30 January 2025
EMA/65469/2025
Human Medicines Division

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/P46/029

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On September 2024, the MAH submitted a completed paediatric study (A3921165) for Xeljanz (tofacitinib) for treatment of systemic juvenile idiopathic arthritis (sJIA), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study A3921165 titled "efficacy, safety, tolerability and pharmacokinetics of tofacitinib for treatment of systemic juvenile idiopathic arthritis (sjia) with active systemic features in children and adolescent subjects" is a global study conducted in accordance with the approved EU Paediatric Investigation Plan, PIP 01 (Treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis)), Study 7 (EMEA-000576-PIP01-09-M16; EMA Opinion date: 31 May 2024).

This study is indeed being submitted in accordance with Article 46 of the Paediatric Regulation (EC) No. 1901/2006 and is also part of the PIP commitments for tofacitinib.

The applicant requested to EMA/PDCO in 2017 (in the context of Modification 07 of the original PIP) to change the study design from a parallel placebo-controlled safety and efficacy trial in children with sJIA to a placebo-controlled withdrawal design. This change was proposed on the basis of significant changes in the context of treatments for JIA since first agreement of the paediatric investigational program (PIP) in 2010.

Indeed, with effective treatments on the market a parallel-group placebo-controlled design was no longer ethical. In the randomized withdrawal design, only responders to open-label treatment with tofacitinib were randomized into the double-blind phase comparing tofacitinib to start placebo.

The PDCO agreed with the proposed modification, in line with CHMP guidance (EMA/CHMP/239770/2014 Rev2) and with recently agreed PIPs for other products for sJIA.

In addition, the proposed primary endpoint (Time to flare in the double-blind phase) for a randomised withdrawal design study was in line with the EMA guideline on the clinical investigation of medicinal products for the treatment of JIA (EMA/CHMP/239770/2014 Rev.2).

Study A3921165 was a two-part study (an open-label, run-in phase, followed by a double blind, placebo-controlled, randomized event-driven withdrawal phase) in 100 patients with systemic JIA with active systemic features (ages 2 to <18 years).

2.2. Information on the pharmaceutical formulation used in the study

Two formulations are available for children: tablets for children ≥40 kg and oral solution for children <40 kg.

Both formulations of tofacitinib have been used in study A3921165 to enable weight-based dosing and achieve comparable tofacitinib exposure 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

The MAH submitted a final report for:

- Study A3921165, an efficacy, safety, tolerability and pharmacokinetics of tofacitinib for treatment of systemic juvenile idiopathic arthritis (sJIA) with active systemic features in children and adolescent subjects;

- A Population PK analysis using data from the multiple dose PK study (A3921103) and safety and efficacy studies (A3921104, A3921165) in paediatric patients with juvenile idiopathic arthritis (in accordance with approved EMEA-000576-PIP01-09-M16; Study 10).

2.3.2 Clinical study

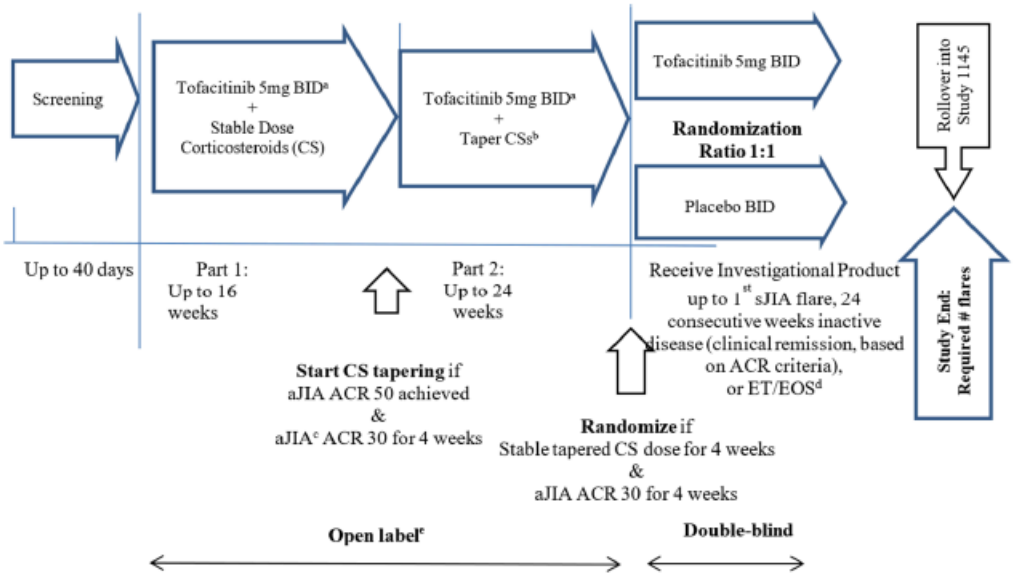
Clinical study A3921165

Study Title: Efficacy, Safety, Tolerability and Pharmacokinetics of Tofacitinib for Treatment of Systemic Juvenile Idiopathic Arthritis (sJIA) With Active Systemic Features in Children and Adolescent Subjects

Description

Study A3921165 was a two-part study (an open-label, run-in phase, followed by a double blind, placebo-controlled, randomized event-driven withdrawal phase) to evaluate efficacy, safety and tolerability, and pharmacokinetics in patients with systemic JIA with active systemic features (age 2 to <18 years).

Figure 1. Study Design



a Subjects <40 kg will receive an equivalent weight based lower dose of tofacitinib 5 mg BID.

b CS Tapering is only required for subjects treated with CS >0.2 mg/kg/day oral prednisone (or equivalent). During the active CS tapering period in Part 2 subjects must maintain an Adapted JIA ACR 50 response.

c aJIA: Adapted JIA.

d Subjects who discontinue Investigational Product in the randomized withdrawal phase continue in study until week 52 after randomization, or until the study concludes, whichever comes first.

e Subjects who discontinue the study in the open-label phase and do not enter A3921145 within 4 weeks, will be required to perform a follow-up visit 28 days after the last dose of Investigational Product.

Methods

The open-label active treatment period consists of two parts:

- **Part 1** designed to identify tofacitinib-treated subjects who are able to achieve and maintain an Adapted JIA ACR 30 response for at least 4 weeks while continuing on the stable CS dose identified during the screening period prior to treatment with tofacitinib.
- **Part 2** to taper CSs in subjects receiving CS doses >0.2 mg/kg/day to a target range. Subjects treated with stable oral prednisone (or equivalent) doses ≤0.2 mg/kg/day who were able to maintain an Adapted JIA ACR 30 response for 4 weeks in Part 1 were allowed to skip Part 2 and be randomized in the Double-Blind Withdrawal Phase of the study.

Before CS tapering can start in the Open-label Phase Part 2, subjects will be required to achieve an Adapted ACR 50 response in the Open-label Phase Part 1 in addition to maintaining an Adapted ACR 30 response for 4 weeks.

After 12 to 40 weeks of treatment with tofacitinib, sJIA patients who were able to taper corticosteroids (CS) while maintaining an Adapted JIA ACR 30 response were identified as "**responders**". These responders proceed to a double-blind withdrawal phase in which they were randomized to either continue with tofacitinib treatment or start placebo treatment. Sustained efficacy of tofacitinib to prevent disease flare was evaluated in the randomized withdrawal phase.

The minimum total duration of treatment with a stable dose of tofacitinib for subjects completing Parts 1 and 2 was 12 weeks to qualify to enter the randomized withdrawal phase of the study, in which "responders" from the open-label phase were randomized in a 1:1 ratio to either continue tofacitinib or start placebo. The **double-blind withdrawal** phase continued until **a sufficient number of flares** were reported. In the double-blind phase "time to sJIA flare" was evaluated as primary endpoint.

sJIA Flare is defined as <u>at least one</u> of the following:

• Recurrence of fever (>38° C on 2 or more consecutive days) considered to be due to SJIA activity.

• Worsening of 30% or more in three or more of the six variables of the JIA core set with no more than one variable of the JIA core set improving by 30% compared to the day of randomization into the withdrawal phase.

An **interim analysis for efficacy and futility** was planned when 28 flares were observed. If either criterion is met, the study will be stopped. If neither criterion is met, the study will continue until the requisite number of flares are observed as determined by the number of flares included in statistical analysis (37 subjects with flares).

Subjects who flare or achieve ACR clinical remission (ie, maintain JIA ACR inactive disease during 24 consecutive weeks) were to be given the opportunity to participate in A3921145 (long-term extension study) and be treated with open-label tofacitinib. Subjects who discontinue Investigational Product in the double-blind phase and who do not enter A3921145 continued in A3921165 for follow up of efficacy and safety endpoints. Subjects should receive standard-of-care treatment in accordance with local treatment guidelines.

Study participants

Key **inclusion** criteria were as follows:

I. Male or female aged 2 to <18 years.

II. Diagnosed with sJIA according to International League Against Rheumatism (ILAR) criteria, and, in the opinion of the investigator, have active disease prior to screening.

Subjects must have active disease at the time of enrolment, defined as:

a. Documented intermittently spiking temperature >38° C for at least 1 day due to sJIA in the screening period and within 1 week before the first dose, and the presence of at least 2 joints with active arthritis at screening and baseline, and an ESR >30 mm/hr. [1.5 X ULN] at screening.

OR

b. <u>Only after cohort review is completed and enrolment is opened without restrictions</u>: The presence of at least 5 joints with active arthritis at screening and baseline, and an ESR >30 mm/hr. [1.5 X ULN] at screening.

III. Treatment with stable doses of methotrexate (MTX) and/or oral CSs is permitted.

a. MTX: Treatment for ≥3 months with MTX and with a stable dose of MTX (dose must be ≤25 mg/wk or ≤20 mg/m2/week, whichever is lower) for at least 4 weeks before the first study drug dose (Day 1).

b. CS: Treatment with a stable dose of oral prednisone (≤1 mg/kg/day up to a maximum of 30 mg/day), or equivalent, for at least 1 week before the first study drug dose (Day 1).

IV. No evidence or history of untreated or inadequately treated active or latent tuberculosis infection.

Key **exclusion** criteria in brief were as follows:

- Previous JIA treatment with tofacitinib
- Current symptoms or findings of myocarditis, endocarditis or more than minimal pericardial effusion associated with sJIA;
- Current symptoms or findings of more than minimal pleuritis with sJIA.
- Subjects who are still within the washout periods for disallowed nonbiological and biological DMARDs.
- Infections:

  a. Chronic infections;

  b. Any infection requiring hospitalization, parenteral antimicrobial therapy or judged to be opportunistic within the 3 months prior to the first dose of study intervention;

  c. Any treated infections within 2 weeks of baseline;

  d. A subject known to be infected with Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C;

  e. History of infected joint prosthesis with prosthesis still in situ

- History of recurrent (more than one episode) herpes zoster or disseminated (at least one episode) herpes zoster, or disseminated (at least one episode) herpes simplex.
- Diagnosis of active Macrophage Activation Syndrome (MAS) within 3 months prior to the first dose of study intervention.

Treatments

In open-label phase: treatment with tofacitinib

In double-blind phase: treatment with tofacitinib or placebo in 1:1 ratio

Tofacitinib was provided as oral tablets (tofacitinib 5 mg) and as an oral solution (CP 690,550 [the compound name for tofacitinib] 1 mg/mL) by the Sponsor.

OL bottles of tofacitinib tablets and CP 690,550 (compound name for tofacitinib) oral solution were provided for the OL phase of the study. Blinded-label bottles of tofacitinib tablets, CP 690,550 (compound name for tofacitinib) oral solution, and matching placebo, for oral administration, were provided for the DB withdrawal phase of the study.

Table 1. Study Treatment dosing and administration

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

Objective(s)

Primary objective

- To assess the sustained efficacy of tofacitinib versus placebo in sJIA patients, as measured by time to sJIA flare in the double-blind randomized withdrawal phase.

Secondary objectives

- To assess efficacy of tofacitinib versus placebo in sJIA patients at various time points in the double-blind randomized withdrawal phase
- To assess the efficacy of tofacitinib in sJIA patients in the open label treatment phase.
- To assess the safety and tolerability of tofacitinib in sJIA patients.
- To assess the pharmacokinetics of tofacitinib in sJIA patients in the open label phase.

Outcomes/endpoints

Primary endpoint

1. Time to sJIA disease flare in the double-blind randomized withdrawal phase.

Secondary endpoints

1. Occurrence of disease flares in the double-blind phase at each visit.
2. Achievement of corticosteroid tapering per protocol at the end of the open label active treatment period in applicable subjects receiving corticosteroids on study Day 1 of the open label phase.
3. Achievement of a corticosteroid dose of ≤0.2 mg/kg/day or 10 mg/day (whichever is lower) at the end of the open label treatment period in subjects receiving corticosteroids on Day 1 of the open label phase.
4. Adapted JIA ACR 30/50/70/90/100 response at every visit from Day 7 onward in the open label and the double-blind phase.
5. Fever (Temp >38 °C) attributed to sJIA at Day 3, Day 7 and Day 14 of the open label phase.
6. CRP ≤10 mg/L at every visit of the open label phase.
7. Absence of fever, defined as absence of fever due to sJIA in the week preceding the assessment at every visit from Day 7 onward in the open label and double-blind phase.
8. Time to first Adapted JIA ACR 30 response in Part 1 of the open label phase.
9. Change from baseline in Juvenile Arthritis Disease Activity Score (JADAS 27) at every visit from Day 7 onward in the open label and double-blind phase.
10. Change from baseline in each JIA ACR core variable at every visit from Day 7 onward in the open label and double-blind phase.
11. Change from baseline in Child Health Questionnaire (CHQ) responses at the end of Part 1 and Part 2 of the open label phase, at randomization and every 6 months thereafter.
12. Change from baseline in Child Health Assessment Questionnaire (CHAQ) at every visit from Day 7 onward in the open label and double-blind phase.
13. Occurrence of inactive disease status and minimal disease activity at every visit from Day 7 onward (JADAS 27) in the open label and double-blind phase.
14. Occurrence of inactive disease status at every visit from Day 7 onward (JIA ACR) in the open label phase.
15. Occurrence of inactive disease status at every visit and clinical remission at every visit starting at Week 24 in the double-blind phase.

Safety Endpoints

1. All adverse events (AEs), including Serious Adverse Events (SAEs).
2. Macrophage activation syndrome (MAS) events.
3. Serious infections, including tuberculosis, varicella and herpes zoster and opportunistic infections.
4. Clinically significant abnormal laboratory parameters, including abnormal haematology parameters, lipid parameter changes, liver enzymes, serum creatinine elevation.
5. Malignancies, including lymphoma and non-melanoma skin cancer.
6. Gastrointestinal perforations.
7. Cardiovascular diseases.
8. Assessments of growth and pubertal development.

Sample size

Approximately 100 subjects were to be enrolled in the open-label run-in phase of the study and based on results from a similarly designed sJIA clinical trial (Ruperto N et al. Two randomized trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis. New England Journal of Medicine 2012), it was estimated that approximately 55% of the subjects enrolled in the open-label run-in phase would enter the randomized withdrawal DB phase of the study.

The primary objective in the DB phase of the study was to test the superiority of tofacitinib (5 mg BID) over placebo as measured by the time to flare. There were potentially 2 planned analyses. The First Analysis was to be performed after 28 subjects had reported flare in the DB phase. If the study did not end for efficacy or futility at the First Analysis, a total of 37 subjects with flares were required for the Final Analysis to yield an overall power of 80% using a log rank test to detect the treatment difference, assuming a 1-sided type I error rate of 2.5% and a 64% improvement in median time to flare (i.e., a hazard ratio of 0.36 and a median time to flare of 236 days for placebo; assumptions based on a similar sJIA randomized withdrawal trial).

Randomisation and blinding (masking)

Only subjects who are able to maintain a minimal clinical response for 4 weeks in the OL phase at an allowed CS dose will proceed to randomization. Eligible subjects were to be randomized in a 1:1 ratio into the double-blind withdrawal phase to either continue tofacitinib treatment or withdraw the tofacitinib dose and start placebo. Randomization was stratified by age group (2 to <6, 6 to <12, and ≥12 years).

Statistical Methods

Primary endpoint

The time to flare was assessed using Kaplan-Meier methods and displayed graphically. The median time to flare and corresponding 2-sided 95% confidence interval (CI) were provided. Difference in time to flare between the two treatment groups (tofacitinib vs. placebo) was assessed using a stratified Log-rank test if enough events were observed in each stratum. Otherwise, the unstratified Log-rank test was used.

As a supportive analysis for the Log-rank test, Hazard ratios (tofacitinib/placebo) and 95% CIs were obtained from a Cox Proportional hazards model with treatment group as covariate.

Subjects who discontinued the study treatment due to inactive disease for at least 24 weeks in the double-blind phase were censored at the time of study drug discontinuation (i.e., their discontinuation was not analyzed as a disease flare). Treatment discontinuations for any other reasons was considered as flares.

Secondary endpoints

As this was a time-to-event trial, participants had varying follow-up times. For efficacy endpoints analyzed by visit, only the data through 52 weeks in the double-blind phase were analyzed statistically.

Secondary binary endpoints such as: occurrence of disease flare or inactive disease status, achieving a response of adapted JIA, absence of fever, etc., were analyzed using statistical methods for binary variables (normal approximation to binomial proportions).

For the continuous endpoints, a mixed model for repeated measures (MMRM) was applied, including fixed effects for treatment (tofacitinib and placebo), visit, treatment by visit interaction, baseline value, baseline value by visit interaction.

Interim analysis for efficacy and futility

Type I error rate was preserved at 0.025 (1-sided test) and the overall study power maintained at 80% (type II error rate $\beta=0.2$), by spending a fraction of α for efficacy and a fraction of β for futility at the First Analysis, so it was accounted for in the overall type I error rate and type II error rate, respectively.

A formal efficacy boundary for rejecting the null hypothesis was constructed by using the spending function methodology of the gamma family design with $\gamma= 4$. Similarly, a formal futility boundary for not rejecting the null hypothesis was constructed by using the spending function methodology of the gamma family design with $\gamma= -4$. Boundaries with 28 flares at the First Analysis are as follows.

If the value of the test-statistic at the First Analysis crosses the efficacy boundary ($z\leq-1.973$, 1-sided $p\leq0.0242$), the trial may be stopped for efficacy.

If the value of the test-statistic at the First Analysis crosses the futility boundary ($z\geq-1.240$, 1-sided $p\geq0.1074$), the trial may be stopped for futility.

Otherwise, the trial was to continue as planned. The Final Analysis was to be performed after flares had been reported in approximately 37 subjects.

Estimands

The **primary estimand** of the primary endpoint was based on a composite strategy (Estimand 1). Patients who completed study participation after maintaining JIA ACR inactive disease for at least 24 weeks (i.e., clinical remission) in the double-blind phase, and patients who were still active in the double-blind withdrawal phase but had to discontinue due to study end were censored at the last available flare assessment. Patients who discontinued study treatment for any other reasons were considered as having a disease flare.

A supplementary estimand for the primary endpoint used the hypothetical strategy (Estimand 4), which estimates the treatment effect if all patients adhere to the protocol and the intercurrent event of treatment discontinuation has not occurred. A second supplementary estimand for the primary endpoint used the treatment policy strategy (Estimand 5) and estimates the treatment difference regardless of whether an intercurrent event occurs.

Secondary binary endpoints were analyzed based on a composite strategy (Estimand 2). For end of study treatment after clinical remission and treatment discontinuation due to study end, last on-

treatment value was carried forward (ie, LOCF) until Week 52. Treatment discontinuations for any other reason were considered as non-response.

A supplementary analysis for aJIA ACR response was performed based on the treatment policy strategy (Estimand 6) and all aJIA ACR data collected while on- and off-treatment were used to derive the endpoints regardless of the intercurrent event.

For the continuous endpoints, the analyses were based on the treatment policy strategy (Estimand 3) and hypothetical strategy (Estimand 7). Estimand 3 included all data collected while on- and off-treatment while Estimand 7 only included on-treatment data.

Population PK model

A population PK model (Module 5.3.4.2 PMAR: EQDD-A392I-sNDA-1703) was developed using the PK concentration data from the Phase 1 PK Study A3921103, Phase 3 efficacy Studies A3921104 and A3921165, and the LTE Study A3921145, where both oral solution and tablet was administered.

