17 August 2023
EMA/338167/2023
Human Medicines Division

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

Benlysta

belimumab

Procedure no: EMEA/H/C/002015/P46/032

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	19/06/2023	19/06/2023	☐
☐	CHMP Rapporteur Assessment Report	24/07/2023	19/07/2023	☐
☐	CHMP members comments	07/08/2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	10/08/2023	n/a	☐
☒	CHMP adoption of conclusions	17/08/2023	17/08/2023	☐

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CRF	Case report form
CRO	Clinical Research Organization
EC	Ethics Committee
EDC	Electronic data capture
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practice
ICF	Informed consent form
ICH GCP	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use – Good Clinical Practices
IDM	Intensive drug monitoring
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Affairs
NSAID	Nonsteroidal Antiinflammatory Drug
PML	Progressive Multifocal Leukoencephalopathy
PT	Preferred term
SAE	Serious adverse event
SAS	Statistical Analysis System
SC	Subcutaneous
SLE	Systemic lupus erythematosus
SOC	System organ class
TB	Tuberculosis
TFL	Tables, Figures and Listings
TNF	Tumour necrosis factor
US	United states
V	Visit
WHO	World Health Organization

1. Introduction

On 18 May 2023, the MAH submitted a completed paediatric study for Benlysta, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that “An Observational Study to Evaluate the Safety of Belimumab in Chinese patients”, study number 213210 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Benlysta (IV formulation) is indicated as add-on therapy in patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy.

The recommended dose regimen for children aged 5 years and older is 10 mg/kg Benlysta on Days 0, 14 and 28, and at 4-week intervals thereafter.

Belimumab for injection (1) 400 mg/vial and (2) 120 mg/vial was administered in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study 213210, “An Observational Study to Evaluate the Safety of Belimumab in Chinese patients”

2.3.2. Clinical study

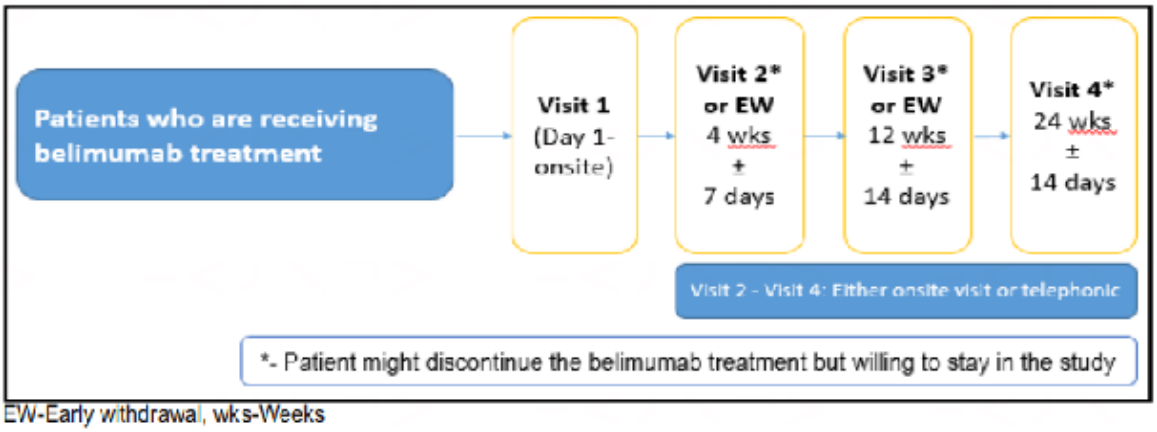
- Study 213210, “An Observational Study to Evaluate the Safety of Belimumab in Chinese patients”

Description

Study 213210 was a multicentre, observational study assessing the safety of belimumab in Chinese patients who have been prescribed belimumab for appropriate medical use based on investigator’s judgement.

Eligible patients were observed when they first start belimumab treatment, while the patients who had been previously treated with belimumab also were included. The investigator enrolled all eligible patients during the predefined surveillance period, unless the patient refuses to be enrolled. All patients were followed up by the treating investigator according to the clinical need. Investigators collected all data at routine clinical visits. The total duration of safety monitoring was 24 weeks.

