29 January 2026
EMADOC-1700519818-3277680
Human Medicines Division

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

Xeljanz

Tofacitinib

Procedure no: EMA/PAM/0000291064

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	18 August 2025	18 August 2025
☐	CHMP Rapporteur AR	22 September 2025	19 September 2025
☐	CHMP comments	6 October 2025	6 October 2025
☐	Updated CHMP Rapporteur AR	9 October 2025	8 October 2025
☐	CHMP outcome - RSI	16 October 2025	16 October 2025
☐	Submission of responses	23 December 2025	19 December 2025
☐	Restart date	31 December 2025	31 December 2025
☐	CHMP Rapporteur AR	14 January 2026	14 January 2026
☐	CHMP comments	19 January 2026	19 January 2026
☐	Updated CHMP Rapporteur AR	22 January 2026	N/A
☒	CHMP outcome	29 January 2026	29 January 2026

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1. Introduction

On 28 July 2025, the MAH submitted a completed paediatric study for Xeljanz, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This study, A3921145, is not part of the Clinical Study commitments in the tofacitinib PIPs but is included as a Category 3 Study in the EU RMP.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study A3921145 (A Long-Term, Open-Label Follow-Up Study of Tofacitinib for Treatment of Juvenile Idiopathic Arthritis (JIA)) is part of a clinical development program.

The rationale of the A3921145 study was to enable participants who potentially benefitted from treatment in a previous qualifying/index study to continue to receive tofacitinib at the same dose (maximum 5 mg BID) and to characterize long-term safety and tolerability of tofacitinib for the treatment of JIA. A summary of results from this paediatric Study A3921145 is presented in this CEO.

2.2. Information on the pharmaceutical formulation used in the study

The MAH provided the following information: Tofacitinib citrate is a heterocyclic, small molecule. Selection of the 5 mg BID dose of tofacitinib for this long-term extension study of tofacitinib in JIA subjects is supported by pharmacokinetic (PK) data from the completed Phase 1 PK study of tofacitinib in JIA subjects (A3921103) and the benefit/risk profile of tofacitinib in adult RA subjects. Tofacitinib clearance is not dependent on body weight for weights >40 kg based on tofacitinib PK in the adult RA population [body weight range of the population studied was 40 kg-140 kg]. Thus, the dose of tofacitinib in adolescents with body weight ≥40 kg was set to 5 mg twice a day (BID), the only approved dose of tofacitinib in adult RA subjects in the EU. The doses for JIA participants with lighter weight were selected to match the predicted steady state concentrations in JIA participants with body weight ≥40 kg after administration of a 5 mg BID dose.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for: A Long-Term, Open-Label Follow-Up Study of Tofacitinib for Treatment of Juvenile Idiopathic Arthritis (JIA) - Study Number: A3921145.

This was a Phase 2/3, long term, open label, follow up study. Participants would have previously participated in qualifying/index studies in the tofacitinib JIA program. Those who had already completed such participation and enrolled outside the 14-day window following completion of the End of Study (EOS) Visit of the qualifying/index study would have participated in a Screening Visit to determine eligibility. A Baseline Visit then occurred within 28 days after the Screening Visit. For participants who completed participation in a qualifying study of tofacitinib and enrolled on the same day of the EOS Visit of the qualifying/index study, the EOS Visit of the qualifying/index study was combined with the Screening and Baseline Visits for this study. The participants enrolled within the 14-day window following completion of the EOS Visit of the qualifying/index study would have participated in a combined Screening and Baseline Visit for this study. After the Baseline Visit, visits occurred at 1 month (1 month=30 days) and 3 months, then every 3 months thereafter as long as the participant remained in the study.

Approximately 340 participants were projected to be enrolled into this open-label extension study after completing a qualifying/index study (Studies A3921103, A3921104 or A3921165) in the JIA program.

The primary focus of this study was the **long-term safety** and tolerability of tofacitinib for treatment of the signs and symptoms of JIA. Safety endpoints included standard laboratory safety data and AE reports. Body weight, height, and Tanner stages were collected to assess growth and physical development.

Analyses for safety are based on Pfizer reporting standards unless otherwise specified or noted.

2.3.2. Clinical study

Study A3921145: A Long-Term, Open-Label Follow-Up Study of Tofacitinib for Treatment of Juvenile Idiopathic Arthritis (JIA)

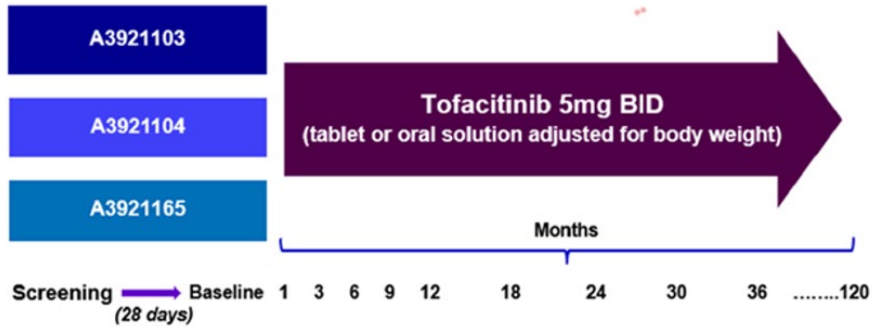
Description

Methods

Serious adverse event (SAE) presentations were derived from clinical study database based on information provided from the case report forms (CRFs)/data collection tools (DCTs). The safety measurements recorded in this clinical study are those employed in most clinical studies, including the recording of AEs. Medical Dictionary for Regulatory Activities (MedDRA) v. 26.1 coding was applied.

This study is complete and ended as of 12 Feb 2025 date, when the last subject, and all other subjects, who entered from study A3921165, completed approximately 1 year in this study.

Figure 1. Study Schematic



Key inclusion criteria were:

1. Paediatric participants with JIA aged from 2 to less than 18 years who had met entry criteria for the qualifying/index study, and in the opinion of the investigator, had sufficient evidence of JIA disease activity to warrant use of tofacitinib as a disease modifying antirheumatic drug (DMARD).

2. Participants previously completed participation in a qualifying study of tofacitinib for the treatment of JIA. Participants who had required earlier discontinuation of treatment in a qualifying study for reasons other than tofacitinib related SAEs may have been eligible.

3. For participants receiving methotrexate (MTX) treatment, MTX was administered either orally or parenterally at doses not to exceed 25 mg/week or 20 mg/m2/week, whichever was lower. Participants who took MTX must have been taking folic acid or folinic acid in accordance with local standards.

4. For participants receiving an oral glucocorticoid, glucocorticoids may have been administered at a maximum dose of 0.20 mg/kg/day or 10 mg/day, prednisone or equivalent, whichever was lower (intramuscular and intravenous corticosteroids were not permitted in the 4 weeks preceding the first

dose of study medication and throughout the study). For participants coming from the systemic JIA Study A3921165, a higher prednisone-equivalent dose may have been continued or started (doses must have been ≤1.0 mg/kg/day up to 30 mg/day oral prednisone [or equivalent]).

5. For participants receiving leflunomide treatment, leflunomide may have been administered according to the following dosing scheme: 10 mg every other day for participants weighing less than 20 kg; 10 mg every day for participants weighing between 20 and 40 kg; 20 mg every day for participants weighing over 40 kg; Or as according to local standards.

6. For participants receiving sulfasalazine, chloroquine, or hydroxychloroquine treatment, these medications may have been administered according to local standards.

Key exclusion criteria were:

For participants who enrolled outside the 14-day window of the EOS Visit of their qualifying/index study (Exclusion 1-3):

1. Blood dyscrasias, including: a. Haemoglobin (Hgb) <10 g/dL or haematocrit <33%. b. White blood cell (WBC) <3.0 × 109/L. c. Neutrophil count <1.2 × 109/L. d. Platelet count <100 × 109/L. e. Lymphocyte count of <0.75 × 109/L.

2. Estimated glomerular filtration rate (GFR) <40 mL/min/1.73 m2 calculated using Bedside Schwartz formula at the Screening Visit.

3. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥1.5 times the upper limit of normal or any other clinically significant laboratory abnormality.

For all participants:

4. Persistent oligoarthritis and undifferentiated JIA.

5. Current or recent history of uncontrolled clinically significant renal, hepatic, haematological, gastrointestinal (GI), endocrine, pulmonary, cardiac, or neurological disease.

6. History of any other rheumatic autoimmune disease, other than Sjogren's syndrome.

7. Infections: a. Chronic infections. b. Any infection requiring hospitalization, parenteral antimicrobial therapy or judged to have been opportunistic by the investigator within the 3 months prior to the first dose of study drug. c. Any treated infections within 2 weeks of baseline visit (excluding those treated with topicals only). d. A participant known to be infected with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C virus. e. History of infected joint prosthesis with prosthesis still in situ.

8. History of recurrent (more than one episode) herpes zoster, or a single episode of disseminated herpes zoster, or a single episode of disseminated (both oral and genital lesions simultaneously, or widespread lesions not contained to oral or genital regions alone) herpes simplex.

9. Any prior treatment with non-B cell-specific lymphocyte depleting agents/therapies (e.g., almetuzumab [CAMPATH®], alkylating agents [e.g., cyclophosphamide or chlorambucil], total lymphoid irradiation, etc.). Participants who had received rituximab or other selective B lymphocyte depleting agents (including experimental agents) were eligible if they had not received such therapy for at least 1 year prior to study baseline and had normal CD 19/20+ counts by fluorescence activated cell sorting analysis.

10. Any factors or clinical characteristics potentially related to the risk of venous thromboembolism (VTE) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Study participants

This study was conducted at 84 sites in 20 countries. This study enrolled and treated a total of 302 participants (26 participants from Study A3921103, 199 participants from Study A3921104, and 77 participants from Study A3921165).

Table 1. Number of Participants (Planned and Analysed)

Population	N	Definition
Planned	340	NA
Screened	302	NA
Enrolled and treated	302	NA
FAS	302	The full analysis set will include all enrolled subjects with at least one dose of tofacitinib during this study.
SAS	302	The safety analysis set will include all enrolled subjects with at least one dose of tofacitinib during this study. SAS is the same as FAS in this study.

NA = not applicable; FAS=full analysis set; SAS=safety analysis set

Analysis Sets

The number of participants included in each analysis set is provided in Figure 2. The majority (199) of participants were enrolled from Study A3921104; 77 participants were enrolled from Study A3921165, and 26 from Study A3921103 (Table 2). No participants were excluded from the analysis sets.

- FAS included all enrolled participants with at least one dose of tofacitinib during this study (302 participants). The SAS included all enrolled participants with at least one dose of tofacitinib during this study and is the same as FAS in this study.

- The sJIA1 analysis set included all participants in the FAS with sJIA (those with active arthritis but without active systemic features [index study A3921104] and those with confirmed active systemic features [index study A3921165]).

- The sJIA2 analysis set was a subset of sJIA1 analysis set. This analysis set includes only sJIA participants who, through their prior enrolment in index study A3921165, were confirmed to have active systemic features prior to their initial screening.

- The pJIA analysis set included all participants in FAS with pJIA (i.e., extended oligoarthritis, polyarthritis RF+, polyarthritis RF-, sJIA with active arthritis but without active systemic features). The pJIA analysis set did not include participants enrolled from index Study A3921165.

- The ERA analysis set consists of all participants in FAS with ERA.

- The PsA analysis set consists of all participants in FAS with jPsA.

Table 2. Participants in Each Data Analysis Set (Protocol A3921145)

	A3921103	A3921104				A3921165				Total Tofacitinib (A3921145)
	n (%)	Tofa OL (not randomized) n (%)	Tofa-Tofa n (%)	Tofa-Placebo n (%)	All n (%)	Tofa OL (not randomized) n (%)	Tofa-Tofa n (%)	Tofa-Placebo n (%)	All n (%)	n (%)
Full Analysis Set (FAS)	26 (100.0)	31 (100.0)	85 (100.0)	83 (100.0)	199 (100.0)	24 (100.0)	26 (100.0)	27 (100.0)	77 (100.0)	302 (100.0)
sJIA Analysis Set (sJIA1)	0	2 (6.5)	5 (5.9)	4 (4.8)	11 (5.5)	24 (100.0)	26 (100.0)	27 (100.0)	77 (100.0)	88 (29.1)
sJIA Analysis Set (sJIA2)	0	0	0	0	0	24 (100.0)	26 (100.0)	27 (100.0)	77 (100.0)	77 (25.5)
pJIA Analysis Set (pJIA)	22 (84.6)	26 (83.9)	69 (81.2)	68 (81.9)	163 (81.9)	0	0	0	0	185 (61.3)
PsA Analysis Set (PsA)	2 (7.7)	2 (6.5)	7 (8.2)	8 (9.6)	17 (8.5)	0	0	0	0	19 (6.3)
ERA Analysis Set (ERA)	2 (7.7)	3 (9.7)	9 (10.6)	7 (8.4)	19 (9.5)	0	0	0	0	21 (7.0)
Safety Analysis Set (SAS)	26 (100.0)	31 (100.0)	85 (100.0)	83 (100.0)	199 (100.0)	24 (100.0)	26 (100.0)	27 (100.0)	77 (100.0)	302 (100.0)

Tofa=Tofacitinib, OL=Open-Label.
The full analysis set (FAS) will include all enrolled participants with at least one dose of tofacitinib during this study.
The sJIA1 analysis set consists of all participants in FAS with systemic JIA (sJIA).
The sJIA2 analysis set is a subset of sJIA1 analysis set, including participants only from index study A3921165.
The pJIA analysis set consists of all subjects in FAS with polyarticular course JIA (participants from index study A3921165 not included).
The PsA analysis set consists of all participants in FAS with psoriatic arthritis.
The ERA analysis set consists of all participants in FAS with enthesitis related arthritis.
The safety analysis set (SAS) is identical as FAS.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2025 (20:00) Source Data: adsl Table Generation: 13MAR2025 (09:05)
(Database snapshot date : 26FEB2025) Output File: ./ra cdisc/A3921145 CSR/seval
Table 14.1.1.1 CP-690,550 is for Pfizer internal use.

Important Protocol Deviations

A formal acknowledgment by the study team was made that deviations were reviewed and GCP compliance was maintained. There were protocol deviations associated with 245 of the 302 enrolled participants. The most frequently reported important protocol deviations were:

- Lab(s) not done at 1 or more visits in 101 (33.4%) of participants.

- Visit more than 7 days outside of window in 85 (28.1%) of participants.

- Uveitis Exam not done annually (applies to pJIA only in 85 (28.1%) of participants).

Treatments

Tofacitinib was the study intervention administered and was provided as oral tablets (tofacitinib citrate 5 mg) and as an oral solution (CP-690,550-10 [tofacitinib citrate] 1 mg/mL) by the sponsor. Tablets and solution were supplied in bottles to the sites.

Objective(s)

The main aim of the study was on safety evaluation.

Safety: To determine the long-term safety and tolerability of tofacitinib for treatment of the signs and symptoms of JIA.

Efficacy: To evaluate the persistence of efficacy of tofacitinib for treatment of the signs and symptoms of JIA.

Outcomes/endpoints

Safety endpoints

Incidence and severity of AEs. Incidence of clinical laboratory abnormalities and change from baseline in clinical laboratory values. Validated assessments of growth (body weight and height) and pubertal

development (Tanner Stage of Development). Incidence of abnormalities in physical examination. Incidence of vital sign abnormalities and change from baseline in vital sign measures.

Efficacy (main) endpoints

Change from baseline in physician global evaluation of disease activity at each visit. Change from baseline in number of joints with active arthritis at each visit. Change from baseline in number of joints with limitation of motion at each visit. Change from baseline in index of inflammation (CRP and ESR) at each visit. CHAQ at each visit: 1) Change from baseline in Parent's Assessment of Physical Function (CHAQ Disability Index) 2) Change from baseline in Parent's Assessment of Child's Arthritis Pain (CHAQ Discomfort Index, VAS) 3) Change from baseline in Parent's Global Assessment of Overall Wellbeing (CHAQ subsection, VAS). The proportion of participants achieving JIA ACR response at each visit. The proportion of participants with occurrence of JIA ACR disease flare at each visit after Month 3. The proportion of participants achieving JIA ACR Clinical Inactive Disease status at each visit, and the proportion of participants achieving clinical remission at each visit after 24 weeks since this study started. Note that clinical remission is counted as 6 months (24 weeks) of inactive disease during study, and 24 weeks will be used in programming. Change from baseline in JADAS 27- CRP and JADAS 27- ESR, and occurrence of JADAS minimum disease activity and inactive disease at each visit.

Sample size

Participants completing any of 3 tofacitinib studies who met the enrolment criteria were eligible to enrol this open-label follow-up study: 302 participants had enrolled in the study (signed informed consent).

Randomisation and blinding (masking)

The study is open label; therefore, no randomization or blinding was adopted.

Statistical Methods

Baseline was defined in the following way for all statistical analyses except for JIA ACR disease flare, and safety monitoring and discontinuation:

- The number of off-study days (enrolment gap) between the last visit date in the qualifying study and the first visit date in this extension study was first determined.

- If the gap is ≤14 days, the baseline value came from the baseline value of the qualifying study, if available. If it was not available, the baseline value would have been missing.

- If the gap is >14 days, the following decision tree was used to determine which baseline value, from the qualifying study or from this extension study, was utilized in the analyses.

Table 3. Baseline value selection from qualifying & extension studies

Qualifying Study Baseline Available [a]	Extension Study Baseline Available [b]	Baseline Value for Use in Analyses, if Gap >14 days
No	No	No Baseline (Missing)
No	Yes	Extension Study
Yes	No	Qualifying study
Yes	Yes	Extension study

[a] The baseline values from the qualifying study with a randomized withdrawal design (ie, A3921104 and A3921165) will come from the open-label period baseline.
[b] The baseline values from this extension study will come from 1) separate screening and baseline visits after EOS visit of the qualifying study, 2) a combined screening/baseline visit after EOS visit, or 3) a screening/baseline visit combined with the EOS visit. More specifically, extension study baseline will be the last non-missing assessment on or before Day 1 and prior to first dose of study drug administration in this extension study. Only data collected in the extension study database will be used. If a baseline value is not available by design (ie, not planned to be collected at screening or baseline visit according to the protocol), extension study baseline availability will be "No" in the above decision tree.

For JIA ACR disease flare, baseline values will be from Month 3 of this extension study regardless of the gap calculated above.

The primary focus of this study is the long-term safety and tolerability of tofacitinib for treatment of the signs and symptoms of JIA. Safety endpoints will include standard laboratory safety data and TEAE reports (including SAE and AEs leading to discontinuation). Growth and pubertal development were also assessed.

The measures of efficacy were summarised using descriptive statistics, such as number and percent for binary endpoints, mean, standard deviation and quartiles for continuous endpoints at each visit where measured.

Results

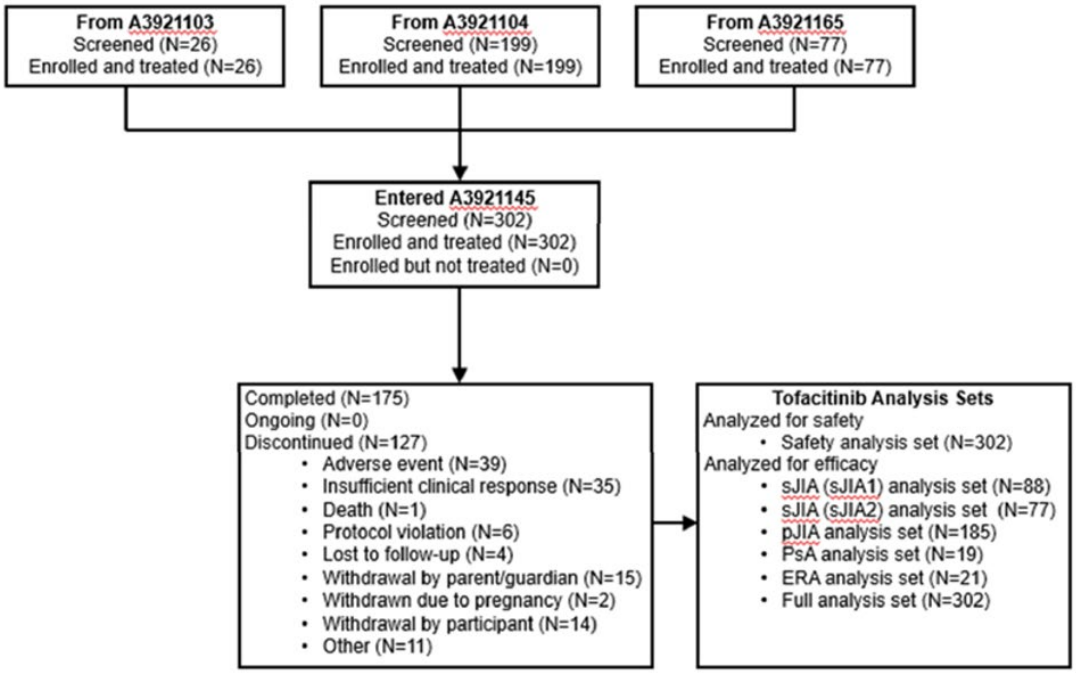
Participant flow

Participants completing any of 3 tofacitinib studies who met the enrolment criteria were eligible to enrol in this open-label follow-up study:

- 302 participants had enrolled in the study (signed informed consent).

- A total of 127 (32%) patients discontinued from OL study. Adverse events and insufficient clinical response were the most common reasons for discontinuation (39 [12.9%] and 35 [11.6%] participants, respectively). Of those who discontinued due to adverse events, 15 (5.0%) participants discontinued from the study due to adverse events (AEs) based on the following Preferred Terms that represent disease exacerbation: Still's Disease, Arthritis, Juvenile Idiopathic Arthritis (JIA), Arthropathy, temporomandibular pain and dysfunction syndrome, condition aggravated, and disease progression. Therefore, the rate of discontinuation due to insufficient clinical response should theoretically be implemented by this 5% of participants with disease progression.

Figure 2. Disposition of Participants



Source: Table 6 and Table 14.1.1.2

Baseline data

Table 4. Participant Demographic Characteristics - FAS, sJIA1, sJIA2, pJIA, ERA and PsA (Protocol A3921145)

	FAS (N=302)	sJIA1 (N=88)	sJIA2 (N=77)	pJIA (N=185)	ERA (N=21)	PsA (N=19)
Age (Years)						
2 - <6	31 (10.3)	11 (12.5)	10 (13.0)	21 (11.4)	0	0
6 - <12	100 (33.1)	43 (48.9)	37 (48.1)	56 (30.3)	5 (23.8)	2 (10.5)
>=12	171 (56.6)	34 (38.6)	30 (39.0)	108 (58.4)	16 (76.2)	17 (89.5)
Mean (SD)	11.86 (4.38)	10.75 (4.51)	10.75 (4.55)	11.90 (4.42)	13.48 (3.19)	14.16 (2.81)
Median (Range)	12.00 (3, 21)	10.00 (4, 21)	10.00 (4, 21)	13.00 (3, 18)	14.00 (7, 18)	15.00 (6, 18)
Q1,Q3	(8.00, 15.00)	(7.00, 15.00)	(7.00, 15.00)	(8.00, 16.00)	(12.00, 16.00)	(13.00, 16.00)
Gender						
Male	100 (33.1)	50 (56.8)	44 (57.1)	42 (22.7)	10 (47.6)	4 (21.1)
Female	202 (66.9)	38 (43.2)	33 (42.9)	143 (77.3)	11 (52.4)	15 (78.9)
Race						
White	229 (75.8)	39 (44.3)	29 (37.7)	165 (89.2)	18 (85.7)	17 (89.5)
Black or African American	11 (3.6)	6 (6.8)	6 (7.8)	4 (2.2)	1 (4.8)	0
Asian	37 (12.3)	37 (42.0)	37 (48.1)	0	0	0
Other	25 (8.3)	6 (6.8)	5 (6.5)	16 (8.6)	2 (9.5)	2 (10.5)

Data collected at extension study are used.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2025 (20:15) Source Data: adsl Table Generation: 13MAR2025 (06:33)
(Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/adsl_s001
Table 14.1.2.1 CP-690,550 is for Pfizer internal use.

