11 June 2026
EMADOC-1700519818-3052509
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xeljanz

International non-proprietary name: Tofacitinib

Procedure No. EMA/VR/0000339481

Note

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

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 27 March 2026 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.3.c	C.3.c) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	Variation type II

Update of sections 4.8 and 5.1 of the SmPC following the outcome of the Article 46 procedure for study A3921145 (EMA/PAM/0000291064).

The requested variation(s) proposed amendments to the Summary of Product Characteristics

2. Overall conclusion and impact on the benefit/risk balance

In order to support the labelling updates that are being proposed to address the following conclusions and recommendations for Procedure EMA/PAM/0000291064 (Article 46 procedure for Study A3921145 CSR submission; CHMP outcome 29 January 2026), the MAH submitted 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. The SmPC changes will impact Sections 4.8 and 5.1 for the tofacitinib 5 mg and 10 mg film-coated tablets and the tofacitinib 1 mg/mL oral solution.

Regarding efficacy data, as expected for a LTE study, the proportion of patients with observed efficacy data declined at later time-points mainly due to reasons other than AEs or insufficient efficacy, particularly beyond Month 45 (the median duration of participation for patients with polyarticular course JIA), with only 25% of patients remaining in the study after Month 60. Thus, the MAH considers that at Month 45 the proportion of patients with observed efficacy data and the proportion of patients imputed as non-responders using the modified NRI approach are considered sufficient to support an interpretable assessment of maintenance of response. At later time-points, increasing attrition due primarily to study completion or non-adverse event/non-efficacy related discontinuations results in a high proportion of missing data, rendering NRI analyses less interpretable. Therefore, the MAH considers Month 45 to be the most appropriate time-point to include in the SmPC to inform prescribers on the long-term efficacy of tofacitinib in pJIA, which is accepted.

Moreover, the MAH's proposes to present in 5.1 section of the SmPC long-term data according to a post-hoc analysis, required during the Article 46 review (EMA/PAM/0000291064), where patients who discontinued due to insufficient clinical response or adverse event were considered non-responders, with the aim to prevent overestimation of treatment (providing a more cautious view of long-term performance), which is acknowledged. However, it is recognized that the impact presented from imputed responses in which patients who discontinued due to AEs (including death) were considered non-responders, may be overly conservative for this long term follow up, thus, in this case observed responses could be preferred. Therefore, also in line with long-term data presentation in 5.1 section of the SmPC of other medicinal products with the same indication, observed data are deemed important to be reported. Considering all of the above, the MAH included upon request in table 28 of the SmPC also observed results, adding a column in the tofacitinib-tofacitinib DB and tofacitinib-placebo DB groups. The tofacitinib OL group is considered less informative for a long-term study, therefore the first column has been deleted.

Regarding the safety, the MAH was asked to 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. Therefore, the MAH amended 4.8 section of the SmPC with the following schematic changes:

- Description of serious infections observed in Study JIA-I.

- Description of serious infections in the long-term extension study, including HZ cases. Of the HZ cases, 2 patients (0.7%) experienced serious events of multidermatomal herpes zoster with an incidence rate of 0.21 events per 100 patient-years.

- Description of liver events: in Study JIA I, ALT elevations > 5 × ULN at 2 consecutive visits were reported in 1 patient (0.4%) tofacitinib and methotrexate; the event was adjudicated as related to tofacitinib and resolved following discontinuation of methotrexate and tofacitinib. In the long term extension study, AST or ALT elevations > 5 × ULN at 2 consecutive visits were reported in 2 patients (0.66%); both events were adjudicated as unrelated to tofacitinib. None of the events in either study met Hy's Law criteria.

In conclusion, no new particular safety concerns seem emerge from the data presented, and the amendment of the SmPC 4.8 section is deemed sufficient to describe the further safety data gained in the JIA studies.

The benefit-risk balance of Xeljanz remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		**Type**
C.3.c	C.3.c) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	Variation type II

Update of sections 4.8 and 5.1 of the SmPC following the outcome of the Article 46 procedure for study A3921145 (EMA/PAM/0000291064).

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I are recommended.

4. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Xeljanz-EMA/PAM/0000291064'

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

In order to support the labelling updates that are being proposed to address the following conclusions and recommendations for Procedure EMA/PAM/0000291064 (Article 46 procedure for Study A3921145 CSR submission; CHMP outcome 29 January 2026), the MAH submitted 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, in particular, regarding the safety, the MAH was asked to 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.

Moreover, 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 was asked in section 5.1 of the SmPC.

The SmPC changes will impact Sections 4.8 and 5.1 for the tofacitinib 5 mg and 10 mg film-coated tablets and the tofacitinib 1 mg/mL oral solution.

