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Human Medicines Division

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

Orencia

Abatacept

Procedure no: EMEA/H/C/000701/P46/072

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	Description	Planned date	Actual Date	Need for discussion[2]
☐	Start of procedure	30 Dec 2024	30 Dec 2024	☐
☐	CHMP Rapporteur Assessment Report	03 Feb 2025	03 Feb 2025	☐
☐	CHMP members comments	17 Feb 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20 Feb 2025	n/a	☐
☐	CHMP adoption of conclusions:	27 Feb 2025	27 Feb 2025	☐
☐	Submission of MAH responses	26 Mar 2025	24 Mar 2025	☐
☐	Re-start of procedure	27 Mar 2025	27 Mar 2025	☐
☐	CHMP Rapporteur Assessment Report	09 Apr 2025	07 Apr 2025	☐
☐	CHMP members comments	14 Apr 2025	14 Apr 2025	☐
☐	Updated CHMP Rapporteur Assessment Report	16 Apr 2025	16 Apr 2025	☐
☒	CHMP adoption of conclusions:	25 Apr 2025	25 Apr 2025	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

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1. Introduction

The Category 3 planned additional pharmacovigilance activity listed in the EU RMP for abatacept (ORENCIA) included a 5-year long-term extension to the Phase 3 IM101-301 study in patients with JIA to evaluate safety of long-term exposure of abatacept administered subcutaneously in JIA patients, aged 2-17 years, including the evaluation of immunogenicity. The MAH has now submitted the final study report of this paediatric study in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The IM101-301 study was a phase 3 multi-center, open-label study 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 (MARD). This Article 46 paediatric submission concerns namely the 5-year long-term results of this study.

The critical expert overview is dated 25th November 2024. On request, the required information on the clinical expert of the MAH i.e. who compiled the expert overview, was provided. As per the pertinent guidance (Article 12(2) of the Directive 2001/83/EC as amended), the expert overview has now been signed and dated and a short curriculum vitae of the expert has been attached.

2. Scientific discussion

2.1. Medicine Overview

Abatacept (Orencia), a selective costimulation modulator, is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T cell-associated CTLA-4 linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human IgG1. Abatacept is approved for the IV treatment of moderate to severe adult RA and PsA in the US, the EU, Japan, Latin America, and other countries/regions. An SC formulation of abatacept in a prefilled syringe and autoinjector has been approved for adult RA and PsA patients in the US, EU, and several other countries. SC abatacept is approved for the treatment of JIA in pediatric patients 2 years of age and older in the US and EU. Abatacept is also approved for IV treatment of JIA in pediatric patients 6 years of age and older in the US, EU, and other countries/regions, as well as for prophylaxis of aGvHD (not in the EU) in adult and pediatric patients 2 years of age and older in the US and 6 years of age and older in some other countries.

Orencia, in combination with MTX, is indicated for the treatment of moderate to severe active RA in adult patients who responded inadequately to previous therapy with one or more DMARDs including MTX or a TNF-alpha inhibitor, the treatment of highly active and progressive disease in adult patients with rheumatoid arthritis not previously treated with MTX. A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with abatacept and MTX.

Orencia, alone or in combination with MTX, is indicated for the treatment of active PsA in adult patients when the response to previous DMARD therapy including MTX has been inadequate, and for whom additional systemic therapy for psoriatic skin lesions is not required.

Orencia in combination with MTX is indicated for the treatment of moderate to severe active pJIA in paediatric patients 6 years of age and older (IV) and 2 years and older (SC) who have had an inadequate response to previous DMARD therapy.

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

2.2. *Disease context*

JIA is one of the most common chronic diseases of childhood and is an important cause of short- and long-term disability. In Europe, one report revealed an incidence rate of JIA in Caucasians of 7.8/100,000 and a prevalence of 32.6/100,000. In the US, the reported prevalence of JIA is estimated to be 1 in 1,000 with an incidence of about 6 to 14 new cases per year per 100,000 children.

JIA is a diagnostic classification designed to encompass a heterogeneous group of chronic childhood and adolescent inflammatory joint diseases. The current JIA classification scheme recognizes distinct clinical subtypes based on the pattern of disease during the first 6 months of illness and on biomarker status: RF positive and negative polyarthritis, extended oligoarthritis, persistent oligoarthritis, enthesitis-related arthritis (ERA), PsA, systemic arthritis, and undifferentiated arthritis.

JIA is characterized by persistent synovitis that has been attributed to autoimmune dysfunction, although what initiates the synovial inflammation and why the synovitis persists is unknown. The fact that some patients have evidence of widespread and multi-system inflammatory features, including elevation of acute phase reactants, anemia, elevated platelets and weight loss, suggests that JIA is a systemic disease- the synovium is not the only area of active inflammation.

2.3. Information on the development program

The SC route of administration was developed to provide patients with a self-administration alternative to IV dosing to allow for greater flexibility and subject acceptance. Treatment with SC abatacept of adults with RA has been demonstrated to be non-inferior to IV treatment as measured by 20% improvement in ACR20 responses at 6 months of treatment. Analysis of data from the IV pJIA and SC and IV adult RA trials indicated that an abatacept steady-state trough serum concentration (Cminss) of ≥10 µg/mL was required for near maximal efficacy.

Study IM101-301 focused on paediatric subjects aged 2 through 17 years with active pJIA and resistant to at least 1 biologic or non-biologic DMARD. The purpose of this study was to evaluate if 4 months of a weekly weight-tiered SC abatacept dosing regimen would deliver steady-state systemic exposures in this population within the therapeutic range associated with maximal efficacy observed with IV abatacept. The doses tested in this study were derived from modeling the exposure-response relationships using data from both adult patients with RA and paediatric patients with JIA treated with IV abatacept. This study included 2 cohorts of subjects with active pJIA: Cohort 1 between the ages of 2 through 5-year-old and Cohort 2 between the ages of 6 through 17-year-old.

