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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/P46/033

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	14 Aug 2023	14 Aug 2023	☐
☐	CHMP Rapporteur Assessment Report	18 Sept 2023	18 Sept 2023	☐
☐	CHMP members comments	02 Oct 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Oct 2023	n/a	☐
☒	CHMP adoption of conclusions:	12 Oct 2023	12 Oct 2023	☐

[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

On 26 June 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.

Belimumab (BENLYSTA) is a BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. Belimumab IV is approved for the treatment of patients (5 years of age and older) with active autoantibody positive SLE. BENLYSTA for SC use is approved only for the treatment of adult patients with SLE.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 200908 is part of a paediatric investigation plan (EMEA-000520-PIP02-13-M04). The variation application consisting of the full relevant data package is planned to be submitted as a Type II Variation to apply for an indication in paediatric patients once additional documentation needed for the variation dossier are available.

2.2. Information on the pharmaceutical formulation used in the study

The investigational product used during this study was belimumab for SC injection via autoinjector as supplied by GSK. Participants were dosed with belimumab according to body weight. Belimumab 200 mg SC was administered as shown in the following table:

Cohort	Body weight at baseline (kg)	Dosing frequency
1	≥50	Every week (QW)
2	≥30 to <50	Every 10 days (Q10d)
3	<30	Every 2 weeks (Q2W)

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study 200908, a Multi-Center, Open-Label Trial to Evaluate the Pharmacokinetics, Safety, and Pharmacodynamics of Subcutaneously Administered Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Participants with Systemic Lupus Erythematosus (SLE) – Open-label Endpoint Analysis (Parts A and B)

2.3.2. Clinical study

Study 200908, a Multi-Center, Open-Label Trial to Evaluate the Pharmacokinetics, Safety, and Pharmacodynamics of Subcutaneously Administered Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Participants with Systemic Lupus Erythematosus (SLE) – Open-label Endpoint Analysis (Parts A and B)

Description

This was a single arm, multi-center open-label study to evaluate the PK, safety, and PD of SC belimumab plus background standard therapy in approximately 28 paediatric participants 5 to 17 years of age and weighing ≥15 kg with active SLE.

Methods

Study design

The study included:

- Part A: Open-label, 12-week treatment phase
- Part B: Optional 40-week open-label continuation phase for any participant who completed Part A
- Post-treatment follow-up assessments at 8 and 16 weeks after the last dose of SC belimumab
- Optional Access Extension Phase: Optional post-Week 52 extension phase exclusively for eligible participants who complete Part B (e.g., participants from countries where the IV formulation is not approved for paediatric use; or participants in whom IV Benlysta is not suitable due to medical reasons or significant logistical challenges). As of this report writing, the optional Access Extension Phase of the study is ongoing

Study participants

Eligible participants were 5 to 17 years of age with clinically active SLE disease, defined as a SELENA SLEDAI disease activity score of ≥6 at screening. Participants had to have 4 or more of the 11 American College of Rheumatology (ACR) criteria for the classification of SLE either at screening or in the past. Participants also had to have an unequivocally positive test result for anti-nuclear antibody (ANA) titer ≥1:80 and/or anti-dsDNA ≥30 IU/mL serum antibody test based on either the study's central laboratory results or the local laboratory results. Participants were to be on a stable SLE treatment regimen at a fixed dose for at least 30 days prior to Day 1.

Key exclusion criteria included severe active CNS lupus or severe lupus nephritis.

Treatments

The investigational product used during this study was belimumab for SC injection via autoinjector as supplied by GSK. Participants were dosed with belimumab according to body weight. Belimumab 200 mg SC was administered as shown in the following table:

Cohort	Body weight at baseline (kg)	Dosing frequency
1	≥50	Every week (QW)
2	≥30 to <50	Every 10 days (Q10d)
3	<30	Every 2 weeks (Q2W)

Part B was an optional 40-week open-label continuation phase, open to all participants who completed **Part A**. Dosing of SC belimumab continued at the same frequency, or it may have required a change in frequency according to change in body weight.

The **Optional Access Extension Phase** provided a mechanism for continued access to belimumab SC from Week 52 onward and was open only for eligible participants who completed Part B. Dosing of SC

belimumab continued at the same frequency or it may have required a change in frequency according to change in body weight.

