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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Xeljanz

tofacitinib

Procedure no: EMEA/H/C/004214/P46/012

Note

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

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1. Introduction

On 27/01/2020, the MAH submitted a completed paediatric study for tofacitinib for treatment of polyarticular course juvenile idiopathic arthritis (JIA), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

This submission is in fulfilment of the Article 46 requirement. Study A3921104 is a deferred study in the JIA PIP (Study 6) with a completion date by February 2020. Study A3921104 was a randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of tofacitinib for treatment of polyarticular course juvenile idiopathic arthritis (JIA) in children and adolescent subjects.
A consequential Type II variation to update the SmPC with the relevant results is planned for submission in June 2020.

2.2. Information on the pharmaceutical formulation used in the study

Two formulations of tofacitinib have been used in study A3921104 to enable weight-based dosing and achieve comparable tofacitinib area under the curve (AUC) for all patients:

- Tofacitinib citrate IR film-coated 5 mg tablet
- Tofacitinib citrate 1 mg/mL oral solution

2.3. Clinical aspects

2.3.1. Introduction

Clinical study number and title

Study Title: Efficacy, Safety, and Tolerability of Tofacitinib for Treatment of Polyarticular Course JIA in Children and Adolescent Subjects

Description

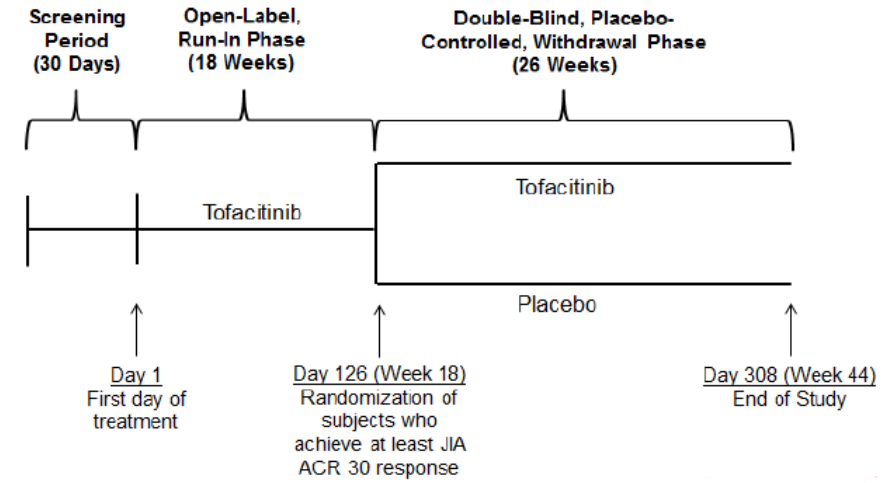
Methods

Objective(s)

Efficacy, safety, tolerability and PK

Study design

Figure 1. Study Design

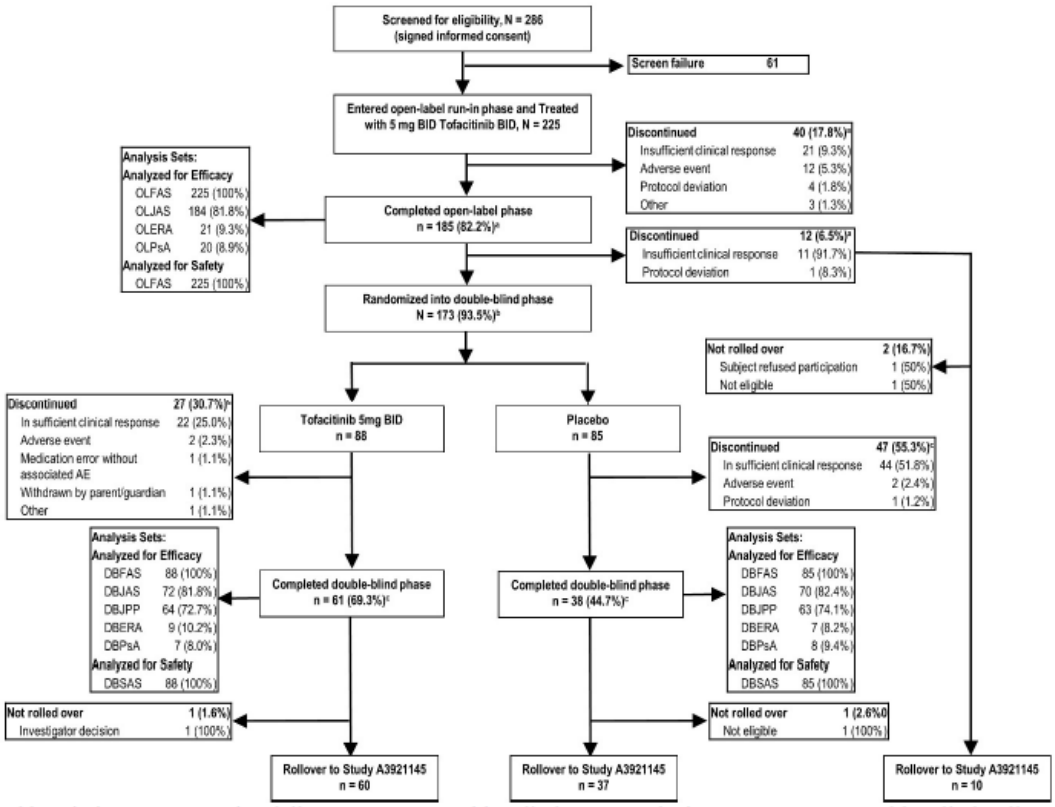


All eligible subjects enrolled in the study initially received open-label tofacitinib for 18 weeks (run-in phase). At the end of the 18-week run-in phase, only subjects who achieved at least a JIA American College of Rheumatology (ACR) 30 response were randomized to the 26-week double-blind, placebo-controlled phase. Subjects who did not achieve a JIA ACR 30 response at this time point were discontinued from the study. Subjects who experienced a single episode of disease flare (according to Pediatric Rheumatology Clinical Study Group/Pediatric Rheumatology International Trials Organization [PRCSG/PRINTO] Disease Flare criteria) at any time during the study (including the open-label run-in and double-blind phase) were also discontinued from the study.
Subjects who were eligible for the 26-week double-blind phase were randomized (1:1 ratio) to either active tofacitinib or placebo.

Study population /Sample size

A total of 286 subjects enrolled in the study, 185 subjects completed the open-label run-in phase, with 173 subjects being randomized into the double-blind phase (88 subjects to tofacitinib 5 mg BID and 85 subjects to placebo).
There were 12 subjects that were withdrawn upon completion of the initial treatment phase because they did not meet the criteria to be randomized into the double-blind phase (insufficient clinical response for 11 subjects and protocol deviation for 1 subject). Of these subjects, 10 were rolled over into Study A3921145 and 2 discontinued (1 subject was not eligible for Study A3921145 and 1 subject refused participation).
A total of **99 subjects completed the double-blind phase** (61 in the tofacitinib 5 mg BID group and 38 in the placebo group). Of those subjects, 97 were rolled over into the A3921145 study and 2 were discontinued. Since flares led to discontinuation during the double-blind phase, insufficient clinical response was the most common discontinuation reason for double-blind discontinuation in both arms, with a higher percentage in the placebo group.

Disposition Events Summary



Abbreviations: BID = twice daily; DBERA = Double-Blind ERA Analysis Set; DBFAS = Double-Blind Full Analysis Set; DBJAS = Double-Blind Polyarticular Course JIA Analysis Set; DBJPP = Double-Blind Polyarticular Course JIA Per Protocol Analysis Set; DBPsA = Double-Blind PsA Analysis Set; DBSAS = Double-Blind Safety Analysis Set; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; OLFAS = Open-Label Run-In Phase Full Analysis Set; OLERA = Open-Label Run-In ERA Analysis Set; OLJAS = Open-Label Run-In Polyarticular Course JIA Analysis Set; OLPsA = Open-Label Run-In PsA Analysis Set; PsA = psoriatic arthritis

a. Percentage based on the number of subjects who entered open-label run-in phase
b. Percentage based on the number of participants who completed the open-label phase
c. Percentage based on the number of participants

Key inclusion/exclusion criteria

Key inclusion criteria:

- ✓ Male or female subjects aged 2 to <18 years.
- ✓ Must have met International League Against Rheumatism (ILAR) JIA classification for 1 of the following categories and, in the opinion of the investigator, had active disease for at least 6 weeks prior to screening:
- ✓ E Oligo;
- ✓ Polyarthritis (RF+);
- ✓ Polyarthritis (RF-);
- ✓ Systemic JIA with active arthritis but without active systemic features in the prior
- ✓ 6 months and at the time of enrolment;
- ✓ PsA;
- ✓ ERA.

-Subjects with PJIA (i.e., E Oligo, polyarthritis RF+, polyarthritis RF-), systemic JIA (with active arthritis but without active systemic features) must have had a minimum of 5 active joints (an active joint was defined as a joint with swelling or, in the absence of swelling, limited range of motion accompanied by either pain on motion or tenderness) at screening and baseline

Subjects with psoriatic- or enthesitis-related arthritis must have had a minimum of 3 active joints (an active joint was defined as a joint with swelling or, in the absence of swelling, limited range of motion accompanied by either pain on motion or tenderness) at screening and baseline

-Treatment with stable doses of a NSAID and/or a stable dose of an oral glucocorticoid, and/or a stable dose of MTX was permitted.
-For subjects who were receiving an oral glucocorticoid: were administered at a maximum dose of 0.2 mg of prednisone equivalent per kilogram per day or 10 mg per day for ≥2 weeks before baseline, whichever was lower.
-For subjects who were receiving MTX treatment: at doses not to exceed 25 mg/week or 20 mg/m2/week (whichever was lower); participants must have taken MTX for ≥3 months and been at a stable dose for at least 6 weeks before baseline.
-For subjects with PsA, the following topical treatments for psoriasis were
allowed: non-medicated emollients for use over the whole body; topical steroids including hydrocortisone and hydrocortisone acetate ≤1% for the palms, soles, face, and intertriginous areas only; tar, salicylic acid preparations, and shampoos free of corticosteroids were permitted only for the scalp.

-Inadequate response or intolerance to at least 1 DMARD, which may include MTX or biologic agents; in the case of ERA and psoriatic arthritis, inadequate response to NSAIDs.
-No evidence or history of untreated or inadequately treated active or latent tuberculosis infection as for standard diagnostic tests

Key exclusion criteria

-Previous JIA treatment with tofacitinib.
-sJIA with any active systemic features other than active joints and elevated acute phase reactants within 6 months of enrollment.
-Persistent oligoarthritis.
-Undifferentiated JIA.
-Infections: Chronic infections; Any infection that required hospitalization, parenteral antimicrobial therapy or judged to be opportunistic by the investigator within the 6 months prior to the first dose of study drug; Any treated infections within 2 weeks of baseline; A subject known to be infected with human immunodeficiency virus, Hepatitis B, or Hepatitis C;
-History of recurrent (more than 1 episode) herpes zoster or disseminated (at least 1 episode) herpes zoster or disseminated (at least 1 episode) herpes simplex.
-Active uveitis within 3 months of enrollment.
-Blood dyscrasias, including (Hemoglobin <10 g/dL or Hematocrit <33%;White Blood Cell count <3.0 x 109/L; Neutrophil count <1.2 x 109/L;Platelet count <100 x 109/L;Lymphocyte count <0.75 x 109/L).
-History of any other rheumatologic disease, other than Sjogren's syndrome. History or current symptoms suggestive of lymphoproliferative disorders
-Vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of study drug or was expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of study drug.
-Subjects without documented evidence of having received at least 1 dose of the varicella vaccine in countries where the vaccine is approved and standard of care or those who did not have evidence of prior exposure to varicella zoster virus based on serological testing.
-Subjects who previously failed more than 3 biologic therapies (with different mechanisms of action) for JIA.

-Subjects with a first degree relative with a hereditary immunodeficiency; IgA deficiency not exclusionary.
-For subjects with PsA, oral and topical medications and alternative treatments that could affect psoriasis were prohibited. This included topical corticosteroids, tars, keratolytics, anthralin, vitamin D analogs, and retinoids which must have been discontinued at least 2 weeks prior to first dose of study drug. Also prohibited was ultraviolet B (narrowband or broadband) phototherapy that must have been discontinued at least 2 weeks prior to first dose of study drug. Psoralens + ultraviolet A phototherapy must have been discontinued at least 4 weeks prior to first dose of study drug.

Treatments

Tofacitinib was provided as oral tablets (tofacitinib citrate 5 mg) and as an oral solution (CP-690,550-10 [tofacitinib citrate] 1 mg/mL) by the Sponsor. Open-label bottles of tofacitinib tablets and tofacitinib citrate oral solution were provided for the run-in phase of the study. Blinded-label bottles of tofacitinib tablets, tofacitinib citrate oral solution, and matching placebo, for oral administration, were provided for the double-blind phase of the study.

Randomization: For subjects with PJIA, randomization was stratified by JIA category and baseline CRP. For subjects with PsA and ERA, randomization was stratified by JIA category.

Dose The dose of tofacitinib in adolescents with body weight ≥40 kg was set to 5 mg BID. Oral solution (1 mg/mL) was used for subjects weighing <40 kg. The tofacitinib doses for the younger JIA subjects were selected to match the predicted steady state concentrations in JIA subjects with body weight ≥40 kg after administration of a 5 mg BID dose.

Table 3. Study Treatment Dosing and Administration

Body Weight (kg)	Dosage Regimen (Run-In Phase: Tofacitinib, Double-Blind Phase: Tofacitinib/Placebo)
5 to <7	2 mg (2 mL oral solution) BID
7 to <10	2.5 mg (2.5 mL oral solution) BID
10 to <15	3 mg (3 mL oral solution) BID
15 to <25	3.5 mg (3.5 mL oral solution) BID
25 to <40	4 mg (4 mL oral solution) BID
≥40	5 mg (one 5 mg tablet or 5 mL oral solution) BID

Source: Appendix 16.1.1, Protocol Table 2

Outcomes/endpoints

Table 1. Study Objectives and Endpoints

Type	Objective	Endpoint[a]
Primary (Type I Error Controlled)		
Efficacy	To compare the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA at Week 44/End of Study (Week 26 of the double-blind phase) as measured by the percentage of subjects with disease flare (according to PRCSG/PRINTO Disease Flare criteria) after Week 18 of the open-label run-in phase.	Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) by Week 44/End of Study (Week 26 of the double-blind phase)
Key Secondary (Type I Error Controlled)		
Efficacy	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by achievement of JIA American College of Rheumatology (ACR) 30, 50, 70 response at various time points in the double-blind phase	Achieving JIA ACR 30, 50, 70 response at Week 44/End of Study (Week 26 of the double-blind phase); open-label run-in baseline will be used to determine ACR response
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in CHAQ responses at various time points in the double-blind phase	Change from double-blind baseline in CHAQ disability index at Week 44/End of Study (Week 26 of the double-blind phase)
Secondary		
Efficacy	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by the percentage of the subjects with disease flare (according to PRCSG/PRINTO Disease Flare criteria) at various time points in the double-blind phase	Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by time to disease flare in the double-blind phase	Time to disease flare in the double-blind phase
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by achievement of JIA ACR 30, 50, 70, 90, 100 responses at various time points in the double-blind phase	Achieving JIA ACR 30, 50, 70, 90, 100 response at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase; open-label run-in baseline will be used to determine ACR response
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in Juvenile Arthritis Disease Activity (JADAS)-27 c-reactive protein (CRP) and JADAS-27 ESR, and percentage of subjects achieving JADAS minimum disease activity and inactive disease at various time points in the double-blind phase	Change from double-blind baseline in JADAS-27 CRP, JADAS-27 ESR, and achieving JADAS minimum disease activity and inactive disease at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase

Type	Objective	Endpoint[a]
	To evaluate the efficacy of tofacitinib versus placebo for treatment of signs and symptoms of JIA as measured by the JIA ACR inactive disease and clinical remission rate at various time points in the double-blind phase	Achieving JIA ACR inactive disease at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase, and achieving clinical remission at Week 44 (Week 26 of the double-blind phase); achieving at least 1 JIA ACR inactive disease during double-blind phase
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in each JIA ACR core set variable at various time points in the double-blind phase	• Change from double-blind baseline in each JIA ACR core set variable at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase • Change from open-label run-in baseline in each JIA ACR core set variable at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in CHQ responses at various time points in the double-blind phase	Change from double-blind baseline in CHQ responses at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in CHAQ responses at various time points in the double-blind phase	Change from double-blind baseline in CHAQ responses at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase
	In subjects with ERA: To evaluate the efficacy of tofacitinib for the treatment of ERA as measured by changes from baseline in the Tender Entheseal Assessment, Modified Schober's Test, and Overall Back Pain and Nocturnal Back Pain responses at various time points in the double-blind phase	In subjects with ERA: Change from double-blind baseline in the Tender Entheseal Assessment, Modified Schober's Test, Overall Back Pain, and Nocturnal Back Pain responses at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase
	In subjects with PsA: To evaluate the efficacy of tofacitinib for the treatment of PsA as measured by changes from baseline in the BSA affected with psoriasis and PGA of psoriasis assessments at various time points in the double-blind phase	In subjects with PsA: Change from double-blind baseline in the BSA affected with psoriasis and PGA of psoriasis assessments at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase
	To evaluate the efficacy of tofacitinib in the open-label run-in phase	• Occurrence of disease flare at each scheduled visit in the open-label phase. • Time to disease flare in the open-label run-in phase. • Achieving JIA ACR 30, 50, 70, 90, 100 response at each scheduled visit in the open-label run-in phase; JIA ACR 30, 50, 70, 90, 100 response is determined based on the open-label run-in baseline. • Change from open-label run-in baseline in JADAS-27 CRP, JADAS-27 ESR, and

Type	Objective	Endpoint[a]
		achieving JADAS minimum disease activity and inactive disease at each scheduled visit in the open-label run-in phase • Achieving JIA ACR inactive disease at each scheduled visit in the open-label run-in phase; percentage of subjects experiencing at least one JIA ACR inactive disease during open-label phase • Change from open-label run-in baseline in each JIA ACR core set variable at each scheduled visit in the open-label run-in phase • Change from open-label run-in baseline in CHQ responses at each scheduled visit in the open-label run-in phase • Change from open-label run-in baseline in CHAQ responses at each scheduled visit in the open-label run-in phase • In subjects with ERA: Change from open-label run-in baseline in the Tender Entheseal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain responses at each scheduled visit in the open-label run-in phase • In subjects with PsA: Change from open-label run-in baseline in the BSA affected with psoriasis and PGA of psoriasis assessments at each scheduled visit in the open-label run-in phase
	To evaluate the taste acceptability of tofacitinib oral solution, if applicable, on Day 14 of the open-label run-in phase	Taste acceptability of tofacitinib oral solution (Like very much, Like a little, Not Sure, Dislike a little, Dislike very much), if applicable, on Day 14 of the open-label run-in phase
PK	To evaluate the PK of tofacitinib in subjects with JIA during the open-label run-in phase.	Plasma tofacitinib concentrations during the open-label run-in phase.
Safety	To evaluate safety and tolerability of tofacitinib in subjects with JIA during the study	• Incidence and severity of adverse events, with focus on serious infections, cytopenias, malignancies, cardiovascular diseases and gastrointestinal (GI) perforations • Incidence of clinical laboratory abnormalities and change from baseline in clinical laboratory values • Incidence of abnormalities in physical examination and incidence of significant changes from baseline at final visit for physical examination

Type	Objective	Endpoint[a]
		• Incidence of vital sign abnormalities and change from baseline in vital sign measures • Validated assessments of growth and pubertal development (Tanner Stage of Development) (see Appendix 16.1.1, Protocol Section 7.2.5)
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by the occurrence of active uveitis (according to standard uveitis nomenclature [SUN] criteria) in the double-blind phase	Occurrence of active uveitis (according to SUN criteria) at each scheduled visit in the open-label run-in and double-blind phase
Exploratory		
Biomarker	To evaluate exploratory biomarker and genomic samples to characterize the effect of tofacitinib	The biobanked exploratory genomic and biomarker samples[b]

a. Endpoints from Appendix 16.1.9, SAP Section 3.
b. Analyses will be presented in a separate report if performed.

