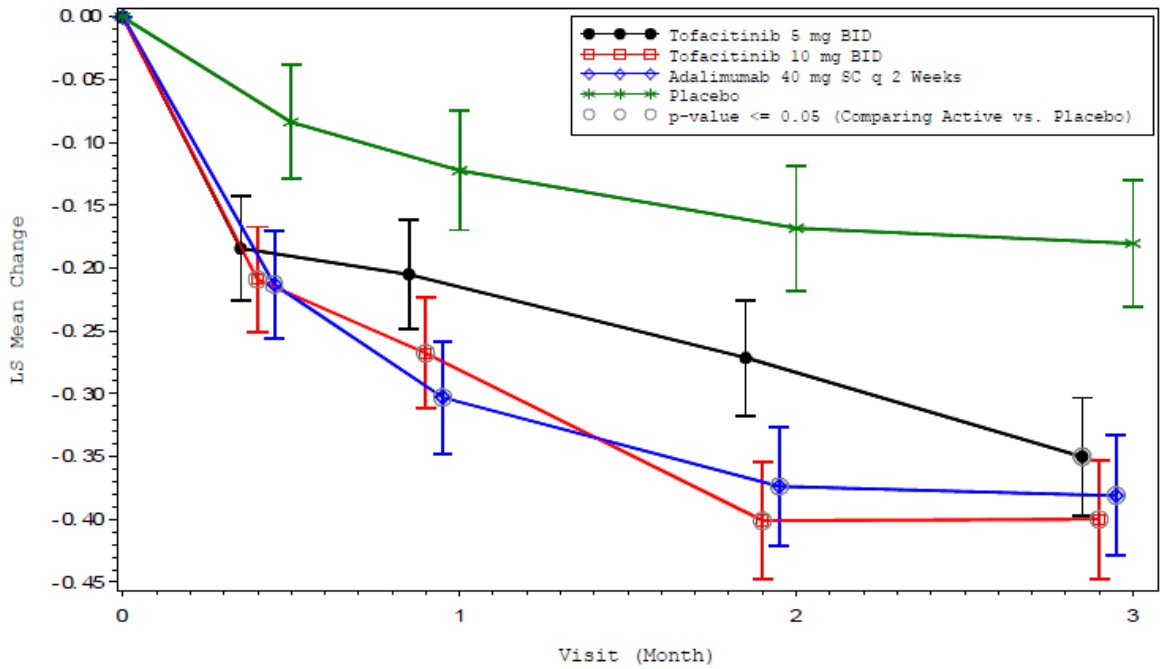
Co-primary endpoint: ΔHAQ-DI at Month 3

Table 13 - Statistical Analysis (Repeated Measures Model) of ΔHAQ-DI at Month 3 (FAS, No Imputation) – Treatment Comparisons - Primary Analysis

Visit	Treatment Group	N	n	LS Mean	SE	Difference				
						Difference	SE of Difference	95% CI		P-value
								Lower	Upper	
Month 3	Tofa 5	107	103	-0.3499	0.04665					
	Tofa 10	104	103	-0.3998	0.04716					
	ADA	106	101	-0.3808	0.04767					
	PBO	104[a]	102	-0.1802	0.05031					
	Tofa 5 vs PBO					-0.1697	0.06173	-0.2910	-0.0483	0.0062
	Tofa 10 vs PBO					-0.2196	0.06184	-0.3411	-0.0980	0.0004
	ADA vs PBO					-0.2005	0.06145	-0.3213	-0.0797	0.0012

Source: Table 14.2.1.3.3.1
Results were based on MMRM1 with the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used.
P-values are nominal.
Abbreviations: Δ = change from baseline; ADA = adalimumab 40 mg SC q 2 weeks; BID = twice daily; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire - Disability Index; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; N = number of unique subjects in the longitudinal model; n = number of subjects evaluable at Month 3; PBO = placebo; q = every; SC = subcutaneous; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs=versus.
a. One placebo subject (11711001) was excluded from the analysis (no postbaseline assessments; Table 16.2.6.02.1).

Figure 15 - Line Graph of Least Squares Mean (±SE) ΔHAQ-DI up to Month 3 From the Repeated Measures Model (FAS, No Imputation) – Comparison to Placebo – Primary Analysis



Source: Figure 14.2.1.3.3.1
Results were based on MMRM1 with the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used.
Abbreviations: Δ = change from baseline; BID = twice daily; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire - Disability Index; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; q = every; SC = subcutaneous; SE = standard error; vs = versus.

Table 14 - Statistical Analysis (MI-JTR) of ΔHAQ-DI at Month 3 (FAS, jump-to-reference multiple imputation) – Treatment Comparisons - Supportive Analysis

Visit	Treatment Group	N	n	LS Mean	SE	Difference				
						Difference	SE of Difference	95% CI		P-value
								Lower	Upper	

MI-JTR (FAS, Multiple Imputation) – Supportive Analysis[b,c]										
Month 3	Tofa 5	107	103	-0.3345	0.04942					
	Tofa 10	104	103	-0.4020	0.04995					
	PBO	104	102	-0.1822	0.05561					
	Tofa 5 vs PBO					-0.1523	0.06121	-0.2728	-0.0319	0.0134
	Tofa 10 vs PBO					-0.2198	0.06115	-0.3401	-0.0995	0.0004
	Tofa 10 vs Tofa 5					-0.0675	0.05993	-0.1854	0.0504	0.2609

Table 15 - Normal Approximation to HAQ-DI Response Rates (Decrease From Baseline ≥0.30 and ≥0.35) at Month 3 (for Subjects With Baseline HAQ-DI ≥0.30 and ≥0.35, Respectively, in FAS, Missing Response = Non-Response) - Treatment Comparisons – Supportive Analysis

Visit	Treatment Group	N	n	Response Rate (%)	SE (%)	Difference				
						Difference (%)	SE of Difference (%)	95% CI		P-value
								Lower (%)	Upper (%)	
Decrease From Baseline ≥0.30 at Month 3 for Subjects With Baseline HAQ-DI ≥0.30 in FAS										
Month 3	Tofa 5	96	51	53.13	5.09					
	Tofa 10	92	51	55.43	5.18					
	ADA	96	51	53.13	5.09					
	PBO	94	29	30.85	4.76					
	Tofa 5 vs PBO					22.27	6.97	8.61	35.94	0.0014
	Tofa 10 vs PBO					24.58	7.04	10.79	38.38	0.0005
	ADA vs PBO					22.27	6.97	8.61	35.94	0.0014
Decrease From Baseline ≥0.35 at Month 3 for Subjects With Baseline HAQ-DI ≥0.35 in FAS										
Month 3	Tofa 5	96	51	53.13	5.09					
	Tofa 10	92	51	55.43	5.18					
	ADA	96	51	53.13	5.09					
	PBO	94	29	30.85	4.76					
	Tofa 5 vs PBO					22.27	6.97	8.61	35.94	0.0014
	Tofa 10 vs PBO					24.58	7.04	10.79	38.38	0.0005
	ADA vs PBO					22.27	6.97	8.61	35.94	0.0014

Source: Table 14.2.1.3.6.2 and Table 14.2.1.3.7.2

Two-sided 95% CIs and p-values were based on the normal approximation for the difference in binomial proportions.

Subjects with baseline HAQ-DI ≥0.30 or ≥0.35 were included in the analysis.

Number of subjects in FAS with baseline HAQ-DI ≥0.30 for tofacitinib 5 mg BID: 96; tofacitinib 10 mg BID: 92; adalimumab 40 mg SC q 2 weeks: 96; placebo: 94.

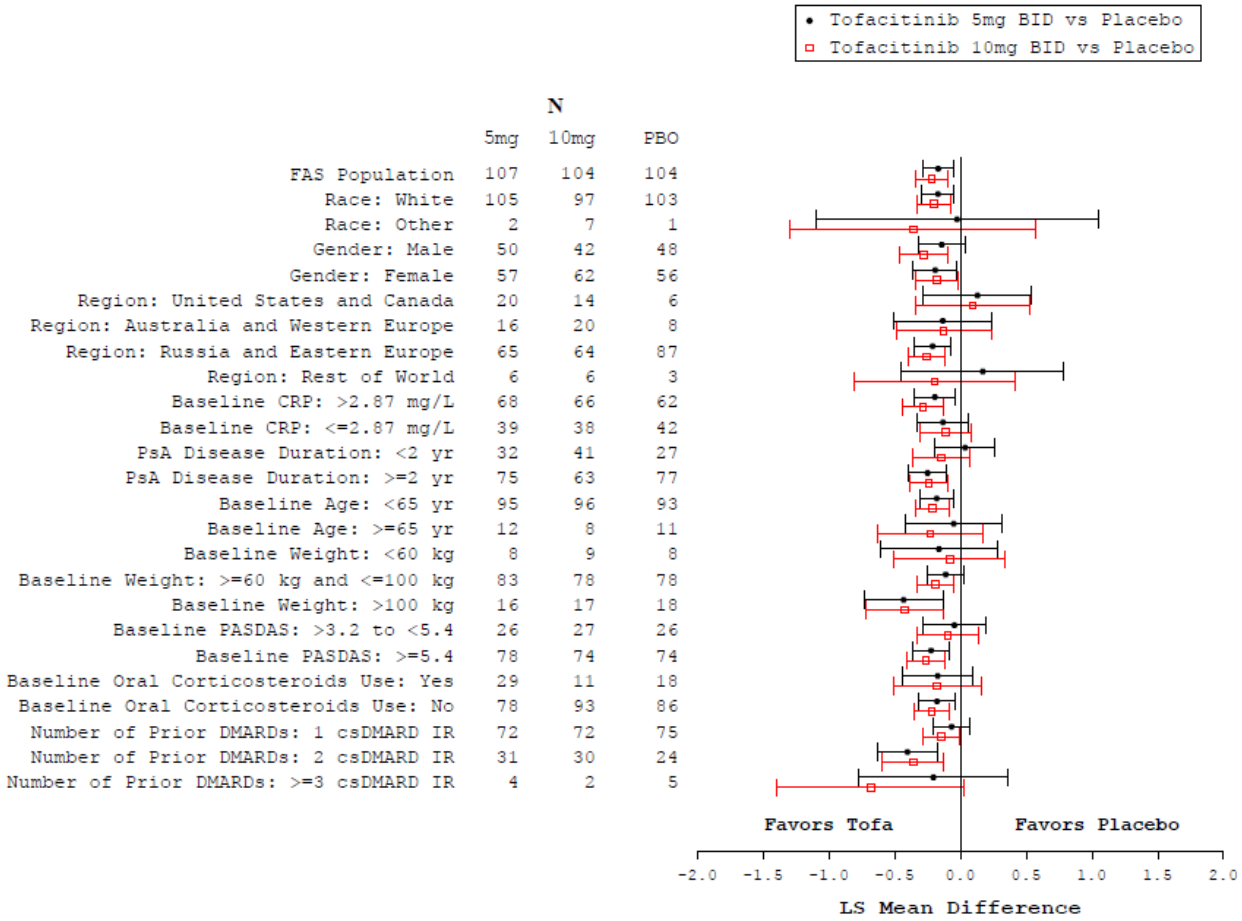
Number of subjects in FAS with baseline HAQ-DI ≥0.35 for tofacitinib 5 mg BID: 96; tofacitinib 10 mg BID: 92; adalimumab 40 mg SC q 2 weeks: 96; placebo: 94.

P-values are nominal.

Abbreviations: ADA = adalimumab 40 mg SC q 2 weeks; BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire - Disability Index; N = number of subjects in FAS with baseline HAQ-DI ≥0.30 or ≥0.35; n = number of responders; PBO = placebo; q = every; SC = subcutaneous; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs=versus.

Subgroup analyses:

Figure 16 - Forest Plot of Least Squares Mean Differences (95% CIs) in ΔHAQ-DI at Month 3 by Subgroup (FAS, Repeated Measures Model, No Imputation) - Comparisons to Placebo

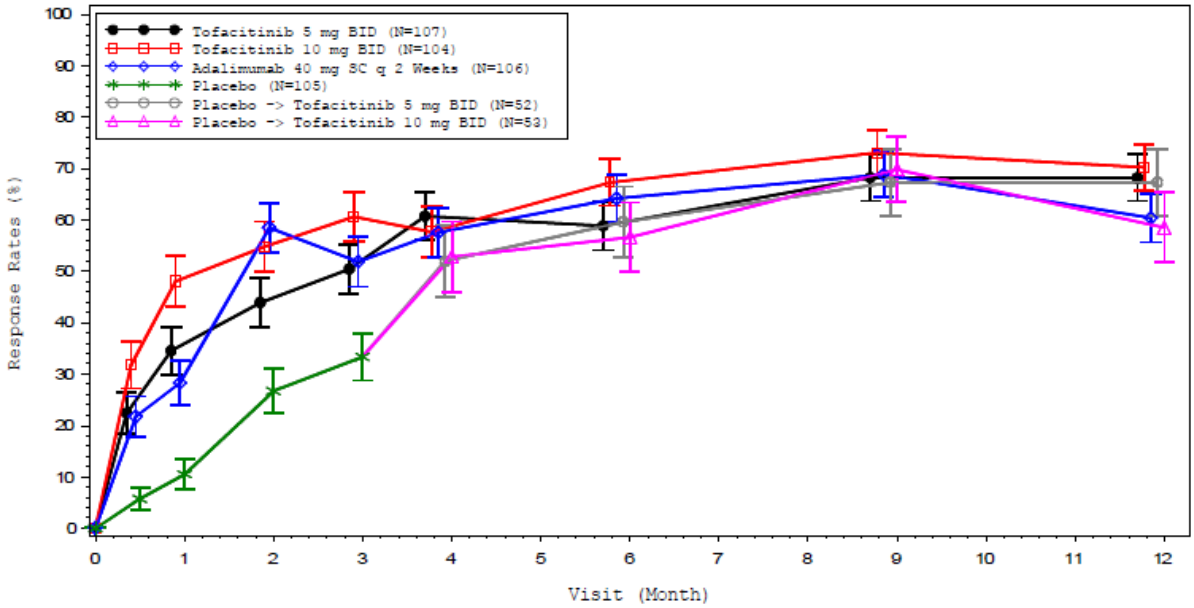


Source: Figure 14.2.1.4.12.1, Tables 14.2.1.4.1 through 14.2.1.4.11, and Table 14.2.1.3.3.1
Western Europe includes Belgium, France, Germany, Spain, and UK. Eastern Europe includes Bulgaria, Czech Republic, Hungary, Poland, and Slovakia. Rest of world includes Mexico and Taiwan.
For each subgroup (eg, gender), the results were based on a repeated measures model with the fixed effects of treatment, visit, treatment by visit interaction, subgroup, subgroup by treatment, subgroup by visit, subgroup by treatment by visit interaction, geographical location, and baseline value; an unstructured covariance matrix was used. Difference was defined as tofacitinib – placebo.
Due to low number of subjects in the categories, Number of prior DMARDs: ≥1 bDMARDs IR and baseline PASDAS: ≤3.2, these categories were dropped from the analysis.
Abbreviations: Δ = change from baseline; bDMARDs IR = biologic DMARDs that resulted in inadequate response; BID = twice daily; CI = confidence interval; CRP = C-reactive protein; csDMARDs IR = conventional synthetic DMARDs that resulted in inadequate response; DMARDs = disease-modifying anti-rheumatic drugs; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire - Disability Index; LS Mean = least squares mean; N = number of subjects; PASDAS = Psoriatic Arthritis Disease Activity Score; PsA = psoriatic arthritis; UK = United Kingdom; vs = versus.

Secondary endpoints

ACR20 responder rates at all time points other than Month 3

Figure 17 - Line Graph of ACR20 Response Rates (±SE) up to Month 12 (FAS, Missing Response = Non-Response)



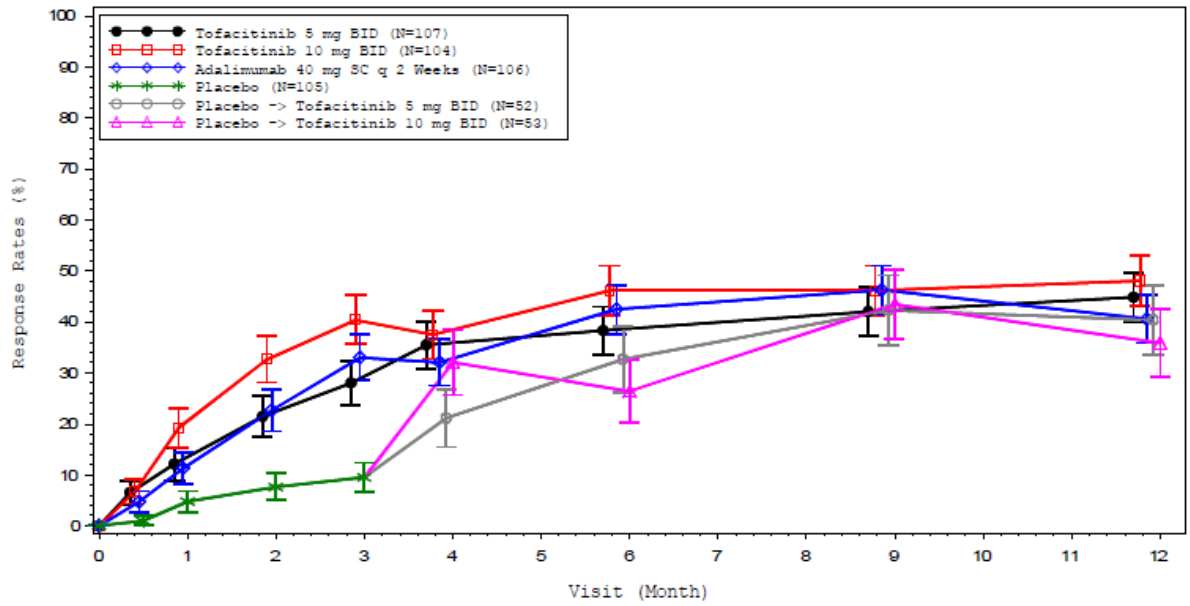
Source: Figure 14.2.1.1.2.2

ACR20 was calculated as a ≥20% improvement from baseline in tender/painful and swollen joint counts and ≥20% improvement from baseline in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.

Abbreviations: ACR20 = American College of Rheumatology Response Criteria ≥20%; BID = twice daily; FAS = Full Analysis Set; N=number of subjects in FAS; SC = subcutaneous; SE = standard error; q = every.

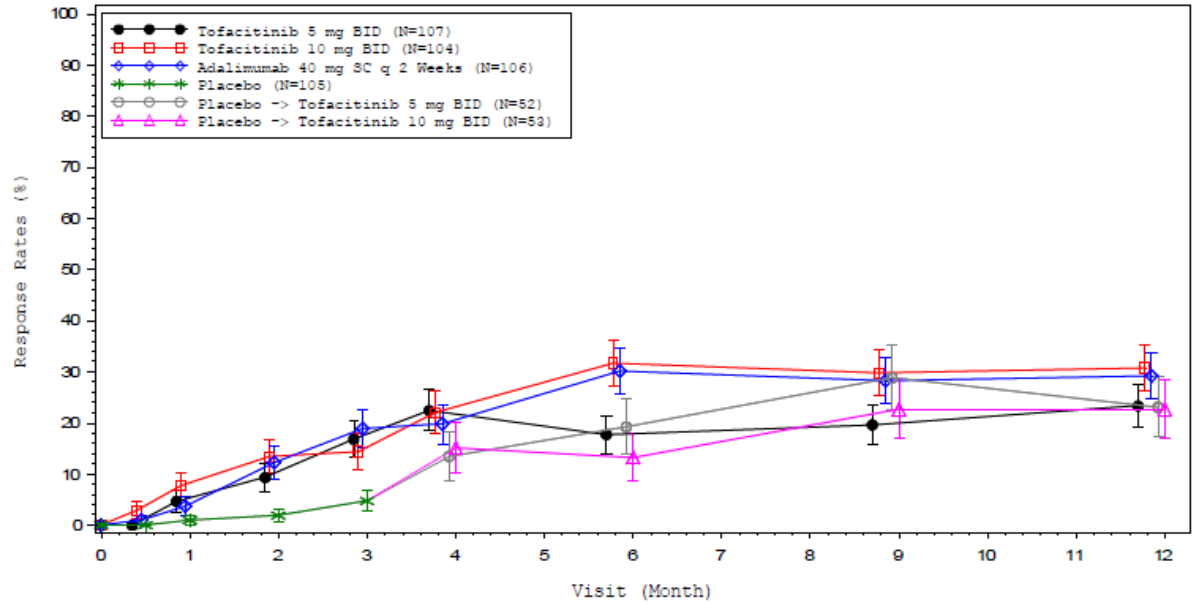
ACR50 and ACR70 responder rates at all time points

Figure 18 - Line Graph of ACR50 Response Rates (±SE) up to Month 12 (FAS, Missing Response = Non-Response)



Source: Figure 14.2.2.3.2.1 and Figure 14.2.2.3.2.2
ACR was calculated as a ≥50% improvement from baseline in tender/painful and swollen joint counts and ≥50% improvement from baseline in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.
Abbreviations: ACR50 = American College of Rheumatology Response Criteria ≥50%; CR = American College of Rheumatology, BID = twice daily; FAS = Full Analysis Set; SC = subcutaneous; SE = standard error; q = every.

Figure 19 - Line Graph of ACR70 Response Rates (±SE) up to Month 12 (FAS, Missing Response = Non-Response)



Source: Figure 14.2.2.4.2.1 and Figure 14.2.2.4.2.2
ACR70 was calculated as a ≥70% improvement from baseline in tender/painful and swollen joint counts and ≥70% improvement from baseline in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.
Abbreviations: ACR70 = American College of Rheumatology Response Criteria ≥70%; BID = twice daily; FAS = Full Analysis Set; SC = subcutaneous; SE = standard error; q = every.

ΔACR response criteria components

HAQ-DI

The Month 6 and Month 12 ΔHAQ-DI are shown in the following table:

Table 16 - Statistical Analysis (Repeated Measures Model) of ΔHAQ-DI at Month 6 and 12 (FAS, No Imputation) – Treatment Comparisons

Visit	Treatment Group	N	n	LS Mean	SE	Difference	SE of Difference	95% CI Lower	95% CI Upper	P-value
Month 6	Tofa 5	107	100	-0.4471	0.05136					
	Tofa 10	104	100	-0.4611	0.05179					
	ADA	106	99	-0.4259	0.05227					
	PBO → Tofa 5	52	48	-0.3142	0.07315					
	PBO → Tofa 10	52	48	-0.3841	0.07369					
	Tofa 10 vs Tofa 5					-0.0140	0.06821	-0.1481	0.1201	0.8372
	Tofa 5 vs ADA					-0.0212	0.06823	-0.1553	0.1130	0.7564
	Tofa 10 vs ADA					-0.0352	0.06828	-0.1694	0.0990	0.6064
Month 12	Tofa 5	107	96	-0.5391	0.05324					
	Tofa 10	104	96	-0.5104	0.05365					
	ADA	106	94	-0.4478	0.05426					
	PBO → Tofa 5	52	44	-0.4104	0.07646					
	PBO → Tofa 10	52	44	-0.4569	0.07704					
	Tofa 10 vs Tofa 5					0.0287	0.07102	-0.1110	0.1683	0.6865
	Tofa 5 vs ADA					-0.0913	0.07114	-0.2312	0.0486	0.2002
	Tofa 10 vs ADA					-0.0626	0.07119	-0.2026	0.0774	0.3798

Source: Table 14.2.1.3.3.2
Results were based on MMRM2 with the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used.
P-values are nominal.
Abbreviations: Δ = change from baseline; ADA = adalimumab 40 mg SC q 2 weeks; BID = twice daily; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire - Disability Index; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; N = number of unique subjects in the longitudinal model; n = number of subjects evaluable at each visit; PBO = placebo; q = every; SC = subcutaneous; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs=versus.

The ΔHAQ-DI is increased at Month 6 and Month 12 in all 3 original treatment groups, compared to Month 3, suggesting at least maintenance of effect.

Tender/painful joint count

A statistically significant reduction in tender/painful joint count was only observed for the comparison of tofacitinib 10 mg BID vs placebo at Month 3.

Swollen joint count

There was a statistically significant reduction in swollen joint count for the 3 active treatments vs placebo at Month 3. For the comparison of tofacitinib 5 mg BID vs placebo, the LS mean difference was -1.7 (95% CI: -3.3, -0.2; p=0.0265).

Patient's Assessment of Arthritic Pain – VAS (mm)

At Month 3, the LS mean difference from baseline in patient's assessment of arthritic pain was -21.5, -27.1 and -21.9 for tofacitinib 5 mg, tofacitinib 10 mg and adalimumab, vs -10.2 for placebo. All comparisons with placebo were statistically significant. These differences from baseline were maintained at Months 6 and 12.

Patient's global assessment of arthritis - VAS (mm)

At Month 3, the LS mean difference from baseline in patient's global assessment of arthritis was -20.1, -25.5 and -21.5 for tofacitinib 5 mg, tofacitinib 10 mg and adalimumab, vs -11.4 for placebo. All comparisons with placebo were statistically significant. These differences from baseline were maintained at Months 6 and 12.

Physician's global assessment of arthritis – VAS (mm)

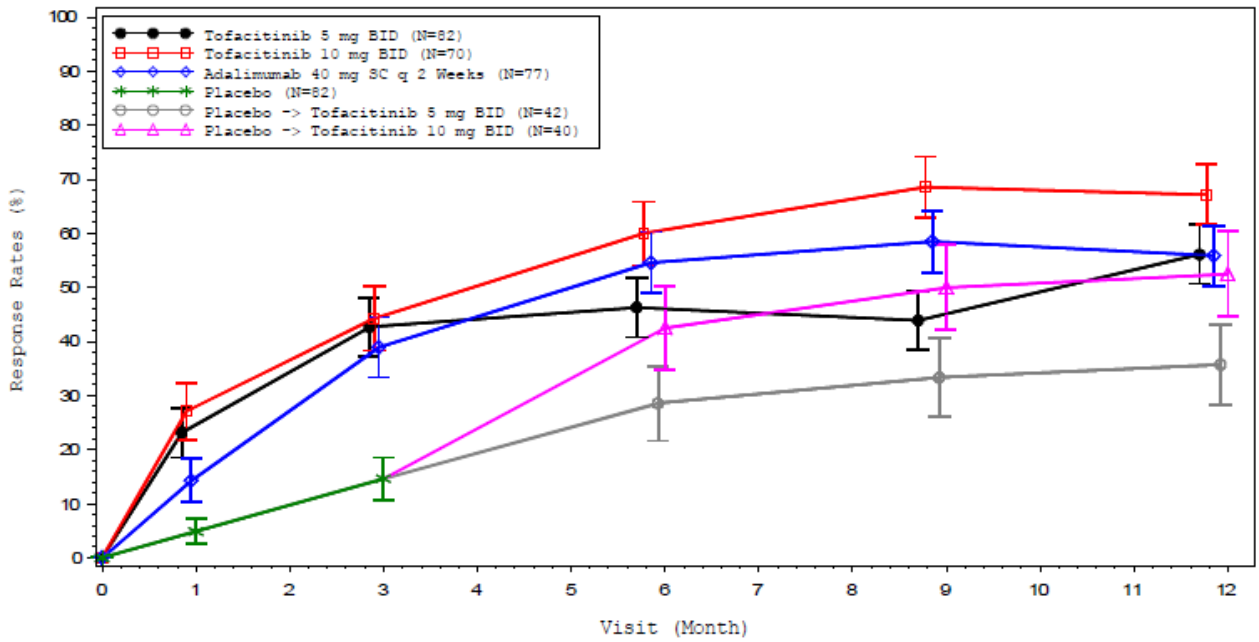
At Month 3, the LS mean difference from baseline in physician's global assessment of arthritis was -27.4, -33.7 and -29.0 for tofacitinib 5 mg, tofacitinib 10 mg and adalimumab, vs -22.3 for placebo. The comparison of tofacitinib 5 mg vs placebo was borderline statistically significant (p = 0.0555). These differences from baseline were maintained at Months 6 and 12.

C-reactive protein

At Month 3, the LS mean difference from baseline in CRP (mg/L) was -5.60, -6.60 and -7.90 for tofacitinib 5 mg, tofacitinib 10 mg and adalimumab, vs -0.86 for placebo. All comparisons with placebo were statistically significant (p<0.0001). These differences from baseline were maintained at Months 6 and 12.

Psoriasis Area and Severity Index 75 (PASI75) response

Figure 20 - Line Graph of PASI75 Response Rates (±SE) up to Month 12 (for Subjects With Baseline BSA ≥3% and Baseline PASI >0 in FAS, Missing Response = Non-Response)



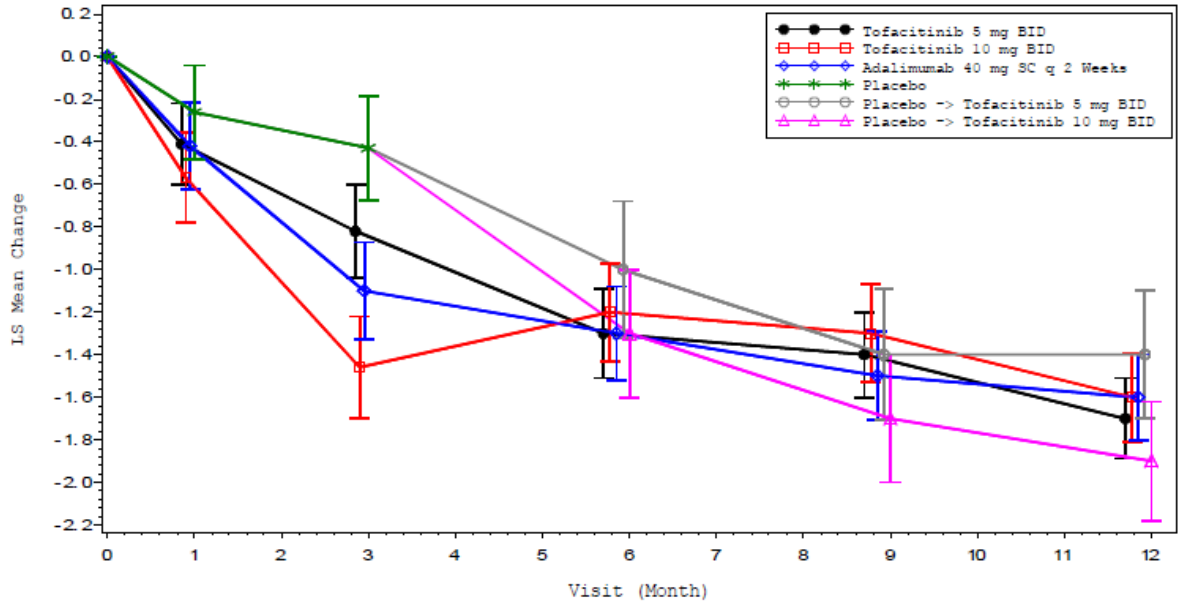
Source: Figure 14.2.2.6.2 and Figure 14.2.2.6.4
PASI75 was defined as a ≥75% reduction from baseline in PASI.
Only subjects with baseline BSA affected ≥3% (per study protocol) and baseline PASI >0 were considered.
Abbreviations: BID = twice daily; BSA = body surface area; FAS = Full Analysis Set; PASI75 = Psoriasis Area and Severity Index 75; SC = subcutaneous; SE = standard error; q = every.

Physician's Global Assessment of Psoriasis (PGA-PsO)

At Month 3, the LS mean difference from baseline in physician's global assessment of arthritis was -1.0, -1.2 and -1.0 for tofacitinib 5 mg, tofacitinib 10 mg and adalimumab, vs -0.4 for placebo. The comparison of tofacitinib 5 mg vs placebo was statistically significant ($p<0.0001$). These differences from baseline were maintained at Months 6 and 12.

Enthesitis

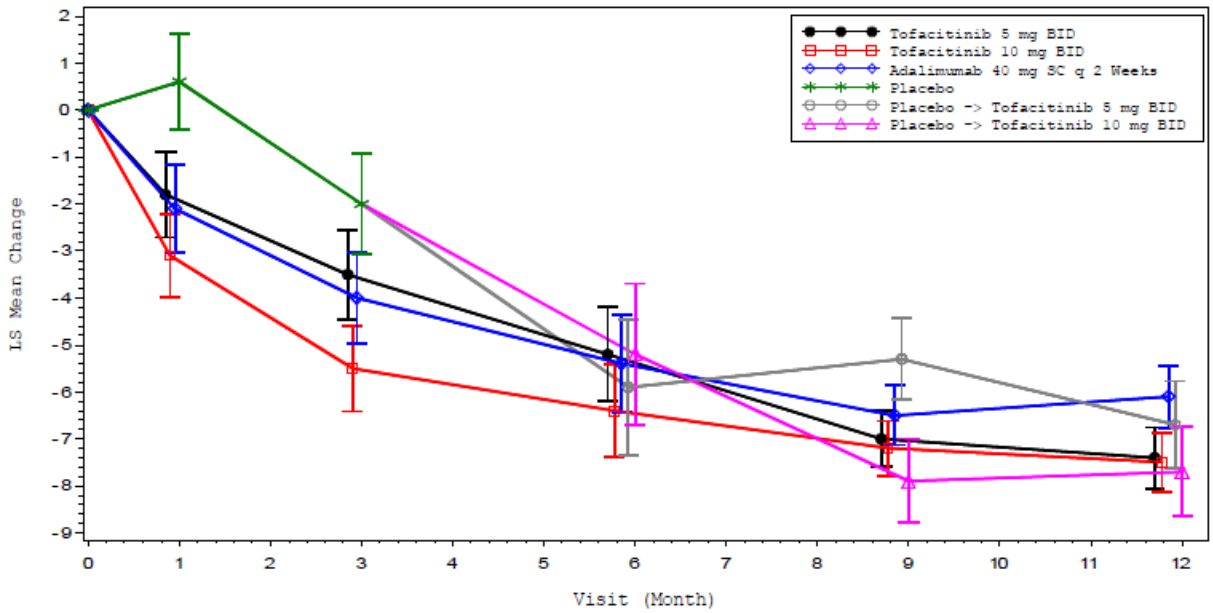
Figure 21 - Line Graph of Least Square Mean (±SE) ΔLeeds Enthesitis Index (LEI) up to Month 12 From the Repeated Measures Model (for Subjects With Baseline Score >0 in FAS, No Imputation)



Source: Figure 14.2.2.18.3.1 and Figure 14.2.2.18.3.2
Two separate analyses were performed. The results for Month 1 to Month 3 were generated using MMRM1 including data from Month 1 to Month 3 (combined placebo). The results for Month 6 to Month 12 were generated using MMRM2 including data from Month 1 to Month 12 (separate placebo treatment sequences; discarding the results for Month 1 to Month 3). Each model with the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used.
Subjects with baseline LEI score = 0 were excluded from the LEI analysis.
Abbreviations: Δ = change from baseline; BID = twice daily; FAS = Full Analysis Set; LEI = Leeds Enthesitis Index; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; SC = subcutaneous; SE = standard error; q = every.

Dactylitis

Figure 22 - Line Graph of Least Square Mean (±SE) ΔDactylitis Severity Score (DSS) up to Month 12 From the Repeated Measures Model (for Subjects With Baseline DSS >0 in FAS, No Imputation)



Source: Figure 14.2.2.17.3.1 and Figure 14.2.2.17.3.2
Two separate analyses were performed. The results for Month 1 to Month 3 were generated using MMRM1 including data from Month 1 to Month 3 (combined placebo). The results for Month 6 to Month 12 were generated using MMRM2 including data from Month 1 to Month 12 (separate placebo treatment sequences; discarding the results for Month 1 to Month 3 for plotting). Each model included the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used.
Subjects with baseline dactylitis score = 0 were excluded from analysis.
Abbreviations: Δ = change from baseline; BID = twice daily; DSS = Dactylitis Severity Score; FAS = Full Analysis Set; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; SC = subcutaneous; SE = standard error; q = every.

Psoriatic Arthritis Response Criteria (PsARC)

At Month 3, the PsARC response rates were 51.4%, 70.2% and 61.3% for tofacitinib 5 mg, tofacitinib 10 mg and adalimumab, vs 44.8% for placebo. The difference between tofacitinib 5 mg and placebo was not statistically significant.