Objective(s)

The primary objective was to o characterize the PK profile of belimumab 200 mg SC in paediatric SLE participants.

Secondary/other objectives were:

- Safety: to evaluate the safety and tolerability of belimumab 200 mg SC in paediatric SLE participants
- Biomarkers: to characterize the pharmacodynamic profile of belimumab 200 mg SC in paediatric SLE participants
- Efficacy: to characterize the impact of belimumab 200 mg SC on disease activity in paediatric SLE participants.

Outcomes/endpoints

Primary endpoints were the PK of observed belimumab concentrations at Week 12, and steady state PK parameters including Cavg (AUC), Cmax, and Cmin (based on population PK estimates).

The secondary endpoints were safety, including the incidence of AEs, SAEs, and AEs of special interest through Week 52, and PD/biomarker endpoints including change from baseline in C3/C4, anti-dsDNA, B cell subsets, and immunoglobulins at Weeks 12 and 52. In addition, other PD parameters that were assessed but were not specified an endpoint for this study were ANA, C reactive protein, and BLyS protein.

To support the other objective/endpoint, and to characterize the impact of belimumab 200 mg SC on disease activity in paediatric SLE participants, the efficacy endpoint in this study was the SELENA SLEDAI Disease Assessment Scale. The outcome for the efficacy endpoint was defined as the percent of participants with a ≥4-point reduction from baseline in SELENA SLEDAI score at Week 12 and Week 52. Additional efficacy endpoints of interest that were assessed but were not supportive of a study objective were proteinuria and prednisone dose.

Sample size

Assuming a 20% screen-failure rate, it was expected that 36 participants would need to be screened so that approximately 28 participants would be enrolled, (treated with at least one dose of study treatment) aiming for 24 evaluable participants at Week 12. The sample size of 24 participants and the specified sampling schedule allow estimation of central clearance and volume of distribution, with a power of 99.9% and 99.7%, respectively (mean 95% confidence intervals were 83.8-116.2% and 80.5-119.5%, respectively).

Randomisation and blinding (masking)

This was an open-label study with a single treatment arm.

Statistical Methods

This study was designed to descriptively evaluate PK, safety, and PD of belimumab during Parts A and B, and as such no formal statistical hypothesis testing was planned.

Results

Participant flow

A total of 28 participants were screened and 25 were enrolled to the study. All 25 enrolled participants received at least 1 dose of study drug. Two (8.0%) participants withdrew from the study prior to Week 52, 1 participant due to an adverse event and 1 participant at the investigator's discretion.

Table 1. Participant Completion Status at Week 12 and Week 52 (ITT Population)

	Number (%) of Participants Belimumab 200 mg N=25
Completed Week 12 visit	25 (100.0)
Withdrawn prior to Week 12	0
Completed Week 52 visit	23 (92.0)
Entered Access Extension Phase	11 (44.0)
Withdrawn prior to Week 52 visit	2 (8.0)
Adverse event	1 (4.0)
Investigator discretion	1 (4.0)

Source: Table 1.04 (Part A) and Table 1.05 (Part B)

Recruitment

This was a multi-center study conducted at 11 sites in 7 countries (Argentina, Germany, Japan, Mexico, Netherlands, Spain, and United States.

Baseline data

Table 2.Summary of Demographics and Baseline Characteristics (ITT Population)

	Number (%) of Participants Belimumab 200mg (N=25)
Country	
Argentina	4 (16.0)
Germany	4 (16.0)
Japan	2 (8.0)
Mexico	3 (12.0)
Netherlands	2 (8.0)
Spain	6 (24.0)
United States	4 (16.0)
Sex	
n	25
Female	21 (84.0)
Male	4 (16.0)
Age at Screening (years)[a]	
n	25
Mean	14.0
SD	2.09
Median	14.0
25th percentile	13.0
75th percentile	16.0
Min.	10
Max.	17
Age Group at Screening (years)[a]	
n	25
<=18	25 (100.0)
19-64	0
>=65	0