Disease assessments at baseline are presented in Table 5 below:

Table 5. Disease Assessments at Baseline - FAS, sJIA1, sJIA2, pJIA, ERA and PsA (Protocol A3921145)

	FAS (N=302)	sJIA1 (N=88)	sJIA2 (N=77)	pJIA (N=185)	ERA (N=21)	PsA (N=19)
Physician's Global Evaluation of Overall Disease Activity [a]						
n	302	88	77	185	21	19
Mean (SD)	6.3 (1.99)	6.7 (2.09)	6.7 (2.14)	6.3 (1.93)	5.4 (1.78)	5.5 (1.77)
Median (range)	6.5 (0.0, 10.0)	7.3 (1.0, 10.0)	7.0 (1.0, 10.0)	6.5 (0.0, 10.0)	5.5 (2.5, 9.0)	5.0 (2.5, 8.5)
Q1, Q3	5.0, 8.0	5.5, 8.0	5.5, 8.0	5.0, 8.0	4.5, 6.5	4.0, 7.0
C-reactive protein (CRP) (mg/dL) [b]						
n	302	88	77	185	21	19
Mean (SD)	1.9 (3.17)	3.9 (4.30)	4.2 (4.43)	1.2 (2.22)	0.5 (0.82)	0.7 (1.58)
Median (range)	0.4 (0.0, 18.5)	2.4 (0.0, 18.5)	2.5 (0.0, 18.5)	0.2 (0.0, 12.5)	0.1 (0.0, 3.1)	0.2 (0.0, 5.9)
Q1, Q3	0.1, 2.3	0.4, 6.2	0.5, 6.6	0.0, 1.3	0.0, 0.5	0.1, 0.4
Normal	172 (57.0%)	52 (59.1%)	48 (62.3%)	98 (53.0%)	14 (66.7%)	12 (63.2%)
Above Normal	130 (43.0%)	36 (40.9%)	29 (37.7%)	87 (47.0%)	7 (33.3%)	7 (36.8%)
Missing	0	0	0	0	0	0
CHAQ: Evaluation of Overall Well-being [c]						
n	283	88	77	169	19	18
Mean (SD)	5.3 (2.56)	6.6 (2.33)	6.8 (2.19)	4.8 (2.53)	4.8 (2.01)	4.7 (2.45)
Median (range)	5.5 (0.0, 10.0)	7.0 (0.0, 10.0)	7.0 (0.5, 10.0)	5.0 (0.0, 10.0)	5.0 (1.0, 8.0)	4.5 (0.0, 8.5)
Q1, Q3	3.5, 7.0	5.0, 8.5	5.0, 8.5	3.0, 7.0	2.5, 6.5	3.0, 6.5
CHAQ: Disability Index [c]						
n	283	88	77	169	19	18
Mean (SD)	1.1 (0.75)	1.3 (0.76)	1.3 (0.75)	1.0 (0.75)	0.8 (0.50)	0.6 (0.53)
Median (range)	1.0 (0.0, 3.0)	1.4 (0.0, 3.0)	1.3 (0.0, 3.0)	1.0 (0.0, 2.9)	0.8 (0.0, 1.6)	0.5 (0.0, 1.9)
Q1, Q3	0.4, 1.6	0.8, 2.0	0.8, 2.0	0.3, 1.6	0.4, 1.3	0.3, 0.9
CHAQ: Discomfort Index [c]						
n	283	88	77	169	19	18
Mean (SD)	5.6 (2.61)	6.6 (2.44)	6.7 (2.34)	5.1 (2.70)	5.8 (1.89)	5.8 (2.20)
Median (range)	6.0 (0.0, 10.0)	7.5 (0.0, 10.0)	7.5 (0.0, 10.0)	5.5 (0.0, 10.0)	6.0 (2.0, 8.0)	6.3 (0.0, 8.5)
Q1, Q3	4.0, 7.5	5.0, 8.5	5.0, 8.5	3.0, 7.0	4.0, 7.5	5.5, 7.0
JADAS-27 CRP Score [d]						
n	283	88	77	169	19	18
Mean (SD)	21.9 (8.14)	24.3 (7.58)	24.6 (7.58)	22.0 (8.29)	14.7 (3.71)	17.0 (5.80)
Median (range)	20.5 (1.7, 51.6)	23.1 (5.5, 43.4)	23.2 (5.5, 43.4)	20.5 (1.7, 51.6)	15.6 (8.1, 23.8)	16.0 (7.5, 29.0)
Q1, Q3	16.2, 26.9	19.5, 27.8	20.0, 28.2	16.5, 27.2	11.0, 16.6	13.5, 20.1
JADAS-27 CRP High Disease Activity						
Yes	278 (92.1%)	88 (100.0%)	77 (100.0%)	166 (89.7%)	18 (85.7%)	17 (89.5%)
No	5 (1.7%)	0	0	3 (1.6%)	1 (4.8%)	1 (5.3%)
Missing	19 (6.3%)	0	0	16 (8.6%)	2 (9.5%)	1 (5.3%)

Baseline disease data are either from the qualifying study or the extension study based on the enrollment gap.
a. Physician's Global: Higher Physician global evaluation of overall disease activity means more JIA disease activity. The possible range of scores is 0 - 10.
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.
d. Higher JADAS-27 scores mean more JIA disease activity. The possible range of scores is 0 - 57.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2025 (20:15) Source Data: adsl adbase Table Generation: 13MAR2025 (09:57)
(Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/bdisease_da
Table 14.1.2.2.1 CP-690,550 is for Pfizer internal use.

The majority of patients (92.1%) had a high disease activity at baseline based on JADAS-27 CRP with a median score of 20.5.

Prior therapy

The majority (232 [76.8%]) of participants were taking analgesic medications prior to enrolment in A3921145 or qualifying/index studies A3921165, A3921103, and A3921104

- 260 [86.1%] were taking csDMARDs (Table 14.1.4.2).
- 216 [71.5%] were taking NSAIDs (Table 14.1.4.1).
- 177 [58.6%] were taking corticosteroids (Table 14.1.4.2).
- 83 [27.5%] were taking bDMARDs (Table 14.1.4.2).
- 71 [23.5%] were taking non-anti-inflammatory analgesics (Table 14.1.4.1).

Concomitant Therapy

The majority (238 [78.8%]) of participants took concomitant analgesic medications

- 215 [71.2%] were taking csDMARDs (Table 14.4.2.3).
- 220 [72.8%] were taking NSAIDs (Table 14.4.2.2).
- 152 [50.3%] were taking corticosteroids (Table 14.4.2.3).
- 2 [0.7%] were taking bDMARDs (Table 14.4.2.3).
- 94 [31.1%] were taking non-anti-inflammatory analgesics (Table 14.4.2.2).

Number analysed

Table 6. Participants in Each Data Analysis Set (Protocol A3921145)

	A3921103	A3921104				A3921165				Total Tofacitinib (A3921145)
	n (%)	Tofa OL (not randomized) n (%)	Tofa-Tofa n (%)	Tofa-Placebo n (%)	All n (%)	Tofa OL (not randomized) n (%)	Tofa-Tofa n (%)	Tofa-Placebo n (%)	All n (%)	n (%)
Full Analysis Set (FAS)	26 (100.0)	31 (100.0)	85 (100.0)	83 (100.0)	199 (100.0)	24 (100.0)	26 (100.0)	27 (100.0)	77 (100.0)	302 (100.0)
sJIA Analysis Set (sJIA1)	0	2 (6.5)	5 (5.9)	4 (4.8)	11 (5.5)	24 (100.0)	26 (100.0)	27 (100.0)	77 (100.0)	88 (29.1)
sJIA Analysis Set (sJIA2)	0	0	0	0	0	24 (100.0)	26 (100.0)	27 (100.0)	77 (100.0)	77 (25.5)
pJIA Analysis Set (pJIA)	22 (84.6)	26 (83.9)	69 (81.2)	68 (81.9)	163 (81.9)	0	0	0	0	185 (61.3)
PsA Analysis Set (PsA)	2 (7.7)	2 (6.5)	7 (8.2)	8 (9.6)	17 (8.5)	0	0	0	0	19 (6.3)
ERA Analysis Set (ERA)	2 (7.7)	3 (9.7)	9 (10.6)	7 (8.4)	19 (9.5)	0	0	0	0	21 (7.0)
Safety Analysis Set (SAS)	26 (100.0)	31 (100.0)	85 (100.0)	83 (100.0)	199 (100.0)	24 (100.0)	26 (100.0)	27 (100.0)	77 (100.0)	302 (100.0)

Tofa=Tofacitinib, OL=Open-Label.
The full analysis set (FAS) will include all enrolled participants with at least one dose of tofacitinib during this study.
The sJIA1 analysis set consists of all participants in FAS with systemic JIA (sJIA).
The sJIA2 analysis set is a subset of sJIA1 analysis set, including participants only from index study A3921165.
The pJIA analysis set consists of all subjects in FAS with polyarticular course JIA (participants from index study A3921165 not included).
The PsA analysis set consists of all participants in FAS with psoriatic arthritis.
The ERA analysis set consists of all participants in FAS with enthesitis related arthritis.
The safety analysis set (SAS) is identical as FAS.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2025 (20:00) Source Data: adsl Table Generation: 13MAR2025 (09:05)
(Database snapshot date : 26FEB2025) Output File: ./ra cdisc/A3921145 CSR/seval
Table 14.1.1.1 CP-690,550 is for Pfizer internal use.

Efficacy results

All efficacy endpoints in this study are secondary endpoints.

The efficacy analysis only provides descriptive information across different endpoints.

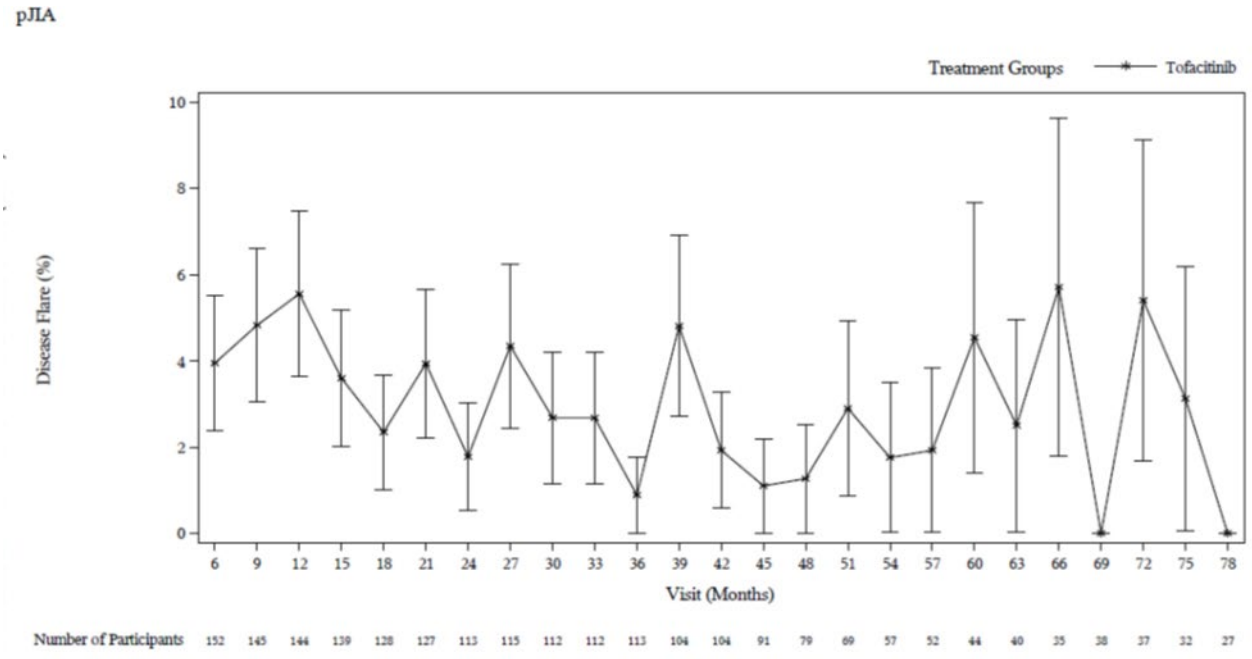
According to SAP, the secondary efficacy endpoints are summarised using descriptive statistics by visit for the binary and continuous endpoints respectively. The percent (for the binary endpoints) and mean change (for the continuous endpoints) over time and associated standard errors have been plotted for analyses in sJIA1, sJIA2 and pJIA analysis sets.

A summary of the long-term efficacy data for the combined systemic JIA population (sJIA1 analysis set; participants with systemic JIA with active arthritis but without active systemic features and with those who had active systemic features), systemic JIA participants with active systemic features (sJIA2 analysis set), pJIA participants (i.e., participants with extended oligoarthritis, polyarthritis RF+, polyarthritis RF-, and systemic JIA with active arthritis but without active systemic features), PsA participants, and ERA participants is included within this report. Limited conclusions can be made due to the small sample sizes for ERA and PsA populations at all timepoints and for pJIA, sJIA1 and sJIA2 populations after the timepoints Month 78, Month 27, and Month 30, respectively. In general, long-term treatment with tofacitinib resulted in maintenance of efficacy over time in patients with JIA.

- **Occurrence of Flare** (primary endpoint in Study A3921104): For all populations, occurrence of disease flare remained overall low and stable throughout the study.

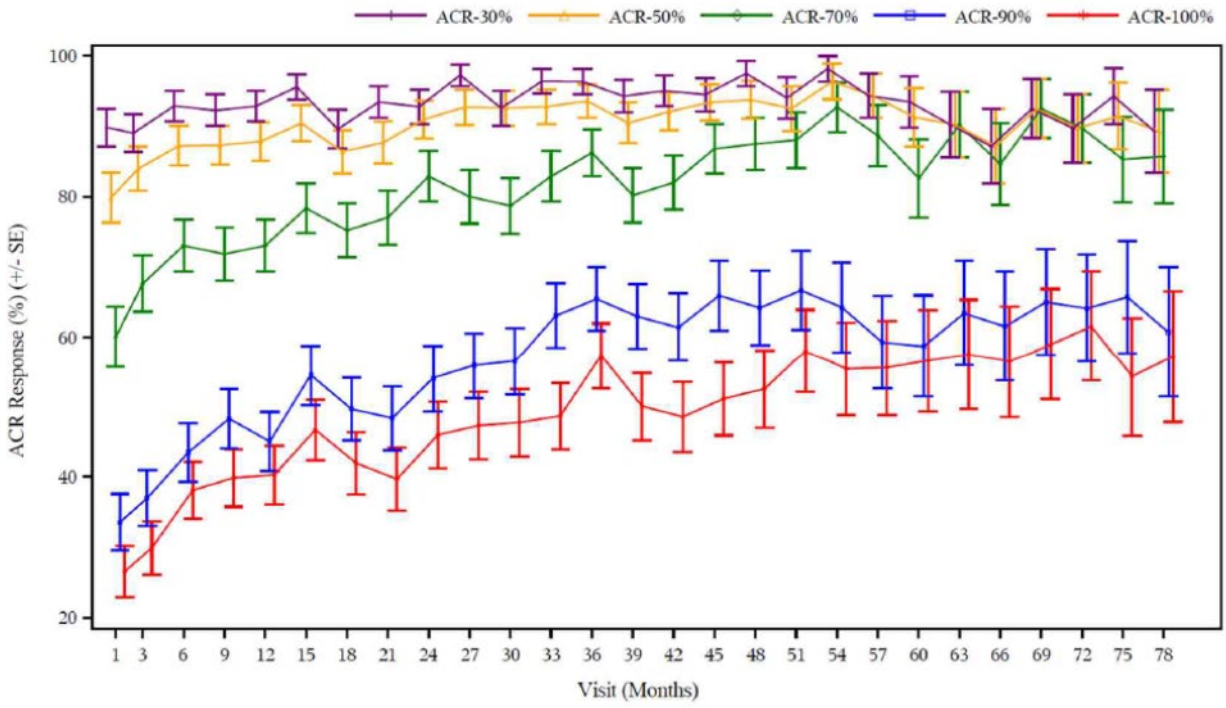
The figure below shows the Occurrence of Disease Flare in **pJIA** population:

Figure 3. Line Graph of Occurrence of Disease Flare (%) (+/- SE) by Visit - sJIA1, sJIA2, pJIA, ERA and PsA who Reached Month 3 Visit (Protocol A3921145)



- **JIA ACR Responses:** JIA ACR30, JIA ACR50, JIA ACR70, JIA ACR90 and JIA ACR100 are defined as achieving at least a 30%, 50%, 70%, 90%, or 100% improvement, respectively, in at least three of six core variables used to assess disease activity, with no more than one variable worsening by more than 30%. For all populations, JIA ACR response rates were generally maintained over the course of the study. For the **pJIA** population the percentage of participants achieving a JIA ACR30 response was at or above 87% at each visit throughout the study with at least 89.05% [2.67] of participants attaining ACR30 at each visit prior to Month 36. The percentage of participants achieving JIA ACR70 was 60.00% [4.30] at Month 1 and improved through Month 6 before remaining stable.

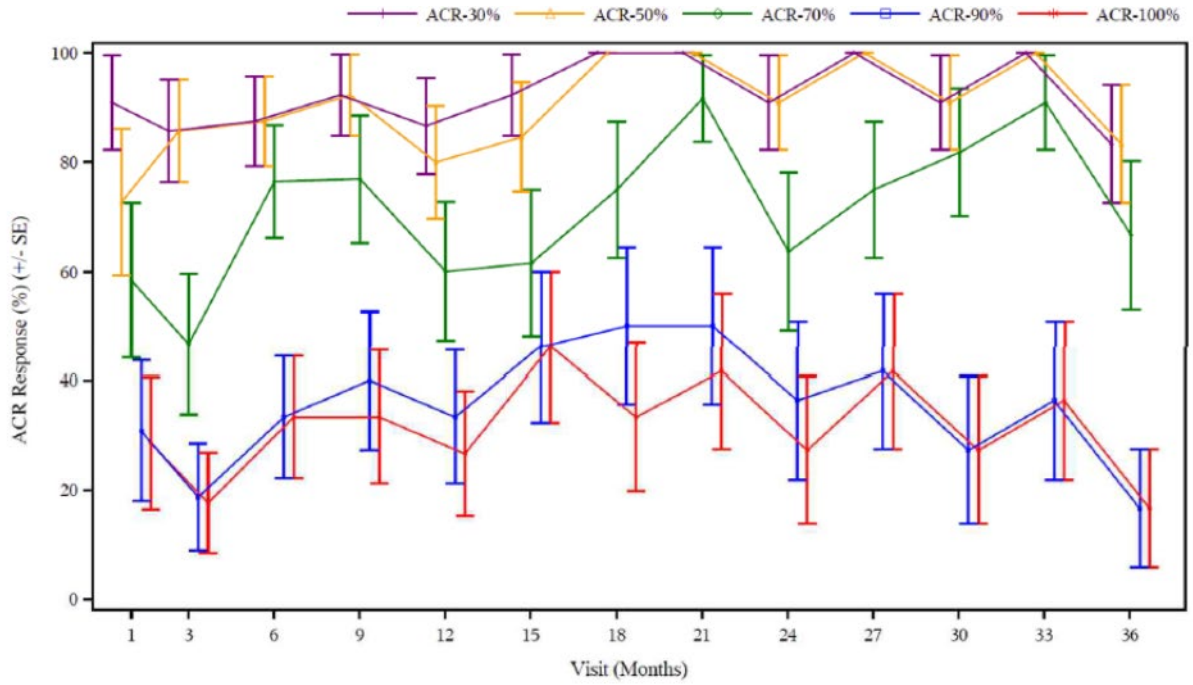
Figure 4. JIA ACR Responses (%) (+/- SE) – pJIA



PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (22:48) Source Data: adsl adacr Table Generation: 13MAR2025 (09:56) (Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/fig_acr_overlay

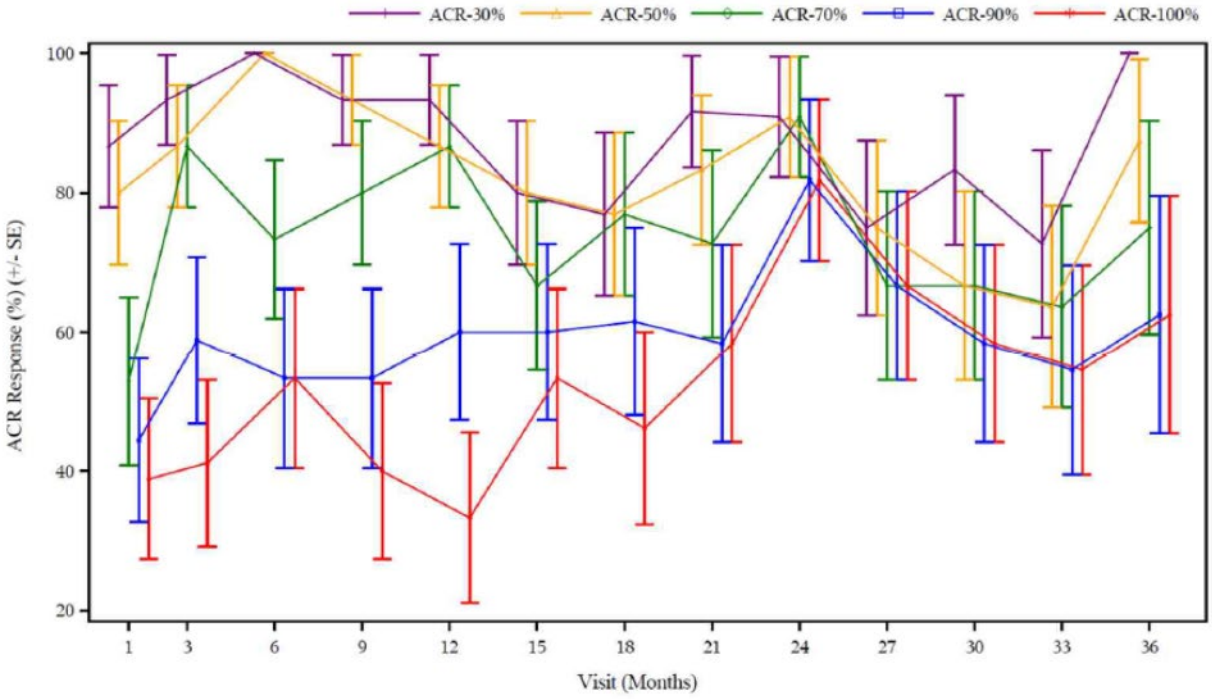
For the **ERA** population, the percentage of participants (standard error [SE]) achieving a JIA ACR30 response was at or above 80% at each visit throughout the study with at least 83.33% [10.76] participants attaining ACR30 at each visit prior to Month 36. The percentage of participants achieving JIA ACR70 was 58.33% [14.23] at Month 1 and remained stable throughout the study (figure below).