The study was extended for up to 5 years (from 03 Jul 2018 through 01 Feb 2023) in some countries in the EU to ensure continued dosing for subjects who demonstrate clinical benefit from SC abatacept at the conclusion of the study. This Article 46 paediatric submission concerns the safety data from this 5-year extension follow-up to the study IM101-301.

2.4. Information on the pharmaceutical formulation used in the study

During the study IM101-301, SC abatacept was administered weekly as a weight-tiered dosing regimen that was predicted to provide a systemic exposure comparable to the therapeutic range observed with IV abatacept treatment. SC administration of 2 mg/kg abatacept relied on 3 different PFS presentations for 3 weight tiers: 10 to < 25 kg (50 mg in 0.4 mL PFS), 25 to < 50 kg (87.5 mg in 0.7 mL PFS), and ≥ 50 kg (125 mg in 1 mL PFS). A maximum of 125 mg was proposed for subjects weighing ≥ 50 kg because it is the current SC abatacept dose for adults with RA. SC abatacept was administered every 7 days, similar to the dosing frequency for adults with RA.

2.5. Clinical aspects

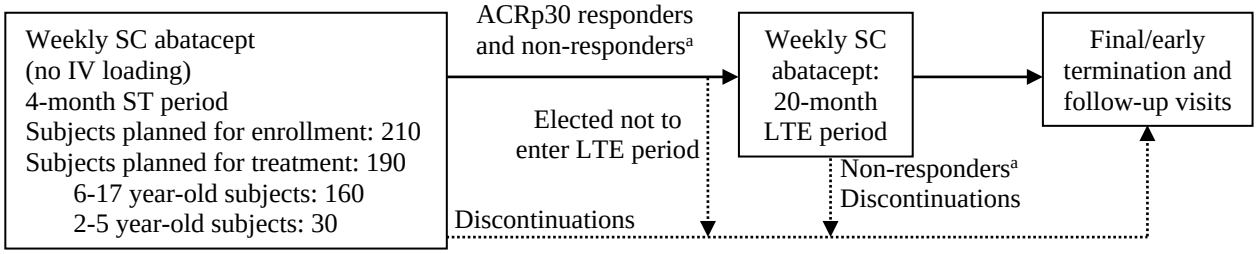
2.5.1. Introduction

Within this Article 46 paediatric submission, the MAH of abatacept has submitted a final study report for the clinical study IM101-301. This submission concerns namely the overall safety results from this 5-year extension, in JIA patient, aged 2-17, on abatacept treatment.

2.5.2. Clinical study IM101-301

IM101-301 was an open-label study to assess PK, safety, and efficacy of SC abatacept in pJIA with no formal hypothesis testing (Figure 2.5.2.1).

Figure 2.5.2.1 Study Design of Study IM101-301



[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.

Source: Figure 3.1-1 of 24-month IM101-301 CSR[i]

Efficacy and PK Data

Not applicable as no efficacy or PK data were collected during the 5 year long term extension of the Phase 3 study IM101-301 intended to evaluate the safety of long-term exposure of abatacept administered subcutaneously in JIA patients, aged 2-17 years.

Safety Data

Methods:

The Adverse Events were assessed from the day of the first subcutaneous injection in the 5-year extension period up to 56 days post the last day of subcutaneous injection in the 5-year extension period or the first dose in post-study therapy period, whichever occurs first. The safety analysis was based on the frequency of deaths, serious adverse events (SAEs), adverse events (AEs) leading to discontinuation and overall AEs. AEs of Special Interest were assessed throughout the study: malignancies, autoimmune disorders, local injection-site reactions, AEs within 24 hours of study drug administration, and infections. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1. All treated subjects were included in the safety analysis.

Immunogenicity to abatacept was assessed in subjects with JIA given weekly weight-tiered doses of SC abatacept. Pre-dose blood samples for immunogenicity were collected at several points in the cumulative period and following the last dose of abatacept administered by the study. According to the MAH, a validated, sensitive, electrochemiluminescence assay (ECL) method will be used to analyse anti-abatacept antibodies in serum. Samples that were confirmed positive for antibodies specific to the CTLA4 region of abatacept and had abatacept serum concentrations of ≤ 1 µg/mL was further analyzed

with a validated, in vitro, cell-based bioassay to determine whether the sera contained abatacept neutralizing activity.

Study participants: The study included 2 cohorts of subjects with active pJIA: one a 2 through 5 year-old cohort and a 6 through 17 year-old cohort. All study subjects could participate in the ST period and the month LTE. Subjects from both cohorts who completed the ST period were given the option to enter a 20-month LTE period where they continued to receive weekly SC abatacept injections. Subjects who entered the LTE period as non-responders per ACRp30 criteria had the opportunity to be treated with SC abatacept for an additional 3 months. If, however, an individual subject did not respond per ACRp30 criteria after a total of 7 months of abatacept therapy (ST period plus 3 months of LTE period), the subject was considered for discontinuation from study drug. All subjects who received a dose of abatacept, subjects who received a dose of abatacept, regardless of the time of termination or discontinuation, were scheduled to participate in a follow up period. At the end of the 20-month LTE period, subjects from selected EU countries who were continuing to derive clinical benefit could move into an optional 5-year extension.

Treatments: 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

Objective(s): To provide additional longer term safety data for pJIA patients on abatacept treatment, between the ages of 2 through 5-year-old and 6 through 17-year-old, in the period after the 2-year database lock through and up to the 5-year extension of the study IM101301.

Outcomes/endpoints: The safety endpoints were the frequency of deaths, serious adverse events (SAEs), adverse events (AEs) leading to discontinuation and overall AEs. AEs of Special Interest were assessed throughout the study: malignancies, autoimmune disorders, local injection-site reactions, AEs within 24 hours of study drug administration, and infections. Assessment of immunogenicity was also included.

Sample size: The number of subjects: in the 2 Through 5-Year Cohort: 30 subjects were planned; in the 6 Through 17-Year Cohort: 160 subjects were planned.