Study A3921103: a phase 1, 5-day, open-label, non-randomized, and multiple-dose study, which has been used to guide weight-based dosing algorithm in subsequent studies (A3921104/A3921165/A3921145) in JIA patients

Study A3921104: a pivotal phase 3, randomized withdrawal study to demonstrate the efficacy and safety of tofacitinib 5 mg or a weight-based dose BID in pJIA subjects

Study A3921165: a pivotal phase 3, randomized withdrawal study to demonstrate the efficacy and safety of tofacitinib 5 mg or a weight-based dose BID in sJIA subjects

Study A3921145: a phase 2/3 long-term, open label, follow-up study in which patients who completed the index studies (A3921103, A3921104 and A3921165)

The objectives of this population pharmacokinetic analysis were to:

1. Describe the pharmacokinetic (PK) of tofacitinib (CP-690,550) in paediatric patients from 2 to less than 18 years of age with JIA

2. Identify potential covariates in the study population(s) which account for the variability in CP-690,550 exposure

Methods

The population PK model was performed using the nonlinear mixed effects modelling Approach.

The population PK of tofacitinib has been previously characterized in pJIA patients by pooling data from two completed paediatric studies, A3921103 and A3921104, and an ongoing long-term extension study A3921145

In the previous developed model, the population PK of tofacitinib in patients with pJIA was described **by a one compartment model parameterized in terms of apparent oral clearance (CL/F), apparent of volume of distribution (V/F), and first order absorption with a lag time.** An allometric weight scaling was inherently built into the model, with clearance and volume parameters being scaled with weight raised to power coefficients. The effect of formulation (oral solution or tablet) on the absorption was identified to be significant.

The previous PK model results were used to characterize the pooled JIA dataset after the inclusion of data from study A3921165.

The final dataset included 4427 records from 324 subjects, **of which 75 are sJIA subjects**.

A list of potential covariates was explored for inclusion in the PK model. Covariate selection was performed using a stepwise covariate model (SCM) approach. The parameter-covariate relationship was evaluated using stepwise forward-inclusion backward-deletion procedures. Sex, age, baseline body surface area, race, patient type, concomitant medications, baseline renal function, baseline C-reactive protein, baseline Alanine transaminase, baseline Alkaline phosphatase were tested as potential covariates on CL/F.

GoF and VPCc were used to evaluate model performance. The quality of the final model predictions was determined by the agreement between the intervals of the simulated percentiles and percentiles of the observed data as observed in Visual Predictive Checks (VPCs).

Finally, simulations were performed to verify the effectiveness of the current weight-based dosing scheme in the drug label (which was developed for pJIA) in all JIA subjects including sJIA.

Results

The study was conducted from 10 May 2018 to 27 March 2024.

Participant flow

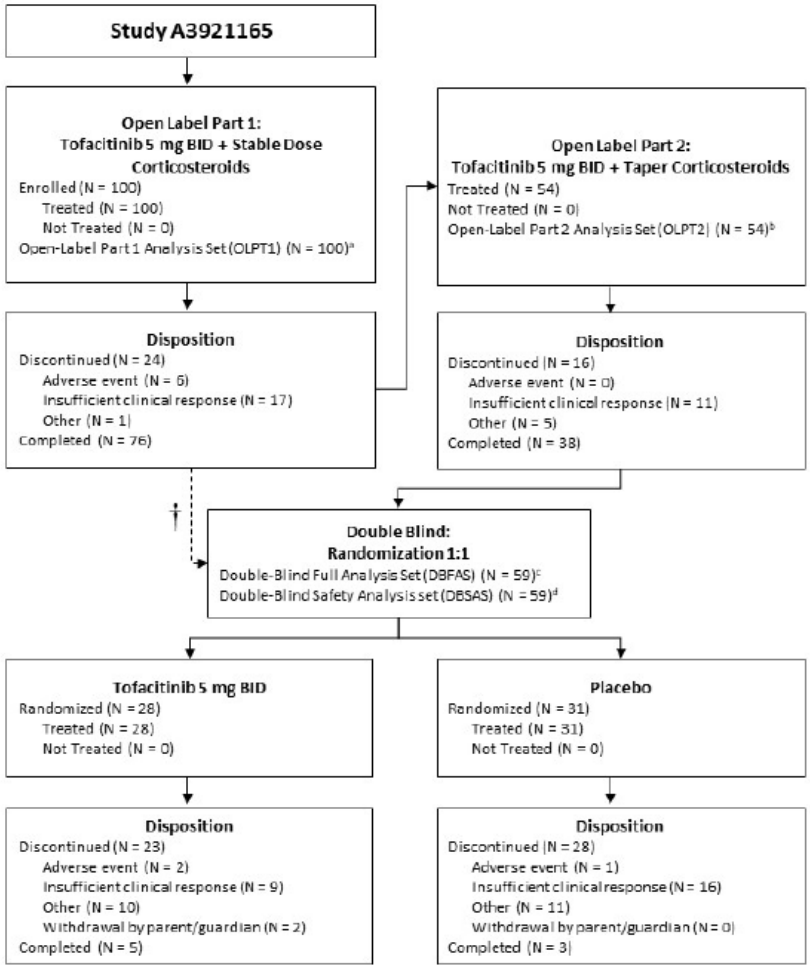
From a total of 101 sites in 23 countries, 167 participants were screened and 100 were enrolled in this study: Argentina (2), Belgium (1), Brazil (3), Canada (2), China (26), Germany (1), India (22), Israel (7), Mexico (4), Poland (1), Russian Federation (3), South Africa (9), Spain (4), Turkey (1), Ukraine (8), and the United States (6).

From the total of 100 participants enrolled into the OL phase of the study, 59 participants were randomized between the treatment groups in the DB phase.

In the DB phase, the proportions of overall discontinuations and underlying reasons for discontinuation were similar between the two treatment groups.

Participant disposition is presented in Figure 2.

Figure 2. Subject Disposition



Source: Table 14.1.1.1, Table 14.1.1.2.1, Table 14.1.1.2.2, and Table 14.1.1.2.3.
†. Some patients not on corticosteroids or on allowable doses of CS at baseline went directly from OL Phase Part 1 to the DB phase.
a. OLPT1 consisted of all participants who were enrolled into the OL part 1 and received at least one dose of investigational product in part 1.
b. OLPT2 consisted of all participants who were enrolled into the OL part 2 and received at least one dose of investigational product in part 2.
c. DBFAS consisted of all randomized participants who received at least one dose of investigational product in the DB phase
d. DBSAS consisted of all randomized participants who received at least one dose of investigational product in the DB phase.

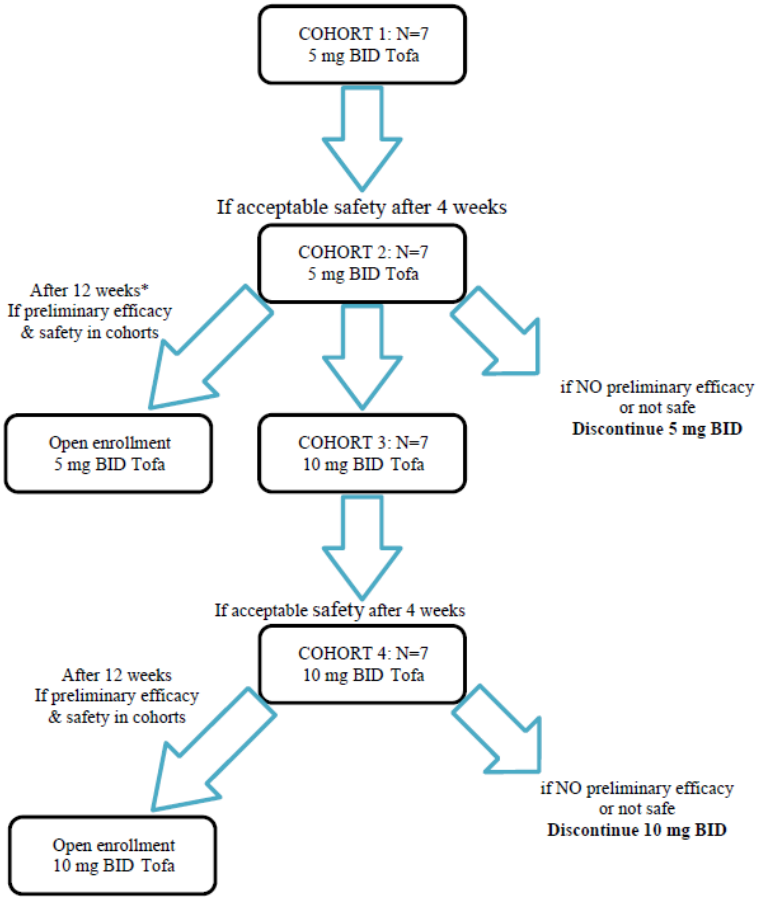
No disposition events or permanent discontinuation of study intervention due to COVID-19 were reported.

Important change in study conduct

The original protocol design included the 10 mg BID dose as it was anticipated that, due to the underlying pathophysiology of sJIA, participants may require a higher dose to achieve efficacy than that needed for pcJIA.

The initially planned dose escalation schema was the following:

Figure 3. Dose Evaluation Schema

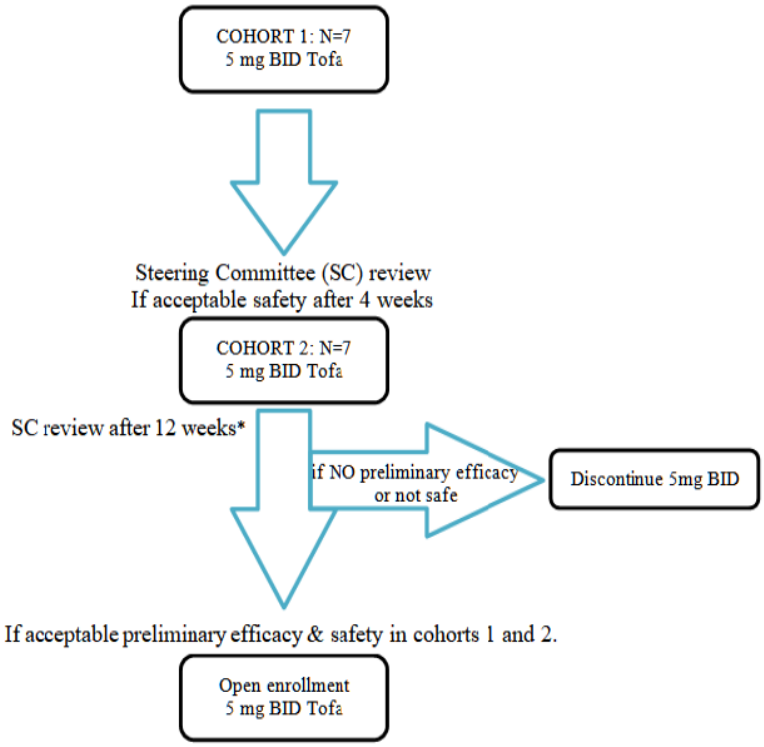


In response to a Special Safety Concern of pulmonary embolism identified in an adult RA study, screening was stopped, administration of the 10 mg BID dose was discontinued, and examination of subjects at each visit to identify potential risk of VTE was implemented (Amendments 2 and 3). The discontinuation of the 10 mg BID dose potentially impacted the efficacy endpoints because dose escalation was no longer possible for participants who were unable to control fever using the 5 mg BID dose.

At the time of Amendment 2, only Cohort 1 (5 mg BID dose evaluation) completed and Cohort 2 (5 mg BID dose evaluation) was ongoing. There were 2 participants that required a dose escalation to 10 mg BID after 14 days of dosing due to uncontrolled fever. One participant discontinued 4 days after the dose increase due to sJIA exacerbation and 1 participant had their dose decreased to tofacitinib 5 mg BID.

The dose evaluation schema after Amendment 2 was the following:

Figure 4. Dose Evaluation Schema



Other changes regarded COVID-19 pandemic and conflict in Ukraine and Russia.

The most frequently reported important protocol deviations in the OL and DB phases were related to sample collection and analysis.

Recruitment/ Number analysed

The analysis of efficacy in each of the analysis sets included all participants who were either enrolled (OL phases) or randomized (DB phase) into the study and received at least 1 dose of investigational product. The analysis of safety data in each of the analysis sets included all participants in each phase who received at least 1 dose of investigational product. All participants in the DB phase were included in the full (DBFAS) and the safety analysis sets (DBSAS).

Baseline data

Table 2. Participant Demographic Characteristics – OLPT1

	Tofacitinib 5mg BID OL (N=100)			
	2 to < 6 Years (N=17)	6 to < 12 Years (N=43)	12 to < 18 Years (N=40)	Total (N=100)
Age (years):				
Mean (SD)	4.18 (0.95)	8.28 (1.62)	14.25 (1.78)	9.97 (4.11)
Median (Range)	4.0 (2.0, 5.0)	8.0 (6.0, 11.0)	14.0 (12.0, 17.0)	10.0 (2.0, 17.0)
Q1, Q3	4.0, 5.0	7.0, 10.0	13.0, 16.0	7.0, 13.0
Gender, n (%)				
Male	11 (64.7)	22 (51.2)	23 (57.5)	56 (56.0)
Female	6 (35.3)	21 (48.8)	17 (42.5)	44 (44.0)
Race, n (%)				
White	8 (47.1)	12 (27.9)	19 (47.5)	39 (39.0)
Black or African American	2 (11.8)	2 (4.7)	3 (7.5)	7 (7.0)
Asian	6 (35.3)	28 (65.1)	15 (37.5)	49 (49.0)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0

The demographic characteristics for OLPT2 were overall similar with characteristics of patients in OLPT1 with lower number of participants for every age group: 2 to <6 years N=10, 6 to <12 years N=21, 12 to <18 years N=23 (total 54 participants).

Table 3. Participant Demographic Characteristics – DBFAS

	Tofacitinib 5mg BID DB (N=28)				Placebo (N=31)			
	2 to < 6 Years (N=3)	6 to < 12 Years (N=12)	12 to < 18 Years (N=13)	Total (N=28)	2 to < 6 Years (N=6)	6 to < 12 Years (N=11)	12 to < 18 Years (N=14)	Total (N=31)
Age (years):								
Mean (SD)	3.67 (1.15)	7.75 (1.66)	14.31 (2.18)	10.36 (4.34)	3.83 (1.17)	8.55 (1.75)	14.57 (1.83)	10.35 (4.55)
Median (Range)	3.0 (3.0, 5.0)	7.0 (6.0, 11.0)	14.0 (12.0, 17.0)	10.5 (3.0, 17.0)	4.0 (2.0, 5.0)	8.0 (6.0, 11.0)	14.5 (12.0, 17.0)	11.0 (2.0, 17.0)
Q1, Q3	3.0, 5.0	6.5, 9.0	12.0, 17.0	7.0, 13.5	3.0, 5.0	7.0, 10.0	13.0, 16.0	7.0, 14.0
Gender, n (%)								
Male	2 (66.7)	8 (66.7)	6 (46.2)	16 (57.1)	3 (50.0)	8 (72.7)	11 (78.6)	22 (71.0)
Female	1 (33.3)	4 (33.3)	7 (53.8)	12 (42.9)	3 (50.0)	3 (27.3)	3 (21.4)	9 (29.0)
Race, n (%)								
White	1 (33.3)	4 (33.3)	6 (46.2)	11 (39.3)	4 (66.7)	3 (27.3)	6 (42.9)	13 (41.9)
Black or African American	0	1 (8.3)	2 (15.4)	3 (10.7)	1 (16.7)	0	1 (7.1)	2 (6.5)
Asian	2 (66.7)	7 (58.3)	4 (30.8)	13 (46.4)	1 (16.7)	7 (63.6)	6 (42.9)	14 (45.2)
American Indian or Alaska Native	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0
Other	0	0	1 (7.7)	1 (3.6)	0	1 (9.1)	1 (7.1)	2 (6.5)

Demographic characteristics were generally similar between the two treatment groups at OL and DB baseline. However, there were more male subjects in the placebo arm (71%) compared to tofacitinib arm (57.1%).

The mean age (SD) of participants in the tofacitinib 5 mg BID and placebo treatment groups was 10.36 (4.34) and 10.35 (4.55) years, respectively.

In the tofacitinib 5 mg BID treatment group, the largest proportion of participants were of Asian descent (46.4%); 39.3% of all participants were White, and 10.7% of participants were Black or African American. Similar proportions were reported in the placebo treatment group.

Table 4. Disease Assessments at Open-Label Baseline – OLPT1, OLPT2, DBFAS

	OLPT1	OLPT2	DBFAS	
	Tofacitinib 5 mg BID OL (N=100)	Tofacitinib 5 mg BID OL (N=54)	Tofacitinib 5mg BID DB (N=28)	Placebo (N=31)
Physician Global Evaluation of Overall Disease Activity [a]				
n	100	54	28	31
Mean (SD)	6.9 (1.89)	6.8 (1.81)	6.9 (1.88)	6.5 (1.98)
Median (range)	7.5 (1.0, 10.0)	7.0 (1.0, 10.0)	7.5 (1.0, 9.0)	7.0 (2.0, 9.5)
Q1, Q3	6.0, 8.3	6.0, 8.0	6.3, 8.0	5.0, 8.0
C-reactive protein (CRP) (mg/dL) [b]				
n	100	54	28	31
Mean (SD)	4.9 (5.22)	4.9 (4.54)	3.4 (4.44)	2.6 (3.58)
Median (range)	2.9 (0.0, 24.6)	3.3 (0.0, 18.1)	1.5 (0.0, 18.5)	1.4 (0.0, 13.9)
Q1, Q3	0.7, 8.2	1.0, 9.1	0.3, 5.6	0.3, 3.2
C Reactive Protein Category				
Normal	15 (15.0%)	7 (13.0%)	7 (25.0%)	7 (22.6%)
Above Normal	85 (85.0%)	47 (87.0%)	21 (75.0%)	24 (77.4%)
CHAQ: Evaluation of Overall Well-being [c]				
n	100	54	28	31
Mean (SD)	6.9 (2.08)	6.7 (2.02)	7.6 (1.51)	6.8 (1.97)
Median (range)	7.0 (1.0, 10.0)	7.0 (1.0, 10.0)	8.0 (4.5, 10.0)	7.0 (1.0, 10.0)
Q1, Q3	5.5, 8.5	5.0, 8.5	6.5, 8.5	5.5, 8.5
CHAQ: Disability Index [c]				
n	100	54	28	31
Mean (SD)	1.3 (0.78)	1.3 (0.79)	1.6 (0.66)	1.1 (0.68)
Median (range)	1.3 (0.0, 3.0)	1.3 (0.0, 3.0)	1.9 (0.0, 2.4)	1.0 (0.0, 2.1)
Q1, Q3	0.6, 2.0	0.6, 2.0	1.3, 2.0	0.5, 1.9
CHAQ: Discomfort Index [c]				
n	100	54	28	31
Mean (SD)	6.8 (2.27)	6.6 (2.35)	7.7 (1.52)	6.3 (2.28)
Median (range)	7.5 (1.0, 10.0)	7.5 (1.0, 9.5)	8.0 (4.0, 10.0)	6.0 (1.0, 9.5)
Q1, Q3	5.0, 8.5	5.0, 9.0	6.8, 9.0	5.0, 8.0
JADAS-27 CRP Score [d]				
n	100	54	28	31
Mean (SD)	26.0 (8.58)	25.7 (8.79)	23.8 (5.75)	22.3 (6.71)
Median (range)	24.0 (11.5, 53.0)	23.4 (12.9, 53.0)	22.5 (13.8, 39.6)	21.0 (11.5, 36.2)
Q1, Q3	20.0, 30.5	19.4, 30.5	20.0, 27.0	17.0, 26.9
JADAS-27 CRP High Disease Activity				

Yes	100 (100.0%)	54 (100.0%)	28 (100.0%)	31 (100.0%)
No	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age at First Diagnosed				
n	99	53	28	30
Mean (SD)	7.2 (4.31)	7.5 (4.44)	7.3 (4.49)	7.9 (4.84)
Median (range)	6.4 (0.2, 16.8)	6.9 (0.2, 16.8)	6.8 (0.2, 16.5)	7.1 (0.2, 16.8)
Q1, Q3	4.0, 10.8	4.4, 11.8	4.5, 11.3	3.9, 11.9
Duration since Onset				
n	99	53	28	30
Mean (SD)	2.8 (3.22)	2.3 (3.01)	3.1 (3.73)	2.4 (3.48)
Median (range)	1.4 (0.1, 15.7)	0.9 (0.1, 14.8)	1.2 (0.1, 15.7)	1.0 (0.1, 14.8)
Q1, Q3	0.3, 4.1	0.2, 3.7	0.4, 5.0	0.1, 2.8

a. Physician's Global: Possible range of scores is 0-10. Higher Physicians' global evaluation of overall disease activity means more JIA disease activity.
b. CRP normal is 0-0.287 mg/dL.
c. CHAQ domains and disability index ranges are 0-3. Overall well-being and discomfort index are 0-10. Higher CHAQ scores mean more disability.

