31 January 2019
EMA/126226/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Orencia

International non-proprietary name: abatacept

Procedure No. EMEA/H/C/000701/X/117/G

Note

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

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List of abbreviations

ACR	American College of Rheumatology
ACRP	American College of Rheumatology Paediatric Criteria
ADA	anti-drug antibodies
AE	adverse event
AUC	area under the concentration-time curve
BP	British Pharmacopoeia
BMS	Bristol-Myers Squibb
CD	cluster of differentiation
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cav	time-averaged serum concentration
Cavss	time-averaged serum concentration at steady-state
Cmax	peak serum concentration
Cmaxss	peak serum concentration at steady-state
Cmin	trough serum concentration
Cminss	trough serum concentration at steady-state
CRP	C-reactive peptide
CSR	clinical study report
CTLA	cytotoxic T-lymphocyte associated antigen
D, d	day
DMARD	disease modifying anti-rheumatic drug
DMC	data monitoring committee
E-R	exposure-response
EMA, EMEA	European Medicines Agency
ERA	enthesitis-related arthritis
EU	European Union
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IL	interleukin
IV	intravenous
JIA	juvenile idiopathic arthritis
LT	long-term
LTE	long-term extension
LOE	loss of efficacy
MAH	Market Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
N, n	number of subjects or observations
NA	not available
ND	not determined
No.	number
PDCO	Paediatric Committee
PFS	prefilled syringe
Ph.Eur.	European Pharmacopoeia
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic, pharmacokinetics
PPK	population pharmacokinetics
PRINTO	Pediatric Rheumatology International Trials Organisation
PRCSG	Pediatric Rheumatology Collaborative Study Group
PsA	psoriatic arthritis
PT	preferred term
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous, subcutaneously
SD	standard deviation

SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SOC	system organ class
ST	short-term
UPLC	Ultra performance liquid chromatography
USP	United States Pharmacopeia

1. Background information on the procedure

1.1. Submission of the dossier

Bristol-Myers Squibb Pharma EEIG submitted on 8 March 2018 a group of variations consisting of an extension of the marketing authorisation and the following variations:

Variations requested		Type
B.II.b.3.a	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	IB
B.II.b.3.a	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	IB
B.II.b.5.z	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	IB
B.II.e.1.z	B.II.e.1.z - Change in immediate packaging of the finished product - Other variation	IB
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	II

Extension application to add 2 new strengths of 50 mg and 87.5 mg for solution for injection in a pre-filled syringe with needle guard, for subcutaneous (SC) administration, grouped with a type II variation (C.I.6.a) to include paediatric use of polyarticular Juvenile Idiopathic Arthritis (2 years and above) for solution for injection (50 mg, 87.5 mg and 125 mg).

The above-described changes are grouped with the following variations:

B.II.b.3.a – To introduce an automated device assembly process for Neopak and Hypak non-printed syringes in all 3 fill volumes (0.4 mL, 0.7 mL and 1.0 ml) as an alternate to the current semi-automatic device assembly process used for the currently approved 1 mL fill in Hypak printed syringes.
B.II.b.3.a - to use all paperboard carton design with the automated secondary packaging process for all fill volumes.
B.II.b.5.z - To add a new machine vision inspection station “Stopper Presence” to the current automated in-process inspection process used for the inspection of the prefilled syringes.
B.II.e.1.b.z – To add two alternate syringe barrels, the current BD Hypak syringe barrel without pre-printed lines and BD Neopak syringe barrel without pre-printed lines to the currently approved BD Hypak syringe barrel with pre-printed lines.

The RMP (version 25.0) is updated in accordance.
In addition, the applicant took the opportunity to implement minor editorial changes in the product information.

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(s) P/0128/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0128/2014 was not yet completed as some

measures were deferred.

However, the PIP P/100/2009 was completed.

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

No CHMP Scientific Advice dedicated to this application was sought by the MAH.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Outi Mäki-Ikola

The application was received by the EMA on	8 March 2018
The procedure started on	29 March 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 June 2018
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	05 July 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 July 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 July 2018
The MAH submitted the responses to the CHMP consolidated List of Questions on	12 October 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	13 November 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 November 2018
The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	05 December 2018
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	13 December 2018
The MAH submitted the responses to the CHMP List of Outstanding Issues on	03 January 2019
The PRAC Rapporteur's Assessment Report was circulated to all PRAC members on	07 January 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 January 2019
The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	23 January 2019
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 Orencia on	31 January 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Juvenile idiopathic arthritis is a broad term that describes a clinically heterogeneous group of arthritis of unknown aetiology that begins before the age of 16 years and persists for at least 6 weeks. JIA is one of the most common chronic diseases of childhood and is an important cause of short- and long-term disability.

2.1.2. Epidemiology

JIA is one of the most common chronic diseases of childhood and is an important cause of short- and long-term disability. The epidemiology for JIA varies depending on different global regions and method of analysis, the reported incidence rates being between 7-100/100,000 and prevalence of 32 to 200/100,000.

2.1.3. Biologic features

Polyarticular JIA is a systemic disease with active synovial inflammation; elevation of platelet, white blood cell counts and acute phase reactants, fever, anaemia, and growth retardation, weight loss and failure to thrive all speak to the systemic nature of this inflammation. Recent evidence in RA, psoriatic arthritis and lupus, as well as other chronic systemic inflammatory disorders suggests that such active inflammation predisposes to accelerated atherosclerosis leading to premature coronary and cerebrovascular disease; there is evidence of a similar linkage in active pJIA.

2.1.4. Clinical presentation, diagnosis

JIA is a diagnostic classification designed to encompass a heterogeneous group of chronic childhood and adolescent inflammatory joint diseases. The current JIA classification recognizes seven clinical JIA subtypes based on phenotype, serology and associated features: rheumatoid factor (RF) positive and negative polyarthritis, extended oligoarthritis, persistent oligoarthritis, enthesitis-related arthritis (ERA), psoriatic arthritis (PsA), systemic arthritis, and undifferentiated arthritis.

2.1.5. Management

Polyarticular JIA is treated with the same medicinal products used for adult RA. Similarly to adult RA, emphasis is on early diagnosis and aggressive therapy, and closer disease monitoring as we 'treat-to-target'. Treatment currently aims at disease remission i.e. minimal disease activity and quality of life approaching that of any other child. With this concept of a 'treatment window of opportunity' instead of a slower 'step-up' pyramid approach, patient care is optimised and better long term outcomes are achieved. A current parallel concept is that of clinical versus immunological remission: that there may be ongoing activity within the immune system, measurable by increasingly sensitive biochemical and radiological markers, even in the absence of clinically apparent disease. Extinguishing even this subclinical immune activity is becoming the new treatment goal.

Current treatment options include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and biologic and non-biologic disease-modifying antirheumatic drugs (DMARDs).

NSAIDs, such as naproxen, ibuprofen, and diclofenac, are indicated for a wide range of rheumatoid conditions and can be used as an initial therapy for paediatric patients with JIA. NSAIDs may be used alone when disease flares are intermittent and only mild to moderate in severity.

Corticosteroids are often used in the long-term management or in the treatment of disease flares for both adults with RA and paediatric patients with JIA. However, the use of corticosteroids is limited due to both short-term and long-term toxicity.

Second-line therapies include conventional non-biologic DMARDs such as MTX (usually the cornerstone of therapy) or leflunomide, typically in combination with NSAIDs. Non-biologic DMARDs have been also used in combination with corticosteroids. Use of single or multiple non-biologic DMARDs is not effective in all patients and has been associated with toxicity or aversion to therapy for some patients.

Several biologic DMARDs are approved to treat JIA typically as second- or third-line therapies. Biologic TNF-alpha inhibitors are recommended for most subtypes of pJIA in patients whose disease inadequately responds to standard non-biologic DMARDs.

Non-biologic DMARDs, anti-TNF-alpha therapies, and cytokine inhibition therapies for JIA are not uniformly effective or tolerated. Some JIA subtypes respond differently, some patients do not respond, and other patients experience secondary loss of efficacy, often with an accompanying production of anti-drug antibodies. These therapies can also have significant toxicities that can force interruption or discontinuation of therapy.

About the product

ORENCIA (abatacept, Bristol-Myers Squibb [BMS]-188667), is a selective costimulation modulator that acts on a key regulatory pathway for immune activation and reduces the inflammatory process associated with rheumatoid arthritis (RA). Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte (T-cell)-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Abatacept binds to CD80/CD86 receptors on antigen-presenting cells, thereby inhibiting binding of these molecules to the costimulatory CD28 receptor on T cells and inhibiting full activation of T cells and the downstream inflammatory cascade.

Orencia (IV and SC formulations) is approved for the treatment of Rheumatoid arthritis and Psoriatic arthritis. Intravenous (IV) abatacept was approved in 2009 for the treatment of moderate to severe active pJIA in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs, including at least one TNF-alpha inhibitor. The paediatric IV Study IM101033 included both MTX-IR and TNF-IR pJIA patients, but was considered to support only the third line pJIA indication, similar to the approved adult RA indication that at that time included only those with insufficient response or intolerance to other DMARDs including at least one TNF-alpha inhibitor.

In 2010, the adult RA indication was extended to include adult patients with RA with inadequate response to previous therapy with one or more DMARDs including MTX or a TNF-alpha inhibitor, which indication was supported by long-term efficacy and safety data from the initial RA studies, as well as by a new study conducted in MTX-naive RA patients (IM101023). Later also SC abatacept was approved for adult RA, supported by the Study IM101174, which demonstrated therapeutic equivalence between IV abatacept and SC abatacept in RA patients.

In 2016, the adult RA indication for IV and SC abatacept was extended to the first line treatment, i.e. treatment of highly active and progressive disease in adult patients with RA not previously treated with MTX.

Type of Application and aspects on development

This application is a grouped variations application that is being submitted together with an Extension Application covering two new strengths (50 mg and 87.5 mg) for an already approved pharmaceutical form (Solution for injection in pre-filled syringe). These 2 new strengths are presented in a pre-filled syringe with needle guard.

The grouped type II variation application consists of the submission of a type II variation (category C.I.6.a) and four quality type IB variations (categories B.II.e.1.b.z, B.II.d.2.a, B.II.b.3.a and B.II.b.3.a).

These changes are submitted as a grouping as the proposed clinical and quality changes are linked to the extension application. In addition, the four proposed quality changes are applicable to both the new paediatric presentations and the currently approved Orencia 125 mg solution for injection in pre-filled syringe.

The proposed changes of indication are as follows:

- Current paediatric indication (IV abatacept)

ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (pJIA) in paediatric patients 6 years of age and older who have had an ~~insufficient~~ ***inadequate*** *response to* ***previous*** *~~other~~ DMARD* ***therapy~~s~~*** *~~including at least one TNF inhibitor.~~*

ORENCIA can be given as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate.

- The currently proposed new paediatric indication for sub cutaneous (SC) abatacept

(ORENCIA 50 mg and 87.5mg solution for injection in pre-filled syringe)

ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (pJIA) in paediatric patients 2 years of age and older who have had an inadequate response to previous DMARD therapy.

ORENCIA can be given as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate.

An updated RMP (version 25.0) was submitted with this application to include data from pivotal study IM101-301, in support of the pJIA indication. The MAH has also revised the content and format of the RMP according to the revised guideline on Good Pharmacovigilance Practices Module V (Rev 2). As a result, “immunogenicity” has been removed from the list of important potential risks.

No CHMP Scientific Advice dedicated namely to this application was sought by the MAH.

2.2. Quality aspects

2.2.1. Introduction

The purpose of this line extension application and variation grouping is to introduce two new strengths of abatacept (ORENCIA 50 mg and 87.5 mg solution for injection in pre-filled syringe (PFS)) of an already approved pharmaceutical form (Orencia 125 mg solution for injection in PFS), for the already approved subcutaneous (SC) route of administration, for a new paediatric population indication, as detailed above. The finished product composition and concentration (125 mg/mL) are the same for all the three strengths. In addition to the currently approved syringe barrel, two alternate syringe barrels are proposed, as detailed below. The device components that come into contact with the solution are the

same as the currently approved ones. The relevant specification (fill volume) and analytical method (glide force distance range) have been updated to reflect the addition of new fill volumes. Minor changes to the proposed manufacturing method of the new strengths, are also applicable to the already marketed products.

2.2.2. Active Substance

There are no changes declared for the active substance part of Module 3.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Abatacept PFS is provided as a 125 mg/mL sterile solution, ready for injection. It is a clear, colourless to pale yellow solution with a pH of 6.8 to 7.4. It is available in three strengths, namely 50 mg and 87.5 mg, subject of this application, and 125 mg (marketed). The product is supplied in a single-use pre-filled syringe (PFS, type I glass) with an automatic needle safety guard and flange extenders. The type I glass syringe has a coated bromobutyl stopper and fixed stainless steel needle covered with a rigid needle shield.The materials comply with Ph. Eur. and EC requirements. The marketed SC formulation is a ready to use single dose formulation available in three presentations (PFS with flange extender; PFS with BD Ultrasafe Automatic Needle Guard and flange extender, CE marked, and PFS in ClickJect autoinjector). In addition to the currently approved BD Hypak syringe barrel with pre-printed lines (for use only for the 1.0 mL fill), two alternate syringe barrels are proposed for the PFS with UltraSafe Automatic Needle Guard, to ensure robust supply: the BD Hypak syringe barrel without pre-printed lines and BD Neopak syringe barrel without pre-printed lines. These two syringe barrels are both supplied by BD and visually look the same. The device components that come into contact with the solution are the same as the currently approved ones. All syringes are manufactured by the currently approved supplier, Becton Dickinson Medical-Pharmaceutical Systems (BD). These syringes use the same Type I borosilicate glass and have the same 0.5 inch, 29-gauge thin-wall stainless steel needle, as the current commercial product .The three strengths are differentiated by the colour of the plunger rod (50 mg-white, 87.5 mg-light blue, and currently approved 125 mg-orange), syringe label and secondary packaging artwork.

Abatacept 125mg/mL contains as excipients sucrose (stabiliser), poloxamer 188 (surfactant), sodium phosphate monobasic monohydrate (buffering agent), sodium phosphate dibasic anhydrous (buffering agent) and water for injection (solvent). All excipients are well known pharmaceutical ingredients and their quality is compliant with pharmacopoeial standards. There are no novel excipients used in the finished product formulation. In view of the paediatric indication for the new strengths (for use in children two years and older) the applicant has been requested to justify suitability of the formulation in accordance with the guideline on Pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2) as part of the development; especially in relation to the quantities of poloxamer 188 and sucrose. A multidisciplinary concern has been raised for quality and safety, which was resolved based on published pre-clinical and clinical findings and taking into consideration the route of administration and the weekly dose of the excipients. Additionally, the applicant has satisfactorily justified that the presence of silicon oil used as lubricant and sprayed to the interior of the syringes does not affect the stability or the safety of the finished product and that it is acceptable for the proposed paediatric patient population.

Manufacture of the product and process controls

The process is a modification of the manufacturing process for an approved product. Satisfactory validation data have been provided for the paediatric presentations. The manufacturing process of the additional two strengths is considered as satisfactorily validated.

Product specification

The release specification includes: appearance, volume in container, pH, osmolality, identity, peptide mapping, isoelectric focusing, protein concentration, sodium dodecyl sulfate polyacrylamide gel electrophoresis, size homogeneity, B7 Binding, human cell IL-2 inhibition assay, sterility, particulate matter, bacterial endotoxins. The analytical methods are the same as the currently approved ones.

Batch analysis

Batch analysis data of the finished product were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Stability of the product

Based on available stability data, the shelf-life of 24 months and storage condition of 2 °C to 8 °C and protected from light, as stated in the SmPC, are acceptable.

Discussion on chemical, and pharmaceutical aspects

The information provided to support this line extension 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.

Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the new presentations of ORENCIA (Abatacept) 50 mg and 87.5 mg solution for injection in PFS is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

No new data has been submitted in this application. To support paediatric development, the MAH has submitted within earlier variation procedures studies on juvenile rats aged from post-natal day 4 (PND4) to PND94, which covers humans from neonates to adulthood. Related to the extension of indication of Orencia to paediatric patient population with pJIA in 6 to 17 years and the post-authorisation commitments thereafter, the MAH has performed non-clinical immunotoxicity studies in adult and juvenile rats to address the potential association of the presence of ADAs and the autoimmunity observed in previous juvenile studies. In these studies, autoimmunity-related findings such as lymphocytic infiltration of the thyroid and pancreatic islands was frequently observed in juvenile rats but only in rare cases in adult rats indicating that juvenile animals might be more sensitive than the adult animals. Additional juvenile study suggested that findings indicative of autoimmunity observed in previous studies might be due to the pharmacological activity of abatacept and not to the occurrence of ADAs.

2.3.2. Ecotoxicity / environmental risk assessment

BMS-188667 (abatacept) is a protein composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk to the environment. As a protein, BMS-188667 is exempt from preparation of an Environmental Risk Assessment under the 1 June 2006 "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00). In conclusion, BMS-188667 and the product excipients do not pose a significant risk to the environment.

2.3.3. Discussion on non-clinical aspects

No new data has been submitted in the frame of this application which is acceptable to the CHMP. In accordance with Appendix 3 to the "Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling", the wording of the Section 4.6 of the SmPC has been modified. In addition, the wording of the Section 5.3 of the SmPC has been modified to reflect the new indication in children aged from 2 years onwards.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considered that this application is approvable from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

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

Table 1 Clinical development program for subcutaneous abatacept in JIA

Study Category and Population	Study Number	Location[a]	Design/Control Type	Study and Control Drugs Dose, Route, Regimen	Duration of Study	# of Subjects Enrolled/Treated
Phase 3						
Children and Adolescents with Active pJIA	IM101301 ST and LTE	WW	Multi-center, Open-label Study to Evaluate Pharmacokinetics, Efficacy and Safety of Abatacept Administered SC in Children and Adolescents with Active pJIA Two cohorts of children (ages 2 to 5 years and 6 to 17 years) received 4 months of weekly weight-tiered dosing of SC abatacept aimed to achieve the target therapeutic steady-state systemic exposure (Cminss of 10 µg/mL or greater).	SC abatacept was administered by prefilled syringe (PFS) once weekly as a weight-tiered dose regimen: (10 to < 25 kg: 50 mg; 25 to < 50 kg: 87.5 mg; ≥ 50 kg: 125 mg)	4 month ST 20 month LTE	N = 187 subjects enrolled and 173 subjects were treated ages 6 to 17 years old N= 47 subjects enrolled and 46 subjects were treated ages 2 to 5 years old

[a] WW: World-Wide (Argentina, Belgium, Brazil, France, Germany, Italy, Mexico, Peru, Russian Federation, South Africa, Spain, and United States of America)

2.4.2. Rationale for extrapolation

An extrapolation approach was proposed to characterize the clinical profile of SC abatacept in pJIA. This approach was agreed on with the Paediatric Committee (PDCO). The rationale for this extrapolation approach is discussed below:

Development of Subcutaneous Abatacept in Adults

The clinical development program for SC abatacept included a direct IV to SC comparison in adults with RA (pivotal Study IM101174) to demonstrate therapeutic equivalence between the formulations. Three other supportive studies (IM101173, IM101167, IM101185) assessed the efficacy, safety, and immunogenicity in adults under clinical scenarios that could potentially increase the development of immunogenicity and to determine the consequences of treating with SC abatacept in this setting (e.g., no IV load, monotherapy, prolonged withdrawal of therapy, switch from IV to SC). An additional clinical pharmacology and safety study (IM101063) was conducted for the selection of an SC abatacept dosing regimen.

The PK and exposure-response (E-R) of IV and SC abatacept have also been characterized in adult subjects with RA. These analyses demonstrated that the PK of IV and SC abatacept is linear, and that steady-state trough concentration (Cminss) is the most appropriate measure of exposure for efficacy in adult subjects with RA.

Clinical Development Program in pJIA

The therapeutic utility of intravenously (IV) administered abatacept in patients with pJIA was demonstrated in the Phase 3 pivotal Study IM101033. IM101033 was a randomized withdrawal study that evaluated the safety and efficacy of IV abatacept in children and adolescents (ages 6 to 17 years) with active pJIA and inadequate response to methotrexate (MTX) and/or biologic DMARDs. Doses were administered once every 2 weeks for the first 4 weeks, and once every 4 weeks thereafter. IV abatacept was found to have a favourable benefit/risk profile in pJIA, resulting in approval to treat pJIA in the EU in 2009 (variation II/24). The approved therapeutic indication was follows:

"ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years of age and older who have had an insufficient response to other disease modifying anti-rheumatic drug(s) (DMARDs) including at least one TNF-alpha *inhibitor. Orencia has not been studied in children under 6 years old"*

The approved IV dose is 10 mg/kg every 4 weeks (q4w) for patients who weigh less than 75 kg; paediatric patients weighing 75 kg or more should follow the adult dosing regimen.

With the IV development program, the PK of IV abatacept have been well characterized in adult patients with RA and in paediatric patients with pJIA, and have been shown to be comparable, after accounting for the effect of body weight. The E-R relationship was also deemed to be comparable between RA and pJIA. The E-R analyses of efficacy suggest that similar levels of abatacept exposure are required to achieve adequate efficacy in adult patients with RA (ACR20) and in paediatric patients with pJIA (JIA ACR30).

Furthermore, the E-R relationship was similar between IV and SC abatacept in RA. Based on the observation of therapeutic equivalence between IV and SC abatacept in adults with RA, it was reasonable to assume that the E-R relationship would be similar between IV and SC abatacept in pJIA. To that end, the existing PK and efficacy data in RA and JIA was leveraged to design a SC dosing regimen that accounts for the changes in body weight that occur with age to maintain similar abatacept exposures throughout the paediatric age range.

Appropriateness of extrapolating abatacept data from adults to paediatric patients

The clinical data from the abatacept adults RA (IV and SC) development programme are considered relevant for both adults and paediatrics as consistent eligibility criteria were employed irrespective of age in both adult and the paediatric studies. Results from comparison of these studies showed that the baseline characteristics of the disease were consistent between the age groups and the studies.

The clinical efficacy and safety endpoint data from the adult RA (IV and SC) and the IV pJIA programmes are considered relevant for both adults and the paediatric patients. The primary and/ key secondary endpoints in adult RA for exposure and efficacy were alike (ACR and ACRp criteria, Cmin) in both paediatric the IV and SC studies. The standard ACR criteria were used to assess and establish efficacy, improvement. Overall, in these studies also the other secondary and explorative outcomes were consistent between adults and paediatrics.

Key steps of the proposed extrapolation strategy

1. Confirm that abatacept is efficacious with a favourable benefit-risk profile in adult subjects with RA (IV and SC). Confirm that abatacept is efficacious with a favourable benefit-risk profile in subjects with pJIA (IV) patients aged 6 to 17 years of age. The data together with current data from study IM101301 form the basis of extrapolation to paediatric pJIA subjects treated with SC abatacept.
2. Confirm that abatacept PK in adults is predictive of PK in paediatrics following both IV administration and SC administration (predictability of the available paediatric data in pJIA 6 to 17 years) and confirm the consistency of the PK of abatacept in both adults and paediatric populations.
3. Provide supportive evidence that abatacept efficacy in adults treated with SC and IV abatacept with RA and paediatric pJIA patients treated with IV abatacept can be extrapolated to the paediatric population (6 to 17 years of age) and that establishing this evidence is sufficient to extend this to the 2 to 5 years age group pJIA patients.
4. Evaluate the safety profile of the SC formulation of abatacept in the paediatric population (aged 2 to 17 years) with pJIA by comparing it with that of the overall phase III IV and SC RA and IV pJIA clinical development programme.
5. Identify and plan for the mitigation of any remaining uncertainty and risk.

This approach, in which limited data was to be collected in the target population, with extrapolation of efficacy and safety data from source populations of the abatacept (IV and SC) in RA and pJIA (IV) development programme, was agreed on with the Paediatric Committee (PDCO). In this context, an open-label Study IM101301 (with PK as the primary endpoint and efficacy and safety were evaluated to confirm that the benefit-risk profile was comparable to that observed with IV abatacept in pJIA) and a PK modelling and simulation evaluation, was considered appropriate to seek approval for the use of SC abatacept in the treatment of 2 to 17 year old children with pJIA and possibly include monotherapy in the IV indication for the older 6 to 17 year-old population.

2.4.3. Pharmacokinetics

In the present application for the subcutaneously administered abatacept in treatment of JIA in paediatric patients 2 years of age and older, pharmacokinetics, efficacy and safety of SC abatacept in children and adolescents (ages 2-17 years) with JIA was investigated in one study IM101301.

A weight-tiered dosing regimen was selected for SC abatacept based on pharmacokinetic and pharmacodynamic modelling and simulation analyses: Doses of 50 mg, 87.5 mg, and 125 mg were administered once per week (q1w) in patients weighing 10 to < 25 kg, 25 to 50 kg, and > 50 kg, respectively. Sparse PK samples, primarily trough concentrations, were collected. Summary statistics for the observed abatacept Cmin by weight-tiered dose are displayed in the table below.

Table 2 Observed abatacept Cmin Values by Weight-tiered Dose (Study IM101301)

	CMIN (ug/mL)		
50mg			
STATISTIC	DAY 57	DAY 85	DAY 113
N	51	53	43
MEAN	42.5	43.8	46.2
S.D.	14.1	16.8	17.1
GEO. MEAN	40.1	40.2	43.0
%CV	33	38	37
MEDIAN	41.4	43.7	44.0
MIN	13.6	8.1	13.4
MAX	79.0	83.4	96.2
87.5mg			
STATISTIC	DAY 57	DAY 85	DAY 113
N	72	65	63
MEAN	40.6	45.8	48.0
S.D.	16.7	17.1	18.2
GEO. MEAN	37.5	42.9	45.1
%CV	41	37	38
MEDIAN	37.5	44.0	45.5
MIN	10.4	13.3	22.4
MAX	114.4	118.8	122.1
125mg			
STATISTIC	DAY 57	DAY 85	DAY 113
N	75	65	59
MEAN	35.1	39.3	38.4
S.D.	11.6	15.9	11.7
GEO. MEAN	33.0	36.0	36.6
%CV	33	40	30
MEDIAN	32.8	38.6	37.2
MIN	9.0	7.4	9.3
MAX	72.0	97.0	73.2

The Cminss levels observed with weight-tiered SC dosing in paediatric patients were higher than average Cminss levels observed in adult RA patients with fixed 125 mg SC dosing. However, the observed Cminss values were comparable to the observed exposures in RA patients with low body weight (<60 kg) (Figure below).

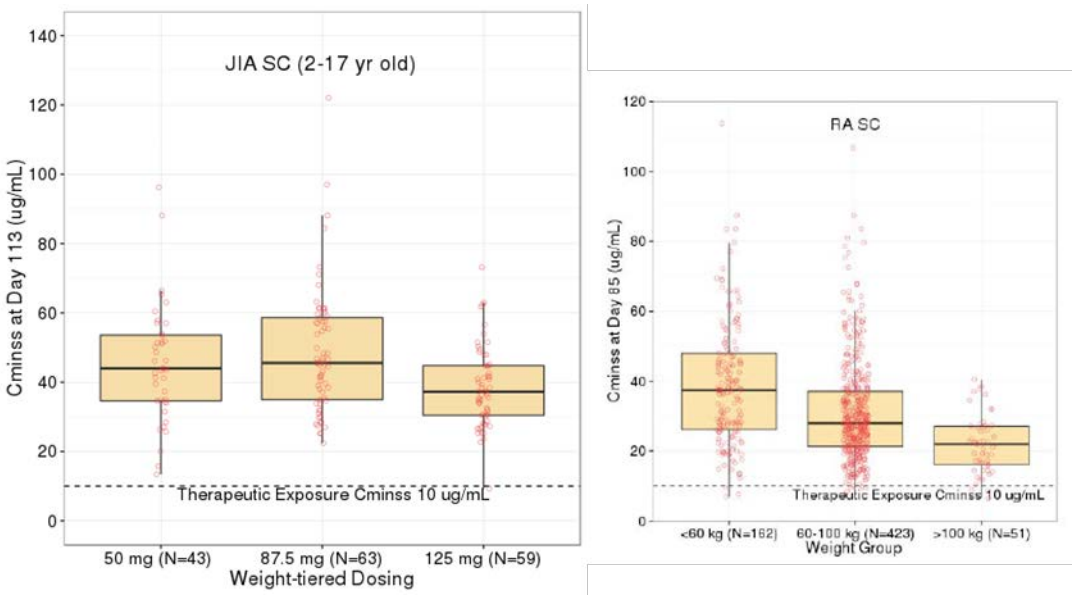


Figure 1 Observed Cminss Distribution Following SC Abatacept Administration in JIA (weight-tiered dosing) and RA (fixed 125 mg dose)

Population PK analysis

Marketing authorization in the EU has been granted for Orencia 125 mg solution for injection in pre-filled syringe for subcutaneous use. Bioavailability and bioequivalence studies were not conducted for the two proposed medicinal products Orencia 87.5 mg solution for injection in pre-filled syringe and Orencia 50 mg solution for injection in pre-filled syringe. This is acceptable because the same drug product is used in the syringes, only the fill volume (0.4 mL, 0.7 mL and 1 mL) is adjusted for each syringe dose strength.

Pharmacokinetics of abatacept in paediatric patients with JIA was evaluated using population PK (PPK) analysis. The data were collected from patients in two JIA studies [Study IM101033, intravenous (IV) abatacept; Study IM101301, subcutaneous (SC) abatacept] and 11 adult RA studies. All available PK data in JIA patients were used, including the open-label lead-in phase (Period A) and randomized double-blind treatment phase (Period B) of Study IM101033 and the open-label short-term and long-term treatment periods of Study IM101301 (database lock March 21, 2017). The PPK analysis was conducted with a total of 12759 serum concentration values from 2213 adult patients with RA, 357 patients aged 6 to 17 years with JIA and 46 patients aged 2 to 5 years with JIA, who received IV and/or SC abatacept.

The final PPK model was a 2-compartment, zero-order IV infusion, first-order SC absorption, and first-order elimination model with a combined residual error model. This is the same structural model that was used in previous abatacept PPK models. Covariate-parameter relationships that have been tested in previous abatacept PPK models were tested in developing the current model. A single round of forward selection was used to select statistically significant (univariate alpha level of 0.01) covariates for inclusion in the full model (Figure below). Covariate-parameter relationships of the full model were assessed using the likelihood ratio test (LRT) within a stepwise backward elimination process using alpha level 0.001. The effect of race and duration of disease on CL were removed in the backward elimination analyses.

