24 June 2021
EMA/CHMP/389275/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xeljanz

International non-proprietary name: tofacitinib

Procedure No. EMEA/H/C/004214/X/0024/G

Note

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

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List of abbreviations

Abbreviation	Term
ACR	American College of Rheumatology
AE	adverse event
ANA	antinuclear antibody
AET	Antimicrobial effectiveness testing
AS	ankylosing spondylitis
ATC	Anatomical Therapeutic Chemical
bDMARD(s)	biological disease-modifying antirheumatic drug(s)
BID	twice daily
BR	benefit:risk
C_{avg}	average concentration
CFR	Code of Federation of Regulation
CHAQ	Childhood Health Assessment Questionnaire
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CISAP	continuous integrated safety analysis population
CK	creatine kinase
CL/F	apparent clearance
C_{max}	maximum observed concentration
CO	Clinical Overview
COX-2	cyclooxygenase-2 inhibitors
CRP	C-reactive protein
csDMARD(s)	conventional synthetic disease-modifying antirheumatic drug(s)
CV	Coefficient of variation
DHPC	Direct Healthcare Professional Communication
DMARD(s)	disease-modifying antirheumatic drug(s)
DVT	deep vein thrombosis
EC	European Community
EMA	European Medicines Agency
E Oligo	extended oligoarthritis
ERA	enthesitis-related arthritis
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
EU	European Union
GI	gastrointestinal
GRAS	Generally recognize as safe
HDPE	High Density Polyethylene
HRQOL	health-related quality of life
HZ	herpes zoster
IA	intra-articular
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFC	Individual folding carton
ILAR	International League of Associations for Rheumatology
ILD	interstitial lung disease
IM	intra-muscular
IOFI	International Organization of Flavour Industry
IR	immediate release
ISAP	integrated safety analysis population
IV	intravenous
JADAS	Juvenile Arthritis Disease Activity Score
JADAS27-CRP	Juvenile Arthritis Disease Activity Score in 27 joints using C-reactive protein
JADAS27-ESR	Juvenile Arthritis Disease Activity Score in 27 joints using erythrocyte sedimentation rate

Abbreviation	Term
JAK	Janus Kinase
JIA	Juvenile Idiopathic Arthritis
JIA ACR	Juvenile Idiopathic Arthritis American College of Rheumatology
JIA ACR30/50/70	3 out of 6 JIA core set variables improved ≥30%, 50%, 70%, respectively, with no more than 1 out of 6 JIA core set variables worsened by ≥30%. In subjects with systemic JIA, the absence of spiking fever related to systemic JIA is also required.
ka	First-order absorption rate constant
LS	least squares
LTE	long-term extension
MAA	marketing authorisation application
MACE	major adverse cardiovascular events
MAH	Marketing Application Holder
MAS	macrophage activation syndrome
mg	milligram
mL	milliliter
MTX	methotrexate
NA	Not applicable
NSAIDs	nonsteroidal anti-inflammatory drugs
OTIS	Organization of Teratology Information Services
PASS	Post-Authorisation Safety Study
PE	Pulmonary embolism
Ph. Eur.	European Pharmacopoeia
PHIS	Pediatric Health Information System
PK	pharmacokinetic
pJIA	Polyarticular Juvenile Idiopathic Arthritis
PMR	post marketing requirement
PMAR	pharmacometric analysis report
PRAC	Pharmacovigilence Risk Assessment Committee
PRINTO-PRCSG	Pediatric Rheumatology Collaborative Study Group and the Pediatric Rheumatology International Trial Organisation
PsA	psoriatic arthritis
PsO	psoriasis
PT	(MedDRA) Preferred Term
PV	pharmacovigilance
PY	patient-years
QOL	quality of life
QTTP	Quality target product profile
RA	rheumatoid arthritis
RA P123LTE	rheumatoid arthritis phase 1, 2, 3 and long-term extension
RF	rheumatoid factor
RH	Relative Humidity
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SC	subcutaneous
SD	standard deviation
sJIA	systemic Juvenile Idiopathic Arthritis
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TB	tuberculosis
TEAEs	treatment-emergent adverse events
TNF	tumor necrosis factor
UC	ulcerative colitis

Abbreviation	Term
ULN	upper limit of normal
UPLC	Ultra high performance liquid chromatography
US	United States
USPI	United States Package Insert
UV	Ultraviolet
VTE	venous thromboembolism
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

Pfizer Europe MA EEIG submitted on 29 May 2020 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation:

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

Extension application to introduce a new pharmaceutical form (oral solution, 1mg/ml) grouped with a type II variation (C.I.6.a) to add a new indication (treatment of active polyarticular course juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older). The RMP (version 12.1) is updated in accordance.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/134/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0134/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Armando Genazzani

The application was received by the EMA on	29 May 2020
The procedure started on	18 June 2020

The Rapporteur's first Assessment Report was circulated to all CHMP members on	8 September 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	N/A
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	16 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 October 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	15 October 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	22 January 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	26 February 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 March 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	25 March 2021
The MAH submitted the responses to the CHMP List of Outstanding Issues on	25 May 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	09 June 2021
The outstanding issues were addressed by the MAH during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Xeljanz on	24 June 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication for tofacitinib oral IR tablet and oral solution 5mg BID is for the treatment of active pJIA in subjects 2 years of age and older.
JIA is an umbrella-term describing a heterogeneous group of conditions characterized by chronic arthritis. Polyarticular JIA is defined as arthritis affecting 5 or more joints during the first 6-month period and includes RF+ polyarthritis and, RF-polyarthritis according to ILAR classification. Subjects with other subtypes of JIA who later develop arthritis in multiple joints can also have polyarticular disease e.g. extended polyarthritis, however they are excluded from the ILAR polyarticular JIA.

Table 1. Subtypes of Juvenile Idiopathic Arthritis

Subtype	Brief description
RF+ Polyarthritis	Symmetric polyarthritis that affects 5 or more joints during the first 6 months of disease. Primarily involves small joints of the hands and feet. Large joints may also be involved. Includes presence of IgM RF on at least 2 occasions. Severe extra-articular manifestations are rare.
RF- Polyarthritis	Asymmetric polyarthritis that affects 5 or more joints during the first 6 months of disease. The most heterogenous subtype and is characterized by the absence of IgM RF. It has 3 distinct subsets that have different manifestations and overall prognoses.
Oligoarthritis	Asymmetric arthritis primarily affecting the legs with knee joints most affected followed by ankles. Is usually accompanied by anti-nuclear antibody (ANA) positivity and anterior uveitis.
Oligoarthritis, persistent[a]	Affects no more than 4 joints at any time
Oligoarthritis, extended[a]	Affects 5 or more joints after the first 6 months of disease
Systemic arthritis	Arthritis with or preceded by fever and 1 or more of the following: non-fixed erythematosus rash, hepatomegaly or splenomegaly, generalized lymphoadenopathy, or serositis.
Psoriatic arthritis	Simultaneous presence of arthritis and typical psoriatic rash or family history of psoriasis, dactylitis, or nail pitting. Frequently at risk for iridocyclitis and can be ANA positive.
Enthesitis-related arthritis	Enthesitis and peripheral arthritis. May also involve the sacroiliac and spinal joints. Most subjects are HLA-B27 positive.
Undefined	Arthritis that does not fulfil any of the above categories or that fulfils more than one category

Source: De Benedetti F and Schneider R 2016, Modified from Rheumatology, 3rd Edition Table 84.3; Ravelli and Martini, 2007.
[a] Subcategory of oligoarthritis
Abbreviations: ANA=antinuclear antibodies; RA=rheumatoid arthritis; RF=rheumatoid factor; RF-=rheumatoid factor negative; RF+=rheumatoid factor positive

2.1.2. Epidemiology and risk factors, screening tools/prevention

JIA is the most common rheumatologic condition of childhood with an annual incidence in developed countries of 2 to 20 per 100,000 and a prevalence of 16 to 150 per 100,000.

Afflicted children have recurrent periods of disease flares which often persist into adulthood leading to long-term morbidity, physical disability and decreased quality of life.

Children with polyarticular JIA tend to have a more refractory course compared to those with fewer involved joints. Due to a prolonged course of active disease, the children are at increased risk for joint damage, resulting in poorer functional outcomes and decreased quality of life.

2.1.3. Biologic features, aetiology and pathogenesis

The pathogenesis of JIA is not well characterized but seems to include both genetic and environmental components.

Genetics are thought to contribute up to a third of the risk of developing JIA and HLA genes are the most important with several identified HLA alleles being associated with different pJIA subtypes.

Polyarticular and oligoarticular JIA are autoimmune diseases involving the adaptive immune system with T lymphocytes playing a central role, releasing proinflammatory cytokines in response to a self-antigen. Soon after the initial autoreactive response, almost the entire immune system (innate and adaptive) is involved in the immune response (Prakken et al, 2011). Similar to RA and other autoimmune diseases, there is an imbalance in the immune system in pJIA which leads to increased production of proinflammatory cytokines such as IL-17, IL-6, IL-1, and TNF- alpha (Hahn et al, 2010). Modulation of these cytokines results in improvement of clinical outcomes which suggests that these cytokines play an important role in pJIA.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Polyarticular JIA diagnosis is based upon clinical observations and examinations requiring exclusion of other known conditions. No laboratory test can confirm the diagnosis.

Chronic pain, joint tenderness and swelling, stiffness, decreased range of motion, decreased muscle strength, poor cardiovascular endurance, increased fatigue and headaches are often reported by children and adolescents with pJIA.

Long-term physical consequences of pJIA include: 1) Local Growth Disturbances and Limb-length Discrepancy; 2) Generalized Growth Disturbance; 3) Osteopenia; 4) Functional disability and decreased quality of life.

Children with pJIA experience functional impairment due to joint and back pain, heel pain, swelling of joints and morning stiffness, contractures, pain, and anterior uveitis leading to blindness. Functional impairment often continues into adulthood, with subjects having continued disease activity, medication-associated morbidity, and life-long disability and risk for emotional and social dysfunction.

Children with pJIA have lower health-related quality of life (HRQOL) compared to normative data. They are less physically active and participate less often in competitive sports and spend more time sedentary compared with their peers without pJIA. This aspect may lead to less ability to make friends, social isolation, depression, and physical deconditioning (Norgaard and Herlin, 2019; Milatz et al, 2019).

2.1.5. Management

Conventional treatment options for pJIA include local glucocorticoid injections, systemic glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (Schiappapietra et al, 2015; Ringold et al, 2014).

csDMARDs are first-line therapy for the treatment of pJIA due to their proven ability to minimize joint damage and improve symptoms. Methotrexate (MTX) is the most widely used csDMARD; side effects such as gastrointestinal and hepatic toxicity are often associated with its use (Ringold et al, 2019; Falvey et al, 2017).

Biological DMARDS (bDMARDs) have revolutionized the treatment of pJIA, especially in those who fail to respond to csDMARDs (Hodge et al, 2016; Ringold et al, 2019). Tumor necrosis factor (TNF) inhibitors were the first bDMARD approved for the treatment of pJIA, are the most widely used class of bDMARDs, and have been shown to lead to significant improvement in the reduction of signs and symptoms of pJIA. Since their approval, several other classes of bDMARDs have also been approved for use in pJIA (IL-1 inhibitors, IL-6 inhibitors, selective T cell costimulation modulator) (Sterba and Ilowite, 2016).

Despite the many benefits of bDMARDs, there are still downsides to their use in children with pJIA such route of administration (parenteral) and the potential development of anti-drug antibodies which can result in loss of efficacy over time.

Early pharmacological and non-pharmacological treatment of the disease is imperative for the prevention of irreversible soft tissue and joint damage (Hashkes, 2011; HaywardandWallace, 2009). Most treatments can be used to control and delay the progression of symptoms of pJIA, as well as prevent joint damage over the long term (Hashkes, 2011; Beukelmann et al, 2011). Consequently, the current treatment approach has shifted from a pyramidal approach to more aggressive therapy with earlier initiation of bDMARDs.

Although treatments are available to control and delay the progression of symptoms of pJIA, as well as prevent joint damage over the long term, however, additional therapy options are still needed as up to 30% of children with pJIA continue to have active disease despite treatment with MTX or biological agents (Lovell, 2006; Otten et al, 2013). For children who have failed currently available bDMARDs, additional therapies with novel mechanisms may be required to control their disease.

Moreover, the effective treatment of many rheumatic diseases requires parenteral administration of medications. There are significant barriers to injections with most children having a fear of injection needles; oral route is the preferred and considered the most appropriate route of administration to pediatric subjects. Repeated injections required for children with JIA may result in long-term consequences such as increased stress and decreased quality of life (Jacobse et al, 2019). In addition, the use of injectables for the treatment of JIA can pose a significant burden for subjects and parents due to the need to either administer them at home or require additional doctor visits for administration (Klein et al, 2012).

Oral agents are welcome to reduce the stress of parenteral administration on children with pJIA and their families. Unmet medical need remains for new effective oral systemic therapies that could provide a favourable benefit-risk assessment.

About the product

Mode of action

Tofacitinib is a potent, selective inhibitor of the JAK family. In enzymatic assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In contrast, tofacitinib has a high degree of selectivity against other kinases in the human genome. In human cells, tofacitinib preferentially inhibits signalling by

heterodimeric cytokine receptors that associate with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal via pairs of JAK2.Inhibition of JAK1 and JAK3 by tofacitinib attenuates signalling of interleukins (IL-2, -4, -6, -7, -9, -15, -21) and type I and type II interferons, which will result in modulation of the immune and inflammatory response.

Pharmacological classification

Tofacitinib belongs to the therapeutic group of Immunosuppressants (L04) and its therapeutic subgroup is L04AA29.

The new proposed extension of indication as initially claimed by the MAH is for the *treatment of active polyarticular course juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older*.

The recommended dose of tofacitinib is 5 mg film-coated tablets twice daily or tofacitinib oral solution weight-based equivalent twice daily, which should not be exceeded (Table 2).

Table 2 Tofacitinib dose for patients with polyarticular juvenile idiopathic arthritis two years of age and older:

Body weight (kg)	Dosage regimen
10 - <20	3.2 mg (3.2 mL oral solution) twice daily
20 - <40	4 mg (4 mL oral solution) twice daily
≥40	5 mg (one 5 mg tablet or 5 mL oral solution) twice daily*

* Patients treated with 5 mL tofacitinib oral solution may be switched to a tofacitinib 5 mg film-coated tablet.

Patients ≥40 kg treated with tofacitinib 5 mL oral solution twice daily may be switched to tofacitinib 5 mg film-coated tablets twice daily. Patients <40 kg cannot be switched from tofacitinib oral solution.

Within this application, a new formulation was presented for children not able to swallow capsules. This is an oral formulation (1mg/mL).

Type of Application and aspects on development

This is an application for a Grouped Type II Variation (new indication) / Line Extension (1 mg/ mL oral solution) for XELJANZ (tofacitinib) for the treatment of active polyarticular course juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older as initially applied by the MAH, in accordance with Article 2(3) and 2(4) of Commission Regulation (EC) No 1234/2008 ('the Variations Regulation'). This application concerns Xeljanz 5 mg IR tablet formulation and a new oral solution formulation at 1 mg/mL.

The tofacitinib clinical development programme for JIA was designed to evaluate the safety and efficacy of tofacitinib 5 mg film-coated tablets twice daily or tofacitinib oral solution weight-based equivalent twice daily for patients aged 2 years to < 18 years. This application in pJIA was supported by 4 clinical studies – Studies A3921103, A3921104, A3921145 (interim analysis – data cutoff date of 04 June 2019), and A3921354.

The 2 tablet formulations used in the pJIA programme (Phase 3 tablet and commercial tablet) were shown to be bioequivalent in Study A3921075. The proposed commercial oral solution formulation includes minor composition differences compared to the clinical oral solution formulation used in the pJIA program, and an *in vivo* study for bridging the commercial oral solution is not considered necessary. The clinical oral solution formulation was bridged to the commercial tablet formulation used in the pJIA program in healthy adults

(A3921354). Therefore, a 5 mg dose of the oral solution (5 mL of the 1 mg/mL oral solution) can be used interchangeably with a 5 mg IR tablet for treatment of JIA.

2.2. Quality aspects

Xeljanz 5 and 10 mg film coated tablets and Xeljanz 11 mg prolonged release tablets are already authorised medicinal products in the EU (EU/1/17/1178/001-014). This is a line extension to register a new pharmaceutical form (oral solution). The finished product is presented as oral solution containing tofacitinib citrate, equivalent to 1 mg tofacitinib as active substance.

Other ingredients are grape flavour [containing propylene glycol (E1520), glycerin (E422), and natural flavour], hydrochloric acid, lactic acid (E270), purified water, sodium benzoate (E211), sucralose (E955), and xylitol (E967)

The product is available in white coloured HDPE bottles with a child resistant, polypropylene cap with PP liner sealed by aluminium-foil heat-induction seal and a 5 mL oral dosing syringe with 3.2 mL, 4 mL, and 5 mL gradations. The container closure system also includes a low-density polyethylene (LDPE) press-in bottle adapter (PIBA) as described in section 6.5 of the SmPC

2.2.1. Introduction

2.2.2. Active Substance

The active substance used to manufacture the new pharmaceutical form is the same as that used in the manufacture of the currently authorised Xeljanz 5 and 10 mg film coated tablets and 11 mg prolonged release tablets (EU/1/17/1178/001-014).

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Tofacitinib oral solution, 1 mg/mL, will be provided as a multi-use, clear, colourless solution.

The oral solution, 1 mg/mL, has been developed for the treatment of juvenile idiopathic arthritis (JIA) and is intended for use in paediatric patients that have difficulty swallowing tablets. Patients who are later able to swallow tablets are expected to transition from the oral solution to the commercial 5 mg tablets.

Other than the active substance properties described in the previously approved marketing authorisation application, the solubility of the active substance, compatibility with the oral solution excipients, and compatibility with the manufacturing materials are of relevance for the new oral solution. The same active substance specification is used for the oral solution product than the already authorised tablet.

*All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except the flavour grape which complies with "in house" specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The components of the grape flavour comply with applicable food flavouring regulations, are approved by the FDA under CFR 21 and/or are considered GRAS (Generally Recognized As Safe), comply with the IOFI (International Organization of the Flavour Industry) Code of Practice and meet the criteria of EC regulation No 1334/2008.*The tofacitinib formulation

concentration of 1 mg/mL was chosen to provide appropriate dose flexibility in the target population. The proposed dosage volume is 3.2 to 5 mL administered twice daily, with the dosing prescribed based on patient weight and optimised background therapy. The nominated concentration, 1 mg/mL, accommodates the delivery of the highest and lowest proposed dosages using practical administration volumes utilizing the dosing device (dose-marked oral syringe).

The proposed commercial manufacturing process was established based on prior knowledge and experience with other oral liquid products, as well as the experience gained from manufacturing clinical and primary stability batches of the finished product. During compounding, the time to dissolve the active substance and in-process pH control are the critical process parameters. During packaging, insertion of the bottles into the secondary packaging is the critical processing parameter.

The primary packaging is HDPE bottles with a child resistant, polypropylene cap with PP liner sealed by aluminium-foil heat-induction seal and a 5 mL CE marked oral dosing syringe with 3.2 mL, 4 mL, and 5 mL gradations. The container closure system also includes a low-density polyethylene (LDPE) press-in bottle adapter (PIBA). The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The suitability of the graduation of the syringe was not shown at the time of submission. Therefore, the CHMP raised a major objection requesting that the precision and accuracy of dosing of the finished product with the syringe should be shown and this precision and accuracy of dosing should be guaranteed from release throughout storage until the end of shelf life. The MAH demonstrated precision and accuracy of dispensing the finished product using the commercial oral syringe. The effect of ageing on dose accuracy and the potential printing ink fading during storage and use were studied using representative oral syringes, identical to the commercial oral syringe in every way except that the representative syringes have generic dose markings instead of custom prescribed dose markings. This was considered satisfactory

Manufacture of the product and process controls

The finished product is manufactured in one manufacturing site.

The manufacturing process consists of 4 main steps: compounding, filtration, filling and packaging using conventional pharmaceutical manufacturing equipment. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC, UV), assay (UPLC), impurities (UPLC), sodium benzoate content (UPLC), pH (Ph. Eur.), and microbial limits (Ph. Eur.)

The specifications in the finished product are set in line with stability studies and current guidelines. This was considered satisfactory.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested as Major Objection) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 22 pilot and commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 24 months at the long term storage conditions of 25°C/40% RH (testing started at 12 months) and 30°C/35% RH and 6 months at the accelerated storage conditions of 40°C/20 % RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.
Samples were tested for appearance, assay, degradation products, as well as preservative efficacy (pH, sodium benzoate content, antimicrobial effectiveness), microbiological quality and weight loss.

Under long term and accelerated conditions, the observed changes in the tested parameters were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

Photostability studies were carried out on all three batches of the finished product according to the ICH Guideline Q1B on Photostability Testing of New Drug Substances and Products. No significant changes were observed in any of the parameters measured for the confirmatory photostability study for samples packaged in the proposed commercial packaging HDPE bottle in a paperboard individual folding carton (IFC)).

Forced degradation experiments were performed to establish the extent and nature of potential degradation pathways and to confirm the suitability of the assay and purity method. The stress conditions included thermal, photolysis, acid/base, peroxide, free radical initiator and metals. The studies conducted showed an increase of degradation was induced under thermal, photolysis and free radical oxidation stress conditions. Under these conditions, one specified degradant increased to a in the free radical oxidation stress condition and another specified degradant increased in the thermal stress condition. These studies confirm that the assay/purity method is selective and stability indicating.

The finished product is a multidose product. In-use stability studies have been performed. One batch was analysed at 3 and 12 months at 30°C/ 35% RH (upright orientation). Additionally, in-use was evaluated for another batch at 24 months and a third batch was evaluated at 36 months at 25°C/ 40% RH (upright orientation) and 30°C/ 35% RH (upright orientation). Based on the in-use stability data an in-use label restriction of 90 days is warranted.

Based on available stability data, the proposed shelf-life of 2 years and store in the original bottle and package in order to protect from light as stated in the SmPC (section 6.3) are acceptable. It should be discarded after 60 days of first opening.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Two issues were raised by CHMP as Major Objections (MO). The first MO requesting the demonstration of precision and accuracy of dosing of the finished product with the syringe to be guaranteed from release throughout storage until the end of shelf life and the second MO requesting the risk evaluation concerning the presence of nitrosamine impurities in the finished product. Responses to both issues were provided by the applicant and considered to be satisfactory by CHMP.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

With this application, the MAH proposes the use of tofacitinib IR tablet or oral solution in the treatment of pJIA in children aged 2 to 18 years. Administration of tofacitinib is by weight-based IR tablet BID at 5 mg or weight-based oral solution BID at 1 mg/mL. Comparable exposure is expected between tablet and oral solution administration. Hence, the nonclinical assessment of the IR tablet and oral solution formulation of tofacitinib for pJIA is supported by the previous nonclinical assessment of the IR tablet formulation of tofacitinib for rheumatoid arthritis.

Assessment of the oral solution formulation impurities has been performed.

2.3.2. Pharmacology

The MAH has not submitted new pharmacology results, which is acceptable to CHMP since the nonclinical assessment for pJIA is supported by the previous nonclinical assessment of the IR tablet formulation of tofacitinib for rheumatoid arthritis.

2.3.3. Pharmacokinetics

The MAH has not submitted new pharmacokinetics results, which is acceptable to CHMP since the nonclinical assessment for pJIA is supported by the previous nonclinical assessment of the IR tablet formulation of tofacitinib for rheumatoid arthritis.

2.3.4. Toxicology

The MAH has only submitted toxicology results on impurities of the oral forumlation, which is acceptable to CHMP since the nonclinical assessment for pJIA is supported by the previous nonclinical assessment of the IR tablet formulation of tofacitinib for rheumatoid arthritis.

Bone toxicity

During the last modification of the Xeljanz JIA PIP (EMEA-000576-PIP01-09-M12), a review of the safety information was provided by the applicant, with regard to the potential risk for bone and joint development. This in light of the potential effects seen in a juvenile rats study with another JAK inhibitor compound of the same class.

Juvenile toxicity studies in rats and cynomolgus monkeys (studies GR307 and 09GR248, respectively) the age of which were selected to support human age of ≥2 years, were conducted.
Since bone and joint were not identified as target organs in adult animals, these tissues were not examined microscopically in juveniles.

In the juvenile rat toxicity and rat fertility studies, no tofacitinib-related clinical observation suggestive of bone or joint abnormalities (change in limb and/or paw use and positioning, gait abnormalities or macroscopic changes in bent bones and fractures) were noted in macroscopic examinations at necropsy. Similar results were seen in the monkey, moreover no effects on bone growth assessed by differences in the rate of radius or tibia lengthening (as per ICH S11) were seen.

Other toxicity studies

Impurities

Study CP-703058 (Hydrolysis Product)

The proposed control limit for CP-703058 is 1.0% in the oral solution. CP-703058 was classified as non-mutagenic (class 5) based on the in-silico assessment in DEREK and SARAH, structural similarity to the Ames negative drug substance, negative Ames data on a large number of relevant structures (internal data), and expert review of the in-silico predictions. CP-703058 has been evaluated in nonclinical toxicity studies, including a 6-week oral rat study at up to 100 mg/kg/day (Study 01-2063-06) and a 39-week juvenile oral monkey study at up to 10 mg/kg/day (Study 2501-010). The highest dose administered of 100 mg/kg/day in the 6-week rat study resulted in effects consistent with the intended inhibition of Janus kinase [JAK] pharmacology. The no observed adverse effect level (NOAEL) in the 39-week oral juvenile monkey toxicity study was 2 mg/kg/day, and adverse findings at 10 mg/kg/day (lowest observed adverse effect level [LOAEL]) were considered related to the exaggerated pharmacology of tofacitinib. The findings in both the rat and juvenile monkey studies were attributed to the pharmacological properties of tofacitinib. CP-703058 was present at 0.10% in Lot 43798-2-1H used in the 6-week rat study and at 0.11% in Lot E01001098 used in the 39-week juvenile monkey study. Therefore, the dose of CP-703058 that corresponds to the high dose in the 6-week rat study was 100 µg/kg/day, and 2.2 µg/kg/day and 11 µg/kg/day in the 39-week juvenile monkey study at the NOAEL and LOAEL doses, respectively. The LOAEL in the juvenile monkey study is used to qualify the CP-703058 impurity as all the effects observed in the study at that

dose can be attributed to the pharmacology of tofacitinib and were completely reversible. The maximum anticipated dose of CP-703058 at 1.0% of the API in humans is 8 µg/kg/day for 2 mg tofacitinib administered BID to a 5 kg child. Therefore, CP-703058 is considered qualified as an impurity in the oral formulation of tofacitinib up to 1.0%.

Study PF-04471928 (Oxidation Product; Rat, Monkey, Human Metabolite M9)

The proposed control limit for PF-04471928 is 1.0% in the oral solution. PF-04471928 was classified as non-mutagenic (class 5) based on the in-silico assessment in DEREK and SARAH and expert review of the in silico predictions and training set structures.

PF-04471928 is present as a metabolite in mass balance studies in rats, monkeys, and humans, and exposures have been estimated for the chronic repeat dose toxicity studies as well as the human exposure following repeat dosing. Calculated exposures at the highest dose in the chronic rat study (in which changes observed were consistent with the intended inhibition of JAK pharmacology) exceeds those of the most conservative human exposure projections, and the additional exposure in humans by contribution from PF-04471928 as an impurity is approximately 5% of the total exposure to the metabolite.

2.3.5. Body burden in the monkey 9-month chronic toxicity study at the LOAEL was generally less than the estimated human body burden. The *in-silico* data and body burden data support the control limit of 1% for PF-04471928. Ecotoxicity/environmental risk assessment

Table 1. Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH: 4 — Log D (OECD 107)[3]: 0.114; pH: 7 — 1.19; pH: 9 — 1.18	Potential PBT (N)
PBT-assessment (not required in light of PBT screening results)			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater, default or refined (e.g., prevalence, literature)	0.1	µg/L	> 0.01 threshold (Y)
Other concerns (e.g., chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106 or …	Sludge Sorption Coefficient K_{oc} =102 Soil Sorption Coefficient K_{oc} = *2042* Sediment Sorption Coefficient K_{oc} = *6918*	

Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 6.3 - 19.0 days $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = 26.3 and 52.8 days % shifting to sediment = 3.3 – 8.8% over 102 days			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	11 (biomass) 11 (growth rate)	mg a.i./	Green Alga *(Pseudokirchneriella subcapitata)*
Daphnia sp. Reproduction Test	OECD 211	NOEC	4.8*	mg a.i./	Daphnids *(Daphnia magna)*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	2.9** (sub-lethal effect) 5.6 (survival)	mg a.i./	Fathead Minnow *(Pimephales promelas)*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>1000	mg a.i./	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism		NOEC	46	mg/kg	*Chiromomus riparius*

*NOEC used to calculate $PNEC_{groundwater}$

** NOEC used to calculate $PNEC_{surfacewater}$

2.3.6. Discussion on non-clinical aspects

In this line extension to add an oral paediatric formulation, the impurities have been adequately qualified (study reports CP-703058 and PF-04471928) in the oral formulation of tofacitinib up to 1.0%. With regards

to bone toxicity after review of the safety information, it is agreed with the PDCO that current non-clinical and clinical data did not suggest an increased risk for lesions of bone tissue or effects on joints.

