NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental BLA
Application Number(s)	BLA 761043/S034 BLA 125370/S085
Priority or Standard	Standard
Submit Date(s)	August 21, 2024
Received Date(s)	August 21, 2024
PDUFA Goal Date	June 21, 2025
Division/Office	DRTM/OII/OND
Review Completion Date	See electronic stamp date
Established/Proper Name	Belimumab
(Proposed) Trade Name	Benlysta
Pharmacologic Class	Monoclonal Anti-BLyS Antibody
Applicant	GlaxoSmithKline (GSK) LLC
Dosage form	200 mg/mL single-dose prefilled autoinjector (no new dosage forms)
Applicant proposed Dosing Regimen	Subcutaneous dosing: Patients greater than or equal to ≥40 kg: 400 mg once weekly x 4 doses, followed by 200 mg once weekly Patients 15 kg to less than <40 kg: 200 mg once weekly x 4 doses, followed by 200 mg once every 2 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of pediatric patients 5 years of age and older with active lupus nephritis who are receiving standard therapy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of pediatric patients 5 years of age and older with active lupus nephritis who are receiving standard therapy
Recommended Dosing Regimen	Subcutaneous dosing: Patients greater than or equal to ≥40 kg: 400 mg once weekly for 4 doses, followed by 200 mg once weekly Patients 15 kg to less than <40 kg: 200 mg once weekly for 4 doses, followed by 200 mg once every 2 weeks

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Signatures

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
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
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
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
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

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 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). An alternative once weekly 200 mg subcutaneously (SC) administered injection formulation, available as a ready to use pre-filled syringe (PFS) and autoinjector (AI), was approved in 2017 for the same indication. The IV formulation has subsequently been approved for the treatment of children 5 years and older with active, autoantibody positive childhood-onset SLE (cSLE, 2019), adults with active lupus nephritis (LN, 2020), and children 5 years and older with active LN (2022). Both PFS and AI presentations for SC administration have been approved for adults with active LN (2020), and only AI presentation for SC administration has been approved for children 5 years and older with active, autoantibody positive cSLE (2024). Table 1 presents the currently approved indications and dosing regimens for belimumab.

Table 1. FDA Approved Indications and Dosing Regimens for Belimumab (IV and SC)

Indications	Dosing Regimens
Belimumab Intravenous	
Patients 5 years of age and older with **active SLE** who are receiving standard therapy	10 mg/kg at 2-week intervals for the first 3 doses, then at 4-week intervals thereafter
Patients 5 years of age and older with **active LN** who are receiving standard therapy	
Belimumab Subcutaneous	
Patients 5 years of age and older with **active SLE** who are receiving standard therapy	Adults: 200 mg once weekly
	Children 5 to less than 18 years of age (autoinjector only): • Weight 15 kg to <40 kg: 200 mg once every 2 weeks • Weight ≥40 kg: 200 mg once weekly
Adults with **active LN** who are receiving standard therapy	400 mg once weekly for 4 doses, then 200 mg once weekly thereafter

IV=intravenous; LN=lupus nephritis; SC=subcutaneous; SLE=systemic lupus erythematosus
Source: Belimumab (Benlysta) USPI, dated June 2024

The Applicant, GlaxoSmithKline, submitted a 351(a) supplemental biologics license application (sBLA) 761043/S-034 seeking marketing approval of belimumab for SC administration via the autoinjector (AI) presentation for the treatment of pediatric patients (5 to less than 18 years of age) with active LN who are receiving standard therapy. The Applicant proposes a weight-tiered dosing regimen with a loading and maintenance dose, as shown in Table 2.

Table 2. Proposed Dosing Regimen for Pediatric Lupus Nephritis (Age 5 to less than 18 years)

Weight Categories	Loading dose (4-weeks)	Maintenance (similar to cSLE regimen)
15 to <40 kg	200 mg QW for first 4 doses	200 mg Q2W
≥40 kg	400 mg (2 x 200 mg) QW for first 4 doses	200 mg QW

The Applicant also submitted BLA 123370/S-085 for the intravenous formulation in order to update the shared labeling. The current supplements serve to fulfill the Pediatric Research Equity Act (PREA) post-marketing required (PMR) pediatric assessment related to the December 16, 2020, approval for belimumab SC formulation as a treatment of adults with active LN who are receiving standard therapy (BLA 761043/S-013).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is approval for belimumab (Benlysta) SC route of administration via the AI presentation for the treatment of children 5 to 17 years of age with active LN who are receiving standard therapy. This recommendation is based on the PK/exposure-matching based extrapolation of efficacy established in adults with active LN and leveraging the existing safety information in children with cSLE, as well as supportive safety data from a postmarketing safety update of pediatric and adult patients with SLE and LN exposed to belimumab. Additionally, the pediatric clinical pharmacology, efficacy, and safety data submitted are adequate to fulfill the PREA PMR 4021-1 (previously, 3994-2) included in the December 16, 2020, approval for BLA 761043/S-013 belimumab SC formulation for adult LN.

Systemic lupus erythematosus (SLE) is a heterogeneous, chronic, autoimmune disease that can affect multiple organ systems that included the skin, musculoskeletal, hematological, renal, nervous and cardiovascular systems. Approximately 10-20% of all SLE cases develop during childhood (cSLE).[1] Renal involvement or lupus nephritis (LN) is one of the most serious manifestations of this disease occurring in approximately 50-70% of the pediatric patients with cSLE.[2] Currently, belimumab IV is the only approved therapy for pediatric LN patients. A full description of pediatric LN and its diagnosis, treatment, and prognosis, which are all highly similar to adult LN, can be found in Sections 2.1 and 2.2.

[1] Hiraki LT, et al. Arth and Rheum 2012; 64:2669-76.
[2] Hahn BH, et al. Arthritis Care Res. 2012; 64:797-808.

No clinical studies have been conducted with belimumab in pediatric LN. Pediatric subjects with active LN were excluded from participating in study 200908, which was a study in pediatric subjects with active, cSLE on stable immunosuppressive medications, used to support expanding belimumab SC's indication to include children ages 5 to 17 years old with active, seropositive cSLE under BLA761043/s-027. As described in Section 6, determination of efficacy in pediatric subjects was instead based on PK matching of systemic exposure in pediatric and adult subjects, which permitted extrapolation of established efficacy of belimumab IV from the pivotal phase 3 study in adults with active LN (study BEL114054). The adult belimumab IV LN study was an adequate and well controlled clinical trial that has been reviewed previously in support of the approval of belimumab IV for adult LN (BLA 125370/S-073). A pediatric population PK model was built based on data from belimumab IV cSLE study BEL114055/C1109, SC cSLE study 200908, and IV adult LN study BEL114054/C1121. Since PK exposure is expected to be similar between adult and pediatric LN patients, it is scientifically justified to extrapolate the efficacy established from the belimumab IV adult LN study to the belimumab SC formulation in pediatric LN patients.

The safety of belimumab SC in pediatric LN is leveraged from the belimumab's safety experience in cSLE (IV and SC) and pediatric LN (IV). Overall, the safety of belimumab in pediatric patients is consistent with the adult patients, and no new safety signals have been identified that warrant discussion of the data contained in this submission at a public advisory committee meeting or an update of 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 as an add-on therapy for the treatment of pediatric patients 5 years and older with active LN who are receiving standard therapy, when 200 mg is administered as a subcutaneous injection once weekly for the first 4 doses, followed by 200mg SC every 2 weeks thereafter for pediatric subjects weighing 15 kg to <40 kg, and 400mg SC weekly for the first 4 doses, followed by 200mg SC weekly thereafter for pediatric subjects weighing ≥40 kg. Approval of belimumab autoinjector for SC injection will provide an additional treatment option for pediatric patients with active LN given the limited number of approved treatment options for this disease in the United States (U.S.). The convenience and availability of a SC formulation will be an advantage for this pediatric patient population.

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. Childhood-onset SLE (cSLE) is a rare disease that is seldom diagnosed in children 9 years old and younger. 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. Renal disease, which is referred to as lupus nephritis (LN), occurs in approximately 50%-70% of all cSLE patients within the first 2 years of diagnosis. Similar to adults, LN in children is diagnosed via characteristic findings on renal biopsy which determines the type of treatment to be administered. Benlysta (belimumab) IV is the only approved treatment for pediatric LN. Pediatric patients with this disease are treated with standard of care therapy that is similar to treatments used in the management of adult patients that consists of induction therapy with corticosteroids and immunosuppressive agents, followed by maintenance therapy with immunosuppressive agents for 3 to 5 years. Despite treatment with current standard of care therapy, patients with LN develop long-term kidney damage which results in kidney failure in approximately 15%-22% of children with this disease within 10-15 years of diagnosis, necessitating long-term treatment with hemodialysis or renal transplant. Additionally, the toxicities associated with the off-label treatments commonly used to treat LN contribute to the long-term toxicities and increased risk for death observed in adult and pediatric patients with LN. The overall survival rate in pediatric patients with cSLE is approximately 89%-97% at 10 years, but it is reduced in pediatric patients with LN to approximately 86% at 10 years. Therefore, there is a significant unmet need for therapeutic options in the pediatric population with LN.

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 for the treatment of adults with active, autoantibody-positive SLE on March 11, 2011. It was subsequently approved for the treatment of children 5 years and older with active, autoantibody-positive cSLE on April 26, 2019, and adults with active LN on December 16, 2020, at the same dosing regimen of 10 mg/kg at 2-week intervals for the first 3 dose and at 4 week intervals thereafter. Under the Pediatric Research Act (PREA), a partial waiver for pediatric studies in lupus nephritis patients <5 years of age, based on the justification that dedicated clinical studies to establish the efficacy of products in pediatric LN would be impossible or highly impracticable to conduct because there are too few children with the disease/condition to study in this subgroup, along with a deferral for a pediatric assessment in lupus nephritis patients >5 to 17 years of age were granted at the time of approval of the adult LN indication. Based on the high degree of disease similarity between adults and pediatric patients with LN, the Agency agreed that the Applicant could fulfil this PREA postmarketing required (PMR) pediatric assessment via a PK matching based extrapolation of efficacy established in adults with LN along with

leveraging safety data from the existing pediatric studies in cSLE. This would permit extrapolation of efficacy based on the expectation of similarity in exposure-response between these two populations, supported by the product's safety database in cSLE, with adequate justification for this approach by the Applicant.

In support of a PK/exposure-matching based extrapolation approach of belimumab IV in adult LN to belimumab SC in pediatric LN , the Applicant provided the following justification: (1) information supporting disease similarity between the adult and pediatric patients with LN; (2) establishment of a PK bridge between adult and pediatric patients; (3) extrapolation of efficacy in pediatric patients from adult subjects with LN; and (4) justification of the relevance of the safety data from cSLE.

Results from the population PK modeling study 217481, which demonstrated the comparability of exposure levels in children with lupus nephritis, when belimumab SC is administered at the proposed dosing regimen, to adults with lupus nephritis, when belimumab IV is administered at a dose of 10 mg/kg every 2 weeks for the first 3 doses and at 4- week intervals thereafter, were found to be adequate to support the extrapolation of efficacy and leverage of safety in pediatric LN patients from the following studies: BEL114054/C1121 (belimumab IV in adult LN), BEL114055/C1109 (belimumab IV in cSLE), and 200908 (belimumab SC in cSLE). Adult LN PK data and cSLE PK data used in study 217481 came from three studies: 1) BEL114054/C1121 was an adequate and well-controlled clinical trial that evaluated 10 mg/kg of belimumab IV in adults with LN on standard of care induction (high dose corticosteroids with cyclophosphamide or mycophenolate mofetil) and maintenance (azathioprine or mycophenolate mofetil) therapy over 104-weeks of treatment; 2) study BEL114055/C1109 also evaluated the 10 mg/kg approved dosing regimen over 52-weeks in pediatric subjects with cSLE on stable immunosuppressive medications; and 3) study 200908 evaluated the 200 mg approved SC dosing regimen in pediatric subjects with cSLE on stable immunosuppressive medications. All these studies have been reviewed previously in support of the approvals for the adult LN indication (belimumab IV) and the cSLE indications (belimumab IV and SC) under sBLA 125370/S-073, sBLA 125370/S-064, and sBLA 761043/S-027, respectively. Since PK exposure is estimated to be similar between adult and pediatric LN patients, extrapolation of efficacy was derived from study BEL114054/C1121, which was the pivotal trial that established belimumab IV's efficacy as a treatment for adults with LN.

The PK exposure is expected to be similar in pediatric patients with LN compared to cSLE patients with the same dosing regimen, notwithstanding the differences in SC loading dose. In addition, there are no significant disease-specific factors that would be expected to impact safety differently. These considerations support the relevance of safety data from cSLE patients to the pediatric LN population. Thus, the safety of belimumab SC in pediatric LN primarily came from leveraging established safety information from cSLE studies (i.e., belimumab IV/SC pediatric study BEL114055/C1109 and study 200908). However, since the safety database from these two studies were small due to the rarity of cSLE, the safety information from adult LN patients provided additional supportive safety data. In this application, review of cumulative safety data collected from the ongoing open-label portion of study 200908 as well as updated spontaneous postmarketing safety data in

children and adults with lupus nephritis did not identify any new or unexpected safety signals associated with the administration of belimumab.

In summary, pediatric lupus nephritis is a rare and serious manifestation of SLE with high unmet medical 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 LN who are receiving standard therapy and support the expansion of the indication of belimumab autoinjector for SC injection as an add-on treatment for active LN in pediatric patients 5 to 17 years old.

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 • 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 • Kidney (renal) involvement or lupus nephritis is one of the most common as well as one of the most severe organ manifestations of SLE • It occurs in approximately 50%-70% of all pediatric patients within the first 2 years of disease diagnosis • Despite treatment with current standard of care therapy, LN causes long term kidney damage that results in kidney failure in 15%-22% of pediatric lupus nephritis patients within 10-15 years of diagnosis necessitating treatment with hemodialysis or renal transplant • The overall survival rate in pediatric patients with cSLE is approximately 89-97% at 10 years but it is reduced in pediatric patients with lupus nephritis to approximately 86% at 10 years	• Lupus nephritis is a serious, life-threatening manifestation of SLE that can have a significant impact on a patient's function and quality of life • Patients with LN are at increased risk for developing chronic kidney disease that can progress to renal failure, the need for hemodialysis and/or renal transplantation, and death • Lupus nephritis in children and adults share similar disease manifestations, disease progression, and similar response to treatment, supporting the similarity of the diseases to support the extrapolation of efficacy from adult LN to pediatric LN based on exposure matching.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Currently, Benlysta IV (belimumab) is the only approved treatment for pediatric patients with LN • Recommendations for treatment are based on expert consensus treatment guidelines which are determined on a case-by-case basis by the following factors: the type of lupus nephritis and inflammatory activity/damage found on renal biopsy, ethnicity, the need to protect fertility, pregnancy, and the presence of high levels of protein in the urine (proteinuria) or disease that fails (refractory) to respond to treatment • Standard of care treatment for pediatric patients with active LN is similar to treatment in adult patients and is comprised of induction therapy followed by maintenance therapy which is administered for the next 3 to 5 years while being monitored for recurring lupus nephritis • Induction therapy regimens currently consist of high dose corticosteroids plus cyclophosphamide or mycophenolate mofetil • Following an induction therapy response (disease remission), patients start maintenance therapy with azathioprine or mycophenolate mofetil • Alternatively, calcineurin inhibitors (tacrolimus or cyclosporin) can be used alone or in combination with mycophenolate mofetil as induction/maintenance therapy particularly in cases that are refractory to treatment • Rituximab is also commonly used as a treatment for refractory lupus nephritis alone or in combination with mycophenolate or cyclophosphamide • Other drugs used in the management of lupus nephritis patients include hydroxychloroquine (to prevent renal flares), angiotensin inhibitors/angiotensin II receptor blockers (to decrease proteinuria as well as control blood pressure although other anti-hypertensive agents may additionally be required) and statins (to treat hyperlipidemia)	• The toxicities associated with the off-label treatments commonly used to treat LN contribute to the long-term toxicities and increased risk for death observed in adult and pediatric patients with LN • There is a significant unmet medical need for safe and efficacious treatments for pediatric lupus nephritis due to the current lack of approved treatments