Table 5. Disease Symptoms at Open-Label Baseline – OLPT1, OLPT2, DBFAS

	OLPT1	OLPT2	DBFAS	
	Tofacitinib 5 mg BID OL (N=100)	Tofacitinib 5 mg BID OL (N=54)	Tofacitinib 5mg BID DB (N=28)	Placebo (N=31)
Number of Joints with Active Arthritis [a]				
n	100	54	28	31
Mean (SD)	10.6 (9.99)	10.5 (9.57)	8.3 (7.00)	8.6 (7.37)
Median (range)	6.0 (2.0, 63.0)	6.0 (2.0, 40.0)	6.0 (2.0, 32.0)	6.0 (2.0, 30.0)
Q1, Q3	5.0, 13.0	4.0, 14.0	5.0, 10.5	5.0, 9.0
Number of Joints with Limitation of Motion				
n	100	54	28	31
Mean (SD)	6.4 (9.93)	6.0 (8.80)	4.9 (7.27)	4.4 (6.99)
Median (range)	2.0 (0.0, 65.0)	2.0 (0.0, 32.0)	1.5 (0.0, 29.0)	2.0 (0.0, 33.0)
Q1, Q3	0.0, 7.5	0.0, 7.0	0.0, 7.5	0.0, 6.0
Number of Swollen Joints				
n	100	54	28	31
Mean (SD)	9.6 (9.40)	9.6 (9.15)	7.5 (6.57)	7.7 (7.21)
Median (range)	6.0 (0.0, 58.0)	6.0 (0.0, 36.0)	5.5 (1.0, 32.0)	5.0 (0.0, 30.0)
Q1, Q3	5.0, 12.0	4.0, 14.0	4.0, 9.0	4.0, 7.0
Number of Painful/Tender Joints				
n	100	54	28	31
Mean (SD)	9.8 (11.29)	9.7 (10.75)	10.0 (9.94)	8.3 (9.60)
Median (range)	6.0 (0.0, 67.0)	5.5 (0.0, 44.0)	7.5 (0.0, 44.0)	6.0 (0.0, 41.0)
Q1, Q3	2.5, 12.0	2.0, 14.0	5.0, 9.5	2.0, 8.0
Duration of Morning Stiffness (min)				
n	100	54	28	31
Mean (SD)	49.1 (87.48)	52.5 (86.52)	37.4 (30.25)	38.3 (50.46)
Median (range)	20.0 (0.0, 500.0)	24.5 (0.0, 500.0)	27.5 (0.0, 120.0)	20.0 (0.0, 180.0)
Q1, Q3	0.0, 60.0	5.0, 60.0	20.0, 47.5	0.0, 40.0
Fever				
Yes	23 (23.0%)	11 (20.4%)	9 (32.1%)	9 (29.0%)
No	77 (77.0%)	43 (79.6%)	19 (67.9%)	22 (71.0%)
Generalized Lymphadenopathy				
Yes	10 (10.0%)	8 (14.8%)	3 (10.7%)	4 (12.9%)
No	90 (90.0%)	46 (85.2%)	25 (89.3%)	27 (87.1%)
Hepatomegaly				
Yes	5 (5.0%)	2 (3.7%)	5 (17.9%)	0 (0.0%)
No	95 (95.0%)	52 (96.3%)	23 (82.1%)	31 (100.0%)
Rash				
Yes	40 (40.0%)	24 (44.4%)	13 (46.4%)	15 (48.4%)
No	60 (60.0%)	30 (55.6%)	15 (53.6%)	16 (51.6%)
Serositis				
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
No	100 (100.0%)	54 (100.0%)	28 (100.0%)	31 (100.0%)
Splenomegaly				
Yes	6 (6.0%)	2 (3.7%)	3 (10.7%)	1 (3.2%)
No	94 (94.0%)	52 (96.3%)	25 (89.3%)	30 (96.8%)

a. 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.

Table 6. sJIA Medications at Open-Label Baseline – OLPT1, OLPT2, DBFAS

	OLPT1	OLPT2	DBFAS	
	Tofacitinib 5 mg BID OL (N=100)	Tofacitinib 5 mg BID OL (N=54)	Tofacitinib 5mg BID DB (N=28)	Placebo (N=31)
Formulation				
Tablet	34 (34.0%)	19 (35.2%)	8 (28.6%)	12 (38.7%)
Solution	60 (60.0%)	32 (59.3%)	18 (64.3%)	16 (51.6%)
Switchers	6 (6.0%)	3 (5.6%)	2 (7.1%)	3 (9.7%)
Oral Corticosteroid Use at Open-Label Baseline				
Yes	93 (93.0%)	54 (100.0%)	25 (89.3%)	27 (87.1%)
No	7 (7.0%)	0 (0.0%)	3 (10.7%)	4 (12.9%)
MTX Use at Open-Label Baseline				
Yes	70 (70.0%)	34 (63.0%)	23 (82.1%)	21 (67.7%)
No	30 (30.0%)	20 (37.0%)	5 (17.9%)	10 (32.3%)
Other csDMARDs Use at Open-Label Baseline				
Yes	77 (77.0%)	39 (72.2%)	24 (85.7%)	23 (74.2%)
No	23 (23.0%)	15 (27.8%)	4 (14.3%)	8 (25.8%)
MTX Use on First Dose Date				
Yes	61 (61.0%)	31 (57.4%)	22 (78.6%)	20 (64.5%)
No	39 (39.0%)	23 (42.6%)	6 (21.4%)	11 (35.5%)

Table 7. Double-Blind Baseline Disease and Other Baseline Characteristics – DBFAS (Protocol A3921165)

	Tofacitinib 5mg BID DB (N=28)	Placebo (N=31)
Number of Joints with Active Arthritis [a]		
n	28	31
Mean (SD)	1.2 (2.29)	0.5 (1.39)
Median (range)	0.0 (0.0, 10.0)	0.0 (0.0, 7.0)
Q1, Q3	0.0, 1.0	0.0, 0.0
Number of Joints with Limitation of Motion		
n	28	31
Mean (SD)	1.8 (4.57)	1.2 (3.83)
Median (range)	0.0 (0.0, 23.0)	0.0 (0.0, 18.0)
Q1, Q3	0.0, 2.0	0.0, 0.0
Number of Swollen Joints		
n	28	31
Mean (SD)	1.1 (2.26)	0.4 (0.75)
Median (range)	0.0 (0.0, 10.0)	0.0 (0.0, 2.0)
Q1, Q3	0.0, 1.0	0.0, 0.0

	Tofacitinib 5mg BID DB (N=28)	Placebo (N=31)
Number of Painful/Tender Joints		
n	28	31
Mean (SD)	1.1 (1.79)	0.8 (3.06)
Median (range)	0.0 (0.0, 7.0)	0.0 (0.0, 17.0)
Q1, Q3	0.0, 2.0	0.0, 0.0
Duration of Morning Stiffness (min)		
n	28	31
Mean (SD)	8.0 (20.34)	0.3 (1.25)
Median (range)	0.0 (0.0, 90.0)	0.0 (0.0, 5.0)
Q1, Q3	0.0, 5.0	0.0, 0.0
Physician's Global Evaluation of Overall Disease Activity [b]		
n	28	31
Mean (SD)	2.6 (1.72)	1.2 (1.52)
Median (range)	2.8 (0.0, 6.0)	0.5 (0.0, 5.5)
Q1, Q3	1.0, 4.0	0.0, 2.5
C-reactive protein (CRP) (mg/dL) [c]		
n	28	31
Mean (SD)	0.9 (1.43)	0.8 (1.83)
Median (range)	0.3 (0.0, 5.0)	0.1 (0.0, 8.0)
Q1, Q3	0.0, 1.0	0.0, 0.4

	Tofacitinib 5mg BID DB (N=28)	Placebo (N=31)
C Reactive Protein Category		
Normal	14 (50.0%)	23 (74.2%)
Above Normal	14 (50.0%)	8 (25.8%)
Erythrocyte Sedimentation Rate (mm/h) [d]		
n	28	30
Mean (SD)	24.2 (24.43)	18.6 (14.80)
Median (range)	20.0 (4.0, 121.0)	15.0 (4.0, 68.0)
Q1, Q3	9.5, 31.0	8.0, 24.0
Erythrocyte Sedimentation Rate Category		
Normal	15 (53.6%)	22 (71.0%)
Above Normal	13 (46.4%)	8 (25.8%)
Missing	0 (0.0%)	1 (3.2%)
CHAQ: Evaluation of Overall Well-being [e]		
n	28	31
Mean (SD)	2.5 (1.60)	1.4 (1.31)
Median (range)	2.8 (0.0, 5.5)	1.0 (0.0, 4.5)
Q1, Q3	1.5, 3.8	0.5, 2.5

	Tofacitinib 5mg BID DB (N=28)	Placebo (N=31)
CHAQ: Disability Index [e]		
n	28	31
Mean (SD)	0.6 (0.58)	0.3 (0.37)
Median (range)	0.4 (0.0, 2.0)	0.1 (0.0, 1.3)
Q1, Q3	0.0, 1.0	0.0, 0.6
CHAQ: Discomfort Index [e]		
n	28	31
Mean (SD)	2.7 (2.08)	1.4 (1.48)
Median (range)	2.8 (0.0, 8.0)	0.5 (0.0, 5.5)
Q1, Q3	1.0, 4.0	0.0, 3.0
JADAS-27 CRP Score [f]		
n	28	31
Mean (SD)	6.7 (3.99)	3.7 (4.13)
Median (range)	7.7 (0.0, 14.0)	2.8 (0.0, 18.0)
Q1, Q3	3.3, 9.6	0.5, 5.5

	Tofacitinib 5mg BID DB (N=28)	Placebo (N=31)
JADAS-27 CRP Inactive Disease		
Yes	4 (14.3%)	12 (38.7%)
No	24 (85.7%)	19 (61.3%)
Missing	0 (0.0%)	0 (0.0%)
JADAS-27 CRP Minimal Disease Activity		
Yes	7 (25.0%)	18 (58.1%)
No	21 (75.0%)	13 (41.9%)
Missing	0 (0.0%)	0 (0.0%)
JADAS-27 CRP Low Disease Activity		
Yes	3 (10.7%)	6 (19.4%)
No	25 (89.3%)	25 (80.6%)
Missing	0 (0.0%)	0 (0.0%)
JADAS-27 CRP Moderate Disease Activity		
Yes	7 (25.0%)	9 (29.0%)
No	21 (75.0%)	22 (71.0%)
Missing	0 (0.0%)	0 (0.0%)

	Tofacitinib 5mg BID DB (N=28)	Placebo (N=31)
JADAS-27 CRP High Disease Activity		
Yes	14 (50.0%)	4 (12.9%)
No	14 (50.0%)	27 (87.1%)
Missing	0 (0.0%)	0 (0.0%)
JADAS-27 ESR Score [f]		
n	28	30
Mean (SD)	6.9 (4.56)	3.6 (3.64)
Median (range)	7.3 (0.0, 19.5)	2.0 (0.0, 13.9)
Q1, Q3	3.3, 9.6	0.5, 6.5
JADAS-27 ESR Inactive Disease		
Yes	4 (14.3%)	13 (41.9%)
No	24 (85.7%)	17 (54.8%)
Missing	0 (0.0%)	1 (3.2%)
JADAS-27 ESR Minimal Disease Activity		
Yes	8 (28.6%)	18 (58.1%)
No	20 (71.4%)	12 (38.7%)
Missing	0 (0.0%)	1 (3.2%)

	Tofacitinib 5mg BID DB (N=28)	Placebo (N=31)
JADAS-27 ESR Low Disease Activity		
Yes	4 (14.3%)	5 (16.1%)
No	24 (85.7%)	25 (80.6%)
Missing	0 (0.0%)	1 (3.2%)
JADAS-27 ESR Moderate Disease Activity		
Yes	7 (25.0%)	7 (22.6%)
No	21 (75.0%)	23 (74.2%)
Missing	0 (0.0%)	1 (3.2%)
JADAS-27 ESR High Disease Activity		
Yes	13 (46.4%)	5 (16.1%)
No	15 (53.6%)	25 (80.6%)
Missing	0 (0.0%)	1 (3.2%)
Fever		
Yes	0 (0.0%)	0 (0.0%)
No	28 (100.0%)	31 (100.0%)
Generalized Lymphadenopathy		
Yes	0 (0.0%)	0 (0.0%)
No	28 (100.0%)	31 (100.0%)

	Tofacitinib 5mg BID DB (N=28)	Placebo (N=31)
Hepatomegaly		
Yes	0 (0.0%)	0 (0.0%)
No	28 (100.0%)	31 (100.0%)
Rash		
Yes	3 (10.7%)	0 (0.0%)
No	24 (85.7%)	31 (100.0%)
Serositis		
Yes	0 (0.0%)	0 (0.0%)
No	28 (100.0%)	31 (100.0%)
Splenomegaly		
Yes	1 (3.6%)	0 (0.0%)
No	27 (96.4%)	31 (100.0%)
Body Weight		
<40 kg	18 (64.3%)	18 (58.1%)
>=40 kg	10 (35.7%)	13 (41.9%)
Missing	0 (0.0%)	0 (0.0%)
Oral Corticosteroid Use at Randomization		
Yes	12 (42.9%)	17 (54.8%)
No	16 (57.1%)	14 (45.2%)
Methotrexate Use at Randomization		
Yes	22 (78.6%)	20 (64.5%)
No	6 (21.4%)	11 (35.5%)

	Tofacitinib 5mg BID DB (N=28)	Placebo (N=31)
Weekly MTX Dose (mg) at Randomization		
n	22	20
Mean (SD)	15.9 (9.40)	12.1 (4.46)
Median (range)	15.0 (7.5, 52.5)	13.8 (5.0, 20.0)
Q1, Q3	10.0, 20.0	7.5, 15.0
Other csDMARDs Use at Randomization		
Yes	22 (78.6%)	20 (64.5%)
No	6 (21.4%)	11 (35.5%)
Oral Corticosteroid and MTX Use at Randomization		
Yes	11 (39.3%)	11 (35.5%)
No	17 (60.7%)	20 (64.5%)

Indicators of more severe disease activity were generally higher in the tofacitinib 5 mg BID treatment group compared with the placebo treatment group at both OL and DB baseline. For example, selected baseline and clinical characteristics of the DB-phase treatment groups were as follows:

- At OL baseline, the mean (SD) Physician's Global Evaluation of Overall Disease Activity was 6.9 (1.88) and 6.5 (1.98) in the tofacitinib 5 mg BID and placebo groups, respectively.

- At OL baseline, mean (SD) CRP, which was used in the efficacy parameters of JADAS, was 3.4 (4.44) and 2.6 (3.58) in the tofacitinib 5 mg BID and placebo groups, respectively.

- At DB baseline, the mean (SD) ESR rate (mm/h), which was used for real-time assessment of ACR, was 24.2 (24.43) and 18.6 (14.80) in the tofacitinib 5 mg BID and placebo groups, respectively.

At DB baseline, the mean and median JADAS-27 CRP and JADAS-27 ESR scores, were numerically higher in tofacitinib 5 mg BID group compared with the placebo Group.

Prior use of:

- NSAIDs was reported by 57 participants (57.0 %)
- csDMARDs was reported by 77 participants (77.0 %)
- CS was reported by 89 participants (89.0 %),
- bDMARDs was reported by 27 participants (27.0 %), of which tocilizumab was the most frequently reported (23 [23.0 %] participants)

Concomitant use of NSAIDS was reported by 59 (59.0%) participants in the OLPT1, 30 (55.6%) participants in the OLPT2, and 13 (46.4%) participants in the tofacitinib arm and 17 (54.8%) participants in the placebo arm of the DB phase. Concomitant use of MTX was reported by 63 [63.0%] participants in the OLPT1, 31 (57.4%) participants in the OLPT2, and 22 (78.6%) participants in the tofacitinib arm and 20 (64.5%) participants in the placebo arm of the DB phase. Concomitant use of corticosteroids was reported by 85 (85.0 %) participants in the OLPT1, 52 (96.3%) participants in the OLPT2, and 12 (42.9%) participants in the tofacitinib arm and 19 (61.3%) participants in the placebo arm of the DB phase. Of note, all 54 (100.0%) participants in OLPT2 were using CS. Two (2) participants tapered off CS during the first 4 weeks of OLPT2 and did not report receiving CS at Week 4 visit during OLPT2. Thus, they were not counted in the frequency tables.

The mean duration of treatment was 90.56 days for the OLPT1 and 84.40 days for the tofacitinib OLPT2. For the DB phase, the mean duration of treatment was greater for the tofacitinib group (385.50 days) than for the placebo group (244.45 days).

Efficacy results

The efficacy analysis conducted was based on the data as of the cutoff date of 03 Jan 2024 (snapshot date of 02 Feb 2024) and is considered final and definitive. Analysis was repeated for selected endpoints based on the final data LPLV date of 27 Mar 2024, final database release date of 24 Apr 2024) as supportive analysis.

During this phase, improvements from baseline were observed for all efficacy endpoints in OLPT1 and these improvements were generally maintained while tapering CSs during OLPT2.

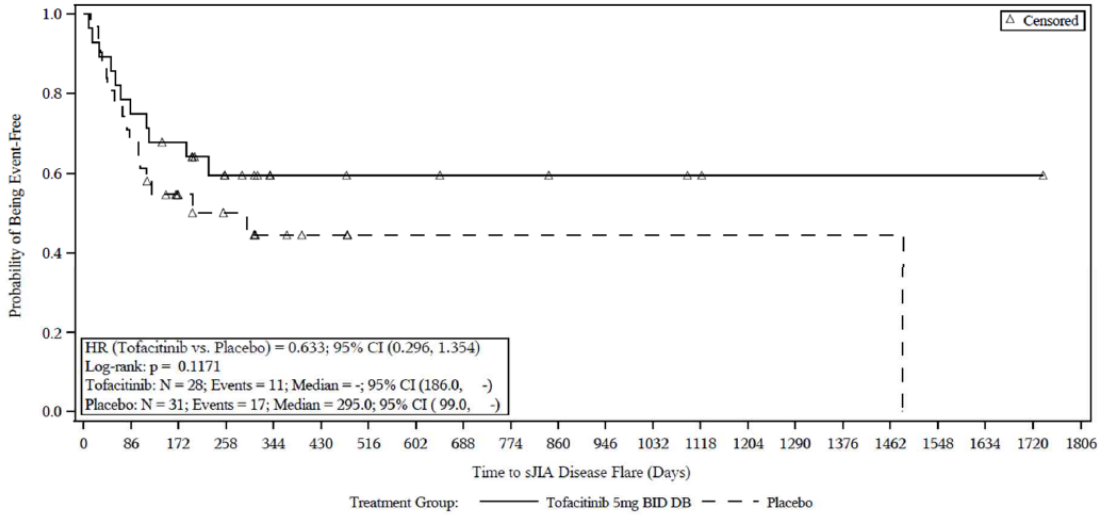
The study met the stopping criteria for futility at the First Analysis. The p-value (1-sided) of 0.1171 from the primary analysis exceeded the First Analysis Futility Stopping Boundary of p-value (1-sided) of 0.1074

Primary endpoint

The study met the pre-specified criteria for futility and the tofacitinib 5 mg BID-treated group did not show statistical superiority over the placebo-treated group in the primary efficacy endpoint. Although

the HR (0.633) favoured the tofacitinib 5 mg BID group, the 95% CI encompassed 1 (95% CI: 0.296, 1.354) and the unstratified 1-sided Log-rank p-value of 0.1171 exceeded the futility boundary of 0.1074. Supplementary analyses supported the primary endpoint result.

