Amsterdam, 19 June 2025
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Committee for Medicinal Products for Human Use (CHMP)

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

Benlysta

Belimumab

Procedure no: EMA/PAM/0000265362

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**
☐	CHMP Rapporteur AR	26 May 2025	22 May 2025
☐	CHMP comments	10 June 2025	n/a
☐	Updated CHMP Rapporteur AR	12 June 2025	n/a
☒	CHMP outcome	19 June 2025	19 June 2025

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1. Introduction

On 7 April 2025, 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 Study 217091, "A Multi-Centre, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Subcutaneously Administered Belimumab Plus Standard Therapy in Chinese Paediatric Participants with Systemic Lupus Erythematosus (SLE)" is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The study intervention was Belimumab 200 mg/mL SC injection (single use autoinjector) provided centrally by the Sponsor. The autoinjector components were manufactured by Scandinavian Health Limited (SHL) and assembled with the pre-filled syringe at GSK, Barnard Castle, UK.

2.3. Clinical aspects

2.3.1. Introduction

Since 2019, Benlysta as powder for concentrate for solution for infusion is approved in the EU as add-on therapy in paediatric patients aged 5 years and older with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy.

The indication for belimumab SC has been extended to include children 5 years and above with SLE in the US on 17 May 2024, followed by Japan on 24 June 2024. The SC formulation for paediatric patients is not yet approved in the EU.

The purpose of this study was to evaluate the pharmacokinetics (PK) and safety of subcutaneously administered belimumab (200 mg/mL) with standard therapy in Chinese paediatric patients with SLE. As the study includes paediatric patients, it is in scope of Article 46. The study has not been conducted according to an agreed paediatric investigation plan.

The MAH submitted a final report for:

- Study 217091, "A Multi-Centre, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Subcutaneously Administered Belimumab Plus Standard Therapy in Chinese Paediatric Participants with Systemic Lupus Erythematosus (SLE)"

2.3.2. Clinical study

Study 217091, "A Multi-Centre, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Subcutaneously Administered Belimumab Plus Standard Therapy in Chinese Paediatric Participants with Systemic Lupus Erythematosus (SLE)"

2.3.2.1. Description

This was a single-arm, multi-center, open-label study of belimumab plus standard of care in participants with SLE who had completed 48 weeks belimumab IV treatment in Study 213560. The study aimed to evaluate the PK and safety of subcutaneously administered belimumab over 12 weeks in approximately 17 paediatric participants aged 5 to 17 years and weighing ≥15 kg. Participants enrolled in this study were, in the Investigator's judgment, expected to benefit from continuing treatment with belimumab. The PK data derived from this study contributed to the update of previous population PK model. Based on the updated population PK model, an appropriate dose regimen of belimumab SC (i.e., dose frequency according to body weight) for Chinese paediatric participants was determined by simulation.

2.3.2.2. Methods

Study participants

This study enrolled Chinese paediatric participants (5 to 17 years of age and body weight ≥15kg) with SLE who had completed 48 weeks treatment in Study 213560 and who, in the opinion of the Investigator, might benefit from continuing treatment with belimumab.

The study aimed to evaluate the PK and safety of subcutaneously administered belimumab over 12 weeks in approximately 17 paediatric participants aged 5 to 17 years and weighing ≥15 kg.

The targeted aim for this study was to recruit participants from Study 213560 who had IV PK samples collected. However, as the targeted number of participants could not be met, 1 additional participant from the non-PK Population in 213560 was also included. The PK samples were collected immediately after the last IV dose in Study 213560 and before the first dose in Study 217091. This ensured that the belimumab PK profile could be accurately characterized for each participant both leading up to and following the switch to SC dosing.