To better evaluate potential tofacitinib effects on bone and joint development and growth, a further juvenile rat toxicity study is currently planned post-approval. The non-clinical study report is expected to be available in November 2021.

Juvenile animal toxicity studies were conducted, and results have been assessed in the initial marketing authorisation application. Section 5.3 of the SmPC is updated with these results.

ERA

Tofacitinib has a log D value <4.5 at all environmentally relevant pHs. Screening for Persistence, Bioaccumulation and Toxicity (PBT) is not required.

The PECsw value is greater than the 0.01 µg/L action limit. Based on the PEC value, a Phase II environmental fate and effects analysis for tofacitinib was required. Biodegradation studies conducted in sludge indicated that tofacitinib may undergo moderate degradation during the wastewater treatment process via mineralization and primary biodegradation. Based on a sludge sorption coefficient (Kd) of 37, a minimal amount (0.6%) may be removed through sorption to sludge during the wastewater treatment process.

Based on an aqueous dissipation half-life of 6.3 –19 days under aerobic conditions, tofacitinib is expected to quickly dissipate from the water to the sediment and continue to degrade once in the environment (primary degradation half-life total system of 26.3 to 52.8 days). Multiple degradation products, all present at <10%, were observed in the sediment compartment sampled throughout the study, indicating that tofacitinib is expected to undergo primary degradation under the aerobic conditions present in the water-sediment system; it is not expected to persist. Tofacitinib is not volatile and therefore will not enter the air compartment.

The chronic aquatic effects of tofacitinib were assessed in green algae, fish and daphnia.

The fathead minnow NOEC, based on sub-lethal effects related to observations of crocked tails, was more conservative than the NOEC established for population relevant of survival.

As per guidance, the chronic NOEC for *Daphnia magna and for sludge* were used to calculate the PNEC ground water and the NOEC for sludge will be used to calculate the PNEC micro-organisms.

The PEC/PNEC values were <1, leading to the MAH conclusion that tofacitinib is unlikely to represent a risk to the aquatic and wastewater environment. No further testing was required.

The present application concerns an extension of indication (JIA) and line extension. Although a new indication may indeed lead to an increase of exposure in the environment, and epidemiological data concerning the new indication should be taken into consideration when updating ERA, calculation of the PECsw was based on the maximum daily dose for all indications (including those previously approved), which is higher than that of JIA one. This is accepted by the CHMP.

2.3.7. Conclusion on the non-clinical aspects

No new pharmacology, pharmacokinetics and toxicity studies were submitted. Impurities present in the tofacitinib oral solution have been adequately qualified in nonclinical evaluations as declared by the MAH and endorsed by the CHMP.

ERA

Tofacitinib is not a PBT substance.

- Considering the above data, tofacitinib is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

The tofacitinib paediatric development programme was designed to demonstrate efficacy and long-term safety in subjects with JIA from 2 to <18 years of age. It consists of one completed Phase 1 pharmacokinetics (PK) Study A3921103, 1 completed Phase 3 pivotal Study A3921104, and 1 ongoing long term extension (LTE) Study A3921145 for subjects with JIA who previously participated in Studies A3921103 and A3921104. There is an additional ongoing Study A3921165 for subjects with systemic JIA with active systemic features which, upon completing study, are eligible to participate in the LTE Study A3921145.

GCP

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

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

- Tabular overview of clinical studies

Overview of Studies in pJIA Clinical Program

Study Number	Study Design/ Primary Objective/ Primary Endpoint/ Duration/Dosage/	Treatment Groups	N
Phase 1 Pharmacokinetic and Safety Study in JIA – Completed			
A3921103	Open-label multiple dose study to evaluate the PK, safety, and tolerability of tofacitinib in subjects with JIA from 2 to <18 years of age. Primary Objective: To characterize the PK and safety of tofacitinib following multiple oral doses in pediatric subjects (from 2 to <18 years) with active JIA (RF+ polyarthritis, RF- polyarthritis, Extended Oligoarthritis, PsA, and ERA). Primary Endpoint: Oral clearance (CL/F) on Day 5 Study treatment duration: 5 days Dosage: 5 mg BID or weight-based equivalent	Cohort 1: 12 to <18 years Cohort 2: 6 to <12 years Cohort 3: 2 to <6 years	8 9 9
Phase 3 JIA Pivotal Study – Completed			
A3921104	Open-label run-in phase followed by randomized withdrawal, double-blind placebo-controlled phase which evaluated efficacy, safety, and tolerability in subjects with JIA from 2 to <18 years of age. Primary Objective: To compare the efficacy and safety of tofacitinib to placebo in subjects with JIA. Primary Endpoint: Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) at Week 44/End of Study (Week 26 of the double-blind phase). Study treatment duration: 44 weeks Dosage: 5 mg BID or weight-based equivalent	All (enrolled in OL and treated) Randomized in DB phase Tofacitinib Placebo	225 173 88 85

Phase 2/3 JIA Long-term Extension Study – Ongoing			
A3921145[a]	Open-label long-term follow-up study in subjects with JIA from 2 to <18 years of age who have previously participated in tofacitinib studies for treatment of JIA. Primary Objective: To assess long-term efficacy and safety of tofacitinib for treatment of subjects with JIA. Primary Endpoint: Incidence and severity of AEs, incidence of abnormalities and changes from baseline in laboratory tests and vital signs, incidence in physical examination abnormalities, and validated assessment of growth and pubertal development. Study treatment duration based on data cut-off date of 04 June 2019 and data snapshot of 03 July 2019: Approximately 5 years Dosage: 5 mg BID or weight-based equivalent	All (enrolled) All (enrolled and treated) Enrolled and treated from A3921103 from A3921104 from A3921165	227 225 26 197 2[b]
Phase 1 Bioequivalence Study (Healthy Participants) – Completed			
A3921354	A randomized, open label, 2 period, cross over, single dose study to demonstrate the area under the curve equivalence between tofacitinib oral solution formulation and tablet formulation under fasted condition in healthy participants. Primary Objective: To demonstrate the equivalence of the extent of exposure between a single dose of tofacitinib 5 mL oral solution (1 mg/mL) relative to 5 mg tablet. Primary Endpoint: AUC_{inf}, AUC_{last}. Study treatment duration: 48 hours Dosage: 5 mg BID or 5 mL oral solution (1mg/mL)	Group A: Period 1, tofacitinib 5 mL oral solution, Period 2, tofacitinib 5 mg tablet Group B: Period 1, tofacitinib 5 mg tablet, Period 2, tofacitinib 5 mL oral solution	5 6

Overview of Studies in pJIA Clinical Program

Study Number	Study Design/ Primary Objective/ Primary Endpoint/ Duration/Dosage/	Treatment Groups	N
Phase 3 sJIA Study – Ongoing			
A3921165[c]	Randomized withdrawal, double-blind placebo-controlled study evaluating the efficacy, safety, tolerability, and pharmacokinetics in subjects with sJIA from 2 to <18 years of age. Primary Objective: To assess the sustained efficacy of tofacitinib versus placebo in sJIA subjects, as measured by time to sJIA flare in the double-blind randomized withdrawal phase. Primary Endpoint: Time to sJIA disease flare in the double-blind randomized withdrawal phase. Subject duration: Based on data cutoff date of 29 March 2019: Approximately 2 years.	Tofacitinib 5 mg BID	8

[a]No subject received tofacitinib 10 mg BID in Study A3921145.
[b] Study A3921165 subjects who rolled over into LTE Study A3921145 are not included in the JIA integrated safety database.
[c]Tofacitinib 10 mg was available per protocol for subjects in Study A3921165 before protocol amendment 2 was issued; 1 subject in Study A3921165 was administered 10 mg dose at the time of the interim data cutoff.
Abbreviations: AE = adverse event; AUC_{inf} = area under the concentration time curve from time zero to infinity; AUC_{last} = area under the concentration time curve from time zero to the time of last measurable concentration; BID=twice daily; CL/F = apparent total clearance of the drug from plasma after oral administration; DB = double-blind; ERA = enthesitis-related arthritis ; JIA = Juvenile Idiopathic Arthritis; N = number of subjects; OL = open-label; pJIA = Polyarticular Course Juvenile Idiopathic Arthritis; PK = pharmacokinetic; PRCSG/PRINTO = Pediatric Rheumatology Clinical Study Group/Pediatric Rheumatology International Trials Organization; PsA = psoriatic arthritis; sJIA = systemic Juvenile Idiopathic Arthritis.

2.4.2. Pharmacokinetics

Study A3921103 was an open-label multiple dose study in subjects from 2 to <18 years of age with Juvenile Idiopathic arthritis. Three cohorts were included, 12 to >18 years (n=8), 6 to <12 years (n=9) and 2 to < 6 years (n=9).

Study A3921104 was an open-label run-in phase study followed by randomised withdrawal double blind placebo-controlled phase which evaluate efficacy in subjects with pJIA aged 2 to <18 years. 225 subjects entered in the open-label phase and 173 in the randomized phase (88 tofacitinib and 85 placebo). The study duration was 44 weeks.

A phase 1 bioequivalence study (A3921354) was also submitted to demonstrate bioequivalence between a single dose of tofacitinib 5 ml oral solution and 5 mg tablet. This was a randomized, open label, 2 period, cross over, single dose study conducted in fasted condition in healthy participants (11).

An HPLC-MS/MS method (Pfizer Validation **A3929023**) was developed and validated at WuXi AppTec (Shanghai, China) with a quantitative range of 0.100 to 350 ng/mLwith quadratic regression. The method was transferred to PPD (Richmond Virginia and Middleton, Wisconsin) and validated (Pfizer Validation **A3929032**) with a truncated quantitative range from 0.100 to 100 ng/mL with linear regression. The truncated assay range from 0.100 to 100 ng/mL was also partially validated at WuXi AppTec (Pfizer Validation **A3929034**). Both WuXi and PPD used solid phase extraction followed by HPLC-MS/MS detection with only minor differences in procedures to accommodate individual lab operational needs. Cross validation (Pfizer Validations **A3929023 addendum 6 and A3929034**) between WuXi and PPD was conducted and assay equivalency was established.

For method **A3929023**, already submitted and validated, the Applicant submitted the addendum 5 (frozen storage matrix stability), the addendum 6 (cross validation among laboratories) and amendment 1 (to update the freezer temperature range).

The full report of **A3929032** with addendum 1 (method transfer from PPD Richmond to PPD Middleton) and addendum 2 (Interference Assessment, Frozen Storage Matrix Stability and Primary Stock Solution Stability) and 3 (Primary Stock Solution Stability, IS Stock and Working Solution Stability and Frozen Storage Matrix Stability) were submitted as well as the partial validation report **A3929034** and addendum 1 (editorial revision).

Bioavailability and bioequivalence

Tofacitinib is well-absorbed, with an oral bioavailability of 74%. On the basis of data already submitted in the initial MA, following the oral administration, systemic exposure of tofacitinib increases in an approximately dose proportional manner in healthy subjects.

Two (2) tofacitinib formulations were used for the treatment of subjects with JIA, age 2 years to <18 years: the oral 5 mg immediate release (IR) tablet and the oral solution formulation (1 mg/mL) developed to support weight-based dosing in the JIA clinical studies. Minor changes in composition of the proposed commercial oral solution formulation relative to the clinical oral solution formulation were implemented: a reduction in the sodium benzoate (preservative) level from 1.5% to 0.9% and the use of natural grape flavour instead of an artificial grape flavour. These changes are not expected to impact the physicochemical property of tofacitinib, therefore an *in vivo* study to bridge the clinical oral solution to the proposed commercial oral solution is not needed.

Study A3921354 was performed to bridge the PK of Tofacitinib IR Tablet and Oral Solution. This is a phase 1, randomized, open label, 2 period, cross over, single dose study to demonstrate the equivalence between 5 ml tofacitinib oral solution formulation and 5 mg tablet formulation under fasted condition in healthy participants. All participants (11) received tofacitinib 5 mL oral solution (1 mg/mL) and 5 mg tablet separated by the washout period of 48 hours. The pharmacokinetic blood samples are collected prior to dosing (0 hours) and post-dose at 0.25, 0.5, 1, 2, 3, 4, 8, 12, 16 and 24 hours in Periods 1 and 2. Statistical summary of plasma tofacitinib PK parameters is provided in Table 3.

Table 3 Statistical summary of plasma tofacitinib PK parameters, Protocol A3921354

Parameter (Units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio[a]
	Test (Tofacitinib 5 mL Oral Solution)	Reference (Tofacitinib 5 mg Tablet)		
AUC_{inf} (ng.hr/mL)	132.4	126.8	104.38	(99.99, 108.97)
AUC_{last} (ng.hr/mL)	131.3	125.7	104.48	(100.16, 108.99)
C_{max} (ng/mL)	38.01	34.56	110.00	(99.90, 121.13)

AUC_{inf} = area under the plasma concentration-time curve from time zero to infinity; AUC_{last} = area under the plasma concentration-time curve from time zero to time of last measurable concentration; CI= Confidence interval; C_{max} = maximum plasma drug concentration; CSR = clinical study report.

[a]The ratios (and 90% CIs) are expressed as percentages.

Pharmacokinetics in target population – Study A3921103

This was an open-label, non-randomized, multi-center, oral tofacitinib, multiple-dose (BID for 5 days) study in pediatric subjects with JIA aged from 2 to <18 years.

The study consisted of 3 cohorts based on the age of the subjects:

- Cohort 1: 12 to <18 years;
- Cohort 2: 6 to <12 years;
- Cohort 3: 2 to <6 years.

Oral formulations of tofacitinib, solution and tablet, were utilized for this study.

In children in the age range of 6 to <18 years, the oral solution was used for those weighing <40 kg. Oral tablets were used for children weighing ≥40 kg in this age range. Children aged 12 to <18 years who were unable to swallow tablets had the option of taking an oral solution. Children aged 6 to <12 years with a BWT of ≥40 kg had the option of taking oral solution or tablets. In the age range 2 to <6 years, children with a BWT <30 kg had the option of taking oral solution or tablets, and children weighing <30 kg were dosed with the oral solution.

The following doses were initially administered:

Body Weight (Kg)	Dose (mg)	Volume (mL)
5-11	1	1
12-18	1.5	1.5
19-24	2	2
25-31	2.5	2.5
32-39	3	3
≥40	5	5

An unplanned interim analysis was conducted in this phase 1 study for subjects enrolled in Cohorts 1 and 2. The interim analysis indicated higher CL/F values (28.09 L/h and 25.48 L/h for Cohorts 1 and 2, respectively) in JIA subjects compared to adult RA subjects (18.4 L/h at 5 mg BID dose), resulting in steady state AUCtau values in JIA subjects in Cohort 1 and Cohort 2 that are 37.9% and 52.9% lower compared to adult RA subjects. The Cmax values in Cohorts 1 and 2 in this study are also 19% and 28% lower compared to adult RA subjects (Cmax: 58 ng/mL). The allometric relationships were re-estimated during this preliminary PK characterization using observed concentration-time data from the first fourteen subjects (6 to <18 year age group) completing the study. The mean estimate of the power scalar for the CL-BWT relationship (Eq. 1) was 0.51, lower than that assumed for the initial dose selection (assuming 0.75 as allometric scaling factor).

Doses for the 2 to <6-year age group were increased from that initially planned based on this analysis, to achieve exposures comparable to that from a 5-mg-BID dose in adult RA subjects. The table below shows the new administered doses:

Table 4 Study Treatment Dosing and Administration for Study A3921103

Body Weight (kg)	Dose (mg, BID)	Volume (mL, BID)
Dosing scheme for age 6 to <18 years		
5-11	1	1
12-18	1.5	1.5
19-24	2	2

Body Weight (kg)	Dose (mg, BID)	Volume (mL, BID)
25-31	2.5	2.5
32-39	3	3
≥40	5	5
Dosing scheme for age 2 to <6 years		
5-6	1	1
7-9	1.5	1.5
10-12	2	2
13-15	2.5	2.5
16-19	3	3
20-22	3.5	3.5
23-26	4	4
27-29	4.5	4.5
≥30	5	5

A total of 26 subjects between 2 and 17 years of age and weighing between 13.9 and 70.9 kg were dosed with 2 to 5mg BID doses of tofacitinib for 5days in Study A3921103.

A summary of PK parameters are presented in the table below.

Table 5 Descriptive Summary of Plasma Tofacitinib Pharmacokinetic Parameters by Age Group – Parameter Analysis Set (A3921103)

	Parameter Summary Statistics[a]			
Parameters, Units	**Cohort 1 12 to <18 Years**	**Cohort 2 6 to <12 Years**	**Cohort 3 2 to <6 Years**	**All Cohorts**
N	8[b]	9[c]	9	26[d]
Dose, mg (BID)	5.0 (3.0-5.0)	2.5 (2.0-5.0)	3.0 (2.5-3.5)	3.0 (2.0-5.0)
AUC_{tau} ng h/mL	156.58 (25)	118.81 (27)	142.51 (32)	138.56 (30)
C_{max}, ng/mL	46.97 (40)	41.67 (29)	66.15 (28)	50.74 (38)
T_{max}, h	0.75 (0.50-6.90)	1.00 (0.50-2.05)	0.50 (0.50-1.92)	0.91 (0.50-6.90)
C_{trough}, ng/mL	2.659 (100)	0.757 (127)	0.756 (119)	1.114 (145)
C_{min}, ng/mL	2.503 (86)	0.816 (95)	0.698 (103)	1.104 (123)
$t_{½}$, h	2.616 ± 0.453	1.949 ± 0.294	1.771 ± 0.406	2.077 ± 0.518
CL/F, L/h	28.09 (22)	25.48 (40)	20.53 (33)	24.32 (34)
V_z/F, L	104.93 (35)	71.00 (40)	51.44 (34)	70.51 (47)

%CV = percent coefficient of variance; AUC_{tau} = area under plasma concentration-time curve over dosing interval; BID = twice a day; CL/F = apparent oral clearance; C_{max} = maximum concentration; C_{min} = minimum concentration; C_{trough} = trough plasma concentration; N = number of subjects; PK = pharmacokinetic; SD = standard deviation; $t_{½}$ = apparent terminal half-life; T_{max} = time of maximum observed plasma concentration; V_z/F = apparent volume of distribution at terminal phase.

[a] Geometric mean (geometric %CV) for all except: median (range) for dose and T_{max}; arithmetic mean ± SD for $t_{½}$.

[b] N = 7 for $t_{½}$ and V_z/F due to lack of a well-characterized terminal phase in 1 subject.

[c] N = 8 for $t_{½}$, V_z/F, CL/F, C_{min}, and AUC_{tau} due to incomplete PK sampling for 1 subject.

[d] N = 24 for $t_{½}$ and V_z/F and N = 25 for C_{min} and AUC_{tau} due to the exceptions noted above.

Population PK model

The popPK Report PMAR-EQDD-A392l-Other-941 was performed in order to: 1) describe the PK of tofacitinib in paediatric patients from 2 to less than 18 years of age with JIA; 2) identify potential covariates in the study population(s) which account for the variability in tofacitinib exposure; 3) assess the formulation effect and relative bioavailability of tofacitinib oral solution versus tablet formulation administered during clinical development; 4) evaluate PK similarity between the two formulations in terms of AUC and Cmax using a model-based simulation approach and the stringent 80-125% bioequivalence; 5) provide individual-level exposure output (concentration profile over time, AUC, Cmax, Cave, etc.) for subsequent analyses. The popPK includes data pooled from studies A3921103, A3921104 and A3921145. A one compartment model parameterized in terms of CL/F and V/F with first-order ka and

absorption lag time was chosen. The final estimates for CL/F, V/F and Ka were 26.1 L/hr, 89.2 L, and 2.78 hr-1, respectively. Absorption was described with a lag time estimated at 0.186 hr. The solution has a 1.64 fold faster absorption rate compared to the reference formulation of the tablet.

The available data indicated that there were no clinically relevant differences in tofacitinib exposure (AUC), based on age, race, gender, patient type or baseline disease severity. The between-subject variability (% coefficient of variation) in (AUC) was estimated to be approximately 24%.

To assess the overall impact of formulation effect, ratios (with 90% CI) for AUC and Cmax relative to a reference patient (body weight 46.3 kg and taking tablet) were calculated using the estimated formulation effect from each bootstrap dataset. Formulation was found to be statistically significant on Ka, which suggests that oral solution is expected to result in 113.9% (95% CI: 108.0%, 120.7%) higher Cmax than tablet for the typical patient.

Formulation is not expected to affect AUC. Hence, the point estimates of the AUC and Cmax ratios and the associated 90% CI indicated no relevant differences in tofacitinib exposure over the formulations across all weights in the study.

The dosing regimen selected for Phase 3 Study A3921104 was based on the popPK model including data from Study A3921103. From the predicted AUC and Cmax values it was evident that over the range of weights examined, higher doses were needed to reach an efficacy target Cavg,ss of 21 ng/ml, the 5 mg BID equivalent in adult RA patients. However, concentrations were within the range of 3 mg BID dose in adult RA patients. The final dosing scheme proposed for Study A3921104 is described in Table 6.

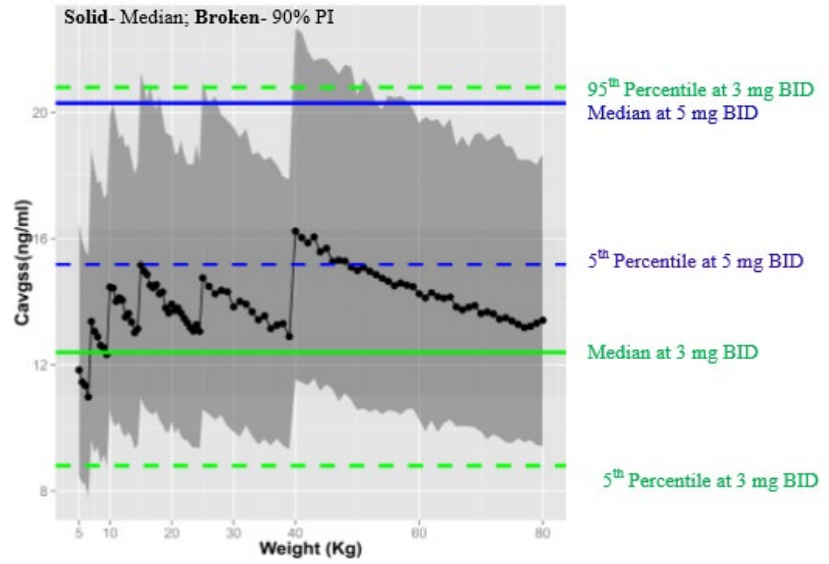
Table 6 Study Treatment Dosing and Administration for Pivotal Phase 3 Study A3921104

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

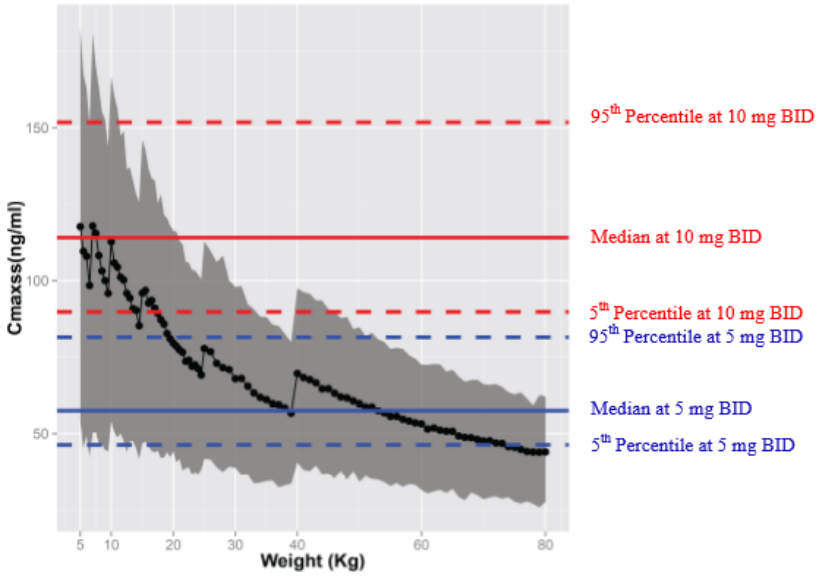
Abbreviations: BID = twice daily; kg=kilograms; mg=milligrams; mL=milliliters.
Subjects with body weight ≥40 kg who are unable to swallow tablets will have the option of taking oral solution (1 mg/mL).

Simulations were performed in order to predict the Cavg,ss and Cmax,ss reached with the dosing regimen of Study A3921104.
The predicted steady state Cavg and Cmax (median and 90% PI) values are depicted in the figures below, overlaid with median and 90% CI of corresponding exposure metrics in RA subjects following 3, 5 and 10mg BID doses as relevant.

Figure 1 Predicted average steady-state concentrations of tofacitinib in paediatric subjects (JIA) with weights ranging from 5-80kg (Red and green solid and broken lines indicate Tofacitinib $C_{avg,SS}$ in adult RA subjects)



ePharm Artifact ID: 10919369



ePharm Artifact ID: 10919369

2.4.3. Pharmacodynamics

No pharmacodynamic evaluations was performed in the context of this application.

An **Exposure-Response Relationships** for efficacy was evaluated in the context of POPULATION MODELING ANALYSIS REPORT PMAR-EQDD-A392I-Other-942. The objectives of this population exposure-response (E-R) analysis were: 1) To develop a longitudinal model characterizing the exposure-response relationship between CP-690,550 and change in JIA American College of Rheumatology (ACR) scores in pediatric patients from 2 to less than 18 years of age with juvenile idiopathic arthritis (JIA) in the open

label phase; 2) To identify potential covariates in the study population(s) which account for the variability in JIA ACR responder rates; 3) To characterize the onset of tofacitinib efficacy.
This analysis included data from the pivotal study A3921104. Exponential model was used to describe the time course and onset of drug effect. Treatment factor and Cave were tested for drug effect. However, linear or non-linear models with exposure metrics (Cave) did not provide better fitting than the simple treatment effect model. Therefore, treatment effect model was used to characterize the drug effect and for further model development. Based on the covariate analysis, number of prior failed DMARDs (NFAIL) was identified as the only significant covariate with NFAIL = 0 and 1 grouped together to be the reference population. Patients who had experienced 2 or more prior DMARDs treatment failures showed significantly lower rates of JIA ACR response. The half-life for drug effect onset was estimated to be 4.2 weeks. The rates of response for ACR scores based on final model parameter estimates can be contextualized through simulation using the final model. The onset of tofacitinib treatment effect was rapid. The simulations using the final model showed that at Week 2, the probabilities of JIA ACR30, 50 and 70 responses were approximately 47%, 26% and 8%, respectively, which were 60%, 36% and 16% of Week 18 efficacy, respectively.

Based on population PK analysis (PMAR-EQDD-A392l-Other-941) a *post hoc* estimated individual PK parameters suggest that consistent Cavg (median 14.8 ng/mL, range 8.9-30.0 ng/mL) were achieved among all JIA subjects and the Cavg in the different weight ranges (10 <15 kg, 15 <25 kg, 25 <40 kg and ≥40 kg) are similar. Therefore it is not feasible to determine an exposure/ response relationship and an exponential model was used to describe the time course and onset of drug effect in terms of ACR30, 50 and 70. Based on the model parameter estimates the half-life for drug effect onset was estimated to be 4.2 weeks. Based on model simulation the probability to reach ACR30, 50 and 70 seems to increase with treatment duration. The number of prior failed DMARDs (NFAIL) was a significant covariate impacting the efficacy outcome. The model simulation showed that the increase of NFAIL results in decreased probability of achieving ACR30, 50 and 70 and this effect is reasonably due to the disease severity.

2.4.4. Discussion on clinical pharmacology

Tofacitinib plasma concentrations were measured through HPLC-MS/MS method developed and validated at Wuxi AppTec (Shangai, China – A3929023) and then transferred at PPD (Richmond and Middleton).

Tofacitinib determinations were performed on samples collected in Study A3921103 (151 samples analysed by Wuxi), in Phase 3 pivotal Study A3921104 (815 samples analysed by Wuxi and 320 analysed by PPD Middleton), in Study A3921145 LTE (124 samples analysed by Wuxi and 363 analysed by PPD Middleton) and the BE Study A3921354 (254 samples analysed by PPD Middleton). As confirmed by the MAH, the samples of studies A3921104 and A3921145 LTE were analysed by both laboratories.

Two cross-validations were submitted:

- Addendum 6 of method validation A3929023 which was a cross validation between Wuxi, BASi (not involved in tofactinib determination for the studies of interest) and PPD Richmond.
- The method validation A3929034 aimed to perform a partial validation with truncated quantitative range (0.100 to 100 ng/ml) and cross validation between Wuxi and PPD including cross validation QC samples and incurred samples (from study A3921104). The MAH confirmed that the PPD laboratory involved in the analysis of QCs was that in Richmond.

A method transfer was performed from PPD in Richmond, VA to PPD in Middleton, WI and an assay performance with respect to precision, accuracy, and specificity was conducted.

No cross-validation was performed between PPD Middleton and Wuxi. However, the MAH considered that since the methods used at Richmond are the same as those used at Middleton, the cross validation between Wuxi and PPD Richmond supports the comparability of data analysis also between Wuxi and PPD Middleton.

This is not fully in line with EMA guideline on Bioanalytical reports that states: *"Where data are obtained from different methods within and across studies or when data are obtained within a study from different laboratories, applying the same method, comparison of those data is needed and a cross validation of the applied analytical methods should be carried out".* However, since the method transfer to PPD Middleton showed that selectivity, carryover, linearity, sensitivity, accuracy, precision, recovery, dilution, and stability were met, the method is considered valid for the extraction and analysis of human lithium heparin plasma. The issue was therefore not further pursued by the CHMP.

