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Human Medicines Evaluation 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/P46/058

Note

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

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1. Introduction

On 23 November 2018, the MAH submitted a clinical study report for a completed clinical study (study number IM101291) for Orencia. In principle, the completed study was not a paediatric study, but since one adolescent (17-year-old) subject had been enrolled into the study, the clinical study report was submitted in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

A clinical expert overview has also been provided. It briefly summarises the results from the overall population, with a focus on the results from the one adolescent subject.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study number IM101291, entitled "A Phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of BMS-188667 (abatacept) or placebo on a background of mycophenolate mofetil (MMF) and corticosteroids in subjects with active class III or IV lupus nephritis", is a stand-alone study.

According to the MAH, the study is not considered a paediatric study (only one adolescent subject participated in the study) and the lupus nephritis development program has been stopped. A line listing of all the studies included in the development program was therefore not considered relevant and was not included in this submission.

The MAH stated that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for Orencia and therefore do not require further regulatory action to be taken on the marketing authorisation for this product.

2.2. Information on the pharmaceutical formulation used in the study

According to the MAH, the formulation of intravenous (IV) abatacept that is currently marketed for use in adult and paediatric subjects with JIA/RA was used in study IM101291. The formulation is a sterile, white, preservative-free, lyophilized powder for "concentrate for solution" IV use. A silicone-free syringe was used to reconstitute the lyophilized powder and for transfer to the infusion bag/bottle.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final abbreviated clinical study report for study IM101291, entitled "A Phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of BMS-188667 (abatacept) or placebo on a background of mycophenolate mofetil (MMF) and corticosteroids in subjects with active class III or IV lupus nephritis." In principle, the study was intended to enrol subjects of at least 18 years of age; however, one adolescent subject (17 years old) was randomised and treated.

2.3.2. Clinical study

Study IM101291

Description

Study IM101291 was a Phase 3 randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of abatacept on a background of mycophenolate mofetil (MMF) and corticosteroids in subjects with active class III or IV lupus nephritis.

Methods

Objective(s)

The primary objective of the study was to compare the proportion of subjects with Complete Renal Response (CRR) of lupus glomerulonephritis at Day 365 following 1 year treatment with abatacept or placebo administered on a background of MMF and corticosteroids.

Secondary objectives included other assessments of changes in disease activity / treatment response, clinical and laboratory assessments for safety and tolerability evaluation, as well as pharmacokinetic and immunogenicity assessments.

Study design

The study was a randomised, double-blind, placebo-controlled Phase 3 study. It comprised a screening period, a 104-week double-blind treatment period, an optional 52 week long-term extension (LTE) period, a maintenance phase extension (beginning on Day 1094 for subjects who were clinically stable and did not require use of alternative therapy to manage active lupus nephritis), and a 6-month follow up period.

Study population /Sample size

According to the main eligibility criteria defined in the study protocol, men or women (not nursing or pregnant) who are at least 18 years old, have systemic lupus erythematosus (SLE) based on American College of Rheumatology criteria and have active Class III or IV lupus glomerulonephritis documented by renal biopsy within 12 months of enrolment, were to be enrolled into the study. At least approximately 40% of subjects were to have nephrotic levels of proteinuria at screening, defined as a urine protein/creatinine ratio (UPCR) of 3 mg/mg or above.

The study was planned to enrol 400 subjects, 200 subjects per treatment group.

Treatments

Study drug was administered IV on Days 1, 15, 29 and every 28 days thereafter.

- For subjects randomised to abatacept, the initial 4 doses were 30 mg/kg. After Day 57, the dose of abatacept was weight tiered approximating 10 mg/kg; subjects weighing < 60 kg received 500 mg, subjects weighing 60 to 100 kg received 750 mg, and subjects weighing > 100 kg received 1 g.
- Subjects randomised to placebo received dextrose 5% in water [D5W]) or normal saline [NS]).
- Investigational sites were responsible for providing the D5W or NS used for reconstitution and dilution.