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of belimumab IV has been previously demonstrated in adult patients with active LN in study BEL114054/C1121, a pivotal phase 3 study submitted in support of the approval of belimumab IV for the treatment of adult patients with active LN receiving standard therapy • PK data were available in 53 pediatric patients with active cSLE between the ages 5 to 17 years old who received belimumab IV 10 mg/kg every 2 weeks for the first 3 doses and at 4-week intervals thereafter (study BEL114055/C1109), in 25 pediatric patients with active cSLE between ages 10 to 17 years old who received belimumab SC 200 mg weekly (study 200908), and in 224 adult patients with active LN who received belimumab IV 10 mg/kg every 2 weeks for the first 3 doses and at 4-week intervals thereafter (study BEL114054) • The SC pharmacokinetics of belimumab in pediatric patients with active lupus nephritis were estimated based on a population pharmacokinetic model developed from studies BEL114055, BEL114054, and 200908. With SC administration of the proposed SC dosing regimen in pediatrics with active LN, the simulated belimumab exposures for pediatrics with active LN 5 to 17-year-old were estimated to be comparable to adults with active lupus nephritis.	• Efficacy of belimumab SC in pediatric patients with LN ages 5 to 17 years old is based on PK exposure matching and extrapolation of established efficacy of belimumab IV in adults with LN from study BEL114054/C1121 • This approach is justified based on similarities of disease manifestations, disease progression, and response to treatment in adults and pediatric patients with lupus nephritis.
Risk and Risk Management	• Lupus nephritis is a serious manifestation of the broader SLE disease. Thus, it is reasonable to leverage safety data from cSLE to pediatric LN. • The PK exposure is expected to be similar (or lower in patients with high proteinuria) in pediatric patients with LN compared to cSLE patients with the same dosing regimen, further supporting the leverage of safety data from cSLE patients to the pediatric LN population • The cumulative safety database for belimumab IV and SC in cSLE was previously reviewed and determined to be similar to the established safety in adults with SLE/LN. In addition, the cumulative safety data from	• Lupus nephritis is an organ manifestation commonly seen in pediatric patients with SLE. As a manifestation of the broader SLE disease, LN shares pathophysiological mechanisms, and the management of both includes chronic immunosuppression. Therefore, it is reasonable to leverage safety data from study BEL114055/C1109 (IV) and 200908 (SC) in pediatric patients

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the open label extension of pediatric cSLE study 200908 and the updated spontaneous postmarketing safety review in pediatric and adult patients exposed to belimumab are sufficient to provide a risk assessment for belimumab SC in the pediatric LN population	with cSLE • Overall, the safety profile of belimumab IV and SC in pediatric cSLE was consistent with what has been observed in the adult SLE and LN • No new safety signals were observed upon review of the cumulative safety data of belimumab in the pediatric cSLE population or from the updated spontaneous postmarketing safety review in pediatric and adult patients exposed to belimumab

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.[3, 4, 5] There is a consistent and striking female predominance, with females comprising approximately 90% of all SLE patients.[6] 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.[7] 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.[8, 9, 10, 11] Although the prevalence of cSLE increases with age, it is rarely diagnosed in children 9 years old and younger.[12]

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.[13]

Renal disease, which is also referred to as lupus nephritis, is one of the most severe organ manifestations of SLE and occurs in approximately 50-60% of adult patients during the first 10 years of their disease and in approximately 50-70% of all pediatric patients within the first 2 years of disease diagnosis.[14] In both adult-onset and childhood-onset SLE, the incidence of lupus nephritis is higher in Blacks, Hispanics, and Asians than in Caucasians as well as in adult

[3] Izmirly PM, et al. Arthrits Rheum 2021: 73:991.
[4] Pons-Estel GJ, et al. Semin Arth and Rheum 2010 Feb.; 39:257-268
[5] Danchenko N, et al. Lupus 2006; 15:308.
[6] Pons-Estel GJ, et al. Semin Arth and Rheum 2010 Feb.; 39:257-268.
[7] Hiraki LT,, et al. Arth and Rheum 2012; 64:2669-76.
[8] Hiraki LT, et al. Arth and Rheum 2012; 64:2669-76.
[9] Nightingale AL, et al. Pharmacoepidemiol Drug Saf. 2007; 16:144-51.
[10] Valenzuela-Almada MO, et al. Arthritis Care and Research 2022; (74)5:728-732.
[11] Oni L, et al. Pediatric Nephrology 2021; 36:1377-1385.
[12] Hiraki et al. Arth and Rheum 2012; 64:2669-76.
[13] Livingston B, et al. Lupus 2011; 20:1345-55.
[14] Hahn BH, et al. Arthritis Care Res. 2012; 64:797-808.

males with SLE.[15, 16] Lupus nephritis also tends to be more severe in these subpopulations as well as in children in general resulting in increased end-organ damage.[17, 18]

Failure to control renal inflammation and/or prevent renal flares leads to accrual of glomerular damage resulting in end-stage renal disease (ESRD) in 10%-20% of adult patients and 15-22% of children with lupus nephritis within 10-15 years of diagnosis.[19] Improvements in the treatment of adult and childhood-onset SLE have resulted in overall survival rates of approximately 95 and 99% at 5 years, and 89% and 97% at 10 years after diagnosis, respectively.[20] However, the overall survival rate in adults and children with lupus nephritis is reduced to approximately 88 and 86% at 10 years, respectively, and is even lower in African Americans.[21, 22]

There are three classification criteria currently available that are used to identify adults and children with SLE: the 1997 revised American College of Rheumatology (ACR) criteria for SLE, the 2012 Systemic Lupus International Collaborating Clinics (SLICC) group classification criteria, and the 2019 European League Against Rheumatism (EULAR)/ACR classification criteria.[23, 24, 25] Although the criteria for lupus nephritis varies between these classification systems (Table 3), all three consider renal biopsy confirmatory for diagnosis.

[15] Johnson SR, et al. J Rheumatol 2006; 33(10):1990-5.
[16] Uribe AG, et al. Curr Rheumatol Rep. 2003; 5 (5):364-9.
[17] Johson SR, et al. J Rheumatol 2006; 33(10):1990-5.
[18] Uribe AG, et. Curr Rheumatol. Rep. 2003; 5(5):364-9.
[19] Anders H-J, et al. Nature Reviews 2020; 6(7):1-25.
[20] Tektonidou MG, et al. Ann Rheum Dis 2017; 76:2009-2016.
[21] Hahn BH, et al. Arthritis Care Res. 2012; 64: 797-808.
[22] Demir S, et al. Nephrol Dial Transplant 2022. 37:1069-1077.
[23] Hochberg MC. Arthritis Rheum 1997; 40:1725.
[24] Petri M, et al. Arthritis Rheum 2012; 64:2677-86.
[25] Arubger M, et al. Arthritis and Rheum 2019;71:1400-12.

Table 3. Lupus Nephritis Criteria

ACR 1997 Revised Classification Criteria for SLE[a]	2012 SLICC Criteria for SLE[b]	EULAR/ACR 2019 Classification Criteria for SLE[c]
Renal criterion 1. Persistent proteinuria >0.5 g/d or >3+ by dipstick 2. Active urinary sediment (>5 RBCs/hpf, >5WBCs/hpf in absence of infection; or cellular casts including RBCs, hemoglobulin, granular tubular or mixed) Optional: 3. Renal biopsy demonstrating immune complex mediated glomerulonephritis compatible with lupus nephritis	Renal criterion 1. Urine protein to creatinine ration (or 24-hour urine protein) representing 500 mg/protein/24 hours OR 2. Red blood cell casts Optional: 3. Biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies	Renal domain criterion 1. Proteinuria >0.5 g/24 hours (4 points) 2. Renal biopsy Class II or V lupus nephritis (8 points) 3. Renal biopsy Class III or IV lupus nephritis (10 points) Note: Patients are additionally required to have a positive ANA > 1:80 titer.

[a]Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40:1725.
[b]Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics Classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64:2677-86.
[c]Arubger M, Costenbader K, Daikh D Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis and Rheum 2019;71:1400-12.

Treatment and prognosis of adult and pediatric lupus nephritis are based on renal biopsy histopathology results using the 2003 International Society of Nephrology and the Renal Pathology Society (ISN/RPS) classification system (Classes I-V).[26] See Table 4 below.

[26] Weening JJ, et al. J Am Soc Nephrol 2004; 15:241-250.

Table 4. ISN/RPS 2003 Classification of Lupus Nephritis

Class I	**Minimal mesangial lupus nephritis**
	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	**Mesangial proliferative lupus nephritis**
	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microsocpy, with mesangial immune deposits
	A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	**Focal lupus nephritis[a]**
	Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	**Diffuse lupus nephritis[b]**
	Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
Class IV-G (A/C)	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	**Membranous lupus nephritis**
	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
	Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed
	Class V lupus nephritis may show advanced sclerosis
Class VI	**Advanced sclerotic lupus nephritis**
	≥90% of glomeruli globally sclerosed without residual activity

Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.
[a]Indicate the proportion of glomeruli with active and with sclerotic lesions.
[b]Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.

Source: Weening, J. J., et al, 2004, The classification of glomerulonephritis in systemic lupus erythematosus revisited, Kidney International, 65(2), 521–530. https://doi.org/10.1111/j.1523-1755.2004.00443.

The long-term therapeutic goal in the management of both adults and pediatric patients with lupus nephritis is preserving renal function and delaying progression to chronic kidney disease (CKD) and end-stage renal disease (ESRD) resulting in the need for renal replacement therapy (i.e., hemodialysis or renal transplantation) by controlling renal inflammation and minimizing lupus nephritis flares as well as minimizing iatrogenic corticosteroid toxicity thus improving quality of life and kidney and patient survival.[27, 28]

2.2. Analysis of Current Treatment Options

Benlysta (belimumab) IV is the only approved treatment for active lupus nephritis in pediatrics. Table 5 lists the treatments that are currently approved for adults and children with lupus nephritis as well as off-label treatments that are available for the treatment of adults and

[27] Almaani S, et al. Clin J Am Soc Nephrol. 2017; 12:825-835.
[28] Groot N, et al. Ann Rheum Dis 2017;76:1965-1973.

children with lupus nephritis.

Table 5. Summary of Treatment Armamentarium for Lupus Nephritis

Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments for Adults with Lupus Nephritis						
Belimumab	Treatment of adult patients with active LN who receiving standard therapy	2020 (IV and SC)	10mg/kg via IV infusion at 2-week intervals for the first 3 doses and then at 4-week intervals thereafter 400 mg (two 200-mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter	IV: One phase 3 study SC: PK bioequivalence	↑risk for serious infections including PML, hypersensitivity reactions, depression and suicidality	Part of induction therapy with MMF and/or IV cyclophosphamide w/o pulse corticosteroids and as maintenance therapy with MMF and/or azathioprine
Voclosporin	In combination with background immunosuppressive therapy regimen for the treatment of adult patients with active LN	2021	Recommended starting dose is 23.7 mg orally twice a day. Dose is modified based on eGFR. Should not be used in patients with a baseline eGFR < 45ml/min/1.73 m^2. Capsules must be swallowed whole on an empty stomach consistently as close to a 12-hr schedule with a minimum of 8-hrs between doses.	One phase 3 study	↑risk for malignancies and serious infections, nephrotoxicity, HTN, neurotoxicity, hyperkalemia, QT prolongation, and red cell aplasia	Part of induction therapy with pulse corticosteroids and MMF and as maintenance therapy with MMF
FDA Approved Treatments for Children with Lupus Nephritis (ages 5 to 17 years-old)						
Belimumab	Treatment of pediatric patients 5 to 17 years old with active LN who are receiving standard therapy	2022 (IV)	10mg/kg at 2-week intervals for the first 3 doses followed by 4-week intervals thereafter	Extrapolation from adult LN studies	↑risk for serious infections including PML, hypersensitivity reactions, depression and suicidality	
Off-Treatments						

Corticosteroids			Pulse doses of up to 1000 mg/day x 3 days; 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: mucocutaneous and musculoskeletal. manifestations; serositis High Dose: Induction therapy for lupus nephritis, CNS disease, and immune cytopenia
Cyclophos-phamide			IV bolus regimens of 0.5- 1g/m body surface area for once monthly for 6 months	Published literature	Myelosuppression, hemorrhagic cystitis, malignancy, lymphoproliferative disorders, infertility and infections	Induction therapy for lupus nephritis especially refractory disease
Mycophenolate Mofetil			500-1500 mg BID	Published literature	Myelosuppression, GI complaints, myalgia, serious infections including reactivation of viruses	Induction and maintenance therapy for lupus nephritis
Rituximab			1000 mg IV infusions x 2 administered 2 weeks apart; readminister 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 cytopenia
Tacrolimus			0.1 mg/kg/day to a trough of 4-6ng/ml	Published literature	Fatal infections, malignancies, nephrotoxicity, neurotoxicity, hypertension, hyperkalemia, red cell aplasia, QT prolongation	Induction and maintenance therapy especially for refractory lupus nephritis
Cyclosporine			2.5-4 mg/kg/day	Published literature	Hepatoxicity, nephrotoxicity, thrombotic microangiopathy, malignancies, serious Infections, neurotoxicity, hyperkalemia, hypertension	Induction and maintenance therapy especially for refractory lupus nephritis

Lupus nephritis patients are generally managed with standard of care (SOC) induction and maintenance therapy regimens based on published, consensus-driven, international treatment

guidelines by the American College of Rheumatology (ACR), European Alliance of Associations for Rheumatology and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA), and Kidney Disease Improving Global Outcomes (KDIGO) for adults and by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and the Single Hub and Access point for pediatric Rheumatology (SHARE) for children.[29, 30, 31, 32,,33] These adult and pediatric treatment guidelines for lupus nephritis are very similar in their approaches with the choice of induction and maintenance therapy based on a number of factors including histopathological class (including both chronicity and activity scores) on renal biopsy, ethnicity, preservation of fertility, pregnancy, and the presence of nephrotic proteinuria or refractory disease. In both adult and pediatric LN, hydroxychloroquine is recommended at the onset of LN and throughout maintenance, unless contraindicated. Current induction regimens in new onset class III or IV LN are comprised of either high dose pulses or moderate oral doses of corticosteroids plus either low-dose cyclophosphamide (CYC) in combination with belimumab, mycophenolate mofetil (MMF) in combination with belimumab, or MMF in combination with a calcineurin inhibitor. Patients who achieve clinical remission of their lupus nephritis following induction therapy undergo concomitant tapering to low-dose daily oral corticosteroids while initiating maintenance therapy with azathioprine (AZA) or MMF which they receive for the next 3 to 5 years while being monitored for recurring lupus nephritis flares. Patients who fail to respond to the aforementioned induction therapies can be switched to other induction regimens. Alternatively, calcineurin inhibitors (tacrolimus or cyclosporin) can be used as monotherapy or in combination with MMF as induction/maintenance therapy particularly in refractory cases.[34] Rituximab is also commonly used as a treatment for refractory lupus nephritis as add-on therapy to MMF or CYC.[35, 36]

In addition to the treatment of co-morbid conditions such as hypertension and hyperlipidemia, the administration of hydroxychloroquine (to prevent renal flares) and angiotensin inhibitors/angiotensin II receptor blockers (to decrease proteinuria) are also recommended as part of the overall management of adult and pediatric patients with lupus nephritis.[37, 38]

In general, the treatment goal for patients with this disease is complete renal response defined as proteinuria <0.5 -0.7g/24 hours with near-normal glomerular filtration rate achieved by 12

[29] Sammaritano LR, et al. Arthritis Rheum 2025; doi:10.1002/art.43212
[30]Fanouriakis et al. Ann Rheum Dis 2024;83:15–29..
[31] Mina R, et al. Arthritis Care Res 2012;64:375-83.
[32] Groot N, et al. Ann Rheum Dis 2017;76:1965-1973.
[33] KDIGO, Kid International 2024; 105: S1-S69.
[34]Fanouriakis A, et al. Ann Rheum Dis 2024;83:15–29.
[35] Hahn BH, et al. Arthritis Car Res 2021;63(6):797-808.
[36] Groot N, et al. Ann Rheum Dis 2017;76:1965-1973
[37] Fanouriakis A, et al. Ann Rheum Dis 2024;83:15–29.
[38] Groot N, et al. Ann Rheum Dis 2017;76:1965-1973.

months of treatment.[39, 40] This includes evidence of improvement in proteinuria at 3 months, but this timeframe may be extended by 6-12 months for patients with nephrotic range proteinuria.[41]

However, administration of these treatments is not always uniformly effective and is associated with significant side effects resulting in accrual of long-term organ damage (chronic kidney disease that progresses to end-stage renal disease) and toxicity resulting in suboptimal responses. The recent approvals of belimumab (December 2020) and the calcineurin inhibitor voclosporin (January 2021) for the treatment of adults with lupus nephritis receiving standard therapy will hopefully result in an improvement of treatment outcomes in adult patients, but a significant unmet medical need remains for safer and more efficacious treatments for the management of pediatric patients with lupus nephritis.

[39] Fanouriakis A, et al. Ann Rheum Dis 2020; 79:713-723.
[40] Groot N, et al. Ann Rheum Dis 2017;76:1965-1973.
[41] Fanouriakis A, et al. Ann Rheum Dis 2020; 79:713-723.