Figure 5. JIA ACR Responses (%) (+/- SE) - ERA



The **PsA** population ACR response rates were maintained over the course of the study. The percentage of participants achieving a JIA ACR30 response was at or above 72% at each visit throughout the study. The percentage of participants achieving JIA ACR70 was 52.94% [12.11] at Month 1 and improved through Month 3 before remaining stable (figure below).

Figure 6. JIA ACR Responses (%) (+/- SE) - PsA



- **Inactive Disease/Clinical Remission**: At least 20% of sJIA1, sJIA2, and ERA participants achieved Clinical Remission based on CRP at least once during the study. For pJIA and PsA, at least 40% of participants achieved Clinical Remission based on CRP at least once during the study. Similar results were seen for Clinical Remission based on ESR.

- **JADAS Score:** A negative mean change from baseline in JADAS-27 CRP score, a measure of disease activity where higher scores represented more disease activity, showed the disease activity decreased from baseline through Month 90 for sJIA1, Month 75 for sJIA2, Month 111 for pJIA, Month 90 for ERA, and Month 72 for PsA. A similar trend was observed for mean change from baseline in JADAS-27 ESR score from baseline throughout the study.

- **JADAS Minimum Disease Activity**: The proportion [SE] of participants with JADAS minimum disease - activity calculated from the JADAS-27 CRP score increased from Month 1 to Month 6 to 56% [5.61], 56% [5.86], and 61.4% [4.11] in sJIA1, sJIA2, and pJIA populations, respectively. In ERA population, JADAS minimum disease activity was achieved by over 35% of participants at each visit. In PsA population, over 50% of participants achieved JADAS minimum disease activity throughout. A similar trend was observed for JADAS minimum disease activity calculated from the JADAS-27 ESR score.

- **JADAS Inactive Disease:** The proportion of participants with JADAS inactive disease activity calculated from the JADAS-27 CRP score initially increased to over 30% by Month 3 and then remained stable over time in the sJIA1, sJIA2, and pJIA populations. JADAS inactive disease activity from JADAS-27 CRP score remained generally stable for PsA and ERA populations at approximately 25% to 50% for PsA and 15% to 30% for ERA. A similar trend was observed for JADAS minimum disease activity calculated from the JADAS-27 ESR score.

- **Joint Assessment:** A negative mean change from baseline in the number of joints with active arthritis and the number of joints with limited range of motion showed decreased number of joints for

both measures from baseline through Month 90 for sJIA1, Month 75 for sJIA2, Month 114 for pJIA, Month 90 for ERA, and Month 75 for PSA.

- **Physician Global Evaluation of Disease Activity:** A negative mean change from baseline in Physician Global Evaluation of disease activity showed decreased disease activity through Month 90 for sJIA1, Month 75 for sJIA2, Month 117 for pJIA, Month 75 for PsA, and Month 90 for ERA.

- **Childhood Health Assessment Questionnaire**: A negative mean change from baseline in CHAQ indicates improvement in sJIA. Mean changes from baseline in CHAQ Disability Index, Discomfort Index, and Parental Evaluation of Overall Well Being all showed decreased scores from baseline through the following period: sJIA1 at Month 90, sJIA2 at Month 75, pJIA at Month 111, ERA at Month 90, PsA at Month 72.

- Tapering (Corticosteroids, MTX/Leflunomiode, and Tofacitinib): Few participants in each analysis set attempted to taper corticosteroids, MTX/leflunomide, or tofacitinib during this study. Of the few participants who did attempt to taper oral corticosteroids or MTX/leflunomide, the majority were generally able to achieve complete tapering success; however, caution should be used interpreting these data due to the small numbers. No conclusions can be made on the ability of participants to taper tofacitinib during the study due to the small numbers who attempted to taper.

- Achieving "Absence of Fever" (sJIA Participants): The majority (>90%) of participants in the sJIA1 and sJIA2 population achieved absence of fever up to Month 90 and Month 75, respectively.

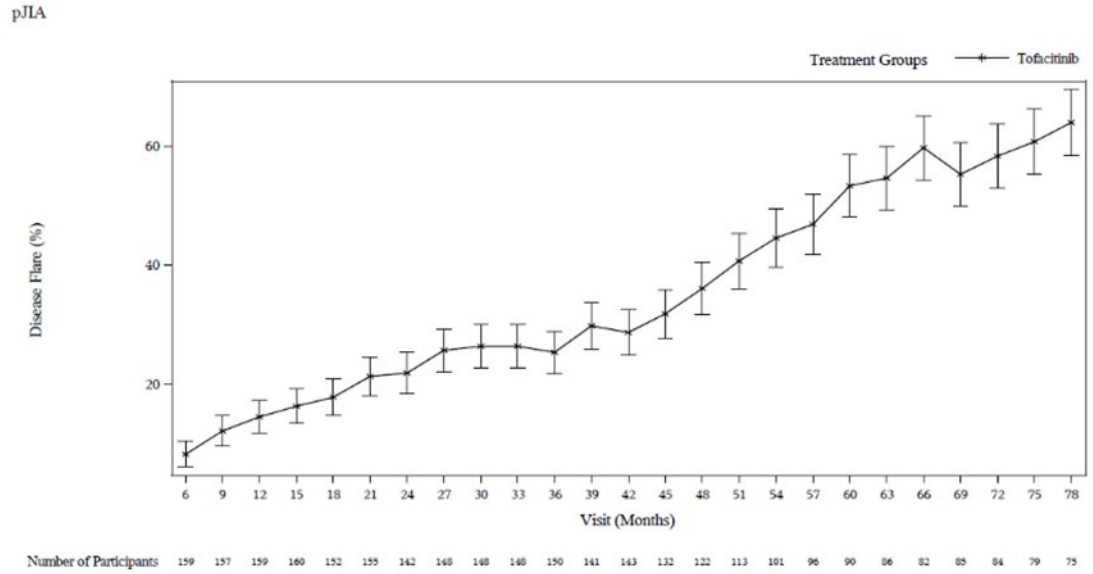
- Inflammatory Markers: Mean change from baseline in ESR and CRP through Month 90 for the sJIA1 population, Month 75 for the sJIA2 population, Month 117 for the pJIA population, Month 90 for the ERA population, and Month 75 for the PsA population remained stable indicating maintained response over course of study.

- TEA score, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain (ERA participants): Limited data are available for ERA participants since the sample size was <20 participants at all visits.

- BSA Affected by Psoriasis and PGA of Psoriasis (PsA Participants): Limited data are available for PsA participants since the sample size was <20 participants at all visits.

The MAH performed upon request additional analyses in which patients who discontinued due to insufficient clinical response or AE (including death) were considered non-responders. Based on this analysis, the occurrence of disease flare increased with time, from 8.2% at Month 6 to 25.3% at Month 36 and to 64.0% at Month 7.

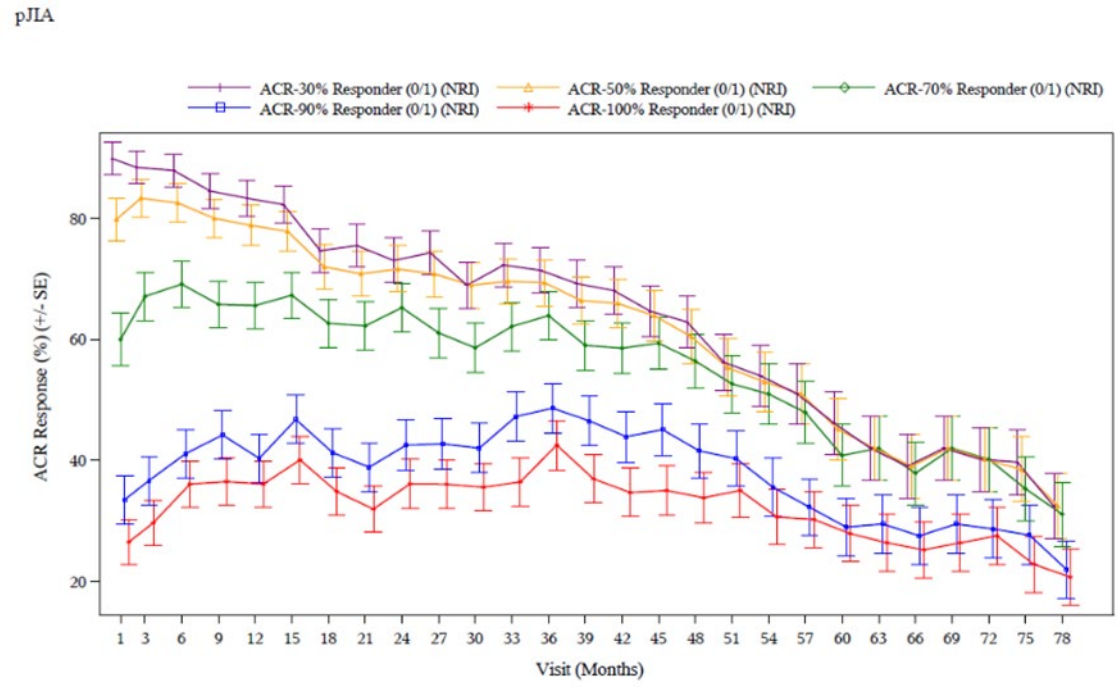
Figure 7. Line Graph of Occurrence of Disease Flare (%) (+/- SE) – pJIA (NRI)



Month 3 is the baseline for disease flare.
Participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death are considered as non-responders at visits post discontinuation.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2025 (20:15) Source Data: adsl adpa Table Generation: 08OCT2025 (08:35)
(Database snapshot date : 26Feb2025) Output File: ./ra_cdisc/SCS509a/fig_flare

Similarly, the proportion of responders declined over time for the JIA ACR endpoints (30 and 50) nd was less evident for the more stringent endpoints such as JIA ACR 70, 90, 100, as well as inactive disease and clinical remission.

Figure 8. Line Graph of JIA ACR Responses (%) (+/- SE) - pJIA (NRI)



Participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death are considered as non-responders at visits post discontinuation.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (22:48) Source Data: adsl adacr Table Generation: 07OCT2025 (06:04)
(Database snapshot date : 26Feb2025) Output File: ./ra_cdisc/SCS509a/fig_acr_overlay

Safety results

Overall, 268/302 (88.7%) participants reported AE(s).

Table 7. Treatment-Emergent Adverse Events (All Causalities) - SAS (Protocol A3921145)

Number (%) of Participants	Tofacitinib n (%)
Participants evaluable for adverse events	302
Number of adverse events	1490
Participants with adverse events	268 (88.7)
Participants with serious adverse events	48 (15.9)
Participants with severe adverse events	30 (9.9)
Participants discontinued from study due to adverse events[a]	41 (13.6)
Participants discontinued study drug due to AE and continue Study[b]	1 (0.3)
Participants with dose reduced or temporary discontinuation due to adverse events	93 (30.8)

Includes data up to 365 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 v27.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (22:48) Source Data: adsl adae Table Generation: 13MAR2025 (06:33)
(Database snapshot date : 26FEB2025) Output File: ./ra cdisc/A3921145 CSR/adae s010
Table 14.3.1.2.1.1 CP-690,550 is for Pfizer internal use.

TEAEs were most frequently reported in the SOCs of Infection and Infestations (198/302 [65.6%] participants), Musculoskeletal and Connective Tissue Disorders (110/302 [36.4%] participants) and GI Disorders (85/302 [28.1%] participants).

Table 8. TEAEs Reported in >=2% Participants by MedDRA PT - SAS (Protocol A3921145)

Number of Participants Evaluable for AEs Number (%) of Participants: by Preferred Term	Tofacitinib (N=302) n (%)
With Any Adverse Event	268 (88.7)
Upper respiratory tract infection	66 (21.9)
Nasopharyngitis	40 (13.2)
Juvenile idiopathic arthritis	31 (10.3)
Urinary tract infection	29 (9.6)
Pyrexia	28 (9.3)
Viral infection	27 (8.9)
Arthralgia	25 (8.3)
Abdominal pain	24 (7.9)
Headache	23 (7.6)
COVID-19	21 (7.0)
Cough	20 (6.6)
Vomiting	20 (6.6)
Influenza	19 (6.3)
Pharyngitis	18 (6.0)
Sinusitis	18 (6.0)
Still's disease	18 (6.0)
Bronchitis	17 (5.6)
Nausea	17 (5.6)
Arthritis	16 (5.3)

SARS-CoV-2 test positive	16 (5.3)
Oropharyngeal pain	15 (5.0)
Blood creatine phosphokinase increased	14 (4.6)
Diarrhoea	14 (4.6)
Ear infection	14 (4.6)
Latent tuberculosis	14 (4.6)
Condition aggravated	13 (4.3)
Disease progression	13 (4.3)
Anaemia	11 (3.6)
Gastroenteritis	11 (3.6)
Neutropenia	11 (3.6)
Rash	11 (3.6)
Abdominal pain upper	10 (3.3)
Acne	10 (3.3)
Ligament sprain	10 (3.3)
Limb injury	10 (3.3)
Skin papilloma	10 (3.3)
Haemoglobin decreased	9 (3.0)
Interferon gamma release assay positive	9 (3.0)
Leukopenia	9 (3.0)
Otitis media acute	9 (3.0)
Pneumonia	9 (3.0)
Alanine aminotransferase increased	8 (2.6)
Joint swelling	8 (2.6)
Pain in extremity	8 (2.6)
Pharyngitis streptococcal	8 (2.6)
Respiratory tract infection	8 (2.6)
Rhinitis allergic	8 (2.6)
Tonsillitis	8 (2.6)
Anxiety	6 (2.0)
C-reactive protein increased	6 (2.0)
Constipation	6 (2.0)
Fall	6 (2.0)
Herpes zoster	6 (2.0)
Hypertransaminasaemia	6 (2.0)
Myopia	6 (2.0)
Respiratory tract infection viral	6 (2.0)

Suicidal ideation	6 (2.0)
Urticaria	6 (2.0)
Viral upper respiratory tract infection	6 (2.0)

Participants are only counted once per treatment per event.
*Percentages of gender specific events are calculated using the corresponding gender count as denominator.
Includes data up to 365 days after last dose of study drug.
(@@) Denotes AE terms that were not coded by the MedDRA dictionary.
MedDRA v27.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (22:48) Source Data: adsl adae Table Generation: 13MAR2025 (06:33)
(Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/adae_s0311
Table 14.3.1.2.5 CP-690,550 is for Pfizer internal use.

Most AEs were mild (125/302 [41.4%]) or moderate (113/302 [37.4%]) in severity.

The most frequent severe AEs were reported in the Musculoskeletal and Connective Tissue Disorders SOC in 8/302 (2.6%) participants, Infections and Infestations SOC in 6/302 (2.0%) participants, and Psychiatric Disorders SOC in 5/302 (1.7%) participant. The most frequent severe AE by PT was Still's Disease in 4/302 (1.3%) participants.

Treatment-related TEAEs were most frequently reported in the SOCs of Infection and Infestations (69/302 [22.8%] participants), Investigations (26/302 [8.6%] participants), and Musculoskeletal and Connective Tissue Disorders (18/302 [6.0%] participants). The most frequently reported TEAEs by PT were: Upper respiratory tract infection (19/302 [6.3%] participants), Juvenile idiopathic arthritis (12/302 [4.0%] participants) and Sinusitis (8/302 [2.6%] participants). Most treatment-related AEs were mild (55/302 [18.2%]) or moderate (44/302 [14.6%]) in severity. Severe treatment-related AEs were reported in 11/302 (3.6%) participants.

There were 48/302 (15.9%) participants with at least 1 treatment-emergent SAE. The most commonly reported SAEs were Still's Disease, in 8 participants (2.6%), and Suicidal ideation, in 5 participants (1.7%).

Table 9. Treatment-Emergent SAEs by MedDRA PT - SAS (Protocol A3921145)

	Tofacitinib (N=302) n (%)
Participants with at least 1 Treatment-Emergent SAE	48 (15.9)
Still's disease	8 (2.6)
Suicidal ideation	5 (1.7)
Herpes zoster	4 (1.3)
Pyrexia	3 (1.0)
Abortion spontaneous	2 (0.7)
Appendicitis noninfective	2 (0.7)
Haemophagocytic lymphohistiocytosis	2 (0.7)
Juvenile idiopathic arthritis	2 (0.7)
Pneumonia	2 (0.7)
Suicide attempt	2 (0.7)
Abdominal pain	1 (0.3)
Abscess limb	1 (0.3)
Anaemia	1 (0.3)
Arthritis	1 (0.3)
Bronchitis	1 (0.3)
COVID-19	1 (0.3)
Chest pain	1 (0.3)
Cholecystitis chronic	1 (0.3)
Cholelithiasis	1 (0.3)
Escherichia pyelonephritis	1 (0.3)
Febrile convulsion	1 (0.3)
Femur fracture	1 (0.3)
Forearm fracture	1 (0.3)
Gastritis	1 (0.3)
Headache	1 (0.3)
Hepatic enzyme increased	1 (0.3)

Homicidal ideation	1 (0.3)
Hypertransaminasaemia	1 (0.3)
Infectious mononucleosis	1 (0.3)
Influenza	1 (0.3)
Major depression	1 (0.3)
Migraine	1 (0.3)
Molluscum contagiosum	1 (0.3)
Muscle spasms	1 (0.3)
Osteoarthritis	1 (0.3)
Osteonecrosis	1 (0.3)
Ovarian cyst	1 (0.3)
Rhinovirus infection	1 (0.3)
Synovial cyst	1 (0.3)
Ureterolithiasis	1 (0.3)
Urinary tract infection	1 (0.3)
Weight decreased	1 (0.3)

Participants are only counted once per treatment per event.
*Percentages of gender specific events are calculated using the corresponding gender count as denominator.
Includes data up to 365 days after last dose of study drug.
(@@) Denotes AE terms that were not coded by the MedDRA dictionary.
MedDRA v27.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (22:48) Source Data: adsl adae Table Generation: 13MAR2025 (06:33)
(Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/adae_s200
Table 14.3.1.3.3.1 CP-690,550 is for Pfizer internal use.

Two **deaths** were reported for participants in this study.

One participant death was due to an AE of weight decreased in a participant with sJIA. On study Day 337 the participant reported decreased weight, night fever and an arthritis flare in the ankles for which study drug was stopped. On study Day 381 participant was switched from latent TB treatment to empirical treatment for possible active tuberculosis. On Day 395 the participant was severely weak, could not walk, had severe ankle edema, ongoing diarrhoea, new onset pleural effusion, tachycardia and was urgently admitted to hospital. Participant died on study Day 414 during a hospital admission. The investigator considered this death related to study intervention; the sponsor considered this death unrelated to study intervention.

One participant death occurred due to an AE of Still’s disease and haemophagocytic lymphohistiocytosis in a participant with sJIA. Participant completed the study and discontinued study drug on study Day 513. Participant developed high fever and rashes 15 days after end of study and was hospitalized with sJIA flare with MAS and died the following day. The event was considered unrelated to study intervention.

The number of participants who permanently **discontinued** from the study due to an AE was 39/302 (12.9%). Infections and infestations (SOC) (9/302 [3.0%] participants) and Musculoskeletal and connective tissues disorders (SOC) (12/302 [4.0%] participants) were the most common cause of study discontinuation. Still’s disease (sJIA disease flare) (7/302 [2.3%] participants), HZ (3/302 [1.0%] participants), and Interferon gamma release assay positive (3 [1.0%] participants) were the most common cause (PT) of permanent discontinuation. Fifteen participants, representing 5% of the study population, permanently discontinued from the study due to adverse events (AEs) based on the following Preferred Terms that represent disease exacerbation: Still's Disease, Arthritis, Juvenile Idiopathic Arthritis (JIA), Arthropathy, temporomandibular pain and dysfunction syndrome, condition aggravated, and disease progression.

There were 93 (30.80%) participants with **dose reductions or temporary discontinuations** due to AEs. Infections and infestations (SOC) (67/302 [22.2%]) and GI disorders (SOC) (15/302 [5.0%]) were the most common cause of dose modification of temporary discontinuation (Table 14.3.1.1.2). Covid-19 (14/302 [4.6%] participants), Upper respiratory tract infection (12/302 [4.0%] participants) and Pyrexia (10/302 [3.3%] participants) were the most common cause (PT) of dose reductions or temporary discontinuations.

AESI – AEs of special interest

- No participants met the criteria for adjudicated major adverse cardiovascular events, malignancy (excluding non-melanoma skin cancer), adjudicated TB, GI perforations, drug induced liver injury and other hepatic events, or interstitial lung disease. There were no events of pulmonary embolism or deep vein thrombosis.

- No participant met the criteria for adjudicated Drug Induced Liver Injury (DILI) and other hepatic events.

- Two participants had an adjudicated event of MAS (Still's disease). Further one participant had an event of MAS adjudicated as possible MAS.

- Fourteen (4.6%) out of 302 participants reported serious infections and 6/302 (2.0) participants reported HZ. TEAE are included in the exposure estimates and incidence rates.

- 2 participants (0.7%) had adjudicated opportunistic infections. Both cases were of HZ and were adjudicated as multidermatomal (nonadjacent or >2 adjacent dermatomes) and met the criteria for being considered an OI.

- 1 participant had a case of HZ on study day 2645 which met the criteria for being considered a special interest infection due to 2 adjacent dermatomes involved. Of note, this participant had a previous mild Varicella event on study day 593 which resolved following antiviral treatment. The participant had rolled over from index study A3921103 and was not required to have documentation of previous varicella vaccination or seropositive result for VZV ELISA screening test.

- 9 participants had renal events, defined as adverse events of increased creatinine or proteinuria. Only 1 participant was discontinued due to meeting renal stopping laboratory criteria of increased creatinine.

- There were 2 (0.7%) cases (mild) and 1 (0.3%) case (moderate) of TEAE Uveitis. The moderate case was considered treatment-related.