Radiographic changes

Table 17 - Statistical Analysis (ANCOVA) of ΔModified Total Sharp Score at Month 12 (FAS, Linear Extrapolation) – Treatment Comparisons

Visit	Treatment Group	N	LS Mean	SE	Difference				
					Difference	SE of Difference	95% CI		P-value
							Lower	Upper	
Month 12	Tofa 5	98	0.01	0.067					
	Tofa 10	99	-0.01	0.067					
	ADA	95	-0.07	0.069					
	PBO → Tofa 5	48	0.00	0.094					
	PBO → Tofa 10	45	0.09	0.099					
	Tofa 10 vs Tofa 5				-0.02	0.083	-0.19	0.14	0.7744
	Tofa 5 vs ADA				0.08	0.084	-0.08	0.25	0.3301
	Tofa 10 vs ADA				0.06	0.084	-0.11	0.22	0.4844

Source: Table 14.2.2.1.3
In FAS, number of subjects in tofacitinib 5 mg BID: 107; tofacitinib 10 mg BID: 104; adalimumab 40 mg SC q 2 Weeks: 106; placebo→tofacitinib 5 mg BID: 52; placebo→tofacitinib 10 mg BID: 53.
Results were based on an ANCOVA model with the fixed effects of treatment, geographic location and baseline value as a covariate.
The linearly extrapolated value at Month 12 was calculated as Y = B+([X – B]/[date of assessment - date of baseline + 1]) × 337, where X was the value obtained prior to Month 12 and B was the baseline value.
P-values are nominal.
Abbreviations: Δ = change from baseline; ADA = adalimumab 40 mg SC q 2 weeks; ANCOVA = analysis of covariance; BID = twice daily; CI= confidence interval; FAS = Full Analysis Set; LS Mean = least squares mean; q = every; N = total number of unique subjects in ANCOVA analysis; PBO = placebo; SC = subcutaneous; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs=versus.

mTSS progressor rates

Table 18 - Normal Approximation to Progressor Rates (>0.5 Increase From Baseline in mTSS) at Month 12 (FAS, Linear Extrapolation) – Treatment Comparisons

Visit	Treatment Group	N	n	Progressor Rate (%)	SE	Difference				
						Difference	SE of Difference	95% CI		P-value
								Lower	Upper	
Month 12	Tofa 5	98	4	4.08	2.00					
	Tofa 10	99	5	5.05	2.20					
	ADA	95	2	2.11	1.47					
	PBO → Tofa 5	48	2	4.17	2.88					
	PBO → Tofa 10	45	4	8.89	4.24					
	Tofa 10 vs Tofa 5					0.97	2.97	-4.86	6.80	0.7445
	Tofa 5 vs ADA					1.98	2.48	-2.89	6.84	0.4260
	Tofa 10 vs ADA					2.95	2.65	-2.25	8.14	0.2661

Source: Table 14.2.2.2.2
In FAS, number of subjects in tofacitinib 5 mg BID: 107; tofacitinib 10 mg BID: 104; adalimumab 40 mg SC q 2 Weeks: 106; placebo→tofacitinib 5 mg BID: 52; placebo→tofacitinib 10 mg BID: 53.
Progressor was defined as a >0.5 increase from baseline in mTSS.
The linearly extrapolated value of mTSS at Month 12 was calculated as $Y = B+([X - B]/[\text{date of assessment - date of baseline} + 1]) \times 337$, where X was the value obtained prior to Month 12 and B was the baseline value.
Two-sided 95% CIs and p-values were based on the normal approximation for the difference in binomial proportions.
P-values are nominal.
Abbreviations: ADA = adalimumab 40 mg SC q 2 weeks; BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; mTSS = modified Total Sharp Score; N = number of subjects evaluable at Month 12 after linear extrapolation; n = number of progressors; PBO = placebo; q = every; SC = subcutaneous; SE = standard error; tofa 5 = tofacitinib 5 mg BID; tofa 10 = tofacitinib 10 mg BID; vs=versus.

Physical function and health outcome measures

SF36v2

For the physical functioning domain, physical component and bodily pain domain at Month 3, LS mean changes are increased for all 3 active treatments vs placebo, reaching statistical significance. The improvements are maintained over the 12-month study.

For the vitality domain at Month 3, LS mean changes are increased for tofacitinib 5 mg and 10 mg vs placebo, reaching statistical significance. The improvements are maintained over the 12-month study.

For the social functioning domain at Month 3, LS mean changes are increased for tofacitinib 5 mg vs placebo, reaching statistical significance. The improvements are maintained over the 12-month study.

For the mental component and role – emotional domain, there is a trend in favour of tofacitinib 5 mg and 10 mg at Month 3.

For role-physical domain, mental health domain and general health domain, there is a trend in favour of all 3 active treatments at Month 3.

EuroQol-5 Dimension Health State Profile (EQ-5D-3-level)

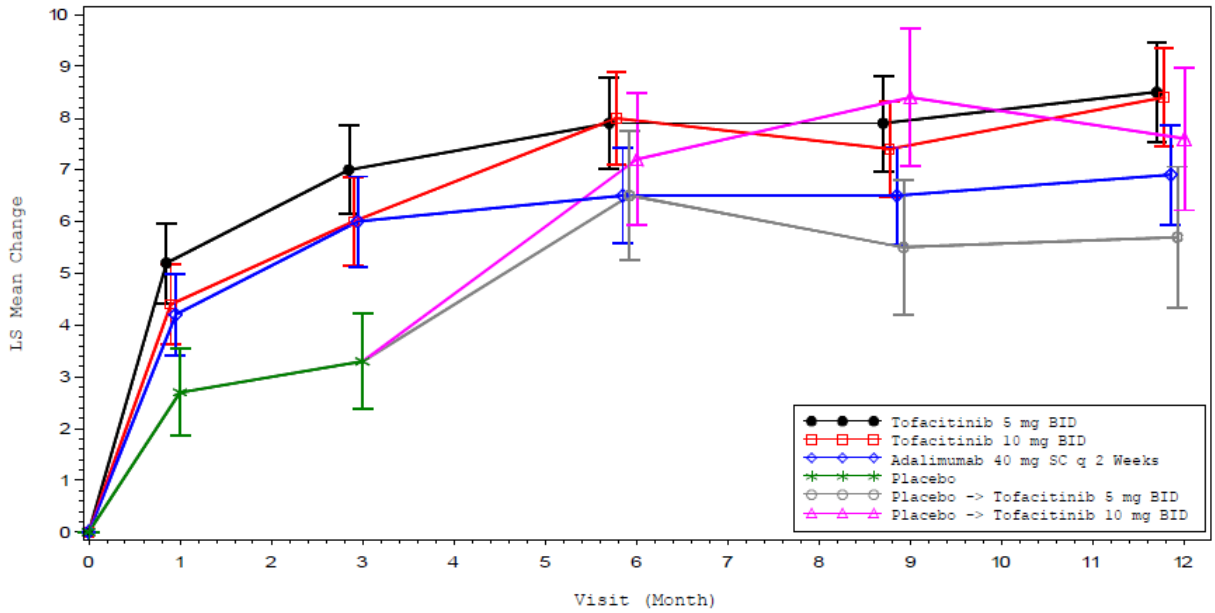
For the mobility domain and the pain/discomfort domain, the LS mean change from baseline at Month 3 was greater for the active treatment groups vs placebo to a statistically significant extent. The changes were maintained during the 12-month study.

For the self-care domain, the usual activities domain and the anxiety/depression domain, there was no statistically significant difference compared to placebo.

Regarding the VAS score (mm) on the subjects' health care state today, the Month 3 LS mean scores (change from baseline) were 14.00, 15.83 and 13.10 for tofacitinib 5 mg, tofacitinib 10 mg and adalimumab, compared to 6.37 for placebo. These treatment differences reached statistical significance. The scores were maintained during the 12-month study.

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

Figure 23 - Line Graph of Least Square Mean (±SE) ΔFACIT-F Total Score up to Month 12 From the Repeated Measures Model (FAS, No Imputation) - Comparisons to Placebo



Source: Figure 14.2.2.20.3.1 and Figure 14.2.2.20.3.2
Two separate analyses were performed. The results for Month 1 to Month 3 were generated using MMRM1 including data from Month 1 to Month 3 (combined placebo). The results for Month 6 to Month 12 were generated using MMRM2 including data from Month 1 to Month 12 (separate placebo treatment sequences; discarding the results for Month 1 to Month 3). Each model included the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used.
Abbreviations: Δ = change from baseline; BID = twice daily; FAS = Full Analysis Set; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; SC = subcutaneous; SE = standard error; q = every.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The numbers included in this analysis are small: 24, 21, 10 and 22 subjects in tofacitinib 5 mg, tofacitinib 10 mg, adalimumab and placebo groups, respectively:

Table 19 - Statistical Analysis (Repeated Measures Model) of ΔBath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Months 1, 3, 6, and 12 (for Subjects With Presence of Spondylitis at Screening and Baseline BASDAI Score >0 cm in FAS, No Imputation) – Treatment Comparisons

Visit	Treatment Group	N	n	LS Mean	SE	Difference				
						Difference	SE of Difference	95% CI		P-value
								Lower	Upper	
Month 1	Tofa 5	24	24	-1.23	0.537					
	Tofa 10	21	21	-1.60	0.508					
	ADA	10	10	-2.30	0.673					
	PBO	22	22	-1.27	0.581					
	Tofa 5 vs PBO					0.05	0.478	-0.91	1.00	0.9210
	Tofa 10 vs PBO					-0.32	0.491	-1.30	0.66	0.5111
	ADA vs PBO					-1.02	0.607	-2.23	0.19	0.0964
	Tofa 10 vs Tofa 5					-0.37	0.481	-1.33	0.59	0.4414
	Tofa 5 vs ADA					1.07	0.602	-0.13	2.27	0.0801
	Tofa 10 vs ADA					0.70	0.610	-0.52	1.91	0.2563
Month 3	Tofa 5	24	24	-1.83	0.579					
	Tofa 10	21	21	-2.78	0.559					
	ADA	10	10	-2.93	0.753					
	PBO	22	22	-1.60	0.624					
	Tofa 5 vs PBO					-0.23	0.572	-1.37	0.91	0.6848
	Tofa 10 vs PBO					-1.18	0.589	-2.36	-0.01	0.0486
	ADA vs PBO					-1.33	0.730	-2.79	0.12	0.0722
	Tofa 10 vs Tofa 5					-0.95	0.577	-2.10	0.20	0.1042
	Tofa 5 vs ADA					1.10	0.724	-0.34	2.54	0.1331
	Tofa 10 vs ADA					0.15	0.735	-1.31	1.62	0.8378
Month 6	Tofa 5	24	23	-2.24	0.580					
	Tofa 10	21	21	-2.35	0.560					
	ADA	10	10	-3.58	0.758					
	PBO → Tofa 5	10	9	-2.85	0.778					
	PBO → Tofa 10	12	11	-3.31	0.744					
	Tofa 10 vs Tofa 5					-0.11	0.593	-1.29	1.08	0.8552
	Tofa 5 vs ADA					1.34	0.774	-0.15	2.82	0.0769
	Tofa 10 vs ADA					1.23	0.753	-0.28	2.73	0.1076
Month 12	Tofa 5	24	23	-2.50	0.594					
	Tofa 10	21	19	-3.30	0.587					
	ADA	10	10	-2.42	0.779					
	PBO → Tofa 5	10	9	-2.31	0.808					
	PBO → Tofa 10	12	9	-2.67	0.806					
	Tofa 10 vs Tofa 5					-0.80	0.631	-2.06	0.46	0.2106
	Tofa 5 vs ADA					-0.08	0.776	-1.63	1.47	0.9202
	Tofa 10 vs ADA					-0.88	0.793	-2.46	0.71	0.2738

Source: Table 14.2.2.19.3.1 and Table 14.2.2.19.3.2

Number of subjects in FAS with presence of spondylitis at screening and baseline BASDAI score >0 cm for tofacitinib 5 mg BID: 24; tofacitinib 10 mg BID: 21; adalimumab 40 mg SC q 2 weeks: 10; placebo: 22; placebo→tofacitinib 5 mg BID: 10; placebo→tofacitinib 10 mg BID: 12.

Subjects with absence of spondylitis at screening or baseline BASDAI = 0 were excluded from the analysis.

Two separate analyses were performed. The results for Month 1 and Month 3 were generated using MMRM1 including data from Month 1 to Month 3 (combined placebo). The results for Month 6 to Month 12 were generated using MMRM2 including data from Month 1 to Month 12 (separate placebo treatment sequences; discarding the results for Month 1 to Month 3). Each model with the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used.

P-values are nominal.

Abbreviations: Δ = change from baseline; ADA = adalimumab 40 mg SC q 2 weeks; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; N = total number of unique subjects in the longitudinal model; n = number of subjects evaluable at each visit; PBO = placebo; q = every; SC = subcutaneous; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs=versus.

Other efficacy evaluations

DAS28-3 (CRP)

Table 20 - Statistical Analysis (Repeated Measures Model) of ΔDAS28-3 (CRP) at Months 3, 6 and 12 (FAS, No Imputation) – Treatment Comparisons

Visit	Treatment Group	N	n	LS Mean	SE	Difference	SE of Difference	95% CI Lower	95% CI Upper	P-value
Month 3	Tofa 5	107	101	-1.329	0.1019					
	Tofa 10	104	103	-1.628	0.1022					
	ADA	106	99	-1.513	0.1038					
	PBO	104	101	-0.773	0.1072					
	Tofa 5 vs PBO					-0.556	0.1384	-0.828	-0.284	<0.0001
	Tofa 10 vs PBO					-0.855	0.1383	-1.127	-0.584	<0.0001
	ADA vs PBO					-0.740	0.1383	-1.012	-0.469	<0.0001
	Tofa 10 vs Tofa 5					-0.300	0.1371	-0.569	-0.030	0.0294
	Tofa 5 vs ADA					0.185	0.1377	-0.086	0.456	0.1804
	Tofa 10 vs ADA					-0.115	0.1376	-0.385	0.155	0.4037
Month 6	Tofa 5	107	100	-1.661	0.1065					
	Tofa 10	104	99	-1.943	0.1073					
	ADA	106	99	-1.806	0.1082					
	PBO → Tofa 5	52	48	-1.719	0.1521					
	PBO → Tofa 10	52	48	-1.617	0.1533					
	Tofa 5 vs PBO					-0.282	0.1446	-0.566	0.003	0.0520
	Tofa 10 vs PBO					0.146	0.1446	-0.139	0.430	0.3149
	ADA vs PBO					-0.136	0.1449	-0.421	0.149	0.3478
Month 12	Tofa 5	107	95	-1.926	0.1101					
	Tofa 10	104	96	-2.048	0.1105					
	ADA	106	93	-1.912	0.1122					
	PBO → Tofa 5	52	44	-2.020	0.1587					
	PBO → Tofa 10	52	44	-1.968	0.1602					
	Tofa 10 vs Tofa 5					-0.122	0.1494	-0.416	0.172	0.4156
	Tofa 5 vs ADA					-0.014	0.1501	-0.310	0.281	0.9245
	Tofa 10 vs ADA					-0.136	0.1500	-0.431	0.159	0.3653

Source: Table 14.2.2.23.3.1 and Table 14.2.2.23.3.2
In FAS, number of subjects in tofacitinib 5 mg BID: 107; tofacitinib 10 mg BID: 104; adalimumab 40 mg SC q 2 weeks: 106; placebo: 105; placebo→tofacitinib 5 mg BID: 52; placebo→tofacitinib 10 mg BID: 53.

Two separate analyses were performed. The results for Month 3 were generated using MMRM1 including data from Month 1 to Month 3 (combined placebo). The results for Month 6 to Month 12 were generated using MMRM2 including data from Month 1 to Month 12 (separate placebo treatment sequences; discarding the results for Month 1 to Month 3). Each model with the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used.
P-values are nominal.
Abbreviations: Δ = change from baseline; ADA = adalimumab 40 mg SC q 2 weeks; BID = twice daily; CI = confidence interval; CRP = C-reactive protein; DAS = Disease Activity Score; FAS = Full Analysis Set; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; N = total number of unique subjects in the longitudinal model; n = number of subjects evaluable at each visit; PBO = placebo; q = every; SC = subcutaneous; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs=versus.

Minimal disease activity

Another exploratory endpoint was minimal disease activity (MDA). A psoriatic arthritis patient is defined as having Minimal Disease Activity (MDA)26 when the patient meets ≥5 of the 7 following criteria: 1) tender joint count ≤1; 2) swollen joint count ≤1; 3) PASI score ≤1 or BSA ≤3%; 4) patient Arthritis Pain (VAS) ≤15; 5) patient's global arthritis assessment (VAS) ≤20; HAQ-DI score ≤0.5; 6) tender entheseal points (using Leed's Index) ≤1.

Table 21 - Normal Approximation to MDA Rates at Months 3, 6, and 12 (FAS, Missing Response = Non-Response) – Treatment Comparisons

Visit	Treatment Group	N	n	Response Rate (%)	SE (%)	Difference				
						Difference (%)	SE of Difference (%)	95% CI Lower (%)	95% CI Upper (%)	P-value
Month 3	Tofa 5	107	28	26.17	4.25					
	Tofa 10	104	27	25.96	4.30					
	ADA	106	27	25.47	4.23					
	PBO	105	7	6.67	2.43					
	Tofa 5 vs PBO					19.50	4.90	9.90	29.10	<0.0001
	Tofa 10 vs PBO					19.29	4.94	9.61	28.98	<0.0001
	ADA vs PBO					18.81	4.88	9.24	28.37	0.0001
	Tofa 10 vs Tofa 5					-0.21	6.04	-12.05	11.64	0.9727
	Tofa 5 vs ADA					0.70	6.00	-11.06	12.45	0.9075
	Tofa 10 vs ADA					0.49	6.03	-11.33	12.31	0.9353
Month 6	Tofa 5	107	28	26.17	4.25					
	Tofa 10	104	39	37.50	4.75					
	ADA	106	38	35.85	4.66					
	PBO → Tofa 5	52	10	19.23	5.47					
	PBO → Tofa 10	53	18	33.96	6.51					
	Tofa 10 vs Tofa 5					11.33	6.37	-1.16	23.82	0.0753
	Tofa 5 vs ADA					-9.68	6.30	-22.04	2.68	0.1247
	Tofa 10 vs ADA					1.65	6.65	-11.38	14.69	0.8040
Month 12	Tofa 5	107	40	37.38	4.68					
	Tofa 10	104	45	43.27	4.86					
	ADA	106	42	39.62	4.75					
	PBO → Tofa 5	52	16	30.77	6.40					
	PBO → Tofa 10	53	18	33.96	6.51					
	Tofa 10 vs Tofa 5					5.89	6.74	-7.33	19.10	0.3828
	Tofa 5 vs ADA					-2.24	6.67	-15.31	10.83	0.7369
	Tofa 10 vs ADA					3.65	6.79	-9.67	16.96	0.5915

Source: Table 14.2.2.8.2 and Table 14.2.2.8.4
The 2-sided 95% CI was based on the normal approximation for the difference in binomial proportions.
P-values are nominal.
Abbreviations: ADA = adalimumab 40 mg SC q 2 weeks; BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; MDA = Minimal Disease Activity; N = number of subjects in FAS; n = number of responders; PBO = placebo; q = every; SC = subcutaneous; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs = versus.

PASDAS

PASDAS is a composite PsA disease activity score that includes the following components: Patient's Global Joint and Skin Assessment (VAS: 0-100 mm), Physician's Global Assessment of Psoriatic Arthritis (VAS: 0-100 mm), swollen and tender/painful joint counts (66/68), LEI score, tender dactylitic digit score, PCS of SF-36v2 and CRP (mg/L).

The ΔPASDAS at Month 3 in Study A3921091 was greater for subjects receiving tofacitinib 5 mg BID (-1.99), tofacitinib 10 mg BID (-2.39), adalimumab (-2.17) versus placebo (-1.21) (the 2-sided 95% CI for the difference between each active treatment group and placebo excluded 0). The improvement in PASDAS was sustained or increased for the 3 active treatment groups at time points after Month 3 through Month 12.

Additional subgroup analyses

Target population

In order to establish if the indication population should be restricted to patients with MTX inadequate response (IR), additional subgroup analyses were performed. At baseline, around 6% of the population of study A3921091 (csDMARD-IR) had an inadequate response to one csDMARD other than MTX. In addition, 1.4% had an inadequate response to >1 csDMARD that did not include MTX. These subgroups are too small for meaningful efficacy or safety analyses. However, the subgroup with an inadequate response to >1 csDMARD can provide supportive information, since patients in this subgroup (>1 csDMARD-IR) had an inadequate response to a csDMARD other than MTX and should represent a more difficult to treat population.

The efficacy outcomes of the >1 csDMARD subgroup vs 1 csDMARD-IR subgroup (predominantly MTX-IR) are presented below:

Table 22 - Comparison of Responder Rates for Selected Efficacy Endpoints at Month 3 by Number of Prior csDMARD-IRs in Study A3921091

	1 csDMARD-IR						≥2 csDMARD-IRs					
	Placebo		Tofa 5		ADA		Placebo		Tofa 5		ADA	
Response Rates	N/ n	% (SE)	N/ n	% (SE or 95% CI)[a]	N/ n	% (SE or 95% CI)[a]	N/ n	% (SE)	N/ n	% (SE or 95% CI)[a]	N/ n	% (SE or 95% CI)[a]
ACR20	76/ 24	31.6 (5.3)	72/ 32	44.4 (5.9)	65/ 34	52.3 (6.2)	29/ 11	37.9 (9.0)	35/ 22	62.9 (8.2)	41/ 21	51.2 (7.8)
Active Treatment vs Placebo				12.9 (-2.7, 28.4)		20.7 (4.7, 36.8)				24.9 (1.1, 48.8)		13.3 (-10.1, 36.7)
ACR50	76/ 6	7.9 (3.1)	72/ 17	23.6 (5.0)	65/ 23	35.4 (5.9)	29/ 4	13.8 (6.4)	35/ 13	37.1 (8.2)	41/ 12	29.3 (7.1)
Active Treatment vs Placebo				15.7 (4.2, 27.3)		27.5 (14.4, 40.6)				23.35 (3.0, 43.7)		15.5 (-3.3, 34.2)
ACR70	76/ 3	4.0 (2.2)	72/ 11	15.3 (4.2)	65/ 13	20.0 (5.0)	29/ 2	6.9 (4.7)	35/ 7	20.0 (6.8)	41/ 7	17.1 (5.9)
Active Treatment vs Placebo				11.3 (1.9, 20.7)		16.05 (5.4, 26.7)				13.1 (-3.0, 29.3)		10.2 (-4.6, 24.9)
PASI75[b]	58/ 9	15.5 (4.8)	56/ 25	44.6 (6.6)	46/ 17	37.0 (7.1)	24/ 3	12.5 (6.8)	26/ 10	38.5 (9.5)	31/ 13	41.9 (8.9)
Active Treatment vs Placebo				29.1 (13.1, 45.1)		21.4 (4.7, 38.2)				26.0 (3.1, 48.9)		29.4 (7.6, 51.3)

a. SE values are provided for the absolute result and 95% CI are provided for comparison to placebo.
b. PASI75 was measured in subjects with baseline BSA ≥3% and PASI >0 in FAS with non-missing concomitant csDMARD use. PASI75 is defined as a ≥75% reduction from baseline in PASI.
Abbreviations: ACR = American College of Rheumatology; ACR20, 50, 70 = ACR Response Criteria ≥20%, ≥50%, ≥70% improvement from baseline, respectively; ADA = adalimumab 40 mg SC q2w; BID = twice daily; BSA = body surface area; CI = confidence interval; csDMARD = conventional synthetic DMARD; DMARD = disease-modifying anti-rheumatic drug; FAS = full analysis set; IR = inadequate response; N = number of subjects in FAS with non-missing concomitant csDMARD use; n = number of responders; PASI = Psoriasis Area and Severity Index; q2w = every two weeks; SC = subcutaneous; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; vs = versus.
Missing values for ACR20, ACR50, ACR70, and PASI75 were considered as non-response to treatment.
Sources Module 5.3.5.3 Efficacy RSI D90 Tables 00061.1.2.1; 00061.1.2.2; 00061.1.2.3; 00061.1.2.4.

Table 23 - Comparison of Change from Baseline in Least Squares Mean for Selected Efficacy Endpoints at Month 3 by Number of Prior csDMARD-IR in Study A3921091

	1 csDMARD-IR						≥2 csDMARD-IRs					
	Placebo		Tofa 5		ADA		Placebo		Tofa 5		ADA	
	N/ n	LSM (SE)	N/ n	LSM (SE or 95% CI)[a]	N/ n	LSM (SE or 95% CI)[a]	N/ n	% (SE)	N/ n	LSM (SE or 95% CI)[a]	N/ n	LSM (SE or 95% CI)[a]
ΔHAQ-DI	75/ 73	-0.20 (0.06)	72/ 68	-0.26 (0.06)	65/ 62	-0.42 (0.06)	29/ 29	-0.15 (0.10)	35/ 35	-0.54 (0.08)	41/ 39	-0.33 (0.08)
Active Treatment vs Placebo				-0.07 (-0.21, 0.08)		-0.23 (-0.37, -0.08)				-0.38 (-0.61, -0.16)		-0.18 (-0.40, 0.04)
ΔLEI[b]	48/ 46	-0.48 (0.28)	51/ 48	-0.62 (0.26)	47/ 45	-1.46 (0.28)	17/ 17	-0.57 (0.44)	23/ 22	-1.41 (0.35)	29/ 28	-0.65 (0.33)
Active Treatment vs Placebo				-0.14 (-0.81, 0.53)		-0.98 (-1.66, -0.30)				-0.84 (-1.82, 0.14)		-0.08 (-1.01, 0.85)
ΔDSS[b]	41/ 39	-0.80 (1.38)	38/ 36	-3.06 (1.28)	34/ 32	-4.02 (1.39)	16/ 16	-4.39 (1.56)	22/ 22	-4.00 (1.33)	24/ 24	-3.71 (1.22)
Active Treatment vs Placebo				-2.27 (-5.52, 0.99)		-3.22 (-6.54, 0.10)				0.39 (-2.90, 3.67)		0.68 (-2.58, 3.93)

a. SE values are provided for the absolute result and 95% CI are provided for comparison to placebo.
b. ΔLEI and ΔDSS were measured in subjects with baseline LEI>0 and DSS>0, respectively.
Abbreviations: Δ = change from baseline; ADA = adalimumab 40 mg SC q2w; BID = twice daily; CI = confidence interval; csDMARD = conventional synthetic DMARD; DMARD = disease-modifying anti-rheumatic drug; DSS = Dactylitis Severity Score; HAQ-DI = Health Assessment Questionnaire-Disability Index; IR = inadequate response; LEI = Leeds Enthesitis Index; LSM = least squares mean; N = total number of unique subjects in the longitudinal model; n = number of subjects evaluable at each visit; q2w = every two weeks; SC = subcutaneous; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; vs = versus.
A longitudinal model was used to analyse the ΔHAQ-DI, ΔLEI, and ΔDSS without imputation for missing values.
Sources: Module 5.3.5.3 Efficacy RSI D90 Tables 00061.1.2.7; 00061.1.2.8; 00061.1.2.9.

Study A3921125: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of 2 Doses of Tofacitinib (CP-690,550) in Subjects with Active Psoriatic Arthritis and an Inadequate Response to At Least One TNF Inhibitor

Methods

Study participants

Inclusion criteria included:

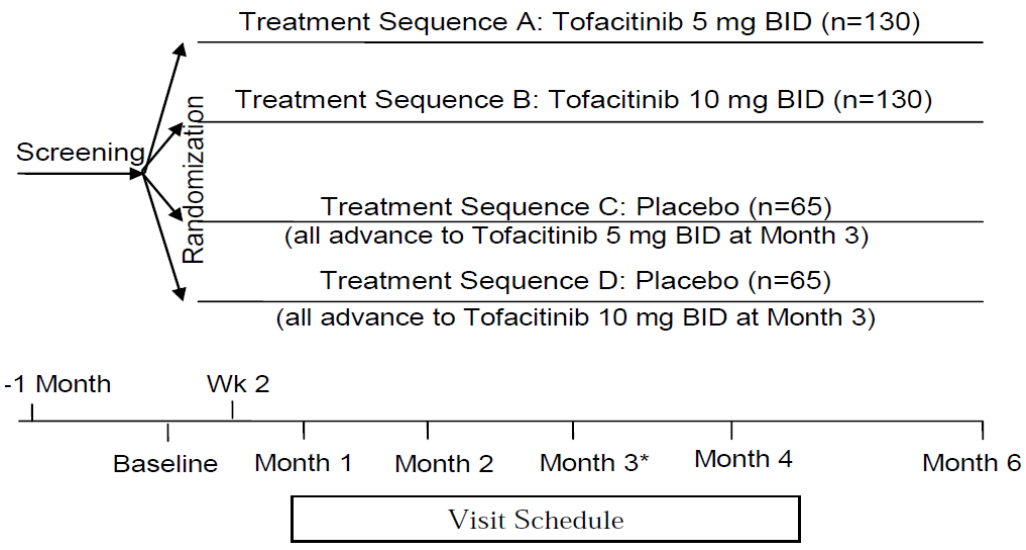
- The subject had signs and symptoms consistent with the diagnosis of PsA for at least 6 months, fulfilled CASPAR criteria at screening and had evidence of active arthritis based upon number of tender/painful and swollen joints.
- Subjects must have received one permitted background csDMARD that was dosed in accordance with the local regulatory label. Subjects remained on a stable dose of that csDMARD throughout the course of the study. Permitted csDMARDs were methotrexate, sulfasalazine, leflunomide, or other csDMARDs not listed as a prohibited concomitant medication after discussion with the Pfizer Study Clinician.
- The subject must have had active arthritis at both screening and baseline, as defined by having both: ≥3 tender/painful joints on motion (out of 68 joints assessed) and ≥ 3 swollen joints (out of 66 joints assessed).
- At screening, the subject must have had active plaque psoriasis that had been diagnosed or confirmed by a dermatologist or a Sponsor-approved rheumatologist.
- Subjects must have received at least one approved TNF inhibiting biologic agent that was administered in accordance with its labelling recommendations and was inadequately effective and/or not tolerated as follows:
    - 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.
- At least 18 years of age at the screening visit.
- No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB).
- Discontinuation of disallowed concomitant medications: biological DMARDs (including TNFi), injectable steroids (except intra-articular steroids used as rescue), certain agents for the treatment of psoriasis, inhibitors and inducers of CYP3A4
- Subjects who were already taking oral corticosteroids (stable dose of ≤ 10 mg per day of prednisone or equivalent for 4 weeks prior to first dose of study drug)
- Subjects who were already taking nonsteroidal anti-inflammatory drugs (NSAIDs)/cyclo-oxygenase 2 (COX-2) inhibitors could have participated in the study provided that the dose was stable for 1 week prior to first dose of study drug.

Exclusion criteria included:

- Currently had non-plaque forms of psoriasis, e.g., erythrodermic, guttate or pustular, except for nail psoriasis.
- Functional Class IV as defined by the ACR classification of functional status for RA, i.e., limited in ability to perform usual self-care, vocational and avocational activities.
- Pregnant females, breastfeeding females, females of childbearing potential not using highly effective contraception
- Criteria related to severe, progressive or uncontrolled organ dysfunction, blood dyscrasias (within 3 months prior to first dose of study drug), immunodeficiency
- Subjects with history of any autoimmune rheumatic disease other than PsA (including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis) or known diagnosis of fibromyalgia, without approval by Sponsor. Prior history of, or current, rheumatic inflammatory disease other than PsA (e.g., gout, reactive arthritis, chronic Lyme disease) without approval by Sponsor.
- History of any lymphoproliferative disorder, such as Epstein-Barr Virus-related lymphoproliferative disorder, history of lymphoma, leukaemia, or signs and symptoms suggestive of current lymphatic disease.
- History of recurrent (more than 1 episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.
- Recent history of active infection, vaccination with live or attenuated vaccines.
- A subject with evidence of skin conditions (e.g., eczema) at the time of the screening or baseline visit that would have interfered with evaluation of psoriasis.
- A subject that was considered at increased risk for GI perforation (e.g., subjects with diverticulitis) by the Investigator or Sponsor.

Treatments

Figure 24 - Overview of study design



Abbreviations: BID = twice daily; n = number of subjects; Wk = week.

*Primary study endpoints of American College of Rheumatology Response Criteria ≥ 20% and change from baseline in score on the Health Assessment Questionnaire – Disability Index were obtained at Month 3. All subjects randomized to placebo treatment sequences were to receive tofacitinib (5 or 10 mg BID, Treatment sequences C and D, respectively) in a blinded manner after Month 3.

At the end of Month 6, eligible subjects may have enrolled into the open-label, long-term extension study A3921092.

During the study, subjects remained on a stable dose of 1 csDMARD, e.g., methotrexate, sulfasalazine, leflunomide, or other drug as approved by the Study Clinician, dosed in accordance with the local regulatory label. Subjects on methotrexate must have received folate supplementation per local methotrexate label guidelines and standard of care. Subjects were also permitted to remain on a stable dose of NSAIDs/COX-2 inhibitor, corticosteroid, opioids (up to potency equivalent of 30 mg oral morphine) and acetaminophen/paracetamol (up to 2.6 g daily) from 1 week prior to first study dose. The only exception was adjustment for safety reasons.

Certain medications were permitted for rescue. Increases of acetaminophen/paracetamol and opioids were allowable as rescue medication. Subjects who required rescue for more than 10 consecutive days were discontinued from the study. Intra-articular corticosteroids or hyaluronate sodium could be administered at or after the Month 3 visit (after study assessments) in no more than 2 joints. Injected joints were considered as having their pre-injection status (tender/painful and swollen joint count) and were not counted for the remainder of the study.

Objectives

Primary objectives:

1. To compare efficacy of tofacitinib at doses of 5 mg BID and 10 mg BID versus placebo for treatment of rheumatological signs and symptoms of active PsA in subjects who have had an inadequate response in PsA to at least 1 TNFi.
2. To compare physical function status after administration of tofacitinib at doses of 5 mg BID and 10 mg BID versus placebo in subjects with active PsA who have had an inadequate response in PsA to at least 1 TNFi.
3. To compare the safety and tolerability of tofacitinib at doses of 5 mg BID and 10 mg BID versus placebo in subjects with active PsA who have had an inadequate response in PsA to at least 1 TNFi.

Secondary objectives were also listed, relating to efficacy for health outcome measures, dermatological signs and symptoms, and pharmacokinetic (PK) characterisation.

Outcomes / endpoints

Primary efficacy evaluation

There were two primary efficacy endpoints: ACR20 responder rates at Month 3, and Δ HAQ-DI at Month 3.

ACR20 was calculated as a ≥20% improvement in tender/painful and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. The specific components of the ACR assessments used in this study were: Tender/Painful Joint count (68); Swollen Joint Count (66); Patient's Assessment of Arthritis Pain (Visual Analog Scale [VAS]); Patient's Global Assessment of Arthritis (VAS); Physician's Global Assessment of Arthritis (VAS); CRP; HAQ-DI.

Secondary efficacy evaluation

Signs and symptoms evaluated by:

- ACR50 and ACR70 responder rates at all time points
- ACR20 responder rates at all time points other than Month 3
- ΔACR response criteria components (except HAQ-DI) at Month 3
- Psoriatic Arthritis Response Criteria (PsARC) at all Months 1, 3 and 6
- Δ Physician's Global Assessment of Psoriasis (PGA-PsO) response at Months 1, 3 and 6
- Psoriasis Area and Severity Index 75 (PASI75) response at Months 1, 3 and 6
- ΔDactylitis Severity Score (DSS) at Months 1, 3 and 6
- ΔEnthesitis (using the Leeds Enthesitis Index [LEI] and Spondyloarthritis Research Consortium of Canada [SPARCC] Enthesitis Index) at Months 1, 3 and 6

Secondary Patient-Reported Outcomes (PROs) of Physical Function and Health Outcome Measures (assessed at Months 1, 3 and 6):

- ΔShort-Form 36 (SF-36) Version 2, Acute
- ΔEuroQol-5 Dimension health state profile (EQ-5D) and ΔEQ-VAS
- FACIT-F (3 endpoints: total score, experience domain score and impact domain score)

Evaluation of spondylitis using ΔBath Anklyosing Spondylitis Disease Activity Index (BASDAI)

Sample size

The sample size and power analysis for the 2 primary endpoints were based on subjects randomised in a 2:2:1:1 ratio where the 2 placebo groups were combined, effectively resulting in a 1:1:1 randomisation for the primary analysis at 3 months. All hypotheses were tested at the nominal alpha level of 2.5% (5% 2-sided).

The sample size for this study was driven by the ACR20 response rate. On the assumption of a placebo response rate of 15%, a sample size of 130 subjects per treatment arm yields approximately 84% power to detect a difference of 15% from placebo in ACR20 response; this sample size would also yield approximately 97% power to detect an ACR20 response difference of at least 20%.

For the analysis of HAQ-DI, the sample size of 130 subjects per treatment arm results in approximately 98% power to detect a difference between the 2 means of 0.3 or greater, assuming a SD of 0.6.

Randomisation

Randomisation was conducted by means of an Interactive Voice Response System (IVRS). The randomisation was not stratified.

Blinding (masking)

This was a double-blind study. Subjects were assigned a combination of active and placebo 5 mg tablets according to the randomisation schedule.

All rheumatological and dermatological assessments including the physician's global efficacy assessments were performed by qualified assessors who were blinded to study drug treatment, laboratory values (including CRP), subject safety and prior efficacy data. The same qualified assessor was requested to score all evaluations for a particular assessment for a given subject throughout the study. Laboratory samples were analysed by a central laboratory.

Statistical methods

General Considerations

The primary efficacy analysis was conducted on data collected during the first 3 months where inferential comparisons to placebo entailed combining treatment sequences C and D to form 1 placebo group. The primary comparisons were between each tofacitinib dose and placebo at Month 3.

All statistical tests for efficacy endpoints were 2-sided at a significance level of 0.05.

In order to control the Type I error, a step-wise testing procedure was used. This implied that a given endpoint for a given dose can only achieve significance (i.e., conclude superiority) if the prior endpoint was significant. The order or fixed sequence for testing against placebo was as follows: tofacitinib 10 mg ACR20 response rate at Month 3, tofacitinib 5 mg ACR20 response rate at Month 3, tofacitinib 10 mg ΔHAQ-DI at Month 3 and tofacitinib 5 mg ΔHAQ-DI at Month 3.

A step-down approach was also applied to certain secondary efficacy endpoints. Key secondary efficacy variables were as follows: PASI75, ΔLEI, ΔDSS, ΔPhysical Functioning Domain of SF-36 and FACIT-F (3 endpoints in order of testing priority: ΔFACIT-F total score, ΔFACIT-F experience domain score and ΔFACIT-F impact domain score) at Month 3. In order to strongly protect the study-wise Type I error rate at the 0.05 (2-sided) level with respect to these key secondary endpoints and the primary endpoints, these endpoints were tested only if all endpoints/doses for the primary endpoints were statistically significant. The order of testing was as listed above; for each endpoint, tofacitinib 10 mg was tested versus placebo first, followed by tofacitinib 5 mg versus placebo. Testing stopped at the first instance in which statistical significance was not achieved.