Treatments

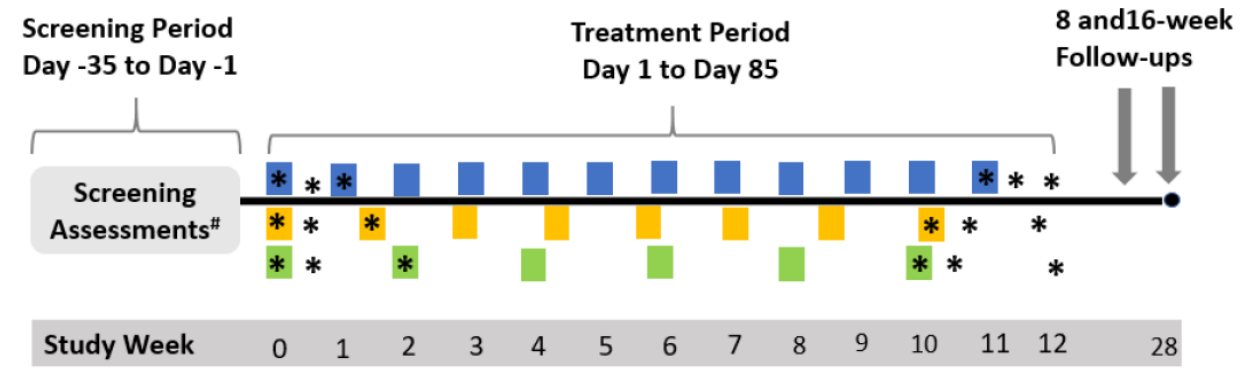
Participants received the first SC dose of belimumab in study 217091 no more than 4 weeks after the last IV dose (administered at Week 48 visit of Study 213560) at the dose level below:

- Dose weight ≥50 kg: 200 mg weekly;
- Dose weight ≥30 kg - <50 kg: 200 mg every 10 days;
- Dose weight ≥15 kg - <30 kg: 200 mg every 2 weeks.

The study included:

- Open-label, 12-week treatment phase.
- Post-treatment follow-up assessments at 8 weeks and 16 weeks after the last dose of SC belimumab.

Figure 1 Study design



Participants ≥50 kg body weight received belimumab 200 mg SC weekly
Participants ≥30 kg to <50 kg body weight received belimumab 200 mg SC every 10 days
Participants ≥15 kg body to <30 kg weight received belimumab 200 mg SC every 2 weeks
* PK sampling
# Participants rolled over from Study 213560 thus the screening period of this study had an overlap with Study 213560.

Objectives and endpoints

This was a single-arm study. No formal statistical hypothesis testing was planned. All analyses were descriptive. There is no adjustment for multiplicity in this study.

Objectives	**Endpoints**
Primary - Pharmacokinetics	
• To characterize belimumab exposure following belimumab 200 mg SC in Chinese paediatric SLE participants who have previously been treated with IV belimumab.	• Exposure parameters: AUCss, 0-τ, Cavg,ss, Cmin,ss, Cmax,ss.
Secondary - Safety	
• To evaluate the safety and tolerability of belimumab 200 mg SC in paediatric participants with SLE who have previously been treated with IV belimumab.	• Occurrence of AEs, SAEs, and AESIs through Week 12.

Abbreviations: AE = adverse event, AESI = adverse event of special interest, AUCss, 0-τ = area under the curve at steady state to the end of the dosing period, Cavg,ss= average serum concentration at steady state, Cmin,ss = minimum serum concentrations at steady state, Cmax,ss = maximum serum concentrations during the dosing interval at steady state, IV = intravenously, SAE = serious adverse event, SC = subcutaneously, SLE = systemic lupus erythematosus

2.3.2.3. Results

This study was conducted at 6 centres in China. There were no formal calculations of power for this study. The planned total sample size was 17. The actual participants in Screened, Enrolled, ITT, and PK Population were 16. All 16 (100%) participants completed the study treatment, the 12-week visit, and the whole study (including the 16-week post-treatment follow-up period) with no Early withdrawal.

Overall, the median (range) age of the participants was 13.0 (7 to 17) years, of which most participants were aged 12 to 17 years (75.0%), predominantly female (68.8%). All participants were of Asian-East Asian heritage (100%). The median (range) weight of the participants was 56.25 (25.0 to 77.5) kg, where numbers of participants in ≥50 kg, ≥30 kg - <50 kg, and ≥15 kg - <30 kg body weight groups were 10 (62.5%), 5 (31.3%), and 1 (6.3%), respectively.

