22 May 2025
EMADOC-1700519818-2197854
Human Medicines Division

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

## Benlysta

Belimumab

Procedure no: EMA/PAM/0000253553

## 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 |
| ☐ | Start of Procedure | 25 February 2025 | 25 February 2025 |
| ☐ | CHMP Rapporteur AR | 31 March 2025 | 31 March 2025 |
| ☐ | CHMP comments | 14 April 2025 | n/a |
| ☐ | Updated CHMP Rapporteur AR | 16 April 2025 | n/a |
| ☐ | Request for supplementary information | 25 April 2025 | 25 April 2025 |
| ☐ | Submission of MAH responses | 29 April 2025 | 29 April 2025 |
| ☐ | Re-start of procedure | 30 April 2025 | 30 April 2025 |
| ☐ | CHMP Rapporteur AR | 07 May 2025 | 08 May 2025 |
| ☐ | CHMP comments | 12 May 2025 | n/a |
| ☐ | Updated CHMP Rapporteur AR | 15 May 2025 | n/a |
| ☒ | CHMP outcome | 22 May 2025 | 22 May 2025 |

[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 11 February 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 "A Multi-Center, Open-Label Study to Evaluate Safety, Efficacy and Pharmacokinetics of Belimumab Plus Standard Therapy in Chinese Pediatric Patients with Active Systemic Lupus Erythematosus (SLE)" (213560) is a stand-alone study. According to the MAH, the study is not a measure of any agreed Benlysta Paediatric Investigation Plan and therefore a line listing is not included in this submission.

*CHMP comment:*

An agreement between centre for drug evaluation (CDE) in China and GSK was made to conduct a post approval commitment (PAC) study (Study 213560) in Chinese paediatric patients.

The study is not a measure of any agreed Benlysta Paediatric Investigation Plan and therefore a line listing is not included in this submission.

## *2.2. Information on the pharmaceutical formulation used in the study*

Treatment was given with Belimumab (10 mg/kg) administered IV. This formulation is approved for children from 5 years of age for the treatment of SLE.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

- 213560, A Multi-Center, Open-Label Study to Evaluate Safety, Efficacy and Pharmacokinetics of Belimumab Plus Standard Therapy in Chinese Pediatric Patients with Active Systemic Lupus Erythematosus (SLE)

### 2.3.2. Clinical study

#### 213560, A Multi-Center, Open-Label Study to Evaluate Safety, Efficacy and Pharmacokinetics of Belimumab Plus Standard Therapy in Chinese Pediatric Patients with Active Systemic Lupus Erythematosus (SLE)

#### Description

This was a multicentre, single arm, prospective, 52-week study to assess the safety and efficacy of belimumab IV administered in combination with background standard therapy in 65 paediatric

participants aged 5 to 17 years with active SLE. The PK profile of belimumab was investigated in a tabsubset of participants. The study was open labelled without randomization and blinding.

## Methods

### *Study participants*

Paediatric participants with SLE as diagnosed with American college of rheumatology (ACR) classification criteria who had active disease (defined as safety of oestrogen in lupus national assessment [SELENA] systemic lupus erythematosus disease activity index [SLEDAI] score ≥8) at screening were enrolled. Participants were on stable standard SLE therapy for at least 30 days prior to baseline.

### *Treatments*

Belimumab (10 mg/kg) was administered IV over a minimum of 1 hour on Day 0, Day 14, Day 28, and then every 28 days through the Week 48 (Day 336) visit. All participants continued to receive their standard SLE therapy with restrictions on the changes that were permitted throughout the 52-week observational period.

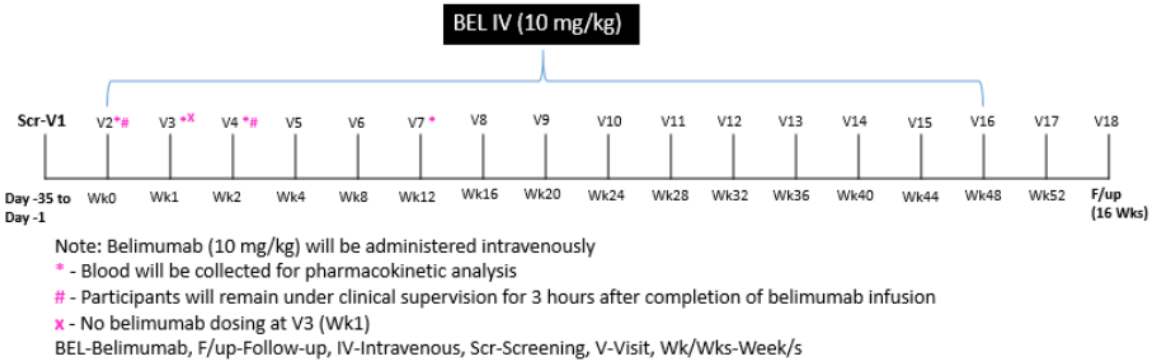
| *CHMP comment:* |
| --- |
| The dose regimen is equal to that of the EU SmPC. |

### *Objectives*

The primary objectives of this study were to evaluate the safety and efficacy of belimumab IV in Chinese paediatric participants with SLE. The secondary objectives included the evaluation of safety, tolerability, efficacy, and PK of belimumab (10 mg/kg) IV in Chinese paediatric participants with SLE.

### *Study design*

Figure 1: Study design




Participants could withdraw or discontinue from the study at any time for any reason. Participants withdrawing from belimumab treatment returned for an Exit Visit, i.e., 4 weeks after their last dose of belimumab, and then continue safety monitoring at the scheduled visit until Day 364 if they were willing to stay in safety monitoring.