Laboratory findings

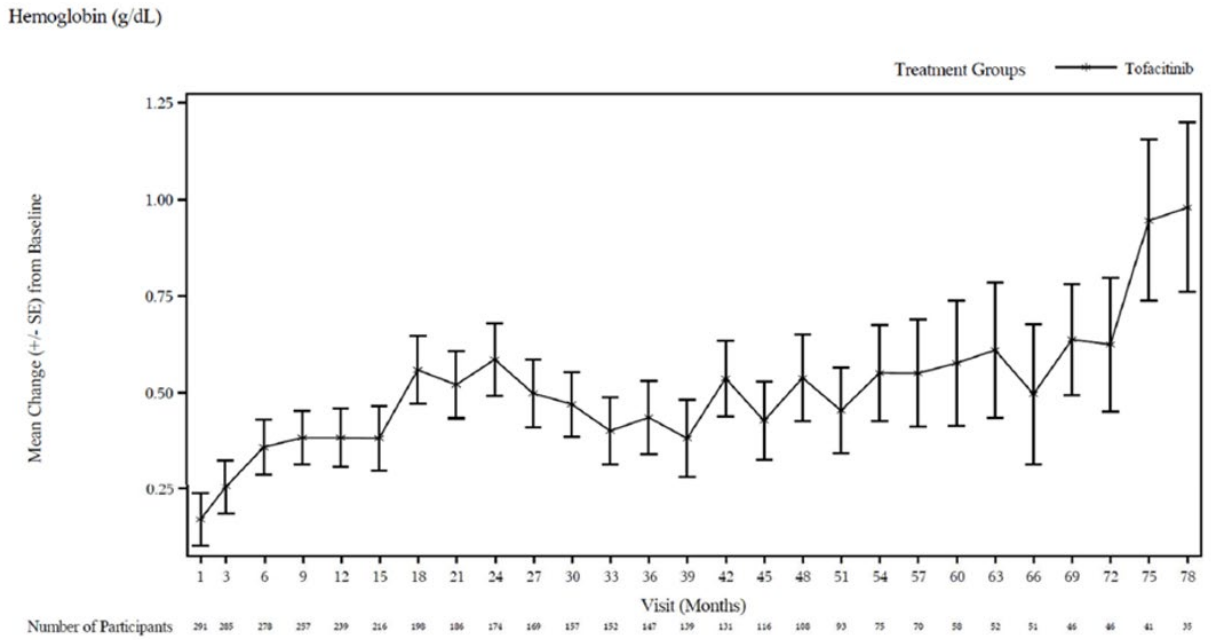
Overall, clinical laboratory values remained stable throughout the treatment period and only 22 events met criteria for discontinuation of study drug for laboratory values. Of the 22 events only 2 led to participant discontinuation, with the remainder either occurring in participants who had already discontinued study drug, or in the case of creatinine criteria, participants were allowed to continue after further assessment.

Table 10. Number (%) of Participants with Laboratory Values meeting Protocol Criteria for Discontinuation - SAS (Protocol A3921145)

	Tofacitinib (N = 302) n (%)
Two sequential hemoglobin 30% from baseline value	1 (0.33)
Two sequential lymphocyte counts	1 (0.33)
Two sequential neutrophil counts	0 (0.00)
Two sequential platelet counts	0 (0.00)
Two sequential AST or ALT elevations >3 x ULN with at least one Total Bilirubin value >2 x ULN	0 (0.00)
Two sequential AST or ALT elevations >3 x ULN accompanied by abnormal INR	0 (0.00)
Two sequential AST or ALT elevations >3 x ULN accompanied by symptoms consistent with hepatic injury	1 (0.33)
Two sequential AST or ALT elevations >5 x ULN regardless of Total Bilirubin	2 (0.66)
Single positive HBc Ab and a negative HBs Ab	0 (0.00)
Two sequential increases in serum creatinine >100% over the average of screening and baseline values[a]	4 (1.32)
Two sequential increases in serum creatinine >50% over the avg. of screening and baseline values OR an absolute increase in serum creatinine >=0.5mg/dL (>=44.2 umol/L) over the avg. of screening and baseline values, AND a confirmed (two sequential) creatinine clearance decrease of >30% over the avg. of screening and baseline values[b]	13 (4.30)

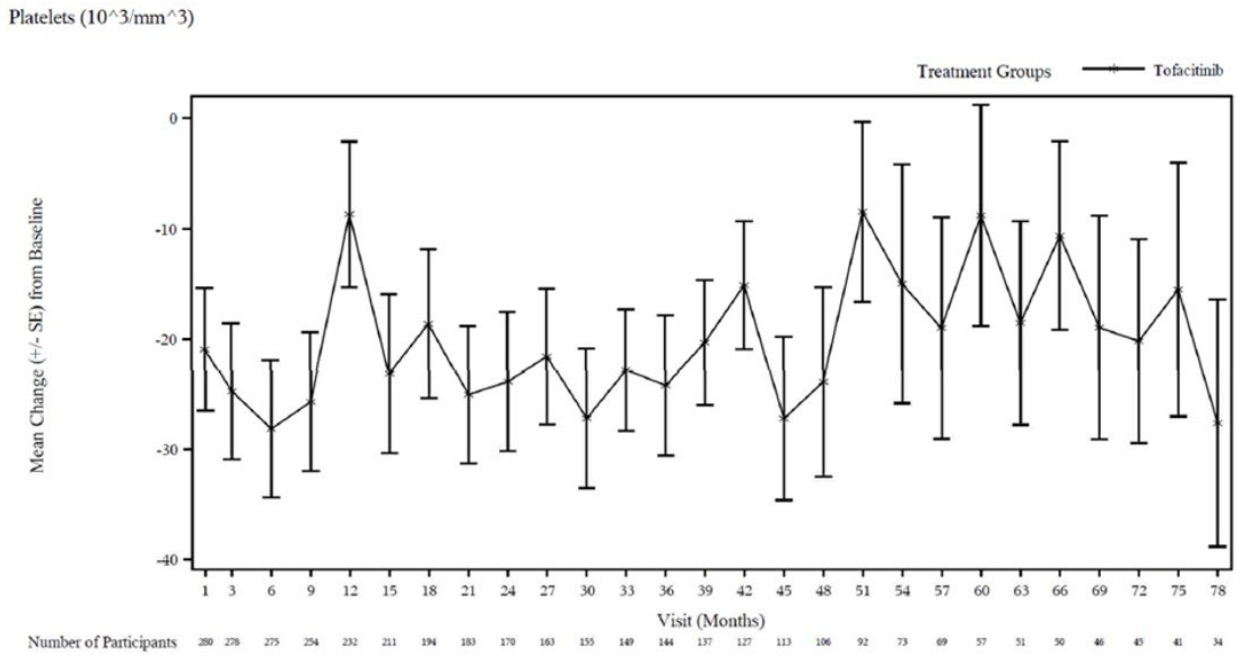
Screening/baseline is either from the qualifying study or the extension study based on the enrollment gap.
Hepatic Injury: PT INR > 1.2
a. Denotes discontinuation criteria for renal functioning from original protocol through Amendment 10.
b. Denotes discontinuation criteria for renal functioning from Amendment 11 onwards.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (23:03) Source Data: adsl adlb2 Table Generation: 13MAR2025 (09:07)
(Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/tab_disc_crit
Table 14.3.4.1.6.2 CP-690,550 is for Pfizer internal use.

Figure 9. Mean Change from Baseline (+/-SE) for Hemoglobin (SAS)



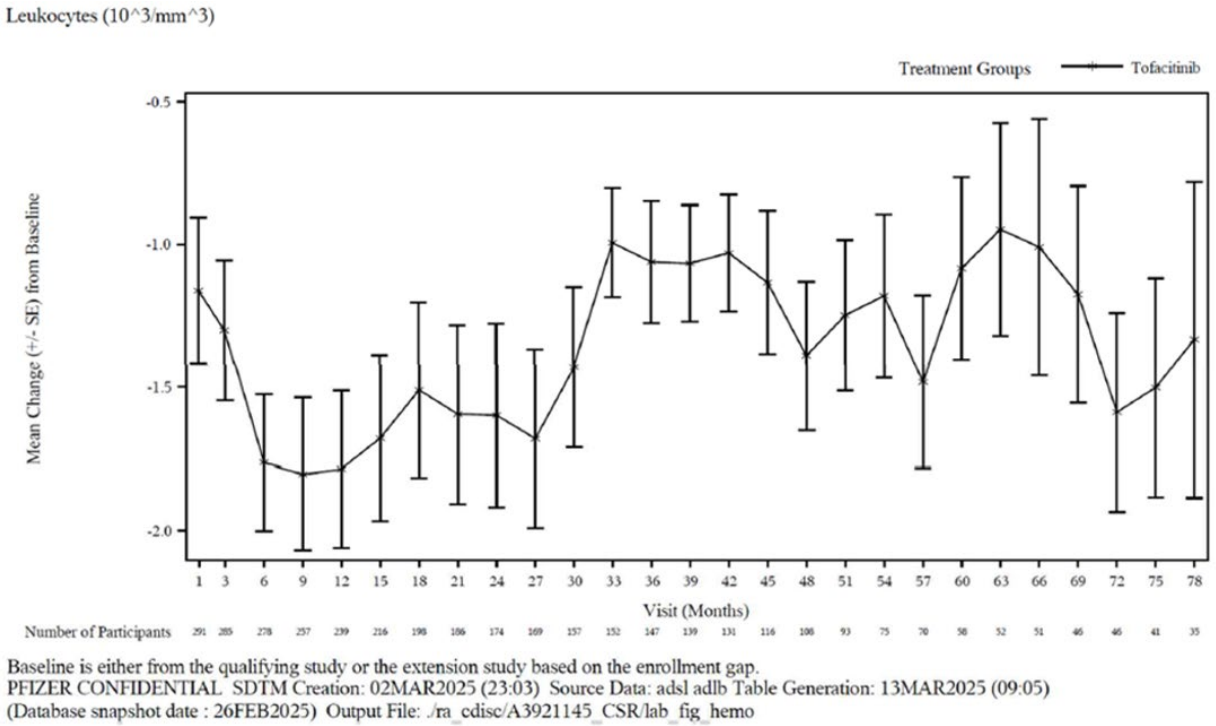
Baseline is either from the qualifying study or the extension study based on the enrollment gap.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (23:03) Source Data: adsl adlb Table Generation: 13MAR2025 (09:05)
(Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/lab_fig_hemo

Figure 10. Mean Change from Baseline (+/-SE) for Platelets (SAS)



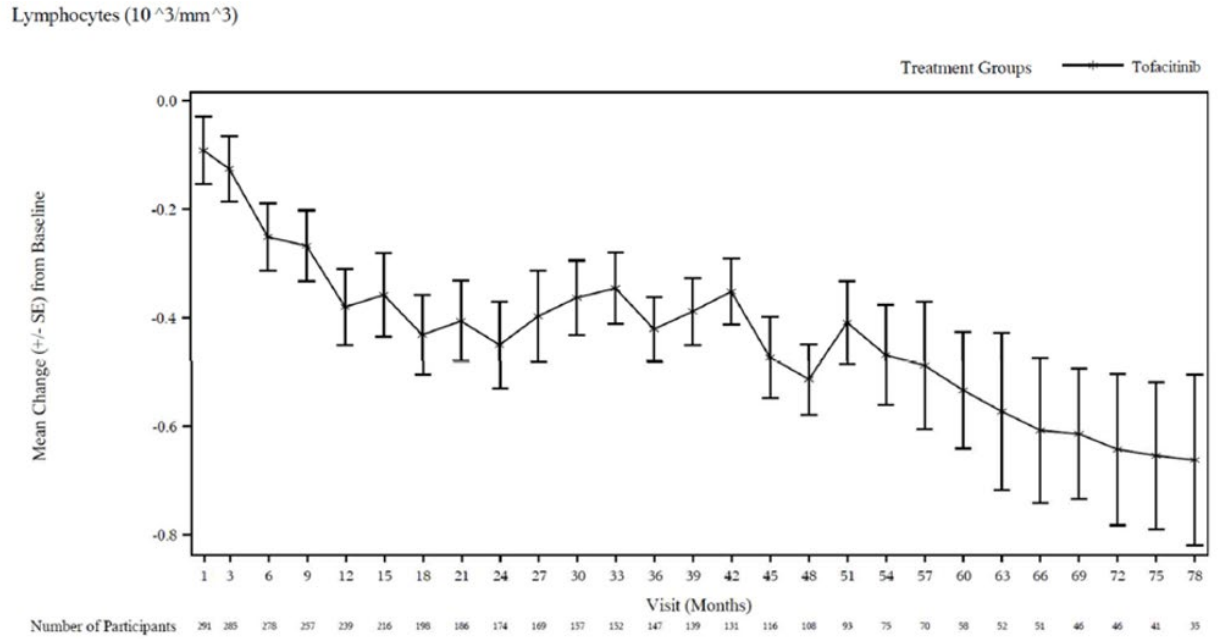
Baseline is either from the qualifying study or the extension study based on the enrollment gap.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (23:03) Source Data: adsl adlb Table Generation: 13MAR2025 (09:05)
(Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/lab_fig_hemo

Figure 11. Mean Change from Baseline (+/-SE) for Leukocytes (SAS)



Baseline is either from the qualifying study or the extension study based on the enrollment gap.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (23:03) Source Data: adsl adlb Table Generation: 13MAR2025 (09:05)
(Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/lab_fig_hemo

Figure 12. Mean Change from Baseline (+/-SE) for Lymphocytes (SAS)



Baseline is either from the qualifying study or the extension study based on the enrollment gap.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (23:03) Source Data: adsl adlb Table Generation: 13MAR2025 (09:05)
(Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/lab_fig_hemo

Figure 13. Mean Change from Baseline (+/-SE) for Neutrophils (SAS)

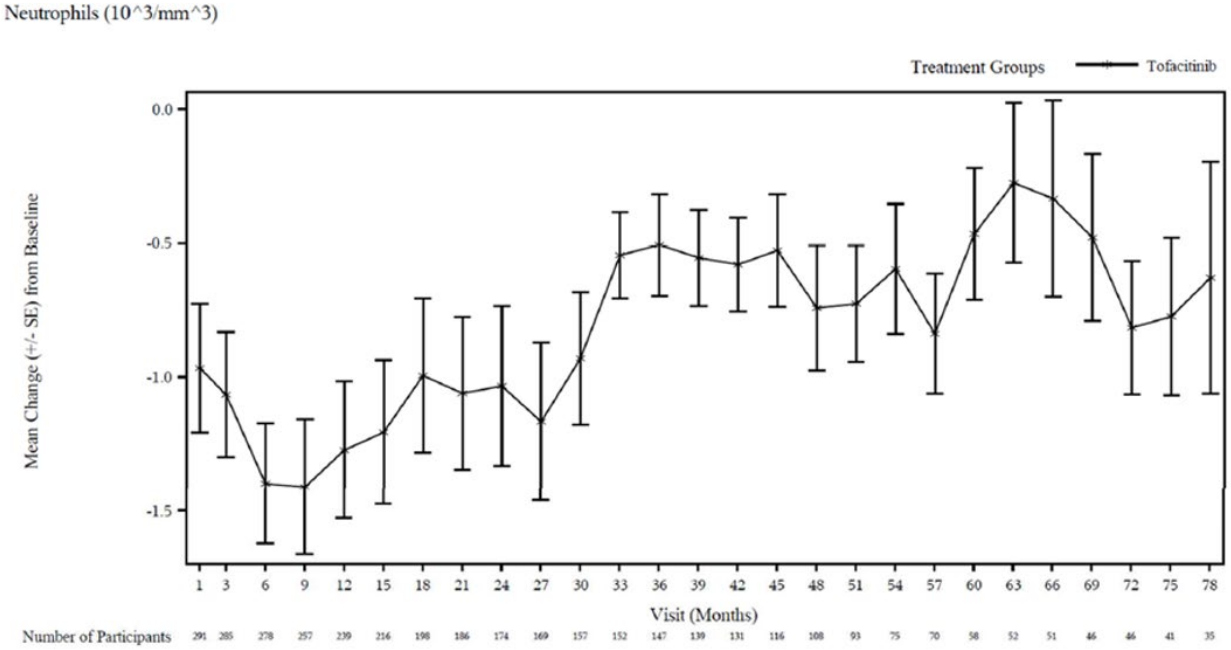


Figure 14. Mean Change from Baseline (+/-SE) for Serum Creatinine (SAS)

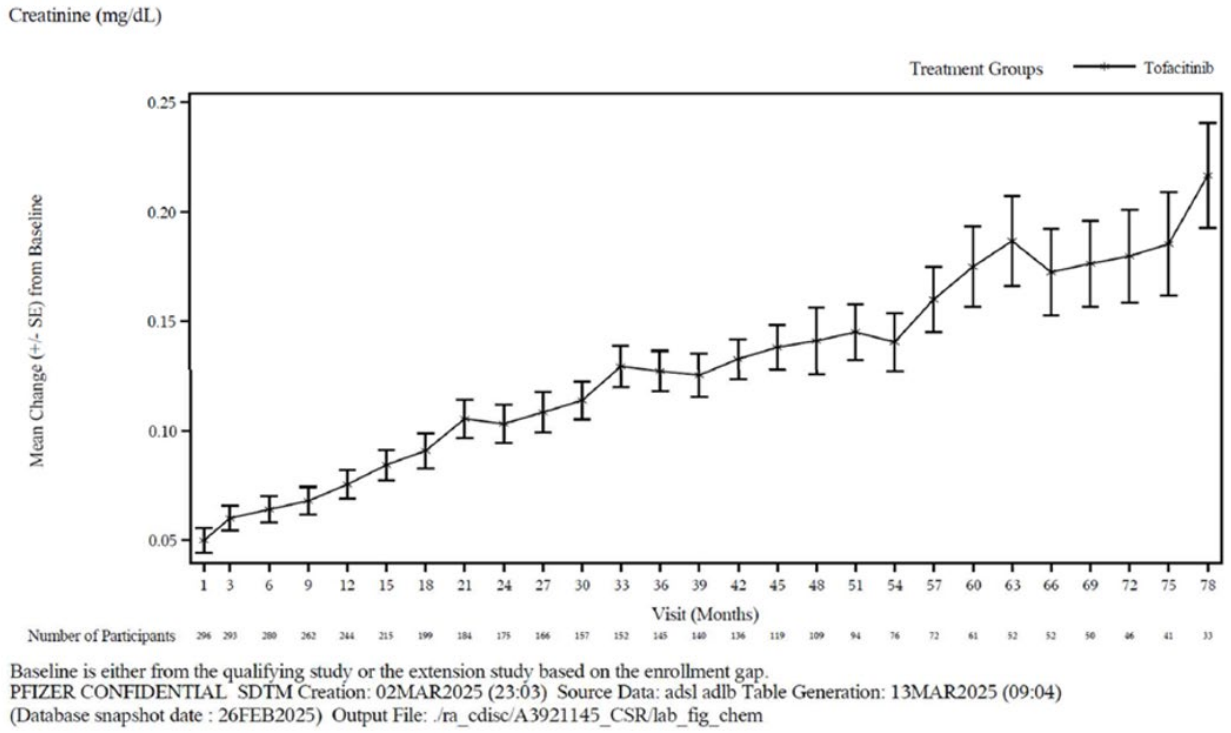
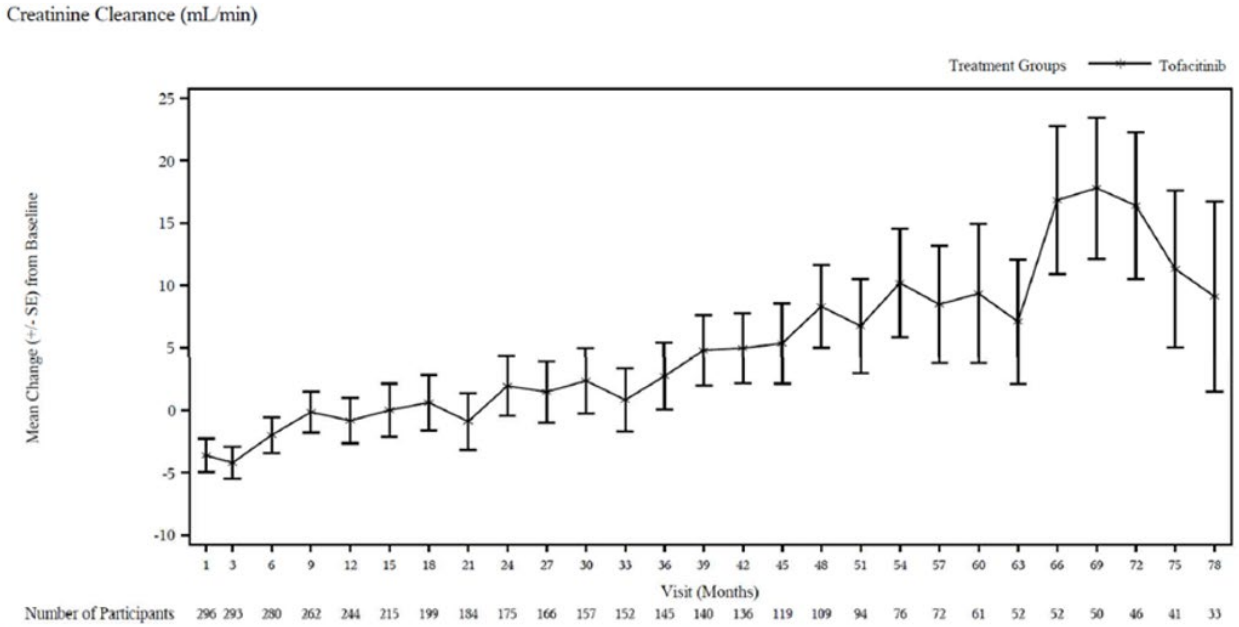
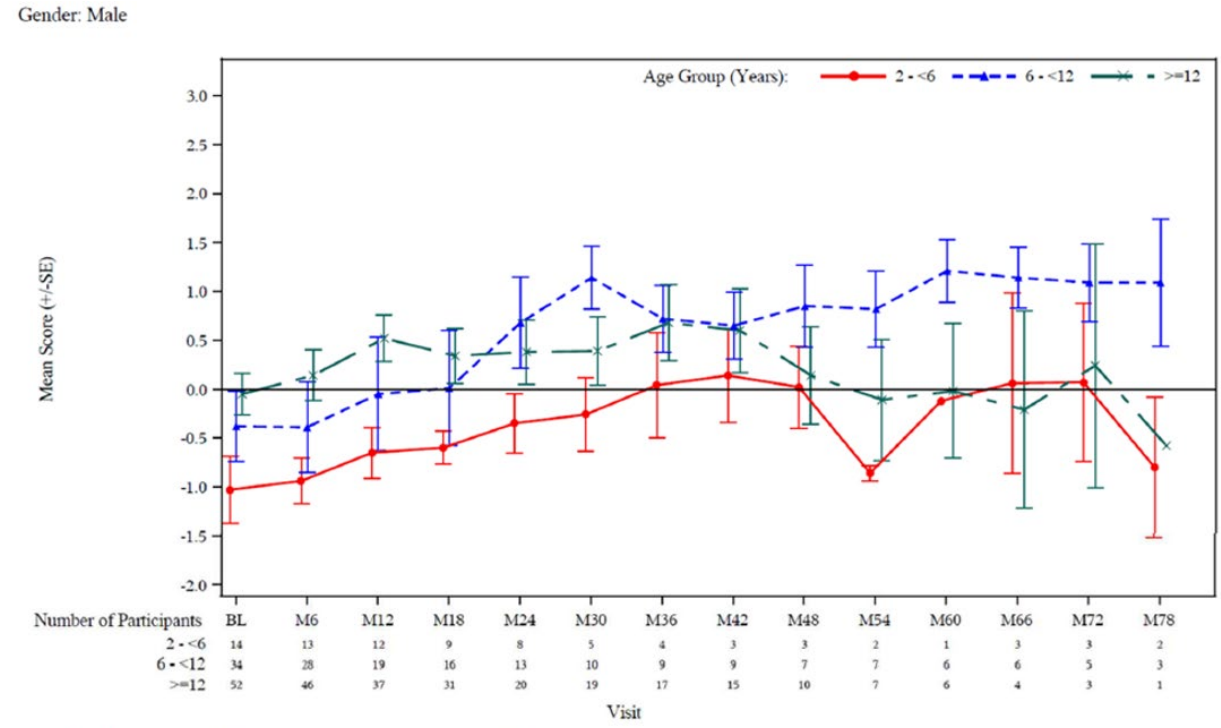