Randomisation and blinding (masking): N/A

Statistical Methods: There was be no formal hypothesis or statistical testing. The analyses were be descriptive within each age cohort except where indicated.

Results

Extent of Exposure: Extent of exposure in both cohorts were as follows:

- 2 Through 5-Year Cohort: For the 31 subjects who entered into the study, the mean (SD) exposure to SC abatacept during the 5-year Extension period was 32.2 (18.74) months with a median duration of 24.9 months. Subjects received a median of 86 SC injections during the 5-year extension period.

- 6 Through 17-Year Cohort: For the 78 subjects who entered into the study, the mean (SD) exposure to SC abatacept during the 5-year Extension period was 38.3 (18.54) months with a median duration of 37.6 months. Subjects received a median of 145.5 SC injections during the 5-year extension period.

Disposition, Demographics, and Other Pertinent Baseline Characteristics:

Subject disposition is presented in Table 1.

Table 1: Subject Disposition

	2 Through 5-Year Cohort Number (%) of Subjects N= 31	6 Through 17-Year Cohort Number (%) of Subjects N=78
No. of Subject Discontinued	21 (67.7)	43 (55.1)
Death	0	0
Adverse Event	6 (19.4)	3 (3.8)
Lack of Efficacy	0	7 (9.0)
Lost to Follow-up	1 (3.2)	1 (1.3)
Withdrawal of Consent	0	1 (1.3)
Subject no longer meets study criteria	0	1 (1.3)
Poor/Non-compliance	0	0
Pregnancy	0	1 (1.3)
Administrative reason by sponsor	0	0
Subject request to discontinue study treatment	0	7 (9.0)
Other	14 (45.2)	22 (28.2)
No. of Subjects Ongoing	0	1 (1.3)
No. of Subjects Completed 5-Year Extension Period	10 (32.3)	34 (43.6)

Baseline data

Table 2 describes the baseline and demographic information of both study cohorts:

Table 2: Baseline Demographic Characteristics - All Treated Subjects Entering 5-Year Extension

		2 Through 5-Year-Old Cohort N = 31	6 Through 17-Year-Old Cohort N = 78
Age (years)	N	31	78
	Mean	4.0	12.4
	SD	1.0	2.8
	Median	4.0	13.0
	Min	2.0	6.0
	Max	5.0	17.0
Weight (Kg)	N	31	78
	Mean	18.0	47.2
	SD	3.4	17.8
	Median	18.0	46.5
	Min	12.0	16.3
	Max	26.0	94.4
Weight Categories	<25kg	29 (93.5%)	8 (10.3%)
	25-50kg	2 (6.5%)	33 (42.3%)
	>=50kg	0	37 (47.4%)
Gender	Male	12 (38.7%)	9 (11.5%)
	Female	19 (61.3%)	69 (88.5%)
Race	White	30 (96.8%)	65 (83.3%)
	Black/African American	1 (3.2%)	8 (10.3%)
	American Indian/Alaska Native	0	0
	Asian	0	0
	Native Hawaiian/Other Pacific Islander	0	0
	Other	0	5 (6.4%)
Ethnicity (US Only)	Hispanic/Latino	0	0
	Not Hispanic/Latino	0	1 (100.0%)
Geographic Region	North America	0	1 (1.3%)
	South America	3 (9.7%)	13 (16.7%)
	Europe	26 (83.9%)	50 (64.1%)
	ROW	2 (6.5%)	14 (17.9%)

Numbers analysed

- 2 Through 5-Year Cohort: 30 subjects were planned, and 31 subjects were treated in 5-year long term extension study.
- 6 Through 17-Year Cohort: 160 subjects were planned, 164 completed short-term period and 78 subjects were treated in the optional 5-year long term extension study.

Efficacy and PK results

Not applicable as no efficacy or PK data were collected during the 5-year long-term extension of the Phase 3 study IM101-301 intended to evaluate the safety of long-term exposure of abatacept administered subcutaneously in JIA patients, aged 2-17 years.

Safety results

AEs that occurred after the first SC injection and up to 56 days post the last day of SC injection in the 5-year extension period or the first dose in the post-study therapy period, whichever occurs first are included in the safety summaries. The overall safety results are briefly summarized below in Table 3.

Table 3: Summary of Safety Results Reported During the 5-Year Extension Period -All Treated Subjects

Category	2 through 5 Year Cohort No. of Subjects (%) N = 31	6 through 17 Year Cohort No. of Subjects (%) N = 78
Deaths	**0**	**0**
Overall SAEs	**4 (12.9)**	**4 (5.1)**
SAEs Related to Study Drug	**1 (3.2)**	**2 (2.6)**
Discontinuations Due to SAEs	**1 (3.2)**	**1 (1.3)**
Overall AEs	**28 (90.3)**	**60 (76.9)**
AEs Related to Study Drug	**20 (64.5)**	**27 (34.6)**
Discontinuations Due to AEs	**6 (19.4)**	**4 (5.1)**
AEs of Special Interest		
Malignancies	0 (0.0)	0 (0.0)
Autoimmune Events	2 (6.5)	3 (3.8)
Local injection site reactions	0 (0.0)	1 (1.3)
AEs Within 24 hours of Drug Administration	4 (12.9)	23 (29.5)

Includes data from the day of the first subcutaneous injection in the 5-year extension period up to 56 days post the last day of subcutaneous injection in the 5-year extension period or the first dose in post-study therapy period, whichever occurs first. Includes all deaths reported during the 5-year extension period including those that occurred > 56 days after the last dose. SAEs include hospitalizations for elective surgical procedures. Related AE or SAE defined as AE or SAE with Related or Missing relationship to study medication. MEDDRA VERSION: 25.1
Source: Table 5 of Closeout CSR for Study IM101-301.

Deaths: No deaths were reported during the 5-year extension period in both the cohorts (Table 3).

