NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sBLA
Application Number(s)	sBLA761043/S-027 and sBLA 125370/S-081
Priority or Standard	Standard
Submit Date(s)	July 17, 2023
Received Date(s)	July 17, 2023
PDUFA Goal Date	May 17, 2024
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM)
Review Completion Date	See Electronic Stamp Date
Established/Proper Name	Belimumab
(Proposed) Trade Name	Benlysta
Pharmacologic Class	Monoclonal Anti-BLyS Antibody
Code name	N/A
Applicant	GSK
Dosage form	Subcutaneous Injection
Applicant proposed Dosing Regimen	Subcutaneous Dosage for Pediatric Patients with SLE: • Weighing greater than or equal to 40 kg: 200 mg once weekly • Weighing 15 to less than 40 kg: 200 mg once every 2 weeks
Applicant Proposed Indication(s)/Population(s)	Patients aged 5 years of age and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Patients aged 5 years of age and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy
Recommended Dosing Regimen	Subcutaneous Dosage for Pediatric Patients with SLE: • Weighing greater than or equal to 40 kg: 200 mg once weekly • Weighing 15 to less than 40 kg: 200 mg once every 2 weeks

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSIS= Office of Study Integrity and Surveillance
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Signatures

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Glossary

AC	advisory committee
ACP	access extension phase
ACR	American College of Rheumatology
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
AI	autoinjector
ANA	anti-nuclear antibody
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
cSLE	childhood-onset systemic lupus erythematosus
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention
DRE	Disease Related Event
ECG	electrocardiogram
eCTD	electronic common technical document
EEA	European Economic Area
ETASU	elements to assure safe use
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007

FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HF	Human Factors
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IFU	Instructions for Use
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LN	lupus nephritis
MedDRA	Medical Dictionary for Regulatory Activities
MG	Medication Guide
mITT	modified intent to treat
MMF	mycophenolate mofetil
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSAIDs	nonsteroidal anti-inflammatory agents
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFS	pre-filled syringe
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PML	progressive multifocal encephalopathy
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PERC	Pediatric Research Committee
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	Preferred Term
QW	every week
Q2W	every 2 weeks
REMS	risk evaluation and mitigation strategy

RRA	Remote Regulatory Assessment
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGE	special government employee
SLE	systemic lupus erythematosus
SOC	standard of care or System Organ Class
TEAE	treatment emergent adverse event
UK	United Kingdom
U.S.	United States

1 Executive Summary

1.1. Product Introduction

Belimumab (Benlysta) is a monoclonal antibody (mAb) that inhibits B-lymphocyte stimulator (BLyS) which modulates B-cell growth and survival. It is an approved therapeutic biologic product that is available and marketed in the U.S. since 2011 as an intravenous (IV) formulation (BLA125730) at a dose of 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter for the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) despite standard therapy. An alternative once weekly 200 mg subcutaneous (SC) administered injection formulation available as a ready to use pre-filled syringe (PFS) and autoinjector (AI) was approved in 2017 (BLA761043) for the same indication. In 2019, the IV formulation's indication was expanded to include the treatment of children 5 years and older with active, autoantibody-positive childhood-onset SLE (cSLE). Both the IV and SC formulation's indications were expanded in 2020 to include the treatment of adults with active lupus nephritis (LN) despite standard therapy. In 2022, the IV formulation's LN indication was expanded to include children 5 year of age or older.

The Applicant, GlaxoSmithKline, submitted a 351(a) supplemental biologics license application (sBLA) seeking marketing approval of belimumab for SC administration to fulfill the Pediatric Research Equity Act (PREA) post-marketing required (PMR) 3239-01 pediatric assessment related to the July 20, 2017 approval for BLA 761043 Benlysta® (belimumab) subcutaneous (SC) formulation as a treatment of adults with SLE who are receiving standard therapy. With this supplement, the Applicant proposes to expand the present indication for belimumab SC administration via the AI presentation to include the treatment of children 5 to 17 years of age with active SLE who are receiving standard therapy. At the time, BLA125370 S-081 Benlysta IV labeling supplement was also submitted to align label.

The Applicant proposed to only develop the AI presentation and not the PFS presentation of belimumab SC for children. The rationale was based on (b) (4) the enhanced ergonomics and needle safety features provided by the AI presentation as compared to the PFS presentation. This proposal was originally submitted in the iPsP in 2014 and was discussed and deemed acceptable at the PeRC meeting held on May 15, 2015.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is approval for belimumab (Benlysta) SC formulation administration via the AI presentation for the treatment of children 5 to 17 years of age with active SLE who are receiving standard therapy. This recommendation is based on extrapolation

of efficacy of belimumab SC established in adults, with active SLE on standard therapy. The phase 2, open-label, pharmacokinetic (PK) bridging, safety study 200908 conducted in pediatric SLE subjects treated with belimumab 200 mg SC administered via the autoinjector and an updated review of pharmacovigilance safety data from pediatric patients exposed to belimumab also provided safety data supportive of this recommendation. Additionally, the pediatric clinical pharmacology, efficacy and safety data submitted are adequate to fulfill the PREA postmarketing requirement (3239-1) included in the July 20, 2017 approval for BLA 761043 Benlysta® (belimumab) subcutaneous (SC) formulation.

As described in Section 6, determination of efficacy in pediatric subjects was based on PK matching of systemic exposure in pediatric and adult subjects, which permitted extrapolation of established efficacy of belimumab SC from the pivotal phase 3 studies in adults with SC belimumab (BEL112341/C1115). The adult belimumab SC study was an adequate and well controlled clinical trial that had been reviewed previously in support of the approvals of belimumab SC for adult SLE (BLA 761043). A pediatric population PK model was built based on data from study 200908 and belimumab IV pediatric study BEL114055/C1109. Since PK exposure is expected to be similar between adult and pediatric SLE patients, it is scientifically justified to extrapolate the efficacy established from the adult SC SLE study to the belimumab SC formulation in pediatric SLE patients.

Belimumab's safety and PK profiles in study 200908 in pediatric patients were consistent with the overall population in the pivotal pediatric and adult studies, and no new safety signals were identified that warranted discussions of the data contained in this submission at a public advisory committee meeting or updating the Warnings and Precautions section of the current belimumab label.

The Applicant has provided adequate data and information to inform the benefit-risk assessment of belimumab SC for the treatment of pediatric patients 5 years and older when administered at a dose of 200 mg as a subcutaneous injection once weekly via the AI to pediatric subjects weighing $\geq$40 kg, and once every 2 weeks via the AI to pediatric patients weighing $\geq$15 kg to <40 kg as add-on therapy for pediatric patients with active SLE who are receiving standard therapy. Approval of belimumab SC will provide an additional treatment option for pediatric patients with SLE given the limited number of approved treatment options for this disease in the United States (U.S).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Systemic lupus erythematosus (SLE) is a chronic, multisystemic, inflammatory, autoimmune disease characterized by autoantibody production and disease flares alternating with periods of remission. Although this disease most commonly develops during early adulthood, approximately 10-20% of patients develop SLE during childhood.[1] Childhood-onset SLE (cSLE) is a rare disease that is seldom diagnosed in children 9 years old and younger.[2] Clinical manifestations of SLE can range from mild to life-threatening, affecting a variety of organs that include the skin, joints, blood, brain, and kidney. The range of disease manifestations are similar in children and adults except children may have more brain and kidney (renal) involvement at disease onset that may be life-threatening.[3] Currently, there is only one approved therapeutic biologic (belimumab) that is administered intravenously (IV) as a treatment for cSLE in the U.S. Thus, an unmet medical need exists for additional therapeutic options for pediatric patients with cSLE.

Belimumab (Benlysta) is a monoclonal antibody (mAb) that inhibits B-lymphocyte stimulator (BLyS) which modulates B-cell growth and survival. The IV formulation was first approved in 2011 for the treatment of adult patients with active, systemic lupus erythematosus (SLE) despite standard therapy. An alternative once weekly 200 mg subcutaneous (SC) formulation, available as a ready to use pre-filled syringe (PFS) and autoinjector (AI) was approved in 2017 for the same indication. Belimumab has been subsequently approved for the treatment of children 5 years and older with active, childhood-onset SLE (cSLE) (IV formulation only), the treatment of adults with active lupus nephritis (LN) despite standard therapy (both IV and SC formulations) in 2020, and the treatment of children 5 years of age or older with active LN despite standard of care (IV formulation only) in 2022. Under the Pediatric Research Act (PREA), a partial waiver for pediatric studies in patients with cSLE $\leq$ 5 years of age based on the justification that dedicated clinical studies to establish the efficacy of products in cSLE would be impossible or highly impracticable to conduct because there were too few children with the disease/condition to study in this subgroup along with deferral for a pediatric assessment in patients with cSLE >5 to 17 years of age were granted at the time of approval of the SC formulation for the adult SLE indication. Based on the high degree of disease similarity between adults and pediatric patients with SLE, the Agency agreed that the Applicant could fulfill this PREA postmarketing required (PMR) pediatric assessment via full extrapolation of efficacy and safety established in children and adults with SLE based on matching of the PK exposures between the SC formulation in children to the IV formulation in children and the SC

[1] Hiraki LT, et al. Arth and Rheum 2012; 64:2669-76.
[2] Hiraki LT, et al. Arth and Rheum 2012; 64:2669-76.
[3] Livingston B, et al. Lupus 2011; 20:1345-55.

and IV formulations in adults based on existing belimumab studies conducted in pediatric and adult patients.

In support of a full extrapolation approach, the Applicant provided the following justification: (1) Information supporting disease similarity between the adult and pediatric patients with SLE; (2) Establishment of a PK bridge (comparable exposures) between pediatric and adult subjects treated with SC formulations of belimumab; (3) Extrapolation of efficacy from belimumab SC Study BEL114054/C1115 in adult subjects with SLE; and (4) Justification of the relevance of the safety data from belimumab IV pediatric study BEL114055/C1109 in children with SLE.

As described in Section 6, determination of efficacy in pediatric subjects was based on PK matching of systemic exposure in pediatric and adult subjects, which permitted extrapolation of established efficacy of belimumab SC from the pivotal phase 3 studies in adults with SC belimumab (BEL112341/C1115). The adult belimumab SC study was an adequate and well controlled clinical trial that had been reviewed previously in support of the approvals of belimumab SC for adult SLE (BLA 761043). A pediatric population PK model was built based on data from study 200908 and belimumab IV pediatric study BEL114055/C1109. Since PK exposure is expected to be similar between adult and pediatric SLE patients, it is scientifically justified to extrapolate the efficacy established from the adult SC SLE study to the belimumab SC formulation in pediatric SLE patients.

Assessment of safety in the SC belimumab program in cSLE was primarily based on leverage of established safety in the pediatric population from the aforementioned belimumab IV pediatric study BEL114055/C1109. The comparable exposure of belimumab SC and belimumab IV in pediatric patients supports the leverage of established safety in the pediatric population from the belimumab IV pediatric study BEL114055/C1109. Review of the safety data from the completed portions (Parts A and B) of study 200908 as well as updated pharmacovigilance postmarketing safety data in pediatric patients with cSLE did not identify any new or unexpected safety signals associated with the administration of belimumab in the pediatric subpopulation. The rate and type of adverse events reported in Study 200908 are consistent with the cSLE population, and the known adverse reaction profile of belimumab. Note that no pediatric patients between 15-30 kg were enrolled in Study 200908. Although the prevalence of cSLE increases with age, it is rarely diagnosed in children 9 years old and younger.[4] Based on the CDC growth chart, the average weight of a 9 year old girl is 28kg. It may be difficult to enroll enough cSLE patients under 30kg to inform on the local safety of Benlysta AI. The IFU of the proposed label includes “For children less than 10 years of age, BENLYSTA must be given by a healthcare provider or a trained caregiver”. This would help to ensure the safe use of the AI in the younger pediatric patients. Overall, the review team concluded that risk/benefit would support the approval of BENLYSTA SC in patients with body weight within the 15-30kg range and provide an important treatment option for this population with high unmet medical need.

[4] Hiraki et al. Arth and Rheum 2012; 64:2669-76.

In summary, cSLE is a rare and serious disease with an unmet need for new therapies. The Applicant has provided adequate data and information to inform the benefit-risk assessment of belimumab SC for the treatment of pediatric patients with active SLE who are receiving standard therapy, and support the expansion of the indication of belimumab SC administered via AI as add-on treatment for active SLE in pediatric patients 5 to 17 years old at a dose of 200 mg once weekly via AI in pediatric subjects weighing ≥ 40 kg, and at a dose of 200 mg once every 2 weeks via AI in subjects weighing ≥15 kg to <40 kg.

This approval will provide an important treatment option for this pediatric population with high unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Systemic lupus erythematosus (SLE) is a chronic, multisystemic, autoimmune disease characterized by alternating periods of disease flares and remission • Approximately 10-20% of SLE patients have disease onset during childhood • Childhood onset SLE (cSLE) is a rare disease that is seldom diagnosed in children 9 years old and younger • Disease manifestations in adults and children are similar affecting a variety of organs that include the skin, joints, blood, brain, and kidney which can range from mild to life-threatening in severity	• SLE is s a serious disease that can impact virtually any organ system. This disease can cause significant morbidity and mortality as well as impact on patients' function and quality of life especially if it first presents during childhood.
Current Treatment Options	• Belimumab IV is currently the only treatment approved for pediatric patients with active SLE despite standard of care. Treatment with belimumab IV requires patients to travel to an infusion center or hospital in order to receive • The following are off-label therapies administered orally or via IV infusion that are currently used to treat pediatric patients with SLE: corticosteroids, hydroxychloroquine and other antimalarials, NSAIDs, rituximab, mycophenolate mofetil, anifrolumab, azathioprine, methotrexate, and cyclophosphamide	• A SC formulation of belimumab would be more convenient and less time consuming since it could be self-administered at home which may result in increased patient compliance • The toxicities associated with the off-label treatments commonly used to treat SLE contribute to the long-term morbidity and mortality observed in patients with SLE.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		• A large unmet medical need for safe and efficacious treatments for children 5 to 17 years old with childhood onset SLE exists
• **Benefit**	• In children 5 to 17 years old with active SLE, the PK of belimumab were estimated based on a population pharmacokinetic model developed from 78 pediatric patients with active SLE. With SC administration, the simulated belimumab exposures for both the < 40kg group and the ≥ 40 kg group were comparable to adults with active SLE, supporting the efficacy extrapolation from adults with active SLE to pediatric subjects with SLE. • Belimumab SC's efficacy as a treatment of adults with SLE has been previously demonstrated. Study BEL114054/C1115 supported the approval of belimumab SC for the treatment of adults with active SLE on standard therapy.	• The comparable exposure of belimumab SC in pediatric and adult patients supports the extrapolation of established efficacy in the adult SLE population from the belimumab SC adult study BEL114054/C1115. • Lower SLE disease activity as well as a decrease in the risk for severe SLE flares may also result in less long-term end-organ damage from patients' underlying disease, less treatment with unapproved immunosuppressive agents commonly used to treat childhood-onset SLE with their own inherent toxicities, as well as fewer hospitalizations with less absent school days and ultimately less morbidity and mortality associated with the disease
Risk and Risk Management	• With SC administration, the simulated belimumab AUC for both the < 40kg group and the ≥ 40 kg group were comparable to the AUC with IV administration in pediatric SLE patients of the same age/weight group, and the Cmax with the SC administration is expected to be lower compared to the approved IV dosing regimen in pediatric SLE. Therefore, the findings of safety in the cSLE program with the approved belimumab IV dosing regimen are relevant and supportive of the safety of belimumab SC in cSLE patients 5 years and older.	• The comparable exposure of belimumab SC and belimumab IV in pediatric patients supports the leverage of established safety in the pediatric population from the belimumab IV pediatric study BEL114055/C1109.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The safety database is comprised of safety data from the phase 2, open-label, pharmacokinetic (PK) bridging safety study 200908 conducted in pediatric SLE subjects treated with belimumab 200 mg SC administered via autoinjector and safety data from the pediatric belimumab IV study (BEL114055/C1109). In addition, an updated review of pharmacovigilance postmarketing safety data from pediatric patients exposed to belimumab was submitted as supportive evidence. Overall, the safety database is sufficient to provide a risk assessment for belimumab SC in the pediatric SLE population. • The safety profile in pediatrics is generally consistent with the belimumab SC adult SLE study BEL112341/C1115 and the belimumab IV adult SLE studies BEL110751/C1056 and BEL110772/C1057 that originally established both the safety and efficacy of belimumab SC and IV in adult SLE patients.	• Available safety data from children treated with belimumab SC in study 200908 and the updated pharmacovigilance postmarketing data from pediatric patients exposed to belimumab suggest that the safety profile of belimumab SC in the pediatric SLE population age 5 years and older will be similar to what has been observed with the belimumab IV formulation in pediatric and adult patients and the belimumab SC formulation in adults

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Systemic lupus erythematosus (SLE) is a heterogeneous, chronic, autoimmune disease characterized by autoantibody production with systemic inflammation as a result of immune dysregulation with disease flares alternating with periods of improvement. Clinical manifestations can range from mild to life-threatening, affecting a variety of organ systems. Estimated incidence rates of SLE in the adult population range from 1 to 25 per 100,000 person-years, with a prevalence in the range of 20 to 73 per 100,000.[5, 6, 7] There is a consistent and striking female predominance, with females comprising approximately 90% of all SLE patients.[8] Although patients with this disease most commonly present between the ages 15 and 40, approximately 10-20% of SLE patients have disease onset during childhood.[9] Childhood-onset SLE (cSLE) is a rare disease with an estimated incidence ranging from 0.3 to 2.2 per 100,000 children, and prevalence in the range of 1.1 to 9.7 per 100,000 children and adolescents depending on world location.[10, 11, 12, 13] Although the prevalence of cSLE increases with age, it is rarely diagnosed in children 9 years old and younger.[14]

In general, the most common SLE manifestations are malar rash, photosensitivity, oral ulcers, arthritis, and renal disease. The range of manifestations in cSLE is similar to that seen in adult onset disease with the exception that children who present with cSLE have more hematological (55-77%), renal (27-59%), and neuropsychiatric (25%) involvement at onset which may present as life-threatening disease.[15]

For the purposes of clinical trials, the European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) established in 2019 classification criteria to assist in uniformly identifying patients with SLE (Figure 1).[16] Generally, adult and pediatric patients are considered to have SLE if they have a positive anti-nuclear antibody (ANA) test in addition to disease activity in one clinical domain and a total score greater than or equal to 10 based on the criteria listed in Figure 1.

[5] Izmirly PM, et al. Arthrits Rheum 2021: 73:991.
[6] Pons-Estel GJ, et al. Semin Arth and Rheum 2010 Feb.; 39:257-268
[7] Danchenko N, et al. Lupus 2006; 15:308.
[8] Pons-Estel GJ, et al. Semin Arth and Rheum 2010 Feb.; 39:257-268.
[9] Hiraki LT, et al. Arth and Rheum 2012; 64:2669-76.
[10] Hiraki LT, et al. Arth and Rheum 2012; 64:2669-76.
[11] Nightingale AL, et al. Pharmacoepidemiol Drug Saf. 2007; 16:144-51.
[12] Valenzuela-Almada MO, et al. Arthritis Care and Research 2022; (74)5:728-732.
[13] Oni L, et al. Pediatric Nephrology 2021; 36:1377-1385.
[14] Hiraki et al. Arth and Rheum 2012; 64:2669-76.
[15] Livingston B, et al. Lupus 2011; 20:1345-55.
[16] Aringer M, et al. Arth and Rheum 2019; 71(9):1400-1412.

Figure 1. 2019 EULAR/ACR Classification Criteria for SLE[17]

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

As there is no cure for this chronic disease, therapeutic goals in the chronic management of SLE include controlling active inflammation and preventing or resolving organ damage while improving quality of life and survival. The current overall 10-year survival in adult patients with SLE has improved to 85-90%.[18] However, pediatric patients with cSLE have a higher

[17]Aringer M, et al. Arth and Rheum 2019; 71(9):1400-1412.
[18] Ipolito A, Petri M, et al. Clin Exp Rheumatol 2008;26 Suppl51:S72-9

relative risk of mortality as compared to patients with adult-onset disease (hazard ratio [HR] 3.1, 95% confidence interval [CI] 1.3-7.3).[19] This disparity in survival has been attributed to the more aggressive disease course seen in cSLE resulting in greater major end-organ damage due to underlying disease activity as well as from the cumulative toxicities and increased risk for infection associated with the immunosuppressive medications used in the management of this disease.

2.2. Analysis of Current Treatment Options

Currently, the IV formulation of belimumab is the only approved treatment for pediatric patients with SLE. Table 1 lists the treatments currently approved for adults and children with SLE as well as off-label treatments that are available for the treatment of adults and children with this disease.

Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments for Children with SLE and LN						
Belimumab	Treatment of active, SLE or LN despite standard of care in patients 5 years of age and older	SLE: 2019 LN: 2022	10mg/kg via IV infusion at 2-week intervals for the first 3 doses and then at 4-week intervals thereafter	IV: One phase 2 study in pediatric subjects with extrapolation of PK/PD, safety, and efficacy from adult phase 3 studies	↑risk for serious and fatal infections, PML, hypersensitivity reactions, depression and suicidality	Musculoskeletal, mucocutaneous, renal, and immunologic manifestations
FDA Approved Treatments for Adults with SLE						
Anifrolumab	Treatment of active, SLE and despite standard of care	2021	300 mg via IV infusion over 30 minutes every 4 weeks	Three phase 3 studies in adults	↑risk for serious and fatal infections, hypersensitivity reactions, and malignancy	Mucocutaneous and musculoskeletal manifestations
Belimumab	Treatment of active, SLE and LN despite standard of care	SLE: 2011 IV formulation; 2017 SC formulation LN: 2022 IV and SC formulations	10mg/kg via IV infusion at 2-week intervals for the first 3 doses and then at 4-week intervals thereafter	IV: Two phase 3 studies SC: One phase 3 study	↑risk for serious and fatal infections, PML, hypersensitivity reactions, depression and suicidality	Musculoskeletal, mucocutaneous, renal and immunologic manifestations

[19] Hersh AO, et al. Arthritis Care Res (Hoboken). 2010;62(8):1152-9.