Within this application, the oral solution formulation was added to treat paediatric patients in a weight-based dosing. A BE study A3921354 was performed to compare the PK of tofacitinib IR tablet and oral solution.

Population PK model

The model is well structured and validated. As expected, the formulation showed an effect on Ka due to a faster absorption of the oral solution. Higher doses and tablet formulation are associated to higher CL and V/f and this is expected considering that in both cases they refer to children in the higher age and weight group. The MAH provided the requested information about the value of η-shrinkage through model development. The value of η-shrinkage is below 20% for both the base model and the final model.

The MAH was requested to show that the model (PopPK Report PMAR-EQDD-A392l-Other-941) can truly capture the concentration-time profile for all children included in the phase 3 trials and to submit pcVPCs of concentration over time stratified on weight. The requested pcVPCs of concentration over time stratified over the 4 weight groups was submitted. pcVPCs demonstrated that the population PK model sufficiently characterized tofacitinib exposure over time across the 4 studied weight range as the majority of observations fall within the predicted range of exposure.

In the SmpC section 5.2 it is reported that the between-subject variability (% coefficient of variation) in (AUC) was estimated to be approximately 24%. The MAH clarified that the information reported in SmPC regarding the % coefficient of variation around AUC value is related to the between-subject variability (%CV) in CL/F.

Bioequivalence

The design (cross over study) of bioequivalence study A3921354 and the wash out period are adequate, considering the half-life of tofacitinib. Although the BE Guideline states that the study should be conducted at the highest strength, tofacitinib is a BCS class III, therefore the use of a lower strength of 5 mg is acceptable also in light of a linearity in the considered range (5 mg and 10 mg).

Following administration of single oral doses of tofacitinib, median time to reach maximum plasma concentration (Tmax) was comparable between oral solution and tablet (0.5 and 1.0 hour, respectively). Mean elimination half-life (t½) values were nearly identical (approximately 3 hours) for both formulations.

Although the 90% CIs for the ratios (Test/Reference) of adjusted geometric means for AUCinf (GM ratio 104.38, CI 99.99-108.97), AUClast (GM ratio 104.48, CI 100.16-108.99) and Cmax (GM ratio 110.00, CI 99.90-121.13) were entirely contained within the acceptance region for bioequivalence (80%, 125%), it is noted that in study A3921354 there were 12 subjects randomised, but only 11 completed both study periods. This is not in compliance with the CHMP guideline on the investigation of bioequivalence, which states that the number of evaluable subjects in a bioequivalence study should not be less than 12. In addition, the subject with data from only one treatment period was not excluded from the statistical analysis, and random, rather than fixed effects were used for the subject term in the statistical model. The MAH was requested to discuss about this deviation from guideline to clarify the reason for not replacing the subject who did not complete both study periods. The MAH clarified that the subject was not replaced as it was confirmed that 11 subjects provided adequate power for demonstrating AUC equivalence (primary study objective), and the study protocol did not mandate replacement of study subjects. Given that the

concerned subject completed protocol requirements for at least one study treatment, this subject was deemed an evaluable subject for inclusion in the PK and safety analyses. All 12 evaluable subjects were included in the ANOVA mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect which is the standard analysis approach for crossover studies, and was pre specified in the analysis plan for this study. Therefore, the CHMP agreed with the MAH's conclusion that the exclusion of data from one subjects in Study A3921354 did not cause a significant deviation in the comparison of tofacitinib exposure profile between the tablets and Oral Solution.

Target population and dose selection

Phase I PK study A3921103 was initially conducted in 26 JIA subjects to inform the dosing regimen in patients with JIA aged 2 through less than 18 years for the subsequent pivotal efficacy study (A3921104) as well as the long-term extension (LTE) study (A3921145). The JIA clinical program evaluated the efficacy and safety of tofacitinib 5 mg BID for ≥40 kg subjects or weight-based lower doses for <40kg subjects to achieve comparable Cavg as those dosed at 5 mg BID. Study A3921103 consisted of 3 cohorts based on the age of the subjects:1) Cohort 1: 12 to <18 years; 2) Cohort 2: 6 to <12 years; 3) Cohort 3: 2 to <6 years.

The doses in paediatric patients were initially calculated using the allometric scaling (0.75) on CL/F in order to obtain exposure similar to that in adults RA patients administered with tofacitinib 5mg BID dosing (assuming 70kg BWT for an adults). The considered PK parameter was the Cavg,ss after 5 mg BID dosing in adult RA (21 ng/ml). An interim analysis of this study indicated higher CL/F values (28.09 L/h and 25.48 L/h for Cohorts 1 and 2, respectively) in JIA subjects compared to adult RA subjects (18.4 L/h at 5 mg BID dose), resulting in steady state AUCtau values in JIA subjects in Cohort 1 and Cohort 2 that are 37.9% and 52.9% lower compared to adult RA subjects. The Cmax values in Cohorts 1 and 2 in this study are also 19% and 28% lower compared to adult RA subjects (Cmax: 58 ng/mL). The allometric relationships were re-estimated and the mean estimate of the power scalar for the CL-BWT relationship was 0.51, lower than that assumed for the initial dose selection.

Doses for the 2 to <6-year age group were increased from that initially planned based on this analysis to achieve exposures comparable to that from a 5-mg-BID dose in adult RA subjects (Table 4).

The dosing regimen selected for Phase 3 Study A3921104 was based on the popPK model including data from Study A3921103. The aim was to select doses to reach the exposure observed in adults administered with 5 mg BID dose. Simulations were performed using the parameters from the final popPK model to predict AUC and Cmax at the doses used in the A3921103 study. From the predicted AUC and Cmax values it was evident that over the range of weights examined, higher doses were needed to reach an efficacy target Cavg,ss of 21 ng/ml, the 5 mg BID equivalent in adult RA patients. However, concentrations were within the range of 3 mg BID dose in adult RA patients.

Simulations were performed in order to predict the Cavg,ss and Cmax,ss reached with the dosing regimen of Study A3921104. The predicted steady state Cavg and Cmax (median and 90% PI) values overlaid with median and 90% CI of corresponding exposure metrics in RA subjects following 3, 5 and 10mg BID doses as relevant. As illustrated in the submitted simulation, in the entire considered weight range, the predicted Cavg,ss is below the median (21 ng/ml), as well as the 5th percentile, of the Cavg,ss observed with 5 mg BID dose in adult RA patient. The MAH stated that the predicted Cavg is similar to that of 3-5 mg BID in adult RA subjects across the expected weight range. However, the median value of Cavg,ss that results in efficacy outcomes is 21 ng/ml (5 mg BID dose) while the 3 mg BID dose did not show efficacy in previously submitted study in the already approved indications.

In the plot (Figure 1) of Cavg,ss versus continuous weight, the subjects weighing 40 kg, that are given the same dose as adults, have an exposure that is lower compared to adults. The MAH was requested to discuss about this unexpected finding. The MAH explained that the results of population PK analysis indicated that the clearance of tofacitinib in a JIA subject with a typical body weight of 46 kg (26.1 L/h)

was approximately 42% higher than in RA subjects (18.4 L/h) and consequently the exposure reached in subjects with JIA (although weighing over that 40 kg) is lower than exposure reached in subjects with RA taking the same dose of 5 mg. Moreover, data from **Schmitt C et al, 2011** showed that the higher clearance in subjects with JIA compared to subjects with RA may be related to the higher inflammatory burden in the adult RA population compared to the JIA population, resulting in greater downregulation of CYP enzymes in RA patients due to the inflammatory stimuli. Moreover, the MAH stated that the predicted Cmax,ss did not exceed those reached with 10 mg BID in most subjects, a dose linked with a worse safety profile. However, as illustrated in the mentioned simulations, subject with a weight range of 5-20 kg showed predicted Cmax,ss above the 95th percentile of 5 mg BID dose and some reached the median Cmax,ss at 10 mg BID dose.

The MAH stated that the predicted Cmax,ss did not exceed those reached with 10 mg BID in most subjects, a dose linked with a worse safety profile. However, as illustrated in the mentioned simulations, subject with a weight range of 5-20 kg showed predicted Cmax,ss above the 95th percentile of 5 mg BID dose and some reached the median Cmax,ss at 10 mg BID dose.

The paediatric data available so far do not give rise to new safety concerns. However, as the observed data is rather limited, especially regarding the longer time perspective, the assessment relies also on extrapolation from the approved adult indications. In this regard, it is critical to demonstrate that the chosen paediatric posology is not likely to result in a higher exposure than what has been seen in the adults. This is underlined by the fact that it is known that important risks associated with tofacitinib are dose dependant.

With regard to long term safety, the MAH was asked to perform a comparison of Cmin, Cmax and Cavg between observed exposure in adults with RA and the simulated exposure children (both studied posology and the new proposed posology). The MAH performed this comparison in terms of exposure (Cmax, Cave and Cmin) between the posology used in study A3921104 and the proposed posology in SmPC are shown to be overlapping and contained within RA exposure in adults.

A more comprehensive popPK was developed including data from studies A3921103, A3921104 and A3921145. Further simulations were performed in order to predict the exposure measures at steady-state using dosing regimen of study A3921104. The predicted median Cavg of 14.8 ng/mL (range 8.9-30.0 ng/mL) was achieved among all JIA subjects. The dose recommendation proposed in the extension of indication was simplified to 3-dose steps instead of the 4-dose step in Study A3921104 with the objective of having consistency between tofacitinib Cavg for <40 kg JIA subjects, and ≥ 40kg JIA subjects taking 5 mg BID dose. The MAH was requested to discuss the choice for dose selection. The MAH submitted the Exposure Ratios of 3-dose-step versus 4-dose-step that are close to 1 for all body weight groups and for each PK parameters concerning exposure (Cmin, Cave, Cmax). The choice to select a more simplified dosing-scheme with 3 dose steps for section 4.2 of the SmPC is therefore supported by the CHMP.

The MAH was requested to clarify why the initial target exposure in paediatrics referred to those obtained with administration of 5 mg BID in adults while, thereafter, a reference to the exposure reached with 3 mg BID dose in adults has been considered. The MAH clarified that the dosing regimen was first established to reach a similar exposure to adults with RA and assuming a similar oral clearance (allometrically scaled using the standard value of 0.75). The POPPK analysis indicated that the oral clearance of tofacitinib in a JIA subject with a typical body weight of 46 kg (26.1 L/h) was approximately 42% higher than in RA subjects (18.4 L/h). Therefore, the MAH concluded that the Cavg after 5 mg BID dose in a JIA subject ≥40 kg body weight is comparable to the Cavg after 3 to 5 mg BID dose in adult RA subjects while doses for JIA subjects <40 Kg were adjusted by body weight, to achieve Cavg similar to that at 5 mg BID in JIA subjects ≥40 kg. On this justification, the MAH based the rationale to set the exposure reached with 3 mg BID dose in adults as a reference for patients with JIA even though the MAH did not explain the choice to set the exposure reached with 3 mg BID in RA patients to drive the dose recommendation in the proposed indication in paediatrics, considering that the effective dose in RA patients is 5 mg dose BID. In addition, population PK

analysis in JIA subjects across clinical studies (EQDD-A392l- Other-941) confirmed that 40 kg is an appropriate cut-off for the 5 mg BID dose in this population and the selected dosing regimen resulted in consistent exposure between recommended weight- based dose groups for JIA subjects. The dosing in JIA subjects is therefore sufficiently appropriately justified.

Drug-drug interaction (DDI)

DDI studies have only been performed in adults and Conventional drug-interaction studies are not expected to be performed in children. The MAH was requested to discuss extrapolation of the adult DDI results to the paediatric target age group or possible differences in CYP contribution. The MAH considered that the dose adjustment recommendation due to DDI from adult RA patients can be extrapolated to JIA patients down to 2 years of age. Indeed, the MAH clarified that the maturation of both CYP3A4 and CYP2C19 enzymes leads to enzymatic activities reaching the adult values before 2 years of age (Salem et al, 2015 and Upreti et al, 2016). The MAH concluded that the contribution of CYP3A4 and CYP2C19 to tofacitinib metabolism in children down to 2 years of age is expected to be comparable to those in adults. The MAH's argumentation is endorsed by the CHMP.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics in paediatric patients with JIA has been sufficiently characterised.

The following posology in JIA patients 2 years of age and older is endorsed by the CHMP:

Body weight (kg)	Dose regimen
10 - < 20	3.2 mg (3.2 mL of oral solution) twice daily
20 - < 40	4 mg (4 mL of oral solution) twice daily
≥ 40	5 mg (5 mL of oral solution or 5 mg film-coated tablet) twice daily

Patients ≥ 40 kg treated with tofacitinib 5 mL oral solution twice daily may be switched to tofacitinib 5 mg film-coated tablets twice daily. Patients < 40 kg cannot be switched from tofacitinib oral solution.

2.5. Clinical efficacy

2.5.1. Dose response study

No dose response study was performed in this application.

2.5.2. Main studies

To support the claimed indication, the MAH submitted the following studies: study A3921104, a completed Phase 3 pivotal and an interim analysis of the ongoing OL long-term extension study A3921145.

Table 7. Overview of pJIA Clinical Efficacy Development Program

Study Number/ Study Population/ Study Phase/ Geographic Region	Study Description/ Background Therapies/ Duration	Objective	Primary Endpoint	Treatment Groups	N
A3921104 Subjects with pJIA Phase 3 Argentina, Australia, Belgium, Brazil, Canada, Israel, Mexico, Spain, Poland, Russia, Turkey, Great Britain, Ukraine, United States	Open-label run-in phase followed by randomized withdrawal, double-blind placebo-controlled phase which evaluated efficacy in subjects with JIA ages 2 to <18 years. Allowed DMARDs (methotrexate only), topical treatments for psoriasis including steroids, oral corticosteroids, injectable steroids. Participant Duration: *44 weeks*	To compare the efficacy and safety of tofacitinib to placebo in subjects with JIA.	Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) by Week 44/EOS (Week 26 of the double-blind phase).	All (enrolled in OL and treated) Randomized in DB phase Tofacitinib Placebo	225 173 88 85
A3921145 Subjects with JIA who have previously participated in Study A3921103, A3921104 or A3921165 Long-term Extension Phase 2/3 All countries from qualifying trials	Ongoing Open-label long-term follow-up study in JIA subjects ages 2 to <18 years who have previously participated in tofacitinib studies for treatment of JIA. Continue with background therapy from qualifying study. Adjustments are allowed due to inadequate efficacy or tapered or discontinued due to disease improvement. Participant Duration: Varies depending upon when the subject entered the trial.	To assess long-term efficacy and safety of tofacitinib for treatment of subjects with JIA.	Standard laboratory safety data and adverse event (AE) reports. Body weight, height and Tanner Stages were collected to assess growth and physical development.	All (enrolled and treated) Enrolled and treated from A3921103 from A3921104 from A3921165	225 26 197 2*

Table 7. Overview of pJIA Clinical Efficacy Development Program

Study Number/ Study Population/ Study Phase/ Geographic Region	Study Description/ Background Therapies/ Duration	Objective	Primary Endpoint	Treatment Groups	N

* Data from these subjects is not included in the interim analysis CSR.
Abbreviations: AE=Adverse events; DB=Double-blind; EOS=end of study; N=number of subjects; OL=open-label; PRCSG=Pediatric Rheumatology Collaborative Study Group; PRINTO=Pediatric Rheumatology International Trials Organisation.
Note: Studies A3921103 and A3921165 are not included in this table as they are not part efficacy analysis

Study A3921104: Randomized withdrawal, double-blind, placebo-controlled study of 5 mg tofacitinib BID IR tablets or weight-equivalent dose of an oral solution in subjects from 2 to <18 years of age with JIA.

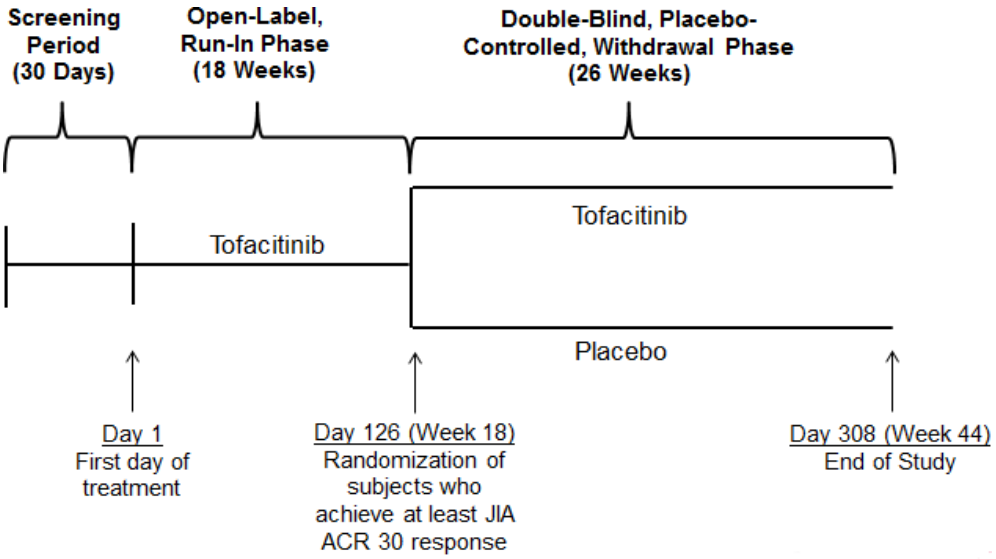
Methods

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

Subjects who were eligible for the 26-week double-blind phase were randomized (1:1 ratio) to either active tofacitinib or placebo.

For subjects with polyarticular JIA (PJIA) (ie, E Oligo, polyarthritis RF+, polyarthritis RF-, and sJIA with active arthritis but without active systemic features), randomization was stratified by JIA category and baseline CRP (normal, above normal). Randomization for subjects with PsA and ERA was stratified by JIA category.

Figure 2 Study design



Study Participants

Key inclusion criteria:

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

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

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

Treatment with stable doses of a NSAID and/or a stable dose of an oral glucocorticoid, and/or a stable dose of MTX was permitted.

For subjects who were receiving an oral glucocorticoid: were administered at a maximum dose of 0.2 mg of prednisone equivalent per kilogram per day or 10 mg per day for ≥2 weeks before baseline, whichever was lower.

For subjects who were receiving MTX treatment: at doses not to exceed 25 mg/week or 20 mg/m2/week (whichever was lower); participants must have taken MTX for ≥3 months and been at a stable dose for at least 6 weeks before baseline.

For subjects with PsA, the following topical treatments for psoriasis were allowed: non-medicated emollients for use over the whole body; topical steroids including hydrocortisone and hydrocortisone acetate ≤1% for the palms, soles, face, and intertriginous areas only; tar, salicylic acid preparations, and shampoos free of corticosteroids were permitted only for the scalp.

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

Key exclusion criteria

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

dose of study drug. Also prohibited was ultraviolet B (narrowband or broadband) phototherapy that must have been discontinued at least 2 weeks prior to first dose of study drug. Psoralens + ultraviolet A phototherapy must have been discontinued at least 4 weeks prior to first dose of study drug.

Treatments

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

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

Table 8 Study Treatment Dosing and Administration for Pivotal Phase 3 Study A3921104

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

Abbreviations: BID = twice daily; kg=kilograms; mg=milligrams; mL=milliliters.
Subjects with body weight ≥40 kg who are unable to swallow tablets will have the option of taking oral solution (1 mg/mL).

Objectives

The study objectives were efficacy, safety, tolerability and PK.

Outcomes/endpoints

Table 9 Study objectives and endpoints

Type	Objective	Endpoint[a]
Primary (Type I Error Controlled)		
Efficacy	To compare the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA at Week 44/End of Study (Week 26 of the double-blind phase) as measured by the percentage of subjects with disease flare (according to PRCSG/PRINTO Disease Flare criteria) after Week 18 of the open-label run-in phase.	Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) by Week 44/End of Study (Week 26 of the double-blind phase)
Key Secondary (Type I Error Controlled)		

Efficacy	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by achievement of JIA American College of Rheumatology (ACR) 30, 50, 70 response at various time points in the double-blind phase	Achieving JIA ACR 30, 50, 70 response at Week 44/End of Study (Week 26 of the double-blind phase); open-label run-in baseline will be used to determine ACR response
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in CHAQ responses at various time points in the double-blind phase	Change from double-blind baseline in CHAQ disability index at Week 44/End of Study (Week 26 of the double-blind phase)
Secondary		
Efficacy	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by the percentage of the subjects with disease flare (according to PRCSG/PRINTO Disease Flare criteria) at various time points in the double-blind phase	Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by time to disease flare in the double-blind phase	Time to disease flare in the double-blind phase
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by achievement of JIA ACR 30, 50, 70, 90, 100 responses at various time points in the double-blind phase	Achieving JIA ACR 30, 50, 70, 90, 100 response at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase; open-label run-in baseline will be used to determine ACR response
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in Juvenile Arthritis Disease Activity (JADAS)-27 c-reactive protein (CRP) and JADAS-27 ESR, and percentage of subjects achieving JADAS minimum disease activity and inactive disease at various time points in the double-blind phase	Change from double-blind baseline in JADAS-27 CRP, JADAS-27 ESR, and achieving JADAS minimum disease activity and inactive disease at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase
	To evaluate the efficacy of tofacitinib versus placebo for treatment of signs and symptoms of JIA as measured by the JIA ACR inactive disease and clinical remission rate at various time points in the double-blind phase	Achieving JIA ACR inactive disease at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase, and achieving clinical remission at Week 44 (Week 26 of the double-blind phase); achieving at least 1 JIA ACR inactive disease during double-blind phase
	To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by changes from baseline in each JIA ACR core set variable at various time points in the double-blind phase	• Change from double-blind baseline in each JIA ACR core set variable at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase • Change from open-label run-in baseline in each JIA ACR core set variable at each scheduled visit up to Week 44 (Week 26 of the double-blind phase) in the double-blind phase

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

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

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

Sample size

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

Randomisation

All eligible subjects enrolled in the study initially received open-label tofacitinib for 18 weeks (run-in phase). At the end of the 18-week run-in phase, subjects who achieved at least a JIA ACR 30 response were randomized to the 26-week double-blind, placebo-controlled phase. Subjects who entered the 26-week double-blind phase were randomized (1:1 ratio) to either active tofacitinib tablets/oral solution or matching placebo. For subjects with PJIA, randomization was stratified by JIA category and baseline CRP. For subjects with PsA and ERA, randomization was stratified by JIA category.

Blinding (masking)

During the double-blind phase of the study, the Sponsor, subject, and investigator site staff were blinded to the subject's treatment assignment. At the initiation of the study, the study site was instructed on the electronic process for breaking the blind using the interactive response technology (IRT) system. Blinding was only to be broken in emergency situations for reasons of subject safety.

Statistical methods

The primary hypothesis is that among subjects who achieve ACR30 response at Week 18 in the OL phase, those who remain on tofacitinib will have a lower rate of disease flare up to Week 44/EoS compared to those on placebo.

Statistical decision rules

Tofacitinib will be considered superior to placebo with respect to occurrence of disease flare by Week 44/End of Study (EoS) (Week 26 of the double-blind phase) for polyarticular JIA subjects if the test for difference in the occurrence rate results in a p-value (two-sided) less than 0.05.

In order to preserve type-I error, the primary endpoint and the key secondary endpoints were assessed sequentially using gate keeping or step-down approach in the order showing below. When an endpoint fails to declare statistical significance, this endpoint and the remaining endpoints lower in the hierarchy will be considered non-significant. A 2-sided p-value ≤0.05 was considered statistically significant.

Analyses other than primary and key secondary analyses were not controlled for type-I error, and such reported p-values are all nominal along with 95% confidence intervals.

The sequence of primary and key secondary endpoints was:

1) Disease flare by Week 44/End of Study (EOS);

2) JIA ACR 50 at Week 44/EOS;

3) JIA ACR 30 at Week 44/EOS; and

4) JIA ACR 70 at Week 44/EOS;

5) Change from baseline in CHAQ Disability Index at Week 44/EOS.

Analyses other than primary and key secondary analyses were not controlled for type-I error.

It has been suggested that achievement of a 30% improvement in disease activity (ie, JIA ACR 30) may not represent a clinically meaningful degree of improvement therefore JIA ACR 50 was chosen to be evaluated in the sequence before JIA ACR 30 and 70 as it represents a more significant reduction in disease activity.

Two tipping point analyses based on two imputation models (Weibull regression and binomial distribution) were planned to be performed to assess impact of dropouts - patients who discontinued from study after randomization prior to the efficacy cutoff date (Week 26 of the double-blind phase) who do not have a primary event (flare) before dropout - on results of primary analysis.

Analysis sets

pJIA: The primary outcome population consists of subjects with the following pJIA subtypes

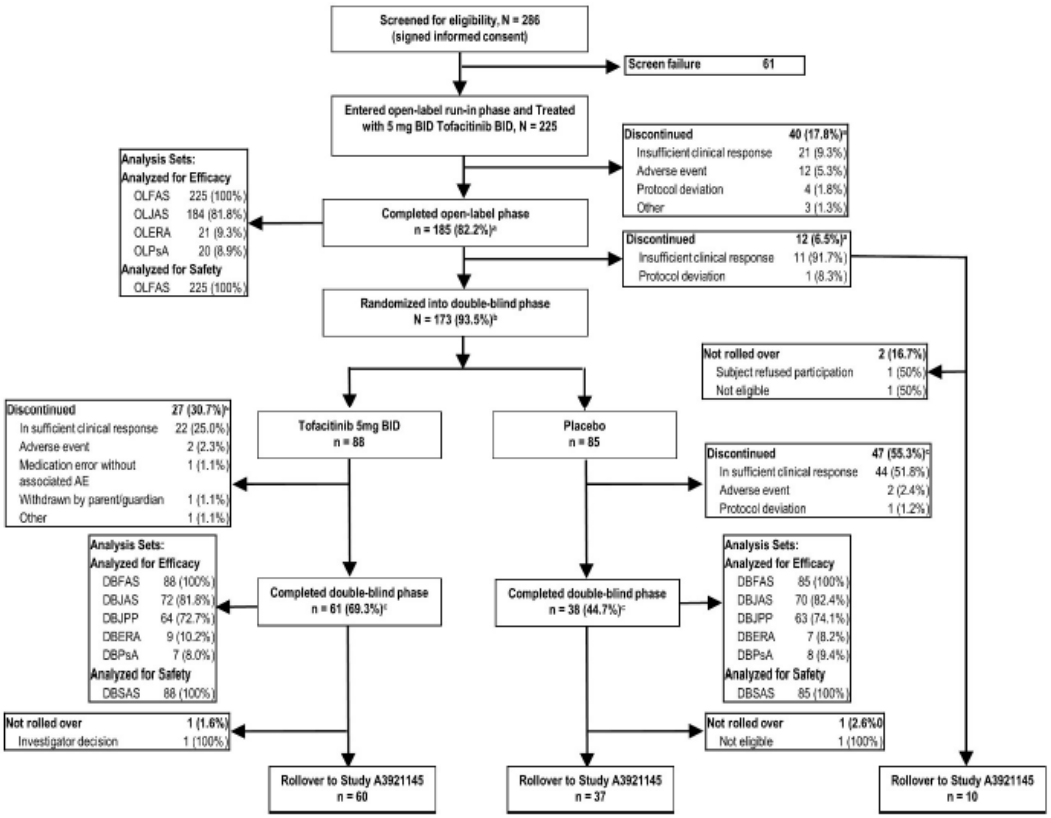
> polyarthritis rheumatoid factor (RF)+, polyarthritis RF-, extended oligoarthritis (E Oligo), and systemic JIA (sJIA) without active systemic features;

JIA: The pooled analysis population when all the subtypes in Study A3921104 are included in an analysis (including pJIA, ERA and PsA) or when the additional subjects from Study A3921145 are included.

Results

Participant flow

Figure 3 Disposition events summary



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

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

Recruitment

Study Initiation Date: First Subject First Visit (FSFV): 10 June 2016

Study Completion Date: Last Subject Last Visit (LSLV): 16 May 2019

Conduct of the study

There were 6 protocol amendments. None of the protocol amendments were substantial.

Key protocol deviations include: investigational product in particular the subcategory missed doses/compliance less than 80% (7.1% OL; 6.8% and 11.8% in the tofacitinib and PLB arms of the DB phase, respectively); concomitant medications not stable (CS or MTX): 5% in the OL phase, 5.7% and 2.4% in the tofacitinib and PLB arms of the DB phase, respectively. The other category including key

deviations was: laboratory analyses not performed/retested (11.6% in the OL phase and 12.5% and 11.8% in the tofacitinib and PLB arms of the DB phase, respectively) and procedure not done (3.1% in the OL phase and 9% and 4.7% in the tofacitinib and PLB arms of the DB phase, respectively).