The exposures of each body weight group were:

- The 1 participant in the ≥15 kg - <30 kg body weight group was exposed to the study treatment for 85 days with 6 injections. The participant was a 7-year old female and weighed 25.0 kg at study entry.
- In 5 participants in the ≥30 kg - <50 kg body weight group, the median (range) duration of exposure was 80.0 (79 to 81) days, and all 5 (100%) participants received 8 injections. The median (range) age of the participants was 12.0 (11 to 15) years. Participants were predominantly female (60.0%). The median (range) weight of the participants was 47.50 (32.8 to 48.9) kg.
- In 10 participants in the ≥50 kg body weight group, the median (range) duration of exposure was 84.5 (83 to 89) days, where 8 (80.0%) participants received 12 injections and 2 (20.0%) participants received 11 injections. The median (range) age of the participants was 14.0 (9 to 17) years. Participants were predominantly female (70.0%). The median (range) weight of the participants was 60.90 (55.8 to 77.5) kg.

Pharmacokinetic results

In ≥50 kg, ≥30 kg - <50 kg, and ≥15 kg - <30 kg body weight groups, the geometric mean pre-dose concentrations before the first dose were 54.90 µg/mL, 45.00 µg/mL, and 38.47 µg/mL, respectively; the geometric mean approximate Cmax after the first dose were 68.87 µg/mL, 63.41 µg/mL, and 92.44 µg/mL, respectively; the geometric mean Ctrough after the first dose were 61.71 µg/mL, 54.55 µg/mL, and 63.47 µg/mL, respectively.

In ≥50 kg and ≥30 kg - <50 kg body weight groups, the geometric mean pre-dose concentrations before the last dose were 83.94 µg/mL and 76.37 µg/mL, respectively; geometric mean approximate Cmax after the last dose were 88.61 µg/mL and 85.11 µg/mL, respectively; the geometric mean Ctrough after the last dose were 85.55 µg/mL and 71.57 µg/mL, respectively. For the single participant in the ≥15 kg - <30 kg body weight group, the pre-dose concentration after the last dose was 22.75 µg/mL, the geometric mean approximate Cmax after the last dose was 28.01 µg/mL, and geometric mean Ctrough after the last dose was 20.44 µg/mL.

Population PK parameters were analyzed. The geometric means of Cmin,ss were 82.63 µg/mL, 70.71 µg/mL, and 80.95 µg/mL in ≥50 kg, ≥30 kg - <50 kg, and ≥15 kg - <30 kg body weight groups, respectively. The geometric means of Cmax,ss were 93.36 µg/mL, 87.15 µg/mL, and 109.59 µg/mL in the 3 body weight groups, respectively. The geometric means of Cavg,ss were 90.47 µg/mL, 80.76 µg/mL, and 97.52 µg/mL in the 3 body weight groups, respectively, which were generally comparable between body weight groups and reflected the designed dosing frequency adjusted to body weight.

Table 1: Summary of Observed Belimumab Concentrations (µg/mL) at Each Timepoint by Body Weight Group

	≥50 kg (N=10)	**≥30 kg - <50 kg (N=5)**	**≥15 kg - <30 kg (N=1)**	**Total Belimumab 200 mg SC (N=16)**
Pre-dose at first dose				
Geomean (GeoCV%)	54.90 (52.42)	45.00 (43.19)	38.47 (NA)	50.46 (47.74)
95% CI of geomean	(38.59, 78.10)	(26.93, 75.21)	(NA, NA)	(39.64, 64.24)
Median	59.90	45.99	38.47	51.09
(Min, Max)	(18.88, 100.87)	(22.92, 69.16)	(38.47, 38.47)	(18.88, 100.87)
Cmax after the first dose				
Geomean (GeoCV%)	68.87 (36.79)	63.41 (31.66)	92.44 (NA)	68.36 (34.04)
95% CI of geomean	(53.37, 88.86)	(43.20, 93.07)	(NA, NA)	(57.30, 81.55)
Median	75.44	73.32	92.44	74.65
(Min, Max)	(38.44, 109.16)	(38.71, 83.21)	(92.44, 92.44)	(38.44, 109.16)
Ctrough after the first dose				
Geomean (GeoCV%)	61.71 (38.47)	54.55 (29.07)	63.47 (NA)	59.48 (33.79)
95% CI of geomean	(47.31, 80.50)	(38.30, 77.69)	(NA, NA)	(49.92, 70.87)
Median	67.27	54.87	63.47	61.67
(Min, Max)	(31.88, 100.52)	(34.89, 76.55)	(63.47, 63.47)	(31.88, 100.52)
Pre-dose at steady state				
Geomean (GeoCV%)	83.94 (27.53)	76.37 (19.18)	22.75 (NA)	75.11 (41.22)
95% CI of geomean	(69.18, 101.85)	(60.32, 96.70)	(NA, NA)	(60.82, 92.76)
Median	87.69	80.38	22.75	85.14
(Min, Max)	(49.52, 118.44)	(54.94, 88.64)	(22.75, 22.75)	(22.75, 118.44)
Cmax at steady state				
Geomean (GeoCV%)	88.61 (27.68)	85.11 (28.71)	28.01 (NA)	81.42 (39.76)
95% CI of geomean	(72.96, 107.62)	(60.01, 120.70)	(NA, NA)	(66.39, 99.86)