Hydroxychloroquine	Treatment of discoid and SLE	1955	200 mg BID	Clinical studies	Retinal and corneal deposits, GI complaints, rash, myalgia. Headache and hemolytic anemia in G6PD deficiency	Constitutional, cutaneous, and musculoskeletal manifestations
Prednisone	During an exacerbation or as maintenance therapy in selected cases of SLE	1955	Up to 80 mg/day; use lowest dose to maintain adequate anti-inflammatory response	Clinical studies	↑risk for infections, glucose intolerance, osteoporosis, glaucoma, cataracts, HTN, osteonecrosis, and ↓growth	Low dose: muco-cutaneous and musculoskeletal manifestations; serositis High Dose: induction therapy for lupus nephritis, CNS disease, and immune cytopenias
Aspirin	Treatment of arthritis and pleurisy of SLE	1948	Initially 3g/d in divided doses; titrate up to plasma salicylate level 150-300mcg/ml for anti-inflammatory effect	Clinical studies	GI bleeding and tinnitus at plasma salicylate levels ≥ 250 mcg/ml	Constitutional and musculoskeletal manifestations and serositis. (No longer used.)
Other Treatments (Off-Label)						
Rituximab	----------	----------	1000mg IV infusions x 2 administered 2 weeks apart; re-administer when disease worsens	Two failed phase 3 studies	Fatal infusion reactions, severe mucocutaneous reactions, Hepatitis B reactivation, serious infections including PML	Treatment of refractory lupus nephritis and immune cytopenias
Mycophenolate Mofetil	----------	----------	500-1500 mg BID	Published literature	Myelosuppression, GI complaints, myalgia, infections	Induction and maintenance therapy for lupus nephritis
Cyclophosphamide	----------	---------	IV bolus regimens of 0.5-1g/m body surface area for once monthly for 6 months	Published literature	Myelosuppression, hemorrhagic cystitis, malignancy, lympho-proliferative disorders, infertility and infections	Induction therapy for lupus nephritis, CNS disease, pulmonary hemorrhage, and systemic vasculitis
Methotrexate	----------	----------	7.5-25 mg/week	Published literature	Mucositis, myelosuppression,	Cutaneous and musculoskeletal manifestations

					hepatotoxicity, cirrhosis, pneumonitis, pulmonary fibrosis, infections	
Azathioprine	----------	----------	2-2.5 mg/kg/d	Published literature	Myelosuppression, hepatotoxicity, malignancies, infections	Steroid sparing and maintenance therapy for lupus nephritis
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	----------	----------	Lowest effective approved dose	Published literature	GI bleeding, CV events, hepatic and renal toxicity, HTN, headache, aseptic meningitis, confusion	Constitutional and musculoskeletal manifestations, headaches and serositis

Based on anecdotal reports and non-registrational studies in the published literature, both adult and pediatric SLE patients are usually treated with a combination of hydroxychloroquine, nonsteroidal anti-inflammatory agents (NSAIDs), and immunosuppressive agents. Toxicities associated with immunosuppressive agents such as corticosteroids and cyclophosphamide contribute to the morbidity and mortality associated with this disease. As noted in Table 1 above, there are currently only 5 treatments approved for the treatment of SLE in adults, of which belimumab IV is the only approved therapeutic biologic product for the treatment of SLE in both adults and children. Its currently approved label contains a limitation of use in patients with severe central nervous system lupus since all the phase 3 adult studies and the phase 2 pediatric study conducted in support of the IV formulation product excluded patients with this disease manifestation. Belimumab's labeling also contains Warning and Precaution statements regarding an increased risk for developing serious infections, progressive multifocal encephalopathy (PML), hypersensitivity reactions including anaphylaxis, and depression and suicidality associated with its administration. The label also includes a Warning and Precaution statement regarding concomitant use with other biologic therapies and the concomitant administration of live vaccines.

Despite the availability of belimumab IV for the treatment of pediatric patients with SLE in the United States, there is an unmet medical need for alternative formulations that potentially could improve patient compliance and quality of life because of increased patient comfort and ease of use including being less time consuming to administer.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Belimumab is an approved therapeutic biologic product that is available and marketed in the U.S. (since 2011) and in all the European Economic Area (EEA) countries, the United Kingdom (UK) and Japan as well as in over 30 other countries worldwide (as of March 2023) as an intravenous (IV) formulation at a dose of 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter for the treatment of adult patients with active, SLE. An alternative once weekly 200 mg subcutaneously (SC) administered injection formulation available as a ready to use PFS and AI was approved in the U.S. in 2017 for the same indication and is also marketed in all EEA countries, the UK and Japan as well as 13 additional countries. In 2019, the IV formulation's indication was expanded in this country and in the other countries where the product is marketed to include the treatment of children 5 years and older with active, childhood-onset SLE. In 2020, the indications for both the IV and SC formulations were further expanded to include the treatment of adult patients with active lupus nephritis on standard of care. The LN indication for belimumab IV was extended to include children ages 5 to 17 years of age in 2022.

Belimumab's initial label contained Warning and Precaution statements regarding increased risk for both mortality and serious infections, the occurrence of hypersensitivity reactions including anaphylaxis and depression including suicidality as well as not administrating live vaccines to patients receiving this product. The product's USPI has subsequently undergone 11 major labeling revisions as follows:

- 2012 and 2013: The Warnings and Precautions section for hypersensitivity reactions including anaphylaxis was updated to reflect post marketing cases of post-infusion/injection systemic reactions.
- 2014: A Warning and Precaution statement regarding the occurrence of PML in SLE patients who had received belimumab IV in addition to concomitant immunosuppressive agents was added to the product's USPI and subsection 17.1 Advice to for the Patient and the Medication Guide were updated to provide information about the risk of PML in patients with SLE receiving belimumab.
- 2016: Section 2.3 Preparations of Solutions was updated to include the recommendation to use a 21- to 25-G needle for reconstitution and dilution of belimumab with half-normal saline or Lactated Ringer's Injection. Sections 5.2 Serious Infections and 6.1 Clinical Trials Experience were updated to include new safety information while Section 8 was updated to comply with the Pregnancy Lactation Labeling Rule (PLLR).
- 2017: Information was added regarding the dose and administration of the SC formulation via PFS and AI as well as a description of the clinical pharmacology and clinical trial data reviewed in support of the marketing approval of the SC formulation to Sections 12 Clinical Pharmacology and 14 Clinical Studies. Information regarding the SC formulation was added to the product's Medication Guide.

- 2019: The IV formulation's indication was expanded to include children aged 5 years and older with cSLE. A description of the clinical trial data reviewed in support of the pediatric indication was added to Section 14.1.
- 2019: The Warnings and Precaution section for Depression and Suicidality was updated to reflect the occurrence of these adverse events in clinical trials of the product including a recently completed, large postmarketing safety study and to advise healthcare providers to assess patients prior to initiating treatment as well as monitor them during treatment.
- First quarter 2020: Deletion of the precautionary statement regarding the treatment of black/African-American patients with belimumab based on the subgroup exploratory analysis of the SRI-4 response rate for black subjects who participated in the two pivotal IV belimumab studies under subsection Effect in Black/African-American Patients under Section 14.1 Clinical Trials. Efficacy and safety results of study BEL115471/C1112 conducted in black/African-American patients with SLE receiving standard of care where applicable was included under Sections 6.1 Clinical Trials with Intravenous Administration, 8.8 Racial Groups and 14.1 Clinical Trials Experience with Intravenous Administration.
- Third quarter 2020: Deletion of the Warnings and Precautions statements regarding all-cause mortality. Under Section 5 Warnings and Precautions for serious infections, PML, depression and suicidality, and hypersensitivity reactions were updated and the results of adverse events of special interest (AESI) from study BEL15467/C1113 were included under the corresponding subsections. Section 17 Patient Counseling Information was updated to reflect the new and updated Warnings and Precautions.
- Last quarter 2020: The indications for both IV and SC formulations were expanded to include the treatment of adult patients with active lupus nephritis on standard of care with the deletion of both lupus nephritis and intravenous cyclophosphamide under Section 1 Indications and Usage and its subsection, Limitations of Use, respectively. The new SC loading regimen 400 mg (two 200-mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter and the associated administration instructions for lupus nephritis in adults were added under Section 2.2 Subcutaneous Dosing Instructions. A description of the clinical trial data from study BEL114054/C1121 reviewed in support of the adult lupus nephritis indication was added to Section 14.2 and safety data regarding the incidence of serious infections in this study and the observation of cases of myelosuppression including febrile neutropenia, leukopenia, and pancytopenia observed in subjects who received induction therapy with cyclophosphamide followed by maintenance therapy with azathioprine or mycophenolate mofetil were added under Section 5.1 Serious infections and Section 6.1 Clinical Trials Experience, respectively. Information regarding increased serum IgG levels and complement levels, and the reduction in autoantibodies, circulating total B cells and B cell subsets in patients treated with belimumab in study BEL114054/C1121 was added under Section 12.2 Pharmacodynamics. PK data for the IV formulation related to proteinuria as well as PK data related to the subcutaneous injection in adults with lupus nephritis was added under Section 12.3 Pharmacokinetics. Other changes included the deletion of intravenous cyclophosphamide under Section 5.7 Concomitant Use with Other Biologic Therapies; the addition of information regarding the lack of formation of anti-belimumab antibodies in

study BEL114054/C1121 under Section 6.4 Immunogenicity; and the addition of cyclophosphamide to the list of concomitantly administered medications under Section 7 Drug Interactions. The Instructions for Use (IFU) and Medication Guide (MG) were also updated to include the instructions for administration of the loading dose of the subcutaneous formulation and to reflect the new information regarding cyclophosphamide and the use of belimumab as a treatment for adult patients with lupus nephritis.

- 2022: The indication for belimumab IV was extended to include children ages 5 to 17 years of age with lupus nephritis who are receiving standard of care. Additionally, "antibody positive" was deleted from the SLE indication as was the text regarding use with other biologics under Section 1 Indications and Usage. (Note: Deletion of "antibody positive" was in line with the new 2019 EULAR/ACR SLE classification criteria which requires all patients with SLE to have a positive ANA and did not impact the originally approved patient population/condition of use.) Other changes to the labeling included updating information under Section 2 Intravenous Preparation and Dosing Indications to include new dosing recommendations for belimumab IV in pediatric patients with lupus nephritis. Clinical safety data under subheadings 5.1 Serious Infections; 5.2 Hypersensitivity Reactions, including Anaphylaxis; 5.3 Infusion Reactions; 5.4 Depression and Suicidality; and 5.5 Malignancy were moved to new corresponding subsections under 6.1 Clinical Trials Experience with Intravenous Administrations. Additional information regarding the increased risk of malignancies with the use of immunosuppressives and the need for the consideration of the benefit-risk for each individual patient in patients with known risk factors for the development or reoccurrence of malignancy prior to prescribing belimumab and continuing treatment in patients who develop malignancies were added under the new subheading 5.5 Malignancy. Subheading 5.6 Not Recommended for Concomitant Use with Other Biologic Therapies was added with the statement that "Benlysta has not been studied in combination with other biologic therapies, including B-cell targeted therapies, therefore, the use of Benlysta is not recommended in combination with biologic therapies." Existing information under Section 6 Adverse Events was re-ordered to improve readability. Section 8.4 Pediatric Use was updated to include the new pediatric lupus nephritis indication and the results from the PK extrapolation of the established efficacy of belimumab plus standard therapy from the phase 3 IV study in adults with lupus nephritis and the pediatric SLE study. Under Section 10 Overdose, the following sentence was deleted: "Adverse reactions reported in association with cases of overdoses have been consistent with those expected for Benlysta." A description of the pediatric dosing for LN based on PK extrapolation from adults with LN was added under Section 12.3 Pharmacokinetics. The sentence, "Ask patients if they have a history of chronic infections and if they are currently on any therapy for an infection," was deleted under Section 17 Patient Counseling Information. The Medication Guide was updated to include the expanded indication of children aged 5 years and older with LN.
- 2023: Label was updated to include the results of clinical study 205646 conducted with Benlysta SC administrated in combination with rituximab in adult patients with SLE under

Section 6.1 Clinical Trials with Subcutaneous Administration and to update the Warning under Section 5.6 Concomitant Use of Other Biological Therapies to include information regarding the increase incidence of serious infections and post-injection systemic reactions in patients receiving Benlysta concomitantly with rituximab compared to patients receiving Benlysta alone. Section 6.2 Immunogenicity was deleted and the information under this section was moved in its entirely to Section 12.6 Immunogenicity. New contact information regarding the recently initiated OTIS Pregnancy Exposure Registry was added under Section 8.1 Pregnancy. Section 17 Patient Counseling Information was updated to remind healthcare providers to inform patients that there is a pregnancy registry to evaluate fetal outcomes of pregnant women with lupus exposed to Benlysta.

- First quarter of 2024: The Warnings and Precautions section for progressive multifocal leukoencephalopathy (PML) was updated to state that healthcare providers must stop treatment with all immunosuppressant therapy including Benlysta in patients with suspected PML until the latter has been excluded. All immunosuppressant therapy including Benlysta must be discontinued in patients with confirmed PML.

3.2. Summary of Presubmission/Submission Regulatory Activity

As part of the approval action on July 20, 2017 for BLA 125370 Benlysta® (belimumab) subcutaneous (SC) formulation as a treatment for adult patients with active SLE, the Agency required a pediatric postmarketing (PMR 3239-01) assessment of belimumab SC under the Pediatric Research Equity Act (PREA) as follows:

> "Conduct a pharmacokinetic and safety study of subcutaneous belimumab in patients with active systemic lupus erythematosus ages 5 to <18 years of age"
>
> | | |
> |---|---|
> | Final Protocol Submission: | April 2019 |
> | Study Completion: | March 2023 |
> | Final Assessment Report Submission: | November 2023 |

On October 24, 2014, the Applicant submitted a draft Initial Pediatric Study Plan (iPsP) which outlined their plans for the pediatric clinical development of belimumab SC utilizing the approved AI presentation. The Applicant's rationale for only developing the AI presentation and not the PFS presentation of belimumab SC for children was based on (b) (4) the enhanced ergonomics and needle safety features provided by the AI presentation as compared to the PFS presentation. Based on feedback comments from the January 7, 2015 meeting of the Agency's Pediatric Review Committee (PeRC), the Applicant submitted an amended draft iPsP on April 15, 2015, that included data demonstrating the use of the AI in children would reliably result in subcutaneous administration in smaller and thinner children where inadvertent intramuscular or intra-osseous administration of the product might occur. This amended draft iPsP was deemed acceptable at the PeRC meeting held on May 15, 2015. The Agency's agreement of the iPsP was communicated to the Applicant on May 15, 2015.

Data generated from the PK bridging study 200908, which was conducted in accordance with the agreed iPSP and supported by full extrapolation of pharmacokinetic, pharmacodynamic, efficacy and safety data from pediatric patients with cSLE and adult patients with SLE, was submitted by the Applicant in a sBLA for the expansion of belimumab SC's approved indication for the treatment of patients with active SLE to include children 5 to less than 18 years of age on July 17, 2023.

Despite the availability of belimumab IV for the treatment of pediatric patients with SLE, the Applicant submitted a priority review request with the sBLA on July 17, 2023, based on the rationale that there is an unmet medical need for alternative formulations that potentially could improve patient compliance and quality of life as a result of increased patient comfort due to a reduction in injection site pain in addition to the increased convenience of administration (e.g., ease of use and less time consuming than receiving an IV infusion) as well as the lower costs associated with self-administration of belimumab via subcutaneous injection versus intravenous administration. Following internal review and discussion, the Applicant's request for a priority review for this sBLA was denied by the Agency on September 9, 2023.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

In September 2023, a Remote Regulatory Assessment (RRA) was conducted of the analytical study site by the Office of Study Integrity and Surveillance (OSIS). While conducting this RRA, OSIS identified data reporting errors in the anti-drug antibody (ADA) validation report (specifically, the intra- and inter-assay precision-titer assay erroneously stated the use of the screening cut point instead of the titer cut point when determining individual sample titers in addition to using an incorrect N-factor). Based on their review of the laboratory's written responses to these issues, OSIS determined that a site inspection was not needed since these errors did not impact data integrity. Refer to the OSIS review by Dr. Folaremi Adeyemo dated Jan 8, 2024, for more details.

4.2. Product Quality

This section is not applicable as no new product quality data were needed or submitted.

4.3. Clinical Microbiology

This section is not applicable as there are no new product quality data submitted or needed for this application.

4.4. Devices and Companion Diagnostic Issues

The Applicant previously submitted Human Factors (HF) study results to support use of belimumab's 200 mg AI in pediatric patients aged 5 to 17 years old. The Division of Medication Error Prevention and Analysis (DMEPA) reviewed this data as part of the sBLA review and concluded that the Applicant has provided HF data to support use of the 200 mg AI in pediatric patients.

An intercenter consult from the Division of Drug Delivery, General Hospital and Human Factors located in CDRH's Office of Product Evaluation and Quality was obtained regarding the appropriateness of the approved AI presentation in pediatric patients as part of the BLA review for this pediatric efficacy supplement. Recommendations made by the CDRH consultants were discussed internally by the clinical review team who agreed that most of their comments are addressed by the Instructions for Use (IFU) for the AI in the current belimumab label. Since no new or unexpected adverse events associated with the use of the AI in the pediatric population were observed in study 200908 (see Section 8 for additional information), the clinical review

team believes that the current risk mitigation and safeguards currently in place for the AI presentation are adequate for its continued safe use in the pediatric subpopulation. Given that the AI presentation proposed for use in the pediatric subpopulation is currently approved for use in adults including obese adults, and the concerns originally raised by PeRC regarding the potential risk for the administration of an intra-muscular and/or intra-osseous injection to a pediatric patient as a result of a longer needle, the clinical review does not believe that conducting an additional HF study in obese pediatric subjects assessing a longer needle in the AI presentation of belimumab SC is warranted.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical studies were submitted or required to support this efficacy supplement.

6 Clinical Pharmacology

6.1. Executive Summary

On July 17, 2023, GlaxoSmithKline LLC submitted an efficacy supplement (Supplement 027) under BLA 761043 seeking approval of Benlysta (belimumab) for the treatment of active systemic lupus erythematosus (SLE) children 5 years and older who are receiving standard therapy. The proposed dosing regimen is 200 mg subcutaneous (SC) administration once weekly in children 40 kg and above and 200 mg SC administration once every two weeks (Q2W) in children 15 to < 40 kg.

Benlysta IV (BLA 125370, initially approved on March 09,2011) is approved for the treatment of patients with active, autoantibody positive SLE who are receiving standard therapy. The approved intravenous (IV) dosing regimen in adult subjects with SLE is 10 mg/kg Q2W for the first 3 doses and Q4W thereafter. The approval is based on two Phase 3 randomized controlled trials in adult subjects with SLE (Study BEL110751/C1056 and Study BEL110752/C1057). Benlysta SC (BLA 761043, initially approved on July 20, 2017) is approved for the treatment of patients with active, autoantibody positive SLE who are receiving standard therapy. The approved SC dosing regimen in adult subjects with SLE is 200mg QW. The approval is based on one Phase 3 randomized controlled trials in adult subjects with SLE (BEL11234/HGS1006-C1115).

Benlysta IV (BLA 125370 Supplement 064, approved on April 26, 2019) is approved for the treatment of patients aged 5 years and older with active, autoantibody positive, SLE who are receiving standard therapy. The approved IV dosing regimen in children is 10 mg/kg Q2W for the first 3 doses and Q4W thereafter. The approval was based on one Phase 3 randomized placebo-controlled trial in pediatric subjects with SLE (BEL 114055/C1109).

The pharmacokinetics (PK) of belimumab following SC administration were characterized in Study 200908 in children 5 to < 17 years of age with active SLE. The belimumab systemic exposure following the proposed dosing regimen in children 5 to < 17 years of age with active SLE resulted in similar exposure levels compared to adults with active SLE following the approved dosing regimen of 200 mg QW. The similar exposure levels along with the similar pharmacodynamic (PD) response (IgG, Anti-dsDNA antibodies, C3/C4 complement, B cell subsets) supported the proposed dosing regimen.

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) and Division of Pharmacometrics (DPM) have reviewed the data and modeling and simulation results included in this sBLA submission and recommend for approval. The Division Signatory agrees with this assessment and recommendations.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Benlysta (belimumab) is a human IgG1λ monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

In children 5 to 17 years old with active SLE, the PK of belimumab were estimated based on a population pharmacokinetic model developed from 78 pediatric patients with active SLE in Study 200908 and Study BEL 114055/C1109 (See section 15.3.3, Table 28). With the proposed belimumab SC dosing regimen in cSLE, the simulated belimumab exposures (i.e., AUCss, Cmax,ss, and Cmin,ss) for both the < 40kg group and the ≥ 40 kg group were generally comparable to the PK exposures in adult SLE patients treated with belimumab SC, supporting the efficacy extrapolation from adults with active SLE to pediatric subjects with SLE.

With the proposed belimumab SC dosing regimen in cSLE, the simulated belimumab AUC for both the < 40kg group and the ≥ 40 kg group were comparable to the AUC with IV administration in pediatric SLE patients of the same age/weight group, and the simulated belimumab Cmax with the SC administration is lower compared to the approved IV dosing regimen in pediatric SLE. Therefore, the findings of safety in the cSLE program with the approved belimumab IV dosing regimen are relevant and supportive of the safety of belimumab SC in cSLE patients 5 years and older.

Safety events related to SC administration, such as injection site reaction, were assessed in Study 200908. See section 8 for more details. None of the pediatric subjects in study 200908 were found to have transient or persistently positive anti-belimumab immunogenic response during Part A or B of the study.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

In pediatric patients 5 years and older with active SLE:

- weighing greater than or equal to 40 kg: 200 mg once weekly
- weighing 15 to less than 40 kg: 200 mg once every 2 weeks

Therapeutic Individualization

None.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The pharmacokinetics of belimumab following subcutaneous administration in children 5 years and older with active systemic lupus erythematosus (SLE) were characterized in Study 200908. Study 200908 was a multi-center, open-label trial to evaluate the pharmacokinetics, safety, and pharmacodynamics of subcutaneously administered belimumab plus standard therapy in pediatric participants with SLE. The study included:

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

Belimumab 200 mg SC was administered as shown in Table 2 below:

Table 2 Studied dosing regimen in Study 200908

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

A total of 28 participants were screened and 25 were enrolled to the study. All 25 (100.0%) enrolled participants completed the study through Week 12 (Part A) and 23 of 25 (92.0%) completed the study through Week 52 (Part B). 13 children were enrolled in Cohort 1 (≥50 kg; 52.0%) and 12 children were enrolled in Cohort 2 (≥30 kg to <50 kg; 48.0%); no participants were included in Cohort 3 (<30kg). Demographics at baseline and SLE medication usage at baseline are summarized in **Table 3** below.

