16 November 2012
EMA/763437/2012
Committee for Medicinal Products for Human Use (CHMP)

Orencia

(abatacept)

Procedure No. EMEA/H/C/000701/A46/039

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

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

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Administrative information

Invented name of the medicinal product:	Orencia
INN (or common name) of the active substance(s):	abatacept
MAH:	Bristol-Myers Squibb Pharma EEIG
Currently approved Indication(s)	Rheumatoid arthritis: Orencia in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or a tumour necrosis factor (TNF)-alpha inhibitor. A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with abatacept and methotrexate. Polyarticular juvenile idiopathic arthritis: 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 DMARDs including at least one TNF inhibitor.
Pharmaco-therapeutic group (ATC Code):	L04AA24
Pharmaceutical form(s) and strength(s):	powder for concentrate for solution for infusion 250 mg
Rapporteur:	**Name** Janne Komi Tel: +358 50 4141 637 Email: janne.komi@fimea.fi

Introduction

On 22nd of May, the MAH submitted a completed paediatric study for Orencia, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Orencia and that no consequential regulatory action is required.

Scientific discussion

Information on the development program

The active substance of Orencia, abatacept, is a fusion protein that consists of the extracellular domain of human CTLA-4 linked to a modified Fc portion of human IgG1. Abatacept reversibly binds to CD 80/86 on antigen presenting cells via its CTLA-4 portion preventing the interaction of CD 80/86 with CD28 on T cells and thus inhibiting full T-cell activation. ORENCIA is available as a 250 mg powder for concentrate for solution for infusion and is to be administered intravenously.

Orencia was initially approved in the EU in 2007 for the treatment of moderate to severe active rheumatoid arthritis in adult patients. The indication was extended in 2010 to include the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years of age and older. The JIA indication was mainly based on Study IM101033: Phase 3, randomized, double-blind, placebo-controlled, multi-national study in children and adolescents (6 to 17 years age) with JIA with a polyarticular course and who had previously failed at least 1 or more DMARDs, including biologic therapy. This study included three periods: A 4-month Lead-in Phase (Period A), a 6-month Double-blind Phase (Period B), and a 5-year Open-label Extension Phase (Period C). At the time of the approval of the JIA indication, Period C was ongoing. The current submission includes the final study report of Period C, providing long-term efficacy and safety data on abatacept treatment in JIA patients.

The MAH stated that the *Phase 3 multi-center, multi-national, randomized, withdrawal study to evaluate the safety and efficacy of abatacept in children and adolescents with active polyarticular juvenile rheumatoid arthritis - Addendum (Open-label Extension Phase [Period C]) (IM101033)* is a stand-alone study.

Information on the pharmaceutical formulation used in the study

The approved pharmaceutical form has been used in the study (ORENCIA 250 mg powder for concentrate for solution for infusion).

Batch numbers of abatacept for injection (250 mg/vial) used during Period C were: 3A64967, 3D66861, 3E75222, 3H65127, 3M60521, 4A75209, 4A79855, 4B80782, 4J88292, 4J88331, 6M11713, 6M16129, 4K84065, 4K88013, 4K88014, 5C10527, 5D05853, 5D05859, 5M08057, 6B21229, 6B21243, 6C11369, 6M16130, 7A26251, 7E25701, 6D16144, 6D20932, 6D20933, 6D20934, 6F16599, 6F16600, 6J14996, 6M11556, 7E27539 7K34655, 7K34659, 7L29720, 7M16254, 7M19525, 8A38476, 8B37768, 8B41044, 8H33138 and 8M25229.