6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

The tofacitinib juvenile idiopathic arthritis (JIA) clinical program was designed as a sequential and integrated development strategy to characterize pharmacokinetics, efficacy, and safety of tofacitinib across JIA subtypes. The program was comprised of an initial phase 1 study (A3921103) to establish paediatric pharmacokinetics and inform dose selection, followed by a pivotal Phase 3 randomized, double-blind, placebo-controlled withdrawal study in polyarticular course JIA (A3921104), which also included patients with juvenile psoriatic arthritis and enthesitis-related arthritis, and a Pivotal phase 3 randomized, double-blind, placebo-controlled withdrawal study in systemic JIA with active systemic features (A3921165). Patients in each of these studies could enter the open-label long-term extension (LTE) study A3921145 if they met eligibility criteria, which allowed continued treatment with tofacitinib and enabled a comprehensive assessment of long-term safety (primary objective) and maintenance-of-efficacy data across JIA subtypes and varying durations of prior exposure. Consequently, patients entering the LTE study differed with respect to underlying disease characteristics, JIA subtype, duration of prior exposure to tofacitinib, and clinical response.

The LTE study continued until the last systemic JIA patient enrolled in study A3921165 completed 1 year of follow-up in the LTE study, which occurred in February 2025. The majority of patients from the A3921104 index study had generally completed the LTE study by the end of 2022 as the protocol specified that their participation end after first marketing approval for polyarticular course JIA, however, there were some polyarticular course JIA patients who were permitted to continue in the study if access to tofacitinib was limited in their specific geographic region. Therefore, the length of exposure to tofacitinib for patients with polyarticular course JIA was highly variable.

As expected for an LTE study of extended duration, patient attrition increased over time due to protocol-defined study completion (51.9%), as described above, discontinuation for reasons other than AEs or insufficient efficacy (20.5%), AE (13.5%), and insufficient clinical response (14.1%). Accordingly, the proportion of patients with observed efficacy data declined at later timepoints, particularly beyond Month 45 (the median duration of participation for patients with polyarticular course JIA), with only 25% of patients remaining in the study after Month 60.

Similar patterns of attrition have been observed with other treatments for polyarticular course JIA, such as **abatacept** and **adalimumab**. Although these programs were conducted as single studies, they incorporated comparable elements, including an open-label run-in phase, a double-blind withdrawal phase, and an open-label LTE phase. In the open-label LTE phases for abatacept and adalimumab, treatment retention was calculated relative to the number of patients enrolled at the start of the open-label run-in phase and was modest, with approximately one-third of patients remaining on study through 6–7 years of follow-up. In both programs, the majority of discontinuations occurred for reasons other than adverse events or lack of efficacy, most commonly withdrawal of consent, loss to follow-up, or other non–drug-related factors. In the abatacept study, discontinuations due to adverse events (including death) or lack of efficacy during the open-label extension phase occurred in 12.1% of double-blind phase responders, 20.3% of double-blind phase placebo-withdrawal patients, and 33.3% of initial open-label phase non-responders. In the adalimumab study, 10.2% discontinued due to adverse events or lack of efficacy. The observed discontinuation rates were considered reflective of the challenges inherent to prolonged follow-up in pediatric chronic disease populations, rather than indicative of cumulative safety concerns or loss of treatment effect.

6.2. Results

The efficacy results for both abatacept and adalimumab studies demonstrated maintenance of efficacy in observed analyses and declining response rates over time when NRI analyses were performed, particularly at the later timepoints when attrition was greatest (Figure 1 and Figure 2).

Figure 1: **Proportion of Patients achieving JIA ACR Responses and Inactive Disease with Observed (A) and NRI (B) Analyses in Abatacept LTE Phase**

