25 June 2026
EMADOC-1700519818-3321070
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/0000325489

## 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 | 30 March 2026 | 30 March 2026 |
| ☐ | CHMP comments | 13 April 2026 | 13 April 2026 |
| ☐ | Updated CHMP Rapporteur AR | 16 April 2026 | 16 April 2026 |
| ☐ | CHMP outcome | 23 April 2026 | 23 April 2026 |
| ☐ | Re-start of Procedure | 27 May 2026 | 27 May 2026 |
| ☐ | CHMP Rapporteur AR | 10 June 2026 | 10 June 2026 |
| ☐ | CHMP Comments | 15 June 2026 | n/a |
| ☐ | Updated CHMP Rapporteur AR | 18 June 2026 | n/a |
| ☒ | CHMP Outcome | 25 June 2026 | 25 June 2026 |

[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 23 January 2026, 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*

Belimumab intravenous (IV) use was approved in the USA in 2011 as an add-on treatment for adult patients with autoantibody positive systemic lupus erythematosus (SLE) despite standard therapy. Belimumab IV has since been approved for adults with SLE in all European Economic Area (EEA) countries, the United Kingdom (UK) and Japan as well as over 25 further countries. Results from a global Phase 2 study (BEL110455) with belimumab IV in paediatric SLE patients have supported approval of belimumab for SLE paediatric indication in children 5-17 years of age in the USA (approval on 26 April 2019), the European Union (EU) (approval on 21 October 2019) and Japan (20 September 2019).

The MAH stated that the study 212670 *BENLYSTA for Intravenous Injection Paediatric Special Drug Use Investigation* 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*

In the majority of cases, the intravenous formulation was used, however some patients received the subcutaneous formulation, see tables 1 and 2.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for study 212670: *BENLYSTA for Intravenous Injection Paediatric Special Drug Use Investigation*.

The objective of this study was to collect and assess the information about the long-term safety and effectiveness of Benlysta in paediatric patients (aged <15 years) in daily clinical practice, and started according to the conditions of approval by targeting all paediatric patients who had received Benlysta after its paediatric dosage was approved. As of the end of registration, 180 patients were registered in total.

### 2.3.2. Clinical study

### Clinical study number and title

212670 BENLYSTA for Intravenous Injection Paediatric Special Drug Use Investigation.

## Description

## Methods

This was a multicenter, single arm, real-world study to assess the safety and efficacy of IV belimumab administered to paediatric patients (aged ≤15 years) in daily clinical practice in Japan. This was an open-label study without randomization and blinding. The observation period was 52 weeks after the start of belimumab treatment, however, patients were followed for adverse events (AEs) until they discontinued belimumab treatment and for up to 3 years after the start of belimumab treatment if they continued receiving belimumab.

### *Study participants*

The study aimed to include paediatric patients to whom Benlysta was administered after approval of the paediatric dosage. In addition, among patients who started administration after approval of the paediatric dosage, those to whom Benlysta has already administered before the conclusion of the contract and those who has already started administration at diagnosis, because of hospital transfer, etc. was intended to be included as well.

### *Objective*

The objective of this study was to collect and assess the information about the long-term safety and effectiveness of Benlysta in paediatric patients (aged <15 years) in daily clinical practice.

### *Outcomes/endpoints*

According to the protocol summary in this study, the safety specifications are as follows, and occurrence of adverse drug reactions (ADRs), etc. will be monitored.

- Serious hypersensitivity
- Serious infections (including tuberculosis (TB), pneumonia, pneumocystis jiroveci pneumonia (PCP), sepsis, and opportunistic infection (OI))
- Reactivation of hepatitis B (HB) virus
- Progressive multifocal leukoencephalopathy (PML)
- Interstitial pneumonia
- Malignant tumour (MT)
- Depression, suicidal ideation and suicide attempt

There were no specified effectiveness considerations.

The following observation items were collected:

- Information about a medical institution
- Patient characteristics (at the start of Benlysta treatment)
- Screening test regarding TB before the start of administration
- Screening test regarding HB before the start of administration
- Pre-treatment drugs for systemic lupus erythematosus (hereinafter referred to as "SLE")
- Administration status of Benlysta
- Withdrawal of consent for publication of the study results
- Concomitant drugs (SLE drugs)
- Concomitant drugs (except SLE drugs)
- Concomitant therapies intended for SLE (except drugs)
- Vaccination
- Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index (hereinafter, SELENA SLEDAI), Physician's global assessment (hereinafter, PGA))
- Laboratory tests
- Continuation status of Benlysta administration at the end of the observation period
- Possibility of study continuation
- Pregnancy

- AEs
- Two-year follow-up investigation after the end of the observation period

***Sample size***

According to the protocol summary, the targeted number of patients were 115 (as safety analysis set).

***Randomisation and blinding (masking)***

The study was an open label observational study; there were no randomisation or blinding.

## Results

***Participant flow and recruitment***

Of 175 patients registered into the study, 24 did not have their Case Report Form (CRF) collected. The remaining 151 patients were included in the safety analysis. Of these, 150 received belimumab for SLE that has not responded adequately to prior treatment and 1 received belimumab for Mixed Connective Tissue Disease (MCTD). 143 of these patients were included in the efficacy analysis set (1 was excluded as they received belimumab off label for MCTD; 7 were excluded as they received SQ belimumab).