Analysis sets

The Full Analysis Set (FAS): All subjects who were randomized to the study and received at least 1 dose of the randomized study drug (tofacitinib, or placebo). The FAS was used for all analyses of all efficacy and PRO endpoints and was the primary dataset for the primary endpoints.

The Per-Protocol (PP) Analysis Set: The PP Analysis Set excluded all subjects who had a protocol deviation thought to have a material impact on the primary efficacy analysis The PP Analysis Set was used in a sensitivity analysis for each of the 2 primary endpoints.

Endpoint Specific Analysis Sets: Subjects were excluded from FAS for a specific endpoint if certain conditions were met for the endpoints based upon baseline criteria. These criteria were used to ensure that only patients with the condition present or severe enough to allow room for response were included in analyses for endpoints where presence of that condition was not an inclusion criterion.

The Safety Analysis Set (Safety): this set included all subjects who received at least 1 dose of the randomized study drug (tofacitinib or placebo).

Analysis of the primary endpoints

The analysis methods were identical to those used for study A3921091, please see above.

Interim analyses

No interim analyses were conducted for this study.

Results

Participant flow

Of 546 subjects screened for entry into the study, 395 subjects were randomized to double-blind treatment; 132 subjects to tofacitinib 5 mg BID, 132 subjects to tofacitinib 10 mg BID, 66 subjects to placebo → tofacitinib 5 mg BID, and 65 subjects to placebo → tofacitinib 10 mg BID.

There were 394 treated subjects included in the FAS as 1 subject in the tofacitinib 5 mg BID sequence was randomized but was not treated; all 394 subjects in the FAS were analysed for safety data and 393 subjects were analysed for laboratory data.

Table 24 - Subject Evaluation Groups by Treatment Sequence, Month 6

Number (%) of Subjects	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo → Tofacitinib 5 mg BID	Placebo → Tofacitinib 10 mg BID	Total
Screened (546)					
Assigned to study drug	132	132	66	65	395
Treated	131 (99.2)	132 (100.0)	66 (100.0)	65 (100.0)	394 (99.7)
Completed	122 (93.1)	111 (84.1)	56 (84.8)	56 (86.2)	345 (87.6)
Discontinued	9 (6.9)	21 (15.9)	10 (15.2)	9 (13.8)	49 (12.4)
Analyzed for efficacy					
FAS	131 (100.0)	132 (100.0)	66 (100.0)	65 (100.0)	394 (100.0)
PP	120 (91.6)	124 (93.9)	64 (97.0)	63 (96.9)	371 (94.2)
Analyzed for safety	131 (100.0)	132 (100.0)	66 (100.0)	65 (100.0)	394 (100.0)
AEs	131 (100.0)	132 (100.0)	66 (100.0)	65 (100.0)	394 (100.0)
Laboratory data	130 (99.2)	132 (100.0)	66 (100.0)	65 (100.0)	393 (99.7)

Source: Table 14.1.1.1.1.
Abbreviations: AE = adverse event; BID = twice daily; FAS = Full Analysis Set; PP = Per-Protocol.
Full Analysis Set (FAS) – All subjects who were randomized to the study and received at least 1 dose of the randomized study drug (tofacitinib or placebo).
Per-Protocol Analysis Set (PP) – All FAS subjects who did not have a protocol deviation thought to have a material impact on the primary efficacy analysis.
Safety Analysis Set (Safety) – All subjects who received at least 1 dose of the study drug (tofacitinib or placebo).
Percentages for the 'treated' row were calculated using the number of randomized subjects as the denominator.
Other percentages were calculated using the number of treated subjects as the denominator.

Table 25 - Subject Discontinuation by Treatment Group/Sequence, Month 3 and Month 6 (Safety Analysis Set)

Number (%) of Subjects	Tofacitinib 5 mg BID (N=131)	Tofacitinib 10 mg BID (N=132)	Placebo (N=131)	Total (N=394)
Discontinuations – Month 3				
Relation to study drug not defined[a]	3 (2.3)	6 (4.5)	10 (7.6)	19 (4.8)
Insufficient clinical response	1 (0.8)	2 (1.5)	4 (3.1)	7 (1.8)
Medication error without associated AE	0	0	2 (1.5)	2 (0.5)
No longer willing to participate in study	1 (0.8)	2 (1.5)	4 (3.1)	7 (1.8)
Protocol violation	1 (0.8)	1 (0.8)	0	2 (0.5)
Withdrawn due to pregnancy	0	1 (0.8)	0	1 (0.3)
Related to study drug[b]	1 (0.8)	4 (3.0)	3 (2.3)	8 (2.0)
AE	1 (0.8)	4 (3.0)	3 (2.3)	8 (2.0)
Not related to study drug[b]	1 (0.8)	0	2 (1.5)	3 (0.8)
AE	1 (0.8)	0	2 (1.5)	3 (0.8)
Total	5 (3.8)	10 (7.6)	15 (11.5)	30 (7.6)

Number (%) of Subjects	Tofacitinib 5 mg BID (N=131)	Tofacitinib 10 mg BID (N=132)	Placebo → Tofacitinib 5 mg BID (N=66)	Placebo → Tofacitinib 10 mg BID (N=65)	Total (N=394)
Discontinuations – Month 6					
Relation to study drug not defined[a]	4 (3.1)	11 (8.3)	8 (12.1)	6 (9.2)	29 (7.4)
Insufficient clinical response	1 (0.8)	4 (3.0)	4 (6.1)	2 (3.1)	11 (2.8)
Medication error without associated AE	0	0	2 (3.0)	0	2 (0.5)
No longer willing to participate in study	1 (0.8)	4 (3.0)	2 (3.0)	3 (4.6)	10 (2.5)
Protocol violation	2 (1.5)	2 (1.5)	0	1 (1.5)	5 (1.3)
Withdrawn due to pregnancy	0	1 (0.8)	0	0	1 (0.3)
Related to study drug[b]	3 (2.3)	8 (6.1)	1 (1.5)	2 (3.1)	14 (3.6)
AE	3 (2.3)	8 (6.1)	1 (1.5)	2 (3.1)	14 (3.6)
Not related to study drug[b]	2 (1.5)	2 (1.5)	1 (1.5)	1 (1.5)	6 (1.5)
AE	2 (1.5)	2 (1.5)	1 (1.5)	1 (1.5)	6 (1.5)
Total	9 (6.9)	21 (15.9)	10 (15.2)	9 (13.8)	49 (12.4)

Source: Table 14.1.1.2.1 and Table 14.1.1.2.2
Abbreviations: AE = adverse event; BID = twice daily; CRF = Case Report Form; N = number of subjects in the analysis set.
Discontinued status was determined from the subject summary page at the end of study.
a. All assessments where the relation to study drug was not defined.
b. Relationship is determined by investigator's assessment of relationship to study drug on the AE CRF page.

Recruitment

The study was conducted in 98 centres in Australia, Brazil, Canada, EU, Mexico, Russian Federation, Taiwan and US.

22/08/2013 (first patient first visit) to 04/04/2016 (last patient last visit).

Conduct of the study

The final protocol document (dated 21 December 2012) had 4 amendments. The amendments were made prior to the first subject first visit and mainly included minor changes to the eligibility criteria. None of the changes made were deemed to impact the primary objective of the study. The SAP was amended 4 times. All updates were made prior to the treatment code unblinding and study database release.

Protocol deviations

Upon entry into the study, 6 subjects were receiving >1 allowable csDMARD: 3 subjects in the tofacitinib 5 mg BID group, 2 subjects in the tofacitinib 10 mg BID group, and one subject in the placebo → tofacitinib 5 mg BID sequence. All but one of these subjects discontinued 1 of the csDMARDs after the Month 3 visit. The most common protocol deviations were related to concomitant medication (40 [10.2%] deviations). Protocol deviations were also identified for inclusion/exclusion criteria (35 [8.9%] deviations). Three subjects were not taking csDMARDs at baseline (2 subjects in the tofacitinib 10 mg BID group and 1 subject in the placebo → tofacitinib 5 mg BID sequence); no csDMARD was initiated during the study. In addition, protocol deviations were identified for procedures/tests (17 [4.3%]). Key protocol deviations that were viewed by the Sponsor to impact the primary efficacy results were excluded from the PP Analysis Set. Twenty-three subjects were excluded from the PP Analysis Set.

Baseline data

Table 26 - Demographic and Baseline Characteristics by Treatment Group (Safety Analysis Set)

Number (%) of Subjects	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Placebo			Overall		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
	67	64	131	58	74	132	51	80	131	176	218	394
Age (years)[a]												
N	67	64	131	58	74	132	51	80	131	176	218	394
	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)
Mean	49.9	49.2	49.5	49.7	52.7	51.3	47.9	49.7	49.0	49.3	50.5	50.0
SD	12.6	12.0	12.3	11.1	10.6	10.9	13.2	12.3	12.6	12.2	11.7	12.0
Range	20-71	24-76	20-76	24-73	30-73	24-73	18-73	22-78	18-78	18-73	22-78	18-78
18-44	21	25	46	19	17	36	23	27	50	63	69	132
	(31.3)	(39.1)	(35.1)	(32.8)	(23.0)	(27.3)	(45.1)	(33.8)	(38.2)	(35.8)	(31.7)	(33.5)
45-64	40	33	73	34	49	83	24	43	67	98	125	223
	(59.7)	(51.6)	(55.7)	(58.6)	(66.2)	(62.9)	(47.1)	(53.8)	(51.1)	(55.7)	(57.3)	(56.6)
65-74	6 (9.0)	5 (7.8)	11 (8.4)	5 (8.6)	8 (10.8)	13 (9.8)	4 (7.8)	8 (10.0)	12 (9.2)	15 (8.5)	21 (9.6)	36 (9.1)
75-84	0	1 (1.6)	1 (0.8)	0	0	0	0	2 (2.5)	2 (1.5)	0	3 (1.4)	3 (0.8)
≥85	0	0	0	0	0	0	0	0	0	0	0	0
Race, n (%)												
White	60	61	121	55	69	124	46	72	118	161	202	363
	(89.6)	(95.3)	(92.4)	(94.8)	(93.2)	(93.9)	(90.2)	(90.0)	(90.1)	(91.5)	(92.7)	(92.1)
Black	1 (1.5)	0	1 (0.8)	0	1 (1.4)	1 (0.8)	1 (2.0)	0	1 (0.8)	2 (1.1)	1 (0.5)	3 (0.8)
Asian	2 (3.0)	0	2 (1.5)	2 (3.4)	1 (1.4)	3 (2.3)	2 (3.9)	6 (7.5)	8 (6.1)	6 (3.4)	7 (3.2)	13 (3.3)
Other	4 (6.0)	3 (4.7)	7 (5.3)	1 (1.7)	3 (4.1)	4 (3.0)	2 (3.9)	2 (2.5)	4 (3.1)	7 (4.0)	8 (3.7)	15 (3.8)
Ethnicity, n (%)												
Hispanic/Latino	13	12	25	6 (10.3)	7 (9.5)	13 (9.8)	15	8 (10.0)	23	34	27	61
	(19.4)	(18.8)	(19.1)				(29.4)		(17.6)	(19.3)	(12.4)	(15.5)
Not Hispanic/Latino	54	52	106	52	67	119	36	72	108	142	191	333
	(80.6)	(81.3)	(80.9)	(89.7)	(90.5)	(90.2)	(70.6)	(90.0)	(82.4)	(80.7)	(87.6)	(84.5)
Weight (kg)												
N	67	64	131	58	74	132	51	80	131	176	218	394
	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)
Mean	92.5	83.2	87.9	92.4	83.0	87.1	86.6	79.2	82.1	90.7	81.7	85.7
SD	20.3	24.6	22.9	18.1	20.0	19.7	14.8	16.5	16.2	18.2	20.3	19.9
Range	52.0-155.0	38.1-159.7	38.1-159.7	46.2-153.8	50.8-144.7	46.2-153.8	53.2-122.7	48.0-117.8	48.0-122.7	46.2-155.0	38.1-159.7	38.1-159.7

Number (%) of Subjects	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			Placebo			Overall		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
	67	64	131	58	74	132	51	80	131	176	218	394
<60	2 (3.0)	10 (15.6)	12 (9.2)	2 (3.4)	7 (9.5)	9 (6.8)	1 (2.0)	10 (12.5)	11 (8.4)	5 (2.8)	27 (12.4)	32 (8.1)
≥60 to ≤100	48 (71.6)	41 (64.1)	89 (67.9)	41 (70.7)	52 (70.3)	93 (70.5)	41 (80.4)	64 (80.0)	105 (80.2)	130 (73.9)	157 (72.0)	287 (72.8)
>100	17 (25.4)	13 (20.3)	30 (22.9)	15 (25.9)	15 (20.3)	30 (22.7)	9 (17.6)	6 (7.5)	15 (11.5)	41 (23.3)	34 (15.6)	75 (19.0)
Height (cm)												
N	67	64	131	58	74	132	51	80	131	176	218	394
	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)
Mean	176.3	162.7	169.7	175.4	163.2	168.6	172.2	162.9	166.5	174.8	163.0	168.3
SD	8.5	6.7	10.2	7.3	7.0	9.4	7.6	7.3	8.7	8.0	7.0	9.5
Range	153.0-196.1	145.0-180.3	145.0-196.1	160.0-193.0	148.0-186.0	148.0-193.0	150.0-187.5	142.0-175.3	142.0-187.5	150.0-196.1	142.0-186.0	142.0-196.1
BMI (kg/m^2)												
N	67	64	131	58	74	132	51	80	131	176	218	394
	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)
Mean	29.5	31.6	30.5	30.5	31.3	31.0	29.2	29.8	29.5	29.8	30.8	30.3
SD	5.8	8.1	7.1	5.8	7.3	6.7	4.3	6.2	5.5	5.4	7.2	6.5
Range	19.2-46.2	18.8-53.2	18.8-53.2	19.8-51.3	19.8-54.6	19.8-54.6	22.9-40.1	19.1-47.5	19.1-47.5	19.2-51.3	18.8-54.6	18.8-54.6
<18.5	0	0	0	0	0	0	0	0	0	0	0	0
18.5 to <25	16	13	29	9 (15.5)	17	26	11	21	32	36	51	87
	(23.9)	(20.3)	(22.1)		(23.0)	(19.7)	(21.6)	(26.3)	(24.4)	(20.5)	(23.4)	(22.1)
25 to <30	23	18	41	20	19	39	18	21	39	61	58	119
	(34.3)	(28.1)	(31.3)	(34.5)	(25.7)	(29.5)	(35.3)	(26.3)	(29.8)	(34.7)	(26.6)	(30.2)
30 to <40	24	22	46	26	27	53	21	36	57	71	85	156
	(35.8)	(34.4)	(35.1)	(44.8)	(36.5)	(40.2)	(41.2)	(45.0)	(43.5)	(40.3)	(39.0)	(39.6)
≥40	4 (6.0)	11 (17.2)	15 (11.5)	3 (5.2)	11 (14.9)	14 (10.6)	1 (2.0)	2 (2.5)	3 (2.3)	8 (4.5)	24 (11.0)	32 (8.1)

Source: Table 14.1.2.1.1.1
Abbreviations: BID = twice daily; BMI = body mass index; DOB = date of birth; N = number of subjects in the analysis set; n = number of subjects that met the criteria; SD = standard deviation.
Weight and Height are from the last assessments prior to the first dose of study drug. Other includes Indian, Mestizo, Mixed, Pacific Islander. Categories of parameters were analyzed as number (%) of subjects in each category. There were no subjects less than 18 years old in the study.
a. Age at screening. Age was calculated as screening date year – birth year. If the screening date month was less than the DOB month, or the screening date month = DOB month and the screening date day was less than the DOB day, then age = (screening date year – DOB year) – 1.

Table 27 - Additional Demographic and Baseline Characteristics by Treatment Group

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 131)	Tofacitinib 10 mg BID (N = 132)	Placebo (N = 131)	Total (N = 394)
Geographic region[a]				
United States and Canada[b]	38 (29.0)	42 (31.8)	38 (29.0)	118 (29.9)
Australia and Western Europe	42 (32.1)	39 (29.5)	41 (31.3)	122 (31.0)
Russia and Eastern Europe	28 (21.4)	36 (27.3)	25 (19.1)	89 (22.6)
Rest of World	23 (17.6)	15 (11.4)	27 (20.6)	65 (16.5)
Smoking classification				
Never smoked	75 (57.3)	76 (57.6)	86 (65.6)	237 (60.2)
Current smoker	21 (16.0)	20 (15.2)	18 (13.7)	59 (15.0)
Ex-smoker	35 (26.7)	36 (27.3)	27 (20.6)	98 (24.9)
Alcohol use				
Yes	44 (33.6)	44 (33.3)	52 (39.7)	140 (35.5)
No	87 (66.4)	88 (66.7)	79 (60.3)	254 (64.5)

Source: Table 14.1.2.1.1.3
Categories of parameters were analyzed as number (%) of subjects in each category.
Abbreviations: BID = twice daily; N = number of subjects in the analysis set; UK = United Kingdom.
a. Western Europe includes Belgium, France, Germany, Spain, and UK. Eastern Europe includes Czech Republic, Poland, and Slovakia. Rest of World includes Brazil, Mexico and Taiwan.
b. No subjects from Canada were enrolled.

Table 28 - Baseline Disease Characteristics by Treatment Group

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 131)	Tofacitinib 10 mg BID (N = 132)	Placebo (N = 131)	Total (N = 394)
Psoriatic arthritis duration (years) since first diagnosed				
<2	9 (6.9)	14 (10.6)	17 (13.0)	40 (10.2)
≥2	122 (93.1)	118 (89.4)	114 (87.0)	354 (89.8)
N	131	132	131	394
Mean (SD)	9.63 (7.580)	9.10 (6.765)	9.37 (8.088)	9.37 (7.480)
Median	7.58	7.96	6.83	7.50
Min, Max	0.4, 39.0	0.5, 31.8	0.6, 43.4	0.4, 43.4
Baseline PsA subtype				
<5 joints	2 (1.5)	3 (2.3)	6 (4.6)	11 (2.8)
≥5 joints	129 (98.5)	129 (97.7)	125 (95.4)	383 (97.2)
Baseline PASDAS				
≤3.2	1 (0.8)	0	1 (0.8)	2 (0.5)
>3.2 to <5.4	35 (26.7)	22 (16.7)	41 (31.3)	98 (24.9)
≥5.4	88 (67.2)	106 (80.3)	86 (65.6)	280 (71.1)
Missing	7 (5.3)	4 (3.0)	3 (2.3)	14 (3.6)
N	124	128	128	380
Mean (SD)	6.09 (1.224)	6.43 (1.205)	5.97 (1.264)	6.16 (1.243)
Median	6.10	6.42	5.95	6.15
Min, Max	3.1, 9.7	3.9, 9.8	2.5, 9.5	2.5, 9.8
Baseline CPDAI for subjects with baseline BSA ≥3%				
≤4	1 (0.8)	0	3 (2.3)	4 (1.0)
>4 to <8	14 (10.7)	10 (7.6)	20 (15.3)	44 (11.2)
≥8	64 (48.9)	69 (52.3)	62 (47.3)	195 (49.5)
Missing	2 (1.5)	2 (1.5)	1 (0.8)	5 (1.3)
N	79	79	85	243
Mean (SD)	10.1 (2.58)	10.7 (2.56)	9.6 (2.86)	10.1 (2.70)
Median	10.0	11.0	10.0	10.0
Min, Max	4, 15	5, 15	4, 15	4, 15
Baseline CPDAI for subjects with baseline BSA ≥3%				
n[a]	81	81	86	248
≤4	1 (1.2)	0	3 (3.5)	4 (1.6)
>4 to <8	14 (17.3)	10 (12.3)	20 (23.3)	44 (17.7)
≥8	64 (79.0)	69 (85.2)	62 (72.1)	195 (78.6)

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 131)	Tofacitinib 10 mg BID (N = 132)	Placebo (N = 131)	Total (N = 394)
Missing	2 (2.5)	2 (2.5)	1 (1.2)	5 (2.0)
Baseline swollen joint count (66)				
N	131	132	131	394
Mean (SD)	12.1 (10.60)	12.8 (11.19)	10.5 (8.97)	11.8 (10.32)
Median	8.0	8.0	7.0	8.0
Min, Max	0, 60	3, 60	0, 49	0, 60
Baseline tender/painful joint count (68)				
N	131	132	131	394
Mean (SD)	20.5 (13.02)	25.5 (17.52)	19.8 (14.85)	22.0 (15.42)
Median	17.0	21.0	16.0	17.0
Min, Max	4, 68	3, 68	3, 66	3, 68
Baseline HAQ-DI				
N	130	132	131	393
Mean (SD)	1.2644 (0.69215)	1.3722 (0.60561)	1.2510 (0.76027)	1.2961 (0.68911)
Median	1.2500	1.5000	1.2500	1.3750
Min, Max	0.000, 2.875	0.000, 2.875	0.000, 3.000	0.000, 3.000
Screening presence of distal interphalangeal joints involvement				
Yes	89 (67.9)	92 (69.7)	72 (55.0)	253 (64.2)
No	42 (32.1)	40 (30.3)	59 (45.0)	141 (35.8)
Screening presence of arthritis mutilans				
Yes	7 (5.3)	11 (8.3)	15 (11.5)	33 (8.4)
No	124 (94.7)	121 (91.7)	116 (88.5)	361 (91.6)
Baseline presence of enthesitis measured by SPARCC Enthesitis Index or LEI (SPARCC >0 or LEI >0)				
Yes	98 (74.8)	112 (84.8)	108 (82.4)	318 (80.7)
No	33 (25.2)	20 (15.2)	23 (17.6)	76 (19.3)
Baseline presence of enthesitis measured by SPARCC Enthesitis Index >0				
Yes	96 (73.3)	108 (81.8)	100 (76.3)	304 (77.2)
No	35 (26.7)	24 (18.2)	31 (23.7)	90 (22.8)
Baseline presence of enthesitis measured by LEI >0				
Yes	83 (63.4)	99 (75.0)	93 (71.0)	275 (69.8)
No	47 (35.9)	33 (25.0)	36 (27.5)	116 (29.4)

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 131)	Tofacitinib 10 mg BID (N = 132)	Placebo (N = 131)	Total (N = 394)
Missing	1 (0.8)	0	2 (1.5)	3 (0.8)
Baseline enthesitis index measured by SPARCC Enthesitis Index (continuous) for those subjects with SPARCC Enthesitis Index >0 at baseline				
N	96	108	100	304
Mean (SD)	5.8 (4.07)	6.9 (4.57)	5.4 (3.48)	6.1 (4.12)
Median	5.0	6.0	5.0	5.0
Min, Max	1, 16	1, 16	1, 16	1, 16
Baseline enthesitis index measured by LEI (continuous) for those with LEI >0 at baseline				
N	83	99	93	275
Mean (SD)	3.0 (1.63)	3.4 (1.77)	2.8 (1.55)	3.0 (1.67)
Median	3.0	3.0	2.0	3.0
Min, Max	1, 6	1, 6	1, 6	1, 6
Baseline presence of dactylitis (DSS>0)				
Yes	66 (50.4)	65 (49.2)	63 (48.1)	194 (49.2)
No	65 (49.6)	67 (50.8)	68 (51.9)	200 (50.8)
Baseline DSS (continuous) for those subjects with DSS >0 at baseline				
N	66	65	63	194
Mean (SD)	7.8 (9.87)	9.5 (8.21)	6.8 (5.74)	8.1 (8.18)
Median	4.0	8.0	4.0	6.0
Min, Max	1, 52	1, 40	1, 26	1, 52
Baseline presence of spondylitis (defined as presence of spondylitis at screening and baseline BASDAI >0)				
Yes	26 (19.8)	26 (19.7)	22 (16.8)	74 (18.8)
No	105 (80.2)	106 (80.3)	109 (83.2)	320 (81.2)
Baseline BASDAI for subjects with presence of spondylitis at screening				
0	0	0	0	0
>0 to <4	1 (0.8)	1 (0.8)	2 (1.5)	4 (1.0)
≥4	25 (19.1)	25 (18.9)	20 (15.3)	70 (17.8)

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 131)	Tofacitinib 10 mg BID (N = 132)	Placebo (N = 131)	Total (N = 394)
Baseline BASDAI for subjects with presence of spondylitis at screening				
n[b]	26	26	22	74
0	0	0	0	0
>0 to <4	1 (3.8)	1 (3.8)	2 (9.1)	4 (5.4)
≥4	25 (96.2)	25 (96.2)	20 (90.9)	70 (94.6)
Baseline BASDAI (continuous) for those subjects with presence of spondylitis at screening and BASDAI >0 at baseline				
N	26	26	22	74
Mean (SD)	6.33 (1.552)	6.71 (1.580)	6.84 (1.834)	6.61 (1.641)
Median	6.38	6.91	6.97	6.75
Min, Max	3.1, 9.5	3.7, 9.0	2.3, 10.0	2.3, 10.0
Baseline total psoriatic BSA (%)				
0	5 (3.8)	4 (3.0)	0	9 (2.3)
>0 to <3	43 (32.8)	46 (34.8)	45 (34.4)	134 (34.0)
≥3	80 (61.1)	81 (61.4)	86 (65.6)	247 (62.7)
Missing	3 (2.3)	1 (0.8)	0	4 (1.0)
Baseline total psoriatic BSA (continuous) for those subjects with BSA >0% at baseline				
N	123	127	131	381
Mean (SD)	9.80 (13.235)	10.74 (13.635)	11.36 (15.954)	10.65 (14.330)
Median	4.00	5.00	5.00	5.00
Min, Max	0.2, 83.0	0.2, 56.0	0.1, 94.0	0.1, 94.0
Baseline PASI				
0	0	0	0	0
>0 to ≤20	72 (55.0)	66 (50.0)	74 (56.5)	212 (53.8)
>20	8 (6.1)	15 (11.4)	12 (9.2)	35 (8.9)
Missing	1 (0.8)	0	0	1 (0.3)
Not assessed[c]	50 (38.2)	51 (38.6)	45 (34.4)	146 (37.1)
Baseline PASI (continuous) for those subjects with BSA ≥3% and PASI >0 at baseline				
N	80	81	86	247
Mean (SD)	9.80 (7.298)	11.16 (8.850)	11.11 (10.883)	10.70 (9.159)

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 131)	Tofacitinib 10 mg BID (N = 132)	Placebo (N = 131)	Total (N = 394)
Median	7.60	8.80	7.10	7.90
Min, Max	0.6, 32.2	0.8, 41.6	1.6, 66.0	0.6, 66.0
Baseline PGA-PsO				
0	7 (5.3)	4 (3.0)	4 (3.1)	15 (3.8)
1	36 (27.5)	38 (28.8)	42 (32.1)	116 (29.4)
2	56 (42.7)	51 (38.6)	55 (42.0)	162 (41.1)
3	25 (19.1)	33 (25.0)	22 (16.8)	80 (20.3)
4	6 (4.6)	5 (3.8)	8 (6.1)	19 (4.8)
Missing	1 (0.8)	1 (0.8)	0	2 (0.5)
Baseline PGA-PsO (continuous) for those subjects with PGA-PsO >0 at baseline				
N	123	127	127	377
Mean (SD)	2.0 (0.83)	2.0 (0.85)	2.0 (0.87)	2.0 (0.85)
Median	2.0	2.0	2.0	2.0
Min, Max	1, 4	1, 4	1, 4	1, 4
Baseline PGA-PsO ≥3, PASI ≥12, and BSA ≥10%				
Yes	18 (13.7)	16 (12.1)	18 (13.7)	52 (13.2)
No	62 (47.3)	64 (48.5)	68 (51.9)	194 (49.2)
Missing	1 (0.8)	1 (0.8)	0	2 (0.5)
Not assessed for PASI	50 (38.2)	51 (38.6)	45 (34.4)	146 (37.1)
Baseline SF-36 Physical Functioning domain				
N	130	132	131	393
Mean (SD)	33.45 (10.429)	32.12 (9.872)	34.03 (10.992)	33.20 (10.444)
Median	32.55	32.55	34.60	32.55
Min, Max	16.2, 57.1	16.2, 57.1	16.2, 57.1	16.2, 57.1
Baseline SF-36 Physical Component Score (PCS)				
N	127	132	131	390
Mean (SD)	33.57 (8.461)	31.73 (8.934)	34.70 (9.550)	33.33 (9.059)
Median	33.42	31.09	35.30	33.20
Min, Max	14.9, 59.4	10.3, 55.1	9.8, 58.7	9.8, 59.4
Baseline SF-36 Mental Component Score (MCS)				
N	127	132	131	390
Mean (SD)	39.76 (12.640)	39.84 (12.277)	40.59 (12.655)	40.07 (12.497)

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 131)	Tofacitinib 10 mg BID (N = 132)	Placebo (N = 131)	Total (N = 394)
Median	38.37	38.93	40.21	39.11
Min, Max	12.0, 68.3	10.8, 69.4	13.8, 65.3	10.8, 69.4
Baseline FACIT-F total score				
N	130	132	131	393
Mean (SD)	26.1 (12.15)	26.1 (10.27)	27.5 (11.58)	26.5 (11.35)
Median	27.0	26.0	28.0	27.0
Min, Max	3, 51	5, 52	4, 51	3, 52
Baseline FACIT-F experience domain score				
N	130	132	131	393
Mean (SD)	8.2 (5.07)	8.1 (4.29)	8.6 (4.80)	8.3 (4.72)
Median	8.0	8.0	8.0	8.0
Min, Max	0, 20	0, 20	0, 19	0, 20
Baseline FACIT-F impact domain score				
N	130	132	131	393
Mean (SD)	17.8 (7.56)	18.0 (6.48)	18.9 (7.36)	18.3 (7.14)
Median	19.0	17.0	19.0	18.0
Min, Max	2, 31	2, 32	4, 32	2, 32
Baseline DLQI				
<5	57 (43.5)	43 (32.6)	54 (41.2)	154 (39.1)
≥5	73 (55.7)	88 (66.7)	77 (58.8)	238 (60.4)
Missing	1 (0.8)	1 (0.8)	0	2 (0.5)
N	130	131	131	392
Mean (SD)	7.8 (7.05)	10.2 (8.20)	8.4 (7.71)	8.8 (7.72)
Median	6.0	9.0	6.0	7.0
Min, Max	0, 27	0, 30	0, 30	0, 30
Baseline CRP (mg/L)				
≤2.87	46 (35.1)	50 (37.9)	51 (38.9)	147 (37.3)
>2.87	85 (64.9)	82 (62.1)	80 (61.1)	247 (62.7)
N	131	132	131	394
Mean (SD)	13.7461 (22.06024)	15.0418 (27.16309)	12.1049 (22.69763)	13.6345 (24.05806)
Median	5.6800	4.8650	4.3700	4.7250
Min, Max	0.199, 126.000	0.199, 163.000	0.199, 164.000	0.199, 164.000

Number (%) of Subjects	Tofacitinib 5 mg BID (N = 131)	Tofacitinib 10 mg BID (N = 132)	Placebo (N = 131)	Total (N = 394)
Baseline rheumatoid factor positive				
Yes	7 (5.3)	5 (3.8)	7 (5.3)	19 (4.8)
No	124 (94.7)	127 (96.2)	123 (93.9)	374 (94.9)
Missing	0	0	1 (0.8)	1 (0.3)
Baseline cyclic citrullinated peptide antibody positive				
Yes	5 (3.8)	10 (7.6)	3 (2.3)	18 (4.6)
No	126 (96.2)	122 (92.4)	127 (96.9)	375 (95.2)
Missing	0	0	1 (0.8)	1 (0.3)

Source: Table 14.1.2.2.1

Abbreviations: BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BID = twice daily; BSA = body surface area; CPDAI = Composite Psoriatic Disease Activity Index; CRP = C-reactive protein; DLQI = Dermatology Life Quality Index; DSS = Dactylitis Severity Score; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI = Health Assessment Questionnaire-Disability Index; LEI = Leeds Enthesitis Index; Max = maximum; Min = minimum; N = number of subjects in the analysis set; n = number of subjects that met the criteria; PASDAS = Psoriatic Arthritis Disease Activity Score; PASI = Psoriasis Area and Severity Index; PGA-PsO = Physician's Global Assessment of Psoriasis; PsA = psoriatic arthritis; SD = standard deviation; SF-36 = 36-Item Short-Form Health Survey; SPARCC = Spondyloarthritis Research Consortium of Canada.

The percentages were calculated using the number of subjects in the Safety Analysis Set as the denominator unless stated otherwise.

a. n is the number of subjects with baseline BSA ≥3% and was used as the denominator for the percent calculation.

b. n is the number of subjects with spondylitis at screening and was used as the denominator for the percent calculation.

c. PASI was not assessed if baseline BSA <3% per study protocol.

Prior drug treatment

All subjects received prior csDMARDs drug treatment and prior biological DMARD treatment.

Table 29 - Summary of prior drug treatment for PsA

	Tofacitinib 5 mg BID (n=131) n (%)	Tofacitinib 10 mg BID (n=132) n (%)	Placebo (n=131) n (%)
csDMARD	131 (100.0)	132 (100.0)	131 (100.0)
bDMARD (all)	131 (100.0)	132 (100.0)	131 (100.0)
TNFi + other bDMARD	11 (8.4)	14 (10.6)	11 (8.4)
TNFi only	120 (91.6)	118 (89.4)	120 (91.6)
Number of prior bDMARDs			
1 TNFi	76 (58.0)	80 (60.6)	79 (60.3)
2 TNFi	23 (17.6)	21 (15.9)	27 (20.6)
≥3 TNFi	21 (16.0)	17 (12.9)	14 (10.7)
Non-DMARDs*	94 (71.8)	98 (74.2)	93 (71.0)
NSAIDs	77 (58.8)	76 (57.6)	76 (58.0)
Joint injections	2 (1.5)	0	1 (0.8)
Oral steroids	42 (32.1)	28 (21.2)	39 (29.8)

* drug treatments for psoriatic arthritis other than DMARDs

Concomitant drug treatment

Table 30 - Summary of baseline (day 1) drug treatment for PsA

	Tofacitinib 5 mg	Tofacitinib 10	Placebo (n=131)

	BID (n=131) n (%)	mg BID (n=132) n (%)	n (%)
Biologic DMARD	0	0	0
Non-DMARDs*	86 (65.6)	88 (66.7)	85 (64.9)
Oral steroids	37 (28.2)	25 (18.9)	31 (23.7)
Joint injections	0	0	0
csDMARDs	131 (100)	129 (97.7)	130 (99.2)
methotrexate	98 (74.8)	91 (68.9)	101 (77.1)
sulfasalazine	21 (16.0)	24 (18.2)	20 (15.3)
leflunomide	12 (9.2)	14 (10.6)	9 (6.9)
hydroxychloroquine	1 (0.8)	1 (0.8)	0
apremilast	1 (0.8)	1 (0.8)	0
chloroquine	1 (0.8)	0	1 (0.8)

* drug treatments for psoriatic arthritis other than DMARDs

Table 31 - New concomitant medications (taken on or after day 2) up to month 6

	Tofacitinib 5 mg BID (n=131) n (%)	Tofacitinib 10 mg BID (n=132) n (%)	Placebo -> tofacitinib 5 mg BID (n=66) n (%)	Placebo -> tofacitinib 10 mg BID (n=65) n (%)
Non-DMARDs*	12 (9.2)	2 (1.5)	3 (4.5)	4 (6.2)
Oral steroids	0	0	1 (1.5)	1 (1.5)
Joint injections	2 (1.5)	4 (3.0)	1 (1.5)	3 (4.6)
Rescue treatment	3 (2.3)	4 (3.0)	1 (1.5)	2 (3.1)
csDMARD				
methotrexate	0	1 (0.8)	0	0
etanercept	0	0	1 (1.5)	1 (1.5)
Biologic DMARD				
adalimumab	1 (0.8)	0	0	0
certolizumab	0	2 (1.5)	1 (1.5)	0
golimumab	0	0	0	1 (1.5)

* drug treatments for psoriatic arthritis other than DMARDs

Numbers analysed

The primary efficacy analysis was conducted in the full analysis set, which included all subjects randomised and treated. There was one randomised patient (randomised to tofacitinib 5mg) who was not treated.

