EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 June 2025
EMA/CHMP/451801/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Benlysta

International non-proprietary name: belimumab

Procedure No. EMEA/H/C/002015/II/0133

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
AEP	Access Extension Phase
AESI	Adverse Event of Special Interest
ANA	Anti-Nuclear Antibody
Anti-dsDNA	Anti-double stranded deoxyribonucleic acid
AUC	Area under concentration-time curve
BAFF	B-cell activating factor
BLA	Biologics License Application
BLyS	B-lymphocyte stimulator
Cavg	Average concentration overdosing period
Cmin	Minimum concentration
CMQ	Customized MedDRA query
COVID-19	Coronavirus disease 2019
CRD	Controlled repeat dose
cSLE	childhood-onset SLE
CSR	Clinical Study Report
dL	deciliter
GCP	Good Clinical Practice
GSK	GlaxoSmithKline Research & Development Limited
IB	Investigator's Brochure
IgG	Immunoglobulin G
ISR	Incurred Sample Re-analysis
ITT	Intent-to-treat
IU	International unit
IV	Intravenous(ly)
LLN	Lower Limit of Normal
LN	Lupus Nephritis
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram

mL	Milliliter
NSAID	Non-Steroidal Anti-Inflammatory Drug
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PIP	Pediatric Investigation Plan
PK	Pharmacokinetics
PMS	Post-Marketing Surveillance
PSP	Pediatric Study Plan
PT	Preferred Term
Q10d	Every 10 days
Q2W	Every 2 weeks
QW	Every week
RMP	Risk Management Plan
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SC	Subcutaneous(ly)
SELENA	Safety of Estrogen in Lupus Erythematosus National Assessment
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SoA	Schedule of Activities
SOC	System Organ Class
TEN	Toxic Epidermal Necrolysis
US	United States
Vs	versus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline (Ireland) Limited submitted to the European Medicines Agency on 1 July 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include add-on therapy in paediatric patients from 5 years of age with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti dsDNA and low complement) despite standard therapy for Benlysta 200 mg in pre-filled pen (injection), based on final results from study 200908; this is a worldwide population pharmacokinetic (PK) analysis of subcutaneous administered belimumab plus standard therapy to paediatric patients aged 5-17 years with SLE, which was aimed to describe the PK analysis of belimumab to support an appropriate weight-based dosing regimen for subcutaneous administration in paediatric patients aged 5-17 years with SLE. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 46.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0395/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the P/0395/2022 was completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder

Timetable	Actual dates
Submission date	1 July 2024
Start of procedure:	20 July 2024
CHMP Rapporteur Assessment Report	11 September 2024
PRAC Rapporteur Assessment Report	11 September 2024
PRAC Outcome	03 October 2024
CHMP members comments	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	09 October 2024
Request for supplementary information	17 October 2025
MAH's responses submitted to the CHMP on:	11 February 2025
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	27 February 2025
CHMP members comments	n/a
Rapporteur's updated assessment report on the MAH's responses circulated on:	20 March 2025
2nd Request for supplementary information	27 March 2025
MAH's responses submitted to the CHMP on:	14 April 2025
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 May 2025
CHMP members comments	10 June 2025
Rapporteur's updated assessment report on the MAH's responses circulated on:	12 June 2025
CHMP opinion:	19 June 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

SLE predominantly affects female patients between the ages of 15 and 40, and in approximately 10%-20% of SLE patients, disease onset occurs prior to 20 years of age [Aggarwal, 2015[1]; Kamphuis,

[1] Aggarwal A, Srivastava P. Childhood onset systemic lupus erythematosus: how is it different from adult SLE? Int J Rheum Dis. 2015;18(2):182-91.

2010[2]; Klein-Gitelman, 2002[3]; Malattia, 2013[4]]. Regardless of the age of onset or time of diagnosis, SLE patients share many immunogenetic and serologic similarities [Aggarwal, 2015[1]; Barron, 1993[5]; Livingston, 2012[6]; Mina, 2013[7]].

SLE incidence and prevalence increase with age during childhood, and diagnosis is uncommon in pediatric patients aged ≤9 years [Hiraki, 2012[8]; Lim, 2009[9]; Nightingale, 2007[10]; Somers, 2007[11]]. In a population-based cohort study in Norway, the average incidence rate of SLE in pediatric patients and adolescents (defined as disease onset at age 15 years or younger) was stable at 0.3 for during 1999-2007 and 0.4 during 2008-2017 per 100 000 people [Haukeland, 2022[12]].

It has been reported that there are some differences in clinical features in cSLE [Aggarwal, 2015[1]; Brunner 2008[14]; Mina, 2013[7]; Tucker, 1995[13]]. Paediatric SLE patients tend to have more active disease both at the time of diagnosis and over time [Kamphuis, 2010[2]; Livingston, 2012[6]; Mina, 2013[7]]. In a study by Brunner et al., the mean SLEDAI score in pediatric SLE patients at diagnosis was 1.8 times the score in adult SLE patients (16.8 vs. 9.3, respectively) [Brunner, 2008[14]].

SLE in paediatric patients can be associated with more rapid accrual of damage and may have a higher degree of morbidity compared with SLE in adult populations [Brunner, 2008[14]; Kamphuis, 2010[2]; Levy, 2012[15]; Malattia, 2013[4]; Tucker, 2008[13]]. In a global study, accumulation of damage was observed in 58.2% of the patients who had disease duration more than 5 years [Gutiérrez-Suárez, 2006[22]]. The range of organ involvements in pediatric SLE is generally similar to adult SLE with some manifestations more prevalent in pediatric patients, such as renal lupus, malar rash, seizures, oral ulcers, hemolytic anemia, and thrombocytopenia [Aggarwal, 2015[1]; Barron, 1993[5]; Brunner, 2008[14]; Fonseca, 2018[19]; Mina, 2013[7]; Webb, 2011[16]]. Glomerulonephritis and neurologic involvement represent significant disease burden in SLE and occurred at higher frequency in pediatric SLE [Amaral, 2014[17]; Ambrose,

[2] Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol. 2010;6(9):538-46.
[3] Klein-Gitelman M, Reiff A, Silverman ED. Systemic lupus erythematosus in childhood. Rheum Dis Clin North Am. 2002;28(3):561-77.
[4] Malattia C, Martini A. Paediatric-onset systemic lupus erythematosus. Best Pract Res Clin Rheumatol. 2013;27(3): 351-62.
[5] Barron KS, Silverman ED, Gonzales J, et al. Clinical serologic and immunogenetic studies in childhood-onset systemic lupus erythematosus. Arthritis Rheum. 1993;36(3):348-54.
[6] Livingston B, Bonner A, Pope J. Differences in autoantibody profiles and disease activity and damage scores between childhood- and adult-onset systemic lupus erythematosus: a meta-analysis. Semin Arthritis Rheum. 2012;42(3):271-80.
[7] Mina R, Brunner HI. Update on differences between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis Res Ther. 2013;15(4):218.
[8] Hiraki LT, Feldman CH, Liu J, et al. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. Arthritis Rheum. 2012;64:2669-76.
[9] Lim SS, Bayakly R, Helmick CG, et al. The Georgia Lupus Registry: A population-based estimate of the incidence and prevalence of childhood-onset SLE [Abstract]. Arthritis Rheum. 2009;60(Suppl 10):714.
[10] Nightingale AL, Farmer RD, de Vries CS. Systemic lupus erythematosus prevalence in the UK: methodological issues when using the General Practice Research Database to estimate frequency of chronic relapsing-remitting disease. Pharmacoepidemiol Drug Saf. 2007;16(2):144-51.
[11] Somers EC, Lewis EE, Francis S, et al. Michigan Lupus Epidemiology & Surveillance (MILES) Program: Preliminary prevalence estimates for SLE in Southeastern Michigan. Presented at Program and Abstracts of the American College of Rheumatology 71st Annual Meeting; November 6-11, 2007, Boston, Massachusetts. [Abstract #798] 2007.
[12] Haukeland H, Moe SR, Brunborg C, et al. Gender differences in the incidence of systemic lupus erythematosus in Norway: a population-based cohort study. The Lancet Rheumatology. 2022 Sep 1;4:S9.
[13] Tucker LB, Menon S, Shaller JG, et al. Adult and childhood systemic lupus erythematosus: a comparison of onset, clinical features, serology, and outcome. Br J Rheumatol. 1995;34(9):866-72.
[14] Brunner HI, Gladman DD, Ibanez D, et al. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis Rheum. 2008;58(2):556–62.
[15] Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. Pediatr Clin North Am. 2012;59(2):345-64.
[16] Webb R, Kelly JA, Somers EC, et al. Early disease onset is predicted by a higher genetic risk for lupus and is associated with a more severe phenotype in lupus patients. Ann Rheum Dis. 2011;70(1):151–6.
[17] Amaral B, Murphy G, Ioannou Y, et al. A comparison of the outcome of adolescent and adult-onset systemic lupus erythematosus. Rheumatology (Oxford). 2014;53:1130-5.

2016[23]; Barron, 1993[5]; Fish, 1977[18]; Fonseca, 2018[19]; King, 1977[20]; Tarr, 2015[21]; Tucker, 2008[13]]. Growth failure and delayed puberty are complications of SLE specific to paediatric patients that may have a serious psychological impact. The frequency of both events increases significantly with the increase in disease duration [Gutiérrez-Suárez, 2006[22]].

Relative risk of mortality is higher in paediatric SLE populations than adult SLE populations [Ambrose, 2016[23]; Hersh, 2010; Tucker, 2008[13]]. In a case-control study of paediatric SLE (≤18 years old at diagnosis) and adult SLE (19-49 years old at diagnosis) patients, mortality after a mean 4.4 years of follow-up was 19.4% in pediatric SLE patients compared to 10.4% in adult SLE patients [Tucker, 2008[13]]. Major causes of death in paediatric SLE and adult SLE include renal disease, severe disease flares, and infections [Bernatsky, 2006[24]; Cervera, 2006[25]; Glidden, 1983[26]; González, 2005[27]].

Management

Belimumab IV formulation is approved for the treatment of paediatric patients with active, autoantibody-positive SLE who are receiving standard therapy. But there remains an unmet medical need for treatments that improve patient compliance, lead to persistence of treatment and increased patient comfort in this patient population. The clinical evidence of effective treatment of childhood rheumatic diseases including SLE is generally based on anecdotal reports [Lehman, 1997[28]]. Similar to adult-onset disease, paediatric SLE is a chronic disease for which there is no cure. All patients require life-long treatment with a variety of medications for disease control. Generally, paediatric patients are treated with the same agents which have been used in the adult population such as corticosteroids, anti-malarial agents, NSAIDs, cytotoxic agents, and immunosuppressive/immunomodulatory agents [Brocard, 2005[29]; Chatham, 2001[30]; Houssiau, 2004[31]; Midgley, 2014[32]; Petri, 2001[33]; Reveille, 2001[34]; Ruiz-Irastorza, 2001[35]; Wallace, 2002[36]].

[18] Fish AJ, Blau EB, Westberg NG, et al. Systemic lupus erythematosus within the first two decades of life. Am J Med. 1977;62(1):99-117.
[19] Fonseca R, Aguiar F, Rodrigues M, et al. Clinical phenotype and outcome in lupus according to age: a comparison between juvenile and adult onset. Reumatol Clin. 2018;14(3):160-3.
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[21] Tarr T, Dérfalvi B, Győri N, et al. Similarities and differences between pediatric and adult patients with systemic lupus erythematosus. Lupus. 2015;24(8):796-803.
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[24] Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum. 2006;54(8):2550–7.
[25] Cervera R, Abarca-Costalago M, Abramovicz D, et al. Systemic lupus erythematosus in Europe at the change of the millennium: lessons from the "Euro-Lupus Project". Autoimmun Rev. 2006;5(3):180–6.
[26] Glidden RS, Mantzouranis EC, Borel Y. Systemic lupus erythematosus in childhood: clinical manifestations and improved survival in fifty-five patients. Clin Immunol Immunopathol. 1983;29(2):196–210.
[27] González B, Hernández P, Olguín H, et al. Changes in the survival of patients with systemic lupus erythematosus in childhood: 30 years experience in Chile. Lupus. 2005;14(11):918–23.
[28] Lehman TJ. Pediatric rheumatology in the 21st century--where's the common sense? J Rheumatol. 1997;24(9):1855-6.
[29] Brocard A, Barbarot S, Milpied B, et al. Thalidomide in the treatment of chronic discoid lupus erythematosus. Ann Dermatol Venereol. 2005;132(11 Pt 1):853-6 [Article in French].
[30] Chatham WW, Kimberly RP. Treatment of lupus with corticosteroids. Lupus. 2001;10(3):140-7.
[31] Houssiau FA, Vasconcelos C, D'Cruz D, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term follow up of patients in the Euro-Lupus Nephritis Trial. Arthritis Rheum. 2004;50(12):3934-40.
[32] Midgley A, Watson L, Beresford MW. New insights into the pathogenesis and management of lupus in children. Arch Dis Child. 2014;99(6):563-7.
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[34] Reveille JD. The treatment of systemic lupus erythematosus. In: Koopman W, ed. Arthritis and Allied Conditions: A Textbook of Rheumatology. 14th ed. Philadelphia, PA: Lippincott Williams and Wilkins 2001;1533-45.
[35] Ruiz-Irastorza G, Khamashta M, Castellino G, et al. Systemic lupus erythematosus. Lancet 2001;357(9261):1027-32.
[36] Wallace DJ. Management of lupus erythematosus: recent insights. Curr Opin Rheumatol. 2002;14(3):212-9.

Paediatric SLE is more often treated with high doses of corticosteroids than adult SLE, contributing to the increased incidence and earlier onset of long-term organ damage in children [Mina, 2010[37]]. More frequent use of immunosuppressants or IV cyclophosphamide was also reported. These therapies can be associated with significant toxicity including increased risks of infections or cancer [Chatham, 2001[38]; Silva, 2016[39]].

To date, the use of rituximab, a B-cell depletion therapy, both in adult and pediatric SLE populations remains off-label.

2.1.2. About the product

Belimumab is a BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B-cells. IV belimumab was initially approved for adult SLE patients with active disease despite standard of care. An alternative 200 mg once weekly SC administered injection formulation (ready to use pre-filled syringe and autoinjector) has also been approved for the same SLE indication in adult patients as the IV formulation.

Paediatric IV Formulation

Study BEL114055 was a Phase 2, multi-center study that evaluated the safety, efficacy, and PK of belimumab plus background standard therapy in paediatric participants 5 years to 17 years of age with active SLE. This study was conducted as part of post-approval commitment agreed in the PIP as part of the belimumab IV adult registration.

Given the rarity of SLE in children, a fully powered paediatric study was not feasible, and the study was designed to be consistent with the larger adult IV belimumab pivotal studies to allow comparability of the adult data to the paediatric setting.

The overall efficacy observed in the paediatric IV study population was similar to that seen in the adult population leading to extension of the adult SLE indication into the paediatric population from 5 years of age for the IV formulation (EMEA/H/C/002015/II/0062).

Paediatric SC Formulation

This variation includes the results from the SC paediatric Study 200908 that evaluated the PK, PD, and safety of repeat doses of 200 mg belimumab administered SC in paediatric participants 5 to 17 years of age and weighing ≥15 kg with active SLE on a background of standard of care therapy.

The bridging PK study (200908) was part of an extrapolation strategy to support the use of SC belimumab in paediatric SLE patients, based on the completed adult SLE study with SC belimumab (BEL112341) and the paediatric SLE study with IV belimumab (BEL114055). Study 200908 was a component of a post-approval commitment to EMA (EMA-000520-PIP02-13-M04).

2.2. Quality aspects

This is an extension of the SLE indication for the subcutaneous presentation using the commercial autoinjector, 200 mg, now proposed for use in pediatric patients. To support the use of the autoinjector in the pediatric population some minor updates in module 3 have been done. A summary of changes has been provided. Sections S.4.5 and P.5.6 were updated to include the maximum allowed

[37] Mina R, Brunner HI. Pediatric lupus--are there differences in presentation, genetics, response to therapy, and damage accrual compared with adult lupus? Rheum Dis Clin North Am. 2010;36(1):53–80.
[38] Chatham WW, Kimberly RP. Treatment of lupus with corticosteroids. Lupus. 2001;10(3):140-7.
[39] Silva CA, Aikawa NE, Pereira RM, et al. Management considerations for childhood onset systemic lupus erythematosus patients and implications on therapy. Expert Rev Clin Immunol. 2016;12(3):301-13.

endotoxin level for the pediatric population with no change in the specification. In P.2.1 and P.2.2, tables were updated to include DS and DP clinical batch numbers and pediatric study numbers. The container closure system section (P.2.4) was updated with some information on the human factors evaluation.

A notified body opinion for self-administration with the general safety and performance requirements fulfilled as well as a human factors evaluation of self-administration in 10-17 years of age are provided, both found in module 3.2.R. No issues were raised.

The MAH declared that risk assessments for elemental impurities, (ICH Q3D), residual solvents in drug product (ICH Q3C), application of ICH M7 to establish reporting thresholds for extractables and leachables, process and product derived impurities relative to SLE pediatric dosing regimen were performed and assessed to be well controlled and to pose low risk to the pediatric population. This is accepted.

The proposed extension for the subcutaneous presentation of belimumab using the commercial autoinjector, 200 mg, and use in paediatric patients was accepted from a quality perspective.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

A justification for not performing an environmental risk assessment (ERA) was submitted. Due to the nature of its constituents, this product is unlikely to result in a significant risk to the environment. This is in accordance with the current EMA guideline Guideline on the environmental risk assessment of medicinal products for human use and agreed by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Identifier (Identifier of Study Report)	Study Objectives	Study Design	Healthy Participants or Diagnosis of Participants	Treatment Details (Test Products; Dosage Regimen; Route; Duration)	Total No. of Participants by Group Entered/ Completed	Study Reporting Status (Type of Report)
Pharmacokinetic Studies in Pediatric Participants with SLE (SC Administration)						
200908	To evaluate the PK, safety, and PD of belimumab 200 mg SC administered with standard therapy in pediatric participants with SLE.	Ph 2, single arm, MC, OL	Pediatric participants 5 to 17 years of age and weighing ≥15 kg with active SLE disease (SELENA SLEDAI score ≥6 at screening).	Belimumab 200 mg SC via autoinjector per body weight **Part A:** Cohort 1 (≥50 kg): QW Cohort 2 (≥30 kg to <50kg): Q10d Cohort 3 (<30 kg): Q2W. **Part B:** optional 40-week OL continuation phase, open to all participants who had completed Part A. **Optional AEP** ongoing optional access extension phase to provide a mechanism for continued access to belimumab SC from Week 52 and is only for eligible participants who completed Part B of the study.	Part A: 25/25 Part B: 25/23 Optional AEP: Ongoing	Part A and B: Completed Full CSR Optional AEP: Ongoing
Pediatric Studies (Controlled Efficacy and Safety Studies in Participants with SLE [IV Administration])						
BEL114055/ HGS1006-C1109 Previously submitted sequence 0202 in IV belimumab BLA125370 in m5.3.5.1.	To evaluate the safety, efficacy, PK, and impact on quality of life of belimumab in pediatric participants with SLE.	MC, R, DB, PG, PC	Pediatric participants 5 to 17 years of age with active SLE defined as SELENA SLEDAI score ≥6.	Placebo or belimumab 10 mg/kg Day 0, Week 2, Week 4 and then every 4 weeks; IV infusion: 52 weeks The double-blind phase (Part A) will be followed by a long-term open label continuation phase (Part B) and a long-term safety follow up phase (Part C).	Double-blind 93/53 Part B: Ongoing Part C: Ongoing	Double-blind endpoint analysis - Full CSR Part B and Part C: Ongoing SAE data[a], data cutoff 24 January 2018
Pivotal Adult Studies (Controlled Efficacy and Safety Studies in Participants with SLE [IV Administration])						
HGS1006-**C1056**/ BEL110751 Previously submitted sequence 0044 in IV belimumab BLA125370 in m5.3.5.1.	To evaluate the efficacy, safety, tolerability, and impact on quality of life of belimumab in participants with SLE.	Ph 3, MC, R, RD, DB, PG, PC	Participants with active SLE disease defined as SELENA SLEDAI score ≥6, stable SLE treatment regimen, positive ANA/anti dsDNA.	Placebo or Belimumab 1 or 10 mg/kg on Days 1, 14, 28 and every 28 days thereafter; IV infusion: 76 weeks.	819/544	Completed Full CSR
HGS1006-**C1057**/ BEL110752 Previously submitted sequence 0000 in IV belimumab BLA125370 in m5.3.5.1	To evaluate the efficacy, safety, tolerability, and impact on quality of life of belimumab in participants with SLE.	Ph 3, MC, R, RD, PG, DB, PC	Participants with active SLE disease defined as SELENA SLEDAI score ≥6, stable SLE treatment regimen, positive ANA/anti dsDNA.	Placebo or Belimumab 1 or 10 mg/kg on Days 1, 14, 28 and every 28 days thereafter; IV infusion: 52 weeks.	865/578	Completed Full CSR

a. SAE data for Part B and Part C

AEP = Access Extension Phase
ANA = Anti-nuclear antibody
Anti-dsDNA = Anti-double stranded DNA
CSR = Clinical Study Report
DB = Double-blind
IV = Intravenous
MC = Multicenter
MD= Multiple dose
OL = Open label
PC = Placebo-controlled
PD = Pharmacodynamics
PG = Parallel group
Ph = Phase
PK = Pharmacokinetics
Q10d = Every 10 days
Q2W = Every 2 weeks
QW = Every week
R = Randomized
RD = Repeat dose
SC = Subcutaneous
SAE = Serious Adverse Event
SELENA = Safety of Estrogen in Lupus National Assessment Trial
SLEDAI = Systemic Lupus Erythematosus Disease Activity Index
SLE = Systemic Lupus Erythematosus

2.4.2. Pharmacokinetics

Belimumab pharmacokinetics (PK) is consistent with other monoclonal antibodies targeting soluble ligands. The PK is linear, dose-proportional and time-independent after both IV and SC administration. Belimumab clinical pharmacology has been reviewed as part of the adult SLE marketing applications for belimumab administered IV and SC.

The aim of Study 200908 was to select and justify an appropriate SC dosing regimen of belimumab for paediatric patients with SLE. Study 200908 enrolled 25 paediatric participants aged 5-17 years with SLE to receive belimumab; of these, 13 participants were recruited into cohort 1 (≥50 kg body weight)

and received 200 mg SC every week, as per the adult regimen; 12 participants were recruited into cohort 2 (≥30 kg to <50 kg body weight) and received 200 mg SC every 10 days; no one was enrolled into cohort 3 (≥15 kg to <30 kg body weight) as recruitment of low body weight participants was challenging due to the low prevalence of disease in young children.

Methods

Bioanalytical methods

There have been no relevant changes to the information presented in the initial marketing authorisation dossier in the treatment of adult SLE for the IV and SC formulations of belimumab.

The immunogenicity methods have been used in previous submissions of Benlysta.