The patient composition is displayed in the figure below:

*Figure 1 Patient Composition*

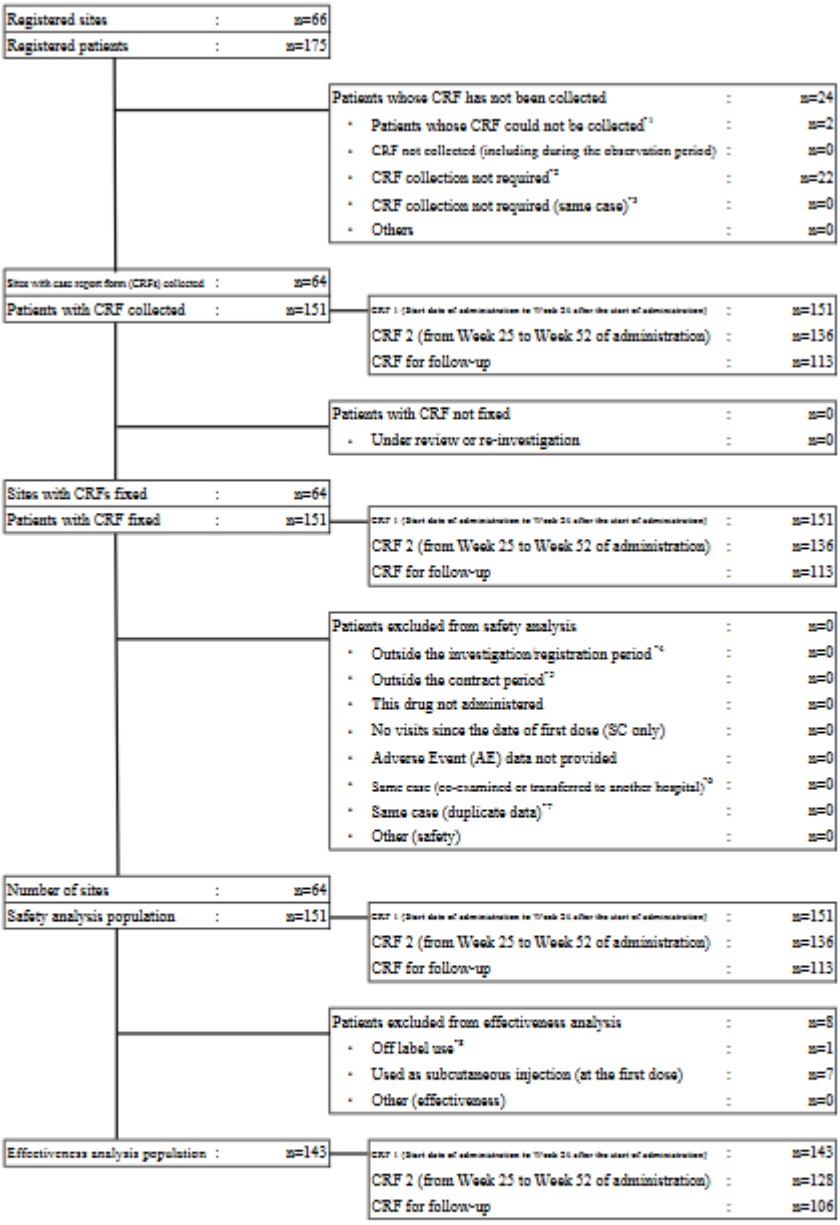


Fig. 2.1-1 Patient Composition

*1: Patients whose CRF could not be collected due to hospital or department closure, etc.
*2: Patients whose CRF collection was not required because they were not subject to CRF collection as agreed with PMDA
*3: Patients for whom collection of the CRF became unnecessary because the patient information was collectively entered at another site due to co-diagnosis, etc.
*4: Patients whose treatment with Benlysta /observation did not end within the study period or those who were registered outside the registration period
*5: Patients whose date of registration is outside the contract period.
*6: Patients who were co-examined or transferred to another hospital and determined to be the same patient
*7: Patients in which the same information was described redundantly and determined to be the same patients
*8: Mixed connective tissue disease(1 patient)

### ***Baseline data***

Among the 151 patients of the safety analysis set, the percentage of females was 82.8% and the age was 11.6±2.4 years. Around 61.5% of the patients were 12 years or above and 3 patients were below 5 years. The number of patients with weight below 40 kg (47.6%) or above 40 kg (51.0%) were similar. The duration of SLE was 1.71±2.01 years. The SELENA SLEDAI score at the start of Benlysta

(baseline) was 8.0±6.6 and the most common affected systems were immune system (72.8%), renal system (42.4%) and the mucocutaneous system (19.2%).

The most common comorbidities were "lupus nephritis" in 78 patients (51.7%), followed by "hypertension" in 29 patients (19.2%), and "constipation" in 18 patients (11.9%).