*Outcomes/endpoints*

*Primary endpoints*

*Safety*

- Incidence of AESIs through 52 weeks:
- All infections of special interest, including serious infections of special interest and opportunistic infections
- Infusion-related systemic reactions and anaphylactic reactions
- Depression, suicidality
- Malignancies

*Efficacy*

- Incidence of patients with ≥4-point reduction from baseline to Week 52 in SELENA SLEDAI

*Secondary endpoints*

- Incidence of AEs through 52 weeks
- Incidence of SAEs through 52 weeks
- Incidence of participants with ≥4-point reduction from baseline in SELENA SLEDAI by visit
- Change from baseline to Week 52 in physician global assessment (PGA)
- Change from baseline to Week 52 in parent global assessment (ParentGA)
- Change from baseline in daily prednisone equivalent dose at Week 52
- Time to first flare/first severe flare over 52 weeks
- Median belimumab concentration levels at Day 0, 7, and 14 post first dose, and pre-infusion and post-infusion at Day 84
- The PK was evaluated with respect to clearance, volume of distribution and half-life, and individual steady state exposures Cmin, Cavg, Cmax and AUC

*Sample size*

Under the assumption that the incidence rate of serious infections is 7.5% (incidence rate in the global paediatric study (Study BEL114055)), it was calculated that a study with 65 participants would have more than 99.0% probability to observe at least one serious infection. Under this sample size, for any other adverse events, there are more than 90% probability to observe at least one event once the incidence rate is larger than 4%.

For the efficacy purpose, as one of the key efficacy endpoints, the estimated percentage of participants with ≥4-point reduction from baseline in SELENA SLEDAI at Week 52 is 54.7% in BEL114055. A sample size of 65 would produce a 95% CI of [41.9%, 67.1%] when the estimate is 54.7%. Under the assumption that the percentage of participants with ≥4 points reduction from baseline in SELENA SLEDAI at week 52 is 54.7%, it was calculated by simulation that a study with 65 participants would have more than 95.0% probability to observe a percentage larger than 43.6%.

*PK Sample Size Determination*

The FDA recommends that for paediatric studies, the 95% confidence interval of the average CL and V estimates are within 60% to 140% of the geometric mean, with at least 80% power [Wang, 2012]. The same principles were applied in this study, but a more stringent criterion was applied requiring the precision of the CL and V to be determined within 80% to 120% of the geometric mean with at least 80% power. It was recommended to collect PK blood samples from 25 Chinese paediatric patients, which was considered the minimum number to meet this more stringent condition and therefore enable a quantitative comparison with the PK in a Western paediatric population.

*Randomisation and blinding (masking)*

This was an open-label study without randomization and blinding.

*Statistical Methods*

This was an open-label study. A descriptive approach was used, and no formal inference was planned in this study. For primary efficacy evaluation, using the proportion of participants with ≥4-point reduction from baseline in SELENA SLEDAI at Week 52 in the placebo group in a Phase 2 paediatric study (Study BEL114055) as the target value to guide the analysis planned for this study. The target for the observed proportion of participants with clinical benefit was >43.6% (the mean placebo group response rate estimate in Study BEL114055).

## Results

*Participant flow*

A total of 89 participants were screened in the study and 22 (24.7%) participants failed screening. The reason for screen failure was due to unmet inclusion/exclusion criteria (22 [100%] participants), Table 1.

Table 1: Reasons for Failing Screening (Screened Population)

| | **Total (N=89)** |
|---|---|
| Screening status | |
| Screened success | 67 (75.3%) |
| Failed screening | 22 (24.7%) |
| Reason for failed screening [1] | 22 |
| Did not meet inclusion/exclusion criteria | 22 (100%) |

Source: Table 1.2
[1] Percentages were based on the number of participants who failed screening.
Note: A participant can have more than 1 reason for failing screening. Percentages may sum to more than 100%.

A total of 67 participants received at least 1 dose of study intervention and thus were included in the ITT population. Among these, 59 (88.1%) participants completed the Week 52 Visit, Table 2. The reasons for withdrawal from the study prior to Week 52 were lack of efficacy (5 [7.5%] participants), followed by AE (2 [3.0%] participants) and lost to follow-up (1 [1.5%] participant).

Table 2: Participant Completion Status (Intent-to-Treat Population)

| | Belimumab (N=67) |
|---|---|
| Completed Week 52 Visit | 59 (88.1%) |
| Withdrawn prior to Week 52 | 8 (11.9%) |
| Adverse event | 2 (3.0%) |
| Lack of efficacy | 5 (7.5%) |
| Lost to follow-up | 1 (1.5%) |

Source: Table 1.3
Note: Percentages were based on the number of Intent-to-Treat Population.

A total of 59 (88.1%) participants completed the study intervention, while 8 (11.9%) participants discontinued the study intervention, Table 3. The reasons for study intervention discontinuation were lack of efficacy (5 [7.5%] participants), followed by AE (2 [3.0%] participants) and lost to follow-up (1 [1.5%] participant). The participant who was lost to follow-up discontinued the study intervention due to COVID-19 pandemic.

Table 3: Study Intervention Completion Status (Intent-to-Treat Population)

| | Belimumab (N=67) |
|---|---|
| Completed the study intervention | 59 (88.1%) |
| Study intervention discontinuation due to the COVID-19 pandemic | 1 (1.5%) |
| Study intervention discontinuation for reasons unrelated to the COVID-19 pandemic | 7 (10.4%) |
| Withdrawn from the study intervention | 8 (11.9%) |
| Adverse event | 2 (3.0%) |
| Lack of efficacy | 5 (7.5%) |
| Lost to follow-up | 1 (1.5%) |

Source: Table 1.5
Note: Percentages were based on the number of Intent-to-Treat Population.

*Recruitment*

This study was conducted at 9 centres that enrolled participants in China.

*Baseline data*

The majority of participants were females (51 [76.1%]). The age of participants at screening ranged from 5 to 16 years with a median of 13.0 years. The majority of participants (51 [76.1%]) were in the 12 to 17 years age group, while the remaining 16 (23.9%) participants were in the 5 to 11 years age group. The mean (standard deviation [SD]) body mass index (BMI) was 21.6 (3.6) kg/m2. The demographic and baseline characteristics by age group (12 to 17 years vs. 5 to 11 years) were similar, with the following exceptions: as expected, height, weight, and BMI were higher in the 12 to 17 years age group than in the 5 to 11 years age group.