Population pharmacokinetic analysis

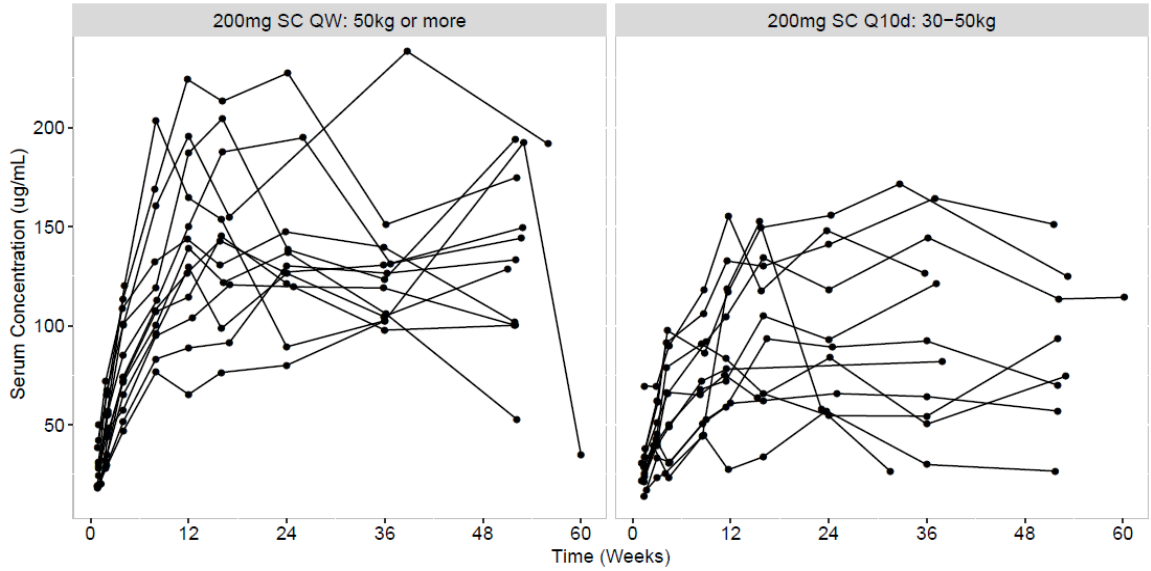
The observed concentrations at Weeks 4, 8, 12, 24 and 52 for the paediatric SC study 200908 are summarized alongside the corresponding adult SC concentrations of study BEL112341 (Table 1).

Table 1: Observed belimumab concentrations (μg/mL) in the Phase 2 paediatric SC Study 200908 and the pivotal Phase 3 adult SC Study BEL112341

Visit Time	**Summary**	**200908 Cohort 1 (≥50 kg) 200 mg SC QW**	**200908 Cohort 2 (≥30 to <50 kg) 200 mg SC Q10d**	**BEL112341 200 mg SC QW**
Week 4 (Day 29/31)	n Median Geo. Mean (CV%) 95% CI	13 73.9 78.7 (31.7%) 65.3 – 94.8	12 57.9 51.9 (56.0%) 37.3 – 72.3	538 65.0 - -
Week 8 (Day 57/61)	n Median Geo. Mean (CV%) 95% CI	13 107.7 115.6 (29.1%) 97.3 – 137.3	12 69.9 70.5 (34.5%) 57.0 – 87.3	527 87.3 - -
Week 12 (Day 85/81)	n Median Geo. Mean (CV%) 95% CI	13 139.2 134.2 (34.7%) 109.5-164.5	12 80.7 82.8 (49.3%) 61.5-111.3	- - - -
Week 24	n Median Geo. Mean (CV%) 95% CI	13 130.3 131.5 (27.7%) 111.6-155.0	12 86.5 88.7 (39.8%) 69.5-113.1	489 105 - -
Week 52	n Median Geo. Mean (CV%) 95% CI	12 138.7 130.8 (39.4%) 102.7 – 166.5	8 84.0 79.4 (59.1%) 50.3 – 125.5	522 86.8 - -

CV% = the coefficient of variation derived as the ratio of standard deviation to the mean and reported as a percentage.

Figure 1: Observed belimumab concentration over time in the paediatric SC Study 200908



Participants ≥50kg received belimumab 200 mg SC QW (study 200908, cohort 1). Participants ≥30 kg to <50 kg received belimumab 200 mg SC Q10d (study 200908, cohort 2).

The 53 belimumab-treated participants from the paediatric IV study BEL114055 were combined with the 25 belimumab-treated participants from the paediatric SC study 200908, and contributed a total of 778 observations to the population PK analysis. The population PK analysis dataset (belimumab treated patients only, does not include the placebo patients of BEL114055) comprised 70 females and 8 males with age at the start of the study ranging from 6 to 18 years (median, 14.0 years; maximum age at screening was 17 years) and body weight ranging from 17.0 to 85.5 kg (median, 52.2 kg). Subject level characteristics in the combined dataset is summarised in Table 2. Overall, 778 PK observations (218 in study 200908) were taken from 78 patients across the two studies and used in the population PK analysis.

Table 2: Subject level characteristics of studies BEL114055 and 200908

	Study 200908 **N=25**	**Study BEL114055** **N=93**	**Population PK Analysis Dataset** **N=78**	**Subject Level Dataset** **N=118**
Median (Range)				
Age (Years)	14.0 (10.0 – 17.0)	15.0 (6.0 – 18.0)	14.0 (6.0 – 18.0)	15.0 (6.0 – 18.0)
Body Weight (kg)	52.0 (34.5 – 78.5)	52.5 (17.0 – 87.0)	52.2 (17.0 – 85.5)	52.4 (17.0 – 87.0)
Fat-free Mass (kg)	35.9 (23.6 – 49.1)	34.8 (12.6 – 57.2)	35.1 (12.6 – 57.2)	35.1 (12.6 – 57.2)
Albumin (g/L)	44.0 (38.0 – 49.0)	43.0 (23.0 – 52.0)	43.0 (29.0 – 52.0))	43.0 (23.0 – 52.0)
IgG (g/L)	11.0 (7.72 – 27.1)	14.6 (4.08 – 31.2)	13.0 (4.08 – 31.2)	13.5 (4.08 – 31.2)
eGFR ($mL/min/1.73m^2$)	112 (64.0 – 200)	106 (68.1 – 200)	107 (64.0 – 200)	108 (64.0 – 200)
Proteinuria (mg/mg)	0.121 (0.045 – 4.40)	0.132 (0.028 – 6.13)	0.130 (0.037 – 4.40)	0.130 (0.028 – 6.13)
White blood cell count (10^9 cells/L)	5.10 (3.40 – 8.50)	5.80 (2.40 – 15.9)	5.80 (2.40 – 13.0)	5.80 (2.40 – 15.9)
BLyS (ng/mL)	0.653 (0.164 – 1.52) [N=24*]	0.780 (0.160 – 4.31) [N=90*]	0.681 (0.160 – 4.31) [N=74*]	0.740 (0.160 – 4.31) [N=114*]
Number (%)				
Sex: Female	21 (84.0%)	88 (94.6%)	70 (89.7%)	109 (92.4%)
Proteinuria: <0.5 mg/mg	24 (96.0%)	80 (86.0%)	73 (93.6%)	104 (88.1%)

*Baseline BLyS levels sample size is smaller than the total study/cohort size

Model Development

The base model used as the starting point for model development was the belimumab IV population PK model previously developed for paediatric patients (Dimelow, 2020[40]), with SC absorption components taken from the adult SC population PK model (Struemper, 2018[41]). The model was 2-compartmental with first order absorption, distribution, and elimination. Between-subject variability was assumed to be log-normally distributed across the population. Residual variability was modelled as the sum of a proportional and additive component, with the standard deviation of the additive component fixed at the lower limit of quantification (0.1 µg/mL). This model was used to predict the individual belimumab concentrations of the analysis dataset without re-fitting to the PK analysis dataset and was a reasonable fit to the paediatric SC data of study 200908. The covariate reference values in the population PK model were updated to reflect the most accurate and reliable estimates of a paediatric SLE population, taking the median values across all paediatric patients in the subject level dataset; that is across all patients of study 200908 and all belimumab and placebo patients of study BEL114055 (Table 2). The allometric effects of fat-free mass were replaced with body weight and the model re-fitted to the PK analysis dataset.

The full covariate method was used to justify inclusion of covariates in the population PK model. For each covariate-parameter pair (e.g., body weight on clearance) the parameter value at the 10th and 90th covariate percentiles in the population PK analysis dataset were expressed relative to the parameter value at the covariate median value; denoted by the ratios R10 and R90, respectively. If the 95% confidence interval around the estimates of R10 and R90 were within the interval 0.8 to 1.25, the covariate was not considered pharmacokinetically relevant and removed from the model. The results indicate that baseline eGFR and baseline proteinuria on CL, and baseline white blood cell count on Vc, have limited influence on informing the PK. These parameter-covariate pairs were removed, and the reduced model re-fitted to the dataset. The full covariate method was then applied confirmed that the remaining covariates were PK-relevant: baseline WT on CL, Q, Vc and Vp, and baseline IgG on CL. Final model selection was confirmed using the backward deletion method (p-value<0.1%).

Baseline body weight and IgG concentrations were identified as pharmacokinetically relevant covariates of belimumab PK in the model. PK model parameters were well estimated with RSE generally less than 25% (Table 3) and the model fitted the data well (Figure 2:). A typical paediatric patient is predicted to have clearance of 154 mL/day, volume of distribution of 3772 mL, and an 18-day terminal phase half-life. The bioavailability estimate in paediatric patients (70.3%) is close to the adult estimate (74.2%) (Struemper, 2018[42]).

[40] Dimelow R, Ji B, Struemper H. Pharmacokinetics of Belimumab in Children With Systemic Lupus Erythematosus. Clin Pharmacol Drug Dev. 2021;(6):622-33. doi: 10.1002/cpdd.889. Epub 2020 Nov 27.
[41] Struemper H, Chen C, Cai, W. Population pharmacokinetics of belimumab following intravenous administration in patients with systemic lupus erythematosus. J Clin Pharmacol. 2013;53:711-20.
[42] Struemper H, Thapar M, Roth D. Population Pharmacokinetic and Pharmacodynamic Analysis of Belimumab Administered Subcutaneously in Healthy Volunteers and Patients with Systemic Lupus Erythematosus. Clin Pharmacokinetics. 2018;57:717-28.

Table 3: Parameter values for the final paediatric Population PK Model

Parameter	Parameter Estimate (RSE%)
Fsc (%)	70.3 (6.52%)
ALAG (days)	0.179 (Fixed)
KA (1/day)	0.287 (26.3%)
CL (mL/day) ×(WT/52.4)$^{\theta}$ ×(IGG/13.5)$^{\theta}$	154 (3.92%) 0.509 (21.4%) 0.576 (15.8%)
Vc (mL) ×(WT/52.4)$^{\theta}$	1935 (4.48%) 0.769 (14.4%)
Q (mL/day) ×(WT/52.4)$^{\theta}$	643 (8.01%) 0.509 (21.4%)
Vp (mL) ×(WT/52.4)$^{\theta}$	1837 (11.6%) 0.769 (14.4%)
Between-Subject Variability (Log-scale variance and covariance)	
ω^2_{CL} $\omega^2_{CL/Vc}$ ω^2_{Vc} ω^2_{Q} ω^2_{Vp}	0.0655 (21.3%) 0.0348 (36.6%) 0.0765 (24.2%) 0 0.401 (23.6%)
Residual Variability (Variance parameters)	
σ^2_{prop} (BEL114055) σ^2_{prop} (200908) σ^2_{add}	0.0896 (18.0%) 0.0329 (17.3%) 0.01 (fixed)

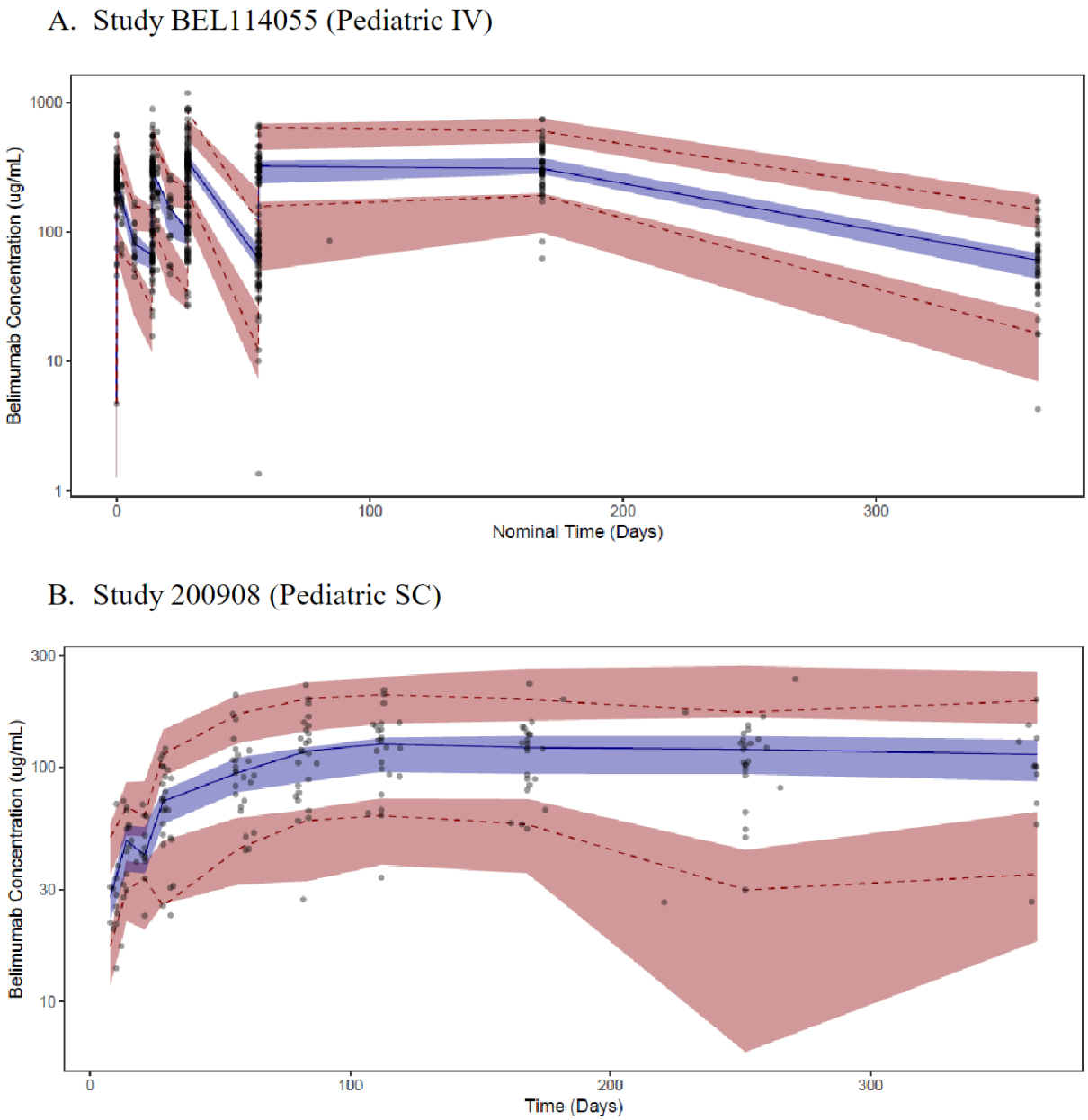
Parameter abbreviations: RSE=Relative standard error; Fsc=Subcutaneous bioavailability; ALAG=Absorption lag time; KA=Absorption rate constant; CL=Clearance; Vc=Central volume of distribution; Q=Inter-compartmental flow rate; Vp=Peripheral volume of distribution.

Baseline covariate abbreviations: WT=Body weight (kg); IGG=Immunoglobulin G concentration (g/L).

Median baseline participant-level characteristics (weight 52.4 kg, IgG 13.5 g/L) were derived from the dataset of all pediatric patients across studies BEL114055 and 200908, which included the placebo participants of study BEL114055.

Residual model: $y = f + f \times \varepsilon_{prop} + \varepsilon_{add}$ where y is the observed value, f is the corresponding model prediction, and ε_{prop} and ε_{add} are normally distributed random variables with variance σ^2_{prop} and σ^2_{add}, respectively.

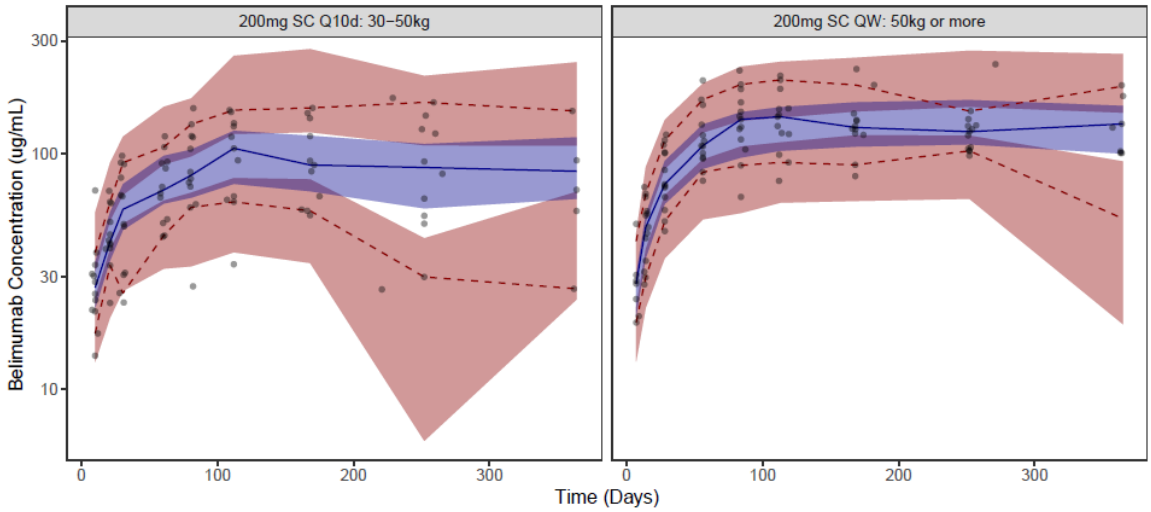
Figure 2: Visual predictive check for the final model (Mod011) for studies (A)BEL114055 and (B) 200908



Median (blue) and 95% variability interval (red) for the observed data (points, lines) and model predictions (red and blue shaded regions).

Upon the CHMP's request, the MAH provided visual predictive checks stratified on body weight groups:

Figure 3: Visual predictive check for the final model (Mod011) for study 200908



Observed data (grey and black points) are shown with the observed median (blue line) and observed 95% prediction interval (red dotted lines), with simulated median (95% CI about the median; blue shaded region) and simulated 95% prediction interval (95% CI about the 2.5th and 97.5th percentiles; red shaded region).
SC = Subcutaneous.

Pharmacokinetics in the paediatric patient population

Individual-predicted PK and exposure parameters are summarized for the paediatric SC study (200908) and the paediatric IV study (BEL114055) (Table 4). Overall, the average concentrations at steady state were comparable between the study 200908 and BEL114055 participants (124 µg/mL vs 112 µg/mL, respectively); however exposures were in general higher in cohort 1 of study 200908 (≥50 kg, 200 mg SC QW) compared to cohort 2 (≥30 kg to <50 kg, 200 mg SC Q10d). The average concentration over the first 12 weeks was higher for study BEL114055 participants compared to study 200908 since the IV regimen of study BEL114055 included the 10 mg/kg IV loading dose at Week 2. Cmin and Cmax were also different for the pediatric SC (200908) and IV (BEL114055) studies due to the larger peak-to-trough ratio exhibited for the IV dosing regimen.

Table 4: Individual PK and exposure parameters for all paediatric participants of Study 200908 and Study BEL114055

	Geometric Mean (CV%) Range			
Parameter	**BEL114055 All Patients N=53**	**200908 All Patients N=25**	**200908 ≥50kg N=13**	**200908 ≥30 and <50kg N=12**
Fsc (%)	-	70.3 (0%) 70.3 – 70.3	70.3 (0%) 70.3 – 70.3	70.3 (0%) 70.3 – 70.3
CL (mL/day)	156 (41.4%) 72.5 - 482	137 (32.1%) 81.2 - 294	137 (25.2%) 93.9 - 210	136 (39.8%) 81.2 - 294
Vss (mL)	3632 (42.4%) 1265 - 7423	3653 (35.9%) 1718 - 7380	4207 (35.0%) 2520 - 7380	3694 (37.1%) 1718 - 5946
Terminal phase Thalf (days)	17.2 (39.6%) 7.9 – 60.0	21.3 (39.3%) 10.6 – 47.6	22.4 (30.9%) 11.1 – 33.5	20.2 (48.1%) 10.6 – 47.6
Cmin.ss[a] (µg/mL)	53.6 (58.7%) 14.5 – 153	112 (41.7%) 38.7 - 203	138 (26.2%) 89.0 - 203	90.1 (43.9%) 38.7 – 159
Cavg.ss (µg/mL)	112 (36.2%) 49.6 - 232	124 (37.3%) 47.9 - 214	146 (25.2%) 95.6 – 214	103 (39.8%) 47.9 – 173

Cmax.ss[a] (µg/mL)	328 (24.1%) 191 – 568	131 (34.9%) 54.1 – 220	151 (24.7%) 99.4 – 220	111 (37.6%) 54.1 - 182
AUC.ss[b] (µg day/mL)	3146 (36.2%) 1389 - 6488	1027 (32.1%) 479 - 1733	1024 (25.2%) 669 – 1498	1031 (39.8%) 479 - 1733
Cavg(Wk 0-12) (µg/mL)	127 (33.7%) 61.7 – 269	82.7 (32.0%) 39.1 – 140	95.4 (25.4%) 60.1 – 140	70.8 (31.5%) 39.1 – 113

CV% = the coefficient of variation derived as the ratio of standard deviation to the mean and reported as a percentage.

[a]Cmin.ss and Cmax.ss are different between the pediatric IV (BEL114055) and SC (200908) studies due to the larger peak-trough ratio of the IV PK profile.

[b]AUC.ss is the area under the curve at steady state over a dosing interval: 4 weeks for BEL114055 patients; 1 week for 200908 patients ≥50kg; 10 days for 200908 patients ≥30 and <50kg.

For children with SLE, subcutaneous bioavailability (Fsc) was estimated to be 70.3%, similar to the adult estimate of 74.2% (Struemper, 2018[42]). The volume of distribution of belimumab in the Study 200908 pediatric population at steady-state (Vss) is 3772 mL. Considering the smaller body size of the pediatric population, these values are consistent with results for other monoclonal antibodies (Dirks, 2010[43]) and a Vss of 5.3 L and 5.0 L estimated, respectively, in the adult IV and SC population PK analyses (Struemper, 2013[41]; Struemper, 2018[42]). Systemic clearance estimated from the pediatric population PK analysis (154 mL/day) was consistent with the systemic clearance estimated in adult IV and SC population PK analyses (215 and 204 mL/day, respectively) considering the smaller body size of the pediatric population (Struemper, 2013[41]; Struemper, 2018[42]). The terminal half-life estimated for the pediatric SLE population is 18 days which is similar to the values estimated in the adult IV and adult SC population PK analyses (19.4 days and 18.3 days, respectively).