Median	92.70	92.11	28.01	91.42
(Min, Max)	(52.39, 121.20)	(52.22, 107.83)	(28.01, 28.01)	(28.01, 121.20)
Ctrough at steady state				
Geomean (GeoCV%)	85.55 (33.52)	71.57 (36.72)	20.44 (NA)	73.99 (49.91)
95% CI of geomean	(67.74, 108.04)	(46.02, 111.31)	(NA, NA)	(57.55, 95.12)
Median	85.20	82.12	20.44	83.53
(Min, Max)	(53.35, 154.23)	(37.98, 87.75)	(20.44, 20.44)	(20.44, 154.23)

Safety results

During the 12-week on-treatment period, of the 16 participants treated with belimumab, 13 (81.3%) participants reported at least 1 adverse event (AE), while 9 (56.3%) participants reported at least 1 AE related to the study intervention. No serious adverse events (SAEs), severe AEs, AEs resulting in study intervention discontinuation, deaths, or adverse events of special interest (AESIs) were reported.

Common (≥2 participants) AEs by system organ class (SOC) were infections and infestations (11 [68.8%] participants); gastrointestinal disorders; hepatobiliary disorders; and respiratory, thoracic and mediastinal disorders (2 [12.5%] participants each). Common (≥2 participants) AEs by preferred term (PT) were upper respiratory tract infection (9 [56.3%] participants), bronchitis (3 [18.8%] participants), and hepatic function abnormal (2 [12.5%] participants). There were no local injection site reactions reported as AEs.

A total of 9 (56.3%) participants experienced AEs related to the study intervention. The common (≥2 participants) AEs related to study intervention by SOC were infections and infestations (9 [56.3%] participants) and hepatobiliary disorders (2 [12.5%] participants). The common (≥2 participants) AEs related to study intervention by PT were upper respiratory tract infection (8 [50.0%] participants) and hepatic function abnormal (2 [12.5%] participants).

The incidence of each category of AEs that occurred during the full period (12-week on-treatment and 16-week post-treatment follow-up period) was the same as the incidence observed during the 12-week on-treatment period. However, there were 8 additional AEs that occurred during the 16-week post-treatment follow-up period, including 3 AEs of upper respiratory tract infection and 1 AE each of non-infective gingivitis, hepatic function abnormal, rash, white blood cell count decreased, and growth retardation. No SAEs, severe AEs, AEs resulting in study intervention discontinuation, deaths, or AESIs were reported during the 16-week follow-up period.

According to the MAH, no new safety concerns in Chinese paediatric SLE participants were observed with belimumab (200 mg) SC.

Conclusion by the MAH

- In Study 217091, the 200 mg SC dosing frequency was adjusted to account for body weight effects on exposure: Participants ≥50 kg received 200 mg SC once a week (N=10); participants ≥30 kg and <50 kg received 200 mg SC Q10d (N=5); participants ≥15 kg and <30 kg received 200 mg SC every 2 weeks (N=1).

- The pre-dose, approximate Cmax, and Ctrough values after the first and the last SC dose were studied in all the enrolled participants. The steady-state PK parameters derived from the population PK analysis were generally consistent with the observed belimumab concentrations from Weeks 10 to 12 of Study 217091.
- No new safety concerns in Chinese paediatric SLE participants were observed with belimumab (200 mg) SC.
    - Incidences of AEs and AEs related to the study intervention were 81.3% and 56.3% (while-on-treatment) respectively. The most commonly reported AE was upper respiratory tract infection (9 [56.3%] participants) during the 12-week on-treatment period.
    - No SAEs, severe AEs, AE resulting in study intervention discontinuation, death, or AESI were reported.