Table 3 Demographics and SLE Medication Usage at Baseline (ITT Population)

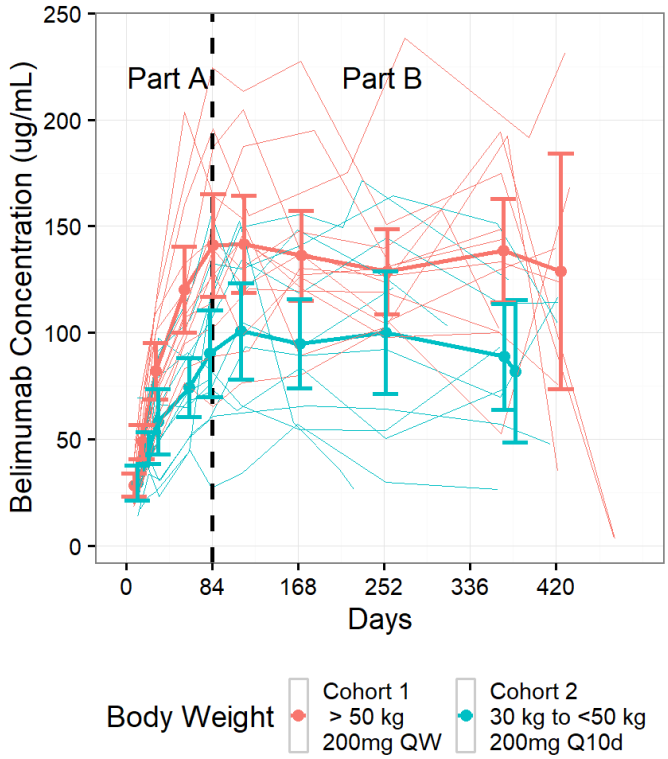
	Number (%) of Participants Belimumab 200mg (N=25)
Country	
Argentina	4 (16.0)
Germany	4 (16.0)
Japan	2 (8.0)
Mexico	3 (12.0)
Netherlands	2 (8.0)
Spain	6 (24.0)
United States	4 (16.0)
Sex	
n	25
Female	21 (84.0)
Male	4 (16.0)
Age at Screening (years)[a]	
n	25
Mean	14.0
SD	2.09
Median	14.0
25th percentile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

	Number (%) of Participants Belimumab 200mg (N=25)
Baseline Body Weight Cohort[b]	
Cohort 1 (>=50kg)	13 (52.0)
Cohort 2 (>=30kg - <50kg)	12 (48.0)
Cohort 3 (<30kg)	0
Average daily Prednisone 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

Source: Table 6 in Clinical Study Report 200908

The observed trough concentrations are depicted in Figure 2.

Figure 2 Observed trough concentration (mean with 90% confidence interval) time profiles in Study 200908



In Part A – Cohort 1 (body weight >50 kg at baseline), samples were collected for assessment of PK pre-dose on Days 8, 15, 29, 57, 85 (i.e., Week 12), and at the 8-week follow-up visit (in case a participant selected not to continue in Part B optional extension phase).

In Part A – Cohort 2 (body weight ≥30 kg to <50 kg at baseline), samples were collected for assessment of PK pre-dose on Days 11, 21, 31, 61, 81 (i.e., Week 12), and at the 8- week follow-up visit (in case a participant selected not to continue in Part B optional extension phase).
In Part B (all Cohorts), samples were collected for assessment of PK pre-dose on Days 113 (Wk 16), 169 (Wk 24), 253 (Wk 36), 365 (Wk 52), and at the 8-week follow-up visit
Source: reviewer's analysis based on adpc.xpt

The PD of belimumab were characterized in children 5 years and older with active SLE in Study 200908. The PD endpoints include IgG, Anti-dsDNA antibodies, C3/C4 complement, B cell subsets. PD responses were consistent with previous experience in adults and children with SLE. The time profiles of these PD endpoints are depicted in Figure 6 to Figure 10 in Section 15.3 OCP Appendices.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

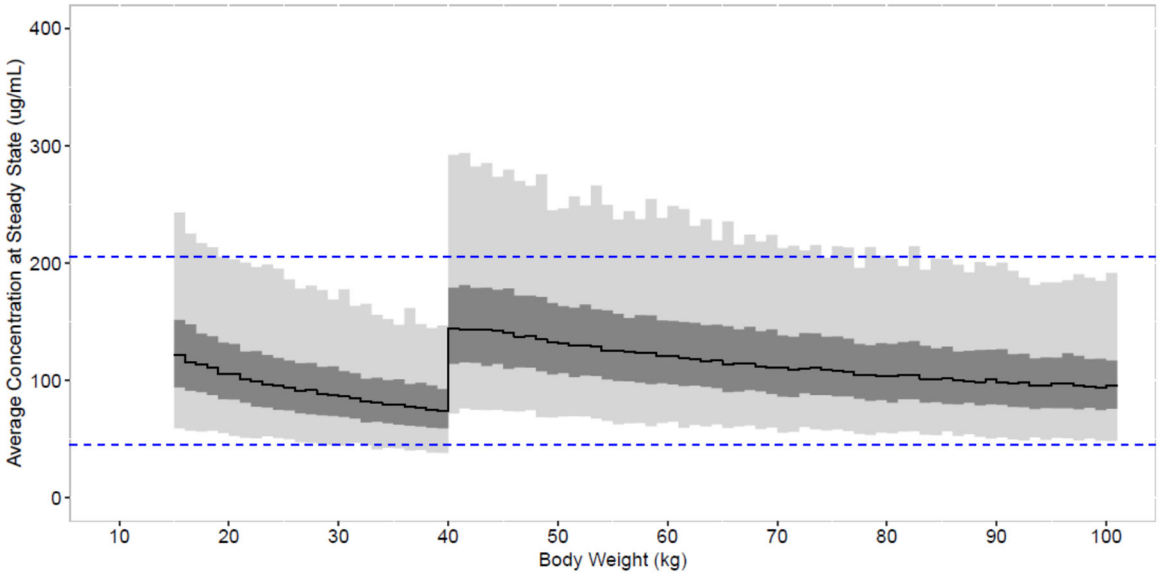
The Applicant proposed the following dosing regimen in children 5 to 17 years old (Table 4):

Table 4 Proposed subcutaneous dosing regimen in children 5 to 17 years old with SLE

Body weight at baseline (kg)	Dosing regimen
≥40	200 mg Every week (QW)
≥15 to <40	200 mg Every 2 weeks (Q2W)

The proposed dosing regimen were based on PopPK modeling and simulation for exposure matching. The Applicant's simulated steady state belimumab average concentration (Cavg) are depicted in **Figure 3**. The proposed dosing regimen resulted in a Cavg that was similar to the Cavg in adults with SLE following the approved dosing regimen of 200 mg QW.

Figure 3 Simulated average concentration at steady state versus body weight for the 2-weight band SC regimen with 40 kg threshold



Average concentrations at steady state for SC in pediatric patients 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).
Source: CPMR, Figure 25A

Model simulations predict steady-state exposures (geometric mean) for Cmin, Cavg, Cmax and AUC for the proposed 2-weight band SC regimen and 10 mg/kg IV Q4W in a pediatric population, and 200 mg SC QW in adults (Table 5). In this Applicant's analysis, equal number of children were simulated across the weight range. However, the prevalence of SLE in younger children with low bodyweight (e.g., 5 to 8 years old) is much lower than older children. Therefore, this reviewer conducted an independent analysis.

Table 5 Simulated Exposure Distribution for the 2-Weight Band Pediatric SC Exposures Compared to Pediatric IV and Adult SC Exposures

	Belimumab Exposures at Steady State Geometric mean (CV%) [95% Prediction Interval]		
	Cmin (µg/mL)	**Cavg (µg/mL)**	**Cmax (µg/mL)**
Pediatric SC ≥40 kg 200 mg SC QW	119 (38.6%) [56.8 - 246]	129 (36.8%) [63.4 – 256]	134 (35.9%) [66.7 – 263]
Pediatric SC 15 kg to <40 kg 200 mg SC Q2W	73.7 (44.6%) [31.8 – 172]	94.8 (37.8%) [47.6 – 198]	110 (34.8%) [58.0 – 217]
Pediatric IV 10 mg/kg IV Q4W	46.8 (78.6%) [10.3 – 157]	101 (42.7%) [45.4 – 226]	301 (31.2%) [167 – 547]

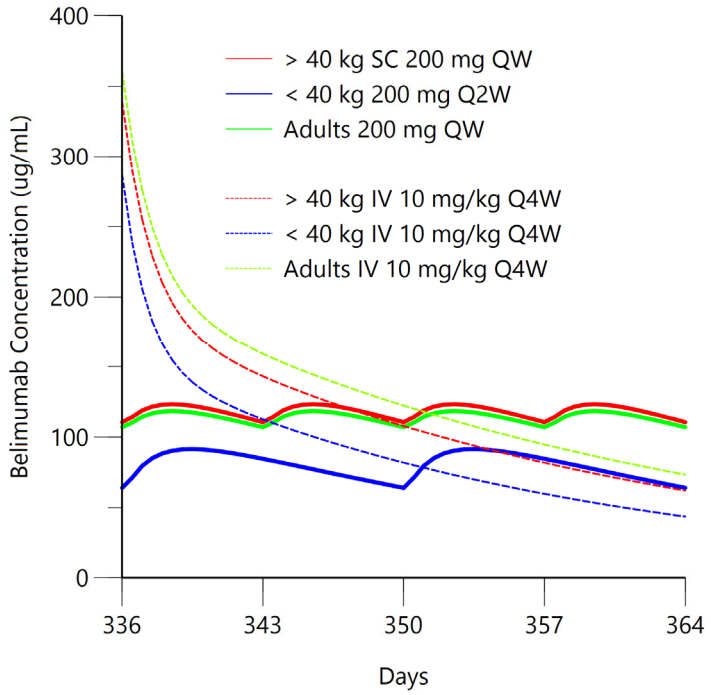
Adult SC (BEL112341) 200 mg SC QW	95.1 (41.0%) [40.2 – 194]	102 (39.2%) [45.1 – 205]	106 (38.4%) [48.1 – 213]

Source: Modified from CPMR, Table 8.1. and PopPK/PD report RA001550188 Table 4-13

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). Cmin and Cmax are different between the pediatric IV and adult and pediatric SC simulations due to the larger peak- trough ratio of the IV PK profile.

Steady state concentration time profiles following IV or SC administration were simulated by the reviewer for a typical adult subject with average bodyweight (68.9 kg) and IgG (15.5 g/L) observed in Study BEL112341 and pediatric subjects with average bodyweight (57.5 kg for the ≥40 kg group, and 32.7 kg for the <40 kg group) and IgG (14.7 g/L for the ≥40 kg group, and 14.3 g/L for the <40 kg group) observed in Studies 200908 and BEL114055/C1109. The simulated concentration time profiles are depicted in Figure 4, and the corresponding PK parameters are listed in Table 6.

Figure 4 Concentration time profiles in a typical subject



Source: Reviewer's analysis

Table 6 Simulate PK Parameters following different subcutaneous and intravenous administration dosing regimens in a typical subject

Route of Administration	PK Parameters	≥ 40 kg 200 mg QW	< 40 kg 200 mg Q2W	Adults 200 mg QW
Subcutaneous Administration	AUC_{ss} (ug.day/mL)[#]	3317	2246	2934
	$C_{max,ss}$ (ug/mL)	123	92	109
	$C_{min,ss}$ (ug/mL)	111	64	98
		≥ 40 kg 10 mg/kg Q4W	< 40 kg 10 mg/kg Q4W	Adults 10 mg/kg Q4W
Intravenous Administration	AUC_{ss} (ug.day/mL) [#]	3391	2611	3594
	C0 (ug/mL)	339	287	355
	$C_{min,ss}$ (ug/mL)	62	44	67

[#] for 4 weeks
Source: reviewer's analysis

The proposed SC dosing regimen of 200 mg QW in children ≥ 40 kg had similar exposure levels (i.e., AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$) compared to adults following the SC administration of the approve dosing regimen 200 mg QW. AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$ of the proposed dosing regimen of 200 mg Q2W in children < 40 kg were 24%, 16%, and 35% lower than adults. The slightly differences in PK parameters are considered not clinically meaningful taking consideration of the known dose response relationship in adults with active SLE. Following IV administration of 1 mg/kg, 4 mg/kg, and 10 mg/kg Q4W, the SELENA SLEDAI percent change from baseline at Week 24 were -23%, -11.3%, and -23.7%, respectively (Study LBSL02 A Phase 2, multi-center, randomized, placebo-controlled trial). Following SC administration of 100 mg Q2W (with a Cmax of 19.9 ug/mL and Cmin of 15 ug/mL) and 3 times a week (with a Cavg of 114 ug/mL), SLENEA SLEDAI percent change form baseline at Week 24 were -40% and -36.7%, respectively, and PGA percent change from baseline at Week 24 were-38.2% and -30.9%, respectively. (Study BEL112232 A Phase 2, multi-center, randomized, open label trial). These Phase 2 dose ranging studies across wide ranges of belimumab exposure levels suggested that belimumab dose response relationship is flat at the approved dosing regimen. The flat exposure response in adult patients with active SLE indicates the efficacy is unlikely to be impacted in a meaningful way in children <40kg with 30% lower exposure. Overall, with the proposed belimumab SC dosing regimen, the simulated belimumab exposures for both the < 40kg group and the ≥ 40 kg group were generally comparable to that of adults patients treated with belimumab SC, supporting the efficacy extrapolation from adults with active SLE to pediatric subjects with SLE.

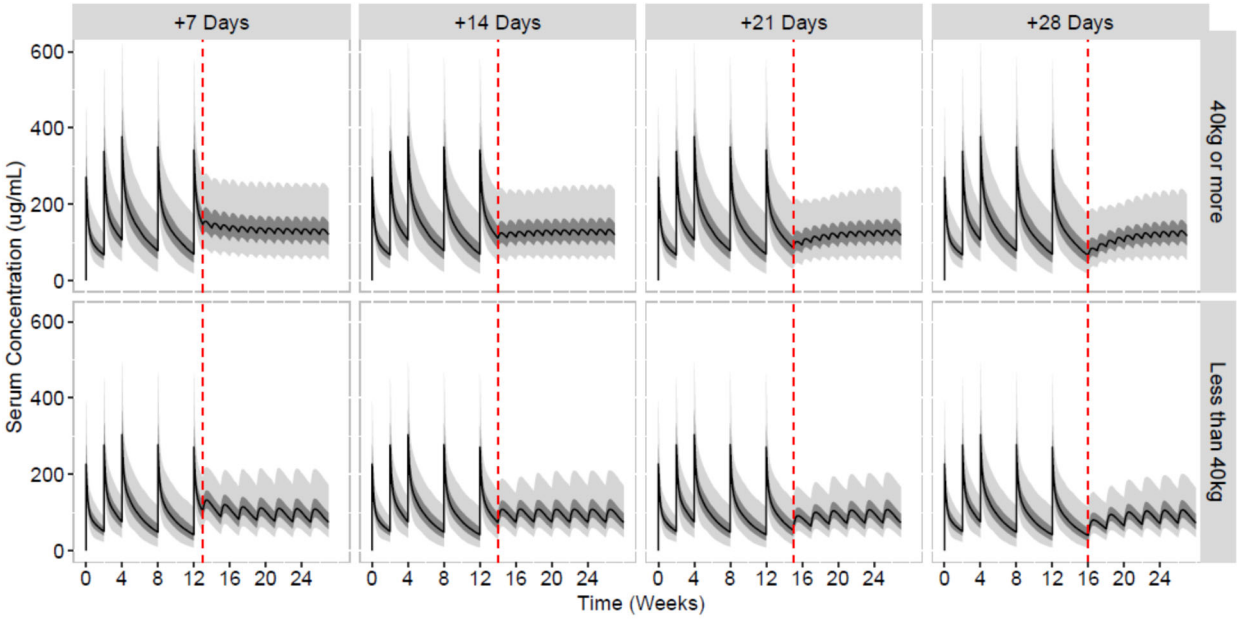
With the proposed belimumab SC dosing regimen, the simulated belimumab AUC for both the < 40kg group and the ≥ 40 kg group were comparable to the AUC with IV administration in pediatric SLE patients of the same age/weight group, and the simulated Cmax with the SC administration is lower compared to the approved IV dosing regimen in pediatric SLE. Therefore, the findings of safety in the cSLE program with the approved belimumab IV dosing regimen are relevant and supportive of the safety of SC belimumab in cSLE patients 5 years and older.

For patients 30-50kg, the proposed dosing regimen (Table 4) was different from what was studied in Study 200908 (Table 2). Specifically, for patients with body weight of 40-50kg, the dosing regimen in Study 200908 was 200 mg Q10D, and the proposed dosing regimen is 200 mg QW. For patients with body weight of 30-40 kg, the dosing regimen in Study 200908 was 200 mg Q10D, and the proposed dosing regimen is 200 mg Q2W. The sponsor proposed that "weekly or every 2 week dosing schedule that is considered 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." As the efficacy is based on PK matching with the proposed SC dosing regimen in pediatric and adult patients, and not based on efficacy findings in the open-label Study 200908, the change of dosing regimen does not affect the conclusion of efficacy in these pediatric patients. As the systemic safety is primarily based on comparable belimumab exposure between IV dosing regimen and the proposed SC dosing regimen in pediatric patients of the same age group, and the leverage of the safety findings in the larger placebo controlled pediatric IV study (Study BEL114055/C1109), the change of dosing regimen does not affect the conclusion of systemic safety in these patients. For local safety related to SC administration, as the proposed dosing regimen only differs in dosing interval, and the to-be-marketed Benlysta SC AI was used in Study 200908 across all age/weight groups, the change of dosing interval does not affect the conclusion on local safety in these patients. Overall, the data support the efficacy/safety of the proposed dosing regimen in patients with body weight of 30-50kg.

Is the proposed dosing regimen for the switch of administration route from IV to SC reasonable?

Yes. The Applicant proposed a dosing regimen for pediatric patients switched from IV administration to SC administration. A pediatric patient with active SLE may transition from intravenous therapy with BENLYSTA to subcutaneous therapy. If transitioning, administer the first subcutaneous dose 1 to 4 weeks after the last intravenous dose. The simulated concentration time profiles and average concentrations are presented in Figure 5 below. The proposed transiting approach is consistent with the approved approach in adults with active SLE. The reviewer found the proposed dosing regimen for switch of route of administration reasonable.

Figure 5 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-subject variability.
Source: CPMR, Figure 15

What is the incidence (rate) of the formation of the anti-drug antibodies (ADA)?

None of the pediatric subjects in study 200908 were found to have transient or persistently positive anti-belimumab immunogenic response during Part A or B of the study. See Section 8.2 for details.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

As part of the approval action on July 20, 2017 for BLA 761043 Benlysta® (belimumab) subcutaneous (SC) formulation as a treatment for adult patients with active systemic lupus erythematosus (SLE), the Agency required PREA PMR 3239-01 as follows:

> "Conduct a pharmacokinetic and safety study of subcutaneous belimumab in patients with active systemic lupus erythematotosus ages 5 to <18 years of age"

In fulfillment of PREA PMR 3239-01 and in support of expanding the indication for belimumab SC to include the treatment of children 5 to 17 years of age with active SLE who are receiving standard therapy, the Applicant submitted the results from a bridging PK/PD and safety study (200908) conducted in pediatric subjects with SLE, along with cross-referenced efficacy, safety and PK/PD data from the phase 2 study BEL114055/C1109 conducted in children 5 to 17 years of age with active SLE and the phase 3 study BEL114054/C1115 conducted in adults with active SLE reviewed previously in support of the marketing approval for the pediatric and adult SLE indications for belimumab's IV and SC formulations, respectively, as well as supportive efficacy, safety and PK data from the pivotal, phase 3 studies, BEL110751/C1056 and BEL110752/C1057, conducted in adults with active SLE that were reviewed previously in support of the original marketing approval for belimumab IV. The key design features of these clinical trials are summarized in **Table 7** below.