Baseline data

Table 10 Demographic Characteristics - DBFAS

	Tofacitinib 5mg BID DB (N=88)			Placebo (N=85)		
	Male (N=22)	Female (N=66)	Total (N=88)	Male (N=21)	Female (N=64)	Total (N=85)
Age (years):						
2 - <6	5 (22.7)	6 (9.1)	11 (12.5)	2 (9.5)	7 (10.9)	9 (10.6)
6 - <12	5 (22.7)	17 (25.8)	22 (25.0)	8 (38.1)	15 (23.4)	23 (27.1)
12 - <18	12 (54.5)	43 (65.2)	55 (62.5)	11 (52.4)	42 (65.6)	53 (62.4)
Mean (SD)	11.0 (5.13)	12.2 (4.04)	11.9 (4.34)	11.3 (3.30)	12.1 (4.29)	11.9 (4.06)
Median (SE)	12.0 (1.09)	13.0 (0.50)	13.0 (0.46)	12.0 (0.72)	13.0 (0.54)	13.0 (0.44)
Q1, Q3	7.0, 15.0	9.0, 15.0	9.0, 15.0	10.0, 14.0	8.5, 16.0	9.0, 15.0
Range (min, max)	2, 17	2, 17	2, 17	4, 16	2, 17	2, 17
Body Weight		<40 kg			36 (40.9)	31 (36.5)
		>=40 kg			52 (59.1)	54 (63.5)
Rheumatoid Factor (IU/mL)		n			59	56
		Mean (SD)			206.3 (1212.58)	60.9 (140.69)
		Median (SE)			15.0 (157.86)	15.0 (18.80)
		Q1, Q3			15.0, 15.0	15.0, 17.0
		Range (min, max)			15, 9335	15, 829
		Positive			14 (15.9)	14 (16.5)
		Negative			45 (51.1)	42 (49.4)
Anti-Cyclin Citrullinated Protein (anti-CCP) Antibodies		Positive			18 (20.5)	12 (14.1)
		Negative			69 (78.4)	69 (81.2)
		Missing			1 (1.1)	4 (4.7)
Antinuclear Antibodies (ANA)		Positive			39 (44.3)	34 (40.0)
		Negative			49 (55.7)	50 (58.8)
		Missing			0	1 (1.2)
Human Leukocyte Antigen B27 (HLA-B27)		Positive			14 (15.9)	11 (12.9)
		Negative			71 (80.7)	71 (83.5)
		Missing			3 (3.4)	3 (3.5)

Table 11 Baseline Disease Characteristics - DBFAS

	Tofacitinib 5mg BID DB (N=88)	Placebo (N=85)
Number of Joints with Active Arthritis[1] (Open-Label Phase)		
n	88	85
Mean (SD)	12.3 (7.07)	11.4 (7.75)
Median (SE)	10.0 (0.75)	9.0 (0.84)
Q1, Q3	7.0, 16.0	6.0, 14.0
Range (min, max)	3, 36	3, 49
Number of Joints with Active Arthritis[1] (Double-Blind Phase)		
n	88	85
Mean (SD)	1.4 (2.27)	1.6 (2.74)
Median (SE)	1.0 (0.24)	1.0 (0.30)
Q1, Q3	0.0, 2.0	0.0, 2.0
Range (min, max)	0, 14	0, 14
Number of Joints with Limitation of Motion (Open-Label Phase)		
n	88	85
Mean (SD)	8.6 (7.67)	6.4 (5.31)
Median (SE)	6.0 (0.82)	5.0 (0.58)
Q1, Q3	3.0, 12.0	3.0, 8.0
Range (min, max)	0, 36	0, 25
Number of Joints with Limitation of Motion (Double-Blind Phase)		
n	88	85
Mean (SD)	1.9 (4.51)	1.4 (2.33)
Median (SE)	0.0 (0.48)	0.0 (0.25)
Q1, Q3	0.0, 2.0	0.0, 2.0
Range (min, max)	0, 33	0, 12
Physician's Global Evaluation of Overall Disease Activity[2] (Open-Label Phase)		
n	88	85
Mean (SD)	6.1 (1.90)	6.0 (1.88)
Median (SE)	6.0 (0.20)	6.0 (0.20)
Q1, Q3	4.5, 7.5	4.5, 7.5
Range (min, max)	2, 9	3, 10
Physician's Global Evaluation of Overall Disease Activity[2] (Double-Blind Phase)		
n	88	85
Mean (SD)	1.6 (1.64)	1.4 (1.46)
Median (SE)	1.0 (0.17)	1.0 (0.16)
Q1, Q3	0.5, 3.0	0.0, 2.5
Range (min, max)	0, 7	0, 6
C-reactive protein (mg/dL)[3] (Open-Label Phase)		
n	88	85
Mean (SD)	1.3 (2.42)	1.0 (1.83)
Median (SE)	0.3 (0.26)	0.2 (0.20)
Q1, Q3	0.1, 1.3	0.1, 0.9

	Tofacitinib 5mg BID DB (N=88)	Placebo (N=85)
Range (min, max)	0, 13	0, 11
C-reactive protein (mg/dL)[3] (Double-Blind Phase)		
n	88	84
Mean (SD)	0.4 (1.09)	0.5 (1.22)
Median (SE)	0.1 (0.12)	0.1 (0.13)
Q1, Q3	0.0, 0.3	0.0, 0.3
Range (min, max)	0, 7	0, 9
Erythrocyte Sedimentation Rate (mm/h)[4] (Open-Label Phase)		
n	88	85
Mean (SD)	24.8 (22.47)	26.4 (26.32)
Median (SE)	19.0 (2.40)	17.0 (2.86)
Q1, Q3	10.0, 31.5	9.0, 35.0
Range (min, max)	1, 120	1, 170
Erythrocyte Sedimentation Rate (mm/h)[4] (Double-Blind Phase)		
n	88	85
Mean (SD)	13.4 (13.42)	13.8 (11.94)
Median (SE)	9.5 (1.43)	9.0 (1.29)
Q1, Q3	5.0, 16.0	6.0, 17.0
Range (min, max)	0, 73	0, 53
CHAQ: Evalution of Overall well-being (Open-Label Phase)		
n	88	85
Mean (SD)	4.7 (2.49)	4.8 (2.57)
Median (SE)	5.0 (0.27)	5.0 (0.28)
Q1, Q3	2.5, 7.0	3.0, 7.0
Range (min, max)	0, 10	0, 10
CHAQ: Evalution of Overall well-being (Double-Blind Phase)		
n	88	85
Mean (SD)	2.0 (1.89)	1.9 (1.91)
Median (SE)	1.5 (0.20)	1.5 (0.21)
Q1, Q3	0.5, 3.0	0.5, 3.0
Range (min, max)	0, 7	0, 8
CHAQ: Disability Index[5] (Open-Label Phase)		
n	88	85
Mean (SD)	0.9 (0.69)	0.9 (0.74)
Median (SE)	0.8 (0.07)	0.9 (0.08)
Q1, Q3	0.4, 1.4	0.3, 1.5
Range (min, max)	0, 3	0, 3
CHAQ: Disability Index[5] (Double-Blind Phase)		
n	88	85
Mean (SD)	0.4 (0.51)	0.4 (0.58)
Median (SE)	0.3 (0.05)	0.3 (0.06)
Q1, Q3	0.0, 0.8	0.0, 0.8
Range (min, max)	0, 3	0, 2

	Tofacitinib 5mg BID DB (N=88)	Placebo (N=85)
CHAQ: Discomfort Index (Double-Blind Phase)		
n	88	85
Mean (SD)	1.9 (1.98)	2.0 (1.91)
Median (SE)	1.5 (0.21)	1.5 (0.21)
Q1, Q3	0.5, 3.0	0.5, 3.5
Range (min, max)	0, 8	0, 8
CHQ-PF50[6]: Physical Summary Score (PhS) (Double-Blind Phase)		
n	87	82
Mean (SD)	45.0 (9.95)	44.3 (10.98)
Median (SE)	48.0 (1.07)	47.6 (1.21)
Q1, Q3	38.9, 52.4	39.4, 52.2
Range (min, max)	8, 57	8, 58
CHQ-PF50[6]: Psychosocial Summary Score (PsS) (Double-Blind Phase)		
n	87	82
Mean (SD)	52.3 (8.60)	51.5 (8.82)
Median (SE)	53.9 (0.92)	52.6 (0.97)
Q1, Q3	46.4, 59.0	46.3, 59.3
Range (min, max)	29, 65	32, 65
JADAS-27 CRP Score[7] (Double-Blind Phase)		
n	88	84
Mean (SD)	5.7 (4.21)	5.5 (4.52)
Median (SE)	4.2 (0.45)	4.7 (0.49)
Q1, Q3	2.2, 8.4	1.7, 8.4
Range (min, max)	1, 17	0, 23
Number of Swollen Joints (Double-Blind Phase)		
n	88	85
Mean (SD)	1.2 (2.25)	1.4 (2.70)
Median (SE)	0.0 (0.24)	0.0 (0.29)
Q1, Q3	0.0, 1.0	0.0, 1.0
Range (min, max)	0, 14	0, 14
Number of Pain/Tenderness Joints (Double-Blind Phase)		
n	88	85
Mean (SD)	2.3 (6.54)	1.8 (3.22)
Median (SE)	0.0 (0.70)	0.0 (0.35)
Q1, Q3	0.0, 2.0	0.0, 3.0
Range (min, max)	0, 56	0, 21
Duration of Morning Stiffness (min) (Double-Blind Phase)		
n	88	85
Mean (SD)	6.3 (15.38)	9.8 (30.46)
Median (SE)	0.0 (1.64)	0.0 (3.30)
Q1, Q3	0.0, 10.0	0.0, 5.0
Range (min, max)	0, 120	0, 240

Open-Label phase baseline is based on Day 1, and Double-Blind phase baseline is based on Week 18.
[1] Active arthritis is defined as any joint with swelling, or in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity.
[2] Physician's Global: Higher Physicians' global evaluation of overall disease activity means more JIA disease activity.
[3] CRP normal is 0 - 0.287 mg/dL.
[4] ESR normal is 0 - 20 mm/h.
[5] Higher CHAQ scores mean more disability.
[6] CHQ-PF50 measures 14 domains, each ranging from 0 to 100, with a higher score indicating better physical function or mental health.
[7] Higher JADAS-27 CRP scores mean more JIA disease activity. The possible range of scores is 0 - 57.

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

Concomitant medications: In the OL phase 171 (76.0%) of subjects used DMARD, corticosteroid, and/or immunosuppressant medications. csDMARDs were used by 149 (66.2%) subjects. MTX and folate were taken by 148 (65.8%) subjects and 145 (64.4%), respectively. Concomitant use of bDMARDs was prohibited during the study. Corticosteroids were used concomitantly by 75 (33.3 %) subjects.
DB phase: A total of 69 (78.4%) and 63 (74.1%) subjects in the tofacitinib and placebo groups, respectively, that used DMARD, corticosteroid, and/or immunosuppressant medications.
csDMARDs (MTX) were used concomitantly by 58 (65.9%) subjects in the tofacitinib group and 58 (68.2%) subjects in the placebo group. Any concomitant DMARD, corticosteroid, and immunosuppressant use was 76 and 74% in the OL and DB phase, respectively. Therefore, a percentage of subjects (24-26%) were treated with Tofacitinib monotherapy.
Corticosteroids were used concomitantly by 35 (39.8%) and 23 (27.1%) subjects in the tofacitinib 5 mg BID and placebo groups, respectively.

Numbers analysed

Numbers per analysis set were the following:

OLFAS: 225; OLJAS: 184; OLERA: 21; OLPSA: 20

DBFAS: 88; DBJAS:72; DBPP:64; BDERA: 9; DBPsA: 7.

Outcomes and estimation

Table 12. Primary and Secondary Efficacy Results from Study A3921104 at Week-44

Primary Endpoint	Treatment Group	N	Occurrence Rate	Difference (%) from Placebo (95% CI)	p-value
Occurrence of disease flare*	XELJANZ 5mg BID	72	29%	-23.7 (-39.4, -8.0)	0.0031
	Placebo	70	53%		
Secondary Endpoints	**Treatment Group**	**N**	**Response Rate**	**Difference (%) from Placebo (95% CI)**	**p-value**
JIA ACR 30*	XELJANZ 5mg BID	72	71%	23.7 (8.0, 39.4)	0.0031
	Placebo	70	47%		
JIA ACR 50*	XELJANZ 5mg BID	72	67%	19.5 (3.6, 35.5)	0.0166
	Placebo	70	47%		
JIA ACR 70*	XELJANZ 5mg BID	72	54%	17.0 (0.9, 33.2)	0.0387
	Placebo	70	37%		
Secondary Endpoints	**Treatment Group**	**N/n**	**LS Mean (SEM)**	**Difference from Placebo (95% CI)**	**p-value**
Change from DB Baseline in CHAQ Disability Index*	XELJANZ 5mg BID	72/49	-0.09 (0.04)	-0.12 (-0.22, -0.01)	0.0292
	Placebo	70/33	0.03 (0.04)		
Change from DB Baseline in JADAS27-CRP Score	XELJANZ 5mg BID	72/49	0.03 (0.91)	-4.36 (-7.02, -1.71)	0.0027
	Placebo	70/32	4.39 (1.00)		

*Endpoints are type-I error-controlled
The Double-Blind (DB) phase is the study period on and after randomization day.

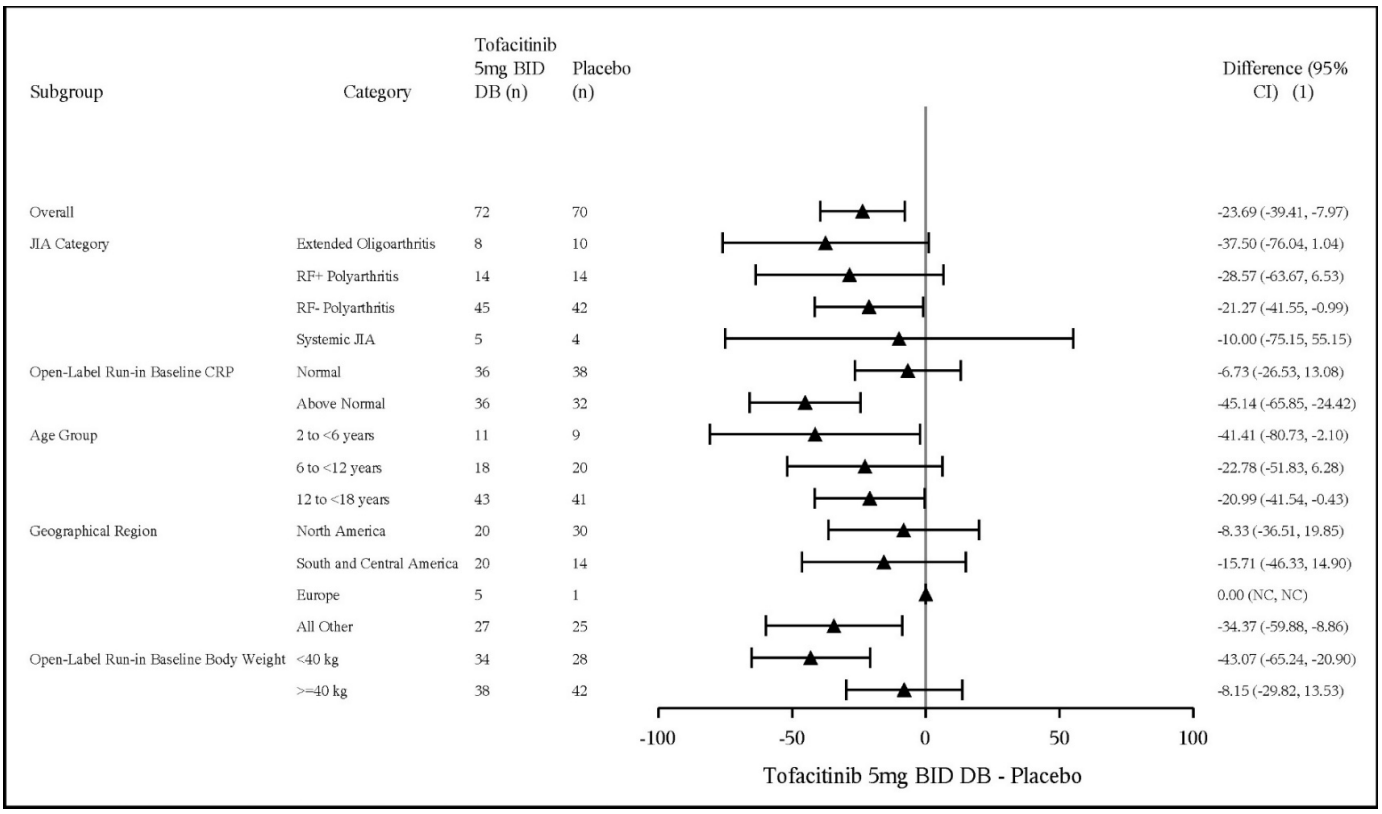
Abbreviations: ACR=American College of Rheumatology; BID=twice daily; CHAQ=Childhood Health Assessment Questionnaire; CI = confidence interval; CRP = C-reactive protein; DB = double-blind; JADAS = Juvenile Arthritis Disease Activity Score; JIA = Juvenile Idiopathic Arthritis; LS = least squares; n=number of subjects with observations at visit; N = number of subjects; SEM = standard error of the mean.

Secondary endpoints results, although only descriptive analysis was conducted, were generally supportive of better activity of tofacitinib as compared to placebo for different endpoints related to disease activity, however it should be highlighted that for more stringent endpoints the numerical difference was lower. Details are reported in the AR.

Ancillary analyses

Subgroup analyses were performed on the primary endpoint (Figure 4).

Figure 4 Forest Plot for Occurrence of Disease Flare at Week 44 of the Study for Overall Population and by Subgroups - DBJAS



(1) Normal approximation.

The DB phase is the study period on and after randomization day.

Europe includes: Poland, Belgium, Great Britain, and Spain; All Other includes: Ukraine, Turkey, Russia, Australia, and Israel.

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

95% CI was not calculated when the flare rates were either 0% in both groups or 100% in both groups.

Sensitivity analyses are consistent with results from the primary analysis.

Sensitivity analysis for the key secondary endpoints were also consistent with the primary analysis.

Summary of main study

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

Table 13 Summary of Efficacy for trial A3921104

Title:	
Study identifier	**A3921104**

Design	randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of tofacitinib for the treatment of **polyarticular** juvenile idiopathic arthritis (pJIA) in children from 2 years of age and older			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks 18 weeks	
Hypothesis	Superiority			
Treatments groups	XELJANZ		5mg BID	
	PLACEBO			
Endpoints and definitions	Primary endpoint		Occurrence of disease flare from double-blind randomization through Week 44	
	Key Secondary		ACR=American College of Rheumatology responses 30/50/70 at week 44 compared to PLB	
	Key Secondary		Change in CHAQ=Childhood Health Assessment Questionnaire at week 44 compared to baseline	
Database lock	15 June 2019			
Results and Analysis				
Analysis description	**Primary Analysis pJIA Double blind phase**			
Descriptive statistics and estimate variability	**Primary Endpoint**	**Treatment Group**	**N**	
	Occurrence of disease	XELJANZ 5mg BID	72	
		Placebo	70	
	Key Secondary Endpoints JIA ACR 30/50/70 JIA ACR 30/50/70 Placebo	XELJANZ 5mg BID Placebo	72/72/72 70/70/70	
	Primary endpoint Occurrence of	**Occurrence Rate**	Xeljanz 29% PLB 53%	
			Difference (%) from Placebo (95% CI), p-value -23.7 (-39.4, -8.0) 0.0031	
	Key Secondary Endpoints JIA ACR 30	**Response Rate**	Xeljanz 71%	
			Difference (%) from Placebo (95% CI), p-value	

	JIA ACR 50	**Response Rate**	Xeljanz 67% PLB 47%
			Difference (%) from Placebo (95% CI), p-value
			19.5 (3.6, 35.5) 0.0166
	JIA ACR 70	**Response Rate**	Xeljanz 54% PLB 37%
			Difference (%) from Placebo (95% CI), p-value
			17.0 (0.9, 33.2) 0.0387
	Change from DB Baseline in CHAQ Disability Index	**LS Mean (SEM)**	
			Difference (%) from
			-0.12 (-0.22, -0.01) 0.0292

Notes	Both the primary and key secondary endpoints were Type-I error protected. Results from secondary are descriptive and not reported in this table.			
Analysis description	Primary Analysis JIA (RF+ polyarthritis, RF- polyarthritis, extended oligoarthritis, and jPsA JIA subtypes) - Double blind phase			
Descriptive statistics and estimate variability	**Primary Endpoint**	**Treatment Group**	**N**	
	Occurrence of disease	XELJANZ 5mg BID	67	
		Placebo	66	
	Key Secondary Endpoints JIA ACR 30/50/70 JIA ACR 30/50/70 Placebo	XELJANZ 5mg BID Placebo	67/67/67 66/66/66	

	Primary endpoint Occurrence of	**Occurrence Rate**	Xeljanz 28% PLB 53%
			Difference (%) from Placebo (95% CI), p-value
			-24.7 (-40.8, -8.5) 0.0028

	Key Secondary Endpoints JIA ACR 30	**Response Rate**	Xeljanz 72% PLB 47%
			Difference (%) from Placebo (95% CI), p-value
			24.7 (8.50, 40.8) 0.0028
	JIA ACR 50	**Response Rate**	Xeljanz 67% PLB 47%
			Difference (%) from Placebo (95% CI), p-value
			20.2 (3.72, 36.7) 0.0163
	JIA ACR 70	**Response Rate**	Xeljanz 55% PLB 38%
			Difference (%) from Placebo (95% CI), p-value
			17.4 (0.65, 34.0) 0.0417
	Change from DB Baseline in CHAQ Disability Index	**LS Mean (SEM)**	
			Difference (%) from
			-0.11 (-0.22, -0.01) 0.0390
Notes	Both the primary and key secondary endpoints were Type-I error protected. Results from secondary are descriptive and not reported in this table.		

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

Results from pivotal Study A3921104 and LTE Study A3921145 were pooled to assess the efficacy of tofacitinib 5 mg BID over the combined exposure to the study drug. Of note subjects participating in 3 qualifying studies (A3921103, A3921104, and A3921165) in the tofacitinib JIA program were enrolled into Study A3921145. However, data from 2 of these studies have been excluded from the integrated efficacy analyses due to the study design of Study A3921103 (a PK study in which tofacitinib was administered for only 1 week), and the study population in Study A3921165, which was conducted in a different population (sJIA) and for which unblinding of the double-blind phase data had not been performed by the cut-off date of the integrated analyses.

The integrated data analysis was conducted in subjects who received at least 1 dose of tofacitinib in Study A3921104 and enrolled or not in the LTE Study A3921145. For subjects enrolled in the LTE, the exposure considered here included, in addition to the pivotal study exposure to tofacitinib, follow up until the cut-off date of Study A3921145. For subjects not rolling over into the extension study, exposure was

limited to the Study A3921104. Subjects coming from A3921103, A3921104 studies and enrolled into Study A3921145 were excluded.

The focus of all the integrated analyses is on subjects randomized in A3921104. Therefore, the double-blind and LTE portions of the data were utilized in the pooled analyses. In addition, subjects randomized to placebo in the qualifying Study A3921104 were included in an analysis aimed at exploring achievement of minimal disease activity upon re-initiation of tofacitinib treatment in the LTE Study A3921145.

Table 14. Overview of Pooled Efficacy Analysis - Studies A3921104 and A3921145

Analysis	Endpoint	Subject Inclusion	Subject Data Inclusion
1	Time to first flare from DB randomization to LTE cut-off	Subjects randomized in the DB phase (including both tofacitinib and placebo subjects) Only include placebo subjects enrolled in LTE	For subjects randomized to tofacitinib, data from randomization until latest available by LTE cut-off. If tofacitinib dose interruption >14 days occurred, included data up to the start of the interruption + 14 days. For subjects randomized to placebo, the data from Day 1 of tofacitinib treatment in LTE until latest available by LTE cut-off. If tofacitinib dose interruption >14 days occurred, included data up to the start of the interruption + 14 days.
2	Number of flares from DB randomization to LTE cut-off	Subjects randomized in the DB phase (including both tofacitinib and placebo subjects) Only include placebo subjects enrolled in LTE	The same as for the analysis of "Time to first flare from DB randomization to LTE cut-off"
3	Incidence rate of flares from DB randomization to LTE cut-off	Subjects randomized in the DB phase (including both tofacitinib and placebo subjects) Only include placebo subjects enrolled in LTE	The same as for the analysis of "Time to first flare from DB randomization to LTE cut-off"
4	Time to JADAS-27 (CRP) MDA from LTE first dose to LTE cut-off	Subjects randomized to placebo in the DB phase and dosed in LTE	Data from LTE first dosing until the last available by LTE cut-off, regardless of the length of dose interruptions
5	Time to ACR inactive disease from LTE first dose to LTE cut-off	Subjects randomized to placebo in the DB phase and dosed in LTE	The same as that for the analysis of "Time to JADAS-27 (CRP) MDA from LTE first dose to LTE cut-off"

Abbreviations: ACR= American College of Rheumatology criteria; CHAQ= Childhood Health Assessment Questionnaire; DB=double-blind; JADAS-27 CRP= Juvenile Arthritis Disease Activity Score 27-joint reduced count with C-reactive protein; LTE=long-term extension; MDA=minimal disease activity.

Methods: No formal hypothesis testing was performed on the pooled trials data. All efficacy analyses were summarized using descriptive statistics.

Disease flares: 138 (81.2%) subjects remained flare free for the entire duration of follow-up. The incidence rate (95% CI) of flares over this follow-up was 20.77 (14.21, 29.32) subjects with flares per 100 subject-years with 24 (14.12%) subjects experiencing a single flare, 7 (4.12%) subjects experiencing 2 flares, and 1 (0.59%) experiencing 3 flares according to PRCSG/PRINTO Disease Flare criteria.

The maximum proportion (standard error [SE]) of subjects with occurrence of disease flare between Month 6 and Month 24 was during the Month 15 visit (4.88% [2.38]) (Figure 2). Limited data (sample size was <20 subjects) are available beyond the Month 24 visit since many subjects in this study were still ongoing and had not yet reached these visits at the time of data cutoff.

ACR response All Subjects with Juvenile Idiopathic Arthritis: The maximum proportion of subjects (SE) with JIA ACR 30/50/70/90/100 responses between Month 1 and Month 24 were during the Month 12 (66.14% [4.20]), Month 15 (62.20 [5.35]), Month 12 (48.82% [4.44]), Month 24 (40.00% [10.95]), and Month 24
(30.00% [10.25]) visits, respectively. Limited data (sample size was <20 subjects) are available beyond the Month 24 visit since many subjects in this study were still ongoing and had not yet reached these visits at the time of data cutoff.

Minimal Disease Activity and Inactive Disease in Subjects with pJIA Limited data (sample size was <20 subjects) are available beyond the Month 21 visit since many subjects in this study were still ongoing and had not yet reached these visits at the time of data cutoff.

JADAS-27 (CRP) MDA was achieved prior to the data cut-off in 65 (79.3%) of the 82 subjects analyzed with a median time (95% CI) to achieving MDA of 12.6 (4.1, 24.4) weeks.

JIA ACR inactive disease was achieved as early as 12 weeks for 10 subjects and for a total of 22 (26.8%) subjects prior to the data cut-off. Median time to inactive disease was not able to be calculated due to the small number of subjects who achieved inactive disease status.

Supportive study

The ongoing Phase 2/3, long-term, open-label, follow-up Study A3921145 was designed to evaluate the safety, tolerability and efficacy of tofacitinib in subjects with JIA.

Approximately 340 subjects were projected to enroll into this open-label extension study after completing a qualifying/index study in the JIA program. For this interim clinical study report (CSR), 26 subjects from A3921103, 197 subjects from A3921104, and 2 subjects from A3921165 were enrolled and treated (excluded from this analysis).

An interim analysis has been completed to summarize the available data based on the data cut-off 04 June 2019.

2.5.3. Discussion on clinical efficacy

The MAH within this procedure intended initially to extend the indication of "*tofacitinib oral IR tablet and oral solution 5 mg BID for the treatment of active polyarticular JIA in subjects 2 years of age and older*".

To support the claimed indication, the MAH submitted the following studies: study A3921104, a completed Phase 3 pivotal and an interim analysis of the ongoing OL long-term extension study A3921145.

Design and conduct of clinical studies

Study A3921104

Study design: This study was a randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of tofacitinib for the treatment of **polyarticular_**juvenile idiopathic arthritis (pJIA) in children from 2 years of age and older. Superiority of tofacitinib versus placebo was analysed.

All eligible subjects enrolled in the study initially received open-label tofacitinib for 18 weeks (run-in phase). At the end of the 18-week run-in phase, only subjects who achieved at least a JIA ACR 30 response were randomized to the 26-week double-blind, placebo-controlled phase. Subjects who did not achieve a JIA ACR 30 response were discontinued from the study. Subjects who were eligible for the 26-week double-blind phase were randomized (1:1 ratio) to either active tofacitinib 5mg BID or placebo. Although for an enrichment study design generalizability issues need to be considered, it is acknowledged that in the context of trials involving autoimmune/rheumatology diseases this approach is commonly used and ACR30 response is an acceptable measure to select responders.

Study endpoints are adequate and explore appropriately the objectives of the study reflecting those recommended in the EMA *Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis* (EMA/CHMP/239770/2014 Rev. 2). Endpoints of low disease activity, which are considered "new" as compared to those classical, have been included and this is acknowledged by the CHMP. Prevention of structural damage is not among study endpoints. Since the MAH is not claiming for such effect this is acceptable to the CHMP. However, the CHMP recommends to add this endpoint in the long-term study.

Statistical hypothesis, decision rules and adopted statistical analyses/methodologies are adequate for the proposed study design characteristics and endpoints.