Figure 15. Mean Change from Baseline (+/-SE) for Creatinine Clearence



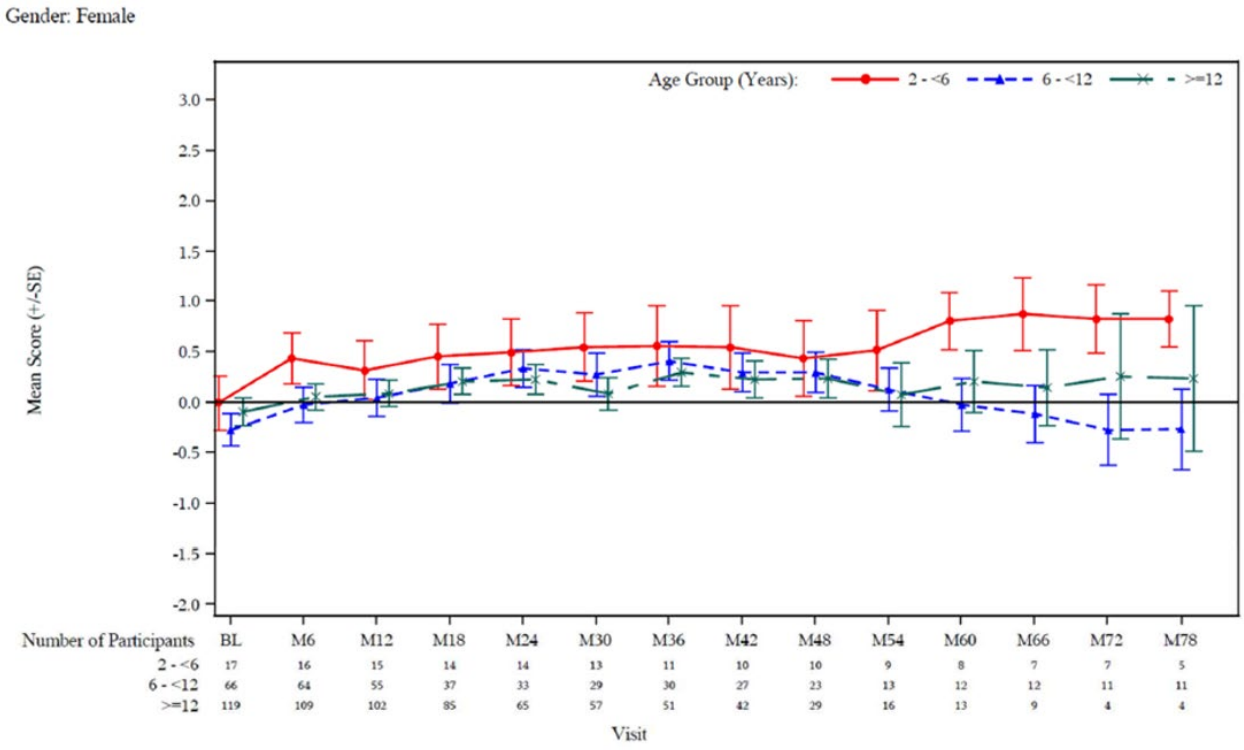
Baseline is either from the qualifying study or the extension study based on the enrollment gap.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (23:03) Source Data: adsl adlb2 Table Generation: 13MAR2025 (09:27)
(Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/lab_fig_chem2

Figure 16. Mean (+/-SE) Weight Z-score by Gender and Age Group for Male Participants - SAS



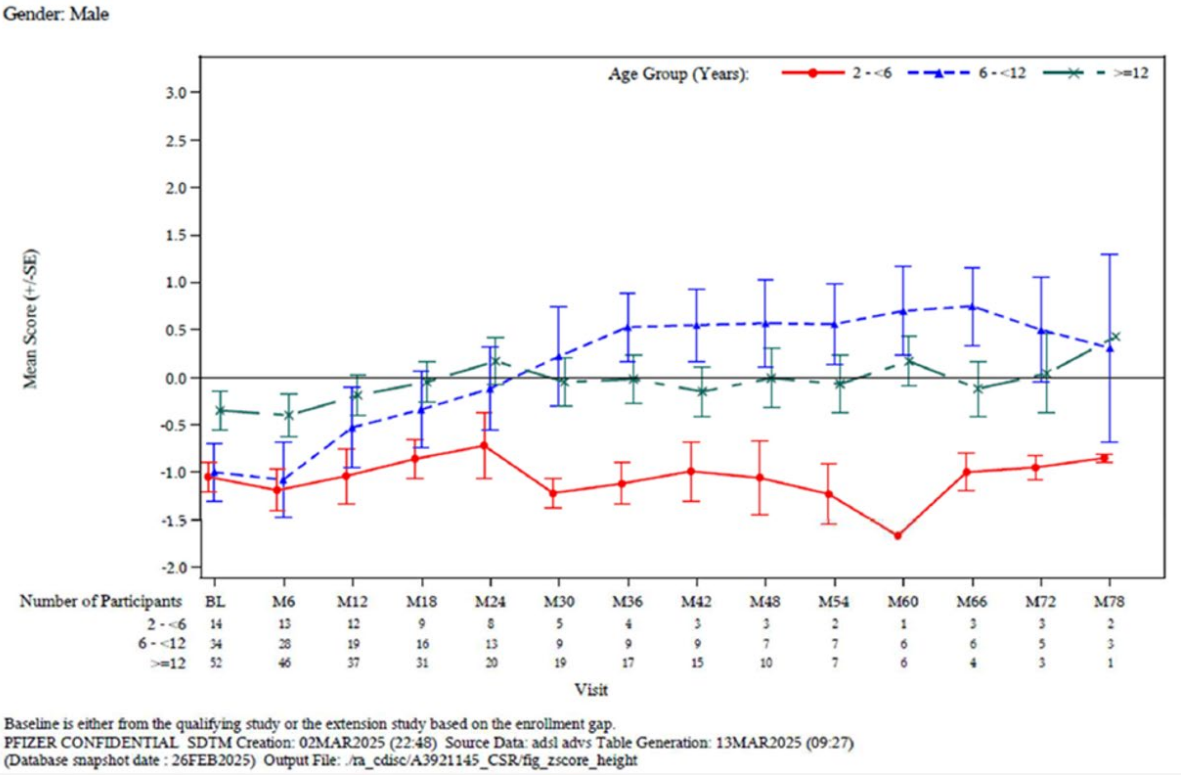
Baseline is either from the qualifying study or the extension study based on the enrollment gap.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (22:48) Source Data: adsl advs Table Generation: 13MAR2025 (09:27)
(Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/fig_zscore_weight

Figure 17. Mean (+/-SE) Weight Z-score by Gender and Age Group for Female Participants - SAS



Baseline is either from the qualifying study or the extension study based on the enrollment gap.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (22:48) Source Data: adsl advs Table Generation: 13MAR2025 (09:27)
(Database snapshot date : 26FEB2025) Output File: ./ra_cdisc/A3921145_CSR/fig_zscore_weight

Figure 18. Mean (+/-SE) Height Z-score by Age Group for Male Participants - SAS



2.3.3. Discussion on clinical aspects

The MAH submitted a final report for the Long-Term, Open-Label Follow-Up Study of Tofacitinib for Treatment of Juvenile Idiopathic Arthritis (JIA) - Study Number: A3921145, a Phase 2/3, long term, open label, follow up study. This study enrolled and treated a total of 302 participants (26 participants from Study A3921103, 199 participants from Study A3921104, and 77 participants from Study A3921165).

The main aim of the study was on safety evaluation. However, also the persistence of efficacy of tofacitinib for treatment of the signs and symptoms of JIA has been described.

Baseline was defined differently (coming from qualifying study or from extension study, depending on enrolment gap), for all statistical analyses except for JIA ACR disease flare. The Applicant specified that 15 (5%) of patients in the FAS had a gap of >14 days between the last visit of the index study (A3921103, A3921104, or A3921165) and the first visit of the extension study (A3921145). Only 9 patients had a gap > 14 days in the authorized indications.

The majority of patients were 12 years of age or older, white and female with a high disease activity at baseline, according to JADAS-27 CRP.

A no negligible number of patients [127 (32%)] patients **discontinued** from OL study, with the most common reasons for discontinuation being adverse events and insufficient clinical response (39 [12.9%] and 35 [11.6%] participants, respectively). Moreover, of those who discontinued due to adverse events, 15 (5.0%) participants discontinued from the study due to adverse events (AEs) based on the following Preferred Terms that represent disease exacerbation: Still's Disease, Arthritis, Juvenile Idiopathic Arthritis (JIA), Arthropathy, temporomandibular pain and dysfunction syndrome, condition aggravated, and disease progression. Therefore, the rate of discontinuation due to insufficient clinical response should theoretically be implemented by this 5% of participants with disease progression. The Applicant clarified upon request the reasons for "Other" category of discontinuations. There were different reasons such as withdrawal consent or availability of commercial Xeljanz. It seems that no

reasons due to lack of efficacy was reported. Two patients discontinued due to safety reasons (a SAE of pyelonephritis and lab abnormalities), which however are already reflected in the SmPC.

The majority (78.8%) of participants took concomitant medications including csDMARDs (71.2%) and NSAIDs (72.8%), as expected. However, it was noticed that half of patients (50.3%) were still taking corticosteroids although no information is provided about dosage. Moreover, the Applicant states that few participants in each analysis set attempted to taper corticosteroids, MTX/leflunomide suggesting a not complete resolution of symptoms with tofacitinib only treatment.

All efficacy endpoints in this study are secondary endpoints, and the efficacy analysis only provides descriptive information across different endpoints. According to SAP, the secondary efficacy endpoints are summarised using descriptive statistics by visit for the binary and continuous endpoints respectively. The percent (for the binary endpoints) and mean change (for the continuous endpoints) over time and associated standard errors have been plotted for analyses in sJIA1, sJIA2 and pJIA analysis sets.

Efficacy

The Applicant states that in general, long-term treatment with tofacitinib resulted in maintenance of efficacy over time in patients with JIA, across different endpoints such as Occurrence of Flare, JIA ACR response, Inactive Disease/Clinical Remission, JADAS score etc. This is in principle acceptable if considering endpoint values at each time point calculated on the total number of patients still in the study as denominator. However, it should be taken into account that the number of patients decreased through the study due to the high number of discontinuations, some of which due to insufficient efficacy (or worsening of disease status), making difficult drawing firm conclusion at the latest time points mainly in the less represented subpopulations (such as ERA). In particular, the number of patients at different time points does not take into account those (about 12%) who discontinued the study due to loss of efficacy or due to AEs (about 13%).

The MAH performed upon request, an additional analysis in which patients who discontinued due to insufficient clinical response or AE (including death) were considered non-responders. Based on this analysis, the occurrence of disease flare increased with time, from 8.2% at Month 6 to 25.3% at Month 36 and to 64.0% at Month 78, which is partially expected due to the increasing number of patients who discontinued for any reason. Similarly, the proportion of responders declined over time for the JIA ACR endpoints (30 and 50). Regarding the more stringent endpoints such as JIA ACR 70, 90, 100, as well as inactive disease and clinical remission, the decline appears to be less evident even with the non-responder imputation. The MAH justifies this different trend arguing that participants achieving a more robust initial response were less likely to experience loss of efficacy over time, which is reasonable. However, it was noted that starting from week 36 the efficacy tends to decrease over time in all the endpoints, including the most stringent ones.

The MAH also provided results coming from an additional analysis in which patients who discontinued due to insufficient clinical response or AE (including death) were excluded from the analysis dataset. The rate of flare was low (≤5%) through Month 42 in this subset of participants and efficacy results seem to be maintained when observing results from the other endpoints (JIA ACR 30/50/70/90/100 Responses, JIA ACR Inactive Disease, and JIA ACR Clinical Remission).

As maintenance of effect of treatment is a relevant clinical aspect, a description of study extension data should be provided in 5.1 section of the SmPC, in order to convey to physicians, the available information on decline of response that emerged in Study A3921145. A proposal for implementation of section 5.1 of the SmPC with long-term data should be presented by the MAH in the requested type II variation.

Safety

Overall, 268/302 (88.7%) participants reported AE(s). TEAEs were most frequently reported in the SOCs of Infection and Infestations (198/302 [65.6%] participants), Musculoskeletal and Connective

Tissue Disorders (110/302 [36.4%] participants) and GI Disorders (85/302 [28.1%] participants). Most AEs were mild (125/302 [41.4%]) or moderate (113/302 [37.4%]) in severity.

Severe AEs were reported in 30 (9.9%) subjects. The most frequent severe AEs were reported in the Musculoskeletal and Connective Tissue Disorders SOC in 8/302 (2.6%) participants, Infections and Infestations SOC in 6/302 (2.0%) participants, and Psychiatric Disorders SOC in 5/302 (1.7%) participant. The most frequent severe AE by PT was Still's Disease in 4/302 (1.3%) participants.

SAEs were reported by 48 participants (15.9%). The most commonly reported SAEs were Still's Disease, in 8 participants (2.6%). Suicidal ideation/attempt was reported in 5 participants (1.7%); considering the age range of the patients, the severity of the underlying disorder, the multidrug treatment, the narratives provided, the Investigator's assessment of the reported cases (invariably reported as "not related to the drug") and the high basal rate of suicidal ideation/attempt in the specific age range, it is shared with the Investigator and the MAH that the reported events do not seem related to tofacitinib treatment.

Death cases: 2 patients died during treatment with the medicinal product. For one of them, the Investigator related the cause of death to the IMP, while the Sponsor was of different opinion: from the narrative available for this case, it seems that the patient had some intercurrent condition, probably extra-pulmonary tuberculosis or/and MAS and it seems non-immediately related to the IMP, and after treatment interruption the condition did not improve. While it is not possible to conclude with certainty about the relationship between IMP and this death case, it is not so clear that the patient died due to IMP-related adverse events, since the clinical picture appeared to be complex. However, Tuberculosis and Opportunistic and serious infections are possible effects of tofacitinib already known and already described in the current SmPC (in 4.8 and 4.4 sections). Therefore, no further actions are required except for the MAH to continue monitoring these AEs.

Laboratory findings showed an increase in creatine in serum with time. At the last visit, the mean was about 0.20 mg/dL compared to baseline. Four (4) patients (1.32%) had a confirmed major increase in creatine >100%, and 13 (4.30%) had a lower (but not negligible) increase in creatine. 22 events met criteria for discontinuation of study drug for laboratory values: of these, 2 led to participant discontinuation, with the remainder either occurring in participants who had already discontinued study drug, or in the case of creatinine criteria, participants were allowed to continue after further assessment. However, an important confounding factor is the age of the patients (young) and the consequent growth development that is physiologically associated to increase in creatinine. In the adults the increase in creatinine was modest; the changes observed in children, taking into account the physiological increase of creatinine during development, do not seem worrisome; moreover, creatinine increase is already listed at the 4.8 table of the SmPC.

According to the SmPC (section 4.8), there are insufficient data regarding the safety profile of tofacitinib used concomitantly with any other csDMARDs in the paediatric population. Additionally, there is a warning for adults with RA, that AEs were more frequent on combination therapy. In study A3921145 the majority (251/302, 81% from Table 14.4.2.3) of patients were taking concomitant csDMARDs.

In the requested type II variation, the MAH should update the 4.8 section of the SmPC with long-term safety data, also describing the 2 cases of multidermatomal HZ in patients treated with concomitant csDMARDs.

In conclusion, no new safety signals or issues were detected with the results submitted. However, an update of 4.8 section of the SmPC is needed.

3. CHMP overall conclusion and recommendation

From the data submitted it seems that the efficacy and safety of tofacitinib in the indication related to this submission is overall confirmed. However, based on an additional non-responder imputation analysis performed by the MAH, a trend of declining response over time is noted. The MAH is requested to submit a type II variation to update sections 4.8 and 5.1 section of the SmPC with long-term safety and efficacy data coming from Study A3921145 outling the following:

- The MAH should update section 4.8 of the SmPC with long-term safety data coming from A3921145, also describing the 2 cases of multidermatomal HZ in patients treated with concomitant csDMARDs.
- In order to convey to physicians, the available information on decline of response that emerged in Study A3921145 and because maintenance of effect of treatment is a relevant clinical aspect, a description of study extension data should be provided in section 5.1 of the SmPC.

In line with the above, the MAH has confirmed its intent to submit a Type II variation no later than 60 days after the receipt of these conclusions.

☒ **Fulfilled:**

In view of the available data regarding long-term efficacy and safety the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

4. Request for supplementary information

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

1. The Applicant should clarify the reasons of discontinuation reported as "other" for 11 subjects.
2. Baseline was defined differently (coming from qualifying study or from extension study, depending on enrolment gap), for all statistical analyses except for JIA ACR disease flare. Therefore, the Applicant is requested to specify the number of patients for all the different subset of patients shown in the table at page 34 of the report body in case of a gap >14 days.
3. With regard to efficacy analysis, in order to have a more reliable estimate of the maintenance of efficacy, the Applicant should: i) provide and discuss efficacy data for, at least, the most informative endpoints (e.g. Occurrence of Flare, JIA ACR Responses, Inactive Disease/Clinical Remission), considering patients who discontinued due to insufficient efficacy and AEs as NRs; ii) provide a more realistic analysis of results up to a time point in which there still is a significant number of patients (e.g. 42 months FU), excluding subjects who discontinued before this time point due to AEs or loss of efficacy.
4. In relation to one case of death (weight decreased in a participant) considering that the event was judged as related to tofacitinib by the investigator and that the Cardiovascular Events Adjudication Committee considered likely cause of death was sepsis with loss of weight and relapsing fevers likely related to extrapulmonary TB, a relationship with study drug, possibly caused by immunosuppression, cannot be excluded. Therefore, the Applicant should discuss the appropriateness of describing this event in 4.8 section of the SmPC.
5. The MAH is asked to perform subgroup analyses for safety (TEAEs, SAEs, infections, serious infections and opportunistic infections), with/without csDMARDS and specified for the csDMARDS most used, such as methotrexate. The MAH should base on these analyses update the paediatric information in section 4.4 and/or 4.8 accordingly.
6. Lab values showed an increase in creatine with time: the MAH should discuss differences with adult data, and the clinical relevance and consequences for the SmPC.

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

MAH responses to Request for supplementary information

Question 1

The Applicant should clarify the reasons of discontinuation reported as "other" for 11 subjects.

Summary of MAH Response

The specific reasons for discontinuation reported as "Other" in Study A3921145 CSR Figure 20 for 11 participants are provided in Table 11 below.

Table 11. Disposition for "Other Category"

Participant ID	Disposition Name	Disposition Event Details
	OTHER	Patient discontinued study as a result of being in clinical remission
	OTHER	The patient withdrew consent
	OTHER	Pregnancy
	OTHER	The patient withdrew consent
	OTHER	Subject was discontinued due to temporary withdrawal of tofacitinib for more than 28 days due to lab abnormalities.
	OTHER	Patient was discontinued due to non-compliance.
	OTHER	Labs now show lupus erythematosus.
	OTHER	Subject became eligible for commercial Xeljanz.
	OTHER	Subject became eligible for commercial Xeljanz.
	OTHER	Subject met the serious infection withdrawal criteria due to SAE of pyelonephritis.
	OTHER	Subject met the discontinuation criteria.

CHMP assessment of MAH's response

The Applicant clarified upon request the reasons for "Other" category of discontinuations. There were different reasons such as withdrawal consent or availability of commercial Xeljanz. It seems that no reasons due to lack of efficacy was reported. Two patients discontinued due to safety reasons (a SAE of pyelonephritis and lab abnormalities), which however are already reflected in the SmPC.

Conclusion

Issue Resolved.

Question 2

Baseline was defined differently (coming from qualifying study or from extension study, depending on enrolment gap), for all statistical analyses except for JIA ACR disease flare. Therefore, the Applicant is requested to specify the number of patients for all the different subset of patients shown in the table at page 34 of the report body in case of a gap >14 days.

Summary of MAH Response

There was a total of 15 (5.0%) participants who had a gap of >14 days between the last visit of the index study (A3921103, A3921104, or A3921165) and the first visit of the extension study (A3921145) as shown in Table 12 for the full analysis set (FAS) and each subset of patients.

Table 12. Baseline Value from Extension Study (A3921145)

	FAS (N=302)	sJIA1 (N=88)	sJIA2 (N=77)	pJIA (N=185)	ERA (N=21)	PsA (N=19)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of participants with gap >14 days between last visit of index study and first visit of extension study	15 (5.0)	6 (6.8)	6 (7.8)	8 (4.3)	1 (4.8)	0

CHMP assessment of MAH's response

The Applicant specified that 15 (5%) of patients in the FAS had a gap of >14 days between the last visit of the index study (A3921103, A3921104, or A3921165) and the first visit of the extension study (A3921145). However, it is not clear which baseline (from qualifying or extension study) was utilized in the analyses for these patients. This information could have been useful in assuring the homogeneity of results. However, considering that only 9 patients had a gap > 14 days in the authorized indications, it is assumed that they did not have an impact on the reliability of results.

Conclusion

Issue not pursued.

Question 3

With regard to efficacy analysis, in order to have a more reliable estimate of the maintenance of efficacy, the Applicant should: i) provide and discuss efficacy data for, at least, the most informative endpoints (e.g. Occurrence of Flare, JIA ACR Responses, Inactive Disease/Clinical Remission), considering patients who discontinued due to insufficient efficacy and AEs as NRs; ii) provide a more realistic analysis of results up to a time point in which there still is a significant number of patients (e.g. 42 months FU), excluding subjects who discontinued before this time point due to AEs or loss of efficacy.

Summary of MAH Response

To address concerns regarding the maintenance of efficacy, the MAH has performed the additional analyses as requested for the following efficacy endpoints for each analysis set (sJIA1, sJIA2, pJIA, ERA, and PsA): occurrence of disease flare, JIA ACR 30/50/70/90/100 responses, JIA ACR Inactive Disease, and JIA ACR Clinical Remission.

i) **Non-responder imputation analysis**: The requested analyses in which patients who discontinued due to insufficient clinical response or AE (including death) were considered non-responders was performed. This approach was applied to the following efficacy endpoints: Occurrence of Disease Flare (Table 509a.2.1), JIA ACR 30/50/70/90/100 Responses (Table 509a.3.1), JIA ACR Inactive Disease (Table 509a.4.1), and JIA ACR Clinical Remission (Table 509a.5.1). For the Occurrence of Flare endpoint, the non-responders were considered as having a flare at the time of discontinuation and carried forward for all visits post-discontinuation. For all other efficacy endpoints, the patients who

discontinued were considered as non-responders at the time of discontinuation and carried forward for all visits post-discontinuation.