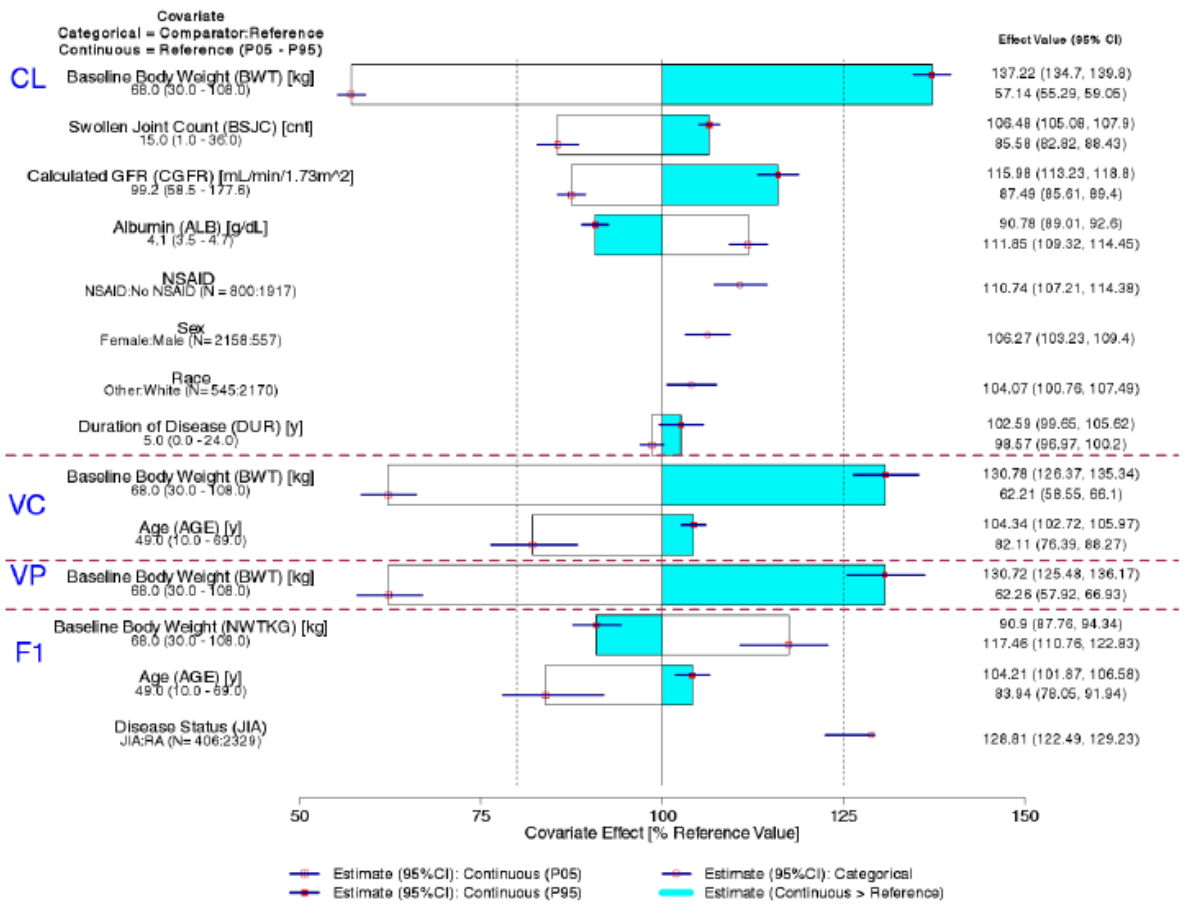


Figure 2 Covariate Effect Forest Plot of the Full PPK Model

The following covariate effects were statistically significant and retained in the final PPK model (Table below): baseline body weight, calculated GFR, albumin, swollen joint count, co-administration of NSAIDs, and gender on CL; baseline body weight and age on VC; baseline body weight on VP; and baseline body weight, age, and disease status on F. Even though several covariates were statistically significant, only body weight effect on clearance (CL) and volume (VC, VP) parameters and disease (JIA vs. RA) effect on bioavailability were considered to have clinical relevance. CL, VC and VP increased with increasing body weight, in line with previous data. Absorption of SC abatacept was more extensive in JIA patients: JIA patients exhibited 28% higher absolute bioavailability for SC formulation than RA patients. Furthermore, absorption rate appeared to be faster in JIA, although this was not formally investigated. The absorption rate constant (KA) was approximately 41.5% higher in the current model than in a previous PPK model that included only adult RA patients. Because typical JIA patients are younger and have lower body weight than RA patients, it is difficult to separate the effects of disease, age and weight on absorption parameters. The magnitudes (i.e. 95% confidence intervals) of the other covariate effects were encompassed within 80% to 125% of reference values and they were considered to be clinically not meaningful, even though they were statistically significant. Co-treatment with methotrexate (MTX) did not have significant effect on clearance (ΔOFV -1.344, P=0.246). This is in line with the observed data in both paediatric trials (study IM101033 and study IM101301) patients with and without MTX had comparable Cmin levels at steady state.

Graphical exploration suggested that anti-drug antibody (ADA) status had no impact on abatacept observed Ctrough and estimated clearance in JIA. However, the results should be interpreted with caution because only few JIA patients treated with abatacept were ADA positive (see Clinical Safety section).

Table 3 Parameter Estimates of the Final PPK Model

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability[a]	
	Estimate	%RSE	Estimate	%RSE
KA: Absorption Rate Constant [1/h]	0.00521	11.0	1.11	24.4
VC: Central Volume [L][b]	3.29	1.57		
$VC_{TV,ref}$: Power of Weight on VC [-][c]	0.603	6.99	0.0464	14.6
VC: Power of Age on VC [-][c]	0.114	23.4		
$CL_{TV,ref}$: Clearance (L/h)[b]	0.0179	1.36		
CL: Power of Weight on CL [-][c]	0.706	2.93	0.0637	4.25
CL: Power of GFR on CL [-][c]	0.259	7.19		
CL: Power of Swollen Joint Count on CL [-][c]	0.0742	12.8		
CL: Exponent of NSAID use on CL [-][c]	0.102	12.5		
CL: Exponent of Male Gender on CL [-][c]	0.0674	21.4		
CL: Power of Albumin on CL [-][c]	-0.722	9.69		
$VP_{TV,ref}$: Peripheral Volume [L][b]	3.67	3.71	0.154	15.9
VP: Power of Weight on VP [-][c]	0.575	7.20		
Q: Intercompartmental Clearance [L/h]	0.0231	7.25	NE	NA
$F1_{TV,ref}$: Bioavailability of SC Formulation [-][b]	0.770	6.09		
F1: Exponent of JIA on F1 [-][c]	3.08	41.3	0.516	15.0
F1: Power of Weight on F1 [-][c]	-0.506	27.3		
F1: Power of Age on F1 [-][c]	0.487	27.1		
Proportional Residual Error	NA	NA	0.0615	3.29
Additive Residual Error	NA	NA	0.00134	69.3
Minimum Value of the Objective Function = 65061.705				

[a] ETA shrinkage: ETA CL: 14.3%, ETA VC: 61.5%, ETA VP: 54.7%, ETA KA: 74.9%, ETA F1: 49.2%; Epsilon Shrinkage: Proportional: 12.3%, Additive: 12.3%

[b] $CL_{TV,ref}$, $VC_{TV,ref}$, $VP_{TV,ref}$, and $F1_{TV,ref}$ are typical values of CL, VC, VP, and F1 at the reference covariate values. Covariate effects were estimated relative to a reference 49-year-old patient with RA who is female, weighing 68 kg, with a CGFR of 99.18 mL/min/1.73m^2, baseline albumin level of 4.1 g/dL, swollen joint count of 15, not on NSAIDs

[c] $$CL_{TV} = CL_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{CL_{BWT}} \times \left(\frac{CGFR_b}{CGFR_{ref}}\right)^{CL_{cGFR}} \times \left(\frac{ALB_b}{ALB_{ref}}\right)^{CL_{ALB}} \times \left(\frac{BSJC_b+1}{BSJC_{ref}+1}\right)^{CL_{SWOL}} \times \exp(SEX \times CL_{SEX} + NSAID \times CL_{NSAID})$$

$$VC_{TV} = VC_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{VC_{BWT}} \times \left(\frac{AGE_b}{AGE_{ref}}\right)^{VC_{AGE}}$$

$$VP_{TV} = VP_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{VP_{BWT}}$$

$$F1_{TV} = F1_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{F1_{BWT}} \times \left(\frac{AGE_b}{AGE_{ref}}\right)^{F1_{AGE}} \times \exp(DISEASE \times F1_{DISEASE})$$

Abbreviations: NA: not applicable; NE: not estimated

Overall, parameters were estimated with good precision, but ETA shrinkage values were high (>49%) for volume (VC, VP) and absorption (F, KA) parameters. At the CHMP's request, the MAH discussed the consequences of high ETA shrinkage for volume and absorption parameters. Multiple diagnostic criteria support the conclusion of the MAH that the population PK model can adequately describe the observed data. The PK parameter estimated with the population PK model and used for exposure-response

modelling was Cmin. The MAH's argument that steady-state Cmin is primarily determined by clearance (CL) and less by absorption and volume parameters is scientifically reasonable. ETA shrinkage for CL was relatively small (14.1%), which indicates that individual CL (and Cmin) estimates are sufficiently reliable for the intended use.

Major deviations were not observed in the typical diagnostic goodness-of-fit plots, and prediction-corrected visual predictive check (pcVPC) analyses indicated that the final model could adequately characterize the pharmacokinetics of abatacept.

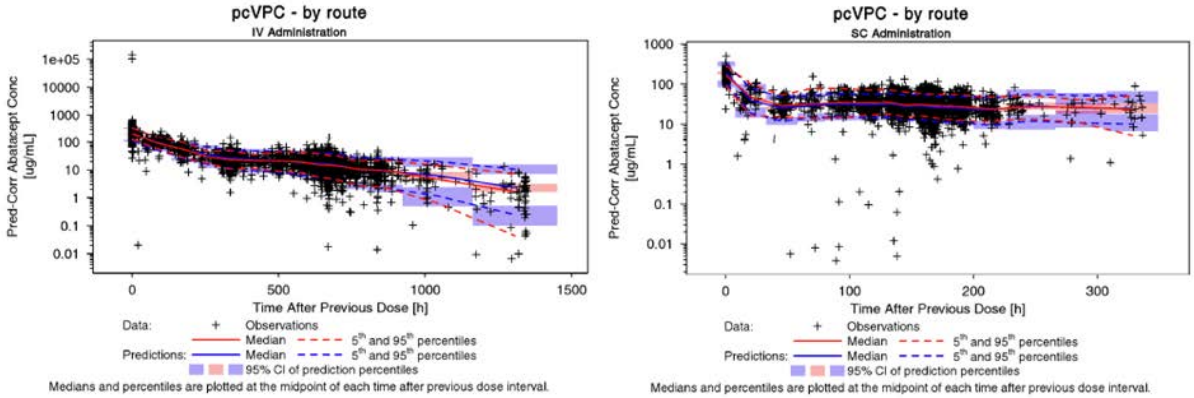
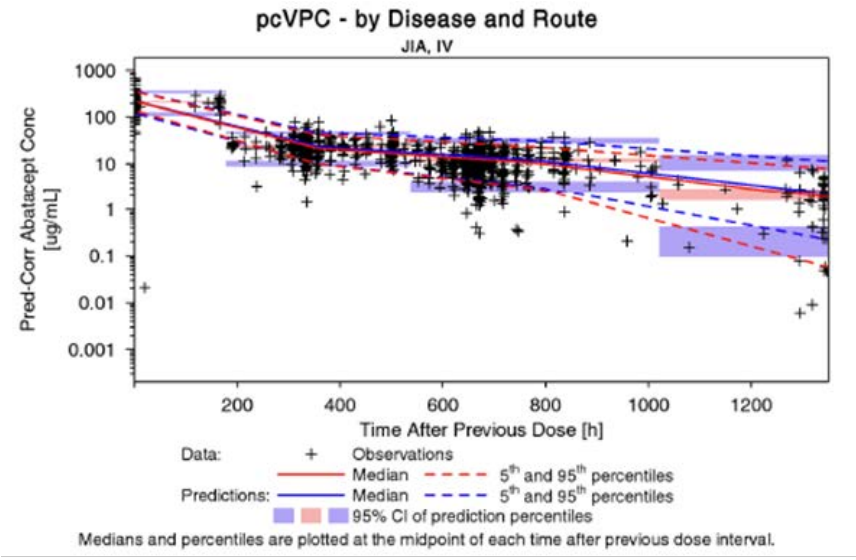


Figure 3 Prediction-Corrected Visual Predictive Check of Concentration vs. Time after Previous Dose, Stratified by Route (All patients)



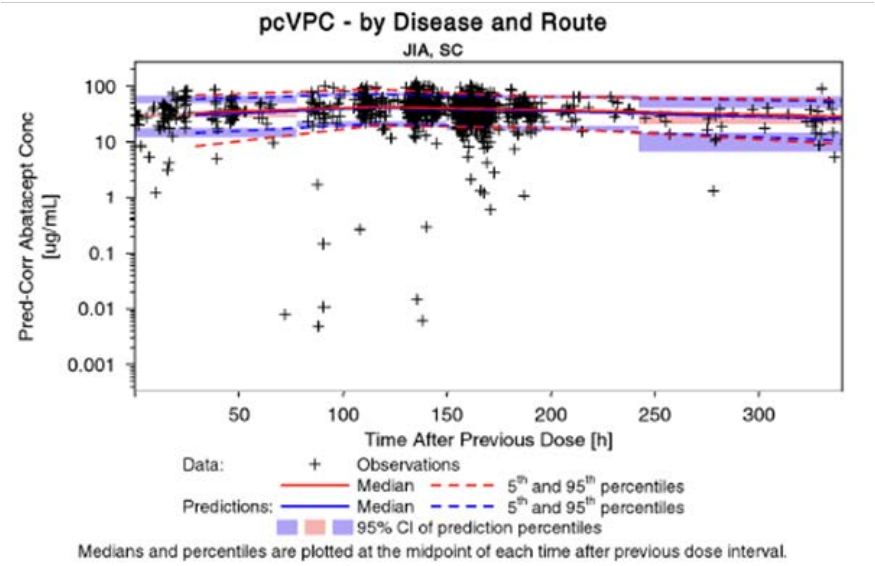


Figure 4 Prediction-Corrected Visual Predictive Check of Concentration vs. Time After Previous Dose, Stratified by Route (JIA patients)

Estimated individual abatacept steady-state minimum, maximum, and average concentrations (Cminss, Cmaxss, and Cavss) for subjects in the PPK dataset were obtained by applying the individual parameter estimates (empirical Bayesian estimates) from the final PPK model to the protocol-specified dose for that patient with the protocol-specified dosing interval. In addition, stochastic simulations of a virtual JIA population of patients were performed to determine the expected range of abatacept exposures. To conduct the stochastic simulations, the JIA efficacy dataset (approximately 400 patients age 2 to 17 years from Study IM101033 and Study IM101301) was resampled using covariate information from patients included in the Phase 3 dataset of patients with JIA to generate a dataset of 2,000 virtual patients. Virtual patients administered weight-tiered SC weekly had comparable distributions of exposure to each other and the Cavss was comparable to that of the 10 mg/kg IV monthly dosing regimen. As expected, SC dosing regimen was associated with higher Cminss and lower Cmaxss than IV dosing regimen.

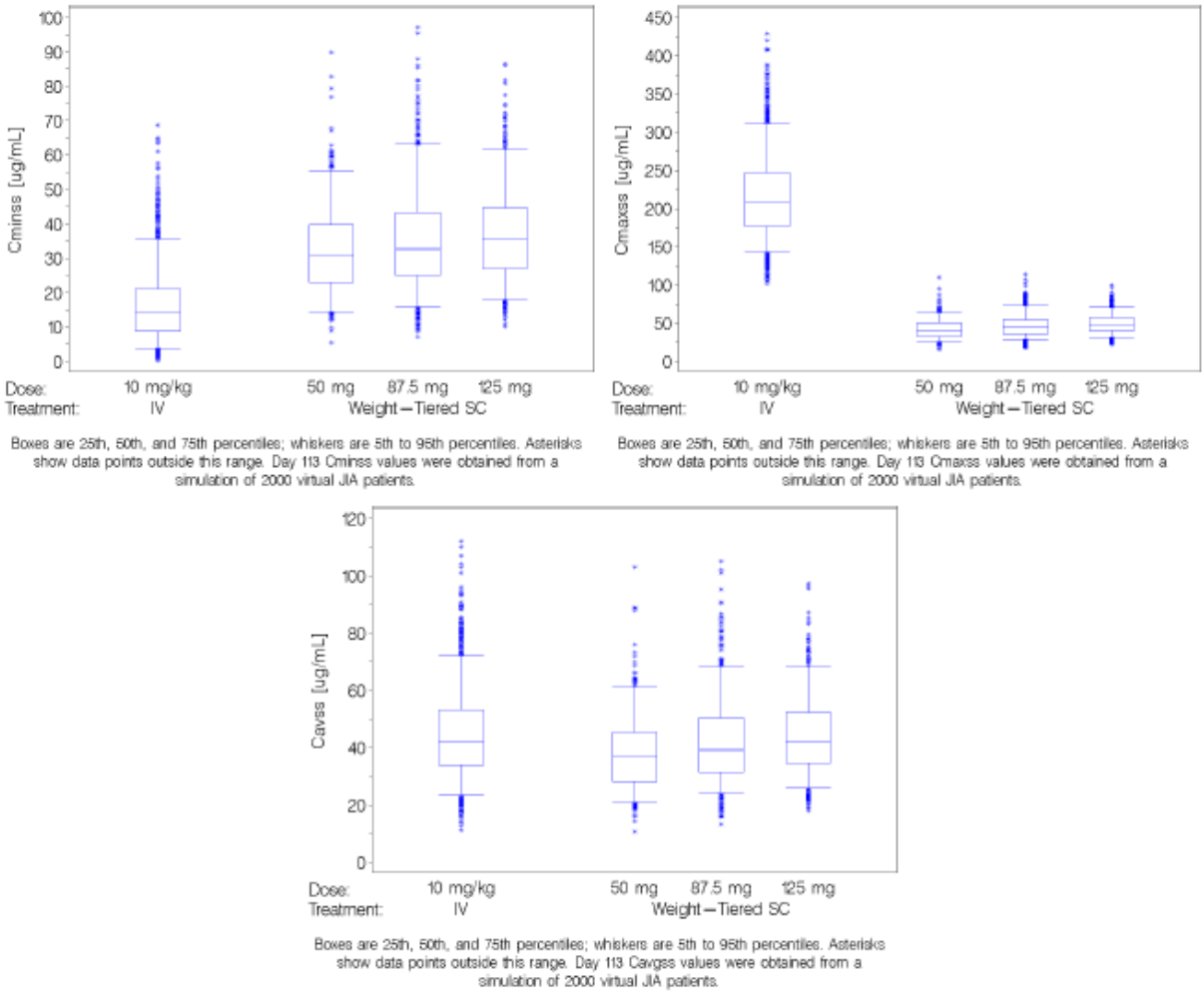


Figure 5 Boxplots of Simulated Abatacept Exposure Measures on Month 4 for Virtual JIA Patients Administered 10 mg/kg IV Monthly and Separate Weight-Tiered SC Weekly Dose Regimens

Pharmacokinetic interaction studies

No new data were provided addressing the pharmacokinetic interactions with other medicinal products and the CHMP considered that they are not required.

Concomitant MTX treatment

The data from the two paediatric studies IM101033 and IM101301 indicated that the achieved steady state (Day 113) abatacept Cmin levels were comparable in subjects with and without concomitant MTX treatment. This was in agreement with and supports the result of population PK analysis, showing that the baseline concomitant MTX use was not a statistically significant (ΔOFV -1.344, P=0.246) covariate on the clearance of abatacept.

Table 4 Abatacept Cmin at Day 113 by MTX use - Evaluable PK Population

	IM101-033 6-17 year old age cohort		IM101-301 2-5 year old age cohort		IM101-301 6-17 year old age cohort		IM101-301 2-17 years	
Cmin at day 113	Abatacept + MTX N=115	Abatacept N=35	Abatacept + MTX N = 25	Abatacept N = 5	Abatacept + MTX N = 103	Abatacept N = 32	Abatacept + MTX N = 128	Abatacept N = 37
Median	9.9	9.9	51.0	51.9	39.0	41.8	41.4	44.8
Mean (Min, Max)	10.9 (0.2, 61.6)	11.9 (0.5, 39.7)	52.0 (20.1, 122.1)	57.5 (43.4, 88.1)	41.5 (9.3, 88.1)	44.2 (15.8, 97.0)	43.6 (9.3, 122.1)	46.0 (15.8, 97.0)

Acronyms: max, maximum; min, minimum; MTX, methotrexate.

2.4.4. Pharmacodynamics

Mechanism of action

Abatacept is a fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte antigen 4 (CTLA4) linked to the modified Fc portion of human immunoglobulin G1 (IgG1). It prevents the interaction of the T-cell's CD28 with the antigen presenting cell's CD80/CD86 by binding avidly to the latter. As a consequence, T-cells are prevented from receiving the required second costimulatory signal needed for full activation resulting in inhibition of multiple aspects of T-cell-driven autoimmunity and inflammation.

Primary and Secondary pharmacology

Therapeutic exposure levels of abatacept were investigated in in vitro and non-clinical in vivo studies that were assessed during the initial marketing authorisation application of Orencia. In vitro studies using human peripheral blood mononuclear cells evaluated the ability of abatacept to inhibit T-cell proliferation and cytokine production. Based on the in vitro findings, it was anticipated that serum trough abatacept concentrations of 10 to 30 µg/mL would be required to observe maximal clinical efficacy. Increasing abatacept concentrations (up to 100 µg/mL) did not result in greater suppression of T-cell proliferation. Consistent with the in vitro results, T cell-dependent immune responses were inhibited in animal models at doses of abatacept where serum trough concentrations were approximately 10 µg/ml or greater. The in vitro studies and in vivo animal model data suggested that trough serum concentrations of abatacept between 10 and 50 µg/mL will provide maximal biologic efficacy.

The relationship between abatacept exposure and efficacy in JIA was characterized by an exposure-response (E-R) model (JIAACR model). The JIAACR model describes the probability of achieving cumulative JIAACR (JIAACR30, JIAACR50, JIAACR70, and JIAACR100) responses at 4 months (113 days) from the initiation of therapy as a function of abatacept exposure using a proportional odds model. Estimated individual abatacept measures (Cminss, Cmaxss, and Cavss) were obtained by applying the individual parameter estimates from the final PPK model to the protocol-specified dose for that patient with the protocol-specified dosing interval. Two JIAACR models were presented in the dossier: The first one was built in year 2012 and had data from study IM101033 (IV abatacept), and the second one was built in year 2018 and had data from both study IM101033 and study IM101301 (SC abatacept). There were no patients treated with placebo in either datasets.

In the most recent and more extensive (year 2018) JIAACR model, initial analyses for the base E-R model indicated that Cminss, compared with Cmaxss and Cavss, was the best (i.e. most statistically significant) abatacept exposure parameter describing the E-R relationship for efficacy. A log-linear function adequately described the drug effect, indicating that increasing Cminss was associated with a higher

probability of JIAACR response. Covariates of interest, e.g. route of administration, baseline age, concomitant medications, disease severity, and JIA category, were tested in the covariate analysis. Covariate-parameter relationships were evaluated using a single round of forward inclusion (univariate alpha level of 0.01) followed by stepwise backward elimination process using alpha level 0.001. None of the covariates were statistically significant predictors of the probability of JIAACR response after the backward elimination step (Tables below). Thus, no other predictors of JIAACR response were identified except abatacept Cminss.

Table 5 Forward Selection of Covariates for JIAACR (year 2018 model)

Parameter Affected	Covariate Added	Functional Form	Ver	Change in VOF[a]	df	*P* value[b]
Reference Model Filename: jiaacr-base-model.ctl (VOF=1172.207)						
Logit	Baseline CRP	Power	01	-9.281	1	2.316E-03
Logit	Age	Power	01	-9.027	1	2.661E-03
Logit	Age	Linear	01	-7.917	1	4.898E-03
Logit	Baseline Swollen Joint Count	Power	01	-7.799	1	5.228E-03
Logit	Weight	Linear	01	-5.367	1	2.053E-02
Logit	Baseline Tender Joint Count	Power	01	-4.183	1	4.084E-02
Logit	White Race	Exponential	01	-3.352	1	6.713E-02
Logit	Prior TNF-alpha Treatment	Exponential	01	-2.794	1	9.462E-02
Logit	Methotrexate Use	Exponential	01	-2.786	1	9.510E-02
Logit	Baseline Physician Global Assessment	Power	01	-2.78	1	9.545E-02
Logit	Corticosteroid Use	Exponential	01	-1.669	1	1.964E-01
Logit	NSAID Use	Exponential	01	-1.283	1	2.574E-01
Logit	Gender	Exponential	01	-1.181	1	2.772E-01
Logit	Route of Administration	Exponential	01	-1.037	1	3.086E-01
Logit	Baseline Tender Joint Count	Linear	01	-1.014	1	3.140E-01
Logit	Baseline Swollen Joint Count	Linear	01	-.926	1	3.360E-01
Logit	Weight	Power	01	-.622	1	4.304E-01
Logit	JIA Category	Exponential	01	-2.308	3	5.110E-01
Logit	Duration of Disease Category	Exponential	01	-2.155	3	5.409E-01
Logit	Duration of Disease Category	Exponential	02	-1.076	2	5.840E-01
Logit	JIA Category	Exponential	02	-1.049	2	5.919E-01
Logit	Baseline Physician Global Assessment	Linear	01	-.245	1	6.207E-01
Logit	Baseline CRP	Linear	01	-.228	1	6.331E-01

[a] Change in the value of the objective function relative to the reference model

[b] Statistical significance ($\alpha = 0.01$)

Abbreviations: df: number of degrees of freedom associated with this addition to the model; Ver: version number of the control stream; VOF: value of the objective function

Table 6 Backward Elimination of Full Covariate Model (year 2018 model)

Step	Parameter Affected	Covariate Removed	Functional Form	Ver	VOF	Change in VOF[a]	df	*P* value[b]
0		Full Multivariable model			1151.428			
1	Logit	Baseline Swollen Joint Count	Power	01	1154.971	3.543	1	5.980E-02
2	Logit	Age	Power	01	1162.927	7.955	1	4.796E-03
3	Logit	Baseline CRP	Power	01	1172.207	9.281	1	2.316E-03
4	No covariate effects remain in the model.							

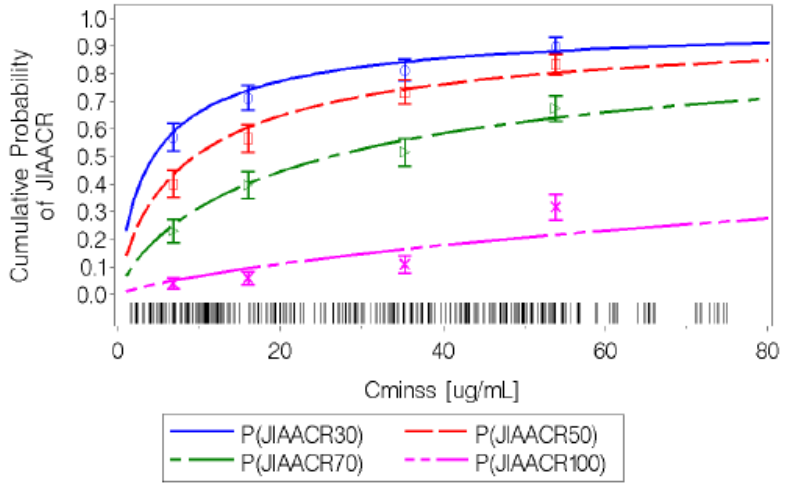
[a] Change in the value of the objective function relative to the reference model

[b] Statistical significance ($\alpha = 0.001$)

Abbreviations: df: number of degrees of freedom associated with this removal from the model; Ver: version number of the control stream; VOF: value of the objective function

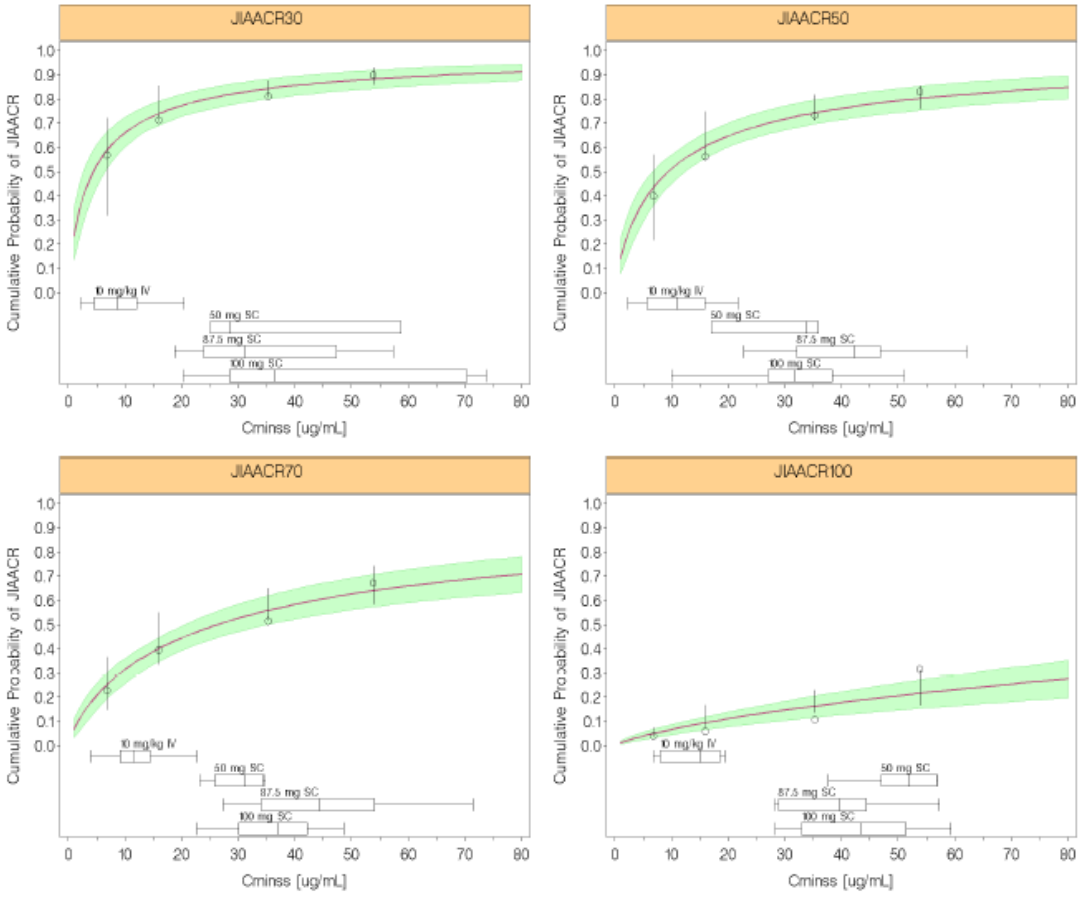
The final model-predicted probability of JIAACR response versus Cminss is presented in the Figure below along with the observed proportion of JIAACR responders in quartiles of Cminss. There was a good agreement between the model-predicted probability of JIAACR response and the proportion of observed JIAACR responders across the range of Cminss. A visual predictive check (VPC) with 1000 replicates of the analysis dataset indicated the data are accurately characterized by the model (Figure below). Of note,

it seems that higher than 10 µg/mL Cminss is required for near maximal JIAACR 50, 70, and 100 responses.



The lines represent the model–based predicted probability of JIAACR responder. The symbols represent the median Cminss of the grouped data and associated observed probabilities. The bars around the symbols represent the standard errors of the observed proportions. The hash marks near the x–axis represent the individual Cminss for JIAACR responders.

Figure 6 Cumulative Probability of JIAACR Response at Month 4 vs. Cminss (year 2018 model)



Note: Boxplots of the distributions of simulated Cminss are at the bottom of the figure for each dosing regimen.

Figure 7 Visual Predictive Check of the Final year 2018 JIAACR Model

Formal E-R analyses for safety endpoints were not conducted. Exploratory graphical analysis of the relationship between abatacept exposure and the most common expected adverse event in JIA patients (infection regardless of seriousness) suggested no relationship between the exposure and time to first infection. Meaningful E-R analyses could not be conducted for serious adverse events (SAEs) because so few SAEs were reported in the clinical studies (see section Clinical Safety).

Abatacept with or without concomitant mtx use As described above, no statistically significant covariates for JIAACR response were identified in the most recent (year 2018) JIAACR model. In contrast, in the earlier (year 2012) JIAACR model that only had data from study IM101033 (IV abatacept), efficacy was significantly better in patients using MTX (Table below). For example, predicted probability of ACR30 response in patients with median Cminss levels (9.99 µg/mL) was 72.2% and 54.7% in patients using and not using MTX, respectively.

Table 7 Predicted Probability of ACRp Responses (year 2012 Model)

Cminss Percentile	Cminss [µg/mL]	With Concomitant Methotrexate			Without Concomitant Methotrexate		
		ACRp30	ACRp50	ACRp70	ACRp30	ACRp50	ACRp70
5%	2.00	54.9%	37.5%	18.6%	36.10%	21.80%	9.60%
50%	9.99	72.2%	56.2%	32.8%	54.70%	37.30%	18.40%
95%	20.55	78.5%	64.3%	40.6%	62.90%	45.50%	24.10%

Abatacept with or without Prior Biologic Failure – second line therapeutic positioning

The results of the E-R analysis with the most recent (year 2018) JIAACR response model also demonstrated that prior use of TNF-alpha inhibitors was not significant covariate and did not affect predicted ACRp responses in subjects with pJIA.