Table 7. Key Design Features of Controlled Studies in Adults and Children with SLE

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Study in Children to Support Safety								
BEL114055/ C1109	NCT-0164 9765	Phase 2, MC, R, DB, PC, parallel group pediatric study (Part A) with a long-term OL safety follow-up for subjects who completed Part A (Part B); and long-term safety follow-up (Part C) for subjects who with-drew any time from Part A or B (Part C ongoing)	Belimumab 10 mg/kg or Placebo intravenous infusions on Days 0, 14, 28 and every 4 weeks thereafter	SRI Response at Week 52 defined as the proportion of patients with: ≥ 4-point reduction from baseline in SELENA SLEDAI score **AND** no worsening (Increase of < 0.30 points from baseline in PGA) **AND** no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline) **AND** subject does not drop out before Week 52 **AND** does not meet treatment failure criteria	Screening and randomization visits with visits on Days 0, 14, 28 and then every 28 days until Week 52. Subjects who completed Part A had the option of entering OL safety extension Part B. Subjects who no longer continued study drug treatment In Parts A or B were followed up for long term safety in Part C.	N=93; n=13 subjects 5-11 years old; n=80 subjects 12-17 years old	Pediatric subjects ≥ 5 to 17 yo with SLE as defined by ACR criteria that is active as per SELENA SLEDAI disease activity score ≥ 6 at screening with + auto-antibodies on stable SLE treatment regimen for ≥ 30 days prior to Day 0. Individuals with severe active LN or CNS lupus were prohibited	Total of 29 sites in 10 countries (Argentina, Canada, Japan, Mexico, Peru, Poland, Russian Federation, Spain, United Kingdom, and United States)
Controlled Study in Adults to Support Efficacy and Safety								

BEL112341/ C1115	NCT01484496	Phase 3, multicenter, randomized, double-blind, placebo-controlled, 52-week comparative parallel group trial	Belimumab 200 mg or Placebo via weekly SC injection All subjects received concomitant SLE standard therapy	SRI Response at Week 52 defined as the proportion of patients with: ≥ 4-point reduction from baseline n SELENA/SLEDASI score AND no worsening (increase of <0.3 points from baseline in PGA) AND no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline) AND subject does not drop out before Week 52 AND does not meet treatment failure criteria	Screening and randomization visits with visits on Days 0, 14, 28 and then every 28 days until Week 52	N=836 Belimumab 200 mg SC = 556 subjects Placebo SC = 280 subjects	Adults age ≥ 18 years with SLE as defined by ACR criteria that is clinically active as per SELENA SLEDAI disease activity score ≥ 4 at screening, with positive auto-antibodies on stable SLE treatment regimen for ≥ 30 days prior to Day 0. Individuals with severe active lupus nephritis or CNS lupus were prohibited	67 sites North America, 53 sites Europe, 25 sites Latin America, and 34 sites Asia
Supportive Controlled Efficacy and Safety Studies in Adults								
BEL110751/ C1056	NCT-00410384	P3, MC, R, DB, PC 76-week comparative parallel group trial	Belimumab 1 mg/kg, 10 mg/kg or Placebo intravenous infusions on Days 0, 14, 28 and every 4 weeks thereafter	SRI Response at Week 52 defined as the proportion of patients with: ≥ 4-point reduction from baseline in SELENA SLEDAI score **AND** no worsening (increase of < 0.30	Screening and randomization visits with visits on Days 0, 14, 28	N=819 BEL 1mg/kg =	Adults age ≥ 18 years with SLE defined by ACR criteria that is clinically active as	65 sites North America, 62 sites Europe and 9 sites Latin America

				points from baseline in PGA) **AND** no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline) **AND** subject does not drop out before Week 52 **AND** does not meet treatment failure criteria	and then every 28 days until Week 52.	271 subjects BEL 10mg/kg = 273 subjects Placebo = 275 subjects	per SELENA SLEDAI disease activity score ≥ 6 at screening, with + auto-antibodies on stable SLE treatment regimen for ≥ 30 days prior to Day 0. Individuals with severe active LN or CNS lupus were prohibited	
BEL110752/ C1057	NCT-0042 4476	P3, MC, R, DB, PC 76-week comparative parallel group trial	Belimumab 1 mg/kg, 10 mg/kg or Placebo intravenous infusions on Days 0, 14, 28 and every 4 weeks thereafter	SRI Response at Week 52 defined as the proportion of patients with: ≥ 4-point reduction from baseline in SELENA SLEDAI score **AND** no worsening (increase of < 0.30 points from baseline in PGA) **AND** no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline) **AND** subject does not drop out before Week 52 **AND** does not meet treatment failure criteria	Screening and randomization visits with visits on Days 0, 14, 28 and then every 28 days until Week 52.	N=865 BEL 1mg/kg = 288 subjects BEL 10mg/kg = 290 subjects PBO = 287 subjects	Same as Study HGS1006/ C1056	41 sites Asian Pacific, 40 sites Latin America and 11 sites Europe
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								

200908	N/A	Phase 2, single arm, MC, OL trial (Parts A and B)	Repeat doses of 200 mg belimumab SC via autoinjector	Primary PK endpoints: belimumab concentrations at Wk 12; Cavg (AUC), Cmax, Cmin) Secondary endpoints: Safety - Incidence of AEs, SAEs, and AESIs; Biomarkers – Change from baseline in C3, C4, anti-dsDNA, B cell subsets and Immunoglobulins Exploratory endpoints: Percent of subjects with a ≥ 4 point reduction from baseline in SELENA SLEDAI at Weeks 12 and 52	Part A: Screening and study visits at Week 0, 1, 2, 4, 8 and 12 Subjects who completed Part A had option of entering 40-Week OL safety extension Part B. Subjects who completed Part B and lived in countries where the IV formulation is not approved for pediatric use or in whom IV belimumab was not suitable due to medical reasons or significant logistic reasons could enroll in the optional access extension phase	N=25 Cohort 1 (≥50 kg) = 13 Cohort 2 (≥30 kg - ≤50 kg) = 12 Cohort 3 (<30 kg) = 0	Pediatric subjects ages 5 to 17 years of age and weighing ≥ 15 kg with active SLE with a SELENA SLEDAI score ≥ 6 at screening	Total of 11 sites in 7 countries (Argenta, Germany, Japan, Mexico, Netherlands, Spain, and United States)

MC= multicenter; R= randomized; DB= double-blind; PC=placebo-controlled; HDCS= high dose corticosteroids; CYC= cyclophosphamide; AZA= azathioprine; MMF= mycophenolate mofetil; OL= open label; OLE= open label extension; uPCR=urine protein to creatinine ratio; eGFR =estimated glomerular filtration rate; ↑=increasing; SOC=standard of care; sCr=serum creatinine; ESRD=end stage renal disease; yo=years old; + = positive; LN= lupus nephritis; CNS= central nervous system; PBO=placebo

7.2. Review Strategy

There were no randomized, placebo-controlled, efficacy studies of belimumab SC conducted in children with active SLE submitted in support of this application. As permitted under 21 CFR 314.55 and per the agreed Pediatric Study Plan (PsP), an assessment of belimumab SC treatment in children aged 5 to less than 18 years old with active SLE was conducted via extrapolation approach from existing efficacy, safety and PK data in children and adults with SLE treated with belimumab IV and SC, respectively. As the efficacy data from the phase 2, randomized, double-blind, placebo controlled study BEL114055/C1109 conducted in children 5 years to 17 years old with active SLE in the unireview dated April 26, 2019, in support of the marketing approval of belimumab IV's pediatric indication for SLE, and the efficacy data from the pivotal, phase 3, randomized, double-blind, placebo-controlled study BEL112341/HGS1006C115 conducted in adults with active SLE receiving standard of care was previously reviewed in support of the marketing approval for belimumab SC 's adult indication for SLE in the clinical review dated June 20, 2017, these data will not be re-presented here as the efficacy of belimumab IV and SC in children and adults with active SLE, respectively, has been previously established. Safety data collected from the 25 pediatric subjects with SLE who participated in the 52-week, phase 2, open-label, bridging PK/PD and safety study 200908 conducted with belimumab SC, will be presented, and discussed in Section 8.2 in support of the SC formulation's safety profile in the pediatric population.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Because efficacy in pediatric SLE is extrapolated from the efficacy established in pediatric SLE with the IV formulation of belimumab and adult patients with SLE with the SC formulation of belimumab, as detailed elsewhere in this review, no new efficacy studies in pediatric SLE were required/submitted with this application.

8.2. Review of Safety

8.2.1. Safety Review Approach

The comparable exposures of the IV and SC formulations of belimumab in pediatric patients supports leveraging of the established safety of belimumab IV in the pediatric population from the following study:

- Study BEL114055/C1109 which was a phase 2, 52-week, randomized, double-blind, placebo-controlled study conducted with belimumab IV in 109 pediatric subjects with active SLE despite standard of care therapy

This application also contained supportive safety data collected from 25 pediatric patients with active SLE (defined as a SELENA SLEDAI score $\geq$ 6 at baseline) despite standard therapy who were administered 200 mg of belimumab subcutaneously via AI while participating in the PK bridging and safety study 200908. This was a 52-week, phase 2, single arm, multicenter, open-label, PK/PD, and safety study conducted in two parts:

- Part A was a 12-week treatment phase that evaluated the PK/PD and safety of 200 mg of belimumab administered subcutaneously via autoinjector in pediatric subjects between 5 to 17 years old weighing >15 kgs. The dosing frequency of belimumab was based on weight bands at baseline as follows:
  - Cohort 1 (N=13) – comprised of subjects weighing $\geq$ 50 kg received a SC injection every week (QW)
  - Cohort 2 (N=12) – comprise of subjects weighing $\geq$ 30 to <50 kg received a SC injection every 10 days (Q10d)
  - Cohort 3 (N=0) – comprised of subjects weighing $\geq$ 15 to <30 kg received a SC injection every 2 weeks (Q2W)
- Part B was an optional 40-week, open-label continuation phase that was open to all subjects who completed Part A. Subjects who participated in Part B either continued receiving belimumab SC via the same dosing regimen or the frequency of the dosing regimen was changed to accommodate changes in subjects' body weight.

Upon completion of Parts A and B, all subjects underwent post- treatment follow-up assessments at 8 and 16 weeks after receiving their last dose of belimumab. Subjects who had completed Part B of the study and were from countries where belimumab IV was not approved

for pediatric use or in whom belimumab IV was not suitable due to medical reason or significant logistical challenges, had the option of continuing to receive belimumab SC in an ongoing post-Week 52 optional access extension phase (AEP). Since study 20908 was an uncontrolled trial, safety data collected from its completed Parts A and B will be presented and discussed in the following subsections as supportive data of the safety profile of belimumab SC in the pediatric SLE population.

Other supportive safety data for belimumab SC contained in this application that have not been previously reviewed are as follows:

- A summary of postmarketing safety reports in pediatric patients collected by the Applicant in their postmarketing safety surveillance database during the time period from Mary 9, 2022 through March 8, 2023
- Data contained in the 120-day safety update:
    - Interim cumulative safety data from the ongoing optional 40-week AEP of study 200908 post submission cut-off date of April 13, 2023 for the time period from April 14, 2023 through July 31, 2023
    - Interim cumulative safety data comprised of adverse events, serious adverse events and adverse events of special interest including deaths collected since the cut-off date of November 1, 2021 through July 31, 2023 from the ongoing Part B (the 10-year, open-label, belimumab treatment continuation phase) and ongoing Part C (the 10-year, safety follow-up phase without belimumab treatment) of the pediatric SLE study BEL114055
    - Updated postmarketing reports for the use of IV and SC belimumab in pediatric subjects during the time period from March 9, 2023 through July 31, 2023
    - Updated postmarketing reports for any new pregnancies or pregnancy outcomes in pediatric subjects from the time period of March 9, 2023 through July 31, 2023

The Applicant also crossed referenced high level safety analyses from the following pivotal studies previously reviewed in support of the adult SLE indications for the SC and IV formulations of belimumab:

- Study BEL112341/C1115 which was the pivotal phase 3, 52-week, randomized, double-blind, placebo-controlled study conducted with the belimumab SC formulation administered as a 200 mg SC injection once weekly in adults with active SLE despite standard of care therapy
- The pivotal phase 3 studies that were concluded with belimumab IV in adults with active SLE receiving standard of care therapy:
    - BEL110751/C1056 which was a 52-week, randomized, double-blind, placebo-controlled trial
    - BEL110752/C1057 which was a 76-week, randomized, double-blind, placebo-controlled trial

As the safety data from the four pivotal studies (BEL114055/C1109, BEL112341/C1115, BEL110751/C1056, BEL110752/C1057) have been previously reviewed in support of the

marketing approval of belimumab IV for adults and children with active SLE and belimumab SC for adults with active SLE (BLA 125370, BLA123570/s-064, and BLA 761043, respectively), data from these studies will not be re-presented here as the safety of belimumab IV as treatment for children and adults with active SLE and the safety of belimumab SC as a treatment for adults with active SLE have been previously established, but are only considered where pertinent in the discussion that follows. The remaining new safety data, which are included in pertinent sections of the following discussion, were examined by this clinical reviewer for any new or unexpected safety signals associated with the administration of belimumab SC in pediatric patients.

8.2.2. Review of the Safety Database

Overall Exposure

The cumulative duration of pediatric exposure to belimumab SC at the 200 mg dose in the completed Parts A and B of study 200908 is shown Table 8. The mean (SD) number of SC injections of belimumab was 42.8 (10.0).

Table 8. Exposure to Belimumab SC in Parts A and B of Study 200908

	Number (%) of Subjects			
	Cohort 1 (≥50 kg) N=13	**Cohort 2 (≥30 kg to <50 kg) N=12**	**Cohort 3 (<30kg) N=0**	**Total N=25**
Total Number of Injections[1]				
1-12	0	0	0	0
13-24	0	1 (8%)	0	2 (4%)
25- 36	0	5 (42%)	0	5 (20%)
37-51	6(46%)	6 (50%)	0	12 (48%)
>51	7 (54%)	0	0	7 (28%)
Mean (SD)	51.2 (2.23)	33.8 (6.59)	0	42.8 (10.0)
Median	52.0	36.5)	0	46.0
Duration of Exposure (days)[2]				
Mean (SD)	366.7	348.1	0	357.8
Median (Min, Max)	366.0	370.0	0	370.0

[1]Total number of injections where dose was given. Note: Dosing frequency is as follows: Cohort 1 = weekly dosing; Cohort 2 + every 10 days, Cohort 3 = every 2 weeks.
[2]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 completed dates are used when calculating duration of exposure. Firs and last injection dates are used, regardless of any missed doses.
Source: Applicant's Table 1.20; p. 115-116 CSR.

Adequacy of the safety database:

Since the safety profile of belimumab IV has been previously established based on safety data from 109 pediatric subjects with cSLE who participated in the belimumab IV study BEL114055/C1109, the size of the safety database for this submission when coupled with the safety database from the supportive, open-label, PK bridging study 200908 in 25 pediatric SLE subjects who received belimumab SC while participating in study 200908, is adequate to provide sufficient basis of belimumab SC's safety for the pediatric SLE population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data quality submitted was well-organized and adequate to perform an updated review of safety in the pediatric population.

Categorization of Adverse Events

Verbatim terms of AEs and Disease Related Events (DRE) recorded in the case report forms (CRF) by investigators were coded by the Applicant using MedDRA dictionary Preferred Term (PT), High-Level Term (HLT), and System Organ Class (SOC) version 25.1. The MedDRA coding of the information generated from study 200908 conducted by the Applicant was generally acceptable. Additionally, the clinical lab and vital sign ranges for clinically significant abnormal results were reviewed and appeared to be appropriate.

Routine Clinical Tests

The following clinical and lab testing were conducted in study 200908 in support of belimumab SC's safety profile in the pediatric population:

- Symptom driven physical exam, height, and weight
- Vital signs: systolic and diastolic blood pressure, respiratory rate, and temperature
- Complete cell count (CBC) with differential and platelet count, hemoglobulin and hematocrit
- PT/PTT (baseline only)
- Serum chemistries
- Urinalysis
- Spot urine for protein to creatinine
- Pregnancy testing
- Hepatitis B and C, HIV testing (baseline only)
- 12-lead ECG (baseline only)
- Serum Immunoglobulins (IgG, IgM, and IgA), autoantibodies (ANA and anti-dsDNA), serum complement (C3 and C4)
- BLyS protein and immunogenicity
- FACS of peripheral B cells

Overall, the types of clinical lab testing and physical assessments as well as the timing of these assessments were appropriate for the pediatric population studies in this trial and are the same as those employed in the adult belimumab SC and pediatric IV studies (refer to reviews of BLA 761043 dated June 20, 2017; and sBLA 125370/s-064 dated April 26, 2019, for additional information).

8.2.4. **Safety Results**

All safety analyses were performed on the population who received at least one dose of study medication (the Intention-to-Treat [ITT] population) in the pivotal adult and pediatric belimumab studies as well as in the pediatric SC bridging study 2000908. Table 9

Table 9 summarizes the adverse events (AEs) that were reported in the safety database for the 52-week, open-label, pediatric SC study 2000908 (completed Parts A and B) as well as the previously reviewed safety data from the adult phase 3 belimumab SC study BEL112341/C1115, the pediatric belimumab IV study BEL14055/C1109, and the pooled adult belimumab IV studies BEL110751/C1056 and BEL110752/C1057. Most subjects experienced at least one AE while participating in these trials. Except for slightly higher rate of infections (72%) observed in the open-label, PK bridging study 2000908, the overall safety profile of belimumab SC pediatric subjects appears to be similar to what has been observed in the pediatric IV belimumab study as well as the both the adult SC and IV belimumab studies. No deaths or malignancies were reported in pediatric subjects while participating in study 2000908, which is consistent with what was observed in the pediatric belimumab IV study BEL14055/C1109. An in-depth examination of the safety data reported in study 2000908 follows below.

Table 9. Summary of Adverse Events and Deaths in the Controlled Portions of the Pivotal Belimumab Studies: Adult SC Study BEL112341/C115, Pediatric IV Study BEL114055/C1109, the Pooled Adult IV Studies BEL110751/C1056 and BEL110752/C1057, and the Pediatric Open-Label SC PK Bridging Study 200908

Number of Subjects with at Least One	Adult SC Study BEL112341/C1115		Pediatric IV Study BEL114055/C1109		Pooled Adult IV Studies BEL110751/C1056 and BEL110752/C1057		OL Pediatric SC PK Bridging Study 200908
	PBO N=280	BEL SC N=556	PBO N=40	BEL 10mg/kg N=53	PBO N=675	BEL 10 mg/kg N=674	BEL SC N=25
Any AE	236 (84%)	449 (81%)	33 (83%)	42 (79%)	623 (92%)	625 (93%)	22 (88%)
Any SAE	44 (16%)	60 (11%)	14 (35%)	9 (17%)	103 (15%)	113 (17%)	1 (4%)
Any Infection	159 (57%)	308 (55%)	28 (70%)	30 (57%)	450 (67%)	471 (70%)	18 (72%)
Any Serious Infection	15 (5%)	23 (4%)	5 (13%)	4 (8%)	35 (5%)	35 (5%)	1 (4%)
Any Malignancy	1 (0.4%)	2 (0.4%)	0	0	3 (0.4%)	3 (0.4%)	0
Any AE Leading to D/C	25 (9%)	40 (7%)	5 (13%)	3 (6%)	48 (7%)	42 (6%)	1 (4%)
Deaths	2 (0.7%)	3 (0.5%)	1 (2.5%)	0	3 (0.4%)	6 (0.9%)	0

Sources: Applicant's Table 7; p. 24 Summary of Clinical Safety; Tables 35 and from the FDA Clinical Review for BLA 125370 dated February 18, 2011, and BLA 761043 dated June 20, 2017, respectively

Deaths

As shown in Table 9 above, there were no deaths reported during the completed portions (Parts A and B) of study 200908. As of the 120-day safety cut-off date of July 31, 2023, there were no deaths reported in the ongoing optional 40-week AEP of study 200908 for the time period from April 14, 2023 through July 31, 2023.

Serious Adverse Events

Table 10 lists the one serious adverse event (SAE) that occurred during Parts A and B of study 200908. This SAE involved an 11-year-old female subject (Subject Number (b) (6)) with SLE who was hospitalized on Day 294 status post first dose of belimumab with fever, musculoskeletal pain, cough, shortness of breath, sore throat, nausea, fatigue, and loss of appetite. This patient was subsequently found to have a positive SARs-COV-2-RNA test and was treated with oxygen, dexamethasone, gentamycin, defuroxime, granisetron, fentanyl, morphine, paracetamol, and diclofenac for a Grade 1 COVID-19 infection. According to the case narrative for this SAE, corticosteroids were initiated and increased due to a possible SLE exacerbation (elevated C-reactive protein) in combination with pulmonary involvement by COVID-19. Although the patient's oxygen saturation levels were within normal limits, oxygen was initiated for comfort. This patient recovered from her COVID-19 infection ten days later without sequalae.

According to the 120-day safety update, no new SAEs have been reported in study 200908's ongoing 40-week AEP.

Table 10. Serious Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class (SOC)/Preferred Term (PT) During Completed Parts A and B of Study 2000908 (ITT Population)

MedDRA System Organ Class/Preferred Term	Belimumab 200 mg N=25
Number of Subjects (%) Who Experienced Any SAE	1 (4%)
Infections and infestations	1 (4%)
COVID-19	1 (4%)

Source: Applicant's Table 3.04; p. 185 of Clinical Study Report for Study 200908.

Overall, the proportion of SAEs observed in the pediatric belimumab SC study 200908 was lower than what was observed in the pediatric belimumab IV and adult SC studies (see Table 9 above) which may be due to study 200908's small sample size. It is not surprising that there was a SAE related to COVID-19 in the study's safety database given that study 200908 was conducted during the COVID pandemic and the majority (72%) of the pediatric subjects who participated in the study were taking concomitant immunosuppressive therapies in addition to belimumab that increased the risk for serious infections.

Dropouts and/or Discontinuations Due to Adverse Effects

A summary of adverse events by MedDRA system organ class (SOC) and preferred term (PT) that resulted in patients discontinuing treatment during study 200908 is shown in Table 11. Further examination of the data in Table 11

Table 11 revealed that all three adverse events (lymphocyte count decreased, neutrophil count decreased, and white blood cell count decreased) occurred on approximately study Day 162 in a 16-year-old Japanese female (Subject Number (b) (6)) taking concomitant hydroxychloroquine and MMF. According to the case narrative, this patient had a Grade 2 lymphocyte count, Grade 2 leukocyte count, and Grade 1 neutrophil count at screening prior to entering the study. These adverse events resolved without sequalae following discontinuation of her concomitant MMF while continuing commercial belimumab following her withdrawal from the study. Cytopenias are not an unexpected finding since both SLE and belimumab (a lymphocyte modulating agent) can affect the hematological system and have been observed in other studies previously reviewed in support of belimumab as a treatment for SLE.

Table 11. Treatment Emergent Adverse Events (TEAEs) Leading to Discontinuation of Randomized Study Medication by MedDRA System Organ Class (SOC)/Preferred Term (PT) During the Completed Parts A and B of Study 200908 (ITT Population)

MedDRA System Organ Class/Preferred Term	Belimumab 200 mg N=25
Number of Subjects (%) With ≥ 1AE Leading to Discontinuation	1 (4%)
Investigations	1 (4%)
Lymphocyte count decreased	1 (4%)
Neutrophil count decreased	1 (4%)
White blood cell count decreased	1 (45)

Source: Applicant's Table 3.05; p. 186 of Clinical Study Report for Study 200908.

Significant Adverse Events

There were no severe adverse events in subjects who participated in Parts A and B of study 200908.