Study population: Overall inclusion and exclusion criteria are appropriate and are representative of the target population. Enrolled subjects must have met ILAR JIA classification criteria for 1 of the following categories and, in the opinion of the investigator, have active disease for at least 6 weeks prior to screening: a) **polyarticular JIA** (pJIA RF+; pJIA RF-; E Oligo; sJIA with active arthritis, but without active systemic features in the prior 6 months and at the time of enrollment); of note polyarticular JIA is defined as arthritis affecting 5 or more joints during the first 6-month period and according to ILAR classification includes RF+ polyarthritis and, RF-polyarthritis. However, for inclusion criteria, subjects with other subtypes of JIA who later develop arthritis in multiple joints and have polyarticular disease, i.e. extended oligoarthritis, and systemic JIA without active systemic features are included in the study. Subjects with sJIA and systemic features within the previous 6 months (sJIA with any active systemic features other than active joints and elevated acute phase reactants within 6 months of enrolment) are not included. Exclusion of this subset is supported by the CHMP in view of a different pathogenesis and disease phenotype. To define disease activity, these subjects must have a minimum of 5 active joints. b) PsA; ERA, these must have a minimum of 3 active joints at screening and baseline to be eligible for study entry.

The selection criteria according to ILAR categories as well as the definition of disease activity are acceptable to the CHMP.

The key exclusion criteria are persistent oligoarthritis and undifferentiated JIA; failure of more than 3 biologic therapies (with different mechanisms of action) for JIA. Regarding safety, in view of the mechanism of action as well as the know safety profile of the drug, particular attention has been paid to infections. Risk factors for thromboembolic events and/or thrombophilia were not included among exclusion criteria since the safety signal was not known at the time of the study design and conduction, moreover in the paediatric setting are less common (mainly genetic risk factors) as compared to adults.
Therefore, in view of the inclusion criteria of the study and results obtained the target population was defined as follow a) polyarticular JIA including pJIA RF+; pJIA RF-; E Oligo; sJIA with active arthritis, but without active systemic features in the prior 6 months and at the time of enrolment subtypes or PsA or ERA; b) subjects with inadequate response or intolerance to at least one DMARD, which may include MTX or biologic agents i.e. naïve or not to a biologic DMARD. The wording of the claimed indication was revised with substantial changes: i) excluding the sJIA with active arthritis (without active systemic features) subgroup among pJIA group; ii) including the PsA subgroup (which was separate from the pJIA) and

excluding the ERA subtype; iii) adding specification to the patient population i.e. responded inadequately to previous therapy with DMARDs (therefore including patients who are either bDMARD naïve or bDMARD experienced); combination therapy with MTX or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. The inclusion of the term "polyarticular **course** juvenile idiopathic arthritis" in the wording of the indication was not agreed by the CHMP. It is considered misleading since there may be different interpretations of what JIA categories are included in this term. In addition, the term '**course**' is not included in previously approved paediatric indications. The term '**course**' was therefore deleted from the agreed indication.

Main baseline characteristics: in the OL phase, the mean age of subjects was 11.9, mean age at first diagnosis 8.1 years and duration of JIA since onset mean of 3.8 years. All age ranges were sufficiently represented: 12-18 y (61.8%), 6-≤12 y (28.4%) and 2-≤6 y (9.8%), reflecting the epidemiology of the disease. Most subjects were White (not Hispanic or Latino (196 [87.1%]), but a minority of subjects were from EU countries 6 (2.7%). This limited representation would affect the external validity of study results to the EU population. The MAH supported the similarity of enrolled pJIA population to the EU pJIA population using different data sources. Although the provided comparison is limited for some characteristics i.e. the populations differ for the respective proportion of subjects being bDMARD naïve as compared to bDMARD experienced (much higher in the tofacitinib study 38% *versus* 3-4% of patients in the German registry none in the British one), the comparison was endorsed by the CHMP.
Subjects had active JIA (mean number of joints with active arthritis 12.2 and number of joints with limitation of motion mean 7.5 and swollen joints 10.4. JADAS-27 CRP score mean 21.5 (0-57).
In the DB phase, baseline characteristics were generally similar between tofacitinib 5 mg BID and placebo groups, with only some minor difference. All age groups were represented in the DB phase substantially reflecting the distribution by age seen in the OL phase.
Overall, 216 (96.0%) of the subjects had prior DMARD, corticosteroid, or immunosuppressant use. bDMARDs and csDMARDs were used by 85 (37.8%) and 206 (91.6%) of subjects, respectively, prior to the open-label run-in phase. The most frequently used bDMARD was etanercept (52 [23.1%] subjects). MTX was the most frequently used csDMARD (204 [90.7%] subjects). Therefore, about40% of the population is bDMARD NOT naïve.

Corticosteroids were used by 111 (49.3%) subjects, with the most common being prednisone (61 [27.1%]. Prior medications are those expected for this population.

Concomitant medications: OL phase csDMARDs were used by 149 (66.2%) subjects. MTX and folate were taken by 148 (65.8%) subjects and 145 (64.4%), respectively. Very similar percentage are replicated in the DB phase. Corticosteroids were used concomitantly by 35 (39.8%) and 23 (27.1%) subjects in the tofacitinib 5 mg BID and placebo groups, respectively. Therefore, a similar percentage of subjects used concomitant medications between tofacitinib and PLB groups with the exception of corticosteroids (12.7% difference between arms). This difference could have impacted efficacy results favouring the tofacitinib arm. Any concomitant DMARD, corticosteroid, and immunosuppressant use was 76 and 74% in the OL and DB phase, respectively. Therefore, a percentage of subjects (24-26%) were treated with Tofacitinib monotherapy. Upon the CHMP's request, the MAH revised the proposed indication to describe the intended use of tofacitinib as combination therapy and/or monotherapy.

Subject's disposition: 185 subjects completed the open-label run-in phase, with 173 subjects being randomized into the double-blind phase (there were 142 patients with pJIA, 15 with juvenile PsA, and 16 with ERA randomised into the double-blind phase of the study). Discontinuation occurred in 27 (30.7%) and 47 (55.3%) subjects in the tofacitinib and PLB arm, respectively; the main reason was lack of efficacy 22 (25%) and 44 (51.8%) subjects in the Tofacitinib and PLB arms, respectively. Safety was a reason for discontinuation in a very limited number of subjects and similar between arms (2 subjects each arm). Discontinuation for lack of efficacy occurred in 30% of subjects who were ACR30 responders at the end of

OL phase and lost response, this is clinically relevant and narrows the subset of responders. A total of 99 subjects completed the double-blind phase (61 in the tofacitinib 5 mg BID group and 38 in the placebo group). Of those subjects, 97 were rolled over into the A3921145 study and 2 were discontinued.

Efficacy data and additional analyses

Results: The primary endpoint was the occurrence of disease flare from double-blind randomization through Week 44 (type I Error Controlled) of study being significantly lower in the tofacitinib 5 mg BID group compared to the placebo group (p-value=0.0031), with a difference of proportions (tofacitinib-placebo) of -23.69%, 95% CI (-39.41%, -7.97%). The results obtained from imputation methods accounting for dropouts supported the primary endpoint conclusion.
Numerical treatment differences were observed in favour of tofacitinib in the reported subgroups. However, the subgroup "geographical region: Europe" and "sJIA" were considered very limited to allow any conclusion (see discussion on therapeutic indication below).
Secondary endpoints measuring occurrence of flares (i.e. at different timepoints of the DB phase) supported the result of the primary endpoint in favour of tofacitinib as compared to PLB (analysis is only descriptive, significant difference is shown).
To support the wide claimed indication, the MAH was requested to provide primary endpoint results for the following categories: i) polyarticular JIA subtypes; ii) bDMARD naïve and experienced subjects; iii) subjects who received tofacitinib as monotherapy as compared to those in combination with DMARDs i.e. MTX. Results from primary and secondary efficacy endpoints for patients with pcJIA (RF+ polyarthritis, RF- polyarthritis, E Oligo) are overall supportive of efficacy and consistent with those of the overall pJIA set. Exclusion of sJIA with active arthritis but without active systemic features in view of the results and limited number is endorsed by the CHMP. The updated results on pJIA group (excluding the subgroup of sJIA with active arthritis but without active systemic features) are reflected in the section 5.1 of the SmPC. Addition of PsA as a separate subgroup in the indication is endorsed by the CHMP in view of the results obtained in this subgroup. Results provided on bDMARD naïve and experienced subjects and on subjects who received tofacitinib as monotherapy as compared to those in combination with DMARDs i.e. MTX support the inclusion of these subgroups as well as use of tofacitinib in combination with MTX or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. The MAH discussed the reasons why a high response is seen in PLB arm in the bDMARD subjects as compared to the experienced ones and on the concomitant therapy MTX+corticosteroids as compared to MTX alone, limited numbers and some imbalance in disease characteristics are those identified. This is agreed by the CHMP.

The efficacy was also supported by key secondary endpoints:
i) **JIA ACR 50, 30, and 70 responses** (at Week 44, Type I Error Controlled), a significantly greater proportion of subjects treated with tofacitinib 5 mg BID achieved ACR 50, 30, and 70 responses compared to subjects treated with placebo (response 48%, delta 19.52 p=0.0166; response 51%, delta 23,69 p=0.0031; response 39% delta 17.02 p=0.0387, respectively). Difference from PLB was statistically significant, consistent across the different measure of ACR response and of clinical value (a percentage ranging from 50% to 30%, for the ACR70 stringent endpoint, showed ACR response).
Subgroups analyses favour tofacitinib treated subjects although the limited number of subjects per subgroup i.e Europe as geographic region and others are too limited to allow a firm conclusion.
Secondary endpoints measuring ACR responses for the entire study support the key secondary endpoint results: a statistically difference (although analyses are descriptive) is shown in favour of tofacitinib for all time points considered and therefore the ACR response is consistent over time; the proportion of responders varies according to the percentage considered for the ACR measure i.e. decrease for higher percentage, in fact for the most stringent ones i.e. ACR 90 and ACR 100 only a numerically difference between Tofacitinib and PLB arms is seen.

ii) **Change from Double-Blind Baseline in CHAQ Disability Index** at Week 44 (Type I Error Controlled) the improvement was statistically greater in subjects treated with tofacitinib 5 mg BID than those treated with placebo, with a LS mean difference in the scores of -0.12, p-value=0.0292. Range of the index is 0-3.

Secondary endpoints results, although descriptive analysis was conducted, were generally supportive of better activity of tofacitinib as compared to placebo for different endpoints related to disease activity, however for endpoints more stringent the numerical difference was lower. Those looking at disease activity i.e. minimal disease activity showed only a numerical trend and not a significant (although formally descriptive) clinical effect. For JIA ACR inactive disease, JIA ACR remission was achieved by 3 subjects per arm, which is very limited; however, it is recognized that this is a very stringent endpoint to meet in view of the definition i.e. clinical inactive disease for 6 months continuously while on medications for JIA. No endpoints aimed at looking the prevention/effect of structural damage are included. Measures of disease activity could serve indirectly as an indicator for the effect on bone. Since pJIA is a chronic disease, long term effect in terms of reducing disease activity sufficiently to prevent life-long damage is an important clinical objective.

Supportive results on tofacitinib activity are from the mean change in number of joints with active arthritis in the DB phase showing a better trend in particular at later endpoints in the subjects treated with tofacitinib. The same trend favouring tofacitinib for number of joints with limited motion (often statistical difference although descriptive in the DB phase) and also for evaluation of disease activity by physician and CHAQ parental is also seen.

Overall, the efficacy results from the pivotal study are supportive of tofacitinib superiority as compared to placebo, although only a subset of pJIA enrolled subjects could be considered responders, this is in line with the agreed therapeutic indication.

Data coming from the OL LTE A3921145 Study (interim analysis, as of the 04 June 2019 data cut-off, 227 subjects were enrolled in; 177 subjects are currently ongoing) are overall supportive of those obtained in the pivotal trial although differences from baseline are sometime not large and of limited clinical value. Upcoming analyses will further inform long term efficacy of tofacitinib in treating JIA subjects.

Stopping rules were discussed and the MAH agreed to update the 4.2 section of the SmPC providing information on when to stop treatment with tofacitinib due to insufficient response. The proposal includes a timeframe of clinical improvement observation of within 18 weeks (more than 4 months, corresponding to the end of induction phase of the study) and a description of the lack of benefit generally described as "no improvement" should be amended to include "clinical improvement". The MAH disagrees to update the 4.2 section of the SmPC providing information on when tofacitinib could be stopped in case of prolonged remission, leaving the decision to physicians and patients/parents. In view of the absence of data in support of the decision the issue is not further pursued by the CHMP.

2.5.4. Conclusions on the clinical efficacy

The Phase 3 study met its primary endpoint, the efficacy was further supported by key secondary endpoints. The claimed indication of tofacitinib *for treatment of active polyarticular course juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older* was revised to reflect the target population as recommended by the CHMP as follows:

> *for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive or negative polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs. Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.*

2.6. Clinical safety

The safety profile of tofacitinib oral 5 mg BID tablet and oral solution formulation (1 mg/mL) dosed twice daily (BID) for the treatment of pediatric subjects with active pJIA is supported by the data from the pivotal Study A3921104 and the Integrated Safety Population JIA (from Studies A3921103, A3921104 and A3921145).

Patient exposure

Integrated safety analysis population

There have been 251 subjects exposed to the tofacitinib 5 mg BID dose in the JIA ISAP safety database. Among the exposed subjects in the ISAP, the overall exposure was 351 PY and the mean duration of exposure was 511 days (median duration 485 days). In the CISAP, representing continuous exposure without interruptions of more than 14 days, 251 subjects were exposed for a total of 253 PY and the mean duration of exposure was 368 days.

Demographic and Disease characteristics

Study A3921104

Table 15 Study A3921104 Demographic Characteristics - DBFAS

	Tofacitinib 5mg BID DB (N=88)			Placebo (N=85)		
	Male (N=22)	Female (N=66)	Total (N=88)	Male (N=21)	Female (N=64)	Total (N=85)
Age (years):						
2 - <6	5 (22.7)	6 (9.1)	11 (12.5)	2 (9.5)	7 (10.9)	9 (10.6)
6 - <12	5 (22.7)	17 (25.8)	22 (25.0)	8 (38.1)	15 (23.4)	23 (27.1)
12 - <18	12 (54.5)	43 (65.2)	55 (62.5)	11 (52.4)	42 (65.6)	53 (62.4)
Mean (SD)	11.0 (5.13)	12.2 (4.04)	11.9 (4.34)	11.3 (3.30)	12.1 (4.29)	11.9 (4.06)
Median (SE)	12.0 (1.09)	13.0 (0.50)	13.0 (0.46)	12.0 (0.72)	13.0 (0.54)	13.0 (0.44)
Q1, Q3	7.0, 15.0	9.0, 15.0	9.0, 15.0	10.0, 14.0	8.5, 16.0	9.0, 15.0
Range (min, max)	2, 17	2, 17	2, 17	4, 16	2, 17	2, 17
Race:						
White	21 (95.5)	55 (83.3)	76 (86.4)	19 (90.5)	55 (85.9)	74 (87.1)
Black or African American	0	4 (6.1)	4 (4.5)	0	1 (1.6)	1 (1.2)
Asian	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
Other	1 (4.5)	7 (10.6)	8 (9.1)	2 (9.5)	8 (12.5)	10 (11.8)
Unknown	0	0	0	0	0	0
Multi-Racial	0	0	0	0	0	0
Not Reported	0	0	0	0	0	0
Geographical Region:						
North America	3 (13.6)	28 (42.4)	31 (35.2)	11 (52.4)	30 (46.9)	41 (48.2)
South and Central America	6 (27.3)	16 (24.2)	22 (25.0)	2 (9.5)	13 (20.3)	15 (17.6)
Europe	3 (13.6)	2 (3.0)	5 (5.7)	0	1 (1.6)	1 (1.2)

	Tofacitinib 5mg BID DB (N=88)			Placebo (N=85)		
	Male (N=22)	Female (N=66)	Total (N=88)	Male (N=21)	Female (N=64)	Total (N=85)
All Other	10 (45.5)	20 (30.3)	30 (34.1)	8 (38.1)	20 (31.3)	28 (32.9)
Ethnicity:						
Hispanic or Latino	7 (31.8)	22 (33.3)	29 (33.0)	3 (14.3)	17 (26.6)	20 (23.5)
Not Hispanic or Latino	15 (68.2)	44 (66.7)	59 (67.0)	18 (85.7)	47 (73.4)	65 (76.5)
Unknown	0	0	0	0	0	0
Not Reported	0	0	0	0	0	0

Data collected at screening are used.
The Double-Blind phase is the study period on and after randomization day.
Age is calculated based on demography collection date and date of birth.
Europe includes: Poland, Belgium, Great Britain, and Spain; All Other includes: Ukraine, Turkey, Russia, Australia and Israel.

Integrated JIA Safety Population Demographics and Baseline Characteristics

Table 16 Tofacitinib Integrated Summary of Safety Other Baseline Characteristics - JIA ISAP (Data Cutoff 04JUN2019)

Number (%) of Subjects	Tofacitinib 5 mg BID (N=251)
Oral Corticosteroid Use at Baseline	
Yes	113 (45.0)
No	138 (55.0)
MTX Use at Baseline	
Yes	226 (90.0)
No	25 (10.0)
Other csDMARDs Use at Baseline	
Yes	56 (22.3)
No	195 (77.7)
Oral Corticosteroid Use on First Dose Date	
Yes	75 (29.9)
No	176 (70.1)
MTX Use on First Dose Date	
Yes	156 (62.2)
No	95 (37.8)
Oral Corticosteroid and MTX Use on First Dose Date	
Yes	55 (21.9)
No	196 (78.1)
Other csDMARDs Use on First Dose Date	
Yes	2 (0.8)
No	249 (99.2)
csDMARDs Use (MTX or Other) on First Dose Date	
Yes	157 (62.5)
No	94 (37.5)

Number (%) of Subjects	Tofacitinib 5 mg BID (N=251)
Weekly MTX Dose (mg) on First Dose Date	
n	156
Mean (SD)	15.1 (5.49)
Median (SE)	15.0 (0.44)
Q1, Q3	10.0, 20.0
Range (min, max)	0.4, 25.0
Previous Biologic DMARDs Received	
bDMARD naive	166 (66.1)
bDMARD experienced (all)	85 (33.9)
1 Prior bDMARD	46 (18.3)
>=2 Prior bDMARDs	39 (15.5)
Formulation [1]	
Tablet	145 (57.8)
Liquid	73 (29.1)
Both (Switchers)	33 (13.1)

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Data collected at index study screening are used except for the formulation categories. Baseline is either prior to or on Day 1.
MTX = Methotrexate
[1] Formulation is from Tofacitinib dosing of the integrated studies. Switchers are identified as subjects with Tofacitinib formulation changes at any time during the integrated studies.

Adverse events

TEAEs in the **double-blind** phase and **entire tofacitinib** exposure period are reported in the tables below.

Table 17 Study A3921104 Treatment-Emergent Adverse Events (All Causalities) in Double-Blind Phase - DBSAS

Number (%) of Subjects	Tofacitinib 5mg BID DB n (%)	Placebo n (%)
Subjects evaluable for adverse events	88	85
Number of adverse events	160	166
Subjects with adverse events	68 (77.3)	63 (74.1)
Subjects with serious adverse events	1 (1.1)	2 (2.4)
Subjects with severe adverse events	0	3 (3.5)
Subjects discontinued from study due to adverse events (a)	16 (18.2)	29 (34.1)
Subjects discontinued study drug due to AE and continue Study (b)	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	9 (10.2)	8 (9.4)

Number (%) of Subjects	Tofacitinib 5mg BID DB n (%)	Placebo n (%)

Includes data up to 28 days after last dose of study drug.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study.
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be discontinued from the study.
MedDRA 22.0 coding dictionary applied.
The Double-Blind phase is the study period on and after randomization day.

Table 9. CP-690,550 Protocol A3921104 Treatment-Emergent Adverse Events (All Causalities) for the Entire Tofacitinib Exposure Period

Number (%) of Subjects	Tofacitinib 5mg BID n (%)
Subjects evaluable for adverse events	225
Number of adverse events	554
Subjects with adverse events	176 (78.2)
Subjects with serious adverse events	8 (3.6)
Subjects with severe adverse events	5 (2.2)
Subjects discontinued from study due to adverse events (a)	42 (18.7)
Subjects discontinued study drug due to AE and continue Study (b)	0
Subjects with dose reduced or temporary discontinuation due to adverse events	25 (11.1)

Includes data up to 28 days after last dose of study drug. Events occurring during placebo exposure are excluded.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be discontinued from Study

Most Frequent All Causality and Treatment-related Adverse Events

Study A3921104

The most frequently reported AEs in the double-blind phase of Study A3921104 (≥ 10% occurrence in tofacitinib, or placebo treatment group) were Upper respiratory tract infection (Tofacitinib: 14.8 %, placebo: 10.6% %), Juvenile idiopathic arthritis (Tofacitinib: 3.4%; placebo: 14.1%), and Disease progression (Tofacitinib: 9.1%; placebo: 15.3%).

Treatment-**related** TEAEs were reported for 64 (28.4%) subjects during the open-label run-in phase. Most treatment-related TEAEs reported were mild to moderate in severity.

Treatment-related TEAEs were reported for 22 (25.0%) subjects in the tofacitinib 5 mg BID group and 33 (38.8%) subjects in the placebo group during the double-blind phase.

Integrated Safety Analysis Population

The most common AEs occurring in the integrated safety population are reported in Table 18.

Table 18 Tofacitinib Integrated Summary of Safety Treatment-Emergent Adverse Events by System Organ Class and Preferred Term with >=2% Occurrence (All Causalities) - ISAP

Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	Tofacitinib 5 mg BID (N=251)
Blood And Lymphatic System Disorders	23 (9.2)
Anaemia	8 (3.2)
Leukopenia	6 (2.4)
Gastrointestinal Disorders	81 (32.3)
Abdominal discomfort	5 (2.0)
Abdominal pain	18 (7.2)
Abdominal pain upper	11 (4.4)
Constipation	9 (3.6)
Diarrhoea	13 (5.2)
Dyspepsia	6 (2.4)
Nausea	23 (9.2)
Vomiting	25 (10.0)
General Disorders And Administration Site Conditions	68 (27.1)
Condition aggravated	12 (4.8)
Disease progression	23 (9.2)
Fatigue	5 (2.0)
Non-cardiac chest pain	5 (2.0)
Pyrexia	22 (8.8)
Infections And Infestations	158 (62.9)
Bronchitis	10 (4.0)
Conjunctivitis	6 (2.4)
Ear infection	11 (4.4)
Gastroenteritis	12 (4.8)
Gastroenteritis viral	5 (2.0)
Influenza	20 (8.0)
Nasopharyngitis	29 (11.6)
Pharyngitis	16 (6.4)
Pharyngitis streptococcal	9 (3.6)
Pneumonia	5 (2.0)
Respiratory tract infection	9 (3.6)
Sinusitis	18 (7.2)
Tinea pedis	5 (2.0)
Upper respiratory tract infection	65 (25.9)
Urinary tract infection	14 (5.6)
Viral infection	19 (7.6)
Viral upper respiratory tract infection	7 (2.8)
Injury, Poisoning And Procedural Complications	49 (19.5)
Contusion	6 (2.4)
Ligament sprain	7 (2.8)
Limb injury	6 (2.4)
Skin abrasion	6 (2.4)
Investigations	53 (21.1)

Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	Tofacitinib 5 mg BID (N=251)
Alanine aminotransferase increased	13 (5.2)
Aspartate aminotransferase increased	13 (5.2)
Blood creatine phosphokinase increased	12 (4.8)
Blood triglycerides increased	6 (2.4)
C-reactive protein increased	6 (2.4)
Haemoglobin decreased	7 (2.8)
Metabolism And Nutrition Disorders	14 (5.6)
Decreased appetite	7 (2.8)
Musculoskeletal And Connective Tissue Disorders	78 (31.1)
Arthralgia	20 (8.0)
Arthritis	7 (2.8)
Back pain	8 (3.2)
Juvenile idiopathic arthritis	27 (10.8)
Pain in extremity	9 (3.6)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	8 (3.2)
Skin papilloma	8 (3.2)
Nervous System Disorders	41 (16.3)
Headache	31 (12.4)
Respiratory, Thoracic And Mediastinal Disorders	51 (20.3)
Cough	17 (6.8)
Epistaxis	10 (4.0)
Oropharyngeal pain	13 (5.2)
Rhinitis allergic	5 (2.0)
Skin And Subcutaneous Tissue Disorders	37 (14.7)
Acne	6 (2.4)
Rash	7 (2.8)
Urticaria	5 (2.0)

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Subjects are only counted once per event. SOCs with at least one PT >=2% are included.
Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events
within the higher level category. The total number of subjects reporting adverse events within a particular SOC reflects all events reported within the SOC,
including events with less than 2% occurrence.
Includes events up to 999 days after the last dose of Tofacitinib. Events occurring during placebo exposure are excluded.
MedDRA 22.0 coding dictionary applied.

Treatment-**related** AEs reported in the integrated safety population, by PT, were reported at rates below 5%, with the exception of upper respiratory tract infection, which was reported in 10% of the population. It should be noted that the rate of treatment-related JIA disease progression in the integrated safety population was below 5%, because it was reported under 2 separate PTs, i.e. Disease progression (4.4%) and JIA (4.8%). All TEAEs with at least 2% occurrence have previously been identified as common AEs in the adult RA population.

Serious adverse event/deaths/other significant events

Study A3921104

In Study A3921104 were reported a total of 10 SAEs, with the majority being reported in the open-label run-in phase (7 SAEs reported by 7 subjects). All SAE Preferred Terms (PT) were reported in 1 subject each.

Integrated Safety Analysis Population

Serious adverse events were reported in **23 subjects (9.2%)** in the integrated safety analysis population, corresponding to an incidence rate of 6.18 (3.87, 9.36) subjects with SAEs/100 PYs. Most SAEs were related to hospitalizations for infections or due to disease worsening/JIA exacerbation.

Table 19. Tofacitinib Integrated Summary of Safety Summary of Serious Adverse Events by System Organ Class and Preferred Terms (All Adverse Events) - ISAP

Number of Subjects Evaluable for Adverse Events	Tofacitinib 5 mg BID (N=251)
Number (%) of Subjects with Serious Adverse Events (a): by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**
Gastrointestinal disorders	3 (1.2)
Abdominal pain	1 (0.4)
Crohn's disease	1 (0.4)
Diarrhoea	1 (0.4)
Vomiting	1 (0.4)
General disorders and administration site conditions	2 (0.8)
Condition aggravated	1 (0.4)
Disease progression	1 (0.4)
Infections and infestations	9 (3.6)
Abscess limb	1 (0.4)
Appendicitis	1 (0.4)
Epidural empyema	1 (0.4)
Herpes zoster	1 (0.4)
Influenza	1 (0.4)
Pilonidal cyst	1 (0.4)
Pneumonia	1 (0.4)
Pyelonephritis acute	1 (0.4)
Sinusitis	1 (0.4)
Subperiosteal abscess	1 (0.4)
Urinary tract infection	1 (0.4)
Injury, poisoning and procedural complications	1 (0.4)
Forearm fracture	1 (0.4)
Musculoskeletal and connective tissue disorders	5 (2.0)
Joint effusion	1 (0.4)
Juvenile idiopathic arthritis	3 (1.2)
Muscle spasms	1 (0.4)
Nervous system disorders	2 (0.8)
Headache	1 (0.4)

Table 19. Tofacitinib Integrated Summary of Safety Summary of Serious Adverse Events by System Organ Class and Preferred Terms (All Adverse Events) - ISAP

Number of Subjects Evaluable for Adverse Events	Tofacitinib 5 mg BID (N=251)
Number (%) of Subjects with Serious Adverse Events (a): by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**
Migraine	1 (0.4)
Psychiatric disorders	3 (1.2)
Homicidal ideation	1 (0.4)
Major depression	1 (0.4)
Suicidal ideation	1 (0.4)
Suicide attempt	1 (0.4)
Total preferred term events (b)	29
Total Number of Cases (c)	24
Total Number of Subjects with Serious Adverse Events (d)	24
Total Number of Subjects with Serious Adverse Events (e)	24

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
A case is a single event or a series of related events not separated in time occurring in a single subject.
(a) SAE's are counted at MedDRA preferred term/Treatment group with each individual SAE counted only once per subject per treatment group.
(b) Total number of events per subject per Treatment group.
(c) Number of cases that started in the Treatment group.
(d) Total number of subjects having an event that started in the Treatment group.
(e) Overall count of subjects that had a Serious adverse Event in any Treatment group.
Source of Actual treatment Group is OC(Oracle Clinical) or PIMS(Phase I Management System). Source of SAE is SDW(Safety Data Warehouse).
Includes events up to 999 days after the last dose of Tofacitinib. Events occurring during placebo exposure are excluded.
MedDRA v22.0 coding dictionary applied.

Deaths

There were no deaths reported in Study A3921104 and no deaths have been reported in the JIA safety population.

Psychiatric Disorders

Psychiatric Disorders were reported in 10 JIA subjects on tofacitinib 5 mg BID in the ISAP, corresponding with a rate of 4.0% and an incidence rate of 2.80 (1.34, 5.15) subjects with Psychiatric Disorders/100 PYs.

There were 3 subjects with **SAEs related to Psychiatric Disorders** in the ISAP.