Clinical aspects

1. Introduction

The MAH submitted a final report for:

- Study IM101033 (Open-label Extension Phase [Period C]), Addendum 3 (Final Report): A Phase 3 multi-center, multi-national, randomized, withdrawal study to evaluate the safety and efficacy of abatacept in children and adolescents with active polyarticular juvenile rheumatoid arthritis

2. Clinical study

Description

Study IM101033 included a 4-month, open-label, lead-in phase (Period A) during which response to abatacept in children and adolescents with active polyarticular JIA was demonstrated; a 6-month, randomized, double-blind, placebo-controlled phase (Period B) in which the clinical efficacy of abatacept was assessed in those subjects with an initial response in the lead-in phase; and an open-label extension phase (Period C) during which the safety, tolerability, and continued clinical activity of long-term abatacept were evaluated. Previous CSRs have provided results for the lead-in phase Period A and double-blind phase Period B and for Period C up to Month 21 (up to 7 May 2008).

The report summarizes efficacy, safety and immunogenicity data from the start of open-label dosing in Period C through the end of treatment and for 6 months of follow up after discontinuation of treatment.

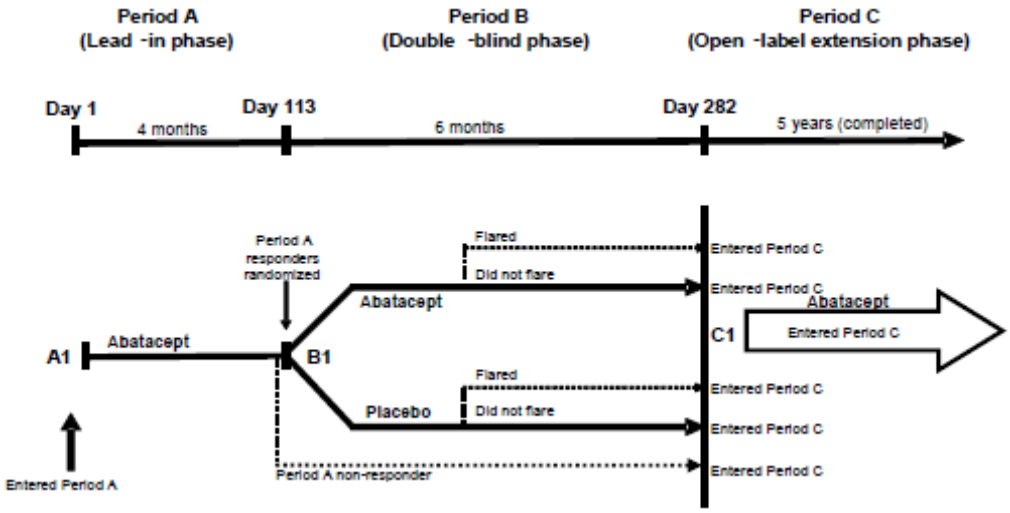
Study Period C Initiation Date: 23-Jul-2004

Study Period C Completion Date: 22-Nov-2011

Methods

- Objective(s)
  - The primary objective of the long-term extension phase was to assess the safety and tolerability of abatacept during long-term administration in subjects with active juvenile rheumatoid arthritis (JRA)/JIA
  - The secondary objective of Period C was to assess the efficacy and immunogenicity of abatacept during long-term treatment
  - The exploratory objective for Period C was to assess growth and development, as measured by changes in height, weight, and Tanner stage. In addition, a substudy was implemented to determine if treatment with abatacept or the development of immunogenicity influences the development and/or titers of autoimmune biomarkers (ie, anti-thyroid peroxidase (TPO), anti-glutamic acid decarboxylase (GAD) and thyroid stimulating hormone (TSH)), and the eventual development of other autoimmune diseases
- Study design
  - Open-label treatment with abatacept (Period C, see *Figure 1*).