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, 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, autoantibody-positive SLE. An alternative once weekly 200 mg subcutaneously (SC) administered injection formulation available as a ready to use pre-filled syringe and autoinjector was approved in the U.S. in 2017 for the same indication and is also marketed in all EEA countries, the United Kingdom and Japan as well as 13 additional countries. In 2019, the IV formulation's indication was expanded in the U.S. to include the treatment of children 5 years and older with active, autoantibody positive childhood-onset SLE. Both the IV and SC formulations were also approved in the U.S. in 2020 for the treatment of adult patients with active lupus nephritis on standard of care. In 2022, the IV formulation's LN indication was expanded to include children 5 years of age or older. In 2024, the SC formulation (autoinjector)'s indication was expanded to include the treatment of children 5 years and older with active, autoantibody positive cSLE. In addition, the SLE indication was revised to be more concise by removal of the "autoantibody-positive" language to reflect updated 2019 EULAR/ACR classification criteria for SLE, which required autoantibody positivity for the diagnosis of SLE.

3.2. Summary of Presubmission/Submission Regulatory Activity

As part of the approval action on December 16, 2020, for belimumab subcutaneous (SC) formulation as a treatment for adult patients with active lupus nephritis (BLA 761043/S-013), the Agency required a pediatric postmarketing (PMR 4021-1, [previously 3994-2]) assessment of belimumab SC under the Pediatric Research Equity Act (PREA) as following:

> "Provide an assessment of subcutaneous belimumab for the treatment of patients ages 5 to less than 18 years of age with lupus nephritis who are receiving standard therapy."
>
> Final Report Submission: November 2023

See Section 10 (Pediatrics) of this review for details regarding the Agency's approach to pediatric lupus nephritis development. The Applicant submitted the final assessment report for the pharmacokinetics modeling study 217481 to the Agency on November 29, 2023, to meet the PREA PMR's final report submission milestone. Based on the data generated from this population pharmacokinetics modeling study, the PK bridge for belimumab SC administration was established to support PK/exposure-matching based extrapolation of efficacy from adults with lupus nephritis to pediatric LN. However, because the safety was to be leveraged from the

safety information in children with cSLE (SC and IV) and the Applicant's supplement for cSLE indication was still under review at that time with goal date of May 17, 2024, the Applicant submitted this sBLA 761043/S-034 to expand the belimumab SC's indication for the treatment of patients with active lupus nephritis to include children 5 to less than 18 years of age on August 21, 2024.

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

4.1. Office of Scientific Investigations (OSI)

This section is not applicable as no clinical data from a study conducted with belimumab SC in pediatric subjects with active lupus nephritis were submitted by the Applicant.

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 Office of Medication Error Prevention and Risk Management, Division of Medication Error Prevention and Analysis 1 evaluated the use-related risk analysis (URRA) and threshold analyses (hereafter, referred to as comparative analyses) submitted under BLA 761043/S-034 for Benlysta (belimumab) autoinjector (AI) to determine whether the Applicant needs to submit human factors (HF) validation study results to support their efficacy supplemental application to expand the use of the AI presentation in pediatric patients 5 years and older with active LN.

The review of the URRA and comparative analyses did not identify any new, differing, or unique risks for the proposed product. As such, the Applicant's justification for not submitting HF validation study results as part of their supplemental application is acceptable. The review team has no HF recommendations for this efficacy supplemental application.

See Use-Related Risk Analysis and Comparative Analyses Review in DARRTS under BLA 761043 dated 03/16/2025 for details.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Not applicable as no new nonclinical data were needed or submitted.

6 Clinical Pharmacology

6.1. Executive Summary

On August 21, 2024, the Applicant submitted a Prior Approval efficacy supplement to BLA 761043 (Benlysta® solution for injection 200 mg/mL) and proposed to expand the use of Benlysta® autoinjector for subcutaneous (SC) injection in treatment of pediatric subjects aged 5 years and older with active lupus nephritis (LN). Concurrently, a labeling supplement was submitted to BLA 125370 (Benlysta® intravenous infusion) on the same date to align the draft labeling, as both BLAs share the same US prescribing information (USPI).

Regulatory History for Belimumab in Treatment of active SLE:
Belimumab IV was initially approved for adults with active SLE on March 9, 2011. The approved IV dosing regimen in adult subjects with SLE is 10 mg/kg Q2W for the first 3 doses and Q4W thereafter. This approved dosing regimen was based on two phase 3 randomized controlled trials in adult subjects with SLE (BEL110751 and BEL110752).

The Applicant later developed a solution for SC injection with two presentations (pre-filled syringe (PFS) and autoinjector (AI)), and both PFS and AI presentations were approved for adults with SLE on July 20, 2017. The approved SC dosing regimen in adults with SLE is 200 mg once weekly. This approved dosing regimen was based on one phase 3 trial conducted in adult subjects with SLE (BEL112341) and a relative bioavailability study between PFS and AI (BEL117100).

Subsequently, belimumab IV was approved for SLE in children aged 5 years and older on April 26, 2019. The approved IV dosage for pediatrics is same as adults based on one randomized controlled trial in pediatric subjects aged 5 to 17 years with SLE (BEL110455). Belimumab SC was approved for SLE in children aged 5 years and older on May 16, 2024, based on the full extrapolation via PK matching, using data from one pediatric PK study (200980) following SC administration using AI. The approved SC dosing regimen for pediatrics is based on body weight, with 15 to < 40 kg dosed at 200 mg every 2 weeks and ≥ 40 kg dosed at 200 mg once weekly. The dosing regimen for ≥ 40 kg pediatric subjects is same as adults.

Regulatory History of Belimumab in Treatment of active LN:
Belimumab IV and SC were approved in adult subjects with active LN on December 16, 2020, based on one phase 3 randomized controlled trials in adults with active LN (BEL114054) and population PK simulation for SC administration. The approved IV dose is same for both active LN and active SLE. The approved SC dosage in adult subjects with LN included a loading dose of 400 mg (two 200 mg injections) once weekly for first 4 weeks followed by 200 mg once weekly.

Belimumab IV was approved in pediatric subjects aged 5 years and older with LN on July 26, 2022, based on a full extrapolation approach using population prediction of comparable exposure between adult and pediatric subjects with LN following IV administration.

Summary of Belimumab SC in Treatment of active LN:
In the current sBLA submission, the Applicant also proposed a full extrapolation approach with a PK modeling and simulation study. The exposure of belimumab is estimated to be comparable in pediatric LN patients following SC and adult LN patients following IV, supporting the extrapolation of efficacy from adult LN patients to pediatric patients with LN. The exposure of belimumab in pediatric LN patients following SC is also estimated to be comparable to adult LN patients following IV and cSLE patients following IV or SC. The safety for belimumab SC administration in pediatric LN patients was leveraged from the safety of belimumab IV and SC in cSLE patients.

The comparable PK in adult and pediatric subjects with LN was supported by a population PK model extrapolated or adapted from multiple models including pediatrics SLE IV+SC model, adult LN IV model and adult SLE SC model. These models were derived from 688 adult subjects with SLE following SC administration from trial BEL112341, 224 adult subjects with LN following IV administration from trial BEL114054 and 53 pediatric subjects with SLE following IV administration from trial BEL114055 and 25 subjects with SLE following SC administration from trial 200908. Of note, a population PK model that was developed to support belimumab IV in pediatric subjects with LN was derived from 224 adult subject with LN following IV from trial BEL114054 and validated with 53 pediatric subjects with SLE following IV from trial BEL114055.

With the proposed 2-weight band dosing for SC in pediatric subjects with LN, a slightly lower exposure was estimated in the sub-body weight group (35 to < 40 kg) in the weight band 15 kg to < 40 kg compared to adults LN following IV, corresponding to a slightly higher percent of subjects estimated below 2.5th percentile of adult exposure (25%). However, the simulated exposure for this sub-body weigh group is still comparable to other sub-body weight groups in this weight band who is estimated to have smaller percent of subjects below 2.5th percentile of adult exposure. The lower exposure in this subgroup is not expected to result in clinically meaningful difference in efficacy, based on the available exposure response relationship observed in adults with LN.

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

Pharmacology
Belimumab is a B-lymphocytes stimulator (BLyS)-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. Belimumab does not bind B cells directly, but by binding BLyS, belimumab inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

Clinical Pharmacokinetics
In children 5 to 17 years old with active LN, the pharmacokinetics of belimumab were estimated based on a population pharmacokinetic model developed from adults with LN following IV, 53 pediatric patients with SLE following IV, and 25 pediatric patients with SLE following SC. With weight bracket dosing, the simulated belimumab exposures for both the 5- to 11-year-old group and the 12- to 17-year-old group were comparable to adults with active LN.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing of belimumab SC via autoinjector in children aged 5 years and older with active LN who are receiving standard therapy is based on body weight:

- Pediatric subjects > 40 kg: 400 mg once weekly for 4 doses, followed by 200 mg once weekly
- Pediatric subjects 15 to < 40 kg: 200 mg once weekly for 4 doses, followed by 200 mg once every 2 weeks.

Subjects with LN may transition from IV to SC after completion of at least 2 IV doses. If transitioning, administer the first weekly (for pediatric subjects weighing ≥ 40 kg) or every 2 weeks (for pediatric subjects 15 to < 40 kg) 200 mg SC dose one or two weeks after last IV dose.

Therapeutic Individualization

None.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

See clinical pharmacology review for BLA125370/S-064 (DARRTS date 4/26/2019) for detailed PK assessment and bioanalytical method in pediatric patients with SLE following IV and clinical pharmacology review for BLA761043/S-027 (DARRTS date 5/6/2024) for detailed PK assessment in pediatric subjects with SLE following SC. No clinical or PK studies were conducted in pediatric patients with active LN.

6.3.2. Clinical Pharmacology Questions

What is the strategy to support the efficacy extrapolation from adult subjects with active lupus nephritis to children 5 years and above?

Similar to the approach supporting belimumab IV in children with active LN, a full extrapolation approach is applied to support the use belimumab SC in this population based on the following four aspects:

(1) Disease similarity between adult and pediatric patients with LN
(2) PK bridge between adult and pediatric subjects
(3) Extrapolation of efficacy in pediatric subjects from adult subjects with LN
(4) Justification of the relevance of safety data from children with SLE.

The safety, efficacy, PK, and immunogenicity data collected from the following four clinical trials (BEL112341, BEL114054, BEL114055 and 200908) were used to support the PK based efficacy extrapolation in children 5 to 17 years old with LN. The description of these clinical trials is shown in Table 6.

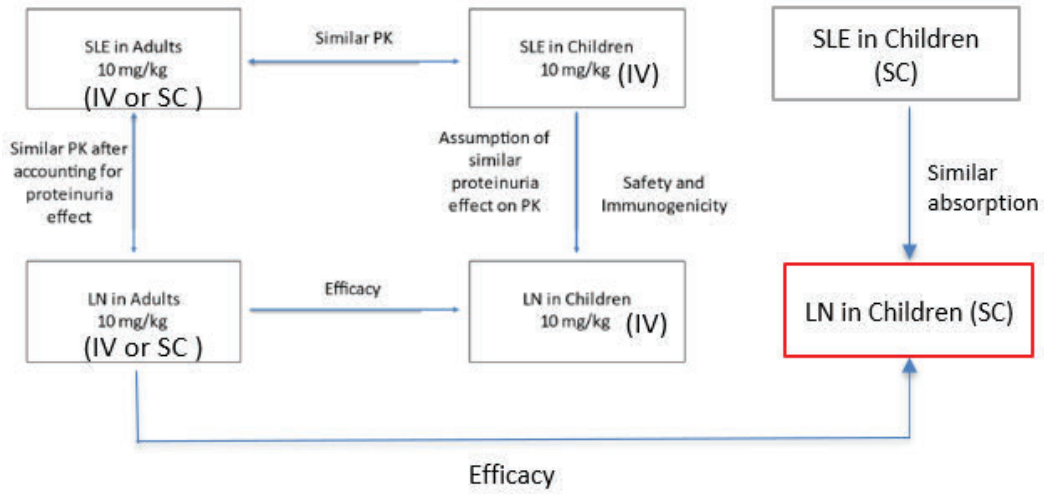
Table 6. Clinical Trials Used to Support PK Based Efficacy Extrapolation for Belimumab SC in Children 5 to 17 Years With LN

Study	Population	Dose and administration	PK sampling times
BEL112341 (BLISS-SC)	Adult SLE patients (n=688). n=4958 observations.	SC, 200 mg, administered weekly for 51 weeks	Pre-dose (day 0), weeks 4,8, 16, 24, and 52, 1-4 weeks after the last dose (for patients exiting before week 52), 8 weeks after the last dose (for patients not entering the extension phase or withdrawing from the study at any time)
BEL114054 (BLISS-LN)	Adult LN patients (n=448; n=224 on placebo and n=224 on 10 mg/kg belimumab). n=2155 observations.	IV 10 mg/kg on days 0, 14 and 28, then every 28 days up to week 100.	Pre-dose (day 0), day 3, weeks 2, 4, 24 (prior to dosing and 0-4 hours after end of infusion), weeks 8 and 52 (prior to dosing), day 171 (week 24 + 3 days, anytime during visit), and week 104 (anytime during visit (or prior to dosing if going into the open-label treatment of the study).
BEL114055 (PLUTO-IV)	Paediatric SLE patients aged 5-17 years, n=93 (n=40 on placebo, n=53 on belimumab). n=560 observations	IV, 10 mg/kg, administered on day 0, 14, 28, then every 28 days (Q28d) until week 48.	Day of dosing on days 0, 14, 28, 56, 168, 364, with additional PK samples collected following the first 2 doses for cohorts 1 and 2.
200908 (PLUTO-SC)	Paediatric SLE patients aged 5-17 years with SLE. n=25. Cohort 1: patients with weight ≥50 kg (n=13), Cohort 2: patients between ≥30 and <50 kg (n=12), Cohort 3: ≥15 to <30 kg (n=0). n=560 observations.	SC, 200 mg, weekly (Cohort 1), Q10d (Cohort 2), or Q2W (Cohort 3).	Cohort 1 and 3: days 8, 15, 29, 57 and 85. Cohort 2: days 11, 21, 31, 61 and 81.

Source: Table 5.1.3. in report for PopPK in pediatric subjects with LN following SC (GSK Document Number RPS-CLIN-089119)

The full extrapolation schema is depicted in Figure 1.

Figure 1. Full Extrapolation Schema for Subcutaneous Belimumab in Pediatric Subjects with Lupus Nephritis



Source: reviewer generated graph. IV=intravenous; SC=subcutaneous; SLE=systemic lupus erythematosus; LN=lupus nephritis; PK=pharmacokinetics.

The disease similarity for active LN between adults and pediatrics was evaluated in Multidisciplinary Review for BLA125370/S-078 (DARRTS date 7/26/2022). Adults and children with LN share the same etiology and pathophysiology, resulting in a similar disease progression and response to standard therapies.

At comparable exposure, similar response between adults and pediatrics subjects with SLE was observed in clinical trials, as similar responder index (SRI) response rates (~50%) was reported for both adults and pediatrics subjects treated with 10 mg/kg IV. The steady state exposure following the same dosing regimen at 10 mg/kg IV was comparable between adults and pediatric subjects with SLE. See Review for sBLA 125370/S-064 (DARRTS Date 4/26/2019). The similar exposure response relationship between adults and pediatrics with SLE support the extrapolation of efficacy from adults to pediatrics for LN, as LN is renal manifestation of SLE. The similarity in disease and response to therapy also supports the extrapolation of efficacy from adults with LN to pediatric subjects with LN.

Although there is no observed PK data available for pediatric subjects with LN, the PK data for pediatric subjects with LN can be reasonably estimated from the available PK data in pediatrics with SLE and adults with SLE and LN. With similar proteinuria effect, the estimated PK data from pediatric subjects with LN following SC is similar to PK data from adult subjects with LN, and support the establishment of a bridge to allow extrapolation of efficacy results from adults with LN.

Based on the previous clinical trial conducted in adult subjects with LN following IV treatment (BEL114054), belimumab clearance was associated with proteinuria. When the proteinuria was decreased to approximately ≤1 g/g after treatment, belimumab clearance and exposure in patients with LN were similar to that observed in patients with SLE who received belimumab 10 mg/kg intravenously. PK would be similar in adults with LN and adults with SLE after accounting for proteinuria impact. The proteinuria impact on PK is expected to be similar between adults and pediatric subjects with LN, which has been discussed in review by Dr. Tao Liu under BLA125370/S-078 (DARRTS date 7/26/2022).