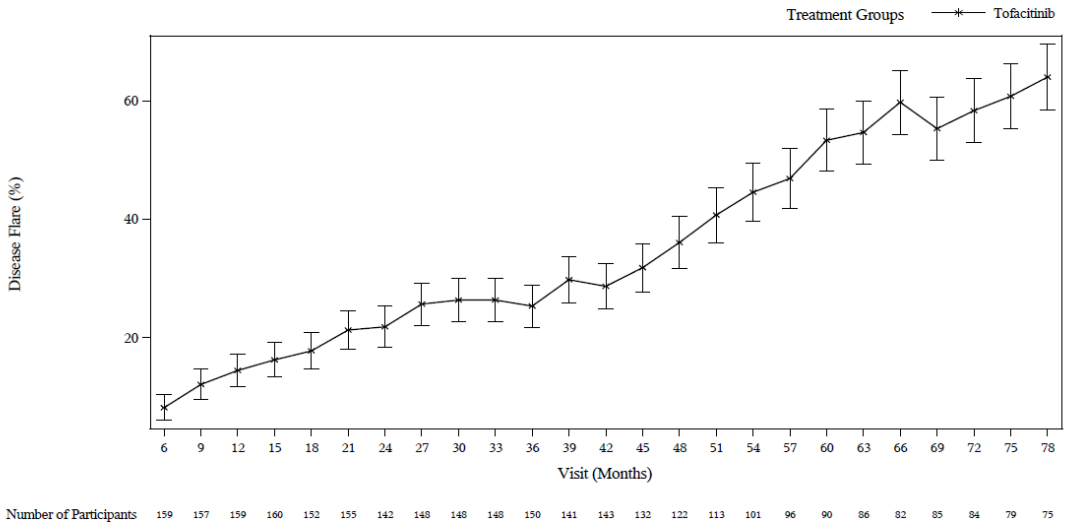
Focusing on the approved pJIA population, which represents the largest analysis set, there were 25 (13.5%) who discontinued due to AE, 26 (14.1%) due to Insufficient Clinical Response, and 0 due to Death (A3921145 CSR Table 14.1.1.2). The remaining participants either discontinued for reasons unrelated to loss of efficacy (38 [20.5%]) or completed the study (95 [51.9%]). The total duration of an individual patient's participation varied depending upon when they entered the trial and the index study they were enrolled in. The median duration of treatment for patients with pJIA was 43.96 (range: 1, 117) months (A3921145 CSR Table 11).

For the non-responder imputation analysis, the occurrence of disease flare increased from 8.2% at Month 6 to 25.3% at Month 36 (Figure 7, Figure 19). Beyond Month 36, the occurrence of disease flare increased to 64.0% at Month 78. This increased rate of flare at the later timepoints is likely attributable to the non-responder imputation method: at later timepoints, participants who discontinued for reasons unrelated to loss of efficacy or who successfully completed the study were missing if their participation ended prior to Month 78, while participants who discontinued due to insufficient clinical response, AEs or death were imputed as disease flares through Month 78. This approach is a more conservative assessment and may inflate the flare rate at the later timepoints in a long-term extension study due the variable length of patient participation.

For the less stringent JIA ACR endpoints (30 and 50), the proportion of responders declined over time (Figure 8, Figure 20). In contrast, the proportion of responders for more stringent endpoints (JIA ACR 70, 90, 100, as well as inactive disease and clinical remission) remained relatively stable through Month 48, even with the non-responder imputation. This suggests that participants achieving a more robust initial response were less likely to experience loss of efficacy over time (Figure 20, Figure 21, Figure 22). The decline in response rate in the less stringent endpoints over time is expected and reflects the natural attrition in long term extensions studies. The stability of response rates for the stringent endpoints supports the durability of response.

Figure 19. Line Graph of Occurrence of Disease Flare (%) (+/- SE) - pJIA (NRI)

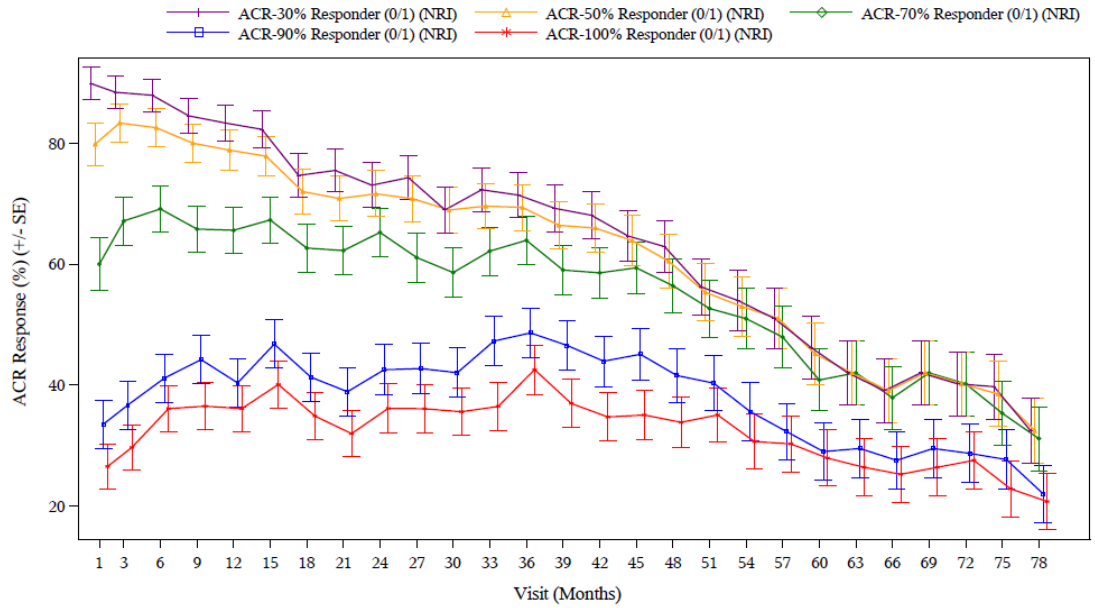
pJIA



Month 3 is the baseline for disease flare.
Participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death are considered as non-responders at visits post discontinuation.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2025 (20:15) Source Data: adsl adpa Table Generation: 08OCT2025 (08:35)
(Database snapshot date : 26Feb2025) Output File: ./ra_cdisc/SCS509a/fig_flare

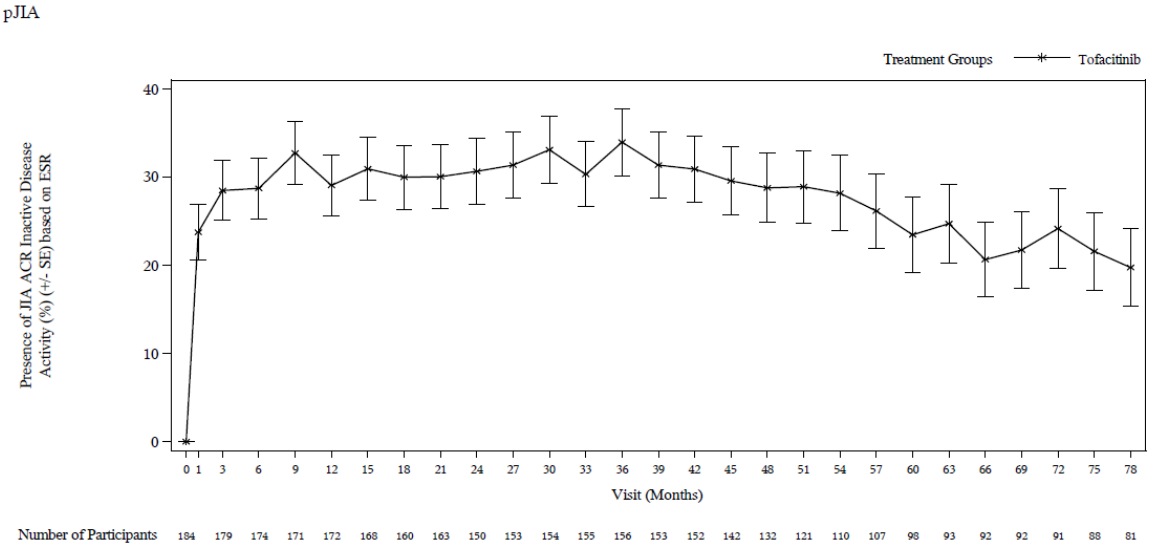
Figure 20. Line Graph of JIA ACR Responses (%) (+/- SE) – pJIA (NRI)

pJIA



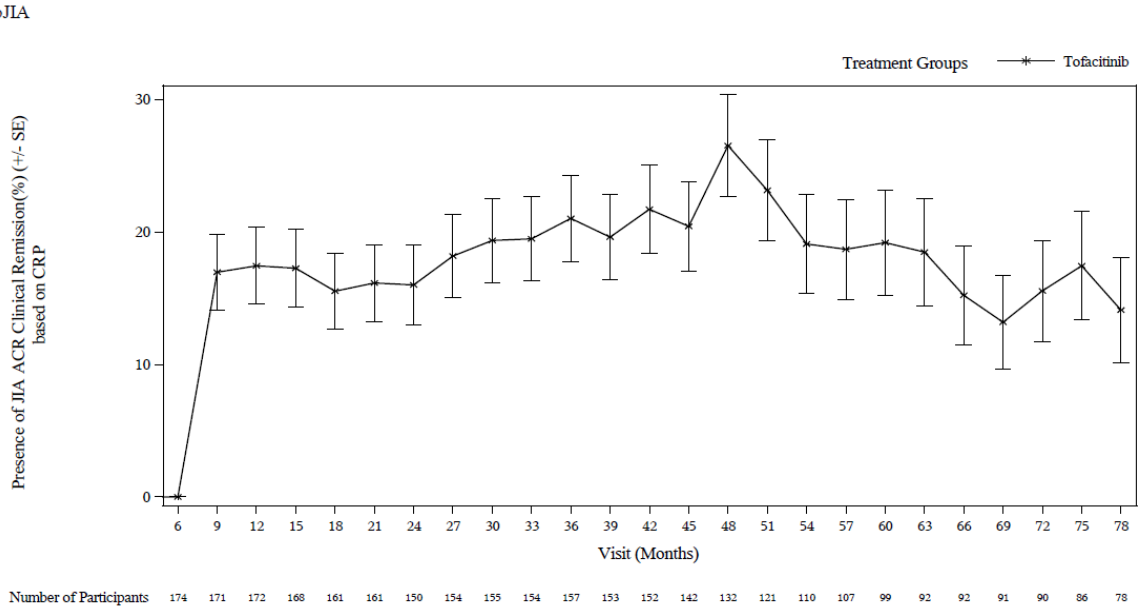
Participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death are considered as non-responders at visits post discontinuation.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (22:48) Source Data: adsl adacr Table Generation: 07OCT2025 (06:04)
(Database snapshot date : 26Feb2025) Output File: ./ra_cdisc/SCS509a/fig_acr_overlay

Figure 21. Line Graph of Presence of JIA ACR Inactive Disease (%) (+/- SE) – pJIA (NRI)



Baseline is either from the qualifying study or the extension study based on the enrollment gap.
Participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death are considered as non-responders at visits post discontinuation.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2025 (20:15) Source Data: adsl adinact Table Generation: 08OCT2025 (08:35)
(Database snapshot date : 26Feb2025) Output File: ./ra_cdisc/SCS509a/fig_acr_inact

Figure 22. Line Graph of Presence of JIA ACR Clinical Remission (%) (+/- SE) – pJIA (NRI)

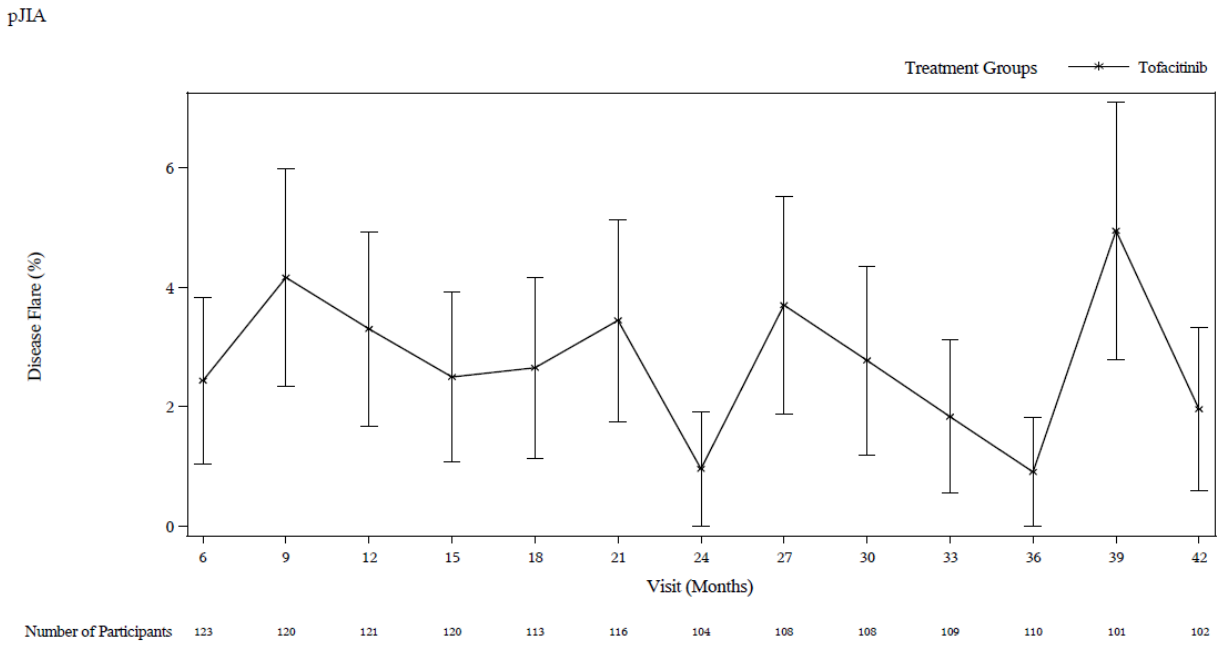


Clinical remission is counted as 6 months (24 weeks) of inactive disease continuously in this extension study A3921145.
Participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death are considered as non-responders at visits post discontinuation.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2025 (20:15) Source Data: adsl adinact Table Generation: 08OCT2025 (08:35)
(Database snapshot date : 26Feb2025) Output File: ./ra_cdisc/SCS509a/fig_acr_cr

ii) **Analysis excluding non-responders**: Analyses have also been performed in which patients who discontinued due to insufficient clinical response or AE (including death) were excluded from the analysis dataset. This approach was also applied to the following efficacy endpoints: Occurrence of Disease Flare (Table 509a.2.2), JIA ACR 30/50/70/90/100 Responses (Table 509a.3.2), JIA ACR Inactive Disease (Table 509a.4.2), and JIA ACR Clinical Remission (Table 509a.5.2).

Again, focusing on the approved pJIA population, the occurrence of disease flare, now excluding those who discontinued due to insufficient clinical response, AEs, or death, is presented in Figure 23 and demonstrates that there was a very low rate of flare (≤5%) through Month 42 in this subset of participants. Based upon the JIA ACR 30 and 50 response rates, there was a high maintenance of efficacy noted through Month 42 and an increase in the proportion of JIA ACR 70, 90 and 100 responders, and those who achieved JIA ACR Inactive Disease through Month 42 (Figure 24, Figure 25, Figure 26).

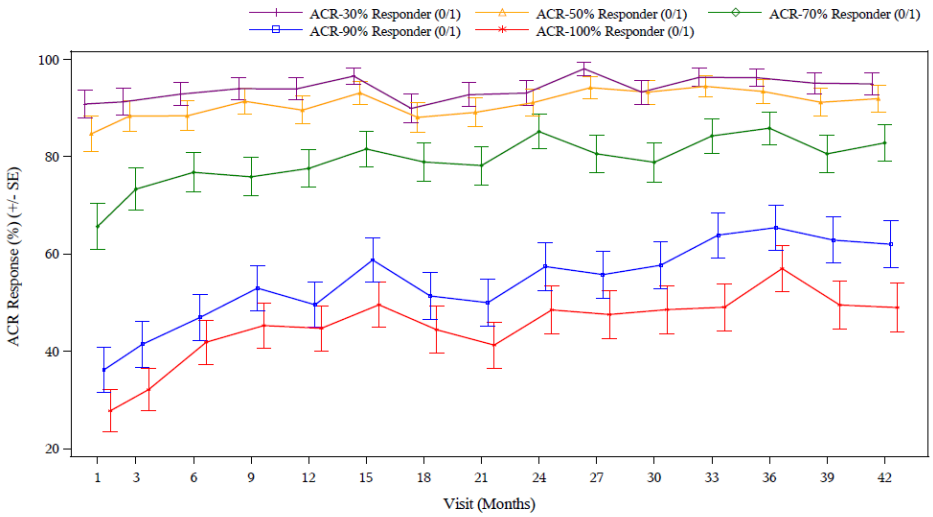
Figure 23. Line Graph of Occurrence of Disease Flare (%) (+/- SE) by Visit - pJIA - who Reached Month 3 Visit Excluding Participants with Discontinuation due to Insufficient Clinical Response or Adverse Events or Death



Month 3 is the baseline for disease flare.
For sJIA1 or sJIA2, participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death on or prior to Month 18 are excluded from the analysis set.
For pJIA, ERA and PsA, participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death on or prior to Month 42 are excluded from the analysis set.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2025 (20:15) Source Data: adsl adpa Table Generation: 08OCT2025 (08:35)
(Database snapshot date : 26Feb2025) Output File: ./ra_cdisc/SCS509a/fig_flare2

Figure 24. Line Graph of JIA ACR Responses (%) (+/- SE) - pJIA - Excluding Participants with Discontinuation due to Insufficient Clinical Response or Adverse Events or Death

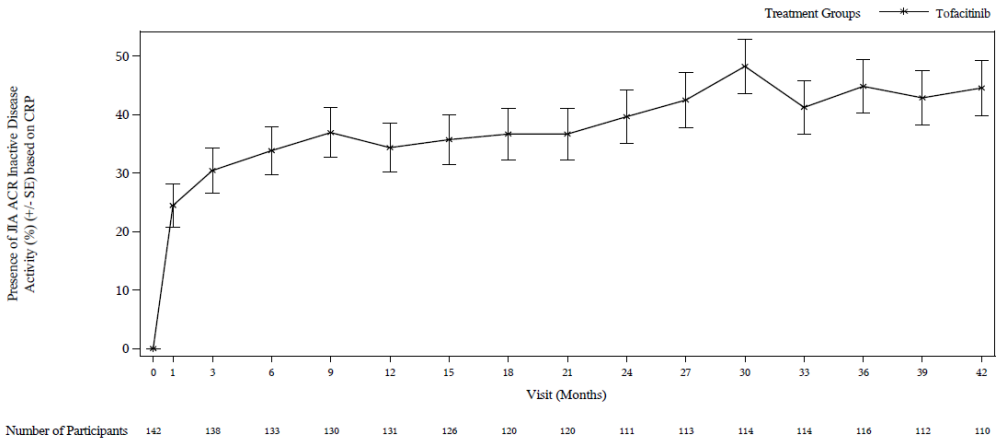
pJIA



For sJIA1 or sJIA2, participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death on or prior to Month 18 are excluded from the analysis set.
For pJIA, ERA and PsA, participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death on or prior to Month 42 are excluded from the analysis set.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (22:48) Source Data: adsl adacr Table Generation: 09OCT2025 (13:20)
(Database snapshot date : 26Feb2025) Output File: ./ra_cdisc/SCS509a/fig_acr_overlay2

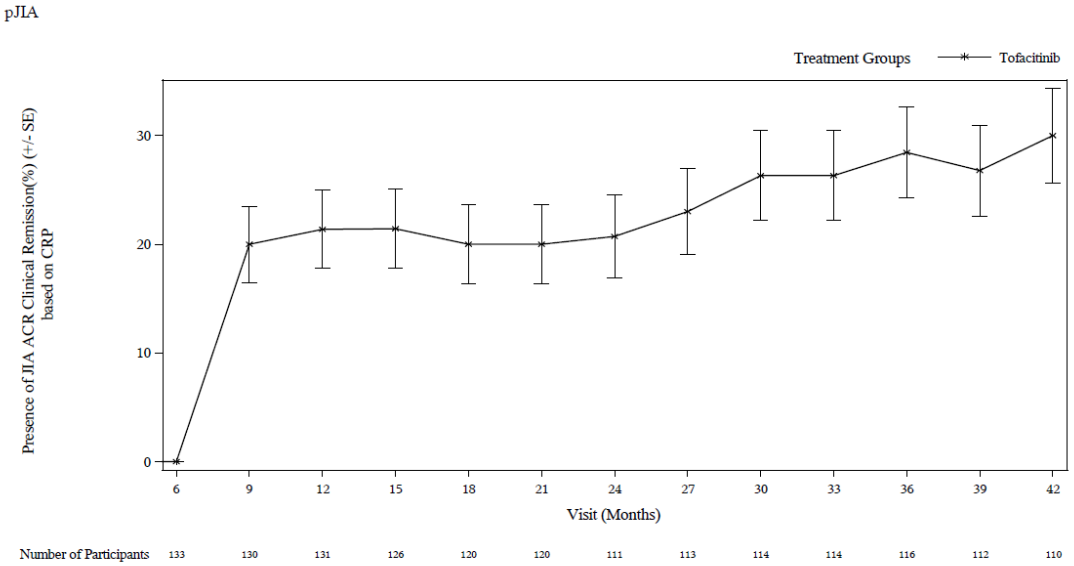
Figure 25. Line Graph of Presence of JIA ACR Inactive Disease (%) (+/- SE) - pJIA - Excluding Participants with Discontinuation due to Insufficient Clinical Response or Adverse Events or Death

pJIA



Baseline is either from the qualifying study or the extension study based on the enrollment gap.
For sJIA1 or sJIA2, participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death on or prior to Month 18 are excluded from the analysis set.
For pJIA, ERA and PsA, participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death on or prior to Month 42 are excluded from the analysis set.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2025 (20:15) Source Data: adsl adinact Table Generation: 08OCT2025 (08:35)
(Database snapshot date : 26Feb2025) Output File: ./ra_cdisc/SCS509a/fig_acr_inact2

Figure 26. Line Graph of Presence of JIA ACR Clinical Remission (%) (+/- SE) - pJIA - Excluding Participants with Discontinuation due to Insufficient Clinical Response or Adverse Events or Death



Clinical remission is counted as 6 months (24 weeks) of inactive disease continuously in this extension study A3921145.
For sJIA1 or sJIA2, participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death on or prior to Month 18 are excluded from the analysis set.
For pJIA, ERA and PsA, participants with discontinuation due to Insufficient Clinical Response, Adverse Events or Death on or prior to Month 42 are excluded from the analysis set.
PFIZER CONFIDENTIAL SDTM Creation: 27FEB2025 (20:15) Source Data: adsl adinact Table Generation: 08OCT2025 (08:35)
(Database snapshot date : 26Feb2025) Output File: ./ra_cdisc/SCS509a/fig_acr_cr2

CHMP assessment of MAH's response

The MAH performed additional analyses in which patients who discontinued due to insufficient clinical response or AE (including death) were considered non-responders. Based on this analysis, the occurrence of disease flare increased with time, from 8.2% at Month 6 to 25.3% at Month 36 and to 64.0% at Month 78, which is partially expected due to the increasing number of patients who discontinued for any reason. Similarly, the proportion of responders declined over time for the JIA ACR endpoints (30 and 50). Regarding the more stringent endpoints such as JIA ACR 70, 90, 100, as well as inactive disease and clinical remission, the decline appears to be less evident even with the non-responder imputation. The MAH justifies this different trend arguing that participants achieving a more robust initial response were less likely to experience loss of efficacy over time, which is reasonable. However, it was noted that starting from week 36 the efficacy tends to decrease over time in all the endpoints, including the most stringent ones.