Statistical Methods

Analysis sets

Table 4. Summary of Analysis Sets

Analysis Set	Brief Description	Efficacy Analysis	Safety Analysis
DBFAS	Subjects randomized to double-blind phase, received at least 1 dose of study medication in double-blind phase, subjects reported under randomized treatment	None	None
DBJAS	PJIA subjects in DBFAS	Primary endpoint, type I error controlled (key) secondary endpoints, and secondary endpoints in double-blind phase for JIA	None
DBERA	ERA subjects in DBFAS	Secondary endpoints in double-blind phase for ERA, ERA specific endpoints in double-blind phase	None
DBPsA	PsA subjects in DBFAS	Secondary endpoints in double-blind phase for PsA, PsA specific endpoints in double-blind phase	None
DBJPP	Subjects with no major protocol violations in the DBJAS	Primary endpoint	None
DBSAS	Subjects received at least one dose of study medication in double-blind phase, subjects reported under received treatment	None	All double-blind safety analyses
OLFAS	Subjects enrolled, received at least one dose of study medication in open-label phase	Taste acceptability	All open-label safety analyses
OLJAS	PJIA subjects in OLFAS	Secondary endpoints in open-label phase for JIA	None
OLERA	ERA subjects in OLFAS	Secondary endpoints in open-label phase for ERA, ERA specific endpoints in open-label phase	None
OLPsA	PsA subjects in OLFAS	Secondary endpoints in open-label phase for PsA, PsA specific endpoints in open-label phase	None

Source: Appendix 16.1.9, SAP Table 2

Missing data handling. During the open-label run-in phase was adjusted as follows for consistency with the double-blind phase. For the composite endpoints flare and JIA ACR 30, 50, 70, 90, 100

responses, LOCF was used to impute the missing component(s) to derive these endpoints at the visits prior to study treatment discontinuation if any component was missing. The LOCF method was also used to impute the binary status of flare, JIA ACR 30, 50, 70, 90, 100 responses, JADAS minimum disease activity, JADAS inactive disease, and JIA ACR inactive disease at intermediate visits with missing values, preceding study treatment discontinuation. Flare, JIA ACR 30, 50, 70, 90, 100 responses, and other binary endpoints (JADAS minimum disease activity and inactive disease, JIA ACR inactive disease) were set to flare/non-responder/active disease, respectively, for observed assessments on or after the treatment discontinuation. Visits without observed assessments after study treatment discontinuation were not imputed.

Analysis of the primary endpoint. Tofacitinib was to be considered superior to placebo in reducing flares if testing the difference between the proportion of subjects with flares by Week 44/end of study (Week 26 of the double-blind phase) would result in a two-sided p-value <0.05. The difference between flare rates in the double-blind phase by Week 44 of the study for subjects with polyarticular course (polyarthritis RF+/RF-, E Oligo, and sJIA with active arthritis but without active systemic features) JIA was tested using the normal approximation approach for binomial populations. Subjects who discontinued from the study treatment for any reason were considered as having a disease flare, except subjects who discontinued after maintaining JIA ACR inactive disease for at least 24 weeks. These discontinuations were considered as non-disease flare.

Sensitivity analyses of the primary endpoint were carried out in support of the primary analysis of flare as follows:

- Using a general linear model with binary outcome (flare/no flare) as response, JIA category and open-label baseline CRP category as factors,
- Using a Cochran-Mantel-Haenszel approach with stratification factors of JIA category and open-label run-in baseline CRP category,
- Analysis where all discontinuations, including those of subjects in clinical remission (at least 24 weeks of inactive disease), were treated as flares,
- Per protocol analysis

Tipping point analyses using 2 model-based multiple imputation approaches (Weibull regression and binomial distribution) to assess the impact of drop-outs (for reasons other than flare) on the primary results.

All secondary endpoints that were collected in the double-blind withdrawal phase were analyzed by treatment group. For the binary endpoints, the normal approximation approach for the binary populations, as used for the primary analysis, was performed. For the continuous secondary endpoints, a mixed effect model was applied. Time to event analyses used Kaplan-Meier methodology and the logrank test.

Tipping point analyses were conducted for the type I error controlled secondary endpoints using model-based multiple imputation—binomial method for ACR 50, 30, 70 responses at Week 44 of the study and missing not at random (MNAR) multiple imputation for the change from baseline in the CHAQ disability index at Week 44 of the study.

For subjects with ERA and subjects with PsA, efficacy endpoints were assessed separately using summary and descriptive statistics by treatment group at each time point in the double-blind phase. The taste acceptability assessment questionnaire was included in the CRF, and summary statistics were provided for each category of the taste acceptability by treatment and by time point.

Sample size Approximately 170 subjects (in the polyarticular course cohort) were to be enrolled in the open-label active treatment run-in phase to provide a power of approximately 90% or above to detect a difference in the rate of disease flares between tofacitinib versus placebo in the double-blind phase, assuming a 54% to 65% response rate of ACR Pedi 30 from the run-in active treatment phase, a 2-sided 5% Type I error, and a true difference of at least 31% in flare rates between tofacitinib and placebo, with a placebo flare rate of 57%. Sample sizes for the PJIA categories were determined from a combination of prevalence data and precedents in the literature.

Biopharmaceutics

Two formulations of tofacitinib have been used in study A3921104 to enable weight-based dosing and achieve comparable tofacitinib area under the curve (AUC) for all patients:

- Tofacitinib citrate IR film-coated 5 mg tablet
- Tofacitinib citrate 1 mg/mL oral solution

The 5 mg tablet formulation has the same qualitative and quantitative composition as the commercial 5 mg tablet formulation and differed only with respect to debossing. Details of tofacitinib 5 mg tablet biopharmaceutics can be found in the Summary of Biopharmaceutic Studies (SBP) in the regulatory submission for RA patients. The clinical oral solution formulation is bridged to the tablet formulation used in the pJIA program using a relative bioavailability study in healthy adults (A3921354).

The composition of the oral solution and the tablet is listed in Table 2 and Table 3, respectively. The resulting tofacitinib plasma concentration from both formulations will be analysed by population pharmacokinetic (PK) approach and reported separately.

Composition of 1 mg/mL CP-690,550-10 Oral Solution (Clinical Formulation)

Component	Function	Quantity (mg/mL)
CP- 690,550-10a	Active	1.62
Lactic Acid, 88.0 – 92.0% Racemic	Buffer	1.013
Sodium Benzoate	Preservative	1.50
Xylitol	Sweetener	200.00
Sucralose	Sweetener	1.00
Flavor Grape (SN355539)	Flavor	3.00
Hydrochloric acid	pH adjuster	Trace, as needed
Sodium Hydroxide Pellets	pH adjuster	Trace, as needed
Purified Water	Solvent	750.00
Purified Water	Solvent	Qs to 1 mL

a Based on a theoretical drug substance potency of 61.9%. The amount of CP-690,550-10 may be adjusted based on the measured potency
Source: Table 3.2.P.2.2-1

Composition of CP-690,550-10 5 mg Film-Coated Commercial Tablets

Component	Function	5 mg Tablet Unit Formula (mg/tab)
CP-690,550-10[a]	Active	8.078
Microcrystalline cellulose	Diluent	122.615
Lactose monohydrate	Diluent	61.307
Croscarmellose sodium	Disintegrant	6.000
Magnesium Stearate	Lubricant	2.000
Core Total		200.000
Opadry II White (HPMC based)	Film coat	6.000
Purified Water[b]	Solvent	(34.000)

a Based on a theoretical drug substance potency of 61.9%. The amount of CP-690,550-10 may be adjusted based on the measured potency
b Purified water is the solvent for the film coating which evaporates during manufacture and, hence, the quantity is indicated within parentheses.
Source: Table 3.2.P.2.2-1

Clinical pharmacology

PK evaluations are as described in Appendix, to Protocol of clinical study **A3921104** and 2 bioanalytical study reports for the determination of tofacitinib in human plasma were submitted one performed at PPD and one performed at Wuxi.
Since there were 2 analytical labs (PPD and Wuxi) used to conduct tofacitinib sample analysis for this study, the applicant stated that a cross validation was conducted to ensure assay equivalency between the 2 labs.
Plasma samples for PK analysis of tofacitinib were collected from all subjects enrolled in the study at various time points.

Analytical methods
PPD Project No. AKPG: **THE DETERMINATION OF CP-690550 IN HUMAN PLASMA SAMPLES BY LC-MS/MS FROM PFIZER CLINICAL PROTOCOL A3921104.**

A 50-µL matrix aliquot is fortified with 50 µL of 10.0 ng/mL PF-04994438 internal standard working solution. Analytes are isolated through solid phase extraction using Phenomenex Strata-X-C (10 mg, 33 µm) 96-well SPE plates and eluted with 400 µL of ethanol/ammonium hydroxide (87:13, v/v). The eluate is evaporated under a nitrogen stream at approximately 50 °C, and the remaining residue is reconstituted with 100 µL of methanol/water (50:50, v/v).
The final extract is analyzed via HPLC and MS/MS detection using positive ion electrospray. A linear, 1/concentration² weighted, least-squares regression algorithm is used to quantitate unknown samples.
A summary of assay methodology is provided in the following table:

Assay Methodology Summary

Matrix	Human Plasma
Anticoagulant	Lithium Heparin
Matrix Modification	None
Sample Preparation	Solid Phase Extraction
Sample Volume Required for Analysis	50 µL
Method Type	LC-MS/MS
Method Instrument	AB Sciex 6500
Data Acquisition and Processing Systems (Software and Version)	Analyst Version 1.6.3 Assist Version 6
Quantification	Peak Area Ratios
Regression, Weighting	Linear, 1/concentration^2
CS Concentrations (in plasma)	0.100, 0.200, 1.00, 5.00, 25.0, 50.0, 90.0, and 100 ng/mL
LLOQ	0.100 ng/mL
ULOQ	100 ng/mL
QC Concentrations (in plasma)	0.300, 10.0, 40.0 and 75.0 ng/mL
Maximum Validated Dilution Factor	1:10
Replicates	Calibration Standards (n=2) QC (n≥2) QCDIL (n≥3) Samples (n=1)
Established Frozen Storage Stability (LTS)	973 Days at -20°C, 973 Days at -70°C A3929032 (PPD, AKEX2), Validation Report Addendum 3
Freeze/Thaw Stability	5 F/T Cycles at -20°C 5 F/T Cycles at -70°C A3929032 (PPD, RGTF2), Validation Report

An Incurred Sample Reanalysis (ISR) assessment was conducted for this study as per Pfizer WWPDM SOP No. 25. The incurred sample reanalysis was performed on 41 study samples, from 33 subjects. Samples were reanalyzed using the same analytical method and same dilution factors as used for the original reported results. The ISR assessment was conducted within freeze/thaw and LTS limits.
Incurred sample repeats were considered acceptable if the original and re-assay values from two-thirds of the repeated samples had a relative percent difference of within ±20.0% for LC-MS/MS assays.
Less than two-thirds of the repeated samples had a relative percent difference of within ±20.0% for LC-MS/MS assays during the initial ISR assessment. A laboratory investigation to evaluate the data was initiated. The investigation resulted in reanalysis of sample runs 2AKPG, 4AKPG, and 5AKPG. After the investigation and reanalysis of runs 2AKPG, 4AKPG, and 5AKPG, the results of the incurred sample repeats met the ISR acceptance criteria. The original analytical results will be reported and used for pharmacokinetic assessments. Results of the ISR study will not be utilized as the reportable values of the samples used for PK analysis.

WuXi AppTec Project No. 15BAS0278: **THE DETERMINATION OF CP-690550 IN HUMAN LITHIUM HEPARIN PLASMA SAMPLES BY HPLC-MS/MS FROM PFIZER CLINICAL PROTOCOL A3921104**

CP-690550 in human lithium heparin samples (50.0 μL) were extracted using solid phase extraction, the extract was injected on a Phenomenex (Synergi Polar-RP column 50 × 2.0 mm, 4 μm, 80 A) column and analyzed by HPLC-MS/MS. The detection was on an API 5000 mass spectrometer in MRM mode with electronic spray ionization (ESI).
A summary of assay methodology is provided in the following table:

Assay Methodology Summary

Matrix	Human Plasma
Anticoagulant	Lithium Heparin
Matrix Modification	None
Sample Volume Required for Analysis	50.0 µL
Sample Preparation	Solid Phase Extraction
Method Type	HPLC-MS/MS
Method Instrument	AB Sciex API 5000
Data Acquisition and Processing Systems (Software and Version)	Analyst™ version 1.4.2/ 1.6.3 (Applied Biosystems) Watson LIMS 7.2.0.02 (Thermo Electron Corporation)
Quantification	Peak Area Ratios
Regression, Weighting	Quadratic regression, $1/X^2$
CS Concentrations (in 100% Matrix)	0.100, 0.200, 1.00, 5.00, 30.0, 150, 300 and 350 ng/mL
LLOQ	0.100 ng/mL
ULOQ	350 ng/mL
QC Concentrations	QCLLOQ: 0.100 ng/mL QCL: 0.300 ng/mL QCGM: 4.00 ng/mL QCM: 40.0 ng/mL QCH: 280 ng/mL
Maximum Validated Dilution Factor	1:10
Replicates	Calibration Standards (n=2) QC (n≥2) Samples (n=1)
Established Frozen Storage Stability (LTS)	943 Days at -20 °C and -80 °C A3929023 Addendum 05 (12BAS0395)
Freeze/Thaw Stability	5 F/T Cycles at -20°C 5 F/T Cycles at -80°C A3929023 Addendum 01 (12BAS0395)

An Incurred Sample Reanalysis (ISR) assessment was conducted for this study as per Pfizer WWPDM SOP No. 25. The incurred sample reanalysis was performed on 91 study samples, composed of 2 samples from 9 subjects, 1 sample from 73 subject. Samples were reanalyzed using the same analytical method and same dilution factors as used for the original reported results. The ISR assessment was conducted within freeze/thaw and LTS limits.
Incurred sample repeats were considered acceptable if the original and re-assay values from two-thirds of the repeated samples had a relative percent difference of within ± 20.0% for LC-MS/MS assays. The results of the incurred sample repeats met the ISR acceptance criteria. The original analytical results will

be reported and used for pharmacokinetic assessments. Results of the ISR study will not be utilized as the reportable values of the samples used for PK analysis.

Pharmacokinetic Results

The result of the population PK analysis (a pooling analysis of data from study A3921104 and other previous studies) will be reported separately in the Type II variation for pJIA. Moreover, the Applicant stated that, a Phase 1 pharmacokinetic (PK) study of tofacitinib in JIA subjects (A3921103) was completed in 2015, and an open-label, non-comparative, long-term extension study (A3921145) is ongoing, as part of this paediatric program. Subjects from **Study A3921104** were eligible to enter Study A3921145 to continue treatment with tofacitinib 5 mg BID IR tablets or weight equivalent dose of oral solution.

Taste Acceptability

Most subjects either liked the taste "very much" (34 [40.00%] subjects) or "a little" (32 [37.65%] subjects). There were few subjects who disliked the taste "a little" (8 [9.41%] subjects) or "very much" (4 [4.71%] subjects) (A3921104 Study Report Section 11.1.1.3.11).

Taste Acceptability of Tofacitinib Oral Solution on Day 14 in Open-Label Run-in Phase - OLFAS

		Tofacitnib 5mg BID (N=225) n (%)
Taste Assessment Category	n	85 (37.78)
	Dislike Very Much	4 (4.71)
	Dislike a Little	8 (9.41)
	Not Sure	6 (7.06)
	Like a Little	32 (37.65)
	Like Very Much	34 (40.00)

The Open-Label Run-in phase is the study period before randomization day (Week 18).
If a subject does not meet randomization criteria and is discontinued, the study period will all be considered Open-Label Run-in phase.
n - Number of subjects on oral solution at Week 2, the corresponding percentage is based on Open Label Full Analysis Set (OLFAS).
The percentage for the taste assessment is based on the number of subjects on oral solution at Week 2 (n).
One subject (i.e., Subject 10081005) on oral solution, did not have taste assessment done at Week 2.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (06:56) Source Data: Table 16.2.6.15 Output File: ./ra_cdisc/A3921104/taste_assmt Date of Generation: 01JUL2019 (16:42)
Table 14.2.24 is for Pfizer internal use.

Results

Recruitment/ Number analysed

All 225 subjects that were assigned to treatment were included in the OLFAS. All 225 subjects in the OLFAS were analyzed for AEs.
All 173 subjects that were treated in the double-blind phase were included in the DBFAS. A total of 142 (82.1%) subjects were included in the double-blind polyarticular course JIA analysis set (DBJAS). There were 127 (73.4%), 16 (9.2%), and 15 (8.7%) subjects in the double-blind per protocol (DBJPP), double-blind ERA (DBERA) and double-blind PsA (DBPsA) analysis sets, respectively. The proportion of subjects excluded from the DBJPP analysis set was similar in both treatment groups. All 173 subjects in the DBFAS were analyzed for safety.