The most common classes of pre-treatment drugs were "immunosuppressants" in 128 patients (84.8%), followed by "steroids" in 123 patients (81.5%), and "antimalarials" in 95 patients (62.9%). The most common classes of concomitant drugs were "steroids" in 149 patients (98.7%), followed by "immunosuppressants" in 147 patients (97.4%), and "antimalarials" in 117 patients (77.5%).

Similar patient characteristics and patterns of drug use were observed in the 143 patients in the efficacy analysis set.

***Efficacy results***

Efficacy was assessed by changes in SELENA SLEDAI score, PGA score, steroid dose and laboratory parameters and by attainment of Lupus Low Disease Activity State (LLDAS). Patients in whom the SELENA SLEDAI score decreased by ≥4 from baseline were regarded as responders in calculating the response rate. The average daily steroid dose was calculated on the basis of prednisolone.

*SELENA SLEDAI*

Of the 143 patients in the efficacy analysis set, the mean±SD of SELENA SLEDAI score at baseline was 7.8±6.1. There were 127 patients with SELENA SLEDAI scores available both at baseline and at discontinuation/completion; the response rate among them was 44.9% (57/127 patients) and the change from baseline. The applicant points out that in the global phase II pediatric study (Study BEL114055), the mean±SD of SELENA SLEDAI score in the Benlysta group at baseline was 10.3±3.34, and the response rate at Week 52 was 54.7% (29/53 patients). In addition, the change in mean SELENA SLEDAI score at Week 52 compared to baseline was -47.58% while in Study BEL114055 it was -50.8%. Therefore, the applicant pointed out that, in this study, the response rate and the change in mean SELENA SLEDAI score at Week 52 were lower than in Study BEL114055. According to the applicant, this is likely due to the fact that the mean SELENA SLEDAI score at baseline was lower in this study compared to study BEL114055, suggesting that the study included more patients with relatively low disease activity compared to study BEL114055 thus leaving less room for reduction in the SELENA SLEDAI score.

The mean PGA score at baseline was 1.21 (n=98), and the change in percentage (mean) was -63.92% at Week 52 (n=66). In Study BEL114055, the mean of PGA score in the Benlysta group (n=53) at baseline was 1.341, and the change in the percentage of PGA score from baseline at Week 52 (adjusted mean) was -63.109%. The applicant stated that the change in PGA at Week 52 in this study was comparable to that in Study BEL114055.

The mean daily steroid dose at baseline (n=137) was 19.35 mg/day, and the mean change was -14.75 mg/day at Week 52 (n=73). The mean anti-dsDNA antibody level was 79.361 IU/mL at baseline (n=121) and 25.515 IU/mL at Week 52 (n=101); the mean C3 was 84.50 mg/dL at baseline (n=140) and 97.36 mg/dL at Week 52 (n=114); and the mean C4 was 13.44 mg/dL at baseline (n=140) and 17.57 mg/dL at Week 52 (n = 115).

To assess efficacy in patients with different organ involvement, response rates were assessed in patients with renal impairment, hepatic impairment, severe lupus nephritis, and CNS lupus. The response rates were 49.3% (37/75) in patients with renal impairment, 76.9% (10/13) in patients with hepatic impairment, 61.3% (19/31) in patients with severe lupus nephritis and 100.0% (2/2) in

patients with severe CNS lupus. Thus, the applicant concluded that the response rate in patients with specific organ involvement was higher than that in the overall patient population

***CHMP comment:***

The provided efficacy data does not evoke any concerns.