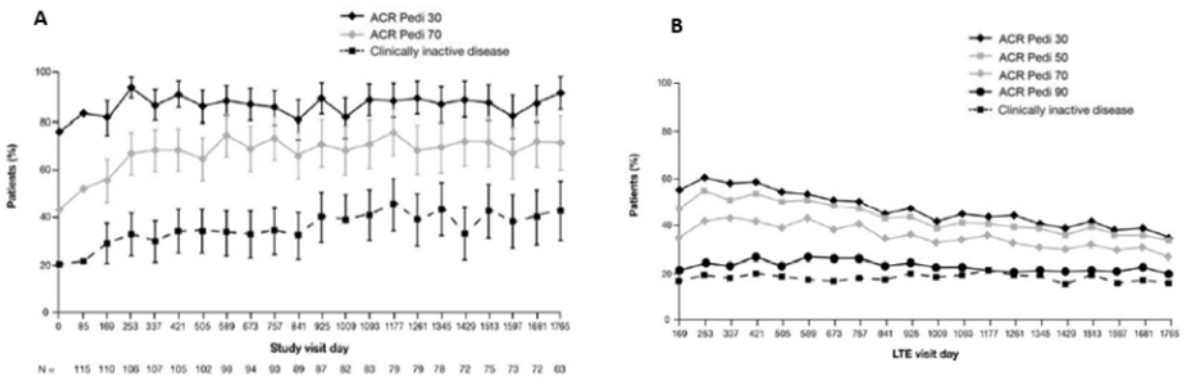
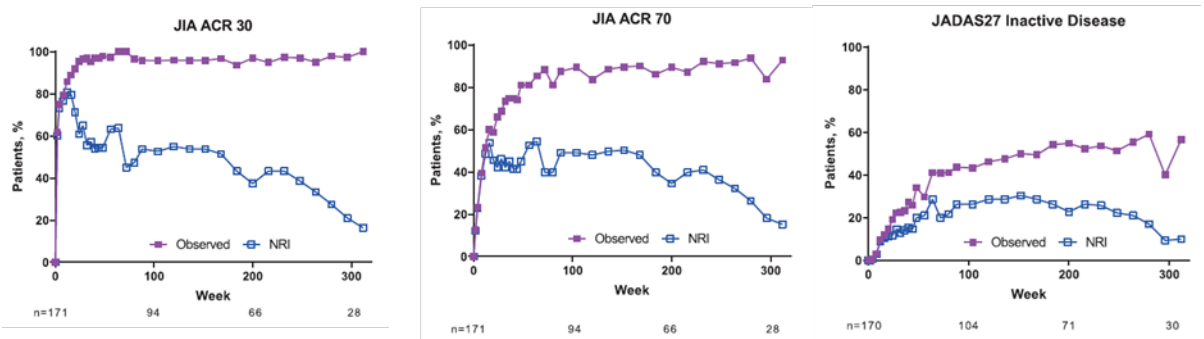
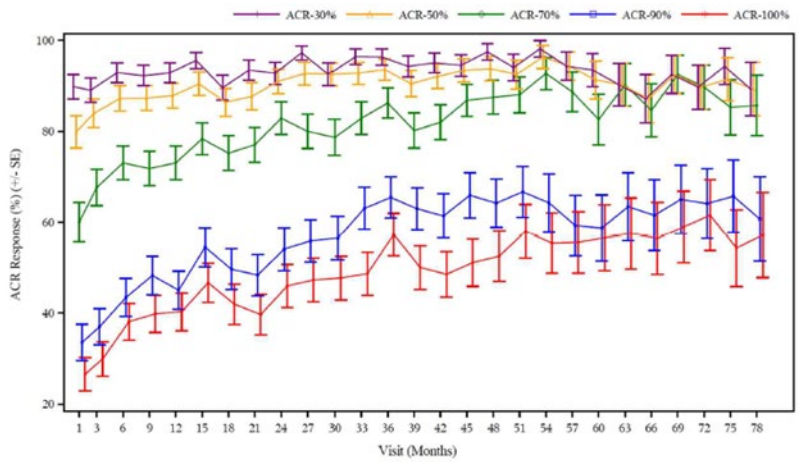


Figure 2: Percentage of Patients achieving JIA ACR30, 70 and Inactive Disease in Adalimumab LTE – Observed and NRI



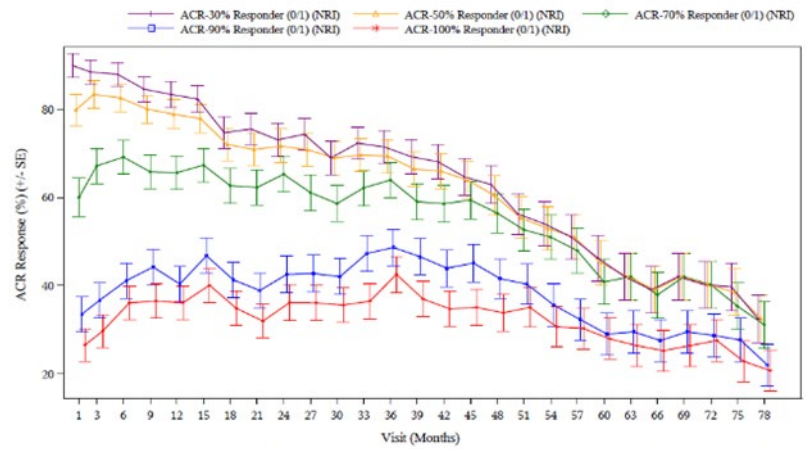
Similar rates of discontinuation and long-term efficacy results were seen in the tofacitinib polyarticular course JIA program. JIA ACR Responses and Inactive Disease based upon observed analyses, which were the analyses pre-specified in the SAP and included in the A3921145 CSR, demonstrated a maintenance of response over time similar to that seen with abatacept and adalimumab (Figure 3). During the Article 46 review of the CSR (EMA/PAM/0000291064), additional post hoc non responder imputation (NRI) analyses were requested and performed for the polyarticular course JIA population. In these analyses, patients who discontinued due to an adverse event or insufficient clinical response were classified as non responders from the time of discontinuation and imputed as non responders at all subsequent visits (modified NRI) (Figure 4).