2.4.3. Exposure-Response Relationships

At the average belimumab concentration following IV and SC dosing in paediatric patients (on average 112 µg/mL for IV, 124 ug/mL for SC), there is a large molar excess of belimumab relative to circulating BLyS homotrimer. Binding to and neutralization of soluble BLyS is expected to be saturated and at these dose levels, downsteam pharmacology and efficacy is expected to be maximal. This expectation was supported by the results of a descriptive exposure-response analysis for SC dosing in paediatric participants of study 200908, and is consistent with the exposure-response analysis in the adult SC study BEL112341 which also indicated maximum efficacy was achieved for similar exposures (Struemper, 2018[42]).

The population PK model was used to derive the average belimumab concentration over the first 12 weeks and the average concentration at steady state, for each participant who received belimumab in the paediatric SC study 200908 and paediatric IV study BEL114055. These measures of belimumab exposure were compared against selected Week 12 and Week 52 pharmacology, efficacy, and safety endpoints.

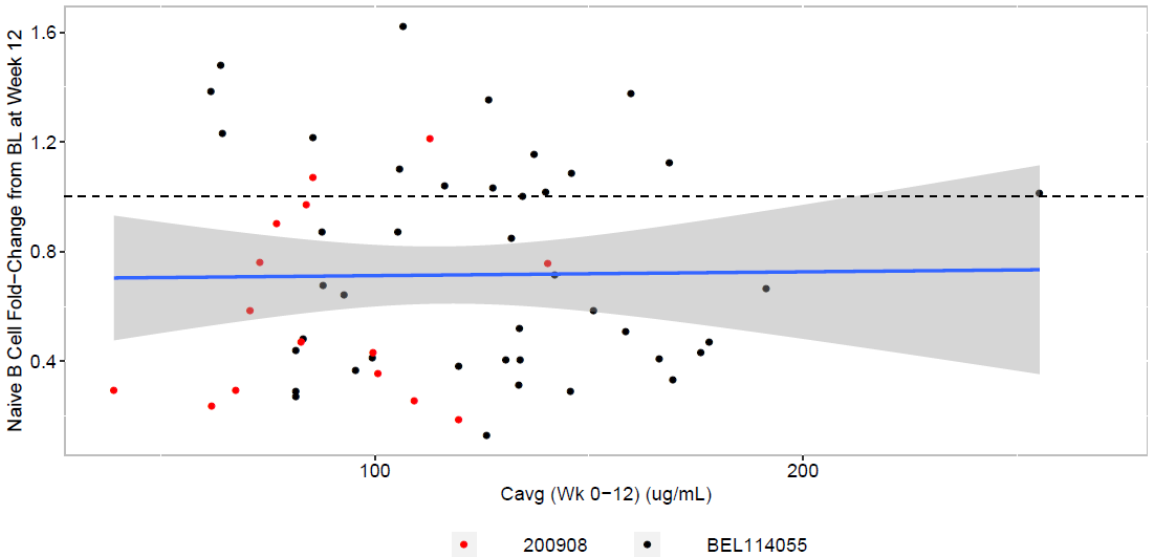
Pharmacology

There was no correlation between pharmacological response and belimumab exposure. Exposure-response analysis showed that the observed pharmacological naïve B cell response did not correlate with belimumab exposure, either over the first 12 weeks of treatment or at steady state after 52 weeks (Figure 4). There was also no statistically significant correlation between belimumab exposure and other pharmacological biomarkers.

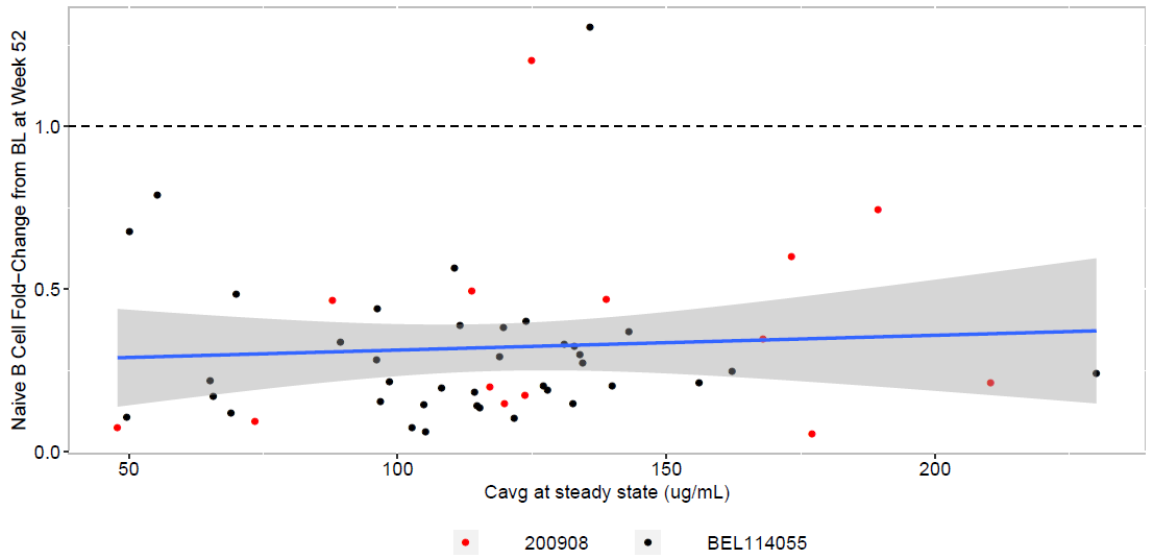
[43] Dirks NL, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet. 2010;49(10):633–59.

Figure 4: Naïve B cell response versus belimumab exposure

A. Naïve-B cell response at Week 12 vs Cavg(Wk 0-12). P-value=0.916



B. Naïve-B cell response at Week 52 vs Cavg.ss. P-value=0.629



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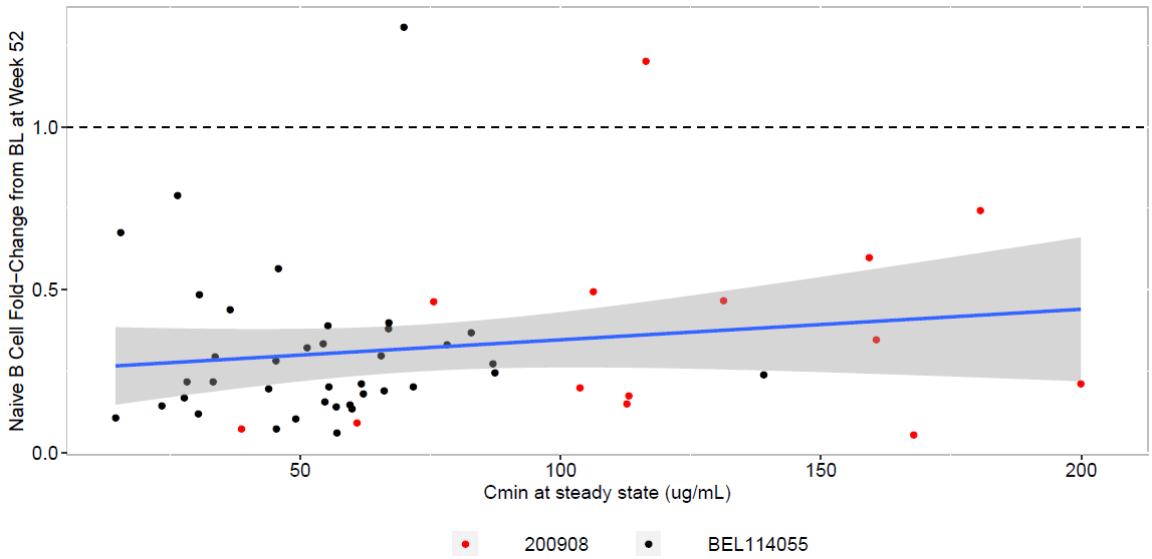
Individual predictions for the pediatric IV study BEL114055 (black) and the pediatric SC study 200908 (red) are shown. The linear regression (blue line) through all data points from studies 200908 and BEL114055 combined is shown with 95% confidence interval (grey shaded region). Baseline levels (fold-change of 1) is represented by the horizontal black line.

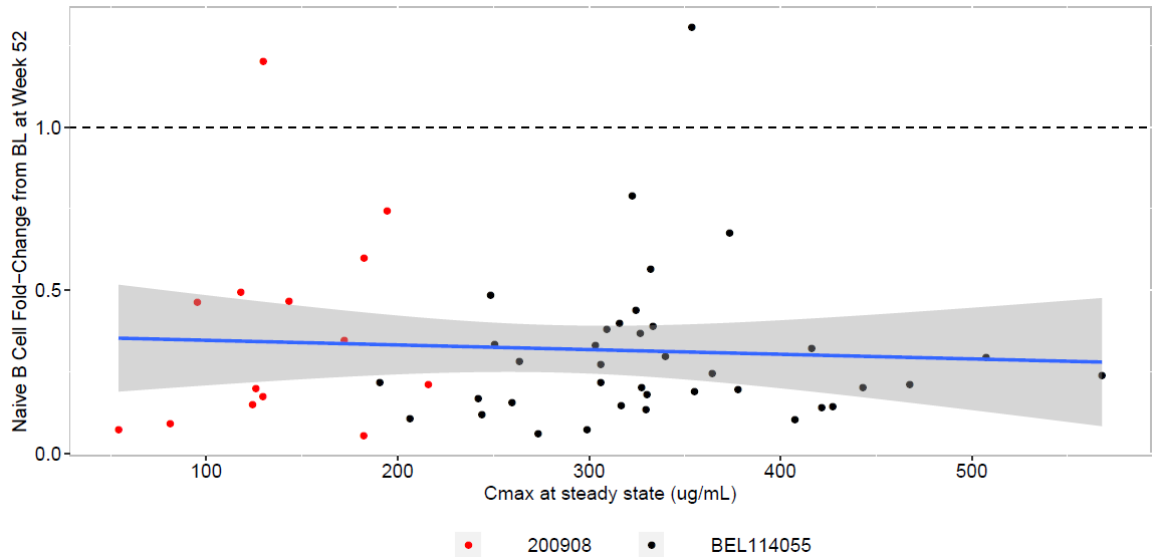
Upon the CHMP's request, the MAH provided graphical analysis of naïve B-cell response according to Cmin and Cmax:

Figure 5: Naïve B-cell response at week 52 vs belimumab exposure

a. Naive B-cell response at week 52 vs Cmin. P-value=0.256



b. Naive B-cell response at week 52 vs Cmax. P-value=0.656



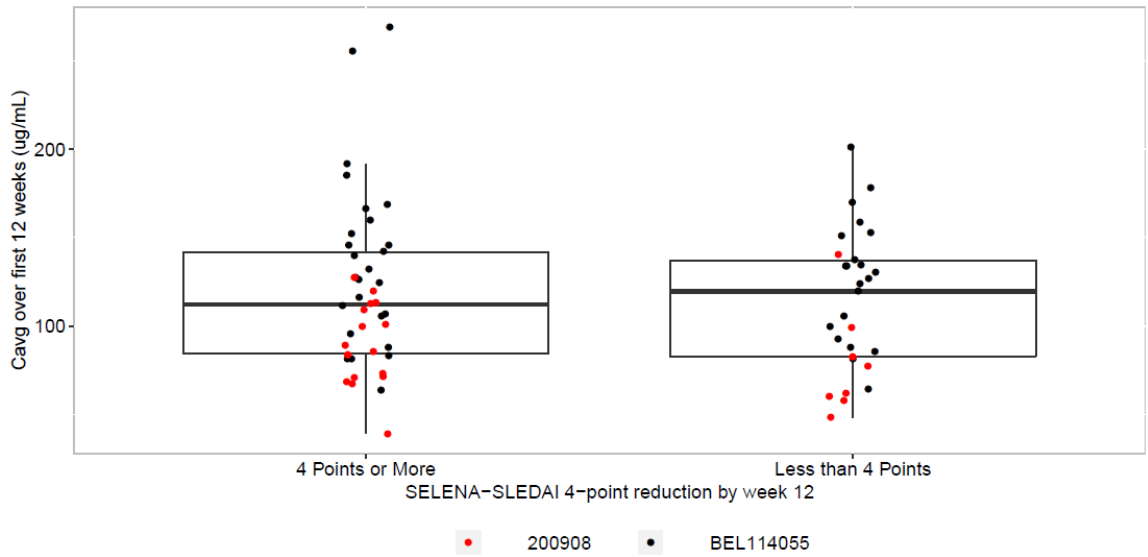
The linear regression (blue line) through all data points from studies 200908 and BEL114055 combined is shown with 95% confidence interval (grey shaded region). Baseline levels (fold-change of 1) is represented by the horizontal black line. Individual predictions for the paediatric IV study BEL114055 (black) and the paediatric SC study 200908 (red) are shown.
BL = Baseline; Cmax = Maximum concentration; Cmin = Minimum concentration.

Efficacy

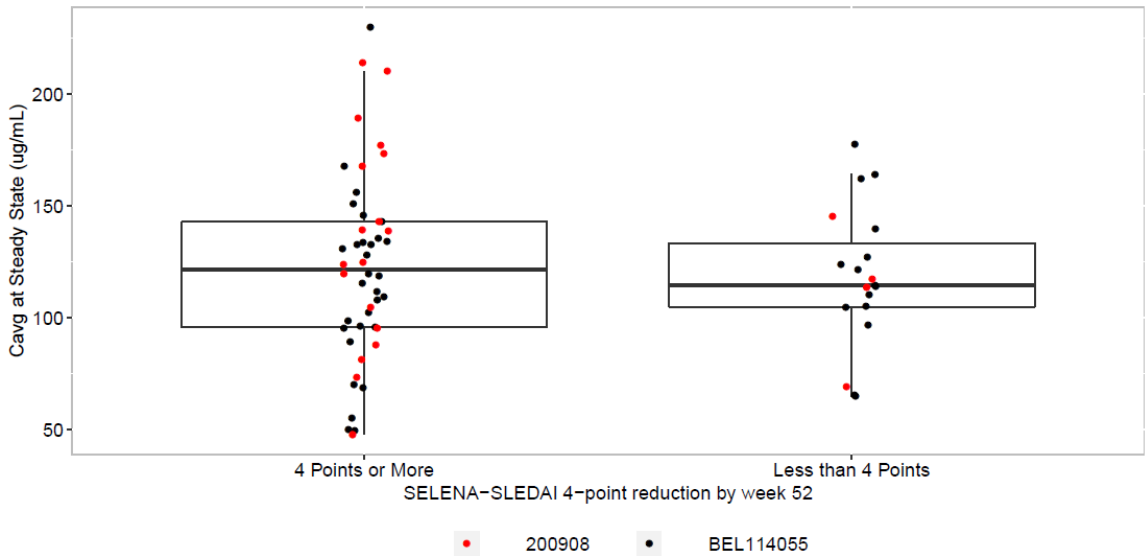
There was no correlation between belimumab exposure and efficacy as described by a binary endpoint: a reduction in SELENA-SLEDAI score of 4 points or more (responders), or less than 4 points (non-responders). The average belimumab concentrations over the first 12 weeks was similar between responders and non-responders at Week 12, and the average belimumab concentration at steady state was similar between responders and non-responders at Week 52 (Figure 6).

Figure 6: SELENA-SLEDAI Response versus belimumab Exposure

A. SELENA-SLEDAI response at Week 12 vs Cavg (Wk 0-12)



B. SELENA-SEDAI response at Week 52 vs Cavg.ss

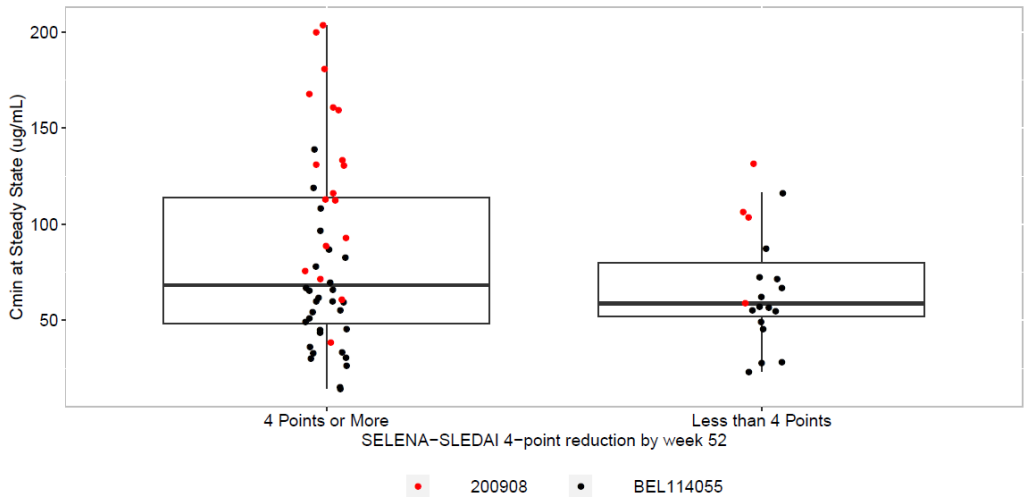


Individual predictions for the pediatric IV study BEL114055 (black) and the pediatric SC study 200908 (red) are shown. Box plots show the median (central bar), inter-quartile range (box) and the nearest data point no more than 1.5 times above and below the box (whisker).

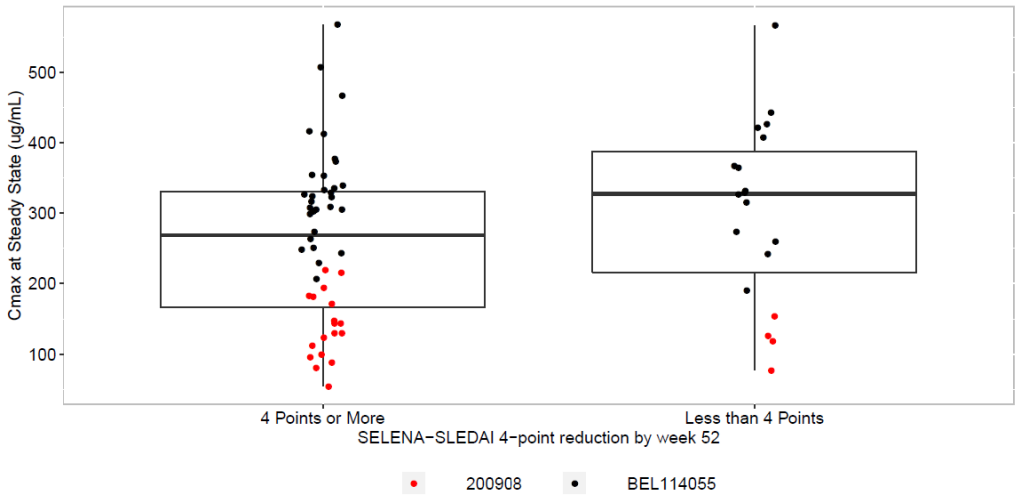
Upon the CHMP's request, the MAH provided graphical analysis of SELENA-SLEDAI response according to Cmin and Cmax:

Figure 7: SELENA-SLEDAI response vs belimumab exposure

a. SELENA-SLEDAI response at week 52 vs Cmin



b. SELENA-SLEDAI response at week 52 vs Cmax



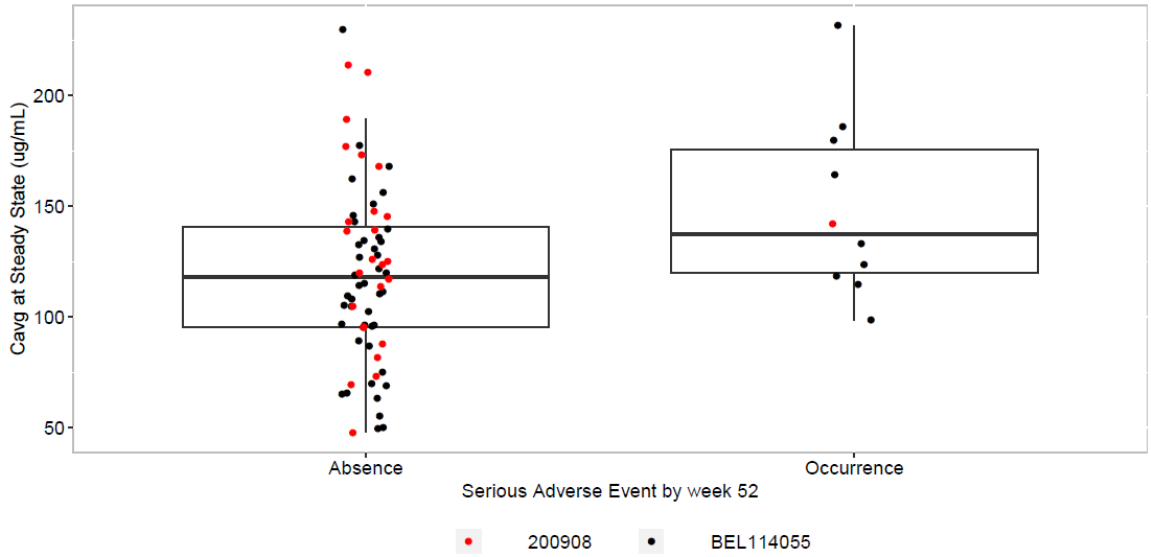
Box plots show the median (central bar), inter-quartile range (box) and the nearest data point no more than 1.5 times above and below the box (whisker). Individual predictions for the paediatric IV study BEL114055 (black) and the paediatric SC study 200908 (red) are shown.
Cmax = Maximum concentration; Cmin = Minimum concentration.