## ***Safety results***

*Table 1 Composition Ratio of treatment with Benlysta*

| | | Safety analysis population | | Effectiveness analysis population | |
|---|---|---|---|---|---|
| | | Number of investigated patients | Composition ratio (%) | Number of investigated patients | Composition ratio (%) |
| Total | | 151 | 100.0 | 143 | 100.0 |
| Route of initial administration *1 | IV | 144 | 95.4 | 143 | 100.0 |
| | SC | 7 | 4.6 | 0 | 0.0 |
| | AI | 7 | 100.0 | - | |
| | PFS | 0 | 0.0 | - | |
| | Unknown | 0 | 0.0 | - | |
| | Unknown | 0 | 0.0 | 0 | 0.0 |
| Route of administration | IV | 130 | 86.1 | 129 | 90.2 |
| | SC | 6 | 4.0 | 0 | 0.0 |
| | Change *2 | 15 | 9.9 | 14 | 9.8 |
| | Unknown | 0 | 0.0 | 0 | 0.0 |
| Duration of treatment [days] | <28 | 5 | 3.3 | 5 | 3.5 |
| | 28≤ - <168 | 7 | 4.6 | 7 | 4.9 |
| | 168≤ - <364 | 71 | 47.0 | 67 | 46.9 |
| | 364≤ | 68 | 45.0 | 64 | 44.8 |
| | Unknown | 0 | 0.0 | 0 | 0.0 |
| Total number of doses (IV) *3 | <6 | 15 | 10.3 | 14 | 9.8 |
| | 6≤ - <11 | 16 | 11.0 | 16 | 11.2 |
| | 11≤ - <15 | 78 | 53.8 | 78 | 54.5 |
| | 15≤ | 36 | 24.8 | 35 | 24.5 |
| | Unknown | 0 | 0.0 | 0 | 0.0 |
| Total number of doses(SC) *4 | <13 | 5 | 23.8 | 5 | 35.7 |
| | 13≤ - <25 | 3 | 14.3 | 3 | 21.4 |
| | 25≤ - <37 | 4 | 19.0 | 4 | 28.6 |
| | 37≤ - <52 | 5 | 23.8 | 2 | 14.3 |
| | 52≤ | 4 | 19.0 | 0 | 0.0 |
| | Unknown | 0 | 0.0 | 0 | 0.0 |
| Total dosage (IV) [mg/kg] *3 | ≤50 | 15 | 10.3 | 14 | 9.8 |
| | 50< - ≤100 | 19 | 13.1 | 19 | 13.3 |
| | 100< - ≤140 | 78 | 53.8 | 78 | 54.5 |
| | 140< | 33 | 22.8 | 32 | 22.4 |
| | Unknown | 0 | 0.0 | 0 | 0.0 |
| Total dosage (SC) [mg] *4 | ≤2400 | 5 | 23.8 | 5 | 35.7 |
| | 2400< - ≤4800 | 3 | 14.3 | 3 | 21.4 |
| | 4800< - ≤7200 | 4 | 19.0 | 4 | 28.6 |
| | 7200< - ≤10200 | 5 | 23.8 | 2 | 14.3 |
| | 10200< | 4 | 19.0 | 0 | 0.0 |
| | Unknown | 0 | 0.0 | 0 | 0.0 |
| Mean single dose (IV) [mg/kg] *3 | <10 | 33 | 22.8 | 32 | 22.4 |
| | 10 | 106 | 73.1 | 105 | 73.4 |
| | 10< | 6 | 4.1 | 6 | 4.2 |
| | Unknown | 0 | 0.0 | 0 | 0.0 |
| Mean single dose (SC) [mg] *4 | <200 | 0 | 0.0 | 0 | 0.0 |
| | 200 | 21 | 100.0 | 14 | 100.0 |
| | 200< | 0 | 0.0 | 0 | 0.0 |
| | Unknown | 0 | 0.0 | 0 | 0.0 |

*1 IV: intravenous infusion; SC: subcutaneous injection; AI: autoinjector; PFS: subcutaneous injection syringe (prefilled syringe)
*2 For IV and SC, the number of patients is calculated excluding changes.
*3 The number of patients who received the drug by route of administration (IV) was tabulated.
*4 The number of patients who received the drug by route of administration (SC) was tabulated.

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*Table 2 Summary Statistics of Administration of Benlysta*

| Descriptor | | Safety analysis population | Effectiveness analysis population |
|---|---|---|---|
| Total | | 151 | 143 |
| Duration of treatment [days] | Number of patients | 151 | 143 |
| | Mean±SD | 329.3±91.9 | 327.1±93.9 |
| | Maximum | 470 | 470 |
| | 75% quartile | 370.0 | 370.0 |
| | Median | 361.0 | 360.0 |
| | 25% quartile | 339.0 | 338.0 |
| | Minimum | 1 | 1 |
| Total number of doses (IV)*1 | Number of patients | 145 | 143 |
| | Mean±SD | 12.1±3.9 | 12.2±3.8 |
| | Maximum | 17 | 17 |
| | 75% quartile | 14.0 | 14.0 |
| | Median | 14.0 | 14.0 |
| | 25% quartile | 11.0 | 11.0 |
| | Minimum | 1 | 1 |
| Total number of doses (SC)*2 | Number of patients | 21 | 14 |
| | Mean±SD | 30.1±19.7 | 20.3±16.2 |
| | Maximum | 57 | 50 |
| | 75% quartile | 46.0 | 33.0 |
| | Median | 33.0 | 16.5 |
| | 25% quartile | 14.0 | 5.0 |
| | Minimum | 1 | 1 |
| Total dosage (IV) [mg/kg]*1 | Number of patients | 145 | 143 |
| | Mean±SD | 118.623±38.597 | 119.050±37.993 |
| | Maximum | 170.00 | 170.00 |
| | 75% quartile | 140.000 | 140.000 |
| | Median | 132.700 | 132.700 |
| | 25% quartile | 110.000 | 110.000 |
| | Minimum | 8.60 | 8.60 |
| Total dosage (SC) [mg]*2 | Number of patients | 21 | 14 |
| | Mean±SD | 6019.0±3931.4 | 4057.1±3239.6 |
| | Maximum | 11400 | 10000 |
| | 75% quartile | 9200.0 | 6600.0 |
| | Median | 6600.0 | 3300.0 |
| | 25% quartile | 2800.0 | 1000.0 |
| | Minimum | 200 | 200 |
| Mean single dose (IV) [mg/kg]*1 | Number of patients | 145 | 143 |
| | Mean±SD | 9.802±0.680 | 9.808±0.679 |
| | Maximum | 12.00 | 12.00 |
| | 75% quartile | 10.000 | 10.000 |
| | Median | 10.000 | 10.000 |
| | 25% quartile | 10.000 | 10.000 |
| | Minimum | 6.00 | 6.00 |
| Mean single dose (SC) [mg]*2 | Number of patients | 21 | 14 |
| | Mean±SD | 200.0±0.0 | 200.0±0.0 |
| | Maximum | 200 | 200 |
| | 75% quartile | 200.0 | 200.0 |
| | Median | 200.0 | 200.0 |
| | 25% quartile | 200.0 | 200.0 |
| | Minimum | 200 | 200 |

*1 The number of patients who received the drug by route of administration (IV) was tabulated.
*2 The number of patients who received the drug by route of administration (SC) was tabulated.