Figure 3: A3921145 JIA ACR Responses (Observed)



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

Figure 4: A3921145 JIA ACR Responses (modified 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

At the conclusion of this review, the MAH agreed to update the SmPC, via a Type II variation, with a description of the LTE study efficacy data. Because the efficacy data presented from Study A3921104 in the SmPC is based on the EU approved indication of polyarticular JIA (pJIA), consisting only of RF+ polyarthritis, RF- polyarthritis, and extended oligoarthritis JIA subtypes, which is a different population than what was included in the A3921145 CSR, observed and modified NRI analyses were performed on the pJIA population from Study A3921104 to support this submission. In addition, the modified NRI analysis was also performed for the 3 subgroups of pJIA patients from Study A3921104 who entered the LTE study: those who discontinued from the open-label (OL) and did not enter the DB phase (Tofacitinib

OL), those who received tofacitinib in the double-blind (DB) phase (Tofacitinib-Tofacitinib DB), and those who received placebo in the DB phase (Tofacitinib-Placebo DB). These subgroups had differing durations of exposure and onset of response to tofacitinib in the index study, which resulted in distinct long term efficacy profiles (Supportive Tables 511a.1.1, 511a.1.2, 511a.2.1, 511a.2.2). Discontinuation rates during the LTE study also differed among groups, with discontinuation due to adverse events or insufficient clinical response occurring in 37.5%, 18.8%, and 21.9% in the Tofacitinib OL, Tofacitinib-Tofacitinib DB, and Tofacitinib-Placebo DB groups, respectively (Table 1).

Table 1. Disposition of pJIA Patients in A3921145 LTE Study by A3921104 Treatment Group

	Tofacitinib OL (N=24) n (%)	Tofacitinib – Tofacitinib DB (N=64) n (%)	Tofacitinib – Placebo DB (N=64) n (%)
Completed	8 (33.3)	36 (56.3)	40 (62.5)
Discontinued	16 (66.7)	28 (43.8)	24 (37.5)
Adverse Event	4 (16.7)	4 (6.3)	10 (15.6)
Insufficient Clinical Response	5 (20.8)	8 (12 .5)	4 (6.3)
Death	0	0	0
All Other	7 (29.2)	16 (25.0)	10 (15.6)

DB = double-blind; n = number of patients with observations; N = total number of patients; OL = open-label
Supportive Table 511a.4.1

Data from Month 45 and Month 60 are presented in Table 2 and Table 3 for the Tofacitinib OL, Tofacitinib-Tofacitinib DB, and Tofacitinib-Placebo DB groups. Results for the Tofacitinib OL group are not discussed due to the small sample size and differing response profile. At Month 45, there were 34 patients ongoing for the Tofacitinib – Tofacitinib DB group and 37 patients in the Tofacitinib-Placebo DB group, representing 53% and 58% of the original population, respectively. For the modified NRI analysis, the analysis populations at Month 45 increased to 43 and 49, respectively, with 9 patients in the Tofacitinib–Tofacitinib DB group and 12 patients in the Tofacitinib–Placebo DB group carried forward as non-responders. Data for the remaining patients (21 and 15, respectively) was missing in the Month 45 analysis because they had completed the study or discontinued for reasons other than adverse events or insufficient clinical response prior to Month 45.

At Month 60, there were 18 patients ongoing for the Tofacitinib – Tofacitinib DB group and 15 patients in the Tofacitinib-Placebo DB group, representing 28% and 23% of the original population, respectively. For the modified NRI analysis, the analysis populations at Month 60 increased to 28 and 29, respectively, with 10 patients in the Tofacitinib–Tofacitinib DB group and 14 patients in the Tofacitinib–Placebo DB group carried forward as non-responders. Data for the remaining patients (36 and 35, respectively) was missing in the Month 60 analysis because they had completed the study or discontinued for reasons other than adverse events or insufficient clinical response prior to Month 60.

Table 2 Proportion of pJIA Patients with JIA ACR Responses or Inactive Disease at Month 45

	Tofacitinib OL		Tofacitinib – Tofacitinib DB		Tofacitinib – Placebo DB	
Endpoint	**Observed N = 9 n (%)**	**mNRI N = 17 n (%)**	**Observed N = 34 n (%)**	**mNRI N = 43 n (%)**	**Observed N = 37 n (%)**	**mNRI N = 49 n (%)**
JIA ACR30	8 (88.9)	8 (47.1)	33 (97.1)	33 (76.7)	34 (91.9)	34 (69.4)
JIA ACR50	8 (88.9)	8 (47.1)	32 (94.1)	32 (74.4)	34 (91.9)	34 (69.4)
JIA ACR70	7 (77.8)	7 (41.2)	29 (85.3)	29 (67.4)	32 (86.5)	32 (65.3)
JIA ACR90	6 (66.7)	6 (35.3)	19 (55.9)	19 (44.2)	26 (70.3)	26 (53.1)
Inactive Disease*	4 (44.4)	4 (23.5)	13 (36.1)	13 (28.9)	17 (43.6)	17 (33.3)

ACR = American College of Rheumatology; DB = double-blind; JIA = juvenile idiopathic arthritis; n = number of patients with observations; N = total number of patients; OL = open-label
*Inactive disease is based upon CRP. N for Inactive disease is 36 for Observed Tofacitinib-Tofacitinib DB, 45 for NRI Tofacitinib-Tofacitinib DB, 39 for Observed Tofacitinib-Placebo DB, and 51 for NRI Tofacitinib-Placebo DB