2.4.5. Discussion on clinical pharmacology

The clinical profile of SC abatacept in treatment of JIA was investigated in one study: Study IM101301. A weight-tiered dosing regimen was used in the study: Doses of 50 mg, 87.5 mg, and 125 mg were administered once per week (q1w) in patients weighing 10 to < 25 kg, 25 to 50 kg, and > 50 kg, respectively. The primary objective was to estimate abatacept Cminss at Day 113; clinical efficacy and safety were secondary objectives. Target Cminss was ≥10 µg/mL in each weight tier, based on prior data indicating that near maximal efficacy in terms of JIAACR 30 response was achieved at Cminss level of approximately 10 µg/mL.

Results of study IM101301 confirmed that Cminss ≥10 µg/mL will be achieved with the selected weight-tiered dosing regimen. Steady state of abatacept was achieved by day 85 following the weekly body-weight–tiered subcutaneous abatacept dosing. Comparable trough concentrations across weight tiers and age groups were achieved by the body-weight–tiered subcutaneous dosing regimen. The mean (range) trough concentration of abatacept at day 113 was 46.2 mcg/mL (13.4 to 96.2 mcg/mL), 48.0 mcg/mL (22.4 to 122.1 mcg/mL), and 38.5 mcg/mL (9.3 to 73.2 mcg/mL) in paediatric pJIA patients weighing 10 to <25 kg, 25 to <50 kg, and ≥50 kg, respectively.

Results of the population PK model suggested that the absorption rate and bioavailability in JIA patients were higher than in adult RA patients, which were used as the prior information for absorption parameters. This is adequately reflected in section 5.2 of the SmPC.

Parameters describing distribution and elimination of abatacept were comparable for JIA and RA patients after adjustment for body size (weight). Consistent with the intravenous data, population pharmacokinetic analyses for subcutaneous abatacept in pJIA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate, corticosteroids, and NSAIDs, did not influence abatacept apparent clearance.

Even though Cminss levels with SC dosing in JIA patients were higher than expected and they are higher than with IV dosing, they were in the range observed in adult RA patients with SC dosing. Abatacept maximum concentrations are, obviously, several folds higher with the q4w IV dosing regimen than with the q1w SC dosing regimen. Exposure parameters were similar in each weight and age category with the dosing regimen used in Study IM101301, which is proposed for the clinical use.

The most recent (year 2018) JIAACR response model that has approximately two times more paediatric JIA patients and wider distribution of Cmin levels than the year 2012 model can more reliably describe the effects of abatacept levels and other parameters on clinical response. The relationship between abatacept exposure and efficacy in JIA was characterized by an exposure-response (E-R) model using efficacy data from the two conducted clinical studies (IM101033 with IV dosing; IM101301 with SC dosing). The model confirmed that, as in RA, the Cminss was a better predictor of efficacy, compared with maximum and average concentrations. As in prior E-R analyses, near maximal JIAACR 30 response was achieved at Cminss level of approximately 10 µg/mL. Limited and exploratory graphical analysis suggested no relationship between the exposure to abatacept and safety endpoints of interest.

Abatacept with or without concomitant mtx use The PK data from the two paediatric studies IM101033 and IM101301 indicated similar exposure/achieved steady state (Day 113) abatacept Cmin levels were comparable in subjects with and without concomitant MTX treatment.

The result of population PK analysis showed that the baseline concomitant MTX use was not a statistically significant (ΔOFV -1.344, P=0.246) covariate on the clearance of abatacept.

Furthermore, modelling showed that MTX was not a significant covariate and did not affect the prediction of ACRp response in subjects with pJIA.

Abatacept with or without Prior Biologic Failure – second line therapeutic positioning

The results of the E-R analysis with the most recent (year 2018) JIAACR response model also demonstrated that prior use of TNF-alpha inhibitors was not significant covariate and did not affect predicted ACRp responses in subjects with pJIA.

2.4.6. Conclusions on clinical pharmacology

The impact of modelling and simulation exercises in the application is high. No major deficiencies in population PK and exposure-response models were observed.

Clinical pharmacology is based on population PK and exposure-response models, which appear to be adequate for the intended use. Pharmacokinetics of abatacept in the target population is adequately summarised in the product information.

The most recent (year 2018) E-R model for efficacy indicated that MTX use was not a statistically significant covariate predicting the JIAACR response and that prior use of TNF-alpha inhibitors was not significant covariate and did not affect predicted ACRp responses in subjects with pJIA.

In conclusion, the pJIA indication for SC abatacept for children 2 to 17 years of age and the change of the indication to introduce abatacept monotherapy in case of MTX intolerance or when treatment with MTX is inappropriate and for positioning abacacept treatment in second line in the treatment of pJIA (i.e. the removal of “following treatment failure with TNF-inhibitors”) for both SC and IV formulations is considered acceptable from a clinical pharmacology perspective.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

For dose-response please refer to the PK section.

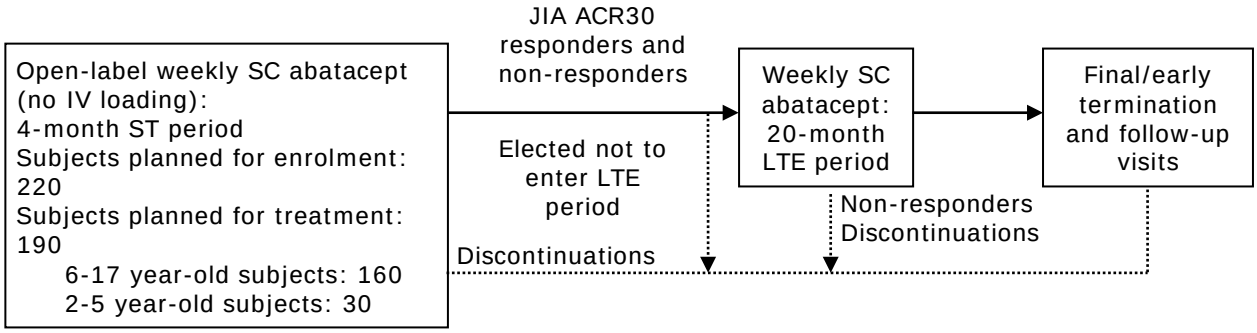
2.5.2. Main study

A Phase 3 Multi-center, Open-label Study im101301 to Evaluate Pharmacokinetics, Efficacy, and Safety of abatacept Administered Subcutaneously (SC) in Children and Adolescents with Active Polyarticular Juvenile Idiopathic Arthritis (pJIA) and Inadequate Response (IR) to Biologic or Non-biologic Disease Modifying Anti-rheumatic Drugs (DMARD).

Methods

This was an uncontrolled open-label study to assess PK, efficacy and safety of SC abatacept in pJIA with no formal hypothesis testing. The clinical study report presents the final results of the 6 to 17 year-old cohort from the 24-month cumulative period (the 4-month short-term [ST] study period plus the

20-month long-term extension [LTE] period) and partial results of the 2 to 5-year-old cohort from the 24-month cumulative period at the time of the latest database closure.



[a]Non-responders per ACRp30 criteria by month 4 were given the opportunity to be treated with SC abatacept for an additional 3 months in the LTE period. If, after 7 total months of treatment, response did not occur, the subject was considered for discontinuation. The study was extended for up to 5 years in some countries by protocol amendment to ensure continued dosing for subjects who demonstrate clinical benefit from SC abatacept at the conclusion of the study.

Figure 8 Study Design

The purpose of this study was to evaluate if 4 months of a weekly weight-tiered dosing regimen of SC abatacept would deliver steady-state systemic exposures within the therapeutic range associated with maximal efficacy observed with intravenous (IV) abatacept in the paediatric population. Subjects were treated with open-label abatacept for a 4-month ST period and 20 month LTE period and evaluated for PK, efficacy, safety and immunogenicity. The study protocol was amended in some countries to extend the study beyond 2 years, up to a total of 7 years.

Investigators and Study Administrative Structure

The study was conducted at 50 sites in 12 countries: Argentina, Belgium, Brazil, France, Germany, Italy, Mexico, Peru, Russian Federation, Spain, South Africa, and US.

Study Participants

Inclusion criteria

Key inclusion criteria for subjects were as follows:

- Ages 2 to 17 years (male or female)
- Diagnosed with active pJIA, extended oligoarthritis, enthesitis-related arthritis, systemic arthritis (with a polyarticular course), or psoriatic arthritis (PsA: but with no other rheumatic disease)
- Naïve to abatacept
- An insufficient therapeutic response (for ≥ 3 months) or prior intolerance to at least 1 biologic or non-biologic DMARD
- A history of a least 5 joints with active disease
- Active articular disease with ≥ 2 active joints and ≥2 joints with limitation of movement at baseline

Subjects with prior inadequate response to TNF-alpha antagonists or other biologic DMARDs were restricted to no more than 30% of the study population. Subjects with systemic JIA at onset were restricted to no more than 10% of the study population. Subjects with active, latent, or recent infections were excluded from enrolment.

Exclusion criteria

Key exclusion criteria were as follows:

1/ Target disease exceptions

a/Subjects with any other rheumatic disease; however, subjects with enthesitis-related arthritis or PsA were included.

2/ Medical history and concurrent diseases

a/ Active systemic disease within a period of 6 months prior to first dose of study medication

b/ Macrophage activation syndrome (per published criteria) anytime within a period of 6 months prior to first dose of study medication

c/ Active uveitis within 6 months of enrollement

d/ Subjects with persistent oligoarthritis JIA

e/ Subjects who have, at any time, received treatment with cytotoxic T-lymphocyte-associated protein (CTLA)4-immunoglobulin (Ig) or abatacept

f/ Subjects who have failed responses to more than 2 TNF-alpha antagonists or other biologic DMARDs

g/ Presence of an active infection, serious infections or history of frequent infection or chronic infections within 3 months prior to the first dose of study medication

j/ Joint replacement surgery required during the anticipated time on study medication, including screening or history of surgery on more than 5 joints

i/ Received live vaccines within 3 months of enrolment

j/ Active vasculitis of a major organ system (except for SC rheumatoid nodules)

(...)

3/ Physical and Laboratory Test Findings

a/ Hepatitis B surface antigen

b/ Hepatitis C antibody

c/ Hemoglobin ≤ 9.0 g/dL

(...)

Treatments

Test product, dose, mode of administration, duration of treatment:

Open-label SC abatacept was administered by prefilled syringe (PFS) once weekly as a weight-tiered dose regimen:

- 10 to < 25 kg: 50 mg in 0.4 mL PFS
- 25 to < 50 kg: 87.5 mg in 0.7 mL PFS
- ≥50 kg: 125 mg in 1.0 mL PFS

Non investigational medicinal products:

Corticosteroid background medications (prednisone or prednisolone) and MTX.

Restricted medications:

Corticosteroid injections (intra-articular or systemic), unless intra-articular injections are used as rescue treatment in the LTE period; MTX doses > 30 mg/m2/week or > 40 mg/week; Any investigational drugs; Non-biologic DMARDs other than MTX; Biologic RA therapies; Cyclosporine (IV or oral) and other calcineurin inhibitors; D-penicillamine; Immunoadsorption columns; Prohibited medications listed in the prescribing label of the subjects' background therapy.

Rescue Treatment:

Non-steroidal anti-inflammatory drugs or analgesics that did not contain aspirin were permitted in subjects experiencing pain not adequately controlled by the baseline medications and study drug. Rescue analgesics or additional NSAIDs were not permitted 12 hours before joint evaluation. Intra-articular corticosteroid injections and addition of nonbiologic conventional DMARDs were permitted only during the LTE period at the Investigator's discretion.

Objectives

- The Primary Objective:

- To estimate abatacept steady-state trough serum concentrations (Cminss) at Day 113 in children and adolescents with pJIA aged 6 to 17 years.

- Secondary Objectives:

- To assess American College of Rheumatology Paediatric 30 (ACRp30) on Day 113 following continuous weekly administration of SC abatacept in children and adolescents with pJIA aged 6 to 17 years
- To assess abatacept Cmin at Day 57, Day 85, and Day 113 during the initial 4-month short-term (ST) period by each weight tiered dosing regimen in 6 to 17-year-old subjects
- To summarize safety (proportion of subjects with AEs, deaths, SAEs, and AEs leading to discontinuation) during the initial 4-month ST (6 to 17-year-old cohort only) and cumulative (ST and LTE periods combined) abatacept periods (in both age cohorts: 2 to 5 years and 6 to 17 years old)
- To assess the proportion of subjects with positive immunogenicity response during the initial 4-month (6 to 17-year-old age cohort only) and cumulative abatacept periods up to 6 months following discontinuation of treatment (in both age cohorts: 2 to 5 years and 6 to 17 years old)

- Exploratory Objectives in Each Age Cohort (in both age cohorts: 2 to 5 years and 6 to 17 years old):

- To assess abatacept Cmin over time
- To assess individual components of ACRp30 over time during the cumulative period
- To assess ACRp30, 50, 70, 90, 100 and inactive disease rates over time
- To assess ACRp30 response rates at Day 113 by weight and by tumour necrosis factor (TNF) naive and TNF-IR subgroups in 6 to 17-year-old subjects only
- To assess ACRp30 response rates at Day 113 by JIA subtypes and for whole population after exclusion of subjects with systemic JIA in 6 to 17-year-old subjects only

- To assess the generation and impact of anti-glutamic acid decarboxylase, anti-thyroperoxidase, and thyroid-stimulating hormone auto antibodies prior, during treatment, and up to 6 months following discontinuation of treatment
- To characterize the PK of SC abatacept in JIA using population PK analysis and exposure-response relationship
- To assess the presence of protective antibody titers to diphtheria and tetanus in paediatric subjects (2 to 5 years of age)
- To assess the change in growth and Tanner stage
- To assess the improvement in quality of life status as measured by the parent version of the Activity Limitation Questionnaire (ALQ) over time
- To assess juvenile arthritis disease activity scores (JADAS) and JADAS low disease activity and remission over time during the cumulative period (post hoc analysis)

Outcomes / endpoints

The achievement of target therapeutic abatacept concentrations was assessed through Cmin values at each pre-specified time point in the cumulative period.

- Efficacy:

Efficacy assessments evaluated the mean and median changes from baseline of the ACRp core components: number of active joints, number of joints with limited range of motion, physician global assessment of disease activity, parent assessment of overall well-being, children's health assessment questionnaire (CHAQ), and C-reactive protein (CRP) level. The proportion of ACRp30, ACRp50, ACRp70, ACRp90, and ACRp100 responders and subjects with inactive disease status was also evaluated. Post hoc analyses of efficacy were conducted using the JADAS during the cumulative period.

- Safety:

Safety assessments were based on medical review of AE reports and the results of vital sign measurements and clinical laboratory tests. Safety assessments included AEs, serious adverse events (SAEs), deaths, discontinuations due to AEs, and AEs related to clinical laboratory test abnormalities reported during the cumulative period safety window. AEs of special interest were assessed throughout the study: malignancies, autoimmune disorders, local injection-site AEs, AEs within 24 hours of study drug administration, and infections.

- Immunogenicity and immunological events:

Pre-dose blood samples for immunogenicity were collected at several points in the cumulative period and following the last dose of abatacept administered in the study. The generation of relevant auto-antibodies (anti-glutamic acid decarboxylase [GAD], anti-thyroid peroxidase [TPO]), was measured to assess the potential for abatacept-induced autoimmune diabetes type 1 or thyroiditis. The potential effect of these antibodies on thyroid function was assessed through the measurement of thyroid stimulating hormone (TSH).

- Outcomes Research Assessments:

Physical function was evaluated using the disability section of the CHAQ, which assesses 8 domains of physical function on 5-point scales: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common activities. A disability index was calculated as the mean of the 8 functional scales. The CHAQ

was completed by the parents. QoL was also evaluated using the ALQ completed by the physician and the parents.

- Tanner Staging:

Tanner staging was assessed at Day 1 and at the final/early termination visit. These results were provided, on request: no clinically significant effects on the children's development were clearly evident, after 2 years of cumulative treatment with abatacept. Results pending final analysis at 24 months.

Sample size

A sample size of 160 subjects aged 6 to 17 years was planned for the primary analysis to allow assessment of the PK parameters as well as the safety and efficacy of SC abatacept in JIA. The sample size approximates the sample size of the 4-month open-label lead-in phase of the original IV JIA abatacept study, which allowed an evaluation of the PK, safety, efficacy, and immunogenicity of SC in JIA abatacept with similar precision as previously obtained for IV abatacept (Period A of Study IM101033).

Anticipated enrolment of approximately 160 subjects into 3 body weight tiers (10 to < 25 kg, 25 to < 50 kg, and ≥ 50 kg) ensures that the half-width of 90% confidence interval (CI) for steady state Cminss is within 18% of the true population mean for each tier based on a log-transformed standard deviation (SD) for steady state Cminss of 0.49 based on population PK modelling. The sample size of 160 subjects also allows an estimation of the proportion of ACRp30 responders after 4 months of SC abatacept treatment with a precision of 7.4% for the half-width of the 95% CI, assuming an underlying true responder rate of 64%, which was the responder rate in the IV JIA trial.

A population of 30 subjects aged 2 to 5 years was predicted to permit descriptive assessments of PK, efficacy, and safety response similar to the 6 to 17-year-old cohort.

As there is no plan for hypothesis testing and no statistical objective per se, no formal sample size calculation is foreseen. The data generated is descriptive in nature. The proposed sample size provides sufficient precision for the descriptive analysis, and thus appears appropriate.

Randomisation / Blinding (masking)

This is not applicable as this was an uncontrolled open-label study.

Statistical methods

- Pharmacokinetics:

Summary statistics (mean, SD, geometric mean and percent coefficient of variation) for Cminss at Day 113 are provided by weight-tiered dose and subject age.

- Efficacy:

The CIs for proportions were computed using the normal approximation, provided that the actual number of events was at least 5. The proportion of ACRp30, ACRp50, ACRp70, ACRp90, and ACRp100 responders and subjects with inactive disease status were summarized at Day 113 using a point estimate and a 95% CI. Missing data was imputed as an ACRp non-responder at all scheduled protocol visits up to Day 113 subsequent to the point of discontinuation. For other missing values, a non-responder imputation was done up to Day 113, except in cases where missing values were between 2 responders. In that case, a response was imputed. Imputed data were included in all analyses of data up to and including that on Day 113. Beyond Day 113, as-observed analyses. In addition, an ad hoc analysis was performed for the ITT population of the 6 to 17-year-old cohort up to Day 729.

Efficacy was also assessed through ad hoc analysis of JADAS27 and JADAS71 scores over time (6 17-year-old cohort only), as well as the proportion of subjects with JADAS low disease activity and remission (both age cohorts). The analysis of JADAS was performed for the ITT population of the 6 to 17-year-old cohort and for ITT population in 2 to 5-year-old cohort up to Day 113 and as-observed beyond Day 113.

- Safety:

All treated subjects were included in the safety analysis. The evaluation of drug safety was based on clinical AEs and laboratory abnormalities reported during the study.

- Immunogenicity:

All treated subjects with at least 1 post-baseline immunogenicity result were included in the immunogenicity analysis population. The frequencies of positive immunogenicity responses were summarized by antibody specificity by study day, and the corresponding titer values were listed by subject and by study day. Listings by subject of efficacy, safety, and PK results for subjects with positive immunogenicity response relative to baseline were generated.

Overall, the statistical methods and analysis appear appropriate for this type of study.

Results

Participant flow

- 6 to 17 year-old:

Cohort 173 subjects entered the ST period and of these, 157 subjects entered the LTE and 132 subjects (76.3%) completed 24 months of treatment. The most common reasons for discontinuation during the cumulative period were lack of efficacy (17 subjects, 9.8%) and AEs (7 subjects, 4.0%). Of the 17 subjects who discontinued due to lack of efficacy, 15 continuously took MTX. There appeared not to be any trend on the reasons for discontinuation. The attrition rate appears acceptable for this type of study.

- 2 to 5 year-old cohort:

Of the 47 enrolled subjects, 46 subjects were treated and 15 subjects (32.6%) were still on-going in the 2 year cumulative period at database closure. Seven subjects (15.2%) prematurely discontinued study drug. Of these, 5 subjects (10.9%) discontinued due to lack of efficacy: 2 subjects in the ST period (Days 66 and 86), and 3 subjects in the LTE period (Days 224, 310, and 650). One subject discontinued due to AEs of pyrexia, rhinitis, and cough, and another subject requested study drug discontinuation.

This part of the study is still ongoing, pending evaluation of the final results. Thus, only the partial cumulative data is presented from the younger age cohort.

Recruitment

Conduct of the study

There were 14 amendments to the original protocol in study conduct; the CHMP was of the opinion that they don't have a significant effect on the results of the study. The presented protocol deviations appear to be minor and unlikely to have a significant impact on the efficacy or present a safety risk to the subjects.

Baseline data

Short term 6 to 17 Year-old Cohort

Table 8 Baseline and Demographic Characteristics - All Treated Subjects – 6 to 17 Year-old Age Cohort

Demographic	All Treated Subjects (n=173)
Age (years)	
Mean (SD)	12.3 (3.1)
Median (Min-Max)	13.0 (6.0-17.0)
Weight (kg)	
Mean (SD)	46.5 (18.8)
Median (Min-Max)	45.0 (16.0-146.3)
Weight Categories (no., [%])	
< 25 kg	18 (10.4%)
25 to < 50 kg	74 (42.8%)
≥ 50 kg	81 (46.8%)
Gender (no., [%])	
Female	136 (78.6%)
Male	37 (21.4%)
Race (no., [%])	
White	144 (83.2%)
Black/African American	14 (8.1%)
American Indian/Alaska Native	0
Asian	0
Native Hawaiian/Other Pacific Islander	0
Other	15 (8.7%)
Geographic Region (no., [%])	
North America	22 (12.7%)
South America	56 (32.4%)
Europe	78 (45.1%)
ROW	17 (9.8%)

Abbreviations: max = maximum; min = minimum; ROW = rest of world; SD = standard deviation

Table 9 Baseline Disease Characteristics - All Treated Subjects – 6 to 17-Year-old Age Cohort

		Total N = 173
Duration of JIA (years)	N	173
	Mean	2.8
	SD	3.3
	Median	2.0
	Min	0.0
	Max	15.0
Duration of JIA Categories	<= 2 years	102 (59.0%)
	2 - <= 5 years	37 (21.4%)
	5 - <= 10 years	30 (17.3%)
	> 10 years	4 (2.3%)
Active Joints	N	173
	Mean	12.4
	SD	8.3
	Median	10.0
	Min	2.0
	Max	42.0
Joints with LOM	N	173
	Mean	10.7
	SD	8.4
	Median	8.0
	Min	0.0
	Max	42.0
CHRQ Disability Index	N	172
	Mean	0.99
	SD	0.68
	Median	0.94
	Min	0.00
	Max	2.88
Parent Global Assessment	N	172
	Mean	45.6
	SD	25.8
	Median	47.8
	Min	0.0
	Max	95.7
Physician Global Assessment	N	173
	Mean	48.5
	SD	21.1
	Median	48.0
	Min	6.0
	Max	94.0
CRP (mg/dL)	N	173
	Mean	1.22
	SD	2.84
	Median	0.20
	Min	0.10
	Max	21.10
JIA Disease Onset Categories	Enthesitis Related Arthritis	4 (2.3%)
	Extended Oligoarthritis	19 (11.0%)
	Persistent Oligoarthritis	4 (2.3%)
	Polyarthritis RF+	46 (26.6%)
	Polyarthritis RF-	94 (54.3%)
	Psoriatic Arthritis	0
	Systemic Arthritis	5 (2.9%)
	Undifferentiated Arthritis	1 (0.6%)
	Other	0
MTX Dose (mg/week)	N	136
	Mean	15.8
	SD	4.7
	Median	15.0
	Min	2.1
	Max	30.0

Baseline is Day 1 of the study or last measurement prior to short-term dose.

The duration of pJIA in the study population ranged from 0 to 15 years, with the majority (59.0%) of subjects experiencing JIA for ≤ 2 years. The most frequent categories of disease at onset in the 6 to 17-year-old cohort met the criteria for pJIA: polyarthritis RF- (54.3%), polyarthritis RF+ (26.6%), extended oligoarthritis (11.0%), and systemic arthritis (2.9%). Four subjects (2.3%) entered the study with persistent oligoarthritis in violation of the study criteria. No subjects with PsA entered the study in this cohort.

The majority of subjects (136 subjects, 78.6%) were taking methotrexate (MTX) at baseline. Relative to body size, mean (SD) MTX dose was 0.388 (0.177) mg/kg/week (12.0 [4.3] mg/m2/week). Prior to enrolment, 26.6% of subjects took a biologic DMARD.

Table 10 Selected Baseline Demographic and Disease Characteristics

	Number (%) of Subjects		
	2-5 age cohort (N=46)	6-17 age cohort (N=173)	2-17 years (N=219)
Age (years)			
– Mean (SD)	4.1 (1.0)	12.3 (3.1)	10.6 (4.4)
– Median (Min, Max)	4.0 (2,5)	13.0 (6,17)	11.0 (2.0,17.0)
Weight Categories			
– <25 kg	43 (93.5)	18 (10.4)	61 (27.9)
– 25 - 50 kg	3 (6.5)	74 (42.8)	77 (35.2)
– >=50 kg	0 (0.0)	81 (46.8)	81 (37.0)
Sex: Female	28 (60.9)	136 (78.6)	164 (74.9)
Race: White	44 (95.7)	144 (83.2)	188 (85.8)
pJIA Duration (years)			
– Mean (SD)	0.8 (1.0)	2.8 (3.3)	2.4 (3.0)
– Median (Min, Max)	0.5 (0, 4)	2.0 (0, 15)	1.0 (0,15)
Active Joints			
– Mean (SD)	9.3 (6.0)	12.4 (8.3)	11.8 (7.9)
– Median (Min, Max)	7 (2, 27)	10 (2, 42)	9 (2,42)
pJIA Disease Onset Categories			
– Polyarthritis RF-	29 (63.0)	94 (54.3)	123 (56.2)
– Polyarthritis RF+	3 (6.5)	43 (24.9)	49 (22.4)
– Extended Oligoarthritis	10 (21.7)	18 (10.4)	29 (13.2)
– Systemic Arthritis	0	5 (2.9)	5 (2.3)
– Enthesitis Related Arthritis	0	3 (1.7)	4 (1.8)
– Persistent Oligoarthritis	0	5 (2.9)	4 (1.8)
– Psoriatic Arthritis	4 (8.7)	0	4 (1.8)
– Undifferentiated Arthritis	0	1 (0.6)	1 (0.5)
MTX dose, mg/m^2/week, n	37	136	173
– Mean (SD)	12.9 (3.8)	12.0 (4.3)	12.3 (4.1)

Previous Treatments:

As per inclusion criteria, subjects received prior nonbiologic DMARD, TNF-alpha antagonist, or other biologic DMARD therapy for JIA. Prior to enrolment, nearly all subjects took MTX (94.8%) and 26.6% of subjects took a biologic DMARD.

At baseline, subjects were restricted from taking biologic DMARDs, and MTX and corticosteroids doses were stabilized for those subjects taking these drugs. Those subjects who took MTX had a mean (SD) dose of 12.0 (4.3) mg/m2/week. Washout of excluded biologic and nonbiologic DMARDs (except for MTX) had occurred for all but 2 subjects at baseline. On Day 1, one subject took chloroquine and sulfasalazine, and one took cyclosporine (oral). Because a 4-week washout period was not enacted prior to the first dose of the study drug, these 2 instances were classified as significant protocol deviations. However, these 2 subjects stopped taking these drugs by Day 1 or 2 of the study.

Other deviations related to prior or concomitant medications include 2 subjects who were enrolled but did not have prior insufficient response to at least 1 biologic or nonbiologic DMARD and one additional subject who was restarted on MTX during the ST period.

Concomitant therapy:

During the ST period, subjects were allowed to remain on stable doses of MTX, corticosteroids, or NSAIDs if they were taking these anti-rheumatic medications at baseline. No other anti-rheumatic medications were allowed during the ST period.

Prior to enrolment, 94,8% of subjects took methotrexate (MTX) and 26.6% of subjects took biologic DMARD. The majority of subjects (78.6% of subjects) took MTX during the ST period. The mean methotrexate dose (mean (SD) MTX dose was 0.388 (0.177) mg/kg/week (12.0 [4.3] mg/m2/week), which appears adequate (usual dose range 10-15 mg/m2 per week). There were some deviations on the prior and concomitant medication use. However, these are not considered significant and are not expected to affect the results or inferences.

Extent of Exposure:

In the ST period, the mean (SD) duration of exposure to SC abatacept was 114.9 (12.22) days, with 172 of 173 subjects with ≥ 90 days of exposure. The majority (95.4%) of 6 to 17 year old subjects received 13 to 16 SC injections, and the median number of injections was 16.

Treatment compliance with investigational treatment was high during the ST period with over 90 % of subjects with no (82,6%) or one (12,1%) missed injection.

Discontinuation of Study Therapy During the ST period:

11 subjects from the 6 to17-year-old cohort discontinued.

Cumulative 2 to 5 Year-old Cohort

The objective of the study in the 2 to 5-year-old cohort was to evaluate the long-term effects of treatment; consequently, results for this cohort are presented only for the entire cumulative period (combined ST and long-term extension [LTE] periods) from baseline up to database closure. For this cohort only partial cumulative data has overall been provided as the 2 year cumulative period is still ongoing. The post treatment data is also pending.

Baseline/Demographic Characteristics:

Demographics At study entry (Day 1), all treated subjects were within the 2 to 5-year age range, with a mean (SD) age of 4.1 (1.0) years. The majority of treated subjects were white (44/46, 95.7%), female (28/46, 60.9%), and weighed < 25 kg (43/46, 93.5%) at baseline.

Exposure:

As of the date of database closure, subjects were still continuing in the 20 months LTE period. For the 46 subjects who entered into the study, the mean (SD) exposure to SC abatacept over the cumulative period was 18.8 (7.26) months with a median duration of 24.1 months. Subjects received a median of 98 SC injections during the cumulative period.

Discontinuations:

Seven subjects in the 2 to 5-year-old cohort discontinued study drug during the 2 year cumulative period. Five subjects discontinued due to lack of efficacy; 1 discontinued due to AEs of pyrexia, rhinitis, and cough; and 1 subject requested to discontinue study treatment.

Baseline Disease Characteristics:

At baseline, study subjects met the criteria for polyarticular disease. The duration of pJIA in the study population ranged from 0 through 4 years, with the majority (42/46, 91.3%) of subjects experiencing JIA for ≤ 2 years. The mean (SD) number of active joints was 9.3 (6.0) and the mean (SD) number of joints with LOM was 8.7 (5.6).

Mean baseline measurements were of the CHAQ (1.08, on a scale of 0-3), Parent Global Assessment (38.6 mm, on a scale of 0-100 mm), and Physician Global Assessment (47.1 mm, on a scale of 0-100 mm), where higher scores in each measurement indicate higher disease activity. Mean (SD) CRP levels were .33 (2.42) mg/dL and ranged from 0.10 mg/dL to 11.30 mg/dL.

The categories of disease onset in the 2 to 5-year-old cohort met the criteria for pJIA: polyarthritis RF- (29/46, 63.0%), extended oligoarthritis (10/46, 21.7%), psoriatic arthritis (4/46, 8.7%), and polyarthritis RF+ (3/46, 6.5%). No subjects presented with systemic arthritis, undifferentiated arthritis, or persistent oligoarthritis.

Baseline Methotrexate Dose:

Most subjects (37/46) were taking MTX at baseline. Relative to body size, baseline mean (SD) MTX dose per week was 12.9 (3.8) mg/m2 body surface area (0.531 [0.172] mg/kg body weight). The mean (SD) total MTX dose per week was 9.5 (2.9) mg/week and ranged from 1.0 mg/week through 15.0 mg/week. The observed range of baseline MTX doses (1.2 through 22.9 mg/m2/week) was comparable to the MTX dose range suggested in the study inclusion criteria (10 to 30 mg/m2/week).