*Table 3 Adverse events*

| | Total | | Serious | |
|---|---|---|---|---|
| Number of investigated patients | 151 | | | |
| Number of patients with ADRs | 31 | | 16 | |
| Incidence rate of ADRs | 20.5 | | 10.6 | |
| Type of ADR | Number of patients with events (%) | | | |
| Infections and infestations | 21 | (13.9) | 11 | (7.3) |
| Herpes zoster | 7 | (4.6) | 4 | (2.6) |
| Cystitis | 2 | (1.3) | | |
| Gastroenteritis | 2 | (1.3) | 1 | (0.7) |
| Nasopharyngitis | 2 | (1.3) | | |
| COVID-19 | 2 | (1.3) | 1 | (0.7) |
| Appendicitis | 1 | (0.7) | 1 | (0.7) |
| Campylobacter gastroenteritis | 1 | (0.7) | 1 | (0.7) |
| Genital candidiasis | 1 | (0.7) | | |
| Paronychia | 1 | (0.7) | | |
| Tonsillitis | 1 | (0.7) | | |
| Adenovirus infection | 1 | (0.7) | | |
| Enterocolitis bacterial | 1 | (0.7) | 1 | (0.7) |
| Oral herpes | 1 | (0.7) | | |
| Aspergillus infection | 1 | (0.7) | 1 | (0.7) |
| Herpes zoster cutaneous disseminated | 1 | (0.7) | 1 | (0.7) |
| General disorders and administration site conditions | 3 | (2.0) | 1 | (0.7) |
| Injection site pain | 1 | (0.7) | | |
| Malaise | 1 | (0.7) | 1 | (0.7) |
| Infusion site pain | 1 | (0.7) | | |
| Immune system disorders | 2 | (1.3) | 2 | (1.3) |
| Hypersensitivity | 1 | (0.7) | 1 | (0.7) |
| Hypogammaglobulinaemia | 1 | (0.7) | 1 | (0.7) |
| Psychiatric disorders | 2 | (1.3) | 1 | (0.7) |
| Depressive symptom | 2 | (1.3) | 1 | (0.7) |
| Intentional self-injury | 1 | (0.7) | 1 | (0.7) |
| School refusal | 1 | (0.7) | | |
| Social avoidant behaviour | 1 | (0.7) | | |
| Suicidal ideation | 1 | (0.7) | 1 | (0.7) |
| Discouragement | 1 | (0.7) | | |
| Gastrointestinal disorders | 2 | (1.3) | 2 | (1.3) |
| Diarrhoea | 1 | (0.7) | 1 | (0.7) |
| Enterocolitis | 1 | (0.7) | 1 | (0.7) |
| Nausea | 1 | (0.7) | 1 | (0.7) |
| Vomiting | 1 | (0.7) | 1 | (0.7) |
| Skin and subcutaneous tissue disorders | 2 | (1.3) | 1 | (0.7) |
| Acne | 1 | (0.7) | | |
| Erythema | 1 | (0.7) | 1 | (0.7) |
| Blood and lymphatic system disorders | 1 | (0.7) | | |
| Hypoglobulinaemia | 1 | (0.7) | | |
| Renal and urinary disorders | 1 | (0.7) | 1 | (0.7) |
| Renal impairment | 1 | (0.7) | 1 | (0.7) |
| Laboratory tests | 1 | (0.7) | | |
| Prothrombin time prolonged | 1 | (0.7) | | |

MedDRA/J (27.1)

*Table 4 Adverse events of special interest*

| Number of patients in the safety analysis set | 151 | | | |
|---|---|---|---|---|
| Safety specification | Serious | | Non-serious | |
| | Number of patients with events | (Incidence rate) | Number of patients with events | (Incidence rate) |
| Important identified risk | - | | - | |
| Important identified risk [Serious hypersensitivity] | 1 | (0.7) | - | - |
| Important identified risk [Serious infections (including tuberculosis, pneumonia, pneumocystis jiroveci pneumonia, sepsis, and opportunistic infection)] | 11 | (7.3) | - | - |
| Important identified risk [Reactivation of hepatitis B virus] | 0 | (0.0) | 0 | (0.0) |
| Important identified risk [Progressive multifocal leukoencephalopathy (PML)] | 0 | (0.0) | 0 | (0.0) |
| Important identified risk [Depression, suicidal ideation, suicide attempt]) | 1 | (0.7) | 1 | (0.7) |
| Important potential risk | - | | - | |
| Important potential risk [Interstitial pneumonia] | 0 | (0.0) | 0 | (0.0) |
| Important potential risk [Malignant tumour] | 0 | (0.0) | 0 | (0.0) |

MedDRA/J (27.1)

ADRs were reported in 31 patients (20.5%). The highest incidence rate of ADRs by system organ class (SOC) was infections and infestations in 13.9% (21/151 patients), followed by general disorders and administration site conditions in 2.0% (3/151 patients).