Figure 1: IM101033 Study Design



- Study population /Sample size:
  - Subjects between the ages of 6 – 17 years at entry into the study, having a diagnosis of either JRA (with pauciarticular, polyarticular, or systemic disease onset and polyarticular course) or JIA (extended oligoarticular, polyarticular [rheumatoid factor, RF, +], polyarticular [RF-], or systemic disease onset and polyarticular course), who had an insufficient response or intolerance to at least 1 disease modifying anti-rheumatic drug (DMARD), and who completed Period A on abatacept without an adequate response, completed Period B on abatacept or placebo without flare, or discontinued Period B on abatacept or placebo due to flare.
  - 153 subjects were enrolled and treated in Period C, including 36 non-responders in Period A and 117 randomized and treated in Period B
- Treatments
  - Subjects received abatacept 10 mg/kg by intravenous (IV) infusion (maximum dose of 1000 mg administered to subjects over 100 kg) at monthly intervals
- Outcomes/endpoints
  - Efficacy: Control of arthritis during Period C was measured by the American College of Rheumatology (ACR) Pediatric (ACRP) response rates. The ACRP30 response criteria were defined as a ≥ 30% improvement over baseline (Day A1) in at least 3 of the 6 JRA/JIA core set variables and a worsening of 30% or more in not more than 1 of the 6 JRA/JIA core set variables. ACRP 50, 70, and 90 responses were defined similarly with 50%, 70%, and 90% improvements required, respectively.
  - Safety: Adverse event (AE) and serious adverse event (SAE), discontinuations due to AEs, changes in laboratory measures, vital signs, and body weight and height
  - Pharmacodynamics: Changes in rheumatoid factor (RF), interleukin-6 [IL-6], soluble interleukin-2 receptor (sIL-2R), tumor necrosis factor-alpha (TNF-α), E-selectin, matrix metalloproteinase-3 [MMP-3], and soluble intercellular adhesion molecule-1 (sICAM-1)
  - Immunogenicity: The number (and percentage) of seropositive subjects was provided by antibody specificity and overall, including frequencies by visit, overall on-treatment, overall post-treatment and overall (on-treatment and post-treatment combined) for Period C for all Period C efficacy cohorts separately and combined. On-treatment incidence rates of

immunogenicity per 100 patient-years (p-y) and associated 95% Poisson confidence intervals were calculated overall and by yearly intervals for Period C. The number (and percentage) of subjects with persistent on-treatment responses (positive responses on 2, 3, 4, >4 consecutive on-treatment visits within the same antibody-reactivity) during Period C was summarized.

  - Autoantibody substudy: An exploratory substudy was performed at selected sites in approximately 60 subjects to collect autoimmune biomarker blood samples coincident with collection of immunogenicity samples. This substudy was to explore biomarkers associated with the development of diabetes and thyroiditis to assess if treatment with abatacept or development of immunogenicity influences development and/or titers of these biomarkers and eventual development of auto-immune disease

- Statistical Methods
  - All data for Period C were analyzed descriptively using as-observed data. Efficacy and pharmacodynamic (PD) analyses were performed using all data for cohorts defined by subject's treatment group assignment in Period B (abatacept 10 mg/kg = Period B-Abatacept cohort; or placebo = Period B-Placebo cohort) or previous participation in the lead-in phase only (Period A Non-responder cohort)

Results

- Recruitment/ Number analysed: All of the 153 subjects entering Period C received treatment with open-label abatacept. A total of 45.1% of subjects (69) completed Period C.

Table 1: Disposition for Period C Treated Subjects (IM101033)

	Period A Non-responders	Period B-Abatacept	Period B-Placebo	Total
Subjects Entering Period C, n	36	58	59	153
Subjects Discontinued from Period C, n (%)	23 (63.9)	29 (50.0)	32 (54.2)	84 (54.9)
Death	0	0	1 (1.7)	1 (0.7)
Adverse Event	1 (2.8)	2 (3.4)	3 (5.1)	6 (3.9)
Lack of Efficacy	11 (30.6)	5 (8.6)	8 (13.6)	24 (15.7)
Lost to Follow-up	2 (5.6)	5 (8.6)	6 (10.2)	13 (8.5)
Withdrawal of Consent	4 (11.1)	6 (10.3)	0	10 (6.5)
Subject no longer meets study criteria	0	1 (1.7)	1 (1.7)	2 (1.3)
Poor/Non-compliance	0	2 (3.4)	2 (3.4)	4 (2.6)
Pregnancy	1 (2.8)	2 (3.4)	3 (5.1)	6 (3.9)
Other	4 (11.1)	6 (10.3)	8 (13.6)	18 (11.8)