Baseline data

OL

Demographic: The mean (standard deviation [SD]) age of subjects entering the open-label run-in phase was 11.9 (4.06) years, and the mean (SD) age when first diagnosed was 8.1 (4.66) years. There were more female (N=169) than male (N=56) subjects in the study, and most subjects in the open-label run-in phase were White (196 [87.1%]). In total, there were 96 (42.7%) subjects from North America (United States and Canada), 47 (20.9%) subjects from South and Central America (Brazil, Argentina, and Mexico), 6 (2.7%) subjects from Europe (Poland, Belgium, Great Britain, and Spain), and 76 (33.8%) from Other (Ukraine, Turkey, Russia, Australia, and Israel).

Age subsets

Table 11. Demographic Characteristics - OLFAS

	Tofacitinib 5mg BID OL (N=225)		
	Male (N=56)	Female (N=169)	Total (N=225)
Age (years):			
2 - <6	7 (12.5)	15 (8.9)	22 (9.8)
6 - <12	20 (35.7)	44 (26.0)	64 (28.4)
12 - <18	29 (51.8)	110 (65.1)	139 (61.8)
Mean (SD)	11.2 (4.12)	12.1 (4.03)	11.9 (4.06)
Median (SE)	12.0 (0.55)	13.0 (0.31)	13.0 (0.27)

	Tofacitinib 5mg BID OL (N=225)		
	Male (N=56)	Female (N=169)	Total (N=225)
Q1, Q3	7.5, 15.0	10.0, 16.0	9.0, 15.0
Range (min, max)	2, 17	2, 17	2, 17

Table 12. Other Baseline Characteristics - OLFAS

		Tofacitinib 5 mg BID OL (N=225)
Body Weight	<40 kg	84 (37.3)
	>=40 kg	141 (62.7)
Rheumatoid Factor (IU/mL)	n	143
	Mean (SD)	152.7 (860.96)
	Median (SE)	15.0 (72.00)
	Q1, Q3	15.0, 22.0
	Range (min, max)	15, 9335
	Positive	39 (17.3)
	Negative	104 (46.2)
Anti-Cyclin Citrullinated Protein (anti-CCP) Antibodies	Positive	38 (16.9)
	Negative	181 (80.4)
	Missing	6 (2.7)
Antinuclear Antibodies (ANA)	Positive	101 (44.9)
	Negative	123 (54.7)
	Missing	1 (0.4)
Human Leukocyte Antigen B27 (HLA-B27)	Positive	32 (14.2)
	Negative	185 (82.2)
	Missing	8 (3.6)
Age at First Diagnosed (years)	n	225
	Mean (SD)	8.1 (4.66)
	Median (SE)	8.0 (0.31)
	Q1, Q3	4.0, 12.3
	Range (min, max)	0.3, 16.3
Duration since Onset (years)	n	225
	Mean (SD)	3.8 (3.52)
	Median (SE)	2.5 (0.23)
	Q1, Q3	1.0, 5.6
	Range (min, max)	0.2, 16.2
Body Mass Index (BMI) (kg/m^2)	n	225
	Mean (SD)	20.2 (4.65)
	Median (SE)	19.7 (0.31)
	Q1, Q3	16.6, 23.0
	Range (min, max)	12, 44
Obesity	Yes	23 (10.2)
	No	202 (89.8)

Table 13. Baseline Disease Characteristics - OLFAS

	Tofacitinib 5mg BID OL (N=225)
Number of Joints with Active Arthritis[1]	
n	225
Mean (SD)	12.2 (8.11)
Median (SE)	10.0 (0.54)
Q1, Q3	6.0, 15.0
Range (min, max)	3, 49
Number of Joints with Limitation of Motion	
n	225
Mean (SD)	7.5 (6.89)
Median (SE)	6.0 (0.46)
Q1, Q3	3.0, 10.0
Range (min, max)	0, 36
Physician's Global Evaluation of Overall Disease Activity[2]	
n	225
Mean (SD)	6.2 (1.88)
Median (SE)	6.0 (0.13)
Q1, Q3	4.5, 7.5
Range (min, max)	2, 10
C-reactive protein (mg/dL)[3]	
n	225
Mean (SD)	1.1 (2.12)
Median (SE)	0.3 (0.14)
Q1, Q3	0.1, 1.0
Range (min, max)	0, 13
Normal	117 (52.0 %)
Above normal	108 (48.0 %)
Missing	0 (0.0 %)
Erythrocyte Sedimentation Rate (mm/h)[4]	
n	225
Mean (SD)	25.3 (24.76)
Median (SE)	17.0 (1.65)
Q1, Q3	10.0, 32.0
Range (min, max)	1, 170
CHAQ: Evalution of Overall well-being	
n	225
Mean (SD)	4.9 (2.53)
Median (SE)	5.0 (0.17)
Q1, Q3	3.0, 7.0

Table 13. Baseline Disease Characteristics - OLFAS

	Tofacitinib 5mg BID OL (N=225)
Range (min, max)	0, 10
CHAQ: Disability Index[5]	
n	225
Mean (SD)	1.0 (0.72)
Median (SE)	0.9 (0.05)
Q1, Q3	0.3, 1.5
Range (min, max)	0, 3
CHAQ: Discomfort Index	
n	225
Mean (SD)	5.3 (2.65)
Median (SE)	6.0 (0.18)
Q1, Q3	3.5, 7.0
Range (min, max)	0, 10
CHQ-PF50[6]: Physical Summary Score (PhS)	
n	223
Mean (SD)	30.6 (15.06)
Median (SE)	30.6 (1.01)
Q1, Q3	19.6, 42.6
Range (min, max)	-5, 59
CHQ-PF50[6]: Psychosocial Summary Score (PsS)	
n	223
Mean (SD)	47.5 (10.74)
Median (SE)	48.2 (0.72)
Q1, Q3	40.6, 56.6
Range (min, max)	16, 66
JADAS-27 CRP SCORE[7]	
n	225
Mean (SD)	21.5 (7.87)
Median (SE)	20.1 (0.52)
Q1, Q3	16.2, 26.6
Range (min, max)	6, 52
Number of Swollen Joints	
n	225
Mean (SD)	10.4 (7.92)
Median (SE)	8.0 (0.53)
Q1, Q3	5.0, 14.0
Range (min, max)	0, 48
Number of Pain/Tenderness Joints	

Table 13. Baseline Disease Characteristics - OLFAS

	Tofacitinib 5mg BID OL (N=225)
n	225
Mean (SD)	11.9 (9.88)
Median (SE)	9.0 (0.66)
Q1, Q3	6.0, 16.0
Range (min, max)	0, 59
Duration of Morning Stiffness (min)	
n	225
Mean (SD)	54.3 (71.00)
Median (SE)	30.0 (4.73)
Q1, Q3	15.0, 60.0
Range (min, max)	0, 600

Open-Label phase baseline data (Day 1) are presented.
[1] Active arthritis is defined as any joint with swelling, or in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity.
[2] Physician's Global: Higher Physicians' global evaluation of overall disease activity means more JIA disease activity.
[3] CRP normal is 0 - 0.287 mg/dL.
[4] ESR normal is 0 - 20 mm/h.
[5] Higher CHAQ scores mean more disability.
[6] CHQ-PF50 measures 14 domains, each ranging from 0 to 100, with a higher score indicating better physical function or mental health.
[7] Higher JADAS-27 CRP scores mean more JIA disease activity. The possible range of scores is 0 - 57.
PFIZER CONFIDENTIAL SDTM Creation: 05NOV2019 (08:44) Source Data: Tables 16.2.6.3.1 16.2.6.5 16.2.6.6.2 16.2.6.7.1 16.2.6.9.1.1 16.2.6.9.5 Output File: ./ra_cdisc/A3921104/base_trt_ol Date of Generation: 05NOV2019 (09:47)
Table 14.1.2.3.1 is for Pfizer internal use.

BD

Table 14. Demographic Characteristics - DBFAS

	Tofacitinib 5mg BID DB (N=88)			Placebo (N=85)		
	Male (N=22)	Female (N=66)	Total (N=88)	Male (N=21)	Female (N=64)	Total (N=85)
Age (years):						
2 - <6	5 (22.7)	6 (9.1)	11 (12.5)	2 (9.5)	7 (10.9)	9 (10.6)

Table 14. Demographic Characteristics - DBFAS

	Tofacitinib 5mg BID DB (N=88)			Placebo (N=85)		
	Male (N=22)	Female (N=66)	Total (N=88)	Male (N=21)	Female (N=64)	Total (N=85)
6 - <12	5 (22.7)	17 (25.8)	22 (25.0)	8 (38.1)	15 (23.4)	23 (27.1)
12 - <18	12 (54.5)	43 (65.2)	55 (62.5)	11 (52.4)	42 (65.6)	53 (62.4)
Mean (SD)	11.0 (5.13)	12.2 (4.04)	11.9 (4.34)	11.3 (3.30)	12.1 (4.29)	11.9 (4.06)
Median (SE)	12.0 (1.09)	13.0 (0.50)	13.0 (0.46)	12.0 (0.72)	13.0 (0.54)	13.0 (0.44)
Q1, Q3	7.0, 15.0	9.0, 15.0	9.0, 15.0	10.0, 14.0	8.5, 16.0	9.0, 15.0
Range (min, max)	2, 17	2, 17	2, 17	4, 16	2, 17	2, 17

Table 16. Baseline Disease Characteristics - DBFAS

	Tofacitinib 5mg BID DB (N=88)	Placebo (N=85)
Number of Joints with Active Arthritis[1] (Open-Label Phase)		
n	88	85
Mean (SD)	12.3 (7.07)	11.4 (7.75)
Median (SE)	10.0 (0.75)	9.0 (0.84)
Q1, Q3	7.0, 16.0	6.0, 14.0
Range (min, max)	3, 36	3, 49
Number of Joints with Active Arthritis[1] (Double-Blind Phase)		
n	88	85
Mean (SD)	1.4 (2.27)	1.6 (2.74)
Median (SE)	1.0 (0.24)	1.0 (0.30)
Q1, Q3	0.0, 2.0	0.0, 2.0
Range (min, max)	0, 14	0, 14
Number of Joints with Limitation of Motion (Open-Label Phase)		
n	88	85
Mean (SD)	8.6 (7.67)	6.4 (5.31)
Median (SE)	6.0 (0.82)	5.0 (0.58)
Q1, Q3	3.0, 12.0	3.0, 8.0
Range (min, max)	0, 36	0, 25
Number of Joints with Limitation of Motion (Double-Blind Phase)		
n	88	85
Mean (SD)	1.9 (4.51)	1.4 (2.33)
Median (SE)	0.0 (0.48)	0.0 (0.25)
Q1, Q3	0.0, 2.0	0.0, 2.0
Range (min, max)	0, 33	0, 12
Physician's Global Evaluation of Overall Disease Activity[2] (Open-Label Phase)		
n	88	85
Mean (SD)	6.1 (1.90)	6.0 (1.88)
Median (SE)	6.0 (0.20)	6.0 (0.20)
Q1, Q3	4.5, 7.5	4.5, 7.5
Range (min, max)	2, 9	3, 10
Physician's Global Evaluation of Overall Disease Activity[2] (Double-Blind Phase)		
n	88	85
Mean (SD)	1.6 (1.64)	1.4 (1.46)
Median (SE)	1.0 (0.17)	1.0 (0.16)
Q1, Q3	0.5, 3.0	0.0, 2.5
Range (min, max)	0, 7	0, 6
C-reactive protein (mg/dL)[3] (Open-Label Phase)		

Table 16. Baseline Disease Characteristics - DBFAS

	Tofacitinib 5mg BID DB (N=88)	Placebo (N=85)
n	88	85
Mean (SD)	1.3 (2.42)	1.0 (1.83)
Median (SE)	0.3 (0.26)	0.2 (0.20)
Q1, Q3	0.1, 1.3	0.1, 0.9
Range (min, max)	0, 13	0, 11
C-reactive protein (mg/dL)[3] (Double-Blind Phase)		
n	88	84
Mean (SD)	0.4 (1.09)	0.5 (1.22)
Median (SE)	0.1 (0.12)	0.1 (0.13)
Q1, Q3	0.0, 0.3	0.0, 0.3
Range (min, max)	0, 7	0, 9
Erythrocyte Sedimentation Rate (mm/h)[4] (Open-Label Phase)		
n	88	85
Mean (SD)	24.8 (22.47)	26.4 (26.32)
Median (SE)	19.0 (2.40)	17.0 (2.86)
Q1, Q3	10.0, 31.5	9.0, 35.0
Range (min, max)	1, 120	1, 170
Erythrocyte Sedimentation Rate (mm/h)[4] (Double-Blind Phase)		
n	88	85
Mean (SD)	13.4 (13.42)	13.8 (11.94)
Median (SE)	9.5 (1.43)	9.0 (1.29)
Q1, Q3	5.0, 16.0	6.0, 17.0
Range (min, max)	0, 73	0, 53
CHAQ: Evalution of Overall well-being (Open-Label Phase)		
n	88	85
Mean (SD)	4.7 (2.49)	4.8 (2.57)
Median (SE)	5.0 (0.27)	5.0 (0.28)
Q1, Q3	2.5, 7.0	3.0, 7.0
Range (min, max)	0, 10	0, 10
CHAQ: Evalution of Overall well-being (Double-Blind Phase)		
n	88	85
Mean (SD)	2.0 (1.89)	1.9 (1.91)
Median (SE)	1.5 (0.20)	1.5 (0.21)
Q1, Q3	0.5, 3.0	0.5, 3.0
Range (min, max)	0, 7	0, 8
CHAQ: Disability Index[5] (Open-Label Phase)		
n	88	85
Mean (SD)	0.9 (0.69)	0.9 (0.74)

Table 16. Baseline Disease Characteristics - DBFAS

	Tofacitinib 5mg BID DB (N=88)	Placebo (N=85)
Median (SE)	0.8 (0.07)	0.9 (0.08)
Q1, Q3	0.4, 1.4	0.3, 1.5
Range (min, max)	0, 3	0, 3
CHAQ: Disability Index[5] (Double-Blind Phase)		
n	88	85
Mean (SD)	0.4 (0.51)	0.4 (0.58)
Median (SE)	0.3 (0.05)	0.3 (0.06)
Q1, Q3	0.0, 0.8	0.0, 0.8
Range (min, max)	0, 3	0, 2
CHAQ: Discomfort Index (Double-Blind Phase)		
n	88	85
Mean (SD)	1.9 (1.98)	2.0 (1.91)
Median (SE)	1.5 (0.21)	1.5 (0.21)
Q1, Q3	0.5, 3.0	0.5, 3.5
Range (min, max)	0, 8	0, 8
CHQ-PF50[6]: Physical Summary Score (PhS) (Double-Blind Phase)		
n	87	82
Mean (SD)	45.0 (9.95)	44.3 (10.98)
Median (SE)	48.0 (1.07)	47.6 (1.21)
Q1, Q3	38.9, 52.4	39.4, 52.2
Range (min, max)	8, 57	8, 58
CHQ-PF50[6]: Psychosocial Summary Score (PsS) (Double-Blind Phase)		
n	87	82
Mean (SD)	52.3 (8.60)	51.5 (8.82)
Median (SE)	53.9 (0.92)	52.6 (0.97)
Q1, Q3	46.4, 59.0	46.3, 59.3
Range (min, max)	29, 65	32, 65
JADAS-27 CRP Score[7] (Double-Blind Phase)		
n	88	84
Mean (SD)	5.7 (4.21)	5.5 (4.52)
Median (SE)	4.2 (0.45)	4.7 (0.49)
Q1, Q3	2.2, 8.4	1.7, 8.4
Range (min, max)	1, 17	0, 23
Number of Swollen Joints (Double-Blind Phase)		
n	88	85
Mean (SD)	1.2 (2.25)	1.4 (2.70)
Median (SE)	0.0 (0.24)	0.0 (0.29)
Q1, Q3	0.0, 1.0	0.0, 1.0

Table 16. Baseline Disease Characteristics - DBFAS

	Tofacitinib 5mg BID DB (N=88)	Placebo (N=85)
Range (min, max)	0, 14	0, 14
Number of Pain/Tenderness Joints (Double-Blind Phase)		
n	88	85
Mean (SD)	2.3 (6.54)	1.8 (3.22)
Median (SE)	0.0 (0.70)	0.0 (0.35)
Q1, Q3	0.0, 2.0	0.0, 3.0
Range (min, max)	0, 56	0, 21
Duration of Morning Stiffness (min) (Double-Blind Phase)		
n	88	85
Mean (SD)	6.3 (15.38)	9.8 (30.46)
Median (SE)	0.0 (1.64)	0.0 (3.30)
Q1, Q3	0.0, 10.0	0.0, 5.0
Range (min, max)	0, 120	0, 240

Open-Label phase baseline is based on Day 1, and Double-Blind phase baseline is based on Week 18.
[1] Active arthritis is defined as any joint with swelling, or in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity.
[2] Physician's Global: Higher Physicians' global evaluation of overall disease activity means more JIA disease activity.
[3] CRP normal is 0 - 0.287 mg/dL.
[4] ESR normal is 0 - 20 mm/h.
[5] Higher CHAQ scores mean more disability.
[6] CHQ-PF50 measures 14 domains, each ranging from 0 to 100, with a higher score indicating better physical function or mental health.
[7] Higher JADAS-27 CRP scores mean more JIA disease activity. The possible range of scores is 0 - 57.
PFIZER CONFIDENTIAL SDTM Creation: 05NOV2019 (08:44) Source Data: Tables 16.2.6.3.2 16.2.6.5 16.2.6.6.3 16.2.6.7.2 16.2.6.9.5 16.2.6.9.1.2 Output File: ./ra cdisc/A3921104/base trt db Date of Generation: 05NOV2019 (09:43)
Table 14.1.2.3.2 is for Pfizer internal use.

