NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sBLA
Application Number(s)	sBLA 125370/s-078 and sBLA 761043/s-021
Priority or Standard	Priority
Submit Date(s)	January 26, 2022
Received Date(s)	January 26, 2022
PDUFA Goal Date	July 26, 2022
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM)
Review Completion Date	See Electronic Stamp Date
Established/Proper Name	Belimumab
(Proposed) Trade Name	BENLYSTA
Pharmacologic Class	Monoclonal Anti-BLyS Antibody
Applicant	GlaxoSmithKline LLC
Doseage form	10mg/kg via Intravenous Infusion
Applicant proposed Dosing Regimen	10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter
Applicant Proposed Indication(s)/Population(s)	Treatment of patients ages 5 to less than 18 years of age with lupus nephritis (LN) who are receiving standard therapy
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of patients aged 5 years and older with active lupus nephritis (LN) who are receiving standard therapy
Recommended Dosing Regimen	10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Susan Rhee
Nonclinical Reviewer	Brett Jones
Nonclinical Team Leader	Ijeoma Uzoma
Office of Clinical Pharmacology Reviewer(s)	Tao Liu
Office of Clinical Pharmacology Team Leader(s)	Youwei Bi Jianmeng Chen
Clinical Reviewer	Rosemarie Neuner
Clinical Team Leader	Nikolay Nikolov
Statistical Reviewer	n/a
Statistical Team Leader	n/a
Cross-Disciplinary Team Leader	Jianmeng Chen
DRTM Director (or designated signatory authority)	Nikolay Nikolov

Additional Reviewers of Application

OPQ	Sean Fitzsimmons/Marjorie Shapiro
Microbiology	Maxwell Van Tassell
OPDP	Kyle Snyder
OSI	n/a
OSE/DEPI	Marie Bradely/Ben Booth
OSE/DMEPA	Teresa McMillan/Idalia Rychlik
DPV	Lisa Wolf

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

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Tao Liu	OCP/DIIP	Section:6, 15.4	**Select one:** _X_ Authored ___ Approved
	Signature: Tao Liu -S Digitally signed by Tao Liu -S Date: 2022.07.25 14:23:40 -04'00'			
Clinical Pharmacology Team Leader	Jianmeng Chen	OCP/DIIP	Section:1, 6, 15.4	**Select one:** _X_ Authored _X_ Approved
	Signature: Jianmeng Chen -S Digitally signed by Jianmeng Chen -S Date: 2022.07.25 12:50:38 -04'00'			
Pharmacometrics Reviewer	Tao Liu	OCP/DIIP	Section:6, 15.4	**Select one:** _X_ Authored ___ Approved
	Signature: Tao Liu -S Digitally signed by Tao Liu -S Date: 2022.07.25 14:24:13 -04'00'			
Pharmacometrics Team Leader	Youwei Bi	OCP/DPM	Section:6, 15.4	**Select one:** _X_ Authored _X_ Approved
	Signature: **Dr. Hao Zhu to sign on behalf of Dr. Youwei Bi** Hao Zhu -S Digitally signed by Hao Zhu -S Date: 2022.07.25 12:12:38 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Rosemarie Neuner	OII/DRTM	Sections: 1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 15.1 and 15.2	**Select one:** __X_ Authored __X_ Approved
	Signature: Rosemarie Neuner -S Digitally signed by Rosemarie Neuner -S Date: 2022.07.25 14:08:49 -04'00'			
Clinical Team Leader/ Division Director/ Signatory	Nikolay Nikolov	OII/DRTM	Sections: All	**Select one:** ___ Authored, 14 _X__ Approved All
	Signature: Nikolay P. Nikolov -S Digitally signed by Nikolay P. Nikolov -S Date: 2022.07.25 14:15:59 -04'00'			

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 subcutaneous (SC) administered injection formulation available as a ready to use pre-filled syringe and autoinjector was approved in 2017 for the same indication. In 2019, the IV formulation's indication was expanded to include the treatment of children 5 years and older with active, autoantibody-positive childhood-onset SLE (cSLE). Both the IV and SC formulation's indications were expanded in 2020 to include the treatment of adults with active lupus nephritis (LN) despite standard therapy.

The Applicant, GlaxoSmithKline, submitted a 351(a) supplemental biologics license application (sBLA) seeking marketing approval of belimumab for IV administration to fulfil the Pediatric Research Equity Act (PREA) post-marketing required (PMR) pediatric assessment related to the December 16, 2020 approval for BLA 125370/s-073 Benlysta® (belimumab) intravenous (IV) formulation as a treatment of adults with active LN who are receiving standard therapy. With this supplement, the Applicant proposes to expand the present indication for belimumab IV administration to include the treatment of children 5 to 17 years of age with active lupus nephritis who are receiving standard therapy. In addition, the SLE indication was revised to be more concise in the description of the population studied with deletion of "antibody positive" since the latter is contained in the description of the studies in Section 14. sBLA 761043/s-021 Benlysta SC labeling supplement was also submitted to align label.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is Approval for belimumab IV for the treatment of active lupus nephritis in children ages 5 to 17 years old. This recommendation is based on the full extrapolation of efficacy established in adults with lupus nephritis and leveraging of safety established in children with cSLE, as well as supportive safety data from a post-marketing safety review update of pediatric and adult patients exposed to belimumab. Additionally, the pediatric clinical pharmacology, efficacy and safety data submitted to sBLA 125370/s-078 are adequate to fulfill the PREA postmarketing requirement (3994-01) related to the December 16, 2020

approval for BLA 125370 Benlysta® (belimumab) intravenous (IV) formulation.

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. It is essentially considered to be the same disease in children with approximately 10-20% of all cases developing 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 there are no approved therapies for pediatric LN patients. A full description of pediatric LN and its diagnosis, treatment and prognosis can be found in Sections 2.1 and 2.2. Similar to the adult SLE studies, pediatric subjects with active LN were prohibited from participating in study BEL114055/C1109 which was a study in pediatric subjects with active, cSLE on stable immunosuppressive medications used to support expanding belimumab IV's indication to include children ages 5 to 17 years old with active, seropositive cSLE under BLA125370/s-064.

In view of the available data with belimumab in adults with SLE and LN, as well as pediatric patients with cSLE, and considering the rarity of pediatric LN, the Applicant has undertaken a PK-bridging approach with full extrapolation of efficacy and leveraging of safety from existing belimumab IV studies in support of this application. The clinical responses to belimumab treatment (at comparable exposures) are similar between adult and pediatric patients with general SLE, as discussed in the review of BLA125370/s-064. Further, the clinical manifestations and management of LN are largely overlapping between pediatric LN and adult LN and evidence suggests that children with pediatric LN should respond to treatment similarly to adults with LN. Thus, the efficacy in pediatric patients with LN can be extrapolated from adults with LN where efficacy has been established from an adequate and well-designed clinical trial (refer to the review of sBLA 125370/s-073).

To establish the PK bridge to pediatric patients with LN, the pharmacokinetics of belimumab in pediatric patients were estimated based on a population pharmacokinetic model developed from 224 adults with active lupus nephritis and validated using data from 53 pediatric patients with SLE. With IV administration of 10 mg/kg on Days 0, 14 and 28 and at 4-week intervals thereafter, the simulated belimumab exposures for both the 5- to 11-year-old group and the 12- to 17-year-old group were estimated to be comparable to adults with active lupus nephritis. Adult LN PK data and pediatric SLE PK data used in population PK modeling study 217143 came from two studies: BEL114054/C1121 which evaluated the same dosing regimen of 10 mg/kg of belimumab IV approved for the 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 and study BEL114055/C1109 which also evaluated the 10 mg/kg approved dosing regimen over 52-weeks

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

in pediatric subjects with cSLE on stable immunosuppressive medications. Both of these studies were adequate and well-controlled clinical trials that had been reviewed previously in support of the approvals for the adult LN indication and the cSLE indications for belimumab IV under sBLA 125370/s-073 and s-064, respectively. Since PK exposure is estimated to be similar between adult and pediatric LN patients, it is scientifically justified to extrapolate the efficacy established from the adult LN study to pediatric patients with LN. Of note, lower exposures were observed in patients with high degree of proteinuria in the adult LN program; however, this observation did not warrant dose adjustments in adults, as discussed in the review of sBLA 125370/s-073. As the proteinuria impact on PK is expected to be similar for adult and pediatric patients with LN, and the exposure is comparable in adult and pediatric patients with SLE, it is reasonable to estimate that the PK would be comparable in adult and pediatric LN patients with proteinuria and respectively would not necessitate dose adjustments in pediatric LN.

Based on the data from the PK-bridging approach supporting full extrapolation of efficacy and leveraging safety from existing studies of belimumab IV reviewed previously, and in view of the unmet medical need for safe and efficacious treatments for pediatric patients with LN, the Applicant has provided adequate information to inform the benefit-risk assessment of belimumab IV for the treatment of pediatric patients with active LN who are receiving standard therapy, to support the expansion of the indication of belimumab IV as add-on treatment for active LN in pediatric patients 5 to 17 years old.

The Division Signatory agrees with this assessment.

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. There are no approved treatments for pediatric LN currently; 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 3-5 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 in adults and children with SLE as well as in adults with LN. Under the Pediatric Research Act (PREA), a partial waiver for pediatric studies in lupus nephritis patients $\leq$ 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 full extrapolation of efficacy established in adults with LN based on matching of the PK exposures between the two populations along with leveraging safety data from the existing adult and pediatric studies conducted with belimumab IV. 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 and by adequate justification for this approach by the Applicant.

In support of a full extrapolation approach of belimumab IV from adults with LN to pediatric patients with 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 children with SLE.

Results from the population PK modeling study 217143, which demonstrated the comparability of exposure levels in children with lupus nephritis 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 bridging of established efficacy and safety in pediatric LN patients from the following studies: BEL114054/C1121, BEL114055/C1109, BEL110751/C1056 and BEL110772/C1057. Adult LN PK data and pediatric SLE PK data used in study 217143 came from two studies: BEL114054/C1121 which evaluated the same dosing regimen of 10 mg/kg of belimumab IV approved for the 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 and study BEL114055/C1109 which also evaluated the 10 mg/kg approved dosing regimen over 52-weeks in pediatric subjects with cSLE on stable immunosuppressive medications. Both of these studies had been reviewed previously in support of the approvals for the adult LN indication and the cSLE indications for belimumab IV under sBLA 125370/s-073 and s-064, respectively. Since PK exposure is estimated to be similar between adult and pediatric LN patients, extrapolation of efficacy was derived from the adult LN study BEL114054/C1121 which was an adequate and well-controlled clinical trial in adult LN patients receiving standard of care induction and maintenance therapy as described above that established belimumab IV's efficacy as a treatment for this disease.

The PK exposure is expected to be similar in pediatric patients with LN compared to pediatric SLE patients with the same dosing regimen. 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 pediatric SLE patients to the pediatric LN population. Leverage of established safety in the pediatric population primarily came from the aforementioned belimumab IV pediatric study BEL114055/C1109. However, since the safety database from this study was small due to the rarity of cSLE and relied upon safety and PK data from the original belimumab IV adult SLE studies BEL110751/C1056 and

BEL110772/C1057 that originally established both the safety and efficacy of belimumab IV in adult SLE patients, the safety database and PK exposure data from these two adult SLE studies were also used in support of the extrapolation process.

Review of cumulative safety data collected from the ongoing open-label portions of study BEL114054/C1121 as well as updated spontaneous postmarketing safety data in pediatric patients with cSLE and in adults with lupus nephritis did not identify any new or unexpected safety signals associated with the administration of belimumab IV.

In summary, pediatric lupus nephritis is a rare and serious manifestation of SLE with high unmet need for new therapies. The Applicant has provided adequate data and information to inform the benefit-risk assessment of belimumab IV for the treatment of pediatric patients with active LN who are receiving standard therapy, and support the expansion of the indication of belimumab IV as 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	• 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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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	
Current Treatment Options	• There are no currently approved treatments 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) • For active lupus nephritis, the pharmacokinetics of belimumab in pediatric patients were estimated based on a population pharmacokinetic model developed from 224 adults with active lupus nephritis and validated using data from 53 pediatric patients with SLE. With IV administration of 10 mg/kg on Days 0, 14 and 28 and at 4-week intervals thereafter, the simulated belimumab exposures for both the 5- to 11-year-old group and the 12- to 17-year-old group were estimated to be comparable to adults with active lupus nephritis.	• Efficacy of belimumab IV 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 in 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 SLE.
Risk and Risk Management	•The PK exposure is expected to be similar or (lower in patients with high proteinuria) in pediatric patients with LN compared to pediatric SLE patients with the same dosing regimen, supporting the leverage of safety data from cSLE patients to the pediatric LN population • The cumulative safety database for belimumab IV in adults with SLE/LN and pediatric cSLE patients, together with the long-term, cumulative safety data from the open label extension of pediatric cSLE study BEL114055/C1109 and the updated spontaneous postmarketing safety review in pediatric and adult patients exposed to belimumab is sufficient to provide a risk assessment for belimumab IV in the pediatric LN population (reviewed under BLA 125370/s-064)	• 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 in pediatric patients with cSLE which was similar to the safety profile of belimumab IV in adults with SLE in studies BEL110751/C1056 and BEL110772/C1057 • Overall, the safety profile of belimumab IV in pediatric cSLE was consistent with what has been observed in the adult SLE and LN • No new safety signals were observed on review

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		of long-term, cumulative safety data of belimumab IV 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 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 1), all three consider renal biopsy confirmatory for diagnosis.