Figure 1. Study design



EW-Early withdrawal, wks-Weeks

Methods

Study participants

Patients eligible for enrolment in the study were required to meet all the following criteria:

1. Patients who had been prescribed belimumab by investigators for their medical condition.
2. Capable of giving signed informed consent, which included compliance with the requirements and restrictions listed in the informed consent form (ICF) and in protocol.

Treatments

Belimumab for IV injection;(1) 400 mg/vial (2) 120 mg/vial.

Objective(s)

The objective of this study was to monitor and evaluate the real-world safety profile of belimumab treatment. The safety information of all adverse events (AEs) and serious adverse events (SAEs) occurring in the observation period were collected and analyzed.

Outcomes/endpoints

The following endpoints were included in the study

- The incidence of AEs through 24 weeks.
- The incidence of SAEs through 24 weeks.
- The occurrence of adverse reactions through 24 weeks.
- The incidence of adverse events of special interests (AESIs) through 24 weeks

Sample size

This was a real-world observational study. A descriptive approach was used and no formal hypothesis was planned for this study. All enrolled patients who were receiving belimumab treatment during this study period were included in the analysis.

Randomisation and blinding (masking)

Not applicable for an observational study.

Statistical Methods

A descriptive approach was used and no formal hypothesis was planned for this study.

All enrolled patients who were receiving belimumab treatment during this study period were included in the analysis. All analyses were performed by SAS version 9.4 or higher (SAS Institute, Cary, NC). Participants who prematurely withdrew from study were not be replaced.

Confidence intervals were use 95% confidence levels unless otherwise specified. Unless otherwise specified, continuous data were summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data were summarized as the number and percentage of participants in each category. For partial dates, if only the date was missing with complete year and month, the date were imputed using “15th”; if the month or year was partial then the date were set to missing. Missing relatedness data were handled using the worst-case scenario. Other missing data were not imputed and set to missing, otherwise specified.

Results

Participant flow

The patient disposition is showed below.

Table 1. Patient Disposition - Enrolled Population

	Belimumab n (%)
Enrolled Population	417*
Safety Population	417(100)
Subject Complete Study	409 (98.1)
Discontinued	8 (1.9)
Lost to follow-up	3 (0.7)
Study termination	0
Subject withdraw informed consent form	1 (0.2)
AE/SAE	0
Major protocol deviation	0
Death	0
COVID-19	0
Other	4 (1.0)

Note: The percentage is calculated based on the Enrolled Population.
*During the implementation of the project, Patient 18 at Site 014 withdrew the informed consent immediately after signing the informed consent form on the day of enrollment, but the ICF was signed by the site and the patient was recorded in EDC. The enrollment page and end of study page were filled in EDC, and other pages were annotated as ND, resulting in no information on whether the screening page was screened or not and this patient was not added at TFL. Therefore, 417 patients were enrolled shown in TFL and 418 patients were actually enrolled

Recruitment

The first patient was enrolled in this study on May 28, 2021, the last visit of last patient was completed on Nov 25, 2022, total 418 patients were enrolled.

Baseline data

Of the patients included in the study, the average age of patients was 35.5 years (SD: 11.92), the median age of patients was 33.0 years; 45 (10.8%) patients were male, 372 (89.2%) patients were female; 400 (95.9%) patients were Han nationality, and 17 (4.1%) patients were other nationalities; 400 patients had weight, height and BMI data, with an average weight of 56.73 kg (SD: 11.050), average height of patients was 160.05 cm (SD:6.928), average BMI of patients was 22.06 kg/m^2 (SD: 3.509) (Table 2).

A total of 14 (3.4%) were paediatric patients (< 18 years), and a total of 5 (1.2%) were geriatrics over 65 years old.

Table 2. Patient demographics

	Belimumab Naïve (N=109)	Belimumab Treated (N=308)	Total (N=417)
Age(years)			
n	109	308	417
Category, n (%)			
<18	9 (8.3)	5 (1.6)	14 (3.4)
18-64	100 (91.7)	298 (96.8)	398 (95.4)
>64	0	5 (1.6)	5 (1.2)
Missing	0	0	0
Mean (SD)	35.0 (12.76)	35.6 (11.63)	35.5 (11.92)
Median (Q1, Q3)	33.0 (25.0, 44.0)	33.0 (27.0, 44.0)	33.0 (27.0, 44.0)
Min, Max	12, 62	12, 74	12, 74
Sex，n (%)			
n	109	308	417
Male	12 (11.0)	33 (10.7)	45 (10.8)
Female	97 (89.0)	275 (89.3)	372 (89.2)
Missing	0	0	0
Race，n (%)			
n	109	308	417
Han	104 (95.4)	296 (96.1)	400 (95.9)
Other	5 (4.6)	12 (3.9)	17 (4.1)
Missing	0	0	0