Outcomes and estimation

Co-primary endpoint: ACR20 response rates at Month 3

Table 32 - Normal Approximation to ACR20 Response Rates at Month 3 (FAS, Missing Response = Non-Response) – Treatment Comparisons – Primary Analysis

Visit	Treatment Group	N	n	Response Rate (%)	SE (%)	Difference				
						Difference (%)	SE of Difference (%)	95% CI Lower (%)	95% CI Upper (%)	P-value
Month 3	Tofa 5	131	65	49.62	4.37					
	Tofa 10	132	62	46.97	4.34					
	PBO	131	31	23.66	3.71					
	Tofa 5 vs PBO					25.95	5.73	14.72	37.19	<0.0001
	Tofa 10 vs PBO					23.31	5.71	12.10	34.51	<0.0001

Source: Table 14.2.1.1.2.1

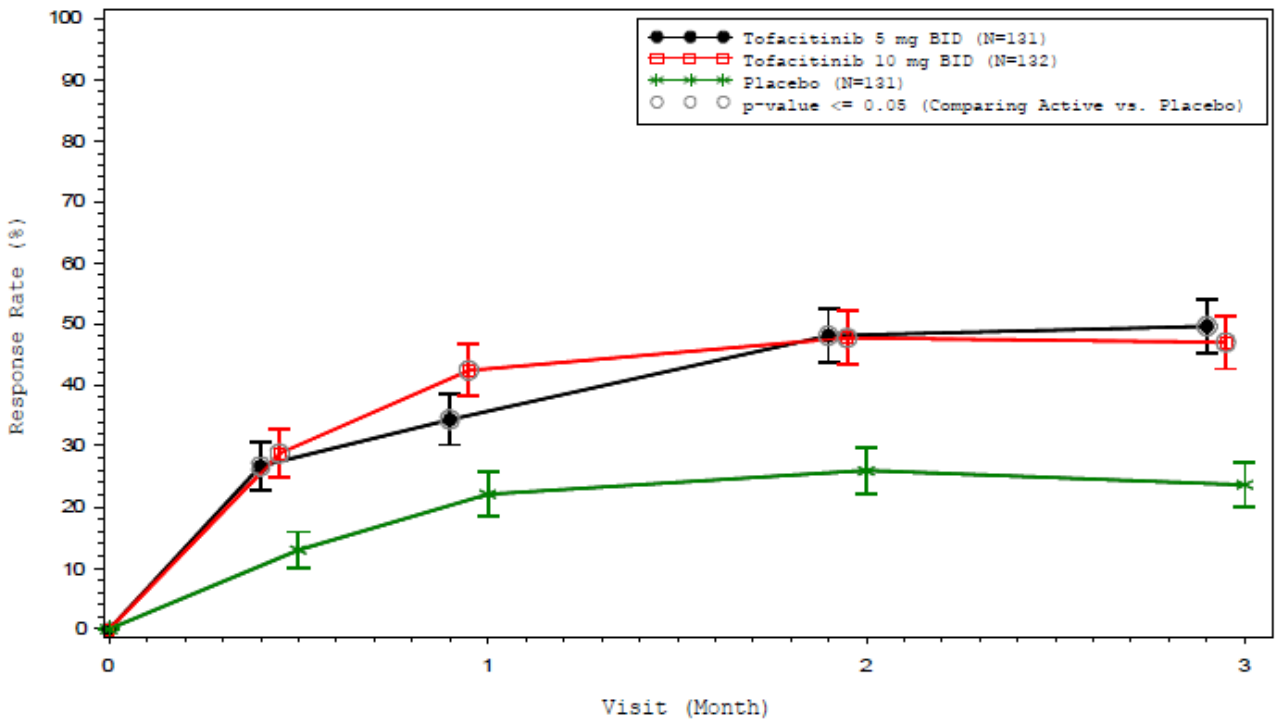
Abbreviations: ACR20 = American College of Rheumatology Response Criteria ≥20%; BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; N = number of subjects in FAS; n = number of responders; PBO = placebo; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs = versus.

ACR20 was calculated as a ≥20% improvement from baseline in tender/painful and swollen joint counts and ≥20% improvement from baseline in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.

Two-sided 95% CI and p-values were based on the normal approximation for the difference in binomial proportions.

P-values are nominal.

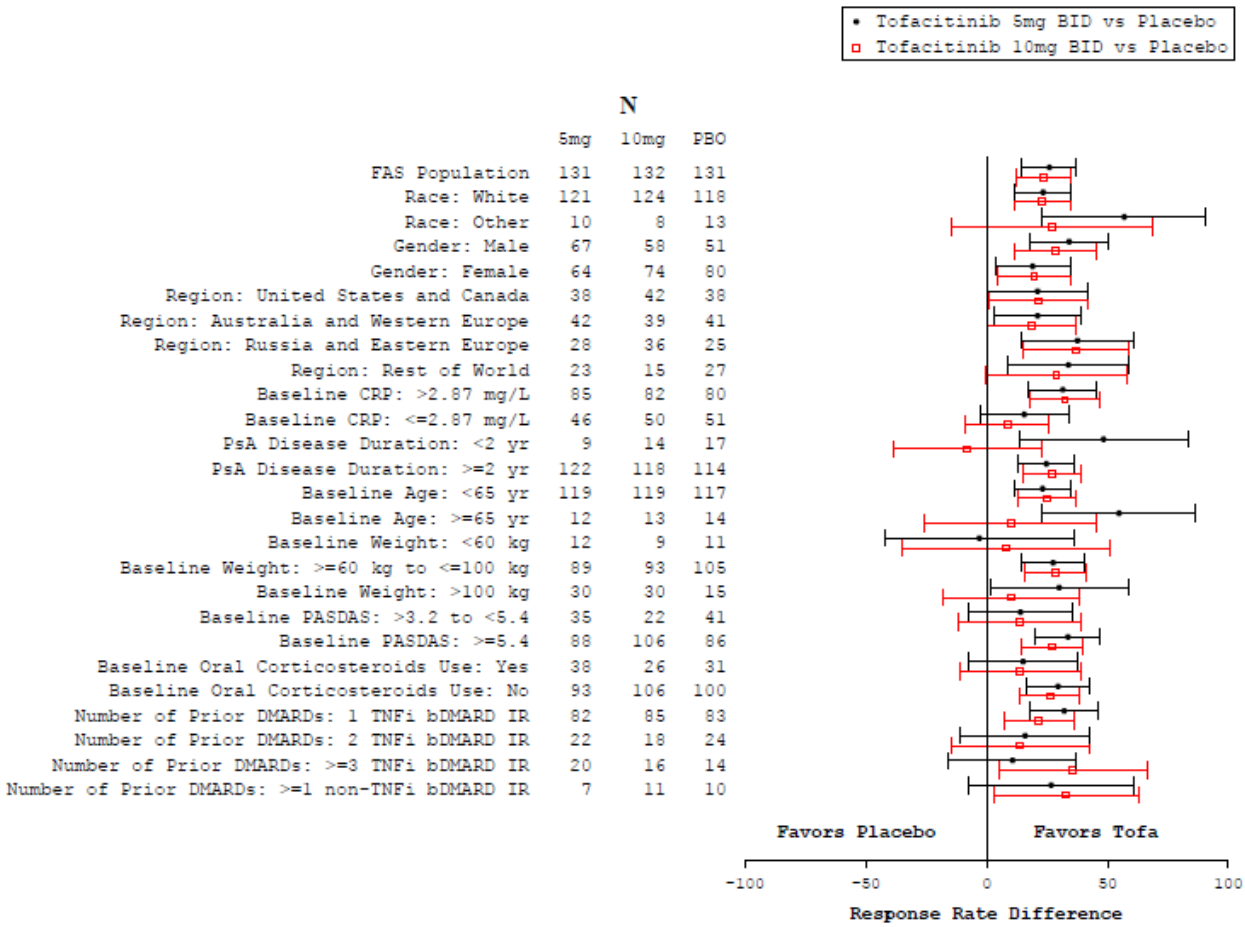
Figure 25 - Line Graph of ACR20 Response Rates (±SE) Up to Month 3 (FAS, Missing Response = Non-Response) – Comparison to Placebo – Primary Analysis



Abbreviations: ACR20 = American College of Rheumatology Response Criteria ≥20%; BID = twice daily; FAS = Full Analysis Set; N = number of subjects in the FAS; SE = standard error.

An analysis of ACR20 response rates at Month 3 by subgroups is presented in the figure below:

Figure 26 - Forest Plot of Differences (95% CIs) in ACR20 Response Rates (%) at Month 3 by Subgroup (FAS, Missing Response = Non-Response) – Comparisons to Placebo



Source: Table 14.2.1.1.2.1, Table 14.2.1.2.1, Table 14.2.1.2.2, Table 14.2.1.2.3, Table 14.2.1.2.4, Table 14.2.1.2.5, Table 14.2.1.2.6, Table 14.2.1.2.7, Table 14.2.1.2.8, Table 14.2.1.2.9, Table 14.2.1.2.11, Figure 14.2.1.2.12.1

Abbreviations: ACR20 = American College of Rheumatology Response Criteria ≥20%; BID = twice daily; CI = confidence interval; bDMARD = biologic DMARD; CI = confidence interval; CRP = C-reactive protein; DMARD = disease modifying anti-rheumatic drug; FAS = Full Analysis Set; PASDAS = Psoriatic Arthritis Disease Activity Score; IR = Inadequate Response; TNFi = Tumor Necrosis Factor inhibitor; Tofa = tofacitinib; UK = United Kingdom; vs = versus.

Western Europe includes Belgium, France, Germany, Spain, and UK. Eastern Europe includes Czech Republic Poland, and Slovakia. Rest of World includes Mexico, Brazil and Taiwan.

ACR20 was calculated as a ≥20% improvement from baseline in tender/painful and swollen joint counts and ≥20% improvement from baseline in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.

Two-sided 95% CI were based on the normal approximation for the difference in binomial proportions.

Difference was calculated as tofacitinib – placebo.

Due to the low number of subjects in the category of baseline PASDAS: ≤3.2, this category was dropped from the analysis.

Co-primary endpoint: Change from baseline (Δ) in Health Assessment Questionnaire - Disability Index (HAQ-DI) at Month 3

Table 33 - Statistical Analysis (Repeated Measures Model) of ΔHAQ-DI at Month 3 (FAS, No Imputation) – Treatment Comparisons – Primary Analysis

Visit	Treatment Group	N	n	LS Mean	SE	Difference				
						Difference	SE of Difference	95% CI		P-value
								Lower	Upper	
Month 3	Tofa 5	129	124	-0.3920	0.04544					
	Tofa 10	132	120	-0.3540	0.04579					
	PBO	131	117	-0.1391	0.04573					
	Tofa 5 vs PBO					-0.2529	0.06422	-0.3792	-0.1266	<0.0001
	Tofa 10 vs PBO					-0.2150	0.06453	-0.3419	-0.0881	0.0009
MI-JTR (FAS, Multiple Imputation) – Supportive Analysis[c,d]										
Month 3	Tofa 5[b]	129	124	-0.4011	0.04536					
	Tofa 10	132	120	-0.3550	0.04613					
	PBO	131	117	-0.1515	0.04557					
	Tofa 5 vs PBO					-0.2497	0.06369	-0.3749	-0.1244	0.0001
	Tofa 10 vs PBO					-0.2035	0.06429	-0.3299	-0.0770	0.0017

Source: Table 14.2.1.3.3.1

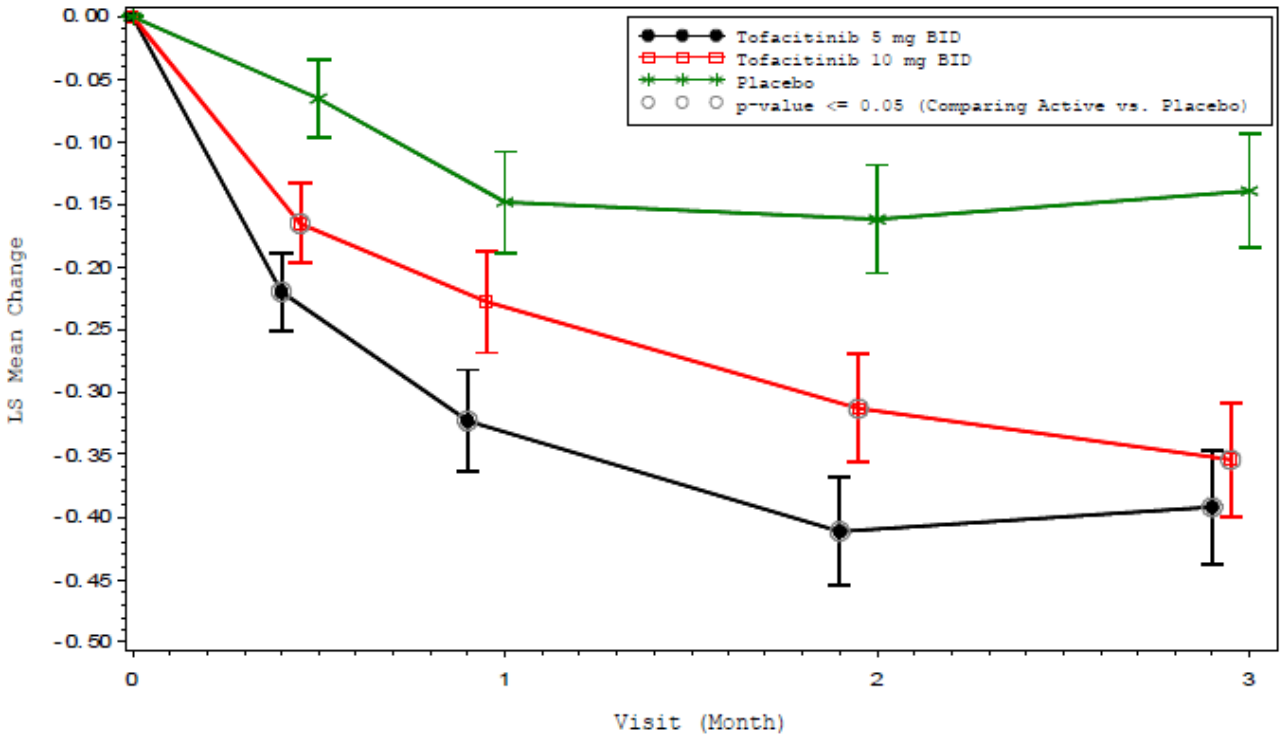
Abbreviations: Δ = change from baseline; BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire-Disability Index; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; N = number of unique subjects in the longitudinal model; n = number of subjects evaluable at Month 3; PBO = placebo; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs = versus.

Results were based on MMRM with the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; and an unstructured covariance matrix was used.

Two subjects in the tofacitinib 5 mg BID group were excluded from the analysis (Subject 11611005 had baseline HAQ-DI missing and Subject 11641003 had no post-baseline HAQ-DI) (Table 16.2.6.02.1).

P-values are nominal.

Figure 27 - Line Graph of Least Squares Mean (±SE) ΔHAQ-DI Up to Month 3 From the Repeated Measures Model (FAS, No Imputation) – Comparison to Placebo – Primary Analysis



Abbreviations: Δ = change from baseline; BID = twice daily; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire-Disability Index; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; SE = standard error. Results were based on MMRM with the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used. The total numbers of unique subjects included in the longitudinal model were 129, 132 and 131, in tofacitinib 5 mg BID, tofacitinib 10 mg BID and placebo, respectively.

A responder analysis was also conducted:

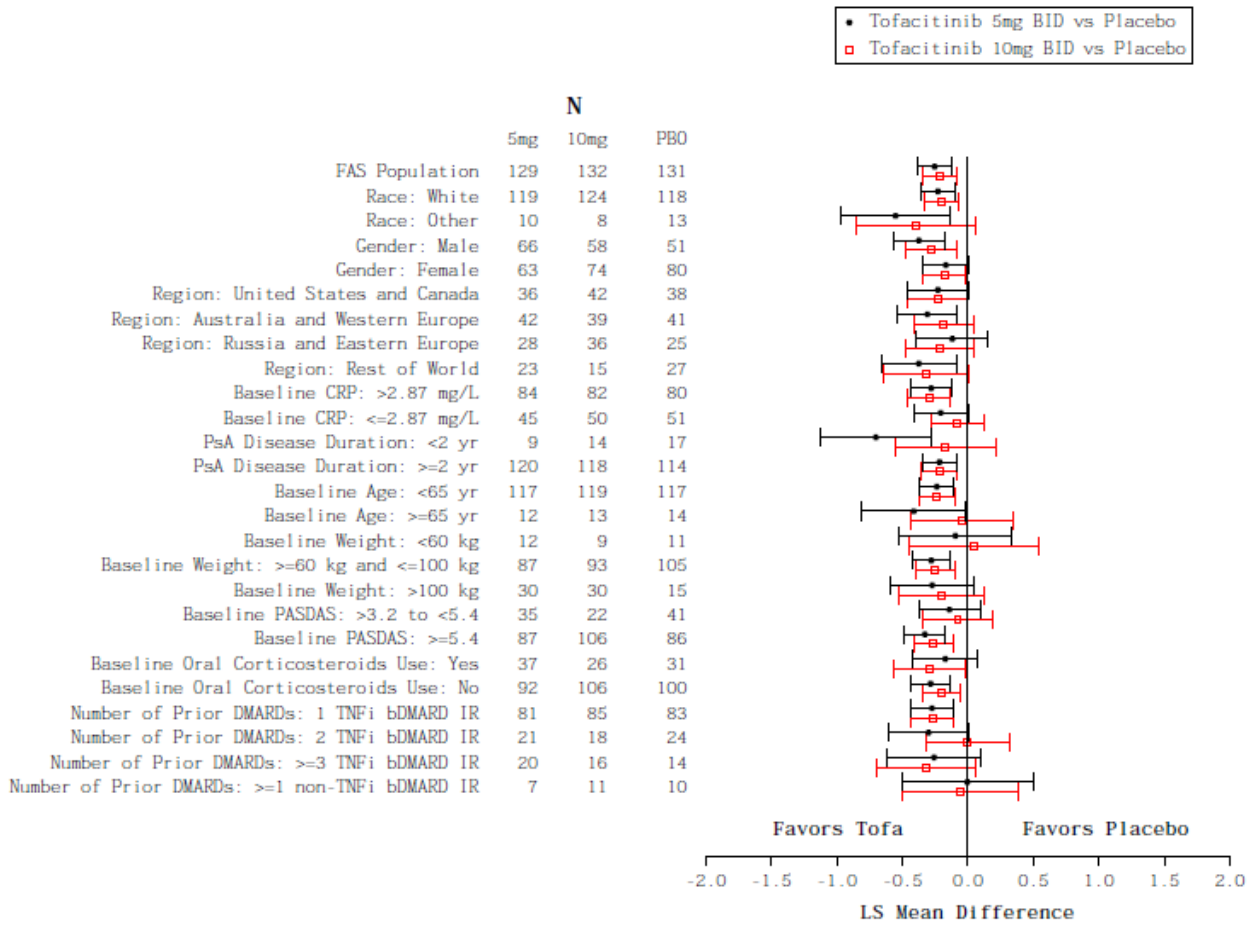
Table 34 - Normal Approximation to HAQ-DI Response Rates (Decrease From Baseline ≥0.30 and ≥0.35) at Month 3 (For Subjects With Baseline HAQ-DI ≥0.30 and ≥0.35, Respectively, in FAS, Missing Response = Non-Response) –Treatment Comparisons – Supportive Analysis

Visit	Treatment Group	N	n	Response Rate (%)	SE (%)	Difference				
						Difference (%)	SE of Difference (%)	95% CI		P-value
								Lower (%)	Upper (%)	
Decrease From Baseline ≥0.30 at Month 3 For Subjects With Baseline HAQ-DI ≥0.30 in FAS										
Month 3	Tofa 5	116	58	50.00	4.64					
	Tofa 10	123	50	40.65	4.43					
	PBO	116	32	27.59	4.15					
	Tofa 5 vs PBO					22.41	6.23	10.21	34.62	0.0003
	Tofa 10 vs PBO					13.06	6.07	1.17	24.96	0.0314
Decrease From Baseline ≥0.35 at Month 3 For Subjects With Baseline HAQ-DI ≥0.35 in FAS										
Month 3	Tofa 5	116	58	50.00	4.64					
	Tofa 10	123	50	40.65	4.43					
	PBO	116	32	27.59	4.15					
	Tofa 5 vs PBO					22.41	6.23	10.21	34.62	0.0003
	Tofa 10 vs PBO					13.06	6.07	1.17	24.96	0.0314

Source: Table 14.2.1.3.6.2 and Table 14.2.1.3.7.2
Abbreviations: BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire-Disability Index; N = number of subjects in FAS with baseline HAQ-DI ≥0.30 or ≥0.35; n = number of responders; PBO = placebo; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs = versus.
Two-sided 95% CI and p-values were based on the normal approximation for the difference in binomial proportions.
Subjects with baseline HAQ-DI ≥0.30 or ≥0.35 were included in the analysis.
Number of subjects in FAS with baseline HAQ-DI ≥0.30 for tofacitinib 5 mg BID: 116; tofacitinib 10 mg BID: 123; placebo: 116.
Number of subjects in FAS with baseline HAQ-DI ≥0.35 for tofacitinib 5 mg BID: 116; tofacitinib 10 mg BID: 123; placebo: 116.
P-values are nominal.

An analysis of ΔHAQ-DI at Month 3 by subgroups is presented in the figure below:

Figure 28 - Forest Plot of Least Squares Mean Differences (95% CIs) in ΔHAQ-DI at Month 3 by Subgroup (FAS, Repeated Measures Model, No Imputation) – Comparisons to Placebo



Source: Table 14.2.1.3.3.1, Table 14.2.1.4.1, Table 14.2.1.4.2, Table 14.2.1.4.3, Table 14.2.1.4.4, Table 14.2.1.4.5, Table 14.2.1.4.6, Table 14.2.1.4.7, Table 14.2.1.4.8, Table 14.2.1.4.9, Table 14.2.1.4.11, Figure 14.2.1.4.12.1

Abbreviations: Δ = change from baseline; bDMARD = biologic DMARD; DMARD = disease modifying anti-rheumatic drug; CI = confidence interval; CRP = C-reactive protein; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire-Disability Index; PASDAS = Psoriatic Arthritis Disease Activity Score; SE = standard error; IR = Inadequate Response; TNFi = Tumor Necrosis Factor inhibitor; Tofa = tofacitinib; UK = United Kingdom; vs = versus.

Western Europe includes Belgium, France, Germany, Spain, and UK. Eastern Europe includes Czech Republic, Poland, and Slovakia. Rest of world includes Mexico, Brazil and Taiwan.

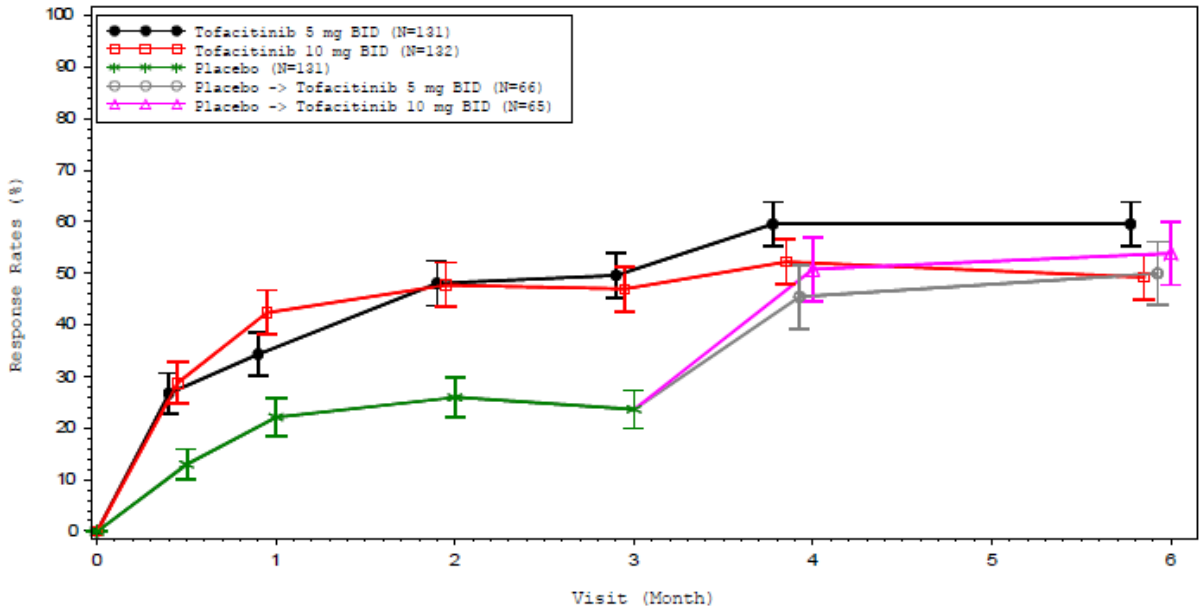
For each subgroup (eg, gender), the results were based on a repeated measures model with the fixed effects of treatment, visit, treatment by visit interaction, subgroup, subgroup by treatment, subgroup by visit, subgroup by treatment by visit interaction, geographic location, and baseline value; an unstructured covariance matrix was used. When subgroup is geographic location, the main effect of geographic location appears only once in the model. Difference was defined as tofacitinib – placebo.

Due to the low number of subjects in the category of baseline PASDAS ≤3.2, this category was dropped from analysis.

Secondary endpoints

ACR20 responder rates at all time points other than Month 3

Figure 29 - Line Graph of ACR20 Response Rates (±SE) Up to Month 6 (FAS, Missing Response = Non-Response)



Source: Figure 14.2.1.1.2.2
Abbreviations: ACR20 = American College of Rheumatology Response Criteria ≥20%; BID = twice daily; FAS = Full Analysis Set; N = number of subjects in the FAS; SE = standard error.
ACR20 was calculated as a ≥20% improvement from baseline in tender/painful and swollen joint counts and ≥20% improvement from baseline in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.

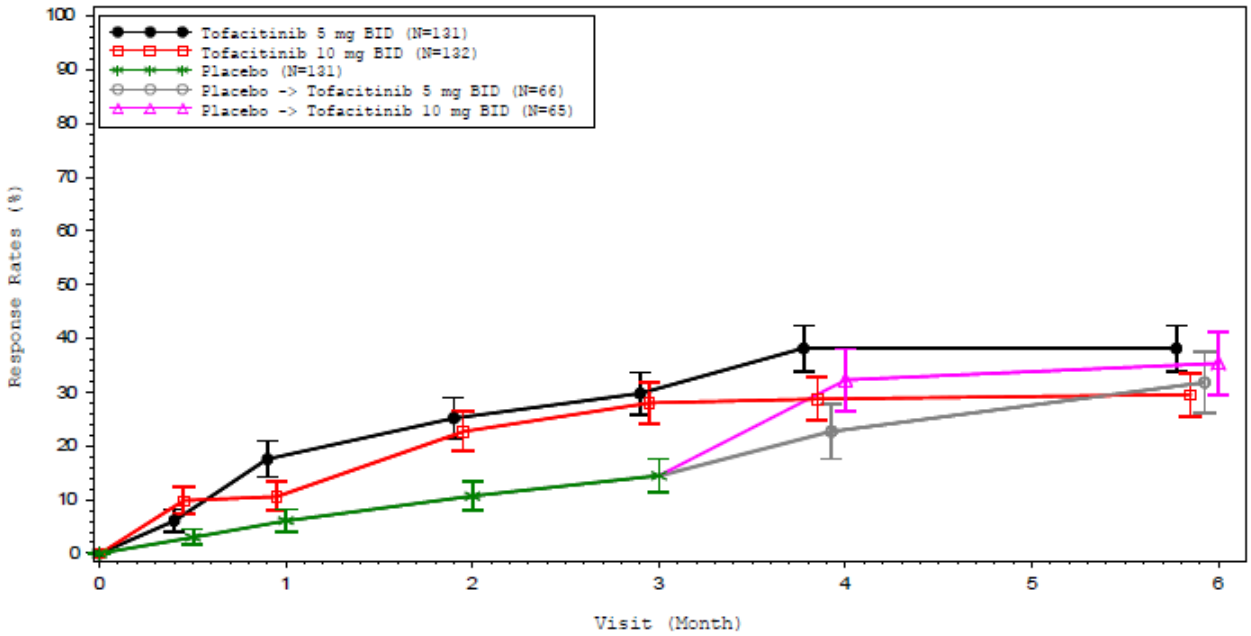
ACR50 response

Table 35 - Normal Approximation to ACR50 Response Rates at Months 3 and 6 (FAS, Missing Response = Non-Response) – Treatment Comparisons

Visit	Treatment Group	N	n	Response Rate (%)	SE (%)	Difference				
						Difference (%)	SE of Difference (%)	95% CI Lower (%)	95% CI Upper (%)	P-value
Month 3	Tofa 5	131	39	29.77	4.00					
	Tofa 10	132	37	28.03	3.91					
	PBO	131	19	14.50	3.08					
	Tofa 5 vs PBO					15.27	5.04	5.38	25.15	0.0025
	Tofa 10 vs PBO					13.53	4.97	3.78	23.28	0.0065
	Tofa 10 vs Tofa 5					-1.74	5.59	-12.70	9.21	0.7555
Month 6	Tofa 5	131	50	38.17	4.24					
	Tofa 10	132	39	29.55	3.97					
	PBO → Tofa 5	66	21	31.82	5.73					
	PBO → Tofa 10	65	23	35.38	5.93					
	Tofa 10 vs Tofa 5					-8.62	5.81	-20.01	2.77	0.1380

Source: Table 14.2.2.1.2.1 and Table 14.2.2.1.2.2
Abbreviations: ACR50 = American College of Rheumatology Response Criteria ≥50%; BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; N = number of subjects in FAS; n = number of responders; PBO = placebo; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs = versus.
ACR50 was calculated as a ≥50% improvement from baseline in tender/painful and swollen joint counts and ≥50% improvement from baseline in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.
Two-sided 95% CI and p-values were based on the normal approximation for the difference in binomial proportions.
P-values are nominal.

Figure 30 - Line Graph of ACR50 Response Rates (±SE) Up to Month 6 (FAS, Missing Response = Non-Response)



Source: Figure 14.2.2.1.2.2
Abbreviations: ACR50 = American College of Rheumatology Response Criteria ≥50%; BID = twice daily; FAS = Full Analysis Set; N = number of subjects in the FAS; SE = standard error.

ACR70 response

Table 36 - Normal Approximation to ACR70 Response Rates at Months 3 and 6 (FAS, Missing Response = Non-Response) – Treatment Comparisons

Visit	Treatment Group	N	n	Response Rate (%)	SE (%)	Difference				
						Difference (%)	SE of Difference (%)	95% CI Lower (%)	95% CI Upper (%)	P-value
Month 3	Tofa 5	131	22	16.79	3.27					
	Tofa 10	132	19	14.39	3.06					
	PBO	131	13	9.92	2.61					
	Tofa 5 vs PBO					6.87	4.18	-1.33	15.07	0.1004
	Tofa 10 vs PBO					4.47	4.02	-3.41	12.35	0.2661
	Tofa 10 vs Tofa 5					-2.40	4.47	-11.17	6.37	0.5915
Month 6	Tofa 5	131	28	21.37	3.58					
	Tofa 10	132	19	14.39	3.06					
	PBO → Tofa 5	66	10	15.15	4.41					
	PBO → Tofa 10	65	12	18.46	4.81					
	Tofa 10 vs Tofa 5					-6.98	4.71	-16.21	2.25	0.1382

Source: Table 14.2.2.2.2.1 and Table 14.2.2.2.2.2
Abbreviations: ACR70 = American College of Rheumatology Response Criteria ≥70%; BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; N = number of subjects in FAS; n = number of responders; PBO = placebo; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs = versus.
ACR70 was calculated as a ≥70% improvement from baseline in tender/painful and swollen joint counts and ≥70% improvement from baseline in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant.
Two-sided 95% CI and p-values were based on the normal approximation for the difference in binomial proportions.
P-values are nominal.

ACR response criteria components

HAQ-DI

At Month 6, the LS mean ΔHAQ-DI was -0.44 for the tofacitinib group and -0.34 for the tofacitinib 10 mg group, indicating that the effect observed at Month 3 is maintained.

Tender/painful joint count

A statistically significant reduction in tender/painful joint count was observed for the comparison of tofacitinib 5 mg BID vs placebo at Month 3. The LS mean difference was -5.4 (95% CI: -8.1, -2.7; p = 0.0001). A maintenance of effect was evident. No dose response was observed.

Swollen joint count

There was a statistically significant reduction in swollen joint count for the comparison of tofacitinib 5 mg vs placebo at Month 3. The LS mean difference was –4.0 (95% CI: -5.7, -2.3; p<0.0001). Maintenance of effect was evident. No dose response was observed.

Patient's Assessment of Arthritic Pain – VAS (mm)

At Month 3, the LS mean difference from baseline in patient's assessment of arthritic pain was -21.7, -20.9 for tofacitinib 5 mg and tofacitinib 10 mg respectively, vs -7.7 for placebo. All comparisons with placebo were statistically significant. These differences from baseline were maintained at Month 6.

Patient's global assessment of arthritis - VAS (mm)

At Month 3, the LS mean difference from baseline in patient's global assessment of arthritis was -21.6, -19.9 for tofacitinib 5 mg and tofacitinib 10 mg respectively, vs 7.1 for placebo. All comparisons with placebo were statistically significant. These differences from baseline were maintained at Month 6.

Physician's global assessment of arthritis – VAS (mm)

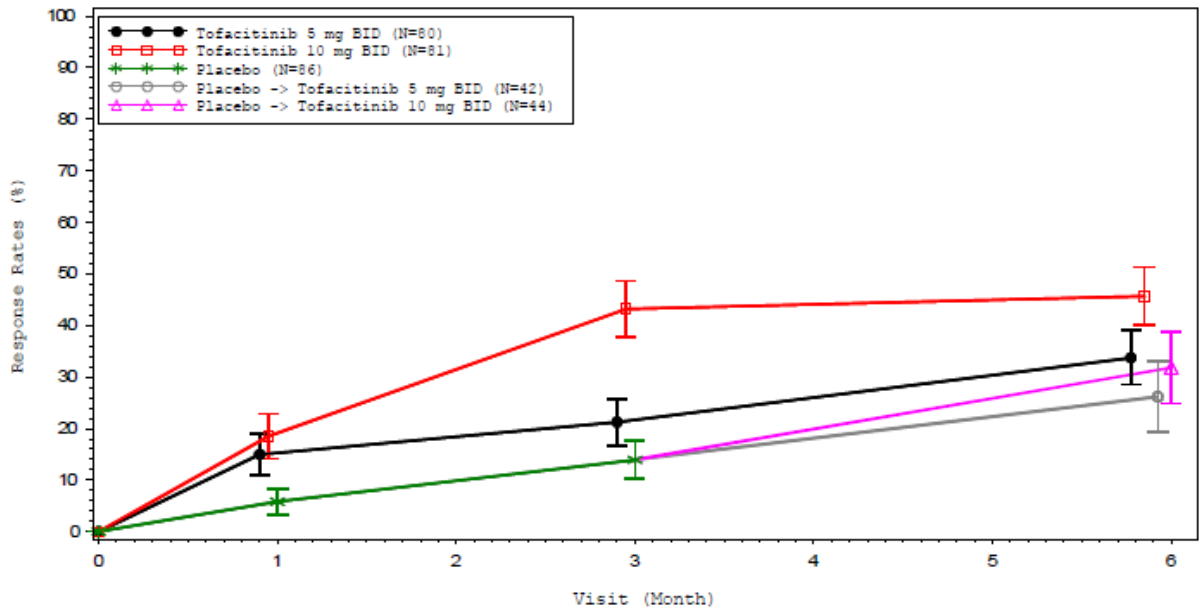
At Month 3, the LS mean difference from baseline in physician's global assessment of arthritis was -27.3, and -29.0 for tofacitinib 5 mg and tofacitinib 10 mg respectively, vs -15.9 for placebo. All comparisons with placebo were statistically significant. These differences from baseline were maintained at Month 6.

C-reactive protein

At Month 3, the LS mean difference from baseline in CRP (mg/L) was -5.47 and -5.91 for tofacitinib 5 mg and tofacitinib 10 mg respectively, vs 1.02 for placebo. All comparisons with placebo were statistically significant. These differences from baseline were maintained at Month 6.

Psoriasis Area and Severity Index 75 (PASI75) response

Figure 31 - Line Graph of PASI75 Response Rates (±SE) up to Month 6 (for Subjects With Baseline BSA ≥3% and Baseline PASI >0 in FAS, Missing Response = Non-Response)



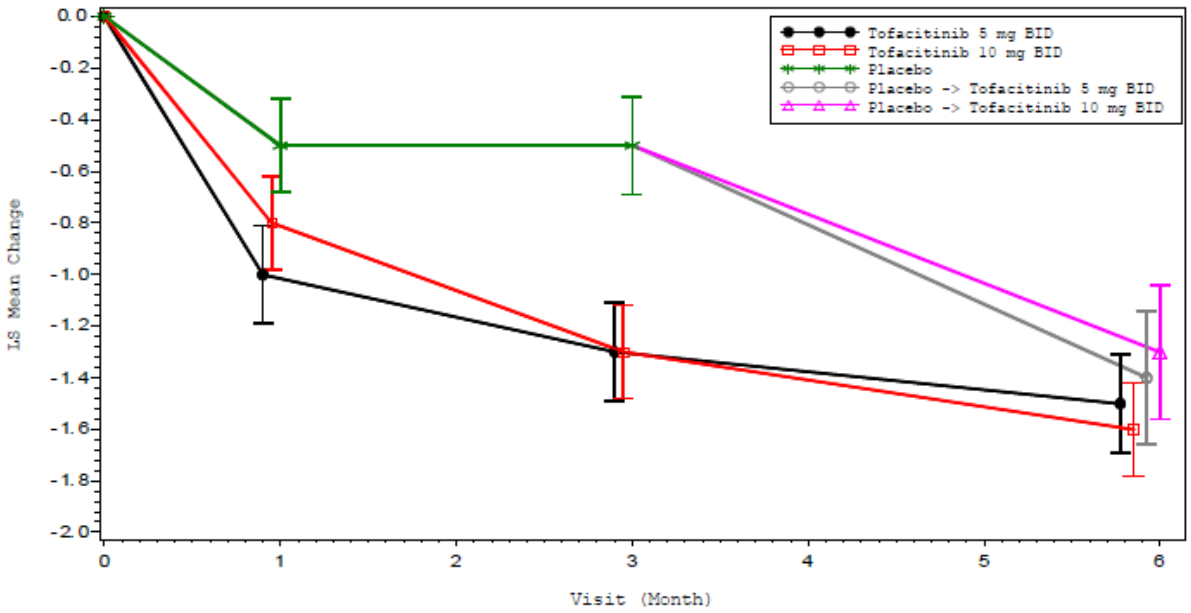
Source: Figure 14.2.2.4.3
Abbreviations: BID = twice daily; BSA = body surface area; FAS = Full Analysis Set; N = number of subjects in the FAS; PASI75 = Psoriasis Area and Severity Index 75; SE = standard error.
PASI75 was defined as a ≥75% reduction from baseline in PASI.
Only subjects with baseline BSA affected ≥3% (per study protocol) and baseline PASI >0 were considered.