Treatment Emergent Adverse Events

Most pediatric subjects experienced a treatment emergent adverse event (TEAE) while participating in Part A and B of study 200908. Table 12 lists the frequency of the TEAEs observed in this study by MedDRA SOC. Infections and infestations, general disorders and administration site conditions, blood and lymphatic system disorders, investigations, and skin and subcutaneous tissue disorders were the most common TEAEs observed. Overall, the types and incidences of common adverse events were consistent with what would be expected for patients with active SLE who had been exposed to immunosuppressive therapies and received an injectable medication. A higher proportion of pediatric subjects in study 200908 experienced infections and infestations (72%) as compared to pediatric subjects in the belimumab IV study BEL114055/C1109 and the adult belimumab SC study BEL112341/C1115 (see Table 9 above). Infections and infestations will be discussed further with the adverse events of special interest (AESIs) section later in this review.

Table 12. Common Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class (SOC)/Preferred Term (PT) During the Completed Parts A and B of Study 200908 (ITT Population)

MedDRA System Organ Class	Belimumab 200 mg N=25
Number of Subjects (%) Who Experienced Any TEAE	22 (88%)
Infections and infestations	18 (72%)
General disorders and administration site conditions	8 (32%)
Blood and lymphatic system disorders	7 (28%)
Investigations	5 (20%)
Skin and subcutaneous tissue disorders	5 (20%)
Eye disorders	4 (16%)
Gastrointestinal disorders	4 (16%)
Injury, poisoning and procedural complications	4 (16%)
Musculoskeletal and connective tissue disorders	4 (16%)
Ear and labyrinth disorders	2 (8%)
Immune system disorders	2 (8%)
Renal and urinary disorders	2 (8%)
Reproductive system and breast disorders	2 (8%)
Cardiac disorders	1 (4%)
Metabolism and nutrition disorders	1 (4%)
Nervous system disorders	1 (4%)
Vascular disorders	1 (4%)

Source: Applicant's Table 3.02; p. 176-180 Clinical Study Report for Study 200908.

Table 13 lists common adverse events by preferred terms reported by 2 or more pediatric subjects while participating in Parts A and B of study 200908. The TEAEs most commonly reported in this study were COVID-19, injection site pain, leukopenia, neutropenia, lymphopenia, nasopharyngitis, upper respiratory tract infection, anemia, erythema, and injection site pain. No new or unexpected safety issues were identified on review of these data but the incidences for injection site pain (16%), leukopenia (16%), neutropenia (16%), lymphopenia (12%), erythema (8%), injection site erythema (8%), neutrophil count decreased (8%), urine protein/creatinine ratio increased (8%), viral infection (8%), and white blood cell count decreased (8%) were all higher in study 200908 as compared to what was observed in the previously reviewed belimumab studies in support of the adult and pediatric SLE indications (refer to the clinical reviews for BLA 125370 belimumab IV dated February 18, 2011; BLA 761043 belimumab SC dated June 20, 2017; and BLA 124370/s-064 belimumab IV for pediatric SLE dated April 26, 2019.).

Since belimumab is a lymphocyte modulating agent, cytopenias associated with its use are not unexpected and have been observed in other belimumab studies. According to information in the application, 7 subjects in the study accounted for the various decreases in white blood cell counts (Subject Numbers: (b) (6)). One of these subjects (Subject (b) (6)) had various cytopenias at study entry and was taking concomitant MMF which is known to cause cytopenias. This patient was subsequently withdrawn from the study (see preceding section on Dropouts/Discontinuations due to Adverse Events for more information). Of the remaining 6 patients, 3 reportedly had mild infections in proximity to their decreased white blood cell counts that resolved within approximately 1 week. Three out of these 6 subjects also had their belimumab dosing interrupted for one week due to other adverse events (2 subjects due to Covid-19 infection and 1 subject due to transient neutropenia). The various cytopenias reportedly resolved in 5 out of these 6 subjects despite continued exposure to belimumab over the course of the study.

The high incidence of COVID-19 infections is also not unexpected since this trial was conducted during the pandemic. Review of the literature suggest that patients with SLE have a higher risk of infection with COVID-19 due to their dysregulated immune system and concomitant use of corticosteroids and other immunosuppressive agents.[20, 21]

Hematology findings and injection site reactions will be discussed further with the laboratory findings and adverse events of special interest (AESIs), respectively.

[20] Patil A, et al. Lupus 2023;32(4):560-564.
[21] Bruera S, et al. Lupus Science and Medicine 2023; 10:e000750, doi:10.1136/Lupus-2022-000750.

Table 13. Summary of Common Treatment Emergent Adverse Events by MedDRA Preferred Term (PR) Occurring in ≥ 2 Subjects in Completed Parts A and B of Study 200908 (ITT Population)

MedDRA Preferred Term	Belimumab 200 mg N=25
COVID-19	9 (36%)
Injection site pain	4 (16%)
Leukopenia	4 (16%)
Neutropenia	4 (16%)
Lymphopenia	3 (12%)
Nasopharyngitis	3 (12%)
Upper respiratory tract infection	3 (12%)
Anemia	2 (8%)
Erythema	2 (8%)
Injection site erythema	2 (8%)
Myalgia	2 (8%)
Neutrophil count decreased	2 (8%)
Urine protein/creatinine ratio increased	2 (8%)
Viral infection	2 (8%)
White blood cell count decreased	2 (8%)

Source: Applicant's Table 3.03; p. 182-184.

Laboratory Findings

Laboratory data from the pediatric SLE subjects who participated in study 200908 were presented as follows: serial changes from baseline at each study visit, serial shifts from baseline to final visit, and worst grade observed. The Applicant provided normal ranges of values for each normal lab parameter assessed. These were reviewed and the clinically acceptable range for normal appeared appropriate.

a. Hematology

Since belimumab is a lymphocyte modulating agent and SLE can also affect the hematological system (e.g., hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia, etc…) and there were reports of cytopenias in the study, the hematological lab data results were examined for possible signs of toxicity. As shown in Table 14, no clinically relevant mean changes from baseline were noted in any of the hematological parameters at the Week 52 visit.

Table 14. Mean Change Over Baseline in Hematology Parameters During Completed Parts A and B of Study 200908 (ITT Population)

Hematological Parameter	Belimumab SC 200 mg N=25	
	Baseline	Week 52
Hematocrit (%)		
N	25	17
Mean (SD)	38.5 (4.15)	38.4 (5.54)
(Min, Max)	(29.8, 50.9)	(29.9, 51.2)
Hemoglobulin (g/L)		
N	25	17
Mean (SD)	126.4 (12.73)	125.2 (15.29)
(Min, Max)	(101, 166)	(102, 160)
Leukocytes (10^9/L)		
N	25	17
Mean (SD)	5.52 (1.72)	5.09 (1.48)
(Min, Max)	(3.4, 8.5)	(3.0, 8.5)
Basophils (10^9/L)		
N	25	17
Mean (SD)	0.034 (0.026)	0.63 (0.295)
(Min, Max)	(0.00, 0.12)	(0.1, 1.1)
Eosinophils (10^9/L)		
N	25	17
Mean (SD)	1.72 (2.00)	0.126 (0.142)
(Min, Max)	(0.2, 8.2)	(0.2, 0.58)
Lymphocytes (10^9/L)		
N	25	17
Mean (SD)	1.55 (0.77)	1.46 90.55)
(Min, Max)	(0.25, 3.03)	(0.74, 2.24)
Monocytes (10^9/L)		
N	25	17
Mean (SD)	0.36 (0.19)	0.35 (0.12)
(Min, Max)	(0.09, 0.95)	(0.09, 0.58)
Neutrophils (10^9/L)		
N	25	17
Mean (SD)	3.48 (1.51)	3.12 (1.27)
(Min, Max)	(1.71, 6.96)	(1.26, 6.11)
Platelets (10^9/L)		
N	25	16
Mean (SD)	285 (79.0)	272 (80.9)
(Min, Max)	(165, 499)	(149, 482)

Source: Modified Applicant's Table 3.18; p. 207-327.

Table 15 lists the hematological parameters that had Grade 3 or 4 values reported post baseline over the course of study 200908. Three subjects had Grade 3 lymphopenia while participating in the study which reportedly resolved without treatment. One of these three subjects (Subject Number (b) (6)) had a Grade 2 lymphocyte count as well as a Grade 2 leukocyte count and a Grade 1 neutrophil count at screening prior to entering the study. This subject was

subsequently withdrawn from the study as a result of these persistent cytopenias that her treating investigator attributed to the concomitant immunosuppressive agent (MMF) the subject was taking. Of the remaining 2 subjects, one subject (Subject Number (b) (6)) had Grade 3 lymphopenia at baseline that reportedly fluctuated between a Grade 2 and Grade 3 throughout the study. The remaining subject (Subject Number (b) (6)), had a Grade 2 lymphopenia at baseline which increased to Grade 3 at Week 8, but deceased to Grade 2 by Week 12 before normalizing by Week 36.

Table 15. Summary of Hematology Parameters by Worst Toxicity Grade During Completed Parts A and B of Study 200908 (ITT Population)

Hematology Parameter Worst Toxicity Grade	Belimumab SC 200 mg N=25
Lymphocytes (10^9/L)	25
Grade 3	3 (12%)
Grade 4	0

Source: Modified Applicant's Table 3.22; p. 454-455.

For completeness, the Applicant also supplied analyses for reference range shifts from baseline and worsening of toxicities at least 2 Grades from baseline for hematological parameters for study 200908 (Table 16). The incidences for any $\geq$ 2 grade shifts in lymphocytes and neutrophils were higher in study 200908 than what was observed in the pediatric belimumab IV study BEL112341/C1109. Since study 200908 was uncontrolled, it is impossible to determine if these cytopenias were due to worsening of underlying SLE disease or additive toxicity due to belimumab and concomitant immunosuppressive agents such as MMF and azathioprine which can also cause cytopenias.

Table 16. Summary of Subjects with Worsening of at Least 2 Grades from Baseline During Completed Parts A and B of Study 200908 (ITT Population)

Hematology Parameter $\geq$2 Grade Shift on Study	Belimumab SC 200 mg N=25
Hemoglobulin (g/L)	25
Any $\geq$ 2 grade shift	1 (4%)
Grade 0 to 2	1 (4%)
Leukocytes (10^9/L)	25
Any $\geq$ 2 grade shift	1 (4%)
Grade 0 to 2	1 (4%)
Lymphocytes (10^9/L)	25
Any $\geq$ 2 grade shift	5 (20%)
Grade 0 to 2	5 (20%)
Neutrophils (10^9/L)	25
Any $\geq$ 2 grade shift	5 (20%)
Grade 0 to 2	5 (20%)

Source: Modified Applicant's Table 3.28; 465-466.

b. Chemistry

Since SLE can affect the renal system and cause an autoimmune hepatitis, test results of renal and hepatic function were also examined (Table 17). Mean liver and renal function parameter values appeared to remain stable over the course of the study treatment. For completeness, mean serum electrolyte values were also reviewed and were found to be generally similar and without clinically meaningful patterns of change (data not shown).

Table 17. Mean Changes Over Baseline in Liver and Renal Function Parameters During Parts A and B of Study 200908 (ITT Population)

Chemistry Parameter	Belimumab SC 200 mg N=25	
	Baseline	Week 52
Alkaline phosphatase (U/L)		
N	25	21
Mean (SD)	102 (57.9)	110 (77.1)
(Min, Max)	(37, 236)	(34, 331)
ALT/SGPT (U/L)		
N	25	21
Mean (SD)	16.4 (13.6)	15.1 (14.1)
(Min, Max)	(5, 60)	(5, 74)
AST/SGOT (U/L)		
N	25	21
Mean (SD)	20 (7.3)	20 (9.6)
(Min, Max)	(7, 45)	(12, 58)
GGTP (U/L)		
N	25	21
Mean (SD)	12.8 (6.41)	12.7 (5.25)
(Min, Max)	(5, 30)	(8, 29)
Bilirubin (µmol/L)		
N	25	21
Mean (SD)	5.2 (2.4)	6.4 (3.5)
(Min, Max)	(2, 12)	(2, 16)
Albumin (g/L)		
N	25	21
Mean (SD)	44 (2.9)	46 (3.0)
(Min, Max)	(38, 49)	(40, 51)
BUN/creatine ratio		
N	25	21
Mean (SD)	79.9 (29.9)	69.0 (20.5)
(Min, Max)	(36.1, 161)	(32.1, 105.1)
BUN (mmol/L)		
N	25	21
Mean (SD)	4.04 (1.14)	4.14 (1.72)
(Min, Max)	(2.18, 6.21)	(1.39, 9.14)
Creatinine (µmol/L)		
N	25	21

Mean (SD)	53 (14)	63 (35)
(Min, Max)	(29, 30)	(36, 202)
eGFR (ml/sec/1.73 m^3)		
N	25	21
Mean (SD)	1.92 (0.38)	1.80 (0.52)
(Min, Max)	(1.07, 3.33)	(0.50, 2.73)
Protein (g/L)		
N	25	21
Mean (SD)	69.6 (6.01)	68.9 (4.08)
(Min, Max)	(59, 82)	(61, 74)

Source: Modified Applicant's Tables 3.19 and 3.20; p. 328-453.

The Applicant also supplied analyses for reference range shifts from baseline and toxicity grades for both liver and renal function as well as serum electrolyte parameters for study 200908 (Table 18). One subject (Subject Number (b) (6)) had Grade 4 hyperkalemia while participating in the study. According to information contained in the application, this subject's potassium level was normal at baseline, but she developed Grade 4 hyperkalemia at Week 30 which returned to normal without treatment by Week 36 while continuing to receive belimumab.

Table 18. Summary of Serum Chemistry Parameters by Worst Toxicity Grade During Completed Parts A and B of Study 200908 (ITT Population)

Chemistry Parameter Worst Toxicity Grade	Belimumab SC 200 mg N=25
Hyperkalemia (mmol/L)	25
Grade 3	0
Grade 4	1 (4%)

Source: Modified Applicant's Table 3.24; p. 458-460.

Table 19 summarizes the abnormal analyses for reference range shifts from baseline and worsening of toxicities at least 2 Grades from baseline for liver, renal, and electrolyte parameters for study 200908. Review of these data did not identify any clinically meaningful patterns of change.

Table 19. Summary of Subjects with Worsening of at Least 2 Grades from Baseline in Chemistry Parameters During Parts A and B of Study 200908 (ITT Population)

Chemistry Parameter ≥2 Grade Shift on Study	Belimumab SC 200 mg N=25
Hyperkalemia (mmol/L)	25
	1 (4%)
	1 (4%)
Creatinine (µmol/L)	25
Any ≥ 2 grade shift	1 (4%)
Grade 0 to 2	1 (4%)
Hypoglycemia (mmol/L)	25
Any ≥ 2 grade shift	3 (12%)
Grade 0 to 2	3 (12%)

Source: Modified Applicant's Tables 3.30 and 3.31; p. 469-473.

c. Urinalysis

Although the protocol for study 200908 prohibited the enrolment of pediatric patients with severe lupus nephritis, some of the participating pediatric patients had disease activity in this organ system. Urinalysis was done via dipstick at each study visit along with collection of spot urines for assessment of protein/creatinine ratio. Protein/Creatinine ratio was the only urinalysis parameter for which any pediatric subject had either a Grade 3 or 4 postbaseline (Table 20). According to information contained in this application, both subjects who had Grade 3 protein/creatinine ratios during the study were receiving concomitant treatment for lupus nephritis.

Table 20. Urinalysis Parameter Worst Toxicity Grade During Parts A and B of Study 200908 (ITT Population)

Urinalysis Parameter Worst Toxicity Grade	Belimumab SC 200 mg N=25
Protein/Creatinine (mg/mg)	25
Grade 3	2 (8%)
Grade 4	0

Source: Modified Applicant's Table 3.26; p. 463.

A summary of the analyses for reference range shifts from baseline in urinalysis parameters are shown in Table 21. Because some of the pediatric subjects who participated in study 200908 had underlying lupus nephritis, it is unclear if the worsening grade shifts in urinary protein and protein/creatinine ratios summarized in Table 21 were due to the worsening of pre-existing renal involvement and/or new renal disease as a result of a lack of response to belimumab.

Table 21. Summary of Pediatric Subjects with Worsening of at Least 2 Grades from Baseline in Urinalysis Parameters During Parts A and B of Study 200908 (ITT Population)

Urinalysis Parameter ≥2 Grade Shift on Study	Belimumab SC 200 mg N=25
Erythrocytes	24
Any ≥ 2 grade shift	3 (13%)
Grade 0 to 2	3 (13%)
Protein (dipstick)	24
Any ≥ 2 grade shift	6 (24%)
Grade 0 to 2	6 (24%)
Protein/Creatinine (mg/mg)	25
Any ≥ 2 grade shift	1 (4%)
Grade 0 to 3	1 (4%)

Source: Modified Applicant's Table 3.32; p. 474.

d. Immunoglobulins

Since the administration of belimumab can cause hypogammaglobulinemia, the Applicant also submitted the results from analyses for reference range shifts from baseline and toxicity grades for serum immunoglobulin levels. Although no pediatric subject in study 200908 had a post baseline Grade 3 or 4 value for serum IgG, 2 subjects had worsening of at least 2 grades from baseline in their serum IgG levels while participating in this study (Table 22) which is consistent with what was observed in the pediatric belimumab IV study BEL114055/C1109 (refer to sBLA 125370/s-064 dated April 26, 2019).

Table 22. Summary of Pediatric Subjects with Worsening of at Least 2 Grades from Baseline in Serum Immunoglobulins During Parts A and B of Study 200908 (ITT Population)

Immunoglobulin Parameter ≥2 Grade Shift on Study	Belimumab SC 200 mg N=25
Immunoglobulin G (g/L)	25
Any ≥ 2 grade shift	2 (8%)
Grade 0 to 2	2 (8%)

Source: Modified Applicant's Table 3.33; . 475.

Vital Signs

According to the protocol for study 200908, subjects underwent measurement of sitting blood pressure (BP), pulse and oral temperature at each visit, but assessment of respiratory rate was not required. Review of the mean changes from baseline by visit for systolic and diastolic BP, pulse, and oral temperature for study 200908 failed to identify any clinically relevant safety issues associated with belimumab SC in pediatric patients (data not shown).

Immunogenicity

None of the pediatric subjects in study 200908 were found to have transient or persistently positive anti-belimumab immunogenic response during Part A or B of the study. This is consistent with what was observed in the pediatric IV study BEL114055/C1109 and similar to what was observed in the adult SC study BEL112341/C1115 and the adult IV studies BEL110751/C1056 and BEL110752/C1057 (refer to BLA 125370/s-064 belimumab IV for pediatric SLE dated April 26, 209; BLA 761043 belimumab SC dated June 20, 2017; and BLA 125370 belimumab IV dated February 18, 2011).

8.2.5. Analysis of Submission-Specific Safety Issues

In support of belimumab SC's safety profile in the pediatric population, the Applicant also submitted analyses of adverse events of interest (AESI) that included deaths, infections, including opportunistic infections, injection site reactions, hypersensitivity reactions including anaphylaxis, depression/suicide/self-injury, and malignancy. The results for the analyses for death and malignancy are discussed in Sections 8.2.3 and 8.2.9, respectively, of this safety review. The remaining analyses of AESIs are discussed in the following subsections.

8.2.5.1. Infections

Because of its mechanism of action, belimumab would also be anticipated to increase the risk of infections, including serious infections which were prespecified as AESI. Although there was only one serious infection (COVID-19) reported during study 200908, the overall incidence of non-serious infections was higher in study 200908 (72%) as compared to the pediatric belimumab IV and adult belimumab SC studies (57% and 55%, respectively) (see Table 9). shows that that most common infection experienced by pediatric subjects during Parts A and B of study 200908 was COVID-19, which accounted for half of the infections that occurred during this study. This is not an unexpected finding since the trial was conducted during the pandemic. The remaining infections listed in **Table 23** are not unusual and are consistent with what one would expect in a pediatric population taking concomitant immunosuppressives and are similar to what was observed in the safety database reviewed in support of the IV formulation of belimumab in pediatric subjects with SLE and the (refer to clinical review of BLA 125370/s-064 belimumab IV dated April 26, 2019).

Table 23. Non-Serious Infections by Preferred Term During Parts A and B of Study 200908 (ITT Population)

MedDRA System Organ Class/Preferred Term	Belimumab 200 mg N=25
Infections and infestations	**18 (72%)**
COVID-19	9 (36%)
Nasopharyngitis	3 (12%)
Upper respiratory tract infection	3 (12%)
Viral infection	2 (8%)
Conjunctivitis	1 (4%)
Gastroenteritis	1 (4%)
Hordeolum	1 (4%)
Oral herpes	1 (4%)
Otitis media acute	1 (4%)
Paronychia	1 (4%)
Pharyngotonsillitis	1 (4%)
Respiratory tract infection viral	1 (4%)
Rhinitis	1 (4%)
Sinusitis	1 (4%)
Tinea versicolour	1 (4%)
Urinary tract infection	1 (4%)

Source: Applicant's Table 3.02; p. 176.

8.2.5.2. Injection Site Reactions

Because belimumab is a protein that contains foreign sequences, a certain level of localized injection site reactions because of it being administered subcutaneously as well as systemic hypersensitivity spectrum reactions including anaphylaxis would be expected. In the marketing application for the adult indication for the SC formulation of belimumab, the occurrence of injection site reactions was prespecified as an AESI along with hypersensitivity spectrum reactions including anaphylaxis which will be discussed in the next subsection. A total of 8 subjects experienced 17 injection site reactions in study 200908 (**Table 24**). All the localized injection site reaction reactions were mild and non-serious in nature and resolved with the continued administration of belimumab. Since injection site reactions are already listed as an adverse event associated with the administration of belimumab SC in the product's label in adults, no strengthening of the existing information describing their occurrence is warranted based on the data shown in **Table 24**.

Table 24. Summary of Treatment Emergent Injection Site Reactions by MedDRA Preferred Term (PT) During Parts A and B of Study 200908 (ITT Population)

System Organ Class/Preferred Term	Belimumab 200 mg N=25
Number of Subjects (%) With ≥ 1 Injection Site Reaction	8 (32%)
Injection site pain	4 (16%)
Injection site erythema	2 (8%)
Injection site hemorrhage	1 (4%)
Injection site swelling	1 (4%)
Injection site urticaria	1 (4%)

Source: Applicant's Table 103.01; p. 648.