- On Day 897 of the LTE, at the investigator's discretion and subject's preference, subjects could have been offered to switch to receive abatacept 125 mg / placebo via subcutaneous injection.

Treatment with MMF (supplied as 500 mg tablets for oral administration; stable dose throughout), and prednisone or prednisone equivalent oral tablets (on a defined tapering schedule), was given throughout the study along with the study medication.

Outcomes/endpoints

The primary endpoint of the study was the proportion of nephrotic subjects with complete renal response (CRR) of lupus glomerulonephritis. CRR was defined as meeting all of the following criteria:

(i) Renal function: estimated glomerular filtration rate (GFR) normal or no less than 85% of baseline value;

(ii) Proteinuria: UPCR less than 0.5 mg/mg;

(iii) Urine sediment: no cellular casts;

(iv) Corticosteroid dose: daily corticosteroid dose equal to or less than 10 mg prednisone or prednisone equivalent for at least 28 days prior to assessment.

Statistical Methods

The primary analysis was carried out after all subjects had completed 52 weeks of double-blind treatment (Day 365) or had discontinued prematurely. The primary comparison of proportion in CRR at Day 365 between the abatacept and placebo groups was assessed using a logistic regression model. A hierarchical approach for statistical testing was to be used for testing treatment group comparisons for key secondary endpoints, provided that the primary efficacy comparison was statistically significant.

Assessor's comment

The study design seems straightforward and comprises no unusual features. For purposes of assessment from the perspective of Article 46, the overall relevance of the study is very limited, as it intended to enrol an adult-only population.

Results

Recruitment/ Number analysed

In total, 406 subjects at 125 sites worldwide were enrolled into the study. Of these, 405 subjects were randomised and treated: 202 subjects into the abatacept group, and 203 subjects into the placebo group. Of particular note for the current assessment, 1 subject randomised into the abatacept group was a 17-year-old Caucasian male weighing 60 kg.

Baseline data

In the overall population, mean age was 33 (SD 11) years, and 89% of the subjects were female. The 405 randomised and treated subjects had been diagnosed with lupus nephritis (LN) for an average of approximately 3 years, and the average time of their current LN episode was approximately 3.5 months. Eighty-eight % of the subjects were receiving an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker (ACEi/ARB) at the time of randomisation. The mean UPCR value at screening was 3.78 mg/mg, and according to the renal biopsy information obtained within

12 months of screening, the majority of subjects had Class IV active proliferative glomerulonephritis (73% of subjects in either Class IV only or Class IV and V).

At the time of randomisation, the 17-year-old adolescent subject [BG1]had been diagnosed with LN for 1 month and was receiving an ACEi/ARB. At screening, his UPCR was 1.6 mg/mg and his estimated glomerular filtration rate (eGFR) was 143.9 mL/min/1.73m^2. Results of the renal biopsy showed Class III focal glomerulonephritis.

Efficacy results

In the overall population, there was no statistically significant difference between the treatment groups in the proportion of subjects with a CRR at Day 365, and the study thus did not meet its primary efficacy endpoint. The odds ratio, based on an adjusted logistic regression analysis comparing the abatacept and placebo groups, was 1.08 (95% CI: 0.7077, 1.6421; p-value = 0.7264).

In accordance with the hierarchical testing approach, further formal statistical testing for the key secondary endpoints was not appropriate, as the difference between treatment groups in the primary endpoint was not statistically significant. Overall, results for the other efficacy endpoints were in agreement with those for the primary endpoint in not showing a difference between the abatacept and placebo groups. Based on the observed pattern of efficacy results not showing differences between the treatment groups, study IM101291 was terminated prematurely by the MAH.

The subject was in partial response (PR) on Study Day 113 and 197 and reached CRR on Study Day 225. His UPRC decreased during the study, and was 0.13 mg/mg at Day 365.