Ethnicity	
n	25
Hispanic or Latino	11 (44.0)
Not Hispanic or Latino	14 (56.0)
High Level Race	
n	25
American Indian or Alaska Native	3 (12.0)
Asian	4 (16.0)
Black or African American	1 (4.0)
Native Hawaiian or Other Pacific Islander	0
White	16 (64.0)
Mixed Race	1 (4.0)
Weight (kg)	
n	25
Mean	52.09
SD	10.898
Median	52.00
25th percentile	43.90
75th percentile	59.00
Min.	34.5
Max.	78.5
Baseline Body Weight Cohort[b]	
Cohort 1 (>=50kg)	13 (52.0)
Cohort 2 (>=30kg - <50kg)	12 (48.0)
Cohort 3 (<30kg)	0

a. Age is imputed when full date of birth is not provided.
b. Dosing frequency is as follows: Cohort 1 = weekly dosing, Cohort 2 = every 10 days, Cohort 3 (not enrolled) = every 2 weeks.

Number analysed

A total of 25 patients was included in the ITT population.

Pharmacokinetic results

Pharmacokinetic assessments, the primary endpoint in this study, were designed to characterize the PK profile of belimumab 200 mg SC in paediatric SLE participants based on observed belimumab concentrations at Week 12, and steady-state PK parameters including Cmin, Cavg, Cmax, and AUC derived from a population PK analysis.

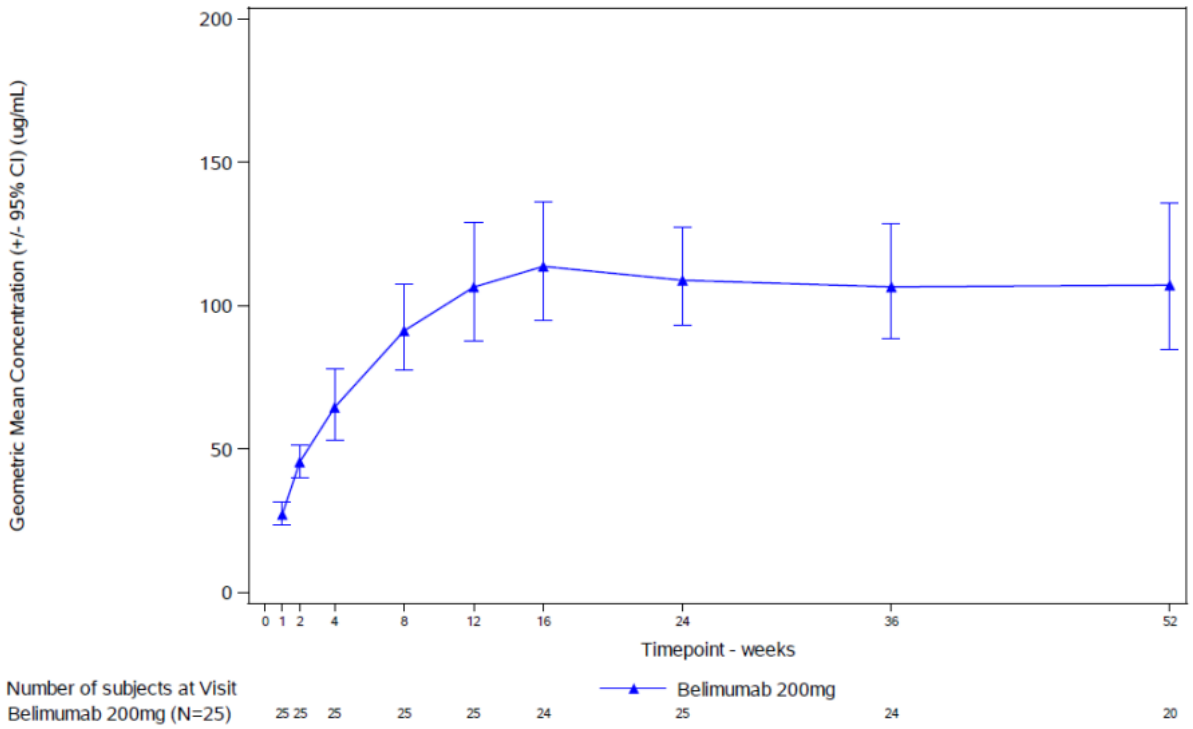
Samples for PK analysis were collected in Part A and Part B. No PK samples are obtained during the optional access extension phase. Observed belimumab concentrations by study week for the paediatric SC study 200908 are graphically illustrated below in Figure 1.