Table 3 Proportion of pJIA Patients with JIA ACR Responses or Inactive Disease at Month 60

	Tofacitinib OL		Tofacitinib – Tofacitinib DB		Tofacitinib – Placebo DB	
Endpoint	**Observed N = 5 n (%)**	**mNRI N = 14 n (%)**	**Observed N = 18 n (%)**	**mNRI N = 28 n (%)**	**Observed N = 15 n (%)**	**mNRI N = 29 n (%)**
JIA ACR30	4 (80.0)	4 (28.6)	17 (94.4)	17 (60.7)	14 (93.3)	14 (48.3)
JIA ACR50	4 (80.0)	4 (28.6)	16 (88.9)	16 (57.1)	14 (93.3)	14 (48.3)
JIA ACR70	3 (60.0)	3 (21.4)	14 (77.8)	14 (50.0)	13 (86.7)	13 (44.8)
JIA ACR90	1 (20.0)	1 (7.1)	9 (50.0)	9 (32.1)	10 (66.7)	10 (34.5)
Inactive Disease*	1 (20.0)	1 (7.1)	8 (44.4)	8 (28.6)	8 (50.0)	8 (26.7)

ACR = American College of Rheumatology; DB = double-blind; JIA = juvenile idiopathic arthritis; n = number of patients with observations; N = total number of patients; OL = open-label
*Inactive disease is based upon CRP. N for Inactive disease is 16 for Observed Tofacitinib-Placebo SB and 30 for NRI Tofacitinib-Placebo DB

At Month 60, the majority of patients from the initially enrolled population were no longer participating in the study, primarily due to protocol defined study completion or discontinuation for reasons unrelated to adverse events or insufficient clinical response. This is consistent with the median duration of tofacitinib exposure of approximately 45 months in the Tofacitinib-Tofacitinib DB and Tofacitinib-Placebo DB treatment groups (Supportive Table 511a.3.1). As a result, the modified NRI analysis at Month 60 is substantially influenced by the carry forward of non responders and by the high proportion of missing data from patients who had completed the study or discontinued for reasons other than adverse event or efficacy related reasons. In contrast, the Month 45 assessment is less affected by missing data and therefore provides a more reliable evaluation of maintenance of response. On this basis, the MAH proposes inclusion of the Month 45 NRI results in the SmPC.

6.3. Discussion

In order to address recommendations coming from a previous Article 46 procedure (EMA/PAM/0000291064) for Study A3921145, asking for the update of 5.1 section of the SmPC with a description of study extension data, the MAH provided a discussion of long-term results in pJIA patients from Study A3921145 and made a comparison with those from other medicinal products authorized in the

same indication (abatacept and adalimumab). Consequently, the MAH is proposing a revision to SmPC Sections 5.1.

As expected for a LTE study, the proportion of patients with observed efficacy data declined at later time-points mainly due to reasons other than AEs or insufficient efficacy, particularly beyond Month 45 (the median duration of participation for patients with polyarticular course JIA), with only 25% of patients remaining in the study after Month 60.

As reported by the MAH, a similar pattern attrition in the long-term was observed for adalimumab and abatacept in pJIA population, suggesting that the observed discontinuation rates were considered reflective of the challenges inherent to prolonged follow up in pediatric chronic disease populations, rather than indicative of cumulative safety concerns or loss of treatment effect, which is reasonable.

When considering different groups in the LTE study, discontinuation due to adverse events or insufficient clinical response occurred in 37.5%, 18.8%, and 21.9% in the Tofacitinib OL, Tofacitinib-Tofacitinib DB, and Tofacitinib-Placebo DB groups, respectively. Results have been presented as "observed data" as well as using a "modified non-responder imputation" (where patients who discontinued due to insufficient clinical response or adverse event were considered non-responders), a post hoc analyses required during the Article 46 review (EMA/PAM/0000291064). Observed data demonstrated a maintenance of response over time while additional post hoc non responder imputation (NRI) analysis showed a trend in declining response rates over time, particularly at the later time-points when attrition was greatest, as expected and in a similar way to what has been observed in abatacept and adalimumab long-term results.

The MAH considers that at Month 45 of the tofacitinib LTE study, the proportion of patients with observed efficacy data and the proportion of patients imputed as non-responders using the modified NRI approach are considered sufficient to support an interpretable assessment of maintenance of response. At later time-points, increasing attrition due primarily to study completion or non-adverse event/non-efficacy related discontinuations results in a high proportion of missing data, rendering NRI analyses less interpretable. Therefore, the MAH considers Month 45 to be the most appropriate time-point to include in the SmPC to inform prescribers on the long-term efficacy of tofacitinib in pJIA, which is accepted.

All that said, the MAH originally proposed to update 5.1 section of the SmPC as follows:

5.1 Pharmacodynamic properties

[….]