Safety results

In the overall study population, mean (SD) duration of treatment during the first year of the double-blind treatment period (i.e. until the time point for the primary analysis) was 326 (92) days in the abatacept group and 330 (82) days in the placebo group. As seen in Table 1, approximately 23% of subjects in the abatacept group and approximately 21% of subjects in the placebo group discontinued the study before the time point for the primary analysis was reached, an adverse event (AE) being the most common reason for premature discontinuation in both groups (10% in the abatacept group and 8% in the placebo group).

Table 1. Subject disposition - year 1 of double-blind period - all randomised and treated subjects

	Number (%) of Subjects		
	Abatacept IV N = 202	Placebo IV N = 203	Total N = 405
NUMBER DISCONTINUED	47 (23.3)	42 (20.7)	89 (22.0)
LACK OF EFFICACY	11 (5.4)	9 (4.4)	20 (4.9)
ADVERSE EVENT	20 (9.9)	17 (8.4)	37 (9.1)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	1 (0.5)	5 (2.5)	6 (1.5)
SUBJECT WITHDREW CONSENT	5 (2.5)	2 (1.0)	7 (1.7)
DEATH	1 (0.5)	1 (0.5)	2 (0.5)
LOST TO FOLLOW-UP	0	2 (1.0)	2 (0.5)
POOR/NON-COMPLIANCE	0	1 (0.5)	1 (0.2)
PREGNANCY	2 (1.0)	0	2 (0.5)
SUBJECT NO LONGER MEETS STUDY CRITERIA	6 (3.0)	2 (1.0)	8 (2.0)
ADMINISTRATIVE REASON BY SPONSOR	0	0	0
OTHER	1 (0.5)	3 (1.5)	4 (1.0)
NUMBER COMPLETED YEAR 1	155 (76.7)	161 (79.3)	316 (78.0)
NUMBER TREATED IN YEAR 2	153 (75.7)	160 (78.8)	313 (77.3)
NUMBER COMPLETED YEAR 1 AND DID NOT ENTER YEAR 2	2 (1.0)	1 (0.5)	3 (0.7)

During the first year of the double-blind treatment period, a total of 12 deaths were reported in the study; 7 in the abatacept group and 5 in the placebo group (Table 2). For 1 subject in each treatment group, the cause of death appeared to be related to the subject's underlying disease (acute kidney failure resulting in sudden death in an abatacept-treated subject, and lupus nephritis in a placebo-

treated subject). For 8 subjects (6 abatacept, 2 placebo), the cause of death was related to an infection. The remaining 2 subjects in the placebo group died as a result of respiratory events.

The number of subjects who experienced a Serious Adverse Event (SAE) during year 1 of the double-blind period, as well as the number of subjects who were discontinued from the double-blind treatment period during year 1 due to an AE or SAE, was higher in the abatacept group compared with the placebo group (Table 2).

Table 2. Adverse event summary - year 1 of double-blind period - all treated subjects

	Number (%) of Subjects	
	Abatacept IV N = 202	Placebo IV N = 203
DEATHs	7 (3.5)	5 (2.5)
SAEs	49 (24.3)	39 (19.2)
RELATED SAEs	26 (12.9)	18 (8.9)
DISCONTINUED DUE TO SAEs	15 (7.4)	11 (5.4)
AEs	188 (93.1)	194 (95.6)
RELATED AEs	95 (47.0)	82 (40.4)
DISCONTINUED DUE TO AEs	21 (10.4)	17 (8.4)

Includes data up to 56 days post last dose in Year 1 of the double-blind period or first dose of year 2 whichever occurs first, except deaths where all deaths that occurred in subjects not treated in year 2 are included.
SAEs include hospitalizations for elective surgical procedures.
Related AE or SAE defined as AE or SAE with Related or Missing relationship to study medication.

Infections were the most common SAEs in both treatment groups, and occurred more frequently in subjects receiving abatacept. The overall occurrence of AEs in the SOC, Infections and Infestations, was similar for the abatacept and placebo groups during year 1 of the double-blind period (74% and 72%, respectively); however, more subjects in the abatacept group had infections/infestations that were serious (14% in the abatacept group vs 10% in the placebo group) or resulted in treatment discontinuation (5% in the abatacept group vs 2% in the placebo group). The most common serious infection was pneumonia, occurring in 5% and 3% of subjects in the abatacept and placebo groups, respectively.