8.2.5.3. Hypersensitivity Spectrum Reactions Including Anaphylaxis

Hypersensitivity spectrum reactions including anaphylaxis were also designated as AESI since the current USPI for belimumab contains Warnings and Precaution statements regarding these types of events. Due to the overlap in symptoms with infusion reactions, hypersensitivity reactions, and anaphylaxis, it is difficult to ensure that these adverse events were adequately captured and classified during the study. Because of this, the Applicant employed various search terms including a MedDRA customized MedDRA query (CMQ) involving broad, narrow, and algorithmic searches for "anaphylactic reactions" as well as the Sampson Criteria[22] preferred by the review division. Cases thus identified were also adjudicated by the Applicant. The results of these various analyses are presented in **Table 25** below.

Table 25. Post-Injection Anaphylaxis/Hypersensitivity Adverse Events During Parts A and B of Study 200908 (ITT Population)

	Belimumab 200 mg N=25
Any post-infusion systemic reaction [a]	3 (12%)
Per anaphylactic reaction CMQ narrow search[a,b]	1(4%)
Per anaphylactic reaction CMQ broad search[a,b]	3 (12%)
Per anaphylactic reaction CMQ algorithmic search[a,b]	1 (4%)
Serious Anaphylaxis per Sampson Criteria	0
Serious acute post-infusion systemic reactions/ hypersensitivity per GSK adjudication[c]	0
Serious acute post-injection syst. react. excluding hypersensitivity per GSK adjudication[c]	0
Serious acute hypersensit. react. per GSK adjud.[c]	0
Serious delayed acute hypersensit. react. per GSK adjudication[c]	0
Serious delayed non-acute hypersensit. react. per GSK adjudication[c]	0

[22] Sampson HA, et al. Allergy Clin Immunol. 2006; 117(2):391-397.

Anaphyl. react.= anaphylactic reaction
Note: Subjects were counted once per category.
Note: Typically: Acute= onset< 1 day; Delayed Acute =Onset 2-3 days; Delayed Non-Acute= Onset 4-21 days. Adjudication primarily uses these windows but may use other clinical factors.
[a] Post-infusion systemic reactions were defined via narrow, broad, or algorithmic search to have occurred on or within 3 days of an infusion date
[b] Per Custom MedDRA query (CMQ v22.0). Preferred terms for broad search included: rash, cough, dyspnea, edema, pruritus, infusion related reaction, erythema, chest discomfort, drug hypersensitivity, hypotension, angioedema, drug eruption, eye pruritus, eyelid edema, face edema, hypersensitivity, sneezing, swelling face, urticaria. Preferred terms for narrow search included: infusion related reaction, drug hypersensitivity, and hypersensitivity. Preferred terms for algorithmic search included: infusion related reaction, drug hypersensitivity, and hypersensitivity.
[c] Per Applicant adjudication

The results from the MedDRA CMQ queries raise concerns regarding their accuracy in capturing and identifying cases of hypersensitivity reactions since the rates of anaphylactic post-injection system reactions for these various searches are higher than the rates observed in the adult SC study BEL112341/C1115 (0% for both belimumab SC and placebo patients) as well as the rates of anaphylaxis observed in the pooled adult SLE belimumab IV studies BEL110751/C1056 and BEL110752/1057 which was low overall (e.g., 0.6% of adult SLE patients who received belimumab IV versus 0.4% placebo patients experienced anaphylaxis). (Refer to clinical reviews of BLA 761043 dated June 20, 2017; and BLA 125370 belimumab IV dated February 18, 2011.) The results from the MedDRA CMQ queries of study 200908's safety database are also unsupported by the results from the search using the Sampson Criteria[23] or the adjudicated searches conducted by the Applicant for hypersensitivity reactions (**Table 25**).

For completeness, the Applicant also submitted the results of an analysis that looked at post injection anaphylactic reactions identified by the MedDRA CMQ broad search during the first six injections of the study 200908 which showed a higher incidence of these types of events occurred following the administration of the first two injections of belimumab that subsequently decreased with continued injections (**Table 26**). Similar to the adult SC and pediatric IV belimumab studies, the majority of the pediatric subjects (72%) who participated in study 200908, were taking concomitant corticosteroids which may have blunted or obscured hypersensitivity responses in this study.

[23] Sampson HA, et al. Allergy Clin Immunol. 2006; 117(2):391-397.

Table 26. Post-Injection Systemic Reactions per Anaphylactic Reactions CMQ Broad Search by Preferred Term, in First Six Injections of Study 200908 (ITT Population)

	Belimumab 200 mg SC – Injection Number						
	1	2	3	4	5	6	All Injections[a]
PISR per Anaphylactic reaction CMQ Broad Search	1 (4%)	1 (4%)	0	0	0	0	3 (12%)
Drug sensitivity	0	0	0	0	0	0	1 (4%)
Erythema	0	0	0	0	0	0	1 (4%)
Injection site urticaria	1 (4%)	1 (4%)	0	0	0	0	1(4%)

[a]Includes all injections through Part A and B of study 200908.
Source: Modified Applicant's Table 3.13; p. 203.

8.2.5.4. Depression, Suicide, and Self-Injury

According to the safety database for 200908 and the 120-day safety update for this application, there were no cases of depression, suicidality or self-injury reported during the completed Parts A and B of the study nor during the ongoing optional 40-week AEP.

8.2.5.5. Malignancy

Because belimumab targets B cells, immunosuppression is an expected effect, and chronic immunosuppression has been associated with an increase in the risk for developing a malignancy. Review of the safety data from the completed portions (Parts A and B) as well as the data from ongoing optional 40-week AEP of study 200908 contained in the 120-day safety update did not identify any cases of malignancy reported by pediatric subjects in this study which is consistent with what was observed in the pediatric belimumab IV study BEL114055/C1109 (see review of BLA 125370/s-064 dated April 26, 2019).

8.2.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Routine pharmacovigilance of belimumab's post marketing safety profile has resulted in the addition of new safety information to the product's label under Section 5 Warnings and Precautions for hypersensitivity reactions including anaphylaxis and the occurrence of PML in SLE patients who received belimumab IV in addition to concomitant immunosuppressive agents.

Review of the index listings and tabulations of postmarketing adverse events by MedDRA SOC contained in the most recent belimumab Periodic Benefit Risk Evaluation Report (PBRER) dated May 17, 2023, which covered the reporting period from March 9, 2022, to March 8, 2023, did not identify any new or unexpected SAEs that needed to be included in belimumab's current

label. According to information contained in the PBRER, the cumulative post marketing exposure to belimumab estimated by the Applicant is 255,082 patient-years based on data through December 31, 2022, out of which 148,815 patient-years were attributed to use of the IV formulation and 76,267 patient-years were attributed to use of the subcutaneous formulation.

Since a review of cumulative postmarketing safety data in the pediatric population collected from the time period from April 26, 2019 to April 8, 2022, had been reviewed in support of BLA 125370/s-078 to broaden the indication for belimumab IV to include children 5 to 17 years old with lupus nephritis, the Applicant submitted an updated review of 145 spontaneous postmarketing safety reports in pediatric patients between the ages 5 to 17 years that had been collected in their postmarketing safety database for belimumab during the time period from March 9, 2022 to March 8, 2023, in support of this current application. Of these 145 spontaneous postmarketing pediatric safety reports, 106 reports were associated with the administration of the IV formulation while the remaining 39 cases were associated with the administration of the SC formulation. The most frequently reported adverse events by MedDRA SOC were attributed to Injury, Poisoning, and Procedural Complications (90 AEs) and Infections and Infestations (33 AEs). The most frequently reported MedDRA PTs under Injury, Poisoning and Procedural Complications were product used in an unapproved therapeutic environment (22 AEs, all non-serious) followed by off-label use (17 AEs, all non-serious) and product use issues (2 AEs). The postmarketing pediatric safety update also included the following AESI: one death due to cardiac arrest, one case report of a suicide attempt, one follow-up case report of suicidal ideation, and one follow-up case report of Hodgkin's lymphoma. There was also one case report from the literature for a pediatric patient who developed Lyell's syndrome (TEN) who had been receiving IV belimumab and recovered from this AE with treatment. Review of the data summarized in the pediatric postmarketing safety update did not reveal any new patterns or safety signals in the pediatric subpopulation.

The 120-day safety update submitted on October 12, 2023, contained an updated search for the period from the cut-off date of March 9, 2023, for the first pediatric postmarketing safety review to July 31, 2023, in which an additional 117 initial or follow-up pediatric case reports comprising a total of 204 adverse events were identified. Of these 117 pediatric case reports, 94 reports were associated with the administration of the IV formulation, 12 reports were associated with the administration of the SC formulation, and 4 reports involved both the IV and SC routes of administration while the route of administration of the remaining 7 cases was unknown. The most frequently reported adverse events by MedDRA SOCs were Injury, Poisoning and Procedural Complications (101 AEs); General Disorders and Administration Site Conditions (25 AEs), Infections and Infestations (11 AEs), and Skin and Subcutaneous Tissue Disorders (11 AEs). Of these 204 AEs reported in pediatric patients, 22 were classified as SAEs. These SAEs include AESI such as herpes zoster, campylobacter gastroenteritis, suicidal ideation, death due to pneumonia, and death due to Hodgkin's lymphoma. The death due to Hodgkin's lymphoma involved an 8-year-old patient treated with IV belimumab for SLE and had been previously reported as a follow-up case report in the original spontaneous postmarketing

pediatric safety review for this application. The current labeling for belimumab contains Warning and Precaution statements regarding the increased risk for serious infections and malignancies to occur in patients receiving belimumab. There was also one SAE case report of leukopenia and neutropenia that involved a 16-year-old female who was receiving treatment with belimumab IV for SLE in addition to monthly pulses of steroids and acetazolamide for intracranial hypertension. According to the limited information regarding this case in the 120-day safety update, the treating pediatric rheumatologist could not tell if the leukopenia and neutropenia were due to an underlying flare of the patient's SLE versus belimumab. Additionally, there were 9 spontaneous postmarketing AE reports involving localized injection site reactions in 7 pediatric patients who had received belimumab via pre-filled pen (n=5), pre-filled syringe (n=1), or via unknown route of administration (n=1). None of these injection site reactions were classified as serious in nature. They included the following: injection site pain (n=6), injection site erythema (n=1), injection site rash (n=1), and injection site swelling (n=1). Four of these patients who reported injection site reactions recovered: two pediatric patients continued SC belimumab, one pediatric patient switch to IV belimumab, and the action undertaken with the remaining patient was not reported. The outcomes for the remaining 3 pediatric subjects with injection site reactions were also not reported or unknown. Injection site reactions are already listed as AEs associated with the administration of belimumab in the product's current labeling.

Expectations on Safety in the Postmarket Setting

The Applicant's postmarketing pediatric safety update suggests that the safety profile of belimumab in the pediatric subpopulation appears to be consistent with that reviewed in support of the IV formulation's pediatric marketing approval. In view of the similar exposure profiles for the IV and SC formulation in children, the safety profile of belimumab SC in children would be expected to be the same as the IV formulation in this subpopulation. No strengthening of the current Warnings and Precautions statements in the product's USPI is indicated.

Currently pending is an FDA recommended post-marketing requirement (PMR 2661-16) for the use of belimumab during pregnancy and an EMA recommended post-marketing AESI registry.

Post-marketing safety data will continue to be assessed through routine pharmacovigilance by OSE's DPV-1.

8.2.7. Integrated Assessment of Safety

No new or unexpected safety signals were identified on review of the safety data from the completed portions (Parts A and B) or from the ongoing AEP of the open-label, PK/PD, and safety study 200908 conducted in pediatric subjects with SLE administered belimumab SC via AI or the updated spontaneous postmarketing safety data in children treated with belimumab. Therefore, no updates of the existing Warnings and Precautions in the current belimumab USPI

are warranted.

As the pediatric belimumab SC safety database does not include safety data from a controlled trial conducted in children with SLE, one of the limitations associated with its review is that it is challenging to draw definitive conclusions regarding the overall safety of belimumab SC in pediatric subjects. Additionally, some of the limitation associated with the safety database from the pediatric belimumab IV study BEL114055/C1109 apply here such as the lack of subjects with central nervous system disease or severe renal lupus, or the inability to perform subpopulation analyses based on race or gender.

For patients enrolled in Study 200908, the minimum weight was 34 kg and the minimum age was 10 year old (**Table 3**). There were no patients with body weight of 15-30kg enrolled in Study 200908. Based on the CDRH review (From Dr. Sreya Tarafdar, DARRT date 4/26/2024), "it is not clear whether one needle size will fit all. Consideration must also be given to factors such as obesity, which may necessitate a longer needle; however, for smaller-sized patients (due to multiple factors) the needle may be too long. Thus, it may be helpful to consider these variables and offer additional needle lengths.". Although the prevalence of cSLE increases with age, it is rarely diagnosed in children 9 years old and younger. Based on the CDC growth chart, the average weight of a 9 year old girl is 28kg. It may not be feasible to enroll enough cSLE patients with a body weight of 15-30kg to explore different needle lengths, and to inform on the local safety of the AI. The IFU of the proposed label stated that "For children less than 10 years of age, BENLYSTA must be given by a healthcare provider or a trained caregiver". This would help to ensure the safe use of the AI in the younger pediatric patients. Overall, the review team concluded that risk/benefit would support the approval of BENLYSTA SC in patients with body weight within the 15-30kg range, and provide an important treatment option for this population with high unmet medical need.

Based on the totality of safety data generated from the pediatric belimumab IV study BEL14055/C1109 and the safety data from the open-label, PK/PD, safety study 200908 that evaluated 200 mg of belimumab SC administered via AI to pediatric subjects between the ages of 5 and 17-years-old, coupled with the updated postmarketing safety review in children administered belimumab, the benefit/risk assessment is favorable for the 200 mg of belimumab SC dosing regimen when administered once weekly via AI in children weighing $\geq$40 kg and administered every 2 weeks via AI in children weighing $\geq$15 kg to <40 kg as add-on therapy for pediatric subjects with active SLE who are receiving standard of care therapy. No additional post-marketing safety studies are warranted based on this submission.

8.3. **Statistical Issues**

Not applicable as no new efficacy or safety data from randomized, controlled trials were included in this application.

8.4. Conclusions and Recommendations

The Applicant proposed a full extrapolation of efficacy and safety established in children and adults with SLE in support of broadening belimumab SC formulation's SLE indication to include children ages 5 to 17-years-old with active SLE on standard of care. Additional supportive safety data comes from the phase 2, open-label, PK-bridging, safety study 200908 conducted in 25 pediatric subjects treated with belimumab 200 mg SC, and an updated review of pharmacovigilance safety data from pediatric patients exposed to belimumab via AI.

The efficacy and safety of belimumab SC is based on PK matching of systemic exposure and extrapolation of established efficacy and safety of belimumab in both pediatric and adult subjects with SLE. As discussed in section 6, the clinical pharmacology review team was able to establish a PK-bridge based on the similarities of serum concentrations of belimumab SC in children and between children and adults treated with belimumab IV and belimumab SC, respectively, at the proposed pediatric dosing regimens of 200 mg once weekly via AI for pediatric subjects weighing $\geq$ 40 kg, and 200 mg once every 2 weeks for pediatric subjects weighing $\geq$ 15 kg to <40 kg when administered via AI. Given that the range of disease manifestations are similar in children and adults with SLE, the establishment of a PK-bridge provided a scientific justification to extrapolate the efficacy and safety of belimumab SC established in children and adults with SLE based on data from adequate and well controlled clinical trials conducted with belimumab IV in children with SLE and with belimumab SC in adults with SLE.

Additional support of safety was provided from the 52-week, phase 2, open-label, PK-bridging, safety study 200908 conducted in 25 pediatric subjects treated with belimumab 200 mg SC, and an updated review of pharmacovigilance safety data from pediatric patients exposed to belimumab between the ages 5 to 17 years collected by the Applicant submitted in support of this application. The safety data from study 200908 coupled with the Applicant's postmarketing pediatric safety update, suggest that the safety profile of belimumab SC in the pediatric SLE population age 5 years and older will be similar to what has been observed with the belimumab IV formulation in pediatric patients. No strengthening of the current Warnings and Precautions statements in the product's USPI is therefore indicated.

The Applicant has provided adequate data and information to inform the benefit-risk assessment of belimumab SC for the treatment of pediatric patients 5 years and older when administered at a proposed dose of 200 mg as a subcutaneous injection once weekly via AI to pediatric subjects weighing $\geq$40 kg, and once every 2 weeks via AI to pediatric patients weighing $\geq$15 kg to <40 kg as add-on therapy for pediatric patients with active SLE who are receiving standard of care. Approval of belimumab SC will provide an additional treatment option for pediatric patients with SLE given the limited number of approved treatment options for this disease in the U.S. Therefore, the review team recommends approval of belimumab SC for the treatment of pediatric patients 5 years and older with active SLE who are receiving standard of care using the proposed weight-based dosing regimen. Additionally, the pediatric clinical

pharmacology, efficacy and safety data submitted to BLA 761043/s-027 are adequate to fulfill the PREA postmarketing requirement (3239-1) as detailed in the Agency letter dated July 20, 2017, related to the approval for BLA 761043 Benlysta® (belimumab) subcutaneous (SC) formulation.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not held for this pediatric PMR efficacy supplement. No issues were identified warranting advisory committee input.

10 Pediatrics

The Agreed Pediatric Study Plan (iPSP) for SC belimumab was previously issued on May 15, 2015, and included an agreement for a partial waiver of pediatric studies in pediatric lupus nephritis patients < 5 years of age and a deferral in pediatric lupus nephritis patients >5 to less than 18 years of age. The results and review findings for this pediatric PMR supplement were presented and discussed at the April 2, 2024, meeting of PeRC who concurred with the review team's recommendation to expand the subcutaneous formulation of belimumab's current indication for the AI presentation to include pediatric patients 5 years and older with active, SLE who are receiving standard therapy based on the data reviewed in this application.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The following is a high-level summary for the product's label changes based on review of the data submitted in support of this application:

1.) On the Highlights page:
   a. Under Recent Major Changes: addition of "Dosage and Administration (2.1, 2.3)" and deletion of "Warnings and Precautions, Concomitant Use with Other Biologic Therapies (5.6)"
   b. Under Indications and Usage, bullet points edited to read as follows:
      - patients 5 years of age and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy
      - patients 5 years of age and older with active lupus nephritis who are receiving standard therapy
   c. Addition of new indication under Dosage and Administration as follows:
      "Subcutaneous Dosage for Pediatric Patients with SLE:
      - weighing greater than or equal to 40 kg: 200 mg once weekly (2.3)
      - weighing 15 to less than 40 kg: 200 mg once every 2 weeks (2.3)"
   d. Index for Full Prescribing Information Contents edited to read: "2.3 Recommended Subcutaneous Dosage"

Under Full Prescribing Information

2.) Under Section 1 Indication and Usage
   a. Bullet points edited to read:
      "-patients 5 years and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy"
      "-patients 5 years and older with active lupus nephritis who are receiving standard therapy"

3.) Under Section 2.1. Important Administration Information
   a. First sentence edited to read: "BENLYSTA may be administered intravenously or subcutaneously [see Dosage and Administration (2.2, 2.3)]" and original sentence deleted.

4.) Under Section 2.3 Recommended Subcutaneous Dosage
   a. The old prescribing information regarding SC administration was deleted and the following new SC dosing information and Table 1 was added:

      "The recommended dosages of BENLYSTA, when administered subcutaneously, are provided in Table 1. When administered subcutaneously, BENLYSTA should be administered in the patient's abdomen or thigh. For patients less than 10 years of age, BENLYSTA must be administered by a healthcare professional or trained caregiver."

Table 1. Recommended Subcutaneous Dosage of BENLYSTA

	Adults[a] (Autoinjector or prefilled syringe)	**Pediatric Patients (5 to less than 18 Years of Age)[a] (Autoinjector**
SLE	200 mg once weekly	Patients>40kg: 200 mg once weekly Patients 15 to <40 kg: 200 mg once **every 2 weeks**
Lupus Nephritis	400 mg[b] once weekly x 4 doses, followed by 200mg once weekly	Safety and efficacy of subcutaneous administration have not been established

[a]Autoinjector only. Note: The prefilled syringe has not been studied in children less than 18 year of age.
[b]The 400-mg dose is recommended for adult patients initiating therapy with BENLYSTA for active lupus nephritis and requires administration of 2 autoinjectors or 2 prefilled syringes.

"Transitioning form Intravenous to Subcutaneous Administration

SLE: Administer the first subcutaneous dose 1 to 4 weeks after the last intravenous dose.

Lupus Nephritis: A patient with lupus nephritis may transition from intravenous therapy with BENLYSTA to subcutaneous therapy ~~any time~~ after the patient completes the first 2 intravenous doses. If transitioning, administer the first subcutaneous dose of 200 mg 1 to 2 weeks after the last intravenous dose."

d. With the addition of the new Table 1 above, the numbering of all subsequent tables and their associated references were updated.
e. Under the subheader "Administration Instructions for Subcutaneous Injection", the following changes were made:

- Under Step 3, Step 5, and Step 6: Added "patient caregiver" to these instruction steps.
- Under Step 6: added to the end of the sentence "or the same day of alternate weeks, as appropriate."
- Under Step 7: deleted "weekly" from the sentence.

5.) Under Section 6.1 Clinical Trials Experience
   a. The subheader has been edited as follows: "Clinical Trials with Intravenous Administration"
   b. Under the subheader "Black/African-American Patients," "adults' was added to clarify the population studied.
6.) Under Section 8.1 Pregnancy
   a. Under the subheader "Data," "area under the curve" and "Immunoglobulin G" were spelled out next to their abbreviations.

b. Under the subheader "Intravenous Use," (b) (4) "intravenous" was added for clarification.
c. Under the subheader "Subcutaneous Use," the following information was deleted: "The safety and effectiveness of subcutaneous administration of BENLYSTA have not been established in pediatric patients younger than 18 years of age."
d. Under the subheader "Subcutaneous Use," the following new information was added:
"Use of BENLYSTA, administered subcutaneously in pediatric patients (5 to less than 18 years of age and weighing at least 15 kg) with SLE, is supported by evidence from on open-label pharmacokinetic trial (subcutaneous administration of BENLYSTA in pediatric patients with SLE) and Trial 6 (a pharmacokinetic, efficacy, and safety study of intravenous dosing in pediatric patients with SLE). The pharmacokinetics of belimumab, following subcutaneous administration in pediatric patients, are estimated to be similar to adults who receive BENLYSTA subcutaneously and pediatric patients who receive BENLYSTA intravenously *[see Clinical Pharmacology (12.3)].*
The safety and effectiveness of the subcutaneous administration of BENLYSTA, in pediatric patients less than 18 years of age with active lupus nephritis, have not been established."
e. Under the subheader "Subcutaneous Use," the following sentence was edited to read: "The safety and effectiveness of BENLYSTA have not been established in pediatric patients less than 5 years of age."