Table 1. 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,	**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	**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

[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.

hemoglobulin, granular tubular or mixed) **Optional:** 3. Renal biopsy demonstrating immune complex mediated glomerulonephritis compatible with lupus nephritis	**Optional:** 3. Biopsy-proven nephritis compatible with SLE in the presence of ANA s or anti-dsDNA antibodies	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 is 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]

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

Table 2. ISN/RPS 2003 Classification of Lupus Nephritis[a]

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 microscopy, with mesangial immune deposits There may be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	**Focal lupus nephritis[a,b]** 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[a,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 sclerosing lupus nephritis** ≥90% of glomeruli globally sclerosed without residual activity

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

[a]Almaani S, et al. Clin J Am Soc Nephrol. 2017; 12:825-835.

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

There are currently no approved treatments for pediatric patients with lupus nephritis. Table 3 lists the treatments that are currently approved for adults with lupus nephritis as well as off-label treatments that are available for the treatment of adults and children with lupus nephritis.

Table 3. Summary of Treatment Armamentarium Relevant to Proposed Indication

Product 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	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 cyclo-phosphamide 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 $\leq$ 45 ml/min/1.73 m^2. Capsules must be swallowed whole on an empty stomach	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

[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.

			consistently as close to a 12-hr schedule with a minimum of 8-hrs between doses.			
Off-Label 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: muco-cutaneous and musculoskel. manifestations; serositis High Dose: induction therapy for lupus nephritis, CNS disease, and immune cytopenias
Cyclophosphamide	----------	----------	IV bolus regimens of 0.5-1g/m body surface area for once monthly for 6 months	Published literature	Myelo-suppression, hemorrhagic cystitis, malignancy, lympho-proliferative disorders, infertility and infections	Induction therapy for lupus nephritis especially refractory disease
Mycophenolate Mofetil	----------	----------	500-1500 mg BID	Published literature	Myelo-suppression, 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; re-administer when disease worsens	Two failed phase 3 studies	Fatal infusion reactions, severe mucocutaneous reactions, Hepatitis B reactivation, serious infections including PML	Treatment of refractory lupus nephritis and immune cytopenias
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

Cyclosporin	----------	----------	2.5-4 mg/kg/day	Published literature	Hepatoxicity, nephrotoxicity, thrombotic micro-angiopathy, 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) and European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) 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] 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. Current induction regimens are comprised of either high dose pulses or moderate oral doses of corticosteroids plus cyclophosphamide (CYC) or mycophenolate mofetil (MMF). 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.[33] Rituximab is also commonly used as a treatment for refractory lupus nephritis as monotherapy or as add-on therapy to MMF or CYC.[34, 35]

In addition to the treatment of co-morbid conditions such as hypertension and hyperlipidemia, the administration of hydroxychloroquine (to prevent renal flares) and angiotensin

[29] Hahn BH et al. Arthritis Care Res 2012;63(6):797-808.
[30] Fanouriakis A, et al. Ann Rheum Dis 2020; 79:713-723.
[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] Fanouriakis A, et al. Ann Rheum Dis 2020;79:713-732.
[34] Hahn BH, et al. Arthritis Car Res 2021;63(6):797-808.
[35] Groot N, et al. Ann Rheum Dis 2017;76:1965-1973

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.[36, 37]

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 months of treatment.[38, 39] 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.[40]

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.

3 Regulatory Background

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 2022) 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 this country to include the treatment of children 5 years and older with active, autoantibody-positive childhood-onset SLE. The indications for both the IV and SC formulations were further expanded in this country in 2020 to include the treatment of adult patients with active lupus nephritis on standard of care.

[36] Fanouriakis A, et al. Ann Rheum Dis 2020;79:713-732.
[37] Groot N, et al. Ann Rheum Dis 2017;76:1965-1973.
[38] Fanouriakis A, et al. Ann Rheum Dis 2020; 79:713-723.
[39] Groot N, et al. Ann Rheum Dis 2017;76:1965-1973.
[40] Fanouriakis A, et al. Ann Rheum Dis 2020; 79:713-723.

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

- 2012 and 2013: The Warnings and Precautions section for hypersensitivity reactions including anaphylaxis was updated to reflect post marketing cases of post-infusion/injection systemic reactions.
- 2014: A Warning and Precaution statement regarding the occurrence of PML in SLE patients who had received belimumab IV in addition to concomitant immunosuppressive agents was added to the product's USPI and subsection 17.1 Advice to for the Patient and the Medication Guide were updated to provide information about the risk of PML in patients with SLE receiving belimumab.
- 2016: Section 2.3 Preparations of Solutions was updated to include the recommendation to use a 21- to 25-G needle for reconstitution and dilution of belimumab with half-normal saline or Lactated Ringer's Injection. Sections 5.2 Serious Infections and 6.1 Clinical Trials Experience were updated to include new safety information while Section 8 was updated to comply with the Pregnancy Lactation Labeling Rule (PLLR).
- 2017: Information was added regarding the dose and administration of the SC formulation as well as a description of the clinical pharmacology and clinical trial data reviewed in support of the marketing approval of the SC formulation to Sections 12 Clinical Pharmacology and 14 Clinical Studies. Information regarding the SC formulation was added to the product's Medication Guide.
- 2019: The IV formulation's indication was expanded to include children aged 5 years and older with cSLE. A description of the clinical trial data reviewed in support of the pediatric indication was added to Section 14.1.
- 2019: The Warnings and Precaution section for Depression and Suicidality was updated to reflect the occurrence of these adverse events in clinical trials of the product including a recently completed, large postmarketing safety study and to advise healthcare providers to assess patients prior to initiating treatment as well as monitor them during treatment.
- First quarter 2020: Deletion of the precautionary statement regarding the treatment of black/African-American patients with belimumab based on the subgroup exploratory analysis of the SRI-4 response rate for black subjects who participated in the two pivotal IV belimumab studies under subsection Effect in Black/African-American Patients under Section 14.1 Clinical Trials. Efficacy and safety results of study BEL115471/C1112 conducted in black/African-American patients with SLE receiving standard of care where applicable was included under Sections 6.1 Clinical Trials with Intravenous Administration, 8.8 Racial Groups and 14.1 Clinical Trials Experience with Intravenous Administration.
- Third quarter 2020: Deletion of the Warnings and Precautions statements regarding all-cause mortality. Under Section 5 Warnings and Precautions for serious infections, PML,

depression and suicidality, and hypersensitivity reactions were updated and the results of adverse events of special interest (AESI) from study BEL15467/C1113 were included under the corresponding subsections. Section 17 Patient Counseling Information was updated to reflect the new and updated Warnings and Precautions.

- 2020: The indications for both IV and SC formulations were expanded to include the treatment of adult patients with active lupus nephritis on standard of care with the deletion of both lupus nephritis and intravenous cyclophosphamide under Section 1 Indications and Usage and its subsection, Limitations of Use, respectively. The new subcutaneous loading regimen 400 mg (two 200-mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter and the associated administration instructions for lupus nephritis in adults were added under Section 2.2 Subcutaneous Dosing Instructions. A description of the clinical trial data from study BEL114054/C1121 reviewed in support of the adult lupus nephritis indication was added to Section 14.2 and safety data regarding the incidence of serious infections in this study and the observation of cases of myelosuppression including febrile neutropenia, leukopenia, and pancytopenia observed in subjects who received induction therapy with cyclophosphamide followed by maintenance therapy with azathioprine or mycophenolate were added under Section 5.1 Serious infections and Section 6.1 Clinical Trials Experience, respectively. Information regarding increased serum IgG levels and complement levels, and the reduction in autoantibodies, circulating total B cells and B cell subsets in patients treated with belimumab in study BEL114054/C1121 was added under Section 12.2 Pharmacodynamics. Pharmacokinetic data for the IV formulation related to proteinuria as well as pharmacokinetic data related to the subcutaneous injection in adults with lupus nephritis was added under Section 12.3 Pharmacokinetics. Other changes included the deletion of intravenous cyclophosphamide under Section 5.7 Concomitant Use with Other Biologic Therapies; the addition of information regarding the lack of formation of anti-belimumab antibodies in study BEL114054/C1121 under Section 6.4 Immunogenicity; and the addition of cyclophosphamide to the list of concomitantly administered medications under Section 7 Drug Interactions. The Instructions for Use (IFU) and Medication Guide (MG) were also updated to include the instructions for administration of the loading dose of the subcutaneous formulation and to reflect the new information regarding cyclophosphamide and the use of belimumab as a treatment for adult patients with lupus nephritis.

3.1. Summary of Presubmission/Submission Regulatory Activity

As part of the approval action on December 16, 2020 for BLA 125370 Benlysta® (belimumab) intravenous (IV) formulation as a treatment for adult patients with active lupus nephritis, the Agency required a pediatric postmarketing (PMR 3994-01) assessment of belimumab IV under the Pediatric Research Equity Act (PREA) as follows:

"Provide an assessment of intravenous belimumab for the treatment of patients ages 5 to less than 18 years of age with lupus nephritis who are receiving standard therapy"

RAP Submission: March 31, 2021
Final Assessment Report Submission: November 30, 2021

The Applicant submitted the final assessment report for the pharmacokinetics modeling study 217143 to the Agency on November 25, 2021. Based on the data generated from this population pharmacokinetics modeling study which was conducted in accordance with an agreed pediatric study plan (iPSP), the PK bridge to pediatric LN was established to support full extrapolation of efficacy established in adults with lupus nephritis and leveraging of safety established in children with cSLE. The Applicant submitted this sBLA125370-s078 for the expansion of belimumab IV's approved indication for the treatment of patients with active lupus nephritis to include children 5 to less than 18 years of age on January 26, 2022. As there are no currently approved treatments for pediatric patients with lupus nephritis and using the rationale that belimumab IV would be a significant improvement over the currently available lupus nephritis treatments for children 5 to less than 18 years of age (e.g., a new subpopulation), the Applicant requested a priority review request for this sBLA which was granted by the Agency on March 31, 2022.

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 IV belimumab 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

Not applicable as there are no new device or companion diagnostic issues associated with the administration of both the intravenous and subcutaneous formulations of belimumab.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

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

5.2. Referenced NDAs, BLAs, DMFs

Not applicable.

5.3. Pharmacology

Not applicable.

5.4. ADME/PK

Not applicable.

5.5. Toxicology

5.5.1. General Toxicology

Not applicable.

5.5.2. Genetic Toxicology

Not applicable.

5.5.3. Carcinogenicity

Not applicable.

5.5.4. Reproductive and Developmental Toxicology

Not applicable.

5.5.5. Other Toxicology Studies

Not applicable.

6 Clinical Pharmacology

6.1. Executive Summary

On January 26, 2022, GlaxoSmithKline LLC submitted an efficacy supplement (Supplement 078) under BLA 125370 seeking approval of Benlysta (belimumab) for the treatment of active lupus nephritis (LN) in children 5 years and older who are receiving standard therapy. The proposed dosing regimen is 10 mg/kg intravenous (IV) administration at 2-week interval (Q2W) for the first 3 doses and at 4-week interval (Q4W) thereafter.

Benlysta IV (BLA125370, initially approved on March 09th, 2011) is approved for the treatment of patients with active, autoantibody-positive systemic lupus erythematosus (SLE) who are receiving standard therapy. The approved dosing regimen in adult subjects with SLE is 10 mg/kg Q2W for the first 3 doses and Q4W thereafter. The approval is based on two Phase 3 randomized controlled trials in adult subjects with SLE (Study BEL110751 and Study BEL110752).

On April 26, 2019, Benlysta IV was approved for the treatment of children with active, autoantibody-positive SLE who are receiving standard therapy. The approved dosing regimen in children 5 to 17 years with active LN is also 10 mg/kg Q2W for the first 3 doses and Q4W thereafter. The approval was based on a Phase 3 randomized controlled trial in children with active SLE (Study BEL114055).

On December 16, 2020, Benlysta IV was approved for the treatment of adult subjects with active LN who are receiving standard therapy. The approved dosing regimen in adult subjects with active LN is also 10 mg/kg Q2W for the first 3 doses and Q4W thereafter. The approval was based on a Phase 3 randomized controlled trial in adult subjects with active LN (Study BEL114054).

In the current sBLA submission, the Applicant proposed a full extrapolation approach with a PK modeling and simulation study to support the PK bridging. No clinical trials were conducted in pediatric patients with active LN. The full extrapolation is based on the following aspects:

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

The exposure of belimumab is estimated to be comparable in pediatric LN patients and adult LN patients, supporting the extrapolation of efficacy from studies in adult LN patients to pediatric patients with LN. The comparable PK in adult and pediatric LN patients was supported by the a population pharmacokinetic model developed from 224 adults with active lupus nephritis and

validated using data from 53 pediatric patients with SLE. With IV administration of 10 mg/kg on Days 0, 14 and 28 and at 4-week intervals thereafter, 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 lupus nephritis.

Of note, lower exposures were observed in patients with high degree of proteinuria in the adult LN program; however, this observation did not warrant dose adjustments in adults, as discussed in the review of sBLA 125370/s-073 (DARRTS date 12/16/2020). As the proteinuria impact on PK is expected to be similar for adult and pediatric patients with LN, and the exposure is comparable in adult and pediatric patients with SLE, it is reasonable to estimate that the PK would be comparable in adult and pediatric LN patients with proteinuria and respectively would not necessitate dose adjustments in pediatric LN.

The PK exposure is estimated to be similar (or lower in patients with high proteinuria) in pediatric patients with LN compared to pediatric SLE patients with the same dosing regimen. 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 pediatric SLE patients to the pediatric LN population.

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 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 224 adults with active lupus nephritis and validated using data from 53 pediatric patients with SLE. With IV administration of 10 mg/kg on Days 0, 14 and 28 and at 4-week intervals thereafter, 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 lupus nephritis.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dose of belimumab in children with active LN is 10 mg/kg administered intravenously at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

Therapeutic Individualization

None.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Benlysta (belimumab) is a human IgG1λ monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA technology in a murine cell (NS0) expression system.