Belimumab concentrations in the pediatric SC study were approaching steady state by Week 12 (Figure 1). Observed Week 12 concentrations (geometric mean) were 106.42 µg/mL (all patients, N=25), 134.23 µg/mL (Cohort 1, N=13) and 82.76 µg/mL (Cohort 2, N=12).

In general, over the 52-week study belimumab concentrations were slightly higher in Cohort 1 (≥50 kg, weekly dosing) compared to Cohort 2 (≥30 kg to <50 kg, every 10-day dosing), indicating the lower dosing frequency of Cohort 2 on exposure. Overall, the observed concentrations were

comparable to the adult SC concentrations observed in study BEL112341 [GSK Study Report 2014N216963_01, 2017] (median concentration of 99 µg/mL at Day 112).

Figure 1 Geometric Mean Pre-injection Belimumab Concentrations (ug/mL) (Observed) (PK Population)



Efficacy results

Efficacy results reported herein should be interpreted with caution due to small sample size and this being an open-label study with no placebo group for comparison.

Table 3. SELENA SLEDAI ≥4 Point Reduction from Baseline to Week 12 and Week 52 by Baseline Weight Cohort (Observed) (ITT Population)

	Number (%) of Participants Belimumab 200 mg			
	Cohort 1 (≥50kg) (N=13)	Cohort 2 (≥30kg - <50kg) (N=12)	Cohort 3 (<30kg) (N=0)	Total (N=25)
Week 12 (Day 85/81)				
n	12	12	0	24
Reduction	9 (75.0)	7 (58.3)	0	16 (66.7)
Week 52				
n	13	9	0	22
Reduction	12 (92.3)	6 (66.7)	0	18 (81.8)

Note: Dosing frequency is as follows: Cohort 1 = weekly dosing, Cohort 2 = every 10 days, Cohort 3 (not enrolled) = every 2 weeks.

Safety results

A summary of adverse events and serious adverse events is shown below.

Table 4. Adverse Events Summary (ITT Population)

	Number (%) of Participants Belimumab 200 mg (N=25)
At least 1 AE	22 (88.0)
At least 1 related AE	14 (56.0)
At least 1 serious AE	1 (4.0)
At least 1 severe AE	0
At least 1 serious and/or severe AE	1 (4.0)
At least 1 AE resulting in study agent discontinuation	1 (4.0)
Death	0

Note: Only treatment-emergent AEs are summarized. Participants are counted once in each row for which they have any AE meeting the criterion. MedDRA version 25.1.

Table 5. Serious Adverse Events by System Organ Class and Preferred Term (ITT Population)

System Organ Class Preferred Term	Number[a] (%) of Participants Belimumab 200 mg (N=25)
ANY EVENT	1 (4.0)
Infections and infestations	
Any event	1 (4.0)
COVID-19	1 (4.0)

Note: Only treatment-emergent AEs are summarized. MedDRA version 25.1

a. Participants only counted once per SOC/PT.

SOCs with ≥20% of participants experiencing an AE were infections and infestations (72.0%), general disorders and administration site conditions (32.0%), blood and lymphatic system disorders (28.0%), investigations (20%), and skin and subcutaneous tissue disorders (20%).

The most common AE overall was COVID-19 (36.0%), followed by injection site pain, leukopenia, and neutropenia, with each occurring in 16.0% of participants.

No deaths, malignancies, infections of special interest, incidents of depression, suicidality, or self-injury were reported through Part A and B of the study.

Post-injection systemic reactions were reported in a total 3 (12.0%) participants through Part A and B of the study. Post-injection systemic reactions per anaphylactic reaction CMQ broad search included the PTs drug hypersensitivity, erythema, and injection site urticaria. There were no serious post-injection systemic reactions AESI and no post-injection systemic reactions AESI which led to discontinuation of study agent.

The incidence of local injection site reactions in all participants was 32%; 8 participants experienced 17 injection site reaction events. All events were mild and non-serious. Belimumab was continued in all 8 participants, and the events resolved. Injection site reactions that occurred in more than 1 participant were injection site pain (16.0%) and injection site erythema (8.0%). Two events in 1 participant (injection site hemorrhage and injection site swelling) were considered by the investigator to be unrelated to belimumab. All other events were considered by the investigator to be related to belimumab.