Baseline disease activity was as expected given the study eligibility criteria and was similar between the 12 to 17 years and 5 to 11 years age groups, with the following exceptions: the median (range) SLE disease duration was 0.71 (0.1, 3.2) years in the 5 to 11 years age group and 1.97 (0.1, 12.7) years in the 12 to 17 years age group; the mean (SD) proteinuria level was 0.8 (1.5) mg/mg in the 5 to 11 years age group and 0.4 (0.8) mg/mg in the 12 to 17 years age group.

The most common SELENA SLEDAI organ system involvement (>20% of participants) at baseline was in the immunologic (57 [85.1%] participants), mucocutaneous (56 [83.6%] participants), musculoskeletal (32 [47.8%] participants), and renal (20 [29.9%] participants) domains.

The majority of participants were positive for anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibody (53 [79.1%] participants) and anti-nuclear antibody (ANA) (63 [94.0%] participants). All 67 (100%) participants were positive for anti-dsDNA antibody and/or ANA. Immunoglobulin G, M, and A (Immunoglobulin G [IgG], Immunoglobulin M [IgM], and Immunoglobulin A [IgA]) levels were within normal ranges for the majority of participants. Complement levels (complement factors C3 and C4 [C3 and C4]) were low in 58.2% and 47.8% of participants, respectively.

The most common (>10% of participants) general medical condition was respiratory tract infection (16 [23.9%] participants), followed by hypertension (8 [11.9%] participants).

*Number analysed*

A total of 89 participants were screened in the study and 22 (24.7%) participants failed screening. The reason for screen failure was due to unmet inclusion/exclusion criteria (22 [100%] participants). A total of 67 participants received at least 1 dose of study intervention and thus were included in the intention-to-treat population. Among these, 59 (88.1%) participants completed the Week 52 Visit.

*Efficacy results*

*Primary Efficacy Endpoint:*

At Week 52 (end of the study), 66.7% of participants (95% CI: 55.3%, 78.0%) were considered SELENA SLEDAI responders, which met the study's target of >43.6%.

Table 4: Disposition of SELENA SLEDAI Response at Week 52 (Intent-to-Treat Population)

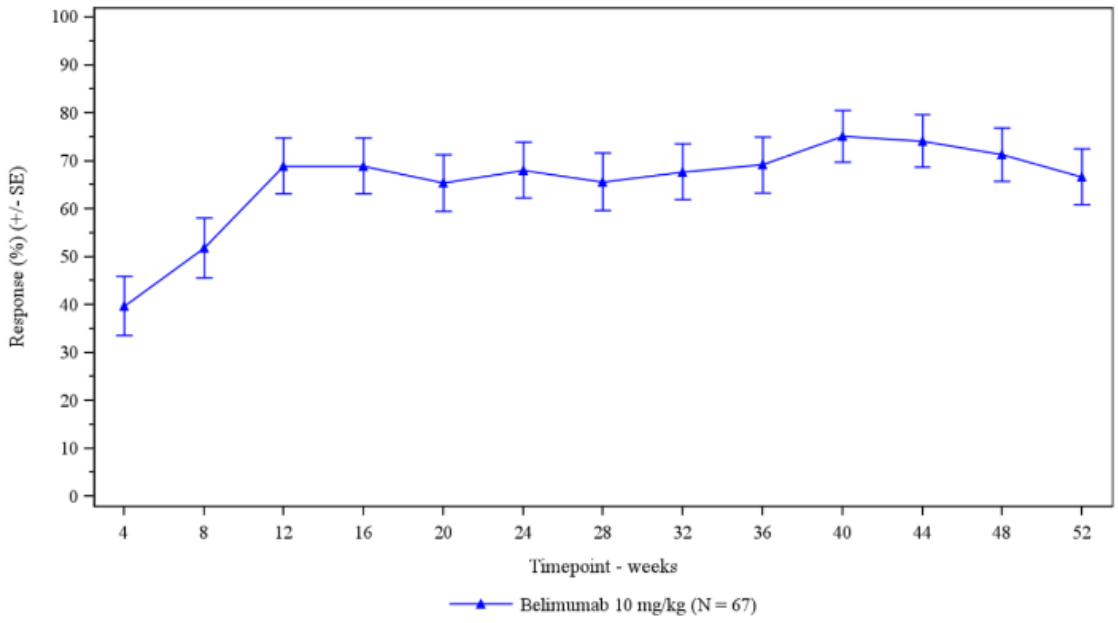
| | **Belimumab (N=67)** |
|---|---|
| n [1] | 66 |
| Responder | 44 (66.7%) |
| Non-responder | 22 (33.3%) |
| <4-point reduction in SELENA SLEDAI | 14 (21.2%) |
| Using prohibited medications | 3 (4.5%) |
| Study intervention discontinuation for any reason | 5 (7.6%) |
| Missing [2] | 0 |

Source: Table 2.2
[1] One participant with baseline SELENA SLEDAI score less than 4 was excluded from the analysis.
[2] If there was any missing data at Week 52, the missing data were to be imputed by MI in the primary estimand.
Note: For participants who used prohibited medications and discontinued study intervention, only the earliest event was counted in this table.

*Secondary Efficacy Endpoints:*

The proportion of SELENA SLEDAI responders showed a continuously rising trend over time, reaching plateau at Week 12 and maintaining through Week 52 (Figure 2).