Previous Treatments:

As per inclusion criteria, subjects had received nonbiologic DMARDs, TNF-alpha antagonist, or other biologic therapy for JIA before enrolling in this study. All but 1 subject (45/46, 97.8%) had taken MTX, 17 subjects (37.0%) had taken oral corticosteroids, and 10 subjects (21.7%) had taken a biologic DMARD (etanercept, adalimumab, or tocilizumab).

At baseline, subjects were restricted from taking biologic DMARDs. MTX and corticosteroid doses were stabilized for those subjects taking these drugs. By Day 1, washout of excluded biologic and nonbiologic DMARDs (except for MTX) and standardization of corticosteroid dose in study subjects were achieved. Those subjects who took MTX at baseline had a mean (SD) dose of 12.9 (3.8) mg/m2/week. No subjects concomitantly took biologic DMARDs or nonbiologic DMARD (other than MTX) when first receiving study drug.

Concomitant Therapy During the Cumulative Period (2 to 5-Year-Old Cohort):

During the study, subjects were allowed to remain on stable doses of MTX, corticosteroids, or NSAIDs if they were taking these anti-rheumatic medications at baseline. No other anti-rheumatic medications were allowed during the study.

Subjects adhered to the study criteria for excluded therapies. All 37 MTX users at Day 1 remained on MTX at the time of database closure. The three subjects who began use of excluded biologic DMARDs after Day 1 did so after discontinuation from the study drug but within the 56-day post-treatment observation period. Thirteen subjects initiated use of corticosteroids after Day 1.

Other therapeutic classes of concomitant medications taken by > 10% of subjects were typical for this patient population.

Cumulative 6 to 17 year-old cohort

Extent of Exposure during the Cumulative Period for the 173 subjects who entered into the study, the mean (SD) exposure to SC abatacept over the cumulative period was 21.8 (6.87) months with a median exposure of 24.3 months (range of 1.9 to28.0 months). Most subjects (129/173) had at least 24 months of abatacept exposure during the cumulative period. Subjects received a median of 102 SC injections during the cumulative period. The majority of subjects received at least 97 injections (122/173, 70.5%).

Discontinuation of Study Therapy

Table 11 Subject Disposition During the Cumulative Period in Study IM101301

	n (%) of subjects		
	2 - 5 year old (N=46)	**6 - 17 year old (N=173)**	**2 - 17 year old (N=219)**
Total discontinuations	7 (15.2)	36 (20.8)	43 (19.6)
Discontinuations due to:			
Adverse event	1 (2.2)	7 (4.0)	8 (3.7)
Lack of efficacy	5 (10.9)	17 (9.8)	22 (10.0)
Withdrawal of consent	0	4 (2.3)	4 (1.8)
Subject no longer meet study criteria	0	2 (1.2)	2 (0.9)
Poor/Non-compliance	0	1 (0.6)	1 (0.5)
Pregnancy	0	1 (0.6)	1 (0.5)
Subject request to discontinue treatment	1 (2.2)	4 (2.3)	5 (2.3)
Number ongoing	15 (32.6)	0	15 (6.8)
Number completing cumulative period	24 (52.2)	132 (76.3)	156 (71.2)
Number completing ST without entering LT	0	5 (2.9)	5 (2.3)

Of the 219 treated subjects, 205 completed the ST period and 200 subjects entered the LTE period. In the 6 to 17 year-old cohort, the majority of subjects reached the primary endpoint at Day 113 (95%), continued into the LTE period, and completed the LT period (76%). In the 2 to 5 year-old cohort, 15 subjects were still ongoing in the LTE period at the time of database lock.

A total of 19.6% of subjects (15.2% in the 2 to 5 year-old cohort and 20.8% of in the 6 to 17 year-old cohort) discontinued during the study cumulative period, the main reason being lack of efficacy. The timing of discontinuation due to lack of efficacy appeared to have no obvious pattern in either cohort.

At database closure, the median length of abatacept exposure was 24.1 months for the 2 to 5 year-old cohort and 24.3 months for the 6 to 17 year-old cohort.

In total, in the 6 to 17 years old cohort, 36 subjects discontinued during the cumulative period: 11 discontinued in the ST period, and 25 subjects discontinued in the LTE period). The most common reason for discontinuation in the cumulative period was a lack of efficacy (17 subjects) or AEs (7 subjects). In addition, after completing the ST period, 5 subjects elected to not enter the LTE period.

Measurements of Treatment Compliance:

The high treatment compliance seen in the ST period continued through the LTE period.

Concomitant Therapy During the Cumulative Period:

During the cumulative period, subjects were allowed to remain on stable doses of MTX, corticosteroids, or NSAIDs if these subjects were taking these anti-rheumatic medications prior to Day 1. No other anti-rheumatic medications were allowed during the cumulative period. A summary of anti-rheumatic medications used up to 56 days past the last dose of SC abatacept during the cumulative period is provided in the table below. Similar proportions of subjects took MTX (80.9%) and/or NSAIDs (83.2%), while 44.5% of all 6 to 17-year-old subjects took oral corticosteroids during the study.

During the cumulative period, 11 subjects were reported as taking prohibited DMARDs concomitantly and were included in the study and analyses up to the last SC injection plus 56 days.

Table 12 Anti-rheumatic Medications Summary During the Cumulative Period up to 56 Days Post the Last Dose in the Cumulative Period – All Treated Subjects – 6 to 17-Year-old Age Cohort

	Number (%) of Subjects
	Total (N=173)
Total Subjects on CONMEDs	168 (97.1)
NSAIDS	144 (83.2)
DMARDS	143 (82.7)
Methotrexate	140 (80.9)
Leflunomide	3 (1.7)
Chloroquine	1 (0.6)
Cyclosporine	1 (0.6)
Hydroxychloroquine	1 (0.6)
Sulfasalazine	1 (0.6)
Biologics	6 (3.5)
Adalimumab	2 (1.2)
Etanercept	2 (1.2)
Tocilizumab	2 (1.2)
Corticosteroids	
Oral and/or injectable	89 (51.4)
Oral	77 (44.5)
Mean Oral Dose (SD)	8.1 (7.64)

The mean oral dose of corticosteroids (prednisone equivalents) includes only subjects who have taken at least 1 dose of oral corticosteroids. Includes data from the day of the first subcutaneous injection in the short-term period up to the day of the last subcutaneous injection in the cumulative period + 56 days or the first day of long-term extension period, whatever comes first.

Numbers analysed

Short term 6 to 17-Year-Old Cohort

- All treated subjects population (also referred to as the ITT population): 173 subjects
- Full PK analysis population: 168 subjects

Full PK analysis population subjects who qualified as part of the evaluable PK analysis population

- Day 57: 158 eligible subjects
- Day 85: 146 eligible subjects
- Day 113: 135 eligible subjects
- Day 309: 120 eligible subjects
- Day 477: 113 eligible subjects

- Day 645: 105 eligible subjects
- Day 729: 79 eligible subjects

Immunogenicity analysis population: 172 subjects

Cumulative 2 to 5 year-old cohort

- All treated subjects population: 46 subjects
- Full PK analysis population: 40 subjects

Evaluable PK analysis population

- Day 57: 40 subjects
- Day 85: 37 subjects
- Day 113: 30 subjects
- Day 309: 25 subjects
- Day 477: 23 subjects
- Day 645: 21 subjects
- Day 729: 19 subjects

Immunogenicity analysis population: 46 subjects

Outcomes and estimation

Efficacy

Results for the short-term period

The proportion of pJIA ACRp30 responders at end of short-term period (4 months) in patients aged 2 to 17 years was 84.5%. Response rates at the end of the short-term exposure are summarised in the Table below:

Table 13 Proportion (%) of polyarticular JIA patients with ACRP responses or inactive disease at end of short-term period (4 months)

	Ages 2 to 17 years
	n=219
ACRP30	84.5%
ACRP50	75.3%
ACRP70	57.1%
ACRP90	34.7%
ACRP100	20.1%
Inactive disease*	34.2%

* No active joints, physician's global assessment of disease severity ≤10 mm and CRP ≤0.6 mg/dL.

6 to 17-year-old cohort

PK results:

A weekly weight-tiered SC abatacept dosing regimen achieved the desired target therapeutic Cmin (≥ 10 µg/mL) in 130 of 131 evaluable PK subjects. The geometric mean Cminss value for the evaluable PK population at Day 113 was 39.7 µg/mL. Similar Cminss levels were observed at Day 57 and Day 85.

The observed Cminss values in the 6 to 17-year-old cohort were similar to or higher than the model-predicted values and were lower than the maximal Cmin for SC abatacept observed in adult subjects with RA (113.8 µg/mL).

Subgroup analyses of Cmin were conducted to evaluate the effect of weight-tiered doses on steady-state trough exposures. From Day 57 through Day 113, mean and median Cminss levels of abatacept were above the target concentration (10 µg/mL) and comparable across dose tiers in the 6 to 17-year-old evaluable PK population. The Cminss ranges among the 3 dose tiers at Day 113 mostly overlapped except for the few subjects with high or low Cminss.

Table 14 Summary Statistics of Abatacept Cmin Values During Short-term Period by Weight-tiered Dose - Evaluable PK Population – 6 to 17-Year-old Age Cohort

	CMIN (µg/mL)		
50mg			
STATISTIC	DAY 57	DAY 85	DAY 113
N	14	17	15
MEAN	31.2	30.1	37.2
S.D.	9.9	11.5	14.7
GEO. MEAN	29.5	27.7	34.3
%CV	32	38	39
MEDIAN	34.7	31.5	35.5
MIN	13.6	8.1	13.4
MAX	45.3	51.5	71.2
87.5mg			
STATISTIC	DAY 57	DAY 85	DAY 113
N	69	63	61
MEAN	38.6	44.9	46.6
S.D.	13.4	14.5	15.8
GEO. MEAN	36.2	42.5	44.2
%CV	35	32	34
MEDIAN	37.1	44.0	45.1
MIN	10.4	13.3	22.4
MAX	72.0	80.8	97.0
125mg			
STATISTIC	DAY 57	DAY 85	DAY 113
N	74	65	55
MEAN	35.0	39.3	38.5
S.D.	11.6	15.9	12.0
GEO. MEAN	33.0	36.0	36.6
%CV	33	40	31
MEDIAN	32.7	38.6	37.2
MIN	9.0	7.4	9.3
MAX	72.0	97.0	73.2

Weight Tiered Dose is based on first dose the subject received.
Program Source: /projects/bms211285/stats/primary/prog/tables/rt-pk-cmin-sub.sas 30JUN2015:07:01:48

Secondary Efficacy Endpoint:

The secondary efficacy objective was an assessment of ACRp30 response at Day 113. ACRp30 responses were observed by Day 29 (103/173, 59.5%), gradually increased to 80.9% (140/173) at Day 85, and remained at this level at Day 113. In study IM101033 the respective values were at Day 113; n=123; 64.7% for ACRp30 and for the more stringent variables: ACRp50 94 (49.5%), ACRp70, 54 (28.4%), ACRp90, 24 (12.6%)

Table 15 Proportion of ACRp30 Response Over Time During the ST Period

Study Day		Total N = 173
Day 29	Number of subjects (%) 95% CI	103/173 (59.5%) (52.2, 66.9)
Day 57	Number of subjects (%) 95% CI	127/173 (73.4%) (66.8, 80.0)
Day 85	Number of subjects (%) 95% CI	140/173 (80.9%) (75.1, 86.8)
Day 113	Number of subjects (%) 95% CI	140/173 (80.9%) (75.1, 86.8)

Comparison Between Efficacy of SC and IV Abatacept in Polyarticular JIA

The ACRp30, ACRp50, and ACRp70 responder results at Day 113 show the efficacy of both routes of administration in pJIA.

Table 16 Proportion of Subjects with ACRp Responses at Day 113 in Studies IM101301 and IM101033

Efficacy Variable at Day 113	IM101301 (SC Abatacept, 2-17 year-old) N=219	IM101301 (SC Abatacept, 6-17 year-old) N=173	IM101033 (IV Abatacept, 6-17 year-old) N=190
ACRp30 Number of responders (%)	185 (84.5%)	140 (80.9%)	123 (64.7%)
95% CI	79.7, 89.3	75.1, 86.8	57.9, 71.5
ACRp50 Number of responders (%)	165 (75.3%)	123 (71.1%)	94 (49.5%)
95% CI	69.6, 81.1	64.3, 77.9	42.4, 56.6
ACRp70 Number of responders (%)	125 (57.1%)	91 (52.6%)	54 (28.4%)
95% CI	50.5, 63.6	45.2, 60.0	22.0, 34.8

ITT with non-responder imputation

In comparison of the two paediatric studies overall higher values were seen for the ACRp30, ACRp50, and ACRp70 responses in SC abatacept-treated subjects (Study IM101301) compared with IV abatacept-treated subjects (Study IM101033). The reason for this was not readily evident. According to the MAH, review of the baseline characteristics did not reveal any clear evidence. However, the results in both studies showed acceptable efficacy on exposure surpassing the target threshold of Cminss of > 10 µg/mL.

Exploratory Efficacy Endpoints for the ST Period (6 to 17-Year-Old Cohort)

ACR Paediatric Responses During the ST Period:

The proportions of ACRp50 and ACRp70 responders increased and plateaued at Day 85: 71.7% (124/173) and 54.9% (95/173), respectively. These proportions of responses remained at these levels through Day 113. The proportions of subjects meeting the ACRp90, ACRp100, and inactive disease criteria increased throughout the ST period.

Table 17 Proportions of ACR Paediatric Responses Over Time During the Short-term Period - All Treated Subjects – 6 to 17-Year-old Age Cohort

Study Day			Total N = 173
Day 29	ACRp50	Number of subjects (%)	75/173 (43.4%)
		95% CI	(36.0, 50.7)
	ACRp70	Number of subjects (%)	29/173 (16.8%)
		95% CI	(11.2, 22.3)
	ACRp90	Number of subjects (%)	11/173 (6.4%)
		95% CI	(2.7, 10.0)
	ACRp100	Number of subjects (%)	4/173 (2.3%)
		95% CI	(0.6, 5.8)
	inactive disease	Number of subjects (%)	10/173 (5.8%)
		95% CI	(2.3, 9.3)
Day 57	ACRp50	Number of subjects (%)	103/173 (59.5%)
		95% CI	(52.2, 66.9)
	ACRp70	Number of subjects (%)	64/173 (37.0%)
		95% CI	(29.8, 44.2)
	ACRp90	Number of subjects (%)	26/173 (15.0%)
		95% CI	(9.7, 20.4)
	ACRp100	Number of subjects (%)	5/173 (2.9%)
		95% CI	(0.4, 5.4)
	inactive disease	Number of subjects (%)	30/173 (17.3%)
		95% CI	(11.7, 23.0)
Day 85	ACRp50	Number of subjects (%)	124/173 (71.7%)
		95% CI	(65.0, 78.4)
	ACRp70	Number of subjects (%)	95/173 (54.9%)
		95% CI	(47.5, 62.3)
	ACRp90	Number of subjects (%)	39/173 (22.5%)
		95% CI	(16.3, 28.8)
	ACRp100	Number of subjects (%)	21/173 (12.1%)
		95% CI	(7.3, 17.0)
	inactive disease	Number of subjects (%)	42/173 (24.3%)
		95% CI	(17.9, 30.7)
Day 113	ACRp50	Number of subjects (%)	123/173 (71.1%)
		95% CI	(64.3, 77.9)
	ACRp70	Number of subjects (%)	91/173 (52.6%)
		95% CI	(45.2, 60.0)
	ACRp90	Number of subjects (%)	50/173 (28.9%)
		95% CI	(22.1, 35.7)
	ACRp100	Number of subjects (%)	25/173 (14.5%)
		95% CI	(9.2, 19.7)
	inactive disease	Number of subjects (%)	51/173 (29.5%)
		95% CI	(22.7, 36.3)

Up to Day 113, a non-responder imputation, except if missing measurement between 2 time points for which a response is observed. In that case a responder is imputed. Inactive disease status is defined as no active joints, physician's global assessment of disease severity <=10 mm and CRP <= 0.6 mg/dL.

Subgroup Analyses of Efficacy During the ST Period (6 to 17-Year-Old Cohort)

The weekly weight-tiered SC abatacept dosing strategy was associated with similar proportions of JIA ACRp30 responders at Day 113 among subgroups in each evaluated category, including weight-tiered dose, age, JIA subtype, concomitant MTX use, prior exposure to biologic DMARDs, baseline CRP (post hoc analysis), and Day 113 Cminss tertiles (post hoc analysis).

Some JIA disease subgroups were small in number and therefore results should be interpreted with care; however, consistent response to SC abatacept treatment was observed at Day 113 among subjects in the different JIA disease subgroups. Although small differences between subgroups were noted, JIA ACR30 responses were 75% through 100% in the polyarthritis and extended oligoarthritis subgroups. Response to SC abatacept among the few subjects with enthesitis-related arthritis, systemic JIA, and persistent oligoarthritis was similar to that of the overall population.

The impact of demographic and clinical parameters, such as prior use of biologic DMARDS, use of MTX, and baseline levels of acute phase reactants (CRP), was assessed. No single parameter seemed to have an effect on the therapeutic response to SC abatacept.

The proportions of JIA ACR30 responders with concomitant MTX use or prior use of biologic DMARDs were generally similar to those of MTX non-users or subjects who were naive to biologic DMARDs. In a post

hoc assessment, similar proportions of subjects with normal or elevated baseline CRP levels were responders.

To account for abatacept exposure in efficacy, response to SC abatacept treatment was assessed by tertile of Day 113 serum abatacept Cminss level in a post hoc analysis. The proportions of responders among the tertiles were similar across all 3 tertiles, confirming that the targeted 10 µg/mL trough concentration represents the lower limit of exposure at steady state that is associated with abatacept response.

Table 18 ACR Paediatric 30 Response Proportions at Day 113 by Subgroups - All Treated Subjects with JIA - 6 to 17-Year-old Age Cohort

	% (no. of responders/no. in subgroup)
	6 through 17-Year-old
	N = 173
All treated subjects	80.9% (140/173)
Weight-tiered dose at Day 1 (weight tier)	
50 mg (10 kg to < 25 kg)	83.3% (15/18)
87.5 mg (25 kg to < 50 kg)	77.0% (57/74)
125 mg (≥ 50 kg)	84.0% (68/81)
Age group at study entry	
6-11 years	77.0% (57/74)
12-17 years	83.8% (83/99)
JIA disease subtype[a]	
Polyarthritis RF-	78.7% (74/94)
Polyarthritis RF+	87.0% (40/46)
Extended oligoarthritis	94.7% (18/19)
Systemic-onset arthritis	80.0% (4/5)
Persistent oligoarthritis	75.0% (3/4)
Enthesitis-related arthritis	100.0% (4/4)
Psoriatic arthritis	NA
Undifferentiated arthritis	100% (1/1)
Prior biologic DMARD use	
Yes	73.9% (34/46)
No	83.5% (106/127)
MTX use on Day 1	
Yes	78.7% (107/136)
No	89.2% (33/37)
Baseline CRP (post hoc analysis)	
Normal (≤ 0.6 mg/dL)	82.5% (99/120)
Elevated (> 0.6 mg/dL)	77.4% (41/53)

Table 19 ACR Paediatric 30 Response Proportions at Day 113 by Subgroups - All Treated Subjects with JIA - 6 to 17-Year-old Age Cohort

Day 113 Cminss tertiles (post hoc analysis)	
≤ 34.746 µg/mL	77.3% (34/44)
34.746 to ≤ 46.039 µg/mL	90.7% (39/43)
> 46.039 µg/mL	86.4% (38/44)

Abbreviations: ACR = American College of Rheumatology; Cminss = minimum concentration at steady state; CRP = C-reactive protein; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate; NA = not applicable; RF = rheumatoid factor.

Other Study Results During the Short-term Period (6 to 17-Year-Old Cohort)

QoL for subjects was assessed from the numbers of days per month of missed activity, paid care, and missed school from the ALQ. At baseline, the mean (SD) values, respectively, for these measures were 4.3 (6.38), 1.7 (5.07), and 3.0 (4.55) days. During treatment in the ST period, the mean numbers of days per month of missed activity, paid care, and missed school, respectively, decreased from baseline by the following values: Day 57 (n = 168 to 170): -2.1, -0.6, and -1.6 days Day 113 (n = 164 to 166): -3.0, -1.1, and -2.2 days.

Results for the cumulative period

Cumulative 2 to 5 Year old Cohort

Pharmacokinetic Results

Cmin values for the 2 to 5-year-old cohort were consistent with those of the 6 to 17-year-old cohort and above the target efficacious range (> 10 µg/mL) for most subjects at each time point. Mean trough values remained stable from Day 57 throughout Day 729. The geometric mean abatacept Cmin value was 47.1 µg/mL on Day 57, 49.5 µg/mL on Day 113, 39.8 µg/mL on Day 309, and 59.1 µg/mL on Day 729. The majority of the Cmin levels for the five subjects who discontinued from study drug due to lack of efficacy were similar to the geometric mean Cmin abatacept levels of the remaining subjects and above the target therapeutic Cmin level (≥ 10 µg/mL).

Table 20 Summary Statistics of Abatacept Cmin Values Over Time During the Cumulative Period: Evaluable PK Population – 2 to 5-Year-old Age Cohort

	CMIN (ug/mL)						
STATISTIC	DAY 57	DAY 85	DAY 113	DAY 309	DAY 477	DAY 645	DAY 729
N	40	37	30	25	23	21	19
MEAN	49.7	52.1	52.9	43.8	53.7	61.2	61.8
S.D.	17.3	18.7	20.9	20.6	28.1	28.0	18.7
GEO. MEAN	47.1	49.1	49.5	39.8	46.6	55.3	59.1
%CV	35	36	39	47	52	46	30
MEDIAN	47.3	51.0	51.2	38.7	50.4	57.0	58.7
MIN	21.4	19.6	20.1	16.9	9.5	24.9	26.5
MAX	114.4	118.8	122.1	100.8	128.0	131.7	103.7

Efficacy Results

Consistent with the results for the 6 to 17 year-old cohort, the proportions of ACRp30, ACRp50, ACRp70, ACRp90, ACRp100 responders, and subjects with inactive disease in the 2 to 5-year-old cohort increased during the cumulative period up to Day 197, when the response rates appeared to plateau (Figure below).

ACRp30 response increased from 65.2% at Day 29 to 89.1% at Day 113 and was 95.3% by Day 197. Responses were maintained throughout the cumulative period. By Day 729, responder rates were 100% for ACRp30, ACRp50, and ACRp70; 90.9% for ACRp90; and 77.3% for ACRp100 and inactive disease.

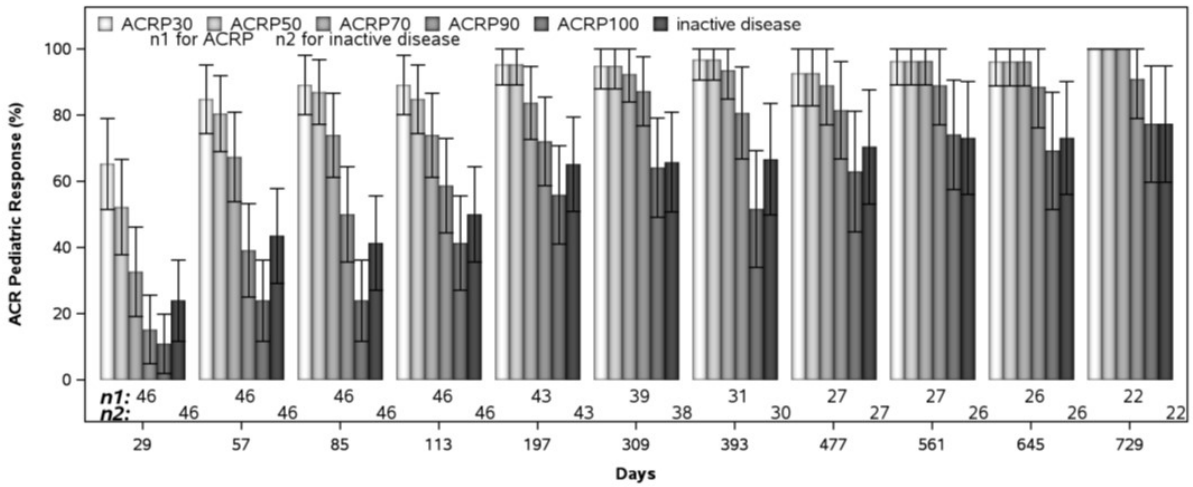


Figure 9 Proportion of ACR Paediatric Responses Over Time During the Cumulative Period - All Treated Subjects – 2 To 5-Year-old Age Cohort Each

Table 21 Proportion of Subjects with ACRP Responses, Inactive Disease, and JADAS Low Disease Activity at the End of the Short-term Period (Day 113) – 2 to 5-Year-Old Age Cohort

	(N=46)
ACRP30 Responder, n/N (%)	41/46 (89.1)
95% CI	80.1, 98.1
ACRP50 Responder, n/N (%)	39/46 (84.8)
95% CI	74.4, 95.2
ACRP70 Responder, n/N (%)	34/46 (73.9)
95% CI	61.2, 86.6
ACRP90 Responder, n/N (%)	27/46 (58.7)
95% CI	44.5, 72.9
ACRP100 Responder, n/N (%)	19/46 (41.3)
95% CI	27.1, 55.5
Inactive disease, n/N (%)	23/46 (50.0)
95% CI	35.6, 64.4
JADAS27/Low Disease Activity, n/N (%)	29/46 (63.0)
95% CI	49.1, 77.0
JADAS71/Low Disease Activity, n/N (%)	28/46 (60.9)
95% CI	46.8, 75.0

Each of the ACRp30 core set variables showed improvement from baseline with SC abatacept treatment. No single set of components dominated the composite results for the ACRp30 responses. Active joints, joints with LOM, and physician's global assessment of disease severity improved from baseline. Most of the improvement in these 3 variables was observed in the first and second months of treatment, followed by more gradual mean improvement for those subjects with longer exposure to abatacept.

Scores for the parental assessment of overall well-being and CHAQ exhibited similar trends, with mean improvement of 46.5% and 36.8%, respectively, from baseline to Day 309, and 24.3% and 36.4% mean improvement, respectively, from baseline to Day 729. Most of the improvement in both measures had occurred by Day 85, and mean scores continued to improve gradually up to Year 2.

Improvement in JADAS27 low disease activity and remission and JADAS71 low disease activity and remission was also observed over time during the cumulative period. The proportion of subjects with JADAS27 and JADAS71 low disease activity and remission increased throughout the study. On Day 729, approximately 90% of subjects met the criteria for JADAS27 and JADAS71 low disease activity, and 50% had achieved JADAS27 and JADAS71 remission.

QoL for subjects was measured by the numbers of days per month of missed activity, paid care, and missed school from the ALQ. These QoL measurements improved during the cumulative period up to Day 113 and then remained relatively stable.

Cumulative 6 to 17 year old cohort

Pharmacokinetic Results

Cmin values for the 6 to 17-year-old cohort were above the target efficacious range (≥ 10 µg/mL) in 130 of 131 evaluable PK subjects at Day 113. The geometric mean Cmin value for the evaluable PK population at Day 113 was 39.7 µg/mL. Similar Cmin levels were observed at Day 57 and Day 85. Mean trough values remained stable from Day 57 throughout Day 729. Geometric mean Cmin values remained ≥ 30 µg/mL during the cumulative period after achievement of steady state at Day 85. Individual Cmin levels remained consistently above the desired 10 µg/mL threshold beyond Day 113 for the subsets of subjects with longer abatacept exposures. Cmin values were similar across the weight- tiered doses at Day 113, suggesting exposure was similar for all weight groups.

Table 22 Summary Statistics of Abatacept Cmin Values over Time During the Cumulative Period - Evaluable PK Population – 6 to 17-Year-old Age Cohort

	CMIN (ug/mL)						
STATISTIC	DAY 57	DAY 85	DAY 113	DAY 309	DAY 477	DAY 645	DAY 729
N	158	146	135	120	113	105	79
MEAN	36.3	40.5	42.2	40.8	40.6	47.7	45.8
S.D.	12.4	15.4	14.6	20.6	20.9	23.3	24.9
GEO. MEAN	34.0	37.4	39.7	35.4	33.4	41.0	31.7
%CV	34	38	35	50	51	49	54
MEDIAN	35.0	38.3	40.5	36.9	39.2	43.2	43.0
MIN	9.0	7.4	9.3	0.2	0.6	1.1	0.0
MAX	72.0	97.0	97.0	146.7	96.8	133.2	105.2

Efficacy Results

The proportions of ACRp30, ACRp50, ACRp70, ACRp90, ACRp100, and inactive disease responders increased during the cumulative period up to Day 309, when the response rates appeared to plateau. By Day 729, the proportions of ACRp30 and ACRp50 responders were 92.7% and 89.0%, respectively; the proportion of ACRp70 responders was 83.5%; and the proportions of ACRp90, ACRp100, and inactive disease responders were 65.1%, 45.0%, and 57.9%, respectively.

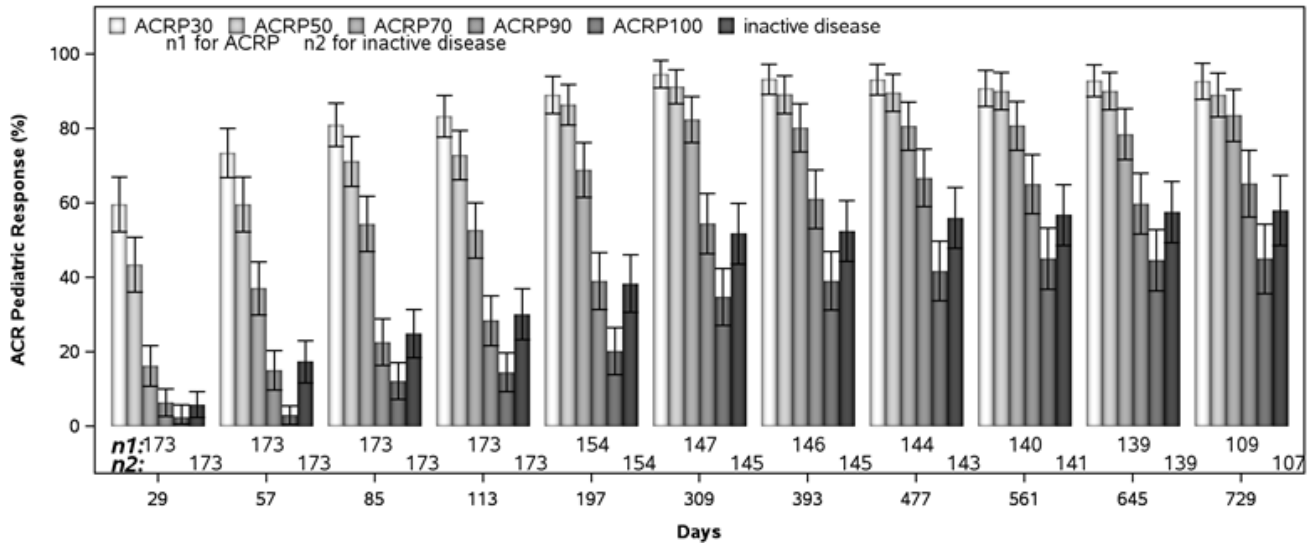


Figure 10 Proportion of ACR Paediatric Responses Over Time During the Cumulative Period - All Treated Subjects – 6 To 17-Year-old Age Cohort

Each of the ACRp30 core set variables showed improvement from baseline with SC abatacept treatment. No single set of components dominated the composite results for the ACRp30 responses. Active joints, joints with limitation of motion (LOM), and physician's global assessment of disease severity improved from baseline. Most of the improvement in these 3 variables was observed in the first and second months of treatment, followed by more gradual mean improvement for those subjects with longer exposure to abatacept.

Table 23 Mean Improvement in JRA/JIA Core Set Variable Results Over Time – 6 to 17-Year-old Age Cohort

	Day 29 n=172	Day 113 n=167	Day 309 n=148	Day 729 n=118
	Mean % (SE) Improvement			
Active Joints	44.1 (3.220)	71.9 (3.286)	89.4 (1.624)	89.3 (2.248)
Joints with LOM	30.3 (4.856)	54.5 (6.811)	78.7 (3.054)	81.8 (3.847)
Physician's Global Assessment of Disease Severity	39.9 (3.028)	69.5 (3.122)	85.0 (1.752)	88.1 (1.761)

Scores for the parental assessment of overall well-being and CHAQ exhibited similar trends, with 39.6% and 46.9% mean improvements, respectively, from baseline to Day 309, and 56.8% and 57.8% mean improvements, respectively, from baseline to Day 729. Most of the improvement in both measures had occurred by Day 85, and mean scores continued to improve gradually up to Year 2.