Prior DMARD, corticosteroid, and immunosuppressant use. Overall, 216 (96.0%) of the subjects had prior DMARD, corticosteroid, or immunosuppressant use. bDMARDs and csDMARDs were used by 85 (37.8%) and 206 (91.6%) of subjects, respectively, prior to the open-label run-in phase. The most frequently used bDMARD was etanercept (52 [23.1%] subjects). MTX was the most frequently used csDMARD (204 [90.7%] subjects), with folate being used by 164 (72.9%) of subjects. Corticosteroids were used by 111 (49.3%) subjects, with the most common being prednisone (61 [27.1%]

Concomitant DMARD, corticosteroid, and immunosuppressant use.Overall, 171 (76.0%) of subjects used DMARD, corticosteroid, and/or immunosuppressant medications. csDMARDs were used concomitantly by 149 (66.2%) subjects. MTX and folate were taken concomitantly by
148 (65.8%) subjects and 145 (64.4%), respectively. Subjects. Concomitant use of bDMARDs was prohibited during the study. Corticosteroids were used concomitantly by 75 (33.3 %) subjects. A total of 69 (78.4%) and 63 (74.1%) subjects in the tofacitinib and placebo groups, respectively, that used DMARD, corticosteroid, and/or immunosuppressant medications. csDMARDs (MTX) were used concomitantly by
58 (65.9%) subjects in the tofacitinib group and 58 (68.2%) subjects in the placebo group. Corticosteroids were used concomitantly by 35 (39.8%) and 23 (27.1%) subjects in the tofacitinib 5 mg BID and placebo groups, respectively.

Efficacy results

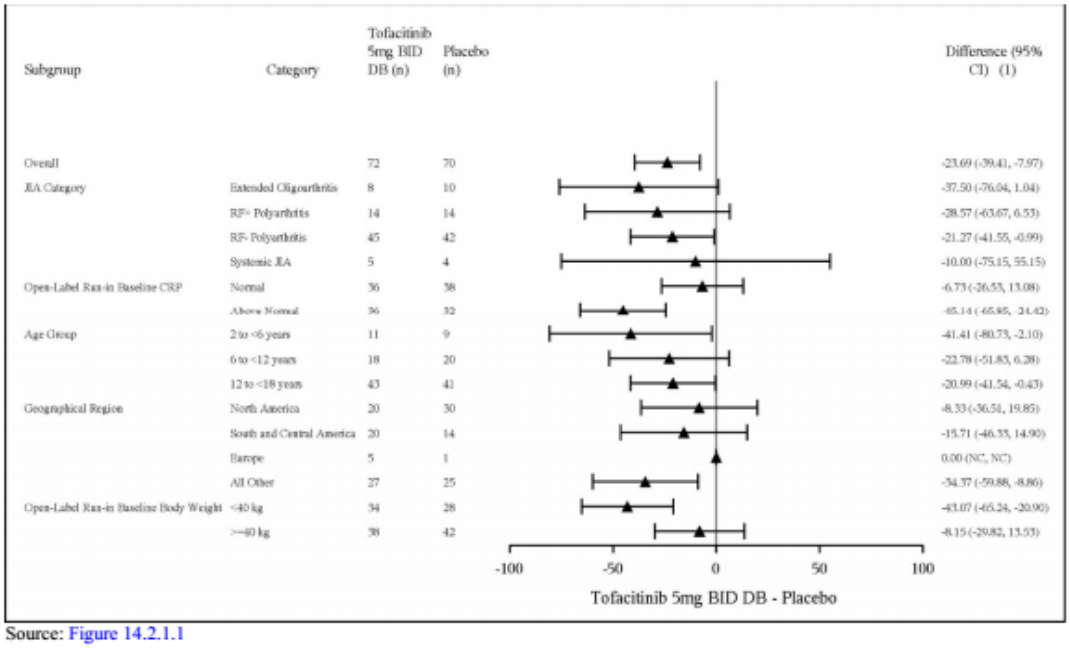
Primary endpoint

Table 17. Occurrence of Disease Flare at Week 44 of the Study - DBJAS

Visit	Treatment	N	Presence n (%)	SE (1)	Tofacitinib - Placebo (1) Diff	SE	95% CI	P-value
Week 44	Tofacitinib 5mg BID DB	72	21 (29.17)	5.36	-23.69	8.02	(-39.41, -7.97)	0.0031
	Placebo	70	37 (52.86)	5.97				

The Double-Blind phase is the study period on and after randomization day.
(1) Normal approximation.
n represents the number of subjects with a flare occurrence at any time from Day 1 to Day 196 of the Double-Blind phase. Once a subject flares or discontinues for
any reason except while in clinical remission (24 weeks of inactive disease) the subject will be counted in the flare category at the discontinuation visit
and at all the subsequent visits in the Double-Blind phase.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (05:56) Source Data: Table 16.2.6.1.1 Output File: ./ra_cdisc/A3921104/binom_flr_dbjas_44 Date of Generation: 09NOV2019 (12:56)
Table 14.2.1.1 is for Pfizer internal use.

Figure 3. Forest Plot for Occurrence of Disease Flare at Week 44 of the Study for Overall Population and by Subgroups - DBJAS



Source: Figure 14.2.1.1
(1) Normal approximation.
The DB phase is the study period on and after randomization day.
Europe includes: Poland, Belgium, Great Britain, and Spain; All Other includes: Ukraine, Turkey, Russia, Australia, and Israel.
LOCF was used for imputing intermittent missing components and assessments. Subjects discontinued study treatment for any reason, except while in clinical remission, were counted as flares as of their discontinuation visit through Week 44. For subjects who discontinued study treatment and met clinical remission at the time of discontinuation, they were considered as non-disease flare from that visit onward through Week 44.
95% CI was not calculated when the flare rates were either 0% in both groups or 100% in both groups.

Sensitivity analyses are consistent with results from the primary analysis.

Key Secondary Endpoint Results (Type I Error Controlled)

-JIA ACR 50, 30, and 70 Responses at Week 44

Table 18. JIA ACR Responses 50/30/70 at Week 44 of the Study - DBJAS

ACR Response	Visit	Treatment	N	Response n (%)	SE (1)	Tofacitinib - Placebo (1) Diff	SE	95% CI	P-value
ACR 50	Week 44	Tofacitinib 5mg BID DB	72	48 (66.67)	5.56	19.52	8.15	(3.55, 35.50)	0.0166
		Placebo	70	33 (47.14)	5.97				
ACR 30	Week 44	Tofacitinib 5mg BID DB	72	51 (70.83)	5.36	23.69	8.02	(7.97, 39.41)	0.0031
		Placebo	70	33 (47.14)	5.97				
ACR 70	Week 44	Tofacitinib 5mg BID DB	72	39 (54.17)	5.87	17.02	8.24	(0.88, 33.17)	0.0387
		Placebo	70	26 (37.14)	5.78				

The Double-Blind phase is the study period on and after randomization day.
(1) Normal approximation.
Response is calculated relative to the Open-Label baseline.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (05:56) Source Data: Table 16.2.6.2.2 Output File: /ra_cdisc/A3921104/acr_db_44 Date of Generation: 09NOV2019 (10:47)
Table 14.2.2.1 is for Pfizer internal use.

Forest plots: In all the subgroups, a numerically greater response was seen in the tofacitinib 5 mg BID group compared to the placebo group, with the exception of ACR 70 response in geographic regions of Europe and South and Central America. ACR 50 and 30 responses were the same between treatment groups for subjects in Europe.

-Change From Double-Blind Baseline in CHAQ Disability Index at Week 44

Table 19. Mean Change from Double-Blind Baseline in Childhood Health Assessment Questionnaire (CHAQ) - Disability Index (MMRM) at Week 44 of the Study - DBJAS

Visit	Treatment	n	LSMean	SEM	95% CI	Tofacitinib - Placebo Diff	SE of diff	95% Confidence Interval Lower	Upper	P-value
Week 44	Tofacitinib 5mg BID DB	49	-0.09	0.04	(-0.17, -0.01)	-0.12	0.05	-0.22	-0.01	0.0292
	Placebo	33	0.03	0.04	(-0.06, 0.12)					

The Double-Blind phase is the study period on and after randomization day. Double-Blind baseline of Week 18 was used.
Abbreviations: MMRM=Mixed Model for Repeated Measures; LS Mean=Least Squares Mean; SEM=Standard Error of LS Mean;
Diff=Difference; SE of Diff=Standard Error of the Difference.
n=number of subjects evaluable at Week 44.
The analysis was based on a MMRM with fixed effects of treatment, visit, JIA category, open-label baseline CRP, treatment-by-visit interaction, and the Double-Blind baseline value;
The Kenward-Roger approximation was used to estimate denominator degrees of freedom.
Unstructured Covariance matrix was used.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (06:56) Source Data: Table 16.2.6.9.1.2 Output File: /ra_cdisc/A3921104/chaq_disabl_mmrm Date of Generation: 18JUN2019 (13:49)
Table 14.2.2.2 is for Pfizer internal use.

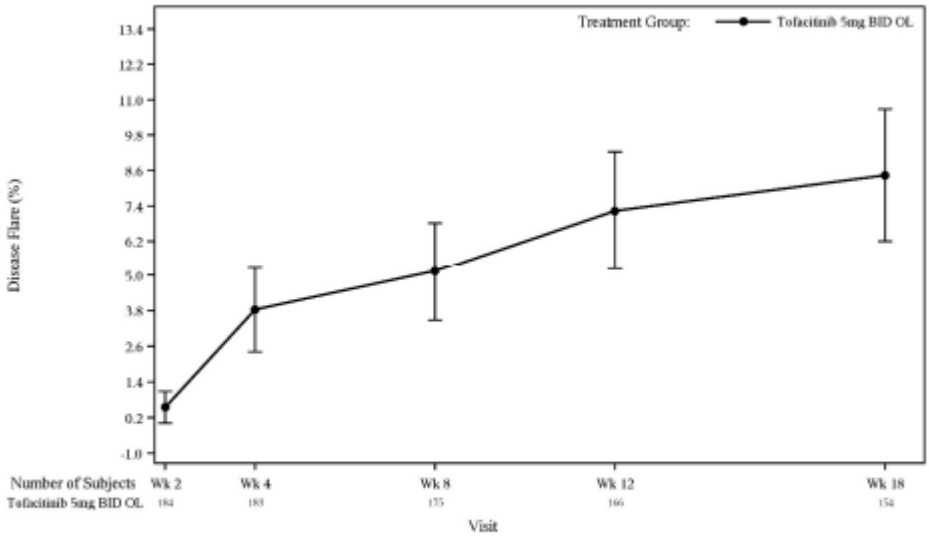
A forest plot for the overall population and by subgroups shows a negative value for the difference in the LSmean changes from baseline(tofacitinib-placebo) had, thus favoring tofacitinib.

Secondary Endpoints Results

-Occurrence of Disease Flare According to PRCSG/PRINTO Disease Flare criteria

Open-Label

Figure 8. Occurrence of Disease Flare (%) (±SE) in Open-Label Run-In Phase – OLJAS



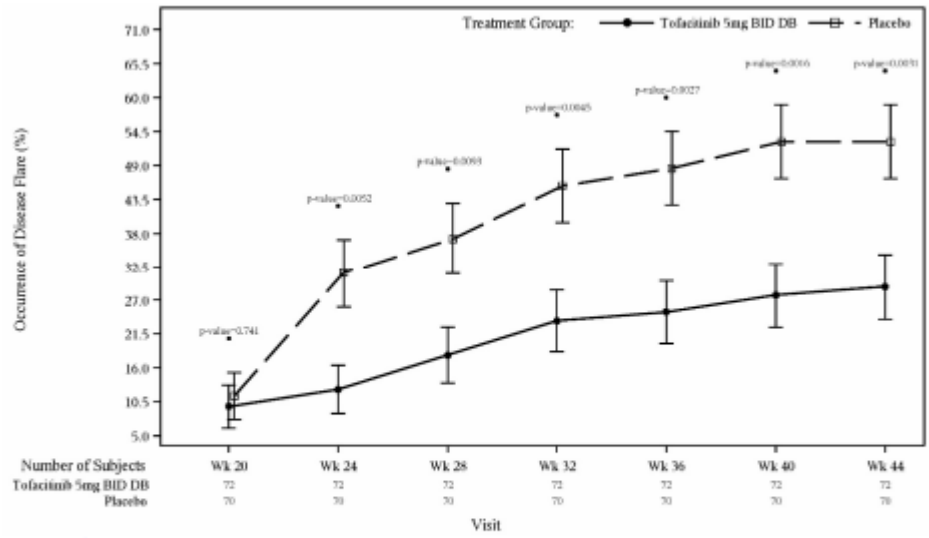
Source: Figure 14.2.11.1

The OL run-in phase is the study period before randomization day (Week 18). If a subject did not meet randomization criteria and was discontinued, the study period was considered the open-label run-in phase. LOCF was used for imputing intermittent missing components and assessments. Discontinuations for any reasons were treated as flares at the visit where they occurred. Figure presents n(%) of subjects with flares at each OL visit.

There were 13 (8.44%) subjects that experienced disease flare at Week 18.

DB

Figure 9. Occurrence of Disease Flare (%) (±SE) in Double-Blind Phase - DBJAS



Source: Figure 14.2.3.1

The DB phase is the study period on and after randomization day. LOCF was used for imputing intermittent missing components and assessments. Subjects discontinued study treatment for any reason, except while in clinical remission, were counted as flares as of their discontinuation visit through Week 44. For subjects who discontinued study treatment and met clinical remission at the time of discontinuation, they were considered as non-disease flare from that visit onward through Week 44.

Time to flare

The Kaplan-Meier median time to event estimate was 155 days for the placebo group and could not be estimated for the tofacitinib 5 mg BID group because there were too few flare events and the probability of flare free was 70.8% (>50%) in this group.

JIA ACR 50, 30, 70, 90, and 100 Responses

ACR50: During the double-blind phase, a significant difference in the number of subjects achieving JIA ACR 50 response was first observed between subjects continuing tofacitinib 5 mg BID and subjects randomized to placebo at Week 24 (p=0.0034). Significantly more subjects in the tofacitinib 5 mg BID group achieved a JIA ACR 50 response compared to the placebo group at each subsequent time point through Week 44 (p=0.0166).

ACR30: A significant difference in the number of subjects achieving JIA ACR 30 response was first observed in the double-blind phase between subjects continuing tofacitinib
5 mg BID and subjects randomized to placebo at Week 24 (p=0.0108). Compared to the placebo group, significantly more subjects in the tofacitinib 5 mg BID group achieved a JIA ACR 30 response at each subsequent time point through Week 44 (p=0.0031).

ACR70: A significant difference in the number of subjects achieving JIA ACR 70 response was first observed in the double-blind phase between subjects continuing tofacitinib 5 mg BID and subjects randomized to placebo at Week 32 (p=0.0258). Significantly more subjects in the tofacitinib 5 mg BID group achieved a JIA ACR 70 response compared to the placebo group at Weeks 36, 40, and 44 (p=0.0149, p=0.0149, and p=0.0387, respectively).

ACR90: significantly more subjects in the tofacitinib 5 mg BID group achieved a JIA ACR 90 response

compared to the placebo group at Week 32 (p=0.0356) and Week 36 (p=0.0115). A numerically higher proportion of subjects in the tofacitinib 5 mg BID group achieved a JIA ACR 90 response compared to the placebo at Weeks 20, 24, 28,
40, and 44.
ACR100: There was a significantly higher proportion of subjects in the placebo group achieving a JIA ACR 100 response at the start of the double-blind phase (Week 18) compared to subjects in the tofacitinib 5 mg BID group. At each subsequent time point in the double-blind phase, a numerically higher proportion of subjects in the tofacitinib 5 mg BID group achieved a JIA ACR 100 response compared to the placebo.

Change from Baseline in JADAS-27 CRP, JADAS-27 ESR, and Achieving JADAS Minimum Disease Activity, and Inactive Disease

Open-Label
Mean change from baseline in JADAS-27 CRP score decreased from baseline to Week 18 (from -6.35 at Week 2 to -15.80 at Week 18).
A similar trend was observed for mean change from baseline in JADAS-27 ESR score (mean changes, -6.38 at Week 2 to -15.94 at Week 18).

The proportion of subjects with JADAS minimum disease activity calculated from the JADAS-27 CRP score increased from baseline at Week 2 and continued through Week 18 (4 [2.19%] to 68 [44.16%] subjects).

A similar trend was observed for JADAS minimum disease activity calculated from the JADAS-27 ESR score (7 [3.83%] at Week 2 to 72 [46.75%] subjects at Week 18).

Inactive disease activity calculated from the JADAS-27 CRP score was first achieved at Week 8 by 5 (2.84%) of the subjects and the proportion of
subjects with inactive disease increased to 12 (7.79%) subjects at Week 18.

JADAS inactive disease activity calculated from the JADAS-27 ESR score was observed in 2 (1.09%) subjects at Week 2 and increased to 36 (23.38%) subjects at Week 18.

Double-Blind Phase
-The LS mean change from the double-blind baseline in JADAS-27 CRP score was significantly lower from Week 20 (p-value=0.0088) through Week 44 (p- value=0.0027) in the tofacitinib 5 mg BID group compared to the placebo group.
-The LS mean change from baseline in JADAS-27 ESR score was also significantly lower in the tofacitinib 5 mg BID group compared to the placebo group from Week 20 (p=0.0172) to Week 44 (p=0.0018).

-The proportion of subjects with JADAS minimum disease activity calculated from the JADAS-27 CRP score was numerically higher from Week 18 through Week 44 in the tofacitinib 5 mg BID group compared to the placebo group.
-A numerically larger proportion of subjects in the tofacitinib 5 mg BID group achieved JADAS minimum disease activity calculated from the JADAS-27 ESR score compared to the placebo group at all time points from Week 18 through Week 44. Statistical significance between the 2 groups was achieved at Week 44 (p=0.0228).

-The proportion of subjects with JADAS inactive disease activity calculated from the JADAS-27 CRP score was statistically higher at Week 40 (p=0.0464) and numerically higher at Weeks 20, 24, 28, 32, 36, and Week 44 in the tofacitinib 5 mg BID group compared to the placebo group.
-A similar numerical trend was observed for JADAS inactive disease activity calculated from the JADAS-27 ESR score in the tofacitinib 5 mg BID group compared to the placebo group.

JIA ACR Inactive Disease at Each Scheduled Visit and Clinical Remission at Week 44
Open-Label
During the open-label run-in phase, there were 2 (1.09%) subjects with JIA ACR inactive disease at Week 4, which increased to 26 (16.88%) subjects at Week 18.

Double-Blind Phase
-The proportion of subjects with JIA ACR inactive disease increased from Week 18 to Week 44 in the tofacitinib 5 mg BID group and decreased in the placebo group during the double-blind phase. There were 3 (4.17%) subjects in the tofacitinib 5 mg BID group and 3 (4.29%) subjects in the placebo group with JIA ACR clinical remission (24 weeks of inactive disease, which may have begun during the open-label phase) by Week 44.