By type, the most frequently reported ADR was herpes zoster in 7 patients, followed by cystitis, gastroenteritis, nasopharyngitis, COVID-19, and depressive symptom in 2 patients each.

Serious ADRs were reported in 16 patients. The most frequently reported serious ADR was herpes zoster (4 patients).

One AE resulting in death was reported in a patient with intra-abdominal haemorrhage. According to the applicant, the investigator reported the event as a complication of microvascular disorder and a relationship with belimumab was unlikely.

**Factors affecting the onset of ADRs**

In order to investigate factors that may affect the onset of ADRs, univariate analyses were performed by patient characteristics in the safety analysis set. In addition, a multivariate analysis was performed using factors in consideration of correlations among variables, etc. Since there were too many factors to calculate appropriately for collected cases, a multivariate analysis was performed again with a reduced number of factors in an *ad-hoc* analysis. "Sex," "age," "duration of SLE," "presence of comorbidity (renal impairment)," "presence of comorbidity (hepatic impairment)," and "SELENA SLEDAI (baseline)" were used as explanatory variables to estimate the adjusted odds ratio.

Factors for which the adjusted odds ratio in the occurrence of ADRs by patient background met the criterion of "the asymptotic 95% confidence interval does not include 1, and the point estimate is >2 or <0.5" were investigated. As a result, factors meeting the above criteria were found in "presence of comorbidity (renal impairment)" and "presence of comorbidity (hepatic impairment)" in both univariate and multivariate analyses.

*Renal impairment:*

For the incidence rate of ADRs by presence of comorbidity (renal impairment), the incidence rate of ADRs in patients who had comorbidity (renal impairment) was 27.3% (24/88 patients), which was higher than that in patients who didn't (11.1%, 7/63 patients). The types, seriousness, etc., of ADRs were investigated by presence of comorbidity (renal impairment). The incidence rate of infections (MedDRA SOC "infections and infestations") as ADRs in patients who had comorbidity tended to be higher (19.3%, 17/88 patients) than in those who didn't (6.3%, 4/63 patients).

The applicant put forward the following: For infections, the electronic package insert of Benlysta states "Serious infections such as pneumonia, sepsis, and TB may occur" as a clinically significant ADR and also provides the following Important Precautions: "Benlysta may increase the risk of infections. Therefore, when Benlysta is administered, patients should be closely monitored and caution should be exercised for the onset or exacerbation of infections. Patients should be instructed to contact their attending physician immediately if any signs or symptoms of infection appear."

The applicant stated that renal impairment is known to be a risk factor of infections in patients with SLE, and it was inferred that concurrent renal impairment may have increased the incidence rate of infections. On the other hand, the outcomes of all infection-related ADRs reported in this study were 'resolved' or 'resolving.' Therefore, the applicant considered it unnecessary to take any additional actions at present, such as revision of the electronic package insert.

*Hepatic impairment*

For the incidence rate of ADRs by presence of comorbidity (hepatic impairment), the incidence rate of ADRs in patients who had comorbidity (hepatic impairment) was 42.9% (6/14 patients), which was higher than that in patients who didn't (18.2%, 25/137 patients).

The types, seriousness, etc. of ADRs were investigated by presence of comorbidity (hepatic impairment). The incidence rate of infections (MedDRA SOC "infections and infestations") as ADRs in patients who had the comorbidity tended to be higher (28.6%, 4/14 patients) than in those who didn't (12.4%, 17/137 patients). The applicant stated that as the number of patients with the comorbidity was small (n=14) compared with those without the comorbidity (n=137), the observed finding may reflect an imbalance in sample sizes between stratification categories. However, the outcomes of all infection-related ADRs reported in this study were 'resolved' or 'resolving.' Therefore, the applicant considered it unnecessary to take any additional actions at present.

In the 31 patients in whom ADRs were reported among the 151 patients in the safety analysis set, the time to onset (initial onset) of ADRs from the first dose of Benlysta was examined by type of ADRs. As a result, ADRs occurred within <140 days of treatment in 41.9% of the patients, but according to the applicant, there was no notable trend in the time to onset of ADRs. For serious infections (including TB, pneumonia, PCP, sepsis, and OI) reported in the 113 patients with the follow-up CRF fixed, ADRs (initial onset) was observed in 2 patients within 588 days, but no notable trend was observed in the onset of ADRs.

Safety specification

There were no ADRs related to reactivation of HB virus, PML, interstitial pneumonia, or malignant tumours (MT).

*Serious hypersensitivity*

The incidence rate of serious hypersensitivity-related ADRs was 0.7% (1/151 patients). The types of reported ADRs were "hypersensitivity" and "erythema" in 1 patient (2 events). The outcome was "recovered/resolved" in all the cases. The incidence, type, and outcome of serious hypersensitivity-related AEs were the same as those of ADRs. The applicant highlighted that in a global phase II

paediatric study (Study BEL114055) (up to Week 52) conducted before approval, the incidence rate of AEs related to "infusion reaction" in the Benlysta group was 7.5% (4/53 patients), including no serious cases.