Post hoc analyses were conducted for the ITT population of the 6 through 17-year-old cohort: subjects with missing data for any reason were imputed as non-responders. The results were consistent with the results of the analyses based on observed data, with response increasing up to Day 113 and remaining generally stable up to Day 645. Thereafter, at Day 729 a large number of subjects had missing efficacy data and, consequently, the responder rates at this time point were lower than those for the observed data analysis due to the imputation of non-response for missing data. At the CHMP's request, the MAH clarified that this phenomenon was unrelated to discontinuation for lack of efficacy.

The results for JADAS27 and JADAS71 low disease activity and remission also followed a similar pattern, with increasing rates over time through Day 645 that decreased due to missing data at Day 729. Median

JADAS27 and JADAS71 scores decreased over time during the cumulative period, reflecting reductions in JIA-associated disability. Median baseline JADAS27 and JADAS71 scores of 19.08 and 21.04, respectively, had declined to 1.25 and 1.30, respectively, by Day 729.

None of the demographic and clinical parameters, such as prior use of biologic DMARDS, use of MTX, and baseline levels of acute phase reactants (CRP), appeared to have an effect on the response to SC abatacept throughout the cumulative period.

Quality of life (QoL) for subjects was measured by the numbers of days per month of missed activity, paid care, and missed school from the ALQ. These QoL measurements improved during the cumulative period up to Day 113 and then remained relatively stable thereafter throughout the 2-year abatacept treatment period.

Subgroup Analysis of Efficacy During the Cumulative Period - 6 to 17 Year Old Cohort

The subgroup analyses of efficacy conducted during the cumulative period were based on the ITT population and imputed non-responder status in cases of missing data. Consistent with the results of the subgroup analysis during the ST period, none of the demographic and clinical parameters, such as prior use of biologic DMARDS, use of MTX, and baseline levels of acute phase reactants (CRP), appeared to have a significant effect on the response to SC abatacept throughout the cumulative period.

Table 24 ACR Paediatric 30 Response Proportions by Subgroups- ITT Population - All Treated Subjects with pJIA – 6 to 17-Year-old Age Cohort (N=173)

	% (No. of responders/no. in subgroup)			
	Day 309	**Day 477**	**Day 645**	**Day 729**
Weight-tiered dose at Day 1 (weight tier)				
50 mg (10 kg to < 25 kg)	72.2% (13/18)	77.8% (14/18)	72.2% (13/18)	55.6% (10/18)
87.5 mg (25 kg to < 50 kg)	83.8% (62/74)	83.8% (62/74)	78.4% (58/74)	60.8% (45/74)
125 mg (≥ 50 kg)	79.0% (64/81)	71.6% (58/81)	71.6% (58/81)	56.8% (46/81)
Age at study entry				
6-11 years	81.1% (60/74)	79.7% (59/74)	75.7% (56/74)	59.5% (44/74)
12-17 years	79.8% (79/99)	75.8% (75/99)	73.7% (73/99)	57.6% (57/99)
JIA disease subtype				
Polyarthritis RF-	76.6% (72/94)	77.7% (73/94)	74.5% (70/94)	55.3% (52/94)
Polyarthritis RF+	91.3% (42/46)	87.0% (40/46)	87.0% (40/46)	71.7% (33/46)
Extended oligoarthritis	84.2% (16/19)	78.9% (15/19)	68.4% (13/19)	52.6% (10/19)
Systemic-onset arthritis	60.0% (3/5)	40.0% (2/5)	40.0% (2/5)	40.0% (2/5)
Persistent oligoarthritis	75.0% (3/4)	75.0% (3/4)	50.0% (2/4)	50.0% (2/4)
Enthesitis-related arthritis	75.0% (3/4)	25.0% (1/4)	50.0% (2/4)	50.0% (2/4)
Psoriatic arthritis	NA	NA	NA	NA
Undifferentiated arthritis	0.0% (0/1)	0.0% (0/1)	0.0% (0/1)	0.0% (0/1)
Prior biologic DMARD use				
Yes	71.7% (33/46)	69.6% (32/46)	69.6% (32/46)	50.0% (23/46)
No	83.5% (106/127)	80.3% (102/127)	76.4% (97/127)	61.4% (78/127)
Concomitant MTX use				
Yes	79.4% (108/136)	78.7% (107/136)	75.7% (103/136)	61.0% (83/136)
No	83.8% (31/37)	73.0% (27/37)	70.3% (26/37)	48.6% (18/37)
Baseline CRP (post hoc analysis)				
Normal (≤ 0.6 mg/dL)	84.2% (101/120)	83.3% (100/120)	78.3% (94/120)	60.0% (72/120)
Elevated (> 0.6 mg/dL)	71.7% (38/53)	64.2% (34/53)	66% (35/53)	54.7% (29/53)

Subgroup Analyses of PK Results During the Cumulative Period

Abatacept Cmin by Weight-tiered Dose During the Cumulative Period Cmin values were stable over time and similar across the weight tiers throughout the cumulative period for the 6 to 17-year-old cohort.

Abatacept Cmin Among Subjects with Serious Infections, Malignancies, or Autoimmune Disorders Among subjects with serious infections, possible opportunistic infections, malignancies, or autoimmune disorders, Cmin at the time of AE onset were within 1 to 2 SD of the mean Cmin at the nearest day of measurement. Opportunistic infections were rare during the study, and Cmin levels for these subjects were comparable to the population mean.

Geometric mean Cmin values remained ≥30 µg/mL during the cumulative period after achievement of steady state at Day 85. Individual Cmin levels remained consistently above the desired 10 ≥g/mL threshold beyond Day 113 for the subsets of subjects with longer abatacept exposures.

The proportions of ACRp30, ACRp50, ACRp70, ACRp90, ACRp100, and inactive disease responders increased during the cumulative period up to Day 309, when the response rates appeared to plateau. By Day 729, the proportions of ACRp30 and ACRp50 responders were 92.7% and 89.0%, respectively; the proportion of ACRp70 responders was 83.5%; and the proportions of ACRp90, ACRp100, and inactive disease responders were 65.1%, 45.0%, and 57.9%, respectively.

Abatacept with or without concomitant mtx use

Baseline data

To interpret the validity of similar efficacy in subgroups of subjects treated with abatacept with MTX and without MTX in both Studies IM101033 and IM101301 analysis of the possible effect of baseline characteristics was further studied. In both the IV study IM101033 and the SC study IM101301, and when comparing results of adult RA trials IM101173 and IM101029 to the pJIA studies, the baseline characteristics were overall similar in the subgroups of subjects treated with MTX and without MTX, excepting that geographic region and higher percentage of subjects treated with abatacept monotherapy were prior biologic users. Clinical response was shown to be similar within each geographic region and disease status, assessed by active joints and CRP values, and within the subgroups with and without prior biologic use, in both studies. Overall, it can be concluded that no clinically meaningful, potentially confounding imbalances according to MTX use, were clearly evident. The Cmin values in the adult studies also showed comparable exposure for the subgroups of subjects treated with abatacept with or without MTX. In additional PK/PD simulations, by comparing the differences between JIAACR responses rates with and without MTX co-treatment, according to weight groups, no clear trends were evident, but numbers in tiers were too small for firm conclusions.

Table 25 Baseline Disease Characteristics by MTX Use - All Treated Subjects

	IM101-033 6-17 year old age cohort		IM101-301 2-5 year old age cohort		IM101-301 6-17 year old age cohort		IM101-301 2-17 years	
	Abatacept + MTX N = 138	Abatacept N = 52	Abatacept + MTX N = 37	Abatacept N = 9	Abatacept + MTX N = 136	Abatacept N = 37	Abatacept + MTX N = 173	Abatacept N = 46
JIA Disease Onset Categories, n (%)								
Enthesitis Related Arthritis	N/A	N/A	0	0	3 (2.2)	1 (2.7)	3 (1.7)	1 (2.2)
Extended Oligoarthritis	14 (10.1)	13 (25.0)	8 (21.6)	2 (22.2)	15 (11.0)	4 (10.8)	23 (13.3)	6 (13.0)
Persistent Oligoarthritis	3 (2.2)	N/A	0	0	1 (0.7)	3 (8.1)	1 (0.6)	3 (6.5)
Polyarthritis RF+	34 (24.6)	4 (7.7)	3 (8.1)	0	36 (26.5)	10 (27.0)	39 (22.5)	10 (21.7)
Polyarthritis RF-	55 (39.9)	29 (55.8)	23 (62.2)	6 (66.7)	75 (55.1)	19 (51.4)	98 (56.6)	25 (54.3)
Psoriatic Arthritis	N/A	N/A	3 (8.1)	1 (11.1)	0	0	3 (1.7)	1 (2.2)
Systemic Arthritis	31 (22.5)	6 (11.5)	0	0	5 (3.7)	0	5 (2.9)	0
Undifferentiated Arthritis	N/A	N/A	0	0	1 (0.7)	0	1 (0.6)	0
Other	N/A	N/A	34 (91.9)	8 (88.9)	126 (92.6)	33 (89.2)	160 (92.5)	41 (89.1)
Duration of JIA disease, years								
Median	3.0	5.0	0	1.0	2.0	2.0	1.0	2.0
Mean (min, max) yrs	3.9 (0.0, 12.0)	5.7 (0.0, 14.0)	0.6 (0, 3)	1.6 (0, 4)	2.7 (0, 15)	3.2 (0, 10)	2.3 (0, 15)	2.8 (0, 10)
Prior Biologic use, n (%)								
Yes	30 (21.7)	27 (51.9)	5 (13.5)	4 (44.4)	27 (19.9)	19 (51.4)	32 (18.5)	24 (52.2)
No	108 (78.3)	25 (48.1)	32 (86.5)	5 (55.6)	109 (80.1)	18 (48.6)	141 (81.5)	22 (47.8)
Prior MTX use, n (%)								
Yes	138 (100)	42 (80.8)	37 (100)	8 (88.9)	134 (98.5)	31 (83.8)	171 (98.8)	39 (84.8)
No	0	10 (19.2)	0	1 (11.1)	2 (1.5)	6 (16.2)	2 (1.2)	7 (15.2)
Prior DMARD use*, n (%)								
Yes	138 (100)	49 (94.2)	37 (100)	8 (88.9)	134 (98.5)	33 (89.2)	171 (98.8)	41 (89.1)
No	0	3 (5.8)	0	1 (11.1)	2 (1.5)	4 (10.8)	2 (1.2)	5 (10.9)
MTX dose, N (mg/m2/week)**								
Median	18.3	0.0	13.3	0.0	11.6	0.0	11.8	0.0

	IM101-033 6-17 year old age cohort		IM101-301 2-5 year old age cohort		IM101-301 6-17 year old age cohort		IM101-301 2-17 years	
	Abatacept + MTX N = 138	Abatacept N = 52	Abatacept + MTX N = 37	Abatacept N = 9	Abatacept + MTX N = 136	Abatacept N = 37	Abatacept + MTX N = 173	Abatacept N = 46
Mean (min, max)	13.4 (11.2, 36.1)	0.0 (0.0, 0.0)	12.9 (1.2, 22.9)	0.0 (0.0, 0.0)	12.1 (1.6, 24.5)	0.0 (0.0, 0.0)	12.3 (1.2, 24.5)	0.0 (0.0, 0.0)
Prednisone equivalents dose (mg/day)								
N	20	8	8	0	46	6	54	6
Median	5.0	9.5	3.1	0	5.0	5.0	5.0	5.0
Mean (min, max)	6.3 (2.5, 15.0)	8.3 (2.5, 12.5)	4.4 (1.3, 10.0)	0 (0, 0)	5.3 (0.7, 20.0)	6.7 (5, 10)	5.2 (0.7, 20.0)	6.7 (5, 10)
Active Joints								
Median	12.5	11.0	9.0	7.0	11.0	7.0	10.0	7.0
Mean (min, max)	16.5 (2.0, 58.0)	15.3 (3.0, 55.0)	10.1 (2.0, 27.0)	6.0 (2, 10)	12.9 (2, 34)	10.8 (2, 42)	12.3 (2, 34)	9.8 (2, 42)
Joints with LOM								
Median	12.5	10.5	9.0	7.0	8.5	7.0	9.0	7.0
Mean (min, max)	17.2 (0.0, 65.0)	14.1 (0.0, 67.0)	9.3 (2.0, 26.0)	6.2 (2, 13)	11.3 (0, 35)	8.5 (1, 42)	10.9 (0. 35)	8.0 (1, 42)
CHAQ Disability Index (mg/dL)								
Median	1.3	1.1	1.3	0.9	1.0	0.9	1.0	0.9
Mean (min, max)	1.3 (0.0, 2.9)	1.2 (0.0, 2.9)	1.1 (0, 2.3)	1.0 (0, 2.1)	1.0 (0, 2.9)	0.9 (0, 2.3)	1.0 (0, 2.9)	0.9 (0, 2.3)
Parent Global Assessment								
Median	47.0	45.0	43.2	40.0	49.0	39.0	48.2	39.5
Mean (min, max)	44.7 (0.0, 96.0)	44.0 (1.0, 100.0)	37.7 (0.0, 83.7)	42.5 (5, 95.8)	47.1 (0, 95.7)	40.3 (0, 89)	45.0 (0, 95.7)	40.8 (0, 95.8)
Physician Global Assessment, N								
Median	50.5	58.5	53.0	28.0	48.0	48.0	49.0	45.5
Mean (min, max)	52.8 (10.0, 99.0)	57.8 (10.0, 100.0)	49.4 (6.9, 75.0)	38.0 (10.9, 79.2)	48.8 (10, 89)	47.5 (6, 94)	48.9 (6.9, 89)	45.6 (6, 94)

	IM101-033 6-17 year old age cohort		IM101-301 2-5 year old age cohort		IM101-301 6-17 year old age cohort		IM101-301 2-17 years	
	Abatacept + MTX N = 138	Abatacept N = 52	Abatacept + MTX N = 37	Abatacept N = 9	Abatacept + MTX N = 136	Abatacept N = 37	Abatacept + MTX N = 173	Abatacept N = 46
CRP, N (mg/dL)***								
Median	1.5	1.1	0.1	0.1	0.3	0.2	0.2	0.2
Mean (min, max)	3.5 (0.0, 26.0)	2.4 (0.0, 16.1)	1.1 (0.1, 6.6)	2.3 (0.1, 11.3)	1.3 (0.1, 21.1)	0.9 (0.1, 8.9)	1.3 (0.1, 21.1)	1.2 (0.1, 11.3)

Abbreviations: CHAQ, Childhood Health Assessment Questionnaire; CRP, C-reactive protein; DMARD, disease modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; kg, kilogram; LOM, limitation of motion; MTX, methotrexate; ROW, rest of world; w, with; w/o, without; yrs, years. * Includes MTX. ** kg/m2 for subjects in Study IM101-033; *** ESR and CRP for IM101-033; CRP for 301.

Efficacy

The clinical response to abatacept in pJIA patients treated with abatacept monotherapy and abatacept on the background of MTX was studied in several settings. The ACRp30, ACRp50, ACRp70, and ACRp90 response results at Day 113 showed overall and consistently similar and acceptable efficacy, in both the IV and SC trials in pJIA. Importantly, similar acceptable efficacy on exposure surpassing the target threshold was also seen between subjects who received abatacept with MTX and those on abatacept monotherapy, in each age cohort, the combined cohort and at each ACRp response level.

Table 26 Proportion of ACR Responses at Day 113 for Subjects by MTX (ITT) - All Treated Subjects

	IM101-033 6-17 year old age cohort		IM101-301 2-5 year old age cohort		IM101-301 6-17 year old age cohort		IM101-301 2-17 years	
	Abatacept + MTX (n=138)	Abatacept (n=52)	Abatacept + MTX (n = 37)	Abatacept (n = 9)	Abatacept + MTX (n=136)	Abatacept (n=37)	Abatacept + MTX (n=173)	Abatacept (n=46)
ACRp30	95 (68.8)	28 (53.8)	33 (89.19)	8 (88.89)	111 (81.6)	33 (89.2)	144 (83.2)	41 (89.1)
ACRp50	70 (50.7)	24 (46.2)	32 (86.49)	7 (77.78)	97 (71.3)	29 (78.4)	129 (74.6)	36 (78.3)
ACRp70	38 (27.5)	16 (30.8)	27 (72.97)	7 (77.78)	68 (50.0)	23 (62.2)	95 (54.9)	30 (65.2)
ACRp90	17 (12.3)	7 (13.5)	22 (59.46)	5 (55.56)	38 (27.9)	11 (29.7)	60 (34.7)	16 (34.8)

Acronyms: ACRp, American College of Rheumatology Paediatrics Criteria; MTX, methotrexate; w, with; w/o, without; yrs, years.

Consistently, no meaningful differences were seen when the clinical responses of subjects on monotherapy due to MTX intolerance or due to lack of efficacy were compared to abatacept with MTX results of both pJIA studies. No formal between-study comparison has been performed that compares the efficacy of abatacept + MTX to the efficacy of abatacept monotherapy due to prior MTX intolerance or due to LOE in subjects with pJIA.

Table 27 Proportion of ACR Responses at Day 113 for Subjects by MTX (Prior MTX Intolerance)

	IM101-033 6-17 year old age cohort		IM101-301 2-5 year old age cohort		IM101-301 6-17 year old age cohort		IM101-301 2-17 years	
	Abatacept + MTX N = 138	Abatacept- prior MTX intolerance N = 21	Abatacept +MTX N = 37	Abatacept - prior MTX intolerance N = 5	Abatacept +MTX N = 136	Abatacept - prior MTX intolerance N = 16	Abatacept + MTX N = 173	Abatacept - prior MTX intolerance N = 21
ACRp n (%)								
ACRp30	95 (68.8)	12 (57.1)	33 (89.19)	4 (80)	111 (81.6)	15 (93.75)	144 (83.2)	19 (90.48)
ACRp50	70 (50.7)	10 (47.6)	32 (86.49)	4 (80)	97 (71.3)	12 (75)	129 (74.6)	16 (76.19)
ACRp70	38 (27.5)	8 (38.1)	27 (72.97)	4 (80)	68 (50.0)	11 (68.75)	95 (54.9)	15 (71.43)
ACRp90	17 (12.3)	5 (23.8)	22 (59.46)	4 (80)	38 (27.9)	4 (25)	60 (34.7)	8 (38.10)

Acronyms: ACRp, American College of Rheumatology Pediatrics Criteria; MTX, methotrexate; w, with; w/o, without.

Table 28 Proportion of ACR Responses at Day 113 by MTX use (Lack of Efficacy)

	IM101-033 6-17 year old age cohort		IM101-301 2-5 year old age cohort		IM101-301 6-17 year old age cohort		IM101-301 2-17 years	
	Abatacept + MTX (n=138)	Abatacept - prior LOE (n = 23)	Abatacept + MTX (n=37)	Abatacept - prior LOE (n = 2)	Abatacept + MTX (n=136)	Abatacept - prior LOE (n=12)	Abatacept + MTX (n=173)	Abatacept - prior LOE (n=14)
ACRp30	95 (68.8)	12 (52.2)	33 (89.19)	2 (100)	111 (81.6)	11 (91.67)	144 (83.2)	13 (92.86)
ACRp50	70 (50.7)	9 (39.1)	32 (86.49)	1 (50)	97 (71.3)	11 (91.67)	129 (74.6)	12 (85.71)
ACRp70	38 (27.5)	5 (21.7)	27 (72.97)	1 (50)	68 (50.0)	9 (75.00)	95 (54.9)	10 (71.43)
ACRp90	17 (12.3)	1 (4.3)	22 (59.46)	0 (0)	38 (27.9)	5 (41.67)	60 (34.7)	5 (35.71)

Acronyms: ACRp, American College of Rheumatology Pediatrics Criteria; LOE, lack of efficacy; MTX, methotrexate; w, with; w/o, without.

Period B of the IV study IM101033 was a randomized, placebo-controlled withdrawal period for subjects who had a clinical response at the end of Period A. At 6 months of Period B, the flare rate of subjects who received abatacept monotherapy versus placebo without MTX (25.0%, 56.3%) was similar to the flare rate of subjects who received abatacept with MTX versus placebo + MTX (18.8% 52.2%). Subjects who received abatacept monotherapy and subjects who received abatacept + MTX had similar flare rates. Similarly, subjects who received placebo monotherapy and placebo with MTX had similar flare rates.

Abatacept with or without Prior Biologic Failure – second line therapeutic positioning

Baseline

Analyses of subjects on prior biologic therapy can be taken to be similar to the analyses of subjects on prior TNF alfa inhibitor therapy, as most of the subjects were indeed treated with a TNF alfa inhibitor in both pJIA studies (57/58 in the IV pJIA study and 53/56 in the SC pJIA study). On the other hand, subjects who failed prior biologic therapy, include subjects who were intolerant to biologics and subjects who had lack of efficacy on biologic therapy.

Table 29 Reasons For Discontinuation of Prior Biologic - All Subjects on Prior Biologics

	IM101-033 6-17 year old age cohort N = 42	IM101-301 2-5 year old age cohort N = 10	IM101-301 6-17 year old age cohort N = 46	IM101-301 2-17 years N = 56
Reasons for Discontinuation*, n (%)				
Intolerance	21 (50.00)	3 (30.00)	3 (6.52)	6 (10.71)
Lack of Efficacy (Null/Partial)	23 (54.76)	7 (70.00)	39 (84.78)	46 (82.14)

*One subject can be counted in more than 1 category.

Efficacy

Table 30 Proportion of ACR Responses at Day 113 and Prior Biologic Use (ITT) - All Treated Subjects

	IM101-033 6-17 year old age cohort		IM101-301 2-5 year old age cohort		IM101-301 6-17 year old age cohort		IM101-301 2-17 years	
	Prior Biologic (n=57)	No Prior Biologic (n=133)	Prior Biologic (n=10)	No Prior Biologic (n=36)	Prior Biologic (n=46)	No Prior Biologic (n=127)	Prior Biologic (n=56)	No Prior Biologic (n=163)
ACRp n (%)								
ACRp30	22 (38.6)	101 (75.9)	10 (100)	31 (86.1)	34 (73.9)	110 (86.6)	44 (78.6)	141 (86.5)
ACRp50	14 (24.6)	80 (60.2)	10 (100)	29 (80.6)	29 (63.0)	97 (76.4)	39 (69.6)	126 (77.3)
ACRp70	6 (10.5)	48 (36.1)	7 (70)	27 (75.0)	21 (45.7)	70 (55.1)	28 (50.0)	97 (59.5)
ACRp90	1 (1.8)	23 (17.3)	3 (30)	22 (61.1)	6 (13.0)	43 (33.9)	11 (19.6)	65 (39.9)

Acronyms: ACRp, American College of Rheumatology Pediatrics Criteria.

Table 31 Proportion of ACR Responses at Day 113 by MTX use and Prior Biologic (ITT) - All Treated Subjects - IM101033 and IM101301 – 2 to 5 year old age cohort

	IM101-033 6-17 year old age cohort				IM101-301 2-5 year old age cohort			
	Abatacept + MTX		Abatacept Monotherapy		Abatacept + MTX		Abatacept Monotherapy	
	Prior Biologic (n=30)	No Prior Biologic (n=108)	Prior Biologic (n=27)	No Prior Biologic (n=25)	Prior Biologic (n=5)	No Prior Biologic (n=32)	Prior Biologic (n=5)	No Prior Biologic (n=4)
ACRp30	13 (43.3)	82 (75.9)	9 (33.3)	19 (76.0)	5 (100)	28 (87.50)	5 (100)	3 (75)
ACRp50	8 (26.7)	62 (57.4)	6 (22.2)	18 (72.0)	5 (100)	27 (84.38)	5 (100)	2 (50)
ACRp70	4 (13.3)	34 (31.5)	2 (7.4)	14 (56.0)	2 (40)	25 (78.13)	5 (100)	2 (50)
ACRp90	1 (3.3)	16 (14.8)	0 (0.0)	7 (28.0)	2 (40)	20 (62.50)	3 (60)	2 (50)

Acronyms: ACRp, American College of Rheumatology Paediatrics Criteria; MTX, methotrexate.

Ancillary analyses

Addendum to Clinical Study Report IM101301

Additional analyses were presented in the Addendum to the study IM101301: subgroup analysis for the primary exposure endpoint Cmin on weight tiers and age strata, was performed (combining the two age pJIA cohorts) on data from the ST period from the evaluable PK population: the results were supportive of the main results of the study Cmin values reaching the target values and showing generally consistent results on weight tiers at each time-point up to Day 113 the geometric mean values ranging from 33.0 to 45.1. Cmin values at Day 113 across three age subgroups (2 to 5 years, 6 to 11 years, and ≥ 12 years) were also comparable.

Other studies

A vaccination sub study in paediatric pJIA patients 2 to 5 years of age was included in the study IM101301 protocol, as agreed in the SC PIP. It showed that in 26 of the total of 29 patients, abatacept at the given weight-tiered dose appeared not to inhibit response to immunisation. Thus, based on this limited amount of pJIA patients, it appears that abatacept does not significantly interfere with the specific antibody response to administered diphtheria and tetanus vaccines. This is in line with previous data (IM101174 and IM101185), which showed that healthy volunteers treated with a single dose and RA patients on abatacept treatment are able to mount an immune response to the vaccines. No label claims or amendments are sought or needed on these data.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In line with the agreed PIP, the only clinical trial data comes from the pivotal uncontrolled open label clinical study IM101301, which included two cohorts of subjects with active polyarticular JIA and subcutaneous abatacept treatment: 46 patients at 2 to 5 years of age and 176 patients at 6 to 17 years of age. Subjects were treated open-label weight tiered abatacept for a 4-month Short Term period (ST). Subjects who completed the ST period were given the option to enter a 20-month Long Term Extension period (LTE) during which they continued to receive weekly SC abatacept injections. Subjects who entered the LTE period as non-responders per ACRp30 criteria were given the opportunity to be treated with SC abatacept for an additional 3 months.

Treatment was discontinued if an individual subject did not achieve ACRp30 response after a total of 7 months of abatacept therapy (4-month ST period plus 3 months of LTE period). All subjects who received a dose of abatacept, regardless of the date of discontinuation, were scheduled to participate in a follow-up period of 168 days post-treatment for safety and immunogenicity monitoring. The data was presented up to year 2 of the study (ST period of 4 months plus a LTE period of 20 months). The study was further extended for up to 5 years in some EU countries extending up to 7 years of treatment with abatacept in 2 to 17 year old subjects with pJIA.

The inclusion and exclusion criteria were relevant and typical for this type of study. These criteria are very similar to those of the IV pivotal study, with the exceptions that subjects with enthesitis-related arthritis (n=3-4 accrued) or PsA were also targeted (n=4 accrued).

The main primary and secondary objectives are in line with the agreed SC PIP and the revised protocol. In the younger age cohort, the primary objective (abatacept steady-state trough serum concentrations [Cminss] at Day 113) was not assessed and the secondary objectives included only safety and immunogenicity. This has implications on the presentation and comparability of the results from the two cohorts. The exploratory objectives were assessed in both age cohorts.

The chosen outcome measures of the efficacy and the safety analysis are well accepted and widely used. Cminss was chosen as it was the most statistically significant abatacept exposure parameter describing the exposure-response relationship for efficacy. The outcome measures for efficacy are validated and were overall comparable with those of the open-label 4-month induction period A of the IV pivotal study IM101033.

The design and conduct of the pivotal study were acceptable to the CHMP.

The 2 year cumumative period in 2-5 years patients is still ongoing, pending evaluation of the final results. For this cohort only partial 2 year cumulative data has overall been provided as the study is still ongoing. The post treatment data is also pending. The MAH should submit the final results (24-month and 5-year data) of the Study IM101301 as a category 3 measure of the RMP. See RMP Section 2.8.

Efficacy data and additional analyses

PK and efficacy of abatacept in the treatment of pJIA was assessed with well accepted and validated outcome measures in this open label study. Main outcomes evaluated the mean and median changes from baseline.

ST period

In the short term period of the study IM101301 (6 Through 17 Year-old Cohort), with the weekly weight-tiered SC abatacept dose the targeted Cmin (≥ 10 µg/mL) was achieved in 130 of 131 evaluable

PK with geometric mean Cminss value 39.7 µg/mL at day 113. Similar Cminss levels were observed at Day 57 and Day 85. These observed values were similar to or higher than the model-predicted values (see PK section 2.4) and were lower than the maximal Cmin for SC abatacept observed in adult subjects with RA (113.8 µg/mL), as also targeted.

ACRp30 (n, %) responses were observed by Day 29 (103/173, 59.5%), gradually increasing to 80.9% (140/173) at Day 85, and remained at this level at Day 113. In study IM101033: Day A113; n=123; 64.7% had ACRP30 response and for the more stringent variables: ACRp50 94 (49.5%), ACRp70, 54 (28.4%), ACRp90, 24 (12.6%).

The results on the exploratory variables and subgroup (among them weight-tiered dose subgroups, age subgroups, prior exposure to biologic DMARDs, concomitant MTX use, the pJIA subtypes, and all non-systemic subjects with pJIA Day 113, post hoc analysis of Cminss tertiles) analyses supported the main results at D113, although some subgroups were too small in numbers for firm conclusion. Overall, the target exposure was reached and therapeutic efficacy of weight tired dose regime of abatacept seems to be maintained up till D113 in this study. There is no evidence for loss of efficacy.

Concomitant MTX use appears not to have a significant effect on efficacy. The ACRp30 response proportions at Day 113 were 78.7% (107/136) for the MTX users and 89.2% (33/37) for those who were not on concomitant MTX. This is in line with the modelling data.

In comparison of the two paediatric studies overall higher values were seen for the ACRp30, ACRp50, and ACRp70 responses in SC abatacept-treated subjects (Study IM101301) compared with IV abatacept-treated subjects (Study IM101033). No clear reasoning could be found to explain these results. However, the results in both studies showed acceptable efficacy in general on exposure surpassing the target threshold of Cminss of > 10 ≥g/mL.

Cumulative period

2 to 5 year-old cohort

In comparison with the older 6 to 17 age cohort, apart from the age and weight related difference in the baseline data of the 2 to 5 year age cohort, the demographic and the disease related baseline characteristics appear similar. The majority of treated subjects were white (44/46, 95.7%) and female (28/46, 60.9%). Although the younger population, overall, may have a slightly less severe disease this is not expected to significantly affect the results or the comparability of data.

Of the originally 46 treated pJIA patients, 24 have completed the 24-month cumulative period and for 15 the 2 year cumulative period is currently still ongoing. The current mean (SD) exposure to SC abatacept in this 2 to 5 year old subgroup over the cumulative period, i.e. up to 24 months, was 18.8 (7.26) months with a median duration of 24.1 months, and subjects received a median of 98 SC injections.

Acknowledging these uncertainties of the data, the Cmin values for the 2 to 5-year-old cohort were above target (≥ 10 µg/mL) for most subjects at each time point. Mean trough values remained stable from Day 57 throughout Day 729. Abatacept remained within the range of exposures observed with SC abatacept in adults with RA: the geometric mean abatacept Cmin value was 47.1 µg/mL on Day 57, 49.5 µg/mL on Day 113, 39.8 µg/mL on Day 309, and 59.1 µg/mL on Day 729. The maximal values of the range were slightly higher than those found in the older population, but remained in the target range i.e. not exceeding those in adults with RA.

Consistent with the results for the 6 to 17 year-old cohort, the proportions of ACRp30, ACRp50, ACRp70, ACRp90, ACRp100 responders, and subjects with inactive disease in the 2 through 5-year-old cohort increased during the cumulative period up to Day 197, when the response rates appeared to plateau. ACRp30 response increased from 65.2% at Day 29 to 89.1% at Day 113 and was 95.3% by Day 197.