The top 3 commonly used concomitant drugs by Anatomical Therapeutic Chemical (ATC) were corticosteroids for systemic use (387 patients, 92.8%), immunosuppressants (386 patients, 92.6%), and vitamins (311 patients, 74.6%). The top-three common concomitant medications were hydroxychloroquine sulfate (265 patients, 63.5%), calcium carbonate;vitamin D3 (214 patients, 51.3%) and mycophenolate mofetil (181 patients, 43.4%).

Number analysed

A total of 418 patients were enrolled. Of these, 417 patients were included in safety population (defined as all patients who received at least one dose and complete one follow-up visit).

Efficacy results

The study did not include any efficacy endpoints.

Safety results

Overview of adverse events

Of the 417 patients included in the safety population, a total of 158 (37.9%) patients experienced 336 AEs, of which 9 (2.2%) patients experienced 13 AEs leading to discontinuation/suspension of medication; 25 (6.0%) patients experienced 37 adverse drug reactions (ADRs); 22 (5.3%) patients experienced 35 SAEs, of which 4 (1.0%) patients experienced 5 SAEs related to the belimumab; 14 (3.4%) patients experienced 16 AESIs (Table 3).

Table 3. Overview of adverse events

	Total N=417	
	Number of events	Number of patients n (%)
Adverse Events(AEs)*	336	158 (37.9)
Adverse Events Leading to Discontinuation/Suspension of medication	13	9 (2.2)
Adverse events leading to dose reduction	0	0
Adverse Drug Reactions(ADRs)*	37	25 (6.0)
Serious Adverse Events(SAEs)*	35	22 (5.3)
SAEs related to drug	5	4 (1.0)
Fatal SAEs	0	0
Fatal SAEs related to treatment	0	0
AE of Special Interest	16	14 (3.4)
COVID-19 Related Adverse Events	0	0

Note: *AEs, ADRs, and SAEs in this study were collected independently, and there was no inclusion relationship among the three, i.e. an adverse event reported as SAE will be included only in SAEs, an non-serious ADR will be included only in ADRs, and a non-serious AE not reported as ADR will be included in AEs.

Classification and terms of AEs

Of the patients included in the safety population, the most frequently reported AEs by SOC were infections and infestations (14.6%), metabolism and nutrition disorders (6.7%), skin and subcutaneous tissue disorders (6.2%), and gastrointestinal disorders (5.8%). The most frequently reported (≥ 2% of patients) AEs by PT were upper respiratory tract infection (4.6%), hypokalemia (4.3%) and anemia (2.6%).

Of the patients included in the safety population, 125 (30.0%) patients had mild AE, 28 (6.7%) patients had moderate AE, and 5 (1.2%) patients had severe AE.

The 5 severe AEs experienced by 5 patients were radius fracture, negative thoughts, back pain, blood urea acid increased and platelet count decreased, respectively.

Adverse events related to drug

Of the patients included in the safety population, a total of 25 patients experienced 37 ADRs considered to be related to the drug. The ADRs by SOC were infections and infestations (44.0%), investigations (24.0%), skin and subcutaneous tissue disorders (16.0%), nervous system disorders (8.0%), immune system disorders (8.0%), general disorders and administration site conditions (8.0%), gastrointestinal disorders (8.0%), respiratory, thoracic and mediastinal disorders (4.0%). The most frequently reported ADRs by PT were urinary tract infection (20.0%), white blood cell count decreased (12.0%), upper respiratory tract infection (8.0%) and vaginal infection (8.0%).

Serious adverse events and deaths

There were no deaths in the study.