Change from Baseline in Each JIA ACR Core Set Variable
Open-Label
The mean change from baseline in the number of joints with active arthritis and the number of joints with limited range of motion decreased throughout the open-label run-in phase.

Table 14.2.16.1.2.1
CP-690,550 Protocol A3921104
Descriptive Statistics of Number of Joints with Active Arthritis in Open-Label Run-in Phase - OLPsA

Visit	Treatment	n	Mean	SD	SE	Min	Q1	Median	Q3	Max
Baseline	Tofacitinib 5mg BID OL	20	10.50	6.45	1.44	3.00	4.50	11.00	15.50	24.00
Week 2	Tofacitinib 5mg BID OL	20	6.45	4.95	1.11	1.00	3.00	5.00	9.00	19.00
Week 4	Tofacitinib 5mg BID OL	20	2.75	3.68	0.82	0.00	0.00	2.00	4.00	16.00
Week 8	Tofacitinib 5mg BID OL	19	2.95	3.63	0.83	0.00	0.00	2.00	4.00	14.00
Week 12	Tofacitinib 5mg BID OL	18	2.33	3.79	0.89	0.00	0.00	1.00	2.00	14.00
Week 18	Tofacitinib 5mg BID OL	16	1.56	3.01	0.75	0.00	0.00	0.50	2.00	12.00

Table 14.2.16.2.2.1
CP-690,550 Protocol A3921104
Descriptive Statistics of Number of Joints with Limited Range of Motion in Open-Label Run-in Phase - OLPsA

Visit	Treatment	n	Mean	SD	SE	Min	Q1	Median	Q3	Max
Baseline	Tofacitinib 5mg BID OL	20	6.65	6.01	1.34	0.00	3.00	5.00	8.00	21.00
Week 2	Tofacitinib 5mg BID OL	20	4.50	5.87	1.31	0.00	1.00	3.00	5.00	24.00
Week 4	Tofacitinib 5mg BID OL	20	5.05	12.46	2.79	0.00	0.00	1.00	3.00	55.00
Week 8	Tofacitinib 5mg BID OL	19	4.84	12.54	2.88	0.00	0.00	1.00	3.00	54.00
Week 12	Tofacitinib 5mg BID OL	18	2.56	4.91	1.16	0.00	0.00	0.50	2.00	17.00
Week 18	Tofacitinib 5mg BID OL	16	3.31	8.46	2.11	0.00	0.00	0.00	1.50	33.00

-JIA disease activity also decreased over the course of the open-label run-in phase as measured by the change from baseline in **physician global evaluation of disease activity**, CHAQ **Parental Evaluation of Overall Well-being, and CHAQ Disability Index.**
The mean (SE) change from baseline activity at Week 2 and Week 18 was -1.81 (0.11) and -4.54 (0.15), respectively, for physician global evaluation of disease activity; -0.94 (0.14) and -2.68 (0.19), respectively, for CHAQ Parental Evaluation of Overall Well-being (Table 14.2.16.5.1.2); and -0.15 (0.03) and -0.49 (0.05), respectively, for CHAQ - Disability Index.

DB

-Subjects in the tofacitinib 5 mg BID group had a significantly greater decrease in the **number of active joints** from the double-blind baseline compared to subjects in the placebo group at Week 36 (p-value=0.0041), Week 40 (p-value=0.0085), and Week 44 (p-value=0.0384).

-Subjects in the tofacitinib 5 mg BID group also had a significantly lower mean change from the double-blind baseline in the **number of joints with limited range of motion** compared to subjects in the placebo group at Week 36 (p-value=0.0251) and Week 40 (p-value=0.0331).

-The mean change from the double-blind baseline in **physician global evaluation of disease activity** was significantly lower in the tofacitinib 5 mg BID group compared to the placebo group at each time point in the double-blind phase, indicating that JIA disease activity was lower in the tofacitinib 5 mg BID group than the placebo group.
-The mean change from the double-blind baseline in **CHAQ Parental Evaluation of Overall Well-being** was significantly lower in the tofacitinib 5 mg BID group compared to the placebo group at all weeks in the double-blind phase except for Week 36 and Week 40.

Change from Baseline in CHQ Responses

OL

Change from baseline in **CHQ responses**: i) the mean (SD) change from baseline in Physical Summary Score was 8.12 (11.18) at Week 4 and increased to 13.36 (12.57) at Week 18. For Psychosocial Summary Score, the mean (SD) change from baseline was 2.46 (8.13) at Week 4 and increased to 4.20 (8.41) at Week 18.

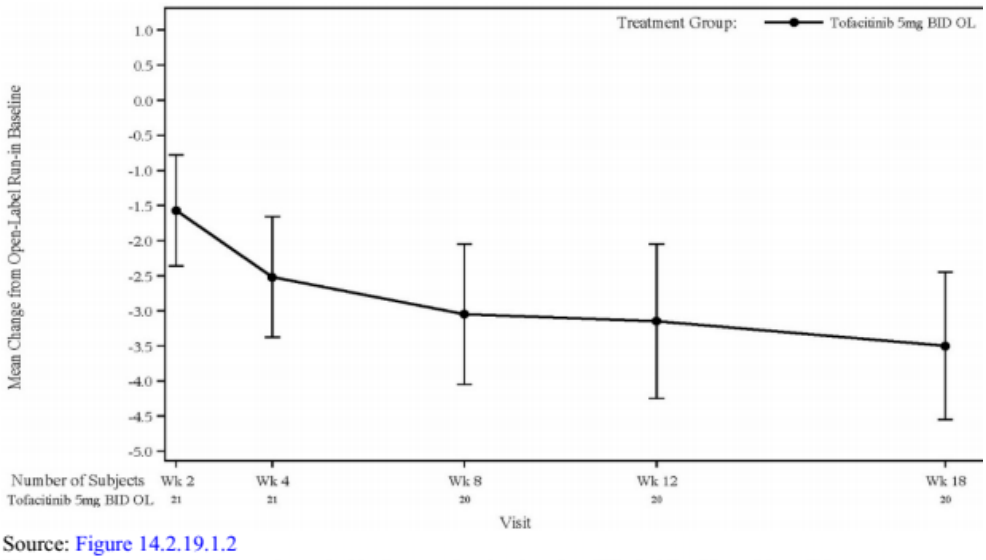
DB

Change from the double-blind baseline in **CHQ responses**: i) the LS mean change from the double-blind baseline was significantly lower for the Family Activities Subscale Standardized Score in the tofacitinib 5 mg BID group compared to the placebo group (LS mean [SE] difference of -8.60 [3.23], 95% CI [-15.03, -2.17], p-value=0.0095). At Week 44, the tofacitinib difference in the LS mean (SE) change from the double-blind baseline from placebo (tofacitinib-placebo) was 3.48 (2.03) for the Physical Summary Score and -0.75 (1.67) for the Psychosocial Summary Score (p-values=0.0902 and 0.6539, respectively).

Subjects with ERA: Change From Baseline in the Tender Entheseal Assessment, Modified Schober's Test, Overall Back Pain, and Nocturnal Back Pain
Responses.

Open-Label
Tender entheseal assessments improved from Week 2 to Week 18.

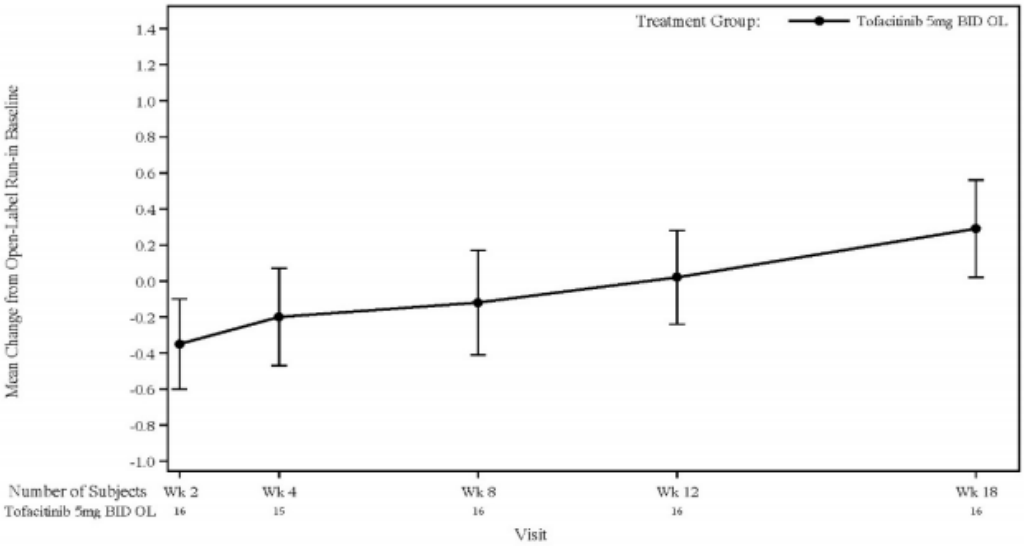
Figure 40. Mean Change (±SE) From Open-Label Run-In Baseline in the Tender Entheseal Assessment in the Open-Label Run-In Phase - OLERA



Source: Figure 14.2.19.1.2
The OL run-in phase is the study period before randomization day (Week 18). If a subject did not meet randomization criteria and was discontinued, the study period was considered open-label run-in phase. OL run-in phase baseline of Day 1 was used. Tender entheseal assessment: high scores are worse. Missing data were not imputed.

Modified Schober's test scores improved from Week 2 to Week 18, indicating an improvement in the ability of subjects to flex their lower back.

Figure 41. Mean Change (±SE) From Open-Label Run-In Baseline in the Modified Schober's Test (cm) in the Open-Label Run-In Phase – OLERA

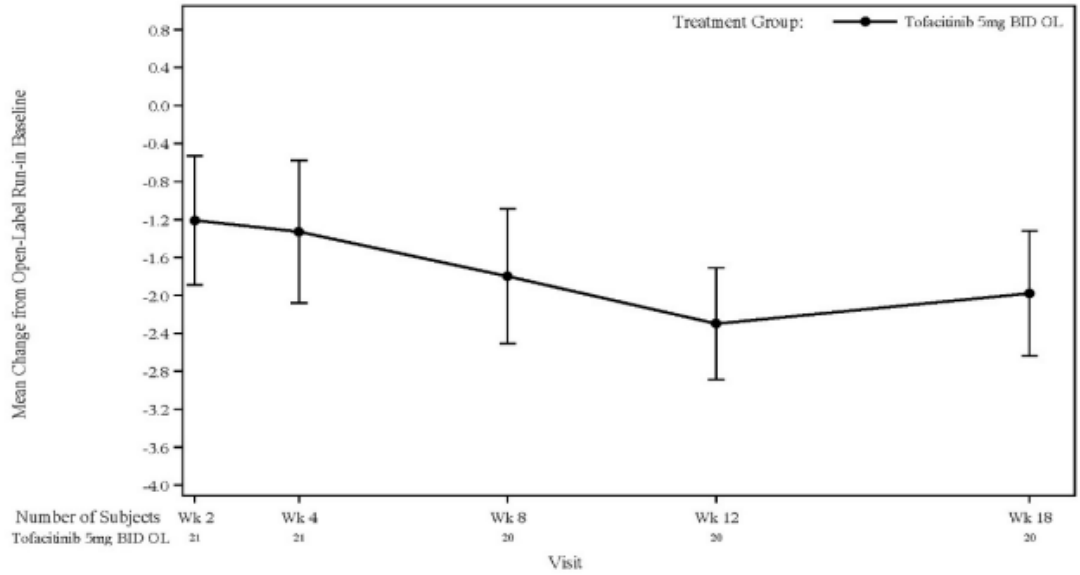


Source: Figure 14.2.20.1.2

The OL run-in phase is the study period before randomization day (Week 18). If a subject did not meet randomization criteria and was discontinued, the study period was considered open-label run-in phase. OL run-in phase baseline of Day 1 was used. Modified Schober's test: higher scores are better. Missing data were not imputed.

The mean change from baseline in both back pain at night and average back pain decreased from baseline over the course of the open-label run-in phase.

Figure 42. Mean Change (±SE) From Open-Label Run-In Baseline in the Overall Back Pain and Nocturnal Back Pain in the Open-Label Run-In Phase - Back Pain at Night - OLERA



Source: Figure 14.2.21.1.2

The OL run-in phase is the study period before randomization day (Week 18). If a subject did not meet randomization criteria and was discontinued, the study period was considered open-label run-in phase. OL run-in phase baseline of Day 1 was used. Overall back pain: higher scores indicate more pain. Missing data were not imputed.

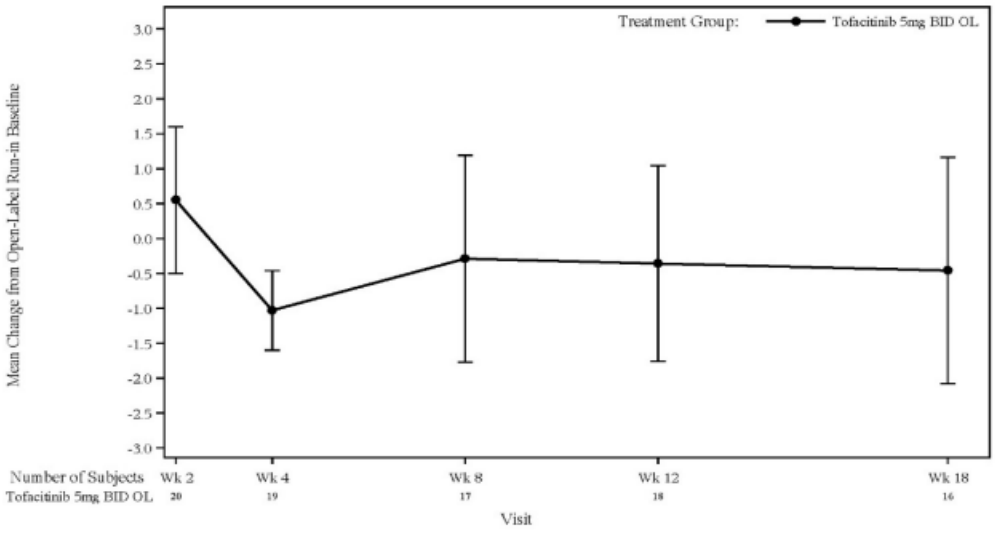
Double-Blind Phase

- **Tender Entheseal Assessment, Modified Schober's Test**: subjects in-both groups demonstrated similar changes from the double-blind baseline, although no conclusions can be drawn because of the small sample size.
-There was a numerical trend for subjects in the tofacitinib 5 mg BID group to have less **back pain at night** compared to subjects in the placebo group, although no conclusions can be drawn because of the small sample size. The mean change from baseline in average back pain was similar between treatment groups.

-**Subjects with PsA:** Change from Baseline in the BSA Affected with Psoriasis and PGA of Psoriasis Assessments in the Open-Label Run-In and Double-Blind Phase.

The mean (SE) change from baseline in **BSA** affected with psoriasis at Week 18 of the open-label run-in phase was -0.46 (1.62).

Figure 48. Mean Change (±SE) From Open-Label Run-In Baseline in the Body Surface Area (BSA) (%) affected with Psoriasis in the Open-Label Run-In Phase - OLPsA

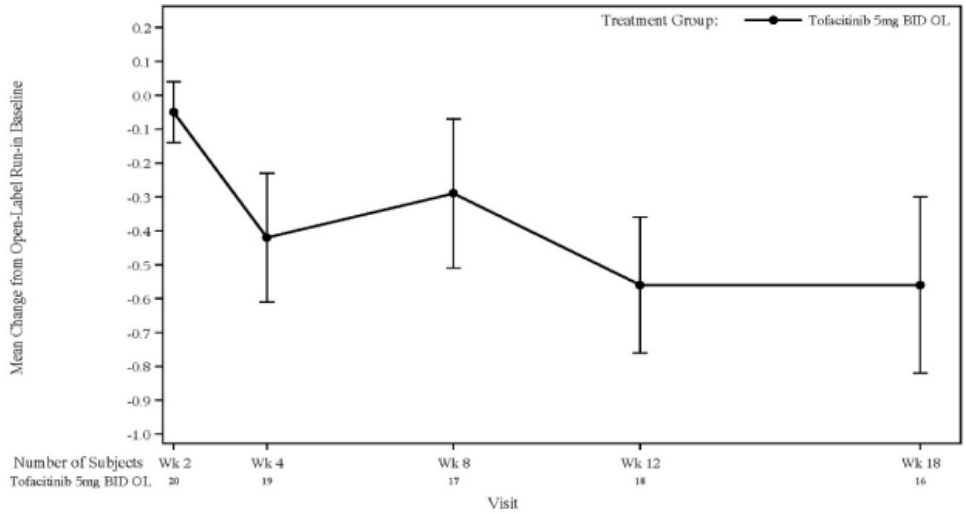


Source: Figure 14.2.22.1.2
The OL run-in phase is the study period before randomization day (Week 18). If a subject did not meet randomization criteria and was discontinued, the study period was considered open-label run-in phase. OL run-in phase baseline of Day 1 was used. Missing data were not imputed.

- **PGA of psoriasis** the mean (SE) change from baseline in the PGA of psoriasis assessments at Week 18 was -0.56

(0.26).

Figure 49. Mean Change (±SE) From Open-Label Run-In Baseline in the Physician's Global Assessment (PGA) of Psoriasis Assessments in the Open-Label Run-In Phase – OLPsA



Source: Figure 14.2.23.1.2

The OL run-in phase is the study period before randomization day (Week 18). If a subject did not meet randomization criteria and was discontinued, the study period was considered open-label run-in phase. OL run-in phase baseline of Day 1 was used. Higher physicians' global evaluation of overall disease activity means more JIA disease activity. Missing data were not imputed.

DB

-**For both PGA and BSA assessments**: subjects treated with tofacitinib 5 mg BID showed a numerically greater decrease in the percentage of BSA affected with psoriasis compared to subjects treated with placebo, although no conclusions can be drawn because of the small sample size.

Taste Acceptability of Tofacitinib Oral Solution

Most subjects either liked the taste "very much" (34 [40.00%] subjects) or "a little" (32 [37.65%] subjects). There were few subjects who disliked the taste "a little" (8 [9.41%] subjects) or "very much" (4 [4.71%] subjects).

Exploratory or Other Endpoints Results

Exploratory or pooled analyses characterizing the effects of tofacitinib utilizing the biobanked exploratory genomic and biomarker samples from this study will be presented in a separate report if performed.