Long term extension study

In the LTE study, 152 patients with pJIA from Study JIA-I received open-label tofacitinib 5 mg twice daily for up to 7.5 years. Patients who discontinued during the open-label (OL) phase of Study JIA-I (tofacitinib OL) and those who entered the double-blind (DB) phase and received tofacitinib 5 mg twice daily (tofacitinib-tofacitinib DB) or placebo (tofacitinib-placebo DB) were eligible to enrol in the LTE study if they met entry criteria. Most patients who entered the DB phase of Study JIA-I entered the LTE study (64/67 from tofacitinib-tofacitinib DB and 64/66 from tofacitinib-placebo DB). Median tofacitinib exposure and response rates at Month 45, using a modified non-responder imputation (where patients who discontinued due to insufficient clinical response or adverse event were considered non-responders), are presented in Table 28 for each group. In addition, among patients who remained in the LTE study through Month 45, 40.5% achieved inactive disease (observed data).

Table 4: **Exposure and Efficacy endpoints at Month 45 of the LTE study in patients with pJIA (modified non-responder imputation**

	Tofacitinib OL (N=24)	*Tofacitinib – Tofacitinib DB (N=64)*	*Tofacitinib – Placebo DB (N=64)*
Median Exposure in months (Range)	*23.6 (1.0, 88.4)*	*46.26 (1.1, 89.4)*	*43.75 (1.5, 89.0)*
JIA ACR30, n / N (%)	*8 / 17 (47.1)*	*33 /43 (76.7)*	*34 / 49 (69.4)*
JIA ACR50, n / N (%)	*8 / 17 (47.1)*	*32 / 43 (74.4)*	*34 / 49 (69.4)*
JIA ACR70, n / N (%)	*7 / 17 (41.2)*	*29 / 43 (67.4)*	*32 / 49 (65.3)*
JIA ACR90, n / N (%)	*6 / 17 (35.3)*	*19 / 43 (44.2)*	*26 / 49 (53.1)*
JIA ACR Inactive Disease, n / N (%)	*4 / 17 (23.5)*	*13 / 45 (28.9)*	*17 / 51 (33.3)*

ACR = American College of Rheumatology; DB = double-blind; JIA = juvenile idiopathic arthritis; n = number of patients with observations at the visit; N = total number of patients; OL= open-label

Updated SmPC section 5.1 & Updated table 28 following receipt of Updated SmPC (02/06/2026):

5.1 Pharmacodynamic properties

[….]

Long term extension study

In the LTE study, 152 patients with pJIA from Study JIA-I received open-label tofacitinib 5 mg twice daily for up to 7.5 years. Patients who discontinued during the open-label (OL) phase of Study JIA-I (tofacitinib OL) and those who entered the double-blind (DB) phase and received tofacitinib 5 mg twice daily (tofacitinib-tofacitinib DB) or placebo (tofacitinib-placebo DB) were eligible to enrol in the LTE study if they met entry criteria. Most patients who entered the DB phase of Study JIA-I entered the LTE study (64/67 from tofacitinib-tofacitinib DB and 64/66 from tofacitinib-placebo DB). Median tofacitinib exposure was 46.3 months (range: 1.0, 88.4) for tofacitinib-tofacitinib DB and 43.8 months (range: 1.5, 89.0) for tofacitinib-placebo DB groups, respectively. JIA ACR ~~and~~ response rates at Month 45, using observed and a modified non-responder imputation (where patients who discontinued due to insufficient clinical response or adverse event were considered non-responders), are presented in Table 28 for the tofacitinib-tofacitinib DB and tofacitinib-placebo DB groups.~~for each group. In addition, among patients who remained in the LTE study through Month 45, 40.5% achieved inactive disease (observed data).~~

Table 5: **Efficacy endpoints at Month 45 of the LTE study in patients with pJIA (observed and modified non-responder imputation analyses)**

	Tofacitinib – Tofacitinib DB (N=64)		**Tofacitinib – Placebo DB (N=64)**	
	Observed	**mNRI**	**Observed**	**mNRI**
JIA ACR30, n / N (%)	33 / 34 (97.1)	33 / 43 (76.7)	34 / 37 (91.9)	34 / 49 (69.4)
JIA ACR50, n / N (%)	32 / 34 (94.1)	32 / 43 (74.4)	34 / 37 (91.9)	34 / 49 (69.4)
JIA ACR70, n / N (%)	29 / 34 (85.3)	29 / 43 (67.4)	32 / 37 (86.5)	32 / 49 (65.3)
JIA ACR90, n / N (%)	19 / 34 (55.9)	19 / 43 (44.2)	26 / 37 (70.3)	26 / 49 (53.1)
JIA ACR inactive disease, n / N (%)	13 / 36 (36.1)	13 / 45 (28.9)	17 / 39 (43.6)	17 / 51 (33.3)

ACR = American College of Rheumatology; DB = double-blind; JIA = juvenile idiopathic arthritis; mNRI = modified non-responder imputation; n = number of patients with observations at the visit; N = total number of patients.