  - The mean (SD) duration of exposure to abatacept in Period C was 48.2 (24.6) months (median [range] = 60.5 [1.9, 80.5] months). By cohort, the mean (SD) duration of exposure was 37.4 (27.0) months for the Period A-Non-responder group; 53.2 (21.0) months for the Period B-Abatacept group; and 50.0 (24.8) months for the Period B-Placebo group.
  - The mean (SD) total exposure across the entire study (Periods A, B, and C) was 53.6 (25.1) months, and by cohort 41.1 (27.0) months for the Period A-Non-responder group; 62.1 (20.9) months for the Period B-Abatacept group; and 52.9 (24.8) months for the Period B-Placebo group. Exposure for 43 subjects was at least 6 years.
  - The original protocol (25-Sep-2003) was amended 5 times. The amendments confirmed the duration of Period C (Amendment 1); lengthened the duration of study drug infusion to 60 minutes for study sites in France (Amendment 2); decreased the frequency of study

assessments beginning with Day C701 and disallowed the concomitant use of abatacept and another biologic therapy for RA (Amendment 3); implemented collection of biomarkers typically associated with diabetes and hypothyroidism to examine the potential relationship between abatacept treatment and the development of immunogenicity in influencing the onset of autoimmune disorders and discontinued all efficacy assessments beyond 5 years of open-label treatment with study drug. (Amendment 4); and terminated the study by December 2011 based on the fact that abatacept was commercially available to treat JRA in the IM101033 participating countries (Amendment 5). Seven administrative letters were implemented.

- Significant protocol violations included seven subjects with single incorrect dosing and two delays in signing the informed consent.

- Baseline data

Table 2: Baseline demographics and disease characteristics of all Period C subjects

Baseline Demographic and Disease Characteristics of Period C Treated Subjects (IM101033)

	Period A-Non-responder N = 36	Period B-Abatacept N = 58	Period B-Placebo N = 59	Total N = 153
Mean Age (years)	12.7	12.4	12.0	12.3
Gender (n, %)				
Male	13 (36.1)	17 (29.3)	17 (28.8)	47 (30.7)
Female	23 (63.9)	41 (70.7)	42 (71.2)	106 (69.3)
Race (n, %)				
White	23 (63.9)	44 (75.9)	46 (78.0)	113 (73.9)
Black	5 (13.9)	5 (8.6)	4 (6.8)	14 (9.2)
Asian	1 (2.8)	0	0	1 (0.7)
Native HI/Other Pacif	0	1 (1.7)	0	1 (0.7)
Other	7 (19.4)	8 (13.8)	9 (15.3)	24 (15.7)
Mean Duration of JIA (years)	4.8	3.8	4.0	4.1
Mean Active Joint Count	14.9	17.8	14.9	16.0

JIA: juvenile idiopathic arthritis; HI: Hawaiian; Pacif: Pacific Islander

- Efficacy results

  - At the end of Year 5, 97% (32/33) of subjects in the Period B-abatacept group and 86.7% (26/30) of Period B-Placebo treated subjects were ACRP 30 responders (see *Table 3*). In the Period A non-responder cohort, rates of ACRP responses gradually increased with continued long-term abatacept therapy (69.2% i.e. 9/13 meeting the ACRP 30 response criteria at DayC1765).

  - At the end of Year 5, 4/13 (30.8%), 17/33 (51.5%) and 11/30 (33.3%) in the Period A non-responder, Period B-abatacept, and Period B-placebo groups, respectively, achieved inactive disease (see *Table 3*).