None of these hospitalizations for psychiatric disorders were considered related to study drug.

Table 20 Listing of Subjects with SAEs related to Psychiatric Disorders - ISAP

Sex/Age/ Race/Country	Verbatim Term/ MedDRA PT	Outcome/ discontinuation study drug	Event Onset Day/ Event Stop Day (Days of tofacitinib treatment)	Investigator Causality/ Sponsor Causality	Outcome/ Seriousness	Relevant Medical History
Female/16/ White/Turkey	Suicide Attempt/ SUICIDE ATTEMPT	Permanently withdrawn/ Study drug discontinued on day 558	544/545	Unrelated / Unrelated	Recovered / Hospitalization	None
Female/11/ Caucasian/USA	Major Depressive Disorder & Homicidal Ideation/ HOMICIDAL IDEATION	Dose not changed	571/578	Unrelated / Unrelated	Recovered Hospitalization	Major Depressive Disorder (MDD)
Female/13/ Caucasian/USA	Suicidal Ideation/ SUICIDAL IDEATION	Permanently withdrawn/ Study drug discontinued on day 92	88/92	Unrelated / Unrelated	Recovered / Hospitalization	ADHD, MDD Recurrent, severe with psychosis, Bipolar 1 Disorder, Suicidal Ideation, Anxiety Disorder, Autism Spectrum Disorder, Bereavement (2 months before study start)

Age = age at date of AE SAE onset. Onset Study Day is calculated as (SDW onset day) – (OC first active therapy date in te index study) + 1. Event Stop Day is calculated SDW SAE stop date) – (OC first active therapy date in the index study) + 1.
SDW = Safety Data Warehouse; OC = Oracle Clinical.; AE = adverse event; SAE = Serious AE.
MedRA v 22.O coding dictionary applied.

Adverse Events of Special Interest

Table 21. Tofacitinib Integrated Summary of Safety Exposure Estimates and Incidence Rates for Adverse Events of Special Interest - ISAP

	Treatment Group	N	n (%)	PD (Subject-Days)	IRD (Subjects with Events / 100 subject-days) (Exact 95% Poisson CI)	PY (Subject-Years)	IRY (Subjects with Events / 100 subjects-years) (Exact 95% Poisson CI)
Death	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)
Serious Infections	Tofacitinib 5 mg BID	251	6 (2.4)	133554	0.004 (0.002, 0.010)	365.65	1.641 (0.602, 3.572)
Opportunistic Infection Excluding TB	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)

Table 21. Tofacitinib Integrated Summary of Safety Exposure Estimates and Incidence Rates for Adverse Events of Special Interest - ISAP

	Treatment Group	N	n (%)	PD (Subject-Days)	IRD (Subjects with Events / 100 subject-days) (Exact 95% Poisson CI)	PY (Subject-Years)	IRY (Subjects with Events / 100 subjects-years) (Exact 95% Poisson CI)
Tuberculosis (TB)	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)
Herpes Zoster	Tofacitinib 5 mg BID	251	3 (1.2)	133241	0.002 (0.000, 0.007)	364.79	0.822 (0.170, 2.403)
Malignancy Excluding NMSC	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)
NMSC (Non-Melanoma Skin Cancer)	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)
Lymphoma	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)
Major Adverse Cardiovascular Events (MACE)	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)
Gastrointestinal Perforations	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)
Interstitial Lung Disease (ILD)	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)
MAS (Macrophage Activation Syndrome)	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)
Venous Thromboembolism	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)
Deep Vein Thrombosis	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)
Pulmonary Embolism	Tofacitinib 5 mg BID	251	0 (0.0)	134391	0.000 (0.000, 0.003)	367.94	0.000 (0.000, 1.003)

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
N: Number of subjects in analysis set; n: Number of subjects with the event in the Tofacitinib risk period.
For subjects who also enrolled in LTE study, total risk period is the sum of index and LTE risk periods.
The gap between index and LTE studies can add a maximum of 28 days to the risk period of exposure to Tofacitinib. Placebo exposure may contribute a maximum of 28 days to the risk period.
PD (subject-day): Sum of total follow-time for all subjects combined. Follow-up time is time from the first dose to the event or total exposure for subjects who did not have any event (to the earliest occurrence of date of: the last dose + 28 days, date of death, or cut-off date).
PY (subject-year): total follow-up time in years defined as PD/365.25.

Serious infections

Overall, there were 6 subjects with **serious infections** in the integrated safety population of the JIA programme, representing an incidence rate of 1.64 events/100 PY. Three subjects had serious infections during exposure to tofacitinib in pivotal Study A3921104 in the open-label run-in phase (1 subject with pneumonia, 1 subject with epidural empyema, pan sinusitis and subperiosteal abscess with a history of craniosynostosis repair, and 1 subject with appendicitis). Three subjects had serious infections in LTE study A3921145: acute pyelonephritis, abscess limb (buttocks) and UTI. The subject with UTI discontinued before the infection was resolved 70 days after onset or UTI

Based on the follow-up period of up to 36 months in the ISAP, there was no evidence of increasing IRs of serious infection over time.

Herpes Zoster

Overall, there were 3 subjects with HZ reported in integrated safety analysis set for JIA, representing an incidence rate of 0.82 events/100 PY (Table 21).

All 3 reported HZ cases were mild to moderate and monodermatomal.

In JIA tofacitinib program, no cases of death, GI perforation, ILD, MACE, malignancy, MAS, opportunistic infection, thromboembolism (no PE or DVT reported), or TB were reported.

Hepatic Function and Drug-Induced Liver Injury

There were 2 subjects with mild liver enzyme elevations; 1 case was adjudicated as possible and 1 case as probable drug-induced liver injury. There was also 1 subject with moderate liver enzyme elevations adjudicated as probable DILI. All 3 hepatic events occurred in the first 4 to 8 weeks of treatment with tofacitinib 5 mg BID in Study A3921104 and all 3 subjects were receiving background MTX. None met Hy's Law criteria.

Uveitis

Uveitis is a common ophthalmologic complication associated with JIA and it is evaluated in all JIA studies.

There was 1 event of mild uveitis reported in the pJIA clinical program. This event occurred in a subject after 511 days of exposure to tofacitinib and was considered resolved at the next visit 23 days later. One other subject reported uveitis symptoms after 639 days of exposure to tofacitinib, but these symptoms were not recorded as an adverse event. Upon querying by the medical monitor, the symptoms were not considered consistent with active uveitis.

Laboratory findings

Haemoglobin

To enroll in the JIA index Study A3921104, subjects were required to have Hb levels ≥10 g/dL and hematocrit ≥33% at the study enrollment visit.

Pivotal Study A3921104

In Study A3921104, the mean (SE) change from baseline in hemoglobin at Week 18 of the open-label run-in phase was 0.21 (0.09) g/dL. The changes from baseline in hemoglobin were similar in both treatment groups during the double-blind phase. At Week 44, the mean (SE) change from the double-blind baseline in hemoglobin was -0.19 (0.19) g/dL for the tofacitinib 5 mg BID group and -0.01 (0.18) g/dL for the placebo group, with a mean hemoglobin level of 12,81 g/dL and 12,86 g/dL in tofacitinib and placebo groups, respectively (Table 14.3.4.1.5.2.2)

Continuous Integrated Safety Analysis Population

There was no evidence of Hb decreases over time in the CISAP, and there were no subject discontinuations due to decreases in Hb.

Neutrophils

To enrol in the JIA index Study A3921104, subjects were required to have a neutrophil count ≥1.2 x 109/L at the study enrolment visit.

Pivotal Study A3921104:

In Study A3921104, mean absolute total neutrophils decreased from baseline to Week 18 of the open-label run-in phase (reference to CSR). At Week 18, the mean (SE) change from baseline in neutrophils was -0.46 (0.17) × $10^3/mm^3$. During the double-blind phase, the mean changes from the double-blind

baseline in absolute neutrophils were similar for subjects in both treatment groups for all week except Week 24. At Week 24, the mean (SE) change from the double-blind baseline in absolute neutrophils was -0.20 (0.30) × $10^3/mm^3$ for the tofacitinib 5 mg BID group and 0.39 (0.24) × $10^3/mm^3$ for the placebo group. The mean (SE) change from the double-blind baseline in absolute neutrophils was -0.43 (0.34) × $10^3/mm^3$ and -0.23 (0.29) × $10^3/mm^3$ for the tofacitinib 5 mg BID and placebo groups, respectively, by Week 44.

Continuous Integrated Safety Analysis Population

Neutrophil count changes over time were monitored in the CISAP. There was no evidence of ANC decreases over time in the JIA population.

Lymphocytes

Pivotal Study A3921104

In Study A3921104, mean lymphocytes initially increased from baseline at Week 2 and decreased to near baseline levels by Week 18 of the open-label run-in phase. The mean (SE) change from baseline in lymphocytes was -0.13 (0.06) × $10^3/mm^3$ at Week 18.

JIA Subjects with Confirmed Lymphopenia

Table 22. Tofacitinib Integrated Summary of Safety Number (%) of Subjects with Confirmed Lymphopenia - CISAP

Age Group	Treatment Group	N	ALC >= 2000/mm³	2000/mm³ > ALC >=1500/mm³	1500/mm³ > ALC >=1000/mm³	1000/mm³ > ALC >=500/mm³	ALC < 500/mm³
2 to < 6 Years	Tofacitinib 5 mg BID	31	22 (71.0%)	5 (16.1%)	4 (12.9%)	0	0
6 to < 12 Years	Tofacitinib 5 mg BID	73	45 (61.6%)	14 (19.2%)	6 (8.2%)	1 (1.4%)	0
12 to < 18 Years	Tofacitinib 5 mg BID	147	49 (33.3%)	43 (29.3%)	43 (29.3%)	2 (1.4%)	0

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Covance LLN for ALC: 2 to < 6 Years: LLN = 1500/mm^3; 6 to < 12 Years: LLN = 1150/mm^3; 12 to < 18 Years: LLN = 950/mm^3.
Covance LLN is based on "Pediatric Reference Intervals" edited by S.J. Soldin, et al, AACC Press, 7th edition, 2011.

Platelets

To enroll in the JIA index Study A3921104, subjects were required to have a platelet count ≥100,000 platelets/mm^3 at the study enrollment visit.

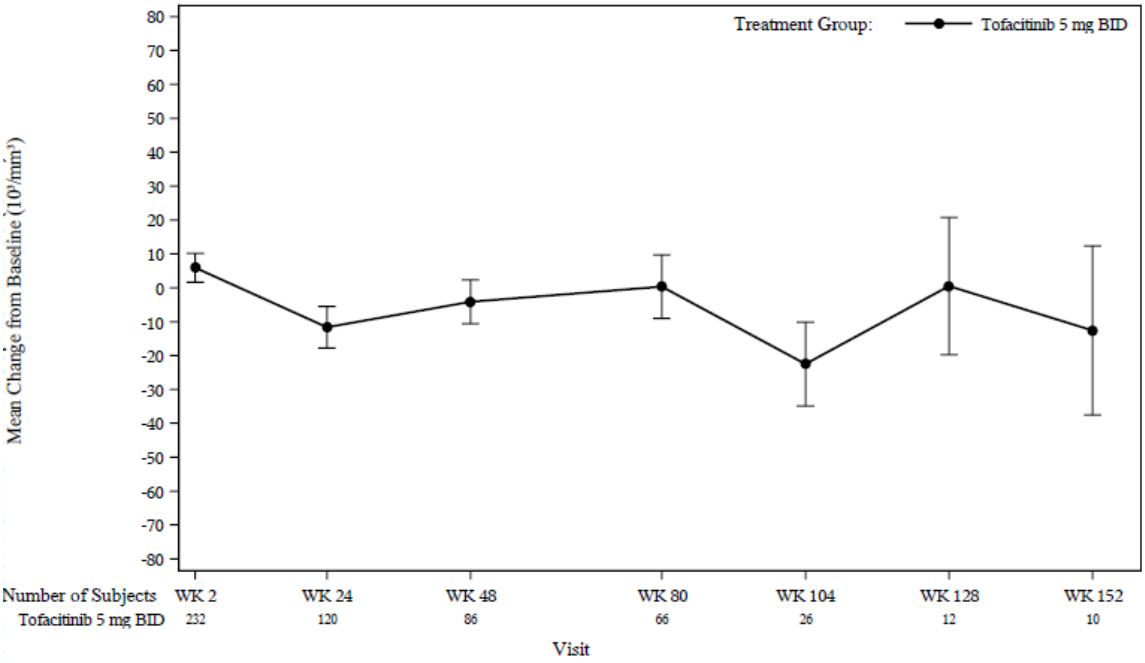
Pivotal Study A3921104

Mean platelet counts initially increased from baseline at Week 2 and decreased by Week 18 during the open-label run-in phase. At Week 18, the mean change from baseline was -14.24 x $10^3/mm^3$. (the mean value was 294,53 $10^3/mm^3$)

During the double-blind phase, the mean change from baseline increased more for subjects on tofacitinib 5 mg BID than on placebo. At Week 44, the mean change from the double-blind baseline was 9.93 x $10^3/mm^3$ and 0.24 x $10^3/mm^3$, for the tofacitinib 5 mg BID and placebo groups, respectively (PLT mean values tofacitinib: 303,03 x $10^3/mm^3$; PLB: 281,57 x $10^3/mm^3$).

Platelet count changes overtime were monitored in the CISAP.

Mean Change (+/- SE) in Platelets (10^3/MM^3) – CISAP



Adjudicated Hepatic Events

In the ISAP there were 2 mild hepatic events, 1 adjudicated as possible DILI and 1 as probable DILI, and 1 moderate hepatic event adjudicated as probable DILI. One mild and 1 moderate event occurred 2 to 4 weeks after start of Study A3921104, and 1 mild event occurred 53 days after the start of Study A3921104. **All 3 subjects were on background MTX therapy.** None met Hy's Law criteria. 1 subject was taking paracetamol and MTX with a concurrent viral illness which was considered a possible cause. The second subject was also taking paracetamol and methotrexate when elevated AST and ALT occurred. All 3 events resolved after discontinuation of methotrexate and interruption or permanent discontinuation of tofacitinib.

No cases of Hy's Law were reported in the integrated safety population of pJIA.

Creatine Kinase

CPK levels in subjects who experienced increased values largely remained within the normal reference range throughout the duration of treatment with tofacitinib.

Regarding **renal function** testing in CISAP there was no extra monitoring required in any JIA subject due to a creatinine increase >50% from the initial value, and no subject had to be discontinued due to creatinine increase >100% from the initial value.

Increases in **lipid parameters** are known effects of tofacitinib treatment and are reported in the SmPC. In the CISAP the percentage change from baseline was fluctuating. However, no major adverse cardiovascular events were reported in the pooled JIA population, even if a long-term safety evaluation is needed mainly for this type of adverse events.

Vital signs

There were no significant changes in **heart rate** and **blood pressure** of pJIA subjects in the integrated safety population

Pubertal Development

Table 23. Tofacitinib Integrated Summary of Safety Shift of Pubertal Development by Gender and Age Group - CISAP

				Tofacitinib 5 mg BID (N1=118)				
				Year 1 Tanner Stage				
Gender	Age Group	Baseline Tanner Stage	N	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Male	6 to < 12 Years	Stage 1	7	6 (85.71)	0 (0.0)	1 (14.29)	0 (0.0)	0 (0.0)
		Stage 2	1	1 (100.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Stage 3	1	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.00)	0 (0.0)
		Stage 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Stage 5	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	12 to < 18 Years	Stage 1	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Stage 2	3	0 (0.0)	0 (0.0)	1 (33.33)	1 (33.33)	1 (33.33)
		Stage 3	3	0 (0.0)	0 (0.0)	1 (33.33)	2 (66.67)	0 (0.0)
		Stage 4	6	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.00)	3 (50.00)
		Stage 5	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.00)
Female	6 to < 12 Years	Stage 1	13	6 (46.15)	6 (46.15)	1 (7.69)	0 (0.0)	0 (0.0)
		Stage 2	6	1 (16.67)	2 (33.33)	2 (33.33)	0 (0.0)	1 (16.67)
		Stage 3	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Stage 4	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Stage 5	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	12 to < 18 Years	Stage 1	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Stage 2	5	0 (0.0)	3 (60.00)	1 (20.00)	1 (20.00)	0 (0.0)
		Stage 3	14	0 (0.0)	0 (0.0)	7 (50.00)	6 (42.86)	1 (7.14)
		Stage 4	21	0 (0.0)	0 (0.0)	0 (0.0)	15 (71.43)	6 (28.57)
		Stage 5	19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (100.00)

N1 is subjects having Tofacitinib exposure and at least one non-missing tanner stage post-baseline result for Year 1.
N is the number of subjects with available tanner stage at both baseline and post-baseline visit for Year 1. Percentages are based on the Ns.
Tanner grades were based on breast development in females and genitalia development in males.
If the breast or genitalia scores were missing, the available pubic hair assessments were used.
In A3921103 study, no tanner stage data were collected.

Growth

Figure 5 Mean Height Z-Score (+/- SE) Over Time in Males – CISAP

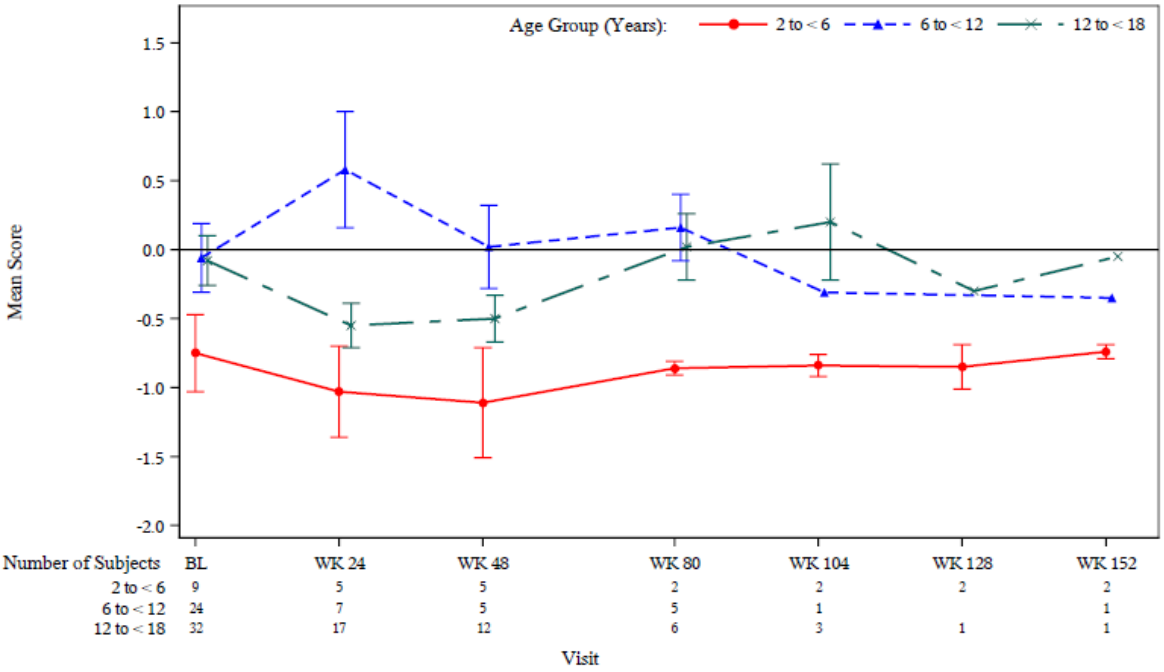
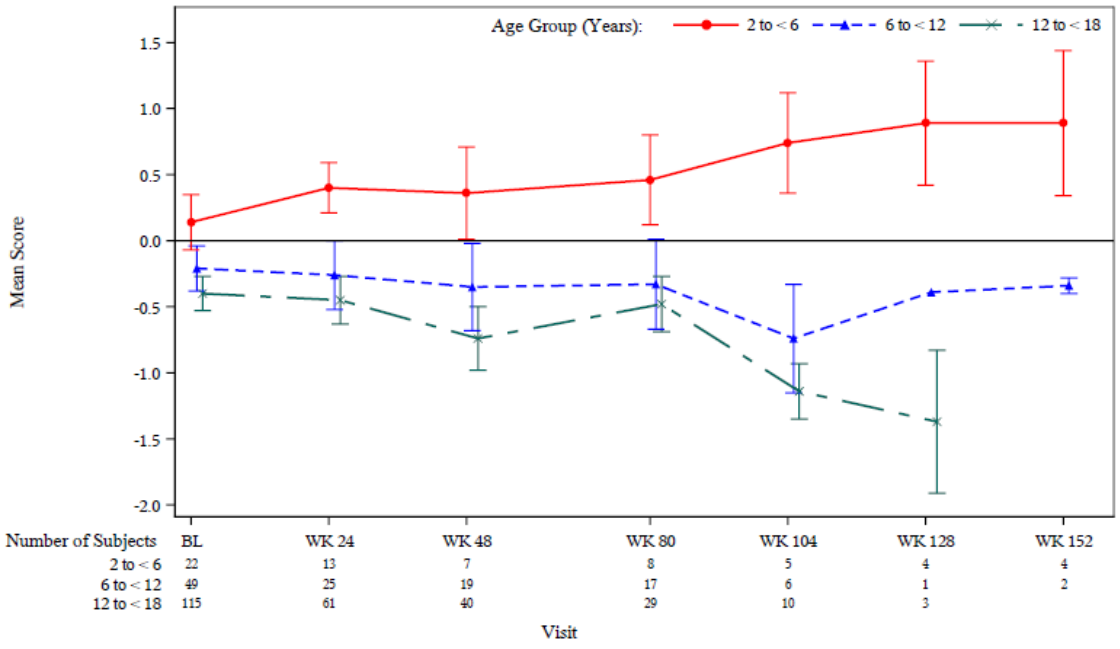


Figure 6 Mean Height Z-Score (+/- SE) Over Time in Females – CISAP



Body Weight

Figure 7 Mean Weight Z-Score (+/- SE) Over Time in Males – CISAP

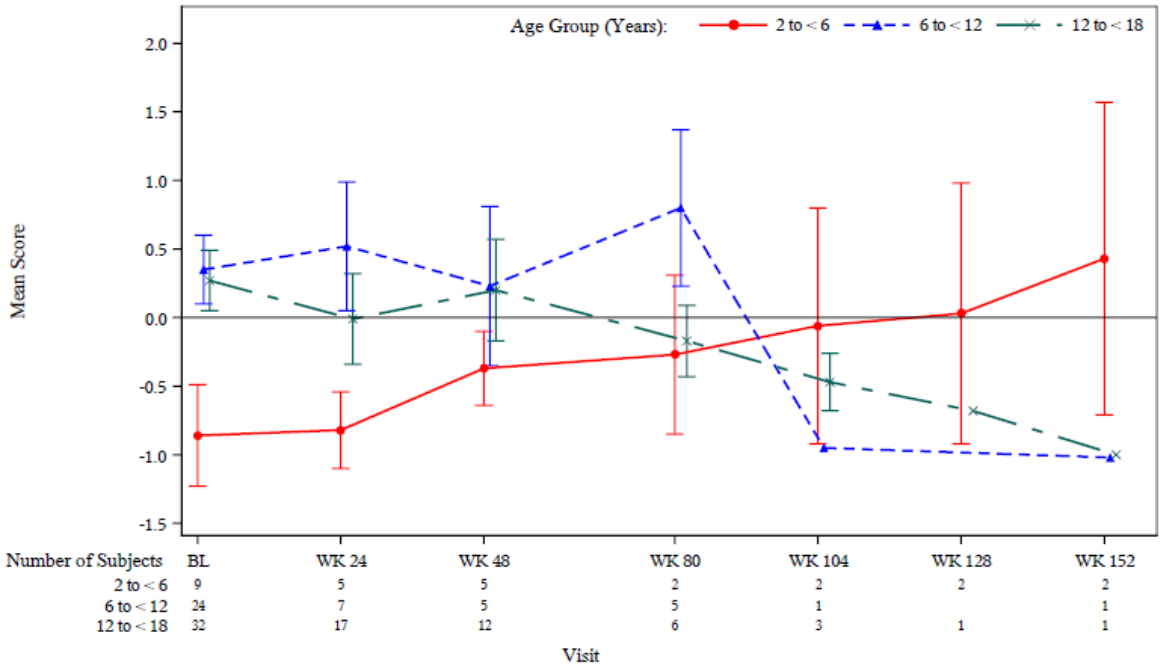
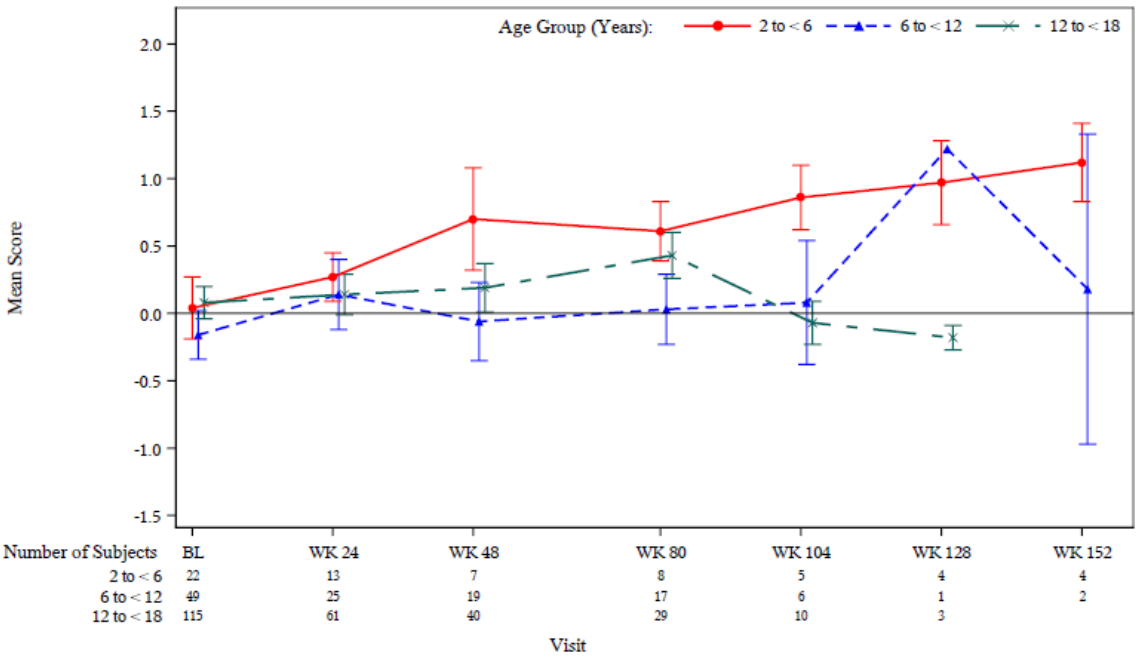


Figure 8 Mean Weight Z-Score (+/- SE) Over Time in Females – CISAP



Safety in special populations

Age

There were no major differences in the safety profile observed between the ages, although the incidence rate of TEAEs and SAEs were numerically lower in the youngest age group than in the others.

Table 24. Tofacitinib Integrated Summary of Safety Treatment-Emergent Adverse Events (All Causalities) by Age Group - ISAP

	Tofacitinib 5 mg BID		
Number (%) of Subjects	**2 to < 6 Years (N=31) n (%)**	**6 to < 12 Years (N=73) n (%)**	**12 to < 18 Years (N=147) n (%)**
Subjects evaluable for adverse events	31	73	147
Number of adverse events	174	313	645
Subjects with adverse events	28 (90.3)	65 (89.0)	134 (91.2)
Subjects with serious adverse events	3 (9.7)	9 (12.3)	11 (7.5)
Subjects with severe adverse events	0	5 (6.8)	10 (6.8)
Subjects discontinued from study due to adverse events (a)	6 (19.4)	22 (30.1)	30 (20.4)
Subjects discontinued study drug due to AE and continue Study (b)	0	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	13 (41.9)	14 (19.2)	31 (21.1)

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Includes events up to 999 days after the last dose of Tofacitinib. Events occurring during placebo exposure are excluded.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be
discontinued from Study
MedDRA 22.0 coding dictionary applied.

The incidence rates of **SAEs** varied from 3.87 subjects with SAEs/100 PY in the youngest age category (2 to < 6 yrs), to 7.71 subjects with SAEs/100 PY in the 6 to <12 yrs age category, and 5.99 SAEs/100 PYs in the oldest age category (12 to <18 yrs age).

In comparison, higher rates of SAEs were reported in the adult RA clinical program, with an incidence rate of 9.73 subjects with SAEs/100 PY at tofacitinib 5 mg BID in the P2P3 RA population and 9.39 subjects with SAEs/100 PY at tofacitinib 5 mg BID in the P123LTE RA population.

Gender

The majority of JIA subjects in the clinical program were female: 186 females, compared to 65 males. Incidence rates of SAE were **9.79** SAEs/100 PY in males and 5.10 SAEs/100 PY in females. Incidence rates for Adverse Events Resulting in Study Discontinuation were 24.68/100 PY in males and 16.58/100 PY in females.