The MAH's proposal of long-term data presentation in 5.1 section of the SmPC with the aim to prevent overestimation of treatment (providing a more cautious view of long-term performance), is

acknowledged. However, it is recognized that the impact presented from imputed responses in which patients who discontinued due to AEs (including death) were considered non-responders, may be overly conservative for this long term follow up, thus, in this case observed responses could be preferred. Therefore, also in line with long-term data presentation in 5.1 section of the SmPC of other medicinal products with the same indication, **observed data** are deemed important to be reported. Considering all of the above, the MAH modified upon request table 28 of the SmPC including also observed results for the tofacitinib-tofacitinib DB and tofacitinib-placebo DB groups. The tofacitinib OL group is considered less informative for a long-term study, therefore the first column was deleted. The text above the table has been revised accordingly:(Please, refer to updated SmPC)

7. Clinical Safety aspects

7.1. Long-term safety

The MAH submitted 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. In particular, regarding the safety, the MAH was asked to 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.

The SmPC changes will impact Sections 4.8 and 5.1 for the tofacitinib 5 mg and 10 mg film-coated tablets and the tofacitinib 1 mg/mL oral solution.

Long-term safety data comes from Study A3921145.

7.2. Results

The MAH amended 4.8 section of the SmPC with the following schematic changes:

- Description of serious infections observed in Study JIA-I.
- Description of serious infections in the long-term extension study, including HZ cases. Of the HZ cases, 2 patients (0.7%) experienced serious events of multidermatomal herpes zoster with an incidence rate of 0.21 events per 100 patient-years.
- Description of liver events: in Study JIA I, ALT elevations > 5 × ULN at 2 consecutive visits were reported in 1 patient (0.4%) tofacitinib and methotrexate; the event was adjudicated as related to tofacitinib and resolved following discontinuation of methotrexate and tofacitinib. In the long term extension study, AST or ALT elevations > 5 × ULN at 2 consecutive visits were reported in 2 patients (0.66%); both events were adjudicated as unrelated to tofacitinib. None of the events in either study met Hy's Law criteria.

The complete amendment to the 4.8 SmPC section is the following:

4.8 Undesirable effects

[….]

Paediatric population

Polyarticular juvenile idiopathic arthritis and juvenile PsA

The adverse reactions in JIA patients in the *Phase 3 pivotal trial (Study JIA-I) and long term extension study, which included paediatric patients with pJIA, jPsA, ERA, and sJIA,* ~~clinical development program~~ were *generally* consistent in type and frequency with those seen in adult RA patients, with the exception of some infections (~~influenza, pharyngitis, sinusitis,~~ *upper respiratory tract infection and* viral infection)

and gastrointestinal or general disorders (abdominal pain, ~~nausea, vomiting,~~ *and* pyrexia~~, headache, cough~~), which were more common in *the* JIA paediatric population. MTX was the most frequent concomitant csDMARD used (on Day 1, 156 of 157 patients on csDMARDs took MTX). There are insufficient data regarding the safety profile of tofacitinib used concomitantly with any other csDMARDs.

Infections

In the double-blind portion of ~~the pivotal Phase 3 trial (~~Study JIA-I~~)~~, infection was the most commonly reported adverse reaction (44.3%). The infections were generally mild to moderate in severity.

In Study JIA-I, serious infections were reported in 3 patients (1.3%) who received tofacitinib, corresponding to an incidence rate of 2.43 patients with events per 100 patient-years. Herpes zoster was reported in 2 patients (0.9%), with an incidence rate of 1.63 patients with events per 100 patient-years. Both events involved a single dermatome and were non-serious.

In the long-term extension study, serious infections occurred in 14 patients (4.6%) receiving tofacitinib, corresponding to an incidence rate of 1.50 patients with events per 100 patient-years. The most frequent serious infections were herpes zoster and pneumonia. Herpes zoster events were reported in 6 patients (2.0%) corresponding to an incidence rate of 0.64 patients with events per 100 patient-years. Of these, two patients (0.7%) experienced serious events of multidermatomal herpes zoster with an incidence rate of 0.21 events per 100 patient-years. In addition, there were three herpes zoster events (two serious and one non-serious) confined to a single dermatome. The remaining herpes zoster event was non-serious, involved two adjacent dermatomes, and occurred in a patient with a prior non-serious varicella event reported 5.8 years earlier in the study).