The applicant put forward the following: Regarding hypersensitivity, the electronic package insert of Benlysta states that "Serious hypersensitivity such as shock and anaphylaxis (blood pressure decreased, urticaria, angioedema, dyspnoea, etc.) may occur. In addition, these symptoms may occur late. These delayed reactions may include rash, nausea, fatigue, myalgia, headache, face oedema, etc." and as Important Precautions, "Hypersensitivity associated with Benlysta has been reported and it can become serious or fatal. In addition, hypersensitivity reactions may occur later. Patients should be instructed to seek medical attention if any signs or symptoms develop."

The applicant also stated that, compared to Study BEL114055, which had no serious cases, AEs (ADRs) related to serious hypersensitivity were reported in 1 patient (2 events) in this study. The outcome of both events was 'recovered.' Therefore, the applicant considered it unnecessary to take any additional actions at present, such as revision of the electronic package insert.

*Serious infections (including TB, pneumonia, PCP, sepsis, and OI)*

The incidence of ADRs related to serious infections (including TB, pneumonia, PCP, sepsis, and OI) was 7.3% (11/151 patients), and the type of reported ADRs was "herpes zoster" in 4 patients. The outcome was "recovered/resolved" or "recovering/resolving" in all the cases. The incidence rate of AEs related to serious infections (including TB, pneumonia, PCP, sepsis, and OI) was 11.9% (18/151 patients), and the types of reported AEs were "COVID-19" in 5 patients, "herpes zoster" in 4 patients, "enterocolitis bacterial" in 2 patients.

The applicant states that in a global phase II paediatric study (Study BEL114055) (by Week 52) conducted before approval, the incidence rate of AEs in the MedDRA SOC "infections and infestations" was 56.6% (30/53 patients) and the incidence rate of serious events was 7.5% (4/53 patients). The applicant points out that the incidence rate of serious infection-related AEs in this study was higher than that in Study BEL114055 and that 97.4% (147/151 patients) of the patients in the safety analysis set used immunosuppressants (drugs) as concomitant medications. In Study BEL114055, 62.3% (33/53 patients) in the Benlysta group used concomitant immunosuppressants. The applicant concludes that since the use of immunosuppressants is associated with a risk of infections , the fact may have made the incidence rate of serious infection higher in this study than in Study BEL114055 but on the other hand the outcomes of all serious infection-related AEs reported in this study were 'resolved' or 'resolving.' Therefore, the applicant considered it unnecessary to take any additional actions at present, such as revision of the electronic package insert.

*Depression, suicidal ideation and suicide attempt*

The incidence rate of ADRs related to depression, suicidal ideation, and suicide attempt was 1.3% (2/151 patients). The type of reported ADRs by seriousness was "depressive symptom" in 2 patients. The outcome was "recovered/resolved" or "recovering/resolving" in all the cases. The incidence rate of AEs related to depression, suicidal ideation, and suicide attempt was 2.6% (4/151 patients). The type of reported AEs was "depressive symptom" in 3 patients. The outcome was "resolved" or "resolving" in 3 patients, and "not resolved" in 1 patient. The applicant highlighted that in the global phase II pediatric study (Study BEL114055) (up to Week 52) conducted before approval, the incidence rate of AEs related to depression and suicide/self-injury with Benlysta was 1.9% (1/53 patients).

The applicant pointed out that for depression, suicidal ideation, and suicide attempt, "events related to depression and suicide/self- injury" were specified in "important potential risks" of the Risk

Management Plan (RMP) when the Benlysta was launched, and then the following safety measures were taken:

- March 2019: Based on the results of the interim analysis of Study BEL115467 (BASE study), a precaution was issued on the risk of serious depression and/or suicidal ideation, suicidal behaviour, or self-injury.
- October 2019: Revision of the package insert: Precautions were added to Section 8 Important Precautions and Section 11.1 Clinically Significant Adverse Reactions.
- December 2019: Revision of RMP: The name of the safety specification was changed to "depression, suicidal ideation, and suicide attempt" and established as "important identified risks."
- December 2019: Revision of RMP materials: RMP materials for healthcare professionals (proper use guide) were revised (precautions for depression, suicidal ideation, and suicide attempt were added)
- January 2025: Results of exploratory analysis of risk factors for depression, suicidal ideation, and suicide attempt were sent to medical institutions by letter

In addition, the applicant points out that the electronic package insert of Benlysta provides the following important precautions: "Since depression, suicidal ideation, and suicide attempt may occur, patients and their families should be fully informed of the possibility of occurrence of these events and instructed to promptly contact the attending physician if any change in mental status such as insomnia and anxiety occurs." In addition, the following precautions concerning patients with specific backgrounds are stated: "Patients with depression, depressive state or its history, or a history of suicidal ideation or suicide attempt: Suicidal ideation or suicide attempt may occur."

The applicant states that incidence rate of AEs related to depression, suicidal ideation, and suicide attempt in this study were similar to those in Study BEL114055, and the outcomes of all ADRs assessed as "related" to Benlysta were 'resolved' or 'resolving.' Therefore, the applicant considers it unnecessary to take any additional actions at present, such as revision of the electronic package insert.