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

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

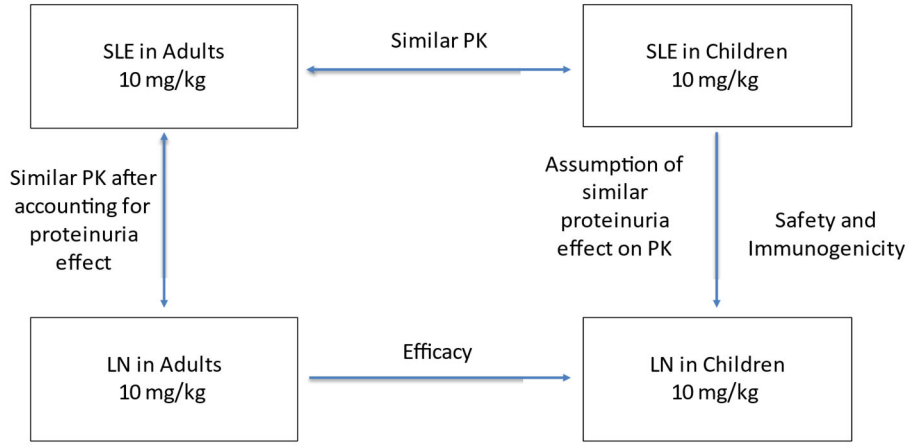
6.3.2. Clinical Pharmacology Questions

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

A full extrapolation approach is applied to support the use of belimumab in children with active LN, and the full extrapolation relied on the following four aspects:
1) Disease similarity between adult and pediatric patients with LN
2) PK bridge between adult and pediatric patients
3) Extrapolation of efficacy in pediatric patients from adult subjects with LN
4) Justification of the relevance of the safety data from children with SLE

The safety, efficacy, PK, and immunogenicity data collected from the following four clinical studies (Study BEL110751, Study BEL110752, Study BEL114055, and Study BEL114054) were used to support the PK based efficacy extrapolation in children 5 to 17 years old with LN. The full extrapolation schema is depicted in Figure 1.

Figure 1 Full Extrapolation Schematic for Intravenous Belimumab



LN is the renal manifestation of SLE. Adults and children with LN share the same etiology and pathophysiology, resulting in similar disease progression and response to standard therapies. The Applicant conducted a literature review in both adults and children with LN who were receiving standard of care (SOC). The responses to SOC were similar between adults and children with LN. (Table 4)

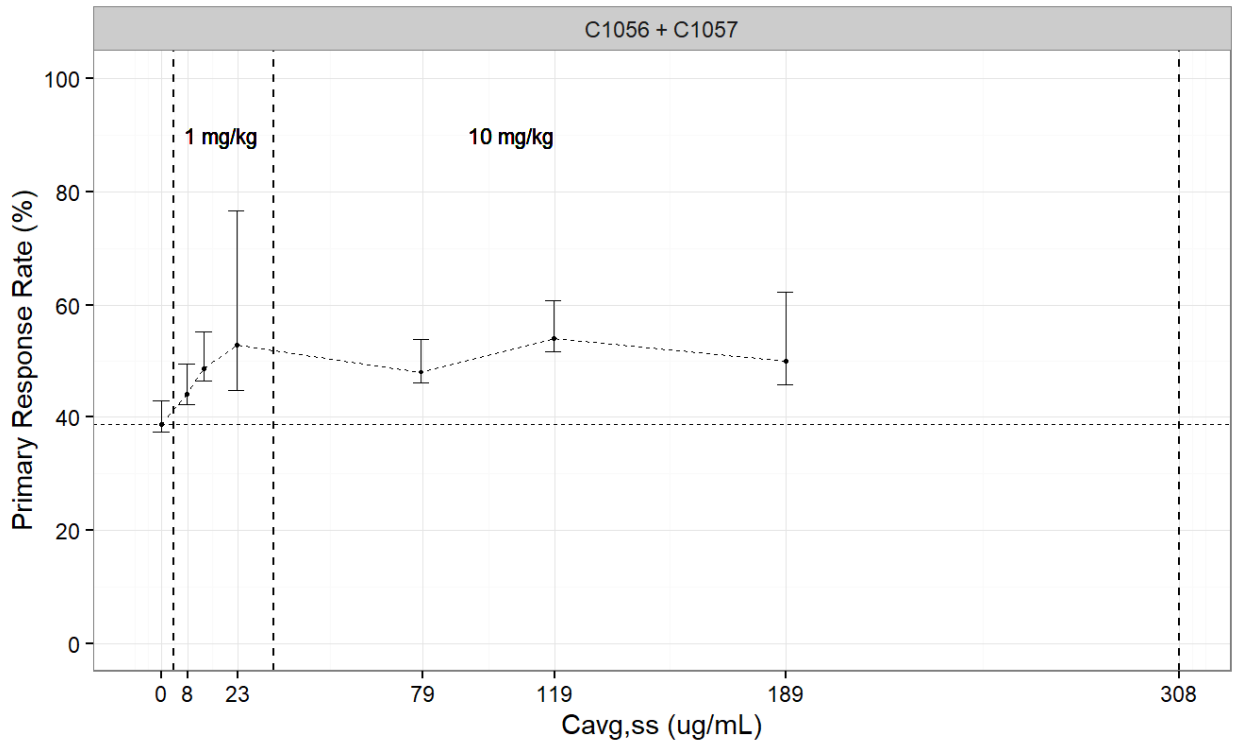
Table 4 Summary of Renal Response Rates (%) over Time in Adults and Children with LN Receiving Standard Therapy (not Belimumab Treated)

Timepoint	Adults with LN Belimumab Study BEL114054 (Placebo Arm)[a]	Adults with LN Published Literature[b]	Children with LN Published Literature[b]
6 months post-baseline	CRR: 19.3 At least PRR: 39.9	CRR: 20 – 31[c] At least PRR: 50 – 59[d]	CRR: 0 – 66.4[g] At least PRR: 57 – 88.3[h]
12 months post-baseline	CRR: 26.9 At least PRR: 43.5	CRR: 8 – 30.6[e] At least PRR: 31 – 52[f]	CRR: 23 – 75[g] At least PRR: 48 – 100[i]

Source: Table 2 in PopPK children LN simulation report [GSK Document Number 2021N491623_00]
a. Post-baseline data are from the placebo group. Source: CSR BEL114054 Table 2.12, Table 2.62
b. Data from the published literature are from the control/standard of care group.
c. ACCESS Trial Group, 2014; Rovin, 2021
d. ACCESS Trial Group, 2014; Rovin, 2021, Sundel, 2012
e. Furie, 2014; Rovin, 2012; Rovin, 2021
f. Furie, 2014; Rovin, 2012; Rovin, 2021
g. Aragon, 2010; Hari, 2009; Lau, 2008; Ruggiero, 2013; Srivastava, 2016
h. Aragon, 2010; Hari, 2009; Lau, 2008; Ruggiero, 2013; Srivastava, 2016; Sundel, 2012; Wei, 2021
i. Aragon, 2010; Hari, 2009; Lau; 2006; Ruggiero, 2013; Srivastava, 2016; Wei, 2021

In the Phase 3 clinical studies (C1056 and C1057) in adults with SLE, the SLE Responder Index (SRI) response rate reached its maximum effect in subjects with an average concentration at steady state above 22.7 ug/mL (Figure 2).
In children with SLE, the proportion of subjects who achieved SRI response at week 52 was found to be greater in belimumab 10 mg/kg IV group (52.8%) compared to the placebo group (43.6%). The clinical responses to belimumab treatment (at comparable exposures) are similar between adult and pediatric patients with general SLE. The similar exposure response relationship of SLE also supported the efficacy extrapolation from adults to children with LN.

Figure 2 : SRI Response vs Average Concentration at Steady State Following Belimumab Dosing at 1 or 10 mg/kg in Adults with SLE



source: Figure 2 in PopPK children LN simulation report [GSK Document Number 2021N491623_00], reproduced by the reviewer
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.

To establish the PK bridge to pediatric patients with LN, PK in children with SLE and adult SLE/LN were considered. In adult patients with lupus nephritis, due to additional clearance associated with proteinuria, belimumab exposure was initially lower than observed in SLE studies and lower belimumab exposure was observed in patients with higher proteinuria. When the proteinuria was decreased to approximately ≤1 g/g after treatment, belimumab clearance and exposure were similar to that observed in patients with SLE who received belimumab 10 mg/kg intravenously. Overall, while the exposure is lower in LN patients with high proteinuria,

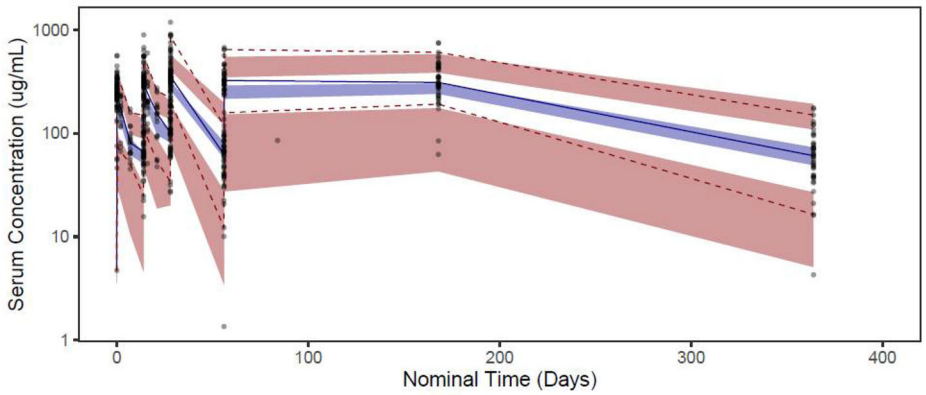
the PK would be similar in adult LN and SLE patients after accounting for the proteinuria impact. As the proteinuria impact on PK is expected to be similar for adult and pediatric patients with LN, and the exposure is comparable in adult and pediatric patients with SLE, it is reasonable to estimate that the PK would be comparable in adult and pediatric patients with LN. Once the PK bridge is established, borrowing efficacy from adequate and well-controlled studies in adult subjects with LN is scientifically justified, if the disease is sufficiently similar in course between the two populations. See clinical pharmacology review below for the simulation based PK bridging.

In addition, safety information from other relevant pediatric populations like SLE and adult patients like LN can be leveraged. For disease similarity and justification of the relevance of safety data from SLE refer to section 2 and 8.

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

Yes. The Applicant's population pharmacokinetics (PopPK) model was developed in adult subjects with active LN. For model development and evaluation in adult subjects with active LN, see clinical pharmacology review by Dr. Tao Liu for BLA 125370 Supplement 73 in DARRTS on 12/16/2020. The identified covariates on belimumab PK includes, fat free mass (FFM), proteinuria (measured by urine protein creatinine ratio, g/g), and albumin (g/L). The Applicant conducted an external evaluation for this PopPK model in children 5 years and older with SLE observed in Study BEL 114055. The external evaluation result is depicted in Figure 3.

Figure 3 Visual Predictive Check of Study BEL114055: Pediatric Systemic Lupus Erythematosus Study

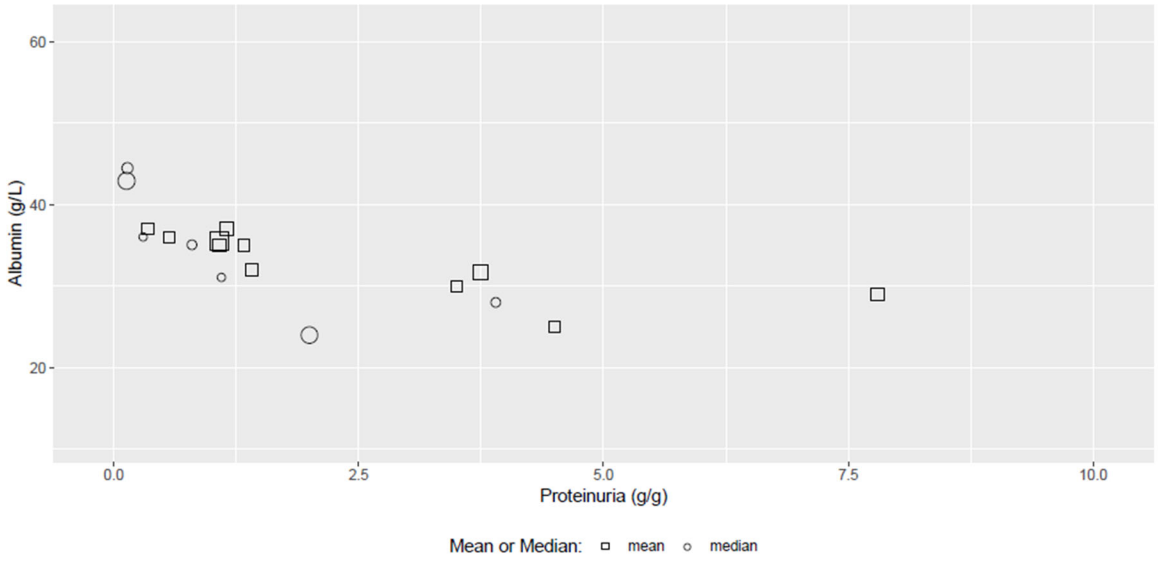


Source: Figure 5 in PopPK children LN simulation report [GSK Document Number 2021N491623_00]
Observed data (black points) are characterized by the median (solid blue line) and 95% prediction interval (dotted red lines). Corresponding model predictions are superimposed as the 95% confidence intervals about the median (blue region) upper and lower percentiles (red regions).