Physician's global assessment of psoriasis (PGA-PsO)

The LS mean change from baseline for PGA-PsO was -0.7, -1.1 and -0.4. for tofacitinib 5 mg, tofacitinib 10 mg and placebo, respectively. The difference between tofacitinib 5 mg and placebo was statistically significant. The response was maintained up to Month 6.

Enthesitis

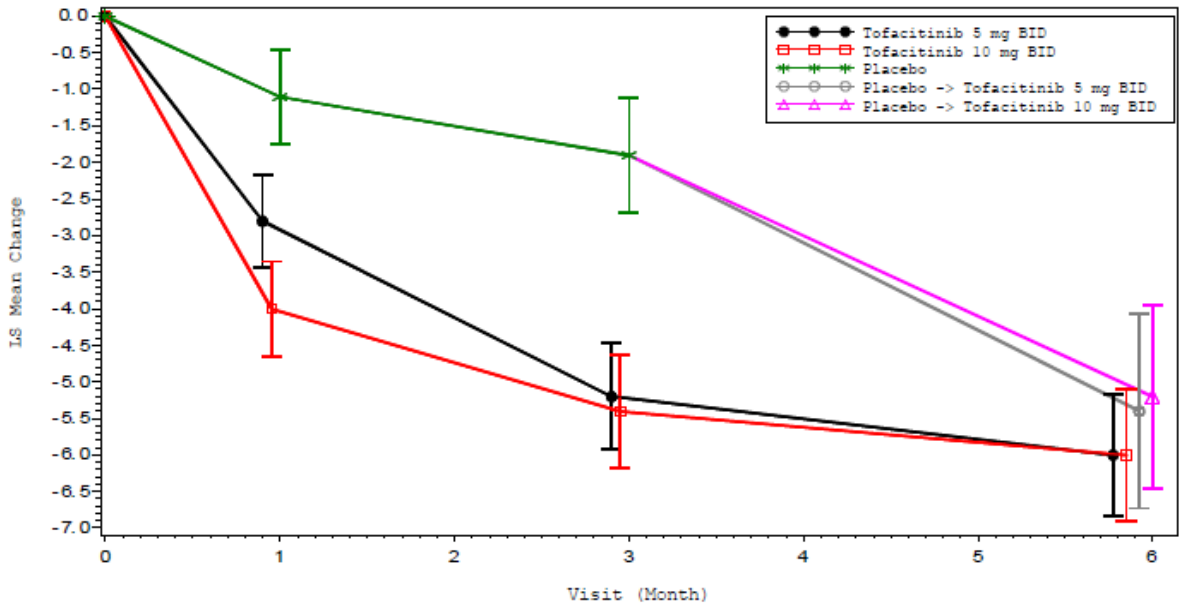
Figure 32 - Line Graph of Least Square Mean (±SE) ΔLeeds Enthesitis Index (LEI) up to Month 6 From the Repeated Measures Model (for Subjects With Baseline Score >0 in FAS, No Imputation)



Source: Figure 14.2.2.16.3.2
Abbreviations: Δ = change from baseline; BID = twice daily; FAS = Full Analysis Set; LEI = Leeds Enthesitis Index; LSMean = least squares mean; MMRM = Mixed Model for Repeated Measures; SE = standard error.
Two separate analyses were performed. The results for Month 3 were generated using MMRM1 including data from Month 1 to Month 3 (combined placebo). The results for Month 6 were generated using MMRM2 including data from Month 1 to Month 6 (separate placebo treatment sequences; discarding the results for Month 1 to Month 3 for plotting). Each model included the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used.
Subjects with baseline LEI score = 0 were excluded from the LEI analysis.
Number of unique subjects included in the MMRM analyses for tofacitinib 5 mg BID: 82; tofacitinib 10 mg BID: 96; placebo: 91; placebo→ tofacitinib 5 mg BID: 45; placebo→ tofacitinib 10 mg BID: 46
(Table 14.2.2.16.3.1 and Table 14.2.2.16.3.2).

Dactylitis

Figure 33 - Line Graph of Least Square Mean (±SE) ΔDactylitis Severity Score (DSS) up to Month 6 From the Repeated Measures Model (for Subjects With Baseline DSS >0 in FAS, No Imputation)



Source: Figure 14.2.2.15.3.2
Abbreviations: Δ = change from baseline; BID = twice daily; DSS = Dactylitis Severity Score; FAS = Full Analysis Set; LSMean = least squares mean; MMRM = Mixed Model for Repeated Measures; SE = standard error.
Two separate analyses were performed. The results for Month 3 were generated using MMRM1 including data from Month 1 to Month 3 (combined placebo). The results for Month 6 were generated using MMRM2 including data from Month 1 to Month 6 (separate placebo treatment sequences; discarding the results for Month 1 to Month 3). Each model included the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used.
Subjects with baseline dactylitis score = 0 were excluded from analysis.
Number of unique subjects included in the MMRM analyses for tofacitinib 5 mg BID: 65; tofacitinib 10 mg BID: 64; placebo: 62; placebo→tofacitinib 5 mg BID: 29; placebo→tofacitinib 10 mg BID: 33
(Table 14.2.2.15.3.1 and Table 14.2.2.15.3.2).

Psoriatic Arthritis Response Criteria (PsARC)

At Month 3, the PsARC response rates were 58.8%, 48.5% and 29.0% for tofacitinib 5 mg, tofacitinib 10 mg and placebo, respectively. The difference between tofacitinib 5 mg and placebo was statistically significant. The response was maintained up to Month 6.

Physical function and health outcome measures

SF-36 version 2

For the physical functioning domain, physical component, vitality domain, social functioning domain and bodily pain domain at Month 3, LS mean changes from baseline are increased for both active treatments vs placebo, reaching statistical significance. The improvements are maintained over the 6-month study.

For role-physical domain, there is a trend in favour of tofacitinib 5 mg vs placebo. For the 10 mg group, a statistically significant difference is observed.

For the mental health domain, mental component general health domain and role-emotional domain, there is a trend in favour of both active treatments at Month 3.

EuroQol-5 Dimension Health State Profile (EQ-5D-3-level)

For the pain/discomfort domain, the LS mean change from baseline at Month 3 was greater for the active treatment groups vs placebo, reaching statistical significance. The changes were maintained during the 6-month study.

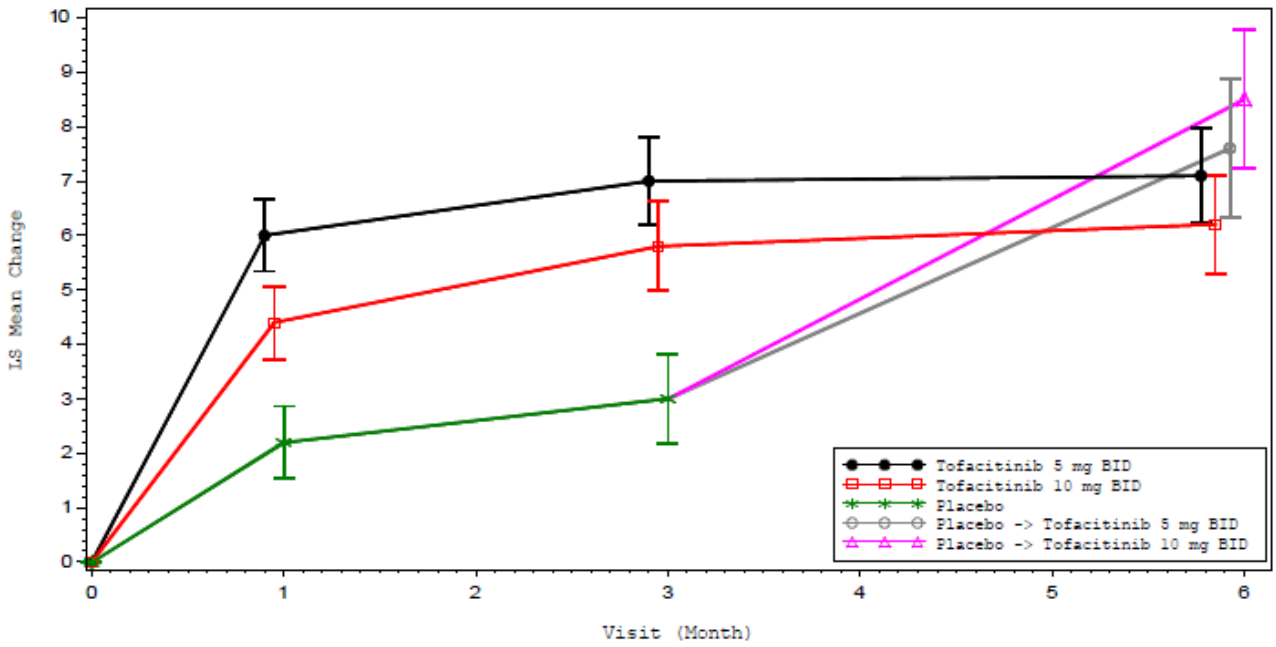
For the mobility domain, the LS mean change from baseline at Month 3 was greater for the active treatment groups vs placebo, reaching statistical significance for the 5 mg group. The changes were maintained during the 6-month study.

For the self-care domain, the anxiety/depression domain and usual activities domain, there was a trend in favour of the active treatments at Month 3.

Regarding the VAS score (mm) on the subjects' health care state today, the Month 3 LS mean scores (change from baseline) were 8.62 and 12.33 for tofacitinib 5 mg and 10 mg respectively, compared to 2.64 for placebo. These treatment differences reached statistical significance. The scores were maintained during the 6-month study.

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

Figure 34 - Line Graph of Least Square Mean (±SE) ΔFACIT-F Total Score up to Month 6 From the Repeated Measures Model (FAS, No Imputation)



Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The numbers included in this analysis are small: 26, 25 and 22 subjects in tofacitinib 5 mg, tofacitinib 10 mg and placebo groups, respectively:

Table 37 - Statistical Analysis (Repeated Measures Model) of ΔBath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Months 1, 3 and 6 (for Subjects With Presence of Spondylitis at Screening and Baseline BASDAI Score >0 cm in FAS, No Imputation) – Treatment Comparisons

Visit	Treatment Group	N	n	LS Mean	SE	Difference				
						Difference	SE of Difference	95% CI		P-value
								Lower	Upper	
Month 1	Tofa 5	26	26	-2.04	0.400					
	Tofa 10	25	25	-1.26	0.412					
	PBO	22	22	-0.34	0.415					
	Tofa 5 vs PBO					-1.70	0.560	-2.82	-0.58	0.0034
	Tofa 10 vs PBO					-0.93	0.558	-2.04	0.19	0.1012
	Tofa 10 vs Tofa 5					0.77	0.529	-0.28	1.83	0.1490
Month 3	Tofa 5	26	26	-2.26	0.465					
	Tofa 10	25	22	-1.92	0.490					
	PBO	22	19	-1.00	0.506					
	Tofa 5 vs PBO					-1.26	0.672	-2.60	0.08	0.0648
	Tofa 10 vs PBO					-0.93	0.681	-2.28	0.43	0.1783
	Tofa 10 vs Tofa 5					0.34	0.638	-0.94	1.61	0.5998
Month 6	Tofa 5	26	25	-2.02	0.463					
	Tofa 10	25	22	-1.56	0.489					
	PBO → Tofa 5	10	8	-2.26	0.756					
	PBO → Tofa 10	12	10	-3.05	0.701					
	Tofa 10 vs Tofa 5					0.46	0.633	-0.80	1.72	0.4694

Source: Table 14.2.2.17.3.1 and Table 14.2.2.17.3.2
Abbreviations: Δ = change from baseline; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; N = total number of unique subjects in the longitudinal model; n = number of subjects evaluable at each visit; PBO = placebo; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs = versus.
Number of subjects in FAS with presence of spondylitis at screening and baseline BASDAI score >0 cm for tofacitinib 5 mg BID: 26; tofacitinib 10 mg BID: 26; placebo: 22; placebo→tofacitinib 5 mg BID: 10; placebo→tofacitinib 10 mg BID: 12.
Subjects with absence of spondylitis at screening or baseline BASDAI = 0 were excluded from the analysis.
Two separate analyses were performed. The results for Month 3 were generated using MMRM1 including data from Month 1 to Month 3 (combined placebo). The results for Month 6 were generated using MMRM2 including data from Month 1 to Month 6 (separate placebo treatment sequences; discarding the results for Month 1 to Month 3). Each model included the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used. P-values are nominal.

Other efficacy evaluations

DAS28-3 (CRP)

Table 38 - Statistical Analysis (Repeated Measures Model) of ΔDAS28-3 (CRP) at Months 3 and 6 (FAS, No Imputation) – Treatment Comparisons

Visit	Treatment Group	N	n	LS Mean	SE	Difference				
						Difference	SE of Difference	95% CI		P-value
								Lower	Upper	
Month 3	Tofa 5	130	123	-1.383	0.0954					
	Tofa 10	132	118	-1.230	0.0969					
	PBO	131	117	-0.613	0.0968					
	Tofa 5 vs PBO					-0.770	0.1353	-1.036	-0.504	<0.0001
	Tofa 10 vs PBO					-0.617	0.1366	-0.866	-0.348	<0.0001
	Tofa 10 vs Tofa 5					0.153	0.1353	-0.113	0.419	0.2587
Month 6	Tofa 5	130	123	-1.567	0.0965					
	Tofa 10	132	113	-1.354	0.0992					
	PBO → Tofa 5	66	56	-1.471	0.1411					
	PBO → Tofa 10	65	55	-1.512	0.1409					
	Tofa 10 vs Tofa 5					0.213	0.1377	-0.058	0.484	0.1224

Source: Table 14.2.2.21.3.1 and Table 14.2.2.21.3.2
Abbreviations: Δ = change from baseline; BID = twice daily; CI = confidence interval; CRP = C-reactive protein; DAS = Disease Activity Score; FAS = Full Analysis Set; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; N = total number of unique subjects in the longitudinal model; n = number of subjects evaluable at each visit; PBO = placebo; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs = versus.
In FAS, number of subjects in tofacitinib 5 mg BID: 131; tofacitinib 10 mg BID: 132; placebo: 131; placebo→tofacitinib 5 mg BID: 66; placebo→tofacitinib 10 mg BID: 65.
Two separate analyses were performed. The results for Month 3 were generated using MMRM1 including data from Week 2 to Month 3 (combined placebo). The results for Month 6 were generated using MMRM2 including data from Week 2 to Month 6 (separate placebo treatment sequences; discarding the results for Week 2 to Month 3). Each model included the fixed effects of treatment, visit, treatment by visit interaction, geographic location and baseline value; an unstructured covariance matrix was used. P-values are nominal.

Minimal disease activity (MDA)

Table 39 - Normal Approximation to MDA Rates at Months 3 and 6 (FAS, Missing Response = Non-Response) – Treatment Comparisons

Visit	Treatment Group	N	n	Response Rate (%)	SE (%)	Difference				
						Difference (%)	SE of Difference (%)	95% CI		P-value
								Lower (%)	Upper (%)	
Month 3	Tofa 5	131	30	22.90	3.67					
	Tofa 10	132	28	21.21	3.56					
	PBO	131	19	14.50	3.08					
	Tofa 5 vs PBO					8.40	4.79	-0.99	17.79	0.0796
	Tofa 10 vs PBO					6.71	4.70	-2.51	15.93	0.1538
	Tofa 10 vs Tofa 5					-1.69	5.11	-11.71	8.33	0.7412
Month 6	Tofa 5	131	31	23.66	3.71					
	Tofa 10	132	31	23.48	3.69					
	PBO → Tofa 5	66	12	18.18	4.75					
	PBO → Tofa 10	65	19	29.23	5.64					
	Tofa 10 vs Tofa 5					-0.18	5.23	-10.44	10.08	0.9727

Source: Table 14.2.2.6.2 and Table 14.2.2.6.3
Abbreviations: BID = twice daily; CI = confidence interval; FAS = Full Analysis Set; MDA = Minimal Disease Activity; N = number of subjects in FAS; n = number of responders; PBO = placebo; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; Tofa 10 = tofacitinib 10 mg BID; vs = versus.
Two-sided 95% CI was based on the normal approximation for the difference in binomial proportions.
P-values are nominal.

PASDAS

ΔPASDAS at Month 3 was greater for subjects receiving tofacitinib 5 mg BID (-1.93) and tofacitinib 10 mg BID (-2.14) versus placebo (-0.83) (the 2-sided 95% CI for the difference between each tofacitinib dose and placebo excluded 0). The improvement in PASDAS was increased for the 2 tofacitinib treatment groups at Month 6 relative to Month 3.

Summary of main studies

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

Table 40 - Summary of Efficacy for trial A3921091

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of 2 Doses of Tofacitinib or Adalimumab in Subjects With Active Psoriatic Arthritis			
Study identifier	A3921091		
Design	Phase 3 randomized, multicentre, 12-month, double-blind, double-dummy, placebo-controlled, parallel treatment group study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months N/A N/A
Hypothesis	Superiority		
Treatments groups	Tofacitinib 5 mg BID		12 months, n=107
	Tofacitinib 10 mg BID		12 months, n=104
	Placebo		3 months (advanced to tofacitinib 5 mg BID or 10 mg BID at Month 3, for 9 months), n=52 (→ 5 mg BID) and n=53 (→ 10 mg BID)
	Adalimumab		40 mg SC q 2 weeks, 12 months, n=106
Endpoints and definitions	Co-Primary endpoint	ACR20	ACR response rate at Month 3

	Co-Primary endpoint	ΔHAQ-DI	Change from baseline in HAQ-DI at Month 3
Database lock	10th November 2016 (clinical study report date)		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Full analysis set (all subjects who were randomized to the study and received at least 1 dose of the randomized study drug), Month 3				
Descriptive statistics and estimate variability	Treatment group	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Adalimumab	Placebo
	Number of subject	107	104	106	105
	ACR20 (%)	50.47	60.58	51.89	33.33
	SE (%)	4.83	4.79	4.85	4.60
	Number of subjects	107	104	106	104*
	ΔHAQ-DI (LS mean)	-0.3499	-0.3998	-0.3808	-0.1802
	SE	0.04665	0.04716	0.04767	0.05031
	* One placebo subject was excluded from the analysis (no post-baseline assessment)				

Effect estimate per comparison	Co-Primary endpoint: ACR20	Comparison groups	Tofacitinib 5 mg BID vs placebo
		Difference (%)	17.13
		95% CI (%)	4.06, 30.21
		P-value	0.0102
	Co-Primary endpoint: ΔHAQ-DI	Comparison groups	Tofacitinib 5 mg BID vs placebo
		Difference	-0.1697
		95% CI	-0.2910, -0.0483
		P-value	0.0062

Table 41 - Summary of Efficacy for trial A3921125

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of 2 Doses of Tofacitinib in Subjects with Active Psoriatic Arthritis and an Inadequate Response to At Least One TNF Inhibitor		
Study identifier	A3921125	
Design	Phase 3 randomized, 6-month, global, double-blind, placebo-controlled, parallel-group study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months N/A N/A
Hypothesis	Superiority	
Treatments groups	Tofacitinib 5 mg BID	6 months, n=132
	Tofacitinib 10 mg BID	6 months, n=132
	Placebo	3 months (advanced to tofacitinib 5 mg BID or 10 mg BID at Month 3, for 3 months), n=66 (→ 5 mg BID) and n=65 (→ 10 mg BID)

Endpoints and definitions	Co-Primary endpoint	ACR20	ACR response rate at Month 3
	Co-Primary endpoint	ΔHAQ-DI	Change from baseline in HAQ-DI at Month 3
Database lock	09 November 2016 (clinical study report)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full analysis set (all subjects who were randomized to the study and received at least 1 dose of the randomized study drug), Month 3			
Descriptive statistics and estimate variability	Treatment group	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
	Number of subject	131	132	131
	ACR20 (%)	49.62	46.97	23.66
	SE (%)	4.37	4.34	3.71
	Number of subjects	129*	132	131
	ΔHAQ-DI (LS mean)	-0.3920	-0.3540	-0.1391
	SE	0.04544	0.04579	0.04573
	* 2 subjects in the tofacitinib 5 mg BID group was excluded from the analysis (no baseline or post-baseline assessment)			

Effect estimate per comparison	Co-Primary endpoint: ACR20	Comparison groups	Tofacitinib 5 mg BID vs placebo
		Difference (%)	25.95
		95% CI (%)	14.72, 37.19
		P-value	<0.0001
	Co-Primary endpoint: ΔHAQ-DI	Comparison groups	Tofacitinib 5 mg BID vs placebo
		Difference	-0.2529
		95% CI	-0.3792, -0.1266
		P-value	<0.0001

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

Pooled analyses

In order to address concerns raised regarding the evidence for use in combination with csDMARDs other than MTX, the MAH has pooled data from study A3921091 (csDMARD-IR) and A3921125 (bDMARD-IR):

Table 42 - Comparison of Responder Rates for Selected Efficacy Endpoints at Month 3 by Concomitant csDMARD Use in Studies A3921091 and A3921125 (Pooled Data)

	Methotrexate Only[a]				Other csDMARD[b]			
	Placebo		Tofa 5		Placebo		Tofa 5	
	N/n	% (SE)	N/n	% (SE or 95% CI)[c]	N/n	% (SE)	N/n	% (SE or 95% CI)[c]
ACR20	192/52	27.1 (3.2)	186/91	48.9 (3. 7)	43/14	32. 6 (7.2)	52/28	53.9 (6.9)
Active Treatment vs Placebo	-	-	-	21.8 (12.2, 31.3)	-	-	-	21.3 (2.2, 40.4)
ACR50	192/24	12.5 (2.4)	186/57	30.7 (3.4)	43/5	11.6 (4. 9)	52/12	23.1 (5.8)
Active Treatment vs Placebo	-	-	-	18.2 (10.1, 26.3)	-	-	-	11.5 (-3.3, 26.3)
ACR70	192/13	6.8 (1.8)	186/32	17.2 (2.8)	43/5	11.6 (4.9)	52/8	15.4 (5.0)
Active Treatment vs Placebo	-	-	-	10.5 (4.0, 16.9)	-	-	-	3. 8 (-9.9, 17.5)
PASI75[d]	139/20	14.4 (3.0)	130/44	33.9 (4.2)	28/4	14.3 (6.6)	32/8	25.0 (7.7)
Active Treatment vs Placebo	-	-	-	19.3 (9.4, 29.2)	-	-	-	10.4 (-8.1, 28.9)

a. Methotrexate Only = subjects who only used concomitant methotrexate or methotrexate sodium up to Month 3.
b. Other csDMARD = subjects who used only 1 concomitant csDMARD other than methotrexate or who used ≥2 csDMARDs (4 receiving tofacitinib 5 mg BID and 1 receiving placebo) up to Month 3.
c. SE values are provided for the absolute result and 95% CI are provided for comparison to placebo.
d. PASI75 was measured in subjects with baseline BSA ≥3% and PASI >0 in FAS with non-missing concomitant csDMARD use. PASI75 is defined as a ≥75% reduction from baseline in PASI.
Abbreviations: ACR=American College of Rheumatology; ACR 20, 50, 70 = ACR Response Criteria ≥20%, ≥50%, ≥70% improvement from baseline, respectively; BID = twice daily; BSA = body surface area; CI = confidence interval; csDMARD = conventional synthetic DMARD; DMARD = disease-modifying anti-rheumatic drug; FAS = full analysis set; N = Number of subjects in FAS with non-missing concomitant csDMARD use; n = number of responders; PASI = Psoriasis Area and Severity Index; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; vs = versus.
Missing values for ACR20, ACR50, ACR70, and PASI75 were considered as non-response to treatment.
Sources: Module 5.3.5.3 D90 RSI Efficacy Tables 00061.3.3.1; 00061.3.3.2; 00061.3.3.3; 00061.3.3.4.

Table 43 - Comparison of Change from Baseline in Least Squares Mean for Select Efficacy Endpoints at Month 3 by Concomitant csDMARD Use in Studies A3921091 and A3921125 (Pooled Data)

	Methotrexate Only[a]				Other csDMARD[b]			
	Placebo		Tofa 5		Placebo		Tofa 5	
	N/n	LSM (SE)	N/n	LSM (SE or 95% CI)[c]	N/n	LSM (SE)	N/n	LSM (SE or 95% CI)[c]
ΔHAQ-DI	192/181	-0.17 (0.04)	185/179	-0.37 (0.04)	42/38	0.16 (0.08)	51/48	-0.48 (0.07)
Active Treatment vs Placebo	-	-	-	-0.19 (-0.29, -0.10)	-	-	-	-0.32 (-0.53, -0.12)
ΔLEI[d]	125/118	-0.55 (0.16)	120/116	-1.11 (0.16)	30/27	-0.53 (0.36)	36/33	-1.37 (0.32)
Active Treatment vs Placebo	-	-	-	-0.56 (-0.99, -0.14)	-	-	-	-0.84 (-1.72, 0.03)
ΔDSS[d]	100/94	-2.79 (0.65)	100/97	-4.90 (0.63)	18/16	-0.83 (2.25)	25/25	-3.61 (1.83)
Active Treatment vs Placebo	-	-	-	-2.12 (-3.75, -0.48)		-	-	-2.78 (-8.38, 2.82)

a. Methotrexate Only = subjects who only used concomitant methotrexate up to Month 3
b. Other csDMARD = subjects who used only 1 concomitant csDMARD other than methotrexate or who used ≥2 csDMARDs (4 receiving tofacitinib 5 mg BID and 1 receiving placebo) up to Month 3.
c. SE values are provided for the absolute result and 95% CI are provided for comparison to placebo.
d. ΔLEI and ΔDSS were measured in subjects with baseline LEI>0 and DSS>0, respectively.
Abbreviations: Δ=change from baseline; BID = twice daily; csDMARD = conventional synthetic DMARD; DMARD = disease-modifying anti-rheumatic drug; DSS = Dactylitis Severity Score; HAQ-DI = Health Assessment Questionnaire-Disability Index; LEI = Leeds Enthesitis Index; LSM = least squares mean; N = total number of unique subjects in the longitudinal model; n = number of subjects evaluable at the visit; SE = standard error; Tofa 5 = tofacitinib 5 mg BID; vs = versus.
A longitudinal model was used to analyse the ΔHAQ-DI, ΔLEI, and ΔDSS without imputation for missing values.
Sources: Module 5.3.5.3 D90 RSI Efficacy Tables 00061.3.3.7; 00061.3.3.8; 00061.3.3.9.

Supportive studies

Study A3921092: A Long-Term, Open-Label Extension Study of Tofacitinib (CP-690,550) for the Treatment of Psoriatic Arthritis

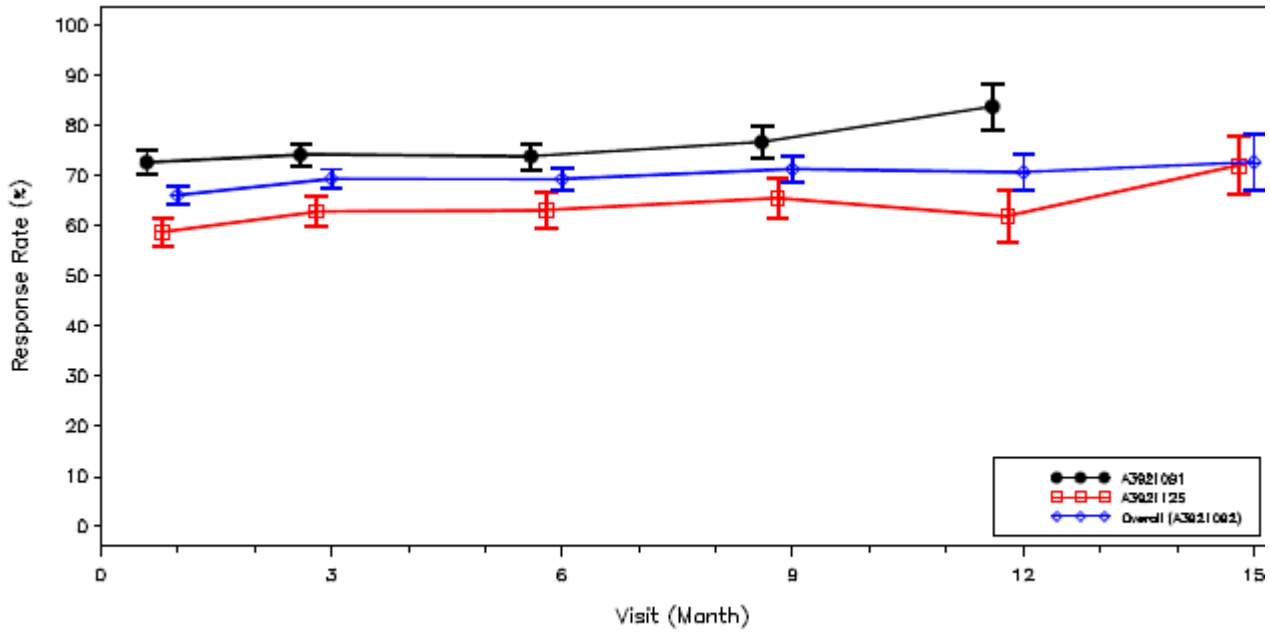
This extension study for protocols A3921091 and A3921125 (see under 'main studies') was initiated 17 February 2014 and is ongoing. A report has been provided based on an interim cut-off date of 04 April 2016. The primary objective was to evaluate the long-term safety and tolerability of treatment with tofacitinib (5 mg BID and 10 mg BID) in adult subjects with active psoriatic arthritis (PsA). The secondary objective was to evaluate long-term efficacy.

All eligible subjects from qualifying Studies A3921091 and A3921125 received open-label tofacitinib 5 mg BID upon entry into A3921092. Starting at Month 1, tofacitinib dose may have been increased to 10 mg BID at study visits if, based upon the Investigator's discretion, subjects receiving tofacitinib 5 mg BID would have benefited from a higher dose and were not experiencing any tofacitinib-related adverse events (AEs), including abnormalities in laboratory parameters that were judged to be related to tofacitinib. Subjects had to be receiving permitted background csDMARDs, eg, methotrexate, sulfasalazine or leflunomide, in accordance with the local regulatory label. Stable doses of oral steroids and NSAIDs were permitted, in line with the protocols of the qualifying studies. The efficacy endpoints matched those evaluated in the qualifying studies, and was evaluated every 3 months.

A total of 685 subjects were enrolled (363 from study 1091 and 322 from study 1125). Of these, 680 were treated and 72 (10.6%) have discontinued at data cut-off. All 680 treated patients were evaluated for efficacy. A total of 661 (97.2%) reported concomitant DMARD treatment on day 1.

Efficacy data is provided up to Month 15:

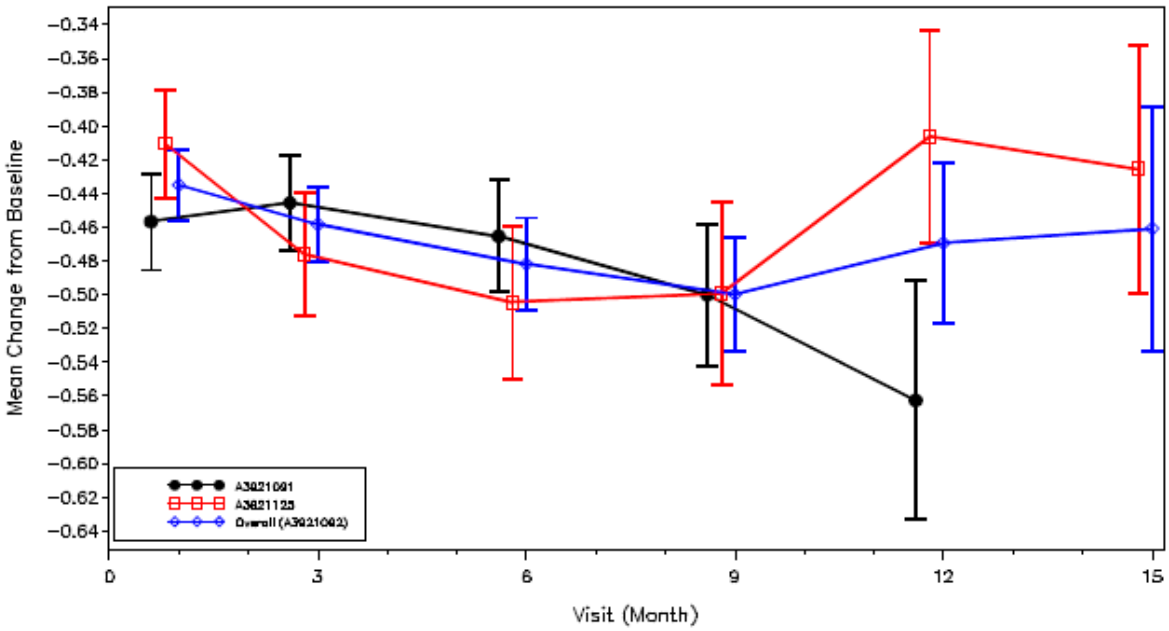
Figure 35 - Line Graph of ACR20 Response Rates (±SE) (FAS, No Imputation) 15 (FAS, No Imputation)



Source: Figure 14.2.1.1.1

The baseline value for each component comes from the baseline of the qualifying study.
Number of subjects evaluable at each visit is the denominator for the calculation of the response rates.
Only visits with ≥50 subjects with evaluable assessments per study are displayed.
Abbreviations: ACR = American College of Rheumatology; CRP = C-reactive protein; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire – Disability Index; SE = standard error.

Figure 36 - Line Graph of Mean (± SE) ΔHAQ-DI (FAS, No Imputation)



Source: Figure 14.2.1.2.2
The baseline value comes from the baseline of the qualifying study.
Only subjects evaluable at each visit contribute to the summary statistics.
Only visits with ≥50 subjects with evaluable assessments per study are displayed.
Abbreviations: Δ = change from baseline; FAS = Full Analysis Set; HAQ-DI = Health Assessment Questionnaire-Disability Index; SE = standard error.

Study A3921119: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose Ranging Study of the Efficacy and Safety of Tofacitinib in Subjects with Active Ankylosing Spondylitis (AS)

This study was conducted between April 2013 and March 2015. This multi-centre study was designed to characterise the dose-response of tofacitinib in adult subjects with active AS per New York classification criteria. Eligible subjects were randomized in a 1:1:1:1 ratio to receive either tofacitinib 2 mg, 5 mg, or 10 mg BID or placebo for 12 weeks. Subjects had to have active AS defined as 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). The primary efficacy endpoint was ASAS20 response rate at 12 weeks of treatment.

A total of 208 subjects were randomised, 52 to each treatment group. Eleven subjects discontinued.

Table 44 - Normal Approximation to ASAS20 Response at Week 12, Comparison to Placebo – Full Analysis Set, NRI /LOCF Mixed Components

					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					

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 in Ankylosing Spondylitis, 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 ASAS 40 response at Week 12 was 42.31%, 46.15%, 38.46% and 19.61% for the tofacitinib 2 mg BID, 5 mg BID, 10 mg BID and placebo groups respectively.

Study A3921137: A Phase 3, Multi Site, Randomized, Double-Blind Study of the Long-Term Safety, Tolerability and Efficacy of 2 Oral Doses of CP 690,550 in Subjects with Moderate to Severe Plaque Psoriasis and/or Psoriatic Arthritis

This study was conducted at 16 centres in Japan. A total of 94 subjects were treated, 87 with psoriasis and 12 with PsA (5 subjects were included in both disease populations). Subjects were randomised 1:1 to tofacitinib 5 mg BID or tofacitinib 10 mg BID. There was a 16-week double-blind period followed by a 36-week open-label period.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The PsA clinical development programme was designed to evaluate the efficacy of tofacitinib 5 mg BID and 10 mg BID in patients with active PsA with inadequate response or intolerance to csDMARD (TNFi naïve) (study 1091) or TNFi (study 1125). Both studies were multi-centre, phase 3 randomised, double-blind, placebo-controlled efficacy and safety studies. Study 1091 lasted one year whereas study 1125 lasted 6 months. Both studies were too short to support claims related to structural progression.

Subjects were selected based on CASPAR criteria, ≥3 tender/painful and ≥3 swollen joints, the presence of signs and symptoms for at least 6 months, and the presence of active psoriasis. These are established criteria with high specificity for PsA diagnosis although are mainly used in research and clinical trials and at a lesser extent in clinical practice. The eligibility criteria were adequate to define a population with active PsA and an inadequate response to a prior DMARD.

Of note, PsA has a multifaceted phenotype that may include arthritis of peripheral joints, skin and nail disease, entheseal involvement, dactylitis and axial disease; however, no formal requirement for skin manifestations, enthesitis, or dactylitis at baseline was included in the studies. Therefore, the target population mainly reflects the PsA phenotype with polyarticular peripheral joint involvement with or without axial disease. This pattern of disease represents the predominant one in the clinical setting, and for this reason it is agreed to be the main population of PsA to be enrolled in clinical trials.

All subjects were required to remain on background csDMARD for the duration of the studies, of which 88% were treated with MTX. Both studies included a 3-month placebo phase, after which placebo patients were allocated (per baseline randomisation) tofacitinib 5 mg BID or 10 mg BID. In addition, study 1091

included the active comparator adalimumab, a TNFα inhibitor approved in Europe for the treatment of active and progressive psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. The inclusion of an active control arm allows contextualisation of study results. The study designs are in line with CHMP scientific advice and are acceptable to demonstrate an effect on signs, symptoms, function and health outcomes, including maintenance of effect. Subjects could continue a stable dose of corticosteroids, opioids, acetaminophen or NSAIDs during the study.