***CHMP comment:***

No new safety data emerged from this observational study. The described events are already sufficiently described in the SmPC 4.8 and/or 4.4 and no additional SmPC updates are considered necessary based on the findings from this study. Upon request from the CHMP, the applicant provided additional information regarding the death case that involved a 15 year-old female patient with a concurrent medical conditions including systemic lupus erythematosus (SLE), bacterial meningitis, and thrombotic microangiopathy. According to the CIOM report she was previous treated with plasmapheresis and haemodialysis. The patient experienced an intra- abdominal haemorrhage (from the gallbladder) 2 days after initiating treatment with belimumab. The investigator reported the event was a complication of microvascular disorder and a relationship with belimumab was unlikely. This was agreed by the CHMP.

### 2.3.3. Discussion on clinical aspects

This was a multicenter, single arm, real-world study to assess the safety and efficacy of IV belimumab administered to paediatric patients (aged ≤15 years) in daily clinical practice in Japan. The study was open-label without randomization and blinding. The observation period was 52 weeks after the start of belimumab treatment, however patients were followed for adverse events (AEs) until they discontinued belimumab treatment and for up to 3 years after the start of belimumab treatment if they continued receiving belimumab. The study aimed to include all paediatric patients to whom Benlysta was administered after approval of the paediatric dosage.

Of 175 patients registered into the study, 24 did not have their Case Report Form collected. The remaining 151 patients were included in the safety analysis and 143 were included in the efficacy analysis set.

The provided efficacy data did not evoke any concerns.

ADRs were reported in 31 patients (20.5%). The highest incidence rate of ADRs by system organ class (SOC) was infections and infestations in 13.9% (21/151 patients), followed by general disorders and administration site conditions in 2.0% (3/151 patients). The most frequently reported ADR was herpes zoster, followed by cystitis, gastroenteritis, nasopharyngitis, COVID-19, and depressive symptom. Serious ADRs were reported in 16 patients. The most frequently reported serious ADR was herpes zoster (4 patients). One AE resulting in death was reported in a patient with intra-abdominal haemorrhage. According to the applicant, the investigator reported the event was a complication of microvascular disorder and a relationship with belimumab was unlikely. Upon request from the CHMP, the case report and CIOM report was provided and it is agreed that the relationship with belimumab is unlikely. There were no ADRs related to reactivation of HB virus, PML, interstitial pneumonia, or malignant tumours.

The frequencies and types of events seen were similar as previously known and adequately addressed in the SmPC Sections 4.4 and/or 4.8. No updates to the SmPC are needed based on the findings from this study. Long term safety in paediatric patients is listed as missing information in the RMP and a long-term follow-up study (PLUTO) is currently ongoing.

# 3. CHMP overall conclusion and recommendation

The MAH has, in accordance with Article 46 of Regulation (EC) No1901/2006, submitted data from study 212670, entitled "BENLYSTA for Intravenous Injection Pediatric Special Drug Use Investigation". This was a multicenter, single arm, real-world study to assess the safety and efficacy of iv belimumab administered to patients below 15 years of age in daily clinical practice in Japan. A total of 151 patients was included in the safety analysis of the study. No new safety data emerged and no updates to the SmPC are needed based on the findings from this study.

☒ **Fulfilled:**

No action required.

# 4. Request for supplementary information

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

1. Please provide the case report regarding the death case in the study.
2. Please provide information regarding the posology used in the study.

The timetable is a 30 day response timetable with clock stop.

## MAH responses to Request for supplementary information

### Question 1

Please provide the case report regarding the death case in the study.

**Summary of the MAHs response**

The reported death occurred in a 15 year-old female patient with relevant concurrent medical condition including systemic lupus erythematosus (SLE), bacterial meningitis, and thrombotic microangiopathy. The patient experienced an intra- abdominal haemorrhage (from the gallbladder) 2 days after initiating treatment with belimumab. The patient died one day after the initial haemorrhage. Reported cause of death was intra-abdominal haemorrhage. Secondary thrombotic microangiopathy was suspected to be the main cause of the event. Please refer to the provided CIOMS form for further details.

**Rapporteurs Assessment of the MAHs response**

The Rapporteur agrees that, based on the review of the case report and provided CIOMS form, concurrent thrombotic microangiopathy is suspected to be the main cause of the intra-abdominal bleeding and the death of the patients.

Issue considered solved.

**Question 2**

Please provide information regarding the posology used in the study.

**Summary of the MAHs response**

Relevant posology details were provided in the CSR Appendix (English translation); please refer to Table 2.2-10 Composition Ratio of Treatment with Benlysta on page 20 and Table 2.2-11 Summary Statistics of Administration of Benlysta on page 21. The CSR Appendix (English translation) was provided in the initial package submitted to the EMA on 23 January 2026, eCTD sequence 0364, under procedure EMA/PAM/0000325489.

**Rapporteurs Assessment of the MAHs response**

The question was slightly misunderstood; the aim of the question was to verify that the posology used was in line or similar to the approved posology for children in EU. However, it is agreed that the provided information in the two tables previous submitted by the applicant provides sufficient information regarding the doses used in the study. Both these tables has now been included in the AR.

Issue considered solved.