Safety

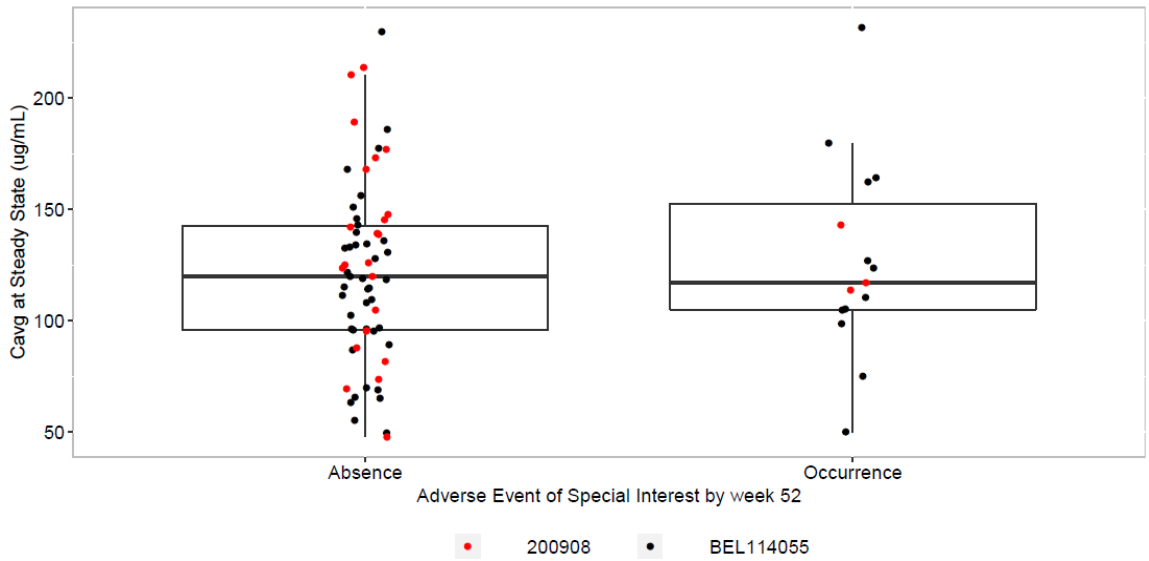
Safety was described by the absence or occurrence of a serious adverse event (SAE), and absence or occurrence of an adverse event of special interest (AESI). In the pediatric SC and IV studies, although belimumab concentrations were slightly higher in patients who experienced a SAE, concentrations in these patients overlapped with those of patients who did not experience an SAE (Figure 8, Panel A). In the paediatric SC study 200908, only one SAE occurred and was related to COVID hospitalization and was not related to belimumab administration. For patients with AESIs, belimumab concentrations were similar to patients without AESIs (Figure 8, Panel B).

Figure 8: Occurrence of Serious Adverse Event versus Belimumab Exposure

A. Occurrence of a serious adverse event over 52 weeks vs Cavg.ss



B. Occurrence of an adverse event of special interest over 52 weeks vs Cavg.ss

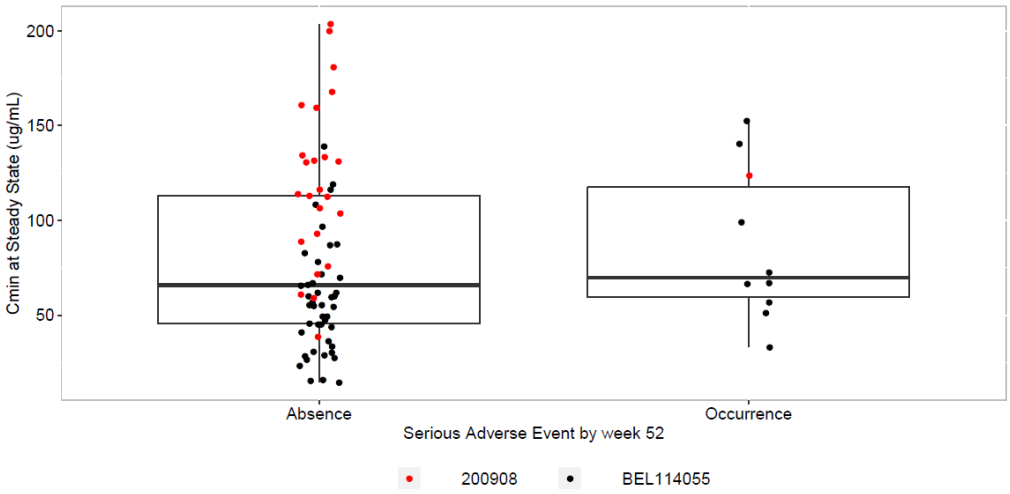


Individual predictions for the pediatric IV study BEL114055 (black) and the pediatric SC study 200908 (red) are shown. Box plots show the median (central bar), inter-quartile range (box) and the nearest data point no more than 1.5 times above and below the box (whisker).

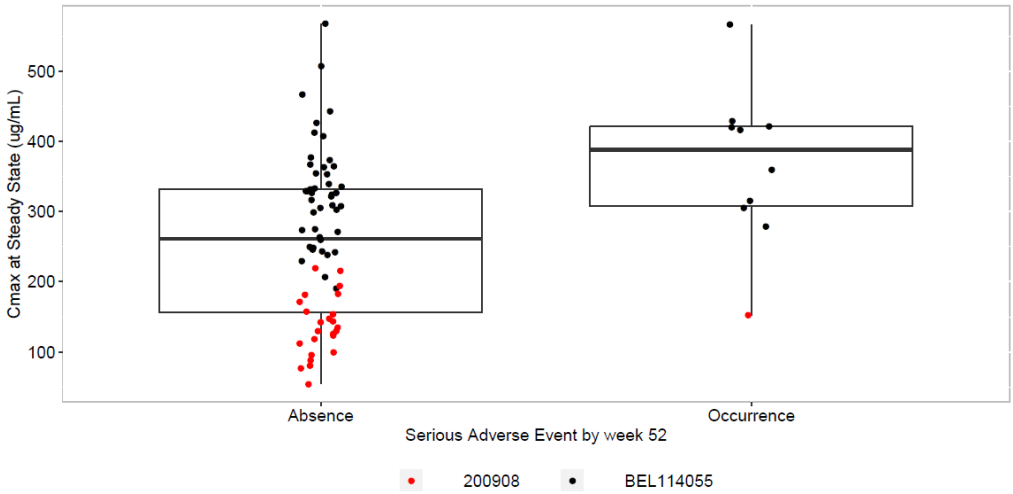
Upon the CHMP's request, the MAH provided graphical analysis of the occurrence of SAE according to Cmin and Cmax:

Figure 9: Occurrence of SAE vs belimumab exposure

a. Occurrence of a SAE over 52 weeks vs Cmin



b. Occurrence of a SAE over 52 weeks vs Cmax



Box plots show the median (central bar), inter-quartile range (box) and the nearest data point no more than 1.5 times above and below the box (whisker). Individual predictions for the paediatric IV study BEL114055 (black) and the paediatric SC study 200908 (red) are shown.
Cmax = Maximum concentration; Cmin = Minimum concentration.

Dose justification

The aim of Study 200908 was to select and justify an appropriate SC dosing regimen of belimumab for paediatric patients with SLE. The study accounted for the allometric effects of body size on belimumab clearance, and SC dosing frequency was reduced in lower body weight participants to ensure that belimumab exposures were consistent across the paediatric weight range. For this purpose, a 3-weight band regimen was utilized in study 200908: 200 mg SC QW for ≥50 kg; 200 mg SC Q10d for ≥30 kg to <50 kg; and 200 mg SC Q2W ≥15 kg to <30 kg.

According to the MAH in the initial submission of this variation, PK simulations derived from the population PK analysis of study 200908 and BEL114055 PK data subsequently demonstrated that a 2-weight band regimen would be appropriate to treat a paediatric population with SLE:

- 200 mg QW for patients ≥40 kg

- 200 mg Q2W for patients ≥15 kg and <40 kg

The final population PK model was used to simulate the Cavg.ss distribution over body weight, in 1 kg intervals, for the SC 3-weight band and 2-weight band dosing regimens, respectively. For each 1 kg body weight interval, 1000 patients were simulated. Between-subject variability was sampled using the PK model, and the subject level covariate of the PK model (baseline IgG) was sampled from the subject level dataset with replacement. It was assumed that body weight is independent of baseline IgG levels, which was confirmed by the data: 6.86% correlation.

The simulated exposure versus body weight indicate that the 3-weight band dosing regimen of Study 200908 enabled consistent belimumab exposure across the paediatric weight range from 15 kg, and that the exposure distribution was similar to that of adults (95% prediction interval 45.1 µg/mL to 205 µg/mL) (Table 5, Figure 10).

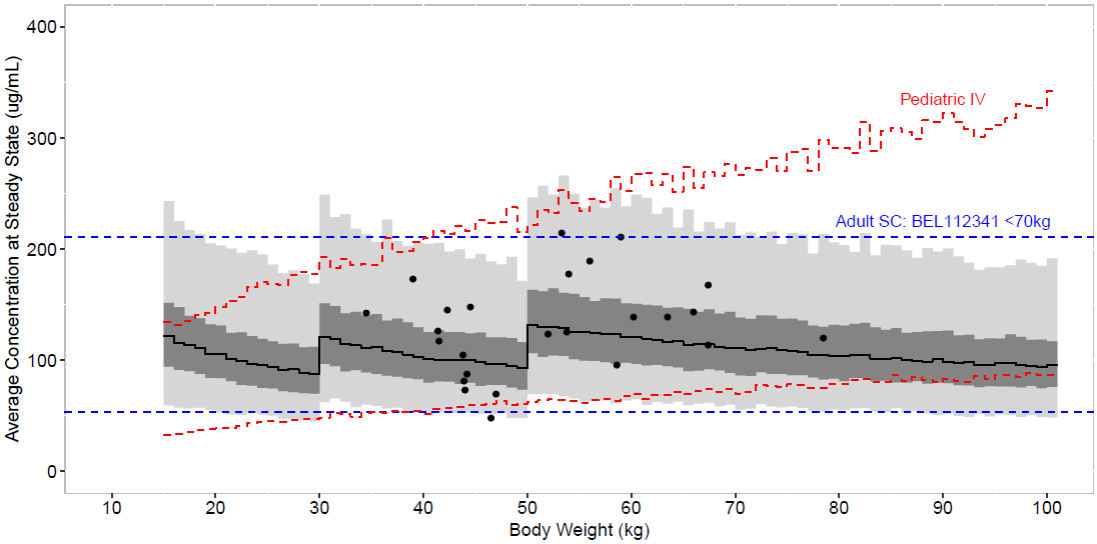
Table 5: Exposure Predictions for Paediatric Patients with SLE Receiving Belimumab SC

	Cavg at steady state Geometric mean (CV%) (95% Prediction Interval)	
	Study 200908 3-weight band SC regimen 200mg QW ≥50 kg 200mg Q10d ≥30 kg to <50 kg 200mg Q2W ≥15 kg to <30 kg	**Proposed 2-weight band SC regimen** 200mg QW ≥40 kg 200mg Q2W ≥15 kg to <40 kg
30-<35 kg	116 (34.4%) (61.6 – 232)	82.9 (34.4%) (44.0 – 166)
35-<40 kg	108 (35.0%) (56.3 – 209)	76.9 (35.0%) (40.2 – 150)
40-45 kg	101 (35.1%) (51.9 – 200)	144 (35.1%) (74.1 – 286)
45-50 kg	96.1 (35.0%) (50.1 – 190)	137 (35.0%) (71.6 – 272)
50-55 kg	130 (34.4%) (68.6 – 254)	130 (34.4%) (68.6 – 254)
Adult SC Study BEL112341 (N=556)	102 (39.2%) (45.1 – 205)	
Pediatric IV Study BEL114055 (N=53)	112 (36.2%) (51.7 – 217)	

CV% = The coefficient of variation derived as the ratio of standard deviation to the mean and reported as a percentage.

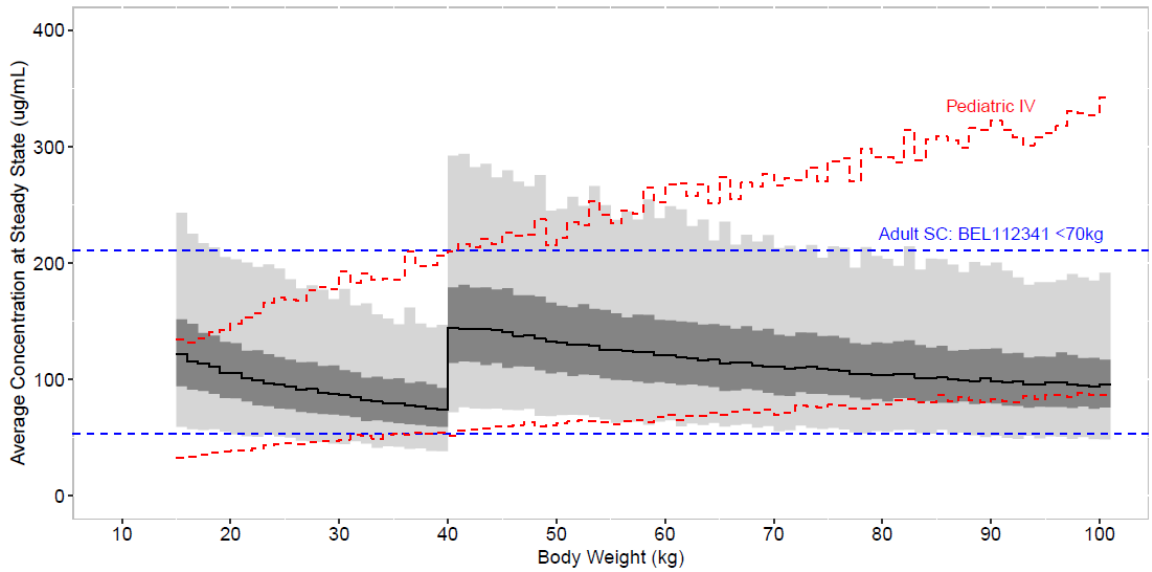
The exposures reported in this table are restricted to the 30-50 kg patients as this is the subgroup affected by the switch from the 3-weight band regimen of study 200908 to the 2-weight band regimen proposed. Exposures in the 50-55 kg weight interval are also reported to support the proposed 2-weight band regimen.

Figure 10: Simulated Average Concentration at Steady State versus Body Weight for the 3-Weight Band Dosing Regimen used in Study 200908



Simulated patients received 200 mg SC every 2 weeks (⩾15 to 30 kg), every 10 days (⩾30 to 50 kg) or every week (⩾50 kg)
Average concentrations at steady state for paediatric SC dosing are shown by the median (black solid line), interquartile range (dark grey region) and 95% prediction interval (light grey region). Individual predicted exposures of study 200908 patients are superimposed (points). The adult exposure distribution derived from the individual estimates of study BEL112341 is shown as the 95% prediction interval (blue dotted lines). The paediatric IV exposure distribution for 10 mg/kg IV every 4 weeks is shown as the 95% prediction interval (red dotted lines).
Cavg = Average observed concentration; IV = Intravenous; SC = Subcutaneous..

Figure 11: Simulated Average Concentration at Steady State versus Body Weight for the 2-Weight Dosing Regimen with a 40 kg Threshold



Simulated patients received 200 mg SC every 2 weeks (≥15 to 40 kg) or every week (≥40 kg).
Average concentrations at steady state for paediatric SC dosing are shown by the median (black solid line), interquartile range (dark grey region) and 95% prediction interval (light grey region).. The adult exposure distribution derived from the individual estimates of study BEL112341 is shown as the 95% prediction interval (blue dotted lines). The paediatric IV exposure distribution for 10 mg/kg IV every 4 weeks is shown as the 95% prediction interval (red dotted lines).
Cavg = Average observed concentration; IV = Intravenous; SC = Subcutaneous.

The 2-weight band regimen exposure was further compared to paediatric IV and adults SC exposure distributions. Model simulations predict steady-state exposures (geometric mean) for Cmin, Cavg, Cmax and AUC for the initially proposed 2-weight band SC regimen and 10 mg/kg IV Q4W in a paediatric population, and 200 mg SC QW in adults (Table 6).

The simulated exposures for SC dosing in paediatric patients by weight band are provided in Figure 12.

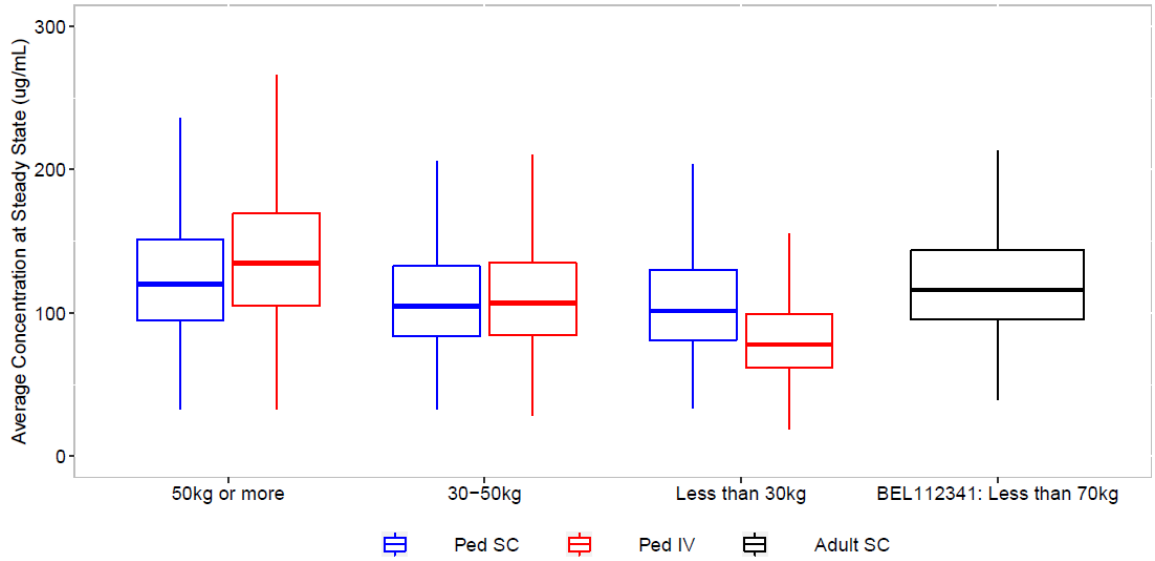
Table 6: Simulated Exposure Distribution for the 3-Weight Band and 2-Weight Band Paediatric SC Exposures Compared to Paediatric IV and Adult SC Exposures

Parameter	Population	Dose	N	GMean	CV	Pct025	Pct25	Pct50	Pct75	Pct975
Cmin.ss	Ped SC: 50kg or more	200mg Every Week	2552	110.8	38.5%	51.5	87.0	111.6	142.2	232.8
	Ped SC: 30-50kg	200mg Every 10 Days	3691	91.4	38.7%	44.2	71.0	91.1	118.2	189.1
	Ped SC: less than 30kg	200mg Every 2 Weeks	3757	79.2	43.8%	35.1	60.1	79.6	105.3	181.3
	Ped SC: 40kg or more	200mg Every Week	4484	119.2	38.6%	56.8	92.8	119.9	153.0	245.7
	Ped SC: Less than 40kg	200mg Every 2 Weeks	5516	73.7	44.6%	31.8	55.2	74.1	98.1	171.9
	Ped IV	10 mg/kg Every Week	10000	46.8	78.6%	10.3	30.8	49.6	75.7	156.5
Cavg.ss	Ped SC: 50kg or more	200mg Every Week	2552	119.2	36.6%	58.2	94.7	120.0	151.2	242.3
	Ped SC: 30-50kg	200mg Every 10 Days	3691	105.1	34.9%	54.4	83.5	104.8	132.6	206.4
	Ped SC: less than 30kg	200mg Every 2 Weeks	3757	102.7	36.2%	53.0	81.1	101.5	130.3	208.1
	Ped SC: 40kg or more	200mg Every Week	4484	128.5	36.8%	63.4	101.4	129.0	163.1	256.3
	Ped SC: Less than 40kg	200mg Every 2 Weeks	5516	94.8	37.8%	47.6	74.0	94.7	120.4	197.8
	Ped IV	10 mg/kg Every Week	10000	100.6	42.7%	45.4	76.0	100.7	133.3	225.7
	Adult SC: BEL112341	200mg Every Week	556	102.1	39.2%	45.1	80.9	105.6	131.5	205.3
Cmax.ss	Ped SC: 50kg or more	200mg Every Week	2552	124.0	35.7%	62.0	99.0	124.6	156.1	249.2
	Ped SC: 30-50kg	200mg Every 10 Days	3691	113.8	33.1%	61.1	91.5	113.3	142.1	218.0
	Ped SC: less than 30kg	200mg Every 2 Weeks	3757	119.1	32.8%	64.8	96.3	117.4	147.1	226.8
	Ped SC: 40kg or more	200mg Every Week	4484	133.8	35.9%	67.7	106.0	134.2	168.8	263.1
	Ped SC: Less than 40kg	200mg Every 2 Weeks	5516	109.6	34.8%	58.0	86.7	109.3	136.8	217.0
	Ped IV	10 mg/kg Every Week	10000	301.0	31.2%	166.5	245.6	301.0	370.4	546.6
AUC.ss	Ped SC: 50kg or more	200mg Every Week	2552	834.2	36.6%	407.3	662.8	840.3	1058.8	1695.8
	Ped SC: 30-50kg	200mg Every 10 Days	3691	1051.4	34.9%	543.9	834.9	1048.5	1325.7	2063.6
	Ped SC: less than 30kg	200mg Every 2 Weeks	3757	1438.3	36.2%	741.4	1134.8	1421.6	1824.3	2912.9
	Ped SC: 40kg or more	200mg Every Week	4484	899.2	36.8%	444.1	709.7	903.0	1141.8	1793.9
	Ped SC: Less than 40kg	200mg Every 2 Weeks	5516	1327.9	37.8%	665.4	1035.5	1325.3	1686.1	2768.4
	Ped IV	10 mg/kg Every Week	10000	2817.2	42.7%	1270.5	2129.0	2819.6	3732.5	6318.7

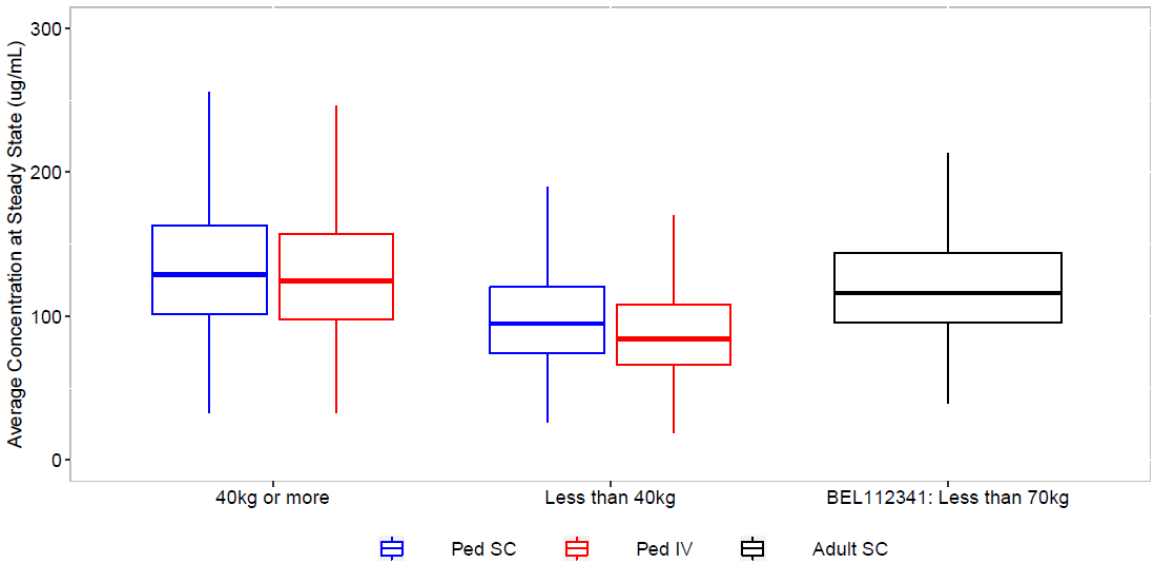
Pediatric exposures derived from a simulation pediatric SLE population (N=10,000) split between ≥40 kg (N=4484) and 15 kg to <40 kg (N=5516). Adult exposure summary (Cavg only) is derived from the individual estimates of study BEL112341 (N=556). The AUC at steady state is calculated over the dosing interval. Cmin.ss and Cmax.ss are different between the pediatric IV and adult and paediatric SC simulations due to the larger peak-trough ratio of the IV PK profile.