The MAH also provided results coming from an additional analysis in which patients who discontinued due to insufficient clinical response or AE (including death) were excluded from the analysis dataset. The rate of flare was low (≤5%) through Month 42 in this subset of participants and efficacy results seem to be maintained when observing results from the other endpoints (JIA ACR 30/50/70/90/100 Responses, JIA ACR Inactive Disease, and JIA ACR Clinical Remission).

As maintenance of effect of treatment is a relevant clinical aspect, a description of study extension data should be provided in 5.1 section of the SmPC, in order to convey to physicians, the available information on decline of response that emerged in Study A3921145. A proposal for implementation of section 5.1 of the SmPC with long-term data should be presented by the MAH in a type II variation.

Conclusion

Issue resolved provided that 5.1 section of the SmPC is updated as part of the requested type II variation, with long-term extension data coming from Study A3921145, as requested above.

Question 4

In relation to one case of death (weight decreased in a participant) considering that the event was judged as related to tofacitinib by the investigator and that the Cardiovascular Events Adjudication Committee considered likely cause of death was sepsis with loss of weight and relapsing fevers likely related to extrapulmonary TB, a relationship with study drug, possibly caused by immunosuppression, cannot be excluded. Therefore, the Applicant should discuss the appropriateness of describing this event in 4.8 section of the SmPC.

Summary of MAH Response

The MAH respectfully believes that it is not appropriate to include this case in Section 4.8 of the Summary of Product Characteristics (SmPC). As outlined in the case narrative in A3921145 CSR Section 14.3.3 and summarised below, the cause of death remains uncertain since there was no autopsy performed. In addition, this event occurred in a patient with sJIA with active systemic features which is not currently an approved indication in the SmPC.

The participant received tofacitinib 5 mg BID in Study A3921165 and then rolled over into Study A3921145. Cumulative tofacitinib exposure for the combined studies was 587 days prior to the onset of the adverse event of decreased weight, at which point treatment was discontinued. The Principal Investigator (PI) noted a family history of tuberculous meningitis; however, there was no confirmed diagnosis linking the participant's symptoms of weight loss and fever to tuberculosis at the time of tofacitinib discontinuation.

Subsequent adverse events, beginning 23 days after withdrawal of tofacitinib (Study Day 359) , were attributed to worsening systemic juvenile idiopathic arthritis (sJIA). Although anti-tuberculosis treatment was initiated approximately 45 days post tofacitinib discontinuation (Study Day 381) for possible active tuberculosis, the participant's condition continued to deteriorate due to an undetermined cause. The PI suggested the possibility of sepsis based on clinical symptoms and laboratory findings; however, no blood culture results were available to confirm this diagnosis, and postmortem examination was declined. Therefore, the cause of death remains undetermined.

While the PI considered the adverse event of weight decreased to be related to tofacitinib, the MAH concluded that, based on the limited information available and noted relevant dominant risk factors, there was not a reasonable possibility that the event weight loss unknown origin with fatal outcome was related to the study drug, concomitants or clinical trial procedure and was more likely related to an intercurrent medical condition. The case was reviewed by the independent cardiovascular adjudication committee who determined that the case met the criteria of non-cardiovascular/non-neurovascular cause of death, and based upon information reported by the PI in the SAE narrative, considered that likely cause of death was sepsis with loss of weight and relapsing fevers likely related to extrapulmonary TB.

It is important to note that both tuberculosis and sepsis are already addressed in Section 4.4 (Special warnings and precautions for use) of the SmPC and in Section 4.8 Undesirable effects where Tuberculosis is listed as an uncommon adverse drug reaction (ADR), and sepsis is listed as a rare ADR. Furthermore, the paediatric safety profile in Section 4.8—based on data from approved indications in polyarticular JIA and juvenile PsA—indicates that adverse reactions in JIA patients are consistent in type and frequency with those observed in adult RA patients. Thus, the potential risk of opportunistic and serious infections is adequately described in the current SmPC, and is also applicable to the paediatric population.

Considering the details provided above, particularly the uncertainty regarding the cause of death and the fact that this event occurred in a patient with sJIA with active systemic features which is not currently an approved indication in the SmPC, the MAH does not consider it appropriate to include this case in Section 4.8 of the SmPC.

CHMP assessment of MAH's response

The clinical case mentioned is very complex, therefore it is very difficult to determine the exact cause of death, probably due to complications of systemic TB. However, it is agreed with the MAH that Tuberculosis and Opportunistic and serious infections are possible effects of tofacitinib already known and already described in the current SmPC (in 4.8 and 4.4 sections). Therefore, no further actions are required except for the MAH to continue monitoring these AEs.

Conclusion

Issue resolved.

Question 5

The MAH is asked to perform subgroup analyses for safety (TEAEs, SAEs, infections, serious infections and opportunistic infections), with/without csDMARDS and specified for the csDMARDS most used, such as methotrexate. The MAH should base on these analyses update the paediatric information in section 4.4 and/or 4.8 accordingly.

Summary of MAH Response

As presented in A3921145 CSR Table 14.4.2.3, a total of 215 participants in the study received concomitant conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Of these, 206 participants received methotrexate. Because only 9 participants received a csDMARD other than methotrexate, subgroup analyses for safety endpoints (TEAEs, SAEs, and infections) were conducted comparing participants who received any csDMARD (primarily methotrexate) versus those who did not receive a csDMARD for both the full safety analysis set (SAS) and for the participants who rolled over from index study A3921104, which is the basis for safety data included in the SmPC.

There was generally little difference overall noted in the subgroup analysis for safety between the group who received csDMARDs and those who did not for both populations.

The summary of TEAEs for both the SAS and the patients who rolled over from A3921104 index study by csDMARD subgroup is presented in Table 13 below. The subgroup without csDMARD use had a somewhat higher proportion of participants who discontinued due to AEs or required temporary discontinuation due to AEs; however, overall proportions of AEs, SAEs, and severe AEs were generally similar between those with and without csDMARD use.

Table 13. Treatment-Emergent Adverse Events (All Causalities) - Subgroup Summary by Concomitant csDMARD Use

	SAS		**Rolled Over From A3921104 Index Study**	
	Tofacitinib csDMARD – Yes (N = 215) n (%)	**Tofacitinib csDMARD – No (N = 87) n (%)**	**Tofacitinib csDMARD – Yes (N = 138) n (%)**	**Tofacitinib csDMARD – No (N = 61) n (%)**
Participants with AEs	186 (86.5)	82 (94.3)	126 (91.3)	58 (95.1)
Participants with SAEs	34 (15.8)	14 (16.1)	22 (15.9)	9 (14.8)
Participants with severe AEs	23 (10.7)	7 (8.0)	17 (12.3)	5 (8.2)
Participants discontinued from study due to AE	26 (12.1)	15 (17.2)	15 (10.9)	11 (18.0)
Participants discontinued study drug due to AE and continue Study	1 (0.5)	0	0	0
Participants with dose reduced or temporary discontinuation due to AEs	54 (25.1)	39 (44.8)	39 (28.3)	28 (45.9)

Includes data up to 365 days after last dose of study drug. Participants are counted only once per treatment in each row. SAEs – according to the investigator's assessment. Tables 509a.7.1, 509a.7.2

The overall frequency of treatment-emergent adverse events (TEAEs), categorized by system organ class (SOC), was comparable between participants who received concomitant csDMARDs and those who did not, in both the SAS and the participants who rolled over from A3921104 index study (Tables 509a.8.1 and 509a.8.2). Differences between groups were generally less than 5%. The only notable exception was the frequency of TEAEs in the Respiratory, Thoracic, and Mediastinal Disorders SOC, which was 9.8% higher among participants who did not receive csDMARDs in the A3921104 index study and 5.4% higher in the SAS.
No meaningful differences were observed for individual preferred terms (PTs), including serious adverse events (SAEs), between the groups. The frequency of serious infections—including herpes zoster—was also similar for both groups, as detailed in Table 14; however, both cases of herpes zoster that were adjudicated as meeting the definition of an opportunistic infection (multidermatomal herpes zoster) occurred in participants who were treated with concomitant csDMARDs (A3921145 CSR Table 16.2.7.4.9).

Table 14. Serious Infections (All Causalities) – Subgroup Summary by Concomitant csDMARD Use

	SAS		**Rolled Over From A3921104 Index Study**	
	Tofacitinib csDMARD – Yes (N = 215) n (%)	**Tofacitinib csDMARD – No (N = 87) n (%)**	**Tofacitinib csDMARD – Yes (N = 138) n (%)**	**Tofacitinib csDMARD – No (N = 61) n (%)**
Participants with at least 1 Treatment-Emergent Serious Infection	10 (4.7%)	4 (4.6%)	6 (4.3%)	3 (4.9%)
Abscess limb	0	1 (1.1)	0	1 (1.6)
Bronchitis	1 (0.5)	0	0	0
COVID-19	1 (0.5)	0	1 (0.7)	0
Escherichia pyelonephritis	1 (0.5)	0	1 (0.7)	0
Herpes zoster	3 (1.4)	1 (1.1)	2 (1.6)	1 (1.6)
Infectious mononucleosis	0	1 (1.1)	0	1 (1.6)
Influenza	1 (0.5)	0	1 (0.7)	0
Molluscum contagiosum	1 (0.5)	0	0	0
Pneumonia	1 (0.5)	1 (1.1)	0	0
Rhinovirus infections	1 (0.5)	0	1 (0.7)	0
Urinary tract infection	1 (0.5)	0	1 (0.7)	0
Includes data up to 365 days after last dose of study drug. Participants are counted only once per treatment in each row. SAEs – according to the investigator's assessment. Tables 509a.9.1, 509a.9.2, 509a.10.1, 509a.10.2				

Based upon these additional subgroup analyses, indicating that the overall proportions of AEs, SAEs, and severe AEs were generally similar between those participants with and without csDMARD use, the MAH does not propose any updates to the paediatric information in Sections 4.4 and 4.8 of the SmPC.

CHMP assessment of MAH's response

We agree with the MAH that no significant differences are seen between patients taking csDMARD and those taking only tofacitinib. However, the MAH specified that 2 cases of HZ in patients treated with concomitant csDMARDs were adjudicated as meeting the definition of an opportunistic infection (multidermatomal herpes zoster). This information should be reflected in 4.8 section of the SmPC under the paragraph of infections. Moreover, in general, the MAH is requested to update, as part of a type II variation, 4.8 section of the SmPC with long-term safety data coming from A3921145 or, at least, with a sentence reassuring the long-term tofacitinib's safety profile in paediatric patients with JIA.

Conclusion

Issue resolved provided that in the requested type II variation the SmPC is updated with long-term safety data as requested above. Moreover, the 2 cases of multidermatomal HZ in patients treated with concomitant csDMARDs should also be described in the same section.

Question 6

Lab values showed an increase in creatinine with time: the MAH should discuss differences with adult data, and the clinical relevance and consequences for the SmPC.

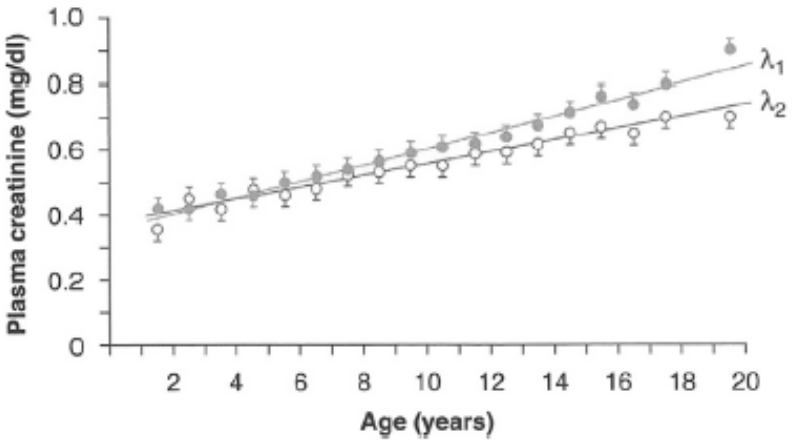
Summary of MAH Response

Background

Serum creatinine (SCr) is produced at a relatively constant rate and eliminated predominantly by glomerular filtration, but it is also influenced by several factors other than glomerular filtration such as diet and illness.[i] Most notably, it is produced from the nonenzymatic degradation of muscle creatine, making it highly dependent on muscle mass. In children, the generation of creatinine is commensurately affected by growth, increasing linearly with age as shown in Figure 27. The ongoing accrual of muscle leads to a progressive rise in SCr, especially in boys, until adolescence when adult levels are achieved.

Normal SCr ranges in children vary by age and sex; for children 1-12 years the range is approximately 0.3 – 0.7 mg/dL, in adolescents 13-18 years the range is approximately 0.5-1.0 mg/dL with values for adolescent females generally being lower than for adolescent males.[ii]

Figure 27. Growth-related change in serum creatinine during childhood

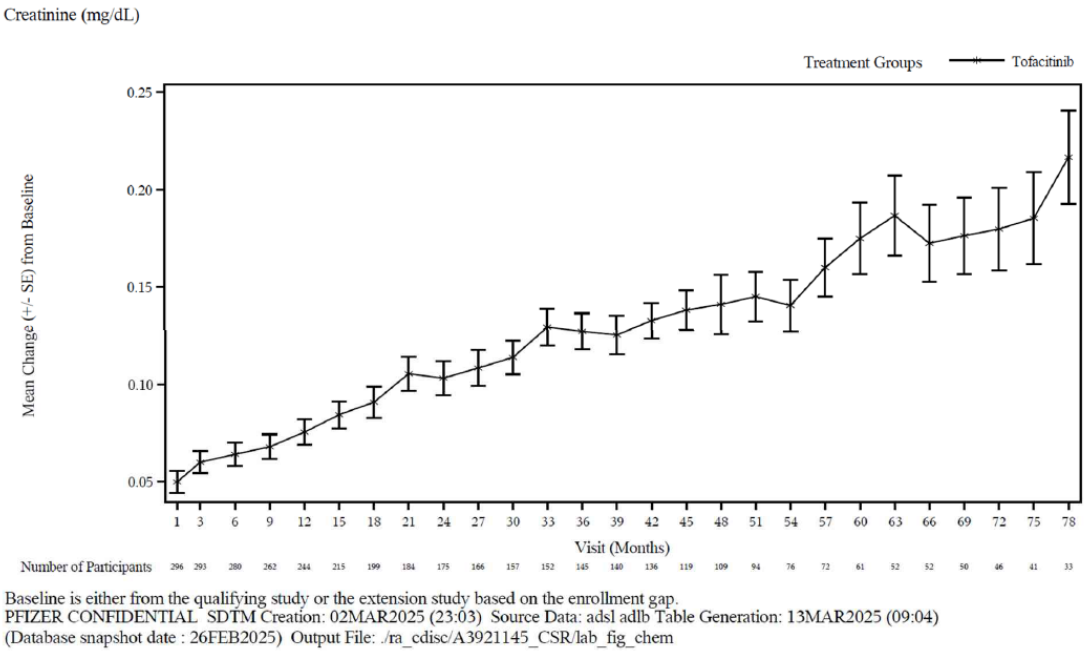


Mean plasma creatinine vs age demonstrating gender difference in serum creatinine beginning in adolescence. Standard error limits for estimates of the mean are shown. λ_1 ~ male λ_2 ~ females.[iii]

Data from A3921145 Long Term Extension Study

The mean change from baseline in SCr over time for this long-term extension study was presented in the A3921145 Clinical Study Report (CSR) and has been included in Figure 28 below. The data demonstrated an increase in the mean change from baseline in SCr levels through Month 78. However, the number of patients contributing data at later timepoints is limited; therefore, these results should be interpreted with caution.

Figure 28. Mean Change from Baseline (+/-SE) in Serum Creatinine (SAS)



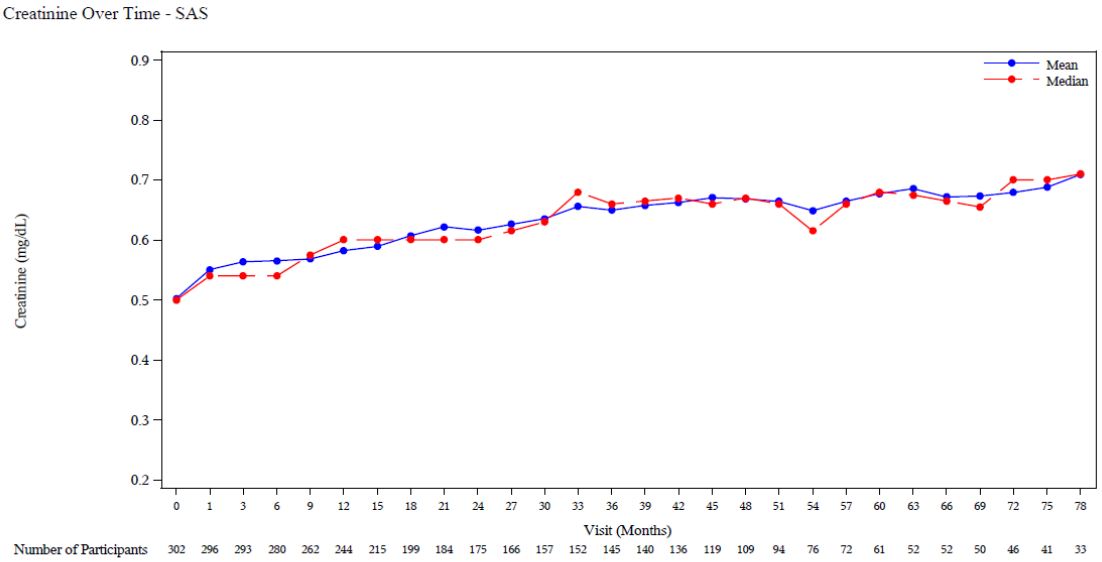
For most patients, baseline SCr values were obtained from the qualifying index study as the enrolment gap between the index studies (A3921103, A3921104, and A3921165) and long-term extension study was <14 days as discussed in Question 2. Due to differences in designs of the index studies and variability in the duration of patient participation, the length of time between the baseline of the index

study and enrolment in this long-term extension study was quite variable and could have been up to a year or more for some patients.

Considering the expected growth in children over time and the resulting increase in SCr levels due to this growth, there are limitations to presenting serum creatinine as mean change from baseline over extended periods of time for a population of paediatric participants with varying ages and duration of participation. At baseline of this study, the median age of participants was 12 years, with ages spanning from 3 to 21 years. The median duration of participation was 33 months, with individual participation ranging from less than 1 month up to 117 months.

To better assess the changes in SCr over time, the mean and median absolute changes are presented in Figure 29 below and in A3921145 CSR Table 14.3.4.1.4. During Study A3921145, a gradual increase in mean and median SCr over time was seen among paediatric patients. Specifically, the mean SCr rose from 0.55 mg/dL at Month 1 to 0.71 mg/dL at Month 78. This pattern closely parallels the expected growth-related changes in serum creatinine as shown in Figure 27.

Figure 29. Line Graph of Mean and Median Values for Serum Creatinine - SAS

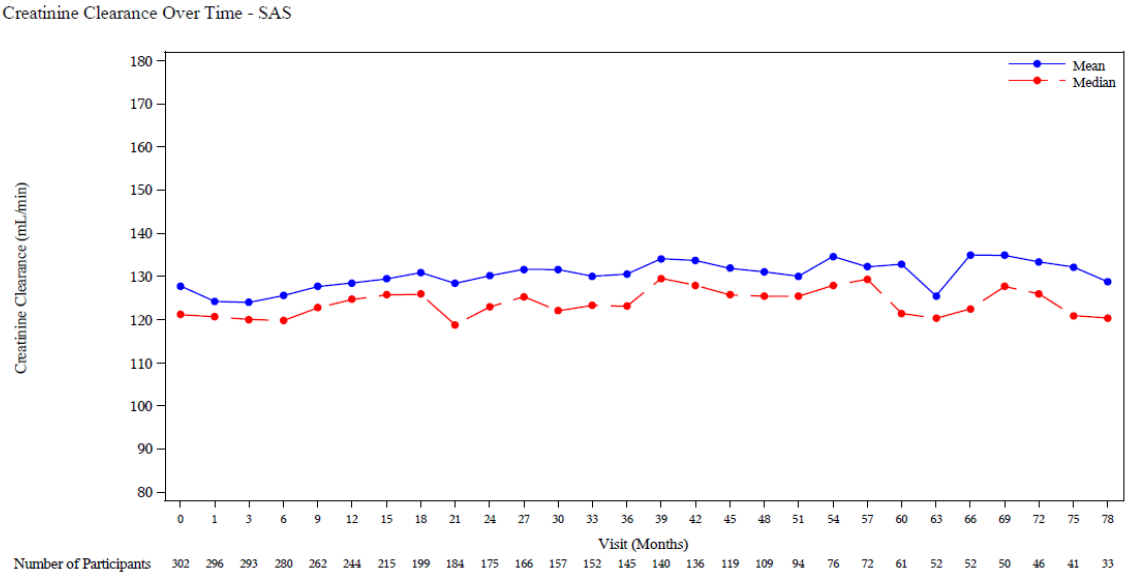


Baseline is either from the qualifying study or the extension study based on the enrollment gap.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (22:03) Source Data: adsl adlb2 Table Generation: 05NOV2025 (18:30)
(Database snapshot date : 26Feb2025) Output File: ./ra_cdisc/SCS509a/lab_fig_chem2

This observed increase in SCr over time appears to be consistent with normal growth and development in children. Supporting data from A3921145 CSR Table 14.3.5.1.1 demonstrate that mean height and weight increased in parallel with SCr levels throughout the study. As discussed above, creatinine is produced in muscle and the amount of creatinine produced is proportional to muscle mass, therefore, the increases in height and weight support the interpretation that the rise in SCr reflects expected physiological changes due to normal growth and development.

To address the limitations of SCr as a renal marker in children and ensure adequate monitoring of renal function, the study also assessed estimated creatinine clearance (CrCl) using equations which consider body surface area, age and sex to better estimate renal function. In this study, CrCl was estimated using Modified Schwartz equation for participants <12 years and the Cockcroft-Gault equation for participants ≥12 years.[iv],[v] Figure 30 shows that, mean and median CrCl remained generally stable over the course of the study, with the mean remaining between 123 ml/min and 135 ml/min at all visits prior to month 78 (where number of participants decreases).