In this external evaluation, the Applicant demonstrated the validity of the PopPK model in predicting the FFM effect on belimumab PK in children. However, children with SLE had no or limited proteinuria and limited changes in albumin levels, the effects of proteinuria and

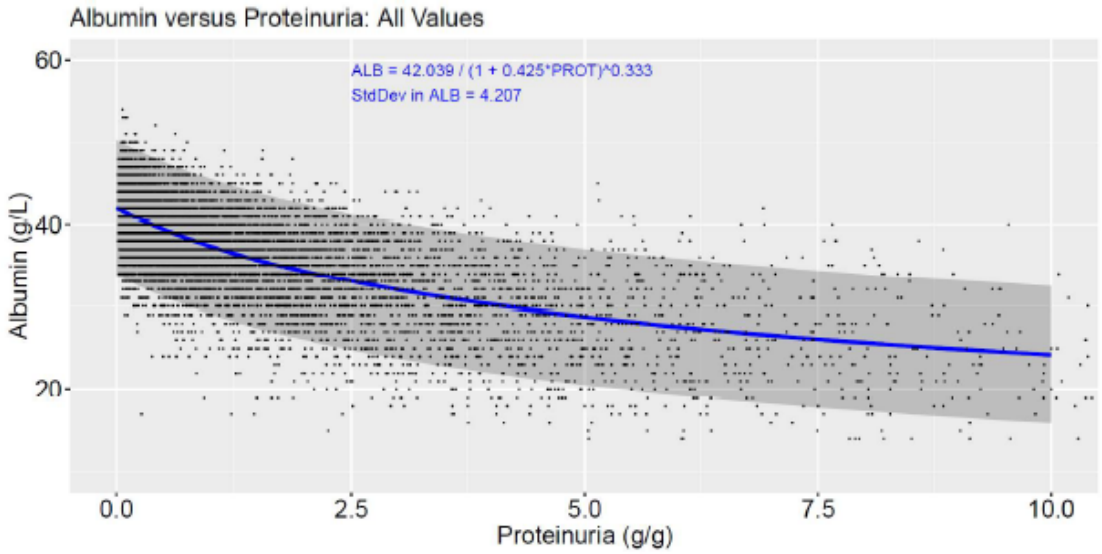
albumin on belimumab PK in children with active LN were not evaluated in this external evaluation. Particularly, proteinuria also decreased albumin level, and the underlying relationship between proteinuria and albumin in children with LN cannot be justified by this external evaluation. The Applicant conducted a literature review on the relationship between proteinuria and albumin in children with SLE or LN. The results are depicted in Figure 4. In comparison with the previously observed proteinuria and albumin relationship in adult subjects with active LN (Figure 5), the Applicant's literature review showed a consistent proteinuria-albumin relationship in adults and children with LN.

Figure 4 Albumin and Proteinuria Relationship in children with Systemic Lupus Erythematosus/Lupus Nephritis



Source: Figure 1 in Response to Information Request dated 04/11/2022
Size of symbols is proportional with number of observations in the underlying data.

Figure 5 Albumin versus Proteinuria Levels Observed in Adults with Lupus Nephritis over The Study Duration



Source: Figure 15 in PopPK adult LN report BLA 125370/S-073 [GSK Document Number 2020N433185_00]
Albumin-proteinuria relationship has been empirically derived to be ALB= $42/(1+0.425*PROT)^{0.333}$. The standard deviation in albumin concentrations is estimated to be 4.207 g/L, constant across all proteinuria levels between 0 and 10 g/g. The median (solid blue) and 95% confidence interval (grey shaded region) is superimposed on the observations (black points)

The similar proteinuria-albumin relationship between adults and children with active LN support the application of adult PopPK model in children:

(1) The potential confounding issue between proteinuria and albumin remained unchanged in children with LN. The re-sampling of proteinuria and albumin time course from adult subjects is reasonable.
(2) The proteinuria effect on protein (e.g., albumin, belimumab) elimination is expected to be similar between adults and children. Therefore, the proteinuria and albumin effects on belimumab clearance in adult subjects with LN can be extrapolated to children.

Overall, the Applicant developed a validated PopPK model in adult patients with active LN and predicted the PK in children 5 years and older with active LN. The model prediction in children 5 years and older assumes the same proteinuria and albumin relationship between adults and children. The proteinuria and albumin relationship in pediatric patients with active LN cannot be estimated due to lack of data, but its relationship appears to be similar between pediatric and adult patients based on literature review. The final PopPK model is acceptable for estimating PK characteristics in children 5 years and older with active LN considering the rarity of disease. See section 15.4.1 pharmacometrics review for additional details for the simulation of demographics and disease characteristics.

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

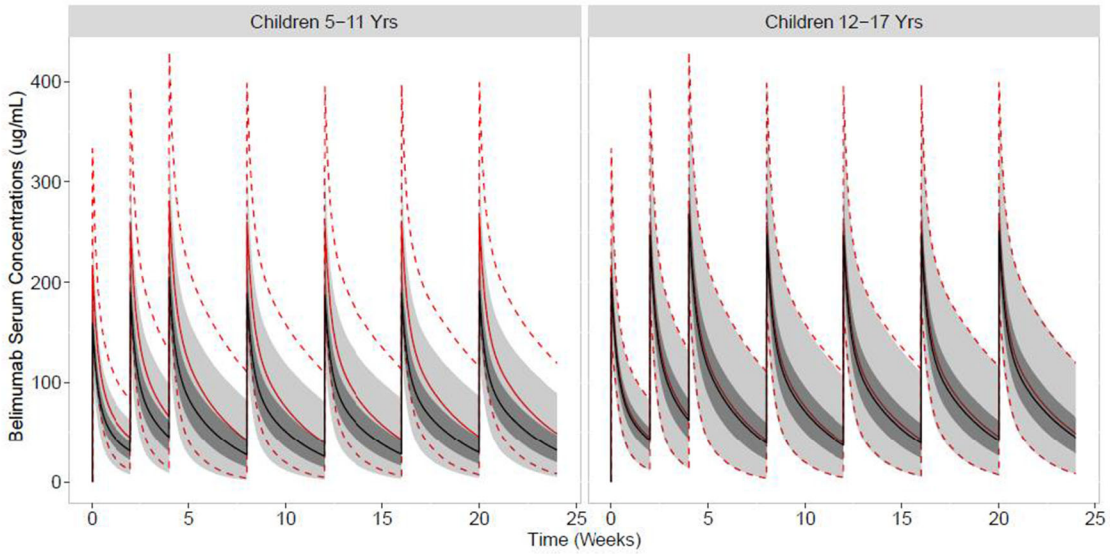
Yes. Based on the PopPK model in subjects with active LN, the Applicant conducted a PK simulation study for the proposed dosing regimen in children 5 years and older. The simulated PK parameters are given in Table 5 for children 5 to 11 years old and 12 to 17 years old, respectively. And the concentration time profiles are depicted in Figure 6 for children 5 to 11 years old and 12 to 17 years old, respectively. See section 15.4.1 pharmacometrics review for additional details for the PK simulation.

Table 5 Belimumab Exposure Summaries in Adults and Children with Lupus Nephritis Receiving Intravenous 10 mg/kg

	Median (95% Prediction Interval) (µg/mL) [% Below Adult 2.5th Percentile Value]		
	Adults with LN	Children with LN 5-11 Yrs	Children with LN 12-17 Yrs
Cavg(Wk 0-12)	96 (42 – 169) [2.5%]	67 (27 - 128) [13.4%]	91 (40–167) [3.4%]
Cavg(Wk 0-24)	96 (44 – 171) [2.5%]	66 (28 – 131) [15.0%]	90 (41 – 171) [3.5%]
Cmin(Wk 12)	40 (5 - 110) [2.5%]	26 (3 - 81) [5.1%]	37 (5 - 106) [2.3%]
Cmin(Wk 24)	49 (8 – 119) [2.5%]	32 (5 – 89) [5.9%]	45 (8 – 119) [2.7%]
Cmax(Wk 8-12)	260 (176 – 398) [2.5%]	189 (122 - 311) [38.4%]	248 (159 - 395) [6.9%]
Cmax(Wk 20-24)	264 (180 - 399) [2.5%]	191 (124 – 313) [39.8%]	251 (163 – 400) [6.8%]

Cmin(Wk 12) and Cmin(Wk 24) are the pre-dose concentration at Weeks 12 and 14, respectively
Source: Table 7 in PopPK children LN simulation report [GSK Document Number 2021N491623_00]

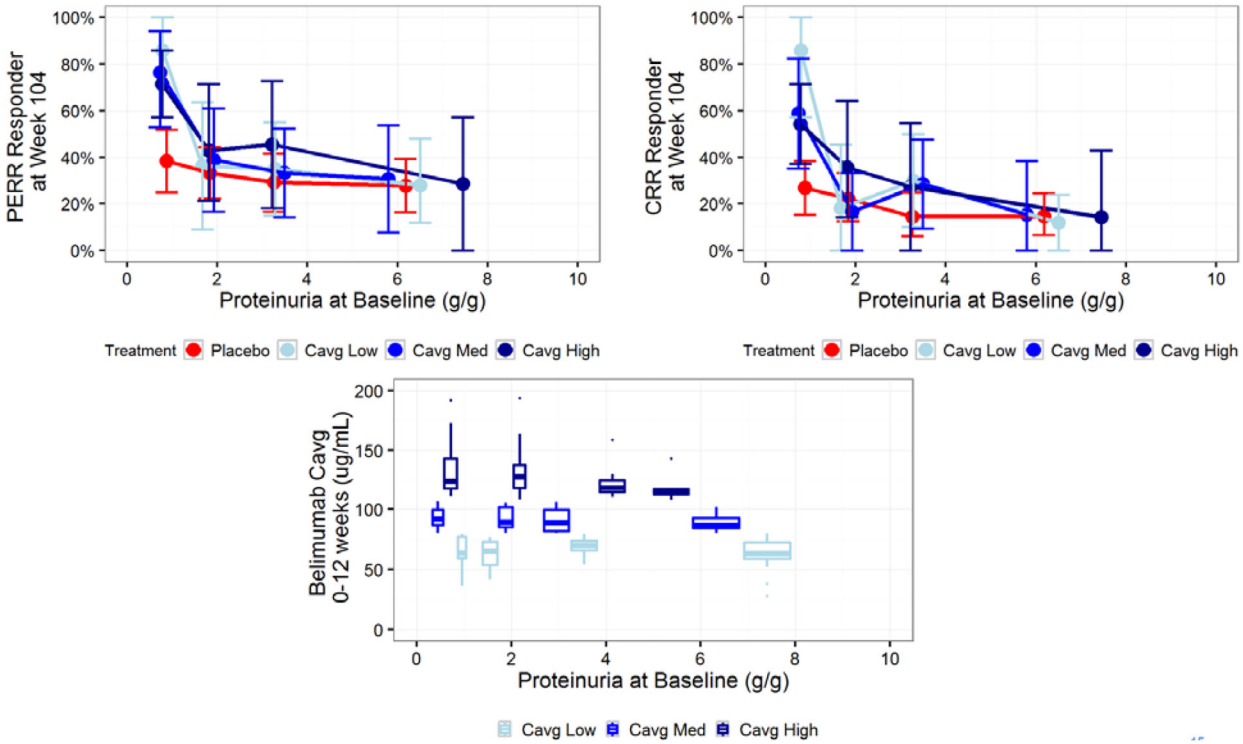
Figure 6 Simulated Concentrations over Time in Adults and Children with Lupus Nephritis Receiving Intravenous Belimumab 10 mg/kg



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).

In pediatric LN patients 5 to 11 years old, the simulation result showed a ~30% lower Cave (67 vs 96 ug/mL) and Cmin (26 vs 40 ug/mL) compared to adult patients with LN. This is driven by children with low body weight (see Table 17 in section 15.4.1 Pharmacometrics review). While equal number of children were simulated across 5 to 11 years old, the prevalence of LN in younger children with low bodyweight (e.g., 5 to 8 years old) is much lower than older children. Therefore, the differences in AUC and Cmax and the percent below adult 2.5th percentile value simulated in children 5 to 11 years old (Table 5) were overestimated. In adult subjects with active LN, the exposure response analyses showed similar PERR and CRR response rates across different exposure levels following IV administration of 10 mg/kg (Figure 7). The flat exposure response in adult patients with active LN indicates the efficacy is unlikely to be impacted in a meaningful way in children 5 to 11 years old with 30% lower exposure. In children 12 to 17 years old, the proposed dosing regimen results in a similar PK profile and supports the efficacy bridging.

Figure 7 Exposure Response in Patients with Different Baseline Proteinuria



Source: Figure 12 in unireview of BLA 125370 S73
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]

In summary, the pharmacokinetics of belimumab in pediatric patients were estimated based on a population pharmacokinetic model developed from 224 adults with active lupus nephritis and validated using data from 53 pediatric patients with SLE. With IV administration of 10 mg/kg on Days 0, 14 and 28 and at 4-week intervals thereafter, the simulated belimumab exposures for both the 5- to 11-year-old group and the 12- to 17-year-old group were estimated to be comparable to adults with active lupus nephritis.

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

The simulated concentrations in pediatric patients with LN were generally within the range of concentrations observed in pediatric SLE patients (Table 5, Table 6). See clinical pharmacology review for BLA125370/S-064 for detailed PK assessment and bioanalytical method in pediatric patients with SLE (DARRTS date 4/26/2019). The point estimate of simulated belimumab concentrations in pediatric patients with LN is numerically lower than the reported average concentration in children with SLE 5 to 11 years old (67 vs 92 ug/mL) and 12 to 17 years old (91 vs 112 ug/mL), respectively. This could be partly due to the impact of proteinuria (see section 15.4.1 Pharmacometrics review) as belimumab concentration is lower in LN patients with high proteinuria. In addition, as the belimumab concentration tends to be lower in pediatric patients

with lower weight, the numerical difference between LN and SLE in the 5-11 years old could be partly due to the age difference in the simulated dataset for LN (Median age=8 years old, Table 17) vs PK dataset in the pediatric SLE study (Median age=10 years old in cohort 2, Study BEL114055, n=10). The comparable systemic exposure in children with LN supports the relevance of safety data from pediatric SLE patients to the pediatric LN population.