7.) Under Section 8.5 Geriatric Use
a. The sentence was edited to read "…subjects, 65 years of age…"

8.) Under Section 12.3 Pharmacokinetics
a. Under the subheader "Specific Populations," under the subsection Pediatric Patients, "…after intravenous administration…" was added to the description of the PK parameters of belimumab in Trial 6.
b. Under the subheader "Specific Populations," under the subsection "Pediatric Patients," the following new information was added after the first paragraph:
"The pharmacokinetic parameters of belimumab, following subcutaneous administration, are based on population pharmacokinetic analysis derived from 25 pediatric patients with SLE who received BENLYSTA subcutaneously and Trail 6 (a phase II study in pediatric patients with SLE receiving BENLYSTA intravenously). Following subcutaneous administration of 200 mg of BENLYSTA in pediatric patients 5 to less than 18 years of age, either weekly (patients weighing > 40 kg) or every 2 weeks (patients weighing 15 to <40 kg), the steady state average belimumab concentration is estimated to be similar to that of adult subjects with SLE following subcutaneous administration of 200 mg weekly and similar to that of pediatric subjects with SLE following

intravenous administration of 10 mg/kg BENLYSTA on Days 0, 14, and 28, and at 4-week intervals thereafter. Simulated steady-state geometric mean Cmax and AUC are estimated to be 110 mcg/mL and 1,328 day.mcg/mL; for pediatric patients (weighing 15 to <40 kg) receiving BENLYSTA every 2 weeks and 134 mcg/mL and 899 day.mcg/ml for pediatric patients (weighing >40 kg) receiving BENLYSTA once weekly. *[See Use in Specific Population (8.4)].”*

c. Under the subheader “Specific Populations,” under the subsection “Pediatric Patients,” “…following intravenous administration…” was added to the first sentence of the third paragraph.
d. Under the subheader “Specific Populations,” under the subsection “Weight,” the following sentence was edited to read: “No dose adjustment is recommended in adults based on weight or BMI for subcutaneous administration.”
e. Under the subheader “Specific Populations,” under the subsection “Weight,” the following paragraph was added:

“The effects of body weight on belimumab exposure, after subcutaneous administration in pediatric patients, have been determined using a population pharmacokinetic model. Pediatric patients with lower body weight have lower belimumab clearance and volume of distribution. To ensure belimumab exposures remain within acceptable limits and are consistent across the pediatric weight range, patients with lower body weight are given BENLYSTA less frequently. *[See Dosage and Administration (2.3).]”*

9.) Under Section 12.6 Immunogenicity
a. The following sentence was added:

“In a 52-week, open-label, pediatric pharmacokinetic trial (subcutaneous dosing in pediatric patients with SLE), none of the 25 patients developed anti-belimumab antibodies.”

10.) Under Section 14.2 Intravenous Administration in Adults with Lupus Nephritis
a. The abbreviation “IVIG” was added, and “intravenous immunoglobulin” was deleted.

11.) Under the Medication Guide
a. Under the header “**What is BENLYSTA?”**, the bullets were edited to read:
- BENLYSTA is a prescription medicine used to treat:
  - adults and children 5 years of age and older with active systemic lupus erythematosus (SLE or lupus) who are receiving other lupus medicines, and
  - adults and children 5 years of age and older with active lupus nephritis (lupus-related kidney inflammation), who are receiving other lupus medicines.

- BENLYSTA contains belimumab which is in a group of medicines called monoclonal antibodies. Lupus is a disease of the immune system (the body system that fights infection). When given together with other medicines for lupus, BENLYSTA decreases lupus disease activity more than other lupus medicines alone.
- It is not known if BENLYSTA is safe and effective in people with severe active central nervous system lupus.
- It is not known if BENLYSTA, given under the skin (subcutaneous), is safe and effective for use in:
    - children less than 5 years of age or less than 33 pounds (15 kg) with SLE.
    - children less than 18 years of age with active lupus nephritis.
- It is not known if BENLYSTA, given in a vein (intravenously), is safe and effective for use in children less than 5 years of age.

b. Under the subheader "**When given under the skin (subcutaneously)**," the bullets were edited to read:

- Your healthcare provider will tell you how often and how much of BENLYSTA you should use. Use BENLYSTA exactly as your healthcare provider tells you to.
- Read the Instructions for Use that comes with BENLYSTA for instructions about the right way to give your injections at home.
- BENLYSTA may be prescribed as a single-dose autoinjector or as a single-dose prefilled syringe.
    - The single-dose autoinjector is for use in adults and children 5 or less than 18 years of age.
    - The single-dose prefilled syringe is for use in adults 18 years of age and older.
- Before you use BENLYSTA, your healthcare provider will show your or your caregiver how to give the injections and review the signs and symptoms of possible allergic reactions.
- For children less than 10 years of age, BENLYSTA must be given by a healthcare provider or a trained caregiver.
- BENLYSTA is injected under the skin (subcutaneously) of your stomach (abdomen) or thigh.
- Use BENLYSTA on the same day each week or the same day every 2 weeks, as your healthcare provider tells you.
- If you miss your dose of BENLYSTA on your planned day, inject a dose as soon as you remember. The, inject your next dose at your regularly scheduled time or continue dosing based on the new day injected. In case you are not sure when to inject BENLYSTA, call your healthcare provider.

12.) Under Instructions for Use, Prefilled Syringe

a. Under the header "**Important Warnings,"** the first bullet was edited to read:
   - The prefilled syringe should be sued only 1 time and then thrown away. See below, **"Step 6-Throw away (dispose of) used prefilled syringe.**"
     - **Do not** share your BENLYSTA prefilled syringe with other people. You may give other people a serious infection or get a serious infection from them.
     - **Do not** shake the prefilled syringe.
     - **Do not** use if dropped onto a hard surface.
     - **Do not** remove the Needle Cap until right before the injection.
     - **Do not** use in children less than 18 years of age. It is not known if the prefilled syringe is safe and effective in children less than 18 years of age.

b. "Step" was added to each section of the IFU.

c. The abbreviation "**Exp**" was added to the step instructing patients to check the expiration date.

d. Step 5 was edited to read "**Step 5 Inject BENLYSTA and Inspect**" with the following bulleted information under Figure J under Step 6 move up as follows:

   Inspect the injection site
   - There may be a small amount of blood at the injection site. If needed, press a cotton ball or gauze pad on the injection site.
   - Do not rub the injection site.

e. Step 6 was edited to read: "**Step 6 Throw away (dispose of) used prefilled syringe**".

13.) Under Instructions for Use, Prefilled Autoinjector

a. Under the header, "Read These Sections First" was deleted.

b. Under the subheader Important Storage Information, the following edits were made to the bullets:
   - Keep refrigerated until 30minutes before use.
   - Keep in the original package until time of use to protect from light.
   - **Do not** freeze BENLYSTA. If the autoinjector has been frozen, do not use the autoinjector even if it is thawed.
   - **Keep away from heat and sunlight.**
   - **Do not** use and do not place back in the refrigerator if BENLYSTA is left out for more than 12 hours.
   - **Keep out of the reach of children.**

c. Under the subheader "**Important Warnings**," the following edits were made to the bullets:
   - The autoinjector should be used only 1 time and then thrown away. See below, "**Step 6 Throw away (dispose of) used autoinjector**."

- **Do not** share your BENLYSTA Autoinjector with other people You may give other people a serious infection or get a serious infection them.
- **Do not** shake the autoinjector.
- **Do not** use if dropped onto a hard surface.
- **Do not** remove the Ring Cap until right before the injection.
- For children less than 10 years of age, BENLYSTA must be given by a healthcare provider or a trained caregiver.

d. "Step" was added to each section of the IFU.
e. Under "**Step 1 Gather and check supplies**", the following edits were made to the bullets:
   - Remove 1 sealed tray containing an autoinjector from the refrigerator.
   - Place any remaining autoinjectors back into the refrigerator.
   - Find a comfortable, well-lit, and clean surface and place the following supplies within reach.
     - BENLYSTA Autoinjector
     - Alcohol swab (not included)
     - Gauze pad or cotton ball (not included)
     - Sharps container (not included)
   - Do not give the injection if you do not have the supplies listed.

   Take out the autoinjector
   - Peel back the film from the corner of the tray. See Figure A.
   - Holding the middle of the autoinjector (near the inspection window), carefully take the autoinjector out of the tray. See Figure B.

   Check expiration (EXP) date
   - Check the expiration date on the autoinjector. See Figure C.
f. Under "Step 4 Prepare for the injection", the following edits were made to the bullets:

   Remove the Ring Cap
   - Do not remove the Ring Cap until right before you give the injection.
   - Remove the Ring Cap by pulling or twisting it off. The Ring Cap may be twisted off in either a clockwise or counterclockwise direction. See Figure H.
g. Step 5 had been edited to read "**Step 5 Inject BENLYSTA and inspect**".
h. Figure H has been renamed Figure J, Figure I has been renamed Figure K, and Figure J has been renamed Figure L.
i. Under subheader, "**Inspect the injection site**" the following bulleted information under Step 6 has been moved up:
   - There may be a small amount of blood at the injection site. If needed, press a cotton ball or gauze pad on the injection stie.

- **Do not** rug the injection site.

j. Step 6 has been edited to read, "**Step 6 Throw away (dispose of) used autoinjector**".

k. Under "**Step 6 Throw away (dispose of) used autoinjector,**" the following bulleted statement has been edited: **Throw away** (dispose of) the used autoinjector and Ring Cap in a Sharps Container. See Figure M.

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary for this pediatric PMR supplement to expand the current indication for SC belimumab to include pediatric patients 5 years and older with active SLE who are receiving standard therapy since no new safety signals were identified on review of the data contained in this submission.

13 Postmarketing Requirements and Commitment

This submission fulfills the PREA PMR 3239-1 related to the July 20, 2017, approval for BLA 761043 belimumab (Benlysta©) described as follows:

> "Conduct a pharmacokinetic and safety study of subcutaneous belimumab inpatients with active systemic lupus erythematosus ages 5 to <18 years of age."

No additional postmarketing requirements or commitments for belimumab SC are recommended at this time.

14 Division Director (Clinical) / Signatory Comments

I agree with the review team's assessment of the data submitted, the benefit-risk assessment, and the conclusions regarding the data supporting the recommended regulatory actions.

The efficacy of belimumab SC is based on PK matching of systemic exposure and extrapolation of established efficacy of belimumab SC in adult subjects with SLE. As discussed in this review, the clinical pharmacology review team was able to establish a PK-bridge based on comparable serum concentrations of belimumab between children and adults treated with belimumab SC, respectively, at the proposed pediatric dosing regimens. Based on the safety data generated from the pediatric belimumab IV study, the safety data from the open-label, PK/PD, safety study that evaluated 200 mg of belimumab SC administered via AI to pediatric subjects between the ages of 5 and 17-years-old and the updated postmarketing safety review in children administered belimumab, the benefit/risk assessment is favorable for the proposed dose of 200 mg of belimumab SC dosing regimen when administered once weekly via AI in children weighing $\geq$40 kg and administered every 2 weeks via AI in children weighing $\geq$15 kg to <40 kg as add-on therapy for pediatric subjects with active SLE who are receiving standard of care therapy.

I agree with the review team that the pediatric clinical pharmacology, efficacy and safety data submitted to BLA 761043/s-027 are adequate to fulfill the PREA postmarketing requirement (3239-1) issued in the July 20, 2017. The recommended regulatory action is approval for belimumab (Benlysta) SC formulation administration via the AI presentation for the treatment of children 5 to 17 years of age with active SLE who are receiving standard therapy.

15 Appendices

15.1. References

1. Bruera S, Lei X, Zhao H, Yazdany J, et al. Risk of mortality and severe coronavirus disease 19 (COVID-19) outcomes in patients with or without systemic lupus erythematosus. Lupus Science and Medicine 2023; 10:e000750, doi:10.1136/Lupus-2022-000750.
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Epidemiology of childhood-onset systemic lupus erythematosus: a population-based study. Arthritis Care and Research 2022; (74)5:728-732.

15.2. Financial Disclosure

See the following completed form.

Covered Clinical Study (Name and/or Number): Study 200908 – A Multi-center, Open-Label Trial to Evaluate the Pharmacokinetics, Safety, and Pharmacokinetics of Subcutaneously Administered Belimumab, A human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Participants with Systemic Lupus Erythematosus

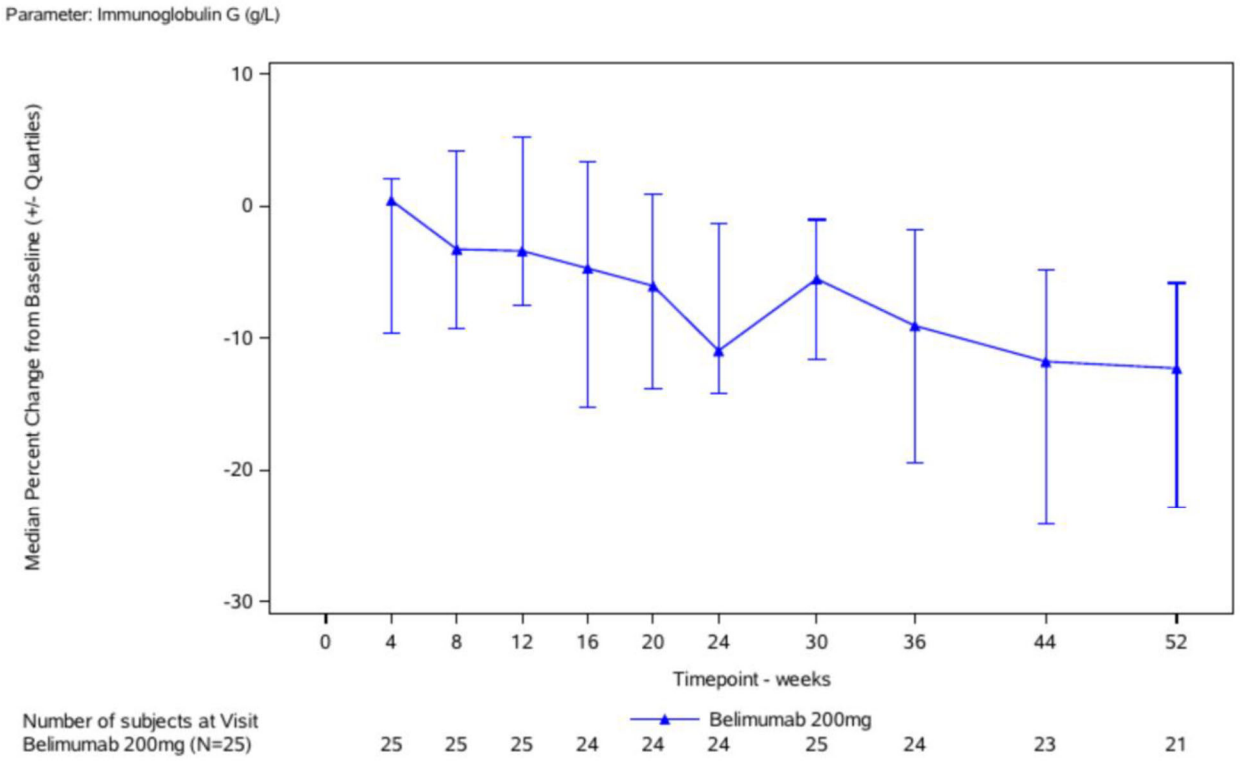
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 14		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Additional Clinical Pharmacology Information

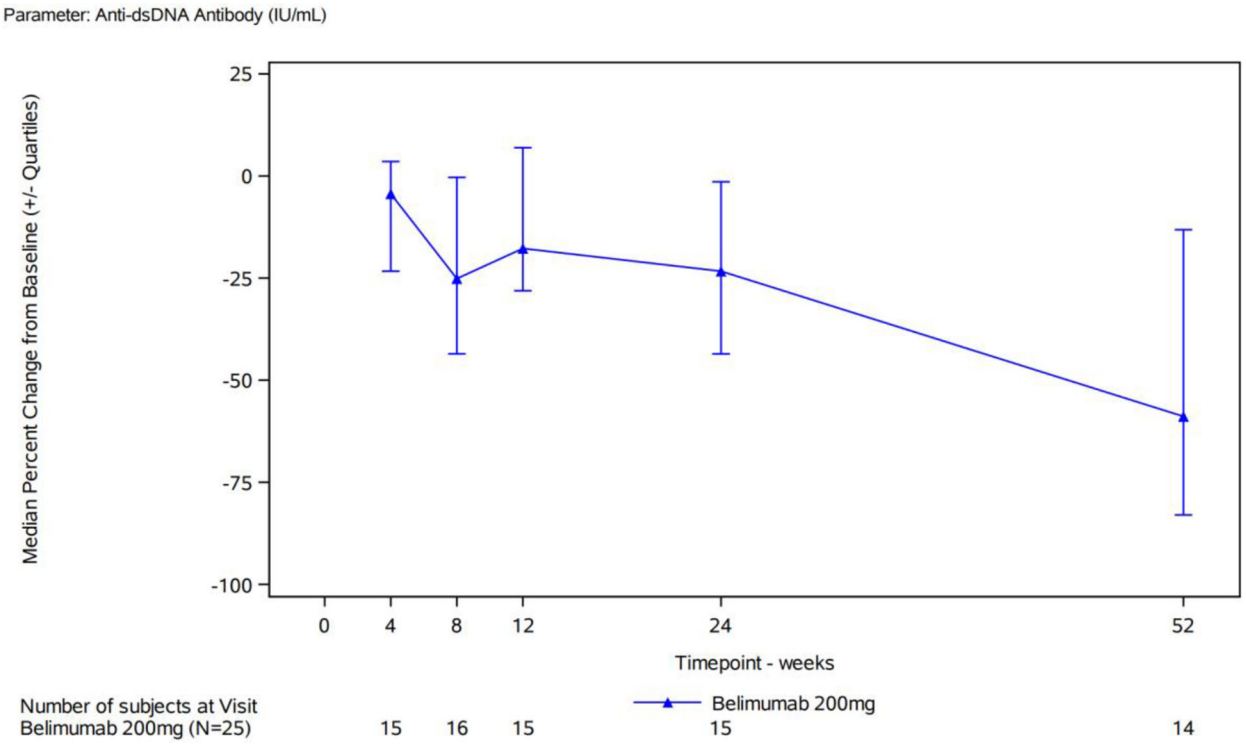
The PD response, including IgG, Anti-dsDNA antibodies, C3/C4 complement, and B cell subsets, were characterized in children 5 years and older in Study 200908. The time profiles are depicted in Figure 6 to Figure 10 below.