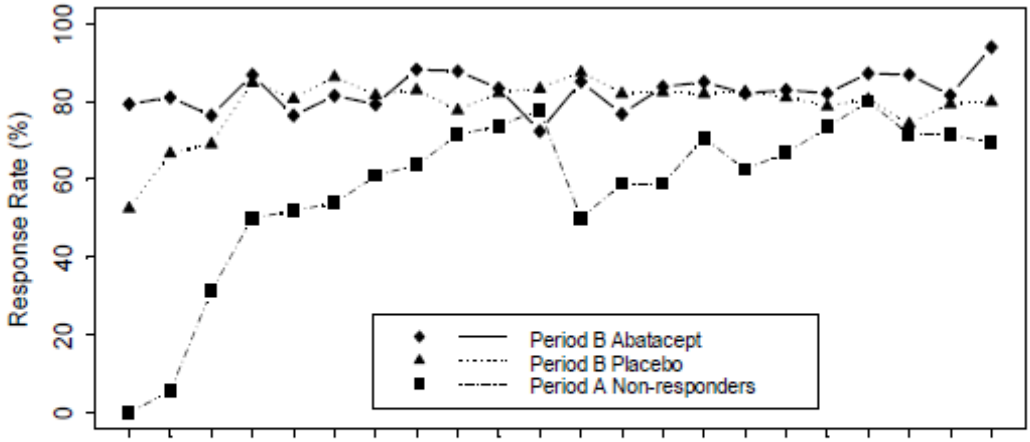
Table 3: Proportion of JIA Subjects with ACR (ESR) Response or Inactive Disease

	Period A Non-responders		Period B-Abatacept		Period B-Placebo	
	Day A113	Day C1765	Day B169	Day C1765	Day B169	Day C1765
No. of Subjects	36	13	58	33	59	30
ACR Pediatric 30 (ESR)	0	69.2%	84.5%	97.0%	67.8%	86.7%
ACR Pediatric 50 (ESR)	0	69.2%	79.3%	93.9%	52.5%	80.0%
ACR Pediatric 70 (ESR)	0	53.8%	55.2%	78.8%	30.5%	63.3%
ACR Pediatric 90 (ESR)	0	38.5%	41.4%	66.7%	15.3%	40.0%
Inactive Disease (ESR)	0	30.8%	31.0%	51.5%	10.2%	33.3%

ESR = erythrocyte sedimentation rate

- Data for ACRP50 response rates over time are shown in *Figure 2*. There is an abrupt decrease after C841 in Period A non-responders. According to the MAH, the raw data did not reveal any notable cause other than the fact that a relatively high proportion of these subjects marginally met ACRP50 criteria, such that any minor change could have impacted the entire (small) cohort, and the observed change in proportion was created by change in only four subjects.

Figure 2: ACR Pediatric 50 (ESR) Response Rates Over Time: All Period C Treated Subjects



Per B Aba (n)	58	58	55	53	55	54	53	51	49	48	47	47	43	43	40	39	41	39	39	38	38	33
Per B Pla (n)	59	57	55	53	52	51	49	47	45	45	42	40	39	40	39	40	37	33	36	35	34	30
Per A Non-resp (n)	36	36	32	28	27	26	23	22	21	19	18	18	17	17	17	16	15	15	15	14	14	13

- Subgroup analyses by age, by JIA disease subtype at diagnosis, by MTX use at entry and by addition of DMARDs did not reveal any clinically relevant differences. Subjects who did not have prior biologics had better response rates than those who had previously failed treatment with biologics.

- JRA/JIA Core Set Variables and Exploratory Efficacy Variables (CHQ, CSHQ, Parent Global Assessment of Pain, and Activity Limitation Questionnaire components) generally supported the long-term efficacy of abatacept.