The MAH reviewed the results of study 217091 and has concluded that they are in line with the approved product information for belimumab in the EU. Therefore, no changes to the Summary of Product Characteristics (SmPC) for belimumab are considered necessary beyond those proposed in the ongoing EU variation (EMEA/H/C/002015/II/0133).

2.3.3. Discussion on clinical aspects

Since 2019, Benlysta as powder for concentrate for solution for infusion is approved in the EU as add-on therapy in paediatric patients aged 5 years and older with active, autoantibody-positive SLE. The subcutaneous formulation for paediatric patients is not yet approved in the EU.

The purpose of this study was to evaluate the PK characteristics and safety of repeat doses of 200 mg belimumab administrated SC in Chinese paediatric participants with SLE. This evaluation followed the China belimumab IV paediatric study (213560), allowing paediatric participants who had completed 48 weeks belimumab of IV treatment to switch to this belimumab SC study. Participants received the first SC dose of belimumab in study 217091 no more than 4 weeks after the last IV dose (administered at Week 48 visit of Study 213560) at the dose level below:

- Dose weight ≥50 kg: 200 mg weekly;
- Dose weight ≥30 kg - <50 kg: 200 mg every 10 days;
- Dose weight ≥15 kg - <30 kg: 200 mg every 2 weeks.

The study included an open-label, 12-week treatment phase, and post-treatment follow-up assessments at 8 weeks and 16 weeks after the last dose of SC belimumab. This was a single-arm study. No formal statistical hypothesis testing was planned. All analyses were descriptive.

All 16 participants completed the full 12+16 weeks. Overall, the median (range) age of the participants was 13.0 (7 to 17) years, of which most participants were aged 12 to 17 years (75.0%), predominantly female (68.8%). The numbers of participants in ≥50 kg, ≥30 kg - <50 kg, and ≥15 kg - <30 kg body weight groups were 10 (62.5%), 5 (31.3%), and 1 (6.3%), respectively.

In ≥50 kg and ≥30 kg - <50 kg body weight groups, the geometric mean pre-dose concentrations at steady state before the last dose were 83.94 µg/mL and 76.37 µg/mL, respectively; geometric mean approximate Cmax after the last dose were 88.61 µg/mL and 85.11 µg/mL, respectively; the geometric mean Ctrough after the last dose were 85.55 µg/mL and 71.57 µg/mL, respectively. For the single

participant in the ≥15 kg - <30 kg body weight group, the pre-dose concentration after the last dose was 22.75 µg/mL, the geometric mean approximate Cmax after the last dose was 28.01 µg/mL, and geometric mean Ctrough after the last dose was 20.44 µg/mL.

In general, the safety profile was consistent with previous experience. A total of 9 (56.3%) participants experienced AEs related to the study intervention. The common (≥2 participants) AEs related to study intervention by PT were upper respiratory tract infection (8 [50.0%] participants) and hepatic function abnormal (2 [12.5%] participants). Upper respiratory tract infection is currently listed as a common adverse reaction in the EU SmPC, but there is no mention of abnormal hepatic function. However, both reported AEs on hepatic function abnormal were non-serious, and the small sample size hampers the conclusions that can be drawn from this data.

As the SC formulation for paediatric patients is not yet approved in the EU, no comparison can be made between this small PK study and the EU label. The benefit-risk of belimumab is considered unchanged and no update to the Summary of Product Characteristics has been proposed because of these data. This is supported by the CHMP.

3. CHMP's overall conclusion and recommendation

No new findings of PK characteristics and safety of repeat doses of 200 mg belimumab administrated SC were observed in the performed post-marketing open-label study of 16 subjects <18 years old with SLE in China. Descriptive data on PK and safety after 12 weeks treatment and 16 weeks follow-up in this population has been presented. The submission of this data under Article 46 is acknowledged and appreciated. No update to the Product Information is required based on the reported study. The benefit-risk balance for Benlysta remains unchanged and positive.

☒ **Fulfilled:**

No regulatory action required.