Figure 5. Kaplan-Meier Plot for Time to sJIA Disease Flare in Double-Blind Phase – Primary Analysis – Estimand 1 - DBFAS



	0		86		172		258		344		430		516		602		688		774		860	
Treatment	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events
Tofacitinib 5mg BID DB	28	0	21	7	18	9	11	11	6	11	6	11	5	11	5	11	4	11	4	11	3	11
Placebo	31	0	21	10	12	14	9	15	5	16	3	16	1	16	1	16	1	16	1	16	1	16

946		1032		1118		1204		1290		1376		1462		1548		1634		1720		1806	
Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events	Risk	Events
3	11	3	11	2	11	1	11	1	11	1	11	1	11	1	11	1	11	1	11	0	11
1	16	1	16	1	16	1	16	1	16	1	16	1	16	0	17	0	17	0	17	0	17

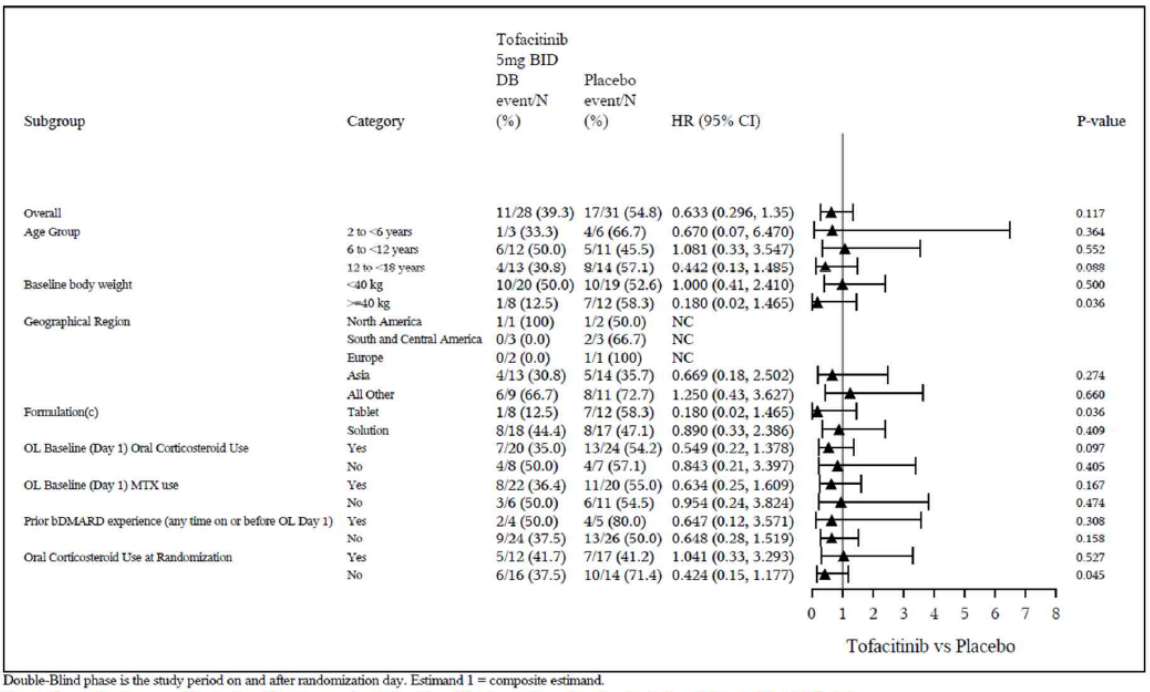
Double-Blind phase is the study period on and after randomization day. Estimand 1 = composite estimand.
Time to disease flare is measured in number of days since randomization (day of first disease flare - day of randomization +1) into the Double-Blind phase.
Hazard ratio (HR) is based on the Cox proportional hazards model.
P-value is from 1-sided log-rank test.

The analysis of time to sJIA disease flare in the DB phase was conducted based on the data as of the cut-off date of 03 Jan 2024 (snapshot date of 02 Feb 2024) with 28 flares. The primary analysis was based on a composite estimand (Estimand 1). Only on-treatment data were included. Participants who discontinued from treatment for reasons other than flare were considered as having a disease flare on the treatment discontinuation day. Participants who completed study participation after maintaining JIA ACR inactive disease for at least 24 weeks (ie, clinical remission) in the DB phase were censored at the last available flare assessment while on treatment.

Seven (7) participants in the tofacitinib 5 mg BID group and 13 participants in the placebo group experienced disease flare and 4 in each group discontinued due to other reasons.

A forest plot of the HRs for the time to disease flare for the overall analysis population and by subgroups is provided in Figure 6. The calculated CIs of the HRs for each of the subgroups encompassed the value of 1, which was consistent with that reported in the overall population.

Figure 6. Forest Plot for Time to sJIA Disease Flare in Double-Blind Phase by Subgroups – Estimand 1 - DBFAS



Double-Blind phase is the study period on and after randomization day. Estimand 1 = composite estimand.
Time to disease flare is measured in number of days since randomization (day of first disease flare - day of randomization +1) into the Double-Blind phase.
a. Hazard ratio (HR) is based on the Cox proportional hazards model.
b. P-value is from 1-sided log-rank test.
c. Switchers who are on both tablet and liquid are not included in this summary.

The probability of being event-free diverged after approximately 80 days and stayed numerically higher in the tofacitinib 5 mg BID group compared with the placebo group for the remainder of the DB phase.

A higher percentage of participants in the tofacitinib 5 mg BID group (14/28 [50.0%]) than in the placebo group (11/31 [35.5%]) remained flare-free through the data cut-off date; 3 in each treatment group completed study participation after achieving clinical remission.

Supplementary analyses supported the primary endpoint result. A HR favouring tofacitinib-treated participant compared to placebo-treated participants was observed but the 95% CIs encompassed 1 with each of the statistical methods.

Secondary efficacy endpoints

During the OL phase, improvements from baseline were observed for all efficacy endpoints in OLPT1, and clinically meaningful responses were obtained for the JADAS-27 and the CHAQ-DI endpoints. These improvements were generally maintained while tapering CSs during OLPT2. (see below)

The secondary efficacy endpoints in the DB randomized withdrawal phase were not Type I error-controlled and any 95% CIs and p-values for secondary analyses are therefore considered nominal.

Occurrence of Disease Flares in the Double-Blind Phase up to Week 52: By Week 8 and at each visit up to Week 52 in the DB phase, the probability of a flare event was lower in the tofacitinib 5 mg BID

group compared to the placebo group. The greatest difference in proportions (-15.0 %) was observed at Week 44 through Week 52.

Table 8. Time to sJIA Disease Flare in Double-Blind Phase – Primary Analysis – Estimand 1 – DBFAS (Protocol A3921165)

	Tofacitinib 5 mg BID DB (N=28) n (%)	Placebo (N=31) n (%)	Tofacitinib vs. Placebo n (%)
Number of Participants	28 (100.0)	31 (100.0)	
Participants with Event	11 (39.3)	17 (54.8)	
Type of Event			
Experienced Disease Flare	7 (25.0)	13 (41.9)	
Discontinued Investigational Product due to Other Reasons	4 (14.3)	4 (12.9)	
Participants Censored	17 (60.7)	14 (45.2)	
Reason for Censoring			
Participant Remained Flare-Free through Data cut-off date [f]	14 (50.0)	11 (35.5)	
Participant Completed Study Participation after achieving Clinical Remission	3 (10.7)	3 (9.7)	

Adapted JIA ACR 30/50/70/90/100 response at every visit from Day 7 onward in the open-label and DB phase: The proportions were numerically higher throughout most of the DB phase in participants treated with tofacitinib 5 mg BID compared to those treated with placebo.

Figure 7. Line graph of Adapted JIA ACR 30 Responses (+/- SE) in Double-Blind Phase up to Week 52 – MR=NR – Estimand 1 - DBFAS

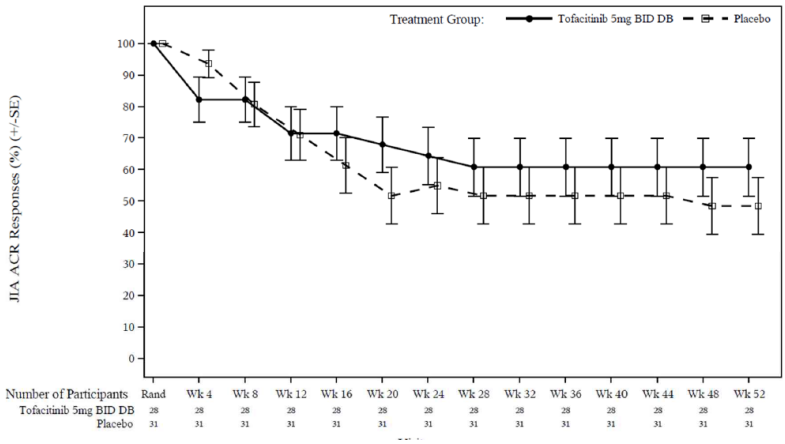


Figure 8. Line Graph of Adapted JIA ACR 50 Responses (+/- SE) in Double-Blind Phase up to Week 52 – MR=NR – Estimand 2 - DBFAS

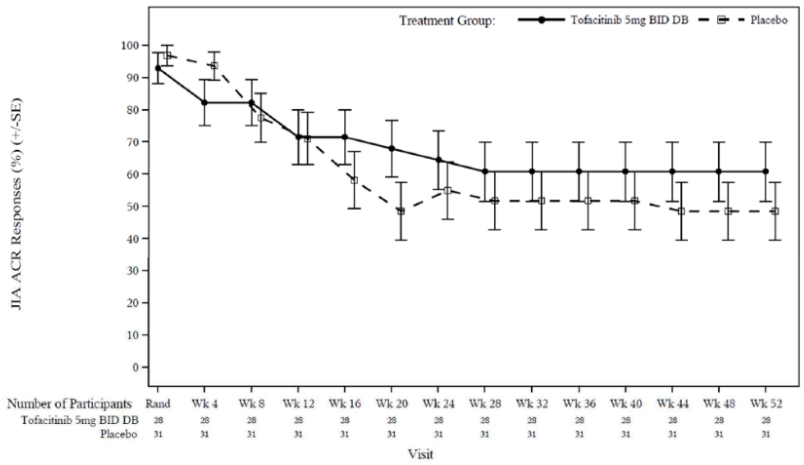


Figure 9. Line Graph of Adapted JIA ACR 70 Responses (+/- SE) in Double-Blind Phase up to Week 52 – MR=NR – Estimand 2 - DBFAS

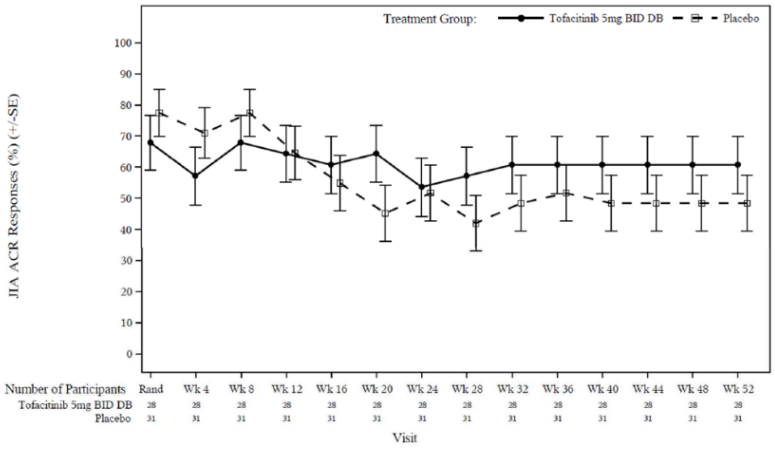
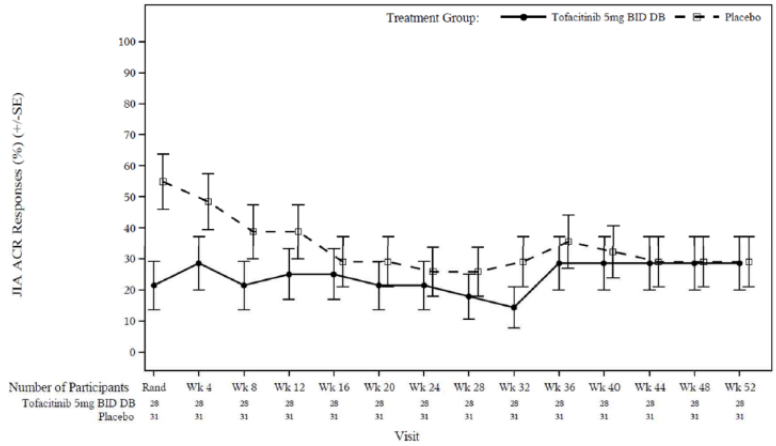
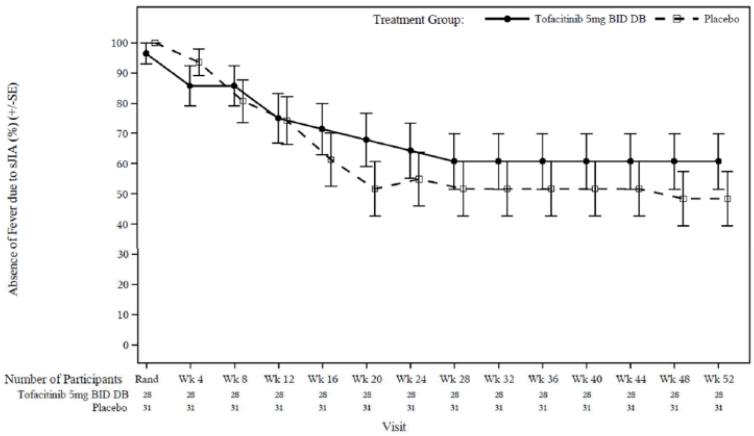


Figure 10. Line Graph of Adapted JIA ACR 90 Responses (+/- SE) in Double-Blind Phase up to Week 52 – MR=NR – Estimand 2 - DBFAS



"Absence of fever", defined as absence of fever due to sJIA in the week preceding the assessment in the DB phase: in a numerically larger proportion of participants treated with tofacitinib 5 mg BID compared to those treated with placebo at the majority of the DB time points. At Week 52, the normal approximation of absence of fever due to sJIA was 60.71% (17/28) in the tofacitinib 5 mg BID group compared with 48.39% (15/31) in the placebo group.

Figure 11. Line graph of Absence of Fever due to sJIA (+/- SE) in Double-Blind Phase up to Week 52 – MR=NR – Estimand 2 - DBFAS



The percentage of participants with absence of fever increased from around 80% at Day 7 to around 95% at Week 16 in OL Phase Part 1. In OL Phase Part 2, the percentage of participants with absence of fever remained above 90%.

Change from baseline in Juvenile Arthritis Disease Activity Score (JADAS-27) in the DB phase: numerical differences in LS mean changes from DB baseline in JADAS-27 CRP or JADAS-27 ESR were observed between the tofacitinib 5 mg BID and placebo groups but the overall pattern of changes was similar between both treatment groups.

Figure 12. Line graph of LS Mean Change (+/- SE) from Double-Blind Baseline for JADAS-27 CRP Score in Double-Blind Phase up to Week 52 – MMRM – Hypothetical Estimand - DBFAS

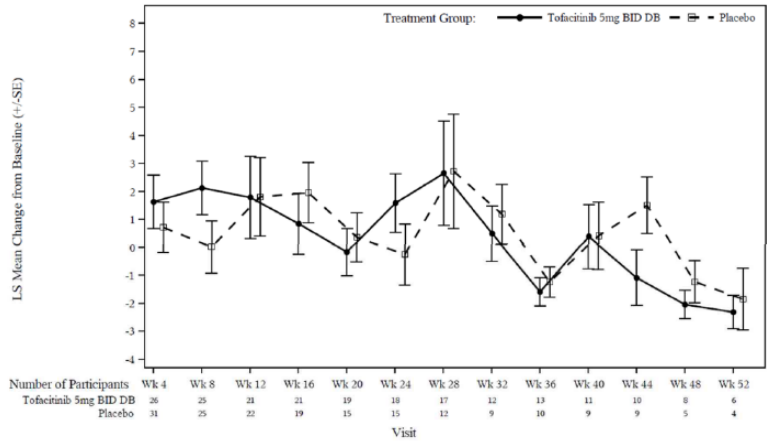
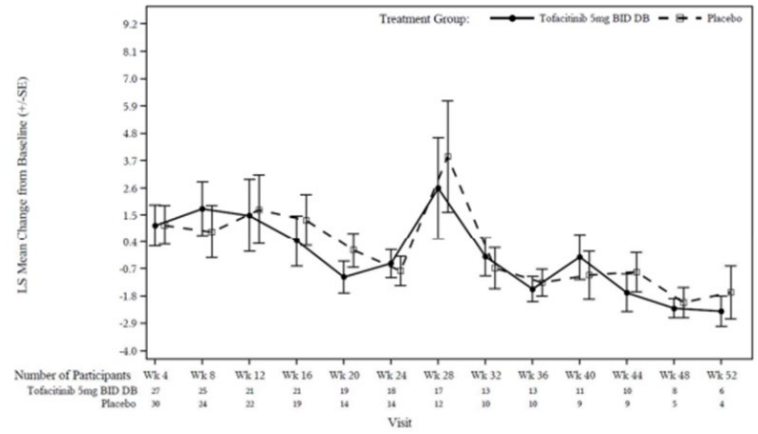


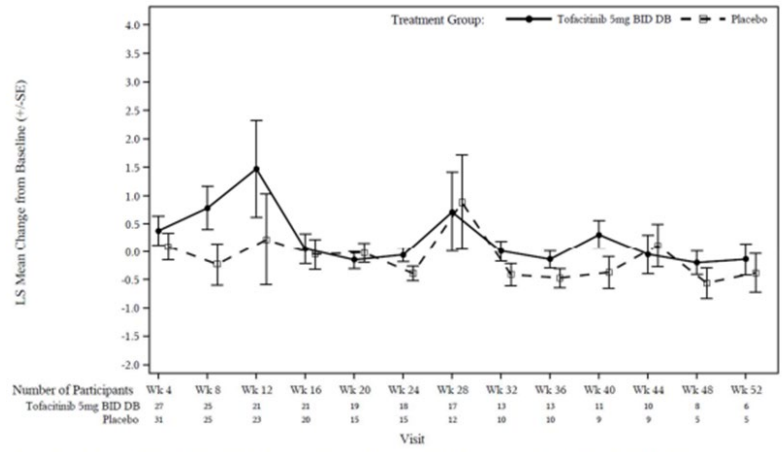
Figure 13. Line Graph LS Mean Change (+/- SE) from Double-Blind Baseline for JADAS-27 ESR Score in Double-Blind Phase up to Week 52 – MMRM – Hypothetical Estimand - DBFAS



Source: Figure 14.2.4.1.2.1

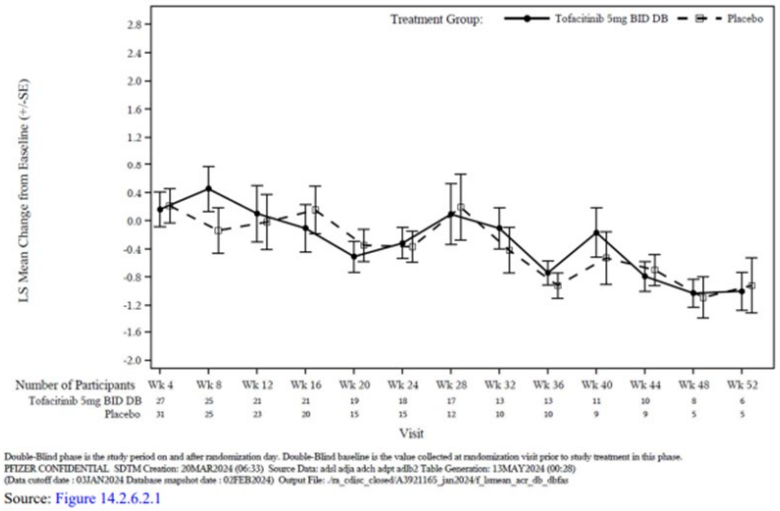
Change from baseline in each JIA ACR core variable at every visit from Day 7 onward in the open-label and DB phase: overall pattern of changes from both OL and DB baselines in the number of active joints with limited range of motion, the number of active joints with active arthritis, CHAQ Disability Index, CHAQ Parental Evaluation of Overall Well-being, and Physician's Global Evaluation of Disease Activity, was similar between the tofacitinib 5 mg BID and placebo treatment groups. There were numerical differences in LS mean change from DB baseline in ESR that favoured the tofacitinib 5 mg BID group compared to the placebo group at all timepoints.