The most frequently reported SAEs by SOC were infections and infestations (1.2%) and nervous system disorders (1.0%). The SAEs by PT of pneumonia and rash were reported in 2 (0.5%) patient respectively, and the SAEs by PT of respiratory tract infection, gingivitis, ureteritis, postherpetic neuralgia, epilepsy, lupus encephalitis, cerebral thrombosis, adnexa uteri cyst, endometrial hyperplasia, uterine polyp, adenomyosis, uterine adhesion, white blood cell count decreased, platelet count decreased, neutrophil count decreased, back pain, systemic lupus erythematosus, pulmonary embolism, tachypnea, ovarian adenoma, benign pancreatic neoplasm, dermatitis contact, oedema, chest discomfort, lupus nephritis, hydronephrosis, ureteral calculus, ileus, and constrictive pericarditis was reported in 1 (0.2%) patient respectively.

Adverse events of special interest

The following AEs were considered adverse events of special interest (AESI):

- Infusion-related systemic and anaphylactic reactions
- Serious infections (including serious opportunistic infections and any event of tuberculosis [TB] or TB reactivation)
- Non-serious opportunistic infections
- Infections of interest: Hepatitis B, Hepatitis C, Herpes Zoster
- Progressive Multifocal Leukoencephalopathy (PML)
- Selected serious psychiatric events (Depression/Suicidal ideation, intent or behaviour)
- Malignancies (excluding non-melanoma skin cancers)
- Non-melanoma skin cancers
- All-cause mortality

Of the patients included in the safety population, AESIs were reported as the erythema, pruritus, urticaria, cold and heat intolerance, headache, hypersensitivity and drug hypersensitivity that related to infusion/injection systemic and anaphylactic reactions, herpes zoster that related to infections and infestations, negative thoughts and depression that related to selected serious psychiatric events. Total 16 AESIs were reported in 14 patients.

Adverse Events of Special Interest by Category are presented below.

Table 4. Adverse Events of Special Interest by Category – Safety Population

	Belimumab Naive N=109		Belimumab Treated N=308		Total N=417	
Category	Number of events	Number of patients n (%)	Number of events	Number of patients n (%)	Number of events	Number of patients n (%)
AESIs	5	5 (4.6)	11	9 (2.9)	16	14 (3.4)
Infusion-related systemic and anaphylactic reactions	3	3 (2.8)	5	4 (1.3)	8	7 (1.7)
Infections of interest	1	1 (0.9)	4	4 (1.3)	5	5 (1.2)
Selected serious psychiatric events	1	1 (0.9)	2	2 (0.6)	3	3 (0.7)

Adverse events in paediatric patients

Of the 417 patients in the enrolled population, a total of 14 (3.4%) were paediatric patients (< 18 years). Of the 417 patients in the safety population, 6 paediatric patients experienced 14 AEs, 2 paediatric patients experienced 3 SAEs (Cerebral thrombosis, oedema and rash, which outcome were recovering), 1 paediatric patient experienced 1 AESI.

CHMP comment:

Of the 417 patients in the enrolled population, a total of 14 (3.4%) were paediatric patients (< 18 years). Overall, AEs were reported in 6/14 paediatric patients (42.9%) and SAEs were reported in 2/14 patients (14.3%). This is slightly higher incidence rates than in the overall population, however given the low number of paediatric patients no firm conclusions can be drawn from the comparison.

Narratives were provided only for serious adverse events considered to be related to study drug. Among these, none were paediatric patients. Therefore, no details could be found on the SAEs in paediatric patients briefly summarised and by the CHMP commented on below:

- Cerebral thrombosis (possibly related to the SLE itself rather than the treatment)
- Oedema (unspecific, could have many causes)
- Rash (could also be related to the SLE)
- AESI without further specification (not possible to further assess).

Overall, no new safety signals were identified among paediatric patients treated with Benlysta.

Pregnancies

The study population included female patients of child-bearing potential and one female patient (belimumab treated) was reported to be pregnant in the study. The patient did not have a delivery prior to database lock, and did not experience any safety events.

Conclusion by the MAH

The MAH concludes that no new safety signals for belimumab have been observed and no additional risk management measures need to be enforced. However, the MAH will routinely conduct pharmacovigilance data collection and the drug safety monitoring work. The MAH states that overall, belimumab has shown favourable safety and tolerability in real-world use in Chinese patients,

2.3.3. Discussion on clinical aspects

Belimumab is a human immunoglobulin-G1λ monoclonal antibody that inhibits B lymphocyte stimulator protein, a member of the tumour necrosis factor (TNF) ligand superfamily that promotes the survival of B lymphocytes. Benlysta is approved for treatment of adult and paediatric patients with SLE, and for adult patients with lupus nephritis.