JIA Subtype

Table 25. Tofacitinib Integrated Summary of Safety Treatment-Emergent Adverse Events (All Causalities) by Subtype of JIA - ISAP

	Tofacitinib 5 mg BID					
	Extended Oligoarthritis (N=32)	RF+ Polyarthritis (N=39)	RF- Polyarthritis (N=122)	Systemic JIA (N=13)	Juvenile Psoriatic Arthritis (N=22)	Enthesitis Related Arthritis (N=23)
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects evaluable for adverse events	32	39	122	13	22	23
Number of adverse events	106	206	541	37	111	131
Subjects with adverse events	27 (84.4)	36 (92.3)	109 (89.3)	12 (92.3)	21 (95.5)	22 (95.7)
Subjects with serious adverse events	2 (6.3)	3 (7.7)	10 (8.2)	2 (15.4)	4 (18.2)	2 (8.7)
Subjects with severe adverse events	0	0	10 (8.2)	1 (7.7)	3 (13.6)	1 (4.3)
Subjects discontinued from study due to adverse events (a)	6 (18.8)	7 (17.9)	27 (22.1)	7 (53.8)	6 (27.3)	5 (21.7)
Subjects discontinued study drug due to AE and continue Study (b)	0	0	0	0	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	6 (18.8)	7 (17.9)	31 (25.4)	2 (15.4)	6 (27.3)	6 (26.1)

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Includes events up to 999 days after the last dose of Tofacitinib. Events occurring during placebo exposure are excluded.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be
discontinued from Study
MedDRA 22.0 coding dictionary applied.

Formulation

Incidence rates of number of subjects with SAEs/100 PY reported in the two formulations were: tablet=6.49, liquid=7.56 and for discontinuations due to AEs were: subjects with events/100 PY: tablets=20.20, liquid=25.71. The spectrum of the AEs **treatment related** seems to be quite similar between the two formulation with abdominal pain, pyrexia and urinary tract infection being more common in liquid compared to tablet formulation, although they occurred in few patients (4, 3, 3 respectively).

Geographical Region

Table 26. Tofacitinib Integrated Summary of Safety Treatment-Emergent Adverse Events (All Causalities) by Geographical Region - ISAP

	Tofacitinib 5 mg BID			
	North America (N=101)	South and Central America (N=47)	Europe (N=27)	All Other (N=76)
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects evaluable for adverse events	101	47	27	76
Number of adverse events	655	149	116	212
Subjects with adverse events	95 (94.1)	40 (85.1)	23 (85.2)	69 (90.8)
Subjects with serious adverse events	10 (9.9)	1 (2.1)	4 (14.8)	8 (10.5)
Subjects with severe adverse events	11 (10.9)	1 (2.1)	1 (3.7)	2 (2.6)
Subjects discontinued from study due to adverse events (a)	19 (18.8)	12 (25.5)	3 (11.1)	24 (31.6)
Subjects discontinued study drug due to AE and continue Study (b)	0	0	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	31 (30.7)	2 (4.3)	14 (51.9)	11 (14.5)

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Includes events up to 999 days after the last dose of Tofacitinib. Events occurring during placebo exposure are excluded.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be
discontinued from Study
MedDRA 22.0 coding dictionary applied.
Europe includes Poland, Belgium, Great Britain, Spain, Germany, Slovakia; All Other includes Ukraine, Turkey, Russia, Australia and Israel.

Table 27. Tofacitinib Integrated Summary of Safety Exposure Estimates and Incidence Rates for Serious Adverse Events by Geographical Region - ISAP

Treatment	Tofacitinib 5 mg BID			
Geographical Region	**North America**	**South and Central America**	**Europe**	**All Other**
Number of Subjects in Analysis Set	101	47	27	76
Number of Subjects with Event n (%)	10 (9.9)	1 (2.1)	4 (14.8)	7 (9.2)
Total PD Exposure for Event	52904	21369	19896	35839
Incidence Rate/100 PD (95 % CI)	0.02 (0.01, 0.03)	0.00 (0.00, 0.03)	0.02 (0.01, 0.05)	0.02 (0.01, 0.04)
Total PY Exposure for Event	144.84	58.51	54.47	98.12
Incidence Rate/100 PY (95 % CI)	6.90 (3.31, 12.70)	1.71 (0.04, 9.52)	7.34 (2.00, 18.80)	7.13 (2.87, 14.70)

Table 27. Tofacitinib Integrated Summary of Safety Exposure Estimates and Incidence Rates for Serious Adverse Events by Geographical Region - ISAP

Treatment	Tofacitinib 5 mg BID			
Geographical Region	North America	South and Central America	Europe	All Other

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
CI: Exact 95% Poisson Confidence Interval.
For subjects who also enrolled in LTE study, total risk period is the sum of index and LTE risk periods.
The gap between index and LTE studies can add a maximum of 28 days to the risk period of exposure to Tofacitinib.
Placebo exposure may contribute a maximum of 28 days to the risk period.
PD (subject-day): Sum of total follow-time for all subjects combined.
Follow-up time is time from the first dose to the event or total exposure for subjects who did not have any event (to the earliest occurrence of date of: the last dose + 28 days, date of death, or cut-off date).
PY (subject-year): total follow-up time in years defined as PD/365.25.
Europe includes Poland, Belgium, Great Britain, Spain, Germany, Slovakia; All Other includes Ukraine, Turkey, Russia, Australia and Israel..

Prior bDMARD Therapy

The majority of subjects with JIA in the clinical program were naive to bDMARDs, with 66% of subjects in the integrated safety population having no previous experience with bDMARDs; **34% had previously received 1 or more bDMARD before study participation**.

Table below presents the TEAEs (All Causality) by previous bDMARDs received.

Table 28. Tofacitinib Integrated Summary of Safety Treatment-Emergent Adverse Events (All Causalities) by Previous Biologic DMARDs Received - ISAP

Number (%) of Subjects	Tofacitinib 5 mg BID			
	bDMARD naive (N=166) n (%)	bDMARD experienced (all) (N=85) n (%)	1 Prior bDMARD (N=46) n (%)	>=2 Prior bDMARDs (N=39) n (%)
Subjects evaluable for adverse events	166	85	46	39
Number of adverse events	730	402	243	159
Subjects with adverse events	146 (88.0)	81 (95.3)	44 (95.7)	37 (94.9)
Subjects with serious adverse events	14 (8.4)	9 (10.6)	4 (8.7)	5 (12.8)
Subjects with severe adverse events	9 (5.4)	6 (7.1)	1 (2.2)	5 (12.8)
Subjects discontinued from study due to adverse events (a)	31 (18.7)	27 (31.8)	10 (21.7)	17 (43.6)
Subjects discontinued study drug due to AE and continue Study (b)	0	0	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	37 (22.3)	21 (24.7)	13 (28.3)	8 (20.5)

Table 28. Tofacitinib Integrated Summary of Safety Treatment-Emergent Adverse Events (All Causalities) by Previous Biologic DMARDs Received - ISAP

Number (%) of Subjects	Tofacitinib 5 mg BID bDMARD naive (N=166) n (%)	bDMARD experienced (all) (N=85) n (%)	1 Prior bDMARD (N=46) n (%)	>=2 Prior bDMARDs (N=39) n (%)

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Includes events up to 999 days after the last dose of Tofacitinib. Events occurring during placebo exposure are excluded.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be
discontinued from Study
MedDRA 22.0 coding dictionary applied.

Also, for incidence rate (IR) calculation, a trend towards a higher IR of TEAEs in bDMARD experienced (404,14/100 PY) than naïve bDMARDs (258,98/PY) was observed.

Baseline MTX

The majority of JIA subjects (62%) were treated with background MTX at the start of tofacitinib treatment (Day 1), at an average dose of 15 mg/week.

Table below present the TEAEs by Use of MTX.

Table 29. Tofacitinib Integrated Summary of Safety Treatment-Emergent Adverse Events (All Causalities) by Use of MTX on First Dose Date - ISAP

Number (%) of Subjects	Tofacitinib 5 mg BID Yes (N=156) n (%)	No (N=95) n (%)
Subjects evaluable for adverse events	156	95
Number of adverse events	664	468
Subjects with adverse events	138 (88.5)	89 (93.7)
Subjects with serious adverse events	10 (6.4)	13 (13.7)
Subjects with severe adverse events	7 (4.5)	8 (8.4)
Subjects discontinued from study due to adverse events (a)	32 (20.5)	26 (27.4)
Subjects discontinued study drug due to AE and continue Study (b)	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	30 (19.2)	28 (29.5)

Table 29. Tofacitinib Integrated Summary of Safety Treatment-Emergent Adverse Events (All Causalities) by Use of MTX on First Dose Date - ISAP

	Tofacitinib 5 mg BID	
	Yes (N=156)	No (N=95)
Number (%) of Subjects	**n (%)**	**n (%)**

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Includes events up to 999 days after the last dose of Tofacitinib. Events occurring during placebo exposure are excluded.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be
discontinued from Study
MedDRA 22.0 coding dictionary applied.

The incidence rate of TEAEs was lower in subjects on background MTX (275.52/100PY) compared to subjects who were MTX-free (338.30/100 PY).

Rates of ALT/AST >1X ULN were doubled in subjects on background MTX versus those who did not receive MTX. There were no subjects with ALT/AST elevations ≥2X ULN in the MTX-free population versus 3.2% and 0.6% in subjects on background MTX. Overall, the rates of LFT elevations were low in both subjects with or without background MTX therapy.

Baseline Corticosteroids

Approximately 30% of JIA subjects received background oral corticosteroids (CS) at the start of tofacitinib 5 mg BID treatment (Day 1). Subjects on background MTX and/or CS were required to maintain a stable dose of these therapies throughout the studies.

Table 30. Tofacitinib Integrated Summary of Safety Treatment-Emergent Adverse Events (All Causalities) by Use of Oral Corticosteroid on First Dose Date - ISAP

	Tofacitinib 5 mg BID	
	Yes (N=75)	No (N=176)
Number (%) of Subjects	**n (%)**	**n (%)**
Subjects evaluable for adverse events	75	176
Number of adverse events	315	817
Subjects with adverse events	67 (89.3)	160 (90.9)
Subjects with serious adverse events	11 (14.7)	12 (6.8)
Subjects with severe adverse events	6 (8.0)	9 (5.1)
Subjects discontinued from study due to adverse events (a)	23 (30.7)	35 (19.9)
Subjects discontinued study drug due to AE and continue Study (b)	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	13 (17.3)	45 (25.6)

Table 30. Tofacitinib Integrated Summary of Safety Treatment-Emergent Adverse Events (All Causalities) by Use of Oral Corticosteroid on First Dose Date - ISAP

	Tofacitinib 5 mg BID	
	Yes (N=75)	No (N=176)
Number (%) of Subjects	**n (%)**	**n (%)**

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Includes events up to 999 days after the last dose of Tofacitinib. Events occurring during placebo exposure are excluded.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be
discontinued from Study
MedDRA 22.0 coding dictionary applied.

The incidence rate of TEAEs (all causalities) was higher in subjects without background CS (313.89/100 PY) compared to subjects who received background CS therapy (262.68/100 PY).

In general, baseline systemic oral CS use did not appear to impact the IR for SI, HZ, OI and MACE, likely due to both the limited number of events and the relatively low use of CS at baseline.

Discontinuation due to adverse events

Study A3921104

In Study A3921104, 26 (11.6%) subjects discontinued from the study because of an AE during the open-label run-in phase.

The most common TEAE by PT that led to discontinuation were JIA [6 (2.7%]), Disease Progression (5 [2.2%]), and Condition Aggravated (3 [1.3%]).

During the double-blind phase of Study A3921104, there were 16 [18.2%] subjects in the tofacitinib 5 mg BID group and 29 [34.1%] subjects in the placebo group that discontinued the study because of an AE. The most frequently reported PTs for the tofacitinib 5 mg BID and placebo groups were Disease progression (8 [9.1%] and 10 [11.8%] subjects, respectively), and Juvenile idiopathic arthritis (3 [3.4%] and 12 [14.1%] subjects, respectively).

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

Integrated Safety Analysis Population

Table 31. Tofacitinib Integrated Summary of Safety Incidence and Severity of Treatment-Emergent Adverse Events Resulting in Study Discontinuations by System Organ Class and Preferred Term (All Causalities) - ISAP

Number of Subjects Evaluable for AEs	Tofacitinib 5 mg BID (N=251)			
Severity(a)	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)
With Any AE Leading to Discontinuation	27 (10.8)	23 (9.2)	8 (3.2)	58 (23.1)
Blood And Lymphatic System Disorders	1 (0.4)	0	0	1 (0.4)
Leukopenia	1 (0.4)	0	0	1 (0.4)
Neutropenia	1 (0.4)	0	0	1 (0.4)
Gastrointestinal Disorders	1 (0.4)	0	1 (0.4)	2 (0.8)
Crohn's disease	0	0	1 (0.4)	1 (0.4)
Tooth impacted	1 (0.4)	0	0	1 (0.4)
General Disorders And Administration Site Conditions	13 (5.2)	11 (4.4)	2 (0.8)	26 (10.4)
Condition aggravated	4 (1.6)	3 (1.2)	1 (0.4)	8 (3.2)
Disease progression	8 (3.2)	7 (2.8)	1 (0.4)	16 (6.4)
Drug intolerance	1 (0.4)	1 (0.4)	0	2 (0.8)
Infections And Infestations	2 (0.8)	2 (0.8)	2 (0.8)	6 (2.4)
Appendicitis	0	1 (0.4)	0	1 (0.4)
Epidural empyema	0	1 (0.4)	0	1 (0.4)
Herpes zoster	1 (0.4)	0	1 (0.4)	2 (0.8)
Pneumonia	0	0	1 (0.4)	1 (0.4)
Sinusitis	0	1 (0.4)	0	1 (0.4)
Subperiosteal abscess	0	1 (0.4)	0	1 (0.4)
Upper respiratory tract infection	1 (0.4)	0	0	1 (0.4)
Investigations	2 (0.8)	2 (0.8)	0	4 (1.6)
Alanine aminotransferase increased	0	2 (0.8)	0	2 (0.8)
Aspartate aminotransferase increased	0	1 (0.4)	0	1 (0.4)
Mycobacterium test positive	1 (0.4)	0	0	1 (0.4)
Mycobacterium tuberculosis complex test positive	1 (0.4)	0	0	1 (0.4)
Musculoskeletal And Connective Tissue Disorders	8 (3.2)	7 (2.8)	1 (0.4)	16 (6.4)
Arthritis	2 (0.8)	0	0	2 (0.8)
Juvenile idiopathic arthritis	6 (2.4)	6 (2.4)	1 (0.4)	13 (5.2)
Still's disease	0	1 (0.4)	0	1 (0.4)
Psychiatric Disorders	0	0	2 (0.8)	2 (0.8)
Suicidal ideation	0	0	1 (0.4)	1 (0.4)
Suicide attempt	0	0	1 (0.4)	1 (0.4)
Skin And Subcutaneous Tissue Disorders	1 (0.4)	1 (0.4)	0	2 (0.8)
Alopecia	1 (0.4)	0	0	1 (0.4)
Dermatitis allergic	0	1 (0.4)	0	1 (0.4)
Surgical And Medical Procedures	0	1 (0.4)	0	1 (0.4)
Pilonidal sinus repair	0	1 (0.4)	0	1 (0.4)
Total preferred term events	29	27	8	64

Table 31. Tofacitinib Integrated Summary of Safety Incidence and Severity of Treatment-Emergent Adverse Events Resulting in Study Discontinuations by System Organ Class and Preferred Term (All Causalities) - ISAP

Number of Subjects Evaluable for AEs	Tofacitinib 5 mg BID (N=251)			
Severity(a)	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is counted.
Subjects are counted only once per treatment per event. For the TESS algorithm any missing severities have been imputed as severe unless the subject experienced
another occurrence of the same event in a given treatment for which severity was recorded.
In this case, the reported severity is summarized. Missing baseline severities are imputed as mild. Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
Includes data up to 999 lag days after last dose of Tofacitinib. Events occurring during placebo exposure are excluded.
MedDRA 22.0 coding dictionary applied.

Post marketing experience

As of 05 May 2019, cumulatively, there have been approximately 209,081 PY of exposure to tofacitinib from marketing experience. There have been a total of 67,075 case reports received. Of the 67,075 cases, 97.6% were from spontaneous sources. The remaining cases were reported from non-interventional studies, the literature, and other non-interventional solicited sources. There was a total of 181,756 AEs reported, of which 28,531 (15.7%) were SAEs.

The most frequently reported AEs in the 67,075 reported cases were drug ineffective (14.7%), condition aggravated (6.9%), headache (6.7%), product use in unapproved indication (6.7%), pain (6.5%), arthralgia (6.3%), fatigue (5.2%), malaise (5%), diarrhoea (4.3%), therapeutic product effect incomplete (4.3%), nausea (4.2%), pain in extremity (4.1%), nasopharyngitis (4.1%), product dose omission (3.4%), herpes zoster (3.2%), joint swelling (3.1%), peripheral swelling (2.9%), cough (2.7%), musculo-skeletal stiffness (2.7%), influenza (2.5%), pneumonia (2.3%), product use issue (2.5%), abdominal discomfort (2.1%), dizziness (2.1%); sinusitis (2.1%), and urinary tract infection (2.0%). The most frequently reported SAEs in the 67,075 cases (≥1%) were rheumatoid arthritis (1.8%), condition aggravated (1.6%), and pneumonia (2.3%).

In summary, the review of the types and frequencies of AE reports from post-marketing spontaneous/non-interventional studies/non-interventional solicited sources supports the known safety profile of tofacitinib identified through the tofacitinib RA clinical development programme. No new safety signals were identified.

2.6.1. Discussion on clinical safety

The safety profile of tofacitinib oral 5 mg BID tablet and oral solution formulation (1 mg/mL) dosed twice daily for the treatment of pediatric subjects with active pJIA is supported by the data coming from the pivotal Study A3921104 and the Integrated Safety Population JIA (ISAP) (from Studies A3921103, A3921104 and A3921145).

In the JIA ISAP safety database 251 patients have been exposed to the tofacitinib 5 mg BID dose with a mean duration of exposure of 511 days. Considering that the tofacitinib safety profile has been established in adults with RA, this is considered acceptable to the CHMP. However, additional long-term safety data is needed to be collected post-marketing from observational studies (i.e. registries) to evaluate the safety in larger populations according to EMA Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis. The MAH proposed as additional pharmacovigilance activities, two non-interventional post-authorisation safety studies (PASS) using existing JIA registries (the German Biologics in Pediatric Rheumatology Registry (BiKeR), the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO), the UK JIA Biologics and the Swedish JIA Clinical Registry), to actively collect and monitor the safety events of interest in tofacitinib treated JIA patients in the post-approval real-world setting, including events that have long latency and the possible effect of tofacitinib on maturation, development, bone growth and response to vaccination. Recommendation on immunization in section 4.4 of the SmPC has been included, recommending that prior to initiating tofacitinib all patients, *particularly JIA patients*, be brought up to date with all immunisations in agreement with current immunisation guidelines. Moreover, in light of the parallel evaluation of signal on MACE and malignancies, in view of the long-term nature of these events, the MAH committed to continue to conduct routine pharmacovigilance on malignancies in JIA patients and to assess all malignancies in the proposed JIA PASS studies (where lymphoma along with other types of malignancies has been included as an event of interest) to further inform risk characterization and minimization measures in this population.

Demographics and baseline disease characteristics were similar between the overall JIA integrated safety set and the pivotal Study A3921104 open-label run-in and double-blind phase analysis sets. All age groups were adequately represented. However, in view of disease epidemiology, the majority of subjects was in the oldest age group of 12 to <18 yrs old. Almost all subjects were treated with MTX at baseline OL run-in phase as well as in the ISAP, suggesting a prevalent second line treatment of tofacitinib. In the Integrated JIA Safety Population most of subjects were b-DMARDs naïve (66%) and 33,9% were bDMARDs experienced and the majority of subjects (62%) were treated with background MTX at the start of tofacitinib treatment (Day 1), at an average dose of 15 mg/week or CCS (approximately 30% of subjects). Other csDMARDs were used only in 2 patients at Day 1 of treatment. Based on these data, the MAH revised the claimed indication to better reflect the population studied (see Section 2.5.3. Discussion on clinical efficacy).

The majority of patients (78,2%) in the Entire Tofacitinib Exposure Period of Study A3921104 experienced AEs and 8 subjects (3,6%) had a SAE. Most TEAEs were mild to moderate in severity, and severe adverse events were reported for 5 (2.2%) subjects. 25 (18,7%) subjects discontinued from study due to AEs. No meaningful differences were observed in the DBSAS of pivotal study between tofacitinib and PLB groups.

The most common AEs occurring with ≥10% for tofacitinib treatment reported in the integrated safety population, by PT, were vomiting (10.0%), Nasopharyngitis (11.6%), and Upper respiratory tract infection (25.9%), JIA (10.8%), and Headache (12.4%). Treatment-related AEs by PT were reported at rates below 5%, with the exception of upper respiratory tract infection, which was reported in 10% of the population. As stated by the MAH, all TEAEs with at least 2% occurrence have previously been identified as common AEs in the adult RA population.

A not negligible proportion of subjects (23.1%) in the ISAP discontinued treatment due to AEs. However, it should be considered that the most frequently reported AEs leading to discontinuation in the integrated analysis were disease progression, JIA, and condition aggravated, rather suggesting a loss of efficacy. 6 (2,4%) subjects discontinued due to infections and infestations.

There were no deaths reported neither in Study A3921104 nor in the JIA safety population**.**

In the ISAP, there were 23 subjects (9.2%) with **SAEs,** corresponding to an incidence rate of 6.18 (3.87, 9.36) subjects/100 PYs. The majority of SAEs were reported in the SOCs of infections and infestations or due to disease worsening/JIA exacerbation.

It was also noted that 3 subjects had SAEs relative to **psychiatric disorders**: one subject aged 11, was hospitalized for Major Depressive Disorder and Homicidal Ideation, one subject aged 13 years for Suicidal Ideation, and one subject aged 16 years for a Suicide Attempt, but none were considered related to study drug. Two of these subjects had a positive relevant medical history for psychiatric disorders. The incidence rate (95% CI) of suicidal and self-injurious behaviors in the ISAP was 0.82 (0.17, 2.39) subjects with events/100 PYs, which was higher than that reported in the RA programme (0.04 subjects with events/100 PYs). However, the different age population and exposure between JIA patients and RA subjects does not allow to draw firm conclusion from this comparison. Unfortunately, as reported by the MAH, although an increased frequency of psychiatric disorders and depression in JIA subjects compared to healthy youth is acknowledged, incidence rates for psychiatric disorders, including MDD and suicidal ideation in JIA patients are not available in literature (Mullick, Nahar, and Haq, 2005; Hanns et al, 2018). However, it is known that suicidality in the child and adolescent population is a major public health concern and that the risk for self-harm, suicidal thinking, and attempted suicide may increase in case of chronic physical and mental conditions *(*Barnes AJ et al. Pediatrics, 2010*).* Therefore, due to these reasons and confounding factors, it is difficult to draw final conclusion on psychiatric disorders and suicidal and self-injurious behaviors in tofacitinib treated JIA population. Data provided from a literature review on the possible impact of jak inhibitors mechanism of actions on psychiatric events as well as on identifying incidence rates among a similar setting of the JIA population, are not sufficiently clear to conclude on an association of psychiatric events with tofacitinib. Moreover, data from the latest PSUR on signal evaluation of Psychiatric Disorders in adult population were considered insufficient to establish a causal relationship between the use of tofacitinib and the development of suicidal/self-injurious behaviour or anxiety. In pJIA subjects, 2 psychiatric disorders were judged by the investigator as related to study drug (aggression and anxiety). However, as re-assessed by the MAH, the event of anxiety occurred in a 17-year old female, was moderate in intensity, started at the 311 study day and did not require a change of the study drug. Moreover, she was taking concomitant medications (lutera and meloxicam) that can be associated with anxiety. The event of aggression ["worsening of behavior Alteration (aggressiveness)"], occurred in a 7-year old male patient, started on Study Day 497, was mild in severity and did not require a change of study drug. Therefore, considering the late onset of the events, which did not require study drug interruption and the confounding factors, the CHMP considers reasonable the MAH's conclusion that a clear causal association of these events with tofacitinib, cannot be established.

The MAH was requested to clary if some related AEs other than serious infections has similar frequency in JIA and RA patients. The MAH identified some related AEs (e.g influenza, pharyngitis, sinusitis, viral infection, abdominal pain, nausea, vomiting, pyrexia, headache, cough), with a higher frequency in paediatric JIA population compared to the adult one. It is however noted that the JIA programme is smaller than the adult programme and that the differences observed are likely due to the background risks associated with the study population. In order to better inform physicians and patients, this information is included in the SmPC Section 4.8.

Adverse events of special interest

There were no cases of GI perforation, ILD, MACE, malignancy, MAS, opportunistic infection, thromboembolism (no PE or DVT reported), or TB. Risk factors for thromboembolic events and/or thrombophilia were not included among exclusion criteria since the safety signal was not known at the time of the study design and conduction. Moreover, in the paediatric setting they are less common as compared to adults. **Serious Infections** and **Herpes Zoster** were the only AEs of Special Interest reported in the ISAP. Serious infections occurred in three subjects during exposure to tofacitinib in pivotal

Study A3921104 in the open-label run in phase (1 subject with pneumonia, 1 subject with epidural empyema, pan sinusitis and subperiosteal abscess with a history of craniosynostosis repair, and 1 subject with appendicitis) and in three subjects in LTE study A3921145: acute pyelonephritis, abscess limb (buttocks) and UTI. In addition, there was one event of pilonidal cyst not originally included in the list of serious infections and in the incidence rate calculation due to a discrepancy between the clinical and the safety databases. The incidence rate for serious infections is 1.92 patients with events per 100 patient-years.

There were 3 subjects with HZ reported in integrated safety analysis set for JIA (incidence rate of 0.82 events/100 PY) and all of these were mild to moderate and monodermatomal. However, a severe multi-dermatomal case in one additional subject (12 days outside of risk period) occurred. Serious and other important infections, and HZ reactivation are important identified risks and RMMs are in place to mitigate them.

Serious infections and HZ are known AESI of tofacitinib treatment and are adequately reported in sections 4.4 and 4.8 of the SmPC.

Laboratory findings

The changes from baseline in **haemoglobin** were similar in both treatment groups during the double-blind phase of Study A3921104. The mean absolute total **neutrophils** decreased from baseline to Week 18 of the open-label run-in phase of Study A3921104 and were similar in the DB phase between the two treatment groups. However, at week 24 a higher difference was observed between tofacitinib and placebo groups [the mean (SE) change from the double-blind baseline in absolute neutrophils was -0.20 (0.30)$\times 10^3/mm^3$ for the tofacitinib 5 mg BID group and 0.39 (0.24) $\times$ $10^3/mm^3$ for the placebo group. No patients were discontinued due to ANC decreases. Upon request from the CHMP, the MAH specified that 5 patients in the integrated safety analysis population had severe neutropenia (absolute neutrophil count <1000 cells/mm3 at one or more visits), which was transient in all patients and did not require treatment discontinuation of the study drug (except in one case in which neutropenia was reported in the last day of the open-label phase). The first patient experienced a concomitant mild viral infection with fever which was considered not related to study treatment. The second patient experienced a mild upper respiratory tract infection before neutropenia and a mild viral infection probably after resolution of neutropenia. No concomitant infections were reported in the other patients. All patients had concomitant medications at the time of the event. In addition, two patients experienced severe anemia which was transient and no action was taken regarding study medication. Changes in Hb and ANC are expected during treatment and they are reflected in the current version of the SmPC with precautions on how the risks can be mitigated or managed. However, the sections 4.2 and 4.4 of the SmPC have been modified recommending not to initiate tofacitinib treatment in paediatric patients with an absolute neutrophil count less than 1,200 cells/mm3 and haemoglobin level less than 10 g/dL according to the inclusion/exclusion criteria of the pivotal study.

Overall, in the JIA clinical programme (CISAP) the majority of patients in different age groups had ALC $\geq$ 2000/mm^3. No subjects met the discontinuation criteria of ALC <500/mm^3. However, according to the Covance classification, 4 patients (12,9%) in the age group of 2 to < 6 Years had LLN for ALC (<1500/mm^3) without experiencing concomitant serious infections.

In the pivotal Study A3921104, an initial increase of platelets count at Week 2 followed by a decrease by Week 18 during the open-label run-in phase was observed. Only patients with a platelet count ≥100,000 platelets/mm^3 at the study A3921104 enrollment visit were allowed to participate in the study and this has been reported in the SmPC.

Treatment with tofacitinib was already associated with an increased incidence of **liver enzyme elevation** in some adult patients. In the ISAP of the paediatric JIA programme, 3 hepatic events were judged as DILI (2 mild hepatic events, 1 adjudicated as possible DILI and 1 as probable DILI, and 1 moderate

hepatic event adjudicated as probable DILI). All 3 subjects were on background MTX therapy and 2 patients were also taking paracetamol, with a concurrent viral illness in one case, as confounding factors of possible causes of DILI. However, they resolved after discontinuation of methotrexate and interruption or permanent discontinuation of tofacitinib. No cases of Hy's Law were reported. This information has been reported in Section 4.8 of the SmPC**.**

Pubertal development has been investigated using Tanner Stage Assessment at the baseline visit in the pivotal Study A3921104 and on a yearly basis after rollover into the LTE Study A3921145. However, very few patients are available for a year or more in the LTE study A3921145 at the time of data cut-off for this submission and this does not allow to draw firm conclusion on pubertal development.