Figure 14. Line graph of LS Mean Change (+/- SE) from Double-Blind Baseline for Number of Active Joints with Active Artithritis in Double-Blind Phase up to Week 52 – MMRM – Hypothetical Estimand - DBFAS



Source: Figure 14.2.6.2.1

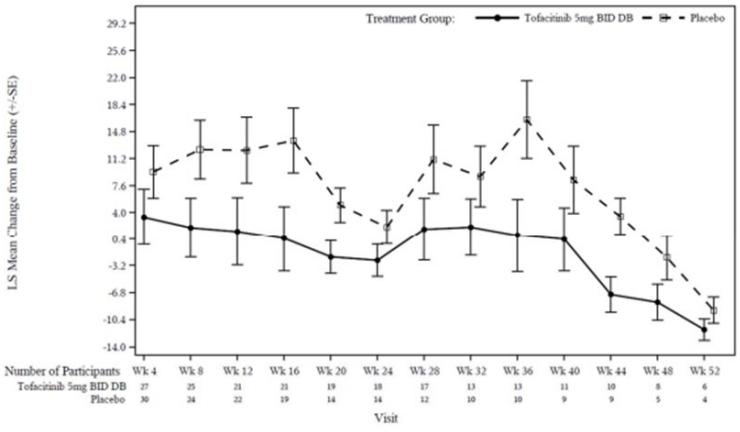
Figure 15. Line Graph of LS Mean Changer (+/- SE) from Double-Blind Baseline for Physician's Global Evaluation of Disease Activity in Double-Blind Phase up to Week 52 – MMRM – Hypothetical Estimand - DBFAS



Double-Blind phase is the study period on and after randomization day. Double-Blind baseline is the value collected at randomization visit prior to study treatment in this phase.
PFIZER CONFIDENTIAL SDTM Creation: 20MAR2024 (06:33) Source Data: adsl adja adch adpr adlb2 Table Generation: 13MAY2024 (00:28)
(Data cutoff date : 03JAN2024 Database snapshot date : 02FEB2024) Output File: /ts_cdisc_closed/A3921165_jan2024/f_lsmean_acr_db_dbfas

Source: Figure 14.2.6.2.1

Figure 16. Line Graph of LS Mean Change (+/- SE) from Double-Blind Baseline for Erythrocyte Sedimentation Rate (mm/h) in Double-Blind Phase up to Week 52 – MMRM – Hypothetical Estimand - DBFAS

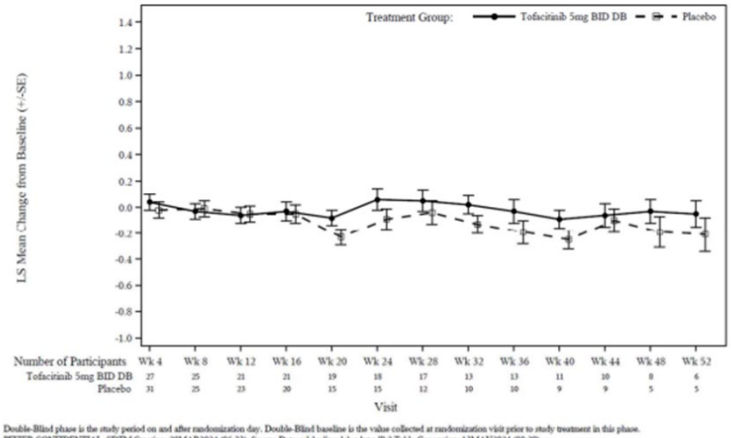


Double-Blind phase is the study period on and after randomization day. Double-Blind baseline is the value collected at randomization visit prior to study treatment in this phase.
PFIZER CONFIDENTIAL SDTM Creation: 20MAR2024 (06:33) Source Data: adsl adja adch adpr adlb2 Table Generation: 13MAY2024 (00:28)
(Data cutoff date : 03JAN2024 Database snapshot date : 02FEB2024) Output File: /ts_cdisc_closed/A3921165_jan2024/f_lsmean_acr_db_dbfas

Source: Figure 14.2.6.2.1

CHAQ-Disability Index and CHAQ-Overall Well-Being: LS mean changes from DB Baseline were generally similar between the tofacitinib 5 mg BID and placebo group through Week 52 of the DB period

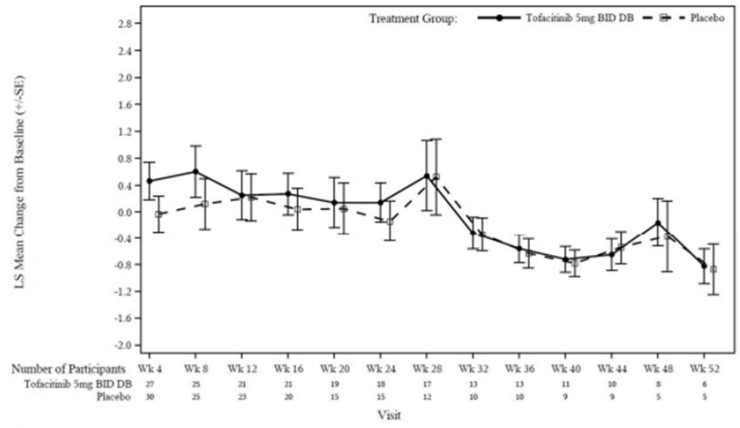
Figure 17. Line Graph of LS Mean Change (+/- SE) from Double-Blind Baseline for CHAQ-Disability Index in Double-Blind Phase up to Week 52 – MMRM – Hypothetical Estimand – DBFAS



Double-Blind phase is the study period on and after randomization day. Double-Blind baseline is the value collected at randomization visit prior to study treatment in this phase.
PFIZER CONFIDENTIAL SDTM Creation: 20MAR2024 (06:33) Source Data: adsl adja adch adpt adlb2 Table Generation: 13MAY2024 (00:28)
(Data cutoff date : 03JAN2024 Database snapshot date : 02FEB2024) Output File: /m_cdisc_closed/A3921165_jan2024/f_lsmean_acr_db_dbfas

Source: Figure 14.2.6.2.1

Figure 18. Line Graph of LS Mean Change (+/- SE) from Double-Blind Baseline for CHAQ-Overall Well Being in Double-Blind Phase up to Week 52 – MMRM – Hypothetical Estimand - DBFAS



Double-Blind phase is the study period on and after randomization day. Double-Blind baseline is the value collected at randomization visit prior to study treatment in this phase.
PFIZER CONFIDENTIAL SDTM Creation: 20MAR2024 (06:33) Source Data: adsl adja adch adpt adlb2 Table Generation: 13MAY2024 (00:28)
(Data cutoff date : 03JAN2024 Database snapshot date : 02FEB2024) Output File: /m_cdisc_closed/A3921165_jan2024/f_lsmean_acr_db_dbfas

Source: Figure 14.2.6.2.1

Occurrence of inactive disease status and minimal disease activity (JADAS-27) in the DB phase.

Figure 19. Line Graph of JADAS Inactive Disease Activity (+/- SE) calculated from JADAS-27 CRP Score in Double-Blind Phase up to Week 52 – MR=NR – Estimand 2 - DBFAS

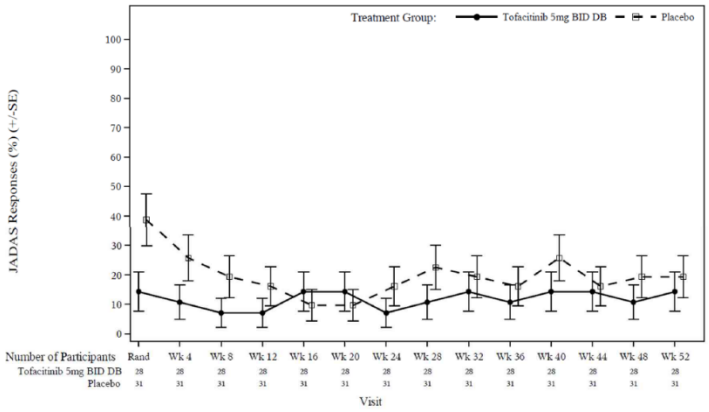
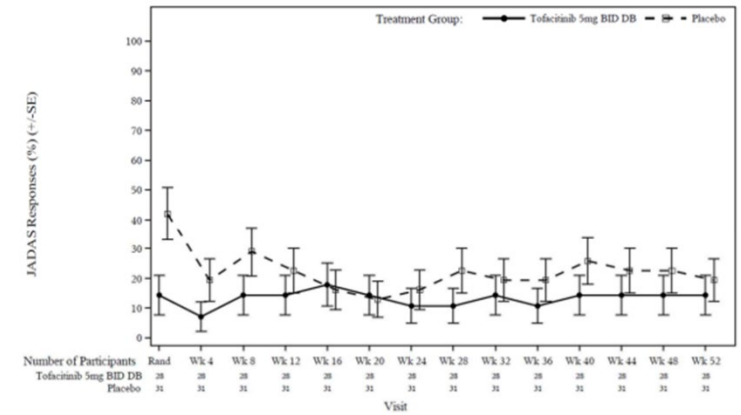


Figure 20. Line Graph of JADAS Inactive Disease Activity (+/- SE) calculated from JADAS-27 ESR Score Score in Double-Blind Phase up to Week 52 – MR=NR – Estimand 2 - DBFAS



Double-Blind phase is the study period on and after randomization day.
PFIZER CONFIDENTIAL SDTM Creation: 20MAR2024 (06:13) Source Data: adjdas Table Generation: 12MAY2024 (09:57)
(Data cutoff date : 03JAN2024 Database snapshot date : 02FEB2024) Output File: /ts_cdisc_closed/A3921165_jan2024/fig_jdas_inacte2

Source: Figure 14.2.4.3.1.1

Figure 21. Line Graph of JADAS Minimum Disease Activity (+/- SE) calculated from JADAS-27 CRP Score in Double-Blind Phase up to Week 52 – MR=NR – Estimand 2 - DBFAS

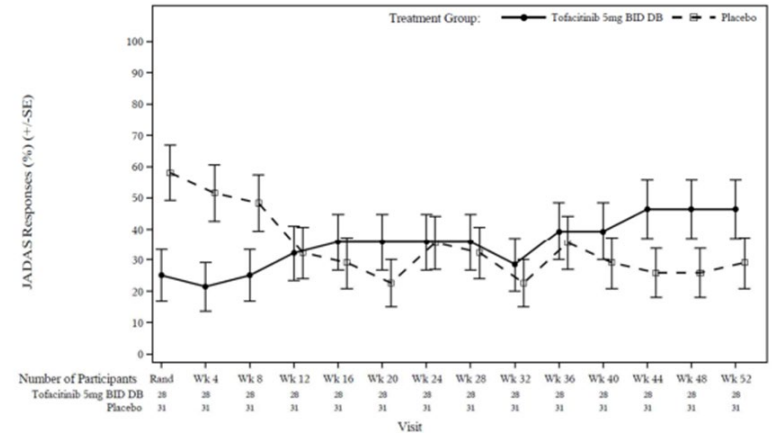
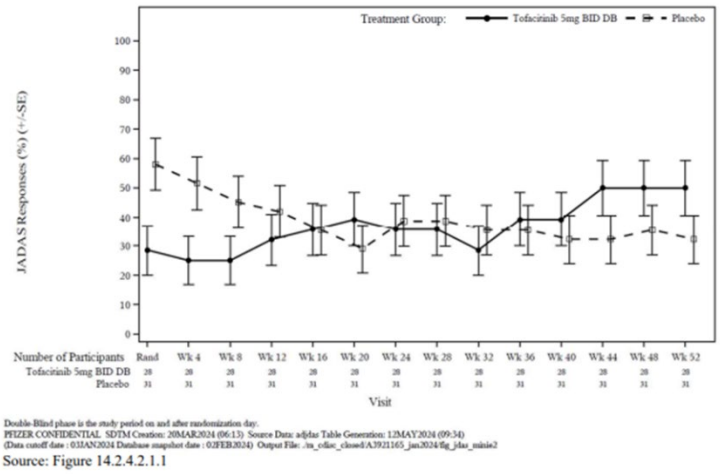


Figure 22. Line Graph of JADAS Minimum Disease Activity (+/- SE) calculated from JADAS-27 ESR Score in Double-Blind up to Week 52 – MR=NR – Estimand 2 - DBFAS



Source: Figure 14.2.4.2.1.1

Achievement of corticosteroid tapering per protocol at the end of the open-label active treatment period in applicable subjects receiving corticosteroids on study Day 1 of the open-label phase: By the end of OL Phase Part 2, the majority of participants (38/54 [70.37%]) successfully tapered their CS dose.

Achievement of a corticosteroid dose of ≤0.2 mg/kg/day or 10 mg/day (whichever is lower) at the end of the open-label treatment period in subjects receiving corticosteroids on Day 1 of the open-label phase: A CS Dose of ≤0.2 mg/kg/day and 10 mg/day was achieved in 59.26% (32/54) of participants by the end of OL Phase.

Fever (>38 °C) attributed to sJIA at Day 3, Day 7 and Day 14 of the open-label phase: The percentage of participants with fever attributed to sJIA was <5% on Day 3, Day 7, and Day 14 (Week 2) in Part 1 of the OL phase compared with 23.00% at baseline.

CRP ≤10 mg/L at every visit of the OL phase: During the OL Phase Part 1, the percentage of participants with CRP ≤10 mg/L increased from 30% (30/100) at Baseline to a peak of 60% (48/80) at Week 8. The percentage of participants with CRP ≤10 mg/L was greater than 50% at the majority of timepoints in OL Phase Part 2.

Time to first Adapted JIA ACR 30 response in Part 1 of the open-label phase: The majority of participants (90.0% [90/100]) achieved an adapted JIA ACR30 response in Part 1 of the OL phase with a median time to achieve an adapted JIA ACR30 response of 27 days.

Occurrence of inactive disease status and clinical remission at every visit from Day 7 onward (JIA ACR) in the DB phase: The percentage of participants with JIA ACR inactive disease or JIA ACR clinical remission was numerically higher in the placebo group compared with the tofacitinib 5 mg BID for the majority of timepoints during the DB phase.

Figure 23. Line Graph of Presence of JIA ACR Inactive Disease Based on ESR (+/- SE) in Double-Blind Phase up to Week 52 – MR=NR – Estimand 2 - DBFAS

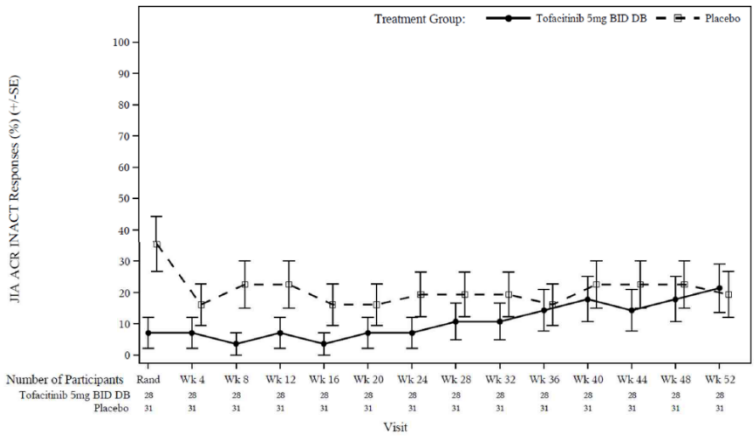
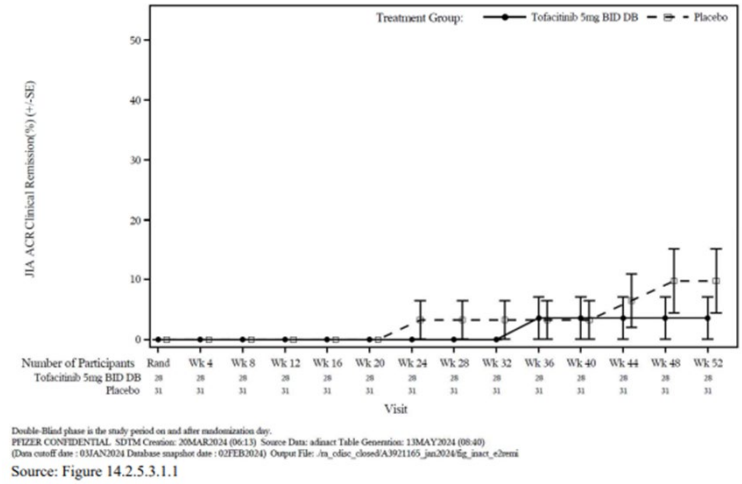


Figure 24. Line Graph of Presence of JIA ACR Clinical Remission (+/- SE) in Double-Blind Phase up to Week 52 – MR=NR – Estimand 2 - DBFAS

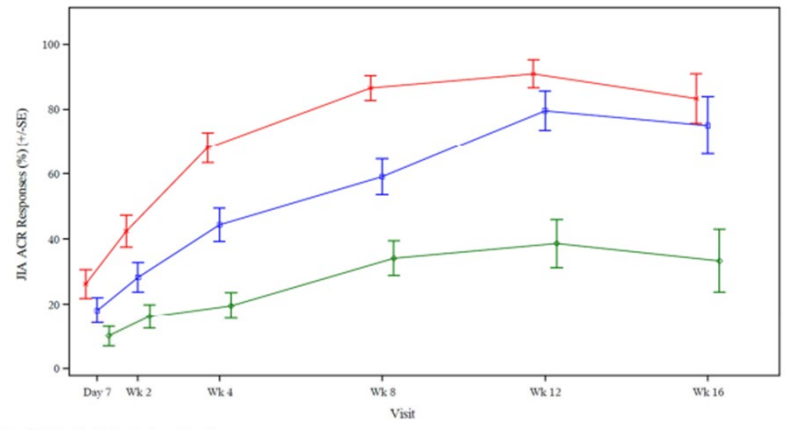


Open-Label Treatment Phase

During the OL phase, improvements from baseline were observed for all efficacy endpoints in OLPT1, and these improvements were generally maintained while tapering CSs during OLPT2.

The majority of participants (90.0% [90/100]) achieved an adapted JIA ACR30 response in Part 1 of the OL phase with a median time to achieve an adapted JIA ACR30 response of 27 days.

Figure 25. Line Graph of Adapted JIA ACR 30/50/70 Responses (+/- SE) in Open Label Phase Part 1 – OLPT1



Open-Label Phase Part 1 is from Day 1 up to 16 weeks.
Response is calculated relative to the Open-Label baseline on Day 1.
PFIZER CONFIDENTIAL SDTM Creation: 20MAR2024 (06:28) Source Data: adsl adacr Table Generation: 02APR2024 (12:28)
(Data cutoff date : 03JAN2024 Database snapshot date : 02FEB2024) Output File: /ts_cdisc_closed/A3921165_jan2024/fig_acr_305070_ol1

Source: Figure 14.2.14.1.1

Conclusions

- **The study met the pre-defined stopping criteria for futility at the first analysis and the primary efficacy endpoint was not met in the DB phase.** The study did not demonstrate a statistically significant prolongation in the time to disease flare in the tofacitinib 5 mg BID-treated group compared to the placebo-treated group in the DB randomized withdrawal phase.
- The secondary endpoint outcomes were consistent with the primary endpoint in that there was a lack of meaningful separation between the tofacitinib 5 mg BID and placebo treatment groups in the DB withdrawal phase.
- During the OL phase, improvements from baseline were observed for all efficacy endpoints in OLPT1, and these improvements were generally maintained while tapering CSs during OLPT2.

Population PK model results

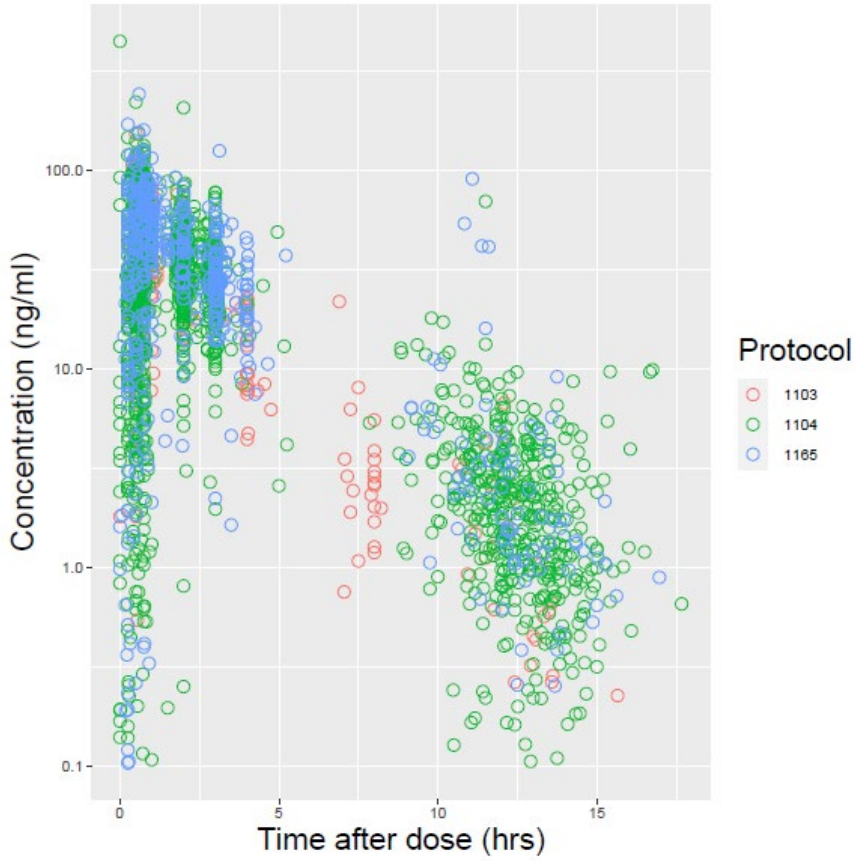
The study population for analysis (n=324) consisted of 107 males and 217 females with ages ranging from 2 to 17 years and weights ranging from 11.1 to 122 kg (median weight of 43.9 kg). **Of the total 324 subjects, 75 were sJIA subjects from study A3921165.**

A total of 2605 plasma concentration records were included in the final analysis.