Figure 12: Cavg distribution stratified by weight band

a. **3-weight band SC regimen used in study 200908**



b. **Proposed 2-weight band SC regimen to treat paediatric patients with SLE**



a. Simulated patients received 200 mg SC every 2 weeks (⩾15 to 30 kg), every 10 days (⩾30 to 50 kg) or every week (⩾50 kg). b. Simulated patients received 200 mg SC every 2 weeks (⩾15 to 40 kg) or every week (⩾40 kg).

Populations are defined as follows: Paediatric SC patients received 200 mg at the specified dosing frequency for the weight band (blue); All paediatric IV patients received 10 mg/kg every 4 weeks with exposure distribution stratified by weight band (red); Adult SC BEL112341 represents the individual estimated exposures for adults of study BEL112341 receiving 200 mg SC QW, restricted to those adult patients less than 70 kg (black).

Cavg = Average observed concentration; IV = Intravenous; SC = Subcutaneous.

Compared to the exposure distributions of 3-weight band regimen of study 200908, paediatric IV dosing regimen, and adult SC dosing regimen, belimumab exposure for the 2-weight band regimen is predicted to be more variable: 30 kg to 40 kg patients would have lower exposure due to Q2W dosing; and 40 kg to 50 kg patients would have higher exposure due to QW dosing. However, the MAH considered that the difference is not large nor clinically relevant, and that the 2-weight band regimen is expected to have the same benefit-risk profile for the following reasons:

1. The lower exposures in the 30 kg to 40 kg subgroup expected from the Q2W dose are generally within the adult SC and paediatric IV exposure range for which efficacy has been established.

   The higher exposures in the 40 kg to 50 kg subgroup expected from the QW dose are less than 50% above adult SC and paediatric IV exposures for which safety has been established (Table 5, Table 6).

2. Furthermore, weekly dosing is proposed in patients 50 kg or more, as administered in study 200908 (Cohort 1), where exposures are expected to be below 254 ug/mL compared to less than 286 ug/mL for 40-50 kg patients (upper bound of the 95% prediction intervals of Table 5). On this basis, no increased safety risk is expected for weekly dosing in the 40-50 kg subgroup.

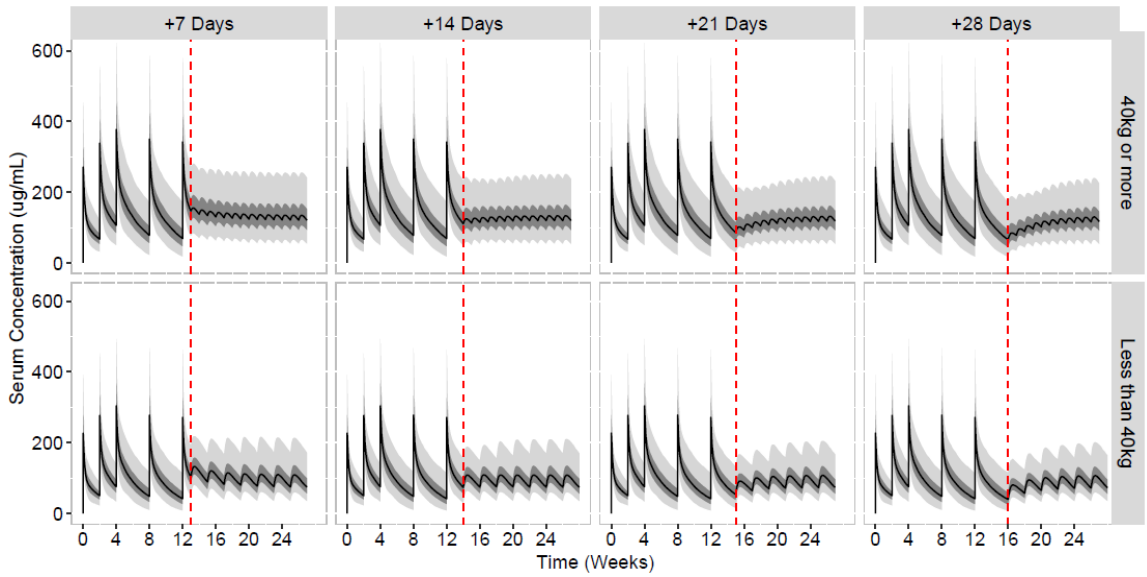
3. The exposure-response relationships derived from study 200908 data show that maximum efficacy is achieved for the 3-weight band SC regimen with no clear exposure-driven safety risk. The slightly wider exposure distribution predicted for the 2-weight band SC regimen is therefore not expected to impact efficacy or increase the safety risk. The 2-weight band regimen is considered safe to treat pediatric patients with SLE.

On this basis, the 2-weight band SC regimen was initially proposed to be recommended to treat paediatric patients with SLE. The MAH also considered that the 2-weight band regimen also benefits from the weekly or every 2 week dosing schedule as it would be more practical in a real-world setting, minimizing the risk of non-compliance that may be associated with a 10-day dosing schedule that was included in the 3-weight band regimen of study 200908.

Transitioning from IV to SC Dosing

When transitioning from IV to SC dosing, the first SC dose should be administered between 1 and 4 weeks after the last IV dose, with the optimal time being 1 to 2 weeks after the last IV dose, since SC exposures are approximately at steady state directly after the first SC dose is administered (Figure 13). This is in line with adult IV to SC switching, recommended to be 1 to 4 weeks after the last IV dose, with the optimal time being 2 weeks.

Figure 13: IV to SC PK Simulation for the 2-Weight Band Regimen



The time of switch is 7, 14, 21 or 28 days after the last IV dose (red dotted line). Median concentrations (solid black line) are shown with inter-quartile range (dark grey region) and 95% prediction interval (light grey region) of the between-participant variability.

2.4.4. Discussion on clinical pharmacology

The dosing recommendation for paediatric SC administration initially proposed was a 2-weight group regimen, 200 mg Q2W ≥15 kg to <40 kg and 200 mg QW ≥40 kg.

Given the rarity of paediatric SLE, the use of SC belimumab in paediatric SLE patients was mainly supported by an extrapolation strategy based on a paediatric SLE study with SC belimumab (study 200908), the adult SLE study with SC belimumab (study BEL112341) and the paediatric SLE study with IV belimumab (study BEL114055). The determination of the dose recommendation for paediatric SC use was based on a modelling and simulation study. This approach has been accepted in the PIP.

The approval of the extension of indication for IV use of belimumab in paedatric SLE patients (variation II/0062, EC decision 21/20/2019) was mainly based on extrapolation from adult SLE patients. Compared with individuals with adult-onset disease, children with SLE have more commonly multiorgan disease, acute disease onset and ongoing active inflammation over time. SLE with childhood onset is also more often associated to rare complement mutations with an increased susceptibility to infections. These differences were discussed in variation II/0062 and it was agreed that these differences do not preclude extrapolation. The CHMP concluded that PK properties for belimumab are similar in the paediatric and adult population. Hence, the extrapolation of efficacy and safety data for belimumab from adults to children with SLE is acceptable also for the paediatric SC formulation.

Study 200908 was a single arm, multi-center, open-label PK/PD/safety study using the belimumab SC formulation in paediatric SLE participants. The aim of Study 200908 was to select and justify an appropriate SC dosing regimen of belimumab for paediatric patients from 5 years of age and weighing ≥15 kg with SLE. As such, the PK analysis and results in paediatric patients is pivotal to support SC dosing recommendation. A total of 13 participants were recruited into cohort 1 (≥50 kg body weight) and received 200 mg SC every week, as per the adult regimen; 12 participants were recruited into cohort 2 (≥30 kg to <50 kg body weight) and received 200 mg SC every 10 days; no one was enrolled into cohort 3 (≥15 kg to <30 kg body weight) as recruitment of low body weight participants was challenging due to the low prevalence of disease in young children. Exposures were in general higher in cohort 1 compared to cohort 2. The average concentrations at steady state were comparable between the paediatric SC study (200908) and paediatric IV study (BEL114055).

A population PK analysis was performed on combined paediatric SC and IV PK data with the aim to compare paediatric and adult belimumab exposure to support the extrapolation of efficacy and safety from SC administration in the adult population. Standard methodology was used and, in general, the analysis was well performed. The PK model previously developed on the paediatric IV data, with the addition of SC absorption components from the adult SC PK model, was used as a base model. The covariate fat-free mass was replaced by body weight, which is accepted. Overall, it is considered that the model describes well the paediatric PK data. Upon the CHMP's request, the MAH provided visual predictive checks stratified on body weight which indicate that the model describes data well independent of body weight.

It is reasonable to use average concentration as the main exposure metric in the comparison between paediatric and adult SC exposure. The fluctuation in belimumab concentration is less after SC administration than after IV administration, Cmax is not of concern since higher levels have been accepted for the IV administration in paediatric patients. Conversely, Cmin levels are higher for the SC administration, so loss of efficacy is not an issue. Nonetheless, the MAH was asked to provide the clinical impact of the covariates selected based on the change on exposure metrics (Cavg, Cmax and

Cmin). No obvious trend between Naive B-cell response or SELENA-SLEDAI and any of the exposure metrics was observed. A slight trend between Cmax and occurrence of SAE was noted, which is also visible for Cavg vs SAE. As expected, the highest Cmax-values and lowest Cmin-values were observed with IV administration. Overall, Cavg was accepted as the main exposure metric for belimumab exposure-matching.

The simulated exposure versus body weight indicate that the 3-weight band dosing regimen of Study 200908 enabled consistent belimumab exposure across the paediatric weight range from 15 kg and that the exposure distribution was similar to that observed for the SC use in adults (200 mg once weekly) and for the IV use in paediatric patients (10 mg/kg body weight on Days 0, 14 and 28, and at 4-week intervals thereafter).

Exposure-response evaluations were provided for average concentration versus Naïve-B cell response, SELENA-SLEDAI, SAE, and SAE of special interest. The CHMP agreed that there is no apparent relationship between the exposure (at studied exposure range) and PD or efficacy. However, the tendency for higher exposure for patients who experienced SAE cannot be neglected given the expected higher exposure for patients ≥50 kg (or ≥40 kg with the 2-weight group dosing regimen).

No patients were included in the ≥15 kg to <30 kg weight group of Study 200908, and thus the dosing recommendation is based on model predictions. A comparison between expected exposure (Cavg) values after IV and SC administration show that higher values are expected after SC administration in the lowest weight groups. Upon the CHMP's request, the MAH provided an overview of the limited information that is available for comparison of subcutaneous bioavailability of monoclonal antibodies (mAbs) between paediatric and adult patients. The comparison was not specific to the body weight group 15 to < 30 kg. Although some of the mAbs showed higher bioavailability between adult and paediatric patients, there does not seem to be any indication that the bioavailability would drastically change below 30 kg compared to paediatric patients 30-50 kg. The population PK analysis of belimumab PK data in paediatric patients results in similar bioavailability between adult and paediatric patients which was considered somewhat reassuring. The predicted exposure range across all body weights (3 weight group dosing regimen) was within the limits of the reference adult exposure (SC administration) and IV exposure in both adults and paediatric patients. In a worst-case scenario, the maximum increase in bioavailability would be 30% (i.e. 100% bioavailability) which still be within the IV exposure range of body weights above approximately 75 kg. Thus, the assumption of constant bioavailability across body weight in the paediatric population was accepted by the CHMP. The proposed dosing regimen of 200 mg Q2W in patients 15 to <30 kg was accepted by the CHMP.

The initially proposed 2-weight group dosing regimen, which is different from the studied 3-weight group regimen, was not agreed by the CHMP since concerns were raised regarding the exposure in patients ≥50 kg considering the exposure-safety trend towards higher exposure for patients who experienced a SAE. Further, the observed exposure in the weight group >50 kg was somewhat higher than the adult reference range. It was even more apparent in the proposed 200 mg QW dosing >40 kg, where a large proportion of the exposure distribution was above the adult reference range between 40-60 kg. In response to the CHMP concerns, the MAH provided a comparison with SC exposure for adult patients <70 kg; the exposure range in this adult patients' subgroup was slightly higher compared to the full adult population. The highest observed Cavg values in the paediatric population were within the adult <70 kg exposure range. The MAH argued that there is no dose(exposure)-response relationship, however, patients with SAEs have exposure values in the upper range of the exposure range. Due to this trend with SAEs at higher exposures, a dosing recommendation that shows expected exposure beyond the studied exposure range was not supported by the CHMP. Given the proposed 2-weight group dosing (cut-off 40 kg), the CHMP considered that the patients between 40-50 kg clearly would exceed the exposure both in adults and paediatric IV exposure. Therefore, the

CHMP concluded that the studied 3-weight group dosing recommendation is favourable and the MAH agreed to revise the posology accordingly.

When transitioning from IV to SC dosing in paediatric SLE patients, the first SC dose should be administered between 1 and 4 weeks after the last IV dose, this in line with the switching recommended in adults from IV to SC (SmPC Sections 4.2 and 5.2).

2.4.5. Conclusions on clinical pharmacology

The following 3-weight group SC dosing recommendation in paediatric SLE patients is endorsed by the CHMP:

Body weight	Recommended dose
≥ 50 kg	200 mg once weekly
30 to < 50 kg	200 mg every 10 days
15 to < 30 kg	200 mg every 2 weeks

2.5. Clinical efficacy

2.5.1. Main study(ies)

Study 200908

Methods

Study 200908 is a Phase 2, single arm, multi-centre, open-label trial to evaluate the PK, safety, and PD of repeat doses of 200 mg belimumab administered subcutaneously in participants 5 to 17 years of age and weighing ≥15 kg with active SLE on a background of standard of care therapy. This bridging PK study is part of an extrapolation strategy to support the use of SC belimumab in paediatric SLE patients, based on the completed adult SLE study with SC belimumab (BEL112341) and the paediatric SLE study with IV belimumab (BEL114055).

Study 200908 includes:

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

Study participants

Key inclusion criteria consisted of paediatric participants who were between 5 and 17 years of age inclusive on Day 1. Participants must have had active SLE disease (defined as a SELENA SLEDAI score ≥6 at screening), who had at least 4 of the 11 manifestations of SLE, had documented positive autoantibody test results with an ANA titre ≥1:80 and/or anti-dsDNA (≥30 IU/mL) serum antibody test, were on a stable SLE treatment regimen, and had a body weight of ≥15 kg.

Key exclusion criteria consisted of an estimated glomerular filtration rate of <30 mL/min; acute severe nephritis defined as significant renal disease; a history of a major organ transplant or hematopoietic stem cell/marrow transplant; clinical evidence of significant, unstable or uncontrolled, acute or chronic diseases not due to SLE; a history of malignant neoplasm within the last 5 years; prior treatment with belimumab; treatment with B-cell targeted therapy, abatacept, or any biologic investigational agent within 364 days of Day 1; treatment with 3 or more courses of systemic corticosteroids within 90 days of Day 1; treatment with cyclophosphamide within 30 days of Day 1; active CNS lupus requiring intervention within 60 days of Day 1.

Treatments

Administration of belimumab 200 mg SC in Part A was as follows:

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

a. No participants were enrolled in Cohort 3.

In Part B, the dosing frequency could change according to pre-defined criteria based on changes in the body weight of the participant.

Objectives, Outcomes/endpoints

Study 200908 was a bridging PK study with a small sample size, and the key objectives were PK and safety.

Objective	Endpoint
Primary - Pharmacokinetics	
• To characterize the pharmacokinetic (PK) profile of belimumab 200 mg subcutaneous (SC) in pediatric SLE participants.	• Observed belimumab concentrations at Week 12. • Steady-state PK parameters: Cavg (AUC), Cmax, Cmin (based on population PK estimates).
Secondary - Safety	
• To evaluate the safety and tolerability of belimumab 200 mg SC in pediatric SLE participants.	• Incidence of adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESI) through Week 52.
Secondary - Biomarkers	
• To characterize the pharmacodynamic (PD) profile of belimumab 200 mg SC in pediatric SLE participants.	• Change from baseline in biomarkers (C3/C4, anti-dsDNA, B cell subsets, and immunoglobulins) at Weeks 12 and 52.
Other – Efficacy	
• To characterize the impact of belimumab 200 mg SC on disease activity in pediatric SLE participants.	• Percent of participants with a ≥ 4 point reduction from baseline in SELENA SLEDAI at Weeks 12 and 52.

Sample size

A total of 25 participants were enrolled and included in the intent-to-treat (ITT) population and the PK population.

Randomisation

Not applicable for a single arm, open-label study.

Blinding (masking)

Not applicable.

Statistical methods

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

All PK analyses were performed on the PK Population. All safety, PD, and other (efficacy) analyses were performed on the ITT Population.

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

Results

Participant flow

A total of 28 participants were screened and 25 were enrolled to the study. All 25 enrolled participants received at least 1 dose of study drug. The most common reason for failed screening was did not meet eligibility criteria (n=2), and 1 participant was excluded based on investigator's discretion.

Table 7: Disposition of patients

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

Recruitment

Table 8: Recruitment by country

	Number (%) of Participants Belimumab 200mg (N=25)
Country	
Argentina	4 (16.0)
Germany	4 (16.0)
Japan	2 (8.0)
Mexico	3 (12.0)
Netherlands	2 (8.0)
Spain	6 (24.0)
United States	4 (16.0)

Conduct of the study

Study Period: 28 November 2019 (first subject enrolled) to Ongoing: last subject last visit 16 January 2023 Part B, open-label endpoint analysis.

Baseline data

The majority of participants were female (84.0%). Sixty four percent (64%) of participants were White (64.0%), followed by Asian (16.0%) and Alaska Native or American Indian (12.0%). The median age of participants at screening was 14.0 years (range 10 to 17 years). The number of participants was evenly distributed between Cohort 1 (≥50 kg; 52%) and Cohort 2 (≥30 kg to <50 kg; 48.0%) at baseline. No participants were included in Cohort 3 (<30 kg). Spain enrolled the largest number of participants (24.0%), followed by the United States (US), Argentina, and Germany with 16.0% each.

Table 9: Summary of demographics and baseline characteristics in the SC belimumab phase 2 paediatric study 200908 (ITT Population)

	Number (%) of Participants Belimumab 200 mg (N=25)
Country	
Argentina	4 (16.0)
Germany	4 (16.0)
Japan	2 (8.0)
Mexico	3 (12.0)
Netherlands	2 (8.0)
Spain	6 (24.0)
United States	4 (16.0)
Sex	
n	25
Female	21 (84.0)
Male	4 (16.0)
Age at Screening (years)[a]	
n	25
Mean	14.0
SD	2.09
Median	14.0
25th percentile	13.0
75th percentile	16.0
Min.	10
Max.	17
Age Group at Screening (years)[a]	
n	25
<=18	25 (100.0)
19-64	0
>=65	0
Ethnicity	
n	25
Hispanic or Latino	11 (44.0)
Not Hispanic or Latino	14 (56.0)
High Level Race	
n	25
American Indian or Alaska Native	3 (12.0)
Asian	4 (16.0)
Black or African American	1 (4.0)
Native Hawaiian or Other Pacific Islander	0
White	16 (64.0)
Mixed Race	1 (4.0)
Weight (kg)	
n	25
Mean	52.09
SD	10.898
Median	52.00
25th percentile	43.90
75th percentile	59.00
Min.	34.5
Max.	78.5
Baseline Body Weight Cohort[b]	
Cohort 1 (>=50 kg)	13 (52.0)

	Number (%) of Participants Belimumab 200 mg (N=25)
Cohort 2 (>=30 kg - <50 kg)	12 (48.0)
Cohort 3 (<30 kg)	0

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

Table 10: Selected baseline disease characteristics in the SC belimumab phase 2 paediatric study 200908 (ITT Population)

	Belimumab 200 mg N=25
SELENA SLEDAI score, n Mean SD Median 25th percentile 75th percentile Min Max	 25 9.5 3.04 8.0 8.0 10.0 6 18
SELENA SLEDAI category, n (%) ≤7 ≥8 SELENA SLEDAI category, n (%) ≤9 ≥10	25 5 (20.0) 20 (80.0) 25 13 (52.0) 12 (48.0)
Proteinuria category (mg/mg) n ≤0.5 >0.5 - <1 1 - <2 ≥2 Proteinuria level (mg/mg) n Mean SD Median 25th percentile 75th percentile Min Max	 25 24 (96.0) 0 0 1 (4.0) 25 0.32 0.855 0.10 0.10 0.20 0 4.4

SELENA SLEDAI organ involvement at baseline in the Phase 2 SC paediatric trial (Study 200908) is presented below. The most common SELENA SLEDAI organ system involvement (in >50% participants) were in the musculoskeletal, mucocutaneous, and immunologic systems.

Table 11: Baseline organ involvement in SC belimumab phase 2 paediatric study 200908 (ITT Population)

Organ Item	Belimumab 200 mg N=25
CNS	
Any Event	2 (8.0%)
Lupus Headache	2 (8.0%)
Vascular	
Any Event	1 (4.0%)
Vasculitis	1 (4.0%)
Musculoskeletal	
Any Event	15 (60.0%)
Arthritis	14 (56.0%)
Myositis	1 (4.0%)
Renal	
Any Event	3 (12.0%)
Hematuria	1 (4.0%)
Proteinuria	1 (4.0%)
Pyuria	1 (4.0%)
Mucocutaneous	
Any Event	21 (84.0%)
Rash	11 (44.0%)
Alopecia	15 (60.0%)
Mucosal Ulcers	6 (24.0%)
Cardiovascular and Respiratory	
Any Event	4 (16.0%)
Pleurisy	4 (16.0%)
Immunologic	
Any Event	19 (76.0%)
Low Complement	18 (72.0%)
Increased DNA Binding	16 (64.0%)
Hematologic	
Any Event	1 (4.0%)
Leukopenia	1 (4.0%)

Concomitant medication

The percentage of participants taking allowable SLE medications at baseline in the Phase 2 SC paediatric trial (Study 200908) is presented in Table 12. The majority of participants were receiving a combination of SLE therapies, with the highest percentage (72%) on steroids, plus an immunosuppressant and an antimalarial.

Table 12: Allowable SLE medication usage at baseline in the SC belimumab phase 2 paediatric study 200908 (ITT Population)

	Number (%) of Participants Belimumab 200mg (N=25)
Average daily Prednisone[a] dose (mg/day), n	25
Mean (SD)	8.55 (6.767)
(Min, Max)	(0.0, 25.0)
Number (%) of Participants Taking:	
Antimalarials	25 (100.0)
Immunosuppressants	21 (84.0)
Steroids	21 (84.0)
NSAIDs	5 (20.0)
Aspirin	0

a. Steroids were converted to prednisone equivalent dose.