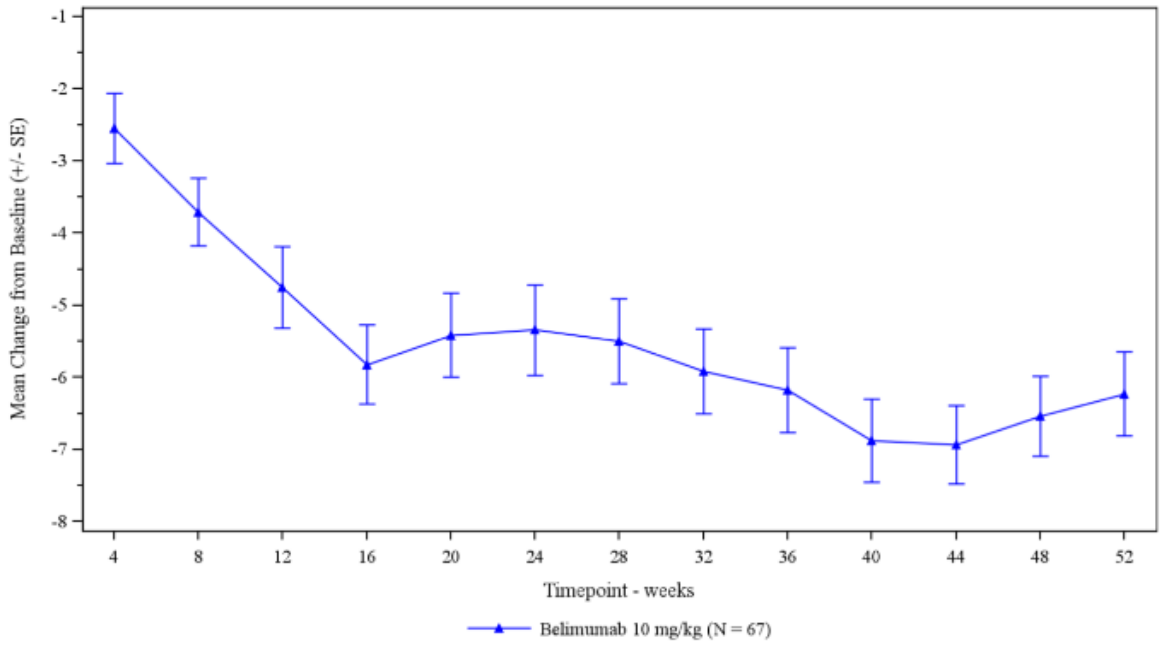
Figure 2: SELENA SLEDAI Response by Visit (Intent-to-Treat Population)




Source: Figure 2.1
Note: One participant with baseline SELENA SLEDAI score less than 4 was excluded from the analysis.
Response at each visit was defined as 1) with ≥4 points reduction from baseline in SELENA SLEDAI, and 2) Not using prohibited medications, and 3) Not discontinuing study intervention for any reason. Each estimate was to be generated for each imputed dataset produced by the MI procedure and the corresponding results were to be combined using Rubin's rules.
In the final datasets, there was no missing data at Week 52, so the MI procedure and Rubin's rules were not used for estimates at Week 52.

The mean change from baseline in SELENA SLEDAI score showed a decreasing trend over time and reached a nadir at Week 44 (Figure 3). A similar trend was observed in the mean percent change from baseline in SELENA SLEDAI score.

Figure 3: Change from Baseline in SELENA SLEDAI by Visit (Intent-to-Treat Population).




Source: Figure 2.2
Note: One participant with baseline SELENA SLEDAI score less than 4 was excluded from the analysis.
Each estimate was generated for each imputed dataset produced by the MI procedure and the corresponding results were combined using Rubin's rules. Hypothetical strategy was applied for ICEs: 1) Initiation of prohibited medications: 2) Study intervention discontinuation.

The mean (standard error [SE]) change from baseline in physician global assessment (PGA) score at Week 52 was a decrease (i.e., improvement) of 0.93 (0.08) (Table 5).

Table 5: Change from Baseline at Week 52 in PGA (Intent-to-Treat Population).

| | **Belimumab (N=67)** |
|---|---|
| n | 67 |
| Mean (SE) | -0.931 (0.0808) |
| SD | 0.6046 |
| Median | -0.966 |
| 25th percentile, 75th percentile | -1.237, -0.563 |
| Min, Max | -2.28, 0.56 |

The mean (SE) change from baseline in parent global assessment (ParentGA) score at Week 52 was a decrease (i.e., improvement) of 2.71 (0.35) (Table 6).

Table 6: Change from Baseline at Week 52 in ParentGA (Intent-to-Treat Population).

| | **Belimumab (N=67)** |
|---|---|
| n | 67 |
| Mean (SE) | -2.71 (0.350) |
| SD | 2.713 |
| Median | -2.90 |
| 25th percentile, 75th percentile | -4.21, -1.15 |
| Min, Max | -9.0, 4.5 |

Based on the observed data, the mean (SE) change from baseline in daily prednisone equivalent dose at Week 52 was a decrease (i.e., improvement) of 6.0 (1.2) mg/day (Table 7).

Table 7: Change from Baseline at Week 52 in Prednisone (Observed) (Intent-to-Treat Population).

| | **Belimumab (N=67)** |
|---|---|
| n | 59 |
| Mean (SE) | -6.020 (1.2104) |
| SD | 9.2970 |
| Median | -7.500 |
| 25th percentile, 75th percentile | -12.500, 0.000 |
| Min, Max | -25.00, 20.00 |

Source: Table 2.23
Note: All corticosteroids were converted to a prednisone equivalent average daily dose (mg/day).

Table 8: Time to First SFI Flare Over 52 Weeks (Intent-to-Treat Population).

| | **Belimumab (N=67)** |
|---|---|
| SFI flare, n (%) [1] | 50 (74.6%) |
| Median days (25th percentile, 75th percentile) [2] | 141.0 (58.0, 333.0) |
| Study day of first SFI flare [3] | |
| n | 50 |
| Median | 96.5 |
| 25th percentile, 75th percentile | 51.0, 147.0 |
| Min, Max | 2, 333 |

Source: Table 2.27
[1] Number (%) of participants with a SFI flare over 52 weeks. Only included post-baseline flares.
[2] Statistics were missing when the number of events was too low to estimate the value.
[3] Among participants experiencing a SFI flare.
Note: Percentages were based on the number of Intent-to-Treat Population.
Severe flares that were triggered only by an increase in SELENA SLEDAI score to >12 were reported as mild/moderate flares if the change from the previous visit was at least 3 points and were excluded otherwise. For participants who used prohibited medications, the event date was the earliest of the first flare date and the date of initiation of prohibited medications. For participants who died during Week 52, the event date was the date of death if no flares. For participants who discontinued from treatment, the date was censored at last flare assessment date if no flares. Time to first flare was defined as (event date - treatment start date + 1).

A total of 50 (74.6%) participants experienced a SLE flare index (SFI) flare over 52 weeks and the median time to the first SFI flare was 141.0 days. Among the participants experiencing any SFI flare, the median time to the first SFI flare was 96.5 days (Error! Reference source not found.).