PK data for pediatric subjects with SLE following both IV and SC have been evaluated in previous trials (BEL110455 for IV and 200908 for SC). PK for pediatrics subjects with SLE following SC or IV is comparable to adults with SLE. The proteinuria effect on PK is also expected to be similar between adults and pediatric subjects with LN, as a similar proteinuria-albumin relationship was demonstrated between these two populations. Therefore, based on similar PK between pediatric and adults with SLE, it is reasonable to estimate that PK for pediatric subjects with LN following SC is also similar to adults with LN, after considering similar proteinuria impact on PK between adults and pediatrics and the absorption component following SC in pediatrics based on previously observed pediatric PK data.

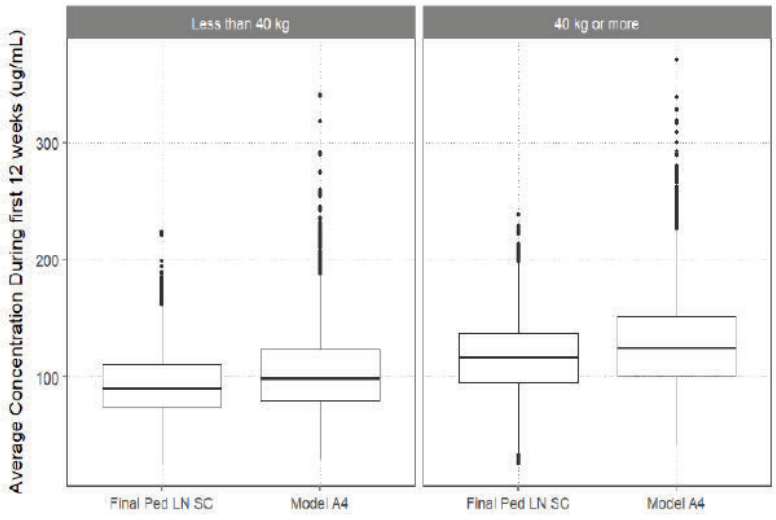
Despite no clinical data with pediatric subjects with LN, safety information from relevant population such as pediatric subjects with SLE and adult subjects with LN based on previously conducted clinical trials can be leveraged.

Is the Applicant's population pharmacokinetics model appropriate for the prediction of pharmacokinetics in children 5 years and older with active lupus nephritis following SC administration?

Yes, the Applicant's population PK (PopPK) model for prediction PK in pediatric subjects with active LN is developed by extrapolation or adaption from multiple models including pediatrics SLE IV+SC model, adult LN IV model and adult SLE SC model.

The Applicant validated the final model for predicting pediatric subjects with LN following SC (final pediatric LN SC model) in pediatric subjects with SLE. The new model adequately predicted belimumab exposure (average concentration during first 12 weeks ($C_{avg,}$(Week 0-12)) in pediatric subjects with SLE and the prediction results were comparable with exposure predicted from the population PK model previously developed on the cSLE IV+SC dataset (Figure 2). The cSLE IV+SC model was previous reviewed by Dr. Tao Liu under BLA761043/S-027 (DARRTS date 5/6/2024).

Figure 2. Comparison of Belimumab C_{avg} (Week 0 to 12) Prediction in Virtual Pediatric Subjects with SLE Between Final Pediatric LN SC Model and Previously Reviewed cSLE IV+SC Model



Each panel represents a weight class. The x-axis represents the population PK models used to predict the average belimumab concentrations during the first 12 weeks in 10,000 virtual pediatric SLE patients aged 5 to 17 years. Box plots show the median (central bar), inter-quartile range (box) and the nearest data point no more than 1.5 time above and below the box (whisker). The simulated dosing regimen was the 2-weight SC band regimen approved for pediatric patients with SLE: 200 mg Q2W for 15 to <40 kg; 200 mg QW for ≥40 kg.
Ped = Pediatric; PK = Pharmacokinetic; SLE = Systemic lupus erythematosus; SC = Subcutaneous(ly); QW = Once every week; Q2W = Once every 2 weeks.

Source: Figure 7.4.6 in report for PopPK in pediatric subjects with LN following SC (GSK Document Number RPS-CLIN-089119). Model A4 is previous reviewed cSLE IV+SC model in BLA761043/S-027 (DARRTS date 5/6/2024).

The proteinuria and albumin component of the final pediatric LN SC model was directly taken from the adult LN population PK model. Adult LN model was reviewed by Dr. Tao Liu under BLA125370/S-073 (DARRTS date 12/16/2020). The justification of using adult proteinuria and albumin in pediatric subjects with LN has been provided and reviewed by Dr. Tao Liu under BLA125370/S-078 (DARRTS date 7/26/2022).

Does the proposed dosing regimen result in similar belimumab exposure in pediatric patients and adult patients with LN?

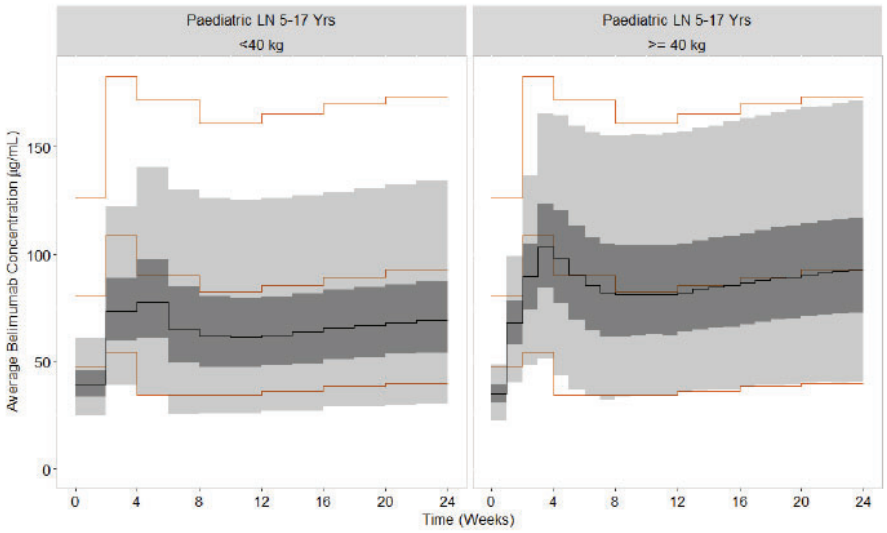
Yes. Based on the PopPK model in pediatric subjects with LN following SC, the Applicant conducted PK simulation for the proposed dosing regimen in pediatric subjects 5 years and older. The simulated belimumab PK parameters in pediatric subjects with LN compared to adult with LN is presented in Table 7 and the simulated concentration time profile in pediatric subjects with LN is depicted in Figure 3. See section 15.4.1 pharmacometrics review for additional details for the PK simulation.

Table 7. Simulated Belimumab Pharmacokinetics Parameters in Virtual Population of Adult and Pediatric Subjects with Lupus Nephritis

	Median (95% Prediction Interval) (µg/mL) [% Below Adult LN IV Cavg 2.5th Percentile Value]		
	Adults with LN IV	Children with LN SC < 40 kg	Children with LN SC ≥ 40 kg
C_{avg} (Week 0-12)	89 (41 – 161) [2.5]	63.3 (30.0-116) [11.7]	81.4 (38.0-140) [3.6]
$C_{avg,ss}$ (Week 24)	92.8 (40 –173) [2.5]	69.2 (30.3-134) [7.8]	92.7 (40.6-171) [2.4]
C_{min} (Week 12)	34 (4 - 101)	45.1 (13.6-105)	73.9 (27.9-148)
$C_{min,ss}$ (Week 24)	44 (6 – 112)	52.6 (17.1-114)	85.3 (33.9-164)
C_{max} (Week 12)	254 (173 – 388)	73.0 (36.0-138)	75.3 (37.8-161)
$C_{max,ss}$ (Week 24)	259 (177 - 392)	80.6 (40.7-147)	96.8 (44.3-177)

Source: Adapted from Table 11.3.20 and in Table 11.3.21 in report for PopPK in pediatric subjects with LN following SC (GSK Document Number RPS-CLIN-089119) for pediatrics simulated PK parameters and Table 7 in report for PopPK amendment 1 in children LN simulation report (GSK Document Number PRS-CLIN_061677) for adult simulated PK parameters.
Note: Cavg(Week 0-12): average concentration over the first 12 weeks of treatment; Cavg(Week 12): average concentration during the last dose interval before 12 weeks; Cavg,ss(Week 24): average concentration during the last dose interval before 24 weeks(steady state); Cmin(Week 12): trough concentration during the last dose interval before 12 weeks; Cmin,ss(Week 24): trough concentration during the last dose interval before 24 weeks (steady state); Cmax(Week12): maximum concentration during the last dose interval before 12 weeks; Cmax,ss(Week 24): maximum concentration during the last dose interval before 24 weeks (steady state).

Figure 3. Simulated Belimumab Average Concentration (C_{avg}) Over Each Dosing Interval in Pediatric Subjects with LN Aged 5-17 Years Following SC By Weight Band (< 40 kg and ≥ 40 kg) Compared to Adults LN with IV



Source: Figure 7.4.9 in report for PopPK in pediatric subjects with LN following SC (GSK Document Number RPS-CLIN-089119). The simulation is based on 2-weight band dosing regimen (15 to < 40 kg: 200 mg once weekly for 4 doses followed by 200 mg once every 2 weeks; ≥ 40 kg: 400 mg once weekly for 4 doses followed by 200 mg once weekly). The median (black solid line), inter-quartile range (dark shaded region), 95% prediction interval (light shaded region) are shown with the adult median and 95% prediction interval (41 to 161 µg/mL orange lines).

Based on the simulation results, the steady state exposure is reached before the 4th loading dose (200 mg once weekly for 15 to <40 kg and 400 mg once weekly for ≥ 40 kg). The simulated average concentration during first 12 weeks (C_{avg} (week 0-12)) and steady-state average concentration during last dosing interval at Week 24 ($C_{avg,ss}$ (Week 24)) for pediatric subjects with LN in ≥ 40 kg are estimated to be similar compared to simulated adults with LN.

However, the simulation results showed around 30% lower median C_{avg} (week 0-12) (63.3 µg/mL vs.89 µg/mL) and median $C_{avg,ss}$ (Week 24) (69.2 µg/mL vs. 92.8 µg/mL) in pediatrics subjects < 40 kg following the proposed SC dosing compared to adults with LN following IV. The lower exposure was mainly driven by children in the higher end of body weight group (35 to < 40 kg) in this weight band, as suggested in the simulated exposure in pediatrics subjects by 10 kg weight bands following proposed SC dosing in comparison to adult exposure (Table 8).

Table 8. Simulated Belimumab C_{avg} (Week 0-12) By 10 Kg Weight Bands in Pediatric Subjects Aged 5 to 17 Years Following SC

	Cavg(Wk 0-12) (μg/mL)		LT025 (%)	LT975 (%)
Weight band	Geometric mean [GeoCV (%)]	Median (95% percentile)		
≥15-<20 kg	75.1 [32.7]	77.3 (38.1-130)	4.0	100
≥20-<25 kg	66.0 [32.5]	68.1 (32.8-113)	8.3	100
≥25-<30 kg	58.9 [32.8]	60.7 (29.7-101)	14.0	100
≥30-<35 kg	53.8 [31.8]	55.1 (27.0-91.0)	18.2	100
≥35-<40 kg	50.0 [32.3]	51.3 (25.3-85.6)	25.2	100
≥40-<45 kg	89.8 [32.3]	92.5 (45.3-155)	1.2	98.4
≥45-<50 kg	85.3 [32.0]	87.9 (43.2-146)	1.7	99.1
≥50-<55 kg	80.7 [31.7]	82.6 (40.2-136)	2.8	99.7
≥55-<60 kg	76.5 [31.6]	78.4 (39.2-129)	3.4	99.9
≥60-<65 kg	73.1 [31.5]	75.4 (37.7-124)	4.4	99.9
≥65-<70 kg	70.0 [31.7]	72.2 (35.7-119)	5.8	100
≥70-<75 kg	67.9 [31.6]	69.9 (35.0-114)	6.6	100
≥75-<80 kg	65.2 [32.0]	67.3 (32.8-110)	8.3	100
≥80-<85 kg	62.9 [31.5]	64.8 (32.1-107)	9.5	100
≥85-<90 kg	60.6 [32.6]	62.4 (30.2-103)	11.9	100
≥90-<95 kg	59.0 [31.4]	60.5 (30.1-99.7)	12.6	100
≥95-<100 kg	57.7 [31.4]	59.6 (29.7-97.1)	14.1	100
Adult LN IV	87.0 [36.0]	89.1 (41.1-161)	2.5	97.5

Source: Table 7.4.12. in in report for PopPK in pediatric subjects with LN following SC (GSK Document Number RPS-CLIN-089119). Adult LN IV denotes the reference values obtained by simulating Cavg (Wk 0-12) for an adult LN IV population6. LT025: percentage of subjects below the adult lower threshold (2.5th percentile) of 41 μg/mL. LT975: percentage of subjects below the adult LN IV upper threshold (97.5th percentile) of 161 μg/mL

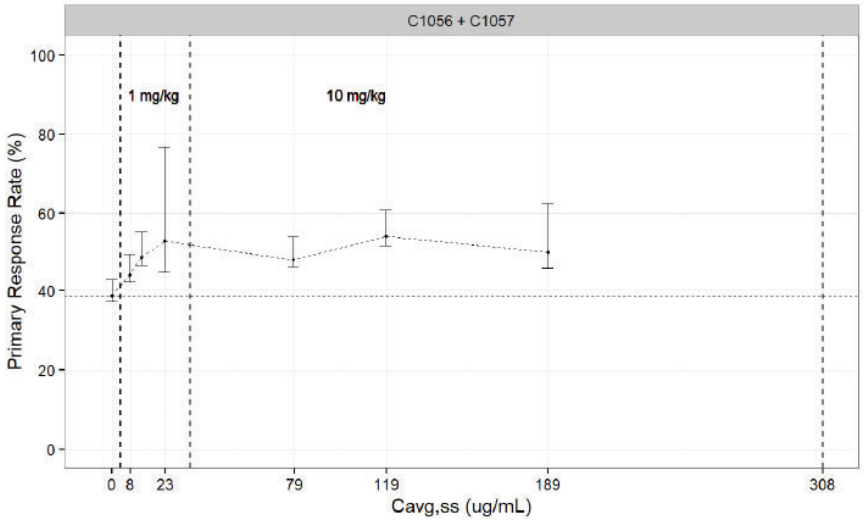
The 35 kg to < 40 kg group is estimated to have 25% subjects below 2.5th percentile of adult exposure. However, the median (51.3 μg/mL) and geometric mean (50 μg/mL) values for C_{avg} (Week 0-12) for this sub-group is similar to other sub-body weight groups in this weight band (e.g., 30 to < 35 kg group with a median of 55.1 μg/mL and geometric mean of 53.8 μg/mL).

The slightly lower exposure estimated in pediatric subjects with LN in 35 to < 40 kg following the proposed SC regimen is not expected to result in clinically meaningful difference in efficacy compared to adults or pediatrics in other body weight groups, based on the exposure response relationship observed in adults with LN and similar response expected in pediatric subjects.

Belimumab was initially investigated in adult subjects with SLE with a wide dose range from 1 mg/kg to 10 mg/kg IV. In the phase 3 clinical trials (BEL110751 and BEL110752), the SLE Responder Index (SRI) response rate reached the maximum effect in subjects with an average

concentration at steady state above 22.7 µg/mL (**Figure 4**). Children with SLE also had similar exposure response relationship as adults based on the previous clinical trial (BEL114055).