Overall SAEs: During the 5-year extension period 4 subjects in each cohort had at least 1 SAE.

2 Through 5-Year Cohort: Overall, 5 SAEs were reported in 4 subjects (12.9%).

- 1 subject had 2 SAEs, limb injury and hand fracture, which are severe and moderate in intensity respectively, both the events are not related to study drug, but the drug was interrupted.
- 2 subjects each had tachycardia and molluscum contagiosum, which are moderate and mild in intensity, both the events are not related to study drug.

- 1 subject had drug-related SAE erythema multiforme which was very severe in intensity, leading to discontinuation.

6 Through 17-Year Cohort: Overall, 6 SAEs were reported in 4 subjects (5.1%).

- 1 subject had 3 SAEs, 2 severe events of peritonitis and small intestinal obstruction, and 1 very severe event of complicated appendicitis, all events are not related to the drug, but the drug was discontinued.
- 2 subjects each had 1 drug-related event of latent tuberculosis and sinusitis, which are mild and moderate in intensity, respectively.
- 1 subject had an event of joint hyperextension, not related to the study drug and moderate in intensity.

Table 4: Overall Adverse Events reported (≥ 5% of Subjects) During the 5-Year Extension Period: All Treated Subjects Entering 5-Year Extension - 2 through 5-Year Cohort

SYSTEM ORGAN CLASS (SOC) PREFERRED TERM (PT)	Abatacept N= 31
TOTAL SUBJECTS WITH AE	28 (90.3)
Infections and infestations	19 (61.3)
Nasopharyngitis	10 (32.3)
Gastroenteritis	4 (12.9)
Upper respiratory tract infection	3 (9.7)
Impetigo	2 (6.5)
Oral herpes	2 (6.5)
Gastrointestinal disorders	7 (22.6)
Abdominal pain	3 (9.7)
Aphthous ulcer	2 (6.5)
Diarrhoea	2 (6.5)
Skin and subcutaneous tissue disorders	7 (22.6)
Dermatitis atopic	2 (6.5)
Psoriasis	2 (6.5)
Respiratory, thoracic and mediastinal disorders	5 (16.1)
Cough	3 (9.7)
Blood and lymphatic system disorders	3 (9.7)
Neutropenia	2 (6.5)
Investigations	3 (9.7)
Aspartate aminotransferase increased	2 (6.5)
Nervous system disorders	2 (6.5)
Headache	2 (6.5)

Table 5: Overall Adverse Events reported (≥ 5% of Subjects) During the 5-Year Extension Period: All Treated Subjects Entering 5-Year Extension – 6 through 17-Year Cohort

SYSTEM ORGAN CLASS (SOC) PREFERRED TERM (PT)	Abatacept N= 78
TOTAL SUBJECTS WITH AE	60 (76.9)
Infections and infestations	51 (65.4)
Nasopharyngitis	26 (33.3)
Upper respiratory tract infection	14 (17.9)
Gastroenteritis	7 (9.0)
Bronchitis	6 (7.7)
Sinusitis	5 (6.4)
Cystitis	4 (5.1)
Influenza	4 (5.1)
Rhinitis	4 (5.1)
Gastrointestinal disorders	15 (19.2)
Toothache	4 (5.1)
Nervous system disorders	8 (10.3)
Headache	5 (6.4)

Overall AEs: Most AEs were reported in the SOC of infections and infestations in both cohorts (Table 3 and Table 5).

- 2 Through 5-Year Cohort: Overall, AEs were reported in 28 (90.3%) subjects and 20 (64.5%) subjects had drug-related AEs. A total of 6 (19.4%) subjects were discontinued from the study due to AEs (Table 3). AEs of very severe intensity were reported in 2 subjects (6.5%), severe intensity was reported in 1 subject (3.2%) and all the other reported AEs were mild or moderate in intensity. The most commonly reported AEs were nasopharyngitis (10 [32.3%]) and gastroenteritis (4 [12.9%]) (Table 4).
- 6 Through 17-Year Cohort: AEs were reported in 60 (76.9%) subjects. Of which, 27 (34.6%) subjects AEs had drug-related AEs, 4 subjects (5.1%) were discontinued from the study due to AEs (Table 3). AEs of very severe intensity was reported in 1 subject (1.3%), severe intensity was reported in 1 subject (1.3%) and all the other reported AEs were mild or moderate in intensity. The most commonly reported AEs were nasopharyngitis (26 [33.3%]) and upper respiratory tract infection (14 [17.9%]) (Table 5).

Adverse Events of Special Interest: AEs of Special Interest including malignancies, autoimmune events, local injection site reactions, and AEs within 24-hr were assessed during the 5-year-extension period. PTs were prespecified for autoimmune events and local injection site reactions.

- 2 Through 5-Year Cohort: No malignancies and local injection site reactions were reported. AEs within 24 hours of drug administration occurred in 4 subjects and autoimmune events were reported in 2 subjects (Table 3).

- 6 Through 17-Year Cohort: No malignancies were reported. AEs within 24 hours of drug administration occurred in 23 subjects, autoimmune events were reported in 3 subjects and local injection site reactions was reported for 1 subject (Table 3).

Clinical Laboratory Evaluations:

- 2 Through 5-Year Cohort: Marked abnormalities in clinical laboratory evaluations during the 5-year extension period were reported in few subjects and were not persistent. The most common Marked abnormalities (> 5% of subjects) include elevated laboratory values of creatinine (51.6%) and eosinophils (29.0%).
- 6 Through 17-Year Cohort: Marked abnormalities in clinical laboratory evaluations during the 5-year extension period were reported in few subjects and not persistent. The most common Marked abnormalities (> 5% of subjects) included creatinine (32.1%) and eosinophils (20.5%).

Other Study Results: All subjects in 2 through 5-year cohort and most subjects in 6 through 17 year cohort had negative anti-GAD and anti-TPO values at baseline. None of the subjects had abnormal TSH value during the 5-year extension in either cohort.