Responses were maintained throughout the cumulative period. By Day 729, responder rates were 100% for ACRp30, ACRp50, and ACRp70; 90.9% for ACRp90; and 77.3% for ACRp100 and inactive disease. Results of the exploratory analyses were supportive of these data. Overall, these results were comparable to those of the older age cohort.

It is acknowledged that the interpretation of the results on the treatment outcome is hampered by the small number of patients in this subpopulation (2 to 5 year age cohort) and by the fact that the study is still ongoing.

At the CHMP's request, the MAH has added "Long-term safety in 2 to 5 year old patients with pJIA" and "Immunogenicity in paediatric patients" as Missing information in the RMP. Additional PhV activities have also been put in place in the RMP (submission of the final results (24-month and 5-year data) of the Study IM101301 and the on-going registry study IM101240, see RMP Section 2.8).

6 to 17 year-old cohort

The cumulative data from study IM101301 for 6 to 17-year-old cohort was overall consistent with the data from the ST period and showed that weekly weight-tiered SC abatacept dosing delivered target Cmin values for the 6 to 17-year-old cohort were above the target therapeutic exposures (> 10 µg/mL) in 130 of 131 evaluable PK subjects at Day 113. The geometric mean Cmin value for the evaluable PK population at Day 113 was 39.7 µg/mL. Similar Cmin levels were observed at Day 57 and Day 85. Mean trough values remained stable from Day 57 throughout Day 729. Geometric mean Cmin values remained ≥ 30 µg/mL during the cumulative period after achievement of steady state at Day 85. Individual Cmin levels remained consistently above the desired 10 µg/mL threshold beyond Day 113 for the subsets of subjects with longer abatacept exposures. Cmin values were similar across the weight- tiered doses at Day 113, suggesting exposure was similar for all weight groups.

Proportions of ACRp30, ACRp50, ACRp70, ACRp90, ACRp100, and inactive disease responders increased during the cumulative period up to Day 309, when the response rates appeared to plateau. By Day 729, the proportions of ACRp30, ACRp50 and ACR70 were 92.7%, 89.0%, and 83.5%, respectively, and the proportions of ACRp90, ACRp100, and inactive disease responders were 65.1%, 45.0%, and 57.9%, respectively.

Results of post hoc analyses (missing efficacy data imputed as non-responder) of ACR response for the ITT population were consistent with the results of the analyses based on observed data after Day 113, with response increasing up to Day 113 and remaining generally stable up to Day 645. Thereafter the number of subjects with data at Day 729 was much lower than at the previous visits; consequently, the responder rates at this time point were lower than those for the observed data analysis due to the imputation of non-response for missing data. At the CHMP's request, the MAH clarified that this phenomenon was unrelated to discontinuation for lack of efficacy.

The results for post hoc JADAS27 and JADAS71 low disease activity and remission analysis also followed a similar pattern, with increasing rates over time through Day 645 that decreased due to missing data at Day 729. Median JADAS27 and JADAS71 scores decreased over time during the cumulative period, reflecting reductions in pJIA-associated disability. Median baseline JADAS27 and JADAS71 scores of 19.08 and 21.04, respectively, had declined to 1.25 and 1.30, respectively, by Day 729.

Consistent with the results of the subgroup analysis during the ST period, none of the demographic and clinical parameters, such as prior use of biologic DMARDS, use of MTX, and baseline levels of acute phase reactants (CRP), appeared to have an effect on the response to SC abatacept throughout the cumulative period. Scores for the parental assessment of overall well-being and CHAQ exhibited similar trends of improvement.

Indication

Abatacept with or without concomitant mtx use Similar efficacy was shown in pJIA subjects treated with Orencia with or without MTX in Study IM101301 (ACRp30 responses at Day 113 78.7% with MTX and 89.2% without MTX). At the CHMP's request, the MAH has provided a detailed description of patient demographic and baseline characteristics including disease characteristics in subgroups of subjects treated with MTX and without MTX in both Studies IM101033 and IM101301. The efficacy results are consistent in all studies and subgroups studied in pJIA subjects treated with Orencia with or without MTX where baseline characteristics were shown to be homogeneous. Hence, the similar efficacy results of these subgroups show that the overall efficacy results /PK results were not confounded by differences in patient characteristics.

Similar descriptive statistics were produced for pharmacokinetic results of Cmin and were shown to be similar in pJIA subjects treated with Orencia with or without MTX and consistent with adult data. These data are in line with the population PK results.

Abatacept with or without Prior Biologic Failure – second line therapeutic positioning

The SC Study IM101301 and the earlier IV study IM101033 provide evidence of efficacy and safety of abatacept mainly in pJIA-patients who had previously been treated with MTX (95.9% and 94.2%, respectively). Of the 219 subjects who entered the Study IM101301, 56 (25.6%) had previously been treated with biologic DMARD therapy, i.e., etanercept (n=45), adalimumab (n=19), or tocilizumab (n=6); in Study IM101033, 57/190 (30.0%) had previously been treated with anti-TNF biologic DMARD therapy. In the SC pJIA study, the number of responders seemed to be slightly less in patients with prior biologic DMARD use compared to those without such (e.g. at day 309 71.7% versus 83.5%), but overall the efficacy seemed similar in all subgroups.

At the CHMP's request, the MAH provided efficacy and safety analyses in patients with and without prior use of biologics. The efficacy results were consistent and similar in the patients with and without prior use of biologics, namely TNF inhibitors.

The presented data show that in both Study IM101033 and Study IM101301, abatacept-treated subjects who did not receive prior biologic therapy had generally higher ACRp response (ACRp30/50/70/90) than subjects who received prior biologic therapy. This finding is not unexpected since subjects who have received previous biologic therapy may be often refractory to further therapy. Importantly, this response rate was independent of MTX use in both the IV and SC pJIA studies.

In the 2-5 year old age cohort of Study IM101301, the number of subjects was too small to draw conclusions about differences in clinical response in subjects with or without prior biologic therapy. However, the efficacy results in the target patient population of pJIA patients treated with SC abatacept in study IM101301 show, acknowledging the limitations of uncontrolled data, consistent and clinically acceptable treatment effect of SC abatacept. Importantly, similar and acceptable efficacy on exposure surpassing the target threshold was also seen, between subjects who received abatacept with MTX and those on abatacept monotherapy. The consistency and persistence effect was shown up to 24 months, also across various efficacy outcome variables and subgroups. Importantly, the data were comparable to treatment effects seen in pJIA patients treated with the IV formulation in study IM101033. Furthermore, the results show consistency throughout the historical data of the abatacept development program in both adult RA and pJIA with both formulations, SC and IV. Thus, the efficacy results support the concept of extrapolation of the therapeutic use of SC abatacept in the treatment of pJIA, also in the younger patient population of 2 to 5 year old children, especially as a robust post approval follow up is in place (see RMP Section 2.8).

At the CHMP's request, the MAH has aligned the wording of pJIA indication for the IV and SC formulations by using the phrasing "*inadequate response to previous DMARD therapy*" also for the IV formulation (instead of "*insufficient response to other DMARDs*").

2.5.4. Conclusions on the clinical efficacy

The main aim of the study, target therapeutic abatacept concentrations (Cmin), were reached and sustained showing consistent results on weight tiers and age strata at each time-point up to Day 113 and beyond up to 24 months. ACRp30 responses rates were of sufficient level of efficacy when compared to previous adult RA and paediatric IV pJIA data. The proportion of pJIA ACRp30 responders at end of short-term period (4 months) in patients aged 2 to 17 years was 84.5%.

From a clinical point of view the efficacy of SC abatacept was acceptable, acknowledging the limitations of descriptive data.

Acknowledging the limitations of uncontrolled data, the efficacy result in the target patient population of pJIA patients treated with SC abatacept in study IM101301, show consistent and clinically acceptable treatment effect of SC abatacept. Similar and acceptable efficacy on exposure surpassing the target threshold was also seen, between subjects who received abatacept with MTX and those on abatacept monotherapy. Overall, the consistency and persistence of effect was shown up to 24 months, also across various efficacy outcome variables and subgroups (including use of MTX and prior use of biologics, namely TNF inhibitors), and were not counfounded by the characteristics of the patient populations in both paediatric studies. Importantly, the data were comparable to treatment effects seen in pJIA patients treated with the IV formulation in study IM101033. Furthermore, the results show consistency throughout the historical data of the abatacept development program in both adult RA and pJIA.

Furthermore, these observed data are in line and supportive of the results of the E-R analysis with the most recent (year 2018) JIAACR response model, where in addition to the baseline MTX use, prior use of TNF-alpha inhibitors was not significant covariate and did not affect predicted ACRp responses in subjects with pJIA (for details see Clinical Pharmacology Section 2.4).

In conclusion, the pJIA indication for SC abatacept for children 2 to 17 years of age and the change of the indication to introduce abatacept monotherapy in case of MTX intolerance or when treatment with MTX is inappropriate and for positioning abacacept treatment in second line in the treatment of pJIA (i.e. the removal of "following treatment failure with TNF-inhibitors") for both SC and IV formulations is considered acceptable from an efficacy perspective.

2.6. Clinical safety

Patient exposure

Altogether 173 6 to 17 year old patients and 47 2 to 5 year old patients were entered to the study. Patient exposure in most subjects (70%) was at least 24 months of treatment. Final results for the 2 to 5 age group are pending, but thus far the duration of exposure was for both age groups essentially same as for the pooled population: for the 6-17 year old patients the mean (SD) exposure to SC abatacept over the cumulative period was 21.8 (6.87) months with a median exposure of 24.3 months and for the 2-5 year old patients the mean (SD) exposure to SC abatacept over the cumulative period was 18.8 (7.26) months with a median duration of 24.1 months. The reported adherence to treatment, measured by diary, was high with over 90 % of subjects with no (82,6%) or one (12,1%) missed injection. Thus, the data allows for analysis of short and long term, up to 24 months, with a reserve on the 2 to 5 age group, because of limited data.

Adverse events

ST period

Overall Adverse Events from the ST period for 6 to 17 Year-old Cohort

The majority (157/173, 90.8%) of subjects completed the ST period and continued into the LTE period. Overall, AEs were reported in 102 subjects (59.0%) during the ST period of which approximately half (20.8%) were deemed treatment related. The most commonly occurring AEs were nasopharyngitis and upper respiratory tract infections (18 subjects, 10.4%, each). Malignancies and autoimmune disorders were single occurrence and the rate of injection site reactions was 5.8%. No fatal cases were reported.

AEs of severe intensity were reported in 7 subjects (4.0%): sepsis, chest pain, headache, traumatic hematoma, anaemia, hypochromic anaemia, and stage III ovarian germ cell teratoma. No AEs were classified as very severe, and all other AEs were mild or moderate. The sole case of sepsis was the only severe AE (or SAE) related to treatment. All other AEs related to study drug were mild or moderate in intensity. There was no apparent trend on the weight tiers. In the ST period no new AE were observed, and the safety profile in the ST of Study IM101301 appear to previously reported for abatacept.

Table 32 Overview of Subjects with Safety Events Reported During the Short-term Period - All Treated Subjects - 6 through 17-Year-old Age Cohort

Safety event	Number (%) of subjects (n = 173)
Deaths	0
SAEs	5 (2.9)
SAEs Related to Study Drug	1 (0.6)
Discontinuations Due to AEs	3 (1.7)
Discontinuations Due to SAEs	2 (1.2)
Overall AEs	102 (59.0)
AEs Related to Study Drug	36 (20.8)
AEs by Weight-tiered Dose Class	
50 mg	14/18 (77.8)
87.5 mg	32/74 (43.2)
125 mg	56/81 (69.1)
AEs of Special Interest	
Malignancies	1 (0.6)
Autoimmune Disorders	1 (0.6)
Local Injection-site Reactions	10 (5.8)
AEs Within 24 Hours of Drug Administration	44 (25.4)
Infections	55 (31.8)

Comparison of AEs between paediatric IV Study IM101033 and SC Study IM101301 in ST period

Apart from age, and a slightly longer duration of disease in the IV study, the baseline characteristics of (of the respective short term periods) of the abatacept paediatric studies the 4-month Period A of the IV study IM101033 and pooled data from the 4-month ST period in the SC study IM101301 was comparable.

The use of concomitant anti-rheumatic medications was similar in both studies. The minor differences observed are unlikely to affect the analysis.

In both the lead-in phase of IM101033 and the ST period of IM101301 the rate of overall AEs (70% and 63.9%, respectively) and SAEs (vs 3.1% vs. 2.7% respectively) were similar. As expected, among the AEs of special interest, infections were overall the most common. The other AEs were few in number, with low frequencies and incidence rates, excepting the twice as high number of AE occurring within 24 hours of drug administration for those on SC abatacept treatment (60/27.4% vs 30/15.8%). The most common AEs in both studies were upper respiratory tract infection and nasopharyngitis.

Table 33 Adverse Events Summary During 4-month Lead-in Period A in Study IM101033 and 4-month ST Period in Study IM101301

	Number (%) of Subjects	
	Study IM101033 N =190	Study IM101301 N = 219
Deaths	0 (0.0)	0 (0.0)
SAEs	6 (3.1)	6 (2.7)
SAEs related to study drug	1 (0.5)	2 (0.9)
Discontinuations due to AEs	1 (0.5)	3 (1.4)
Adverse events of special interest		
Malignancies	1 (0.5)	1 (0.5)
Autoimmune disorders	2 (1.1)	1 (0.5)
AEs within 24 hours of drug administration	30 (15.8)	60 (27.4)
Infections	68 (35.8)	84 (38.4)
Overall AEs	133 (70.0)	140 (63.9)
AEs related to study drug	52 (27.4)	55 (25.1)

Results from the cumulative period

Table 34 Adverse Events Summary During the Cumulative Period (IM101301) (both age cohort and pooled cohort)

	Number (%) of Subjects		
	2-5 age Cohort N =46	6-17 age cohort N = 173	2-17 years N = 219
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	3 (6.5)	14 (8.1)	17 (7.8)
SAEs related to study drug	1 (2.2)	1 (0.6)	2 (0.9)
Discontinuations due to AEs	1 (2.2)	7 (4.0)	8 (3.7)
Discontinuations due to SAEs	0 (0.0)	4 (2.3)	4 (1.8)
Adverse events of special interest			
Malignancies	0 (0.0)	1 (0.6)	1 (0.5)
Autoimmune disorders	0 (0.0)	3 (1.7)	3 (1.4)
Local injection-site reactions	2 (4.3)	12 (6.9)	14 (6.4)
AEs within 24 hours of drug administration	26 (56.5)	82 (47.4)	108 (49.3)
Infections	36 (78.3)	118 (68.2)	154 (70.3)
Overall AEs	43 (93.5)	152 (87.9)	195 (89.0)
AEs related to study drug	27 (58.7)	54 (31.2)	81 (37.0)

Overall Adverse Events During the Cumulative Period (2 to 5-Year-Old Cohort)

AEs were reported in 93.5% (43/46) of pJIA patients in the younger cohort during the cumulative period. The most frequently reported AEs were nasopharyngitis (33%), Pyrexia (30%), and Upper respiratory tract infection (24%). No AEs were reported as severe or very severe in intensity; three (6.5%) of the 46 subjects experienced three SAEs. AEs with an incidence of > 10 subjects per 100 person-years were nasopharyngitis, pyrexia, upper respiratory tract infections, cough, rhinitis, gastroenteritis, headache, pharyngitis, conjunctivitis, and vomiting. AEs were classified by the study investigators as related to study drug for 27 (58.7%) subjects. No drug-related AE was reported as severe or very severe in intensity.

Table 35 Frequently Reported (≥10% of Subjects) Adverse Events During the Cumulative Period – 2 through 5-Year-old Age Cohort Cumulative Period

System Organ Class Preferred Term	Number (%) of subjects (n=46)
Infections and Infestations	36 (78.3)
Nasopharyngitis	15 (32.6)
Upper Respiratory Tract Infection	11 (23.9)
Rhinitis	8 (17.4)
Gastroenteritis	6 (13.0)
Pharyngitis	6 (13.0)
Conjunctivitis	5 (10.9)
Gastrointestinal Disorders	19 (41.3)
Vomiting	5 (10.9)
General Disorders and Administration Site Conditions	17 (37.0)
Pyrexia	14 (30.4)
Respiratory, Thoracic, and Mediastinal Disorders	11 (23.9)
Cough	9 (19.6)
Nervous System Disorders	9 (19.6)
Headache	6 (13.0)

Overall Adverse Events During the Cumulative Period (6 through 17-Year-Old Cohort)

In the cumulative period in the in the 6 to 17 age cohort, AEs were reported by 152 (87.9%) in pJIA patients. The safety profile was similar to that of the 2 -5 age cohort with the most common AEs being infections and infestations. The majority of AEs were of mild or moderate intensity. In the 2 -5 age cohort no AEs of severe intensity were observed, whereas nine (5.2%) subjects in the 6 to 17 age cohort reported AEs were severe intensity. These included the AEs of sepsis, chest pain, headache, traumatic haematoma, synovitis, nephrolithiasis, anaemia, hypochromic anaemia, nephrolithiasis, and ovarian germ cell teratoma. All other AEs were mild or moderate in intensity. No subject reported an AE of very severe intensity in this cohort.

Table 36 Most Frequently Reported Adverse Events Reported During the Cumulative Period (in at Least 10 percent of Subjects) – Study IM101301

	Number (%) of Subjects		
	2-5 age cohort (N=46)	6-17 age cohort (N=173)	2-17 years (N=219)
Overall AEs	43 (93.5)	152 (87.9)	195 (89.0)
Most Frequently Reported AEs (>10% in each cohort)			
NASOPHARYNGITIS	15 (32.6)	52 (30.1)	67 (30.6))
UPPER RESPIRATORY TRACT INFECTION	11 (23.9)	32 (18.5)	43 (19.6)
PYREXIA	14 (30.4)	21 (12.1)	35 (16.0)
HEADACHE	6 (13.0)	24 (13.9)	30 (13.7)
NAUSEA	4 (8.7)	19 (11.0)	23 (10.5)
GASTROENTERITIS	6 (13.0)	15 (8.7)	21 (9.6)
RHINITIS	8 (17.4)	9 (5.2)	17 (7.8)
PHARYNGITIS	6 (13.0)	11 (6.4)	17 (7.8)
COUGH	9 (19.6)	8 (4.6)	17 (7.8)
VOMITING	5 (10.9)	11 (6.4)	16 (7.3)
CONJUNCTIVITIS	5 (10.9)	7 (4.0)	12 (5.5)
AEs Related to Study Drug	27 (58.7%)	54 (31.2)	81 (37.0)

Related Adverse Events

Eighty-one (81) (37%) of the overall reported AEs were assessed to be related to the study drug during the cumulative period. All related AEs were of mild or moderate intensity except 1 AE of sepsis that was of severe intensity.

The frequency of related AEs was similar in the ST period of this study and Period A of IM101033 (25.1% and 27.4% respectively). In both age cohorts, the most frequent reported related AE was nasopharyngitis. The Adverse Reactions during the first 4-month open-label period in the 409 pJIA patients were similar in nature and frequency to that observed in the RA trials, with the exception of pyrexia haematuria and otitis (media and externa). All related AEs in both cohorts were considered mild or moderate in intensity with the exception of 1 AE in the older age cohort that was severe in intensity (sepsis).

A greater percentage of subjects in the 2 to 5 age cohort experienced AEs that were seen to be related to study drug(58.7% vs. 31.2%).. These related AEs were typically upper respiratory tract infections. Considering the data limitations, follow-up data was requested (see section 2.6.1 Discussion on clinical safety).

Comparison of AEs in the During 4-month Lead-in Period A in Study IM101033 and 4-month ST Period in Study IM101301

In both the ST period of IM101301 and the lead-in phase of Study IM101033, the most common reason for discontinuation was lack of efficacy and the most common AEs were upper respiratory tract infection and nasopharyngitis. In both the ST period of IM101301 and the lead- in phase of IM101033, the percent of overall AEs (63.9% and 70%) and SAEs (2.7% vs 3.1%) were similar. Most AEs reported in both studies during these early 4-month periods were mild or moderate in intensity. With few exceptions, most SAEs were determined by the investigator to be unrelated to abatacept and did not cause study

discontinuation in either study. Similar to Study IM101301, related non-serious AEs did not lead to treatment discontinuation in Study IM101033. No deaths were reported in either study in the 4-month ST/lead-in phase.

Table 37 Adverse Events Summary During 4-month Lead-in Period A in Study IM101033 and 4-month ST Period in Study IM101301

	Number (%) of Subjects	
	Study IM101033 N =190	Study IM101301 N = 219
Deaths	0 (0.0)	0 (0.0)
SAEs	6 (3.1)	6 (2.7)
SAEs related to study drug	1 (0.5)	2 (0.9)
Discontinuations due to AEs	1 (0.5)	3 (1.4)
Adverse events of special interest		
Malignancies	1 (0.5)	1 (0.5)
Autoimmune disorders	2 (1.1)	1 (0.5)
AEs within 24 hours of drug administration	30 (15.8)	60 (27.4)
Infections	68 (35.8)	84 (38.4)
Overall AEs	133 (70.0)	140 (63.9)
AEs related to study drug	52 (27.4)	55 (25.1)

Serious adverse event / deaths / other significant events

Overall, no deaths were reported in the study IM 101301.

Results for ST period (6 to 17 Year Cohort)

Five subjects of 173 (2.9%) experienced a total of 7 SAEs. A case of severe sepsis was assessed as related to the study drug, whereas the SAEs teratoma, anaemia, and chest pain, and a case of hypomagnesemia (considered mild in intensity) where not related. Three SAEs were severe in intensity: teratoma, anaemia, and chest pain. Overall, each SAE was a single case.

Results for Cumulative period

2 to 5 Years Cohort:

In the cumulative period three (6.5%) of the 46 subjects in the 2 to 5 age cohort experienced SAEs. The SAEs included drug overdose related to the study drug, and a febrile convulsion and tendon disorder deemed not related. This part of the study IM101301 is still ongoing and the pending data will be provided as described in the RMP (see Section 2.8).

6 To 17 Year-old Cohort:

During the cumulative period, in the 6 to 17 age cohort, 14 of 173 (8.1%) subjects reported SAEs. The SAEs of nephrolithiasis, stage III ovarian germ cell teratoma, sepsis, anaemia, and chest pain were classified as severe in intensity. SAEs of teratoma, sepsis, autonomic nervous system imbalance, and vertigo led to discontinuation of study drug. No SAE was reported to be very severe in intensity.

The event of sepsis occurred during the ST period, was severe, and led to the discontinuation of study drug. The event of sinusitis occurred after the end of the LTE period, was moderate in intensity, led to the interruption of study drug, resolving after 5 days.

In the cumulative period, 7 of 173 subjects (4.0%) discontinued due to AEs. Four subjects had a treatment-related AE that led to discontinuation (mild fatigue, severe sepsis, rash and aphthous ulcer, which were moderate in intensity).

Overall, in the cumulative period the no clear trends were seen and incidence rates were low. The total number of subject in the category infections and infestations was four, for renal and urinary disorders, two and for injury and poisonings two. Otherwise SAEs were single occurrences. The number of subjects with SAEs in the 2 to 5 age group was too low for any meaningful comparison.

Adverse Events of Special Interest

Malignancies:

Overall, only one subject was diagnosed with a malignancy (stage III teratoma).

Local injection site reactions:

Local injections site reactions rates appeared comparable between age group 4.3% (2) in 2 – 5 age group; 5.8% (10/173)and 6.9% (12/173)in the ST and cumulative periods in the 6-8 age group. These were either mild or moderate in intensity and the numbers appeared not to increase with time.

Infections:

In the ST period, infections occurred in 31.8% (55/173) in the older age cohort. The most commonly occurring infections were nasopharyngitis and upper respiratory tract infection, at a rate of 10.4% each (18 subjects each).

In the cumulative period in the 6 to 17-year-old cohort infections were reported by 68.2% (118/173) of subjects. The most common infections were nasopharyngitis (52 subjects, 30.1%) and upper respiratory tract infection (32 subjects, 18.5%). The corresponding numbers for the 2 to 5 age cohort were 15 subjects, 32.6% and 11 subjects, 23,9%, respectively. In the cumulative period in the 2 to 5-year-old cohort infections were reported by 36 subject 78.3%).

All infections, except the sole case of sepsis (which was serious and severe) were of mild or moderate in intensity. Four subjects had a serious infection (appendicitis, pneumonia, pyelonephritis, and sepsis). Most subjects with nasopharyngitis or upper respiratory tract infections experienced only one occurrence of the event during the cumulative period.

Opportunistic infections were rare overall. Three subjects in the older age cohort had AEs classified as autoimmune disorders (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), psoriasis, and Takayasu's arteritis). None were identified among the pJIA patients of the younger age cohort, pending final 24-month data from some patients. Associations suggesting causality were not evident on the basis of these single occurrences. The relatedness of these AEs to study drug (abatacept) was determined by clinical judgement of the investigator and none were assessed to be related to abatacept therapy.

Laboratory findings

Results for ST period: 6 To 17 Year-old Cohort_

During the ST period, Marked laboratory abnormalities, MAs that occurred in more than 5% of subjects were (no. of subjects with an MA/no. of subjects tested, % of subjects tested) as follows:

- Red blood cell (RBC), urine: 19/70, 27.1%
- WBC, urine: 21/78, 26.9%
- Blood, urine (dipstick test): 24/171, 14.0%
- Glucose, serum (high): 18/172, 10.5%
- Leukocytes (high): 9/171, 5.3%

Marked laboratory abnormalities in this study were infrequently associated with AEs and generally not persistent upon continued dosing.

Table 38 Laboratory Values Meeting the Marked Abnormality Criteria During the Short-term Period – All Treated Subjects – 6 through 17-Year-old Age Cohort

	N	LOW(*)	HIGH(*)
Hematology I			
Erythrocyte/Platelet Attributes			
Hemoglobin	171	2 (1.2)	NE
Hematocrit	171	2 (1.2)	NE
Erythrocytes	171	1 (0.6)	NE
Platelet Count	171	0	2 (1.2)
Hematology II			
Quantitative WBC			
Leukocytes	171	0	9 (5.3)
WBC differential count			
Neutrophils + Bands (absolute)	172	0	NE
Eosinophils (absolute)	172	NE	6 (3.5)
Basophils (absolute)	172	NE	0
Monocytes (absolute)	172	NE	0
Lymphocytes (absolute)	172	1 (0.6)	0
Liver and Kidney Function			
Liver function tests			
Alkaline Phosphatase (ALP)	172	NE	0
Aspartate Aminotransferase (AST)	171	NE	0
Alanine Aminotransferase (ALT)	171	NE	0
G-Glutamyl Transferase (GGT)	172	NE	0
Bilirubin, Total	172	NE	0
Kidney function tests			
Blood Urea Nitrogen	172	NE	2 (1.2)
Creatinine	172	NE	3 (1.7)
Electrolytes			
Electrolytes			
Sodium, Serum	172	0	0
Potassium, Serum	171	0	3 (1.8)
Chloride, Serum	172	0	0
Calcium, Total	172	0	0
Phosphorus, Inorganic	172	1 (0.6)	0
Other Chemistry Testing			
Glucose tests			
Glucose, Serum	172	18 (10.5)	1 (0.6)
Protein tests			
Protein, Total	172	1 (0.6)	1 (0.6)
Albumin	172	3 (1.7)	NE
Endocrine tests			
Thyroid Stimulating Hormone (TSH)	164	NE	0
Urinalysis I			
Qualitative urine chemistry			
Protein, Urine	171	NE	2 (1.2)
Glucose, Urine	171	NE	0
Blood, Urine	171	NE	24 (14.0)
Urinalysis II			
Urine WBC + RBC			
RBC, Urine	70	NE	19 (27.1)
WBC, Urine	78	NE	21 (26.9)

In the short term period among the 6 to 17 year-old children, six patients (3.5%) had markedly elevated eosinophil values in the WBC differential count. This was also evident in the cumulative period (13.4%), in also in the younger age group (26.1%).

The MAH provided, on request, further data on the eosinophilia, frequently reported in both age cohorts (up to 26.1% in the cumulative period among 2 to 5 year-old children) among marked abnormality criteria (MLA). However, on the basis of the provided data, no definitive reasons or associations could be

found. A high incidence of upper respiratory infections was acknowledged, but review of the data for AEs reported within ±21 days of the MLA for eosinophils, showed that few AEs in both age groups could be considered associated with the occurrence of eosinophilia, and overall none were associated with injection site reactions. Only one case was reported on the same day as a SAE (pneumonia, considered unrelated to study drug). Furthermore, occurrence of eosinophilia coincided only infrequently and discrepantly with the lack of clinical response.

Results for the Cumulative period

2 To 5 Year-old Cohort

Mean values for laboratory parameters fluctuated over time, but no obvious trends were observed and mean values generally remained within normal limits. Marked normalities in clinical laboratory evaluations during the cumulative period were generally few in number and not persistent. The most common marked abnormalities (> 5% of subjects) were as follows:

- WBC, urine: 8/25, 32.0%
- Glucose, serum (low): 10/46, 21.7%
- Leukocytes (low): 3/46, 6.5%
- Leukocytes (high): 5/46, 10.9%
- Potassium, serum (high): 4/46, 8.7%
- Eosinophils (absolute) (high): 12/46, 26.1%
- Lymphocytes (absolute) (high): 3/46, 6.5%
- Alanine aminotransferase (high): 3/46, 6.7%
- Creatinine (high): 4/46, 8.7%

Table 39 Laboratory Values Meeting the Marked Abnormality Criteria During the Cumulative Period- All Treated Subjects – 2 through 5-Year-old Age Cohort

	Abatacept		
	N	LOW(*)	HIGH(*)
Hematology I			
Erythrocyte/Platelet Attributes			
Hemoglobin	46	1 (2.2)	NE
Hematocrit	46	0	NE
Erythrocytes	46	0	NE
Platelet Count	46	0	0
Hematology II			
Quantitative WBC			
Leukocytes	46	3 (6.5)	5 (10.9)
WBC differential count			
Neutrophils + Bands (absolute)	46	1 (2.2)	NE
Eosinophils (absolute)	46	NE	12 (26.1)
Basophils (absolute)	46	NE	0
Monocytes (absolute)	46	NE	0
Lymphocytes (absolute)	46	0	3 (6.5)
Liver and Kidney Function			
Liver function tests			
Alkaline Phosphatase (ALP)	46	NE	2 (4.3)
Aspartate Aminotransferase (AST)	45	NE	0
Alanine Aminotransferase (ALT)	45	NE	3 (6.7)
G-Glutamyl Transferase (GGT)	46	NE	2 (4.3)
Bilirubin, Total	46	NE	0
Kidney function tests			
Blood Urea Nitrogen	46	NE	0
Creatinine	46	NE	4 (8.7)

Electrolytes			
Sodium, Serum	46	0	0
Potassium, Serum	46	0	4 (8.7)
Chloride, Serum	46	0	0
Calcium, Total	46	0	0
Phosphorus, Inorganic	46	0	0
Other Chemistry Testing			
Glucose tests			
Glucose, Serum	46	10 (21.7)	0
Protein tests			
Protein, Total	46	1 (2.2)	0
Albumin	46	1 (2.2)	NE
Endocrine tests			
Thyroid Stimulating Hormone (TSH)	45	NE	0
Urinalysis I			
Qualitative urine chemistry			
Protein, Urine	46	NE	0
Glucose, Urine	46	NE	0
Blood, Urine	46	NE	0
Urinalysis II			
Urine WBC + RBC			
RBC, Urine	22	NE	0
WBC, Urine	25	NE	8 (32.0)

Marked abnormalities were examined for persistence and for classification as AEs. Abnormal laboratory values typically reverted to within normal ranges during continued treatment. Four subjects had persistent MA for 2 or more consecutive laboratory test days; for 3 of these subjects, these abnormal values were reported as AEs.

The AEs associated with abnormal laboratory values reported in more than 1 subject included anaemia (3 subjects, 6.5%) and hepatic enzyme increased (2 subjects, 4.3%). AEs of hyperphosphatemia, ALT increased, AST increased, GGT increased, leukocytosis, and thrombocytosis each occurred in 1 subject (2.2%). These events were mild or moderate in intensity and resolved without the need for study drug interruption or discontinuation. One event of neutropenia occurred after the 24-month treatment period. Marked laboratory abnormalities in this study were infrequently associated with AEs and generally not persistent upon continued dosing.