Benlysta (IV formulation) is indicated as add-on therapy in patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy.

Methods

Study 213210 was a multicentre, observational study assessing the safety of belimumab in Chinese patients who have been prescribed belimumab for appropriate medical use based on investigator's judgement.

Eligible patients were observed when they first start belimumab treatment, while the patients who had been previously treated with belimumab also were included. The investigator enrolled all eligible patients during the predefined surveillance period, unless the patient refuses to be enrolled. Since this was a non-interventional study and was observational in nature, all the enrolled patients were followed up by the treating investigator according to the clinical need. Data generated as a result of clinical practice, if any, were captured. Investigators collected all data at routine clinical visits. The total duration of safety monitoring was 24 weeks.

Patients eligible for enrolment in the study must meet all the following criteria:

3. Patients who had been prescribed belimumab by investigators for their medical condition.
4. Capable of giving signed informed consent, which included compliance with the requirements and restrictions listed in the informed consent form (ICF) and in protocol.

The objective of this study was to monitor and evaluate the real-world safety profile of belimumab treatment. The safety information of all adverse events (AEs) and serious adverse events (SAEs) occurring in the observation period were collected and analyzed. A descriptive approach was used and no formal hypothesis was planned for this study.

Results

Overall population

A total of 418 patients were enrolled. Of these, 417 patients were included in safety population. Of the 417 patients in the enrolled population, a total of 14 (3.4%) were paediatric patients (< 18 years).

Of the 417 patients included in the safety population, a total of 158 (37.9%) patients experienced 336 AEs and 22 (5.3%) patients experienced 35 SAEs. The most frequently reported AEs by SOC were infections and infestations (14.6%), metabolism and nutrition disorders (6.7%), skin and subcutaneous tissue disorders (6.2%), and gastrointestinal disorders (5.8%).

There were no deaths in the study.

The most frequently reported SAEs by SOC were infections and infestations (1.2%) and nervous system disorders (1.0%).

Paediatric population

A total of 14 patients(3.4%) were paediatric (< 18 years). AEs were reported in 6/14 paediatric patients (42.9%) and SAEs were reported in 2/14 patients (14.3%). This is slightly higher incidence rates than in the overall population, however given the low number of paediatric patients no firm conclusions can be drawn from the comparison.

Narratives were provided only for serious adverse events considered to be related to study drug. Among these, none were paediatric patients. Therefore, no details could be found on the SAEs in paediatric patients briefly summarised and by the CHMP commented on below:

- Cerebral thrombosis (possibly related to the SLE itself rather than the treatment)
- Oedema (unspecific, could have many causes)

- Rash (could also be related to the SLE)
- AESI without further specification (not possible to further assess).

Overall, no new safety signals were identified among paediatric patients treated with Benlysta.

“Limited data on long-term safety in paediatric patients” is included as missing information in the Benlysta RMP. A dedicated paediatric safety study is ongoing (category 3):

Pediatric Safety Study BEL114055/PLUTO-open label Ongoing	To evaluate the safety and tolerability, pharmacokinetics and efficacy of belimumab and the effects of belimumab on the quality of life in the pediatric SLE population.	Infections, Limited data on long-term safety in paediatric patients	Final End of Study CSR	31Dec2028

More safety data on the use of Benlysta in paediatric patients is expected in future PSURs and when the final report from the PLUTO study is provided.

3. CHMP overall conclusion and recommendation

The MAH has within this P46 submitted the final results from study 213210 which was a multicentre, observational study assessing the safety of belimumab in Chinese patients. The study included 418 patients, whereof a total of 14 (3.4%) were paediatric patients (< 18 years).

AEs were reported in 6/14 paediatric patients (42.9%) and SAEs were reported in 2/14 patients (14.3%). This is slightly higher incidence rates than in the overall population, however given the low number of paediatric patients no firm conclusions can be drawn from the comparison.

“Limited data on long-term safety in paediatric patients” is included as missing information in the Benlysta RMP. A dedicated paediatric safety study is ongoing (category 3). More safety data on the use of Benlysta in paediatric patients is expected in future PSURs and when the final report from the PLUTO study is provided.

Based on the information submitted, the CHMP concluded that no update of the product information for Benlysta is required.

☒ Fulfilled:

No regulatory action required.