~~In the integrated safety population, 7 patients had serious infections during treatment with tofacitinib within the reporting period (up to 28 days after the last dose of study medication), representing an incidence rate of 1.92 patients with events per 100 patient-years: pneumonia, epidural empyema (with sinusitis and subperiosteal abscess), pilonidal cyst, appendicitis, escherichia pyelonephritis, abscess limb, and UTI.~~

~~In the integrated safety population, 3 patients had non-serious events of herpes zoster within the reporting window representing an incidence rate of 0.82 patients with events per 100 patient-years. One (1) additional patient had an event of serious HZ outside the reporting window.~~

Hepatic events

Patients in the JIA pivotal study were required to have AST and ALT levels less than 1.5 times the upper limit of normal to be eligible for enrolment. *In Study JIA-I, ALT elevations >5 × ULN at two consecutive visits were reported in 1 patient (0.4%) receiving tofacitinib who was receiving background methotrexate; the event was adjudicated as related to tofacitinib and resolved following discontinuation of methotrexate and tofacitinib. In the long-term extension study, AST or ALT elevations >5 × ULN at two consecutive visits were reported in 2 patients (0.66%); both events were adjudicated as unrelated to tofacitinib. None of the events in either study met Hy's Law criteria.* ~~In the integrated safety population, there were 2 patients with ALT elevations ≥ 3 times the ULN at 2 consecutive visits. Neither event met Hy's Law criteria. Both patients were on background MTX therapy and each event resolved after discontinuation of MTX and permanent discontinuation of tofacitinib.~~

Laboratory tests

Changes in laboratory tests in JIA patients in the clinical development program were consistent with those seen in adult RA patients. Patients in the JIA pivotal study were required to have a platelet count ≥100,000 cells/mm^3 to be eligible for enrolment, therefore, there is no information available for JIA patients with a platelet count <100,000 cells/mm^3 before starting treatment with tofacitinib.

7.3. Discussion

The MAH submitted 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, in particular, regarding the safety, the MAH was asked to 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.

Upon further assessment, the MAH clarified that only 1 of the 2 patients was receiving a csDMARD (MTX) at the time of onset of herpes zoster. The second patient was on MTX at study entry, but had discontinued MTX on study day 175, which was prior to the onset of the herpes zoster on study day 489. Among the remaining 4 patients who experienced herpes zoster involving a single dermatome or 2 adjacent dermatomes, 1 (0.5%) was receiving concomitant MTX and 3 (3.5%) were not receiving any csDMARDs at the time of the event.

Because the frequency of herpes zoster did not differ based on concomitant csDMARD use, no additional language regarding csDMARD co-administration has been included in Section 4.8. A summary of the frequency and incidence rates of herpes zoster in each study, including the multidermatomal cases adjudicated as opportunistic infections, was provided.

The MAH amended 4.8 section of the SmPC with the following schematic changes:

- Description of serious infections observed in Study JIA-I.

- Description of serious infections in the long-term extension study, including HZ cases. Of the HZ cases, 2 patients (0.7%) experienced serious events of multidermatomal herpes zoster with an incidence rate of 0.21 events per 100 patient-years.

- Description of liver events: in Study JIA I, ALT elevations > 5 × ULN at 2 consecutive visits were reported in 1 patient (0.4%) tofacitinib and methotrexate; the event was adjudicated as related to tofacitinib and resolved following discontinuation of methotrexate and tofacitinib. In the long term extension study, AST or ALT elevations > 5 × ULN at 2 consecutive visits were reported in 2 patients (0.66%); both events were adjudicated as unrelated to tofacitinib. None of the events in either study met Hy's Law criteria.

In conclusion, no new particular safety concerns seem emerge from the data presented, and the amendment of the SmPC 4.8 section is deemed sufficient to describe the further safety data gained in the JIA studies.

8. Changes to the Product Information

As a result of this variation, section(s) 4.8, and 5.1 of the SmPC are being updated to update clinical information, following the outcome of the Article 46 procedure EMA/PAM/0000291064, based on the final study data for Study A3921145 (A Long Term, Open Label Follow Up Study of Tofacitinib for Treatment of JIA) to evaluate long term safety and tolerability in pJIA and juvenile PsA patients (e.g., growth or development disturbances).

9. Request for supplementary information

9.1. Major objections

Clinical aspects

9.2. Other concerns

Clinical aspects

The MAH's proposal of long-term data presentation in 5.1 section of the SmPC with the aim to prevent overestimation of treatment (providing a more cautious view of long-term performance), is acknowledged. However, it is recognized that the impact presented from imputed responses in which patients who discontinued due to AE (including death) were considered non-responders, may be overly conservative for this long term follow up, thus, in this case observed responses could be preferred. Therefore, also in line with long-term data presentation in 5.1 section of the SmPC of other medicinal products with the same indication, observed data are deemed important to be reported. All the above considering, the MAH should reflect in table 28 of the SmPC also observed results adding a column in the tofacitinib-tofacitinib DB and tofacitinib-placebo DB groups. The tofacitinib OL group is considered less informative for a long-term study, therefore the first column can be deleted. The text above the table should be revised accordingly.

Summary of MAH answer

On the 2nd of June 2026, the MAH submitted an updated SmPC to update details regarding the long-term extension study. Table 28 of the SmPC was also updated to include observed results for the tofacitinib-tofacitinib DB and tofacitinib-placebo DB groups. The original proposal including the tofacitinib OL group is considered less informative for a long-term study and therefore the first column was deleted.

Conclusion:

Issue considered resolved.

The CHMP AR has been updated accordingly.

10. Assessment of the responses to the request for supplementary information

N/A