Immunogenicity: Sample collection for immunogenicity testing was not included in the original protocol amendment that outlined the 5-year extension period (Amendment 13, approved 12-Jul-2015). Sample collection for immunogenicity testing for participants in France was included in response to a request from the French Health Authority (Amendment 14, approved 05-Oct-2015). A later request for immunogenicity testing led to protocol amendment 15 (approved 27-Jan-2020) for ongoing participants participating in Argentina, Belgium, Italy, Russia and South Africa. Collected samples were tested for the presence of ADAs using the same methodology previously described and eligible samples further tested in NAb analysis.

In all, as previously reported, 109 subjects entered the 5-year extension (31 subjects in the 2-5 age cohort and 78 in the 6-17 age cohort). Overall, only 5 of these subjects tested positive in the ADAs assay at any point during the 5-year follow-up extension period in Study IM101301, 3 in the 2-5 age cohort and 2 in the 6-17 age cohort. Table 6 shows the results per age cohort, which align with the incidences reported in the 24-month data.

Table 6: Proportion of subjects with positive antibody response to abatacept relative to baseline (ECL method) during the 5-year extension period, immunogenicity analysis population

Age Group	Response	CTLA4 and Possible IG n/N (%)	IG and/or Junction Region n/N (%)	Total n/N (%)
2-5 years old	Negative	0/14	0/14	0/14
	Positive	3/14 (21.4)	0/14	3/14 (21.4)
6-17 years old	Negative	0/45	0/45	0/45
	Positive	1/45 (2.2)	1/45 (2.2)	2/45 (2.2)
Overall	Negative	0/59	0/59	0/59
	Positive	4/59 (6.8)	1/59 (6.8)	5/59 (6.8)

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Listing for all of the immunogenicity testing performed in the 2-5 age cohort during this period, were provided, with the 3 subjects showing detectable ADAs. It also shows that no subjects had detectable ADAs on the last day of the initial 2-year observation period (Day 729). Included were also a listing of the positive test including specificity and titers for these 3 subjects.

- Subject was a 3-year old female at the time of enrollment in a site in France. She tested positive for 3 successive visits (Day 1086 through 1626) with the highest titer on Day 1626.

The ADAs were no longer detectable resolved with no detectable ADAs from Day 1817 onwards. Review of the safety listings showed 3 AEs reported during this timeframe; constipation, pharyngitis and nasopharyngitis with the infections considered mild in intensity. The subject completed the 5-year extension.

- Subject was a 5-year old female at the time of enrollment in a site in France. She had detectable ADAs only on the last collection date at the end of the 5-year extension, Day 2555, at a titer of 50.9. Review of the safety listings showed no new AEs were reported at the time of the positive ADA testing. The subject completed the 5-year extension.
- Subject was a 4-year old female at the time of enrollment in a site in Germany. On Day 728, she tested positive for ADA with a titer of 113. On Day 729 (last collection date), she had abatacept Cmin level of 0.3 ug/ml. Review of the safety listings noted that no AEs were reported around the time of ADA detection. The subject discontinued the extension study, approximately 21 months after starting the 5-year extension.

A listing of the immunogenicity results in the 6-17 age cohort, with 2 subjects showing detectable ADAs were appended. It also shows that no subjects had detectable ADAs on the last day of the initial 2-year observation period (Day 729.) and the listing of the positive test included specificity and titers for these 2 subjects.

- Subject was a 15-year old female at the time of enrollment in a site in Belgium. On Day 1377, she tested positive for ADA with a titer of 43. Review of the safety listings noted that no AEs were reported around the time of ADA detection. She discontinued the study, after approximately 20 months in the extension. Subject was a 12-year old female at the time of enrollment in a site in Belgium. On Day 2542, she tested positive with a low titer of 18.6 for the IGG specificity. Review of the safety listings noted that no AEs were reported around the time of ADA detection. The subject completed the 5-year extension.

In both cohorts, none of the samples analyzed were positive for NAb. Cmin values from Day 729 were provided, however, PK assessments were not an objective for the 5-year follow-up period and impact of ADA on PK could not be evaluated.

Clinical Laboratory Evaluations: Clinical Laboratory Evaluations:

- 2 Through 5-Year Cohort: Marked abnormalities in clinical laboratory evaluations during the 5-year extension period were reported in few subjects and not persistent. The most common Marked abnormalities (> 5% of subjects) include creatinine (51.6%) and eosinophils (29.0%).
- 6 Through 17-Year Cohort: Marked abnormalities in clinical laboratory evaluations during the 5-year extension period were reported in few subjects and not persistent. The most common Marked abnormalities (> 5% of subjects) include creatinine (32.1%) and eosinophils (20.5%).

Other Study Results: All subjects in 2 through 5 year cohort and most subjects in 6 through 17 year cohort had negative anti-GAD and anti-TPO values at baseline. None of the subjects had abnormal TSH value during the 5-year extension in either cohort.

2.5.3. Discussion on clinical aspects

Within this Article 46 paediatric submission, the MAH has submitted the safety results from a 5-year extension of study IM101301. This study sample was a selected subset of the study patients who demonstrated clinical benefit from SC abatacept in the initial 24-month open-label study period.

Study IM101301 was a phase 3 multi-center, open-label study to evaluate pharmacokinetics, efficacy, and safety of abatacept administered subcutaneously (SC) in children and adolescents with active polyarticular juvenile idiopathic arthritis (pJIA) with inadequate response (IR) to biologic or non-biologic disease modifying anti-rheumatic drugs (DMARD). Results for the initial study period, described and submitted previously, constitute the main source of information for interpretation of the study results. The current Orencia PI was also referred to.

Abatacept (Orencia), a selective costimulation modulator, is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T cell-associated CTLA-4 linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human IgG1.

Abatacept is indicated for the IV treatment of moderate to severe adult RA and PsA in the US, the EU, Japan, Latin America, and other countries/regions. An SC formulation of abatacept in a prefilled syringe and autoinjector has been approved for adult RA and PsA patients in the US, EU, and several other countries.