Figure 4. SRI Response vs. Average Concentration at Steady State Following Belimumab 1 mg/kg to 10 mg/kg In Adults with SLE

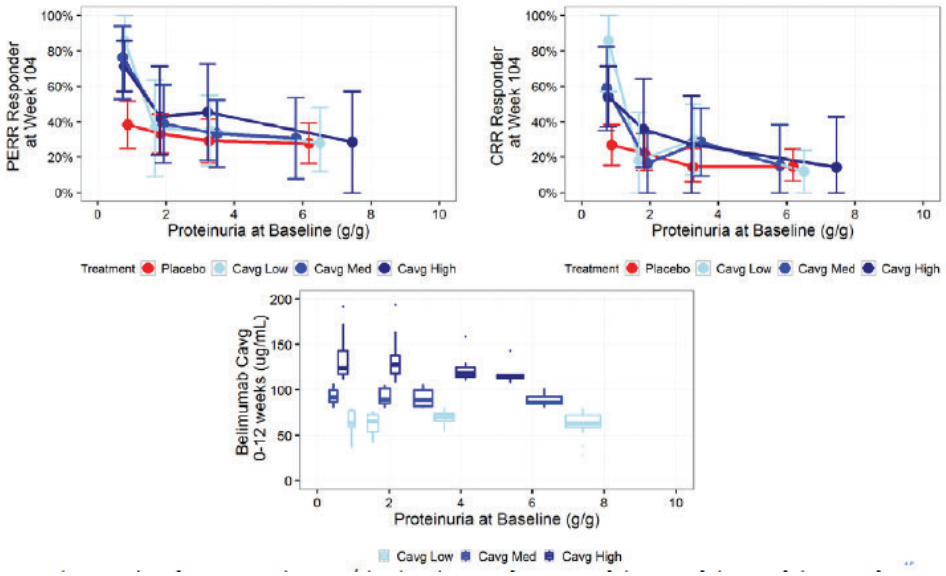


Source: Figure 2, Multidisciplinary review for BLA 125370/S-08 by Dr. Tao Liu (DARRTS date 7/26/2022)
Cavg,ss is the individual predicted average belimumab concentration at steady state, derived from the population PK analysis of the adult IV phase 3 studies BEL110751 and BEL110752. The response rate for each concentration category is displayed as the median (points) with 95% confidence interval (vertical bars). The response rate for placebo is also shown as the horizontal broken line. The vertical dash lines represent the observed Cavg,ss range for 1 mg/kg and 10 mg/kg, respectively. The response rate of placebo subjects is shown by the Cavg,ss=0 category.

LN is a serious manifestation of SLE with renal involvement. The highest dose (10 mg/kg IV) evaluated in adult subjects with SLE were investigated and approved in adult subjects with LN. In patients with active LN, a greater belimumab clearance is associated with worse proteinuria. With various levels of proteinuria at baseline and different resolution of proteinuria during treatment, belimumab clearance can differ between subjects with LN who have different proteinuria at baseline and the clearance can also change over time within each individual due to the resolution of proteinuria.

The need of dose adjustment based on proteinuria has been evaluated from clinical trial results in adults with LN (BEL114057). The exposure response analysis stratified by baseline proteinuria did not indicate exposure dependent efficacy response in terms of primary efficacy renal response (PERR) and complete renal response (CRR) at Week 104 within each baseline proteinuria quartiles (Figure 5).

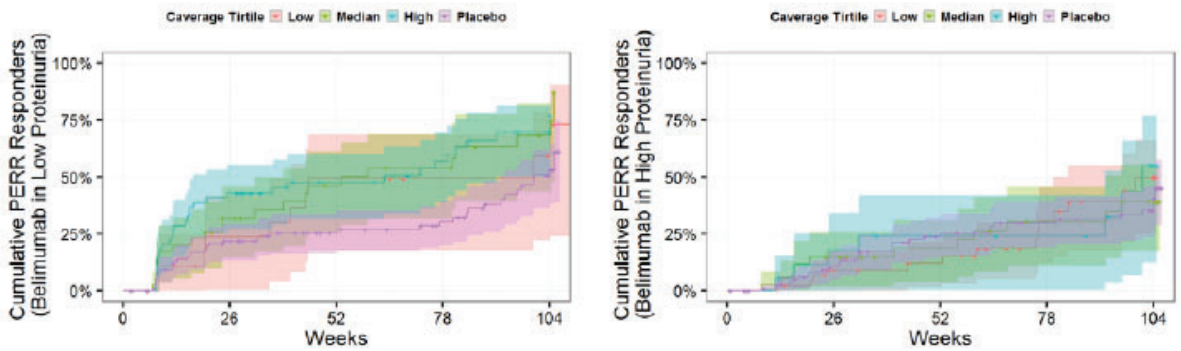
Figure 5. Exposure Response in Subjects with LN Over Different Baseline Proteinuria



Source: Figure 12. Multidisciplinary review for BLA 125370/S-073 by Dr. Tao Liu (DARRTS date 12/16/2020)
Note: The quartiles of proteinuria (uPCR, g/g) at baseline are: [0.159, 1.24], (1.24, 2.5], (2.5, 4.6], (4.6, 35.1]
The tertiles of Caverage (week 0 to 12) are: [28, 80], (80, 107], (107, 194]

Based on trial BEL114057 in adult subjects with LN, only subjects with low proteinuria (uPCR < 2.5 g/g) at baseline demonstrated a higher and faster response to belimumab, while subjects with high proteinuria (uPCR ≥ 2.5 g/g) showed lower CRR and PERR response rate at Week 104. In subjects with high baseline proteinuria, higher exposure did not result in a better efficacy in time to PERR, as shown in **Figure 6**.

Figure 6. Time to PERR Response for Adult Subjects with Lupus Nephritis by Treatment and Exposure Tertiles



Source: Figure 13. Multidisciplinary review for BLA 125370/S-073 by Dr. Tao Liu (DARRTS date 12/16/2020)
Note: The tertiles of Caverage (week 0 to 12) are: [28, 80], (80, 107], (107, 194]. PERR= primary efficacy renal response, Low proteinuria: uPCR < 2.5 g/g, High proteinuria: uPCR >= 2.5 g/g

Although there was only one dosing regimen 10 mg/kg IV Q4W evaluated in the clinical trial for adult subjects with active LN (BEL114054), which may limit the interpretation for exposure response analysis, the available exposure response findings based on BEL114054 stratified by baseline proteinuria indicates that dose adjustment is not warranted for high proteinuria.

Pediatric subjects with LN are expected to respond similarly to belimumab as adults, based on the disease similarity between the two populations and similar responses observed in SLE. LN is one of the severe manifestations of SLE. The mechanism of action for belimumab remains the same in treatment of SLE and LN in reducing autoimmune response by blocking the binding of soluble BLyS to inhibit the survival of B cells including autoreactive B cells and reduce the differentiation of B cells into immunoglobulin-producing plasma cells. Circulating BLyS protein are reported to be elevated in both adults and pediatric subjects with SLE, suggesting phenotypic similarity between pediatrics and adults with SLE.[42]

Overall, based on the available exposure response relationship observed in adults with LN, a similar efficacy response is expected in pediatrics with LN based on comparable belimumab exposure following the proposed dosing regimen, and a higher percent of subjects with systemic exposure below 2.5th percentile of adult exposure is not expected to result in a clinically meaningful difference in efficacy.

Does the proposed dosing regimen result in similar belimumab exposure in pediatric patients with SLE?

The simulated exposure ($C_{avg,ss}$) for pediatric subjects with LN following SC is generally within the range compared to concentration observed in pediatric subjects with SLE following IV and simulated concentration for pediatrics with SLE following SC, with numerically lower point of estimates (Table 9). This is consistent with the previous comparison results between simulated pediatric subjects with LN following IV and pediatric subjects with SLE, as proteinuria effect can impact the exposure (see section 15 for Pharmacometrics Review). The similar or lower exposure in pediatric subjects with LN following SC supported leveraging the safety information from cSLE following IV and SC.

[42] Hong SD, Reiff A, Yang HT, et al. B lymphocyte stimulator expression in pediatric systemic lupus erythematosus and juvenile idiopathic arthritis patients. Arthritis Rheum. 2009;60(11):3400-3409. doi:10.1002/art.24902

Table 9. Simulated Exposure (Steady State Average Concentration $C_{avg,ss}$) in Pediatric Subjects with LN Following SC or IV Compared to Simulated or Derived from Observed Exposure in Pediatric Subjects with SLE Following SC or IV

		Median (95% Percentile Interval)	
		Pediatric LN (SC)	**cSLE (SC)**
$C_{avg,ss}$ (µg/mL)	< 40 kg 200 mg Q2W	69.2 (30.3-134)	94.7 (47.6- 197.8)
	≥40 kg 200 mg QW	92.7 (40.6-171)	129 (63.4- 256.3)
		Pediatric LN (IV)	**cSLE (IV)[a]**
$C_{avg,ss}$ (µg/mL)	5 to 11 years 10 mg/kg	64 (26.3- 131.3)	92 (49-142)
	12 to 17 years 10 mg/kg	86.2 (37.6-86.2)	112 (21-238)
	Total	71.8 (28.8-153.4)	108 (21-238)

Source: Adapted from Table 11.3.20 in report for PopPK in pediatric subjects with LN following SC (GSK Document Number RPS-CLIN-089119); Table 8.1 in PopPK report for pediatric subjects with SLE following SC (GSK Document Number TMF-1637375) and Table 7.2 in PopPK report amendment 1 in pediatric subjects with LN following IV (GSK Document Number RPS-CLIN-061677) and Table 7 in CSR BEL115044 Attachment 2 PopPK report in pediatric subjects with SLE following IV and SC (GSK Document Number 2017N343626_01)
[a]Geometric mean (range) was reported
$C_{avg,ss}$=average concentration at steady state

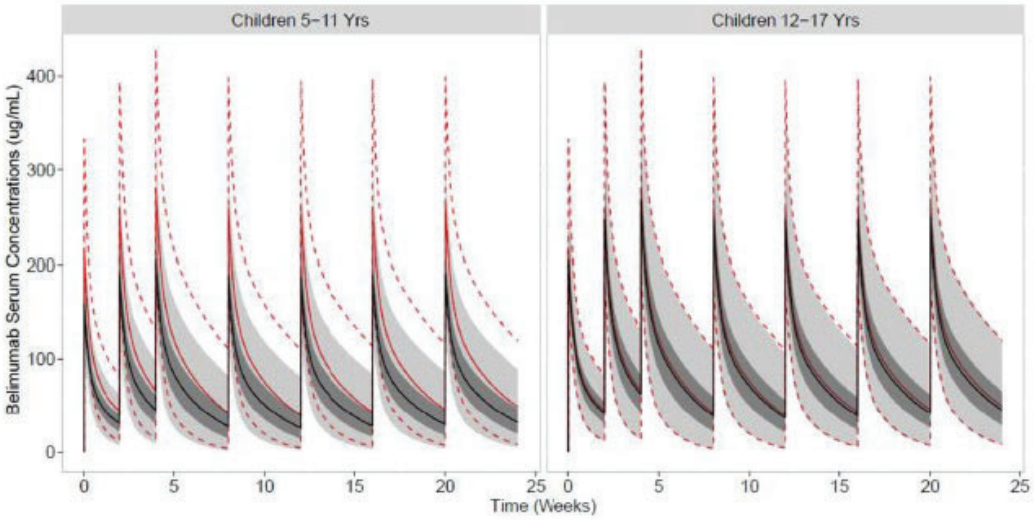
Is the proposed transition schedule from IV to SC adequate for pediatric subjects with LN?

Yes. The proposed transition schedule is adequate and is in line with approved transition schedule for adult subjects with LN.

Adult subjects with LN may transition from IV to SC after subjects completed the first 2 IV doses and the first SC 200 mg weekly should be administered 1 to 2 weeks after last IV dose.

For pediatric subjects, the Applicant proposed that at least 2 IV doses should be administered first to ensure belimumab exposure reaches steady state and are comparable across the pediatric range. Based on simulated PK results for belimumab IV in children with LN, steady state is reached after first 2 IV doses of 10 mg/kg, as shown in Figure 7.

Figure 7. Simulated Concentrations over Time in Adults and Children with LN Receiving Intravenous Belimumab 10 mg/kg



Source: Figure 7 in PopPK children LN simulation report [GSK Document Number 2021N491623_00]
Simulated dosing regimen: 10 mg/kg IV on days 0, 14 and 28 then every 4 weeks. The pediatric median (black solid line), inter-quartile range (dark shaded region) and 95% prediction interval (light shaded region) are shown with the adult median (solid red line) and 95% prediction interval (broken red lines).

The Applicant proposed that the first 200 mg SC weekly dose (for ≥ 40 kg) or every 2 weeks dose (for 15 to < 40 kg) should be administered 1 to 2 weeks after last dose of IV. The duration is the same as for adults with LN. Given that the systemic exposure is estimated to be similar between adults and pediatrics with LN following SC, it is acceptable to include the same duration between last dose of IV and first dose of SC.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

No new clinical data were submitted to support this application. Rather, the Applicant relied on data from already completed studies in adult lupus nephritis (belimumab IV) and cSLE (belimumab IV and belimumab SC). The key design features of the pertinent clinical trials are summarized in Table 8 below.

Table 8. Listing of Clinical Trials Relevant to this BLA

Trial Identity NCT no. *No. of Centers/ Countries*	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
Adult Studies in SLE and LN to Support Efficacy						
BEL114054 **BLISS-LN** NCT-01639339 *107 sites in 21 countries*	Phase 3, MC, R, DB, PC, 104-week study to evaluate efficacy, safety, and tolerability of belimumab in **adults with lupus nephritis**	Belimumab IV 10mg/kg on days 0, 14, and 28, then every 28 days thereafter up to Week 100. All subjects received concomitant standard SLE therapy.	Primary endpoint: primary efficacy renal response (ratio of urine protein to creatinine of ≤0.7, eGFR no worse than 20% below the pre-flare value or at least 60mL/minute, and no use of rescue therapy) at Week 104 Secondary endpoints: complete renal response (urine protein to creatinine ratio <0.5, eGFR no worse than 10% below pre-flare value of ≥90 mL/minute, and no rescue therapy) at Week 104, primary renal response at Week 52, and ordinal renal response without urinary sediment at Week 104.	Screening and randomization visits on Day 0, 14, 28, and then every 28 days until Week 104, plus one follow-up visit 8 weeks after the last dose Subjects who completed the study through Week 100 were eligible to enter into a 6 month open-label extension.	N = 448 Belimumab 10mg/kg IV = 224 Placebo = 224	Adults age ≥18 years with autoantibody-positive SLE fulfilling ACR criteria, urine protein/creatinine ratio ≥1, and biopsy-proven Class III or IV LN, with or without coexisting Class V, or pure class V LN within 6 months before or during screening. Individuals with dialysis within 1 year, GFR <30, failures of prior CYC or MMF induction, or receipt of B-cell-targeted therapy within 1 year were excluded.
Pediatric Studies in cSLE to Support Efficacy and Safety						

BEL114055/C1109 (PLUTO) NCT-01649765 *Total of 29 sites in 10 countries (Argentina, Canada, Japan, Mexico, Peru, Poland, Russian Federation, Spain, United Kingdom, and United States)*	Phase 2, MC, R, DB, PC, parallel group study in **children with SLE** (Part A) with a long-term OL safety follow up for subjects who completed Part A (Part B), and the long-term safety follow up for subjects who withdrew any time from Part A or B (Part C, ongoing)	Belimumab 10mg/kg or Placebo IV 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 subject does not drop out before Week 52 AND does not meet treatment failure criteria	Screening and randomization visits with visits on Day 0, 14, 28, and then every 28 weeks thereafter 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 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 years old with SLE as defined by ACR criteria that is active per SELENA SLEDAI disease activity score ≥6 at screening with +autoantibodies on stable SLE treatment for ≥30 days prior to Day 0. Individuals with severe active LN or CNS lupus were prohibited.
200908 (PLUTO-SC) *Total of 11 sites in 7 countries (Argentina, Germany, Japan, Mexico, Netherlands, Spain, and United States)*	Phase 2, single arm, MC, OL trial (Parts A and B) in **children with SLE** Part A: 12-week treatment phase Part B: optional 40 Week OL continuation phase	Belimumab 200mg via autoinjector Weight ≥40 kg: weekly Weight ≥15 kg to <40 kg: every 2 weeks	Primary PK endpoints: belimumab concentrations at Week 12; Cavg (AUC), Cmax, and 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 – 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 Weeks 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 logistical reasons could enroll in the optional access extension phase	N=25 Cohort 1 (≥50kg) = 13 Cohort 2(≥30kg-<50kg) = 12 Cohort 3 (<30kg) = 0	Pediatric subjects ages 5 to 17 years of age and weighing ≥15kg with active SLE with a SELENA SLEDAI score ≥6 at screening

7.2. Review Strategy

The Applicant did not submit any clinical studies of belimumab SC conducted in pediatric subjects with active lupus nephritis to support this application. As permitted under 21 CFR 314.55, an assessment of belimumab SC treatment in children with active lupus nephritis was conducted via an extrapolation approach from existing efficacy, safety, and PK data in children and adults with SLE and in adults with LN treated with belimumab IV and SC. As the efficacy and safety of belimumab in children and adults with active SLE and adults with active LN has been previously established, these data will not be reviewed again here.

- Data from study BEL114054 (BLISS-LN) were submitted under BLA 125370/S-073 to support the approval of belimumab IV and SC for the treatment of adults with active LN. See the review dated December 16, 2020, for details of this study.
- Data from study BEL114055 (PLUTO) were submitted under BLA 1253770/S-064 to support the approval of belimumab IV for the treatment of children with active SLE. See the review dated April 26, 2019, for details of this study.
- Data from study 200908 (PLUTO-SC) were submitted under BLA 761042/S-027 and BLA 125370/S-081 to support the approval of belimumab SC for the treatment of children with active SLE. See the review dated May 16, 2024, for details of this study.