Infusion-related AEs were reported at comparable rates in both treatment groups, with no serious infusion-related AEs reported.

In the adolescent subject, an SAE of pneumonia was reported with onset on Day 54; the event was assessed as being of moderate intensity and related to study drug. The subject was treated with acetaminophen, piperacillin, and tazobactam. Cefixime was started on Day 57. The pneumonia resolved on Day 68. The subject reported 3 additional AEs during the study (Table 3).

Table 3. Adverse events in the adolescent subject during the cumulative study period

SUBJECT NUMBER (AGE/GENDER/RACE) TREATMENT GROUP	STUDY PERIOD ONSET DAY	ONSET DATE RESOLUTION DATE	DUR TYPE	SYSTEM ORGAN CLASS (SOC) PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
[redacted] (17/M/C) ABATACEPT IV	ST1NI29 54	12JUL2015 15JUL2015	3D SAE	# INFECTIONS AND INFESTATIONS PNEUMONIA PNEUMONIA	6 2	1 1
	ST1NI29 58	16JUL2015 26JUL2015	10D AE	INFECTIONS AND INFESTATIONS PNEUMONIA PNEUMONIA	6 2	1 1
	ST1NI85 90	17AUG2015 13MAR2017	574D AE	# INFECTIONS AND INFESTATIONS FUNGAL SKIN INFECTION CUTANEOUS MYCOSES	6 1	1 1
	ST1NI141 151	17OCT2015 24OCT2015	7D AE	# INFECTIONS AND INFESTATIONS BRONCHITIS BRONCHITIS	6 1	1 1
	LT1NI897 916	20NOV2017 20DEC2017	30D AE	INFECTIONS AND INFESTATIONS FUNGAL SKIN INFECTION CUTANEOUS MYCOSIS	6 1	1 1

# Indicates counted events during the cumulative period up to 56 days post last dose in the study.
Study Period ST1PI(n), ST2PI(n), LT1PI(n) / ST1NI(n), ST2NI(n), LT1NI(n): onset of AE within 24h / AE > 24h after infusion on planned study day n in ST1, ST2, LT study periods.

According to the MAH, no new or unusual safety signals were detected in this study.

Assessor's comment

As the study was prematurely terminated due to lack of efficacy and has not been submitted to support any indication claims, the efficacy data per se is of little relevance for the current assessment.

Infectious disorders were the most common adverse events reported in the study, with the majority of subjects in both treatment groups experiencing at least one infection-related adverse event during year 1. While the overall frequency was similar between the treatment groups, the number of serious infections and infections resulting in treatment discontinuation was higher in the abatacept group than in the placebo group. Considering the known safety profile of abatacept, this finding in itself is not unexpected, and the reported safety data overall does not seem to contain unusual or new safety signals requiring additional action.

From the perspective of Article 46, meaningful conclusions on the efficacy or safety of abatacept in the paediatric population in the studied indication cannot be made based on one single subject.

2.3.3. Discussion on clinical aspects

The current study does not seem to support the use of abatacept in the treatment of lupus nephritis, and no claims thereto are made by the MAH. In terms of paediatric use, the study was intended to enrol adult subjects, and no conclusions relevant to Article 46 can be made based on a single treated adolescent subject. Overall, the results of the study do not change the benefit-risk profile of abatacept in its currently approved indications for use.

3. Rapporteur's overall conclusion and recommendation

No conclusions can be drawn about the efficacy and safety of abatacept in paediatric lupus nephritis patients based on results in one single adolescent subject in this study. Moreover, based on the data reported for the overall study population in the study, there is no meaningful change in the general benefit-risk profile of abatacept in its currently approved indications for use. No changes to the current product information are warranted.

☒ Fulfilled:

No regulatory action required.

4. Additional clarification requested

NA