For both studies, the co-primary endpoints were ACR20 response rate and ΔHAQ-DI at Month 3. These primary endpoints measure signs, symptoms, and function. ACR20 has been widely used as a primary endpoint in PsA registration studies. Secondary endpoints further evaluated the signs and symptoms of psoriasis, enthesitis, dactylitis and axial spondylitis, as well as health outcomes and quality of life. In addition, change from baseline in mTSS at one year was evaluated in study 1091, to assess prevention of structural progression. The choice of primary and secondary endpoints was in line with CHMP advice, and with the EMA *Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis* (CHMP/EWP/438/04).

A total of 422 subjects were randomised in study 1091, and 395 in study 1125. More than two-thirds of subjects in Study 1091 (TNFi-naïve) were recruited in Eastern Europe and Russia (68.2%), while in Study A3921125 (TNFi-IR), the geographical distribution of subjects was more balanced. This may be due to differences in access to TNFi across regions. Across both studies, the number of EU subjects studied (n=462) was adequate. Across both studies, mean age was 49 years, 54% of subjects were female and 95% of subjects were white. The baseline disease characteristics were consistent with a population with active PsA, and a severity level recognised to require treatment change. Baseline characteristics were generally balanced between treatment groups.

The full analysis set was analysed in both studies. This corresponded to an ITT population and is acceptable. The overall discontinuation rates were low (3.8 - 5.6% in the tofacitinib 5 mg BID arm up to Month 3).

Efficacy data and additional analyses

Study 1091 outcomes

For the co-primary endpoint of ACR20 at Month 3, the response rate for the proposed dose of tofacitinib 5 mg BID was 50.5%, in line with the active comparator adalimumab. This represented a 17.1% increase over placebo, which is statistically significant and clinically relevant. The ACR20 response is maintained up to Month 12 for the active treatment groups. A separation from placebo is observed as early as 2 weeks for tofacitinib 5 mg BID. A dose response is evident.

For the co-primary endpoint of ΔHAQ-DI at Month 3, the LS mean treatment difference for tofacitinib 5 mg BID vs placebo was -0.17. This difference was in line with that observed for adalimumab. The effects are maintained until Month 12. The MCID (change from baseline) for HAQ-DI is 0.35. For the 90% of subjects with baseline HAQ-DI ≥0.35, 53.1% of the tofacitinib 5 mg BID group reported a decrease of ≥0.35, the minimum clinically relevant difference, compared to 30.9% for the placebo group. This responder analysis supports the clinical relevance of the HAQ-DI results.

Sensitivity analyses demonstrated the robustness of the results on the primary endpoints, and generally consistent findings were seen across subgroups.

Secondary endpoints included the ACR50, for which a clear separation from placebo was observed, with a treatment difference of 28.0% for tofacitinib 5 mg BID and 33.0% for adalimumab at Month 3, and a maintenance of the effect until Month 12. A dose response is evident. For ACR70, the respective treatment differences were 16.8% and 18.9%. For MDA, the respective treatment differences were

19.5% and 18.8%. Regarding the radiographic evaluations, the mean changes from baseline and the progressor rates were low, providing reassurance of a lack of deleterious effect. No specific claim on treatment effect on joint damage is possible based on these data. In general, the secondary endpoint results were supportive of the primary outcomes. In particular, there was evidence of consistent benefit for health outcome measures such as SF36 and FACIT-F.

Study 1125 outcomes

For the co-primary endpoint of ACR20 at Month 3, the response rate for the proposed dose of tofacitinib 5 mg BID was 49.6%, in line with study 1091. This represented a 26.0% increase over placebo, which is statistically significant and clinically relevant. The ACR20 response is maintained up to Month 12 for the active treatment groups. A separation from placebo is observed as early as 2 weeks for tofacitinib 5 mg BID.

For the co-primary endpoint of ΔHAQ-DI at Month 3, the LS mean treatment difference for tofacitinib 5 mg BID vs placebo was -0.25. This difference was in line with that observed for study 1092. The effects are maintained until Month 12. For the 90% of subjects with baseline HAQ-DI ≥0.35, 50.0% of the tofacitinib 5 mg BID group reported a decrease of ≥0.35, the MCID, compared to 27.6% for the placebo group. This responder analysis supports the clinical relevance of the HAQ-DI results.

Sensitivity analyses demonstrated the robustness of the results on the primary endpoints, and generally consistent findings were seen across subgroups.

Secondary endpoints included the ACR50, for which a clear separation from placebo was observed, with a treatment difference of 15.3% for tofacitinib 5 mg BID, and maintenance of the effect until Month 12. Benefits for tofacitinib 5 mg BID in terms of ACR70 response rate and % subjects with MDA were less clear. This may reflect a more treatment resistant population, compared to study 1091. In general, the other secondary endpoint results were supportive of the primary outcomes. In particular, there was evidence of consistent benefit for health outcome measures such as SF36, FACIT-F and EQ-5D.

Skin involvement

The evaluation of tofacitinib treatment effect on skin manifestations is partially hampered by the lack of a pre-determined minimum number of psoriatic plaques at baseline. The main endpoint to test tofacitinib efficacy on skin manifestations was PASI75 at month 3. Patients were evaluated only if their body surface area was affected by psoriasis for > 3% (BSA >3%), and their PASI score was >0. Although BSA >3% cut-off includes patients with a relatively low involvement of skin in their clinical presentation of the disease, recent data from the Consortium of Rheumatology Investigators of North America (Corrona) indicate a direct relation between skin and joint disease and show a link between BSA > 3% and worse outcomes in PsA patients.

In the csDMARD-IR subjects, both 5mg (PASI75 met by 42.68% of patients) and 10mg (PASI75 met by 44.29% of patients) tofacitinib doses were statistically superior to placebo (PASI75 met by 14.63%) at a similar extend. The effect increased over time, resulting more pronounced with the 10 mg BID dose at both 6 and 12 months after treatment initiation (10 mg BID dose: 44.29% at month 3; 60% at month 6 and 67.14% at month 12; 5mg dose:42.68% at month 3; 46.34% at month 6 and 56.10% at month 12).

In the TNF-IR population, only the high tofacitinib dose showed superiority over placebo at month 3. Treatment effect was stable, with no substantial increase at month 6 observed with the 10 mg BID dose. The low tofacitinib dose did show some improvement in the response rate over time.

Enthesitis

Enthesitis is a major feature of PsA, and is generally measured both as an indicator of disease activity and treatment response. No specific requirement for enthesitis was included in the eligibility rules.

Consequently, only a proportion of enrolled subjects presented at baseline with enthesitis (66.4%and 70.1% of subjects in Study A3921091 and A3921125, respectively), and were thus assessed for treatment effect. Mean baseline LEI values ranged from 2.3 to 3 across the 4 treatment groups of study A3921091 and from 2.8 to 3.4 across the 3 treatment groups of study A3921125.

In the csDMARD-IR population, only the 10 mg BID tofacitinib dose proved statistically superior to placebo at month 3, albeit with a difference in mean LEI of only 1.0 (0.29) point, rather similar the 0.7 point that was observed as maximal difference of LEI values across treatment groups at baseline. Treatment effect slightly increased over time for both tofacitinib doses, resulting in similar differences from placebo at both 6 and 12 months of treatment (6 months: -1.2 and -1.3 for 10 mg BID and 5 mg BID respectively; 12 months: 1.6 and -1.7 for 10 mg BID and 5 mg BID respectively).

A post hoc supportive analysis on enthesitis resolution showed consistent results. Moreover, results obtained using the SPARCC index for the evaluation of enthesitis were in line with those obtained using the LEI index, with tofacitinib 5 mg BID (-1.84) not achieving nominal statistical significance compared to placebo.

In the TNF-IR population the effect on enthesitis (mean ∆LEI at Month 3) was nominally superior (the step wise approach was stopped at prior step, therefore P are nominal) to placebo for both doses, of similar extent, and maintained over time. However, the difference from placebo was 0.9 and 0.8 for tofacitinib 5 mgBID and 10 mg BID, respectively, again rather similar to the maximum difference in mean LEI baseline values (0.6) observed across the 3 treatment groups at baseline. Evaluation of enthesitis using the ∆SPARCC index at month 3, and the supportive analysis of the enthesitis resolution rate resulted in overall consistent results with the ∆LEI analysis, although an expected worse performance of the 10 mg BID dose was observed at 3 months in terms of resolution of enthesitis. In conclusion, tofacitinib effect on enthesitis appears of limited magnitude. Indeed, low mean baseline values prevent the evaluation of treatment effect in patients with larger enthesitis burden.

The MAH provided stratified data on tofacitinib effect on enthesitis according to baseline Leeds Enthesitis Index (LEI) (≤3, >3 and ≤4, >4) and Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index scores (≤4, >4 and ≤10, >10) to facilitate assessment of the impact of baseline disease burden on patient responsiveness to tofacitinib. For both indexes the highest cutoffs (>4 or >10 for the LEI and SPARCC, respectively) were not provided due to the low number of patients per treatment group.

In general, the maximum response observed for improvements in enthesitis occurred later on treatment, beyond the placebo-controlled period of 3 months, indicating a lower onset of clinically relevant effect. The comparison with adalimumab further confirmed the tofacitinib delayed onset of action, particularly when absence of enthesitis was selected as outcome measure. When LSM change from baseline in LEI and SPARCC enthesitis index scores are considered, tofacitinib 5 mg BID treatment effect is observed independently of disease burden, with a trend towards larger magnitude of effect in patients with higher burden of the disease, similar to what observed in the adalimumab group. However, when the more stringent endpoint, absence of enthesitis, is considered, patients with higher burden of the disease tended to respond to tofacitinib treatment with smaller improvement (especially in terms of SPARCC score) and much more slowly compared to those with lower disease burden.

In conclusion, efficacy towards enthesitis appears limited and delayed in onset.

Dactylitis

Dactylitis is a common and painful extra-articular manifestation of PsA, representing a combination of synovitis and inflammation of tendon and ligament insertions. It has been shown that digits with dactylitis are associated with a greater degree of radiological damage than those which occur in digits not affected by dactylitis, thus treatment efficacy on dactylitis is a relevant outcome measure for patients with PsA. No baseline pre-requisite for dactylitis was specified in the inclusion criteria of the pivotal studies, thus only a

proportion of patients were affected with dactylitis at baseline (56% and 49% of subjects in A3921091 and A3921125 study, respectively), and differences in baseline ranges of the Dactylitis Severity Score were observed among treatment groups, with the lowest severity range of dactylitis detected in the placebo group of study A3921125.

In the csDMARD-IR population at month 3, only the tofacitinib 10 mg BID dose was nominally superior (the step wise approach was stopped at prior step, therefore P are nominal) to placebo in ameliorating the Dactylitis Severity Score (DSS). However, the effect of the tofacitinib 5 mg BID dose improved over time, reaching magnitudes similar to those obtained with the 10 mg BID dose from month 6 onwards. Similar slower onset of treatment effect was observed with the 5 mg BID dose also in terms of resolution rates, although in this case the magnitude of treatment effect was always lower than that obtained with the 10 mg BID dose. In TNFi-IR patients, improvements in ∆DSS at month 3 were similar and nominally higher than placebo for both tofacitinib doses (-5.2 and -5.4 LS mean for the 5mg and 10mg bid, respectively), with only minor further improvements over time. Consistent results were seen when resolution rates were analyzed. Differences in baseline dactylitis severity, with a greater number of affected digits and greater DSS at baseline in TNFi naïve pts vs TNFi experienced patients, may have contributed to the different outcomes in the two study populations.

CHMP considered that the discussion provided by the MAH satisfactorily addressed the different performance of tofacitinib 5mg bid in the two studies.

Axial domain

The numbers included in the BASDAI analysis were small, due to the low numbers with spondylitis that were enrolled. Even more important, the BASDAI is not considered the optimal tool to investigate treatment induced amelioration of axial spondylitis and no confirmation of treatment effect on axial damage by imaging data has been provided.

Results are considered not satisfactory with only the 10 mg BID dose showing some effect in the csDMARD-IR population, and no nominal difference from placebo for both tofacitinib doses in the TNFi-IR population. In both cases, no substantial improvement of treatment effect over time was observed. Negative results for both tofacitinib doses were also obtained in the subset of csDMARD-IR and TNFalpha-IR subjects with higher disease activity (BASDAI $\geq$4 cm), where the mean ∆BASDAI at Month 3 was not nominally higher than placebo. On the contrary, nominally significant differences from placebo were obtained, in this setting, with adalimumab.

In the attempt to support the limited information on treatment effect on axial spondylitis, the MAH provided results from the A3921119 study, investigating tofacitinib efficacy in adult subjects with imaging-verified axial spondylitis, and suggesting efficacy of both tofacitinib doses in axial disease. However, supportive data in AS patients, although overall supporting of tofacitinib efficacy on axial disease, cannot overcome the limitations in the assessment of axial damage in PsA patients of the two pivotal studies (small sample size, lack of imaging verification and specific assessment for axial spondylitis). As such, at present, it is difficult to soundly conclude on tofacitinib efficacy in axial disease, on the basis of the data provided.

A statement has been included in section 5.1 of the SmPC that the number of PsA patients with axial involvement/predominant spondylitis was too small to allow meaningful assessment.

Supportive studies

Study 1092 is the on-going extension study for protocols A3921091 and A3921125. Eligible subjects received open-label tofacitinib 5 mg BID with concomitant csDMARD on entry for up to 3 years. A total of 685 subjects were enrolled (363 from study 1091 and 322 from study 1125). Of these, 680 were treated and 72 (10.6%) have discontinued at data cut-off. In general, the improvements observed during the

main studies were maintained over the 12-month observation period of the extension study. For this interim analysis, numbers of subjects included in the analyses at each visit decreased over time because of staggered entry in the study and subject discontinuation from the study. However, the results provide reassurance regarding long-term efficacy.

Target population

Most data derive from (i) subjects that were taking methotrexate at baseline and/or (ii) subjects that were treated with methotrexate concomitantly.

Around 6% of the population of study A3921091 (csDMARD-IR) had an inadequate response to one csDMARD other than MTX. In addition, 1.4% had an inadequate response to >1 csDMARD that did not include MTX. These subgroups are too small for meaningful efficacy analyses. However, the subgroup with an inadequate response to >1 csDMARD can provide supportive information, since this patients in this subgroup (>1 csDMARD-IR) had an inadequate response to a csDMARD other than MTX, and should represent a more difficult to treat population. The MAH has compared the efficacy outcomes of the >1 csDMARD subgroup vs 1 csDMARD-IR subgroup (predominantly MTX-IR). Regarding efficacy at Month 3, the >1 csDMARD subgroup appear to derive more benefit from tofacitinib but less benefit from adalimumab, compared to the 1 csDMARD subgroup, across most of the relevant endpoints. The MAH also provided a supportive analysis of the RA clinical efficacy dataset. The ACR response rates and HAQ-DI change from baseline at Month 3 were comparable for 'csDMARD-IR but not MTX-IR or bDMARD-IR' and MTX-IR subgroups. This provides additional evidence that patients who are csDMARD-IR but not MTX-IR would be expected to benefit from tofacitinib. The low level of recruitment to study A3921091 of patients who failed a csDMARD other than MTX reflects clinical practice. Most patients will receive MTX as first-line. Patients with a contraindication or intolerance to MTX, and an inadequate response to an alternative csDMARD, were not studied in large numbers. It would be difficult to design a study to include more of these patients, given current treatment guidelines. It seems unlikely that this group would benefit less from tofacitinib treatment compared to MTX-IR patients.

To address concerns regarding the evidence for use in combination with csDMARDs other than MTX, the MAH has pooled data from study A3921091 (csDMARD-IR) and A3921125 (bDMARD-IR). This strategy is acceptable since the studies were similar in design. Across both studies 21.8% received concomitant csDMARD other than MTX. The pooled group corresponding to 'other csDMARD' included 52 patients in the tofacitinib 5 mg BID group and 43 in the placebo group. Of the 52 patients in the tofacitinib 5 mg BID group, 30 patients took sulfasalazine and 19 patients took leflunomide. Overall the efficacy outcomes across a range of endpoints were comparable. Efficacy as measured by ACR response rates favoured the 'MTX only' group but efficacy as measured by ΔHAQ-DI, ΔLEI and ΔDSS favoured the 'other csDMARD' group. Supportive evidence from the RA database also suggests comparable efficacy outcomes irrespective of concomitant csDMARD. However, there is insufficient data to conclude on the safety of Xeljanz, in combination with csDMARDs other than MTX (see benefit risk discussion).

2.4.4. Conclusions on the clinical efficacy

For the co-primary endpoints of ACR20 response rate and ΔHAQ-DI, superiority to placebo has been demonstrated for the 5 mg BID dose, on background csDMARD therapy, in PsA subjects with inadequate response to or intolerance to prior DMARDs. These endpoints relate mainly to signs and symptoms of peripheral arthritis which however are predominant in most PsA patients compared to other clinical manifestations of the disease. A statement has been included in section 5.1 of the SmPC that the number of PsA patients with axial involvement/predominant spondylitis was too small to allow meaningful assessment. There is no evidence of a deleterious effect on joint structure.

Outcomes for the secondary endpoints are generally in line with the primary endpoints. However, for disease manifestations of skin involvement, dactylitis and enthesitis, the outcomes are less convincing and less consistent across the two pivotal studies. This may be due in part to the inclusion of patients without these manifestations, and therefore reduced power to demonstrate statistically significant treatment effects within study. The secondary endpoint outcomes are adequately reflected in section 5.1 of the SmPC.

There is some evidence that a dose of 10 mg BID may be associated with increased benefit compared to 5 mg BID, although a difference is not consistently observed across all endpoints. This finding is in line with the PK-PD modelling (see section 2.3.4). The proposed dose of 5 mg BID has been justified based on safety considerations, in particular the dose dependency of serious infections, opportunistic infections and laboratory parameters.

The approved indication and posology are adequately supported by the available clinical efficacy data.

2.5. Clinical safety

Introduction

Tofacitinib is already approved for the treatment of moderate to severe RA. Tofacitinib causes neutropenia and lymphopenia, and is associated with a risk of serious infections (e.g. pneumonia) and opportunistic infections (e.g. herpes zoster). The incidence rate for serious infection was 3.6 per 100 patient year (PY) during the RA programme compared to 1.7 for placebo; there was a higher incidence in the elderly. Neoplasms represent an important potential risk due to the mechanism of action. Common ADRs include headache, URTI, nasopharyngitis, diarrhoea, nausea, hypertension.

Studies A3921125 and A3921091, the two pivotal studies for this application, were pooled for the evaluation of safety, as follows:

- Cohort 1 (placebo-controlled comparison) is derived from the 0-3 month placebo-controlled phase of both studies, and is used to compare tofacitinib with placebo (and with adalimumab for study 1091)
- Cohort 2 (6-month dose comparison) is derived from the 6 months of active treatment in both studies, and is used to compare tofacitinib doses (and with adalimumab for study 1091); subjects originally allocated to placebo are not included.
- Cohort 2a (12-month dose comparison) is derived from 6 months of treatment in study 1125 and 12 months of treatment in study 1091 and is used to compare tofacitinib doses (and with adalimumab for study 1091). This cohort includes the active treatment phase of subjects originally allocated to placebo (‘All Tofa 5mg’ and ‘All Tofa 10mg’).
- Cohort 3 (All PsA) is derived from the entire tofacitinib experience for subjects with PsA, including extension study 1092. The 5 mg and 10 mg doses are combined. Using this cohort, analyses were conducted based on average total daily dose, and for subjects while receiving tofacitinib 5 mg BID (constant 5 mg BID dosing group). This cohort was used to evaluate AEs over time.

External independent adjudication committees were established for reviews of potential AEs of opportunistic infections (OIs), malignancies, cardiovascular (CV) events, hepatic events, and gastrointestinal (GI) perforations.

In addition, the following sets of supportive safety data, to complement the main safety data set, have also been provided:

- Integrated safety datasets of Tofacitinib in the Rheumatoid Arthritis and Psoriasis Development Programs. These data will provide context to compare the similarity of rates, risk factor analysis, and to assess rates of certain safety events, especially those with long-latency periods (such as malignancies) after exposures to tofacitinib for longer periods than have been studied in PsA to date.
- Safety Data from the Literature (Clinical Trial and Observational). These data will allow to contextualize IR for infections of interest, malignancies and CV events in the tofacitinib PsA programme and to complement the adalimumab active control from the A3921091 study.

Safety Data from an External Comparison Cohort. Since the type of data available from published observational sources or published clinical study are limited, in terms of populations and outcomes, data from an external population ('comparison cohort') are presented. This comparison cohort is a retrospective descriptive cohort of adults age 18 years of age and older with moderate to severe PsA from the Antirheumatic Therapies in Sweden (ARTIS) database, a Swedish biologics registry.

Patient exposure

A total of 738 PsA subjects were treated with tofacitinib in the clinical development programme. There were 1237.89 patient-years of exposure, as of the data lock point of 07/03/2017. The exposure to tofacitinib is summarised in the following table:

Table 45 - Number of Subjects and Drug Exposure by Treatment Duration All PsA (Cohort 3)

	Tofacitinib All Doses	Average Tofacitinib 5 mg BID[a]	Average Tofacitinib 10 mg BID[b]
Number of Subjects	783	482	301
Duration			
≤1 Week	2	2	0
>1 week – 1 month	12	7	5
>1 month - 2 months	12	6	6
>2 months - 3 months	12	6	6
>3 months - 6 months	39	14	25
>6 months - 12 months	78	46	32
>12 months - 18 months	150	105	45
>18 months - 24 months	158	95	63
>24 months - 30 months	181	117	64
>30 months - 36 months	131	78	53
>36 months - 42 months	7	5	2
>42 months - 48 months	1	1	0
>48 months	0	0	0
Mean Duration (Days)	577.1	588.5	558.9
Median Duration (Days)	594	595.5	591
Range (Days)	1-1196	1-1196	12-1101
Total Drug Exposure (PY)	1237.89	NA	NA

Abbreviations: BID = twice daily; NA = not available; PY = patient-years; PsA = psoriatic arthritis.
a. Subjects with an average total daily dose of <15 mg over the course of observation.
b. Subjects with an average total daily dose of ≥15 mg over the course of observation.
Duration is defined as the total number of dosing days from the first day of dosing up to and including the last day of each study treatment.
Month = 28 days.
Cohort 3 includes all tofacitinib exposed subjects.
Source: Module 5.3.5.3 SCS Tables C3.3.12.1; C3.3.13.3

Adverse events

Definitions and calculations

Incidence rate (IR) estimates and the corresponding number (%) of subjects with an event are calculated by inclusion of events occurring up to 28 days beyond the last dose (or to the data-lock point date for ongoing studies).

Exposure (PY) is defined as the total follow-up time calculated up to the day of the first event within the event counting period for subjects with the event or the last dose day plus a risk period of 28 days beyond the last dose (or to the data data-lock point date for ongoing studies) for subjects without events.

These definitions were chosen because reporting to the company safety database may occur at any time regardless of the time elapsed from the last administration of study drug or since study completion. Inclusion of all events without regard to elapsed time may inflate IR estimations as the exposure time (denominator) is not similarly increased.

In order to provide a measure of comparison (controlled for study) of the estimated IRs between treatment groups in Cohorts 1, 2 and 2a, hazard ratio (HR) for the treatment effect were calculated from a Cox regression model with treatment arm and study as covariates.

Placebo-controlled comparison

Treatment-emergent AEs were reported by 47.9%, 49.6%, 40.3% and 46.2% of subjects in the tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo and adalimumab groups respectively. Severe AEs were reported by 1.7%, 2.5%, 2.5% and 1.9%, respectively.

Table 46 - Treatment Emergent Adverse Events with Preferred Term ≥2% Occurrence in Any Treatment Group, by System Organ Class and Preferred Term (All Causalities): Placebo-Controlled Period (Cohort 1)

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Adalimumab (A3921091)
Subjects Evaluable For Adverse Events	238	236	236	106
Number (%) of Subjects with Adverse Events				
Gastrointestinal disorders				
Diarrhoea	8 (3.4)	9 (3.8)	1 (0.4)	1 (0.9)
Dyspepsia	5 (2.1)	2 (0.8)	2 (0.8)	1 (0.9)
Nausea	6 (2.5)	5 (2.1)	7 (3.0)	4 (3.8)
General disorders and administration site conditions				
Injection site erythema	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.7)
Injection site swelling	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.8)
Fatigue	0 (0.0)	7 (3.0)	1 (0.4)	1 (0.9)
Infections and infestations				
Bronchitis	6 (2.5)	4 (1.7)	0 (0.0)	0 (0.0)
Nasopharyngitis	14 (5.9)	13 (5.5)	6 (2.5)	5 (4.7)
Pharyngitis	1 (0.4)	7 (3.0)	3 (1.3)	1 (0.9)
Upper respiratory tract infection	12 (5.0)	11 (4.7)	11 (4.7)	3 (2.8)
Urinary tract infection	3 (1.3)	6 (2.5)	5 (2.1)	1 (0.9)
Investigations				
Alanine aminotransferase increased	1 (0.4)	2 (0.8)	1 (0.4)	4 (3.8)
Aspartate aminotransferase increased	0 (0.0)	1 (0.4)	0 (0.0)	3 (2.8)
Nervous system disorders				
Headache	9 (3.8)	20 (8.5)	11 (4.7)	5 (4.7)
Dizziness	6 (2.5)	1 (0.4)	3 (1.3)	0 (0.0)
Skin and subcutaneous tissue disorders				
Acne	3 (1.3)	5 (2.1)	0 (0.0)	0 (0.0)
Vascular disorders				
Hypertension	4 (1.7)	5 (2.1)	3 (1.3)	1 (0.9)

Abbreviations: BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities.
MedDRA (v19.0) coding dictionary applied.
Subjects are counted only once per treatment in each row.
Source: Module 5.3.5.3 SCS Table C1.1.7.1

6-month dose comparison

Treatment-emergent AEs were reported by 64.7%, 67.4% and 65.1% of subjects in the tofacitinib 5 mg BID, tofacitinib 10 mg BID and adalimumab groups respectively. Severe AEs were reported by 5.0%, 4.7% and 3.8%, respectively.

Table 47 - Treatment Emergent Adverse Events with Preferred Term ≥2% Occurrence in Any Treatment Group, by System Organ Class and Preferred Term (All Causalities): 6-month dose comparison (Cohort 2)

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Adalimumab (A3920191)
Subjects Evaluable For Adverse Events	238	236	106
Number (%) of Subjects with Adverse Events			
Gastrointestinal disorders			
Constipation	5 (2.1)	3 (1.3)	1 (0.9)
Diarrhoea	13 (5.5)	12 (5.1)	2 (1.9)
Abdominal pain	3 (1.3)	6 (2.5)	1 (0.9)
Dyspepsia	6 (2.5)	3 (1.3)	1 (0.9)
Nausea	8 (3.4)	11 (4.7)	6 (5.7)
General disorders and administration site conditions			
Injection site erythema	0	0	5 (4.7)
Injection site swelling	0	0	3 (2.8)
Fatigue	4 (1.7)	8 (3.4)	1 (0.9)
Infections and infestations			
Bronchitis	7 (2.9)	12 (5.1)	1 (0.9)
Lower respiratory tract infection	3 (1.3)	7 (3.0)	0
Nasopharyngitis	20 (8.4)	22 (9.3)	8 (7.5)
Pharyngitis	3 (1.3)	9 (3.8)	3 (2.8)
Sinusitis	4 (1.7)	7 (3.0)	0
Upper respiratory tract infection	19 (8.0)	17 (7.2)	5 (4.7)
Urinary tract infection	5 (2.1)	10 (4.2)	2 (1.9)
Oral herpes	4 (1.7)	2 (0.8)	3 (2.8)
Injury, poisoning and procedural complications			
Contusion	3 (1.3)	3 (1.3)	3 (2.8)
Investigations			
Blood creatine phosphokinase increased	7 (2.9)	8 (3.4)	3 (2.8)
Alanine aminotransferase increased	3 (1.3)	4 (1.7)	7 (6.6)
Aspartate aminotransferase increased	1 (0.4)	2 (0.8)	6 (5.7)
Gamma-glutamyltransferase increased	3 (1.3)	1 (0.4)	3 (2.8)
Weight increased	2 (0.8)	5 (2.1)	1 (0.9)
Musculoskeletal and connective tissue disorders			
Psoriatic arthropathy	5 (2.1)	2 (0.8)	1 (0.9)
Back pain	5 (2.1)	3 (1.3)	1 (0.9)
Nervous system disorders			
Headache	14 (5.9)	23 (9.7)	6 (5.7)
Dizziness	7 (2.9)	2 (0.8)	1 (0.9)
Skin and subcutaneous tissue disorders			

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Adalimumab (A3920191)
Subjects Evaluable For Adverse Events	238	236	106
Number (%) of Subjects with Adverse Events			
Psoriasis	4 (1.7)	1 (0.4)	3 (2.8)
Acne	3 (1.3)	5 (2.1)	0
Vascular disorders			
Hypertension	9 (3.8)	7 (3.0)	4 (3.8)

Abbreviations: BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with event.
MedDRA (v19.0) coding dictionary applied.
Subjects are counted only once per treatment in each row.
Source: Module 5.3.5.3 SCS Table C2.1.7.1

All PsA

Treatment-emergent AEs were reported by 83.0%, 79.5% and 88.7% of subjects in the Tofacitinib All Doses, Average Tofacitinib 5 mg BID and Average Tofacitinib 10 mg BID, respectively. Severe AEs were reported by 11.0%, 10.4% and 12.0%, respectively.

Table 48 - Treatment Emergent Adverse Events with Preferred Term ≥2% Occurrence in Any Treatment Group, by System Organ Class and Preferred Term (All Causalities): All PsA (Cohort 3)

System Organ Class Preferred Term	Tofacitinib All Doses	Average Tofa 5 mg BID[a]	Average Tofa 10 mg BID[b]
Subjects Evaluable For Adverse Events	783	482	301
Number (%) of Subjects with Adverse Events	534 (68.2)	309 (64.1)	225 (74.8)
Ear and labryrinth disorders			
Vertigo	8 (1.0)	2 (0.4)	6 (2.0)
Gastrointestinal disorders			
Gastritis	11 (1.4)	4 (0.8)	7 (2.3)
Constipation	14 (1.8)	8 (1.7)	6 (2.0)
Diarrhoea	43 (5.5)	23 (4.8)	20 (6.6)
Gastrooesophageal reflux disease	15 (1.9)	8 (1.7)	7 (2.3)
Abdominal pain	21 (2.7)	11 (2.3)	10 (3.3)
Abdominal pain upper	19 (2.4)	13 (2.7)	6 (2.0)
Dyspepsia	16 (2.0)	9 (1.9)	7 (2.3)
Nausea	39 (5.0)	27 (5.6)	12 (4.0)
General disorders and administration site conditions			

System Organ Class Preferred Term	Tofacitinib All Doses	Average Tofa 5 mg BID[a]	Average Tofa 10 mg BID[b]
Fatigue	16 (2.0)	6 (1.2)	10 (3.3)
Oedema peripheral	16 (2.0)	5 (1.0)	11 (3.7)
Infections and infestations			
Acute sinusitis	10 (1.3)	4 (0.8)	6 (2.0)
Bronchitis	58 (7.4)	32 (6.6)	26 (8.6)
Gastroenteritis	22 (2.8)	15 (3.1)	7 (2.3)
Lower respiratory tract infection	21 (2.7)	11 (2.3)	10 (3.3)
Nasopharyngitis	106 (13.5)	59 (12.2)	47 (15.6)
Pharyngitis	37 (4.7)	19 (3.9)	18 (6.0)
Respiratory tract infection	15 (1.9)	10 (2.1)	5 (1.7)
Rhinitis	14 (1.8)	8 (1.7)	6 (2.0)
Sinusitis	33 (4.2)	14 (2.9)	19 (6.3)
Tooth abscess	12 (1.5)	6 (1.2)	6 (2.0)
Upper respiratory tract infection	117 (14.9)	67 (13.9)	50 (16.6)
Urinary tract infection	53 (6.8)	29 (6.0)	24 (8.0)
Herpes simplex	12 (1.5)	4 (0.8)	8 (2.7)
Herpes zoster	24 (3.1)	15 (3.1)	9 (3.0)
Influenza	18 (2.3)	12 (2.5)	6 (2.0)
Oral herpes	21 (2.7)	12 (2.5)	9 (3.0)
Injury, poisoning and procedural complications			
Contusion	17 (2.2)	8 (1.7)	9 (3.0)
Fall	25 (3.2)	14 (2.9)	11 (3.7)
Investigations			
Blood creatine phosphokinase increased	47 (6.0)	24 (5.0)	23 (7.6)
Alanine aminotransferase increased	28 (3.6)	14 (2.9)	14 (4.7)
Aspartate aminotransferase increased	18 (2.3)	10 (2.1)	8 (2.7)
Gamma-glutamyltransferase increased	18 (2.3)	11 (2.3)	7 (2.3)
Weight increased	13 (1.7)	6 (1.2)	7 (2.3)
Metabolism and nutritional disorders			
Hypercholesterolaemia	12 (1.5)	5 (1.0)	7 (2.3)
Musculoskeletal and connective tissue disorders			
Spinal pain	15 (1.9)	11 (2.3)	4 (1.3)
Arthralgia	22 (2.8)	13 (2.7)	9 (3.0)
Osteoarthritis	15 (1.9)	9 (1.9)	6 (2.0)
Psoriatic arthropathy	29 (3.7)	14 (2.9)	15 (5.0)
Back pain	33 (4.2)	21 (4.4)	12 (4.0)
Pain in extremity	14 (1.8)	7 (1.5)	7 (2.3)
Nervous system disorders			
Headache	61 (7.8)	37 (7.7)	24 (8.0)
Dizziness	22 (2.8)	15 (3.1)	7 (2.3)
Paraesthesia	12 (1.5)	6 (1.2)	6 (2.0)
Sciatica	19 (2.4)	11 (2.3)	8 (2.7)
Psychiatric disorders			
Depression	11 (1.4)	10 (2.1)	1 (0.3)
Respiratory, thoracic and mediastinal disorders			
Cough	21 (2.7)	15 (3.1)	6 (2.0)

System Organ Class Preferred Term	Tofacitinib All Doses	Average Tofa 5 mg BID[a]	Average Tofa 10 mg BID[b]
Oropharyngeal pain	18 (2.3)	12 (2.5)	6 (2.0)
Skin and subcutaneous tissue disorders			
Psoriasis	21 (2.7)	14 (2.9)	7 (2.3)
Rash	18 (2.3)	10 (2.1)	8 (2.7)
Vascular disorders			
Hypertension	51 (6.5)	31 (6.4)	20 (6.6)

Abbreviations: BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with event; PsA = psoriatic arthritis.

a. Subjects with an average total daily dose of <15 mg over the course of observation.

b. Subjects with an average total daily dose of ≥15 mg over the course of observation.

Treatment emergent events are those on-treatment events which are new or worsened in severity relative to the pre-treatment period prior to Day 1 in the qualifying study.

MedDRA (v19.1) coding dictionary applied.

Subjects are counted only once per treatment in each row.

Source: Module 5.3.5.3 SCS Table C3.1.7.1

Serious adverse event / deaths / other significant events

Deaths

Five deaths were reported up to 07/03/2017 during the PsA clinical development programme, all in subjects receiving tofacitinib 5 mg BID. The preferred terms were: pancreatic cell carcinoma metastatic, cardiac arrest, acute cardiac failure, chronic obstructive pulmonary disease and pulmonary embolus. Three deaths occurred more than 28 days after the last dose. All deaths were considered by the Investigator to be unrelated to study drug.

Serious adverse events

There were 4 (1.7%) subjects with SAEs in each of the tofacitinib 5 mg BID, 10 mg BID and placebo treatment groups, and 1 subject (0.9%) with a SAE for adalimumab during the 3-month placebo-controlled period.

For the 12-month dose comparison cohort, there were 15 events each in the All Tofacitinib 5 mg BID (4.3%) and All Tofacitinib 10 mg BID (4.4%) groups. For study 1091, the incidence rates for SAEs over 12 months were 8 (7.5%), 4 (3.8%), and 9 (8.5%).

There were three SAEs of malignancy in the 12-month cohort, all in the tofacitinib 5 mg BID group. These are discussed in more detail below under 'adverse events of special interest'. The incidence rates of infections and infestations SAEs during this time were low and comparable between tofacitinib and adalimumab, affecting 2 (0.8%), 3 (1.3%) and 1 (0.9%) of subjects in the tofacitinib 5 mg BID, tofacitinib 10 mg BID and adalimumab groups, respectively.

For the all PsA cohort, the incidence rates for SAEs were 12.7% (61 subjects) and 11.6% (35 subjects) in the Average Tofacitinib 5 mg BID and Average Tofacitinib 10 mg BID groups.