The Applicant provided the following information to support the proposed PK/exposure-matching approach to extrapolate the efficacy of belimumab IV in adults with active LN to belimumab SC in children with active LN:

- Support for the disease similarity of pediatric and adult LN as discussed in Section 2.1 Analysis of Condition
- Justification that PK of belimumab SC would be expected to be similar in adult LN and pediatric LN as discussed in Section 6.3 Comprehensive Clinical Pharmacology Review
- Justification and information to support the extrapolation of efficacy of belimumab in pediatric LN from the efficacy established for belimumab in an adequate and well controlled study in adult LN

In addition, to support safety, the Applicant provided justification and information to support the relevance of the safety data in cSLE to pediatric LN (Studies BEL114055/C1109 and 200908), as well as the established safety of belimumab IV in pediatric LN and belimumab (SC and IV) in adult SLE and LN.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Integrated Assessment of Effectiveness

Study BEL114054 (BLISS-LN) was the pivotal trial that established the efficacy of belimumab IV in adults with LN. The study was previously reviewed under BLA 761043/S-013.

The extrapolation of efficacy for belimumab SC from adults with active LN to children (ages 5 to 17 years of age) is based on the similarity of disease between pediatric LN and adult LN (Section 2). In addition, the Applicant provided adequate justification of the PK bridge from adults with LN to children with LN based on comparable PK data from adults with LN (belimumab IV) and children with SLE (belimumab IV and SC), as reviewed in Section 6. Therefore, based on the submitted information, it is reasonable to extrapolate efficacy of belimumab from adult LN to pediatric LN based on a PK/exposure-matching approach.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of belimumab SC in pediatric patients with active LN is leveraged from the safety of belimumab SC and IV in cSLE and further supported by belimumab IV in adult LN.

The Applicant referenced the safety data from the following clinical trials:

- Study BEL114055, a 52-week, randomized, double blind, placebo-controlled study conducted with belimumab IV in pediatric patients with active SLE despite standard of care. Data from this study were submitted under BLA 125370/S-064. Please see review dated April 26, 2019.
- Study 200908 was a phase 2, single-arm, multicenter, open-label study conducted with belimumab SC in pediatric patients with active SLE who weighed ≥15 kg. Data from this study were submitted under BLA 761043/S-027. Please see review dated May 16, 2024.

Since the safety data from these two studies were previously reviewed in support of the marketing approval of belimumab IV as treatment for pediatric patients aged 5 to 17 years old with active SLE or LN and belimumab SC as treatment for pediatric patients aged 5 to 17 years old with active SLE, these data will not be re-presented here. In addition, the safety of belimumab IV as treatment for pediatric patients aged 5 to 17 years old with active LN was

reviewed as part of BLA 125370/S-078 and was supportive of its approval. Although there were no clinical trials conducted in pediatric LN, the safety was leveraged from cSLE and was determined to be consistent with the known safety profile in adult SLE and LN. The safety databases that established safety in adults with SLE and LN were previously reviewed at the time of submission for BLA 125370 (belimumab IV for adult SLE), BLA 761043 (belimumab SC for adult SLE), BLA 125370/S-073 (belimumab IV for adult LN), and BLA 761043/S-013 (belimumab SC for adult LN), and the safety of adult SLE and LN will not be reviewed here.

To supplement the safety from the previously reviewed clinical trials, the Applicant provided a brief update to the optional post-Week 52 access extension phase (AEP) of Study 200908 in cSLE. In addition, the Applicant submitted the postmarketing experience of belimumab in cSLE and adult SLE and LN. These data will be reviewed briefly below.

8.2.2. Integrated Assessment of Safety

The safety profile of belimumab has been previously established based on safety data from more than 7400 clinical trial subjects exposed to belimumab in SLE trials, include 347 adult subjects with active LN and 109 pediatric subjects with SLE.

Important identified risks are infections, hypersensitivity reactions, and psychiatric events including depression and suicidality, and important potential risks include progressive multifocal leukoencephalopathy (PML) and malignancies. The safety profile of belimumab has largely been informed by the experience of belimumab IV and SC in adult patients with SLE and LN. Five large double-blind, randomized, controlled efficacy and safety trials and a large double-blind, randomized, controlled safety trial contributed to the safety database in adult SLE. The safety from study BEL114054 in adult LN was comparable to the safety profile established in adult SLE.

Overall, from clinical trials in pediatric patients aged 5 to 17 years with active SLE, belimumab IV and SC plus standard therapy demonstrated an acceptable safety profile consistent with the known safety profile of belimumab IV and SC plus standard therapy in adult SLE/LN patients. At the time of review of belimumab IV for pediatric LN, the safety assessment based on updated data from study BEL114054 (belimumab IV in cSLE) and postmarketing data did not reveal new safety signals. Safety data collection is ongoing in the optional post-Week 52 AEP of study 200908 (belimumab SC in cSLE). As of June 10, 2024, no new serious adverse events (SAEs) or safety findings were reported.

The cumulative post-marketing exposure through December 31, 2023, was estimated at 281,758 patient-years (174,578 patients-years for the IV formulation and 107,180 for the SC formulation). The postmarketing experience in cSLE or pediatric LN is limited. From the Periodic Benefit-Risk Evaluation Report (PBRER, dated March 8, 2024), based on number of belimumab prescriptions between July 1, 2011, to December 31, 2023, there has been 1 prescription for

cSLE (age 0 to 17 years). Also, as of March 8, 2024, there were very few reports (14 references) of belimumab use in children in the literature. Most articles included data from study BEL114055 and a small number of additional cases in children with limited safety data.

In conclusion, it is reasonable to leverage the safety data from clinical trials of belimumab SC and IV in cSLE. No new or unexpected safety signals were identified on review of the cumulative safety data from the ongoing open-label extension of study 200908 or the updated spontaneous postmarketing safety data in children or adults with SLE or LN. No updates of the existing Warnings and Precautions in the current belimumab USPI are warranted, and no additional postmarketing safety studies are necessary based on this submission.

8.3. Statistical Issues

As no new clinical data were submitted as part of this submission, there are no statistical issues.

8.4. Conclusions and Recommendations

The recommended regulatory action is approval for belimumab autoinjector for SC administration for the treatment of children ages 5 years and older with active LN on standard of care.

The effectiveness of belimumab SC is based on PK matching in pediatric and adult subjects, which permitted extrapolation of efficacy of belimumab from adults with LN (study BEL114054 [BLISS-LN]). The belimumab IV study in adult LN was an adequate and well-controlled clinical trial that has been previously reviewed and supported the approval of belimumab IV for adult LN. A pediatric population PK model was built based on data from this study as well as studies of belimumab SC in cSLE (study 200908) and belimumab IV in cSLE (study BEL114055/C1109). As discussed above in section 6, the clinical pharmacology review team was able to establish a PK-bridge based on similarities in exposure-response between adults and pediatric SLE patients and expected similar response between adult and pediatric LN patients. Given that the etiology, pathophysiology, and disease manifestations are highly similar in children and adults with LN, it is scientifically justified to extrapolate the efficacy established in adult LN for the belimumab SC formulation to pediatric patients with LN.

The safety of belimumab SC in pediatric patients with LN was leveraged from the safety database in cSLE, a population relevant to pediatric LN since LN is a renal manifestation of SLE. In addition, the safety of belimumab IV in pediatric LN was established based on the cumulative safety data from studies in cSLE. Belimumab SC and IV clinical trials in cSLE (studies 200908 and BEL114055/C1109, total N=109) demonstrated an acceptable safety profile consistent with the known safety profile of belimumab in adult SLE and LN. Additional supportive data from the open-label extension of study 200908 in cSLE and postmarketing data in pediatric and adult SLE and LN did not reveal new safety signals.

The Applicant has provided adequate data and information to inform the benefit-risk assessment of belimumab SC administered at the proposed dose of 400 mg once weekly for 4 doses followed by 200 mg once weekly (weight category: ≥40 kg) or 200 mg once weekly for 4 doses followed by 200 mg every 2 weeks (weight category: 15 to <40 kg) for the treatment of pediatric patients (ages 5 to less than 18 years-old) with active LN who are receiving standard of care therapy. Approval of belimumab autoinjector for SC administration in pediatric LN will provide an additional treatment option, given the limited number of approved treatment options for this disease in the U.S. The convenience and availability of a SC formulation will be an advantage for the pediatric patient population. Therefore, the review team recommends

approval of belimumab autoinjector for SC administration for the treatment of pediatric patients 5 years and older with active LN who are receiving standard of care, using the proposed weight-tiered dosing regimen. Additionally, the data submitted to this sBLA 761043/S-034 and sBLA 125370/S-085 are adequate to fulfill the PREA PMR 4021-1.

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

In July 2019, the Applicant submitted an initial Pediatric Study Plan (iPSP) for belimumab for LN. In review of this iPSP, which requested a full waiver of pediatric studies from ages 0 to 17 years, the Agency commented that a successful study in adults with LN may support a PK-based extrapolation to pediatric LN. This extrapolation could be based on PK data from the adult LN study and the cSLE study, potentially without the need for additional PK data in pediatric patients with LN. This led to an agreed iPSP for belimumab IV (February 6, 2020) describing the similarities between adult and pediatric LN as well as a deferral for the pediatric assessment with possible reliance on a PK-based extrapolation approach after completion of the adult study in LN.

In the approval letter for adult patients with active LN (dated December 16, 2020), the Agency required the Applicant to provide assessments of belimumab IV and SC for patients 5 to 17 years of age with LN based on extrapolation, due by November 2021 and November 2023, respectively.

PREA PMR 4021-1 (previously, 3994-2) stated the following:

> "Provide an assessment of subcutaneous belimumab for the treatment of patients ages 5 to less than 18 years of age with lupus nephritis who are receiving standard therapy."
>
> Final Report Submission: November 2023

The assessment of belimumab SC for pediatric LN patients based on PK/exposure-matching extrapolation (i.e., the population PK report) was submitted to the Agency under BLA 761043 on November 29, 2023, to meet PREA PMR's final report submission milestone. Based on this assessment, the Applicant submitted BLA 761043/S-034 and BLA 125370/S-085 to expand the indication of belimumab SC formulation's current indication to include pediatric patients 5 years and older with active lupus nephritis who are receiving standard therapy. The results and review findings for this supplement were presented and discussed at the April 29, 2025, meeting of the Pediatric Review Committee (PeRC) who concurred with the review team's recommendation that the benefit-risk assessment supports the proposed indication and the PREA-PMR 4021-1 should be considered fulfilled.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
The following is a high-level summary for the product label changes based on review of the data submitted in support of this application, as well as major editorial changes to update the content and format of the BENLYSTA label:

1. Throughout USPI
    a. Because BENLYSTA is indicated specifically for active SLE and active lupus nephritis, the Agency recommended being consistent when referring to these conditions throughout the labeling to not imply or suggest use in unapproved populations.
    b. The terms "trial" and "study" are used in labeling. Recommended utilizing "trial" throughout the labeling for consistency.
    c. Recommended referencing a participant in a study as "subject," whereas references to a person with a disease or condition external to the study as "patient."
    d. Assigned numbers to each clinical trial described to reduce redundancy of repeating study descriptions throughout label
    e. Utilized trial numbers to replace description of trials in several locations of the USPI to avoid repeating the study design and study population
    f. Minor revisions to several tables for clarity
2. Indications and Usage in Highlights and Section 1
    a. Revised language of indication to reduce redundancy to the following:
    BENLYSTA is a B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of patients five years and older with:
        - *Active systemic lupus erythematosus (SLE) who are receiving standard therapy*
        - *Active lupus nephritis who are receiving standard therapy*
3. Section 2 Dosage and Administration
    a. Agreed with proposed dosage for pediatric patients with active LN and its addition to the table describing "recommended subcutaneous dosage of BENLYSTA"
    b. Multiple revisions throughout Section 2 to improve readability and organization
        i. Moved "Precautions Prior to Intravenous Use" to subsection 2.1 to precede discussion of IV dosage, preparation, and administration
        ii. Modified heading of subsection 2.2 to include preparation and administration instructions, and clarified indication to be active SLE or LN, rather than SLE or LN
        iii. Changed language from passive to active voice in administration

instructions

iv. Modified subsection 2.3 for 'Subcutaneous Dosing' to specify both adult dosing for SLE and LN via autoinjector and pre-filled syringe, as well as two-tiered pediatric dosing for SLE and LN via autoinjector.
v. Clarified heading of subsection 2.3 to include preparation and administration instructions as well as both adult and pediatric patients with active SLE or Lupus Nephritis
vi. Replaced symbols with wording to clarify greater than or less than
vii. Created subsection 2.4 with new header "Switching from Intravenous to Subcutaneous Administration" with clarifying language to guide in transitioning from IV to SC use of belimumab for both active SLE and active LN

4. Section 6 Adverse Reactions
    a. In subsection 6.1 Clinical Trials Experience, divided trial information by administration route, indication, and specific adverse events associated with each indication and administration route
5. Section 8 Use in Specific Populations
    a. Under heading "Subcutaneous Use" of subsection 8.4 Pediatric Use, added language to reflect that the basis for use of belimumab SC in pediatric patients with active LN is the extrapolation of efficacy from the IV belimumab trial in adults with active LN and that this extrapolation was supported by PK, efficacy, and safety data from this same trial as well as the IV trial in pediatric patients with active SLE and the SC trial in pediatric patients with active SLE.
6. Section 12 Clinical Pharmacology
    a. Under subsection 12.3 Pharmacokinetics, under heading of 'Specific Populations', added language to describe the systemic exposure in pediatrics with active lupus nephritis following the proposed bodyweight tiered dosing regimen is comparable to that of adults with active lupus nephritis.
7. Section 14 Clinical Studies
    a. Created new subsection 14.1 "Overview of Clinical Trials" to clearly label information providing brief summaries of all included trials.
    b. Removed language under the description of Trial 1 that implied that the current indication is "autoantibody-positive SLE patients." See edits below. The deletion is presented as a strikethrough below.
    The results of this trial informed the design of Trials 2 and 3 and led to the selection of a target population ~~and indication that is~~ limited to autoantibody-positive SLE patients.

Other Prescription Drug Labeling
Revisions to patient labeling were made to align with the revised prescribing information.

In the Medication Guide, the Applicant proposed to revise the statements regarding use in children in the "What is BENLYSTA?" section by removing wording stating (b) (4) [redacted] The Applicant proposed instead just the following statement:

- *It is not known if BENLYSTA is safe and effective for use in children less than 5 years of age*

The Agency agreed but also recommended the following statement:

- *It is not known if BENLYSTA, given under the skin (subcutaneously), is safe and effective for use in children who weigh less than 33 pounds (15 kg)*

Additionally, in the "What is BENLYSTA?" section, the common age group was moved to the introductory sentence to align with the revisions in the Indications and Usage section. The revised language is as follows:
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*
- *active lupus nephritis (lupus related kidney inflammation), who are receiving other lupus medicines.*

In the section "How will I receive BENLYSTA?", language describing the population was also revised to reflect the changes made in the Indications and Usage section. The updated language is as follows:
The single dose autoinjector is for use in adults and children 5 years of age and older.

No revisions were made to the Instructions For Use (IFU).

Labeling consultants, including DMEPA, OPDP, and DMPP, reviewed the submitted labeling and their recommendations, which pertain primarily to internal consistency, improving readability, and clarity of the labeling, have been considered and conveyed to the Applicant.

All labeling changes were agreed upon with the Applicant.

12 Risk Evaluation and Mitigation Strategies (REMS)

No new clinical data were submitted as part of this supplement. No new safety signals were identified as part of this review. Therefore, a REMS is not necessary to expand the current indication for belimumab SC to include pediatric patients 5 years and older with active lupus nephritis who are receiving standard therapy.

13 Postmarketing Requirements and Commitment

There are no potential or new safety or efficacy issues identified in this review that warrant further assessment with a postmarketing requirement or commitment.

14 Division Director (DRTM)/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 for pediatric patients with active LN is based on PK matching of systemic exposures in pediatric and adult subjects, allowing extrapolation of established efficacy of belimumab IV study in adults with active LN. As discussed in Section 6 of this review, the clinical pharmacology review team established a PK bridge from adults with LN to children with LN based on comparable PK data from adults with LN (belimumab IV) and children with SLE (belimumab IV and SC).