Table 6 Belimumab Exposure Summaries in Adults and Children with SLE Receiving Intravenous 10 mg/kg

Parameter	Summary	Baseline Age 5-11 Years (Cohort 2) N=10	Baseline Age 12-17 Years (Cohorts 1 and 3) N=43	Total Pediatric 5-17 Years (Cohorts 1-3) N=53	Adult N=563
Cmax,ss (µg/mL)	Geo. Mean (%CV)	305 (22.1%)	317 (33.1%)	315 (31.2%)	311 (20.3%)
	95% CI	267 - 350	288 - 350	290 - 342	306 - 316
	Range	193 - 403	81 - 587	81 - 587	173 - 573
Cmin,ss (µg/mL)	Geo. Mean (%CV)	42 (61.8%)	52 (69.7%)	50 (68.3%)	46 (57.1%)
	95% CI	30 - 60	43 - 63	42 - 59	44 - 48
	Range	15 - 95	4 - 146	4 - 146	4 - 222
Cavg,ss (µg/mL)	Geo. Mean (%CV)	92 (42.9%)	112 (42.8%)	108 (43.2%)	100 (34.6%)
	95% CI	71 - 118	99 - 126	96 - 120	98 - 103
	Range	49 - 142	21 - 238	21 - 238	34 - 308
AUC,ss (day µg/mL)	Geo. Mean (%CV)	2569 (42.9%)	3126 (42.8%)	3012 (43.2%)	2811 (34.6%)
	95% CI	1992 - 3314	2765 - 3533	2695 - 3367	2734 - 2890
	Range	1381 - 3988	589 - 6654	589 - 6654	954 - 8627

Source: CSR BEL114055 (Table 7 in attachment 2, page 1537)

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

As part of the approval action on December 16, 2020 for BLA 125370 Benlysta® (belimumab) intravenous (IV) formulation as a treatment for adult patients with active lupus nephritis, the Agency required PREA PMR 3994-01 as follows:

> "Provide an assessment of intravenous belimumab for the treatment of patients ages 5 to less than 18 years of age with lupus nephritis who are receiving standard therapy"

In fulfillment of PREA PMR 3994-01 and in support of expanding the indication for belimumab IV to include the treatment of children 5 to 17 years of age with active lupus nephritis who are receiving standard therapy, the Applicant submitted the results from a population pharmacokinetics (PK) modeling study (217143), along with cross-referenced efficacy, safety and PK data from the phase 3 study BEL114054/C1121 conducted in adults with active lupus nephritis and the phase 2 study BEL 114055/C1109 conducted in children 5 to 17 years of age with active, seropositive SLE reviewed previously in support of the marketing approval for belimumab IV's lupus nephritis indication in adults and pediatric SLE indication, respectively, as well as supportive efficacy, safety and PK data from the pivotal, phase 3 studies, HGS1006/C1056 and HGS1006/C1057, conducted in adult SLE patients reviewed previously in support of the original marketing approval for belimumab IV. The key design features of these clinical trials are summarized in Table 7 below.

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Table 7. Key Design Features of Controlled Studies in Adults with Lupus Nephritis, Children and Adults with SLE, and Population PK Modeling Study

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Study in Adults to Support Efficacy and Safety						
BEL114054/ HGS1006-C1121	NCT-01639339	Phase 3, MC, R, DB, PC, parallel group trial	Standard of care (SOC) induction/maintenance regimens: • HDCS + CYC for induction followed by AZA for maintenance **OR** • HDCS + MMF for induction followed by MMF for maintenance Placebo or BEL 10 mg/kg via intravenous infusion on Days 1, 14, 28, and every 28 days thereafter until Week 100. Subjects who completed Week 104 final study visit assessments had the option of entering a 6-month OLE	**1º endpoint: P**rimary **E**fficacy **R**enal **R**esponse (PERR) at Week 104 • Responder: uPCR ≤ 0.7 and eGFR no more than 20% below pre-flare value or ≥60mL/min/1.73 m^2 and not a treatment failure (received prohibited meds or an ↑SOC therapies) • Non-responder: Not meeting criteria for PERR renal response **Key 2º endpoints:** -**C**omplete **R**enal **R**esponse (CRR) at Week 104 • Responder: uPCR ≤ 0.5 and eGFR no more than 10% below pre-flare value or ≥90mL/min/1.73 m^2 and not a treatment failure • Non-responder: not meeting criteria for CRR response -PERR at Week 52 -Time to renal-related event or death (defined as death, ESRD, doubling of sCr, renal worsening or renal disease-related treatment failure) -**O**rdinal **R**enal **R**esponse (ORR) (complete, partial or no response) at Wk 104	Screening and randomization visits with visits on Days 1, 14, 28 and then every 28 days until Week 104	N=446 BEL 10mg/kg =223 Placebo =223	Adults age ≥ 18 yo with clinically active, biopsy-proven lupus nephritis Class III, IV, and/or V using 2003 ISN/RPS criteria	107 sites in 21 countries in Asia (China, Hong Kong, Korea, Philippines, Taiwan, Thailand), Europe (Belgium, Czech Republic, France, Germany, Hungary, Netherlands, Russian Federation, Spain, United Kingdom), North America (United States and Canada), and South and Central America (Argentina, Brazil, Columbia, and Mexico)
		Controlled Study in Children to Support Safety						

BEL114055/ C1109	NCT-0164 9765	Phase 2, MC, R, DB, PC, parallel group pediatric study (Part A) with a long-term OL safety follow-up for subjects who completed Part A (Part B); and long-term safety follow-up (Part C) for subjects who with-drew any time from Part A or B (Part C ongoing)	Belimumab 10 mg/kg or Placebo intravenous infusions on Days 0, 14, 28 and every 4 weeks thereafter	SRI Response at Week 52 defined as the proportion of patients with: ≥ 4-point reduction from baseline in SELENA SLEDAI score **AND** no worsening (Increase of < 0.30 points from baseline in PGA) **AND** no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline) **AND** subject does not drop out before Week 52 **AND** does not meet treatment failure criteria	Screening and randomization visits with visits on Days 0, 14, 28 and then every 28 days until Week 52. Subjects who completed Part A had the option of entering OL safety extension Part B. Subjects who no longer continued study drug treatment In Parts A or B were followed up for long term safety in Part C.	N=93; n=13 subjects 5-11 years old; n=80 subjects 12-17 years old	Pediatric subjects ≥ 5 to 17 yo with SLE as defined by ACR criteria that is active as per SELENA SLEDAI disease activity score ≥ 6 at screening with + auto-antibodies on stable SLE treatment regimen for ≥ 30 days prior to Day 0. Individuals with severe active LN or CNS lupus were prohibited	Total of 29 sites in 10 countries (Argentina, Canada, Japan, Mexico, Peru, Poland, Russian Federation, Spain, United Kingdom, and United States)
		Supportive Controlled Efficacy and Safety Studies in Adults						
HGS1006/ C1056	NCT-0041 0384	P3, MC, R, DB, PC 76-week	Belimumab 1 mg/kg, 10 mg/kg or Placebo intravenous	SRI Response at Week 52 defined as the proportion of patients with:	Screening and randomization	N=819	Adults age ≥ 18 years with SLE	65 sites North America, 62 sites Europe

		comparative parallel group trial	infusions on Days 0, 14, 28 and every 4 weeks thereafter	≥ 4-point reduction from baseline in SELENA SLEDAI score **AND** no worsening (increase of < 0.30 points from baseline in PGA) **AND** no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline) **AND** subject does not drop out before Week 52 **AND** does not meet treatment failure criteria	visits with visits on Days 0, 14, 28 and then every 28 days until Week 52.	BEL 1mg/kg = 271 subjects BEL 10mg/kg = 273 subjects Placebo = 275 subjects	defined by ACR criteria that is clinically active as per SELENA SLEDAI disease activity score ≥ 6 at screening, with + auto-antibodies on stable SLE treatment regimen for ≥ 30 days prior to Day 0. Individuals with severe active LN or CNS lupus were prohibited	and 9 sites Latin America
HGS1006/C1057	NCT-0042 4476	P3, MC, R, DB, PC 76-week comparative parallel group trial	Belimumab 1 mg/kg, 10 mg/kg or Placebo intravenous infusions on Days 0, 14, 28 and every 4 weeks	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	Screening and randomization visits with visits on Days 0, 14, 28	N=865 BEL 1mg/kg =	Same as Study HGS1006/ C1056	41 sites Asian Pacific, 40 sites Latin America and 11 sites Europe

			thereafter	from baseline in PGA) **AND** no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline) **AND** subject does not drop out before Week 52 **AND** does not meet treatment failure criteria	and then every 28 days until Week 52.	288 subjects BEL 10mg/kg = 290 subjects Placebo = 287 subjects		

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

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7.2. Review Strategy

There were no clinical studies of belimumab IV conducted in children with active lupus nephritis submitted in support of this application. As permitted under 21 CFR 314.55 and per the agreed Pediatric Study Plan (PsP), an assessment of belimumab IV treatment in children aged 5 to less than 18 years old with active lupus nephritis was conducted via a full extrapolation approach from existing efficacy, safety and PK data in adults with lupus nephritis and children with SLE treated with belimumab IV. As the efficacy data from the pivotal, phase 3, randomized, double-blind, placebo-controlled study BEL114054/HGS1006-C1121 conducted in adults with active lupus nephritis receiving standard of care was previously reviewed by this division in the unireview dated December 16, 2020 in support of the marketing approval for belimumab IV 's adult indication for lupus nephritis, it will not be re-presented here.

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8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Because efficacy in pediatric LN is extrapolated from the efficacy established in adult patients with LN, as detailed elsewhere in this review, no new efficacy studies in pediatric LN were required/submitted with this application.

8.2. Review of Safety

8.2.1. Safety Review Approach

While no dedicated clinical trials have been conducted/required in pediatric patients with LN, the safety in that population has been supported by the safety experience with belimumab in pediatric patients with general SLE, as well as in adults with SLE and LN, supported by an adequate justification, provided by the Applicant, of the relevance of these safety data to pediatric LN.

In support of the safety profile of belimumab IV in children with active lupus nephritis, the Applicant submitted summaries of safety data from the following clinical trials:

- Part A of study BEL114055/C1109 which was the 52-week, randomized, double-blind, placebo-controlled portion of this study conducted with belimumab IV in children with active SLE despite standard of care therapy
- Study BEL114054/C1121 which was the 104-week, randomized, double-blind, placebo controlled study of belimumab IV in adults with active lupus nephritis despite standard of care therapy
- The pivotal phase 3 studies that were conducted with belimumab IV in adults with active SLE receiving standard of care therapy:
    - BEL110751/C1056 which was a 52-week, randomized, double-blind, placebo-controlled trial
    - BEL11072/C1057 which was a 76-week, randomized, double-blind, placebo-controlled trial

Since the safety data from these four studies were previously reviewed by this clinical reviewer in support of the marketing approval of belimumab IV as a treatment for pediatric patients ages 5 to 17 years old (BLA 123570/s-064), adult patients with active lupus nephritis (BLA 123570/s-073) and for adults with active SLE (the original BLA 123570), respectively, these data will not be re-presented here as the safety of belimumab IV as a treatment for adults and children with active SLE and adults with active lupus nephritis has been previously established.

Additionally, the Applicant included the following supportive safety data:

- A 10-year summary of post-marketing safety data for belimumab

- A review of safety reports associated with the administration of belimumab in children less than 18 years of age from Applicant's postmarketing Argus safety surveillance database during the time period from April 26, 2019 through September 8, 2021
- Interim cumulative safety data comprised of adverse events, serious adverse events and adverse events of special interest including deaths collected since the cut-off date of November 20, 2018 of the 120-day safety update report submitted in support of BLA 125370/s-064 from the ongoing Part B (the 10-year, open-label, belimumab treatment continuation phase) and ongoing Part C (the 10-year, safety follow-up phase without belimumab treatment) of the pediatric SLE study BEL114055/C1109
- Interim cumulative safety from the ongoing, open label, subcutaneous belimumab pharmacokinetics study 200908 being conducted in children between the ages 5 to 17 years old

The interim cumulative safety from the ongoing study 200908 will not be reviewed here because it involves a different formulation of belimumab administered via a different route that is not currently approved for use in the pediatric population. The remaining new safety data, which are the focus of this review and are included in pertinent sections of the following discussion, were examined by this clinical reviewer for any new or unexpected safety signals associated with the administration of belimumab IV in pediatric patients.

8.2.2. Review of the Safety Database

Overall Exposure

Not applicable since this application did not contain any safety data from pediatric patients with active lupus nephritis treated with belimumab IV.

Adequacy of the safety database:

The safety profile of belimumab IV has been previously established based on safety data from more than 7400 clinical trial subjects exposed to belimumab in SLE trials, including 347 adult subjects with active lupus nephritis and 109 pediatric subjects with SLE which is adequate to provide sufficient basis for extrapolation of belimumab IV's safety to the subpopulation of pediatric patients with active lupus nephritis.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data quality submitted was well-organized and adequate to perform an updated review of safety in the pediatric population. An information request was sent to the Applicant during this

review for additional updated pediatric safety data which was satisfactory and received in a timely manner.

Categorization of Adverse Events

Verbatim terms of adverse events (AEs) Disease Related Events (DRE) recorded in the case report forms (CRF) by investigators participating in Parts B and C of ongoing pediatric SLE study BEL114055/C1109 were coded by the Applicant using MedDRA dictionary Preferred Term (PT), High-level Term (HTL), and Systems Organ Class (SOC) version 24.1.

8.2.4. Safety Results

Refer to Sections 8.2.8 through 8.2.11 for details.