Table 49 - Incidence of Serious Adverse Events by System Organ Class: All PsA (Cohort 3)

System Organ Class	Tofacitinib All Doses (N=783)	Average Tofacitinib 5 mg BID (N=482)[a]	Average Tofacitinib 10 mg BID (N=301)[b]
Number of Subjects (%)			
Blood and lymphatic system disorders	1 (0.1)	0	1 (0.3)
Cardiac disorders	9 (1.1)	4 (0.8)	5 (1.7)

System Organ Class	Tofacitinib All Doses (N=783)	Average Tofacitinib 5 mg BID (N=482)[a]	Average Tofacitinib 10 mg BID (N=301)[b]
Number of Subjects (%)			
Ear and labyrinth disorders	1 (0.1)	1 (0.2)	0
Endocrine disorders	1 (0.1)	0	1 (0.3)
Eye disorders	1 (0.1)	1 (0.2)	0
Gastrointestinal disorders	5 (0.6)	3 (0.6)	2 (0.7)
General disorders and administration site conditions	18 (2.3)	10 (2.1)	8 (2.7)
Hepatobiliary disorders	3 (0.4)	2 (0.4)	1 (0.3)
Infections and infestations	18 (2.3)	12 (2.5)	6 (2.0)
Injury, poisoning and procedural complications	10 (1.3)	6 (1.2)	4 (1.3)
Investigations	1 (0.1)	1 (0.2)	0
Metabolism and nutrition disorders	3 (0.4)	3 (0.6)	0
Musculoskeletal and connective tissue disorders	16 (2.0)	9 (1.9)	7 (2.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (1.9)*	12 (2.5)*	3 (1.0)*
Nervous system disorders	7 (0.9)	5 (1.0)	2 (0.7)
Pregnancy, puerperium and perinatal conditions	1 (0.1)	1 (0.2)	0
Product issues	1 (0.1)	1 (0.2)	0
Psychiatric disorders	1 (0.1)	0	1 (0.3)
Renal and urinary disorders	5 (0.6)	2 (0.4)	3 (1.0)
Reproductive system and breast disorders	3 (0.4)	2 (0.4)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	9 (1.1)	8 (1.7)	1 (0.3)
Skin and subcutaneous tissue disorders	4 (0.5)	3 (0.6)	1 (0.3)
Vascular disorders	5 (0.6)	3 (0.6)	2 (0.7)
Total number of cases [c]	128	82	46
Total number of subjects with serious adverse events [d]	101	66	35

Abbreviations: BID = twice daily; incl = including; N = number of subjects evaluable; MedDRA = Medical Dictionary for Regulatory Activities; PsA = psoriatic arthritis.

a. Subjects with an average total daily dose of <15 mg over the course of observation.
b. Subjects with an average total daily dose of ≥15 mg over the course of observation.
c. Number of cases that started in the treatment group.
d. Total number of subjects having an event that started in the treatment group.

* The average tofacitinib 5 mg BID group contains 2 benign events and 10 malignancies (excluding non-melanoma skin cancer [NMSC]) and 4 NMSC; the average tofacitinib 10 mg BID group contains 1 benign event and 2 malignancies (In the All Tofa group, 1 malignancy [excluding NMSC] and 1 NMSC) for a total of 3 benign events and 12 malignancies.

MedDRA v19.1 coding dictionary applied.

Source: Module 5.3.5.3 SCS Table C3.10.1.1.1

The AEs of special interest (AESIs) are serious infections, herpes zoster, opportunistic infections, haematological events, malignancies, major adverse cardiovascular events (MACE), hepatic events, renal events, GI perforations and interstitial lung disease. The SAEs related to the AESIs are considered below.

Adverse events of special interest

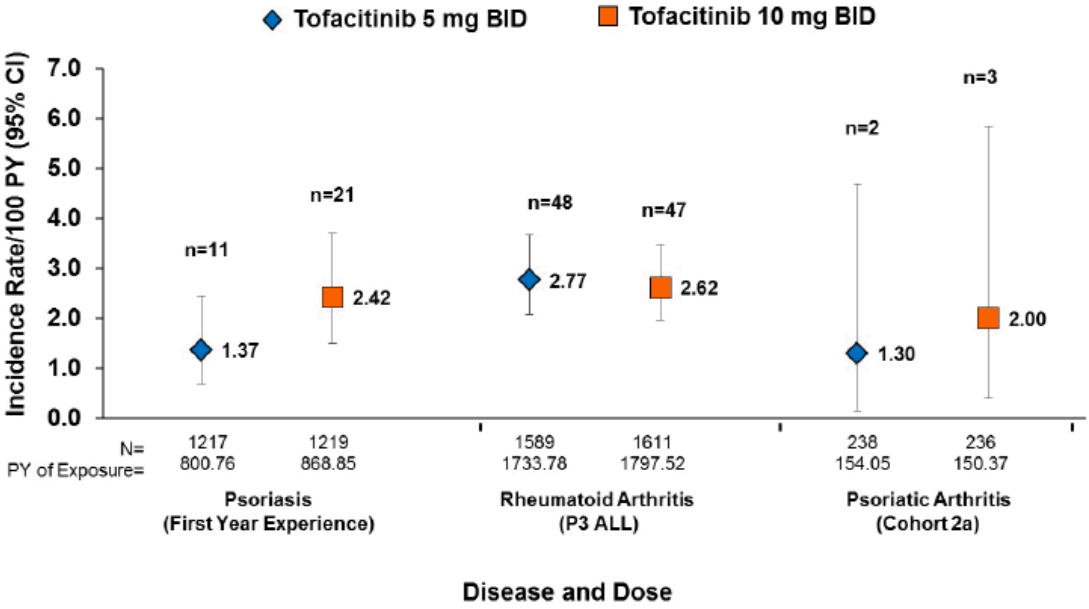
Serious infections (SIs)

In the PsA program, SIs was defined, per protocol, as infections that required parenteral antimicrobial therapy or hospitalisation for treatment or management, or met other criteria that required that the event be classified as serious.

During the 3-month placebo-controlled period, two subjects, both on tofacitinib 10 mg BID, reported a SI.

For the 12-month dose comparison cohort (including tofacitinib-exposed period for subjects that were initially randomised to placebo), the incidence rates (per 100 patient year) were 1.99, 1.53 and 1.08 for All Tofacitinib 5 mg BID, All Tofacitinib 10 mg BID and adalimumab. An analysis of incidence rates for SIs in the psoriasis, RA and PsA tofacitinib development programmes in comparable cohorts (NB the PsA cohort does not include subjects initially randomised to placebo) was provided:

Figure 37 - Incidence Rates for Serious Infections in PsA, RA, and psoriasis 12-month dose-comparison



For the All PsA cohort, including longer-term treatment, the incidence rate for SI was 1.43 per 100 PY for all doses, with little difference between the Average Tofacitinib 5 mg BID group and the Average Tofacitinib 10 mg BID group (1.53 vs 1.28).

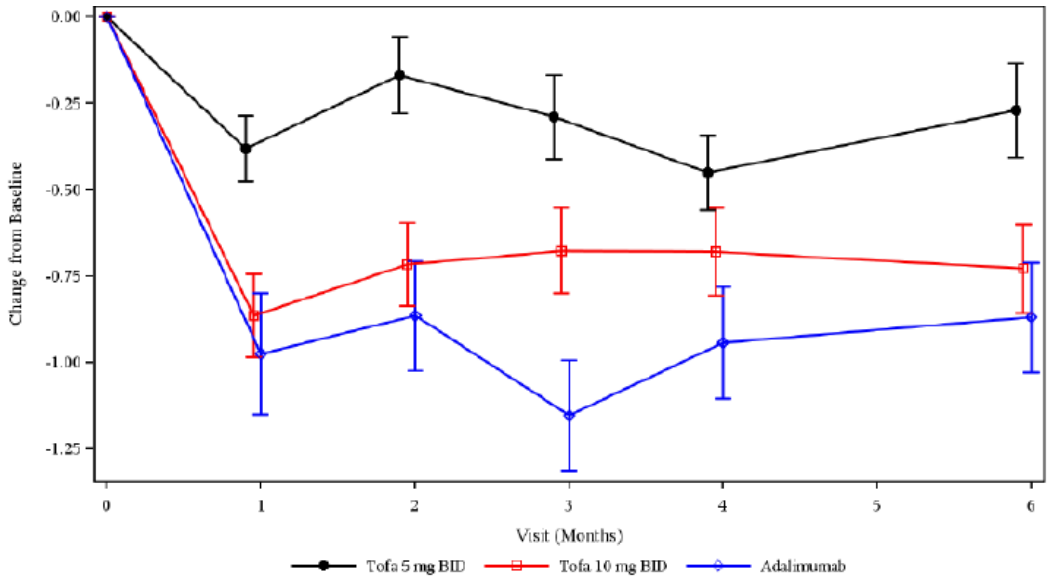
Incidence rates of SIs by months of exposure, at 6-monthly intervals has also been presented. There is no evidence of an association between duration of exposure and incidence rate. A risk factor analysis was also conducted. Trends are observed for higher incidence rates for subjects with a history of diabetes, prior TNFi experience (versus the TNFi naïve population), and concomitant systemic corticosteroid use at baseline.

Eighteen SIs were reported during the PsA clinical development programme; none were fatal. By PT, the commonest SI was pneumonia (4 cases).

<u>Neutrophils</u>

For the 6-month dose comparison cohort, the incidence rate (per 100 PY) for neutropenia was 1.68, 1.71 and 1.71 for tofacitinib 5 mg BID, tofacitinib 10 mg BID and adalimumab. There was one discontinuation due to absolute neutrophil count (ANC) $<1000 \times 10^3/mm^3$. There was no clear association between the incidence of SI, and the confirmed ANC prior to the event.

Figure 38 - Mean change from baseline (SE) in absolute neutrophil count by visit (6-month dose comparison, cohort 2)



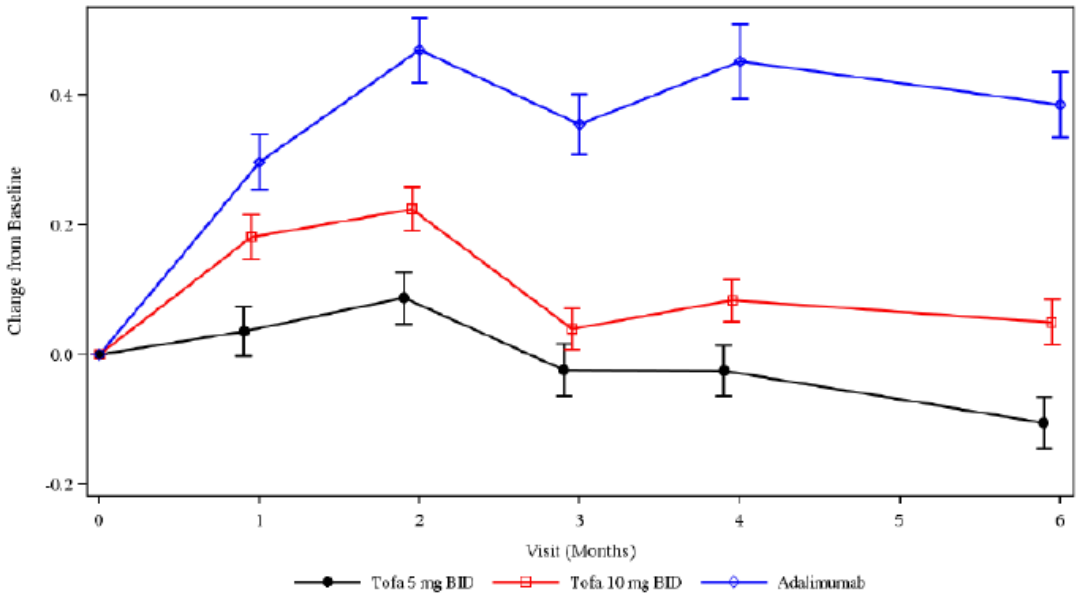
Abbreviation: BID = twice daily; SE = standard error; Tofa = tofacitinib.
Error bars represent standard error.
Includes subjects with a Baseline measurement and at least one post Baseline measurement. Baseline is the latest pre-dose measurement.
Tofacitinib 5 mg BID and 10 mg BID is pooled data from studies A3921125 and A3921091, while adalimumab is from study A3921091 only.
Source: Module 5.3.5.3 SCS Figure C2.6.1.2.

A similar pattern is evidence for mean change from baseline in ANC for study 1091 only.

Lymphocytes

The effect of tofacitinib on absolute lymphocyte count was biphasic:

Figure 39 - Mean Change from Baseline (+/- SE) in Absolute Lymphocyte Count ($10^3/mm^3$) (6-month dose comparison, Cohort 2)



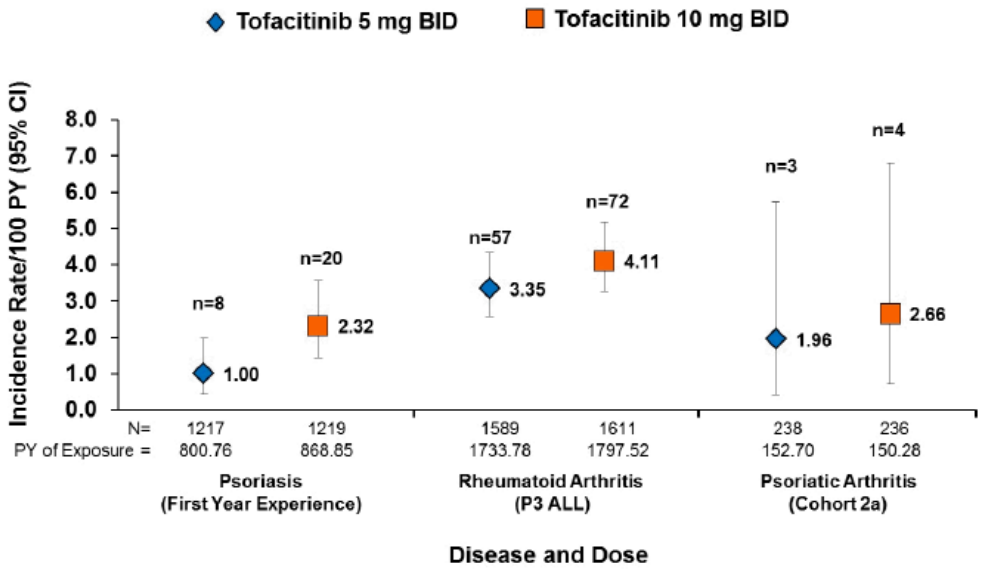
Abbreviation: BID = twice daily; SE = standard error; Tofa = tofacitinib.
Error bars represent standard error.
Includes subjects with a Baseline measurement and at least one post Baseline measurement. Baseline is the latest pre-dose measurement. Tofacitinib 5 mg BID and 10 mg BID is pooled data from studies A3921125 and 1091, while adalimumab is from study A3921091 only.
Source: Module 5.3.5.3 SCS Figure C2.6.1.2.

Fluorescence-activated cell sorting (FACS) evaluation of lymphocyte subsets in tofacitinib-treated patients (6-month dose comparison cohort) showed an increase in B cell (CD19+) counts and a decrease in T cell (CD3+, CD4+, CD8+) counts and natural killer (NK) (CD16+CD56+) counts. The largest mean % reduction from baseline was for NK (-9.68% in the combined tofacitinib group). In general, the reductions from baseline were greater at 6 months compared to 3 months.

Herpes zoster

For the 3-month placebo-controlled cohort, there were 2 herpes zoster (HZ) events for tofacitinib 5 mg BID, one for tofacitinib 10 mg BID and none for adalimumab or placebo. For the 12-month dose comparison (cohort 2a), the incidence rates (per 100 PY) were 1.50, 2.04, and 0.00 for All Tofacitinib 5 mg BID, All Tofacitinib 10 mg BID and adalimumab. An analysis of incidence rates for SIs in the psoriasis, RA and PsA tofacitinib development programmes in comparable cohorts (NB the PsA cohort does not include subjects initially randomised to placebo) has been provided:

Figure 40 - Incidence Rates for HZ in PsA, RA, and psoriasis 12-month dose- comparison



Abbreviations: BID = twice daily; CI = confidence interval; N = number of subjects evaluable; n = number of subjects with an event; PY = Patient Years; PsA = psoriatic arthritis; PsO = psoriasis; RA = rheumatoid arthritis.
Vertical bars represent 95% CI of the IR.
Source: Module 5.3.5.3 SCS Table C2a.2.1.1; SCS PsO Table 2.1.1.1.2 Data as of 21 March 2014; SCS RA Table 777.s18.17 Data as of 28 April 2014

In the All PsA cohort (cohort 3), 26 cases (in 26 subjects) of HZ were reported, with incidence rates 2.07 and 2.17 (per 100 PY) in Average Tofacitinib 5 mg BID and Average Tofacitinib 10 mg BID, respectively. The majority of cases (22) involved a single dermatome. One event was graded severe. None were disseminated, as determined by the adjudication committee.

Incidence rates of SIs by months of exposure, at 6-monthly intervals has also been presented. There is no evidence of an association between duration of exposure and incidence rate. A risk factor analysis was also conducted. Trends are observed for higher incidence rates for subjects with a history of prior TNFi experience (versus the TNFi naïve population), age and Asian ethnicity.

Opportunistic infections (including tuberculosis)

Three HZ cases were classified as opportunistic infection. No other types of opportunistic infection were identified during the PsA programme. No subjects were reported to have developed an active TB infection during the PsA programme.

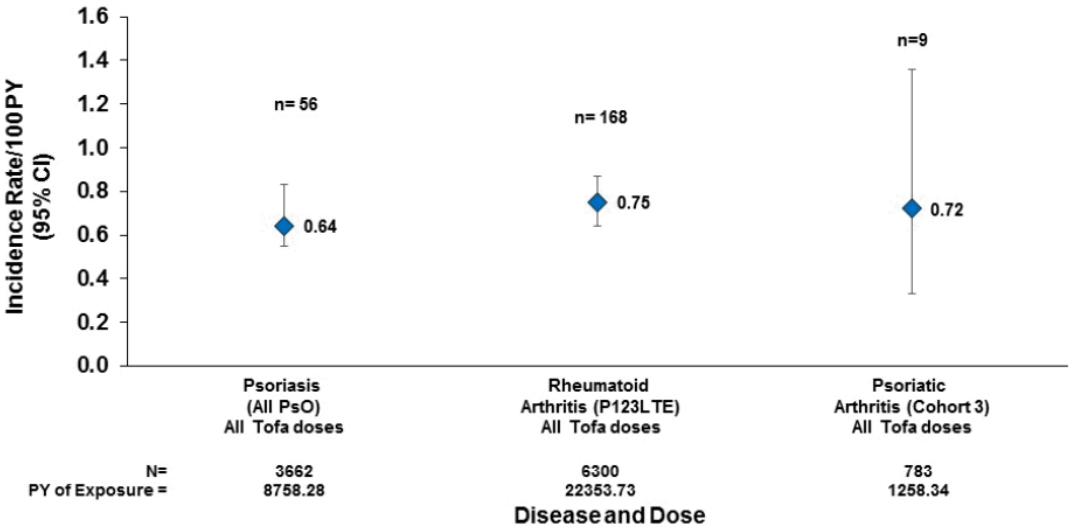
Malignancies

All treatment-emergent reports of malignancies (eg, those occurring following at least one dose of study drug) are described regardless of how long study drug was discontinued prior to event onset. However, only events occurring within the 28 days after the last dose of study drug are included in the IR calculations. All events identified as potential malignancies were assessed by a Malignancy Adjudication Committee.

For the 3-month placebo-controlled cohort, 2 malignancies (bladder transitional cell carcinoma and vulva squamous cell carcinoma) were reported in subjects taking tofacitinib 5 mg BID. No additional cases were seen for the 6-month dose comparison cohort. One additional malignancy was reported for the 12-month dose comparison cohort (invasive ductal breast cancer) in a subject taking tofacitinib 5 mg BID, giving an incidence rate of 1.49 per 100 PY for All Tofacitinib 5 mg BID, compared to 0.00 for tofacitinib 10 mg BID or adalimumab.

A total of 9 malignancies other than non-melanoma skin cancer (NMSC) were identified during tofacitinib treatment of up to 28 days after stopping treatment. Eight cases occurred in subjects receiving tofacitinib 5 mg BID and one case occurred in a subject receiving tofacitinib 10 mg BID at the time of the events. Two cases were randomised to adalimumab prior to the extension study. The six cases identified during the extension study were: renal cell carcinoma, pancreatic carcinoma, prostate adenocarcinoma, medullary thyroid carcinoma, colorectal adenocarcinoma and Huerthle cell carcinoma of the thyroid. This gives an overall incidence rate for tofacitinib of 0.72 per 100 PY. An analysis of incidence rates for SIs in the psoriasis, RA and PsA tofacitinib development programmes has been provided:

Figure 41 - Exposure Estimates and Incidence Rates for Malignancies (Excluding NMSC) in PsA, RA, and PsO



Abbreviations: CI = confidence interval; LTE = long-term extension; N = number of subjects evaluable; n = number of subjects with an event; NMSN = non-melanoma skin cancer; PY = Patient Years; PsA = psoriatic arthritis; PsO = psoriasis; RA = rheumatoid arthritis; Tofa = tofacitinib.
Vertical bars represent 95% CI of the IR.
Source: Module 5.3.5.3 SCS Table C3.2.2.1; SCS PsO Table 198.2.1.2 SCS request #198 Data as of 04 April 2016: SCS RA Table 1182.2.6 P123LTE Data as of 12 Aug 2016

Incidence rates of SIs by months of exposure, at 6-monthly intervals has also been presented. There is no evidence of an association between duration of exposure and incidence rate.

An additional case (bladder papillary transitional cell carcinoma) was identified after the 28-day post-treatment period and was therefore not included in the incidence rate calculations.

Non-melanoma skin cancer (NMSC)

No cases were reported for the 3-month placebo-controlled cohort. One case was reported in the 12-month dose comparison cohort, in a subject taking tofacitinib 10 mg BID. This equates to an incidence rate of 0.66 per 100 PY, which is in line with the rates of 0.58 (5 mg BID) and 0.50 (10 mg BID) observed for RA in a similar cohort.

Seven cases were reported for the All PsA cohort, 2 squamous cell carcinomas and 5 basal cell carcinomas. Of these, 3 were reported in the first year. This equates to an incidence rate of 0.51 (Average 5 mg BID) and 0.64 (Average 10 mg BID).

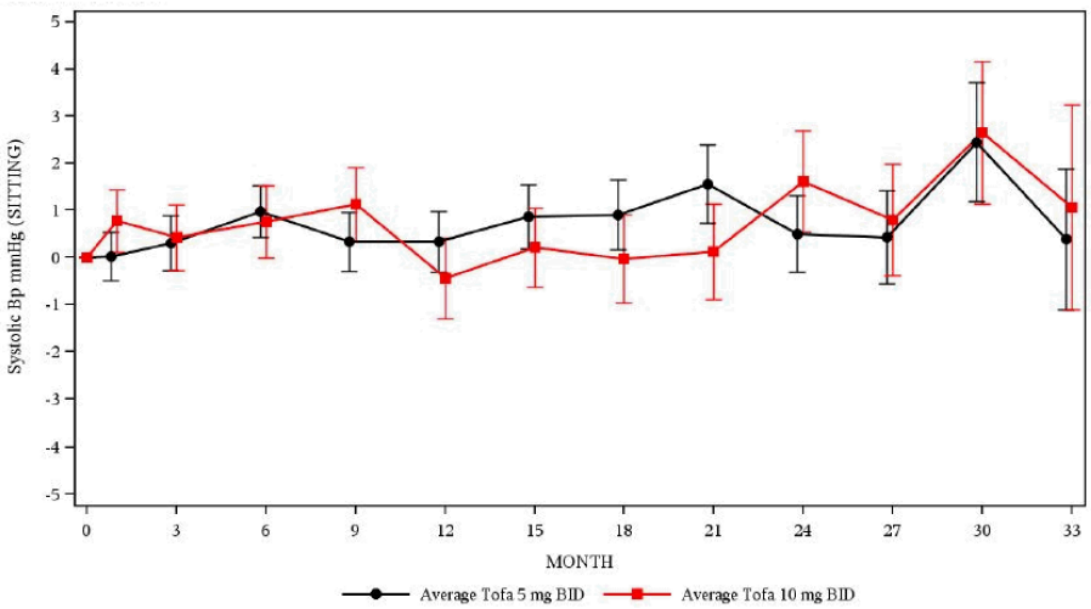
Cardiovascular safety

Lipids

For the 3-month placebo-controlled cohort, the mean % increase in total cholesterol at Month 3 was 8.48, 12.13, 1.87 and 9.88 for tofacitinib 5 mg BID, 10 mg BID, placebo and adalimumab respectively. Data from the 12-month cohort shows that levels stabilise at Month 3. For LDL-cholesterol, the respective mean % changes are 9.20, 14.03, 3.98 and 9.17. For HDL-cholesterol, the respective mean % changes are 10.02, 13.95, -0.81 and 6.91.

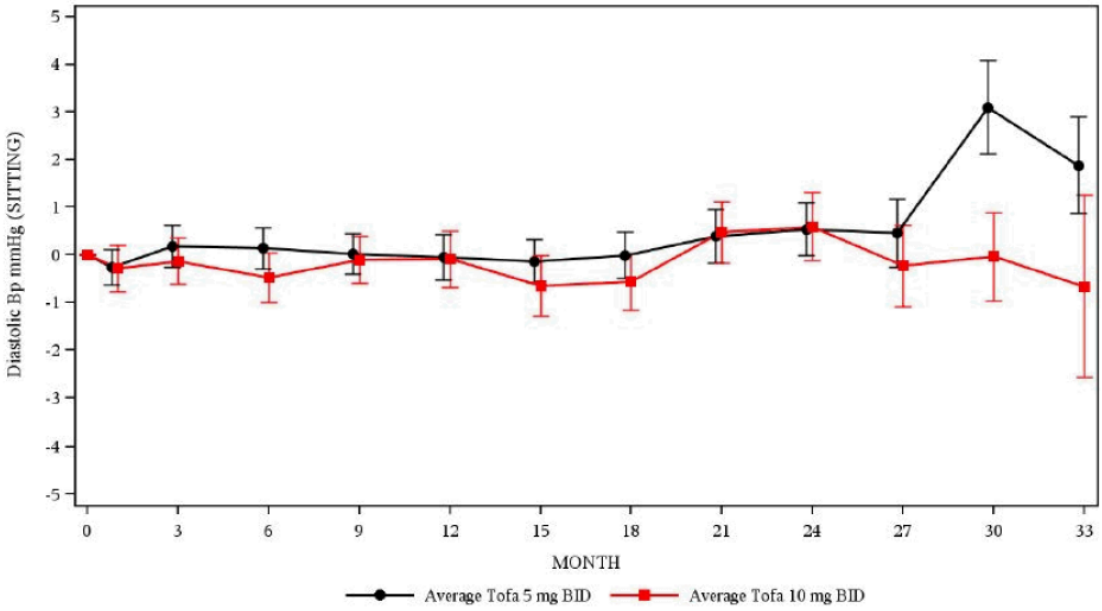
Blood pressure

Figure 42 - Mean (SE) Change from Baseline in Systolic Blood Pressure by Visit All PsA (Cohort 3)



Abbreviation: BID = twice daily; Bp = blood pressure; PsA = psoriatic arthritis; SE = standard error; Tofa = tofacitinib.
Error bars represent standard error.
Includes subjects with a Baseline measurement and at least one post Baseline measurement. Only includes visits with data from at least 20 subjects in any treatment group.
Average Tofa 5 mg: Subjects with an average total daily dose of <15 mg over the course of observation.
Average Tofa 10 mg: Subjects with an average total daily dose of ≥15 mg over the course of observation.
Source: Module 5.3.5.3 SCS Figure C3.7.1.2.1

Figure 43 - Mean (SE) Change from Baseline in Diastolic Blood Pressure by Visit All PsA (Cohort 3)



Abbreviation: BID = twice daily; Bp = blood pressure; PsA = psoriatic arthritis; SE = standard error; Tofa = tofacitinib.
Error bars represent standard error.
Includes subjects with a Baseline measurement and at least one post Baseline measurement. Only includes visits with data from at least 20 subjects in any treatment group.
Average Tofa 5 mg: Subjects with an average total daily dose of <15 mg over the course of observation.
Average Tofa 10 mg: Subjects with an average total daily dose of ≥15 mg over the course of observation.
Source: Module 5.3.5.3 SCS Figure C3.7.1.2.1.

There is some evidence of increase after 18 months, although confidence intervals are wide.

AEs of hypertension were identified based on the standardised MedDRA query (SMQ) for Hypertension (narrow). For the 12-month dose comparison cohort (2), the incidence rate was 8.55, 7.00 and 6.93 per 100 PY for tofacitinib 5 mg BID, 10 mg BID and adalimumab, respectively. For the All PsA cohort, the incidence rate was 4.81 for all tofacitinib doses, with no difference between average doses. Four hypertension events resulted in discontinuation from tofacitinib for the All PsA cohort. There were 3 SAEs of hypertension.

MACE

Major Adverse Cardiovascular Events (MACE) were adjudicated externally. For the 12-month dose comparison period (cohort 2a), there were 3 MACE events, one each for tofacitinib 5 mg BID, 10 mg BID and adalimumab. For All PsA (cohort 3), there was one additional MACE, which equates to an incidence rate of 0.24 per 100 PY (all doses). This is in line with the incidence rate of 0.38 observed for tofacitinib in RA. A further 2 MACE occurred after 28 days from the last dose of tofacitinib. The 5 MACE events associated with tofacitinib were 2 sudden cardiac deaths, 2 myocardial infarctions and one ischaemic stroke.

Rates of MACE in PsA from observational studies were presented. The UK THIN database reported an incidence rate of 0.46 per 100 PY among DMARD-exposed PsA patients. Rates were 0.49 – 0.55 for ARTIS cohorts.

Gastrointestinal perforations

The PsA programme specifically excluded subjects considered at increased risk for GI perforations, e.g. those with a history of diverticulitis. A single event of GI perforation occurred during the PsA programme

up to the data-lock point of 07/03/2017. This was a perforated appendix in a 45-year-old male subject on day 18 of tofacitinib 5 mg BID.

Hepatotoxicity

Table 50 - Number (%) of Subjects with Confirmed Liver Function Test Values as Multiples of Upper Limit of Normal, without Regard to Baseline Abnormality: 6-month dose comparison (Cohort 2)

	Tofacitinib 5 mg BID N=237	Tofacitinib 10 mg BID N=236	Adalimumab N=106
ALT	n (%)	n (%)	n (%)
>1 × ULN	36 (15.2)	47 (19.9)	27 (25.5)
≥2 × ULN	4 (1.7)	2 (0.8)	7 (6.6)
≥3 × ULN	1 (0.4)	0 (0.0)	1 (0.9)
≥5 × ULN	0 (0.0)	0 (0.0)	1 (0.9)
≥10 × ULN	0 (0.0)	0 (0.0)	0 (0.0)
AST			
>1 × ULN	23 (9.7)	31 (13.1)	13 (12.3)
≥2 × ULN	1 (0.4)	2 (0.8)	1 (0.9)
≥3 × ULN	0 (0.0)	0 (0.0)	0 (0.0)
≥5 × ULN	0 (0.0)	0 (0.0)	0 (0.0)
≥10 × ULN	0 (0.0)	0 (0.0)	0 (0.0)
Total Bilirubin			
>1 × ULN	5 (2.1)	4 (1.7)	1 (0.9)
≥2 × ULN	0 (0.0)	0 (0.0)	0 (0.0)
≥3 × ULN	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; N = number of subjects who had a post-baseline visit for AST, ALT or total bilirubin, ULN = upper limit of normal.
Confirmed=at least 2 measurements with the subject.
Source: Module 5.3.5.3 SCS Table C2.6.7.9; C2.6.7.10; C2.6.7.11

For the All PsA cohort, 6 subjects (0.8%) had 2 consecutive elevated ALT ≥3x ULN; 2 subjects had 2 consecutive elevated ALT ≥5x ULN; one subjects had 2 consecutive elevated ALT ≥10x ULN. One subject had 2 consecutive AST ≥3x ULN and one subject had 2 consecutive elevated AST ≥5x ULN. No subjects had 2 consecutive bilirubin ≥2x ULN. There were no discontinuations due to liver enzyme elevations in tofacitinib-treated subjects.

There were 4 reported cases of hepatic steatosis in the 6-month dose comparison cohort, one case each for tofacitinib 5 mg BID and adalimumab, and 2 cases for the tofacitinib 10 mg BID. Nine cases were reported in the All PsA cohort; giving an incidence rate of 0.64 per 100 PY for all tofacitinib doses. In addition, there were 3 cases of 'liver disorder' in the PsA cohort. One case was assessed by the external adjudication committee as a possible drug-induced liver injury, but did not meet the criteria for Hy's Law.

Interstitial lung disease

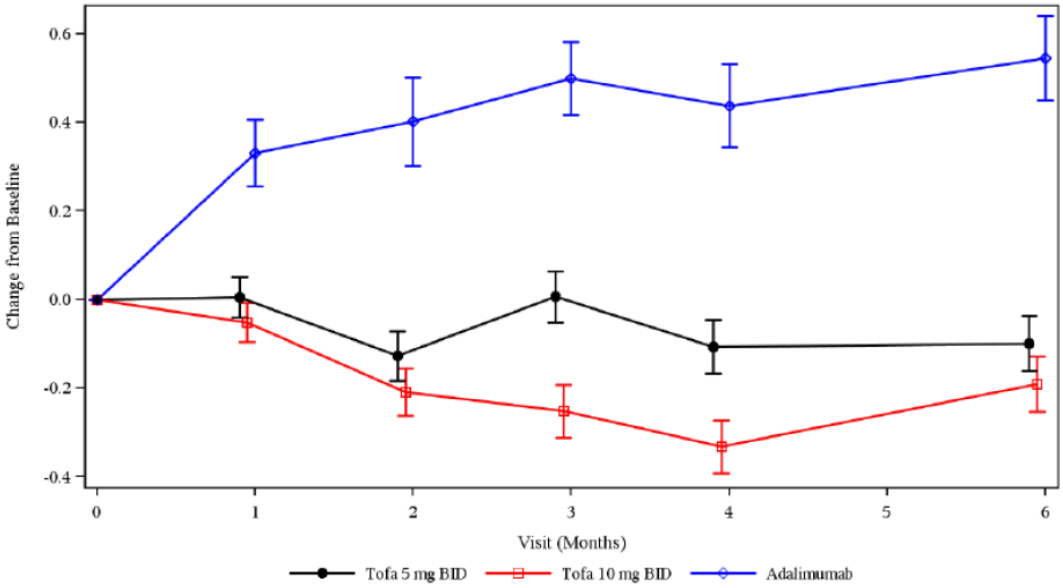
No cases of adjudicated ILD were reported for the PsA programme

Laboratory findings

Laboratory parameters not already discussed under AESIs are summarised and discussed below.

Haemoglobin

Figure 44 - Mean (SE) Change from Baseline in Hb (g/dL) by Visit: 6-month dose comparison (Cohort 2)



Abbreviation: BID = twice daily; SE = standard error; Tofa = tofacitinib.
Error bars represent standard error.
Includes subjects with a Baseline measurement and at least one post Baseline measurement. Baseline is the latest pre-dose measurement. Tofacitinib 5 mg BID and 10 mg BID is pooled data from studies A3921125 and 1091, while adalimumab is from study A3921091 only.
Source: Module 5.3.5.3 SCS Figure C2.6.1.2.

In the All PsA cohort, the median change from baseline to last visit for all doses was -0.1 g/dL. Eleven subjects (1.4%) had confirmed Hb decreases of 3g/dL or Hb <7 g/dL. Thirteen (1.7%) AEs of anaemia were reported, of which 12 were mild.

An exposure-response analysis for change in Hb has been submitted. Placebo-adjusted incidences of >2 g/dL decrease in Hb (90% CI) were predicted to be 1.08% (0.61, 1.64) and 3.01% (1.48, 4.93) at median C_{avg} values of 17.6 ng/mL and 36.1 ng/mL respectively, corresponding to tofacitinib 5 mg BID and 10 mg BID. Individual C_{avg} exposures in the upper quartile of the 10 mg BID dose group showed an increase in the proportion of patients experiencing a decrease in Hb of > 2 g/dL. For example, at the 90th percentile C_{avg} (54.8 ng/mL) in the 10 mg BID group, the estimated incidence was ~8%.

Platelets

For the 3-month placebo-controlled cohort, median changes in platelets were -16.0 x 10^3/mm^3, -5.0 x 10^3/mm^3, -3.5 x 10^3/mm^3 and -27.0 x 10^3/mm^3 for tofacitinib 5 mg BID, 10 mg BID, placebo and adalimumab. There were 2 events of thrombocytopenia in subjects treated with tofacitinib 10 mg BID and one in a subject treated with placebo.

Changes in all treatment groups remained relatively stable after Month 3. In All PsA (cohort 3), overall the median change from baseline in platelets was -4 x 10^3/mm^3. There was 1 subject receiving tofacitinib who had confirmed platelet counts <75 x 10^3/mm^3. There were 3 events of thrombocytopenia.

Creatine kinase

For the 3-month placebo-controlled cohort, the median increase in creatine kinase from baseline was 31 U/L, 49 U/L, 2 U/L and 6.0 U/L for tofacitinib 5 mg BID, 10 mg BID, placebo and adalimumab, respectively. Up to Month 6, the tofacitinib-associated increases remained stable. For All PsA (cohort 3), the median change from baseline to last visit was 73 U/L (all doses). Four (4) subjects (0.5%) in Cohort 3 who received either tofacitinib dose had confirmed CK levels >5x ULN; no subjects had CK levels >10x ULN. There were no subjects reporting AE in the SMQ of rhabdomyolysis in the PsA programme.

Serum creatinine

For the 3-month placebo-controlled cohort, the median increase in creatine kinase from baseline was 0.011 mg/dL, 0.034 mg/dL, 0 U/L and 0 U/L for tofacitinib 5 mg BID, 10 mg BID, placebo and adalimumab, respectively. Up to Month 6, the tofacitinib-associated increases remained stable. In the All PsA cohort (cohort 3), the median change from baseline in serum creatinine was 0.0. In this cohort, 3 (0.4%) subjects reported AE of increased creatinine by Acute Renal Failure SMQ. The incidence rate for all doses was of 0.24 per 100 PY.

Heart rate

There were no clinically meaningful changes in heart rate in subjects from either tofacitinib treatment group, and decreases in heart rate of approximately 1 beat per minute. No significant changes were seen when evaluating the All PsA experience (cohort 3) values.