Safety results

Extent of Exposure

Table 24. Duration of Treatment (Actual Period Dosing Day) in Open-Label Run-in Phase - OLFAS

	Tofacitinib 5mg BID OL (N=225)
Duration of Treatment (Days) [1]	
n	225
Mean	115.16
Median	126.00
Std Dev	27.56
Range(min,max)	(4.00, 153.00)
Category (Days) [1]	
<28	5 (2.2)
28-56	14 (6.2)
57-84	12 (5.3)
85-112	6 (2.7)
113-140	186 (82.7)
141-168	2 (0.9)
>168	0

[1] The Total Number of Dosing Days on which study drug was actually administered
The Open-Label Run-in phase is the study period before randomization day (Week 18).
If a subject does not meet randomization criteria and is discontinued, the study period will all be considered Open-Label Run-in phase.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (09:07) Source Data: Table 16.2.5.1.1 Output File: ./ra cdisc/A3921104/adex s003 Date of Generation: 23JUN2019 (00:23)
Table 14.4.1.1 is for Pfizer internal use.

Table 25. Duration of Treatment (Actual Period Dosing Day) in Double-Blind Phase - DBSAS

	Tofacitinib 5mg BID DB (N=88)	Placebo (N=85)
Duration of Treatment (Days) [1]		
n	88	85
Mean	143.68	114.36
Median	180.00	129.00
Std Dev	61.60	68.53
Range(min,max)	(14.00, 202.00)	(8.00, 193.00)
Category (Days) [1]		
<28	8 (9.1)	11 (12.9)
28-56	7 (8.0)	17 (20.0)
57-84	4 (4.5)	7 (8.2)
85-112	4 (4.5)	6 (7.1)
113-140	4 (4.5)	2 (2.4)
141-168	2 (2.3)	4 (4.7)
>168	59 (67.0)	38 (44.7)

[1] The Total Number of Dosing Days on which study drug was actually administered
The Double-Blind phase is the study period on and after randomization day.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (09:07) Source Data: Table 16.2.5.1.1 Output File: ./ra cdisc/A3921104/adex s003 db Date of Generation: 23JUN2019 (00:26)
Table 14.4.1.2 is for Pfizer internal use.

Adverse Events (TEAEs)

OL phase

Table 26. Treatment-Emergent Adverse Events (All Causalities) in Open-Label Run-in Phase - OLFAS

Number (%) of Subjects	Tofacitinib 5mg BID OL n (%)
Subjects evaluable for adverse events	225

Table 26. Treatment-Emergent Adverse Events (All Causalities) in Open-Label Run-in Phase - OLFAS

Number (%) of Subjects	Tofacitinib 5mg BID OL n (%)
Number of adverse events	411
Subjects with adverse events	153 (68.0)
Subjects with serious adverse events	7 (3.1)
Subjects with severe adverse events	5 (2.2)
Subjects discontinued from study due to adverse events (a)	26 (11.6)
Subjects discontinued study drug due to AE and continue Study (b)	0
Subjects with dose reduced or temporary discontinuation due to adverse events	20 (8.9)

Includes data up to 28 days after last dose of study drug.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study.
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be discontinued from Study.
MedDRA 22.0 coding dictionary applied.
The Open-Label Run-in phase is the study period before randomization day (Week 18). If a subject does not meet randomization criteria and is discontinued, the study period will be considered Open-Label Run-in phase.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (06:56) Source Data: Table 16.2.7.1 Output File: ./ra cdisc/A3921104/adae s010 Date of Generation: 22JUN2019 (23:49)
Table 14.3.1.2.1.1 is for Pfizer internal use.

During the open-label run-in phase, TEAEs were reported for 153 (68.0%) subjects. The majority of TEAEs reported were mild to moderate in severity.

All causality TEAEs with ≥2% occurrence are summarized in the table below:

Table 28. Incidence and Severity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term with >=2% Occurrence (All Causalities) in Open-Label Run-in Phase - OLFAS

Number of Subjects Evaluable for AEs	Tofacitinib 5mg BID OL (N=225)			
Severity(a)	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)
Infections And Infestations	66 (29.3)	22 (9.8)	1 (0.4)	89 (39.6)
Upper respiratory tract infection	20 (8.9)	4 (1.8)	0	24 (10.7)
Nasopharyngitis	9 (4.0)	1 (0.4)	0	10 (4.4)
Influenza	5 (2.2)	3 (1.3)	0	8 (3.6)
Pharyngitis	4 (1.8)	1 (0.4)	0	5 (2.2)
Pharyngitis streptococcal	4 (1.8)	1 (0.4)	0	5 (2.2)
Viral infection	4 (1.8)	1 (0.4)	0	5 (2.2)
Gastrointestinal Disorders	45 (20.0)	3 (1.3)	1 (0.4)	49 (21.8)
Nausea	12 (5.3)	1 (0.4)	0	13 (5.8)
Vomiting	11 (4.9)	2 (0.9)	0	13 (5.8)
Abdominal pain	8 (3.6)	0	0	8 (3.6)
Diarrhoea	5 (2.2)	1 (0.4)	0	6 (2.7)
Abdominal pain upper	5 (2.2)	0	0	5 (2.2)
General Disorders And Administration Site Conditions	19 (8.4)	6 (2.7)	2 (0.9)	27 (12.0)
Pyrexia	10 (4.4)	1 (0.4)	0	11 (4.9)
Disease progression	3 (1.3)	1 (0.4)	1 (0.4)	5 (2.2)
Musculoskeletal And Connective Tissue Disorders	17 (7.6)	8 (3.6)	1 (0.4)	26 (11.6)
Juvenile idiopathic arthritis	3 (1.3)	2 (0.9)	1 (0.4)	6 (2.7)
Arthralgia	3 (1.3)	2 (0.9)	0	5 (2.2)
Back pain	4 (1.8)	1 (0.4)	0	5 (2.2)
Respiratory, Thoracic And Mediastinal Disorders	23 (10.2)	0	0	23 (10.2)
Cough	7 (3.1)	0	0	7 (3.1)
Investigations	14 (6.2)	5 (2.2)	0	19 (8.4)
Aspartate aminotransferase increased	3 (1.3)	4 (1.8)	0	7 (3.1)
Alanine aminotransferase increased	2 (0.9)	4 (1.8)	0	6 (2.7)
Blood creatine phosphokinase increased	4 (1.8)	1 (0.4)	0	5 (2.2)
Nervous System Disorders	18 (8.0)	1 (0.4)	0	19 (8.4)
Headache	15 (6.7)	1 (0.4)	0	16 (7.1)
Blood And Lymphatic System Disorders	7 (3.1)	3 (1.3)	0	10 (4.4)
Anaemia	3 (1.3)	2 (0.9)	0	5 (2.2)
Metabolism And Nutrition Disorders	7 (3.1)	1 (0.4)	0	8 (3.6)
Decreased appetite	6 (2.7)	0	0	6 (2.7)

Table 28. Incidence and Severity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term with >=2% Occurrence (All Causalities) in Open-Label Run-in Phase - OLFAS

Number of Subjects Evaluable for AEs	Tofacitinib 5mg BID OL (N=225)			
Severity(a)	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)

SOCs with no PT >=2% are excluded.
If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is counted.
Subjects are counted only once per treatment per event. For the TESS algorithm any missing severities have been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity is summarized. Missing baseline severities are imputed as mild. Treatment (Trt) column gives study treatment at time of adverse event.
Includes data up to 28 days after last dose of study drug. Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
MedDRA 22.0 coding dictionary applied.
The Open-Label Run-in phase is the study period before randomization day (Week 18). If a subject does not meet randomization criteria and is discontinued, the study period will be considered Open-Label Run-in phase.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (06:56) Source Data: Table 14.3.1.2.3.1 Output File: ./ra cdisc/A3921104/adae s041 ol 2pct mod Date of Generation: 01JUL2019 (18:02)
Table 14.3.1.2.3.1.1 is for Pfizer internal use.

DB

Overall, TEAEs were reported for 68 (77.3%) subjects in the tofacitinib 5 mg BID group and 63 (74.1%) subjects in the placebo group during the double-blind phase.
Most TEAEs reported by both groups were mild to moderate in severity.

All causality TEAEs with ≥2% occurrence are summarized in the Table below:

Table 29. Incidence and Severity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term with >=2% Occurrence (All Causalities) in Double-Blind Phase - DBSAS

Number of Subjects Evaluable for AEs	Tofacitinib 5mg BID DB (N=88)				Placebo (N=85)			
Severity(a)	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Infections And Infestations	28 (31.8)	11 (12.5)	0	39 (44.3)	20 (23.5)	5 (5.9)	1 (1.2)	26 (30.6)
Upper respiratory tract infection	11 (12.5)	2 (2.3)	0	13 (14.8)	8 (9.4)	1 (1.2)	0	9 (10.6)
Nasopharyngitis	6 (6.8)	1 (1.1)	0	7 (8.0)	3 (3.5)	0	0	3 (3.5)
Sinusitis	3 (3.4)	1 (1.1)	0	4 (4.5)	1 (1.2)	0	0	1 (1.2)
Influenza	2 (2.3)	1 (1.1)	0	3 (3.4)	1 (1.2)	1 (1.2)	0	2 (2.4)
Respiratory tract infection	2 (2.3)	1 (1.1)	0	3 (3.4)	1 (1.2)	0	0	1 (1.2)
Gastroenteritis	2 (2.3)	0	0	2 (2.3)	0	0	0	0
Pharyngitis	1 (1.1)	1 (1.1)	0	2 (2.3)	1 (1.2)	0	0	1 (1.2)
Pharyngitis streptococcal	1 (1.1)	1 (1.1)	0	2 (2.3)	0	0	0	0
Rhinitis	2 (2.3)	0	0	2 (2.3)	1 (1.2)	0	0	1 (1.2)
Viral infection	0	2 (2.3)	0	2 (2.3)	1 (1.2)	0	0	1 (1.2)
Respiratory tract infection viral	1 (1.1)	0	0	1 (1.1)	2 (2.4)	0	0	2 (2.4)
Tonsillitis	1 (1.1)	0	0	1 (1.1)	2 (2.4)	0	0	2 (2.4)
Urinary tract infection	1 (1.1)	0	0	1 (1.1)	1 (1.2)	2 (2.4)	0	3 (3.5)
General Disorders And Administration Site Conditions	12 (13.6)	5 (5.7)	0	17 (19.3)	7 (8.2)	8 (9.4)	1 (1.2)	16 (18.8)
Disease progression	4 (4.5)	4 (4.5)	0	8 (9.1)	4 (4.7)	8 (9.4)	1 (1.2)	13 (15.3)
Pyrexia	4 (4.5)	0	0	4 (4.5)	1 (1.2)	0	0	1 (1.2)
Condition aggravated	1 (1.1)	1 (1.1)	0	2 (2.3)	2 (2.4)	0	0	2 (2.4)
Skin And Subcutaneous Tissue Disorders	11 (12.5)	0	0	11 (12.5)	1 (1.2)	0	0	1 (1.2)
Rash	2 (2.3)	0	0	2 (2.3)	0	0	0	0
Gastrointestinal Disorders	8 (9.1)	2 (2.3)	0	10 (11.4)	13 (15.3)	0	1 (1.2)	14 (16.5)
Dyspepsia	2 (2.3)	0	0	2 (2.3)	1 (1.2)	0	0	1 (1.2)
Diarrhoea	1 (1.1)	0	0	1 (1.1)	2 (2.4)	0	0	2 (2.4)
Abdominal pain	0	0	0	0	3 (3.5)	0	0	3 (3.5)
Vomiting	0	0	0	0	4 (4.7)	0	0	4 (4.7)
Musculoskeletal And Connective Tissue Disorders	7 (8.0)	3 (3.4)	0	10 (11.4)	15 (17.6)	6 (7.1)	1 (1.2)	22 (25.9)
Back pain	2 (2.3)	1 (1.1)	0	3 (3.4)	1 (1.2)	0	0	1 (1.2)
Juvenile idiopathic arthritis	1 (1.1)	2 (2.3)	0	3 (3.4)	7 (8.2)	4 (4.7)	1 (1.2)	12 (14.1)
Arthralgia	2 (2.3)	0	0	2 (2.3)	4 (4.7)	0	0	4 (4.7)
Arthritis	1 (1.1)	0	0	1 (1.1)	2 (2.4)	1 (1.2)	0	3 (3.5)
Pain in extremity	1 (1.1)	0	0	1 (1.1)	2 (2.4)	0	0	2 (2.4)
Investigations	7 (8.0)	2 (2.3)	0	9 (10.2)	7 (8.2)	3 (3.5)	0	10 (11.8)
Aspartate aminotransferase increased	4 (4.5)	0	0	4 (4.5)	0	1 (1.2)	0	1 (1.2)

Table 29. Incidence and Severity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term with >=2% Occurrence (All Causalities) in Double-Blind Phase - DBSAS

Number of Subjects Evaluable for AEs	Tofacitinib 5mg BID DB (N=88)				Placebo (N=85)			
Severity(a)	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Alanine aminotransferase increased	2 (2.3)	1 (1.1)	0	3 (3.4)	1 (1.2)	1 (1.2)	0	2 (2.4)
Blood creatine phosphokinase increased	2 (2.3)	1 (1.1)	0	3 (3.4)	0	1 (1.2)	0	1 (1.2)
C-reactive protein increased	0	1 (1.1)	0	1 (1.1)	2 (2.4)	0	0	2 (2.4)
Haemoglobin decreased	0	0	0	0	1 (1.2)	1 (1.2)	0	2 (2.4)
White blood cell count decreased	0	0	0	0	2 (2.4)	0	0	2 (2.4)
Respiratory, Thoracic And Mediastinal Disorders	8 (9.1)	1 (1.1)	0	9 (10.2)	8 (9.4)	1 (1.2)	0	9 (10.6)
Epistaxis	2 (2.3)	1 (1.1)	0	3 (3.4)	1 (1.2)	0	0	1 (1.2)
Cough	2 (2.3)	0	0	2 (2.3)	1 (1.2)	0	0	1 (1.2)
Nasal congestion	2 (2.3)	0	0	2 (2.3)	1 (1.2)	0	0	1 (1.2)
Oropharyngeal pain	2 (2.3)	0	0	2 (2.3)	2 (2.4)	1 (1.2)	0	3 (3.5)
Blood And Lymphatic System Disorders	2 (2.3)	0	0	2 (2.3)	6 (7.1)	1 (1.2)	0	7 (8.2)
Lymphadenitis	1 (1.1)	0	0	1 (1.1)	2 (2.4)	0	0	2 (2.4)
Leukopenia	0	0	0	0	2 (2.4)	0	0	2 (2.4)
Ear And Labyrinth Disorders	2 (2.3)	0	0	2 (2.3)	2 (2.4)	0	0	2 (2.4)
Ear pain	2 (2.3)	0	0	2 (2.3)	1 (1.2)	0	0	1 (1.2)
Eye Disorders	2 (2.3)	0	0	2 (2.3)	4 (4.7)	0	0	4 (4.7)
Uveitis	0	0	0	0	2 (2.4)	0	0	2 (2.4)
Nervous System Disorders	2 (2.3)	0	0	2 (2.3)	5 (5.9)	1 (1.2)	0	6 (7.1)
Headache	2 (2.3)	0	0	2 (2.3)	5 (5.9)	1 (1.2)	0	6 (7.1)

SOCs with no PT >=2% are excluded.
If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is counted.
Subjects are counted only once per treatment per event. For the TESS algorithm any missing severities have been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity is summarized. Missing baseline severities are imputed as mild. Treatment (Trt) column gives study treatment at time of adverse event.
Includes data up to 28 days after last dose of study drug. Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
MedDRA 22.0 coding dictionary applied.
The Double-Blind phase is the study period on and after randomization day.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (06:56) Source Data: Table 14.3.1.2.3.2 Output File: ./ra_cdisc/A3921104/adae_s041_db_2pct_mod Date of Generation: 01JUL2019 (12:55)
Table 14.3.1.2.3.2.1 is for Pfizer internal use.

Treatment-related TEAEs

OL

Treatment-related TEAEs were reported for 64 (28.4%) subjects during the open-label run-in phase. Most treatment-related TEAEs reported were mild to moderate in severity. Treatment-related TEAEs occurring with ≥2% are summarized in the table below:

Table 30. Incidence and Severity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term with >=2% Occurrence (Treatment Related) in Open-Label Run-in Phase - OLFAS

Number of Subjects Evaluable for AEs	Tofacitinib 5mg BID OL (N=225)			
Severity(a)	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)
Infections And Infestations	18 (8.0)	13 (5.8)	1 (0.4)	32 (14.2)
Upper respiratory tract infection	7 (3.1)	3 (1.3)	0	10 (4.4)
Gastrointestinal Disorders	20 (8.9)	0	0	20 (8.9)
Nausea	6 (2.7)	0	0	6 (2.7)
Abdominal pain	5 (2.2)	0	0	5 (2.2)
Nervous System Disorders	8 (3.6)	0	0	8 (3.6)
Headache	7 (3.1)	0	0	7 (3.1)

SOCs with no PT >=2% are excluded.
If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is counted.
Subjects are counted only once per treatment per event. For the TESS algorithm any missing severities have been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity is summarized. Missing baseline severities are imputed as mild. Treatment (Trt) column gives study treatment at time of adverse event.
Includes data up to 28 days after last dose of study drug. Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
MedDRA 22.0 coding dictionary applied.
The Open-Label Run-In phase is the study period before randomization day (Week 18). If a subject does not meet randomization criteria and is discontinued, the study period will be considered Open-Label Run-in phase.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (06:56) Source Data: Table 14.3.1.3.3.1 Output File: ./ra_cdisc/A3921104/adae_s043_ol_2pct_mod Date of Generation: 01JUL2019 (18:06)
Table 14.3.1.3.3.1.1 is for Pfizer internal use.