Although there were no clinical trials in pediatric subjects with active LN, the safety of belimumab SC for pediatric patients with active LN is leveraged from the safety of belimumab SC and IV in children with SLE and was assessed to be consistent with the known safety profile of belimumab in adults with SLE and LN. Additional cumulative safety data that the Applicant submitted did not show any new safety concerns.

I agree with the review team that this submission fulfills PREA-PMR 4021-1. The recommended regulatory action is approval of belimumab (Benlysta) autoinjector for SC administration for the treatment of patients 5 years of age and older with active LN who are receiving standard therapy.

15 Appendices

15.1. References

1. Anders H-J, Sexena R, Zhao M, Parodis I, Salmon JE, Mohan C. Lupus nephritis. Nature Reviews 2020; 6 (7): 1-25.
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15.2. Financial Disclosure

This section is not applicable, as no new clinical trial data were submitted.

15.3. Nonclinical Pharmacology/Toxicology

This section is not applicable, as no new nonclinical data were needed or submitted.

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

15.4.1. Population PK Analysis

15.4.1.1. Executive Summary

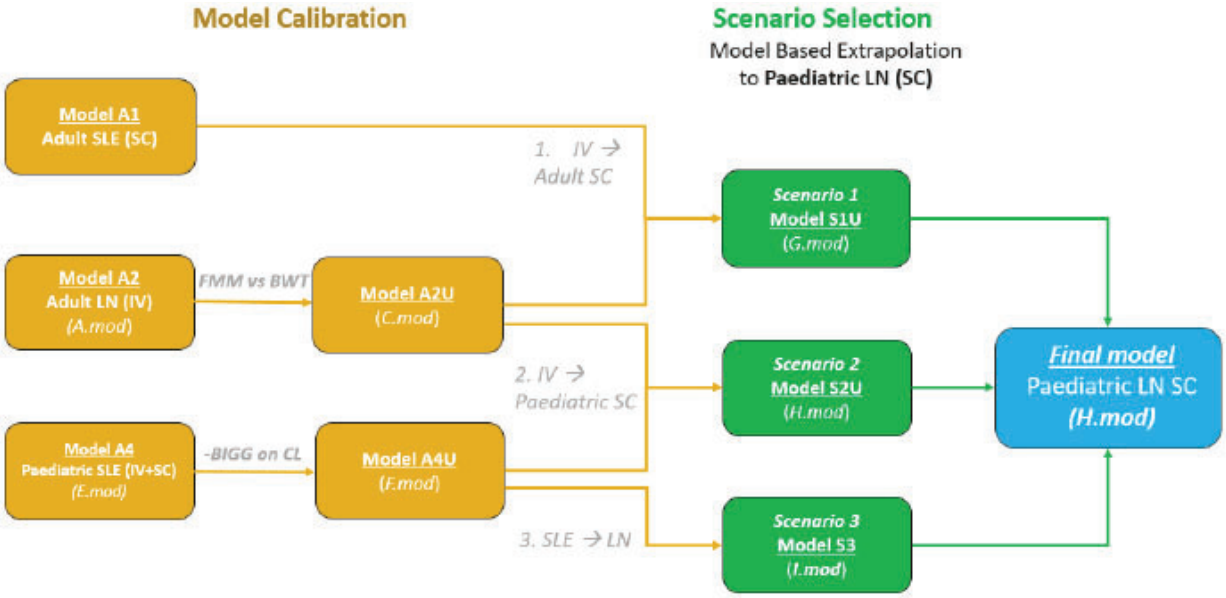
Due to the lack of PK data in pediatric LN with belimumab SC or IV, population PK models for this patient population were constructed by combining previously developed population PK models (i.e., IV belimumab in adult LN, SC belimumab in adult SLE, IV+SC belimumab in cSLE) in various ways which were subsequently assessed using existing adult LN IV data and cSLE IV+SC data. The final extrapolated model was validated by model prediction and model performance in cSLE patients which showed good agreement. This model was then applied to predict PK profiles in virtual pediatric LN patients to justify the proposed dosage whose exposure (Cavg(wk0-12)) in general aligns with that in adult LN with IV belimumab.

15.4.1.2. Population Pharmacokinetics Assessment Summary

PPK model construction	Final model constructed by absorption from cSLE IV+SC model and adult LN IV 2-cmpt model with anthropometric effect by total body weight replacing lean body weight (Figure 8)
Key assumptions	• Absorption (F, ALAG, Kabs) is the same in cSLE and LN and does not require additional covariates • Albumin/proteinuria covariate distributions similar between adult and pediatric LN patients • Covariates effect (e.g., weight, albumin, proteinuria) similar between adult and pediatric LN patients • PK difference between SLE and LN is driven by albumin and proteinuria • Extrapolation from SLE to LN was the same in adult and pediatric patients
PPK data	Data of adult LN IV and cSLE IV+SC were used to compare amongst models (Figure 9)
Final model	Model *H.mod* (Table 10) showed best OFV evaluated with both adult LN IV data and cSLE IV+SC data compared to the other two composite models (i.e., *G.mod*, *I.mod*)
Validation	Part 1: Model prediction in cSLE patients (Table 11) Part 2: Model performance on a virtual cSLE population (Figure 10)
Virtual patients	• SLE: weights sampled and corrected (Figure 11) from NHANES and proteinuria and albumin data sampled jointly from cSLE SC datasets with replacement (for Part 2 validation) • LN: weights sampled and corrected from NHANES and proteinuria and albumin sampled jointly from adult LN IV datasets with replacement (for simulation)

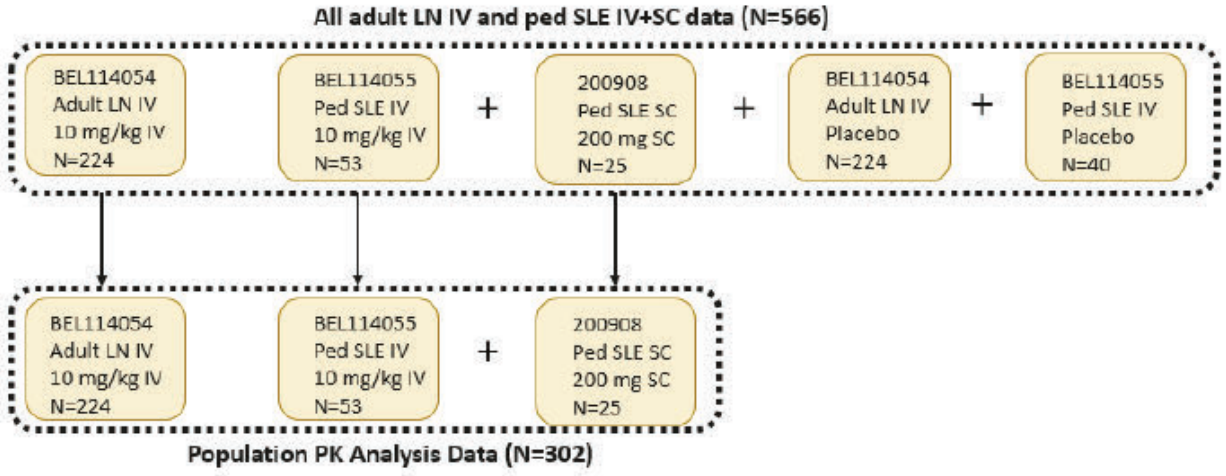
Analysis based on simulation	With 2-weight band dosage, belimumab exposures were comparable between pediatrics ≥40 kg and adult LN, but lower for pediatrics <40 kg (Figure 12, Table 12). Refer to PPK review issues (19.4.1.3) and additional analysis conducted by the Reviewer (19.4.1.4).

Figure 8. Graphical Representation of Final Model Selection.



Source: Figure 7.2:7 of Applicant's popPK report 217481.
Yellow boxes: population PK models earlier developed on clinical studies (left) and calibrated models (right). Green boxes: model extrapolation scenarios. Blue box: final model.

Figure 9. Summary of Data Used for Analysis during PK Model Development.



Source: Figure 7.1:4 of Applicant's popPK report 217481.

Table 10. Simulation Parameter Values for the Final Pediatric Lupus Nephritis Subcutaneous Model (*H.mod*).

Parameter	Implementation	Estimate (fixed)	Source model
F (fraction)	θ	0.703	Model A4 (E.mod)
ALAG (day)	θ	0.179	Model A4 (E.mod)
Kabs (1/day)	θ	0.287	Model A4 (E.mod)
CL (mL/day)	θ	175	Model A2 (A.mod)
V1 (mL)	θ	2728	Model A2 (A.mod)
Q (mL/day)	θ	487	Model A2 (A.mod)
V2 (mL)	θ	1992	Model A2 (A.mod)
Covariates			
Body size on CL	$(BWT/60)^{\theta}$	0.526	Model A2U (C.mod)
Body size on V1	$(BWT/60)^{\theta}$	0.604	Model A2U (C.mod)
Body size on Q	$(BWT/60)^{\theta}$	0.526	Model A2U (C.mod)
Body size on V2	$(BWT/60)^{\theta}$	0.604	Model A2U (C.mod)
ALB on CL	$(ALB/42)^{\theta_1/(1+\theta_2 \cdot PROT)}$	-1.74	Model A2 (A.mod)
PROT on ALB		0.0832	Model A2 (A.mod)
PROT on CL	$1+\theta \cdot PROT$	0.0663	Model A2 (A.mod)
IIV			
CL	ω^2	0.0593	Model A2 (A.mod)
V1	ω^2	0.0322	Model A2 (A.mod)
V2	ω^2	0.133	Model A2 (A.mod)
Prop	ω^2	0.346	Model A2 (A.mod)
Residual variability			
Proportional	σ^2	0.240	Model A2U (C.mod)
Additive	σ^2	0.1	Model A2 (A.mod)

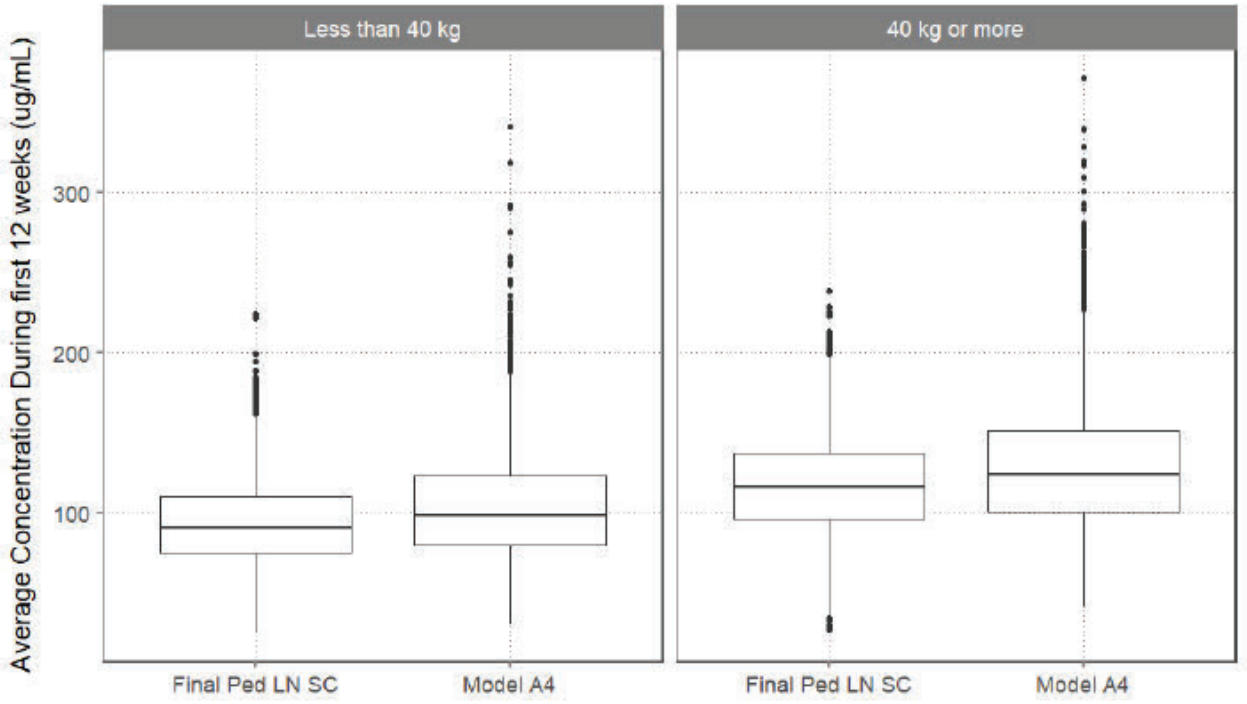
Source: Table 7.3:8 of Applicant's popPK report 217481. For each parameter estimate, the source model, in which the parameter was originally estimated, is listed.

Table 11. Statistical Comparison amongst Composite Models.

dOBJF	*Reference Model*	**Scenario 1/2**	**Scenario 3**
Data:			
Adult LN IV	Model A2 (*A.mod*)	13	771
Ped SLE IV + SC	Model A4 (*E.mod*)	26	20

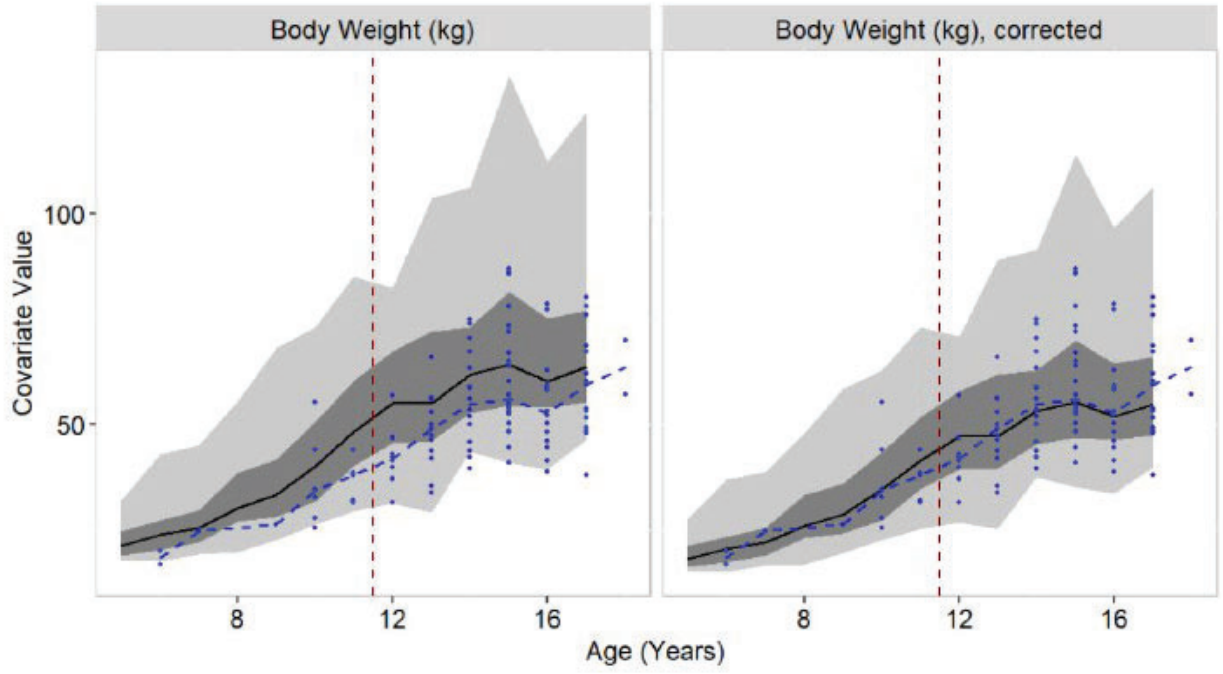
Source: Table 11.3:18 (modified) of Applicant's popPK report 217481.

Figure 10. Comparison of Belimumab Cavg (Wk 0-12) Predictions in a Virtual cSLE Population Between the Final Pediatric LN SC model (*H.mod*) and Model A4 (*E.mod*).