SC abatacept is indicated for the treatment of JIA in pediatric patients 2 years of age and older in the US and EU. Abatacept is also approved for IV treatment of JIA in pediatric patients 6 years of age and older in the US, EU, and other countries/regions, as well as for prophylaxis of aGvHD (not in the EU) in adult and pediatric patients 2 years of age and older in the US and 6 years of age and older in other countries.

The currently provided safety results extend the length of safety observation in paediatric JIA patients of 2-17 years of age up to 5-year. Some uncertainty can be expected in interpretation of these data as, by design, the study sample was a highly selected one, limited to a subset of the overall subjects of all the patient that completed the open label study IM101-301. It is also noted that no efficacy or PK data were accrued.

Overall, no new or unexpected safety signals or toxicities were identified for ORENCIA during the 5-year extension to Study IM101-301 in paediatric patients with pJIA on ORENCIA treatment, aged 2-17, with prior inadequate response to MTX and/or other biologic DMARDs. Most AEs were reported in the SOC of infections and infestations. SAEs related to study drug were rare, as were discontinuations due to SAE. Prespecified AEs of special interest, autoimmune events and local injection site reactions, were also rare. No serious allergic reactions were reported. No deaths were reported. Some differences were noted between the safety results of the two different age cohorts. AEs occurring within 24 hours of abatacept administration was more common in the older patient cohort. On the other hand, the overall AEs, AEs related to study drug and discontinuations due to AEs were somewhat higher in the patients of the younger cohort of 2 to 5 year olds, giving an impression of a slightly more vulnerable safety profile in these younger patients. However, any possible reasons for these disparities were not clearly evident. Overall, firm conclusions on this type of study are restricted. Nevertheless, the safety results appeared overall consistent with the safety results at 24-month and were consistent with the known safety profile of abatacept overall and namely in pJIA patients on abatacept therapy.

Full data on immunogenicity in the follow-up period could not be retrieved from the submitted data, but were subsequently provided by the MAH. Testing was performed using validated instruments and methodology appeared to comply with pertinent guidance. Testing positive for ADA in this study sample was infrequent and transient and none of the samples analysed were positive for NAb. Acknowledging the small numbers overall and namely in the two age cohorts, there appeared to be no association between positive ADA response and the safety data available. The immunogenicity results were broadly similar for both age cohorts. In all, again acknowledging the limitations of the data, these results from the 5-year follow-up extension period were consistent with the results of the previously

reported ADA testing during the initial 2-year reporting period of the study IM101301 of paediatric JIA patients ages 2-17 on SC abatacept treatment.

On the overall assessment, in all three other concerns arose. These concerns were adequately and sufficiently addressed by the MAH.

In conclusion, taking into consideration all available data, it is agreed with the MAH that the findings of the 5-year extension to study IM101-301 do not to change the previous conclusions on the risk-benefit of abatacept. This submission is considered to fulfill the provisions of Article 46 of Regulation (EC) No1901/2006, as amended.

3. CHMP overall conclusion and recommendation

The Category 3 planned additional pharmacovigilance activity listed in the EU RMP for abatacept (ORENCIA) included a 5-year long-term extension to the Phase 3 IM101-301 study in patients with JIA to evaluate safety of long-term exposure of abatacept administered subcutaneously in JIA patients, aged 2-17 years, including the evaluation of immunogenicity. The MAH has now submitted the final study report of this paediatric study in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The IM101-301 study was a phase 3 multi-center, open-label study 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 (MARD). This Article 46 paediatric submission concerns namely the 5-year long-term results of this study.

On assessment, three other concerns arose. These concerns were adequately and sufficiently addressed by the MAH. No changes to the product information are called for.

In conclusion, taking into consideration all available data, it is agreed with the MAH that the findings of the 5-year extension to study IM101-301 do not to change the previous conclusions on the risk-benefit of abatacept.

☒ Fulfilled

No regulatory action required.

4. Request for supplementary information

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

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

1. A critical expert overview, dated 25th November 2024, was provided on request by the MAH. However, no mention of who the clinical expert of the MAH is i.e. who compiled the expert overview. As per the pertinent guidance [Article 12(2) of the Directive 2001/83/EC as amended], the expert overview shall be prepared by a suitably qualified and experienced person and must be signed and dated by the expert. Attached to the report shall be brief information about the educational background, training and professional experience of the expert (curriculum vitae breve). This information must be provided.
2. The immunogenicity results of the 5-year follow-up extension period could not be readily found in the submitted dossier. For example the expert statement does not mention these results at all. The

addendum to the study IM101-301 present results only for the younger cohort. No discussion was found on this issue in the final CSR. The immunogenicity results must be provided collated, as per pertinent guidance (including EMEA/CHMP/BMWP/14327/2006, Rev 1), with a discussion on the relevance and validity of the results and complemented with an overall discussion on the immunogenicity in this patient sample.

3. The MAH is requested to fill in the Annex 1

5. MAH responses and the Assessment of the MAH responses to the Request for supplementary information

Question 1

A critical expert overview, dated 25th November 2024, was provided on request by the MAH. However, no mention of who the clinical expert of the MAH is i.e. who compiled the expert overview. As per the pertinent guidance [Article 12(2) of the Directive 2001/83/EC as amended], the expert overview shall be prepared by a suitably qualified and experienced person and must be signed and dated by the expert. Attached to the report shall be brief information about the educational background, training and professional experience of the expert (curriculum vitae breve). This information must be provided.

The MAH Response

A signed and dated clinical expert statement including a CV breve is provided with this response submission under Module 1.4.3.

Assessment of the MAH Response

The MAH has provided the requested information on the clinical expert of the MAH for this submission i.e. the expert who compiled the expert overview. The MAH clinical expert of this submission is the Company Clinical Development Lead for Abatacept Immunology and Fibrosis R&D. As per the pertinent guidance (Article 12(2) of the Directive 2001/83/EC as amended), the expert overview has now been signed and dated and a short curriculum vitae of the expert has been attached.