Table 31. Incidence and Severity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term with >=2% Occurrence (Treatment Related) in Double-Blind Phase - DBSAS

Number of Subjects Evaluable for AEs	Tofacitinib 5mg BID DB (N=88)				Placebo (N=85)			
Severity(a)	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Infections And Infestations	5 (5.7)	4 (4.5)	0	9 (10.2)	7 (8.2)	4 (4.7)	1 (1.2)	12 (14.1)
Upper respiratory tract infection	3 (3.4)	0	0	3 (3.4)	3 (3.5)	1 (1.2)	0	4 (4.7)
Sinusitis	1 (1.1)	1 (1.1)	0	2 (2.3)	1 (1.2)	0	0	1 (1.2)
Urinary tract infection	1 (1.1)	0	0	1 (1.1)	1 (1.2)	2 (2.4)	0	3 (3.5)
General Disorders And Administration Site Conditions	5 (5.7)	0	0	5 (5.7)	4 (4.7)	4 (4.7)	0	8 (9.4)
Disease progression	2 (2.3)	0	0	2 (2.3)	4 (4.7)	4 (4.7)	0	8 (9.4)
Pyrexia	2 (2.3)	0	0	2 (2.3)	0	0	0	0
Musculoskeletal And Connective Tissue Disorders	1 (1.1)	2 (2.3)	0	3 (3.4)	4 (4.7)	3 (3.5)	1 (1.2)	8 (9.4)
Juvenile idiopathic arthritis	1 (1.1)	2 (2.3)	0	3 (3.4)	3 (3.5)	3 (3.5)	1 (1.2)	7 (8.2)
Investigations	2 (2.3)	0	0	2 (2.3)	4 (4.7)	2 (2.4)	0	6 (7.1)
Alanine aminotransferase increased	1 (1.1)	0	0	1 (1.1)	1 (1.2)	1 (1.2)	0	2 (2.4)
Nervous System Disorders	0	0	0	0	3 (3.5)	0	0	3 (3.5)
Headache	0	0	0	0	3 (3.5)	0	0	3 (3.5)

SOCs with no PT >=2% are excluded.
If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is counted.
Subjects are counted only once per treatment per event. For the TESS algorithm any missing severities have been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity is summarized. Missing baseline severities are imputed as mild. Treatment (Trt) column gives study treatment at time of adverse event.
Includes data up to 28 days after last dose of study drug. Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
MedDRA 22.0 coding dictionary applied.
The Double-Blind phase is the study period on and after randomization day.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (06:56) Source Data: Table 14.3.1.3.3.2 Output File: ./ra cdisc/A3921104/adae s043 db 2pct mod Date of Generation: 01JUL2019 (13:01)
Table 14.3.1.3.3.2.1 is for Pfizer internal use.

AEs of special interest

Table 39. Exposure Estimates and Incidence Rates for Adverse Events of Special Interest for the Entire Tofacitinib Exposure Period (Subject-day)

	Treatment Group	N	n (%)	PD (Subject-Days)	IR (Subjects with Events / 100 subject-days) IR (95% CI) (Exact Poisson)	IR (95% CI) (Poisson Regression with Dispersion Parameter)
Death	Tofacitinib 5mg BID OL	225	0 (0.0)	45132	0.00 (0.00, 0.01)	-
Serious Infections	Tofacitinib 5mg BID OL	225	3 (1.3)	45044	0.01 (0.00, 0.02)	0.01 (0.00, 0.06)
Opportunistic Infections Excluding TB	Tofacitinib 5mg BID OL	225	0 (0.0)	45132	0.00 (0.00, 0.01)	-
Tuberculosis (TB)	Tofacitinib 5mg BID OL	225	0 (0.0)	45132	0.00 (0.00, 0.01)	-
Herpes Zoster	Tofacitinib 5mg BID OL	225	2 (0.9)	44907	0.00 (0.00, 0.02)	0.00 (0.00, 0.14)
Malignancy Excluding NMSC	Tofacitinib 5mg BID OL	225	0 (0.0)	45132	0.00 (0.00, 0.01)	-
NMSC (Non-Melanoma Skin Cancer)	Tofacitinib 5mg BID OL	225	0 (0.0)	45132	0.00 (0.00, 0.01)	-
Lymphoma	Tofacitinib 5mg BID OL	225	0 (0.0)	45132	0.00 (0.00, 0.01)	-
Major Adverse Cardiovascular Events (MACE)	Tofacitinib 5mg BID OL	225	0 (0.0)	45132	0.00 (0.00, 0.01)	-
Gastrointestinal Perforations	Tofacitinib 5mg BID OL	225	0 (0.0)	45132	0.00 (0.00, 0.01)	-
Interstitial Lung Disease (ILD)	Tofacitinib 5mg BID OL	225	0 (0.0)	45132	0.00 (0.00, 0.01)	-
MAS (Macrophage Activation Syndrome)	Tofacitinib 5mg BID OL	225	0 (0.0)	45132	0.00 (0.00, 0.01)	-

N: Number of subjects in analysis set.
n: Number of subjects with the event.
PD (subject-days): Sum of total follow-time for all subjects combined. Follow-up time is time from the first dose to the event or total exposure for subjects who did not have any event (to the earliest occurrence of date of: the last dose date +28 days or date of death).
Placebo exposure may contribute a maximum of 28 days to the risk period.
PFIZER CONFIDENTIAL SDTM Creation: 19AUG2019 (15:17) Source Data: Tables 16.2.7.1 16.2.7.4.1 16.2.7.4.2 16.2.7.4.3 16.2.7.4.9 16.2.7.4.11 Output File: ./ra_cdisc/A3921104/ir_trt_ae_entire Date of Generation: 20AUG2019 (11:56)
Table 14.3.1.5.8.2.1 is for Pfizer internal use.

Drug induced liver injury There were 3 events adjudicated as possible or probable drug induced liver injury during the open-label run-in phase; 2 were mild and 1 was moderate. None met Hy's Law criteria. One subject was on paracetamol with a concurrent viral illness, which was considered a possible cause. This subject was also taking MTX at the time of the event. The second subject was also on paracetamol, when elevated AST and ALT occurred. This was considered moderate with probable relation.

The third subject was not on paracetamol and had a finding consistent with mild hepatocellular effects that were deemed of probable relationship. All 3 events resolved. No drug induced liver injury events were adjudicated during the double-blind phase.

Opportunistic infections and special interest infections, there were 2 cases of herpes zoster adjudicated during the open-label run-in phase and none during the double-blind phase. Both events were in a single dermatome, did not meet the criteria for being considered an opportunistic infection, and resolved.

Four subjects had serious infections that occurred during the study. Three subjects during the open-label run-in phase had serious infections: pneumonia, epidural empyema and sinusitis in a child with a history of craniosynostosis repair, and appendicitis. During the double-blind phase, there was 1 serious infectious event (appendicitis) in a subject being treated with placebo. One SAE/infection, pilonidal sinus repair, was coded to the SOC Surgical and medical procedures instead of Infections even though the subject was admitted to the hospital after surgery to treat a pilonidal cyst because of the infection, large incision site, and the need for wound vac placement. This event was inadvertently not captured in the programmed list of serious infection events. It was adjudicated as not meeting opportunistic infection criteria.

There were no cases of **deep vein thrombosis, pulmonary embolus, or arterial or venous thromboembolism**.

There were 2 events in the open-label run-in phase and 1 event in the double-blind phase reviewed for **GI perforation**; none were adjudicated as GI perforation.

Discontinuation due to AEs

OL

Table 32. Summary of Subjects who Discontinued from Study Due to Adverse Events in Open-Label Run-in Phase - OLFAS

Number of Subjects Evaluable for AEs	Tofacitinib 5mg BID OL (N=225)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**
Gastrointestinal Disorders	1 (0.4)
Crohn's disease	1 (0.4)
General Disorders And Administration Site Conditions	10 (4.4)
Condition aggravated	3 (1.3)
Disease progression	5 (2.2)
Drug intolerance	2 (0.9)
Infections And Infestations	4 (1.8)
Appendicitis	1 (0.4)
Epidural empyema	1 (0.4)
Herpes zoster	1 (0.4)
Pneumonia	1 (0.4)
Sinusitis	1 (0.4)
Subperiosteal abscess	1 (0.4)
Investigations	2 (0.9)
Alanine aminotransferase increased	2 (0.9)
Aspartate aminotransferase increased	1 (0.4)
Musculoskeletal And Connective Tissue Disorders	8 (3.6)
Arthritis	1 (0.4)
Juvenile idiopathic arthritis	6 (2.7)
Still's disease	1 (0.4)
Skin And Subcutaneous Tissue Disorders	1 (0.4)
Dermatitis allergic	1 (0.4)

Subjects are only counted once per treatment per event. Only treatment emergent events are included.
Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
Includes data up to 28 days after last dose of study drug.
MedDRA 22.0 coding dictionary applied.
The Open-Label Run-in phase is the study period before randomization day (Week 18). If a subject does not meet randomization criteria and is discontinued, the study period will be considered Open-Label Run-in phase.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (06:56) Source Data: Table 16.2.7.1 Output File: ./ra cdisc/A3921104/adae s182 olfas Date of Generation: 16AUG2019 (11:50)
Table 14.3.1.1.1.1 is for Pfizer internal use.

Table 33. Summary of Subjects who Discontinued from Study Due to Condition Aggravated Adverse Events in Open-Label Run-in Phase – OLFAS

Number of Subjects Evaluable for AEs Number (%) of Subjects: Preferred Term	Tofacitinib 5mg BID OL (N=225) n (%)
With Any adverse event	16 (7.1)
Arthritis	1 (0.4)
Condition aggravated	3 (1.3)
Disease progression	5 (2.2)
Juvenile idiopathic arthritis	6 (2.7)
Still's disease	1 (0.4)

Subjects are only counted once per treatment per event.
Includes data up to 28 days after last dose of study drug.
MedDRA 22.0 coding dictionary applied.
The Open-Label Run-in phase is the study period before randomization day (Week 18). If a subject does not meet randomization criteria and is discontinued,
the study period will be considered Open-Label Run-in phase.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (06:56) Source Data: Table 16.2.7.1 Output File: ./ra_cdisc/A3921104/adae_intext_ol Date of Generation: 29AUG2019 (11:00)
Table 14.3.1.2.2.1.1 is for Pfizer internal use.

DB

Table 34. Summary of Subjects who Discontinued from Study Due to Adverse Events in Double-Blind Phase - DBSAS

Number of Subjects Evaluable for AEs	Tofacitinib 5mg BID DB (N=88)	Placebo (N=85)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**
Gastrointestinal Disorders	1 (1.1)	1 (1.2)
Intussusception	0	1 (1.2)
Tooth impacted	1 (1.1)	0
General Disorders And Administration Site Conditions	10 (11.4)	12 (14.1)
Condition aggravated	2 (2.3)	2 (2.4)
Disease progression	8 (9.1)	10 (11.8)
Infections And Infestations	0	1 (1.2)
Appendicitis	0	1 (1.2)
Investigations	0	1 (1.2)
Haemoglobin decreased	0	1 (1.2)
Musculoskeletal And Connective Tissue Disorders	4 (4.5)	15 (17.6)
Arthritis	1 (1.1)	3 (3.5)
Juvenile idiopathic arthritis	3 (3.4)	12 (14.1)
Surgical And Medical Procedures	1 (1.1)	0
Pilonidal sinus repair	1 (1.1)	0

Subjects are only counted once per treatment per event. Only treatment emergent events are included.
Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
Includes data up to 28 days after last dose of study drug.
MedDRA 22.0 coding dictionary applied.
The Double-Blind phase is the study period on and after randomization day.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (06:56) Source Data: Table 16.2.7.1 Output File: ./ra cdisc/A3921104/adae s182 dbsas Date of Generation: 16AUG2019 (11:47)
Table 14.3.1.1.1.2 is for Pfizer internal use.

Table 35. Summary of Subjects who Discontinued from Study Due to Condition Aggravated Adverse Events in Double-Blind Phase – DBSAS

Number of Subjects Evaluable for AEs	Tofacitinib 5mg BID DB (N=88)	Placebo (N=85)
Number (%) of Subjects: Preferred Term	**n (%)**	**n (%)**
With Any adverse event	14 (15.9)	27 (31.8)
Arthritis	1 (1.1)	3 (3.5)
Condition aggravated	2 (2.3)	2 (2.4)
Disease progression	8 (9.1)	10 (11.8)
Juvenile idiopathic arthritis	3 (3.4)	12 (14.1)

Subjects are only counted once per treatment per event.
Includes data up to 28 days after last dose of study drug.
MedDRA 22.0 coding dictionary applied.
The Double-Blind phase is the study period on and after the randomization day.
PFIZER CONFIDENTIAL SDTM Creation: 15JUN2019 (06:56) Source Data: Table 16.2.7.1 Output File: ./ra cdisc/A3921104/adae intext db Date of Generation: 29AUG2019 (11:08)
Table 14.3.1.2.2.2.1 is for Pfizer internal use.

Dose Reductions or Temporary Discontinuations Due to Adverse Events

There were 20 (8.9%) subjects with dose reduced or dose temporarily discontinued because of an AE in the OL phase. During the double-blind phase, there were 9 (10.2%) subjects in the tofacitinib 5 mg BID group and 8 (9.4%) subjects in the placebo group with dose reduced or dose temporarily discontinued because of an AE.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths occurred during the study.

Other Serious Adverse Events

During the open-label run-in phase, a total of 10 SAEs were reported by 7 subjects.

Table 36. Summary of Serious Adverse Events by System Organ Class and Preferred Terms (All Adverse Events) in Open-Label Run-in Phase - OLFAS Reporting period: Cumulative Through - Cut off date 14JUN2019

Number of Subjects Evaluable for Adverse Events	Tofacitinib 5mg BID OL (N=225)
Number (%) of Subjects with Serious Adverse Events (a): by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**
Gastrointestinal disorders	2 (0.9)
Crohn's disease	1 (0.4)
Diarrhoea	1 (0.4)
Vomiting	1 (0.4)
General disorders and administration site conditions	1 (0.4)
Condition aggravated	1 (0.4)
Infections and infestations	3 (1.3)
Appendicitis	1 (0.4)
Epidural empyema	1 (0.4)
Pneumonia	1 (0.4)
Sinusitis	1 (0.4)
Subperiosteal abscess	1 (0.4)
Musculoskeletal and connective tissue disorders	1 (0.4)
Juvenile idiopathic arthritis	1 (0.4)
Total preferred term events (b)	10
Total Number of Cases (c)	7
Total Number of Subjects with Serious Adverse Events (d)	7
Total Number of Subjects with Serious Adverse Events (e) 7	

A case is a single event or a series of related events not separated in time occurring in a single subject.
(a) SAEs are counted at MedDRA preferred term/Treatment group with each individual SAE counted only once per subject per treatment group
(b) Total number of events per subject per Treatment group
(c) Number of cases that started in the Treatment group
(d) Total number of subjects having an event that started in the Treatment group
(e) Overall count of subjects that had a Serious adverse Event in any Treatment group
Source of Actual treatment Group is OC(Oracle Clinical) or PIMS(Phase I Management System). Source of SAE is SDW(Safety Data Warehouse)
MedDRA v.22.0J coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 24JUN2019 (18:19) Source Data: Table 14.3.2.2.1.1 Output File: ./ra_cdisc/A3921104/adsae_s001 Date of Generation: 01JUL2019 (14:52)
Table 14.3.2.2.2.1 is for Pfizer internal use.

In the **double-blind phase**, 1 SAE was reported by 1 subject in the tofacitinib 5 mg BID group and a total of 3 SAEs were reported by 2 subjects in the placebo group.

Table 37. Summary of Serious Adverse Events by System Organ Class and Preferred Terms (All Adverse Events) in Double-Blind Phase - DBSAS Reporting period: Cumulative Through - Cut off date 14JUN2019

Number of Subjects Evaluable for Adverse Events	Tofacitinib 5mg BID DB (N=88)	Placebo (N=85)
Number (%) of Subjects with Serious Adverse Events (a): by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**
Gastrointestinal disorders	0	1 (1.2)
Intussusception	0	1 (1.2)
Infections and infestations	1 (1.1)	1 (1.2)
Appendicitis	0	1 (1.2)
Pilonidal cyst	1 (1.1)	0
Musculoskeletal and connective tissue disorders	0	1 (1.2)
Juvenile idiopathic arthritis	0	1 (1.2)
Total preferred term events (b)	1	3
Total Number of Cases (c)	1	2
Total Number of Subjects with Serious Adverse Events (d)	1	2
Total Number of Subjects with Serious Adverse Events (e) 3		

A case is a single event or a series of related events not separated in time occurring in a single subject.
(a) SAEs are counted at MedDRA preferred term/Treatment group with each individual SAE counted only once per subject per treatment group
(b) Total number of events per subject per Treatment group
(c) Number of cases that started in the Treatment group
(d) Total number of subjects having an event that started in the Treatment group
(e) Overall count of subjects that had a Serious adverse Event in any Treatment group
Source of Actual treatment Group is OC(Oracle Clinical) or PIMS(Phase I Management System). Source of SAE is SDW(Safety Data Warehouse)
MedDRA v.22.0J coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 24JUN2019 (18:19) Source Data: Table 14.3.2.2.1.2 Output File: ./ra_cdisc/A3921104/adsae_s001_db Date of Generation: 01JUL2019 (14:55)
Table 14.3.2.2.2.2 is for Pfizer internal use.

Laboratory abnormalities

OL

Table 14.3.4.1.1.1
CP-690,550 Protocol A3921104
Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) in Open-Label Run-in Phase - OLFAS

Laboratory Abnormalities: Number of Subjects Evaluable for Laboratory Abnormalities: Number (%) of Subjects with Laboratory Abnormalities:			**Tofacitinib 5mg BID OL** **225** **211 (93.8%)**	
Group	**Parameter (Units)**	**Primary Criteria**	**N**	**n (%)**
HEMATOLOGY	Hemoglobin (g/dL)	<0.8x LLN	224	1 (0.4)
	Hematocrit (%)	<0.8x LLN	224	1 (0.4)
	Erythrocytes (10^6/mm^3)	<0.8x LLN	224	2 (0.9)
	Ery. Mean Corpuscular Volume (um^3)	<0.9x LLN	224	3 (1.3)
		>1.1x ULN	224	4 (1.8)
	Platelets (10^3/mm^3)	<0.5x LLN	224	1 (0.4)
		>1.75x ULN	224	2 (0.9)
	Leukocytes (10^3/mm^3)	<0.6x LLN	224	1 (0.4)
		>1.5x ULN	224	2 (0.9)
	Lymphocytes (10^3/mm^3)	<0.8x LLN	224	7 (3.1)
		>1.2x ULN	224	2 (0.9)
	Lymphocytes/Leukocytes (%)	<0.8x LLN	224	15 (6.7)
		>1.2x ULN	224	20 (8.9)

NOTE: N = total number of subjects with at least one observation of the given laboratory test while on study treatment or during lag time.
n = number of subjects with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.
Percentages are displayed for the laboratory tests having a category with greater or equal to 1 evaluable subjects.
The Open-Label Run-in phase is the study period before randomization day (Week 18). If a subject does not meet randomization criteria and is discontinued, the study period will all be considered Open-Label Run-in phase.