- Safety results
  - Overall, 140 (91.5%) subjects reported adverse events (see *Table 4*). AEs were similar in type to those seen in adult subjects treated with abatacept. The most common SOC was Infections or infestations (78.4% of subjects) with nasopharyngitis and upper respiratory tract infection being the most frequently reported ones. The incidence rate of infections during Period C was 64.72 / 100 p-y and cumulatively (all Period A treated subjects) 83.80 / 100 p-y. The incidence rate had a decreasing tendency during period C.
  - Serious adverse events (SAEs) were reported for 30 (19.6%) subjects. With the exception of arthritis and arthralgia, no individual SAE was reported by more than 2 subjects in any cohort. The incidence rate of serious adverse events including infections was stable over the 5 year period. 9 (5.9%) SAEs were considered related to study treatment by the investigator (herpes zoster; hypersensitivity to abatacept; fibroadenoma of the breast; temporal lobe epilepsy and multiple sclerosis; appendicitis; tooth abscess, varicella/encephalitis; bacterial arthritis; and limb abscess). One death (fatal motorcycle accident) was reported. Serious infections were reported in 10 (6.5%) subjects and in 6 subjects they were assessed as related to study treatment (appendicitis, impetigo, herpes zoster, varicella, limb abscess and bacterial arthritis).
  - 6 subjects (3.9%) discontinued due to an AE (urticaria and bronchospasm; worsening of vitiligo; temporal lobe epilepsy and multiple sclerosis; appendicitis; skin lesions; and bacterial arthritis). Three of these events were SAEs (temporal lobe epilepsy and multiple sclerosis; appendicitis; and bacterial arthritis).

Table 4: Safety Results for Period C Treated Subjects (IM101033)

	Period A Non-responders(N=36)	Period B-Abatacept N=58)	Period B-Placebo (N=59)	Total (N=153)
Deaths, n (%)	0	0	1 (1.7)	1(0.7)
Serious Adverse Events, n (%)	9 (25.0)	9 (15.5)	12 (20.3)	30 (19.6)
Adverse Events,(AE) n (%)	31 (86.1)	55 (94.8)	54 (91.5)	140 (91.5)
Discontinuation Due to AE, n (%)	1 (2.8)	2 (3.4)	3 (5.1)	6 (3.9)

  - AEs of special interest: Specific events within the categories of autoimmune disorders, malignancies, and infusional events were prospectively identified and classified as AEs of special interest.

    Seven (7) subjects (4.6%) had pre-specified autoimmune disorders reported during Period C (worsening vitiligo in a subject who had a history of this condition prior to study entry; cutaneous vasculitis which resolved while on continued abatacept treatment; multiple sclerosis which was serious and resulted in treatment discontinuation; psoriasis, uveitis, type I diabetes and Raynaud's phenomenon). The incidence rate of autoimmune events was stable or decreasing over time.

    No malignant neoplasms were reported during Period C.

Acute infusional AEs (reported within 1 hour of the start of study drug infusion) were reported in 6 (3.9%) subjects, including two subjects with hypersensitivity. One acute infusional AE was serious (hypersensitivity) and one was severe (bronchospasm and urticaria) resulting in study drug discontinuation. There was no increase in the frequency of acute infusional AEs following the re-introduction of abatacept during Period C.

Peri-infusional AEs (occurring within 24 hours after the start of the infusion) were reported for 22 (14.4%) of subjects. The most common ones were dizziness (n = 4, 2.6%), nausea (n = 4, 2.6%) and vomiting (n = 4, 2.6%). One event of arthralgia was considered serious and very severe.