8.2.5. Analysis of Submission-Specific Safety Issues

Not applicable since this application did not contain any safety data from a clinical trial of belimumab IV conducted in children with active lupus nephritis.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable since this application did not contain any safety data from a clinical trial of belimumab IV conducted in children with active lupus nephritis.

8.2.7. Safety Analyses by Demographic Subgroups

Not applicable since this application did not contain any safety data from a clinical trial of belimumab IV conducted in children with active lupus nephritis.

8.2.8. Specific Safety Studies/Clinical Trials

Safety data from Part A, which was the 52-week, randomized, double-blind, placebo controlled portion of study BEL114055/C1109 conducted with belimumab IV in children with active SLE despite standard of care therapy, were reviewed in support of expanding belimumab IV's SLE indication to include children ages 5 to 17 years old under BLA 123570/s-064. A total of 75 out of the 76 pediatric subjects who completed Part A enrolled in Part B of this study which is the ongoing 10-year, open-label extension in which pediatric patients randomized to placebo treatment during Part A were switched to treatment with belimumab IV while patients randomized to belimumab IV continued receiving belimumab IV at the approved dose of 10 mg/kg once monthly via IV infusion. At the time the Applicant submitted their amendment to this application on April 28, 2022 in response to the review division's information request dated April 19, 2022 for updated safety data from the ongoing Parts B and C of study BEL114055/C1109, a total of 39 pediatric subjects who either completed or discontinued treatment in Part B had enrolled in Part C of this study which is the ongoing 10-year, safety

observational period off belimumab. This amendment contained cumulative interim safety data from both Parts B and C comprised of adverse events, serious adverse events and adverse events of special interest including deaths collected during the time period from November 20, 2018 (the cut-off date of the 120-day safety update report that was submitted in support of BLA 125370/s-064) to the cut-off date of November 10, 2021. These new data are reviewed below starting with deaths.

Deaths

A total of three deaths have occurred in the ongoing Parts B and C of study BEL114055/C1109 during the time period from November 20, 2018 through November 10, 2021 (Table 8). Since two of the deaths (Subjects BEL114055/(b) (6) and BEL114055/(b) (6)) occurred during Part C when subjects were no longer receiving belimumab, they should not be attributed to the product. The third death involving Subject BEL14055/(b) (6) as a result of cardiopulmonary arrest due to septic shock following infectious gastroenteritis occurred during Part B while the subject was receiving open-label belimumab IV. In the adult belimumab studies, the most common cause of death was due to infectious etiologies, so this finding is not unexpected. The current USPI for belimumab contains a Warning statement regarding serious infections resulting in fatalities.

Table 8. Summary of Deaths During the Ongoing, Uncontrolled, Open-Label Part B and the Off-Treatment Safety Observation Part C of Study BEL 114055 (ITT Population) (Reporting Interval November 20, 2018 through November 10, 2021)

Subject No.	Age/Sex	Cause of Death	Days Since 1st Infusion	Days Since Last Infusion	Pertinent History
BEL114055/(b) (6)	15yo/F	Cardiopulmonary arrest	690	48	On study Day 690 and approximately 46 days since last study infusion, patient developed infectious gastroenteritis followed by septic shock and died 48 hours later due to cardiopulmonary arrest
BEL114055/(b) (6)	12yo/F	Severe respiratory insufficiency	1205	534	On study Day 1205 and approximately 534 days S/P last study infusion, patient developed acute appendicitis and died

					72 hours later due to severe respiratory insufficiency
BEL114055/ (b) (6)	23yo/F	COVID-19 pneumonia	Unknown	Approximately 2.7 years	H/O cardiac insufficiency, pulmonary artery thrombosis and pulmonary HTN. Concomitant meds: sildenafil, acenocoumarin, prednisone and MTX. Death reported via submission of death certificate.

H/O= history of; S/P= status post; MTX= methotrexate
Source: Applicant's Listing 2.1, p. 11 and Listing 2.2, p. 9 of information response submitted April 28, 2022 and p. 584 of the 2021 Period Benefit Risk Evaluation Report (PBRER) submitted May 17, 2021.

Serious Adverse Events

Table 9 summarizes the serious adverse events (SAEs) observed during the uncontrolled, open-label portion of the pediatric study BEL114055/C1109 by MedDRA system organ class (SOC) and preferred term (PT). Overall, a higher proportion of pediatric subjects experienced treatment-emergent SAEs in the placebo group switched to belimumab IV than in the group that continued to receive belimumab IV during the Part B. Numeric imbalances in SAEs not in favor of the placebo group switched to belimumab IV include the Infections and Infestations , Musculoskeletal and Connective Tissue Disorders, and Renal and Urinary Disorder system organ classes. Review of the data in Table 9 revealed that most of the SAEs were due to manifestations of pediatric patients' SLE which is similar to what was observed during the review of the double-blind, controlled portion (Part A) of the pediatric study BEL114055/C1109. No potential patterns or safety signals due to the small number of SAEs observed during this open-label portion of the ongoing pediatric study were noted on review of the SAE data shown in Table 9. Serious infections and infestations will be discussed further with adverse events of special interest (AESIs).

Table 9. Cumulative Serious Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class (SOC)/Preferred Term (PT) During Open-Label Portion of BEL114055/C1109 (Part B) (ITT Population)

MedDRA System Organ Class (SOC)/Preferred Term (PT)	Placebo Switched to Belimumab IV	Belimumab IV Continuing Belimumab IV	Total (N=75)

	(N=31)	(N=44)	
Number of Subjects with ≥ 1 Serious Adverse Event (SAE)	**14 (45%)**	**13 (30%)**	**27 (36%)**
Infections and Infestations	**8 (26%)**	**4 (9%)**	**12 (16%)**
Cellulitis	3 (10%)	0	3 (4%)
Gastroenteritis	1 (3%)	1 (2%)	2 (3%)
Appendicitis	0	1 (2%)	1 (1%)
Atypical pneumonia	1 (3%)	0	1 (1%)
Escherichia infection	1 (3%)	0	1 (1%)
Gastroenteritis viral	1 (3%)	0	1 (1%)
Infection	1 (3%)	0	1 (1%)
Influenza	1 (3%)	0	1 (1%)
Ovarian abscess	0	1 (2%)	1 (1%)
Pneumonia	1 (3%)	0	1 (1%)
Pneumonia bacterial	0	1 (2%)	1 (1%)
Pyelonephritis acute	0	1 (2%)	1 (1%)
Septic shock	0	1 (2%)	1 (1%)
Urinary tract Infection	1 (3%)	0	1 (1%)
Varicella	1 (3%)	0	1 (1%)
Musculoskeletal and Connective Tissue Disorders	**6 (19%)**	**2 (5%)**	**8 (11%)**
Systemic lupus erythematosus	5 (16%)	0	5 (7%)
Arthralgia	1 (3%)	0	1 (1%)
Arthritis	0	1 (2%)	1 (1%)
Bursitis	1 (3%)	0	1 (1%)
Joint swelling	1 (3%)	0	1 (1%)
Lupus myositis	0	1 (2%)	1 (1%)
Renal and Urinary Disorders	**2 (7%)**	**1 (2%)**	**3 (4%)**
Acute kidney injury	1 (3%)	0	1 (1%)
Glomerulonephritis	1 (3%)	0	1 (1%)
Renal disorder	0	1 (2%)	1 (1%)
Gastrointestinal Disorders	**1 (3%)**	**1 (2%)**	**2 (3%)**
Acute abdomen	1 (3%)	0	1 (1%)
Diarrhea	0	1 (2%)	1 (1%)
Injury, Poisoning and Procedural Complications	**0**	**2 (5%)**	**2 (3%)**
Gunshot wound	0	1 (2%)	1 (1%)
Multiple injuries	0	1 (2%)	1 (1%)
Blood and Lymphatic System Disorders	**0**	**1 (2%)**	**1 (1%)**
Immune thrombocytopenia	0	1 (2%)	1 (1%)
Cardiac Disorders	**0**	**1 (2%)**	**1 (1%)**
Cardio-respiratory arrest	0	1 (2%)	1 (1%)
General Disorders and Administration Site Conditions	**0**	**1 (2%)**	**1 (1%)**
Pyrexia	0	1 (2%)	1 (1%)
Hepatobiliary Disorders	**0**	**1 (2%)**	**1 (1%)**
Drug-induced liver injury	0	1 (2%)	1 (1%)
Metabolism and Nutrition Disorders	**0**	**1 (2%)**	**1 (1%)**

Dehydration	0	1 (2%)	1 (1%)
Nervous System Disorders	**1 (3%)**	**0**	**1 (1%)**
Headache	1 (3%)	0	1 (1%)
Respiratory, Thoracic, and Mediastinal Disorders	**0**	**1 (2%)**	**1 (1%)**
Dyspnea	0	1 (2%)	1 (1%)
Vascular Disorders	**0**	**1 (2%)**	**1 (1%)**
Vasculitis	0	1 (2%)	1 (1%)

Source: Applicant's Table 2.1; April 28, 2022 Information Request Response

For completeness, the SAE data from the ongoing open-label safety observation portion (Part C) of pediatric study BEL114055 was also reviewed by this clinical reviewer (data not shown) and were found to be similar to the data displayed in Table 9.

Treatment Emergent Adverse Events and Adverse Reactions

Most pediatric subjects experienced a treatment emergent adverse event (TEAE) during the open-label portion of study BEL114055. Table 10 lists the frequency of the TEAEs observed in Part B by SOC and treatment group. The proportions of pediatric subjects who had TEAEs were comparable for the two treatment groups. Infections and infestations, Gastrointestinal Disorders, Musculoskeletal and Connective Tissue Disorders, Blood and Lymphatic System Disorders and Skin and Subcutaneous Tissue Disorders were the most common TEAEs observed. Overall, the types and incidences of common TEAEs were consistent with what would be expected for patients with active SLE who had been exposed to immunosuppressive therapies. Although these findings are similar to what was observed in Part A of this study, some frequencies are higher probably as a result of long-term exposure to belimumab and observation (refer to clinical review of sBLA 125370/s-064 belimumab IV for children 5 to 17 years of age with SLE dated April 26, 2019). The frequency of TEAEs in Part C (the observation period – data not shown) were not unexpectedly lower since the patients were no longer exposed to the product.

Table 10. Common Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class During the Open-Label Portion of BEL114055/C1109 (Part B) (ITT Population)

MedDRA System Organ Class (SOC)	Placebo Switched to Belimumab IV (N=31)	Belimumab IV Continuing Belimumab IV (N=44)	Total (N=75)
Number of Subjects (%) Who Experienced Any TEAE	29 (94%)	41 (93%)	70 (93%)
Infections and Infestations	24 (77%)	33 (75%)	57 (76%)
Gastrointestinal Disorders	18 (58%)	17 (39%)	35 (47%)
Musculoskeletal and Connective Tissue Disorders	11 (36%)	17 (39%)	28 (37%)
Blood and Lymphatic System Disorders	10 (32%)	14 (32%)	24 (32%)
Skin and Subcutaneous Tissue Disorders	9 (29%)	13 (30%)	22 (29%)
Investigations	8 (26%)	12 (27%)	20 (27%)

Injury, Poisoning and Procedural Complications	7 (23%)	10 (23%)	17 (23%)
General Disorders and Administration Site Conditions	7 (23%)	9 (21%)	16 (21%)
Nervous System Disorders	5 (16%)	11 (25%)	16 (21%)
Eye Disorders	9 (29%)	3 (7%)	12 (16%)
Respiratory, Thoracic and Mediastinal Disorders	4 (13%)	8 (18%)	12 (16%)
Psychiatric Disorders	7 (23%)	4 (9%)	11 (15%)
Renal and Urinary Disorders	4 (13%)	7 (16%)	11 (15%)
Reproductive and Urinary Disorders	4 (13%)	6 (14%)	10 (13%)
Metabolism and Nutrition Disorders	2 (7%)	3 (7%)	5 (7%)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	2 (7%)	3 (7%)	5 (7%)
Cardiac Disorders	2 (7%)	1 (2%)	3 (4%)
Ear and Labyrinth Disorders	1 (3%)	2 (5%)	3 (4%)
Hepatobiliary Disorders	0	2 (5%)	2 (3%)
Vascular Disorders	0	2 (5%)	2 (3%)
Endocrine Disorders	1 (3%)	0	1 (1%)
Uncoded	1 (3%)	0	1 (1%)

Source: Applicant's Table 2.1; April 28, 2022 Information Request Response

8.2.9. Additional Safety Explorations

The Applicant also submitted analyses of adverse events of special interest (AESIs) that included deaths, infections including opportunistic infections, hypersensitivity spectrum reactions including anaphylaxis, depression/suicide/self-injury, malignancy and hepatotoxicity. The results of the analysis for death are discussed in Sections 8.2.8 of this safety review. The remaining analyses of AEIs are discussed in the following section.

a. Infections:

Because of its mechanism of action, belimumab would also be anticipated to increase the risk of infections, including serious infections which were prespecified as AESIs.