Based on the covariate analysis results, tofacitinib does not require dose modification or restrictions for any covariates, except for weight, to account for differences in exposure.

Plasma concentrations observations at sampling times after dose for each dose in log scale and per protocol are shown in the following figure:

Figure 26. Observed Plasma Concentrations vs. Time after Dose by Each Protocol



Repository artifact ID FI-55646772.

Base Model Results

The previous PK model developed based on data from pJIA sufficiently described the pooled data from both pJIA and sJIA, suggesting comparable PK between the two populations. This is support by the similarity in parameter estimates between the final base model and the previous PK model as shown in Table 9 and Table 10 here below.

Table 9. Parameter Estimates for Base Model

Parameter	Estimate	RSE(%)	95% CI	SIR Estimate	SIR 95% CI
$\theta_{CL/F}(L/hr)$	24.648	1.84	(23.759 - 25.536)	24.628	(23.956, 25.363)
$\theta_{V}(L)$	86.216	1.86	(83.066 - 89.366)	86.586	(84.178, 89.211)
$\theta_{\text{Exponent on CL/F}}$	0.314	11.73	(0.242 - 0.386)	0.318	(0.268, 0.367)
$\theta_{\text{Exponent on V/F}}$	0.558	5.90	(0.494 - 0.623)	0.563	(0.518, 0.615)
$\theta_{\text{Covariance between CL/F and V/F}}$	0.374	25.27	(0.189 - 0.559)	0.374	(0.249, 0.483)
$\theta_{\text{Lag time}}(hr)$	0.164	2.69	(0.155 - 0.172)	0.193	(0.188, 0.198)
$\theta_{Ka}(hr^{-1})$	2.65	10.67	(2.10 - 3.21)	3.05	(2.58, 3.67)
$\theta_{\text{Error}}(\%)$	47.834	4.09	(44.003 - 51.666)	47.74	(44.816, 50.722)
$\theta_{\text{Error before TAD=1.08hr}}(\%)$	73.38	5.07	(66.08 - 80.67)	73.500	(68.88, 78.12)
$\theta_{\text{Formulation Effect}}$	1.336	30.51	(0.537 - 2.135)	1.61	(1.001, 2.447)
$\omega_{CL/F}$	0.047	18.46	(0.030 - 0.064)	0.047	(0.036, 0.059)
$\omega_{\text{CL/F-Ka}}$*	-0.030	-82.33	(-0.080 - 0.019)	-0.040	(-0.082, 0.002)
ω_{Ka}	1.428	14.52	(1.022 - 1.834)	1.723	(1.347, 2.144)
$\omega_{\text{CL/F-Error}}$*	0.037	33.57	(0.013 - 0.061)	0.036	(0.021, 0.052)
$\omega_{\text{Ka-Error}}$*	-0.539	-10.20	(-0.646 - -0.431)	-0.616	(-0.725, -0.508)
ω_{Error}	0.245	9.92	(0.197 - 0.293)	0.261	(0.218, 0.305)

Repository artifact ID FI-55923983. Line 1 substituted.

*ω represents the off-diagonal elements of the omega block; CI=Confidence Interval; RSE=Relative standard error; SIR=Sampling Importance Re-sampling; TAD=Time After Dose.

Table 10. Parameter Estimates for the Previous PK Model Based on pJIA

Parameter	Estimate	RSE(%)	95% CI	SIR Estimate	SIR 95% CI
$\theta_{CL/F}(L/hr)$	26.053	2.30	(24.880 - 27.226)	26.069	(25.200, 27.127)
$\theta_{V}(L)$	89.217	2.55	(84.755 - 93.679)	89.316	(86.117, 92.905)
$\theta_{Ka}(hr^{-1})$	2.779	12.04	(2.123 - 3.435)	2.768	(2.292, 3.440)
$\theta_{\text{Exponent on CL/F}}$	0.310	13.40	(0.228 - 0.391)	0.310	(0.248, 0.372)
$\theta_{\text{Exponent on V/F}}$	0.537	9.57	(0.436 - 0.637)	0.537	(0.475, 0.598)
$\theta_{\text{Covariance between CL/F and V/F}}$	0.273	38.91	(0.065 - 0.481)	0.271	(0.136, 0.414)
$\theta_{Error}(\%)$	40.98	5.95	(36.20 - 45.76)	41.00	(37.84, 44.46)
$\theta_{\text{Lag time}}(hr)$	0.186	5.02	(0.167 - 0.204)	0.18	(0.172, 0.195)
$\theta_{\text{Error before TAD=1.08hr}}(\%)$	67.96	6.17	(59.74 - 76.18)	67.991	(62.99, 73.44)
$\theta_{\text{Formulation Effect}}$	1.641	38.37	(0.407 - 2.875)	1.61	(0.947, 2.677)
$\omega_{CL/F}$	0.055	18.27	(0.036 - 0.075)	0.056	(0.043, 0.070)
$\omega_{CL/F\text{-}Ka}$*	-0.099	-33.97	(-0.166 - -0.033)	-0.097	(-0.148, -0.051)
ω_{Ka}	1.461	16.31	(0.994 - 1.928)	1.478	(1.133, 1.902)
$\omega_{CL/F\text{-}Error}$*	0.074	24.09	(0.039 - 0.109)	0.072	(0.053, 0.095)
$\omega_{Ka\text{-}Error}$*	-0.567	-11.47	(-0.695 - -0.440)	-0.555	(-0.679, -0.440)
ω_{Error}	0.247	13.61	(0.181 - 0.313)	0.245	(0.198, 0.309)

Repository artifact ID FI-197280. Line 1 substituted.

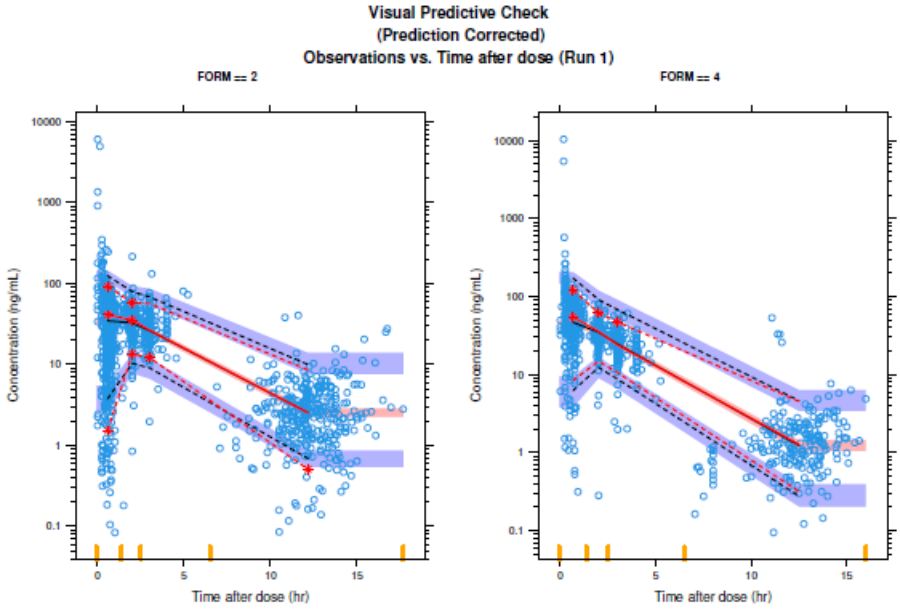
*ω represents the off-diagonal elements of the omega block; CI=Confidence Interval; RSE=Relative standard error; SIR=Sampling Importance Re-sampling; TAD=Time After Dose. Results from previous population PK model conducted in pJIA subjects (PMAR-EQDD-A3921-Other-941 [1])

The final base model (updated with data from study **A3921165)** is a one compartment disposition model with first order absorption and a lag time, where the first order absorption rate is dependent on formulation (oral solution or tablet).

Plots of observed versus predicted (PRED or IPRED) of the final base model showed random scatter around the identity line and plots of CWRES versus PRED and Time showed random scatter around the zero line, demonstrating that the model appropriately described the observed tofacitinib concentration data.

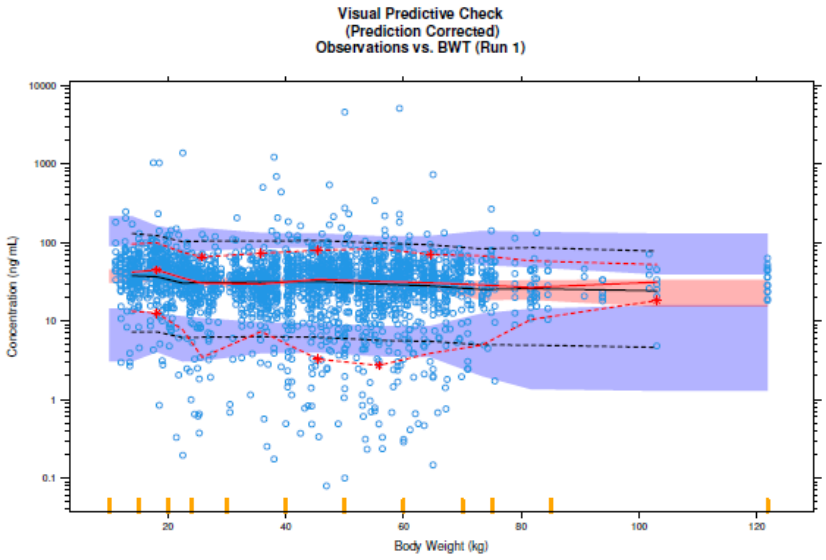
The model was used to simulate data. Simulation of PK profiles over time (stratified by formulation) as well as across body weight and age, as presented in Figure 27, Figure 28 and Figure 29, respectively.

Figure 27. Prediction Corrected Visual Predictive Check for Base PK Model by Formulation



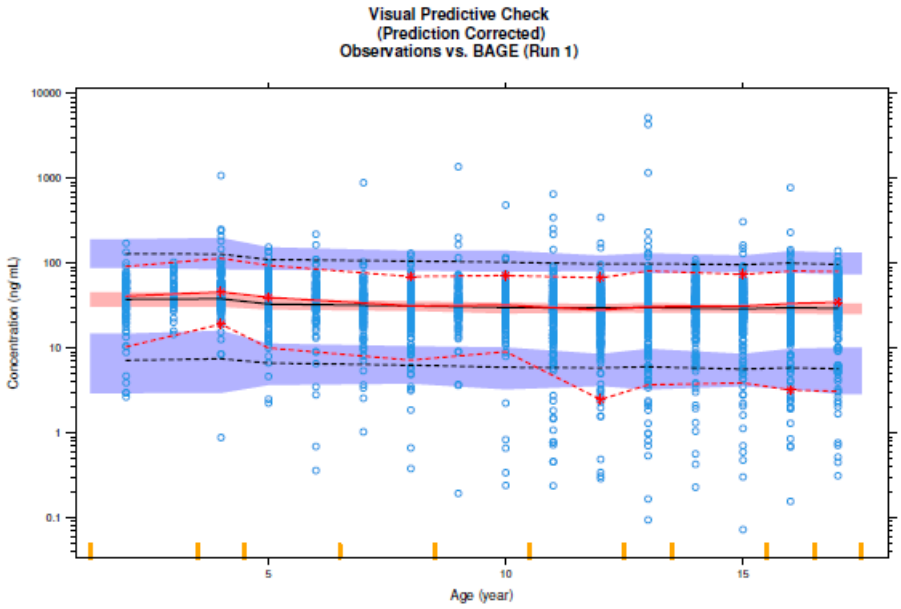
Repository artifact ID FI-55926189.
FORM=2 represents Tablet, and FORM=4 Solution; Red dashed lines represent 90% confidence interval (95% upper limit and 5% lower limit) of observed data. Red solid line is median (50%) of observed data. Black dashed lines represent 90% predictive interval (95% upper limit and 5% lower limit) based on simulations. Black solid line represents median based on simulations. Shaded area is predicted 95% confidence interval of upper limit, lower limit or median (50%) based on simulations.

Figure 28. Prediction Corrected Visual Predictive Check for Final PK Model vs. Baseline Body Weight



Repository artifact ID FI-56265354.
Red dashed lines represent 90% confidence interval (95% upper limit and 5% lower limit) of observed data. Red solid line is median (50%) of observed data. Black dashed lines represent 90% predictive interval (95% upper limit and 5% lower limit) based on simulations. Black solid line represents median based on simulations. Shaded area is predicted 95% confidence interval of upper limit, lower limit or median (50%) based on simulations.

Figure 29. Prediction Corrected Visual Predictive Check for Final PK Model vs. Baseline Age



Repository artifact ID FI-57190722.
Red dashed lines represent 90% confidence interval (95% upper limit and 5% lower limit) of observed data. Red solid line is median (50%) of observed data. Black dashed lines represent 90% predictive interval (95% upper limit and 5% lower limit) based on simulations. Black solid line represents median based on simulations. Shaded area is predicted 95% confidence interval of upper limit, lower limit or median (50%) based on simulations.

Stepwise Covariate Model

The primary covariates of interest had been predefined for this analysis in the Population Modeling and Analysis Plan (PMAP). The correlation among continuous covariates shows that covariates such as age, body weight, BMI, height, BSA are highly correlated as expected.

Since body weight is a structural covariate on CL/F and V/F, alternative highly correlated covariates were not tested, except for BSA and age, which were required by the Pediatric Investigation Plan.

Hence the final reduced set of covariates tested included: age (CAGE), baseline creatinine clearance (BCCL), C-reactive protein (BCRP), alkaline phosphatase (BALK), alanine transaminase (BALT), gender (SEX), race (RACE), oral steroids use (OSTER), NSAID or COX-2 inhibitor use (NDCOX), number of DMARD failures (NFAIL), anti-TNF inhibitor use (TNF), methotrexate use (MTRX), patient type (PTST). Of note, as BCRP and BALT have very skewed distributions, they were log-transformed.

Final Model Results

The predefined covariates were introduced to CL/F in the base structural model to create a covariate model. In the forward selection, BALK, BSA and TNF were kept on CL/F.

After the backward elimination, the final model was reached with no significant covariate. As a result, the final model is identical to the base model and all the base model diagnostic plots apply to the final model as well.

Parameter estimates and SIR results of the final model are presented in Table 9, reported above in this paragraph.

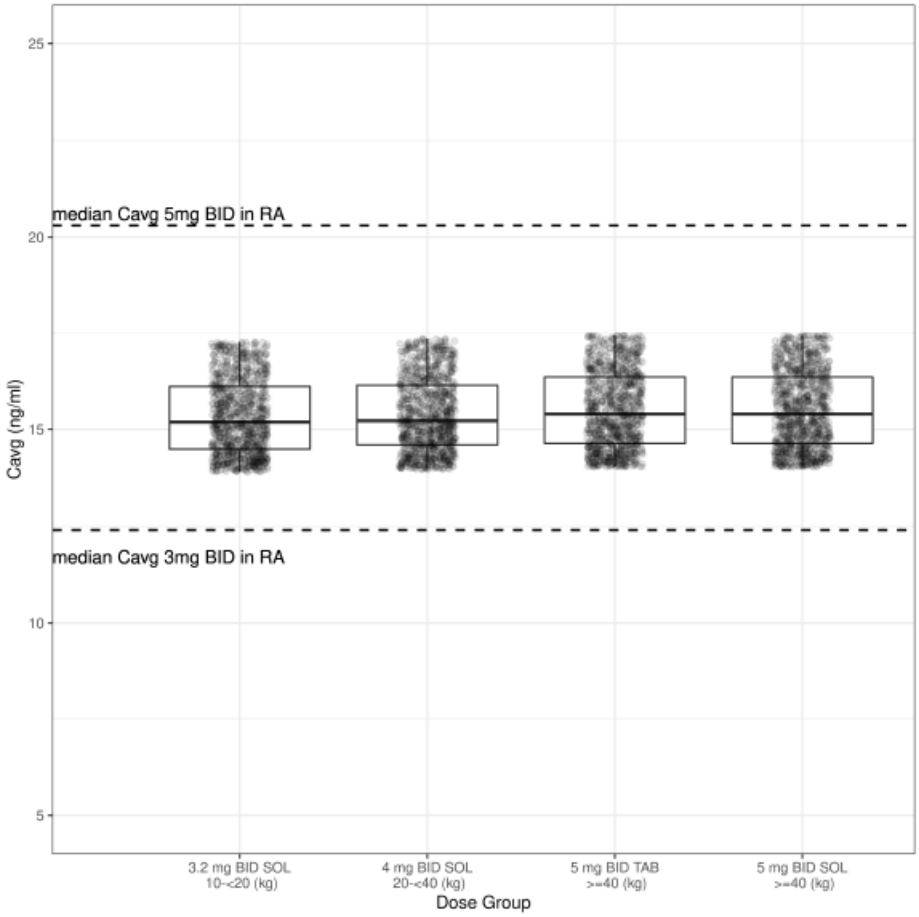
Final Model Predictive Performance

Considering that the final model is the same as the base model, previous base model validation based on VPC plots supports the sufficiency of the final model in characterizing tofacitinib PK in JIA subjects.

The MAH claims that to the similarities of PK in pJIA and sJIA, the weight-based dosing scheme developed for pJIA (as shown below) is effective in achieving consistent tofacitinib Cavg as has been demonstrated by the simulation Figure 30.

- 3.2 mg BID solution for 10 to 20 kg, excluded
- 4 mg BID solution for 20 to 40 kg, excluded
- 5 mg BID tablet or solution for 40 kg and above

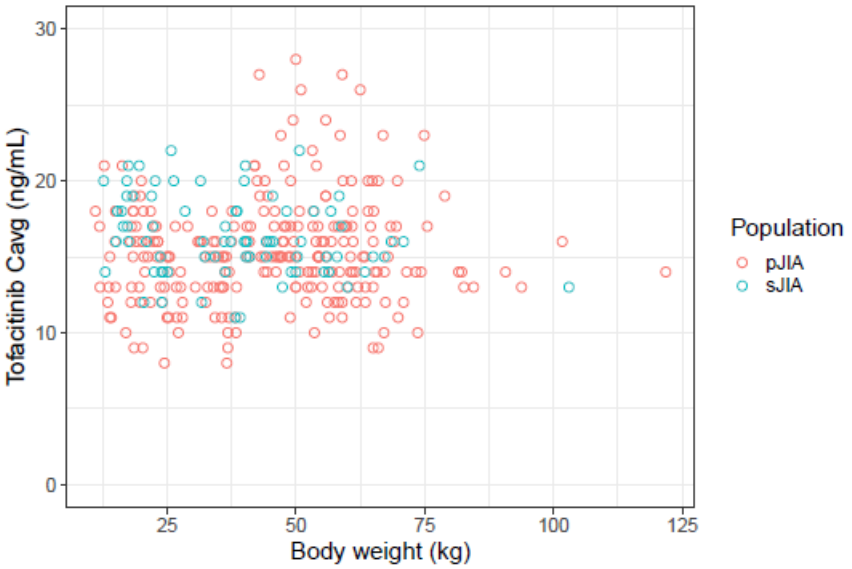
Figure 30. Predicted Steady-State Average Concentrations with Proposed Dosing Scheme (5mg BID Equivalent) in Increasing Weight Cohorts



Repository artifact ID FI-56993057.
BID=Twice a day; RA=Rheumatoid arthritis; SOL=Solution; TAB=Tablet; Cavg=Average concentration; Jitter dots are actual values to visualize the distribution of typical values in each body weight group. The dashed horizontal lines are predicted median values from adult RA popPK model.

Post Hoc estimated Tofacitinib Average Concentration vs body weight was shown in Figure 31 for both pJIA and sJIA Subjects.

Figure 31. Post Hoc Estimated Tofacitinib Average Concentrations vs Body Weight for Both pJIA and sJIA Subjects



Repository artifact ID FI-56967340.
Cavg = Average concentration. Red and green circles represent pJIA and sJIA subjects, respectively.

Safety results

Study A3921165

The safety analysis was conducted with final data which had a LPLV of 27 Mar 2024.

For the DB phase, the mean and median duration of treatment was greater for the tofacitinib group than for the placebo group:

- The mean duration of treatment was 244.45 days for the placebo group and 385.50 days for the tofacitinib 5 mg BID group.

- The median (range) duration of treatment was 169.00 (15.00, 1484.00) days in the placebo group and 283.00 (10.00, 1841.00) days in the tofacitinib 5 mg BID group.

Exposure

The duration of treatment for the majority of participants was longer than 61 days.