A total of 18 (26.9%) participants experienced a severe SFI flare over 52 weeks and the median time to the first severe SFI flare was not able to be calculated. Among the participants experiencing a severe SFI flare, the median time to the first severe SFI flare was 59.5 days.

*CHMP comment:*

The target for the observed proportion of participants with clinical benefit was >43.6% (the mean placebo group response rate estimate in Study BEL114055). The study 213560 met its primary efficacy endpoint as 66.7% of the participants were considered SELENA SLEDAI responders at week 52. The proportion of responders was numerically higher compared with study PLUTO (54.7%), which is the study that the paediatric approval in the EU is based on. However, the proportion of patients experiencing a severe flare was higher in study 213560 (26.9%) compared with PLUTO (17.0%).

The inclusion criteria and demographics differed slightly between the two studies. To be included in study 213560, the patient had to have a SELENA SLEDAI score of ≥8 compared with ≥6 in study PLUTO. In study 213560, 79.1% of the participants were positive for anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibody and 94.0% were positive for anti-nuclear antibody (ANA). In PLUTO, all study participants had to be positive for either anti-dsDNA or ANA. Regarding demographics, study 213560 had fewer females (76.1% vs 94.6%) and a slightly lower median age (13 vs 15 years). Due to these differences, inter-study comparisons should be performed with caution.

*Safety results*

Throughout the 52-week on-treatment period:

A total of 56 (83.6%) participants experienced at least 1 adverse event (AE).

A total of 31 (46.3%) participants experienced at least 1 study intervention-related AE.

A total of 19 (28.4%) participants experienced at least 1 serious adverse event (SAE). SAEs by preferred term that were reported in ≥2 participants were rash (4 [6.0%] participants), bronchitis, SLE (both reported in 3 [4.5%] participants), headache, pyrexia, and interstitial lung disease (all reported in 2 [3.0%] participants).

The majority of AEs were mild or moderate in intensity. A total of 7 (10.4%) participants experienced at least 1 severe AE.

A total of 20 (29.9%) participants experienced at least 1 SAE and/or severe AE.

A total of 2 (3.0%) participants experienced at least 1 AE leading to discontinuation of study intervention.

No deaths were reported in the study.

None of the participants reported the following adverse events of special interest (AESIs): malignant neoplasm, post-infusion systemic reaction (PISR), or depression/suicide/self-injury.

No infection AEs met the protocol-defined AESI criteria of serious infections of special interest or opportunistic infections.

Table 9: Adverse Events by System Organ Class (≥5% of Participants) (Intent-to-Treat Population).

| System Organ Class | Belimumab (N=67) |
|---|---|
| Any event | 56 (83.6%) |
| Infections and infestations | 51 (76.1%) |
| Respiratory, thoracic and mediastinal disorders | 13 (19.4%) |
| Skin and subcutaneous tissue disorders | 13 (19.4%) |
| Gastrointestinal disorders | 11 (16.4%) |
| Hepatobiliary disorders | 10 (14.9%) |
| Investigations | 10 (14.9%) |
| General disorders and administration site conditions | 9 (13.4%) |
| Musculoskeletal and connective tissue disorders | 7 (10.4%) |
| Eye disorders | 6 (9.0%) |
| Metabolism and nutrition disorders | 6 (9.0%) |
| Blood and lymphatic system disorders | 5 (7.5%) |
| Injury, poisoning and procedural complications | 5 (7.5%) |
| Nervous system disorders | 5 (7.5%) |

Source: Table 3.2
Note: Percentages were based on the number of Intent-to-Treat Population.
Participants only counted once per SOC.
Only on-treatment AEs were summarized.
AEs were presented in descending order from the MedDRA SOC with the highest overall incidence. If the overall incidence for any 2 or more AE SOCs were equal, the events were presented in alphabetical order.
MedDRA version 27.0.

Table 10: Adverse Events by Preferred Term (≥5% of Participants) (Intent-to-Treat Population).

| Preferred Term | Belimumab (N=67) |
|---|---|
| Any event | 56 (83.6%) |
| Upper respiratory tract infection | 29 (43.3%) |
| COVID-19 | 10 (14.9%) |
| Coronavirus pneumonia | 9 (13.4%) |
| Cough | 9 (13.4%) |
| Hepatic function abnormal | 8 (11.9%) |
| Rash | 8 (11.9%) |
| Bronchitis | 7 (10.4%) |
| Pyrexia | 7 (10.4%) |
| Lymphocyte count decreased | 5 (7.5%) |
| Gastroenteritis | 4 (6.0%) |
| White blood cell count decreased | 4 (6.0%) |

Source: Table 3.4
Note: Percentages were based on the number of Intent-to-Treat Population.
Participants only counted once per PT.
Only on-treatment AEs were summarized.
AEs were presented in descending order from the MedDRA PT with the highest overall incidence. If the overall incidence for any 2 or more AE PTs were equal, the events were presented in alphabetical order.
MedDRA version 27.0.

Table 11: Severe Adverse Events by System Organ Class and Preferred Term (Intent-to-Treat Population).

| System Organ Class<br>Preferred Term | Belimumab<br>(N=67) |
|---|---|
| Any event | 7 (10.4%) |
| Immune system disorders | 2 (3.0%) |
| Hypogammaglobulinaemia | 2 (3.0%) |
| Blood and lymphatic system disorders | 1 (1.5%) |
| Thrombocytopenia | 1 (1.5%) |
| Cardiac disorders | 1 (1.5%) |
| Myocarditis | 1 (1.5%) |
| General disorders and administration site conditions | 1 (1.5%) |
| Pyrexia | 1 (1.5%) |
| Infections and infestations | 1 (1.5%) |
| H1N1 influenza | 1 (1.5%) |
| Investigations | 1 (1.5%) |
| Lymphocyte count decreased | 1 (1.5%) |
| Musculoskeletal and connective tissue disorders | 1 (1.5%) |
| Systemic lupus erythematosus | 1 (1.5%) |

Source: Table 3.9
Note: Percentages were based on the number of Intent-to-Treat Population.
Participants only counted once per SOC/PT.
Only on-treatment AEs were summarized.
AEs were presented in descending order from the MedDRA SOC/PT with the highest overall incidence. If the overall incidence for any 2 or more AE SOCs or PTs were equal, the events were presented in alphabetical order.
MedDRA version 27.0.