Heart rate as well as supine and sitting diastolic and systolic BP were measured before study drug injection at prespecified office visits. Mean and median heart rate and blood pressure were within normal ranges and remained stable throughout the cumulative period.

6 To 17 Year-old Cohort

Marked laboratory abnormalities were generally few in number and not persistent upon continued dosing during the cumulative period. MAs observed in the highest proportions (> 5%) of subjects were (no. of subjects with MAs/no. of subjects tested, % of subjects tested):

- WBC, urine: 67/127, 52.8%
- RBC, urine: 48/118, 40.7%
- Blood, urine (dipstick): 52/171, 30.4%
- Glucose, serum (low): 36/172, 20.9%
- Leukocytes (high): 20/171, 11.7%
- Eosinophil count (high): 23/172, 13.4%

Table 40 Laboratory Values Meeting the Marked Abnormality Criteria During the Cumulative Period – All Treated Subjects – 6 through 17-Year-old Age Cohort

	Abatacept		
	N	LOW(*)	HIGH(*)
Hematology I			
Erythrocyte/Platelet Attributes			
Hemoglobin	171	4 (2.3)	NE
Hematocrit	171	4 (2.3)	NE
Erythrocytes	171	1 (0.6)	NE
Platelet Count	171	0	3 (1.8)
Hematology II			
Quantitative WBC			
Leukocytes	171	0	20 (11.7)
WBC differential count			
Neutrophils + Bands (absolute)	172	0	NE
Eosinophils (absolute)	172	NE	23 (13.4)
Basophils (absolute)	172	NE	0
Monocytes (absolute)	172	NE	0
Lymphocytes (absolute)	172	2 (1.2)	2 (1.2)
Liver and Kidney Function			
Liver function tests			
Alkaline Phosphatase (ALP)	172	NE	0
Aspartate Aminotransferase (AST)	171	NE	0
Alanine Aminotransferase (ALT)	171	NE	5 (2.9)
G-Glutamyl Transferase (GGT)	172	NE	1 (0.6)
Bilirubin, Total	172	NE	0
Kidney function tests			
Blood Urea Nitrogen	172	NE	5 (2.9)
Creatinine	172	NE	6 (3.5)
Electrolytes			
Electrolytes			
Sodium, Serum	172	0	1 (0.6)
Potassium, Serum	171	1 (0.6)	4 (2.3)
Chloride, Serum	172	0	0
Calcium, Total	172	0	0
Phosphorus, Inorganic	172	2 (1.2)	1 (0.6)
Other Chemistry Testing			
Glucose tests			
Glucose, Serum	172	36 (20.9)	1 (0.6)
Protein tests			
Protein, Total	172	1 (0.6)	2 (1.2)
Albumin	172	4 (2.3)	NE
Endocrine tests			
Cortisol, Total	1	0	NE
Thyroid Stimulating Hormone (TSH)	165	NE	2 (1.2)
Urinalysis I			
Qualitative urine chemistry			
Protein, Urine	171	NE	11 (6.4)
Glucose, Urine	171	NE	1 (0.6)
Ketones, Urine	2	NE	1 (50.0)
Blood, Urine	171	NE	52 (30.4)
Leukocyte Esterase, Urine	1	NE	0
Urinalysis II			
Urine WBC + RBC			
RBC, Urine	118	NE	48 (40.7)
WBC, Urine	127	NE	67 (52.8)

These MAs were examined for persistence, age of subject, sex of subject, accompanying SAEs and AEs of special interest, and classification as AEs. No clinically meaningful patterns were observed in the data. Mean values for all parameters were stable and within normal ranges throughout the study.

AEs associated with abnormal laboratory values were infrequently reported. The AEs associated with abnormal laboratory values (Investigations SOC) or blood and lymphatic disorders that occurred in more than 1 subject included anaemia (5 subjects, 2.9%), ALT increased (4 subjects, 2.3%), AST increased (3 subjects, 1.7%), GGT increased (3 subjects, 1.7%), and neutrophilia (2 subjects, 1.2%). None of the elevated liver function tests values met the criteria for Hy's Law; most of the abnormalities were mild and transient and resolved without the need for treatment interruption or discontinuation.

Most of the AEs associated with abnormal laboratory values were mild or moderate in intensity and resolved without the need for study drug interruption or discontinuation.

Vital Signs During the Cumulative Period

In both age cohorts mean and median heart rate and blood pressure were within normal ranges and remained stable throughout the cumulative period. In the 6 to 17-Year-Old Cohort AEs associated with abnormal vital signs included tachycardia (2 subjects), hypotension (2 subjects), and abnormal pulse (1 subject). These events were mild or moderate in severity, considered unrelated to treatment, and resolved without the need for treatment interruption or discontinuation.

Safety related to drug-drug interactions and other interactions

No dedicated studies were performed on drug-drug interactions. The results of the vaccination study are described in the efficacy section 2.5.

Immunogenicity and Immunological events

Bioanalytical methods

The bioanalytical methods used for determination of the drug concentration, anti-drug-antibodies and neutralizing antibodies in patient sera were previously validated using sera from adults with RA. During Study IM101301 the suitability of the methods for use in the juvenile patient group was evaluated. The assay accuracy (bias: -0.3 - 5.0%) and precision (%CV: 4.1 - 5.9%) were at acceptable level for the drug concentration determination method. The ADA method was cross-validated for the JIA/JRA patient group and study specific cut points were determined for patients with JIA/JRA.

In general, the used approach is acceptable. However, due to the lack of follow-up data, it is not possible to conclude whether the ADA profile in the 2 to 5 year old cohort is similar to that seen in the 6-17 year old group, where ADAs were typically seen after the treatment period.

Sampling

Immunogenicity samples were collected at Days 1, 57, 85, and 113 of the 4-month ST period, at 6-month intervals during the LTE period, at the Final/Early Termination visit, and at follow-up visits 28, 85, and 168 days after the last dose of abatacept.

An earlier sampling time point before reaching the steady state kinetics for abatacept would have been useful.

Results

Altogether, 234 patients were enrolled, and 219 were evaluated for safety. Forty-six subjects were treated in the 2 to 5-year-old cohort. All 46 subjects were evaluated for efficacy, safety, and immunogenicity whereas in the 6 through 17-year-old cohort the immunogenicity population included 172 subjects.

AEs that may be associated with the use of immunomodulatory drugs were recorded. These included infections, malignancies, autoimmune disorders/events, local injection reaction AEs, and AEs within 24 hours of study drug administration. Immune-mediated adverse events were rare, with no obvious differences between the two age categories. In the pooled 2 to 17 year age group, nearly all subjects (95.9%) had received MTX prior to enrolment and most took MTX at Day 1 (79%).

Anti-drug antibodies

Results for short term period

Cohort 6 to 17 years:

During the ST-treatment period, 2 of the 171 subjects (1.2%) in the immunogenicity population tested positive for antibodies to abatacept relative to baseline while on-treatment, and overall (on and off treatment), 3 subjects tested positive for antibodies to abatacept relative to baseline. The one subject who tested positive for CTLA4 and possibly Ig region relative to baseline was not tested for neutralization activity.

Most anti-abatacept-positive sera were reactive with the Ig-part of abatacept.

Results for the long-term period

2 to 5 Year-old Population

Five of 46 subjects (10.9%) developed anti-abatacept antibodies in the cumulative period, including one patient with positive off-treatment sample. Titers for most of the positive results were low, the highest titer was 1940. Three patients had an on-treatment persistent ADA-response (at least two consecutive ADA-positive samples). Among the subjects with ADA response during the cumulative period, 1 subject missed one abatacept injection, and 1 subject missed two abatacept injections.

All patients with anti-abatacept antibodies had concomitant methotrexate at Day 1.

6 to 17 Year-old Population

In this cohort, 8 (4.7%) subjects out of 172 tested positive for antibodies to abatacept relative to baseline in the cumulative period. Five of 8 subjects were positive for CTLA4 and possibly Ig. Of these 5 subjects, 3 subjects tested negative for neutralizing antibodies and 2 were not tested for neutralizing antibodies.

Immunogenicity to abatacept was classified as “persistent” if at least 2 or more consecutive positive test results relative to baseline with the same antibody reactivity were observed while on treatment. Three patients fulfilled these criteria.

As in previous studies in RA, psoriasis, and JIA/JRA, ADA-positive samples were rare. Data on neutralizing antibodies is limited because of the poor drug tolerance of the assay, which results in many samples not meeting criteria for analysis.

The analysis of the clinical correlations will only be explorative due to the rarity of ADAs. In previous studies, ADAs appeared after discontinuation of abatacept treatment in some patients. Late appearing ADAs can be detected in post treatment samples where abatacept levels are low and thus the samples meet the criteria for analysis..

All patients with anti-abatacept antibodies had concomitant methotrexate at Day 1.

Immunogenicity Comparison in pJIA Patients by Route of Administration (SC vs IV)

There was no head-to-head comparison between the SC and IV administrations in JIA/JRA. In order to compare the use of SC and IV abatacept in patients 6 to 17 years of age with pJIA, data from the 4-month ST period of Study IM101301 (S.C. abatacept) were summarized and compared with pooled data from the 4-month lead-in phase (Period A) of Study IM101033 (I.V. abatacept). In IV Study IM101033 (Period A, 6 to 17 Year-old), 1/189 subjects (0.5%) were seropositive for anti-CTLA4 antibodies at the last treatment visit whereas in the SC Study IM101301 6 to 17 Year-old Cohort: 0/171 subjects (0.0%) had

positive antibodies specific to CTLA4 and possibly Ig and 2/171 subjects (1.2%) had positive antibodies specific to IG and/or junction region.

Impact of immunogenicity on pharmacokinetics, safety and efficacy

Abatacept concentration values were similar for both ADA negative and positive status. According to the model-predicted clearance of abatacept in patients with JIA stratified by ADA status, there was no obvious difference in clearance when stratified by ADA status. The trough abatacept concentrations decreased neither in the older nor in the younger age cohort over time.

In both cohorts, efficacy was similar between subjects, with and without positive ADA-response. Most discontinuations were due to lack of efficacy. In both the 6 to 17 year-old and the 2 to 17 year-old cohort, safety was similar between subjects with or without positive immunogenicity. The mean duration of treatment was shorter in the 2.5 years cohort. No AEs were attributed to immune-mediated events in ADA-positive subjects.

Immunological events

Anti-Glutamic Acid Decarboxylase and Anti-Thyroid Peroxidase Antibodies

The generation of relevant auto-antibodies (anti-glutamic acid decarboxylase [GAD], anti-thyroid peroxidase [TPO]), was measured to assess the potential for abatacept-induced autoimmune diabetes type 1 or thyroiditis. TSH was measured as a biomarker to assess the potential effect of the antibodies on thyroid function. In the older paediatric population six and in the younger two subjects had seroconversion (from negative at baseline to positive on treatment). Titers were low and transient and were not associated with autoimmune AEs. Overall, these positive results were generally transient, occurred at a single visit, and were of low titer. Only one subject had a transient shift of TSH on Day 477. These findings appear not to be suggestive of any severe loss of immunological tolerance.

The MAH briefly discussed the possible immunogenic effect/adjuvant potential of the silicon contained in the different types of syringes, in vivo in children, especially in the younger age cohort of 2 to 5 years, and noted the numbers too small for firm conclusion.

Discontinuation due to adverse events

During the cumulative period, a total of 8 of 219 subjects (3.7%) discontinued due to AEs. Overall, the discontinuations related to AEs were single occurrences.

Post marketing experience

The MAH's post marketing observational registries study IM101240 for paediatric pJIA patients aged 6 to 17 years old, was created in cooperation with the Paediatric Rheumatology Collaborative Study Group (PRCSG) and the Paediatric Rheumatology International Trials Organisation (PRINTO) to monitor safety in paediatric patients with JIA on abatacept treatment. The planned enrolment is 900 patients, including at least 500 patients with 10 years of follow-up at the end of the study. The primary objective of the registry is to describe the long term safety of abatacept treatment for JIA in routine clinical practice by quantifying the incidence rates of serious/targeted infections, autoimmune disorders, and malignancies. Targeted infections include Epstein-Barr virus, cytomegalovirus, papilloma virus, herpes zoster, tuberculosis, and opportunistic infections. A secondary objective is to compare the accrued data to historical patients and future recruitees.

At the time of the latest data base lock (31-Mar-2017) 354 of the enrolled 367 are included in this summary, 265 patients are receiving the IV formulation of abatacept. 57% patients have at least one year of observation time. Overall, 29 AEs have been reposted in 22 patients, with 28 SAEs. Most AEs reported were of single occurrence with the exception of hip pain which occurred in 3 patients. These results appear

reassuring also in that no deaths, malignancies, no new autoimmune diseases or targeted infections have been reported.

Abatacept with or without concomitant mtx use

To further justify the proposed amendments to the pJIA indication, the MAH has provided analysis of safety data on abatacept treatment with or without MTX. In Period A of the IV study IM101033, the percentages of SAEs and AEs were similar in subjects who received abatacept with MTX and subjects who received abatacept monotherapy. In Period B of Study IM101033 (controlled phase), subject treated with MTX had more AEs compared to treatment without MTX in both placebo- treated (59.6% placebo + MTX vs. 40.0%; placebo monotherapy) and abatacept-treated subjects (67.3% abatacept + MTX vs. 36.4% abatacept monotherapy) possibly implying MTX treatment in this finding.

During the ST period of the SC study IM101301, the frequency of overall AEs and AEs assessed to be related to study drug were similar among subjects who received abatacept monotherapy and subjects who received abatacept with MTX. No subjects who received abatacept monotherapy reported SAEs, but six subjects who received abatacept + MTX (3.5%) reported SAEs.

Abatacept with or without Prior Biologic Failure – second line therapeutic positioning

The overall safety (SAE, AE, and relatedness) of abatacept, for subjects with pJIA, who received prior biologic therapy and subjects who did not receive prior biologic therapy was similar during the 4-month, open-label periods of both studies IM101033 and IM101301.

2.6.1. Discussion on clinical safety

Exposure

Patient exposure in most subjects (70%) was at least 24 months of treatment. Final results for the 2 – 5 age group are pending, but thus far the duration of exposure was for both age groups essentially same as for the pooled population: for the 6-17 year old patients the mean (SD) exposure to SC abatacept over the cumulative period was 21.8 (6.87) months with a median exposure of 24.3 months and for the 2-5 year old patients the mean (SD) exposure to SC abatacept over the cumulative period was 18.8 (7.26) months with a median duration of 24.1 months. The reported adherence to treatment, measured by diary, was high with over 90 % of subjects with no (82,6%) or one (12,1%) missed injection. Thus, the data allows for analysis of short and long term safety, up to 24 months, with a reserve on the 2 to 5 age group, because of incompleteness of data.

In some European centres the study IM101301 was extended up to five years, thus safety data will be collected to further accrue long-term, up to five years (in all the total 7 year length of the study), safety data for SC abatacept. The LT data will be submitted as described in the RMP (see Section 2.8).

Discontinuation

During the cumulative period, a total of 8 of 219 subjects (3.7%) discontinued due to AEs. Overall, the discontinuations related to AEs were not numerous. No consistent pattern or associations to certain time points were evident.

Adverse events - short term period (ST) 6 to 17 age cohort

In ST period of the study IM101301 overall, AEs were reported in 102 subjects (59.0%) during the ST period of which approximately half (20.8%) were deemed treatment related. The most commonly occurring AEs were nasopharyngitis and upper respiratory tract infections (18 subjects, 10.4%, each).

Malignancies and autoimmune disorders were single occurrence and the rate of injection site reactions was 5.8%. No fatal cases were reported.

AEs of severe intensity were reported in 7 subjects (4.0%): sepsis, chest pain, headache, traumatic hematoma, anaemia, hypochromic anaemia, and stage III ovarian germ cell teratoma. No AEs were classified as very severe, and all other AEs were mild or moderate. The sole case of sepsis was the only severe AE (or SAE) related to treatment. All other AEs related to study drug were mild or moderate in intensity. There was no apparent trend on the weight tiers. In the ST period no new AE were observed and the safety profile in the ST of Study IM101301 appear to be similar to that previously reported for abatacept.

Comparison of the SC study IM101301 and the IV study IM101033

When comparing the two paediatric studies, apart from age, and a slightly longer duration of disease in the IV study, the baseline characteristics of the populations were alike. The minor differences observed are unlikely to affect the analysis.

The Adverse Reactions during the first 4-month open-label period in the 409 pJIA patients were similar in nature and frequency to that observed in the RA trials, with the exception of pyrexia (frequency is “Common” in Section 4.8 of the SmPC) and haematuria and otitis (media and externa) (frequency is “Uncommon” in Section 4.8 of the SmPC). This is adequately reflected in the SmPC.

In both the lead-in phase of IM101033 and the ST period of IM101301 the rate of overall AEs (70% and 63.9%, respectively) and SAEs (2.7% vs 3.1%, respectively) were similar. As expected, among the AEs of special interest, infections were overall the most common. Others were few in number, with low frequencies and incidence rates, excepting the twice as high number of AE occurring within 24 hours of drug administration for those on SC abatacept treatment (60/27.4% vs 30/15.8%). The most common AEs in both studies were upper respiratory tract infection and nasopharyngitis.

Overall, the safety profiles appear similar in the short term period of the two studies. However, upon submission of the final results (24-month and 5-year data) of the Study IM101301, the MAH should re address this issue.

AE in the cumulative period

In the cumulative period in the younger age cohort AEs were reported in 93.5% (43/46) of pJIA patients. The most frequently reported AEs were nasopharyngitis (33%), Pyrexia (30%), and Upper respiratory tract infection (24%). No AEs were reported as severe or very severe in intensity; three (6.5%) of the 46 subjects experienced three SAEs. AEs with an incidence of > 10 subjects per 100 person-years were nasopharyngitis, pyrexia, upper respiratory tract infections, cough, rhinitis, gastroenteritis, headache, pharyngitis, conjunctivitis, and vomiting. AEs were classified by the study investigators as related to study drug for 27 (58.7%) subjects. No drug-related AE was reported as severe or very severe in intensity.

In the cumulative period in the older age cohort, AEs were reported by 152 (87.9%) of pJIA patients.

The safety profile was similar to that of the 2 to 5 age cohort with the most common AEs being infections and infestations. The majority of AEs were of mild or moderate intensity. In the 2-5 age cohort no AEs of severe intensity were observed, whereas nine (5.2%) subjects in the 6 to 17 age cohort reported AEs were severe intensity. These included the AEs of sepsis, chest pain, headache, traumatic haematoma, synovitis, nephrolithiasis, anaemia, hypochromic anaemia, nephrolithiasis, and ovarian germ cell teratoma. All other AEs were mild or moderate in intensity. No subject reported an AE of very severe intensity in this cohort.

A greater percentage of subjects in the 2 to 5 age cohort experienced AEs that were seen to be related to study drug (58.7% vs. 31.2%). The MAH attributed this difference in relatedness to study drug, with references to literature, to the knowledge that upper respiratory tract infections are the most common in children of similar age as those in the younger age cohort. This explanation was accepted by the CHMP. However, considering the data limitations, the MAH should follow-up on this point upon submission of the final results (24-month and 5-year data) of the Study IM101301 and discuss the possible reasons in more detail with the aim of excluding putative age dependency of the (iatrogenic) effects of abatacept treatment.

SAE

In the short term period (6 to age cohort), five subjects of 173 (2.9%) experienced a total of 7 SAEs. A case of severe sepsis was assessed as related to the study drug, whereas the SAEs teratoma, anaemia, and chest pain, and a case of hypomagnesemia (considered mild in intensity) where not related. Three SAEs were severe in intensity: teratoma, anaemia, and chest pain. Overall, the each of the SAE was a single case.

In the cumulative period three (6.5%) of the 46 subjects in the 2 to 5 age cohort experienced SAEs. The SAEs included drug overdose related to the study drug, and a febrile convulsion and tendon disorder deemed not related.

During the cumulative period, among the 6 to 17 age cohort, 14 of 173 (8.1%) subjects reported SAEs. The SAEs of nephrolithiasis, stage III ovarian germ cell teratoma, sepsis, anaemia, and chest pain were classified as severe in intensity. SAEs of teratoma, sepsis, autonomic nervous system imbalance, and vertigo led to discontinuation of study drug. No SAE was reported to be very severe in intensity.

The event of sepsis occurred during the ST period, was severe, and led to the discontinuation of study drug. The event of sinusitis occurred after the end of the LTE period, was moderate in intensity, led to the interruption of study drug, resolving after 5 days.

During the cumulative period, among the 6 to 17 age cohort, 7 of 173 subjects (4.0%) discontinued due to AEs. Four subjects had a treatment-related AE that led to discontinuation (mild fatigue, severe sepsis, rash and aphthous ulcer, which were moderate in intensity).

Overall, in the cumulative period there is no clear trend for observed SAE as the incidence rates are low. The total number of subject in the category infections and infestations was four, for renal and urinary disorders, two and for injury and poisonings two. Other SAEs were single occurrences. The number of subjects with SAEs in the 2 to 5 age group was too low to draw meaningful comparison. However, these data do not raise major concerns at present. However, the MAH should re address this point upon submission of the final results of the Study IM101301.

AEs of special interest

Overall, only one subject was diagnosed with a malignancy (stage III teratoma). Local injections site reactions rates appeared comparable between age group 4.3% (2) in 2 – 5 age group; 5.8% (10/173) and 6.9% (12/173) in the ST and cumulative periods in the 6-8 age group. These were either mild or moderate in intensity and the numbers appeared not to increase with time. There were no reports of anaphylaxis in the paediatric patients.

In the ST period, infections occurred in 31.8% (55/173) in the older age cohort. The most commonly occurring infections were nasopharyngitis and upper respiratory tract infection, at a rate of 10.4% each (18 subjects each). In the cumulative period in the 6 to 17-year-old cohort infections were reported by 68.2% (118/173) of subjects. The most common infections were nasopharyngitis (52 subjects, 30.1%)

and upper respiratory tract infection (32 subjects, 18.5%). The corresponding numbers for the 2 to 5 age cohort were 15 subjects (32.6%) and 11 subjects (23,9%) respectively. In the cumulative period in the 2 to 5-year-old cohort infections were reported by 36 subjects (78.3%).

All infections, except the sole case of sepsis (which was serious and severe) were of mild or moderate in intensity. Four subjects had a serious infection (appendicitis, pneumonia, pyelonephritis, and sepsis). Most subjects with nasopharyngitis or upper respiratory tract infections experienced only one occurrence of the event during the cumulative period.

Opportunistic infections were rare overall. Three subjects in the older age cohort had AEs classified as autoimmune disorders (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), psoriasis, and Takayasu's arteritis). None were identified among the pJIA patients of the younger age cohort pending final 24-month data from some patients. The lack of causality and relatedness cannot unequivocally be excluded (pending data and small sample size); therefore, this issue will be addressed in the pJIA registry (see RMP section 2.8).

The AEs of special interest were few in number, with low frequencies and incidence rates. Local injection site reactions and infections possibly indicative of immunosuppression were rare. No clustering was evident, suggesting that the risk of these AEs did not increase with long-term exposure.

Laboratory findings

In the urine analysis up to a third of the children had significant findings, including haematuria, RBC in urine and WBC in urine. The MAH was asked to clarify possible reasons for MLA findings in urine (haematuria, RBC and WBC) in both studies IM101301 and IM101033. On the basis of the provided data, the possible reasons for this concern appear multifactorial. The most common possibly related AEs being gastroenteritis urinary tract infection and dysmenorrhea, with all other AEs being single occurrences. Reassuringly, most often these MLA were transient. Data were presented also on past medical history and menses, as possible causes of these urinary findings. No definitive causal or clinically meaningful associations were evident in either of the studies, in either male of female children. This explanation was accepted by the CHMP. However, considering the data limitations, the MAH should follow-up the issue upon submission of the final results (24-month and 5-year data) of the Study IM101301.

In addition, eosinophilia was frequently reported in both age cohort (up to 26.1% in the cumulative period among the 2 to 5 year-old children) among the marked abnormality criteria. The MAH provided, on request, further data on the eosinophilia, frequently reported in both age cohorts (up to 26.1% in the cumulative period among 2 to 5 year-old children) among marked abnormality criteria (MLA). No definitive reasons or associations could be found. A high incidence of upper respiratory infections was acknowledged, but review of the data for AEs reported within ±21 days of the MLA for eosinophils, showed that few AEs in both age groups could be considered associated with the occurrence of eosinophilia, and overall none were associated with injection site reactions. Only one case was reported on the same day as a SAE (pneumonia, considered unrelated to study drug). Furthermore, occurrence of eosinophilia coincided only infrequently and discrepantly with the lack of clinical response. This explanation was accepted by the CHMP. Considering the data limitations, the MAH should follow-up on the issue upon submission of the final results (24-month and 5-year data) of the Study IM101301.

Immunogenicity

It appears that the SC administration of abatacept to pJIA patients does not change its immunogenicity or the incidence of potentially immune-associated adverse effects. The immunogenicity of abatacept in patients at the age of 2 to 5 seems not to be significantly different from that of the patients at 6 to

17 years of age. A trend for slightly higher incidence of ADAs in the younger cohort was observed, but the significance of this finding is uncertain due to small number of patients in the dataset.

On the basis of the currently available data, firm conclusion on either a putative effect of MTX on immunogenicity or on the characteristic, including age dependency, of the ADA response cannot be made, because of the small number of patients in the datasets and low ADA incidence rates in study IM101033 and Study IM101301.

Acknowledging the uncertainty in indirect cross study comparisons, the CHMP agreed that, on the current data, there was no clear evidence of effects of immunogenicity on occurrence of PK, loss of efficacy, and the occurrence of AEs, in subjects who were ADA positive in study IM101033 and Study IM101301. Furthermore, the occurrence of ADAs was comparable or less to that in adults with SC abatacept or children treated with the IV formulation.

However, since the immunogenicity of paediatric patients of different age groups may differ and that ADAs may be more frequently observed in the younger patient cohort of 2 to 5 years. Hence, at the CHMP's request, immunogenicity in the paediatric population is judged as missing information and is addressed in the RMP. In addition, upon submission of the final results (24-month and 5-year data) of the Study IM101301, the MAH should follow-up on the issue of the possible effect of MTX on ADA formation and the age dependency of the ADA response.

The MAH briefly discussed the possible immunogenic effect/adjuvant potential of the silicon contained in the different types of syringes, *in vivo* in children, especially in the younger age cohort of 2 to 5 years, and noted the numbers too small to conclude on this issue but gave sufficient reassurance for granting the indication. However, upon submission of the final results (24-month and 5-year data) of the Study IM101301, the MAH should follow-up on the issue.

No safety signal has been identified in the post marketing registry data.

Long-term safety data from the study IM101033 has demonstrated sustained tolerability of up to 7 years of continuous IV abatacept treatment of JIA, with no new safety signals and no increases in incidence rates of AEs, SAEs, infections, malignancies, or autoimmune diseases.

Indication

The safety profiles of patient treated with SC abatacept with or without MTX appear alike and similar to previous reported abatacept safety data. No new or clinically significant safety signals were evident and discontinuations were rare, with no evident clustering.

The overall safety (SAE, AE, and relatedness) of abatacept, for subjects with pJIA, who received prior biologic therapy and subjects who did not receive prior biologic therapy was similar during the 4-month, open-label periods of both studies IM101033 and IM101301.

From the safety database the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Acknowledging the open label nature of the pivotal study IM101301, the safety profile of abatacept administered SC in children and adolescent 2 to 17 years of age, appears overall, similar to the paediatric patients treated with the IV and the adults population.

The safety profiles of patient treated with SC abatacept with or without MTX and for subjects with pJIA, who received prior biologic therapy and subjects who did not receive prior biologic therapy, appear alike and similar to previous reported abatacept safety data.

The currently available safety data are supported by the presented interim registry data.

However, the data is limited and as with adults, infections, autoimmunity and malignancies remain potential serious risks. Thus, post approval management are required to monitor the long-term safety of abacacept in the 2-17 years old patients. The ongoing registry study protocol already recruits children from both age groups and will be updated with the current data of this application. The LT part of the study IM101301 has been extended up to five years, the duration of the study totalling 7 years in all. "Long-term safety in 2 to 5 year old patients with pJIA" and "Immunogenicity in paediatric patients" are stated as Missing information in the RMP and additional pharmacovigilance actions are implemented for these safety concerns. The abatacept long term database will in time be complemented by these data.

The MAH should submit the final results (24-month and 5-year data) of the Study IM101301 as a category 3 measure of the RMP. At the time of submission, the MAH should address the following safety aspects: MLA eosinophils, MLA (haematuria, RBC and WBC) in urine, the effect of MTX on ADA formation, age dependency of ADA response, AEs occurring within 24 hours in the pJIA studies, relatedness of AEs to study drug, immunogenic potential of the lubricant silicon oil.

In conclusion, the pJIA indication for SC abatacept for children 2 to 17 years of age and the change of the indication to introduce abatacept monotherapy in case of MTX intolerance or when treatment with MTX is inappropriate and for positioning abacacept treatment in second line in the treatment of pJIA (i.e. the removal of "following treatment failure with TNF-inhibitors") for both SC and IV formulations is considered acceptable from a safety perspective.

2.7. Conclusions on the extrapolation of previous IV paediatric data and the adult IV and SC data to the SC paediatric population

1. Confirm that abatacept is efficacious with a favourable benefit-risk profile in adult subjects with RA (IV and SC). Confirm that abatacept is efficacious with a favourable benefit-risk profile in subjects with pJIA (IV) patients aged 6 to 17 years of age. These data together with current data from study IM101301 form the basis of extrapolation to paediatric pJIA subjects treated with SC abatacept.

The data from development programmes for abatacept have shown that abatacept is efficacious with a positive benefit risk in both the adult RA (IV and SC) patients and in subjects with pJIA (IV) patients aged 6 to 17 years of age. These data together with current data from study IM101301 where consistent and acceptable efficacy and persistence of effect up 24 months, also across various efficacy outcome variables and subgroups (including use of MTX use and prior use of biologics, namely TNF inhibitors) was shown. Importantly, the data were comparable to treatment effects seen in pJIA patients treated with the IV formulation in study IM101033, and showed consistency with historical efficacy data of the abatacept development program with both formulations (SC and IV) in adult RA and pJIA. Thus, overall, the provided data and the consistency of the efficacy results support the the extrapolation of the therapeutic use of abatacept in the treatment of pJIA.

2. Confirm that abatacept PK in adults is predictive of PK in paediatrics following both IV administration and SC administration (predictability of the available paediatric data in pJIA 6 to 17 years) and confirm the consistency of the PK of abatacept in both adults and paediatric populations.

Pharmacokinetics of abatacept in paediatric patients with pJIA was evaluated using population PK (PPK) analysis with data from all patients in two pJIA studies (Study IM101033, IV abatacept; Study IM101301, with SC abatacept) and 11 adult RA studies. The final model appeared to appropriately characterize the pharmacokinetics of abatacept in both paediatric pJIA and adult RA patients. Clearance and volume parameter values of the final PPK model were within ±15% to those of the previous IV abatacept model for adult RA patients and pJIA assessed previously in variation II/24.

3. Provide supportive evidence that abatacept efficacy in adults treated with SC and IV abatacept with RA and paediatric pJIA patients treated with the IV abatacept formulation can be extrapolated to the SC paediatric population (2 to 17 years of age) and that establishing this evidence is sufficient to extend this to the 2 to 5 years age group pJIA patients.

Overall, the results of the open-label study IM101301 appear to support SC abatacept as an effective treatment option in pJIA. Overall, the main aim of the study, target therapeutic abatacept concentrations (Cmin), were reached and sustained showing consistent results on weight tiers and age strata at each time-point up to Day 113 and beyond up to 24 months. ACR paediatric 30 responses are considered as sufficient level of efficacy when compared to previous adult RA and paediatric IV pJIA data. From a clinical point of view the efficacy of SC abatacept was acceptable, acknowledging the limitations of uncontrolled data. The proportion of JIA ACRp30 responders increased over time and reached 80.9% at Day 113 in the 6 to 17 year-old cohort (secondary efficacy endpoint), with similar result (89.1%) observed in the 2 to 5 year-old cohort. The results were similar across various endpoints and subgroups, and were also consistent with the IV study IM101033 data.