Adverse Events

For the open-label run-in phase, 113 TEAEs were experienced by 55 (55.0%) participants in the OLPT1, and 52 TEAEs experienced by 24 (44.4%) participants in the OLPT2. During the DB phase, there were 62 TEAEs experienced by 23 (82.1%) participants in the tofacitinib 5 mg BID group, and 73 TEAEs experienced by 25 (80.6%) participants in the placebo group. The majority of the TEAEs in each analysis set were mild to moderate.

Open-Label Treatment Phase

Table 11. Treatment-Emergent Adverse Events (All Causalities) in Open-Label Phase Part 1 – OLPT1

Number (%) of Participants	Tofacitinib 5mg BID OL (N=100) n (%)
Number of TEAEs	113
Participants with:	
TEAEs	55 (55.0)
Treatment-emergent SAEs	7 (7.0)
Severe TEAEs	3 (3.0)
TEAEs leading to death	0
Discontinuations from study due to TEAEs [a]	6 (6.0)
Permanent discontinuations from any study intervention due to TEAEs [b]	6 (6.0)
Dose reductions of any study intervention due to TEAEs	0
Dosing interruptions of any study intervention due to TEAEs	7 (7.0)

Table 12. Treatment-Emergent Adverse Events (All Causalities) in Open-Label Phase Part 2 – OLPT2

Number (%) of Participants	Tofacitinib 5mg BID OL (N=54) n (%)
Number of TEAEs	52
Participants with:	
TEAEs	24 (44.4)
Treatment-emergent SAEs	0
Severe TEAEs	0
TEAEs leading to death	0
Discontinuations from study due to TEAEs [a]	0
Permanent discontinuations from any study intervention due to TEAEs [b]	0
Dose reductions of any study intervention due to TEAEs	0
Dosing interruptions of any study intervention due to TEAEs	2 (3.7)

Double-Blind Randomized Withdrawal Phase

Table 13. Treatment-Emergent Adverse Events (All Causalities) in Double-Blind Phase - DBSAS

Number (%) of Participants	Tofacitinib 5mg BID DB (N=28) n (%)	Placebo (N=31) n (%)
Number of TEAEs	62	73
Participants with:		
TEAEs	23 (82.1)	25 (80.6)
Treatment-emergent SAEs	0	2 (6.5)
Severe TEAEs	0	2 (6.5)
TEAEs leading to death	0	0
Discontinuations from study due to TEAEs [a]	10 (35.7)	16 (51.6)
Permanent discontinuations from any study intervention due to TEAEs [b]	11 (39.3)	16 (51.6)
Dose reductions of any study intervention due to TEAEs	0	0
Dosing interruptions of any study intervention due to TEAEs	0	4 (12.9)

Double-Blind phase is the study period on and after randomization day.
Includes data up to 9999 days after last dose of study drug.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
b. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Participant to be discontinued from Study.
MedDRA v26.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 17APR2024 (21:36) Source Data: adsl adae Table Generation: 16MAY2024 (13:01)
(Database snapshot date : 16APR2024) Output File: ./ra_cdisc/A3921165_CSR/adae_s010_dbsas
Table 14.3.1.2.1.3 CP-690,550 is for Pfizer internal use.

Common Adverse Events

All-causality TEAEs evaluated in the OL phase analysis sets were most frequently reported in the Infections and infestations SOC. In the DB phase, all-causality TEAEs were most frequently reported in the Musculoskeletal and connective tissue disorders SOC. The majority of TEAEs reported were mild to moderate in severity.

The most frequently reported all causality TEAEs (≥3% of participants) by PT in the OL phase included:

- OLPT1: Upper respiratory tract infection (10 [10.0%]), Nasopharyngitis (6 [6.0%]), and Pyrexia (6 [6.0%]).

- OLPT2: Upper respiratory tract infection (7 [13.0%]), and COVID-19 (5 [9.3%]).

The most frequent all causality TEAEs (≥2 participants) by PT in the DB phase included:

- Placebo: Still’s disease (14 [45.2%]), Upper respiratory tract infection (5 [16.1%]), Bronchitis, Urinary tract infection (3 [9.7%] each), COVID-19, Diarrhoea, Myalgia, and Pharyngitis (2 [6.5%] each).

- Tofacitinib 5 mg BID: Still’s disease* (8 [28.6%]), Pyrexia (4 [14.3%]) Upper respiratory tract infection, Vomiting (3 [10.7%]), Fall, Haemoglobin decreased, Hypertransaminasaemia, Hypertriglyceridaemia, and Nasopharyngitis (2 [7.1%] each). All of these, except Still’s disease and Upper respiratory tract infection, are more common in Tofacitinib 5 mg than in placebo group.

** sJIA flare (coded as Still's disease)*

Treatment-related AEs

In the OL phase, the proportion of subjects with treatment-related TEAEs was 10.0% and 3.7% in the OLPT1 and OLPT2 phases, respectively. In the DB phase, the proportion of subjects with treatment-related TEAEs was 32.3% and 17.9% in the respective placebo and tofacitinib 5 mg BID treatment groups.

Open-Label Treatment Phase

For the treatment-related AEs in the OL phase, the following observations were noted:

- No severe treatment-related TEAEs were reported in the OLPT1 and OLPT2.
- There were 2 participants (2.0%) in the OLPT1 with at least 1 reported treatment-related SAEs (**Histiocytic necrotising lymphadenitis and Overdose**).
- One (1) participant (1.0%) in the OLPT1 and no participants in the OLPT2 discontinued the study due to treatment-related AEs.
- Four (4) participants (4.0%) in the OLPT1 and no participants in the OLPT2 had a temporary discontinuation due to a treatment-related AE.

Double-Blind Randomized Withdrawal Phase

For the treatment-related AEs in the DB phase, the following observations were noted:

- Treatment-related TEAEs were either mild or moderate in the tofacitinib 5 mg BID group. One (1) severe treatment-related TEAE (Hepatic enzyme increased) was reported in the placebo group; all other treatment-related TEAEs were either mild or moderate in this group.
- There was 1 participant (3.2%) in the placebo group with a treatment-related SAE (**Bronchitis**).
- Five (5) participants (16.1%) in the placebo group and 2 participants (7.1%) in the tofacitinib 5 mg BID group discontinued the study due to treatment-related AEs.
- Three (3) participants (9.7%) in the placebo group and no participants in the tofacitinib 5 mg BID group had a temporary discontinuation due to a treatment-related AE.

Deaths

No deaths occurred during the study.

Serious Adverse Events

A total of 8 SAEs was reported in 7 participants in the OL phase:

- The most frequently reported SAE was Still's disease (3 [3.0%]); depression and overdose (sertraline) were reported for 1 participant. All other events occurred in a single participant: haemophagocytic lymphohistiocytosis; histiocytic necrotizing lymphadenitis; and Hodgkin's disease.

- There were no SAEs reported in OLPT2.

In the DB phase, a total of 2 SAEs was reported in 2 participants in the placebo group (Bronchitis and Nephrolithiasis). There were no SAEs experienced by participants in the tofacitinib 5 mg BID group.

Permanent Discontinuations

The 6 participants discontinued from study intervention due to adverse events in the OL phase were all in the OLPT1 and 4 of these experienced an SAE that led to permanent discontinuation.

- The reported relevant SAEs were haemophagocytic lymphohistiocytosis (resolved), histiocytic necrotising lymphadenitis (resolved), Hodgkin's disease (not resolved), and Still's disease (resolved).

Twenty-seven (27) additional participants permanently discontinued from study intervention due to adverse events in the DB phase. Eleven (39.3%) participants discontinued study intervention due to AEs in the tofacitinib 5 mg BID group compared with 16 (51.6%) participants in the placebo group.

- The majority of discontinuations in the DB phase were due to sJIA flare (coded as Still's disease) with 8 [28.6%] participants in the tofacitinib 5 mg BID group and 14 [45.2%] participants in the placebo group. Moreover, 2 [7.1%] participants in the tofacitinib 5 mg BID group discontinued due to Haemoglobin decreased. Both were considered as not related by the investigator.

Adverse Events of Special Interest

Six (6) AESIs were reported in the OL phase. Two (2) AESIs were reported in the DB phase.

In the **OL phase**:

- Two (2) events of MAS were adjudicated in the OLPT1 phase; 1 was assessed as definite, the other as probable. No participants experienced MAS in the OLPT2.

- One (1) malignancy excluding non-melanoma skin cancer (NMSC) was confirmed by adjudication in the OL phase (Hodgkin's disease; which the PI considered to be present prior to enrollment, resulting in a misdiagnosis of sJIA).

- Three (3) hepatic events in the OL phase were adjudicated. One (1) event (Haemophagocytic lymphohistiocytosis), which was assessed as possible DILI, occurred in a patient receiving concomitant diclofenac. The 2 other events (Hepatic lesion, Hepatic steatosis) were assessed as unlikely DILI

In the **DB phase**, exposure estimates (per 100 PY) and IRs were calculated for the following AESIs:

- Non-adjudicated: Serious infection events including tuberculosis, varicella and herpes zoster.

- Adjudicated: cardiovascular events, gastrointestinal perforation events, MAS events, malignancy events, and opportunistic infections.

- One (1) AESI reported in the DB phase was a hepatic event (Hepatic enzyme increased) assessed as possible DILI by adjudication, which occurred concurrently with a sJIA flare.

- One (1) serious infection (bronchitis) was reported in 1 participant in the placebo group.

- The percentage of participants reporting TEAEs and their respective incidence rates were similar between the tofacitinib 5 mg BID and placebo group.

- The percentage of participants reporting SAEs and their respective incidence rates were numerically higher in the placebo group compared with the tofacitinib 5 mg BID group.

- No additional AESIs were reported in either the tofacitinib 5 mg BID group or placebo group in the DB phase.

Clinical Laboratory Evaluations

Changes in selected haematology parameters, liver enzymes, creatinine, CK, and lipid profiles, as well as inflammatory markers, were observed in the OL and DB phases of Study A3921165. The laboratory changes observed were consistent with those seen in the RA datasets.

Haemoglobin, platelet, leukocyte, lymphocyte, neutrophil, creatinine, creatine kinase, cholesterol, HDL cholesterol, and LDL cholesterol values remained stable throughout the OL and DB phases. There were no participants who were discontinued due to decreases in lymphocyte, neutrophil, or platelet counts as defined by the protocol.

There was no evidence of clinically meaningful increases over time in ALT, AST, or total bilirubin. There were no Hy's Law cases. No participants in either the DB phase or OL phase who had elevations of either AST or ALT that met criteria for monitoring in Study A3921165 were discontinued. Of the 6 participants in the DB phase that met criteria for discontinuation due to changes in haemoglobin or creatinine, 2 with haemoglobin abnormalities were discontinued from the study.

Vital Signs

There were no clinically meaningful median changes from baseline in supine/sitting systolic and diastolic blood pressure, pulse rate, height, weight, temperature, or BMI in the OL phase or in either treatment group in the DB phase.

Tanner Stage of Development

Tanner Stage of Development data in the OLPT1 and DB phases were collected and summarized by gender and age group. At the last assessment of the study, it was expectedthat there would be little if any changes in participants <12 years of age across the Tanner Stage of Development and changes in distribution for those ≥12 years was generally consistent with expected increase in age and stage of development.

Weight and Height Z-scores

There were no clinically meaningful median changes from baseline in weight or height Z-scores in the OL phase or in either treatment group in the DB phase. As expected in participants with sJIA and evidenced by mostly negative height and weight z-scores, both male and female participants were smaller than average for their age and were similar between treatment groups.

2.3.3. Discussion on clinical aspects

The MAH submitted a completed paediatric study for tofacitinib for treatment of Systemic Juvenile Idiopathic Arthritis (sJIA) with or without active systemic features, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. Study A3921165 is a deferred study in the JIA PIP (Study 7) with a completion date by September 2024.

The MAH requested to EMA/PDCO in 2017 to change the study design from a parallel placebo-controlled safety and efficacy trial in children with sJIA to a placebo-controlled withdrawal design. This change was proposed on the basis of significant changes in the context of treatments for JIA since first agreement of the paediatric investigational program (PIP) in 2010.

Indeed, with effective treatments on the market a parallel-group placebo-controlled design was no longer ethical. In the randomized withdrawal design, only responders to open-label treatment with tofacitinib were randomized into the double-blind phase comparing tofacitinib to start placebo.

The proposed change was agreed, in line with CHMP guidance (EMA/CHMP/239770/2014 Rev2) and with recently agreed PIPs for other products for sJIA.

Study design: The trial was a Phase 3 randomized withdrawal study (A3921165) to evaluate efficacy, safety and tolerability, and pharmacokinetics of tofacitinib (5 mg BID tablet in participants ≥40 kg or weight adjusted oral solution in participants <40 kg) as a treatment for sJIA. The participants should have been diagnosed with sJIA according to ILAR criteria and the treatment with stable dose of MTX and/or oral CSs was permitted. Responders (adapted JIA ACR 30) to open-label treatment with tofacitinib (up to 40 weeks) were randomized in a 1:1 ratio to tofacitinib or placebo in a double-blind phase; "time to sJIA flare" was evaluated as primary endpoint.

The assumptions used in the sample size calculation based on the canakinumab (that is from a different class) seem too optimistic. Likely, the applicant should have considered increasing the sample size also to have a better representation for each age subset.

Subjects who discontinued the study treatment due to inactive disease for at least 24 weeks in the DB phase were censored (i.e., their discontinuation was not analyzed as a disease flare). Treatment discontinuations for any other reasons was considered as flares.

Primary and secondary endpoints were analyzed using several estimands (treatment policy, composite and hypothetical strategy). Statistical methods used for time to event endpoints (Kaplan-Meier method with Log-rank test), binary endpoints (normal approximation to binomial proportions), and continuous endpoints (linear mixed model) are considered appropriate.

The original protocol design included the 10 mg BID dose as it was anticipated that, due to the underlying pathophysiology of sJIA, participants may require a higher dose to achieve efficacy than that needed for pcJIA. Due to a special safety concern of pulmonary embolism identified in an adult RA study, the administration of the 10 mg BID dose was discontinued. Potentially the suboptimal dose of 5 mg BID (instead of 10 mg BID initially foreseen for escalation if needed) could had impact on efficacy results.

Overall, study design of the Phase 3 study, objectives and clinical hypotheses are acceptable.

Study population: From 100 participants enrolled into the OL phase of the study, 59 were randomized (28 tofacitinib and 31 placebo) in the DB phase.

During the open label phase 40 patients discontinued the study drug (from whom 28 for insufficient clinical response and 6 for adverse events).

Although in the DB phase the proportions of overall discontinuations and underlying reasons for discontinuation were similar between the two treatment groups (however with more patients in the placebo group with insufficient clinical response (n=16) vs tofacitinib arm (n=9)), the very high rate of discontinuation is noted. Indeed, only 5 subjects in tofacitinib arm and 3 subjects in placebo arm completed the DB phase. The MAH provided information regarding the reasons for discontinuation reported as "other" in the DB randomized event-driven withdrawal phase (10 patients in tofacitinib group and 11 patients in placebo group). All participants in tofacitinib arm and all but one in placebo arm discontinued as their participation had ended being the study terminated due to the achievement of 28 total flares in the DB phase. The remaining 1 participant in the placebo group had achieved remission during treatment after usage of more than 4 years and the investigator decided to withdraw the participant.

Out of total 100 subjects, the majority were Asian (49%) or White (39%); only 17 subjects were of age 2 to <6 years (median age 10, range 2-17 years). In the DB phase there were more males in placebo (78.6%) vs tofacitinib arm (57%). Moreover, in the group 2 to < 6 years there were only 3 subjects in tofacitinib arm vs 6 subjects in placebo arm. Parameters of a more severe disease activity were generally quite higher in the tofacitinib 5 mg BID treatment group compared with the placebo treatment group at both OL and DB baseline, potentially favouring patients in placebo arm.

Results: The interim analysis for efficacy and futility was conducted after 28 subjects reported flarein the double-blind phase with the aim of early stopping the study.

The study met the pre-specified criteria for futility and the tofacitinib 5 mg BID group did not show statistical superiority over the placebo group in the primary efficacy endpoint. Although the HR (0.633)

favoured the tofacitinib 5 mg BID group, the 95% CI encompassed 1 (95% CI: 0.296, 1.354) and the unstratified 1-sided Log-rank p-value of 0.1171 exceeded the futility boundary of 0.1074. Subgroups analysis for the primary endpoint was consistent with that reported in the overall population.

Secondary endpoints did not show significant differences between tofacitinib and placebo, this supporting results of primary endpoint.

Improvements from baseline were observed for all efficacy endpoints in OLPT1 that were generally maintained while tapering CSs during OLPT2. Adapted JIA ACR 30/50/70 responses seem to reach a plateau at 12 weeks timepoint. By the end of OL Phase Part 2, the majority of participants (38/54 [70.37%]) successfully tapered their CS dose.

In the DB phase a higher percentage of participants in the tofacitinib 5 mg BID group (14/28 [50.0%]) than in the placebo group (11/31 [35.5%]) remained flare-free through the data cutoff date; however only 3 in each treatment group completed study participation after achieving clinical remission. The proportions of participants with Adapted JIA ACR 30/50/70 responses were slightly higher throughout most of DB phase in participants treated with tofacitinib 5 mg BID compared to those treated with placebo. However, the overall pattern of LS means changes from DB baseline in JADAS-27 CRP or JADAS-27 ESR were similar between treatment groups.

Overall, a clinically relevant effect has not been demonstrated for tofacitinib 5 mg BID in the target population of children and adolescents with sJIA who have responded inadequately to conventional therapy.

No new clinical pharmacology studies were conducted to support the use of tofacitinib in subjects with sJIA and the sparse PK sampling design precluded non-compartmental analysis for each individual.

The previous PK model developed based data from pJIA was updated with data from study A3921165, pooling plasma concentration time data from this study with results from other clinical studies using a nonlinear mixed effects modelling approach for analysis. Parameter estimates appear similar between the final base model and the previous PK model. Similar trends in the concentration-time curve were observed across different protocols showing rapid absorption followed by approximately first order elimination and similar pharmacological profile between patients with pJIA and patients with sJIA. The updated final model seems to be able to capture observed concentrations, mainly central values, indeed the observed median was similar to the simulated median and generally contained within the 95% CI. Some miss-pecifications can be noted for the pcVPC for the final PK Model vs. baseline Body Weight where the model seems to overpredict lower concentrations. This is not observed for PK profiles over time stratified by formulation and across age.

Although the PK model developed based the pooled data from both pJIA and sJIA subjects confirmed that tofacitinib PK is comparable between pJIA and sJIA subjects and that the weight-based dosing is effective in achieving consistent tofacitinib exposure across the range of body weight studied, this does not automatically imply that the previous weight-based dosing regimen is applicable to sJIA subjects.

The lack of an evaluable exposure-response study does not allow to clearly conclude that the same dosing regimen is able to provide the same clinical effect, considering that pJIA and sJIA are not similar diseases. Different inflammatory status, leading to a different target expression (and consequent need for dose adjustment) resulting in a different efficacy outcome, cannot be excluded.

Considering all the above and that the study has been stopped for futility, at present the update of section 5.1 with pediatric information coming from this study is not warranted.

The **safety profile** seems to be overall in line to that of tofacitinib in other adult and paediatric indications, with a similar frequency of TEAEs between tofacitinib (82.1%) and placebo (80.6%) group in the DB phase which were for the majority mild to moderate in severity. The most frequently reported all-causality TEAEs were in the SOC of Infections and infestations in OL phase and Musculoskeletal and connective tissue disorders in DB phase. The most frequently reported TEAEs by PT were: Still's disease (8 [28.6%]), pyrexia (4 [14.3%]), upper respiratory tract infection, vomiting (3 [10.7%]), fall, haemoglobin decreased, hypertransaminasaemia, hypertriglyceridaemia, and nasopharyngitis (2 [7.1%] each). However, Still's disease (sJIA flare coded as Still's disease) is more common in placebo group and is probably related to lack of efficacy. No deaths occurred.

A total of **8 SAEs** was reported in 7 participants in the OL phase. The most frequently reported SAE was Still's disease (3 [3.0%]); depression and overdose (sertraline) were reported for 1 participant. All other events occurred in a single participant: haemophagocytic lymphohistiocytosis; histiocytic necrotizing lymphadenitis and Hodgkin's disease. There were no SAEs reported in OLPT2. There were no SAEs experienced by participants in the tofacitinib 5 mg BID group in DB phase.

With regard to the event of **histiocytic necrotizing lymphadenitis**, the causality of the event with study drug was discussed by the MAH.