Body weight

There were mean changes from baseline of 1.99 kg for subjects receiving tofacitinib 5 mg BID, 2.2 kg for tofacitinib 10 mg BID, and 0.77 kg for adalimumab up to Month 6.

Electrocardiogram

A maximum QTcF interval of ≥500 msec was reported for one subject in the tofacitinib 10 mg BID group, in the 6-month dose comparison cohort. There were two AEs of Electrocardiogram QT prolonged, both of mild severity, in the All PsA cohort, all doses.

Safety in special populations

Age

A total of 72 subjects ≥65 years received tofacitinib in the PsA programme. The proportion of subjects with adverse events, SAEs, severe AEs and discontinuations due to AE was generally increased for subjects ≥65 years compared with subjects <65 years for tofacitinib 5 mg BID, 10 mg BID, placebo and adalimumab. Subjects on tofacitinib (All PsA) who were ≥65 years of age also experienced increased rates of several specific AEs compared with those in the <65 years, including SI (incidence rate 2.63 vs 1.31 per 100 PY), HZ (3.52 vs 1.96) and MACE (2.64 vs 0).

Gender

Overall, the proportion of subjects with adverse events, SAEs, severe AEs and discontinuations due to AE was similar for male and female subjects.

Race

Most subjects were White. No consistent pattern of difference in AEs or SAEs was evident regarding race.

Pregnancy and lactation

In the PsA clinical development programme, there were 7 cases of exposure to tofacitinib during pregnancy; of these 7 cases, 4 involved maternal exposure and 3 involved paternal exposure. Exposure to tofacitinib occurred in the first trimester in all 7 cases. In 2 of the maternal exposure cases, the tofacitinib dose taken was 5 mg BID; the outcomes were 1 spontaneous abortion and 1 premature birth (37 weeks with normal newborn). In the other 2 maternal exposure cases, the tofacitinib dose taken was 10 mg BID, and the outcomes were elective abortion and normal newborn. The dose taken in the paternal exposure cases was 5 mg BID in 1 case and 10 mg BID in the other 2 cases. The outcomes of the paternal exposure cases were 1 normal newborn, 1 spontaneous abortion, and 1 outcome pending.

Prior TNFi therapy

In terms of TEAEs the TNFi inadequate responder population tended to have a higher proportion of subjects reporting AE (all causalities) compared to the TNFi naïve subjects. Up to 6 months of exposure, the pooled data displayed a higher number of events reported for the 5 mg BID dose compared to the 10 mg BID and placebo groups (Cohort 2). In Cohort 3, SOC distribution was overall similar with two exceptions: there were fewer percentages of subjects with events reported in the Neoplasms benign, malignant and unknown including cysts and polyps in the TNFi inadequate responder population, and there were a higher percentage of events in the Infections and Infestations SOC.

SAEs reported in the programme showed a different trend between the 2 subpopulations with the TNFi inadequate responder population (A3921125 study) reporting 8 events in the 10 mg BID dose and 5 in the 5 mg BID dose, while in the TNFi naïve population (A3921091 study) more events were reported for tofacitinib 5 mg BID relative to 10 mg BID (8 versus 4).

AE leading to discontinuation occurred in 27 subjects the TNFi inadequate responder population compared to 25 subjects in the TNFi naïve populations, and was more frequent in subjects receiving tofacitinib 10 mg BID versus 5 mg BID in the TNFi inadequate responder population.

Risk factor analysis for SIs showed an IR of 1.83 per 100 PY for TNFi experienced subjects compared to an IR of 1.13 per 100 PY for TNFi naïve subjects. With regards to HZ, the IR was 2.80 per 100 PY for TNFi experienced subjects and 1.57 per 100 PY for TNFi naïve subjects. With regards to OI, the IR was 0.37 per 100 PY for TNFi experienced subjects and 0.14 per 100 PY for TNFi naïve subjects.

Additional sub-group analyses

The CHMP discussed whether the indication should be restricted to patients with an inadequate response to MTX, since only around 6% of the population of study A3921091 (csDMARD-IR) had an inadequate response to one csDMARD other than MTX. In addition, 1.4% had an inadequate response to >1 csDMARD that did not include MTX. These subgroups are too small for meaningful safety analyses. However, the subgroup with an inadequate response to >1 csDMARD could provide supportive information, since this patients in this subgroup (>1 csDMARD-IR) had an inadequate response to a csDMARD other than MTX, and should represent a more difficult to treat population. The MAH has compared the efficacy and safety outcomes of the >1 csDMARD subgroup vs 1 csDMARD-IR subgroup (predominantly MTX-IR). Safety outcomes were comparable between the 1 csDMARD and >1 csDMARD subgroups of study A3921091.

CHMP were also concerned regarding the evidence for use in combination with csDMARDs other than MTX. The MAH has pooled data from study A3921091 (csDMARD-IR) and A3921125 (bDMARD-IR). This strategy is acceptable since the studies were similar in design. Across both studies 21.8% received concomitant csDMARD other than MTX. Of the 52 patients in the tofacitinib 5 mg BID who used a non-MTX csDMARD, 30 patients took sulfasalazine and 19 patients took leflunomide. The MAH pooled 6-month (Cohort 2) data across the 2 pivotal studies. Safety outcomes were comparable for the 'MTX only' and 'other csDMARD' groups. Over 12 months, the percentage of subjects reporting SAEs was higher for the 'MTX only' group compared to the 'other csDMARD' group. Hepatic enzyme outcomes were also comparable between the subgroups.

The csDMARDs cannot be considered a single class of drug. Due to the small numbers of patients using individual non-MTX csDMARD at the proposed dose, it is not possible to extrapolate safety conclusions for the combination with MTX. Therefore, the indications is restricted to combination with MTX.

Safety related to drug-drug interactions and other interactions

No new data was submitted which was considered acceptable by CHMP.

Discontinuation due to adverse events

During the 3-month placebo-controlled period, the AEs leading to discontinuation were reported for 5 (2.1%), 10 (4.2%), 6 (2.5%) and 2 (1.9%) subjects in the tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo and adalimumab groups, respectively. AEs leading to dose reductions or interruptions were reported for 19 (8.0%), 33 (14.0%), 18 (7.6%) and 3 (2.8%) respectively. Most discontinuations were reported in the SOC of infections and infestations. Five (2.1%) of subjects receiving tofacitinib 10 mg BID group were discontinued due to this SOC, compared to one (0.4%) receiving tofacitinib 5 mg BID group; no subjects receiving placebo or adalimumab discontinued for this reason.

For the 6-month dose comparison, discontinuations due to AE were reported for 10 (4.2%), 14 (5.9%) and 4 (3.8%) for the Tofacitinib 5 mg BID, Tofacitinib 10 mg BID and adalimumab groups, respectively. AEs leading to dose reductions or interruptions were reported for 32 (13.4%), 50 (21.2%), and 14 (13.2%) respectively. In the Infections and Infestations SOC, there were 5 events, 4 events and one event leading to discontinuation in subjects receiving tofacitinib 10 mg BID, tofacitinib 5 mg BID and adalimumab, respectively. There were 3 events in the Neoplasms benign, malignant and unspecified SOC, in the tofacitinib 5 mg BID group.

When the All PsA cohort is considered, discontinuations due to AE were reported for 48 (10.0%) and 35 (11.6%) for the Average Tofacitinib 5 mg BID and Average Tofacitinib 10 mg BID groups, respectively. The commonest SOC was Infections and Infestations SOC: 15 (3.1%) and 13 (4.3%) affected subjects in the Average Tofacitinib 5 mg BID and Average Tofacitinib 10 mg BID groups, respectively. The Neoplasms benign, malignant and unspecified SOC also featured: 11 (2.3%) and 2 (0.7%) affected subjects in the Average Tofacitinib 5 mg BID and Average Tofacitinib 10 mg BID groups, respectively.

Post marketing experience

Xeljanz was first approved in the US in 2012 at a dose of 5 mg BID for the treatment of RA in adults. As of 05/11/2016, cumulatively, there have been approximately 61,043 PY of exposure to tofacitinib from post-marketing experience. There have been a total of 20,074 case reports received by the MAH during this 4-year reporting period. The most common AEs reported in the 20,074 cases were drug ineffective (14.0%), headache (8.2%), condition aggravated (7.1%), arthralgia (6.5%), pain (6.2%), fatigue (5.9%), nausea (5.4%) and diarrhoea (5.4%). The most common SAEs reported in the 20,074 cases (≥1%) were RA (3.9%), condition aggravated (3.3%) and pneumonia (2.3%).

2.5.1. Discussion on clinical safety

A total of 738 PsA subjects were treated with tofacitinib 5 mg BID or 10 mg BID during the clinical development programme; 713 PsA subjects were exposed to ≥6 months and 635 subjects were exposed to ≥12 months of tofacitinib, corresponding to 1237.89 patient-years of exposure. The exposure is considered to be adequate.

To supplement the relatively short exposure time and to contextualize the safety profile of tofacitinib in PsA, the MAH has performed comparisons with integrated safety datasets of tofacitinib in the Rheumatoid Arthritis and Psoriasis Development Programmes, and with safety data from the literature and from a Swedish biologics registry (the ARTIS database). These comparisons are of some interest as they provide a more comprehensive picture of tofacitinib safety profile, although there are significant differences in the study populations, study designs and exposures by dose that need to be considered when analysing results.

Overall the safety profile of tofacitinib in the PsA population does not differ significantly in terms of both AE types as well as AE incidence rates from what is already known in the RA indication, and no new safety concerns have emerged from the analysis of safety data provided in the present extension of indication.

The most common AEs (up to ~ 5%) by preferred term (PT) in the tofacitinib 5 mg BID group were nasopharyngitis, upper respiratory tract infection, headache and diarrhoea. The frequencies are in line with the RA safety profile; no new safety signal is identified. Severe AEs were reported by 11.0% of the All PsA cohort (combined doses, including extension study data).

Five deaths were reported up to 07/03/2017 during the PsA clinical development programme, all in subjects receiving tofacitinib 5 mg BID. The causes of death (i.e., CV events, malignancies and COPD) were consistent with what is expected in the PsA population as reported in the literature. It was considered that the deaths were likely to be due to causes other than study drug.

SAEs and AEs graded as severe were few and occurred with generally similar frequency in all treatment groups in the first 6 months of treatment. However, the IRs per 100 PY for SAEs were lower for the tofacitinib 5 mg BID dose than for the 10 mg BID, both in the csDMARD-IR as well as the TNFi-IR patients.

For the 12-month dose comparison cohort (including tofacitinib-exposed period for subjects that were initially randomised to placebo), the incidence rate for serious infection (per 100 patient year) were 1.99, 1.53 and 1.08 for tofacitinib 5 mg BID, tofacitinib 10 mg BID and adalimumab. This suggests that the risk is higher for tofacitinib compared to adalimumab. For the All PsA cohort, the incidence rate for serious infection was 1.43 per 100 PY. The commonest serious infection was pneumonia. There was no evidence of an association between duration of exposure and incidence rate. Trends were observed for higher incidence rates for subjects with a history of diabetes, prior TNFi experience (versus the TNFi naïve population), and concomitant systemic corticosteroid use at baseline. The rates of serious infection appear lower than those observed for RA, although confidence intervals are wide. This could possibly be due to the larger use of corticosteroids in the RA programme. A dose response trend is evident for PsA and PsO but not RA.

Tofacitinib is associated with a dose-dependent decrease in neutrophil and lymphocyte counts; the latter was found to be associated with an increased risk of SI or HZ for the RA database. These reductions were reproduced in the PsA database. The incidence rate for neutropenia was around 1.7 per 100 PY. Fluorescence-activated cell sorting (FACS) evaluation of lymphocyte subsets in tofacitinib-treated patients (6-month dose comparison cohort) showed an increase in B cell (CD19+) counts and a decrease in T cell (CD3+, CD4+, CD8+) counts and natural killer (NK) (CD16+CD56+) counts. The largest mean % reduction from baseline was for NK (-9.68% in the combined tofacitinib group). Median change in haemoglobin (Hb) was negligible, but 11 subjects (1.4%) had confirmed Hb decreases of 3g/dL or Hb <7 g/dL, in line with an ADR frequency of common in the current SmPC. An exposure-response analysis suggests that the risk of anaemia is increased with increasing exposure; this may reflect JAK2 inhibition.

Higher IRs were observed for TNFi experienced (2.80) versus TNFi naïve subjects (1.57), and for subjects who were 65 years of age or older (3.52) compared to subjects in the <65 age (1.96).

The incidence rate of herpes zoster, based on data up to Month 12, was 1.5 per 100 PY for tofacitinib 5 mg BID. Incidence rates of HZ in PsA were higher for tofacitinib 10 mg BID than tofacitinib 5 mg BID. Rates appeared comparable to PsO and lower than RA. No cases of HZ were reported in adalimumab or placebo-treated subjects. Of the 26 cases reported for the All PsA cohort, 22 cases involved a single dermatome and no case was disseminated. There is no evidence of an association between duration of exposure and incidence rate. A risk factor analysis was also conducted. Trends are observed for higher incidence rates for subjects with a history of prior TNFi experience (versus the TNFi naïve population),

age and Asian ethnicity. Information on prophylactic zoster vaccination as mitigation prior to tofacitinib treatment in accordance with vaccination guidelines is also included in the current SmPC. No other types of opportunistic infection were identified, and there were no cases of active TB, during the PsA programme.

A total of 10 malignancies have been identified for the PsA programme; no lymphomas were reported. Observational studies of similar PsA populations treated with other therapies report incidence rates of around 0.35-0.50 per 100 PY. The rate for tofacitinib is higher at 0.72, and its mechanism of action provides some biological plausibility for causation. However, this rate is in line with that observed for the tofacitinib RA program (0.75 per 100 PY). Malignancy remains an important potential risk, for which there are additional pharmacovigilance activities including a post-authorisation safety study in RA (A3921133).

Effects on lipids were in line with those observed for RA. Total cholesterol, LDL-cholesterol and HDL-cholesterol showed a mean % increase of 8-10%, stabilising at Month 3. Mean blood pressure was essentially unchanged, but incidence rates of hypertension AEs were 4.81 per 100 PY for the All PsA cohort, in line with the ADR frequency based on the RA database. For the 12-month dose comparison period (cohort), there were 3 MACE events, one each for tofacitinib 5 mg BID, 10 mg BID and adalimumab. For All PsA, there was one additional MACE, which equates to an incidence rate of 0.24 per 100 PY (both doses). This is in line with the incidence rate of 0.38 observed for tofacitinib in RA. A PASS is planned.

Transaminase elevations were in line with the ADR frequencies as stated in the approved SmPC. There were 4 cases of hepatic steatosis, listed as an uncommon ADR currently. 'Transaminase elevation and potential for drug-induced liver injury' is retained as an important identified risk.' Elevations in creatine kinase and creatinine were also observed, in line with the known safety profile.

A total of 72 subjects ≥65 years received tofacitinib in the PsA programme. The proportion of subjects with adverse events, SAEs, severe AEs and discontinuations due to AE was generally increased for subjects ≥65 years compared with subjects <65 years for tofacitinib and comparators, reflecting increased morbidity in older subjects. Serious infections are a particular concern in this subgroup; appropriate warnings are included in the SmPC.

There were 7 cases of exposure during pregnancy, but no definite evidence of teratogenicity. Tofacitinib is contraindicated in pregnancy.

During the 3-month placebo-controlled period, AEs leading to discontinuation were reported for 2.1%, 4.2%, 2.5% and 1.9% subjects in the tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo and adalimumab groups, respectively. This suggests that tofacitinib was well-tolerated, particularly at the 5 mg BID dose level. Discontinuations from tofacitinib were most commonly due to infections. Considering the All PsA cohort, the rate was 10.0% for subjects averaging 5 mg BID.

Cumulative post-marketing data from 2012 to 2016 was consistent with the current SmPC table of ADRs.

2.5.2. Conclusions on clinical safety

The observed safety profile for the PsA population is in line with the known safety profile based on the RA clinical database and post-marketing experience. No new safety concerns are identified.

Regarding section 4.8, the proposed ADR table is based on pooled datasets for RA and PsA. The MAH has clarified that the ADR frequencies at the time of initial MAA were calculated from long-term extension (LTE) studies only. The MAH has revised the ADR frequencies, based on data from LTEs and RCTs in RA and PsA. This has resulted in the reduction of some ADR frequencies. A concern might be that the

frequencies are biased by the pooling strategy, if they are lower in the PsA population. However, the MAH has presented the frequencies from RA (RCT + LTE) only. This demonstrates that the PsA data has no effect on the frequency calculations. The pooling strategy, which includes data from RCTs and LTE studies, although different to the methodology used at the time of initial MAA, is in line with the SmPC guideline, and can be accepted.

No new safety concerns are proposed for inclusion in the RMP; this is appropriate.

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 CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.2 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 3.2 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	Serious and other important infections
	Herpes zoster reactivation
	Decrease in neutrophil counts and neutropenia
	Decrease in lymphocyte counts and lymphopenia
	Decrease in haemoglobin levels and anaemia
	Lipid elevations and hyperlipidaemia
	Nonmelanoma skin cancer
	Transaminase elevation and potential for drug-induced liver injury
Important potential risks	Malignancy
	Cardiovascular risk
	Gastrointestinal perforation
	Interstitial lung disease

Summary of Safety Concerns	
	Progressive multifocal leukoencephalopathy
	Increased immunosuppression when used in combination with biologic DMARDs and immunosuppressants including B lymphocyte depleting agents
	Increased risk of adverse events when tofacitinib is administered in combination with MTX
	Primary viral infection following live vaccination
	Increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors
	Off-label use including children with JIA
	Higher incidence and severity of adverse events in the elderly
Missing information	Effects on pregnancy and the foetus
	Use in breastfeeding
	Effect on vaccination efficacy and the use of live/attenuated vaccines
	Use in paediatric patients
	Use in RA and PsA patients with mild, moderate, or severe hepatic impairment
	Use in RA and PsA 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

CYP=cytochrome P450; DMARD=disease-modifying antirheumatic drug; JIA=juvenile idiopathic arthritis; MTX=methotrexate; PsA=psoriatic arthritis; RA=rheumatoid arthritis

Pharmacovigilance plan

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
Study A3921133: Phase 3B/4 randomized safety endpoint study of 2 doses of tofacitinib in comparison to a TNF inhibitor in subjects with RA 3	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)	The safety of tofacitinib at 2 doses versus adalimumab (co-primary endpoints include adjudicated MACEs and adjudicated malignancies excluding NMSC, secondary endpoint will evaluate adjudicated opportunistic OI events including TB and adjudicated hepatic events).	Started	Submission of the protocol by 09/2017 2020 (planned)
A lymphocyte subset sub-study within the LTE Study A3921024 3	To confirm the conclusions of analyses previously conducted between the risk of infections and lymphocyte subset levels. To evaluate whether monitoring of lymphocyte subset levels provides additional information beyond monitoring and discontinuation criteria based on total lymphocyte	Serious infections, lymphopenia	Started	September 2017

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
	counts that could be used to mitigate the risk of infections			

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
An EU-based survey for prescribers (RMM effectiveness assessment) 3	To assess prescribers' knowledge and understanding of the key risks associated with tofacitinib	Serious and other important infections, HZ reactivation, malignancies (including NMSC), changes in laboratory parameters, GI perforation, liver injury, increased immunosuppression when tofacitinib is used with bDMARDS, 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	Planned	RA: October 2019 PsA: November 2021

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
An EU-based drug utilization study using electronic health care records (RMM effectiveness assessment) 3	To assess prescription trends over time, as well as evaluate compliance with risk minimisation measures	Extent to which patient screening and laboratory monitoring recommendations and recommendations regarding limitations of use (and concurrent conditions, such as pregnancy, hepatic impairment, or concomitant use of bDMARDs) are followed, and off-label use.	Planned	RA: December 2021 PsA: March 2023
Prospective, non-interventional active surveillance study embedded within the ARTIS RA registry 3	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting	Serious infections,HZ reactivation, NMSC, malignancy, CV risk, GI perforation, PML, increased risk of adverse events in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of adverse events in elderly patients	Planned	March 2024

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
Prospective, non-interventional active surveillance study embedded within the BSRBR RA registry 3	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting	Serious infections, HZ reactivation, NMSC, malignancy, CV risk, GI perforation, PML, increased risk of adverse events in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of adverse events in elderly patients	Planned	March 2024
Prospective, non-interventional active surveillance study embedded within the RABBIT RA registry 3	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting	Serious infections, HZ reactivation, NMSC, malignancy, CV risk, GI perforation, PML, increased risk of adverse events in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of adverse events in elderly patients	Planned	March 2024

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
Prospective, non-interventional active surveillance study embedded within the BIOBADASER RA registry 3	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting	Serious infections, HZ reactivation, NMSC, malignancy, CV risk, GI perforation, PML, increased risk of adverse events in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of adverse events in elderly patients	Planned	March 2024
Prospective, non-interventional active surveillance pregnancy study embedded within the US OTIS registry 3	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	Started	RA: 31 August 2018 PsA: March 2024
Prospective, non-interventional active surveillance	To provide additional longitudinal safety data regarding the	Serious infections, HZ reactivation, malignancies, NMSC,	Started	October 2018

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
study embedded within the Corrona registry (RA) 3	use of tofacitinib in the US for RA patients.	cardiovascular events, PML, GI perforation, increased risk of adverse events in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of adverse events in elderly patients		

ARTIS=Antirheumatic Therapies in Sweden; bDMARDs=biologic disease-modifying antirheumatic drugs; BIOBADASER=Registro Español de Acontecimientos Adversos de Terapias Biológicas en Enfermedades Reumáticas; BSRBR= British Society for Rheumatology Biologics Register; CV=cardiovascular; EU=European Union; GI=gastrointestinal; HZ=herpes zoster; LTE=long-term extension; MACE=major adverse cardiac event; MTX=methotrexate; NMSC=nonmelanoma skin cancer; OI=opportunistic infection; OTIS=Organization of Teratology Information Specialists; PhV =pharmacovigilance; PML= Progressive multifocal leukoencephalopathy; PsA=psoriatic arthritis; RA=rheumatoid arthritis; RABBIT=Rheumatoide Arthritis – Beobachtung der Biologika-Therapie; RMM=risk minimisation measure; TB=tuberculosis; TNF=tumour necrosis factor; US=United States

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Serious and other important infections	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Herpes zoster reactivation	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure, safety educational website).
Decrease in neutrophils counts and neutropenia	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Decrease in lymphocyte counts and lymphopenia	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Decrease in haemoglobin levels and anaemia	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Lipid elevations and hyperlipidaemia	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Nonmelanoma skin cancer	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure, safety educational website).
Transaminase elevation and potential for drug-induced liver injury	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Important Potential Risks		
Malignancy	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
		website).
Cardiovascular risk	Labelling	None proposed_
Gastrointestinal perforation	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Interstitial lung disease	Labelling	Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Progressive multifocal leukoencephalopathy	None proposed	None proposed
Increased immunosuppression when used in combination with biologic DMARDs and immunosuppressants including B lymphocyte depleting agents	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Increased risk of adverse events when tofacitinib is administered in combination with MTX	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure, safety educational website).
Primary viral infection following live vaccination	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors	Labelling	Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Prescriber Brochure, safety educational website).
Off-label use including children with JIA	Labelling	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Higher incidence and severity of adverse events in the elderly	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure, safety educational website), specific to the higher risk of infections.
Missing Information		
Effects on pregnancy and the foetus	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Use in breastfeeding	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Effect on vaccination efficacy and the use of live/attenuated vaccines	Labelling	Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Use in paediatric patients	Labelling	None proposed
Use in RA and PsA patients with mild, moderate, or severe hepatic impairment	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Use in RA and PsA patients with moderate or severe renal impairment	Labelling	None proposed
Use in patients with evidence of hepatitis B or C infections	Labelling	None proposed
Use in patients with elevated transaminases	Labelling	None proposed
Use in patients with	Labelling	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
malignancy		

CYP=cytochrome P450; DMARD=disease-modifying antirheumatic drug; JIA=juvenile idiopathic arthritis; MTX=methotrexate; PsA=psoriatic arthritis; RA=rheumatoid arthritis

Please see Annex 10 for more information on the additional risk minimisation measures.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

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 5 mg film-coated tablets. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

PsA is a chronic progressive inflammatory arthritis associated with psoriasis, which may result in permanent joint damage and disability.

3.1.2. Available therapies and unmet medical need

Mild PsA is generally treated with NSAIDs. When only few joints are involved, local injections of steroids might be effective. For more extensive or severe PsA, disease-modifying anti-rheumatic drugs (DMARDs) are recommended. Conventional synthetic DMARDs (csCMARDs) such as methotrexate, sulfasalazine and leflunomide, are standard therapies. For patients in whom csDMARDs are not effective, biological DMARDs (bDMARDs) or targeted DMARDs are recommended by guidelines such as EULAR. These include tumour necrosis factor inhibitors (TNFi) (e.g. etanercept, infliximab, adalimumab, golimumab, certolizumab pegol), bDMARDs with novel mechanisms of action such as ustekinumab (IL-12/23 antagonist) and secukinumab (IL-17A antagonist), and the PDE4 inhibitor apremilast.

3.1.3. Main clinical studies

The tofacitinib PsA development programme is based on 3 global studies, including 2 completed Phase 3 double-blind, placebo-controlled efficacy and safety studies investigating tofacitinib 5 mg BID and 10 mg BID (Studies A3921125 and A3921091, also referred to as pivotal studies) and one ongoing Phase 3 open-label, long-term extension (LTE) study (Study A3921092).

3.2. Favourable effects

The benefit of tofacitinib on PsA has been shown both in terms of signs and symptoms of peripheral arthritis, measured by the ACR20 response, as well as on the decrease in physical function associated with the PsA disease, measured by HAQ-DI, in both csDMARD-IR and TNFi-IR patient populations.

Study 1091 (csDMARD non-responders, TNFi naïve)

For the co-primary endpoint of ACR20 at Month 3, the response rate for the proposed dose of tofacitinib 5 mg BID was 50.5%, in line with the active comparator adalimumab. This represented a 17.1% increase over placebo, which is statistically significant and clinically relevant. The ACR20 response is maintained up to Month 12.

For the co-primary endpoint of ΔHAQ-DI at Month 3, the LS mean treatment difference for tofacitinib 5 mg BID vs placebo was -0.17. This difference was in line with that observed for adalimumab. The effects are maintained until Month 12. The MCID (change from baseline) for HAQ-DI is 0.35. For the 90% of subjects with baseline HAQ-DI ≥0.35, 53.1% of the tofacitinib 5 mg BID group reported a decrease of ≥0.35, the minimum clinically relevant difference, compared to 30.9% for the placebo group. This responder analysis supports the clinical relevance of the HAQ-DI results.

Sensitivity analyses demonstrated the robustness of the results on the primary endpoints, and generally consistent findings were seen across subgroups.

Secondary endpoints included the ACR50, for which a clear separation from placebo was observed, with a treatment difference of 28.0% for tofacitinib 5 mg BID and 33.0% for adalimumab at Month 3, and maintenance of the effect until Month 12. For ACR70, the respective treatment differences were 16.8% and 18.9%. For MDA, the respective treatment differences were 19.5% and 18.8%. Regarding the radiographic evaluations, the mean changes from baseline and the progressor rates were low, providing reassurance of a lack of deleterious effect. In general, the secondary endpoint results were supportive of the primary outcomes. There was evidence of consistent benefit for health outcome measures such as SF36 and FACIT-F.

Study 1125 (TNFi non-responders)

For the co-primary endpoint of ACR20 at Month 3, the response rate for the proposed dose of tofacitinib 5 mg BID was 49.6%, in line with study 1091. This represented a 26.0% increase over placebo, which is statistically significant and clinically relevant. The ACR20 response is maintained up to Month 12.

For the co-primary endpoint of ΔHAQ-DI at Month 3, the LS mean treatment difference for tofacitinib 5 mg BID vs placebo was -0.25. This difference was in line with that observed for study 1092. The effects are maintained until Month 12. For the 90% of subjects with baseline HAQ-DI ≥0.35, 50.0% of the tofacitinib 5 mg BID group reported a decrease of ≥0.35, the MCID, compared to 27.6% for the placebo group. This responder analysis supports the clinical relevance of the HAQ-DI results.

Sensitivity analyses demonstrated the robustness of the results on the primary endpoints, and generally consistent findings were seen across subgroups.

Secondary endpoints included the ACR50, for which a clear separation from placebo was observed, with a treatment difference of 15.3% for tofacitinib 5 mg BID, and maintenance of the effect until Month 12. In general, the secondary endpoint results were supportive of the primary outcomes. There was evidence of consistent benefit for health outcome measures such as SF36 and FACIT-F.

Target population

Around 6% of the population of study A3921091 (csDMARD-IR) had an inadequate response to one csDMARD other than MTX. In addition, 1.4% had an inadequate response to >1 csDMARD that did not include MTX. These subgroups are too small for meaningful efficacy or safety analyses. However, the subgroup with an inadequate response to >1 csDMARD can provide supportive information, since this patients in this subgroup (>1 csDMARD-IR) had an inadequate response to a csDMARD other than MTX, and should represent a more difficult to treat population. The MAH has compared the efficacy and safety outcomes of the >1 csDMARD subgroup vs 1 csDMARD-IR subgroup (predominantly MTX-IR). Regarding efficacy at Month 3, the >1 csDMARD subgroup appear to derive more benefit from tofacitinib but less benefit from adalimumab, compared to the 1 csDMARD subgroup, across most of the relevant endpoints. In the RA clinical efficacy dataset, ACR response rates and HAQ-DI change from baseline at Month 3 were comparable for 'csDMARD-IR but not MTX-IR or bDMARD-IR' and MTX-IR subgroups. This provides additional supportive evidence that patients who are csDMARD-IR but not MTX-IR would be expected to benefit from tofacitinib. Regarding safety, outcomes are comparable between the 1 csDMARD and >1 csDMARD subgroups of study A3921091. Regarding the RA safety dataset, as for the efficacy comparison, there is no evidence of a worse safety outcomes for 'csDMARD-IR but not MTX-IR or bDMARD-IR' vs MTX-IR subgroups.

The low level of recruitment to study A3921091 of patients who failed a csDMARD other than MTX reflects clinical practice. Most patients will receive MTX as first-line. Patients with a contraindication or intolerance to MTX, and an inadequate response to an alternative csDMARD, were not studied in large numbers. It would be difficult to design a study to include more of these patients, given current treatment guidelines. It seems unlikely that this group would benefit less, or be at more risk, from tofacitinib treatment compared to MTX-IR patients.

3.3. Uncertainties and limitations about favourable effects

A benefit for tofacitinib 5 mg BID in terms of ACR70 response rate and MDA was not demonstrated for study 1125. This may reflect a more treatment resistant population, compared to study 1091.

For disease manifestations of skin involvement, dactylitis and enthesitis, the outcomes are less convincing and less consistent across the two pivotal studies. This may be due in part to the inclusion of patients without these manifestations, and therefore reduced power to demonstrate statistically significant treatment effects within study.

Only a small number of patients with predominantly axial PsA were recruited to the pivotal studies. Therefore, a meaningful assessment of efficacy in this sub-group is not possible. Study 1119 in AS patients provides some supportive evidence for the efficacy of tofacitinib 5 mg BID in predominantly axial PsA.

Combination treatment

In order to provide evidence for use in combination with csDMARDs other than MTX, the MAH has pooled data from study A3921091 (csDMARD-IR) and A3921125 (bDMARD-IR). This strategy is acceptable since the studies were similar in design. Across both studies 21.8% received concomitant csDMARD other than MTX. The pooled group corresponding to 'other csDMARD' included 52 patients in the tofacitinib 5 mg BID group and 43 in the placebo group. Of the 52 patients in the tofacitinib 5 mg BID group who used a non-

MTX csDMARD, 30 patients took sulfasalazine and 19 patients took leflunomide. Although efficacy outcomes in the non-MTX group were generally in line with the outcomes in the MTX groups, the numbers were considered too small to support robust efficacy conclusions in the non-MTX group (see also section 3.5).

3.4. Unfavourable effects

The key risks for tofacitinib are serious infections and opportunistic infections. During the first 12 months of treatment the incidence rate of serious infection was 2.0 per 100 PY for the 5 mg BID dose. The commonest serious infection was pneumonia. No fatal serious infections were reported. The incidence rate for herpes zoster during the first 12 months was 1.5 per 100 PY for the 5 mg BID dose. 85% of the cases in the tofacitinib PsA database involved one dermatome, and no cases were disseminated. No other types of opportunistic infection were identified, and there were no cases of active TB, during the PsA programme. Rates of serious infection and herpes zoster were lower than those observed for RA, although confidence intervals are wide.

The commonest AEs (up to ~ 5%) by preferred term (PT) in the tofacitinib 5 mg BID group were nasopharyngitis, upper respiratory tract infection, headache and diarrhoea. The frequencies are in line with the RA safety profile; no new safety signal is identified. Discontinuation rates for tofacitinib 5 mg BID were 2.1% during the first 3 months, rising to 10.0% for the long-term all dose cohort. Tofacitinib appears to be relatively well-tolerated in PsA patients.

3.5. Uncertainties and limitations about unfavourable effects

The number of events of HZ observed in the PsA programme was limited, and robust conclusions on risk factors for HZ in the PsA population is not possible at present.

A total of 10 malignancies have been identified for the PsA programme; no lymphomas were reported. Observational studies of similar PsA populations treated with other therapies report incidence rates of around 0.35-0.50 per 100 PY. The rate for tofacitinib is higher at 0.72, and its mechanism of action provides some biological plausibility for causation. Malignancy remains an important potential risk, for which there are additional pharmacovigilance activities including a post-authorisation safety study in RA (A3921133).

Combination treatment

To provide evidence for use in combination with csDMARDs other than MTX, the MAH has pooled data from study A3921091 (csDMARD-IR) and A3921125 (bDMARD-IR). This strategy is acceptable since the studies were similar in design. Across both studies 21.8% received concomitant csDMARD other than MTX. The pooled group corresponding to ‘other csDMARD’ included 52 patients in the tofacitinib 5 mg BID group and 43 in the placebo group. Of the 52 patients in the tofacitinib 5 mg BID group who used a non-MTX csDMARD, 30 patients took sulfasalazine and 19 patients took leflunomide.

Safety outcomes were comparable for the ‘MTX only’ and other csDMARD’ groups. Over 12 months, the percentage of subjects reporting SAEs was higher for the ‘MTX only’ group compared to the ‘other csDMARD’ group. Hepatic enzyme outcomes were also comparable between the subgroups. Supportive evidence from the RA database also suggests comparable safety outcomes irrespective of concomitant csDMARD. However, csDMARDs cannot be considered a single class. For individual non-MTX csDMARDs, the patient numbers are small. Therefore, it is not possible to extrapolate safety conclusions from the combination with MTX.

3.6. Effects Table

Table 51 - Effects Table for Xeljanz for the treatment of psoriatic arthritis (10th November 2016)

Effect	Short Description	Unit	Treatment (TOF 5mg BID)	Control (placebo)	Control (adalimumab)	Uncertainties/ Strength of evidence
Favourable Effects						
ACR20 in TNFi naïve	Response rate at Month 3	%	50.5	33.3	51.9	P = 0.0102 (tofacitinib vs placebo)
ACR20 in TNFi inadequate responders	Response rate at Month 3	%	49.6	23.7	N/A	P < 0.0001 (tofacitinib vs placebo)
ΔHAQ-DI in TNFi naïve	LS mean at Month 3	-	-0.35	-0.18	-0.38	P = 0.0062 (tofacitinib vs placebo)
ΔHAQ-DI in TNFi inadequate responders	Ls Mean at Month 3	-	-0.39	-0.14	N/A	P < 0.0001 (tofacitinib vs placebo)
Unfavourable Effects						
Nasopharyngitis	% subjects with AE up to Month 3	%	5.9	2.5	4.7	
Upper respiratory tract infection	% subjects with AE up to Month 3	%	5.0	4.7	2.8	
Headache	% subjects with AE up to Month 3	%	3.8	4.7	4.7	
Diarrhoea	% subjects with AE up to Month 3	%	3.4	0.4	0.9	
Serious infections	Incidence rates up to Month 12	Per 100 PY	1.99	N/A	1.08	
Herpes zoster	Incidence rates up to Month 12	Per 100 PY	1.50	0	0	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A clinically relevant benefit for tofacitinib in combination with MTX has been demonstrated for signs, symptoms, function and health outcomes in patients with active PsA who have not responded to, or are intolerant of, a csDMARD or TNF. Tofacitinib offers a different mode of action and safety profile, compared to other targeted treatments for this setting. The oral formulation may also be an advantage for some patients.

The risks of serious or opportunistic infections are important. However, these risks are mitigated by the precautions and warnings included in the SmPC, and these adverse reactions are generally manageable. Tofacitinib was well-tolerated. The potential risk of malignancy continues to be investigated.

3.7.2. Balance of benefits and risks

The benefits of Xeljanz 5 mg film-coated tablets outweigh the risks, when used in combination with MTX for the treatment of adult acive PsA patients who have had an inadequate response or who have been intolerant to a DMARD.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Xeljanz is positive.

4. Recommendations

Outcome

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

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

Extension of Indication: Xeljanz in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy, supported by data from studies A3921091, A3921092, A3921125. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the Annex II with minor editorial changes. The RMP version 3.2 has also been submitted.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

Extension of Indication: Xeljanz in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy, supported by data from studies A3921091, A3921092, A3921125. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the Annex II with minor editorial changes. The RMP version 3.2 has also been submitted.

Summary

Please refer to the scientific discussion Xeljanz EMEA/H/C/004214/II/006.

Attachments

1. SmPC, Annex II, Labelling, Package Leaflet (changes highlighted) as adopted by the CHMP on 26 April 2018.