Height and **weight** were compared with data from standard growth charts and summarized using Z-scores. Despite limitations due to the limited number of subjects with 2 years follow up, it seems from data provided that no significant changes from baseline in height were observed over time in pJIA subjects continuously evaluated over 2 years in the CISAP. In the youngest age group (2 to <6 years) in the female JIA subjects in the CISAP was observed mild weight Z-score increases. However, due to the very few subjects in the CISAP in which weight was assessed continuously for ≥2 years, no firm conclusions can be drawn.

Almost all patients in each **age** group experienced AEs. No meaningful differences in TEAEs and SAEs were observed across age groups. However, it was noted that the incidence rates of SAEs are lower (3.87 subjects with SAEs/100 PY) in the youngest age category (2 to < 6 yrs) compared to 7.71 subjects with SAEs/100 PY in the 6 to <12 yrs age category, and 5.99 SAEs/100 PYs in the oldest age category (12 to <18 yrs age) and this is of some reassurance for the youngest group, although, due to the limited number of patients, these observation should be interpreted with caution.

With regards to **gender**, a higher IR of SAEs were observed in males 9.79 SAEs/100 PY compared to female 5.10 SAEs/100 PY. The MAH was asked to specify if a trend in any specific SAE was observed in males. The majority of SAEs and discontinuations due to AEs for males were related to flare/JIA worsening. The other SAEs or AEs leading to discontinuations occurred in few patients and were single events. Therefore, no specific trend of SAEs in males was identified.

Percentage and IR of SAEs are higher in patients with sJIA (as expected due to the different clinical aspect of the disease) and juvenile psoriatic arthritis,.

Regarding the distribution of AEs among different **regions**, it was noted that SAEs occurred less frequently (only in one patient, IR/100 PY 1.71) in South and Central America compared to North America (IR/100 PY 6.90), Europe (IR/100 PY 7.34) and other (IR/100 PY 7.13), even if in most cases were considered unrelated by both investigators and sponsor and the difference seems to decrease when considering only serious infections. Moreover, an imbalance between rate of discontinuation (25.5%) and reduced or temporary discontinuation due to AEs (4.3%) in South and Central America was observed, but the rates of discontinuations seem to become similar among regions when JIA flares are removed from calculation, suggesting that most discontinuations were due to loss of efficacy. The same did not occur for reduced or temporary discontinuation, which are reported to be not related to flares but rather to certain laboratory abnormalities or were up to investigator discretion. Therefore, in this case a specific reason of difference in frequencies was not identified by the MAH. Only one SAE (2.1%) of pneumonia occurred in the South and Central America which was considered related to study drug. A higher frequency of SAEs was reported in the other regions (range: 8.9% to 11.1), even if in most cases were considered unrelated by both investigators and sponsor and the difference seems to decrease when considering only serious infections. Therefore, even though no certain conclusion can be drawn, the differences among regions seem to reduce when considering the provided justifications. Therefore, the issue was not further by the CHMP.

As expected, there was a slightly higher rate of subjects experiencing AEs, SAEs, severe AEs and discontinuations in **bDMARDs experienced** patients compared to bDMARDs naïve subjects, mainly driven by the subgroup of patients with ≥ 2 prior bDMARDs. Subjects who had previously received 2 or more bDMARDs discontinued at a rate of 43.6% compared to 18.7 % for bDMARD naive subjects. Also, for IR calculation, a trend towards a higher IR of TEAEs in bDMARD experienced (404,14/100 PY) than naïve bDMARDs (258,98/PY) was observed.

The majority of patients (62%) in the ISAP was treated with MTX at the start of tofacitinib. Overall, the tofacitinib safety profile with background MTX therapy did seem worse than on monotherapy**.** There were only 3 patients taking concomitant csDMARDs other than MTX (one leflunomide and 2 hydroxychloroquine), therefore there are no sufficient information about the tofacitinib safety profile with csDMARDs different to MTX as background treatment and this is reflected in the SmPC.

As expected, a higher rate of SAEs, severe and discontinuation due to AEs was noted in the JIA subjects who received background oral corticosteroids compared to the others.

The MAH took also the opportunity to update the summary of safety profile for patients with rheumatoid arthritis, to indicate the frequency of the adverse reactions:

The most common serious adverse reactions were serious infections (see section 4.4). In the long-term safety all exposure population, the most common serious infections reported with tofacitinib were pneumonia (1.7%), herpes zoster (0.6%), urinary tract infection (0.4%), cellulitis (0.4%), diverticulitis (0.3%), and appendicitis (0.2%). Among opportunistic infections, TB and other mycobacterial infections, cryptococcus, histoplasmosis, oesophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus, BK virus infections and listeriosis were reported with tofacitinib. Some patients have presented with disseminated rather than localised disease. Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

The most commonly reported adverse reactions during the first 3 months in controlled clinical trials were headache (3.9%), upper respiratory tract infections (3.8%), viral upper respiratory tract infection (3.3%), diarrhoea (2.9%), nausea (2.7%), and hypertension (2.2%).

The proportion of patients who discontinued treatment due to adverse reactions during first 3 months of the double-blind, placebo or MTX controlled studies was 3.8% for patients taking tofacitinib. The most common infections resulting in discontinuation of therapy during the first 3 months in controlled clinical trials were herpes zoster (0.19%) and pneumonia (0.15%).

This is agreed by the CHMP.

2.6.2. Conclusions on the clinical safety

The safety profile related to the JIA paediatric population is considered generally similar to that of the already approved tofacitinib indications, without new clinically important safety signals related to tofacitinib treatment identified. In particular, the adverse reactions in JIA patients were consistent with those seen in adult RA patients, with the exception of some infections and gastrointestinal or general disorders, which were more common in JIA paediatric population. This is appropriately reflected in the SmPC.

The only adverse events of interest were serious infections (no opportunistic) and HZ.

The long-term safety in JIA patients is identified as missing information and will be further evaluated through additional pharmacovigilance activities (PASS studies) in the post-marketing setting, as agreed in the RMP.

2.7. Risk Management Plan

The MAH submitted an updated RMP version with this application.

The PRAC considered that the risk management plan version 12.4 is acceptable. The CHMP endorsed the Risk Management Plan version 12.4 with the following content:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Venous thromboembolic events (DVT/PE)	<u>Routine risk minimisation measures:</u> SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		[A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC) •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. •Biospecimen Testing Study (Study Number Pending) (please note this study has completed after the DLP of this RMP and assessed in the EU RMP version 14.1, which is currently under PRAC review)
Serious and other important infections	<u>Routine risk minimisation measures:</u> SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	(including Treatment Checklists, Prescriber Brochure).	•Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (Swedish National Quality Registry for Inflammatory Bowel Disease [SWIBREG] – A3921344, and the United Registries for Clinical Assessment and Research [UR-CARE] – A3921352), over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		administrative healthcare claims database (UC)
HZ reactivation	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Decrease in neutrophil counts and neutropenia	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Decrease in lymphocyte counts and lymphopenia	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Decrease in Hgb levels and anaemia	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Lipid elevations and hyperlipidaemia	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
NMSC	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.
Transaminase elevation and potential for DILI	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor.
Important Potential Risks		
Malignancy	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Cardiovascular risk	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
GI perforation	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
ILD	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register
PML	Routine risk minimisation measures: Not applicable Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.
All-cause mortality	<u>Routine risk minimisation measures:</u> SmPC Section 5.1 Pharmacodynamic properties <u>Additional risk minimisation measures:</u> None proposed	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Course Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years •A3921133: A large, post-approval long-term clinical safety trial with an active comparator arm with primary focus of evaluating the safety of tofacitinib at 2 doses versus TNF inhibitor. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (in-hospital mortality)
Increased immunosuppression when used in combination with biologics and immunosuppressants including B-	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 Special warnings and precautions for use <u>Additional risk minimisation measures:</u> Development of an educational programme including additional	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u>

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
lymphocyte depleting agents	communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	•A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment)
Increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment)
Primary viral infection following live vaccination	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Shingrix study
Increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Higher incidence and severity of AEs in the elderly	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921329 (UC): observational PASS within the Corrona Registry over 5 years •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over t 5 years.
Missing Information		
Effects on pregnancy and the foetus	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, pregnancy, and lactation Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Monitoring via an established pregnancy registry (US OTIS). •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment)
Use in breastfeeding	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, pregnancy, and lactation Additional risk minimisation measures: Development of an educational programme including additional	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	
Effect on vaccination efficacy and the use of live/attenuated vaccines	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment)
Use in patients with mild, moderate, or severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 5.2 Pharmacokinetic properties Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921334 (RA, PsA, UC): An EU-based survey for prescribers (aRMM effectiveness assessment) •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment)
Use in patients with moderate or severe renal impairment	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 5.2 Pharmacokinetic properties Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with evidence of hepatitis B or C infection	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients with malignancy	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances)	Routine risk minimisation measures: None Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Additional pharmacovigilance activities: •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the Swedish JIA Clinical Registry •Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry •A nonclinical juvenile rat toxicity study to address the potential for tofacitinib to adversely affect bone development and growth

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•Study A3921145: A Long Term, Open Label Follow Up Study of Tofacitinib for Treatment of JIA

Conclusion

The CHMP and PRAC considered that the risk management plan version 12.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication initially applied was "*tofacitinib oral IR tablet and oral solution 5 mg BID for the treatment of active polyarticular course JIA in subjects 2 years of age and older*".

JIA is an umbrella-term describing a heterogeneous group of conditions characterized by chronic arthritis with onset before the age of 16 years, persisting for at least 6 weeks, and having no other identifiable cause.

Polyarticular JIA is defined as arthritis affecting 5 or more joints during the first 6-month period and includes RF+ polyarthritis and, RF- polyarthritis according to ILAR classification. Subjects with other subtypes of JIA who later develop arthritis in multiple joints can also have polyarticular disease, however

they are excluded from the ILAR polyarticular JIA subgroup (Oberle et al, 2014). These subjects, along with those with polyarticular JIA, could have polyarticular JIA.

Aim of the treatment is to delay the progression of symptoms of pJIA, as well as prevent joint damage over the long term (Hashkes, 2011; Beukelmann et al, 2011). Consequently, the current treatment approach has shifted from a pyramidal approach to more aggressive therapy with earlier initiation of bDMARDs.

3.1.2. Available therapies and unmet medical need

Conventional treatment options for pJIA include local glucocorticoid injections, systemic glucocorticoids, NSAIDs, and csDMARDs (Schiappapietra et al, 2015; Ringold et al, 2014).

csDMARDs are first-line therapy for the treatment of pJIA due to their proven ability to minimize joint damage and improve symptoms. MTX is the most widely used csDMARD; side effects such as gastrointestinal and hepatic toxicity are often associated with its use (Ringold et al, 2019; Falvey et al, 2017).

Biological DMARDS, which are directed at extracellular targets such as individual soluble cytokines, have revolutionized the treatment of pJIA, especially in those who fail to respond to csDMARDs (Hodge et al, 2016; Ringold et al, 2019). TNF inhibitors were the first bDMARD approved for the treatment of pJIA, are the most widely used class of bDMARDs, and have been shown to lead to significant improvement in the reduction of signs and symptoms of pJIA. Since their approval, other classes of bDMARDs have also been approved for use in pJIA (IL-1 inhibitors, IL-6 inhibitors, selective T cell costimulation modulator) (Sterba and Ilowite, 2016).

Despite benefits of bDMARDs, there are still downsides to their use in children with pJIA such as response in only a percentage of subjects, route of administration (parenteral) and the potential development of anti-drug antibodies which can result in loss of efficacy over time.

3.1.3. Main clinical studies

Study A3921104 was a randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of tofacitinib for the treatment of **polyarticular** juvenile idiopathic arthritis (including not only the classical pJIA subsets but also extended oligoarthritis and sJIA with arthritis and without systemic features) in children from 2 years of age and older. Superiority of tofacitinib versus placebo was analysed.

3.2. Favourable effects

The primary endpoint (occurrence of disease flare from double-blind randomization through Week 44 (type I Error Controlled) of study was significantly lower in the tofacitinib 5 mg BID group compared to the placebo group (p-value=0.0031), with a difference of proportions (tofacitinib-placebo) of -23.69%, 95% CI (-39.41%, -7.97%). The results obtained from imputation methods accounting for dropouts supported the primary endpoint conclusion.

Numerical treatment differences were observed in favour of tofacitinib in the reported subgroups. Secondary endpoints measuring occurrence of flares (i.e. at different timepoints of the DB phase) supported the results of the primary endpoint (analysis is only descriptive, significant difference is shown).

Efficacy is consistent across the different JIA subtypes, bDMARD naïve and experienced groups included in the indication.

The secondary (type I controlled) endpoints were also supportive of superiority of tofacitinib over PLB:

i) **JIA ACR 50, 30, and 70 responses** (at Week 44, Type I Error Controlled), a significantly greater proportion of subjects treated with tofacitinib 5 mg BID achieved ACR 50, 30, and 70 responses compared to subjects treated with placebo (response 48%, delta 19.52 p=0.0166; response 51%, delta 23,69 p=0.0031; response 39% delta 17.02 p=0.0387, respectively). Difference form PLB was statistically significant, consistent across the different measure of ACR response and of clinical value (a percentage ranging from 50% to 30%, for the ACR70 stringent endpoint, showed ACR response). Subgroups analyses favour tofacitinib treated subjects.

Secondary endpoints measuring ACR responses for the entire study support the key secondary endpoint results.

ii) **Change from Double-Blind Baseline in CHAQ Disability Index** at Week 44 (Type I Error Controlled) the improvement was statistically greater in subjects treated with tofacitinib 5 mg BID than those treated with placebo, with a LS mean difference in the scores of -0.12, p-value=0.0292. Range of the index is 0-3.

Secondary endpoints (not type I controlled) results, although descriptive analysis was conducted, were generally supportive of better activity of tofacitinib as compared to placebo for different endpoints related to disease activity.

Supportive results on tofacitinib activity are from the mean change in number of joints with active arthritis in the DB phase showing a better trend in particular at later endpoints in the tofacitinib treated. Same trend favouring tofacitinib for number of joints with limited motion (often statistical difference although descriptive in the DB phase) and also for evaluation of disease activity by physician and CHAQ parental is also seen.

Overall efficacy results from the pivotal study are supportive of tofacitinib superiority as compared to placebo.

Data coming from the OL LTE A3921145 Study (interim analysis, as of the 04 June 2019 data cut-off, 227 subjects were enrolled in; 177 subjects are currently ongoing) are overall supportive of those obtained in the pivotal trial.

The oral formulation is considered an advantage to reduce the stress of parenteral administration on children with pJIA and their families.

3.3. Uncertainties and limitations about favourable effects

Although EU population is very limited represented, potentially affecting the external validity of study results to EU population, the similarity of enrolled pJIA population to the EU pJIA population needs was supported using different data sources.

Secondary endpoints results were generally supportive of primary/key secondary, however analysis is only descriptive so limits on robustness of results apply.
Efficacy on endpoints aimed at evaluating disease activity is not or only partially demonstrated i.e. minimal disease activity showed only a numerical trend and not a significant (although formally descriptive) clinical effect. For JIA ACR inactive disease, JIA ACR remission was achieved by 3 subjects per arm, which is very limited; although it is recognized that this is a very stringent endpoint.

No endpoints aimed at looking the prevention/effect of structural damage are included. Measures of disease activity could serve indirectly as an indicator for the effect on bone. Being pJIA a chronic disease, long term effect in terms of reducing disease activity sufficiently to prevent life-long damage is an important clinical objective. This remains an uncertainty. This is agreed by the CHMP since no effect is claimed.

Long term efficacy of tofacitinib in treating JIA subjects will be further substantiated by upcoming analyses, results are from an interim analysis with most subjects still ongoing. The MAH has agreed to submitted to submit final results of Study A3921145 which is listed as category 3 in the RMP.

3.4. Unfavourable effects

Safety data set is an acceptable number of JIA paediatric patients and all age ranges were represented.

As expected, there was a slightly higher rate of subjects experiencing AEs, SAEs, severe AEs and discontinuations in **bDMARDs experienced** patients compared to bDMARDs naïve subjects, mainly driven by the subgroup of patients with ≥ 2 prior bDMARDs. Moreover, a higher rate of SAEs, severe and discontinuation due to AEs was noted in the JIA subjects received background oral corticosteroids compared to the others.

The majority of patients in the Entire Tofacitinib Exposure Period of Study A3921104 experienced AEs. Most TEAEs were **mild to moderate** in severity, and severe adverse events were reported for 5 (2.2%) subjects.

The **most common AEs** occurring with ≥10% for tofacitinib treatment reported in the integrated safety population, by PT, were **Vomiting**, **Nasopharyngitis**, **Upper respiratory tract infection**, **JIA** and **Headache**. Treatment-**related** AEs by PT were reported at rates below 5%, with the exception of upper respiratory tract infection, which was reported in 10% of the population. The adverse reactions in JIA patients were consistent with those seen in adult RA patients, with the exception of some infections and gastrointestinal or general disorders, which were more common in JIA paediatric population. This is appropriately reflected in the Section 4.8 of the SmPC.

A large proportion of subjects (23.1%) in the ISAP **discontinued** treatment due to AEs. However, the most frequently reported AEs leading to discontinuation in the integrated analysis were disease progression, JIA, and condition aggravated, suggesting a loss of efficacy. 6 (2,4%) subjects discontinued due to infections and infestations.

In the ISAP, there were 23 subjects (9.2%) with SAEs, the majority reported in the SOCs of infections and infestations or due to disease worsening/JIA exacerbation. 3 subjects had SAEs relative to psychiatric disorders.

There were no cases of GI perforation, ILD, MACE, malignancy, MAS, opportunistic infection, thromboembolism (no PE or DVT reported), or TB.

Serious Infections and **Herpes Zoster** were the only AEs of Special Interest reported in the ISAP. Serious infections occurred in 7 subjects in the integrated safety analysis set for JIA (pneumonia, epidural empyema, pan sinusitis and subperiosteal abscess with a history of craniosynostosis repair, pilonidal cyst, appendicitis, acute pyelonephritis, abscess limb (buttocks) and UTI). Overall, there were 3 subjects with HZ reported in the integrated safety analysis set for JIA and all of these were mild to moderate and monodermatomal. One (1) additional patient had an event of serious HZ outside the reporting window.

It is known that treatment with tofacitinib was associated with an increased incidence of liver enzyme elevation in some patients. In the ISAP of the paediatric JIA programme, 3 hepatic events were judged as **DILI** (2 mild hepatic events, 1 adjudicated as possible DILI and 1 as probable DILI, and 1 moderate

hepatic event adjudicated as probable DILI). All 3 subjects were on background MTX therapy, the events resolved after discontinuation of MTX and interruption or permanent discontinuation of tofacitinib. No cases of Hy's Law were reported.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile was described in a sufficient number of JIA paediatric patients and all age groups were represented, even if, in view of disease epidemiology, the majority were in the oldest age group of 12 to <18 yrs old. No meaningful differences in TEAEs and SAEs were observed across age groups. However, a better trend seems to be observed in the youngest age category (2 to < 6 yrs), even though, due to the limited number of patients, this observation should be interpreted with caution.

Although the tofacitinib safety profile has been established in adults with RA, the long-term safety profile in paediatric JIA population as well as possible effects on maturation, development, bone and the potential impact on the immune system, are at present not completely known due to the limited number of patients and exposure and will be further investigated in planned PASS studies, as agreed in the RMP.

The majority of SAEs were reported in the SOCs of infections and infestations or due to disease worsening/JIA exacerbation.

Serious Infections and **Herpes Zoster** were the only AEs of Special Interest reported in the ISAP. Although Herpes Zoster cases were in the majority (all 3 subjects) mild to moderate and monodermatomal, however a severe multi-dermatomal case in one additional subject (12 days outside of risk period) occurred. Serious and other important infections, and HZ reactivation are important identified risks and RMMs are already in place to mitigate them.

3.6. Effects Table

Table 32 Effects Table for tofacitinib in patients with pJIA.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint: Occurrence of disease flare from double-blind randomization through Week 44	**Occurrence Rate**	%	29%	53%	primary endpoint was significantly lower in the tofacitinib 5 mg BID group compared to the placebo group in the overall population. Efficacy supported by data from key subgroups in the JIA subtypes of RF+ or RF– polyarthritis, E Oligo, PsA), bDMARD naïve and experienced, and for the group who received tofacitinib as monotherapy or concomitantly to cDMARD. Secondary endpoints results were generally supportive of primary/key secondary, however analysis is only	Study A3921104

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
					descriptive so limits on robustness of results apply. Although activity on disease flare is shown, the impact on disease activity is not or only partially demonstrated i.e. minimal disease activity showed only a numerical trend and not a significant clinical effect. Reducing disease activity sufficiently to prevent life-long damage is an important clinical objective. No endpoints aimed at looking the prevention/effect of structural damage are included. This is at present an uncertainty. Long term efficacy of tofacitinib in treating JIA subjects needs will be further substantiated by upcoming analyses, results are not definitive	
Key secondary endpoints: ACR=American College of Rheumatology responses 30/50/70 at week 44 compared to PLB	**Response Rate**		ACR30 71% ACR50 67% ACR70 54%	47% 47% 37%	secondary endpoints were significantly lower in the tofacitinib 5 mg BID group compared to the placebo group in the overall population.	Study A3921104
Key secondary endpoints: Change in CHAQ=Childhood Health Assessment Questionnaire at week 44 compared to baseline	**LS Mean (SEM)**		-0.09 (0.04)	0.03 (0.04)	Statistically significant	Study A3921104
Unfavourable Effects						
AEs	Rate	77,3 % in tofacitinib arm	*Study A3921104:* DBSAS	74,1% in PLB arm	Similar trend	Study A3921104

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
		78,2 %	Entire Tofacitinib Exposure Period of Study			
SAEs	N. of subjects Rate Incidence rate	1 in the tofacitinib arm 9.2% IR: 6.18(3.87, 9.36)	*Study A3921104:* double-blind phase *Integrated Safety Analysis Population*	2 in the placebo group.	3 psychiatric disorders	Study A3921104 Studies A3921103, A3921104 and A3921145
AESI: Serious infections HZ	Number of subjects Incidence rate Number of subjects Incidence rate	7 subjects (IR: 1.92 events/100 PY) 3 subj (IR: 0.82 events/100 PY)	*Integrated Safety Analysis Population* *Integrated Safety Analysis Population*		All mild to moderate and monodermatomal, but with a severe multi-dermatomal case in one additional subject	Studies A3921103, A3921104 and A3921145
Discontinuations	Rate	23.1 %	*Integrated Safety Analysis Population*		The most frequently reported AEs leading to discontinuation were disease progression, JIA, and condition aggravated	Studies A3921103, A3921104 and A3921145

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite the available treatments for pJIA, additional therapy options are still needed as up to 30% of children with pJIA continue to have active disease despite treatment with MTX or biological agents.

Results from the pivotal study support a beneficial effect of tofacitinib for relevant clinical signs and symptoms of the disease i.e. disease flare, ACR responses in a clinically meaningful percentage of subjects. Efficacy for relevant groups which potentially are included in the claimed broad indication has been provided and the wording of indication has been revised accordingly.

Moreover, the safety profile related to the JIA paediatric population is generally similar to that of the already approved tofacitinib indications in adults with the exception of some infections and gastrointestinal or general disorders, which were more common in JIA paediatric population. The only adverse events of interest were serious infections (no opportunistic) and HZ. The long-term safety profile

will be further evaluated through additional pharmacovigilance activities in the post-marketing setting, as agreed in the RMP.

3.7.2. Balance of benefits and risks

The results from study A3921104 show a statistically and clinically relevant effect for tofacitinib on the primary and secondary efficacy endpoints. The efficacy in JIA was demonstrated in patients with active polyarticular JIA subtypes of rheumatoid factor positive or negative polyarthritis and extended oligoarthritis, and in patients juvenile psoriatic arthritis (PsA); in bDMARD naïve and experienced patients and for patients who received tofacitinib as monotherapy or concomitantly to cDMARD.

The safety in the JIA population shows the same pattern as the known safety profile of tofacitinib in adult RA patients with the exception of some infections and gastrointestinal or general disorders, which were more common in JIA paediatric population. The long-term safety in JIA patients will be further characterized in the post-marketing setting.

The initially sought indication '*treatment of active polyarticular course juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older'* was not agreed by the CHMP since considered too broad. The wording of the agreed indication was revised according to the in/exclusion criteria of study A3921104 and therefore restricted to patients who responded inadequately to previous therapy with DMARDs. The indication was also restricted to the JIA subgroups where the efficacy was demonstrated: rheumatoid factor positive [RF+] or negative [RF-] polyarthritis, extended oligoarthritis and juvenile PsA. The inclusion of the term "polyarticular **course** juvenile idiopathic arthritis" in the wording of the indication was not agreed by the CHMP since there may be different interpretations of what JIA categories are included in this term and it is not included in previously approved paediatric indications.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Xeljanz is positive in the following indication:

Juvenile idiopathic arthritis (JIA)

*Tofacitinib is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive or negative polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs. Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate***.**

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Xeljanz new pharmaceutical form is favourable in the following indication:

Juvenile idiopathic arthritis (JIA)

Tofacitinib is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive or negative polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs. Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Xeljanz subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Additional risk minimisation measures

Prior to launch of XELJANZ in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The MAH shall ensure that in each Member State where XELJANZ is marketed, healthcare professionals who intend to prescribe XELJANZ have been provided with an educational package.

The main objective of the programme is to increase awareness about the risks of the product, specifically in regards to serious infections, venous thromboembolism (deep vein thrombosis [DVT]

and pulmonary embolism [PE]), herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy, gastrointestinal perforations, interstitial lung disease, and laboratory abnormalities.

The MAH shall ensure that in each Member State where XELJANZ is marketed, all healthcare professionals and patients/carers who are expected to prescribe or use XELJANZ have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

- **The physician educational material** should contain:
  - The Summary of Product Characteristics
  - Guide for healthcare professionals
  - Prescriber checklist
  - Patient alert card
  - A reference to the website with the educational material and patient alert card

- **The Guide for healthcare professionals** shall contain the following key elements:
  - Relevant information of the safety concerns addressed by the aRMM (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable)
  - Details of the population at higher risk for the safety concern addressed by the aRMM (i.e. contraindications, risk factors, increased risk by interactions with certain medicine)
    - The above key element needs to be updated with details on the VTE risk including the VTE risk factors as well as with details on the risk of serious infections in patients >65 years old.
  - Details on how to minimise the safety concern addressed by the aRMM through appropriate monitoring and management (i.e. what to do, what not do, and who is most likely be impacted according to different scenarios, like when to limit or stop prescribing/ingestion, how to administer the medicine, when to increase/decrease the dosage according to laboratory measurements, signs and symptoms)
    - The above key element should be updated with details on the VTE risk should be minimised in clinical practice, i.e., that tofacitinib should be used with caution in patients with known VTE risk factors and that 10 mg twice daily is not recommended for maintenance treatment in UC patients with known VTE risk factors unless there is no suitable alternative treatment available. In addition, details on how to minimize the risk of serious infections in patients >65 years old should be provided as well.
  - Key message to convey in patients counselling
  - Instructions on how to handle possible adverse events
  - Information about the BSRBR, ARTIS, RABBIT and BIODABASER and UC registries and the importance of contributing to these

- **The Prescriber checklist** shall contain the following key messages:
  - Lists of tests to be conducted during the initial screening and maintenance of the patient
  - Vaccination course to be completed before treatment
  - A specific reference to the fact that the patient has been informed and understands that tofacitinib is contraindicated during pregnancy and breast-feeding and women of childbearing potential should use effective contraception during treatment with tofacitinib and for at least 4 weeks after the last dose
  - That the benefit risk of tofacitinib should be discussed with the patient, and the patient alert card should be given to and discussed with the patient
  - Relevant comorbidities for which caution is advised when XELJANZ is administered and conditions in which XELJANZ should not be administered
  - List of concomitant medications which are not compatible with treatment with XELJANZ
  - The need to discuss with the patients the risks associated with the use of XELJANZ, specifically in regards to infections, venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]), herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy, gastrointestinal perforations, interstitial lung disease, and laboratory abnormalities
  - The need to monitor for any signs and symptoms and laboratory abnormalities for early identification of the abovementioned risks.

- **The Patient alert card** shall contain the following key messages:
  - A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using XELJANZ

- That treatment with XELJANZ may increase the risk of infections and non melanoma skin cancer
- That patients should inform health professionals if they are planning to receive any vaccine or become pregnant
- Signs or symptoms of the following safety concern and/or when to seek attention from a HCP: infections, venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]), herpes zoster reactivation, non-melanoma skin cancer, transaminase elevation and potential for drug-induced liver injury, gastrointestinal perforation, interstitial lung disease, increased immunosuppression when used in combination with biologics and immunosuppressants including B lymphocyte depleting agents, increased risk of adverse events when XELJANZ is administered in combination with MTX, increased exposure to XELJANZ when co-administered with CYP3A4 and CYP2C19 inhibitors, effects on pregnancy and foetus, use in breast-feeding, effect on vaccination efficacy and the use of live/attenuated vaccines.
- Contact details of the prescriber

- **The website repository** shall contain:
  - The educational material in digital format
  - The patient alert card in digital format

- **The patient information pack** should contain:
  - Patient information leaflet
  - The patient alert card
  - Instructions for use

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0134/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

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

Extension application to introduce a new pharmaceutical form (oral solution, 1mg/ml) grouped with a type II variation (C.I.6.a) to add a new indication (treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive or negative polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older), for the new formulation and the 5mg film-coated tablet formulation, only. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP (version 12.4) is also agreed.