- Laboratory data did not indicate any specific safety concerns. The most frequently occurring marked abnormalities were elevated blood in the urine (47.7%), high urine white blood cells (41.9%) and red blood cells (73.5%), elevated eosinophils (32.7%), high urine protein (22.9%), high creatinine (23.5%), and low lymphocytes (13.7%). Increases from baseline in eosinophil counts were observed over time. For ANA, 85 subjects had data at baseline (Day A1) and at the last visit of Period C. 5 subjects seroconverted positive and 6 of the 24 subjects who were positive at baseline turned negative at the last visit. For anti-dsDNA, 83 subjects had data at baseline and at the last visit of Period C. 2 subjects seroconverted positive and each of the 11 subjects who were positive at baseline turned negative at the final visit.
- No safety issues emerged from the evaluation of vital signs, Tanner stage and physical measurements.
- PD biomarkers showed mean decreases throughout the collection period of up to the end of year 2.
- Auto-antibody substudy was initiated after year 4 (amendment finalized in April 2010) and included 55 subjects. Overall, results were inconclusive due to outside of stability baseline samples and collection of few on-treatment samples. Three subjects with autoimmune events (cutaneous vasculitis, type 1 diabetes, Raynaud´s disease) in Period C had samples obtained for determination of auto-antibodies, and two of these subjects had positive on-treatment and/or post-treatment samples for anti-GAD and anti-TPO.
- Immunogenicity: 26 of 150 evaluable subjects (17.3%) developed antibodies to abatacept (anti-abatacept or anti-CTLA4) at least once during Period C, including 7 newly positive subjects since the previous data lock of May 2008. 19/148 (12.8 %) subjects were positive during treatment and of these, 11 (7.4%) subjects were seropositive at isolated (non-consecutive) visits. The on-treatment incidence rate (per 100 p-y) did not increase during the study (see *Table 5*). The antibody titers were generally low and transient and their presence did not correlate with adverse events representative of immune mediated responses. 9.1% (3/33) of those not receiving methotrexate versus 11.1 % (13/117) of those receiving methotrexate developed anti-CTLA4 antibodies. Thus, concomitant use of MTX did not have a significant impact on the immunogenicity.

Table 5: Overall and Yearly Incidence Rates of Positive Abatacept-induced Antibody Response On-treatment (ELISA Method) During Period C: Period C Immunogenicity Population

Treatment Group: All Combined

Period	Specificity	Seropositive Subjects (%)	Exposure (person-years)	Incidence Rate (a)	Poisson 95% CI
Overall	ANTI-ABATACEPT	8 (5.76)	529	1.51	(0.65, 2.98)
	ANTI-CTLA4-T	12 (8.11)	557	2.15	(1.11, 3.76)
	Total	19 (12.84)	536	3.54	(2.13, 5.53)
Days 2 - 360	ANTI-ABATACEPT	1 (0.72)	130	0.77	(0.02, 4.30)
	ANTI-CTLA4-T	9 (6.08)	132	6.80	(3.11, 12.90)
	Total	9 (6.08)	132	6.80	(3.11, 12.90)
Days 361 - 720	ANTI-ABATACEPT	5 (4.00)	109	4.58	(1.49, 10.69)
	ANTI-CTLA4-T	2 (1.89)	113	1.77	(0.21, 6.40)
	Total	7 (5.56)	109	6.42	(2.58, 13.22)
Days 721 - 1080	ANTI-ABATACEPT	0	93	0.00	N/A
	ANTI-CTLA4-T	1 (0.93)	98	1.02	(0.03, 5.69)
	Total	1 (0.98)	94	1.06	(0.03, 5.93)
Days 1081 - 1440	ANTI-ABATACEPT	2 (2.22)	83	2.42	(0.29, 8.74)
	ANTI-CTLA4-T	0	87	0.00	N/A
	Total	2 (2.22)	83	2.42	(0.29, 8.74)
Days 1441 - 1800	ANTI-ABATACEPT	0	73	0.00	N/A
	ANTI-CTLA4-T	0	79	0.00	N/A
	Total	0	73	0.00	N/A
Days 1801 - last	ANTI-ABATACEPT	0	40	0.00	N/A
	ANTI-CTLA4-T	0	47	0.00	N/A
	Total	0	44	0.00	N/A

(a) Incidence Rate = Number of Subjects with a positive immunogenicity response during the on-treatment period/Overall total exposure expressed in 100 person years for subjects with on-treatment measurements. Subjects with a positive immunogenicity response have their exposure censored at the time of the first on-treatment occurrence.

For subjects who discontinued or completed the study, days of exposure per subject= (date of last abatacept dose - date of first abatacept dose) + 42.
Exposure (person-years) = the sum of the days of exposure over all subjects, divided by 365.25.