It seems that at first the investigator considered there was a reasonable possibility that the event was related to study medication, due mainly to a temporal association between the event and tofacitinib treatment. However, confounding factors such as the underling disease (sJIA) and a possible EBV reactivation, adds uncertainties making difficult drawing conclusions on the causality. Moreover, based on a literature review, no association between tofacitinib and histiocytic necrotizing lymphadenitis could have been identified, while there are also some reports in the literature of cases of Kikuchi-Fujimoto disease (KFD) being associated with Still's disease [adult onset and paediatric onset (also known as systemic JIA)], although the number of cases is limited. Finally, the MAH reports that this case was adjudicated by a panel of 3 experts (paediatric rheumatologists) who reached consensus that it was consistent with an episode of Macrophage Activation Syndrome [MAS]), a complication of sJIA, although with not typical manifestations. In conclusion, all the above considered, the MAH assessed that there is insufficient evidence for a causal association between histiocytic necrotizing lymphadenitis and tofacitinib treatment which can be considered acceptable.

The other SAEs initially reported as related were Haemophagocytic lymphohistiocytosis and Overdose (sertraline) and Depression. However, through the narrative provided, the Investigator assessed the causality of the event of **Haemophagocytic lymphohistiocytosis** as not related to the study intervention, clinical trial procedure, and concomitant medications. However, the event appeared to be related to flaring sJIA and the participant flared despite being on the tofacitinib therapy. Also, for the SAEs of **Overdose** (sertraline), the Investigator later confirmed the event of may not be related to the study intervention and that the causality of the event of **Depression** was not related to the study intervention, concomitant medications, or study procedure. The Sponsor concurred with the Investigator's causality assessment. Behavioural and emotional disorders, which can usually develop in childhood and adolescence, were present in the participant prior to the clinical study participation and the correlation evaluation was updated from probably irrelevant to definitely irrelevant. Therefore, further update of the SmPC with these events seems not to be needed, at present.

A high number of patients (27) permanently **discontinued** from study intervention due to adverse events in the DB phase, with a lower incidence (39.3%) in the tofacitinib 5 mg BID group compared to the placebo group [16 (51.6%)], mainly due to sJIA flare (coded as Still's disease). The majority of TEAEs that led to permanent discontinuation were not considered to be treatment-related and were not resolved.

Regarding laboratory changes 2 patients with haemoglobin abnormalities were discontinued from the study. However, in the narratives provided it is reported that these events were considered not related to tofacitinib.

Overall, no new signals were identified and the majority of TEAEs are already reported in the SmPC. However, even though it is acknowledged that Still's disease is defined by the Applicant as the expression of sJIA flare and therefore rather as lack of efficacy, 2 AEs of Still's disease during the entire study were considered related to study drug by the investigator in participants who were receiving tofacitinib treatment at the time of the AE. However, after re-discussion the MAH concluded that, at present there is insufficient evidence of a causal association between tofacitinib and events of Still's disease and that will continue the monitoring of pharmacovigilance data for adverse events of Still's disease.

3. Overall conclusion and recommendation

☒ Not fulfilled:

Based on the data submitted, the MAH should provide the additional clarifications requested per study A3921165 as part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

Efficacy

1) The Applicant should clarify the reasons of discontinuation reported as "other" in DB phase for 10 subjects in tofacitinib arm and 11 subjects in placebo arm in DB phase

Safety

2) The Applicant should provide a detailed description of the reported case of histiocytic necrotizing lymphadenitis with a critical discussion about possible relatedness of the event to tofacitinib. Based on this review, the Applicant should discuss the need to update the SmPC including the event of histiocytic necrotizing lymphadenitis in section 4.8.

3) Even though it is reported by the Applicant that AEs coded as Still's disease are the expression of sJIA flare and therefore rather as lack of efficacy, it was noticed from narratives that some of them are considered adjudicated as related to study drug by the investigator. The

Applicant should clarify the relatedness of Still's disease with tofacitinib and discuss if this kind of event is to be reflected in the SmPC.

The timetable is a 30-day response timetable without clock stop.

MAH responses to Request for supplementary information

Question 1

Efficacy

The Applicant should clarify the reasons of discontinuation reported as "other" in DB phase for 10 subjects in tofacitinib arm and 11 subjects in placebo arm in DB phase

Response

The reason for discontinuation reported as "other" for the 10 participants in the tofacitinib 5 mg BID arm in the DB phase was that all had reached the end of the study per the study protocol, specifically that their participation had ended as the study was terminated due to achievement of 28 total flares in the DB phase. The reason for discontinuation reported as "other" for all but 1 participant in the placebo arm was also that they had reached the end of the study per the study protocol. The remaining 1 participant in the placebo arm reported as 'other" had achieved remission during treatment after usage of more than 4 years and the investigator decided to withdraw the participant.

This information is included in the CSR in Table 16.2.1.2 Disposition Events (Module 5.3.5.1 A3921165 CSR Table 16.2.1.2) for Treatment Groups "Tofacitinib 5 mg BID OL – Tofacitinib 5 mg BID DB" and "Tofacitinib 5 mg BID OL – Placebo" (pages 5 through 18).

Assessment of the MAH's response

The MAH provided information regarding the reasons for discontinuation reported as "other" in the double- blind randomized event-driven withdrawal phase (10 patients in tofacitinib group and 11 patients in placebo group). All participants in tofacitinib arm and all but one in placebo arm discontinued as their participation had ended being the study terminated due to the achievement of 28 total flares in the DB phase. The remaining 1 participant in the placebo group had achieved remission during treatment after usage of more than 4 years and the investigator decided to withdraw the participant.

Conclusion

Issue resolved

Question 2

Safety

The Applicant should provide a detailed description of the reported case of histiocytic necrotizing lymphadenitis with a critical discussion about possible relatedness of the event to tofacitinib. Based on this review, the Applicant should discuss the need to update the SmPC including the event of histiocytic necrotizing lymphadenitis in section 4.8.

Response

Background

Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a rare, self-limiting inflammatory condition that usually recedes within six months even without drug treatment, but recurrences (3-4%) and fatal cases have been reported [1,2]. It can affect all age-groups; however, it typically affects young individuals and an increased prevalence has been noted in Asians. Patients usually present with tender cervical lymphadenopathy and systemic symptoms like fevers, malaise, myalgia, leukopenia, and anemia [1,2]. Diagnosis is confirmed through excisional lymph node biopsy, which shows specific immunohistochemical markers [1,2]. Treatment is symptomatic with nonsteroidal anti-inflammatory drugs or with corticosteroids or other immunosuppressants in cases of more aggressive disease or persistent symptoms of more than 4 weeks.

The cause remains uncertain but KFD may represent a hyperimmune reaction to an infectious agent, possibly EBV although other infectious etiologies have been proposed, or perhaps an autoimmune process [3]. It has been postulated that the hyperimmune reaction is a T-cell-mediated response to a variety of antigens in genetically susceptible individuals [4]. Compared with the general population, patients with KFD more frequently have particular human leukocyte antigen (HLA) class II alleles, specifically HLA-DPA1 and HLA-DPB1 [4]. These alleles are more prevalent in Asians and are extremely rare or absent in whites, which may account for the more common occurrence of this condition among Asians [4].

An association between KFD and autoimmune diseases has been observed, in particular with systemic lupus erythematosus, but also with Sjogren syndrome, macrophage activation syndrome (MAS), and Graves' disease [2,5]. There are also some reports in the literature of cases of KFD being associated with Still's disease [adult onset and pediatric onset (also known as systemic JIA)], but the number of cases is limited [6,7]. However, because the individual rarity of KFD and Still's disease make independent co-expression of the 2 diseases unlikely [5], it has been suggested that the co-occurrence may represent an overlap syndrome based upon similar pathogenic mechanisms and responses to therapy [5].

Case Summary

A 13-year-old male patient with a medical history of systemic juvenile idiopathic arthritis (SJIA; ongoing, diagnosed Dec 2016), myocardial injury, mild anaemia and liver function impairment received tofacitinib citrate, tablet, from 28 Feb 2023 to 29 Mar 2023 at 5 mg 2x/day, oral for still's disease (sJIA). Patient's concomitant medications included prednisone, diclofenac sodium, bicyclol and ornithine aspartate (all were ongoing). Previously, the patient had been treated with oral ibuprofen for anti-inflammatory therapy and oral cetirizine hydrochloride for hypersensitivity, but these treatments had been discontinued. One week before hospitalization the patient had fever accompanied by neck and axillary lymph node enlargement, which was considered related to lymphadenitis and was hospitalized on 30 March 2023. During the hospitalization various tests were conducted and findings included elevated liver enzymes/c-reactive protein/serum ferritin, low white blood count and low platelet count. Ultrasound examinations revealed enlarged lymph nodes in the axillary, inguinal, and cervical regions. An axillary lymph node biopsy confirmed the diagnosis of histiocytic necrotizing lymphadenitis. Systemic lupus erythematosus was ruled out due to very low titer positive antinuclear antibody (ANA) results (1:10), negative dsDNA, and normal C3 and C4 results. Testing to rule out Epstein-Barr Virus (EBV) was performed, and the participant had negative EBV-CA-IgM and EBV-EA-IgA but positive EBV-NA-IgG and EBV-CA-IgG, suggesting possible reactivation of EBV. The patient was then treated with calcium carbonate and cholecalciferol (Vitamin D3) granules, alfacalcidol, ibuprofen, and glucurolactone. The patient also received several short-term treatments, including Human immunoglobulin, etamsilate, glutathione, glycine, glycyrrhizic acid, ammonium salt, and methylprednisolone. The drug tofacitinib citrate was temporarily withdrawn on 29 Mar 2023. The patient's condition improved and he was discharged on 13 Apr 2023 with outcome resolved. The investigator considered there was a reasonable possibility that the event was related to study medication and was considered unrelated to concomitant medications and clinical trial procedures. The investigator considered the SAE to be primarily related to sJIA disease activity which was not aggravated from baseline but could be related to potential EBV infection.

Signal Evaluation

As a result of the regulatory query, the MAH has evaluated the signal of histiocytic necrotizing lymphadenitis and tofacitinib use, based on a review of the available literature, in conjunction with clinical and safety database searches. Relevant Preferred Term (PT) search criteria used included the following preferred terms: Histiocytic necrotizing lymphadenitis or Kikuchi disease or necrotizing lymphadenopathy.

Literature Review

From the cumulative literature review through 06 November 2024, a total of 4 publications were retrieved. Upon review, all identified publications were deemed non-relevant to the safety signal of interest, as they did not specifically address or provide substantive discussion on the association between tofacitinib and histiocytic necrotizing lymphadenitis. Two case reports were identified: one by Fan et al [8], which reported tofacitinib as ineffective in reducing the steroid requirement for VEXAS syndrome, but noted no adverse events, and another by Fahmy et al [9], where tofacitinib was started for provisional diagnosis of Kikuchi-disease like inflammatory pattern (KLIP) which was later confirmed to be vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome. The patient showed improvement within 2 months of starting tofacitinib and no adverse effects. A cross-sectional study by Ting et al [10], mentioned tofacitinib as a potential confounding factor in exacerbating rheumatic disease among Coronavirus Disease (COVID) vaccine recipients. The remaining publication by Shen et al [11], discussed tofacitinib as a treatment strategy for pre-existing Kikuchi-Fujimoto disease in pediatric patients, which falls outside the scope of our current safety evaluation.

In conclusion, these publications do not contribute meaningful data to the assessment of a potential causal relationship between tofacitinib and histiocytic necrotizing lymphadenitis.

Clinical and Safety Database

The MAH's Clinical and Safety Database was searched as of 06 Nov 2024 using the following PTs: Histiocytic necrotizing lymphadenitis or Kikuchi disease or necrotizing lymphadenopathy. Only 1 serious

case (AER: PV202300060178) from China was retrieved using this search strategy, which has been summarized above.

Considering that the event occurred within a reasonable time frame after drug initiation, there is a temporal relationship between the drug and event. Therefore, the MAH also considered the event as possibly related to study drug. The specific laboratory testing and lymph node biopsy results also confirmed the event diagnosis. Although a causal association cannot be excluded, the patient's underlying autoimmune condition and potential EBV reactivation are possible alternative aetiologies. Furthermore, this case was adjudicated by a panel of 3 experts (paediatric rheumatologists) who reached consensus that it was consistent with an episode of Macrophage Activation Syndrome [MAS]), a complication of sJIA, although recognizing the unusual feature of the resolution with minimal therapy, and that occurrences of histiocytic necrotizing lymphadenitis in sJIA have been previously reported in the literature. Further, they commented that the laboratory values were suggestive of MAS, including low white blood cell (WBC) and platelet count, and elevated ferritin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH), which is itself a known complication of sJIA, and was a likely contributory factor to the MAS event.

Conclusion

Based on the consideration of the totality of the available data regarding KFD pathophysiology, data from the event safety narrative, the conclusions of the MAS adjudication committee, and the literature review, the MAH assessed that there is insufficient evidence for a causal association between histiocytic necrotizing lymphadenitis and tofacitinib treatment. Therefore, inclusion of this event in Section 4.8 of the tofacitinib SmPC is not warranted at this time.

Assessment of the MAH's response

The MAH provided further information and re-discussed the case of histiocytic necrotizing lymphadenitis, as required. It seems that at first the investigator considered there was a reasonable possibility that the event was related to study medication, due mainly to a temporal association between the event and tofacitinib treatment. However, confounding factors such as the underling disease (sJIA) and a possible EBV reactivation, adds uncertainties making difficult drawing conclusions on the causality. Moreover, from a literature review, no association between tofacitinib and histiocytic necrotizing lymphadenitis could have been identified, while there are also some reports in the literature of cases of Kikuchi-Fujimoto disease (KFD) being associated with Still's disease [adult onset and pediatric onset (also known as systemic JIA)], although the number of cases is limited. Finally, the MAH reports that this case was adjudicated by a panel of 3 experts (paediatric rheumatologists) who reached consensus that it was consistent with an episode of Macrophage Activation Syndrome [MAS]), a complication of sJIA, although with not typical manifestations. In conclusion, all the above considered, the MAH assessed that there is insufficient evidence for a causal association between histiocytic necrotizing lymphadenitis and tofacitinib treatment and therefore, inclusion of this event in Section 4.8 of the tofacitinib SmPC is not warranted at this time, which can be considered acceptable with the recommendation to continue the monitoring within routine pharmacovigilance activity.

Conclusion

Issue resolved

Question 3

Safety

Even though it is reported by the Applicant that AEs coded as Still's disease are the expression of sJIA flare and therefore rather as lack of efficacy, it was noticed from narratives that some of them are considered adjudicated as related to study drug by the

investigator. The Applicant should clarify the relatedness of Still's disease with tofacitinib and discuss if this kind of event is to be reflected in the SmPC.

Response

The Phase 3 pivotal study for systemic JIA was a 2-phase randomized withdrawal study in which participants received open-label tofacitinib in the first phase and were required to achieve at least an adapted JIA ACR30 response for 4 weeks to be eligible for randomization. Participants who were receiving corticosteroids at baseline, per the protocol criteria, were also required to taper corticosteroids to a predefined level in open-label phase part 2 before being eligible for randomization. In the double-blind phase, eligible participants were randomized to the tofacitinib 5 mg BID arm (ie, remain on tofacitinib) or to the placebo arm (ie, have tofacitinib withdrawn) during which time investigators were blinded to treatment assignment. Participants were then followed to assess the time to occurrence of disease worsening or flare. The Phase 3 pivotal study for polyarticular JIA (Study A3921104) had a similar design except that there was no mandatory steroid tapering in the open-label phase and the primary endpoint during the double-blind phase was occurrence of disease flare at Week 44. For Study A3921165, occurrence of disease flare was assessed as a secondary efficacy endpoint in the double-blind withdrawal phase.

For clinical trials with a primary endpoint evaluating the efficacy of a treatment based upon the loss of efficacy/occurrence of disease flare, it is expected that both the active treatment arm and the control arm will each have participants who are unable to maintain the level of disease control achieved in Part 1. Additionally, it is not uncommon for an investigator to report this disease worsening or flare as an AE and, consequently, to assess the potential relationship of the AE to study drug. Such causality assessment may be difficult considering that the investigator is blinded to study treatment and investigators may consider the flare to be related to study drug, on the basis that the role of study drug cannot be entirely excluded.

During the double-blind randomized withdrawal phase of Study A3921165, there were 8 (28.6%) participants in the tofacitinib 5 mg BID arm who had AEs of worsening of sJIA (coded as Still's disease) reported, with 2 (7.1%) events (both mild in severity) being considered by the investigator as related to study drug. For the placebo arm, there were 14 (45.2%) participants who had AEs of Still's disease reported, with 5 (16.1%) events (all moderate in severity) being considered by the investigator as related to study drug. There were no SAEs of Still's disease in either treatment arm that were considered to be related to study drug by the investigator throughout the study. In addition, none of the AEs of Still's disease reported during the open-label phase of Study A3921165 [4 (4.0%) participants during Open Label Part 1 and 3 (5.6%) participants during Open Label Part 2] were considered to be related to study drug by the investigator. Therefore, only 2 AEs of Still's disease during the entire study were considered related to study drug by the investigator in participants who were receiving tofacitinib treatment at the time of the AE.

To further contextualize the reporting of sJIA flares in Study A3921165, the JIA flare events that were reported during the double-blind phase of the A3921104 pivotal Phase 3 study in polyarticular JIA were evaluated. In Study A3921104, there were 13 (14.8%) participants in the tofacitinib 5 mg BID arm who had AEs of JIA flare (PT of JIA, disease progression, and condition aggravated) reported, with 6 (6.8%) considered by the investigator to be related to study drug. For the placebo arm, there were 27 (31.8%) participants who had AEs of JIA flare, with 15 (17.6%) that were considered related to study drug by the investigator. Overall, the proportion of AEs of sJIA flare (7.1%) that were considered related to study drug in tofacitinib treated participants was generally similar to the proportion of AEs of JIA flare (6.8%) in Study A3921104.

Signal Evaluation

To further evaluate the potential signal of Still's disease (worsening of sJIA) and tofacitinib use, a search of the tofacitinib clinical and safety databases was conducted. Relevant search criteria used included the Lowest Level Terms 'Systemic juvenile idiopathic arthritis', 'sJIA', and 'Still's disease', and the Preferred Term 'Condition aggravated'.

As of 12 Nov 2024, the cumulative search of MAH safety database retrieved 11 cases in total, all from clinical studies. Out of these 11 cases, 6 were reported from Study A3921145, 4 cases were reported from Study A3921165 (1 case occurred in the screening period, prior to study drug treatment), and 1 case was reported from Study A3921104. Out of those identified, 9 cases were confounded by the underlying medical condition of the patient which included polyarticular JIA or systemic JIA, whereas the remining 2 cases occurred either post-discontinuation of tofacitinib or occurred during the screening period prior to initiation of tofacitinib. The cases were reported in 7 males and 4 females, and all cases were serious. Case outcome was reported as recovered in 9 cases, recovering in 1 case, and unknown in the remaining case. The concomitant medications were present in all cases, while patient history was known in 10 cases and unknown in 1 case. None of the cases reported other co-suspect drugs. The reporting countries were China (6), United States (2), Germany, South Africa, and Turkey (1 each).

Summary

Based upon the low proportion of AEs of Still's Disease reported in participants in Study A3921165 who were receiving tofacitinib at the time of the event, the similar frequency of AEs of disease worsening/flare reported in the sJIA and pJIA pivotal studies, and the cumulative clinical and safety review of Still's disease cases, the MAH has concluded that there is insufficient evidence of a causal association between tofacitinib and events of Still's disease. Therefore, the MAH's position is that the addition of Still's disease to the tofacitinib SmPC is not warranted. The MAH will continue the monitoring of pharmacovigilance data for adverse events of Still's disease.

Assessment of the MAH's response

The MAH clarified that it is not uncommon for an investigator to report the disease worsening or flare (considered as primary endpoint) as an AE and, consequently, to assess the potential relationship of the AE to study drug. Such causality assessment may be difficult considering that the investigator is blinded to study treatment and investigators may consider the flare to be related to study drug, on the basis that the role of study drug cannot be entirely excluded. Only 2 AEs of Still's disease during the entire study were considered related to study drug by the investigator in participants who were receiving tofacitinib treatment at the time of the AE. Moreover, the MAH reported a similar frequency of AEs of disease worsening/flare in the sJIA and pJIA pivotal studies, concluding that there is insufficient evidence of a causal association between tofacitinib and events of Still's disease. The addition of Still's disease to the tofacitinib SmPC is therefore not warranted at this time, which is accepted. The MAH will continue the monitoring of pharmacovigilance data for adverse events of Still's disease and this is agreed.

Conclusion

Issue resolved

5. Overall conclusion and recommendation

☒ Fulfilled:

No further action required.