Numbers analysed

A total of 25 participants were enrolled and included in the intent-to-treat (ITT) population and the PK population.

Outcomes and estimation

Efficacy endpoints

The efficacy assessment in Study 200908 was an exploratory endpoint.

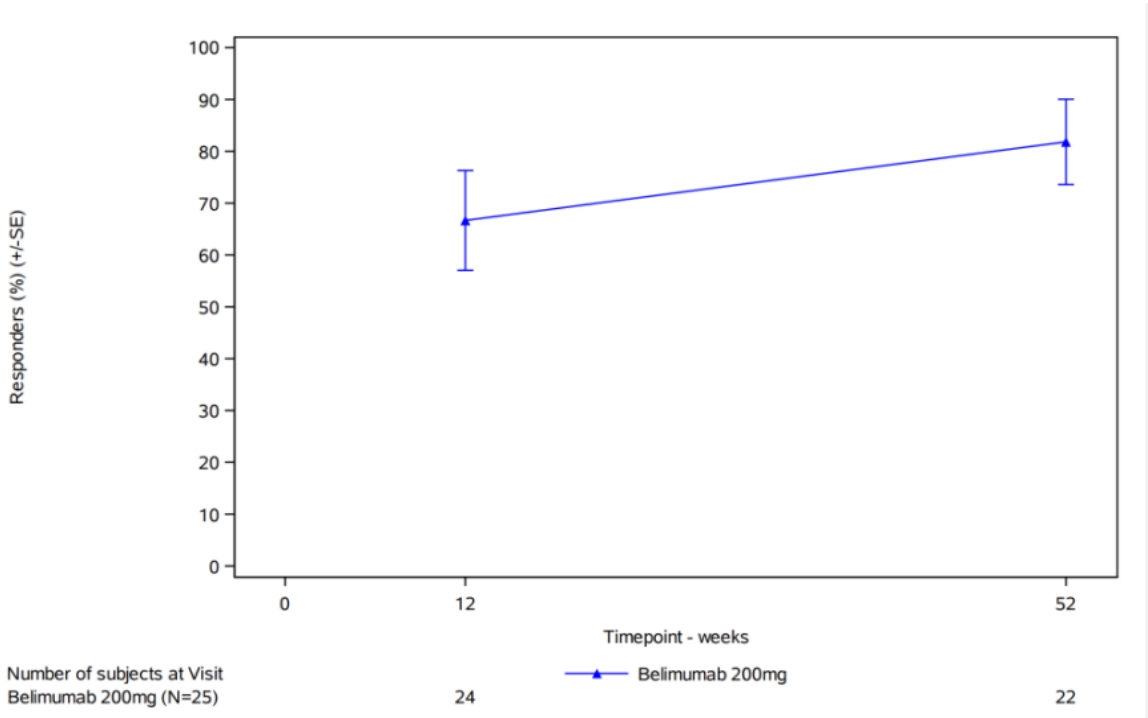
The total percentage of participants with a ≥4 point reduction from baseline in SELENA SLEDAI increased from Week 12 (66.7%) to Week 52 (81.8%) (Table 13 and Figure 14).

Table 13: SELENA SLEDAI ≥4 point reduction from baseline to week 12 and week 52 by baseline cohort for the SC belimumab phase 2 paediatric study 200908 (ITT Population)

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

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

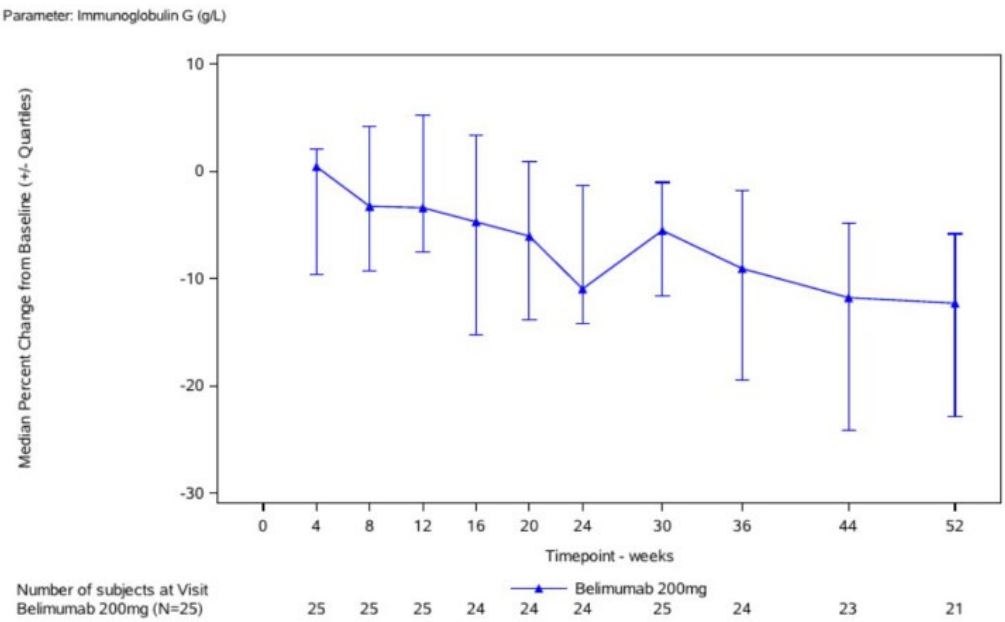
Figure 14: SELENA SLEDAI ≥4 point reduction by visit for the SC belimumab phase 2 paediatric study 200908 (Observed) (ITT Population)



PD endpoints

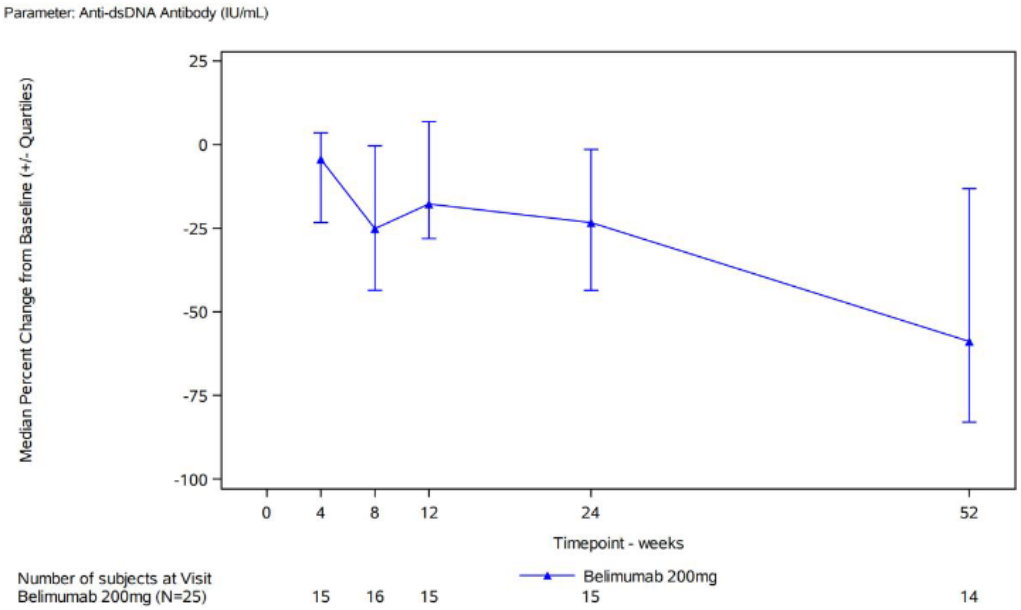
Overall, IgG levels decreased over time. At Week 12 and Week 52, there was a median decrease of 3.40% and 12.29%, respectively. Consistent results were observed for absolute change from baseline in IgG. Reductions in IgA and IgM levels were also observed following belimumab administration. For IgA, the median percent change from baseline was a decrease of 3.13% and 13.06% at Week 12 and Week 52, respectively. For IgM, the median percent change from baseline was a decrease of 10.41% and 30.79% at Week 12 and Week 52, respectively. Similar results were observed for absolute change from baseline in IgA and IgM.

Figure 15: Immunoglobulin G Levels Percent Change from Baseline by Visit (ITT Population)



Overall, anti-dsDNA antibody levels decreased over time. At Week 12 and Week 52, there was a median decrease of 17.74% and 58.88%, respectively. Consistent results were observed for absolute change from baseline in anti-dsDNA antibody levels among participants positive at baseline.

Figure 16: Anti-dsDNA Levels Percent Change from Baseline by Visit among Participants Positive at Baseline (ITT Population)



Source: Figure 4.02
Note: Anti-dsDNA positive (>=30 IU/mL); ANA positive (>=80 Titer); CRP positive (>=4 mg/L).

Among participants who had low complement (C3 <90 mg/dL; C4 <13 mg/dL) at baseline, at Week 12 there was a median increase of 8.26% in C3 and 31.03% in C4; at Week 52, median increases of 23.46% in C3 and 67.52% in C4 were observed. Similar results were observed for absolute change from baseline in complement levels among participants with low complement at baseline by visit.

Figure 17: Complement C3 Level Percent Change from Baseline by Visit Among Participants with Low Complement at Baseline (ITT Population)

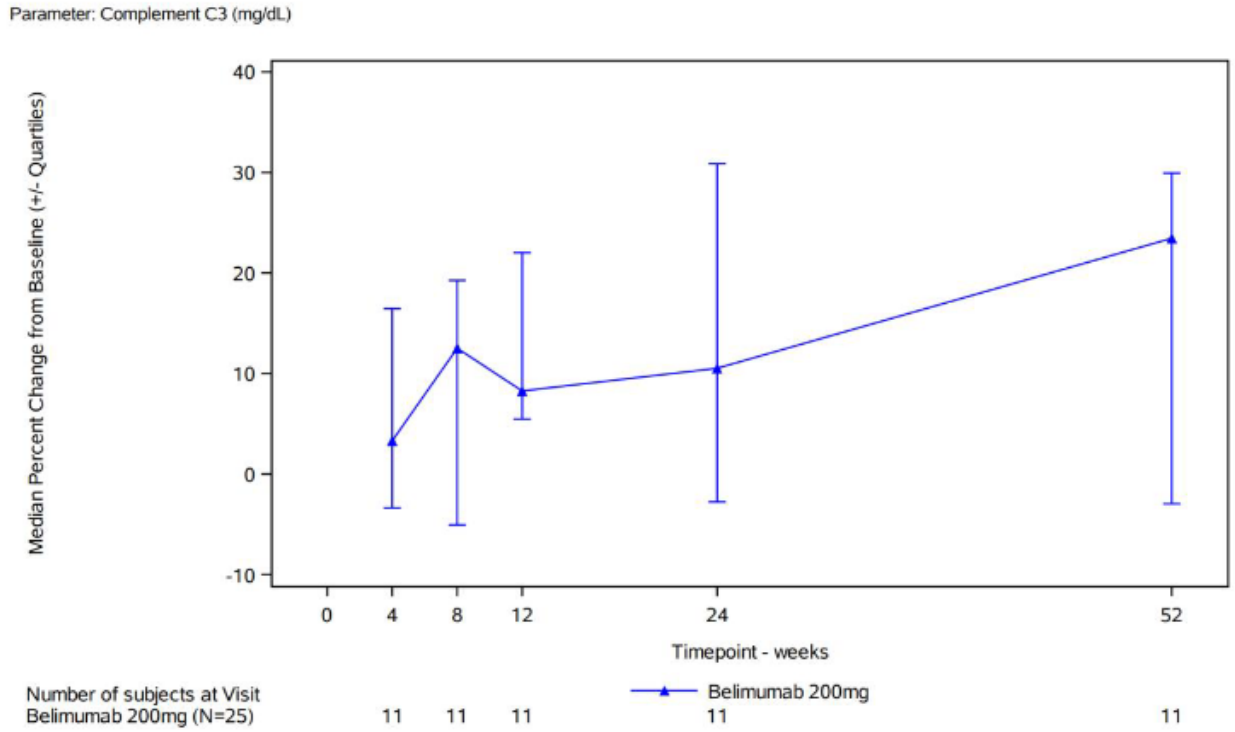
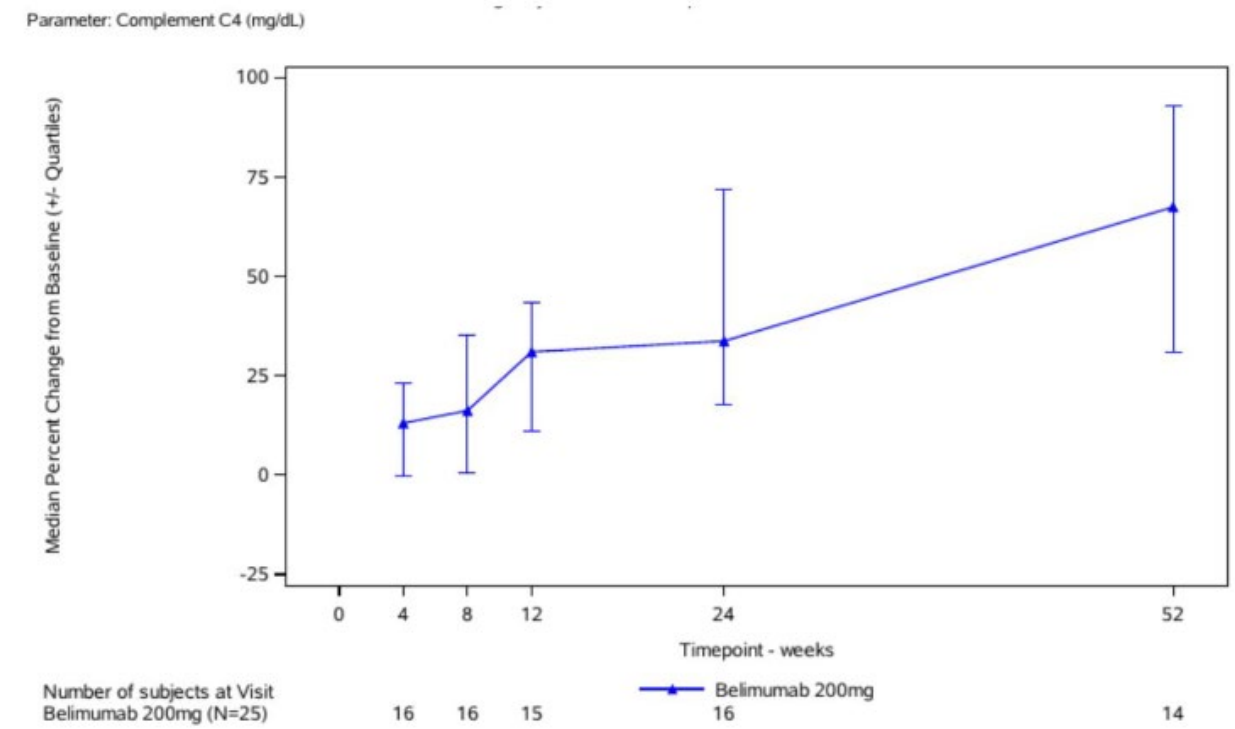


Figure 18: Complement C4 Level Percent Change from Baseline by Visit Among Participants with Low Complement at Baseline (ITT Population)



The median percent reduction in CD19+ B cells was 42.97% and 61.32% at Week 12 and Week 52, respectively. Median percent reductions in CD20+ B cells were similar to what was observed for CD19+ B cells. Median percent reductions in naïve B cells of 53.19% at Week 12 and 72.13% at Week 52 were observed. For memory B cells, median percent increases were observed: 69.06% at Week 12

and 27.10% at Week 52. A median percent increase in plasmablasts of 9.40% was observed at Week 12 and a decrease of 70.07% was observed at Week 52. Similar results were observed for median absolute change from baseline in these B cell subsets by visit.

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14: Summary of Efficacy for trial 20098 in comparison with previous belimumab studies

Study	Treatment Arm	No. Enrolled/ Completed	Efficacy Endpoint	
200908	SC Belimumab 200 mg	25/25	**Percent of Participants with a ≥4 Point Reduction from Baseline in SELENA SLEDAI at Weeks 12 and 52**	
			Cohort 1 (≥50 kg) Belimumab 200 mg Weekly N=13	**Cohort 2 (≥30 kg - <50 kg) Belimumab 200 mg Every 10 Days N=12**
			Week 12 Reduction: 9/12 (75.0%)	**Week 12** Reduction: 7/12 (58.3%)
			Week 52 Reduction: 12/13 (92.3%)	**Week 52** Reduction: 6/9 (66.7%)
BEL112341	SC Belimumab 200 SC	559/556	**≥4 Point Reduction from Baseline in SELENA SLEDAI at Week 52 (Component of SRI Response)**	
	Placebo	280/280	**Placebo N=280 n/n (%)**	**Belimumab 200 mg N=556 n/n (%)**
			137/279 (49.1)	345/554 (62.3) Odds ratio (95% CI) vs placebo: 1.69 (1.26, 2.27) p-value: 0.0005
BEL114055	IV Belimumab 10 mg/kg	53/45	**≥4 Point Reduction from Baseline in SELENA SLEDAI at Week 52 (Component of SRI Response)**	
	Placebo	40/31	**Placebo N=40 n/n (%)**	**Belimumab 10 mg/kg N=53 n/n (%)**
			17/39 (43.6)	29/53 (54.7) Odds ratio (95% CI) vs placebo: 1.62 (0.69,3.78)

Study	Treatment Arm	No. Enrolled/ Completed	Efficacy Endpoint		
C1056	IV Belimumab 1 mg/kg	271/199	**≥4 Point Reduction from Baseline in SELENA SLEDAI at Week 52 (Component of SRI Response)**		
	IV Belimumab 10 mg/kg	273/191	**Placebo N=275 n/n (%)**	**Belimumab 1 mg/kg N=271 n/n (%)**	**Belimumab 10 mg/kg N=273 n/n (%)**
	Placebo	275/186	98/275 (35.6)	116/271 (42.8) Odds ratio (95% CI) vs placebo: 1.38 (0.96, 1.93) p-value: 0.0740	128/273 (46.9) Odds ratio (95% CI) vs placebo: 1.63 (1.15, 2.32) p-value: 0.0062
C1057	IV Belimumab 1 mg/kg	288/240	**≥4 Point Reduction from Baseline in SELENA SLEDAI at Week 52 (Component of SRI Response)**		
	IV Belimumab 10 mg/kg	290/241	**Placebo N=287 n/n (%)**	**Belimumab 1 mg/kg N=288 n/n (%)**	**Belimumab 10 mg/kg N=290 n/n (%)**
	Placebo	287/226	132/287 (46.0)	153/288 (53.1) Odds ratio (95% CI) vs placebo: 1.51 (1.07, 2.14) p-value: 0.0189	169/290 (58.3) Odds ratio (95% CI) vs placebo: 1.71 (1.21, 2.41) p-value: 0.0024

2.5.2. Discussion on clinical efficacy

With this variation, the MAH applied for extension of the SLE indication for the SC formulation (pre-filled pen only) to include also children aged 5 to 17 years of age and weighing ≥15 kg.

Given the rarity of paediatric SLE, the use of SC belimumab in paediatric SLE patients was mainly supported by an extrapolation strategy based on the paediatric SLE study with SC belimumab (study 200908), the adult SLE study with SC belimumab (study BEL112341) and the paediatric SLE study with IV belimumab (study BEL114055). Based on an extrapolation approach, as explained in Discussion on Clinical Pharmacology (Section 2.4.4.), the efficacy of SC belimumab under the 3-weight band regimen (200 mg SC QW for ≥50 kg; 200 mg SC Q10d for ≥30 kg to <50 kg; and 200 mg SC Q2W ≥15 kg to <30 kg) in paediatric patients is expected to be similar to that of the approved SC formulation in adults (200 mg once weekly) and of the approved IV formulation in paediatric patients (10 mg/kg body weight on Days 0, 14 and 28, and at 4-week intervals thereafter).

Design and conduct of clinical studies

The basis for the variation, study 200908, is a Phase 2, single arm, open-label trial to evaluate the PK, safety, and PD of repeat doses of 200 mg belimumab administered subcutaneously in participants 5 to 17 years of age and weighing ≥15 kg with active SLE on a background of standard of care therapy. This bridging PK study is part of an extrapolation strategy to support the use of SC belimumab in

paediatric SLE patients, based on the completed adult SLE study with SC belimumab (BEL112341) and the paediatric SLE study with IV belimumab (BEL114055).

Study 200908 includes:

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

Benlysta was administered through a pre-filled autoinjector with 200 mg SC QW in patients with body weight ≥50 kg and 200 mg every 10 days in patients with body weight ≥30 to <50 kg.

According to the MAH, human factor evaluations have been completed to support self-injection using the autoinjector device in eligible SLE patients from 10 years of age and older. Hence, the SmPC Section 4.2 states that, for patients under 10 years of age, Benlysta pre-filled pen must be administered by a healthcare professional or trained caregiver. Subcutaneous administration of Benlysta with the pre-filled syringe in patients below 18 years of age has not been evaluated.

The key objectives of the study were PK and safety. Secondary endpoints included biomarkers and efficacy endpoints.

A total of 25 participants were included in the study. The majority of participants were female. The median age at screening was 14 years. The number of participants was evenly distributed between Cohort 1 (≥50 kg; 52%) and Cohort 2 (≥30 kg to <50 kg; 48.0%) at baseline. The mean body weight was 52 kg.

All participants were receiving an antimalarial medication, and 84% participants were receiving steroids and immunosuppressants. The mean (SD) average daily prednisone dose was 8.55 (6.767) mg/day.

Efficacy data and additional analyses

The primary efficacy endpoint, SELENA SLEDAI ≥4 point reduction from baseline to week 12 and week 52, was achieved by 66.7% of the patients at week 12 and 81.8% of the patients at week 52. This can be compared to the paediatric Phase 2 belimumab IV trial where 54.7% of the patients had a 4-point reduction in SELENA SLEDAI scores at Week 52 and to the adult SC study where 62.3% had a 4-point reduction in SELENA SLEDAI scores at Week 52.

The results for the PD endpoints support efficacy of belimumab SC in children, with observed increases in complement levels and decreases in anti-dsDNA antibody titres through week 12 and 52.

Overall, although no firm conclusions can be drawn with regards to efficacy given the small sample size, the data indicate efficacy of the SC formulation in children. However, the basis for this variation is primarily PK extrapolation.

2.5.3. Conclusions on the clinical efficacy

The SC use of belimumab in paediatric SLE patients is mainly supported by extrapolation of data from the approved use of the SC formulation in adults and of the IV formulation in children with SLE. Limited efficacy data from study 200908 supports the efficacy of SC Benlysta in children with SLE.

Overall, the CHMP concluded that the efficacy of SC belimumab under the 3-weight band regimen (200 mg SC QW for ≥50 kg; 200 mg SC Q10d for ≥30 kg to <50 kg; and 200 mg SC Q2W ≥15 kg to <30 kg) in paediatric SLE patients is demonstrated.