Table 12: Serious Adverse Events by System Organ Class and Preferred Term (Intent-to-Treat Population).

| **System Organ Class**<br>**Preferred Term** | **Belimumab**<br>**(N=67)** |
|---|---|
| Any event | 19 (28.4%) |
| Infections and infestations | 7 (10.4%) |
| Bronchitis | 3 (4.5%) |
| COVID-19 | 1 (1.5%) |
| Gastroenteritis | 1 (1.5%) |
| H1N1 influenza | 1 (1.5%) |
| Pneumonia | 1 (1.5%) |
| Upper respiratory tract infection | 1 (1.5%) |
| Urinary tract infection | 1 (1.5%) |
| Skin and subcutaneous tissue disorders | 4 (6.0%) |
| Rash | 4 (6.0%) |
| Alopecia | 1 (1.5%) |
| Musculoskeletal and connective tissue disorders | 3 (4.5%) |
| Systemic lupus erythematosus | 3 (4.5%) |
| Nervous system disorders | 3 (4.5%) |
| Headache | 2 (3.0%) |
| Cerebral infarction | 1 (1.5%) |
| General disorders and administration site conditions | 2 (3.0%) |
| Pyrexia | 2 (3.0%) |
| Respiratory, thoracic and mediastinal disorders | 2 (3.0%) |
| Interstitial lung disease | 2 (3.0%) |
| Pulmonary arterial hypertension | 1 (1.5%) |

| System Organ Class<br>Preferred Term | Belimumab<br>(N=67) |
|---|---|
| Blood and lymphatic system disorders | 1 (1.5%) |
| Thrombocytopenia | 1 (1.5%) |
| Cardiac disorders | 1 (1.5%) |
| Myocarditis | 1 (1.5%) |
| Eye disorders | 1 (1.5%) |
| Eyelid oedema | 1 (1.5%) |
| Gastrointestinal disorders | 1 (1.5%) |
| Gastrointestinal haemorrhage | 1 (1.5%) |
| Immune system disorders | 1 (1.5%) |
| Hypogammaglobulinaemia | 1 (1.5%) |

Source: Table 3.6
Note: Percentages were based on the number of Intent-to-Treat Population.
Participants only counted once per SOC/PT.
Only on-treatment AEs were summarized.
AEs were presented in descending order from the MedDRA SOC/PT with the highest overall incidence. If the overall incidence for any 2 or more AE SOCs or PTs were equal, the events were presented in alphabetical order.
MedDRA version 27.0.

Table 13: Adverse Events Leading to Discontinuation of Study Intervention by System Organ Class and Preferred Term (Intent-to-Treat Population).

| **System Organ Class**<br>**Preferred Term** | **Belimumab (N=67)** |
|---|---|
| Any event | 2 (3.0%) |
| Blood and lymphatic system disorders | 1 (1.5%) |
| Thrombocytopenia | 1 (1.5%) |
| Infections and infestations | 1 (1.5%) |
| Pneumonia | 1 (1.5%) |
| Nervous system disorders | 1 (1.5%) |
| Cerebral infarction | 1 (1.5%) |

Source: Table 3.15
Note: Percentages were based on the number of Intent-to-Treat Population.
Participants only counted once per SOC/PT.
Only on-treatment AEs were summarized.
AEs were presented in descending order from the MedDRA SOC/PT with the highest overall incidence. If the overall incidence for any 2 or more AE SOCs or PTs were equal, the events were presented in alphabetical order.
MedDRA version 27.0.

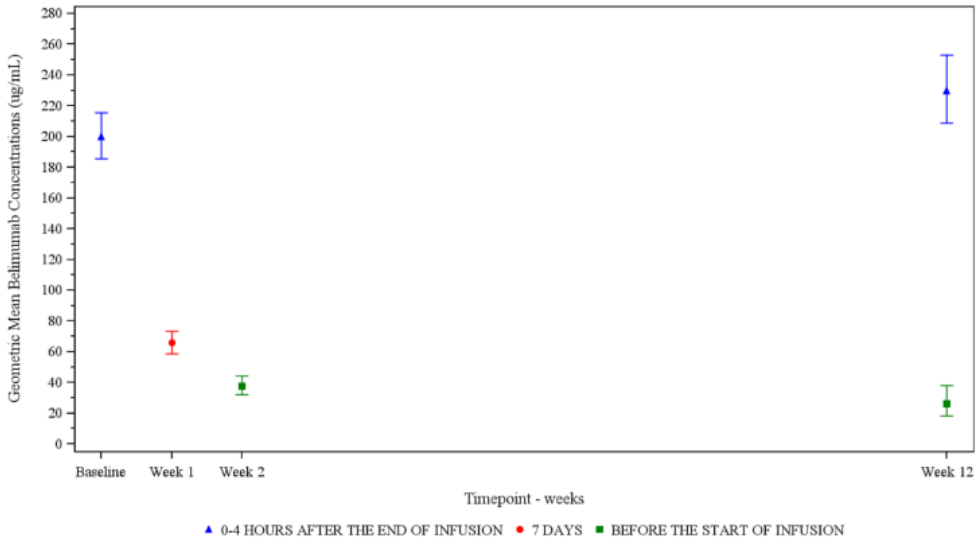
*CHMP comment:*

There were no deaths in this study. None of the study participants reported any of the following adverse events of special interest (AESIs): malignant neoplasm, post-infusion systemic reaction (PISR), or depression/suicide/self-injury. In general, the numbers and type of AEs were similar as already known. However, two cases of interstitial lung disease were reported as SAEs. This condition is not listed as an undesirable effect in the SmPC of Benlysta but could be associated with the underlying disease. The appendix with the narratives referred to by the applicant is however missing and should be provided. Upon request, the applicant summarized the narratives for the two cases with interstitial lung disease. It is agreed with the applicant that these events are considered to be unrelated to belimumab.