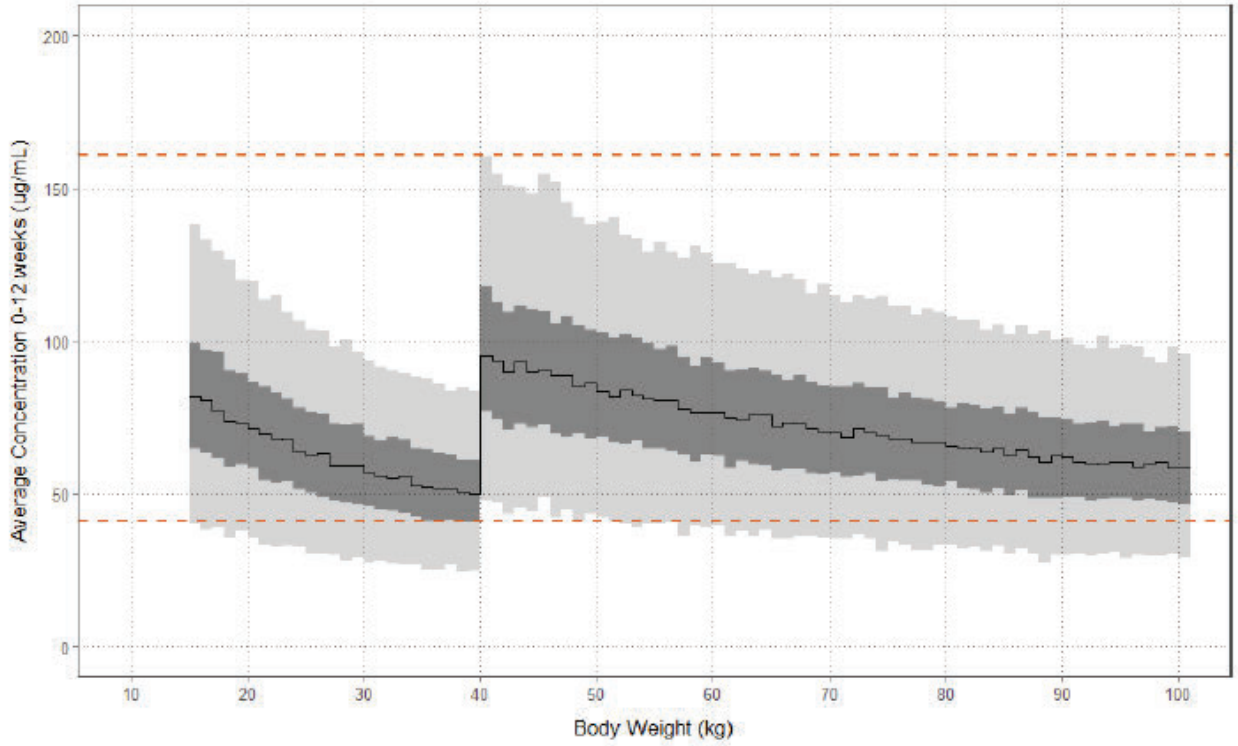
Source: Table 7.4:6 of Applicant's popPK report 217481. The x-axis represents the population PK models used to predict the average belimumab concentrations during the first 12 weeks in 10.000 virtual cSLE patients aged 5-17 years. Simulated maintenance dosing regimen was the 2-weight band regimen.

Figure 11. Baseline Body Weight Metrics versus Age.



Source: Table 11.3:17 of Applicant's popPK report 217481. Sampled NHANES Population versus cSLE patients. Left: original data. Right: NHANES BWT values multiplied by a factor 86%. Sample weights 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 cSLE study BEL114055 are shown (blue points) with the median calculated at each age (blue dotted line). The age groups 5-11 years and 12-17 years are separated by the vertical red dotted line drawn at 11.5 years.

Figure 12. Simulated Belimumab Cavg (Wk 0-12) over Body Weight in Simulated 1-Kg Groups of Pediatric Lupus Nephritis Patients Aged 5-17 Years (N=1000 per Group).



Source: Table 7.4:7 of Applicant's popPK report 217481. Simulated dosing regimen was the 2-weight band regimen. The median (black solid line), inter-quartile range (dark shaded region), 95% prediction interval (light shaded region) are shown. Dashed red lines represent the 2.5 and 97.5 percentiles of Cavg(Wk 0-12) in the adult LN IV patients, 41 and 161 µg/mL, respectively.

Table 12. Simulated Belimumab Cavg (Wk 0-12) Statistics per Weight Band in Simulated 1-Kg Groups of Pediatric Lupus Nephritis Patients Aged 5-17 Years (N=1000 per Group).

Weight band	Cavg(Wk 0-12) (μg/mL)		LT025 (%)	LT975 (%)
	Geometric mean [GeoCV (%)]	Median (95% percentile interval)		
≥15-<20 kg	75.1 [32.7]	77.3 (38.1-130)	4.0	100
≥20-<25 kg	66.0 [32.5]	68.1 (32.8-113)	8.3	100
≥25-<30 kg	58.9 [32.8]	60.7 (29.7-101)	14.0	100
≥30-<35 kg	53.8 [31.8]	55.1 (27.0-91.0)	18.2	100
≥35-<40 kg	50.0 [32.3]	51.3 (25.3-85.6)	25.2	100
≥40-<45 kg	89.8 [32.3]	92.5 (45.3-155)	1.2	98.4
≥45-<50 kg	85.3 [32.0]	87.9 (43.2-146)	1.7	99.1
≥50-<55 kg	80.7 [31.7]	82.6 (40.2-136)	2.8	99.7
≥55-<60 kg	76.5 [31.6]	78.4 (39.2-129)	3.4	99.9
≥60-<65 kg	73.1 [31.5]	75.4 (37.7-124)	4.4	99.9
≥65-<70 kg	70.0 [31.7]	72.2 (35.7-119)	5.8	100
≥70-<75 kg	67.9 [31.6]	69.9 (35.0-114)	6.6	100
≥75-<80 kg	65.2 [32.0]	67.3 (32.8-110)	8.3	100
≥80-<85 kg	62.9 [31.5]	64.8 (32.1-107)	9.5	100
≥85-<90 kg	60.6 [32.6]	62.4 (30.2-103)	11.9	100
≥90-<95 kg	59.0 [31.4]	60.5 (30.1-99.7)	12.6	100
≥95-<100 kg	57.7 [31.4]	59.6 (29.7-97.1)	14.1	100
Adult LN IV	87.0 [36.0]	89.1 (41.1-161)	2.5	97.5

Source: Table 7.4:7 of Applicant's popPK report 217481. Simulated dosing regimen was the 2-weight band regimen. Adult LN IV denotes the reference values obtained by simulating Cavg (Wk 0-12) for an adult LN IV population. LT025: percentage of subjects below the adult lower threshold (2.5th percentile) of 41 μg/mL. LT975: percentage of subjects below the adult LN IV upper threshold (97.5th percentile) of 161 μg/mL. GeoCV: geometric coefficient of variance.

15.4.1.3. Population Pharmacokinetics Review Issues

Two-weight band regimen (i.e., 200 mg QW x 4 doses → 200 mg Q2W and 400 mg QW x 4 doses → 200 mg QW for ≥15kg-<40kg and ≥40 kg, respectively) was proposed to match exposure in adult LN receiving recommended belimumab IV dosage (10 mg/kg Q2W x 3 doses → 10mg/kg Q4W). It was noted that ~1 in 4 pediatric patients weighing 35-40 kg were expected to be underexposed (Cavg(Wk 0-12) < 2.5th percentile of adult exposure), posing efficacy uncertainty in this subgroup.

Due to the lack of E-R analysis conducted with various doses for LN, potential efficacy reduction due to underexposure in pediatrics weighing 35-40 kg receiving the lower dose of the two-

weight band regimen with SC belimumab could not be ruled out from the viewpoint of the pharmacometrics reviewer.

Additional analysis was conducted to explore ways to align exposure of pediatric LN better with that of adult LN, especially in the highlighted subgroup (35-40 kg) (see 19.4.1.4). Compared to altering QW/Q2W dosing interval or fixed dose amount in an autoinjector, exploring different weight cutpoints for the two-weight band regimen was favored considering feasibility. The result showed that 35 kg as a new cutpoint dividing patients into two weight bands for the same dosage could improve exposure matching of the highlighted subgroup with adults.

Pediatric LN with IV dosage was previously assessed via simulation where a subgroup was also likely associated with an increased risk of underexposure --- ~26% in pediatric in the lowest bodyweight subgroup (15-20 kg). However, efficacy concern is low for this pediatric subgroup due to 1) rarity of this subgroup, and 2) improved exposure matching with adults after factoring in empirical maturation function[43] on CL in young pediatrics in the simulation, where % of underexposed patients reduced to 13% (results not included).

For SC dosage in pediatric LN patients, despite a better exposure matching with adult LN patients, the different cutpoint in pediatric LN compared to cSLE for the two-weight band regimen could be prone to medication error. Refer to Section 6 regarding further dosage justification from clinical pharmacology perspective.

15.4.1.4. Reviewer's Independent Analysis

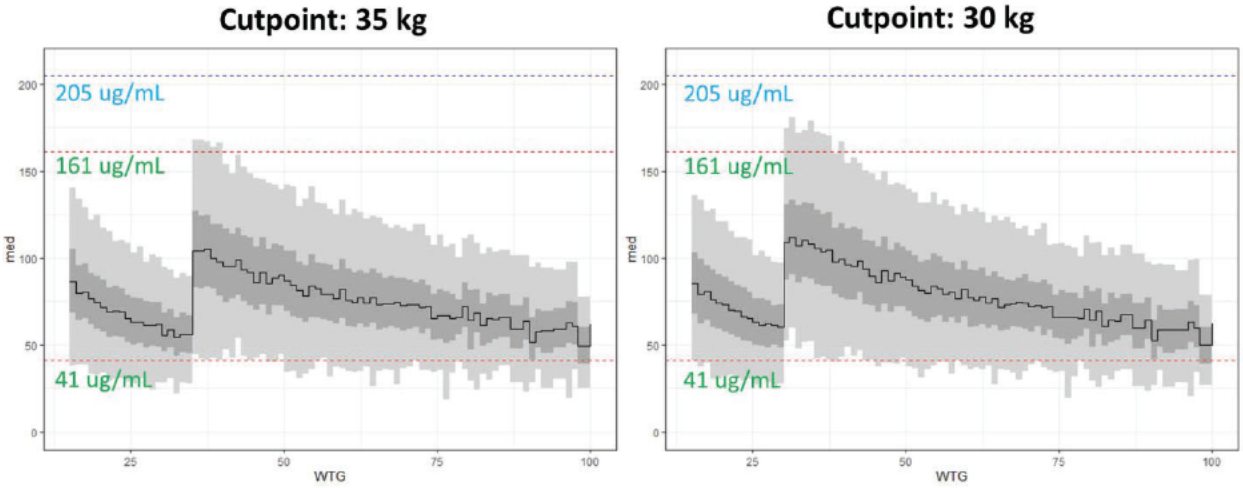
As highlighted in Table 12, pediatrics weighing 35-40 kg receiving the Applicant proposed dosage will likely result in underexposure in 25% of patients. To improve exposure matching with adults, various measures were considered including changing dosing interval, dosing amount, and cutpoint for two-weight bands. The former two are considered less feasible for the following reasons: weekly increments in dosing interval from a compliance perspective will likely result in a substantial change in exposure, dose amount of 200 mg is fixed in prefilled syringe. Therefore, the additional simulation was conducted to explore lower cutpoints.

When moving cutpoints to lower weights, it is expected that pediatrics patients weighing 35-40 kg (when cutpoint is 35 kg) and those weighing 30-35 kg (when cutpoint is 30 kg) will have the highest average concentrations across all weight subgroups. Given the current 97.5th percentile of Cavg(Wk 0-12) of pediatrics weighing 40-45 kg is pressing the upper bound of exposure in adult LN (Figure 12), the exposure range in SLE patients was also assessed to provide safety

[43] Robbie GJ, Zhao L, Mondick J, Losonsky G, Roskos LK. Population pharmacokinetics of palivizumab, a humanized anti-respiratory syncytial virus monoclonal antibody, in adults and children. Antimicrob Agents Chemother. 2012 Sep;56(9):4927-36. Epub 2012 Jul 16. Erratum in: Antimicrob Agents Chemother. 2012 Oct;56(10):5431

assurance. In adult SLE with SC belimumab, the 2.5th to 97.5th percentile range of exposure is 45.1-205 µg/mL; in cSLE with IV belimumab, the 2.5th to 97.5th percentile range of exposure is 51.7-217 µg/mL. As shown in Figure 13, both cutpoints ensure that exposure distribution falls under the upper bounds of SLE patients. While the cutpoint of 30 kg will enable a better exposure matching in an additional subgroup of pediatrics weighing 30-35 kg, the geometric mean/median in this body weight subgroup will be slightly higher than other body weight subgroups. (Table 13).

Figure 13. Simulated Belimumab Cavg (Wk 0-12) over Body Weight in Simulated 1-Kg Groups of Pediatric LN Patients Aged 5-17 Years (N=1000 per Group).



Source: Reviewer's analysis. Simulated dosing regimen was the 2-weight band regimen with indicated cutpoint. The median (black solid line), inter-quartile range (dark shaded region), 95% prediction interval (light shaded region) are shown. Dashed red lines represent the 2.5 and 97.5 percentiles of Cavg(Wk 0-12) in the adult LN IV patients, 41 and 161 µg/mL, respectively. Dashed blue line represents the 97.5th percentile of Cavg(Wk 0-12) in the adult SLE SC patients.

Table 13. Simulated Belimumab Cavg (Wk 0-12) Statistics per Weight Band in Simulated 1-Kg Groups of Pediatric LN Patients Aged 5-17 Years (N=1000 per Group).

Weight band	Cutpoint: 35 kg				Cutpoint: 30 kg			
	Geometric mean [GeoCV(%)]	Median (95% percentile interval)	LT025 (%)	LT975 (%)	Geometric mean [GeoCV(%)]	Median (95% percentile interval)	LT025 (%)	LT975 (%)
≥15-<20 kg	76.3 [33.9]	79.2 (36.0-132)	4.6	100	76.0 [34.5]	79.0 (35.7-130)	4.8	100
≥20-<25 kg	65.9 [34.7]	68.7 (30.0-112)	8.8	100	66.2 [35.2]	68.8 (31.0-115)	8.5	100
≥25-<30 kg	59.5 [34.5]	61.9 (27.5-102)	13.3	100	59.3 [34.3]	61.5 (27.9-101)	13.4	100
≥30-<35 kg	54.5 [32.0]	56.2 (27.4-92.0)	16.9	100	106 [31.8]	109 (52.4-176)	0.9	99.6
≥35-<40 kg	97.3 [35.2]	102 (41.7-167)	2.3	99.9	97.5 [35.7]	102 (41.7-169)	2.3	99.8
≥40-<45 kg	91.3 [32.5]	94.6 (44.3-153)	1.6	99.9	91.2 [32.9]	94.8 (44.0-154)	1.7	99.9

≥45-<50 kg	85.6 [33.0]	88.2 (41.8-143)	2.3	100	85.4 [33.7]	89.1 (39.3-144)	3.1	100
≥50-<55 kg	79.2 [35.8]	82.7 (33.6-137)	4.9	100	79.5 [35.3]	83.3 (36.3-137)	4.2	100
≥55-<60 kg	77.4 [32.1]	79.9 (37.7-131)	3.7	100	77.8 [32.0]	80.0 (38.8-130)	3.4	100
≥60-<65 kg	73.4 [33.8]	75.9 (34.4-125)	5.3	100	73.4 [33.7]	76.1 (35.6-125)	4.9	100
≥65-<70 kg	70.9 [33.1]	73.3 (34.5-119)	6.0	100	70.9 [32.6]	73.5 (34.1-120)	6.2	100
≥70-<75 kg	69.2 [29.9]	70.8 (36.6-115)	4.9	100	68.9 [29.4]	70.7 (37.0-114)	4.8	100
≥75-<80 kg	64.8 [33.1]	67.1 (31.0-109)	7.7	100	64.3 [33.0]	66.4 (30.2-108)	7.8	100
≥80-<85 kg	62.6 [33.2]	64.8 (30.6-107)	10	100	62.5 [32.8]	64.6 (30.3-106)	10	100
≥85-<90 kg	61.5 [32.0]	63.2 (29.9-103)	9.1	100	61.6 [33.0]	63.6 (28.0-103)	9.9	100
≥90-<95 kg	55.6 [32.0]	56.7 (28.2-95.6)	16.1	100	55.6 [32.3]	57.2 (28.0-94.9)	16.5	100
≥95-<100 kg	55.5 [33.5]	57.2 (25.8-93.1)	15.9	100	55.5 [34.0]	56.9 (27.1-96.8)	16.4	100
Adult LN IV	87.0 [36.0]	89.1 (41.1-161)	2.5	97.5	87.0 [36.0]	89.1 (41.1-161)	2.5	97.5

Source: Table 7.4:7 of Applicant's popPK report 217481. Simulated dosing regimen was the 2-weight band regimen. Adult LN IV denotes the reference values obtained by simulating Cavg (Wk 0-12) for an adult LN IV population6. LT025: percentage of subjects below the adult lower threshold (2.5th percentile) of 41 µg/mL. LT975: percentage of subjects below the adult LN IV upper threshold (97.5th percentile) of 161 µg/mL.

15.5. Additional Clinical Outcome Assessment Analyses

Not applicable.

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