Similar proportions developed anti-abatacept antibodies during treatment (19/148; 12.8%) or after the final dose of abatacept (12/115; 10.4%). Post-treatment immunogenicity was highest at Day 113 post-treatment (18.2 %) and decreased thereafter up to the final assessment at Day 169 (13.0 %). In those subjects who switched to commercial abatacept (i.e, the marketed product) after study drug discontinuation, the seroconversion rate at Day 169 post study drug treatment was 6.7% (one of 15 subjects) versus 16.1 % in those who discontinued abatacept permanently.

Neutralizing antibodies were detected in 3 of 6 evaluable subjects.

3. Discussion on clinical aspects

Period C of Study IM101033 provides long-term efficacy and safety data on abatacept treatment in JIA patients. The mean duration of exposure to abatacept in Period C was 48.2 months (4 years), and the mean duration of exposure across the entire Study IM101033 (Periods A, B, and C) was 53.6 months (4.5 years).

Efficacy of abatacept remained stable in those subjects continuing the study. At the end of Period C (Day C1765), ACR Pediatric 30 response to abatacept was maintained in 97 % of subjects with continuous abatacept treatment (Period B-Abatacept; N=33). Among those treated with placebo during Period B, 68 % were still in remission based on ACR Pediatric 30 response at the end of Period B (DayB169), and the response rate increased to 87 % by Day C1765. Nine (69.2%) of the total of 13 Period A-Non-responders reached ACR Pediatric 30 at DayC1765. Thus, the primary efficacy endpoint was reached in some subjects only following continuous therapy of over 4 months (i.e. after the 4-month Period A).

The rate of discontinuation during Period C was rather high. Among the initial responders of Period A, 50 % (29/58) of the Period B-Abatacept subjects and 54.2 % (32/59) of the Period B-Placebo subjects discontinued. Relatively few, however, discontinued due to lack of efficacy (8.6 % and 13.6 %, respectively). Among the Period A-Non-responders, 64% (23/36) discontinued from Period C and the lack of efficacy was the predominant reason for discontinuation (11/36 subjects, 30.6%), as expected.

Safety of long-term abatacept treatment in JIA patients was consistent with that of adults with RA. The most common SOC was Infections or infestations whose incidence rate decreased over time. The rate of acute infusional and peri-infusional AEs was stable. Importantly, no malignancies were reported during Period C.

As pointed out upon extension of the indication to JIA, the overall immunogenicity (including on-treatment and post-treatment immunogenicity) of abatacept in paediatric JIA patients was higher than that in adult RA patients. The on-treatment immunogenicity (12.8 %) remained stable while the post-treatment immunogenicity was clearly less than that reported for patients in Period B who were randomized to placebo (10.4 % vs. 40.7 %, respectively). This is partly due to the fact that several subjects who discontinued the study were subsequently switched to commercial Orencia, i.e. the samples drawn do not represent real post-treatment values. Based on the immunogenicity data currently available, it can be concluded that anti-abatacept antibody response is rather infrequent, mostly transient and does not appear to have an impact of the efficacy and safety of abatacept treatment.

Abatacept SmPC contains data on paediatric JIA subjects in Sections 4.2, 4.4, 4.8 and 5.1. The wording regarding the currently finalized Study IM101033 should be updated in Section 4.8 (under the subheading: *Adverse reactions in paediatric patients with polyarticular juvenile idiopathic arthritis / Description of selected adverse reactions*) and Section 5.1 (under the subheading: *Paediatric population in polyarticular juvenile idiopathic arthritis*).

Rapporteur's overall conclusion and recommendation

Overall conclusion

Based on long-term efficacy and safety results of Study IM101033, benefit-risk of abatacept in children and adolescent patients with JIA remains favourable.

Recommendation

☒ **Fulfilled** –

Type II variation to be requested from the MAH by October 2012 to amend the product information as follows:

The wording regarding the currently finalized Study IM101033 should be updated in SmPC Sections 4.8 and 5.1.

Additional clarifications requested

N/A