*Pharmacokinetics*

The PK population comprised 26 participants who received at least 1 dose of belimumab and for whom at least 1 post belimumab PK sample was obtained and analysed. The belimumab concentration-time results are presented in Figure 4 and the belimumab concentrations are summarized by time point in Table 12. During the interval of the first loading dose, the geometric mean belimumab concentrations of post-infusion (Cmax), Week 1 (Day 7), and pre-infusion of dose at Week 2 (Cmin) were 199.8841 µg/mL, 65.6513 µg/mL, and 37.7244 µg/mL, respectively. At Week 12 (steady state), the pre-infusion (Cmin) and post-infusion (Cmax) geometric mean concentrations were 26.2064 µg/mL and 229.8049 µg/mL, respectively.

Figure 4: Geometric Mean Belimumab Concentrations (µg/mL) (PK Population)




Source: Figure 5.2
Note: Vertical bars represented 95% CIs.

Table 12: Belimumab Concentrations (µg/mL) (Observed) (PK Population).

| Visit<br>Time | Summary | Belimumab (N=26) |
|---|---|---|
| Baseline | n | 24 |
| 0-4 hour post-end of infusion | Geo. Mean (CV%) | 199.8841 (17.3940) |
| | 95% CI | 185.5225, 215.3574 |
| | Median | 197.1173 |
| | Min, Max | 141.9326, 257.3748 |
| Week 1 | n | 26 |
| 7 days | Geo. Mean (CV%) | 65.6513 (25.1695) |
| | 95% CI | 58.7464, 73.3679 |
| | Median | 71.3616 |
| | Min, Max | 35.9532, 100.5913 |
| Week 2 | n | 26 |
| Pre-dose | Geo. Mean (CV%) | 37.7244 (37.3986) |
| | 95% CI | 32.0072, 44.4627 |
| | Median | 37.8585 |
| | Min, Max | 14.5944, 74.1679 |
| Week 12 | n | 25 |
| Pre-dose | Geo. Mean (CV%) | 26.2064 (64.4373) |
| | 95% CI | 18.0892, 37.9660 |
| | Median | 28.2415 |
| | Min, Max | 2.3467, 89.0718 |
| 0-4 hour post-end of infusion | n | 25 |
| | Geo. Mean (CV%) | 229.8049 (22.6740) |
| | 95% CI | 208.6140, 253.1484 |
| | Median | 238.5688 |
| | Min, Max | 139.1862, 357.0316 |

Source: Table 5.1.
Note: Participants 000462 and 000463 were excluded because PK samples of these 2 participants were not collected after study intervention per protocol and the results were below limit of quantitation (<0.1 ug/mL).

*CHMP comment:*

The geometric mean concentrations for Cmax and Cmin at steady state (Week 12) were slightly lower when compared with the values reported in the European SmPC for the same age group. No reason to update the SmPC section 5.2.

### 2.3.3. Discussion on clinical aspects

Since 2019, Benlysta 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. Study 213560 was not a measure of any agreed Benlysta Paediatric Investigation Plan but was based on an agreement between the centre for drug evaluation (CDE) in China and the MAH to conduct a post approval commitment (PAC) study in Chinese paediatric patients.

Hence, study 213560 was a multicentre, single arm, prospective, 52-week study to assess the safety and efficacy of belimumab IV administered in combination with background standard therapy in a target number of 65 paediatric participants aged 5 to 17 years with active SLE. The PK profile of belimumab was investigated in a subset of participants. The study was open-labelled without randomization and blinding.

Participants were enrolled from 9 centres in China. A total of 89 participants were screened and a total of 67 participants received at least 1 dose of study intervention and thus were included in the intention-to-treat population. Among these, 59 (88.1%) participants completed the Week 52 Visit.

Belimumab (10 mg/kg) was administered IV over a minimum of 1 hour on Day 0, Day 14, Day 28, and then every 28 days through the Week 48 (Day 336) visit. The dose regimen is equal to that of the EU SmPC.

The study 213560 met its primary efficacy endpoint as 66.7% of the participants were considered SELENA SLEDAI responders at week 52. The target for the observed proportion of participants with clinical benefit was >43.6% (the mean placebo group response rate estimate in Study BEL114055).

The proportion of responders was numerically higher compared with study PLUTO (54.7%), which is the study that the paediatric approval in the EU is based on. However, the proportion of patients experiencing a severe flare was higher in study 213560 (26.9%) compared with PLUTO (17.0%).

The inclusion criteria and demographics differed slightly between the two studies. To be included in study 213560, the patient had to have a SELENA SLEDAI score of ≥8 compared with ≥6 in study PLUTO. In study 213560, 79.1% of the participants were positive for anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibody and 94.0% were positive for anti-nuclear antibody (ANA). In PLUTO, all study participants had to be positive for either anti-dsDNA or ANA. Regarding demographics, study 213560 had fewer females (76.1% vs 94.6%) and a slightly lower median age (13 vs 15 years). Due to these differences, inter-study comparisons should be performed with caution.

Overall, the efficacy results of this study are in line with what is previously known about Benlysta in the treatment of paediatric SLE.

With regards to safety, there were no deaths in this study. None of the study participants reported any of the following adverse events of special interest (AESIs): malignant neoplasm, post-infusion systemic reaction (PISR), or depression/suicide/self-injury. In general, the numbers and type of AEs were similar as already known. However, two cases of interstitial lung disease were reported as SAEs. This condition is not listed as an undesirable effect in the SmPC of Benlysta but could be associated with the underlying disease. The appendix with the narratives referred to by the applicant is however missing and should be provided. Upon request, the applicant summarized the narratives for the two cases with interstitial lung disease. It is agreed with the applicant that these events are considered to be unrelated to belimumab.

# 3. CHMP overall conclusion and recommendation

In summary, the efficacy results were in line with the PLUTO study which the EU approval for paediatric use was based on. With regards to safety, the adverse events are in line with those reflected in section 4.8 of the SmPC. Some additional information regarding two cases of interstitial lung disease reported as SAE was requested, and the applicant has provided narratives and a summary of the two cases. It is agreed with the applicant that these events are considered to be unrelated to belimumab. No new safety concerns are evoked.

☒ Fulfilled:

No regulatory action required.