2.6. Clinical safety

Introduction

The IV formulation of belimumab is currently approved in children from 5 years of age based on a randomized double-blind placebo-controlled clinical trial of IV belimumab in paediatric participants (BEL114055).

The purpose of the current study 200908, was to evaluate the PK, safety, and PD of repeat doses of 200 mg SC belimumab in paediatric participants 5 to 17 years of age with SLE on a background of standard of care therapy.

In addition to safety data from study 200908 and IV paediatric study BEL114055, safety data from a pooled analysis of previously conducted SLE studies in adults (at least 18 years of age) were presented. This pooled safety analysis includes integrated data through the 52-week double-blind treatment period from 4 randomized, placebo-controlled, repeat-dose studies: Studies BEL112341, C1056 (also reported as GSK Study ID BEL110751), C1057 (also reported as GSK Study ID BEL110752), and LBSL02 (Table 15). Study BEL112341 includes safety data from adult SLE participants treated with 200 mg SC belimumab, and studies C1056, C1057, and LBSL02 include safety data from adult SLE participants treated with 1, 4, and 10 mg/kg IV belimumab.

Table 15: CRD Studies Included in Pooled Safety Analysis

Study	Phase	Doses Administered	Participants Planned	Participants Enrolled
BEL112341	3	Placebo, 200 mg; SC	816	839
LBSL02	2	Placebo, 1, 4, and 10 mg/kg; IV	412	449
C1056	3	Placebo, 1 and 10 mg/kg; IV	810	819
C1057	3	Placebo, 1 and 10 mg/kg; IV	810	865

Patient exposure

A total of 25 participants were enrolled in study 200908, all of whom received at least 1 dose of study agent and were included in the ITT population.

All 25 enrolled participants completed Part A (12-week treatment phase) through Week 12.

In Part A, 13 participants were in Cohort 1 (≥50 kg at baseline; dosing every week) and 12 participants were in Cohort 2 (≥30 kg to <50 kg at baseline; dosing every 10 days); no participants were in Cohort 3 (<30 kg at baseline; dosing every 2 weeks). One participant who was in Cohort 2 at baseline shifted to Cohort 1 (≥50 kg) by last study observation.

All 25 participants continued into Part B. Most participants (92.0%) completed both Part A (12-week treatment phase) and Part B (optional 40-week continuation phase) of study 200908, through Week 52 (Table 16). The percentage of participants who withdrew from the study prior to Week 52 was 8.0%. There was 1 participant who withdrew due to adverse events and 1 participant who withdrew due to investigator discretion. Both participants who withdrew continued to receive commercial belimumab 200 mg from the investigator. The access extension phase is currently ongoing. Further limited safety data will be collected in that phase that is not reported at this time.

Table 16: Participant Completion Status by Week 52 (Part B) (ITT Population, Study 200908)

	Number (%) of Participants
	Belimumab 200 mg N = 25
Completed Week 52 visit	23 (92.0)
Entering access extension phase	11 (44.0)
Withdrawn prior to Week 52	2 (8.0)
Adverse event	1 (4.0)
Protocol deviation	0
Pregnancy	0
No subreasons	0
Study closed/terminated	0
Lost to follow-up	0
Investigator site closed	0
Investigator discretion	1 (4.0)
Withdrew consent	0

The median (range) duration of exposure in study 200908 was 370 (172 to 395) days (Table 17).

Table 17: Study Drug Exposure through Week 52 by Baseline Weight Cohort (ITT Population, Study 200908)

Duration of exposure (days)	Number (%) of Participants Belimumab 200 mg			
	Cohort 1 (≥50kg) N=13	Cohort 2 (≥30kg - <50kg) N=12	Cohort 3 (<30kg) N=0	Total N=25
Duration of Exposure (days)[a]				
n	13	12	0	25
Mean	366.7	348.1		357.8
SD	13.81	60.16		42.95
Median	366.0	370.0		370.0
25th percentile	364.0	361.5		364.0
75th percentile	371.0	372.0		371.0
Min.	330	172		172
Max.	395	388		395
Total Number of Injections[b]				
1 - 12	0	0	0	0
13 - 24	0	1 (8.3)	0	1 (4.0)
25 - 36	0	5 (41.7)	0	5 (20.0)
37 - 51	6 (46.2)	6 (50.0)	0	12 (48.0)
>51	7 (53.8)	0	0	7 (28.0)
Total Number of Injections[b]				
n	13	12	0	25
Mean	51.2	33.8		42.8
SD	2.23	6.59		10.02
Median	52.0	36.5		46.0
25th percentile	51.0	33.0		37.0
75th percentile	53.0	37.0		52.0
Min.	46	15		15
Max.	53	39		53

b. Duration of Exposure (days) = (Last Injection date - First Injection date + X), where X is 7, 10, or 14 for cohorts 1, 2, and 3, respectively. Only complete dates are used when calculating duration of exposure. First and last Injection dates are used, regardless of any missed doses.

c. Total number of injections where a dose was given. Note: Dosing frequency is as follows: Cohort 1 = weekly dosing, Cohort 2 = every 10 days, Cohort 3 = every 2 weeks.

Adverse events

An overall summary of the incidence of AEs reported during study 200908 is provided in Table 18.

Table 18: Adverse Event Summary (ITT Population, Study 200908 and IV+SC Adult Pooled Safety Analysis)

	Number (%) of Participants		
	Adult Pooled IV + SC		200908 SC Pediatric
Participants with at least one:	Placebo N=955	Belimumab N=2014	Belimumab 200 mg[b] N=25
At least 1 AE	859 (89.9)	1803 (89.5)	22 (88.0)
At least 1 related AE	355 (37.2)	759 (37.7)	14 (56.0)
At least 1 serious AE	147 (15.4)	308 (15.3)	1 (4.0)
At least 1 severe[a] AE	139 (14.6)	275 (13.7)	0
At least 1 serious and/or severe[a] AE	197 (20.6)	410 (20.4)	1 (4.0)
At least 1 AE resulting in study agent discontinuation	73 (7.6)	128 (6.4)	1 (4.0)
Death	5 (0.5)	14 (0.7)	0

Note: Only treatment-emergent AEs are summarized.

a. Severe or life threatening for IV+SC Adult Pooled Safety Analysis.

b. Participants are counted once in each row for which they have any AE meeting the criterion.

The most common AE experienced in study 200908 was COVID-19 infection (36.0%). Study BEL114055, BEL112341, and the studies included in the IV+SC Adult Pooled Safety Analysis were all conducted prior to the COVID-19 pandemic and therefore had no incidences of COVID-19 infection.

Table 19: Adverse Events Occurring in ≥2 Participants in Study 200908 by Preferred Term (ITT Population, Study 200908 and IV+SC Adult Pooled Safety Analysis)

	Number[a] (%) of Participants		
	Adult Pooled IV + SC		200908 SC Pediatric
Preferred Term	Placebo N=955	Belimumab N=2014	Belimumab 200 mg N=25
Any Event	859 (89.9)	1803 (89.5)	22 (88.0)
COVID-19	0 (0)	0 (0)	9 (36.0)
Injection site pain	1 (0.1)	10 (0.5)	4 (16.0)
Leukopenia	15 (1.6)	60 (3.0)	4 (16.0)
Neutropenia	10 (1.0)	38 (1.9)	4 (16.0)
Lymphopenia	7 (0.7)	21 (1.0)	3 (12.0)
Nasopharyngitis	64 (6.7)	149 (7.4)	3 (12.0)
Upper respiratory tract infection	135 (14.1)	287 (14.3)	3 (12.0)
Anemia	38 (4.0)	72 (3.6)	2 (8.0)
Erythema	13 (1.4)	38 (1.9)	2 (8.0)
Injection site erythema	1 (0.1)	10 (0.5)	2 (8.0)
Myalgia	51 (5.3)	105 (5.2)	2 (8.0)
Neutrophil count decreased	4 (0.4)	7 (0.3)	2 (8.0)
Urine protein/creatinine ratio increased	4 (0.4)	7 (0.3)	2 (8.0)
Viral infection	5 (0.5)	13 (0.6)	2 (8.0)
White blood cell count decreased	2 (0.2)	7 (0.3)	2 (8.0)

Note: Only treatment-emergent AEs are summarized

a. Participants only counted once per PT.

Among these AEs, injection site pain (16.0%), leukopenia (16.0%), neutropenia (16.0%), lymphopenia (12.0%), erythema (8.0%), injection site erythema (8.0%), neutrophil count decreased (8.0%), urine protein/creatinine ratio increased (8.0%), viral infection (8.0%), and white blood cell count decreased

(8.0%) were reported at a higher (>5%) frequency in study 200908 compared with the belimumab group in IV paediatric study BEL114055, SC adult study BEL112341, and the IV+SC Adult Pooled Safety analysis.

By SOC, the most frequent AE categories were infections and infestations (72.0%), general disorders and administration site conditions (32.0%), and blood and lymphatic system disorders (28.0%) (Table 20).

Table 20: Adverse Events by System Organ Class (ITT Population, Study 200908)

System Organ Class	Number[a] (%) of Participants Belimumab 200mg N=25
Any Event	22 (88.0)
Infections and infestations	18 (72.0)
General disorders and administration site conditions	8 (32.0)
Blood and lymphatic system disorders	7 (28.0)
Investigations	5 (20.0)
Skin and subcutaneous tissue disorders	5 (20.0)
Eye disorders	4 (16.0)
Gastrointestinal disorders	4 (16.0)
Injury, poisoning and procedural complications	4 (16.0)
Musculoskeletal and connective tissue disorders	4 (16.0)
Ear and labyrinth disorders	2 (8.0)
Immune system disorders	2 (8.0)
Renal and urinary disorders	2 (8.0)
Reproductive system and breast disorders	2 (8.0)
Cardiac disorders	1 (4.0)
Metabolism and nutrition disorders	1 (4.0)
Nervous system disorders	1 (4.0)
Vascular disorders	1 (4.0)

a. Participants only counted once per SOC.

Serious adverse event/deaths/other significant events

Serious adverse events and deaths

There were no deaths in the study. SAE was reported in 1 (4.0%) participant due to COVID-19.

Other significant adverse events

Injection site reactions

The incidence of local injection site reactions was 32% (Table 21). Injection site reactions that occurred in more than 1 participant were injection site pain (16.0%) and injection site erythema (8.0%).

Eight participants experienced 17 injection site reaction events. All events were mild and non-serious. Belimumab was continued in all 8 participants, and the events resolved. Most events were considered by the investigator to be related to belimumab.

Table 21: Local Injection Site Reactions (ITT Population, Study 200908)

Preferred Term	Number[a] (%) of Participants Belimumab 200 mg N=25
Any Event	8 (32.0)
Injection site pain	4 (16.0)
Injection site erythema	2 (8.0)
Injection site hemorrhage	1 (4.0)
Injection site swelling	1 (4.0)
Injection site urticaria	1 (4.0)

Note: Only treatment-emergent AEs are summarized.
d. Participants only counted once per PT.

In SC belimumab adult study BEL112341, injection site reaction events were reported in 6.1% of participants in the belimumab group and 2.5% of participants in the placebo group. The PTs with the highest incidence were injection site pain (1.8% belimumab, 0.4% placebo) and injection site hematoma (1.4% belimumab, 0.7% placebo).

The MAH stated that for children, high levels of fear are associated with perceived pain during needle procedures (McMurtry, 2015[44]). They referred to a study in children with juvenile idiopathic arthritis that showed over one-third of children with an average age of 9 years requiring methotrexate injections or blood tests reported often or almost always feeling a fear of injections (Mulligan, 2013[45]). In the adult population, a fear of needles is estimated to be 22% (Wright, 2009[46]).

Post-injection systemic reactions

In study 200908, the incidence of post-injection systemic reactions per anaphylactic reaction CMQ broad search was 12.0% (Table 22). Post-injection systemic reactions per anaphylactic reaction CMQ broad search included the PTs drug hypersensitivity, erythema, and injection site urticaria. There were no serious post-injection systemic reactions AESI and no post-injection systemic reactions AESI which led to discontinuation of study agent.

In IV belimumab paediatric study BEL114055, post-infusion systemic reaction AESI were reported in 7.5% of participants in the belimumab group and 7.5% of participants in the placebo group.

In SC belimumab adult study BEL112341, post-injection systemic reaction AESI were reported in 6.8% of participants in the belimumab group and 8.9% of participants in the placebo group.

There were no clinically meaningful differences between post-injection AESIs in study 200908 compared with the post-infusion/injection AESIs in the IV+SC Adult Pooled Safety Analysis (Table 22).

[44] McMurtry CM, Riddell RP, Taddio A, et al. Far from "just a poke": common painful needle procedures and the development of needle fear. Clin J Pain. 2015;31(10 Suppl):3– 11.
[45] Mulligan K, Kassoumeri L, Etheridge A, et al. (2013). Mothers' reports of the difficulties that their children experience in taking methotrexate for juvenile idiopathic arthritis and how these impact on quality of life. Pediatr Rheumatol. 2013;11(1):23.
[46] Wright S, Yelland M, Heathcote K, et al. Fear of needles-nature and prevalence in general practice. Aust Fam Physician. 2009;38(3):172-6.

Table 22: Post-Infusion/Injection Reactions Adverse Events of Special Interest by Category (ITT Population, Study 200908 and IV+SC Adult Pooled Safety Analysis)

	Number[a] (%) of Participants		
	Adult Pooled IV + SC		200908 SC Pediatric
Adverse Events of Special Interest Category	Placebo N=955	Belimumab N=2014	Belimumab 200 mg N=25
Post-Infusion/Injection Systemic Reactions	90 (9.4)	236 (11.7)	3 (12.0)
Post-Infusion/Injection System Reactions per Anaphylactic Reaction CMQ Narrow Search[b]	8 (0.8)	31 (1.5)	1 (4.0)
Post-Infusion/Injection System Reactions per Anaphylactic Reaction CMQ Broad Search[b]	89 (9.3)	236 (11.7)	3 (12.0)
Post-Infusion/Injection System Reactions per Anaphylactic Reaction CMQ Algorithmic Search[b]	11 (1.2)	33 (1.6)	1 (4.0)
Serious Anaphylaxis per Sampson Criteria[c]	0	4 (0.2)	0
Serious Acute Post-Infusion/Injection Systemic Reactions/Hypersensitivity[c]	2 (0.2)	12 (0.6)	0
Serious Acute Post-Infusion/Injection Systemic Reactions Excluding Hypersensitivity[c]	2 (0.2)	5 (0.2)	0
Serious Acute Hypersensitivity Reactions[c]	0	7 (0.3)	0
Serious Delayed Acute Hypersensitivity Reactions[c]	0	0	0
Serious Delayed Non-Acute Hypersensitivity Reactions[c]	1 (0.1)	0	0

Note: Only treatment-emergent AEs are summarized.
e. Participants are counted only once per category.
f. Per CMQ (version 25.1).
g. Per GSK adjudication.

Immunogenicity

Immunogenicity was assessed using a tiered approach. All samples were first screened against a screening cut-point. Samples with signal above the screening cut-point were to be confirmed by inhibition of signal when excess drug was added. Samples confirming positive were then to be assayed for the presence of neutralizing antibodies as well as titrated in order to determine the relative amount of antibodies present in the sample.

No participants in study 200908 had a transient or persistent positive anti-belimumab immunogenic response through Part A and B of the study.

Laboratory findings

Participants with any post-baseline Grade 3 or Grade 4 clinical laboratory parameters for study 200908 are presented below (Table 23).

Table 23: Summary of Participants with Worst Post-Baseline Toxicity Grade of 3 or 4 (ITT Population, Study 200908)

Clinical Laboratory Parameter Worst Toxicity Grade	Number (%) of Participants Belimumab 200 mg N=25
Lymphocytes, n Grade 3 Grade 4	25 3 (12.0) 0
Hyperkalemia, n Grade 3 Grade 4	25 0 1 (4.0)
Protein/Creatinine, n Grade 3 Grade 4	25 2 (8.0) 0

Source: CSR 200908, Table 3.22, Table 3.23, Table 3.24, Table 3.25, Table 3.26, Table 3.27
Note: Toxicity grades are defined in Appendix 2 of the protocol.

All grade 3 events resolved without intervention.

Safety in special populations

No pregnancies were reported through Part A and B of the study.

Safety related to drug-drug interactions and other interactions

Belimumab as a monoclonal antibody is not metabolized by the cytochrome P450 system. Thus, the types of drug interactions that occur between 1 or more drugs that compete for metabolism by this family of enzymes are not expected with belimumab. The population PK analysis including study 200908 evaluated impact of SLE standard of care concomitant medications. Belimumab does not interact with transporters or hepatic/renal receptors. Drug-drug interactions are not anticipated, and there was no evidence of any DDIs when previously assessed in the paediatric IV study BEL114055.

Discontinuation due to adverse events

In study 200908, 1 participant (4.0%) experienced 3 AEs that led to the discontinuation of study agent (Table 24). By preferred term, the AEs leading to discontinuation of study agent were lymphocyte count decreased, neutrophil count decreased, and white blood cell count decreased. The AEs resolved, and the investigator continued to administer belimumab 200 mg SC. The participant had a Grade 2 value for leukocytes and a Grade 2 value for lymphocytes at baseline.

Table 24: Adverse Events Resulting in Study Agent Discontinuation by Preferred Term (ITT Population, Study 200908)

	Number[a] (%) of Participants
Preferred Term	Belimumab 200 mg N=25
Any Event	1 (4.0)
Lymphocyte count decreased	1 (4.0)
Neutrophil count decreased	1 (4.0)
White blood cell count decreased	1 (4.0)

Note: Only treatment-emergent AEs are summarized.
h. Participants only counted once per PT.

In the IV+SC Adult Pooled Safety Analysis, 6.4% of participants in the belimumab group and 7.6% of participants in the placebo group experienced AEs that led to the discontinuation of study agent. The PTs with the highest incidence were lupus nephritis (0.7% belimumab, 1.0% placebo) and pneumonia (0.1% belimumab, 0.1% placebo).

In IV belimumab paediatric study BEL114055, 5.7% of participants in the belimumab group and 12.5% of participants in the placebo group experienced AEs that led to the discontinuation of study agent. The only PT that occurred in more than 1 participant was lupus nephritis (1.9% belimumab, 5.0% placebo).

In SC belimumab adult study BEL112341, 7.2% of participants in the belimumab group and 8.9% of participants in the placebo group experienced AEs that led to the discontinuation of study agent. The PTs with the highest incidence were lupus nephritis (0.7% belimumab, 0.7% placebo) and thrombocytopenia (0 belimumab, 1.1% placebo).

Post marketing experience

The 200908 Access Extension Phase provides continued access to SC belimumab in paediatric participants after they have completed Part A and Part B of the clinical trial in countries where SC belimumab is not licensed for this population. As such, reports received during the 200908 Access Extension Phase are categorized as "PMS" reports as per GSK reporting processes and included in this section.

Study BEL114055 was the basis for approval of IV belimumab for paediatric use. Currently, SC belimumab is not approved for paediatric use in any country. From the launch of BENLYSTA to 08 March 2023, GSK has received 441 paediatric reports (205 spontaneous and 236 PMS). Details of post-marketing reports for use of belimumab in the paediatric population during the PBRER reporting period 09 March 2022 to 08 March 2023 are described below. Of the 441 reports received cumulatively, 145 were received during the reporting period, and of these, 39 were the SC route of administration. The 145 paediatric reports (111 non-serious and 34 serious) were received from China (39), Japan (36), the US (26), Saudi Arabia (20), Columbia (6), Brazil (4), Italy (4), Argentina (3), Germany (2), Russian Federation (2), and 1 each from Canada, France, and Switzerland.

Of the 145 spontaneous and PMS reports received during the reporting period 09 March 2022 to 08 March 2023, 90 were attributed to the Injury, Poisoning, and Procedural Complications SOC and included 22 reports of non-serious events of the PT product used in an unapproved therapeutic environment, with no additional AEs reported in these cases. In addition, 17 events of non-serious off-label use were reported. Two reports were received for product use issues.

A total of 33 events of infection were reported during the reporting period. Serious infections (1 event each PT) were anal abscess, appendicitis, bacteremia, bronchiolitis, campylobacter gastroenteritis, cytomegalovirus infection, gastroenteritis rotavirus, sepsis, sinusitis, herpes zoster, and upper respiratory tract infection. None of these infections were fatal. The outcomes of these serious infections were either recovering/resolving or recovered/resolved. The appendicitis and sepsis events had an unknown outcome.

One report of suicide attempt was received for a paediatric patient treated with belimumab SC for SLE during the reporting period. The outcome of the event was recovered/resolved. A follow-up report of suicide ideation was also received during the reporting period for a patient treated with belimumab IV for SLE. Follow-up included a comment that the suicide ideation might have disappeared at the time when the belimumab administration interval became longer, and the causality could not be ruled out.

A follow-up report was received for a patient treated with belimumab IV for SLE for an unknown duration who was diagnosed and treated for Hodgkin's disease. The outcome of the Hodgkin's disease was recovered/resolved. The case was updated during the period of this report with outcomes for other AEs of skin eruption and arthralgia, both recovered/resolved, and persistent malaise.

A spontaneous case of Lyell's syndrome (TEN) received during the period of this report was reported in the literature in 2021 for a patient who received belimumab IV for SLE. The patient was hospitalized and intensive therapy was performed, plasmapheresis synchronized with pulse therapy with glucocorticoids, followed by the administration of albumin, human immunoglobulin, and calcium gluconate. The patient's condition gradually stabilized, relapses of new rashes stopped, epithelialization of damaged skin began, and general well-being improved. The case was considered related to belimumab by the reporter and the MAH.

A single report of paediatric fatality was received during the reporting period. This fatality was a consumer report of cardiac arrest in a patient who was receiving belimumab IV monthly for SLE. Belimumab dosing was reported to be monthly for an unknown duration.

2.6.1. Discussion on clinical safety

Given the rarity of paediatric SLE, the use of SC belimumab in paediatric SLE patients was mainly supported by an extrapolation strategy based on the paediatric SLE study with SC belimumab (study 200908), the adult SLE study with SC belimumab (study BEL112341) and the paediatric SLE study with IV belimumab (study BEL114055). Based on an extrapolation approach, as explained in Discussion on Clinical Pharmacology (Section 2.4.4.), the safety profile of SC belimumab under the 3-weight band regimen (200 mg SC QW for ≥50 kg; 200 mg SC Q10d for ≥30 kg to <50 kg; and 200 mg SC Q2W ≥15 kg to <30 kg) in paediatric patients is expected to be similar to that of the approved SC formulation in adults (200 mg once weekly) and of the approved IV formulation in paediatric patients (10 mg/kg body weight on Days 0, 14 and 28, and at 4-week intervals thereafter).

Supportive safety data are available from the Study 200908 where the PK, safety, and PD of repeat doses of 200 mg SC belimumab was evaluated in paediatric participants 5 to 17 years of age with SLE on a background of standard of care therapy. In addition to safety data from study 200908 and IV paediatric study BEL114055, safety data from a pooled analysis of previously conducted SLE studies in adults (at least 18 years of age) were presented. This pooled safety analysis includes integrated data through the 52-week double-blind treatment period from 4 randomized, placebo-controlled studies including safety data from adult SLE participants treated with SC or IV belimumab.