Conclusion

Issue resolved

Question 2

The immunogenicity results of the 5-year follow-up extension period could not be readily found in the submitted dossier. For example the expert statement does not mention these results at all. The addendum to the study IM101-301 present results only for the younger cohort. No discussion was found on this issue in the final CSR. The immunogenicity results must be provided collated, as per pertinent guidance (including EMEA/CHMP/BMWP/14327/2006, Rev 1), with a discussion on the relevance and validity of the results and complemented with an overall discussion on the immunogenicity in this patient sample.

The MAH Response

The MAH acknowledges the lack of immunogenicity data in the final Clinical Study Report (CSR) for the IM101-301, 5-year follow-up extension period. At the time of study closeout, formal outputs for the immunogenicity testing were not completed and were, therefore, not included in the closeout CSR.

Anti-drug antibodies (ADAs) testing had been performed using validated methods and reviewed routinely on an ongoing basis, so the study team was aware that there were no unexpected results which aligned with the findings of the more robust initial 2-year observation period. The immunogenicity results of the 5-year follow-up extension period are presented below.

Sample collection for immunogenicity testing was not included in the original protocol amendment that outlined the 5-year extension period (Amendment 13, approved 12-Jul-2015). Sample collection for immunogenicity testing for participants in France was included in response to a request from the French Health Authority (Amendment 14, approved 05-Oct-2015). A later request for immunogenicity testing led to protocol amendment 15 (approved 27-Jan-2020) for ongoing participants participating in Argentina, Belgium, Italy, Russia and South Africa. Collected samples were tested for the presence of ADAs using the same methodology previously described4 and eligible samples further tested in NAb analysis.

As previously reported, 109 subjects entered the 5-year extension (31 subjects in the 2-5 age cohort and 78 in the 6-17 age cohort). Overall, only 5 of these subjects tested positive in the ADAs assay at any point during the 5-year follow-up extension period in Study IM101301, 3 in the 2-5 age cohort and 2 in the 6-17 age cohort. Table 1 shows the results per age cohort, which align with the incidences reported in the 24-month data.

Table 1: Proportion of Subjects with Positive Antibody Response to Abatacept Relative to Baseline (ECL Method) During the 5-years Extension Period, Immunogenicity Analysis Population

Age Group	Response	CTLA4 and Possible IG n/N (%)	IG and/or Junction Region n/N (%)	Total n/N (%)
2-5 years old	Negative	0/14	0/14	0/14
	Positive	3/14 (21.4)	0/14	3/14 (21.4)
6-17 years old	Negative	0/45	0/45	0/45
	Positive	1/45 (2.2)	1/45 (2.2)	2/45 (2.2)
Overall	Negative	0/59	0/59	0/59
	Positive	4/59 (6.8)	1/59 (6.8)	5/59 (6.8)

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Appendix 4a is a listing for all of the immunogenicity testing performed in the 2-5 age cohort during this period with the 3 subjects showing detectable ADAs. It also shows that no subjects had detectable ADAs on the last day of the initial 2-year observation period (Day 729.) Appendix 2a is a listing of the positive test including specificity and titers for these 3 subjects (NOTE: reported titers of “10” indicate a negative result for ADA).

- Subject was a 3-year old female at the time of enrollment in a site in France. She tested positive for 3 successive visits (Day 1086 through 1626) with the highest titer on Day 1626. The ADAs were no longer detectable resolved with no detectable ADAs from Day 1817 onwards. Review of the safety listings (Appendix 3a) showed 3 AEs reported during this timeframe; constipation, pharyngitis and nasopharyngitis with the infections considered mild in intensity. The subject completed the 5-year extension.
- Subject was a 5-year old female at the time of enrollment in a site in France. She had detectable ADAs only on the last collection date at the end of the 5-year extension, Day 2555, at a titer of 50.9. Review of the safety listings showed no new AEs were reported at the time of the positive ADA testing. The subject completed the 5-year extension.
- Subject was a 4-year old female at the time of enrollment in a site in Germany. On Day 728, she tested positive for ADA with a titer of 113. On Day 729 (last collection date), she had abatacept Cmin level of 0.3 ug/ml. Review of the safety listings noted that no AEs were

reported around the time of ADA detection. The subject discontinued the extension study, approximately 21 months after starting the 5-year extension.

Appendix 4b is a listing of the immunogenicity results in the 6-17 age cohort, with 2 subjects showing detectable ADAs. It also shows that no subjects had detectable ADAs on the last day of the initial 2-year observation period (Day 729.). Appendix 2b is the listing of the positive test including specificity and titers for these 2 subjects.

- Subject was a 15-year old female at the time of enrollment in a site in Belgium. On Day 1377, she tested positive for ADA with a titer of 43. Review of the safety listings noted that no AEs were reported around the time of ADA detection (Appendix 3b). She discontinued the study, after approximately 20 months in the extension. Subject was a 12-year old female at the time of enrollment in a site in Belgium. On Day 2542, she tested positive with a low titer of 18.6 for the IGG specificity. Review of the safety listings noted that no AEs were reported around the time of ADA detection. The subject completed the 5-year extension.

In both cohorts, none of the samples analyzed were positive for NAb. Appendices 4a and 4b include Cmin values from Day 729, however, PK assessments were not an objective for the 5-year follow-up period and impact of ADA on PK could not be evaluated.

Overall, testing positive for ADA was infrequent and transient. There was no association between positive ADA response and observed safety events. The immunogenicity results were similar for both age cohorts. These results were consistent with the previously reported ADA testing of the initial 2-year reporting for the use of SC abatacept to treat JIA in children ages 2-17.

REFERENCES

Method validation of an electrochemiluminescent immunoassay for the detection of abatacept specific antibodies in human rheumatoid arthritis serum, 170606 (2008) BMS Document Control No. 930026379.