Two device malfunctions were reported with the use of belimumab autoinjectors during this study. The 2 device malfunctions that were reported are "cannot push needle to activate injection" and "device leaking." All device functional issues were evaluated and considered to have no impact on safety. In addition, SAEs were reviewed, and none were attributed to be a medical device "incident or near incident".

2.3.3. Discussion on clinical aspects

Belimumab is a BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. Belimumab IV is approved for the treatment of patients (5 years of age and older) with active autoantibody positive SLE. BENLYSTA for SC use is approved only for the treatment of adult patients with SLE.

On 26 June 2023, the MAH submitted a completed paediatric study for Benlysta, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The study is part of a paediatric investigation plan (EMEA-000520-PIP02-13-M04). Based on this study, the MAH plans to submit a Type II Variation to apply for an indication in paediatric patients.

Study 200908 was a single arm, multi-centre open-label study to evaluate the PK, safety, and PD of SC belimumab plus background standard therapy in paediatric participants 5 to 17 years of age with active SLE. This submission includes data from the open-label endpoint analysis (Parts A and B).

Eligible participants were 5 to 17 years of age with clinically active SLE disease, defined as a SELENA SLEDAI disease activity score of ≥6 at screening. Participants were to be on a stable SLE treatment regimen at a fixed dose for at least 30 days prior to Day 1. Patients with severe active CNS lupus or severe lupus nephritis were excluded from the study.

Participants were dosed with SC belimumab 200 mg via autoinjector according to body weight (dosing frequency every week, every 10 days or every 2 weeks). The study included the following parts:

- Part A: Open-label, 12-week treatment phase
- Part B: Optional 40-week open-label continuation phase for any participant who completed Part A

- Post-treatment follow-up assessments at 8 and 16 weeks after the last dose of SC belimumab
- Optional Access Extension Phase: Optional post-Week 52 extension phase exclusively for eligible participants who complete Part B (e.g., participants from countries where the IV formulation is not approved for paediatric use; or participants in whom IV Benlysta is not suitable due to medical reasons or significant logistical challenges). As of this report writing, the optional Access Extension Phase of the study is ongoing

The primary objective was to o characterize the PK profile of belimumab 200 mg SC in paediatric SLE participants. Secondary objectives were safety biomarkers and efficacy. No formal statistical hypothesis testing was planned.

A total of 25 patients were included in the study and received at least 1 dose of study drug. The mean age of the patients was 14 years (range 10-17). Two (8.0%) participants withdrew from the study prior to Week 52, 1 participant due to an adverse event and 1 participant at the investigator's discretion.

No patient was included in Cohort 3 (<30 kg), 12 patients received every 10 day-dosing (Cohort 2, ≥30 kg to <50 kg), and 13 patients received QW dosing (Cohort 1, >50 kg). Overall, the median concentration at week 12 was similar to the concentration observed in the adult population (Study BEL 112341).

A total of 22/25 patients (88%) experienced at least 1 adverse event (AE) and 1/25 patients (4%) experienced at least 1 serious AE (COVID-19). The most common system organ classes affected were infections and infestations (72.0%), general disorders and administration site conditions (32.0%), blood and lymphatic system disorders (28.0%), investigations (20%), and skin and subcutaneous tissue disorders (20%). The most common AE overall was COVID-19 (36.0%), followed by injection site pain, leukopenia, and neutropenia, with each occurring in 16.0% of participants.

No deaths, malignancies, infections of special interest, incidents of depression, suicidality, or self-injury were reported through Part A and B of the study.

No new safety concerns were identified during the study.

3. CHMP's overall conclusion and recommendation

Study 200908 was a single arm, multi-centre open-label study to evaluate the PK, safety, and PD of SC belimumab in paediatric participants 5 to 17 years of age with active SLE. A total of 25 patients were included. No new safety concerns were identified.

The MAH stated that study 200908 is part of a paediatric investigation plan (EMEA-000520-PIP02-13-M04). The MAH indicated that a variation application consisting of the full relevant data package is planned to be submitted as a Type II Variation to apply for an indication in paediatric patients once additional documentation needed for the variation dossier are available.

☒ **Fulfilled:**

No regulatory action required.