Previous E-R analyses have shown that Cminss is the exposure parameter that best predicts the efficacy in RA. E-R efficacy analyses were now conducted in pJIA patients using combined data from studies IM101033 (IV abatacept) and IM101301 (SC abatacept). As in RA, Cminss was the best exposure parameter predicting the efficacy, defined as JIAACR response. No statistically significant covariates affecting the response were found in this analysis. Overall, it can be concluded that Cminss predicts the JIAACR response.

The effect of concomitant MTX on the efficacy of abatacept in pJIA was further clarified and the results showed consistent and acceptable efficacy and safety results in the subgroups according to MTX use, prior biologics use, on subgroups on monotherapy, and with no imbalances in baseline values.

The observed PK data were in line with modelling and were consistent with the historical data of the Orencia development programme.

Thus, overall, the data show the consistency of the PK of abatacept in both adults and paediatric populations and support the current extrapolation concept.

4. Evaluate the safety profile of the SC formulation of abatacept in the paediatric population (aged 2 to 17 years) with pJIA by comparing it with that of the overall phase III IV and SC RA and IV pJIA clinical development programme.

No new or clinically important safety signals were observed in the sole clinical study IM101301 relative to that for IV abatacept or relative to the overall Orencia safety database. AEs associated with the weekly body-weight-tiered SC abatacept dosing regimen in Study IM101301 were low in frequency, mostly mild, and consistent with the overall safety profile of abatacept. The AEs and SAEs, including events of interest related to immunomodulatory agents (i.e., infections, malignancies, and autoimmune disorders), were overall comparable to those seen in the larger abatacept program in RA. Discontinuations related to AEs were not numerous (8/173). No consistent pattern or associations to certain time points were evident.

Though the low prevalence of pJIA and small sample size, relative to studies of RA, could limit the ability of the trial to detect rare, but important safety events, results from abatacept trials support the long-term safety and tolerability of abatacept. Long-term safety data from the study IM101033 demonstrated sustained tolerability of up to 7 years of continuous IV abatacept treatment of JIA, with no new safety signals and no increases in incidence rates of AEs, SAEs, infections, malignancies, or autoimmune diseases. In Study IM101301, overall, the safety profile if abatacept both age groups were similar to previous data.

The presented interim safety results from the registry study IM101240 (database lock 31-Mar-2017) are also reassuring in that the safety profile of abatacept appears consistent with previous data. No deaths, malignancies or new autoimmune disease or targeted infections have been observed.

In conclusion, the overall safety profile of SC abatacept in children and adolescents with active pJIA in study IM101301 appears consistent with the previously described safety profile of IV and SC abatacept both in adults and in the paediatric population and thus, overall, support the current extrapolation concept.

Likewise, the current the safety profiles of patient treated with SC abatacept with or without MTX and for subjects with pJIA, who received prior biologic therapy and subjects who did not receive prior biologic therapy, appears alike and similar to previous reported abatacept safety data.

5. Identify and plan for the mitigation of any remaining uncertainty and risk.

The data is limited and as with adults, infections, autoimmunity and malignancies remain potential serious risks. Hence, at the CHMP's request "Long-term safety in 2 to 5 year old patients with pJIA" and "immunogenicity in paediatric patients" have been added as missing information in the RMP. Two additional pharmacovigilance actions are linked to these safety concerns: submission of study IM101301, extending up to 7 years of treatment with abatacept in 2 to 17 year old subjects with pJIA and the ongoing observational registry study (IM101240), which already allows the recruitment of pJIA patient treated with the SC formulation in the 2 to 17 years old paediatric population, with the aim of accruing long term safety and effectiveness data in the SC abatacept treatment of pJIA. In addition, at the time of submission of the final results (24-month and 5-year data) of the Study IM101301, the MAH should address the following safety aspects: MLA eosinophils, MLA (haematuria, RBC and WBC) in urine, the effect of MTX on ADA formation, age dependency of ADA response, AEs occurring within 24 hours in the pJIA studies, relatedness of AEs to study drug, immunogenic potential of the lubricant silicon oil (see RMP section 2.8).

2.8. Risk Management Plan

Safety concerns

Safety concerns

Summary of safety concerns	
Important identified risks	• Infections • Infusion-related reactions (IV abatacept only) • Injection reactions (SC abatacept only)
Important potential risks	• Malignancies • Autoimmune symptoms and disorders • Adverse pregnancy outcomes • PML • Infections associated to immunization with live vaccines
Missing information	• Combination therapy including biologic therapy • Elderly patients • Long-term safety in 2-5 year old patients with JIA • Immunogenicity in paediatric patients

Pharmacovigilance plan

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
IM101121: Abatacept Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project An Extension Study Ongoing	To estimate risk of major congenital anomalies/birth defect patterns in offspring of patients exposed to abatacept during pregnancy	A prospective, observational study of pregnancy outcome in women with RA who are exposed to abatacept during pregnancy.	1. Interim data 2. Final study report	Summary report each February Dec 2018
IM101213: Post-Marketing Observational Study Assessing the Long-Term Safety of Abatacept Using a Population-Based Cohort of Rheumatoid Arthritis Patients in the Province of British Columbia Ongoing	To estimate incidence of infections, malignancies, mortality, and multiple sclerosis in abatacept exposed patients vs. patients exposed to DMARDs & biologics	Prospective, observational, 10-year cohort study of a population-based longitudinal cohort of all RA patients in the Province of British Columbia (BC), Canada.	1. Interim data 2. Final study report	Summary report each February Dec 2018
IM101125: A Nationwide Post-Marketing Study on the Safety of Abatacept Treatment in Sweden Using the ARTIS Register Ongoing	To assess short- and long-term SAEs and mortality among patients exposed to abatacept vs. other biologics, and DMARDs	A prospective cohort study with accrual and observation for a period up to 10 years.	1. Interim data 2. Final study report	Summary report each February Dec 2018
IM101127: Long-Term Observation of Treatment with Biologics in Rheumatoid Arthritis RABBIT Ongoing	To assess short- and long-term safety (AEs) and mortality among registry patients exposed to abatacept vs. other biologics, DMARDs	RABBIT is a prospective observational cohort study.	1. Interim data 2. Final study report	Summary report each February Dec 2018

IM101211: Multinational Surveillance of Abatacept- Treated Patients Using Disease Registries Ongoing	To assess abatacept patient demographics and incidence of malignancies, infections, infusion reactions, autoimmune events, and mortality	Prospective, longitudinal, observational cohort study	1. Interim data 2. Final study report	Summary report each February Dec 2018
IM101240: An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis Ongoing	To characterize and evaluate the safety of abatacept in JIA in routine clinical practice: infections, malignancy, autoimmune disorders	This study is an observational, multi-center registry.	1. Recruiting Update 2. Interim data 3. Final Study Report	Annually each February beginning in 2011 30- Jun- 2014 30- Jun- 2019 30- Jun- 2029
IM101301: A Phase 3 Study of Abatacept in Patients with Juvenile Idiopathic Arthritis	To evaluate pharmacokinetics, efficacy and safety of abatacept administered subcutaneously in JIA patients	Long-term safety of abatacept in JIA patients 2-5 years of age	24-month Clinical Study Report Final study report	30-Jun-2029 Feb 2019 Aug 2024

Risk minimisation measures

Safety concern	***Risk Minimisation Measures***	***Pharmacovigilance Activities***
Infections	Routine risk minimization measures: SmPC Sections 4.3, 4.4 and 4.8 Additional risk minimization measures: Patient Alert Card: the card highlights the need for an adequate history and screening related to infections, such as TB and hepatitis, prior to treatment with abatacept, as well as the need to seek immediate medical attention when symptoms of infections occur during treatment.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Postmarketing infections questionnaire (Annex 4) Supplemental case report forms for clinical studies Additional pharmacovigilance activities: Postmarketing epidemiology studies: IM101125 IM101127 IM101213 IM101240 IM101211
Infusion-related reactions (IV abatacept only)	Routine risk minimization measures: SmPC Sections 4.3, 4.4 and 4.8 Additional risk minimization measures: Patient Alert Card: the Card highlights risk of hypersensitivity after use of abatacept and instructs patients to seek immediate medical attention should symptoms of serious allergic reactions develop.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology studies IM101125 IM101127 IM101211 IM101240
Injection reactions (SC abatacept)	Routine risk minimization measures: SmPC Sections 4.3, 4.4 and 4.8 Additional risk minimization measures: Patient Alert Card: the Card highlights risk of hypersensitivity after use of abatacept and instructs patients to seek immediate medical attention should symptoms of serious allergic reactions	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Postmarketing injection reactions questionnaire (see Annex 4). Additional pharmacovigilance activities:

	develop.	Postmarketing pharmacoepidemiology studies IM101125 IM101127
Malignancies	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • • Supplemental case report forms for clinical studies Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology studies IM101125 IM101127 IM101213 IM101240 IM101211
Autoimmune disease	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Postmarketing autoimmune disease questionnaire (see Annex 4).Supplemental case report forms for clinical studies Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology studies IM101125 IM101127 IM101213 IM101240 IM101211
Adverse Pregnancy Outcome	Routine risk minimization measures: SmPC Section 4.6 and 5.3	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Postmarketing pregnancy questionnaire (see Annex 4) Additional pharmacovigilance

	Additional risk minimization measures: None	activities: Postmarketing pharmacoepidemiology studies IM101121 IM101240 IM101127
PML	Routine risk minimization measures: SmPC Section 4.4. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Postmarketing PML questionnaire (see Annex 4). Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology studies IM101125 IM101127 IM101213
Infections associated to immunization with live vaccines	Routine risk minimization measures: SmPC Section 4.4, 4.5 and 4.6. Additional risk minimization measures: Patient Alert Card highlights the need to inform a child's physician before any vaccination is given if the child was exposed to ORENCIA in utero	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Combination therapy including biologic therapy	Routine risk minimization measures: SmPC Section 4.4 and 4.5. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology studies: IM101213
Elderly patients	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse

	SmPC Section 4.4 and 4.8. Additional risk minimization measures: None.	reactions reporting and signal detection: None. Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology studies: IM101125 IM101127 IM101213 IM101211
Long-term safety in 2-5 year old patients with JIA	Routine risk minimization measures: SmPC Section 4.8. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Post-marketing pharmacoepidemiology study: IM101240 Clinical study: IM101301
Immunogenicity in paediatric patients	Routine risk minimization measures: SmPC section 4.8. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Clinical study: IM101301

Conclusion

The CHMP and PRAC considered that the risk management plan version 25.2 is acceptable.

2.9. 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.

2.10. Product information

2.10.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to ORENCIA 125 mg solution for injection in pre-filled syringe. The bridging report submitted by the MAH has been found acceptable.

2.11. Significance of paediatric studies

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Juvenile idiopathic arthritis is a broad term that describes a clinically heterogeneous group of arthritis of unknown aetiology that begins before the age of 16 years and persists for at least 6 weeks. JIA is one of the most common chronic diseases of childhood and is an important cause of short- and long-term disability. The epidemiology for JIA varies depending on different global regions and method of analysis, the reported incidence rates being between 7-100/100,000, with a prevalence of 32 to 200/100,000.

The current JIA classification scheme identifies seven clinical JIA subtypes based on phenotype, serology and associated features: rheumatoid factor (RF) positive and negative polyarthritis, extended oligoarthritis, persistent oligoarthritis, enthesitis-related arthritis (ERA), psoriatic arthritis (PsA), systemic arthritis, and undifferentiated arthritis. Polyarticular JIA is a chronic disease that requires long-lasting treatment.

3.1.1. Disease or condition

Polyarticular JIA is treated with the same medicinal products used for adult RA. Similarly to adult RA, emphasis is on early diagnosis and aggressive therapy, and closer disease monitoring (treat-to-target). Treatment now aims for disease remission i.e. minimal disease activity and quality of life approaching that of any other child. With this concept of a treatment window of opportunity, instead of a slower step-up pyramid approach, better long term outcomes are achieved.

3.1.2. Available therapies and unmet medical need

Current treatment options include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and biologic and non-biologic disease-modifying antirheumatic drugs (DMARDs). NSAIDs may be used alone when disease flares are intermittent and only mild to moderate in severity. Corticosteroids are used in the long-term management or in the treatment of disease.

Second-line therapies include conventional non-biologic DMARDs such as MTX (usually the cornerstone of therapy) or leflunomide, typically in combination with NSAIDs. Several biologic DMARDs are approved to treat JIA typically as second- or third-line therapies. Commercially available biologic therapies for JIA can be classified into 3 broad categories by mechanism of action: TNF-alpha signalling inhibitors, interleukin (IL) signalling inhibitors, and T-cell or B-cell inhibitors.

Non-biologic DMARDs, anti-TNF-alpha therapies, and cytokine inhibition therapies for JIA are not uniformly effective or tolerated. Some JIA subtypes respond differently, some patients do not respond, and other patients experience secondary loss of efficacy, often with an accompanying production of

anti-drug antibodies. These therapies can also have significant toxicities that can force interruption or discontinuation of therapy.

3.1.3. Main clinical studies

Given similarities in the clinical presentation of adult and paediatric disease states (RA vs. pJIA) and formulations (IV vs. SC), consistency in therapeutic approach, consistency of abatacept mechanism of action, consistency of the PK/PD in both adults and children and relevance of the clinical endpoints for both efficacy and safety, an extrapolation approach was considered suitable to characterize the clinical profile of SC abatacept in pJIA. This approach, in which limited data was to be collected in the target population, with extrapolation of efficacy and safety data from source populations of the abatacept (IV and SC) in RA and pJIA (IV) development programme, was agreed on with the Paediatric Committee (PDCO). In this context, an open-label study and a PK modelling and simulation evaluation was considered appropriate in seeking approval for the use of SC abatacept to treat 2 to 17 year old children with moderate to severe active pJIA.

The main study IM101301 was a Phase 3 Multi-center, Open-label to Evaluate Pharmacokinetics, Efficacy, and Safety of abatacept Administered Subcutaneously (SC) in Children and Adolescents with Active Polyarticular Juvenile Idiopathic Arthritis (pJIA) and Inadequate Response (IR) to Biologic or Non-biologic Disease Modifying Anti-rheumatic Drugs (DMARD).

The study included two age cohorts (2 to 5 years and 6 to 17 year old).Paediatric patients with pJIA patients were treated with SC abatacept in short term for four months, followed by a long term treatment period 20 months (for a total of 24 months). Altogether 173 6 to 17 year old patients and 47 2 to 5 year old patients were entered to the study. Patient exposure in most subjects (70%) was at least 24 months of treatment. Final results on the long-term extension period for the 2 to 5 age group are pending, but thus far the duration of exposure was for both age groups essentially same as for the pooled population: for the 6-17 year old patients the mean (SD) exposure to SC abatacept over the cumulative period was 21.8 (6.87) months with a median exposure of 24.3 months and for the 2-5 year old patients the mean (SD) exposure to SC abatacept over the cumulative period was 18.8 (7.26) months with a median duration of 24.1 months. The aim of the study was to demonstrate that providing a PK exposure (Cminss) similar to IV abatacept, using weight tiered fixed dosing of SC abatacept, would result in a similar efficacy and safety profile to that already established with IV abatacept.

Study IM101033, a double-blind, placebo-controlled withdrawal trial was the basis for approval of IV abatacept to treat children with pJIA 6 to 17 years old whose disease inadequately responded to other treatment options.

3.2. Favourable effects

Limited, short term and long term, up to 24 months, clinical efficacy data is available from study IM101301. Target therapeutic abatacept concentrations (Cminss≥10 µg/mL), were reached and sustained showing consistent results also on weight tiers and age strata at each time-point up to day 113 and beyond up to 24 months.

ACR paediatric 30 responses rates were of sufficient level of efficacy when compared to previous adult RA and paediatric IV pJIA data. The proportion of pJIA ACRp30 responders increased over time and reached 80.9% in the 6 to 17 year-old cohort, with similar result (89.1%) observed in the 2 to 5 year-old cohort.

The results were overall similar across various endpoints and other subgroups, including concomittant treatment with MTX and prior use of biologics, namely TNF inhibitor. The data were also consistent with historical IV abatacept data of study IM101033 and overall data of the Orencia development programme.

Further analysis was performed on treatment effect and safety of abatacept with or without MTX treatment and the results were in line with the previous data of the Orencia development programme.

The PK data from the two paediatric studies IM101033 and IM101301 indicated similar exposure/achieved steady state (Day 113) abatacept Cmin levels were comparable in subjects with and without concomitant MTX treatment. This was in agreement with and supports the result of population PK analysis, showing that the baseline concomitant MTX use was not a statistically significant covariate on the clearance of abatacept. Furthermore, modelling showed that MTX was not a significant covariate and did not affect the prediction of ACRp response in subjects with pJIA.

Furthermore, no clinically meaningful, potentially confounding imbalances were clearly evident in baseline values. The Cmin values in the adult studies showed comparable exposure for the subgroups of subjects treated with abatacept with or without MTX.

The clinical response to abatacept in pJIA patients treated with abatacept monotherapy and abatacept with MTX was studied in several settings. The ACRp30, ACRp50, ACRp70, and ACRp90 response results at Day 113 showed overall and consistently similar and acceptable efficacy, in both the IV and SC trials in pJIA. Importantly, similar acceptable efficacy on exposure surpassing the target threshold was also seen between subjects who received abatacept with MTX and those on abatacept monotherapy, in each age cohort, the combined cohort and at each ACRp response level.

The presented data also showed that in both IM101033 and IM101301 studies, abatacept-treated subjects who did not receive prior biologic therapy had generally higher ACRp response (ACRp30/50/70/90) than subjects who received prior biologic therapy. This finding is not unexpected since subjects who have received previous biologic therapy are often refractory to further therapy. Importantly, this response rate was independent of MTX use in both the IV and SC pJIA studies.

Furthermore, these observed data are in line and supportive of the results of the E-R analysis with the most recent (year 2018) JIAACR response model, where in addition to the baseline MTX use, prior use of TNF-alpha inhibitors was not significant covariate and did not affect predicted ACRp responses in subjects with pJIA.

The relationship between abatacept exposure and efficacy in pJIA was characterized by an exposure-response (E-R) model using efficacy data from the two conducted clinical studies (IM101033 with IV dosing; IM101301 with SC dosing). The model confirmed that, as in previous analyses in RA population, the Cminss is the best PK parameter predicting efficacy. Near maximal JIAACR 30 response was achieved at Cminss level of approximately 10 µg/mL.

3.3. Uncertainties and limitations about favourable effects

From quality point of view, the formulation composition is the same as the currently approved one and, for the new proposed pre-filled syringes, the device components, coming into contact with the solution, are the same as the approved one.

The impact of modelling and simulation exercises in the application is high. No major deficiencies in population PK and exposure-response models were observed.

Limited uncontrolled data is available for paediatric pJIA patients from study IM101301 and in agreement with the extrapolation approach, it is only supportive. Acknowledging the limitations of uncontrolled open label descriptive data, from a clinical point of view the efficacy of SC abatacept appears acceptable.

3.4. Unfavourable effects

In Study IM101301, overall, the safety profile of abatacept in both age groups were similar to previous data.

Acknowledging the limited numbers in paediatric patients treated with SC abatacept, and the open label nature of the clinical trial the overall safety profile appears similar to that of the IV trial IM101033 and in adults.

In Study IM101301, the most frequently reported AEs were nasopharyngitis and upper respiratory infection in both the younger and the older age cohorts. No consistent pattern or associations to certain time points were evident.

Overall, the SAE incidence rates were low. In the younger patients three (6.5%) and 14 (8.1%) of the older age group reposted SAEs. The SAEs of nephrolithiasis, stage III ovarian germ cell teratoma, sepsis, anaemia, and chest pain were classified as severe in intensity. SAEs of teratoma, sepsis, autonomic nervous system imbalance, and vertigo led to discontinuation of study drug. No SAE was reported to be very severe in intensity. Overall, in the cumulative period no clear trends were observed and the incidence rates were low. Each SAE occurred only once during the study and no clustering around any time point or age group was clearly evident.

Discontinuations related to AEs were not numerous, and were reported in all for eight persons. The majority (95%) of subjects completed the 4 month ST period and 71% had completed the cumulative period at the time of DBL.

No deaths were reported during the study.

Overall infections were the most common AE of special interest. The rate and incidence of infections was similar across age groups and the duration of treatment.

Only one malignancy was reported, but it was thought not to be related the study drug (teratoma).

There were no reports of anaphylaxis in the paediatric patients. The rate of local injection site reactions appeared to be similar in both age groups and did not increase over time. They were few and mild or moderate in intensity.

The current the safety profiles of patient treated with SC abatacept with or without MTX appears alike and similar to previous reported abatacept safety data.

The overall safety (SAE, AE, and relatedness) of abatacept, for subjects with pJIA, who received prior biologic therapy and subjects who did not receive prior biologic therapy was also similar during the 4-month, open-label periods of both studies IM101033 and IM101301.

No new safety signal has been identified in the post marketing registry data.

Long-term safety data from the study IM101033 have demonstrated sustained tolerability of up to 7 years of continuous IV abatacept treatment of JIA, with no new safety signals and no increases in incidence rates of AEs, SAEs, infections, malignancies, or autoimmune diseases.

3.5. Uncertainties and limitations about unfavourable effects

The paediatric clinical trial safety database for the abatacept SC formulation in treatment of moderate to severe pJIA is so far limited to data from the pivotal study IM101301 and comprises of 173 pJIA patients in the 6 to17 age cohort and 47 pJIA patients in the 2 to 5 age cohort. A total of 220 paediatric patients were treated with at least one dose of the SC abatacept in the only SC pJIA clinical trial. The size of this safety data relative to studies of RA may limit the ability of the trial to detect rare safety concerns. Thus,

adequate post approval management were included in the RMP to monitor the long-term safety of abacacept in the 2-17 years old patients (clinical trial IM101301 and the ongoing pediatric pJIA registry).

The immunogenicity of abatacept in patients at the age of 2 to 5 seems not to be significantly different from that of the patients at 6 to 17 years of age. However, there was a trend for somewhat higher incidence of ADAs in the younger cohort. Acknowledging the uncertainty in indirect cross study comparisons, the CHMP agreed that, on the current data, there was no clear evidence of effects of immunogenicity on occurrence of PK, loss of efficacy, and the occurrence of AEs, in subjects who were ADA positive in study IM101033 and Study IM101301. Furthermore, the occurrence of ADAs was comparable or less to that in adults with SC abatacept or children treated with the IV formulation. However, the immunogenicity of paediatric patients of different age groups may differ and ADAs may be more frequently observed in the younger patient cohort of 2 to 5 years. Hence, at the CHMP's request, immunogenicity in the paediatric population was addressed as missing information in the RMP. In addition, further insight on the possible effect of MTX on ADA formation and the age dependency of the ADA response will be provided by the MAH post authorisation by submission of the final results (24-month and 5-year data) of the Study IM101301 as outlined in the RMP..

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

A SC route of administration provides pJIA patients and caregivers a self-administration alternative to IV dosing allowing for greater flexibility and subject compliance.

In agreement with the Paediatric Committee (PDCO), an extrapolation approach was considered suitable to characterize the clinical profile of SC abatacept in pJIA. In line with this approach, limited data was collected in the target population (an open label, exposure, efficacy and safety study in pJIA patients), with extrapolation of efficacy and safety data from source populations of the studies of the abatacept (IV and SC) in RA and pJIA (IV) development programmes.

The evidence to support an extrapolation strategy is based on the overlap in the clinical presentation of adult and paediatric, RA and pJIA, patients, consistency of formulations, consistency in the therapeutic approach, consistency of abatacept mechanism of action, consistency of the PK/PD in both adults and children and relevance of the clinical endpoints for both efficacy and safety. Given these similarities, an extrapolation approach is considered suitable to characterize the clinical profile of SC abatacept in treatment of pJIA.

The MAH's choice to characterize the clinical profile of SC abatacept in JIA using an extrapolation from IV abatacept in JIA is adequately justified. The population PK model and exposure-response model for efficacy appear to be adequate for the intended use. Clinical pharmacology aspects such as drug-drug interactions and effects of renal and/or hepatic dysfunction on PK have been previously addressed in the application for the IV formulation in treatment of JIA, and the highest strength of the proposed SC formulation has been approved for adult patients. Additional clinical pharmacology studies are not required in paediatric patients for the SC formulation in the applied indication.

Results of study IM101301 confirmed that Cminss ≥10 µg/mL will be achieved with the selected weight-tiered dosing regimen. The most recent (year 2018) E-R model for efficacy indicated that MTX use was not a statistically significant covariate predicting the JIAACR response and that prior use of TNF-alpha inhibitors was not significant covariate and did not affect predicted ACRp responses in subjects with pJIA.

The clinical data from the abatacept adults RA (IV and SC) development programme are considered relevant for both adults and paediatrics as consistent eligibility criteria were employed irrespective of age. The primary and key secondary endpoints in adult RA for exposure and efficacy were alike (ACR based

efficacy endpoints, Cmin). Overall, also other secondary and explorative outcomes were consistent between adults and paediatrics. In conclusion, the clinical efficacy and safety endpoint data from the adult RA (IV and SC) and the IV and SC pJIA programmes are considered relevant for both adults and the paediatric patients.

From a clinical point of view the efficacy of SC abatacept was acceptable, acknowledging the limitations of uncontrolled data. The proportion of JIA ACRp30 responders increased over time and reached 80.9% at Day 113 in the 6 to 17 year-old cohort (secondary efficacy endpoint), with similar result (89.1%) observed in the 2 to 5 year-old cohort. The results were in general similar across various endpoints and subgroups, and were also consistent with historical IV abatacept data.

Overall, the main aim of the study IM101301, target therapeutic abatacept concentrations (Cmin), were reached and sustained showing consistent results on weight tiers and age strata at each time-point up to Day 113 and beyond up to 24 months. ACR paediatric 30 responses are considered as sufficient level of efficacy when compared to previous adult RA and paediatric IV pJIA data.

No new or clinically important safety signals were observed in the sole clinical study IM101301 relative to that for IV abatacept or relative to the overall Orencia safety database. AEs associated with the weekly body-weight-tiered SC abatacept dosing regimen in Study IM101301 were low in frequency, mostly mild, and consistent with the overall safety profile of abatacept. The AEs and SAEs, including events of interest related to immunomodulatory agents (i.e., infections, malignancies, and autoimmune disorders), were overall comparable to those seen in the larger abatacept program in RA. Discontinuations related to AEs were not numerous (8/173). No consistent pattern or associations to certain time points were evident.

Though the low prevalence of pJIA and small sample size, relative to studies of RA, could limit the ability of the trial to detect rare, but important safety events, results from abatacept trials support the long-term safety and tolerability of abatacept. Long-term safety data from the study IM101033 demonstrated sustained tolerability of up to 7 years of continuous IV abatacept treatment of JIA, with no new safety signals and no increases in incidence rates of AEs, SAEs, infections, malignancies, or autoimmune diseases. In Study IM101301, overall, the safety profile if abatacept both age groups were similar to previous data.

3.6.2. Balance of benefits and risks

Acknowledging the nature of uncontrolled data and that the study for some patients is still on-going, the study IM101301 in the target population of 2 to 17 year old pJIA patients with active disease (a total of 220 subjects), showed that therapy with weight tiered dosing of SC abatacept, targeted exposures and clinically relevant efficacy (measured with accepted and valid outcome measures) were reached and sustained up to the end (24 months) of the long-term extension period of the study. These results appeared consistent with historical data.

Similar efficacy was shown in pJIA subjects treated with Orencia with or without MTX in Study IM101301 (ACRp30 responses at Day 113 78.7% with MTX and 89.2% without MTX). The exposure-response modelling supports the proposed claim that SC Orencia can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. The same claim is supported also for IV abatacept. Likewise, similar efficacy was shown in pJIA subjects who received prior biologic therapy and subjects who did not receive prior biologic therapy (ACRp30 responses at Day 113 X% and Y%, respectively).

The overall safety profile of SC abatacept in children and adolescents with active pJIA in study IM101301 appears consistent with the previously described safety profile of IV and SC abatacept both in adults and in the paediatric population and thus, overall, support the current extrapolation concept. Likewise, the safety profiles of patient treated with SC abatacept with or without MTX and for subjects with pJIA, who

received prior biologic therapy and subjects who did not receive prior biologic therapy, appears alike and similar to previous reported abatacept safety data.

As with adults, infections, autoimmunity and malignancies remain potential serious risks for abacacept. Thus, adequate post approval management were included in the RMP to monitor the long-term safety of abacacept in the 2-17 years old patients e.g. the currently ongoing open label clinical trial IM101301 and the ongoing pediatric pJIA registry.

Considering the results from the population PK modelling analyses, and on the basis of the totality of the PK, efficacy and safety data provided, the CHMP concluded that the extrapolation exercise adequately supports the use of Orencia with the posology described in Section 4.2 of the SmPCs in the treatment of 2-17y old pJIA patients. Thus, a new subcutaneous administration route for the 2 to 17 year age group, and thus a new patient group (namely paediatric pJIA patients of 2 to 6 years of age), and transitioning Orencia treatment of pJIA patients from 3rd line, after TNF inhibitors, to 2nd line (after 1st line treatment, e.g. methotrexate), and also use as monotherapy without methotrexate in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate are approvable. In addition, two new strengths of an already approved pharmaceutical form and some other minor quality variations are approvable.

3.7. Conclusions

The overall B/R of Orencia is positive.

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 Orencia 50 mg, 87.5 mg and 125 mg solution for injection in pre-filled syringe is favourable in the following indication:

Polyarticular juvenile idiopathic arthritis

ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (pJIA) in paediatric patients 2 years of age and older who have had an inadequate response to previous DMARD therapy.

ORENCIA can be given as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Orencia 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

The MAH should provide a patient alert card in each pack, the text of which is included in Annex III.

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/0128/2014 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 variations to the terms of the marketing authorisation, concerning the following changes:

Variations approved		**Type**	**Annexes affected**
B.II.b.5.z	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	Type IB	None
B.II.e.1.z	B.II.e.1.z - Change in immediate packaging of the finished product - Other variation	Type IB	I, IIIA and IIIB
B.II.b.3.a	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	Type IB	None
B.II.b.3.a	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	Type IB	None
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 of application to add 2 new strengths of 50 mg and 87.5 mg for solution for injection in a

pre-filled syringe with needle guard for subcutaneous administration. Extension of indication to include paediatric use of polyarticular Juvenile Idiopathic Arthritis (pJIA) (2 years and above) for solution for injection in pre-filled syringe (50 mg, 87.5 mg and 125 mg) and to update the pJIA indication transitioning Orencia treatment of pJIA patients from 3rd line (after TNF inhibitors) to 2nd line (after 1st line treatment, e.g. methotrexate) and also use as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate for the subcutaneous formulation (Orencia solution for injection in pre-filled syringe 50 mg, 87,5 mg and 125 mg) and intravenous formulation (Orencia 250 mg powder for concentrate for solution for infusion). Consequential updates have been made to the SmPC of Orencia 125 mg solution for injection in pre-filled pen. The labelling and package leaflet are updated accordingly.

The above-described changes are grouped with the following variations:

B.II.b.3.a – To introduce an automated device assembly process for Neopak and Hypak non-printed syringes in all 3 fill volumes (0.4 mL, 0.7 mL and 1.0 ml) as an alternate to the current semi-automatic device assembly process used for the currently approved 1 mL fill in Hypak printed syringes.
B.II.b.3.a - to use all paperboard carton design with the automated secondary packaging process for all fill volumes.
B.II.b.5.z - To add a new machine vision inspection station “Stopper Presence” to the current automated in-process inspection process used for the inspection of the prefilled syringes.
B.II.e.1.b.z – To add two alternate syringe barrels, the current BD Hypak syringe barrel without pre-printed lines and BD Neopak syringe barrel without pre-printed lines to the currently approved BD Hypak syringe barrel with pre-printed lines.

The RMP (version 25.2) is updated in accordance.

In addition, the applicant took the opportunity to implement minor editorial changes in the product information and to update the list of local representatives in the package leaflet.