Validation of a Cell-based Bioassay for Determination of Neutralizing Antibodies to Abatacept (BMS-188667) in Human Serum, Assay Validation Report 14BASM158 (China, 2016). BMS Document Control No. 930103655.

Validation of a Cell-Based Bioassay for Determination of Neutralizing Antibodies to Abatacept (BMS-188667, CTLA4-Ig) in Human Serum, Assay Validation Report, TNJR06-007 (West Trenton, NJ, Covance, 2006). BMS Document Control No. 930020396.

A Phase 3 multi-center, open-label study to evaluate pharmacokinetics, efficacy, and safety of abatacept administered subcutaneously in children and adolescents with active polyarticular juvenile idiopathic arthritis and inadequate response to biologic or non-biologic disease modifying anti-rheumatic drugs (Study IM101301); 24-month Clinical Study Report. Bristol-Myers Squibb Company; 2019. Document Control No: 930135902.

Validation of a Cell-based Bioassay for Determination of Neutralizing Antibodies to Abatacept (BMS-188667) in Human Serum, Assay Validation Report 14BASM158 (China,2016). BMS Document Control No. 930103655.

Validation of a Cell-Based Bioassay for Determination of Neutralizing Antibodies to Abatacept (BMS-188667, CTLA4-Ig) in Human Serum, Assay Validation Report, TNJR06-007 (West Trenton, NJ, Covance, 2006). BMS Document Control No. 930020396.

Assessment of the MAH Response

The MAH has provided an acceptable justification and discussion why the immunogenicity results of the 5-year follow-up extension period were not submitted initially within this submission.

Sample collection for immunogenicity testing was not included in the original protocol amendment that outlined the 5-year extension period (Amendment 13, approved 12-Jul-2015). Sample collection for

immunogenicity testing for participants in France was included in response to a request from the French Health Authority (Amendment 14, approved 05-Oct-2015). A later request for immunogenicity testing led to protocol amendment 15 (approved 27-Jan-2020) for ongoing participants participating in Argentina, Belgium, Italy, Russia and South Africa. Collected samples were tested for the presence of ADAs on validated instruments and eligible samples further tested in NAb analysis.

Further, the MAH has now presented and discussed, with due diligence, the immunogenicity results available. Six pertinent references were included, covering relevant method validations and the 24 month CSR of the study IM101301. In all, six appendices were attached containing data from the 5-year extension period separately for both of the paediatric age cohorts (2-5 and 6-17 year old patients) as follows: titer and neutralising listings for subjects with positive antibody response, safety listings for subjects with positive antibody response and listings of Cmin values for abatacept and corresponding immunogenicity assessment for the evaluable PK population (data not shown for brevity). Short unstructured case descriptions were also provided, within the MAH response text, for each of the five patients implicated. Anti-drug antibodies (ADAs) testing was performed using validated instruments and methodology, which, in all, appeared to comply with pertinent guidance.

As previously reported, 109 subjects entered the 5-year extension (31 subjects in the 2-5 age cohort and 78 in the 6-17 age cohort). Overall, only 5 of these subjects tested positive in the ADAs assay at any point during the 5-year follow-up extension period in Study IM101301, 3 in the 2-5 age cohort and 2 in the 6-17 age cohort. In both cohorts, none of the samples analysed were positive for NAb. Firm conclusions on any possible associations with the safety data available cannot be made, because of the small numbers overall and consequently in the two age cohorts. It is also noted that PK assessments were not an objective for the 5-year follow-up period and impact of ADA on PK could not be evaluated.

In conclusion, the MAH has with due diligence provided and discussed the immunogenicity results available from the 5-year follow-up extension period of study IM101301. Testing was performed using validated instruments and methodology and appeared to comply with pertinent guidance. It can overall be agreed with the MAH that during the 5-year extension period of the study IM101301 testing positive for ADA was infrequent and transient and none of the samples analysed were positive for NAb. Acknowledging the small numbers overall and namely in the two age cohorts, there appeared to be no association between positive ADA response and the safety data available. The immunogenicity results were broadly similar for both age cohorts. In all, again acknowledging the limitations of the data, these results from the 5-year follow-up extension period were consistent with the results of the previously reported ADA testing during the initial 2-year reporting period of the study IM101301 of paediatric JIA patients ages 2-17 on SC abatacept treatment.

Conclusion

Issue resolved

Question 3

The MAH is requested to fill in the Annex 1

The MAH Response

The completed Annex 1 is provided as an attachment to the Cover Letter of this response.

Assessment of the MAH Response

As stated, it is acknowledged that the requested completed Annex 1 has been provided as an attachment to the Cover Letter of the MAH response.

Conclusion

Issue resolved

Annex 1. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Product Name: **ORENCIA** Active substance: **abatacept**

Non clinical studies

Study title	Study number	Date of completion	Date of submission of final study report
NA	NA	NA	NA

Clinical studies

Study title	Study number	Date of completion	Date of submission of final study report
Pharmacokinetic modelling and simulation study Exposure-Efficacy Response of Intravenously Administered Abatacept and Dose Selection for Subcutaneously Administered Abatacept in Patients with Juvenile Idiopathic Arthritis Data used from Period A of study IM101033 was used *(A Phase III, Multi-Center, Multi-National, Randomized, Withdrawal Study to Evaluate the Safety and Efficacy of BMS-188667 in Children and Adolescents with Active Polyarticular Juvenile Rheumatoid Arthritis (JRA))*	Data used from IM101033 Study 2, part of PIP: EMEA-000118-PIP02-10-M03	28-April-2012	14-Dec-2012 as part of EMEA-C1-000118-PIP02-10-M01
A Phase 3 Multi-center, Open-Label Study 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 (DMARDs)	IM101301 Study 3, part of PIP: EMEA-000118-PIP02-10-M03	Short term period 12-Mar-2015 Long term extension 01-Feb-2023	29-Nov-2024 eCTD 0351