Figure 6 Immunoglobulin G Levels Percent Change from Baseline by Visit



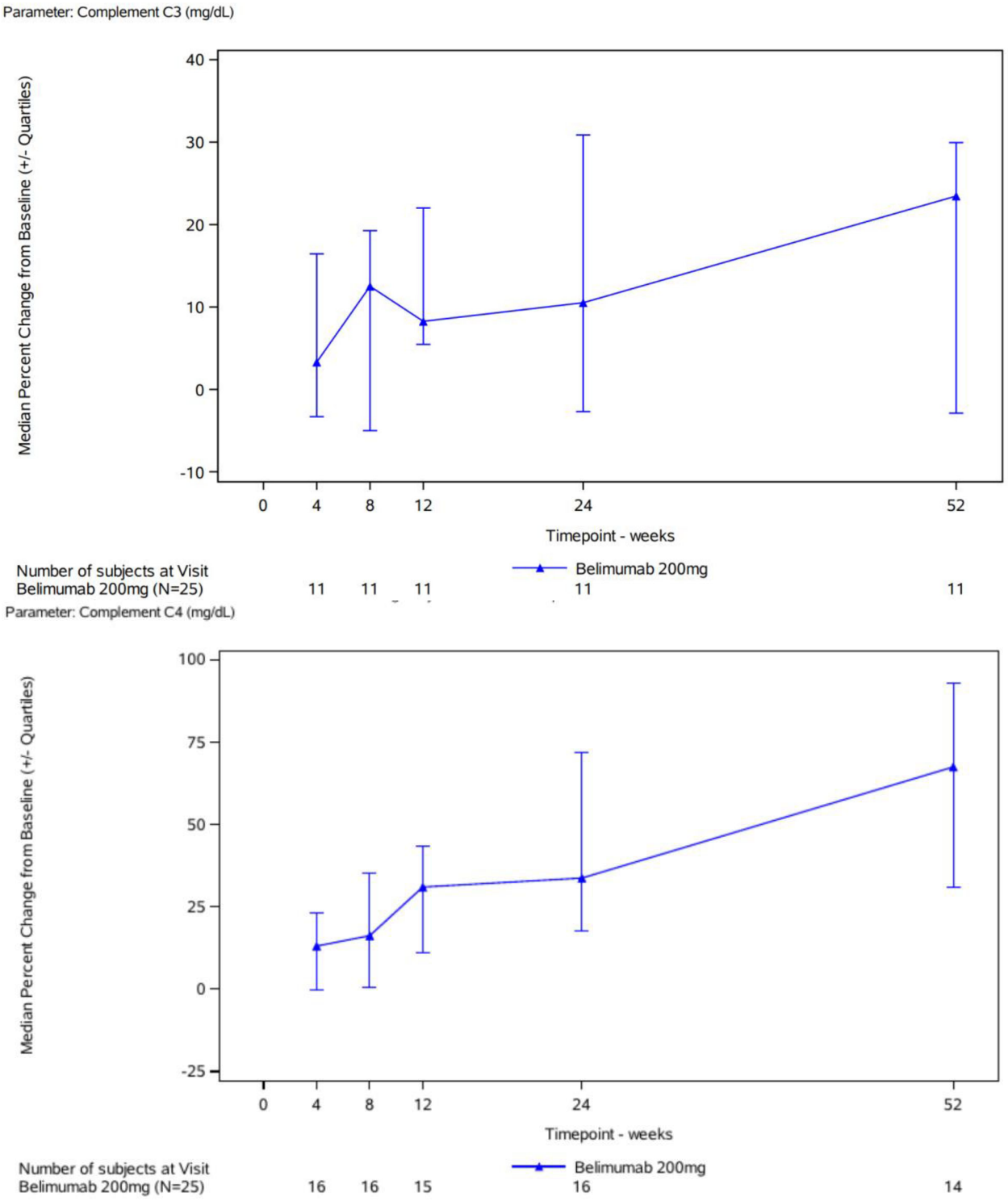
Source: Figure 3 in in Clinical Study Report 200908

Figure 7 Anti-dsDNA Levels Percent Change from Baseline by Visit among Participants Positive at Baseline



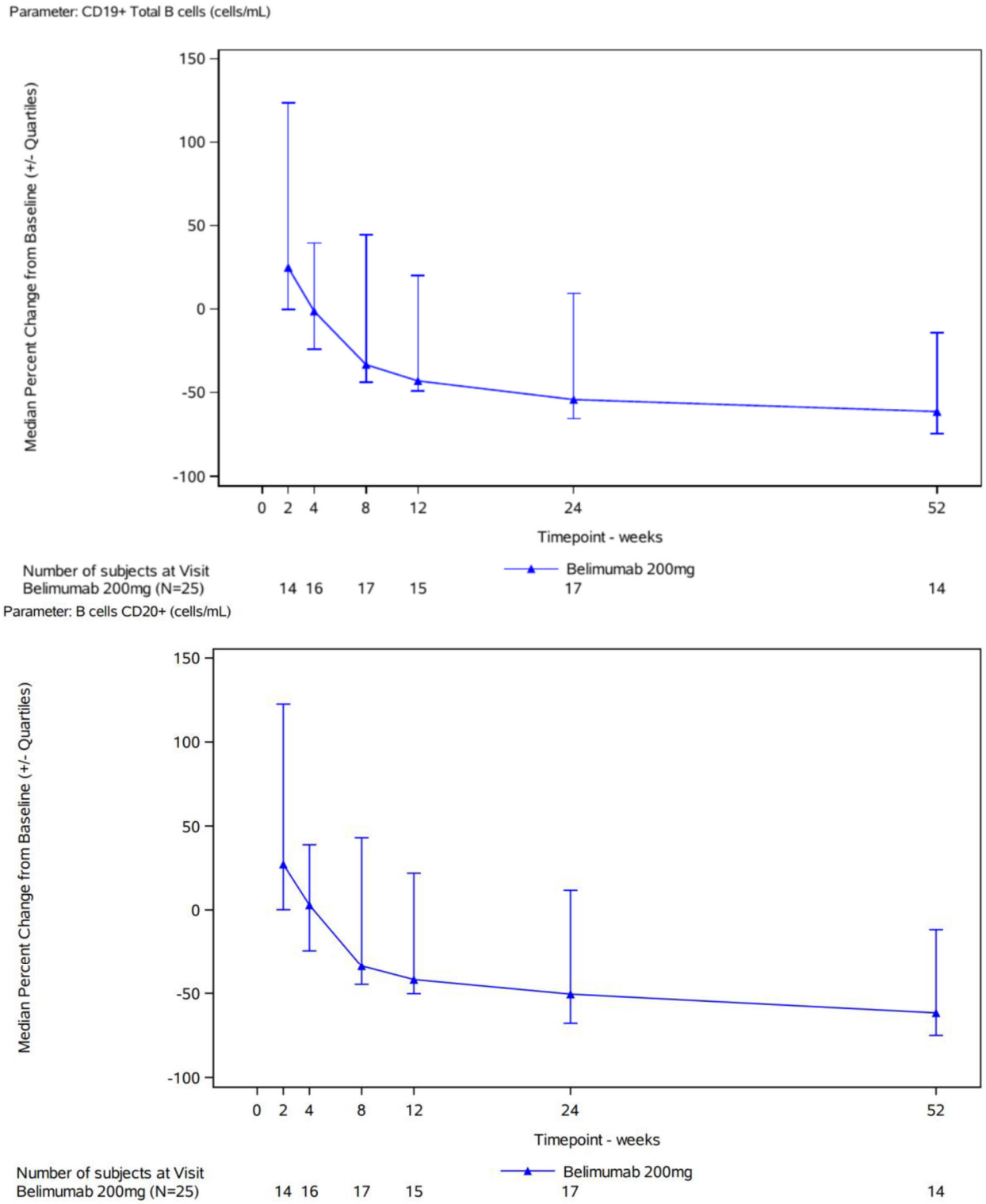
Note: Anti-dsDNA positive (>=30 IU/mL); ANA positive (>=80 Titer); CRP positive (>=4 mg/L).
Source: Figure 4 in Clinical Study Report 200908

Figure 8 Complement Level Percent Change from Baseline by Visit Among Participants with Low Complement at Baseline



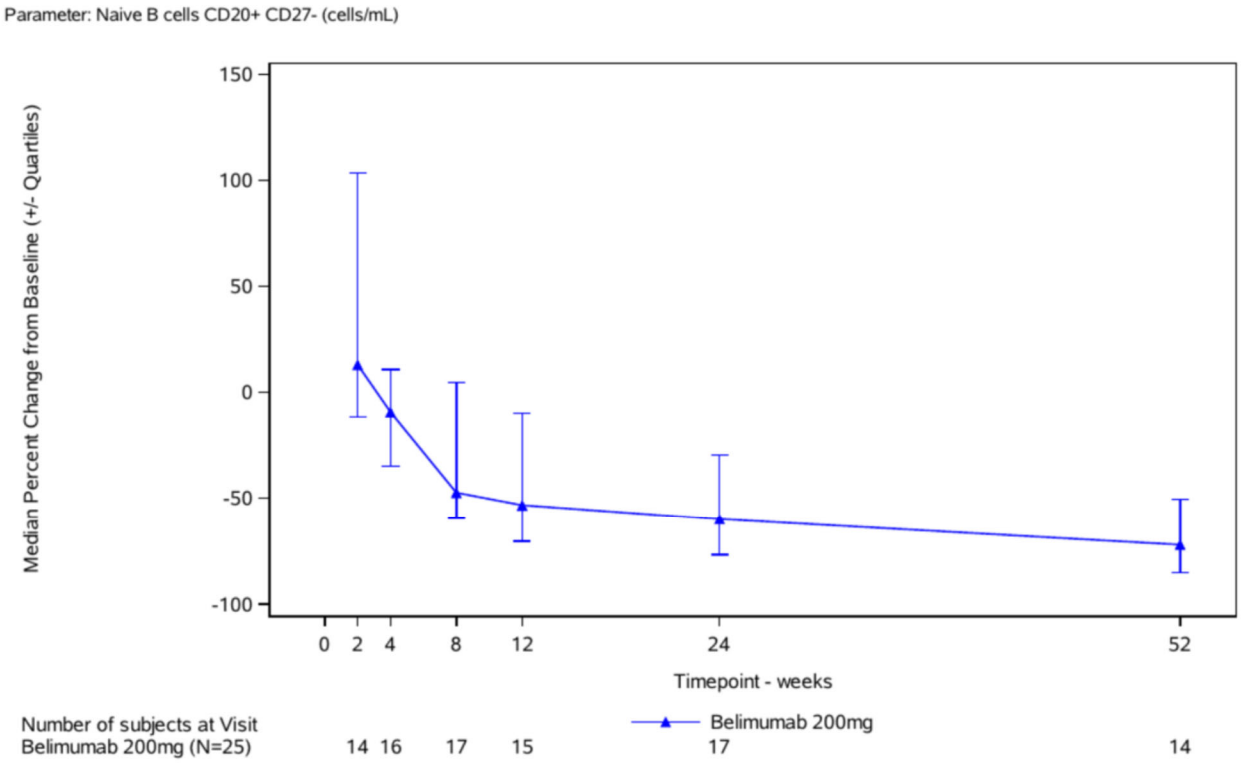
Note: Low C3 (<90 mg/dL); Low C4 (<13 mg/dL)
Source: Figure 5 in Clinical Study Report 200908

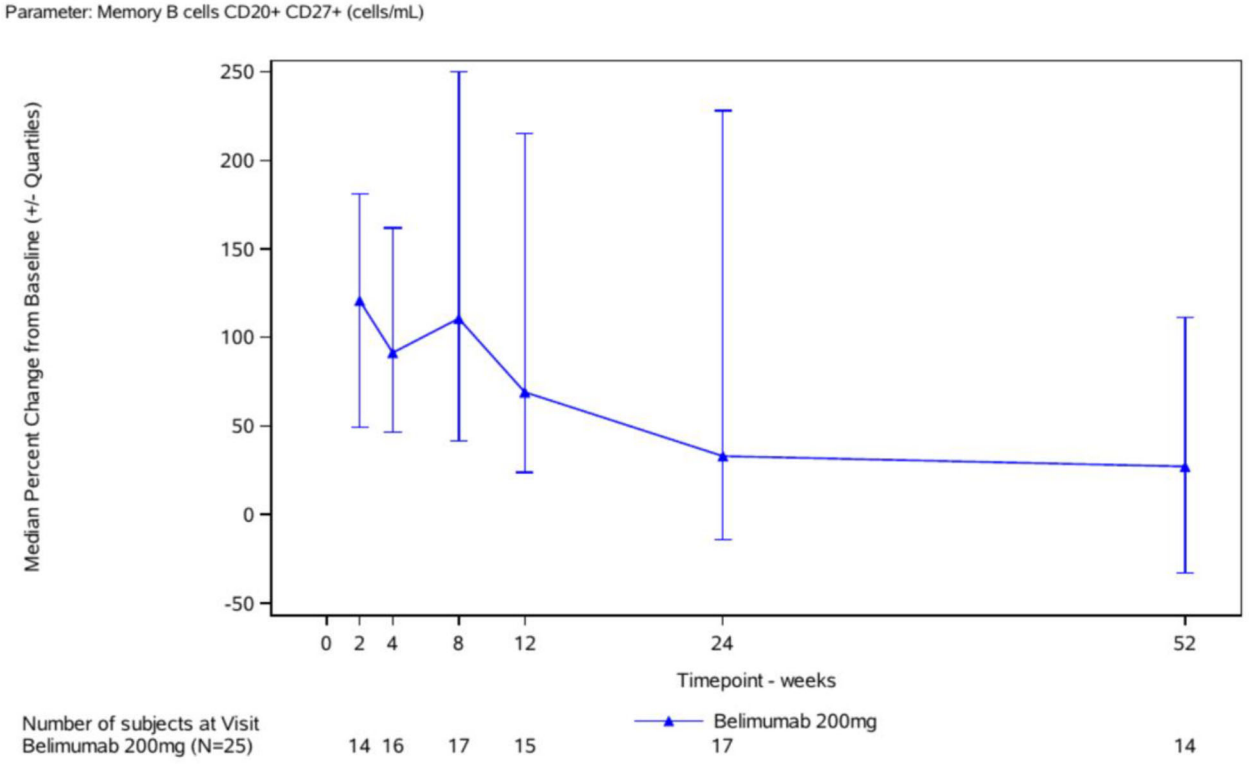
Figure 9 CD19+ and CD20+ B Cells Median Percent Change from Baseline



Source: Figure 6 in Clinical Study Report 200908

Figure 10 Naïve and Memory B Cell Median Percent Change from Baseline





Source: Figure 7 in Clinical Study Report 200908

15.3.2. Bioanalytical Method

The Analytical Method, ECL-0130, been previously validated under Study Number 8278-984 Validation of an ECL Method for the Quantitation of Benlysta (belimumab) in Human Serum (b) (4) This is a re-developed method based on a previous validated method ECL-0083. The original method validation report (Sponsor Sample Analysis Report Number 2015N228352_00) was submitted under BLA 125370/s-068 on 03/21/2019. The bioanalytical method was reviewed by Dr. Justin Penzenstadler. See Multi-Disciplinary Review in DARRTS for sBLA 125370/s-068. A summary of the key method validation parameters is listed in Table 27.

Table 27 Validated Method Parameters

Validation Study Number:	8278-984
Mnemonic:	CB-1145
Method Type:	ECL
Curve Fit; Weighting Factor	5PL, weighting factor 1/ Y^2
Analyte Name(s):	Benlysta (belimumab)***
Species Matrix:	Human Serum
Sample Volume:	0.5 mL requested (0.2 mL minimum)
Calibrator/Control:	Benlysta in human serum matrix
Plate type:	MSD Streptavidin coated, standard
Capture Reagent:	Biotin-BlyS
Detection Reagents:	Detection reagent-1: Rabbit Anti-Benlysta (Rabbit Anti-LSB) Detection reagent-2: Sulfo-Tag-Goat Anti- Rabbit Antibody
Lower Limit of Quantitation (LLOQ):	100.000 ng/mL
Upper Limit of Quantitation (ULOQ):	12800.000 ng/mL
Sample Storage Temperature:	-60 to -80°C
Freeze/Thaw Stability:	Up to 7 cycles at -60 to -80°C
Room Temperature Stability:	Up to 24 hours (1 day)
Refrigerated Temperature (2 to 8ºC) Stability:	Up to 168 hours (7 days)
Long Term Stability:	Up to 3.25 years or 1186 days at -60 to -80°C* Up to 37 months or 1134 days at -15 to -20°C**
Dilutional Linearity:	Up to 1 to 800 prior to MRD
Specificity:	Specific to Benlysta***
Incurred Sample Reproducibility	Study No. 8278-363 Matrix: Human Serum
Method Partially Validated By:	(b) (4).

*Long Term Stability was not performed as part of the validation of assay at (b) (4). LTS Information was provided by the Sponsor and listed in validation study 8478-984.

**Long Term Stability was not performed as part of the validation of assay at (b) (4) but was established by (b) (4) under validation study 8307-474.
Source: Bioanalytical report 2020N462169_00

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for (b) (4) See OSIS Bioequivalence Establishment Inspection Report Review in DARRTS under BLA 761043 dated 01/08/2024.

15.3.3. Pharmacometrics review

The Applicant conducted a PopPK analysis to characterize belimumab PK in children 5 years and old following SC administration and to support the proposed SC dosing regimen for exposure matching. Baseline subject level characteristics are summarized for the pediatric SC (200908) and pediatric IV (BEL114055) studies in Table 28.

Table 28 Subject level characteristics over 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%)

Source: CPMR, Table 2

The final model was 2-compartment with first order absorption, distribution, and elimination. The final parameter estimates are listed in Table 29.

Table 29 Parameter values of the final model

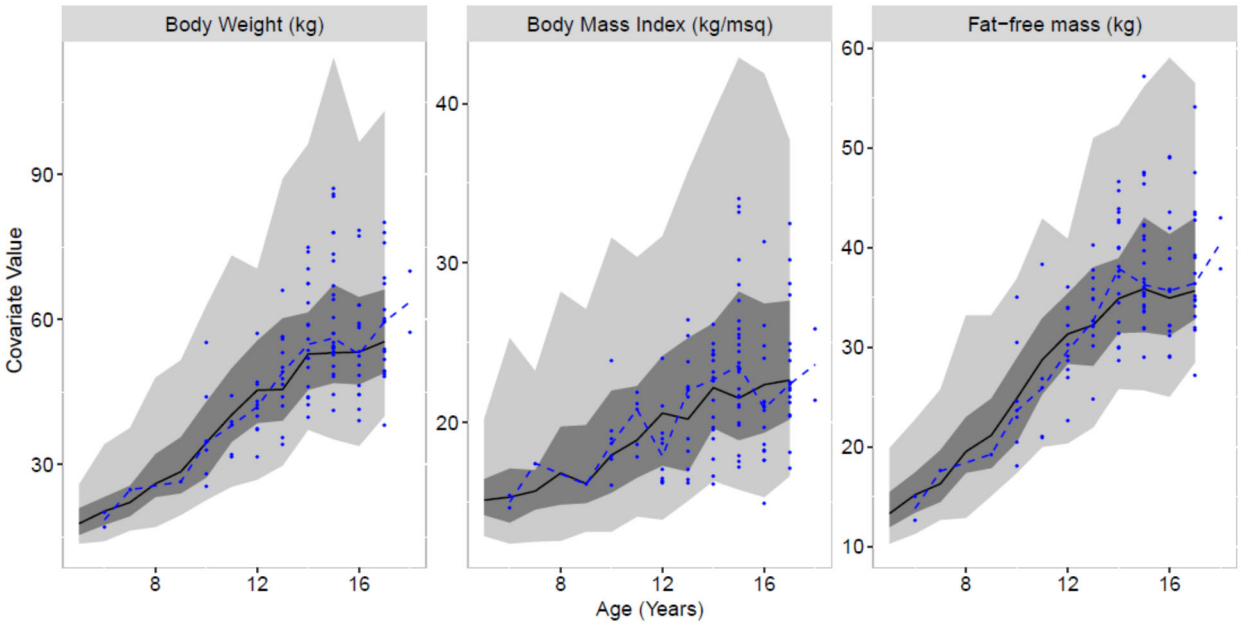
Parameter	Parameter Estimate (RSE%)
Fsc (%)	70.3 (6.52%)
ALAG (days)	0.179 (Fixed)
KA (1/day)	0.287 (26.3%)
CL (mL/day) ×(WT/52.4)$^{\theta}$ ×(IGG/13.5)$^{\theta}$	154 (3.92%) 0.509 (21.4%) 0.576 (15.8%)
Vc (mL) ×(WT/52.4)$^{\theta}$	1935 (4.48%) 0.769 (14.4%)
Q (mL/day) ×(WT/52.4)$^{\theta}$	643 (8.01%) 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^2CL ω^2CL/Vc ω^2Vc ω^2Q ω^2Vp	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)

Source: CPMR, Table 3.12.
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 εadd are normally distributed random variables with variance σ^2_{prop} and σ^2_{add}, respectively.

In PK simulation, the healthy volunteer CDC National Health and Nutrition Examination Survey (NHANES) database was sampled by individual (N=10,000), restricted to the target 5 to 17-year age range and with 90% bias towards females typical of SLE. Fat-free mass was derived from body weight, BMI, and gender. The distribution of body weight, BMI and fat-free mass of this sampled population was in general higher than for pediatric patients with SLE enrolled in the pediatric SLE study BEL114055. Sampled body weights and BMI values were therefore corrected to represent a pediatric SLE population, and a reduction to 86% (body weight) and to 94% (BMI)

of the sampled values was found to minimize the difference in the median values summed over all ages with respect to pediatric patients with SLE. (Figure 11)

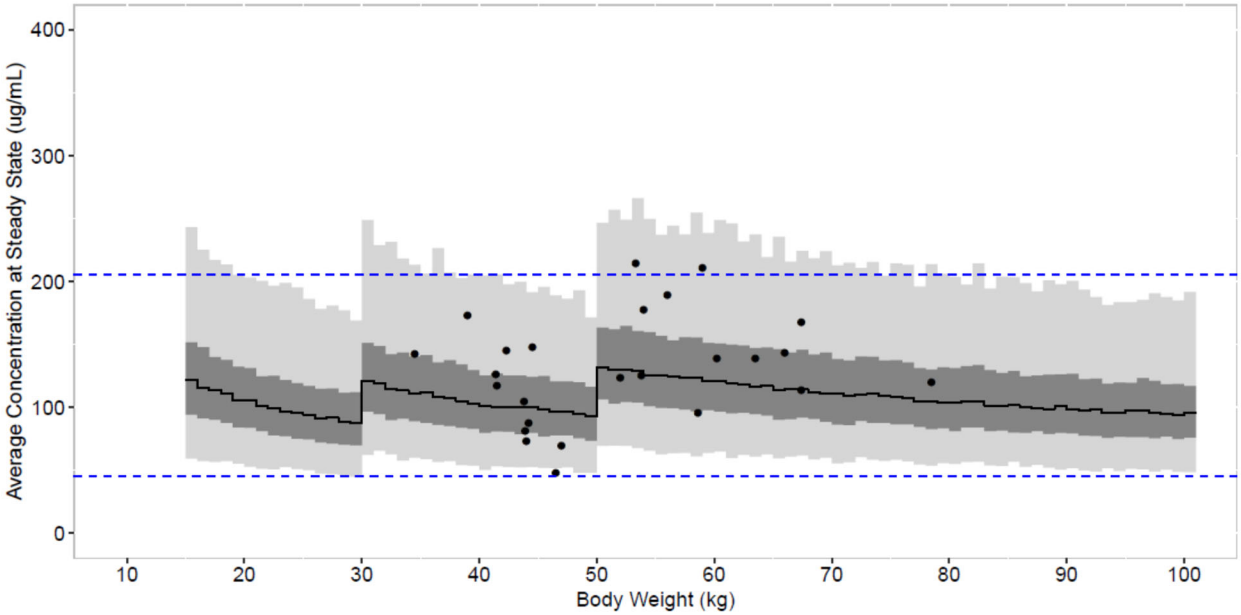
Figure 11 Body size metrics versus age: sampled NHANES population with body weight and BMI correction



Sample covariates from the NHANES database are shown as 95% prediction interval (light grey region), inter-quartile range (dark grey region) and median (solid black line). The observed values from the active and placebo patients of study BEL114055 plus the observed values from study 200908 patients are shown (blue points) with the median calculated at each age (blue dotted line).
Source: CPMR, Figure 16

The final population PK model (Mod011) was used to simulate the Cavg distribution over body weight, in 1 kg intervals, for the SC dosing regimen used in study 200908: 200 mg QW for ≥50kg; 200 mg Q10d for ≥30kg and <50kg; 200 mg Q2W for <30kg, and the proposed dosing regimen: 200 mg QW for ≥40kg; 200 mg Q2W for <40kg. For each 1 kg body weight interval, 1000 patients were simulated. The Pop PK model simulated Cavg is depicted in Figure 12 for the studied dosing regimen and in Figure 3 for the proposed dosing regimen.

Figure 12 Simulated average concentration at steady state versus body weight for the 3-weight band SC regimen of study 200908



Average concentrations at steady state for SC in pediatric patients 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).
Source: CPMR, Figure 24A

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