Table 11. Infections of Special Interest During the Open-Label Portion of BEL114055/C1109 (Part B) (ITT Population)

Infections of Special Interest	Placebo Switched to Belimumab IV (N=31)	Belimumab IV Continuing Belimumab IV (N=44)	Total (N=75)
All infections of Special Interest[a]	**4 (13%)**	**4 (9%)**	**8 (11%)**
Serious	0	0	

All Opportunistic infections per GSK Adjudication[b]	**0**	**2 (5%)**	**2 (3%)**
Serious	0	0	0
Opportunistic Infections per GSK Adjudication Excluding Tuberculosis and Herpes Zoster	0	1 (2%)	1 (1%)
Active Tuberculosis[a]	**0**	**0**	**0**
Serious	0	0	0
Non-Opportunistic	0	0	0
Opportunistic	0	0	0
All Herpes Zoster[a,c]	**3 (10%)**	**3 (7%)**	**6 (8%)**
Serious	0	0	0
Non-Opportunistic	3 (10%)	2 (5%)	5 (7%)
Opportunistic per GSK Adjudication	0	1 (2%)	1 (1%)
Recurrent	0	1 (2%)	1 (1%)
Disseminated	0	0	0
Sepsis[a]	**0**	**0**	**0**

Source: Applicant's Table 2.1; April 28, 2022 Information Request Response
[a] Per Custom MedDRA query CMQ, (v. 24.1)
[b] In situations where the CMQ identifies multiple preferred terms for a given case, medical review determines one preferred term for this summary. All preferred terms are presented in the subject listing.
[c] Not all Herpes Zoster will be recurrent or disseminated.

b. Hypersensitivity Spectrum Reactions Including Anaphylaxis

Serious infusion reactions and hypersensitivity reactions including anaphylaxis were also designated as adverse events of special interest in study C1121 since the USPI for belimumab contains a Warning and Precautions statement regarding these types of events. Due to the overlap in symptoms with infusion reactions, hypersensitivity reactions, and anaphylaxis, it is difficult to ensure that these adverse events were adequately captures and classified during the study. Because of this, the Applicant employed various search terms including a customized MedDRA query (CMQ) involving broad, narrow and algorithmic searches for "anaphylactic reactions" using preferred terms as well as the Sampson Criteria preferred by the review division.[41] Cases thus identified were also adjudicated by the Applicant. The results of these various analyses are presented in Table 12 below.

Table 12. Post-Infusion Anaphylaxis/Hypersensitivity Adverse Events During the Open-Label Portion of BEL114055/C1109 (Part B) (ITT Population)

	Placebo Switched to Belimumab IV (N=31)	Belimumab IV Continuing Belimumab IV (N=44)	Total (N=75)
Any Post-Infusion Systemic Reaction	**1 (3%)**	**6 (14%)**	**7 (9%)**
Per anaphylactic reaction CMQ narrow search[a]	0	0	0

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

Per anaphylactic reaction CMQ broad search[a]	1 (3%)	6 (13%)	7 (9%)
Per anaphylact. reaction CMQ algorithmic search[a]	0	0	0
Serious Anaphylaxis per Sampson Criteria	**0**	**0**	**0**
Serious Acute Post-Infusion Systemic Reactions/ Hypersensitivity per GSK Adjudication[c]	**0**	**0**	**0**
Serious Acute Post-Injection Syst. React. Excluding Hypersensitivity per GSK Adjudication[c]	0	0	0
Serious Acute Hypersensit. React. per GSK Adjud.[c]	0	0	0
Serious Delayed Acute Hypersensit. React. per GSK Adjudication[c]	**0**	**0**	**0**
Serious Delayed Non-Acute Hypersensit. React. per GSK Adjudication[c]	**0**	**0**	**0**

Source: Applicant's Table 3.1; April 28, 2022 Information Request Response
[a] Per Custom MedDRA query CMQ, (v. 24.1)

A higher frequency of post-infusion systemic reactions for the group of pediatric patients who continued receiving belimumab IV compared to placebo patients who were switched to belimumab IV in Part B is seen in Table 12. This rate of 14% is also higher than the rate of anaphylaxis observed in Part A (8%) of study BEL114055/C1109 and may be the result of sensitization due to long- term exposure to belimumab (refer to clinical review of sBLA 125370/s-064 belimumab IV for children 5 to 17 years of age with SLE dated April 26, 2019). Not unexpectedly, there were no reports of post-infusion hypersensitivity reactions during Part C of the study since patients were no longer receiving treatment with belimumab.

c. Depression, Suicide and Self Injury

Since a safety signal for depression and suicidality was noted during the review of the safety database in adults with generalized SLE in support of the IV formulation of belimumab which resulted in a Warning and Precaution statement in the product's USPI, and was confirmed in the long-term belimumab safety study in adults, depression and suicidality were also prespecified as AESI for belimumab IV in the pediatric population. Although the protocol for study BEL114055/C1109 prohibited enrollment of potential subjects with evidence of serious suicide risk and/or any suicidal ideation on the Columbia Suicide Severity Rating Scale (C-SSRS) and required suicidality assessments at each study visit in subjects $\geq$ 12 years old, there were pediatric subjects who experienced depression in both treatment groups during Part A of the study as well as suicide /self-injury in the placebo group during Part A. During Part B, the higher rates of depression and self-injury observed in the placebo group A during Part A carried over to Part B of the study.

Table 13. Depression, Suicide, and Self-Injury Adverse Events of Special Interest by Category During the Open-Label Portion of BEL114055/C1109 (Part B) (ITT Population)

	Placebo Switched to Belimumab IV	Belimumab IV Continuing Belimumab IV	Total (N=75)

	(N=31)	(N=44)	
Depression/Suicide/Self-injury[a]	**7 (23%)**	**1 (2%)**	**8 (11%)**
Depression	5 (16%)	1 (2%)	6 (8%)
Serious	0	0	0
Suicide/Self-injury[b]	2 (7%)	0	2 (3%)
Serious	0	0	0
Serious suicide/Self-injury per GSK Adjudication	**0**	**0**	**0**
Suicidal behavior per GSK Adjudication	0	0	0
Completed suicide per GSK Adjudication	0	0	0
Suicidal ideation per GSK Adjudication	0	0	0
Self-injurious Behavior w/o Suicidal Intent per GSK Adjud.	0	0	0

Source: Applicant's Table 3.1; April 28, 2022 Information Request Response
[a,b] Per Custom MedDRA query CMQ, (v. 24.1)

d. Malignancy

Because belimumab targets B cells, immunosuppression is an expected effect, and chronic immunosuppression has been associated with an increase in the risk for developing a malignancy. According to the Applicant there were no malignancies reported during the time period from November 20, 2018 through November 10, 2021 in pediatric subjects participating in the ongoing Parts B and C of study BEL 114055/C1109.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

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

Review of the index listings and tabulations of postmarketing adverse events by SOC contained in the most recent belimumab Periodic Benefit Risk Evaluation Report (PBRER) dated May 2022, which covered the reporting period from March 9, 2021 to March 8, 2022 did not identify any new or unexpected SAEs that needed to be included in belimumab's current label. According to information contained in this application, the cumulative post marketing exposure to belimumab estimated by the Applicant is 146,388 patient-years based on data through March 31, 2021, out of which 111,986 patient-years were attributed to use of the IV formulation and 34,402 patient-years were attributed to use of the subcutaneous formulation.

In support of this application, the Applicant submitted an updated review of 278 initial (266 cases) or follow-up (12 cases) spontaneous postmarketing safety reports in pediatric patients

between the ages 5 to 17 years identified via query of their Argus postmarketing safety database during the time period from April 26, 2019 to April 8, 2022. These 278 spontaneous postmarketing cases resulted in a total of 572 adverse events. The most frequently reported adverse events (at least 20 occurrences) by MedDRA SOCs were: Injury, Poisoning and Procedural complications (241 AEs); General Disorders and Administration Site Conditions (55 AEs); Infections and Infestations (34 AEs); Gastrointestinal Disorders (34 AEs); Skin and Subcutaneous Tissue Disorders (40 AEs); Psychiatric Disorders (26 AEs); Musculoskeletal and Connective Tissue Disorders (21 AEs); and Pregnancy, Puerperium and Perinatal Conditions (20 AEs). The most frequently reported AE under Injury, Poisoning and Procedural Complications was off-label use (131 cases/131 events), out of which 36 cases reported that belimumab was used to treat lupus nephritis and approximately eight of these cases involved the use of the subcutaneous formulation of belimumab which is not approved for use in the pediatric population. Cases of AESIs included: three deaths (one case of death unknown, one case of perinatal death S/P in utero exposure to belimumab, and one case of death due to septic shock, five cases of herpes zoster (reportedly non-disseminated), two cases of suicidality/intentional self-injury in adolescences, and once case of malignancy (8 year-old with SLE who developed chest and back pain and was found to have a mediastinal tumor consistent with Hodgkin's lymphoma on MRI). Review of the other AEs by MedDRA preferred term failed to reveal any new patterns or safety signals in the pediatric subpopulation.

This application also contained a summary review of 758 spontaneous postmarketing safety reports in adults (≥ 19 years old) identified on query of the Applicant's Argus postmarketing safety database that were collected during the time period from the date of approval of the lupus nephritis indication in adults on December 16, 2020 to April 1, 2022. These 758 spontaneous postmarketing reports resulted in a total of 2564 AEs. The most frequently reported adverse events by MedDRA SOCs were Injury, Poisoning and Procedural Complications (707 AEs); General Disorders and Administration Site Conditions (436 AEs), and Infections and Infestations (302 AEs). Of note, there were a total of 112 AEs reported under the Renal and Urinary Disorders SOC during this time period. According to the Applicant, the high number of AEs reported under the Injury, Poisoning and Procedural Complications were due to the AE coded under the preferred terms (PT) "off label use" and "product used in unapproved indication" for a combined total of 408 AEs. Under the General Disorders and Administration Site Conditions SOC, the PTs with the highest number of AE cases were "drug ineffective" (60 AEs), "malaise" (46 AEs), "pain" (39 AEs), and "pyrexia" (34 AEs). The PTs with the highest combined number of reports Under the Infections and Infestations SOC were "urinary tract infection/E.coli urinary tract infection/bacterial urinary tract infection" for a total of 75 AEs, followed by "influenza" with 33 AEs, "COVID-19/Coronavirus infection/Suspected COVID-19 infection" with 27 AEs. Review of the AEs by PT under the Renal and Urinary Disorders SOC showed that "lupus nephritis/nephritis/glomerulonephritis/tubulointerstitial nephritis" accounted for 27 AEs, followed by "renal failure/renal impairment/renal disorder/chronic kidney disease/nephropathy/end-stage renal disease" with 20 AEs and proteinuria with 18 AEs. These AEs under the Renal and Urinary Disorders are not unexpected since the majority of

lupus nephritis patients randomized to treatment with belimumab in study BEL114054/C1121 failed to respond to treatment with the product. The Applicant also reported that 151 out of these 758 case reports were classified as serious in nature (1382 SAEs). The Infections and Infestations SOC accounted for the highest number of SAEs with 212 events which is not unexpected in view of belimumab's mechanism of action. Of the 8 case reports of fatalities, 3 did not contain adequate information to determine causality while the remaining 5 deaths were due to urosepsis, SARS-COVID-19 infection, cardiac failure, suicide via insulin overdose, and macrophage activation syndrome. Review of these spontaneous postmarketing safety data failed to reveal any new patterns or safety signals in the adult SLE/lupus nephritis population associated with the administration of belimumab.

The Applicant also performed a review of the worldwide published literature for reports of belimumab used in the treatment of children or in adults with lupus nephritis. As of their query's end date of October 31, 2021 they noted few publications in either subpopulation, many of which described data from the belimumab IV pediatric SLE study BEL14055/C1109 and the adult lupus nephritis study BEL114054/C1121.

In support of this safety review, post-marketing safety consultants in the Division of Pharmacovigilence-1 (DPV-1) located in the agency's Office Of Pharmacovigilance and Epidemiology (OSE) conducted a review of spontaneous post-marketing adverse event reports in pediatric patients less than 18 years of age associated with the administration of belimumab collected by the FDA's Adverse Event Reporting System (FAERs) during the time period from March 9, 2011 through March 22, 2022, as well as a review of the published literature for additional case reports for adverse events associated with belimumab in the pediatric population during the same time period. Based on their review, these internal consultants did not identify any new pediatric safety signals for belimumab and recommended no regulatory safety action at this time.

Expectations on Safety in the Postmarket Setting

The Applicant's postmarketing pediatric safety update and lupus nephritis update in adults suggest that the safety profile of belimumab IV in the pediatric population and in the adult subpopulation with lupus nephritis appears to be consistent with that reviewed in support of its initial marketing approval in adults and children and no strengthening of the current Warnings and Precautions statements in the product's USPI is indicated. This is supported by the lack of new post-marketing pediatric safety findings associated with the administration of belimumab identified by internal post-marketing safety consultants in OSE's DPV-1.

Currently pending is an FDA recommended post-marketing commitment for the use of belimumab during pregnancy (b) (4) Since belimumab's current USPI also contains a limitation of use for the product concomitantly with other biologics, the Applicant has completed a phase 3, randomized, double-blind, placebo

controlled study evaluating the efficacy and safety of belimumab subcutaneous formulation when administered in combination with rituximab to adult subjects with SLE (b) (4)
(b) (4)

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

8.2.11. Integrated Assessment of Safety

No new or unexpected safety signals were identified on review of the cumulative interim safety data from the ongoing open-label extension of the pediatric SLE study BEL14055/C1109 or the updated spontaneous postmarketing safety data in children and adults with SLE/lupus nephritis. Therefore, no updates of the existing Warnings and Precautions in the current belimumab USPI are unwarranted.

Since this pediatric belimumab IV safety database does not include safety data from a controlled trial conducted in children with lupus nephritis, some of the limitations associated with the safety database from the adult lupus nephritis study BEL114054/C1121 apply here such as the lack of concomitant biologics including those that target B cells (e.g., rituximab) or calcineurin inhibitors use to treat lupus nephritis or the inability to perform subpopulation analyses based on race or gender.

Based on the totality of safety data generated from the adult lupus nephritis study BEL114054/C1121 and the adult and pediatric SLE studies BEL110751/C1056, BEL110772/C1057 and BEL14055/C1109, respectively, as well as the cumulative interim safety data from study BEL14055/C1109's ongoing open-label extension coupled with the updated postmarketing safety review in both children and adults with SLE/lupus nephritis, the benefit/risk assessment is favorable for extrapolation of the approved 10 mg/kg belimumab dosing regimen when administered as an intravenous infusion every 2 weeks for the first 3 doses and at 4-week intervals thereafter as add-on therapy for pediatric patients with active lupus nephritis who are receiving standard of care induction and maintenance therapy. No additional post-marketing safety studies are warranted based on this submission.