Table 14.3.4.1.1.1
CP-690,550 Protocol A3921104
Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) in Open-Label Run-in Phase - OLFAS

Laboratory Abnormalities: Number of Subjects Evaluable for Laboratory Abnormalities: Number (%) of Subjects with Laboratory Abnormalities:			**Tofacitinib 5mg BID OL** **225** **211 (93.8%)**	
Group	**Parameter (Units)**	**Primary Criteria**	**N**	**n (%)**
	Neutrophils (10^3/mm^3)	<0.8x LLN	224	8 (3.6)
		>1.2x ULN	224	18 (8.0)
	Neutrophils/Leukocytes (%)	<0.8x LLN	224	19 (8.5)
		>1.2x ULN	224	0
	Basophils (10^3/mm^3)	>1.2x ULN	224	0
	Basophils/Leukocytes (%)	>1.2x ULN	224	37 (16.5)
	Eosinophils (10^3/mm^3)	>1.2x ULN	224	53 (23.7)
	Eosinophils/Leukocytes (%)	>1.2x ULN	224	32 (14.3)
	Monocytes (10^3/mm^3)	>1.2x ULN	224	3 (1.3)
	Monocytes/Leukocytes (%)	>1.2x ULN	224	38 (17.0)
	Prothrombin Time (sec)	>1.1x ULN	4	0
	Prothrombin Intl. Normalized Ratio	>1.1x ULN	4	0
	Erythrocyte Sedimentation Rate (mm/hr)	>1.5x ULN	224	65 (29.0)
CLINICAL CHEMISTRY	Bilirubin (mg/dL)	>1.5x ULN	225	1 (0.4)

NOTE: N = total number of subjects with at least one observation of the given laboratory test while on study treatment or during lag time.
n = number of subjects with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.
Percentages are displayed for the laboratory tests having a category with greater or equal to 1 evaluable subjects.
The Open-Label Run-in phase is the study period before randomization day (Week 18). If a subject does not meet randomization criteria and is discontinued, the study period will all be considered Open-Label Run-in phase.

Table 14.3.4.1.1.1
CP-690,550 Protocol A3921104
Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) in Open-Label Run-in Phase - OLFAS

Laboratory Abnormalities: Number of Subjects Evaluable for Laboratory Abnormalities: Number (%) of Subjects with Laboratory Abnormalities:			**Tofacitinib 5mg BID OL** **225** **211 (93.8%)**	
Group	**Parameter (Units)**	**Primary Criteria**	**N**	**n (%)**
	Direct Bilirubin (mg/dL)	>1.5x ULN	225	0
	Indirect Bilirubin (mg/dL)	>1.5x ULN	225	1 (0.4)
	Aspartate Aminotransferase (U/L)	>3.0x ULN	225	4 (1.8)
	Alanine Aminotransferase (U/L)	>3.0x ULN	225	5 (2.2)
	Gamma Glutamyl Transferase (U/L)	>3.0x ULN	225	1 (0.4)
	Lactate Dehydrogenase (U/L)	>3.0x ULN	1	0
	Alkaline Phosphatase (U/L)	>3.0x ULN	225	1 (0.4)
	Protein (g/dL)	<0.8x LLN	225	0
		>1.2x ULN	225	0
	Albumin (g/dL)	<0.8x LLN	225	0
		>1.2x ULN	225	1 (0.4)
	Blood Urea Nitrogen (mg/dL)	>1.3x ULN	225	0
	Creatinine (mg/dL)	>1.3x ULN	225	1 (0.4)
	HDL Cholesterol (mg/dL)	<0.8x LLN	223	2 (0.9)

NOTE: N = total number of subjects with at least one observation of the given laboratory test while on study treatment or during lag time.
n = number of subjects with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.
Percentages are displayed for the laboratory tests having a category with greater or equal to 1 evaluable subjects.
The Open-Label Run-in phase is the study period before randomization day (Week 18). If a subject does not meet randomization criteria and is discontinued, the study period will all be considered Open-Label Run-in phase.

DB

Table 14.3.4.1.1.2
CP-690,550 Protocol A3921104
Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) in Double-Blind Phase - DBSAS

Laboratory Abnormalities: Number of Subjects Evaluable for Laboratory Abnormalities: Number (%) of Subjects with Laboratory Abnormalities:			Tofacitinib 5mg BID DB 88 81 (92.0%)		Placebo 85 74 (87.1%)	
Group	**Parameter (Units)**	**Primary Criteria**	**N**	**n (%)**	**N**	**n (%)**
HEMATOLOGY	Hemoglobin (g/dL)	<0.8x LLN	87	1 (1.1)	85	3 (3.5)
	Hematocrit (%)	<0.8x LLN	87	0	85	2 (2.4)
	Erythrocytes (10^6/mm^3)	<0.8x LLN	87	0	85	2 (2.4)
	Ery. Mean Corpuscular Volume (um^3)	<0.9x LLN	87	2 (2.3)	85	1 (1.2)
		>1.1x ULN	87	1 (1.1)	85	2 (2.4)
	Platelets (10^3/mm^3)	<0.5x LLN	88	1 (1.1)	84	0
		>1.75x ULN	88	0	84	0
	Leukocytes (10^3/mm^3)	<0.6x LLN	87	0	85	1 (1.2)
		>1.5x ULN	87	1 (1.1)	85	0
	Lymphocytes (10^3/mm^3)	<0.8x LLN	87	5 (5.7)	85	1 (1.2)
		>1.2x ULN	87	1 (1.1)	85	0
	Lymphocytes/Leukocytes (%)	<0.8x LLN	87	9 (10.3)	85	5 (5.9)
		>1.2x ULN	87	5 (5.7)	85	7 (8.2)
	Neutrophils (10^3/mm^3)	<0.8x LLN	87	1 (1.1)	85	3 (3.5)

NOTE: N = total number of subjects with at least one observation of the given laboratory test while on study treatment or during lag time.
n = number of subjects with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.
Percentages are displayed for the laboratory tests having a category with greater or equal to 1 evaluable subjects.
The Double-Blind phase is the study period on and after randomization day.

Table 14.3.4.1.1.2
CP-690,550 Protocol A3921104
Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) in Double-Blind Phase - DBSAS

Laboratory Abnormalities: Number of Subjects Evaluable for Laboratory Abnormalities: Number (%) of Subjects with Laboratory Abnormalities:			**Tofacitinib 5mg BID DB** **88** **81 (92.0%)**		**Placebo** **85** **74 (87.1%)**	
Group	**Parameter (Units)**	**Primary Criteria**	**N**	**n (%)**	**N**	**n (%)**
		>1.2x ULN	87	7 (8.0)	85	5 (5.9)
	Neutrophils/Leukocytes (%)	<0.8x LLN	87	5 (5.7)	85	6 (7.1)
		>1.2x ULN	87	0	85	0
	Basophils (10^3/mm^3)	>1.2x ULN	87	1 (1.1)	85	0
	Basophils/Leukocytes (%)	>1.2x ULN	87	14 (16.1)	85	15 (17.6)
	Eosinophils (10^3/mm^3)	>1.2x ULN	87	27 (31.0)	85	18 (21.2)
	Eosinophils/Leukocytes (%)	>1.2x ULN	87	21 (24.1)	85	14 (16.5)
	Monocytes (10^3/mm^3)	>1.2x ULN	87	2 (2.3)	85	2 (2.4)
	Monocytes/Leukocytes (%)	>1.2x ULN	87	18 (20.7)	85	19 (22.4)
	Prothrombin Time (sec)	>1.1x ULN	3	0	2	1 (50.0)
	Prothrombin Intl. Normalized Ratio	>1.1x ULN	3	0	2	0
	Erythrocyte Sedimentation Rate (mm/hr)	>1.5x ULN	88	26 (29.5)	85	19 (22.4)
CLINICAL CHEMISTRY	Bilirubin (mg/dL)	>1.5x ULN	88	1 (1.1)	85	0
	Direct Bilirubin (mg/dL)	>1.5x ULN	88	1 (1.1)	85	0

NOTE: N = total number of subjects with at least one observation of the given laboratory test while on study treatment or during lag time.
n = number of subjects with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.
Percentages are displayed for the laboratory tests having a category with greater or equal to 1 evaluable subjects.
The Double-Blind phase is the study period on and after randomization day.

Table 14.3.4.1.1.2
CP-690,550 Protocol A3921104
Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) in Double-Blind Phase - DBSAS

Laboratory Abnormalities: Number of Subjects Evaluable for Laboratory Abnormalities: Number (%) of Subjects with Laboratory Abnormalities:			Tofacitinib 5mg BID DB 88 81 (92.0%)		Placebo 85 74 (87.1%)	
Group	**Parameter (Units)**	**Primary Criteria**	**N**	**n (%)**	**N**	**n (%)**
	Indirect Bilirubin (mg/dL)	>1.5x ULN	88	1 (1.1)	85	0
	Aspartate Aminotransferase (U/L)	>3.0x ULN	88	0	85	0
	Alanine Aminotransferase (U/L)	>3.0x ULN	88	1 (1.1)	85	2 (2.4)
	Gamma Glutamyl Transferase (U/L)	>3.0x ULN	88	1 (1.1)	85	0
	Alkaline Phosphatase (U/L)	>3.0x ULN	88	0	85	0
	Protein (g/dL)	<0.8x LLN	88	0	85	0
		>1.2x ULN	88	0	85	0
	Albumin (g/dL)	<0.8x LLN	88	0	85	0
		>1.2x ULN	88	0	85	0
	Blood Urea Nitrogen (mg/dL)	>1.3x ULN	88	0	85	0
	Creatinine (mg/dL)	>1.3x ULN	88	0	85	0
	HDL Cholesterol (mg/dL)	<0.8x LLN	70	0	61	2 (3.3)
	LDL Cholesterol (mg/dL)	>1.2x ULN	5	0	4	0
	LDL Chol Friedewald Est PEG (mg/dL)	>1.2x ULN	70	0	60	0

NOTE: N = total number of subjects with at least one observation of the given laboratory test while on study treatment or during lag time.
n = number of subjects with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.
Percentages are displayed for the laboratory tests having a category with greater or equal to 1 evaluable subjects.
The Double-Blind phase is the study period on and after randomization day.

Laboratory tests median changes across the study

Table 14.3.4.1.4.2
CP-690,550 Protocol A3921104
Laboratory Test Data: Median Changes from Open-Label Run-in Baseline to Last Observation in Double-Blind Pha

	Tofacitinib 5mg BID DB			Placebo		
		Baseline	Change From Baseline		Baseline	Change From Baseline
Parameter (Units)	N	Median	Median	N	Median	Median
Hemoglobin (g/dL)	87	12.4	0.2	85	12.5	0.0
Hematocrit (%)	87	0.4	0.0	85	0.5	0.0
Erythrocytes (10^6/mm^3)	87	4.40	-0.10	85	4.50	0.00
Ery. Mean Corpuscular Volume (um^3)	87	86	3	85	83	1
Platelets (10^3/mm^3)	88	297	-3	84	305	-11
Leukocytes (10^3/mm^3)	87	7.5	-0.7	85	6.6	-0.4
Lymphocytes (10^3/mm^3)	87	2.03	-0.06	85	2.21	-0.19
Lymphocytes/Leukocytes (%)	87	28.6	3.0	85	32.0	-0.1
Neutrophils (10^3/mm^3)	87	4.51	-0.74	85	4.08	-0.32
Neutrophils/Leukocytes (%)	87	62.8	-1.8	85	59.2	-0.5
Basophils (10^3/mm^3)	87	0.05	-0.01	85	0.05	-0.01
Basophils/Leukocytes (%)	87	0.7	0.0	85	0.7	0.0
Eosinophils (10^3/mm^3)	87	0.15	-0.02	85	0.14	-0.01
Eosinophils/Leukocytes (%)	87	1.8	-0.1	85	2.0	0.2
Monocytes (10^3/mm^3)	87	0.41	-0.04	85	0.40	-0.04
Monocytes/Leukocytes (%)	87	5.5	-0.1	85	5.4	-0.1
Erythrocyte Sedimentation Rate (mm/hr)	88	19.0	-4.5	85	17.0	-4.0
Bilirubin (mg/dL)	88	0.3	0.0	85	0.3	0.0
Direct Bilirubin (mg/dL)	88	0.1	0.0	85	0.1	0.0
Indirect Bilirubin (mg/dL)	88	0.3	0.0	85	0.3	0.0
Aspartate Aminotransferase (U/L)	88	20	2	85	20	-1
Alanine Aminotransferase (U/L)	88	13	1	85	13	0
Gamma Glutamyl Transferase (U/L)	88	12	1	85	11	0

Last observation is defined as the last observation while on study drug or during the lag of the treatment phase.
The Double-Blind phase is the study period on and after randomization day.
Baseline for Open-Label Run-in phase was Day 1.

Clinical pharmacology

Pharmacokinetic Results

Tofacitinib plasma concentrations for individual patients are listed in Appendix to clinical report for study A3921104.

The sparse PK sampling design precluded non-compartmental analysis (NCA) for each individual. Instead, the results this study will be pooled with other clinical studies to enable population PK analysis. The result of the population PK analysis will be reported separately in the Type II variation for pJIA.

2.3.2. Discussion on clinical aspects

The MAH submitted a completed paediatric study for tofacitinib for treatment of polyarticular course juvenile idiopathic arthritis (JIA), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This submission is in fulfilment of the Article 46 requirement. Study A3921104 is a deferred study in the JIA PIP (Study 6) with a completion date by February 2020.

A consequential Type II variation to update the SmPC with the relevant results is planned for submission in June 2020.

Study design: Study A3921104 was a randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of tofacitinib for treatment of polyarticular course juvenile idiopathic arthritis (JIA) in children and adolescent subjects. Superiority of tofacitinib versus placebo was analysed.

All eligible subjects enrolled in the study initially received open-label tofacitinib for 18 weeks (run-in phase). At the end of the 18-week run-in phase, only subjects who achieved at least a JIA American College of Rheumatology (ACR) 30 response were randomized to the 26-week double-blind, placebo-controlled phase. Subjects who did not achieve a JIA ACR 30 response at this time point were discontinued from the study. Subjects who were eligible for the 26-week double-blind phase were randomized (1:1 ratio) to either active tofacitinib or placebo.

Study population: 185 subjects completed the open-label run-in phase, with 173 subjects being randomized into the double-blind phase (88 subjects to tofacitinib 5 mg BID and 85 subjects to placebo). A total of 99 subjects completed the double-blind phase (61 in the tofacitinib 5 mg BID group and 38 in the placebo group). Of those subjects, 97 were rolled over into the A3921145 study and 2 were discontinued. Since flares led to discontinuation during the double-blind phase, insufficient clinical response was the most common discontinuation reason for double-blind discontinuation in both arms, with a higher percentage in the placebo group.

Enrolled population reflects the International League Against Rheumatism (ILAR) JIA classification criteria. A minority of subjects were from EU countries 6 (2.7%). All age ranges were represented as follow: 12-18 y (61.8%), 6-≤12 y (28.4%) and 2-≤6 y(9.8%). Subjects had active JIA (mean number of joints with active arthritis (12.2 for OL) and number of joints with limitation of motion (mean 7.5 for OL).

Results: Overall efficacy results were supportive of tofacitinib superiority as compared to placebo for the treatment of JIA subjects. Detailed assessment will be made within the variation the MAH will submit.
Primary endpoint was the occurrence of disease flare from double-blind randomization through Week 44 (type I Error Controlled) of study being significantly lower in the tofacitinib 5 mg BID group compared to the placebo group (p-value=0.0031), with a difference of proportions (tofacitinib-placebo) of -23.69%, 95% CI (-39.41%, -7.97%).
Efficacy was supported also by key secondary endpoints: i) JIA ACR 50, 30, and 70 responses (at Week 44, Type I Error Controlled), a significantly greater proportion of subjects treated with tofacitinib 5 mg BID achieved JIA ACR 50, 30, and 70 responses compared to subjects treated with placebo (p=0.0166, p=0.0031, and p=0.0387, respectively); ii) Change From Double-Blind Baseline in CHAQ Disability Index at Week 44 (Type I Error Controlled) the improvement was statistically greater in subjects treated with tofacitinib 5 mg BID than those treated with placebo, with a LS mean difference in the scores of -0.12, p-value=0.0292.
Secondary endpoints results, although descriptive analysis was conducted, were generally supportive of better activity of tofacitinib as compared to placebo for different endpoints related to disease activity, however for endpoints more stringent the numerical difference was lower.

Safety: In the OL phase, treatment-related TEAEs were reported for 64 (28.4%) subjects during the open-label run-in phase. Most treatment-related TEAEs reported were mild to moderate in severity.

In the DB phase, treatment-related TEAEs were seen in 22 (25.0%) subjects in the tofacitinib 5 mg BID group and 33 (38.8%) subjects in the placebo group during the double-blind phase. Most treatment-related TEAEs reported were mild to moderate in severity. The most common was infections and infestations occurring in 14.1% and 10.2% respectively in the OL and DB phase. Regarding severity in the OL phase only 1 case was classified as severe, in the DB phase no severe cases were reported in the tofacitinib arm and 1 case in the PLB arm.
Regarding AEs of special interest, considering the entire tofacitinib exposure period, there were 3 cases of serious infections, 2 cases of zoster, no opportunistic infections, malignancies, deep vein thrombosis, pulmonary embolus, or arterial or venous thromboembolism.
Overall the safety profile seems to not raise specific main safety concerns related to the paediatric age and it could be considered generally similar to that of the already approved tofacitinib indications. Detailed assessment of the data and potential SmPC changes will be done within the variation procedure the MAH will submit.

Pharmacokinetic: The sparse PK sampling design precluded non-compartmental analysis (NCA) for each individual. Instead, the results this study will be pooled with other clinical studies to enable population PK analysis.
The result of the population PK analysis will be reported separately in the Type II variation for pJIA

3. CHMP's overall conclusion and recommendation

■ Fulfilled:

The MAH submitted a completed paediatric study (Study A3921104) for tofacitinib for treatment of polyarticular course juvenile idiopathic arthritis (JIA), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This submission is in fulfilment of the Article 46 requirement. Study A3921104 is a deferred study in the JIA PIP (Study 6) with a completion date by February 2020.
A consequential Type II variation to update the SmPC with the relevant results is planned for submission in June 2020.
No further action required; however further data are expected in the context of a type II variation prior any conclusion on product information amendments is made.

The submission of this variation application is due by June 2020.