Figure 30. Line Graph for Mean and Median Values for Creatinine Clearance - SAS



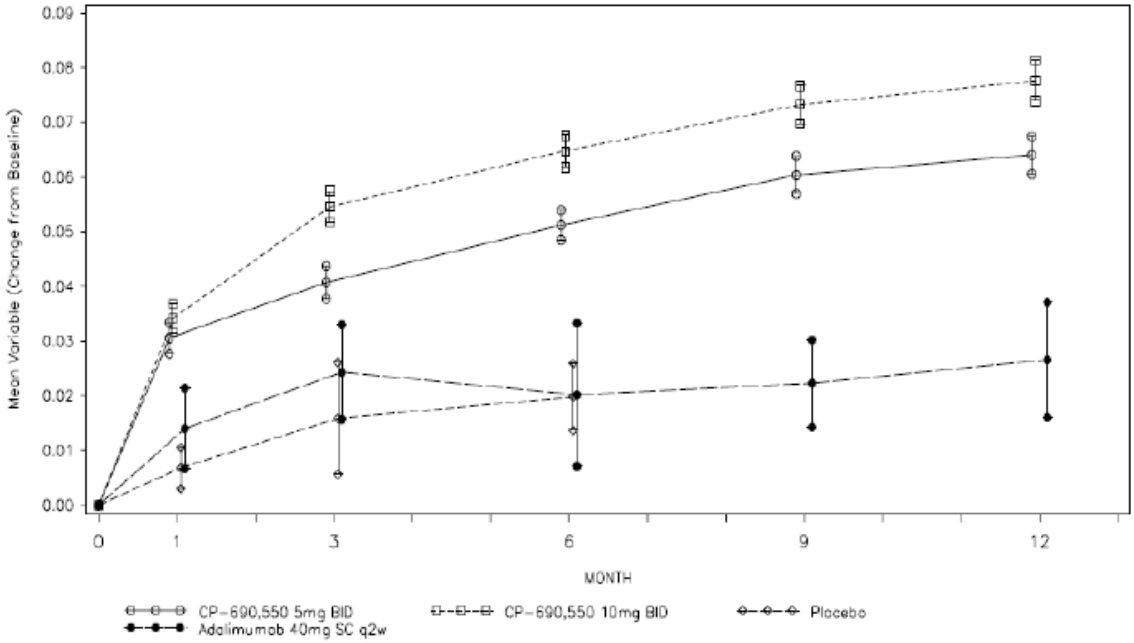
Baseline is either from the qualifying study or the extension study based on the enrollment gap.
PFIZER CONFIDENTIAL SDTM Creation: 02MAR2025 (22:03) Source Data: adsl adlb2 Table Generation: 05NOV2025 (18:28)
(Database snapshot date : 26Feb2025) Output File: ./ra_cdisc/SCS509a/lab_fig_chem2b

Creatinine Data from Tofacitinib Adult RA Clinical Program

The adult clinical program in participants with RA has the greatest tofacitinib exposure and is the most relevant for comparison purposes due to similarity to paediatric JIA. For the purposes of this response, this discussion will focus on the data for tofacitinib 5 mg BID.

Treatment with tofacitinib in the pooled Phase 3 studies over the 12-month treatment period resulted in mean increases from baseline in creatinine levels of approximately 0.06 mg/dL for tofacitinib 5 mg BID (Figure 31). The increases occurred primarily within the first 3 months and generally plateaued thereafter.

Figure 31. Mean (+/-SE) Change from Baseline in Serum Creatinine (mg/dL) in All Phase 3 Studies (0 to 12 Months)

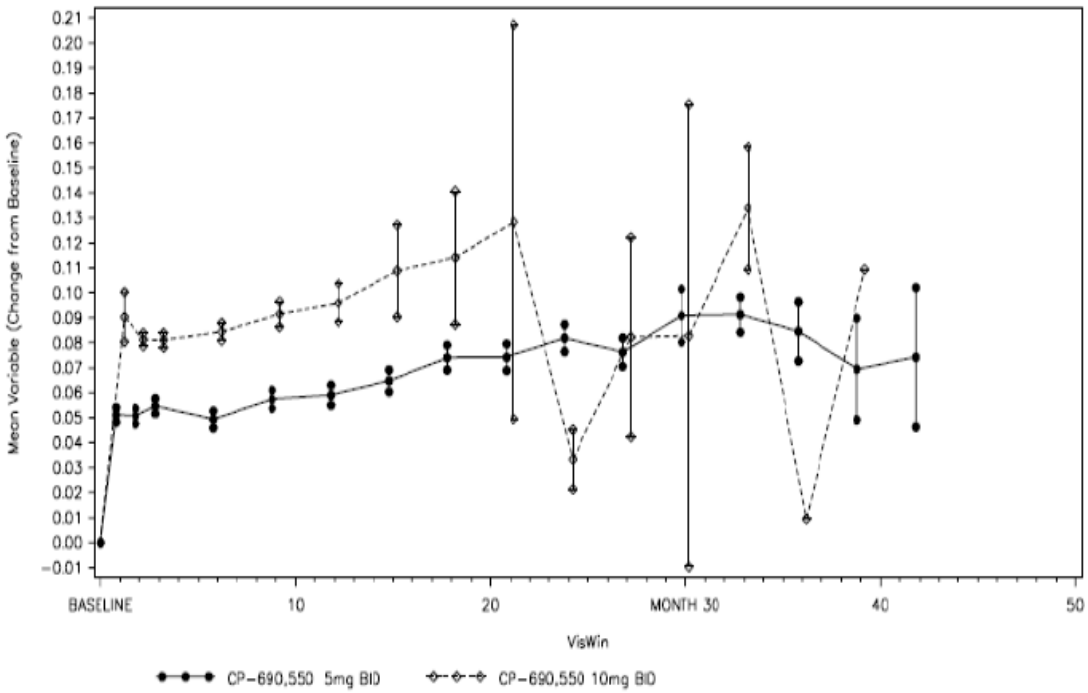


BID=twice daily, q2w=every 2 weeks, SC-subcutaneous, SE=standard error.
Includes Protocols A3921032, A3921044(1 year), A3921045, A3921046 and A3921064.
Source: P3ALL Figure 14.5.1.

The estimated (least squares) mean increases from baseline at Month 3 were larger (0.07 mg/dL) for the tofacitinib 5 mg BID group than the placebo (0.04 mg/dL) or adalimumab (0.06 mg/dL) groups. The difference between the tofacitinib 5 mg BID group and the placebo group in mean increase from baseline was estimated to be 0.02 mg/dL. The upper limit of the corresponding 95% confidence interval for the difference in the mean change was 0.04 mg/dL for tofacitinib 5 mg BID.

In long-term extension studies in adults with RA, changes from baseline in mean creatinine levels were not further increased from that observed in the Phase 3 studies. Mean increase in creatinine of approximately 0.05 mg/dL for tofacitinib 5 mg BID patients was observed at the Month 3 visit, with little changes thereafter. Mean change in creatinine levels remained stable for up to 3 years of follow-up in the tofacitinib 5 mg BID group.

Figure 32. Mean (+/-SE) Change from Baseline in Serum Creatinine (mg/dL) in Long-Term Extension Studies (All Patients)



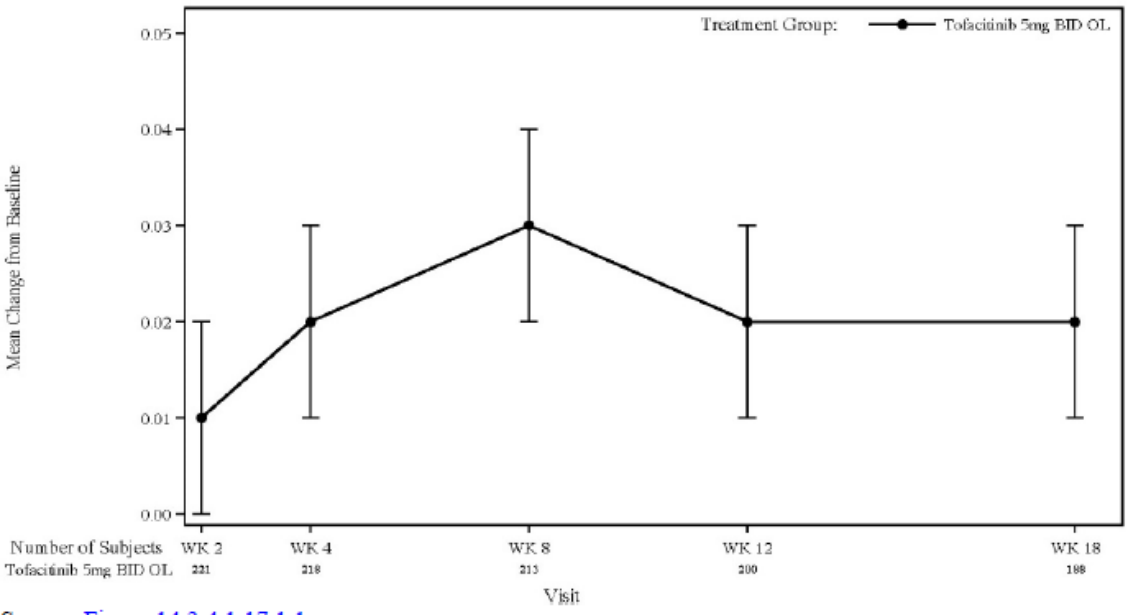
BID=twice daily, SE=standard error.
Source: LTE Figure 14.5.1.

Creatinine Data in JIA Phase 3 Pivotal Studies

The effect of tofacitinib 5 mg BID on SCr over time has been assessed in paediatric participants in 2 Phase 3 pivotal studies (A3921104 in pJIA and A3921165 in sJIA). SCr results over time in these studies were consistent with the results seen in the Phase 3 studies in adults with RA.

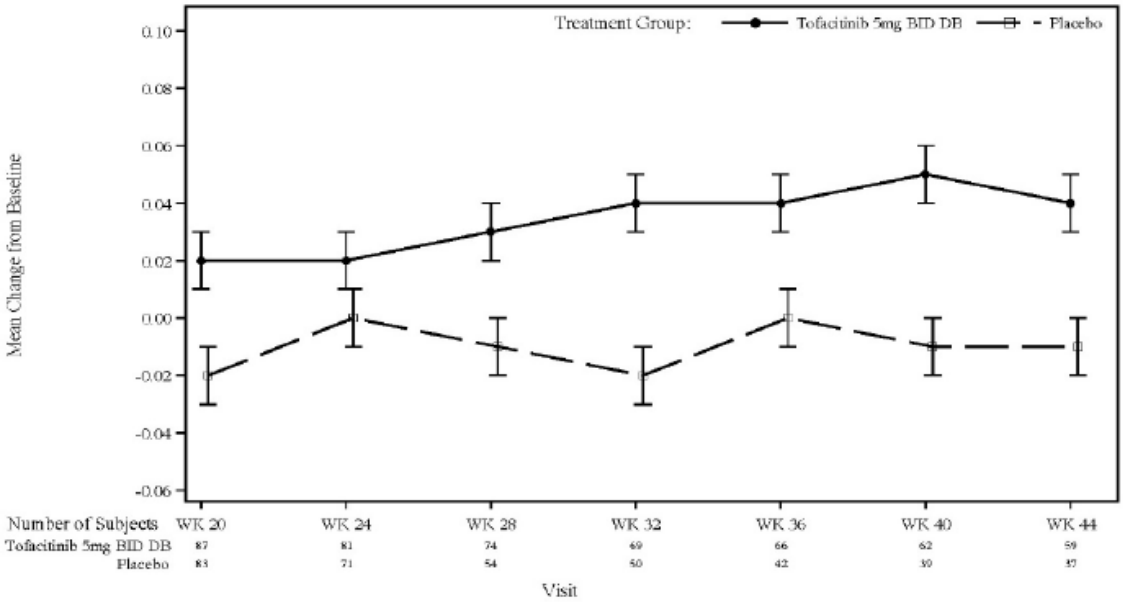
In Study A3921104, mean change from baseline in creatinine in paediatric participants with pJIA increased mildly from baseline to Week 18 of the open-label run-in phase (mean range, 0.01 to 0.03 mg/dL) (Figure 33). During the double-blind phase, a higher mean change from the double-blind baseline in creatinine was observed in the tofacitinib 5 mg BID group (mean range, 0.02 to 0.05 mg/dL) when compared to the placebo group (mean range, -0.02 to 0.00 mg/dL) (Figure 34).

Figure 33. Mean Change from Baseline (SE) in Creatinine (mg/dL) for Open-Label Run-In Phase - All Patients (OLFAS)



Source: Figure 14.3.4.1.17.1.1
The OL run-in phase is the study period before randomization day (Week 18). If a subject did not meet randomization criteria and was discontinued, the study period was considered the open-label run-in phase.

Figure 34. Mean Change from Baseline (SE) in Creatinine (mg/dL) for Double-Blind Phase (DBSAS)

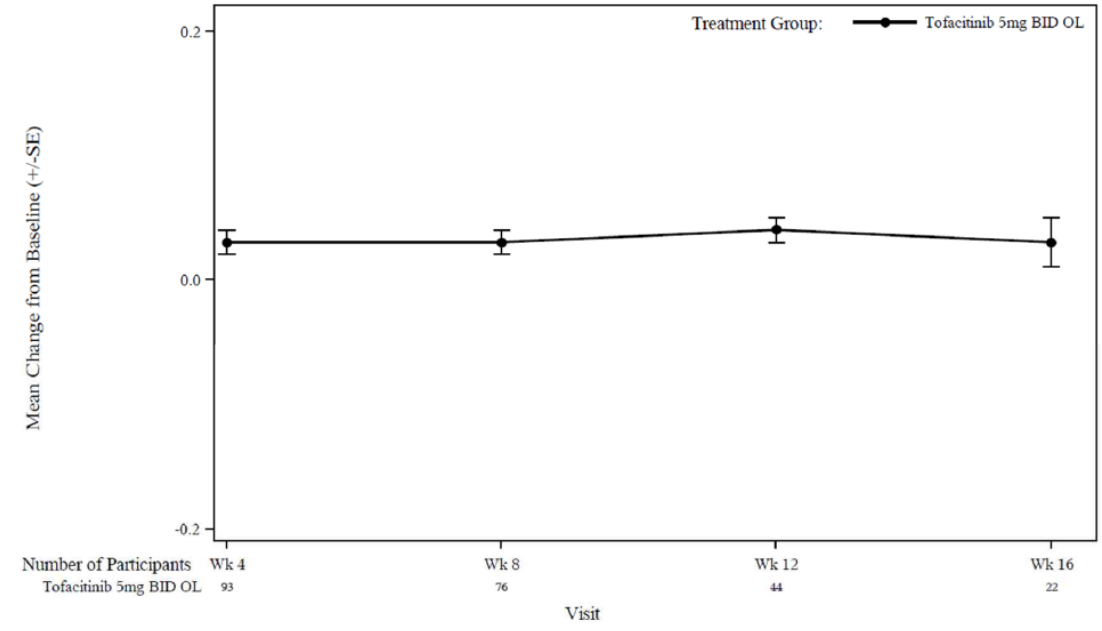


Source: Figure 14.3.4.1.17.2.2
The DB phase is the study period on and after randomization day.

Data from Study A3921165 in participants with sJIA, demonstrated similar results. Creatinine increased mildly from OL baseline in paediatric participants with sJIA during OLPT1 (range of mean change from baseline, 0.03 to 0.04 mg/dL; Figure 35) and was sustained up to Week 20 in the OLPT2, after which the mean change from baseline approached 0 at Week 24 (range of mean change from baseline, 0.00 to 0.09 mg/dL; Figure 36) likely influenced by the decreasing number of participants at this timepoint. Up to Week 52 of the DB phase, the mean changes from the DB baseline in creatinine

were similar in the tofacitinib 5 mg BID (range of mean change from DB baseline, -0.01 to 0.01 mg/dL) and the placebo (range of mean change from DB baseline, -0.04 to -0.01 mg/dL) treatment groups (Figure 37).

Figure 35. Line Graph of Mean Change (+/-SE) from Open-Label Baseline for Creatinine (mg/dL) in Open-Label Phase Part 1 - OLPT1



Open-Label baseline is the last value collected prior to Day 1 of study treatment.
PFIZER CONFIDENTIAL SDTM Creation: 17APR2024 (21:36) Source Data: adsl adlb Table Generation: 16MAY2024 (13:11)
(Database snapshot date : 16APR2024) Output File: ./ra_cdisc/A3921165_CSR/fig_line_lb1

Source: Figure 14.3.4.1.3.1.1

Figure 36. Line Graph of Mean Change (+/-SE) from Open-Label Baseline for Creatinine (mg/dL) in Open-Label Phase Part 2 - OLPT2

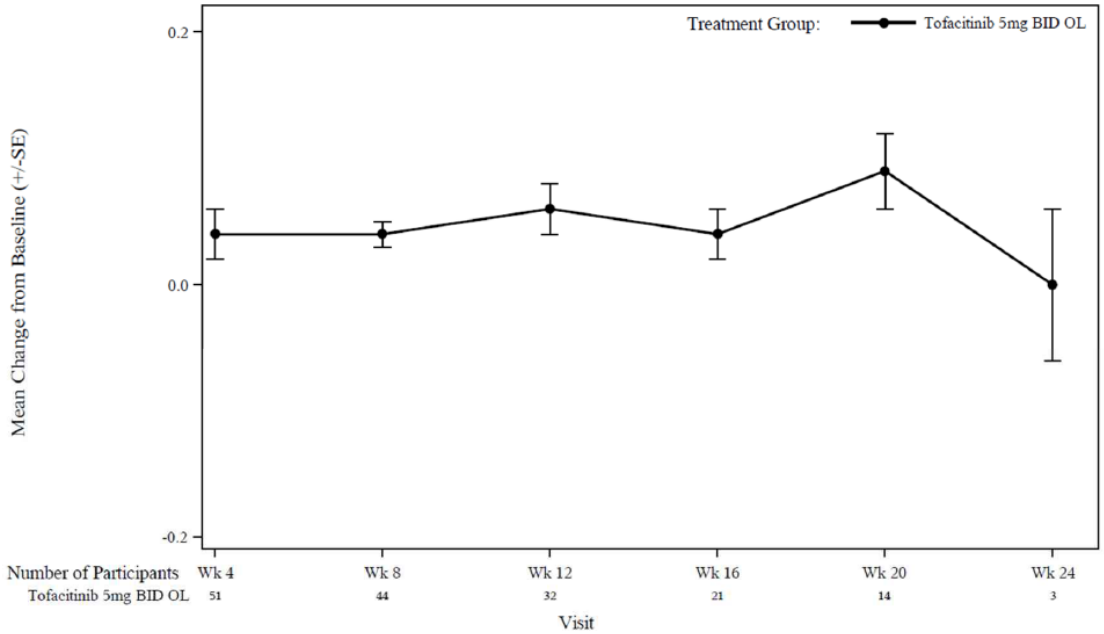
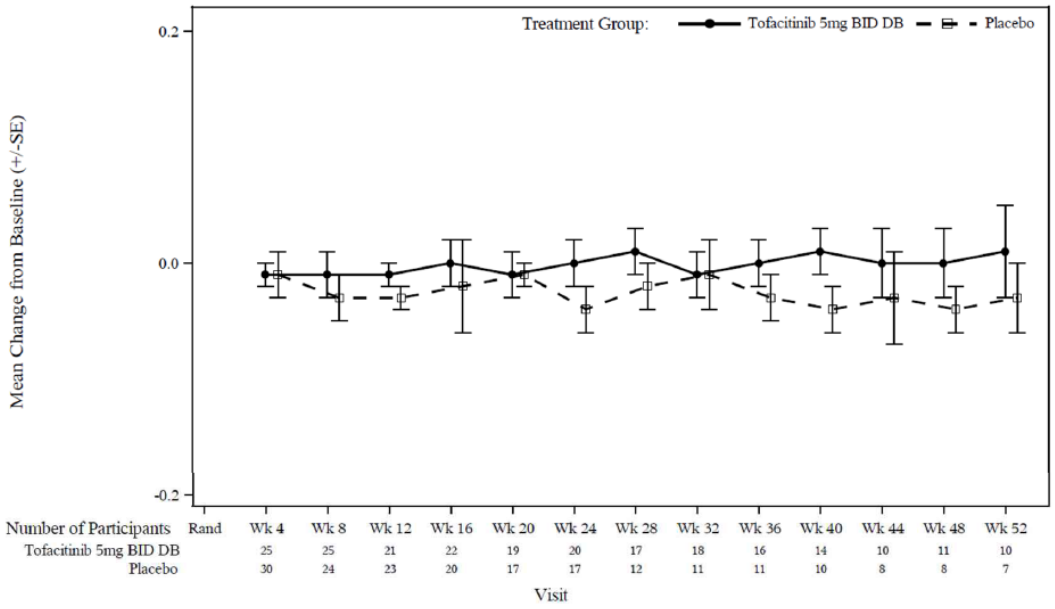


Figure 37. Line Graph of Mean Change (+/-SE) from Open-Label Baseline for Creatinine (mg/dL) in Double-Blind Phase - DBSAS



Double-Blind phase is the study period on and after randomization day. Double-Blind baseline is the values collected at the randomization.
Observations with data entry issues for creatinine were excluded from the summary: 1 data point at each of the following visits in DB phase: Week 28, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 72, Week 156, Week 164, Week 168, Week 172, Week 176, Week 180, Week 184, Week 200.
PFIZER CONFIDENTIAL SDTM Creation: 17APR2024 (21:36) Source Data: adsl adlb2 Table Generation: 22MAY2024 (06:15)
(Database snapshot date : 16APR2024) Output File: ./ra_cdisc/A3921165_CSR/fig_line_lb_adhoc

Source: Figure 14.3.4.1.3.6.1

Summary

In conclusion, the MAH considers the observed increase in SCr over time in paediatric patients in Study A3921145 to be attributed to normal growth and increased muscle mass. The mean SCr rose from 0.55 mg/dL at Month 1 to 0.71 mg/dL at Month 78, paralleling expected growth-related changes.

In the adult RA studies, mean increases from baseline in SCr with tofacitinib were modest (about 0.06 mg/dL), occurring mainly in the first 3 months and plateauing thereafter with stable levels over time in long-term extension studies. The magnitude of SCr changes from baseline in the pivotal Phase 3 paediatric studies were similar to those seen in adults. The paediatric safety profile is considered consistent with adults, and no new safety signals have been identified.

There is no specific information in either Section 4.4 or 4.8 of the SmPC regarding the modest increases in serum creatinine levels over time in adults. Currently, SmPC Section 4.8 "Paediatric population" states that "Changes in laboratory tests in JIA patients in the clinical development program were consistent with those seen in adult RA patients." The MAH continues to believe that safety profile specific to SCr changes over time in paediatric participants with JIA is consistent with that seen in adults with RA and that the current labelling remains appropriate. Therefore, the MAH does not propose an update to the SmPC based upon the results from Study A3921145.

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CHMP assessment of MAH's response

In the long-term extension study (Figure 28) there is an increase in the mean change from baseline in SCr levels through Month 78. The MAH's statement that "the number of patients contributing data at later timepoints is limited" does not appear acceptable since the increase in SCr is evident already in the first months, when the number of patients is good. However, when the absolute mean and median values are plotted it seems that the increase is similar to what expected due to normal growth. Moreover, the MAH calculated the estimated creatinine clearance, and the plot seems to show a stable clearance throughout the study. In the adults the increase in SCr was modest, and the changes observed in children, taking into account the physiological increase of SCr during development, do not seem worrisome. In addition, creatinine increase is already listed at the 4.8 table of the SmPC

Conclusion

Issue resolved.