# 4. Requested supplementary information in first round

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. There were two cases of interstitial lung disease reported as SAEs. The applicant is requested to submit the full narratives and also to summarize the narratives for these two patients.

## MAH responses to Request for supplementary information

Request 1: There were two cases of interstitial lung disease reported as SAEs. The applicant is requested to submit the full narratives and also to summarize the narratives for these two patients.

RESPONSE 1:

The narrative summaries below are for participants in study 213560 (A Multi-Centre, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Subcutaneously Administered Belimumab Plus Standard Therapy in Chinese Pediatric Participants With Systemic Lupus Erythematosus (SLE)). The summaries utilize information from both the GSK Safety Database and Clinical Line Listings. Full narratives from the GSK Safety Database are provided in Appendix 1.

Participant

This was a 13-year-old female with a history of SLE who presented with fever and chest tightness 153 days following her first dose of belimumab was hospitalized with a diagnosis of interstitial pneumonia and pleural effusion (both Grade 2). The events resulted in interruption of her belimumab dosing. No further dosing of belimumab occurred as the participant was withdrawn from the study due to lack of efficacy.

Treatment medications included methylprednisolone, prednisone, fluconazole, sulfamethoxazol/trimethoprim, piperacillin/tazobactam and ibuprofen.

These events resolved in 21 days (positive rechallenge) and the investigator considered them to be unrelated to belimumab. Key concomitant medications included mycophenolate mofetil, hydroxychloroquine and steroids.

Participant

This was a 14-year-old female with a history of SLE who presented with dyspnoea and was hospitalized with a diagnosis of interstitial lung disease, fever, and pulmonary arterial hypertension (all Grade 2) 6 days following her first dose of belimumab. The events did not result in interruption of her belimumab dosing.

Event treatment medications included dipyridamole, cilastatin sodium/imipenem, prednisone, voriconazole, vancomycin injection, azithromycin, linezolid, furosemide, Qidongyixinkoufuye, cyclophosphamide, potassium chloride, methylprednisolone succinate injection, budesonide inhaled, phytomenadione (Vitamin K1 Injection), desloratadine, ibuprofen and milrinone.

The interstitial lung disease remained unresolved at the time of the participant's withdrawal from the study, 3 months following the onset of these events, while the event of fever resolved within 2 days of onset and the pulmonary arterial hypertension resolved within 4.5 months of onset. The investigator considered these events to be unrelated to belimumab.

Key concomitant medications for SLE included steroids and mycophenolate mofetil.

Summary

The two events summarized above consist of one case of interstitial pneumonia and one case of interstitial lung disease, both requiring hospitalizations. Interstitial pneumonia is generally considered to be part of the broader category of interstitial lung disease as below:

Interstitial Pneumonia refers specifically to a group of inflammatory conditions affecting the lung interstitium. It may be used to describe acute or chronic inflammation in this area, typically caused by infection, autoimmune processes, idiopathic reasons. Examples include idiopathic interstitial pneumonias (IIPs) idiopathic pulmonary fibrosis (IPF) or nonspecific interstitial pneumonia (NSIP).

Interstitial Lung Disease (ILD) is a broader umbrella term encompassing a wide range of disorders that involve the interstitium, leading to inflammation, scarring, or both. ILD includes interstitial pneumonias but also covers other conditions caused by factors like environmental exposures (e.g., asbestosis), connective tissue diseases (e.g., rheumatoid arthritis-associated ILD), or drug reactions.

Reviewing the two cases in question, one appears to be an infectious interstitial pneumonia as evidenced from her presentation and subsequent treatment. In this instance, the investigator did not attribute this event to treatment with belimumab. The second case has an event that appears to be consistent with an underlying ILD process. The event was reported 6 days after initiation of belimumab and considering the nature of the event and the fact that this was reported within days after the first dose, it was not considered to be related to belimumab. Drug-induced interstitial lung disease (DILD) is often categorized into acute (days to weeks), subacute (weeks to months), and chronic (months to years) forms. Literature suggests that most cases occur within the first 6 months of treatment, with a peak incidence often reported around 2 to 3 months. Certain drugs associated with drug induced ILD may have more rapid onset of ILD after initiation of treatment such as nitrofurantoin (days) and immune checkpoint inhibitors (as early as one to 2 weeks). The pathophysiology of these drugs which are related to acute DILD include oxidative stress and immune related hypersensitivity (Type I or III) in the case of nitrofurantoin and immune hyperactivation and cytokine release in the case if immune checkpoint inhibitors. These are mechanisms distinct from the known physiologic effects of belimumab and BlyS inhibition. [Bridi, 2024 Sep 27,][Jiang, 1177][Fujiwara, 2024]

It is important to note that ILD associated with SLE is a recognized condition which may occur in these patients. The prevalence of ILD in patients with SLE is thought to be below 5%, though has been noted as high as 29% in a Japanese study.[Richter, 2023 May 28][Lee, 1097][Narváez, 1186][Amarnani, 2020][Toyoda, 2019 Jun 21]

*CHMP comment:*

The applicant has provided narratives for the two cases in which interstitial lung disease were reported.

The first case was a 13-year-old female with SLE who was diagnosed with infectious pneumonia and pleural effusion 153 days after her first dose of belimumab. She was hospitalized, treated with antibiotics, and the condition resolved after 21 days.

The second case was a 14-year-old female with SLE who was diagnosed with interstitial lung disease, fever, and pulmonary arterial hypertension 6 days after her first dose of belimumab. She was hospitalized and treated with antibiotics, diuretics, and corticosteroids. Belimumab treatment was however not interrupted. The fever resolved after 2 months, but the interstitial lung disease was still unresolved after 3 months. The pulmonary arterial hypertension resolved within 4.5 months.

It is agreed with the applicant that the first case likely was an infectious interstitial pneumonia, and that the second case might be an underlying interstitial lung disease associated with SLE. Hence, the conclusion that these events were unrelated to belimumab is supported. Nonetheless, for the second case, an association with belimumab cannot be completely ruled out. Since only two cases of interstitial lung disease were reported and the type of interstitial lung disease apparently differ between these two cases, the matter is not further pursued.