A total of 25 participants were enrolled in Study 200908, all of whom received at least 1 dose of study agent and were included in the ITT population. All 25 enrolled participants completed Part A (12-week

treatment phase) through Week 12 and continued into Part B. Most participants (92.0%) completed both Part A (12-week treatment phase) and Part B (optional 40-week continuation phase) of study 200908, through Week 52. The percentage of participants who withdrew from the study prior to Week 52 was 8.0%. There was 1 participant who withdrew due to adverse events (leukopenia) and 1 participant who withdrew due to the investigator's discretion. Both participants who withdrew continued to receive commercial belimumab 200 mg from the investigator.

Adverse events

The incidence of participants experiencing at least 1 AE during the study was 88.0%. One participant (4.0%) experienced an SAE (COVID-19). There were no deaths in the study. The most common AE was COVID-19 infection (36.0%).

Local injection site reactions were more common in children than in adults treated with SC Benlysta (32% vs 6.1%). All events were mild and non-serious. The MAH argued that high levels of fear for needle procedures in children are associated with perceived pain during needle procedures children. Athough this might lead to discomfort for the children, the risk was considered outweighed by the advantages with a SC formulation over the IV formulation.

The incidence of post-injection systemic reactions was 12.0%, which is slightly higher than in the paediatric IV study (7.5%) and adult SC study (6.8%). The differences are not considered to be clinically meaningful due to the small number of cases in each arm. It was further reassuring that no cases led to discontinuation of study agent. Hence, no product information update was deemed necessary.

No participants in Study 200908 had a transient or persistent positive anti-belimumab immunogenic response through Part A and B of the study.

Post-marketing data

From the launch of Benlysta to 08 March 2023, the MAH received 441 paediatric reports. Most reported cases concern "Injury, Poisoning, and Procedural Complications" SOC and infections. There has been one case of suicide attempt for a paediatric patient treated with SC belimumab. Although of some concern, the risk for suicidal ideation is sufficiently covered by the product information (SmPC Sections 4.4 and 4.8). Further, one case each of Hodgkin's disease, toxic epidermal necrolysis and fatal cardiac arrest was reported among children treated with IV belimumab. A cumulative and periodic reports of post-marketing surveillance are submitted and reviewed in the belimumab PSUSA.

Limited data on long-term safety in paediatric patients is missing information in the Risk Management Plan (RMP). This safety concern is expected to be further characterised in the ongoing open label Paediatric SLE study with IV formulation (Study BEL114055). No new pharmacovigilance activities are deemed necessary.

2.6.2. Conclusions on clinical safety

The SC use of belimumab in paediatric SLE patients is mainly supported by extrapolation of data from the approved use of the SC formulation in adults and of the IV formulation in children with SLE. No new safety concerns were raised in Study 200908 conducted in paediatric SLE patients with SC formulation. However, it is acknowledged that only 25 patients were exposed to SC belimumab in this study and the study was open-label without comparator.

The CHMP concluded that the safety profile in paediatric patients receiving SC belimumab is expected to be consistent with the known safety profile for belimumab.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The MAH submitted an updated RMP version 46.2 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 46.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 46.2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Infections Psychiatric events including depression and suicidality
Important potential risks	Progressive multifocal leukoencephalopathy Malignancies
Missing information	Limited data in pregnant and lactating patients Limited data in elderly patients Limited data on long-term safety in paediatric patients Lack of data in SLE patients with severe active CNS lupus

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
5-Year Safety Registry HGS1006-C1124 (BEL116543/ SABLE) Ongoing	To provide a data report on a long-term controlled safety registry where all patients are followed for a minimum of 5 years, based on a protocol agreed with CHMP. The safety registry will evaluate the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus. These adverse events of special interest include serious infections (including opportunistic infections and	Infections (including PML), Psychiatric events including depression and suicidality, Malignancies	Final CSR	28Feb2026

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	PML), selected serious psychiatric events, and malignancies (including non-melanoma skin cancer).			
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
None				
Category 3- Required additional pharmacovigilance activities				
Belimumab and Lupus Pregnancy Study (213928/bMUM) Ongoing	Prospective cohort study of Benlysta exposed and unexposed pregnancy. Primary objectives are to evaluate pregnancy and infant outcomes following Benlysta exposure and health status of live infants at 1 year.	Limited data in pregnant patients	Final CSR	31May2030
Elderly Subject Analyses BEL116559 Ongoing	Pooled analyses of elderly patients (aged ≥ 65 years) who participated in select belimumab clinical trials	Limited data in elderly patients	Report 5	Feb2026
Pediatric SLE IV Formulation Study BEL114055/PLUTO-open label Ongoing	To evaluate the safety and tolerability, pharmacokinetics and efficacy of belimumab and the effects of belimumab on the quality of life in the pediatric SLE population.	Infections, Limited data on long-term safety in paediatric patients	Final End of Study CSR	31Dec2028

Risk minimisation measures

Important Identified Risks		
Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Infections	Routine risk minimization measures: SmPC Sections 4.4, 4.8 This is a prescription only medicine. Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire on infections for patients 5 to 11 years old. Additional pharmacovigilance activities:

Important Identified Risks		
Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
	None	Analysis of additional safety data that may arise from ongoing studies, including serious infections and infections of special interest from ongoing open-label study BEL114055 in the pediatric population. Evaluation of data on serious infections including opportunistic infections, tuberculosis, and herpes zoster from long-term safety registry (BEL116543/SABLE)
Psychiatric events including depression and suicidality	Routine risk minimization measures: SmPC Sections 4.4, 4.8 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Analysis of additional safety data that may arise from ongoing studies • Specific adverse reaction follow-up questionnaires for Depression and Suicidality: Belimumab and Possible Suicidal Behavior/Suicidal Ideation (Including Potential Self Harm such as Intentional Overdose) Additional pharmacovigilance activities: • Prospective assessment of suicidality in randomized controlled trials and BEL116543/SABLE (5-year registry study)

Important Potential Risks		
Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Progressive Multifocal Leukoencephalopathy	Routine risk minimization measures: **The IV and SC SmPC** Routine activity includes appropriate labelling. Section 4.4 Special warnings and precautions for use of the SmPCs contains text noting PML has been reported with Benlysta treatment for SLE	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted Follow-up Questionnaire for PML • Analysis of additional safety data that may arise from ongoing studies Additional pharmacovigilance activities:

Important Potential Risks		
Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
	and patients should be monitored for PML. Recommendations for HCPs on what to do if PML is suspected are provided. This is a prescription only medicine. Additional risk minimization measures: None	• Evaluation of data on opportunistic infections, including PML, tuberculosis, and herpes zoster from long-term safety registry (BEL116543/SABLE)
Malignancies	Routine risk minimization measure: SmPC Section 4.4 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Analysis of additional safety data that may arise from ongoing studies Additional pharmacovigilance activities: • Evaluation of data on malignancies, including hematologic malignancies and NMSC from the long-term safety registry (BEL116543/SABLE)

Missing Information		
Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Limited data in pregnant and lactating patients	Routine risk minimization measures: SmPC Section 4.6, 5.3 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Analysis of additional safety data that may arise from ongoing studies Additional pharmacovigilance activities: • Ongoing Belimumab & Lupus Pregnancy Study (213928/bMUM) in the United States and Canada that has replaced the Benlysta Pregnancy Registry (BEL114256)
Limited data in elderly patients	Routine risk minimization measures: SmPC Section 4.2, 5.2 This is a prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Evaluation of safety and efficacy data from ongoing and future studies

Missing Information		
Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
	Additional risk minimization measures: None	Additional pharmacovigilance activities: • Analysis plan for BEL116559 has been agreed with EMA
Limited data on long-term safety in pediatric patients	Routine risk minimization measures: SmPC Section 4.2 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaires on infections for pediatric patients 5 to 11 years of age Additional pharmacovigilance activities: • Evaluation of long-term safety (adverse events of special interest, including infections, other autoimmune disease, immunogenicity, and malignancies) in subjects in BEL114055 until 10 years after their first belimumab dose •
Lack of data in SLE patients with severe active CNS lupus	Routine risk minimization measures: SmPC Section 4.4, 5.1 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated for Benlysta 200 mg in pre-filled pen (injection). The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with QRD template version 10.4 and with the excipients guideline.

In addition, the list of local representatives in the PL has been revised.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- extensions for the same route of administration
- reference to test on same class of medicinal product
- reference to test with same safety issues
- reference to test with common design, layout and style of writing

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

SLE is a chronic autoimmune disorder characterized by autoantibody production and abnormal B-lymphocyte function [Choi, 2012[47]; Pisetsky, 2001[48]]. Compared with adult SLE, childhood-onset SLE (cSLE) patients often have more active disease both at the time of diagnosis and over time [Kamphuis, 2010[2]; Livingston, 2012[6]; Mina, 2013[7]]. cSLE can be associated with more rapid accrual of damage, and may have a higher degree of morbidity compared with SLE in adult populations [Brunner, 2008[14]; Kamphuis, 2010[2]; Levy, 2012[15]; Malattia, 2013[4]; Tucker, 2008[13]]. The range of organ involvements in paediatric SLE is generally similar to adult SLE with some manifestations more prevalent in paediatric patients, such as renal lupus, malar rash, seizures, oral ulcers, hemolytic anemia, and thrombocytopenia [Aggarwal, 2015[1]; Barron, 1993[5]; Brunner, 2008[14]; Fonseca, 2018[19]; Mina, 2013[7]; Webb, 2011[16]]. Growth failure and delayed puberty are complications of SLE specific to paediatric patients that may have a serious psychological impact. Relative risk of mortality is higher in paediatric SLE populations than adult SLE populations [Ambrose, 2016[23]; Hersh, 2010[49]; Tucker, 2008[13]].

3.1.2. Available therapies and unmet medical need

Paediatric SLE is more often treated with high doses of corticosteroids than adult SLE, contributing to the increased incidence and earlier onset of long-term organ damage in children [Mina, 2010[37]]. More frequent use of immunosuppressants or IV cyclophosphamide was also reported. These therapies can be associated with significant toxicity including increased risks of infections or cancer [Chatham, 2001[30]; Silva, 2016[39]].

To date, the use of rituximab, a B-cell depletion therapy, both in adult and paediatric SLE populations remains off-label.

Belimumab IV formulation is approved for the treatment of paediatric patients with active, autoantibody-positive SLE who are receiving standard therapy. But there remains an unmet medical need for treatments that improve patient compliance, lead to persistence of treatment and increased patient comfort in this patient population. Similar to adult-onset disease, paediatric SLE is a chronic disease for which there is no cure. All patients require life-long treatment with a variety of medications for disease control. Generally, paediatric patients are treated with the same agents which have been used in the adult population such as corticosteroids, anti-malarial agents, NSAIDs, cytotoxic agents,

[47] Choi J, Kim ST, Craft J. The pathogenesis of systemic lupus erythematosus-an update. Curr Opin Immunol. 2012;24(6):651-7.
[48] Pisetsky DS. Systemic lupus erythematosus: epidemiology, pathology, and pathogenesis. In: Primer on the Rheumatic Diseases. Arthritis Foundation, Atlanta 2001;17:329-35.
[49] Hersh AO, Trupin L, Yazdany J, et al. Childhood-onset disease as a predictor of mortality in an adult cohort of patients with systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2010;62(8):1152-9.

and immunosuppressive/immunomodulatory agents [Brocard, 2005[29]; Chatham, 2001[30]; Houssiau, 2004[31]; Midgley, 2014[32]; Petri, 2001[33]; Reveille, 2001[34]; Ruiz-Irastorza, 2001[35]; Wallace, 2002[36]].

3.1.3. Main clinical studies

Given the rarity of paediatric SLE, the use of SC belimumab in paediatric SLE patients was mainly supported by an extrapolation strategy based on a paediatric SLE bridging PK study with SC belimumab (study 200908), the adult SLE study with SC belimumab (study BEL112341) and the paediatric SLE study with IV belimumab (study BEL114055).

Study 200908 was a single arm, multi-center, open-label study using the belimumab SC formulation in paediatric SLE patients from 5 years of age and weighing ≥15 kg. Patients had active SLE defined as SLE diagnosis confirmed by revised ACR criteria and SELENA SLEDAI score ≥6 at screening, with at least 12 participants with a SELENA SLEDAI score of ≥8 at screening.

The study included:

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

The administration of belimumab 200 mg SC in Part A was as follows:

Cohort	Body weight at baseline (kg)	Dosing frequency
1 (N=13)	≥50	Every week (QW)
2 (N=12)	≥30 to <50	Every 10 days (Q10d)
3 (N=0)	≥15 to <30	Every 2 weeks (Q2W)

The Cohort 1, Cohort 2, and Cohort 3 were recruited in parallel.

Study 200908 was a bridging PK study with a small sample size, and the key objectives were PK and safety. Descriptive efficacy and PD endpoints were also included. A total of 25 patients were included.

A population PK model was used to derive the average belimumab concentration for each participant who received belimumab in the paediatric SC study 200908 and paediatric IV study BEL114055. The dose recommendation was then based on a modelling and simulation study.

3.2. Favourable effects

In Study 200908, results were available for cohort 1 (patients weighing ≥50 kg) and cohort 2 (patients weighing ≥30 to <50) only, as no patients were included in cohort 3 (patients weighing ≥15 to <30 kg). The steady-state Cavg were 146 µg/mL and 103 µg/mL in cohort 1 and cohort 2, respectively. The average concentrations at steady state were comparable between the paediatric SC study (200908) and the paediatric IV study (BEL114055).

A population PK analysis and simulation integrating combined paediatric SC (Study 200908) and paediatric IV (Study BEL114055) PK data were performed. Standard methodology was used and, in

general, the analysis was well performed. The model was considered to describe well the paediatric PK data independent of body weight. Cavg was accepted as the main exposure metric for belimumab exposure-matching. The simulated exposure versus body weight indicates that the 3-weight band dosing regimen of Study 200908 enabled consistent belimumab exposure across the paediatric weight range from 15 kg and that the exposure distribution of paediatric SC was similar to that of adults SC (Study BEL112341) and paediatric IV (Study BEL114055). Further, as agreed during the extension of indication for the paediatric IV formulation (variation II/0062), PK properties of belimumab are considered similar in the paediatric and adult population. On this basis, the efficacy and safety of SC belimumab under the 3-weight band regimen in paediatric patients are considered similar to that of the SC formulation in adults and of the IV formulation in children, under the approved posology.

In Study 200908, the total percentage of participants with a ≥ 4 point reduction from baseline in SELENA SLEDAI increased from Week 12 (66.7%) to Week 52 (81.8%). At Week 12 and Week 52, there was a median decrease of anti-dsDNA antibody levels of 17.74% and 58.88%, respectively. Among participants who had low complement (C3 <90 mg/dL; C4 <13 mg/dL) at baseline, at Week 12 there was a median increase of 8.26% in C3 and 31.03% in C4; at Week 52, median increases of 23.46% in C3 and 67.52% in C4 were observed. Efficacy results from Study 200908 are descriptive only and are supportive of SC belimumab efficacy in children with SLE.

3.3. Uncertainties and limitations about favourable effects

Study 200908 was small (n=25) and primarily a PK/safety study. All efficacy/PD endpoints were descriptive. This is acceptable as the SC use in paediatric SLE patients is mainly supported by an extrapolation approach considering the IV use in paediatric SLE patients and the SC use in adult SLE patients.

There were no patients in cohort 3 (patients weighing ≥15 to <30 kg) of Study 200908, thus the dosing recommendation in this patient's category is based on model predictions, which is agreed as a constant bioavailability across body weight in the paediatric population is assumed.

3.4. Unfavourable effects

The safety of SC belimumab in SLE paediatric patients is mainly based on the extrapolation of belimumab safety data in adults to children as explained under Section 3.2. Hence, the safety profile of SC belimumab under the 3-weight band regimen in paediatric patients is considered similar to that of the SC formulation in adults and of the IV formulation in children, under the approved posology.

In Study 200908, adverse events were reported in 22/25 patients (88%) and serious adverse events in 1/25 (4%). There were no deaths. The most common AE was COVID-19 infection (36.0%). Adverse events were most commonly reported within the SOCs of infections and infestations (72.0%), general disorders and administration site conditions (32.0%), and blood and lymphatic system disorders (28.0%). The incidence of local injection site reactions was 32%, all events were mild and non-serious. The incidence of post-infusion/injection systemic reactions was 12%, no cases led to discontinuation of study agent. No new safety concerns were raised in Study 200908, however, it is acknowledged that safety results from Study 200908 are supportive only.

3.5. Uncertainties and limitations about unfavourable effects

Only 25 patients were exposed to belimumab in Study 200908 and the study was open-label without comparator. This is acceptable as the safety for SC use in paediatric patients is derived from an extrapolation approach and results from Study 200908 are considered supportive only.

Limited data on long-term safety in paediatric patients is missing information in the RMP. This safety concern is expected to be further characterised in the ongoing open label Paediatric SLE study with IV formulation (Study BEL114055). No new pharmacovigilance activities are deemed necessary.

3.6. Effects Table

Table 25: Effects Table for SC Benlysta in peadiatric SLE (data cut-off: 16 January 2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Cavg, ss (µg/mL)	Steady-state average concentration	Geometric mean (Range)	[Cohort1] 146 (95.6 – 214) [Cohort2] 103 (47.9 – 173)	[Adults] 104	Model predicted	[Cohorts 1 and 2]: Study 200908 [Adults]: Study BEL112341
Percentage of participants with a ≥4 point reduction from baseline in SELENA SLEDAI	At week 12	%	66.7%	-	Open-label, uncontrolled study	Study 200908
Percentage of participants with a ≥4 point reduction from baseline in SELENA SLEDAI	At week 52	%	81.8%	-	Open-label, uncontrolled study	Study 200908
Unfavourable Effects						
Adverse event		N (%)	22/25 (88%)	-	Open-label, uncontrolled study	Study 200908
Serious adverse event		N (%)	1/25 (4%)	-	Open-label, uncontrolled study	Study 200908
Injection site reactions		N (%)	8/25 (32%)	-	Open-label, uncontrolled study	Study 200908

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Given the rarity of paediatric SLE, the basis for approval of a SC formulation of Benlysta in children is mainly based on PK extrapolation.

The approval of the extension of indication for IV use of belimumab in paedatric SLE patients (variation II/0062, EC decision 21/20/2019) was mainly based on data extrapolation from adult SLE patients. Compared with individuals with adult-onset disease, children with SLE have more commonly multiorgan disease, acute disease onset and ongoing active inflammation over time. SLE with childhood onset is also more often associated to rare complement mutations with an increased susceptibility to infections. These differences were discussed in variation II/0062 and it was agreed that these differences do not preclude extrapolation. The CHMP concluded that PK properties for belimumab are similar in the paediatric and adult population. Hence, the extrapolation of efficacy and safety data for belimumab from adults to children with SLE applies also to the paediatric SC formulation.

A bridging PK study (200908) utilizing a 3-weight band regimen (200 mg SC QW for ≥50 kg; 200 mg SC Q10d for ≥30 kg to <50 kg; and 200 mg SC Q2W ≥15 kg to <30 kg) was performed in 25 patients. No patients were included in the lowest body weight group, hence the dosing regimen in this patient subgroup is based on simulation only. Comparable exposure were observed at steady state between the paediatric SC study (200908) and the paediatric IV study (BEL114055).

The PK of belimumab in the paediatric SC study (200908) was described by a population PK model, where both IV and SC paediatric belimumab data were used. The simulated exposure under the 3-weight band dosing regimen (200 mg SC QW for ≥50 kg; 200 mg SC Q10d for ≥30 kg to <50 kg; and 200 mg SC Q2W ≥15 kg to <30 kg) indicates similar exposure to that observed in the approved regimens for the adults SC formulation (200 mg SC QW) and for the paediatric IV formulation (belimumab 10 mg/kg body weight on Days 0, 14 and 28, and at 4-week intervals).

Clinical data from Study 200908 are limited and only supportive. A reduction in SELENA SLEDAI and decrease of anti-dsDNA antibody levels were observed, hence, these results are supportive of SC belimumab efficacy in children with SLE.

The safety profile in paediatric patients receiving belimumab subcutaneously appeared consistent with the known safety profile for belimumab. Limited data on long-term safety in paediatric patients is missing information in the RMP. This safety concern is expected to be further characterised in the ongoing open label Paediatric SLE study with IV formulation (Study BEL114055).

Hence, the 3-weight band dosing regimen for belimumab 200 mg SC QW for ≥50 kg; 200 mg SC Q10d for ≥30 kg to <50 kg; and 200 mg SC Q2W ≥15 kg to <30 kg is acceptable to the CHMP.

The paediatric SC use is recommended only for the pre-filled pen as Benlysta with the pre-filled syringe in paediatric patients has not been evaluated.

3.7.2. Balance of benefits and risks

The extension of indication of Benlysta for injection in prefilled-pen to paediatric patients is considered approvable for the following reasons:

- The extrapolation is mainly based on PK data with the SC formulation in paediatric patients, showing a similar exposure of the SC use in paediatric patients compared to the approved use for the SC formulation in adults and the IV formulation in children.
- As agreed in the extension of indication for IV use of belimumab in paedatric SLE patients (variation II/0062, EC decision 21/20/2019), the similarity of belimumab PK in adults and children supports the extrapolation of the efficacy and safety results for Benlysta in adults to the paediatric SLE population.
- The limited efficacy/PD data available support that SC Benlysta can be effective in children with SLE.
- No new safety concerns were identified from the limited safety results available with SC use of belimumab in SLE paediatric patients. The long-term safety of Benlysta treatment in children remains carefully monitored post-approval as described in the RMP.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall benefit risk of Benlysta 200 mg solution for injection in prefilled pen is positive as add-on therapy in patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti dsDNA and low complement) despite standard therapy (see section 5.1).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include add-on therapy in paediatric patients from 5 years of age with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti dsDNA and low complement) despite standard therapy for Benlysta 200 mg in pre-filled pen (injection), based on final results from study 200908; this is a worldwide population pharmacokinetic (PK) analysis of subcutaneous administered belimumab plus standard therapy to paediatric patients aged 5-17 years with SLE, which was aimed to describe the PK analysis of belimumab to support an appropriate weight-based dosing regimen for subcutaneous administration in paediatric patients aged 5-17 years with SLE. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated.

Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC for Benlysta (belimumab, solution for injection in pre-filled syringe, 200 mg) to reflect the paediatric data available for belimumab.

Update of sections 4.8 and 5.2 of the SmPC for Benlysta (belimumab powder for solution for infusion 120 mg and 400 mg) to reflect the paediatric data available for the subcutaneous formulation.

The Package Leaflet is updated in accordance. Version 46.2 of the RMP is agreed.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4 and with the excipients guideline.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0395/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Benlysta-H-C-002015-II-0133’