8.3. Statistical Issues

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

8.4. Conclusions and Recommendations

The Applicant proposed a full extrapolation of efficacy approach along with supportive safety data in pediatric SLE and adult SLE and LN, to support this efficacy supplement to broaden belimumab's IV lupus nephritis indication to include children ages 5 to 17 years old with active lupus nephritis on standard of care. In view of the available data with belimumab in adults with SLE and LN, as well as pediatric patients with cSLE, and considering the rarity of pediatric LN, the Applicant has undertaken a PK-bridging approach with full extrapolation of efficacy and leveraging of safety from existing belimumab IV studies in support of this application. The clinical responses to belimumab treatment (at comparable exposures) are similar between adult and pediatric patients with general SLE, as discussed in the review of BLA125370/s-064. Further, the clinical manifestations and management of LN are largely overlapping between pediatric LN and adult LN and evidence suggests that children with pediatric LN should respond to treatment similarly to adults with LN. Thus, the efficacy in pediatric patients with LN can be extrapolated from adults with LN where efficacy has been established from an adequate and well-designed clinical trial (refer to the review of sBLA 125370/s-073). The efficacy of belimumab in pediatric patients was extrapolated based on a population pharmacokinetic model (study 217143) developed from 224 adults with active lupus nephritis and validated using data from 53 pediatric patients with SLE. With IV administration of 10 mg/kg on Days 0, 14 and 28 and at 4-week intervals thereafter, the simulated belimumab exposures, which included weight-based dose adjustments and the impact of proteinuria on serum concentrations of the product, for both the 5- to 11-year-old group and the 12- to 17-year-old group were estimated to be comparable to adults with active lupus nephritis. The results from this population PK study were deemed adequate by the clinical pharmacology review team to support PK-bridging of both efficacy and safety data from previously reviewed belimumab IV studies in adults with lupus nephritis (BEL114054/C1121), and children and adults with general SLE (studies BEL114055/C1109, BEL110751/C1056 and BEL110772/C1057, respectively) since the etiology, pathophysiology, manifestations, the overall disease course and management of SLE and lupus nephritis are similar in the adult and pediatric populations.

Based on the efficacy and safety data from the adequate and well-controlled studies BEL114054/C1121 conducted in adults with lupus nephritis, BEL114055/C1109 conducted in children with cSLE, and BEL110751/C1056 and BEL110772/C1057 conducted in adults with SLE with belimumab IV reviewed previously under BLA 125370 when coupled with the reviewed postmarketing safety data collected since the approval of the adult LN and the pediatric cSLE indications and the unmet medical need for safe and efficacious treatments for pediatric patients with LN, the benefit/risk assessment favors approval of the 10 mg/kg dosing regimen of belimumab when administered as an intravenous infusion every 2 weeks for the first 3 doses and at 4-week intervals thereafter as add-on therapy for pediatric patients with active lupus nephritis who are receiving standard of care induction and maintenance therapy. Additionally, the pediatric clinical pharmacology, efficacy and safety data submitted to sBLA 125370/s-078 are adequate to fulfill the PREA postmarketing requirement (3994-01) related to the December 16, 2020 approval for BLA 125370 Benlysta® (belimumab) intravenous (IV) formulation.

9 Advisory Committee Meeting and Other External Consultations

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

10 Pediatrics

The Agreed Pediatric Study Plan (iPSP) for IV belimumab was previously issued on February 06, 2020 and submitted to BLA 125370/s-073 on November 20, 2020 that included an agreement for a partial waiver of pediatric studies in pediatric lupus nephritis patients ≤ 5 years of age and a deferral in pediatric lupus nephritis patients >5 to less than 18 years of age. The results and review findings for this pediatric PMR supplement were presented and discussed at the June 7, 2022 meeting of PeRC who concurred with the review team's recommendation to expand the intravenous formulation of belimumab's current indication to include pediatric patients 5 years and older with active lupus nephritis who are receiving standard therapy based on the data reviewed in this application.

APPEARS THIS WAY ON ORIGINAL

11 Labeling Recommendations

11.1. Prescription Drug Labeling

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 as per the *2018 Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* guidance document:

1) Under Section 1 Indications and Usage
    a. Revised the SLE indication to be more concise in the description of the population studied with deletion of "antibody positive" since the latter is contained in the description of the studies in Section 14. (Note: This change is in line with the new 2019 EULAR/ACR SLE classification criteria which requires all patients with SLE to have a positive ANA, and doesn't impact the originally approved patient population/condition of use.)
    b. Expand the approved active lupus nephritis indication in adults to include children aged 5 years and older with active lupus nephritis who are receiving standard therapy
    c. Deleted text regarding the use with other biologics
2) A new Section 2 Intravenous Preparation and Dosing Instructions
    a. Added a new subsection 2.1 Recommended Intravenous Dosage for Adult and Pediatric Patients with SLE or Lupus Nephritis
    b. Added information to include pediatric patients with lupus nephritis
    c. Added a new sub header "Dosage"
    d. Under sub-header "Precautions Prior to Intravenous Use" moved the following "BENLYSTA should be administered by healthcare providers prepared to manage anaphylaxis [see Warnings and Precautions]" from where it was located under sub-header "Administration Instructions for Intravenous Use"
    e. Added new subsection 2.3 " Recommended Subcutaneous Dosage for Adult Patients with SLE or Lupus Nephritis"
    f. Modified the sub-header "Adult Patients with Lupus Nephritis" by deleting the rest of the sub-header for clarity
3) Under Section 5 Warnings and Precaution
    a. Deleted first sentence of the second paragraph as follows: "The population had a mean age of 39 years (range: 18 to 75), 94% were female, and 52% were White"
    b. Relocation of clinical safety data under sub-header 5.1 Serious Infections to under sub-header 6.1 Clinical Trials Experience with Intravenous Administration, subsection Serious Infections
    c. Relocation of clinical safety data under sub-header 5.2 Hypersensitivity

Reactions, including Anaphylaxis to under sub-header 6.1 Clinical Trials Experience with Intravenous Administration, Hypersensitivity Reactions, including Anaphylaxis

d. Relocation of clinical safety data under sub-header 5.3 Infusion Reactions to sub-header 6.1 Clinical Trials Experience with Intravenous Administration, subsection Infusion-related reactions and incorporating the remaining text under sub-header 5.2 Hypersensitivity Reactions, including Anaphylaxis
e. Relocation of clinical safety data under sub-header 5.4 Depression and Suicidality to under sub-header 6.1 Clinical Trials Experience with Intravenous Administration, subsection Depression and Suicidality
f. Relocation of clinical safety data under sub-header 5.5 Malignancy to under sub header 6.1 Clinical Trials Experience with Intravenous Administration, new subsection Malignancy
g. Adding introductory sentence about the increased risk of malignancies with the use of immunosuppressives to the beginning of the paragraph along with healthcare professionals should consider the benefit-risk for each individual patient in patients with known risk factors for the development or reoccurrence of malignancy prior to prescribing BENLYSTA and in continuing treatment in patients who develop malignancies under subheader 5.5 Malignancy
h. Relocation of last sentence under new sub-header 5.5 Immunization to the beginning of the same paragraph
i. Amended new sub header 5.6 to read “Not Recommended for Concomitant Use with Other Biologic Therapies” and amended the information under it as follows: BENLYSTA has not been studied in combination with other biologic therapies, including B-cell targeted therapies. Therefore, use of BENLYSTA is not recommended in combination with biologic therapies.”

4) Under Section 6 Adverse Events
   a. Relocated “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice” to under new sub header 6.1 Clinical Trials Experience
   b. Renamed subleaders as follows: Clinical Trials with Intravenous Administration in Adult and Pediatric Patients; Adult Patients with SLE
   c. Relocated the following sentences in the first and second paragraphs under subsection Infections to subsection Serious infections: “Serious infections occurred in 6.0% of patients receiving BENLYSTA and in 5.2% of patients receiving placebo. The most frequent serious infections included pneumonia, urinary tract infection, cellulitis, and bronchitis. Fatal infections occurred in 0.3% (4/1,458) of patients receiving BENLYSTA and in 0.1% (1/675) of patients receiving placebo” and “Serious infections occurred in 14% of patients receiving BENLYSTA and in 17% of patients receiving placebo. Fatal infections occurred in

0.9% (2/224) of patients receiving BENLYSTA and in 0.9% (2/224) of patients receiving placebo."

d. Relocation of safety data under subsections/sub-headers Section 5 Warnings and Precautions to corresponding subsections/subleaders under Section 6 Adverse Events (see above)
e. Changed "Preferred Term" to "Adverse Reactions" in Table 1

5) Under Section 8.4 Pediatric Use
   a. Added "Safety and effectiveness of BENLYSTA have been established for the treatment of SLE and lupus nephritis in pediatric patients 5 to 17 years old" and deleted "Intravenous administration of BENLYSTA in patients with SLE or lupus nephritis is indicated in pediatric patients aged 5 years and older."
   b. Deleted "the adverse event profile in pediatric patients with SLE was consistent with the overall population in the Phase 3 studies in adults with SLE."
   c. Added "Use of BENLYSTA in pediatric patients with active lupus nephritis is based on the extrapolation of efficacy from the intravenous study in adults (n = 224) with active lupus nephritis, and supported by pharmacokinetic data from intravenous studies in adults (n = 224) with active lupus nephritis and from pediatric patients (n = 53) with SLE. Estimated belimumab exposures for pediatric patients were comparable to adults with active lupus nephritis"
6) Under Section 10 Overdosage
   a. Deleted "Adverse reactions reported in association with cases of overdose have been consistent with those expected for belimumab."
7) Under Section 12.3 Pharmacokinetics
   a. Adding the description of the pediatric PK for lupus nephritis based on PK estimation from population pharmacokinetics model.
8) Under Section 17 Patient Counseling Information
   a. Deleted "Ask patients if they have a history of chronic infections and if they are currently on any therapy for an infection."
9) The Medication Guide was updated to include the expanded indication of children aged 5 years and older with lupus nephritis

<u>All labeling has been reviewed by the labeling consultants and agreed upon with the Applicant.</u>

12 Risk Evaluation and Mitigation Strategies (REMS)

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

13 Postmarketing Requirements and Commitment

This submission fulfills the PREA PMR 3994-1 related to the December 16, 2020 approval for BLA 125370 belimumab (Benlysta) described as follows:

> "Provide an assessment of intravenous belimumab for the treatment of patients ages 5 to less than 18 years of age with lupus nephritis who are receiving standard therapy."

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

APPEARS THIS WAY ON ORIGINAL

14 Division Director (Clinical)/Signatory Comments

I concur with the team's review, assessment, and recommendations of this submission.

The action to expand the indication for belimumab IV administration to include the treatment of children 5 to 17 years of age with active lupus nephritis who are receiving standard therapy is Approval. This action is supported by the data from a PK-bridging approach supporting full extrapolation of efficacy established in adults with active LN and leveraging safety from existing studies of belimumab IV reviewed previously, and in view of the unmet medical need for safe and efficacious treatments for pediatric patients with LN. The Applicant has provided adequate data and information to support the favorable benefit-risk assessment of belimumab IV for the treatment of pediatric patients with active LN who are receiving standard therapy, to support the expansion of the indication of belimumab IV as add-on treatment for active LN in pediatric patients 5 to 17 years old.

This submission also fulfills the PREA PMR 3994-1 related to the December 16, 2020 approval for BLA 125370/s-073.

No Risk Evaluation and Mitigation Strategies, postmarketing requirements or commitments for belimumab IV are warranted based on this submission.

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.
2. Almaani S, Meara A, and Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017; 12: 825-835.
3. 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.
4. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus 2006; 15:308.
5. Demir S, Gulhan B, Ozen S, et al. Long-term renal survival of pediatric patients with lupus nephritis. Nephrol Dial Transplant 2022. 37:1069-1077.
6. Farnouriakis A, Kostopoulou M, Cheema K, Anders HJ, Aringer M, Bajema I, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association- European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis 2020; 79: 713-723.
7. Groot N, de Graeff N, Marks SD, et al. European evidence-based recommendations for the diagnosis and treatment of childhood-onset lupus nephritis: the SHARE initiative. Ann Rheum Dis 2017;76:1965-1973.
8. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Car Res. 2012; 64: 797-808.
9. Hiraki LT, Feldman CH, Liu J, et al. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. Arth and Rheum 2012; 64:2669-76.
10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40:1725.
11. Izmirly PM, Parton H, Wang L, et al. Prevalence of systemic lupus erythematosus in the United States: estimates from a meta-analysis of the Centers for Disease Control and Prevention National Lupus Registries. Arthritis Rheum 2021: 73:991.
12. Johnson SR, Urowitz MB, Ibanez D, Gladman DD. Ethnic variation in disease patterns and health outcomes in systemic lupus erythematosus. J Rheumatol. 2006; 33(10): 1990-5.
13. Livingston B, Bonner A, Pope J. Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: a meta-analysis. Lupus 2011; 20:1345-55.
14. Mina R, von Scheven E, Ardoin SP, et al. Consensus treatment plans for induction therapy of newly diagnosed proliferative lupus nephritis in juvenile systemic lupus erythematosus. Arthritis Care Res 2012;64:375-83.

15. Nightingale AL, Farmer RDT, de Vries CS. Systemic lupus erythematosus prevalence in the UK: methodological issues when using the General Practice Research Database to estimate frequency of chronic relapsing-remitting disease. Pharmacoepidemiol Drug Saf. 2007; 16:144-51.
16. Oni L, Wright RD, Marks S, Beresford MW, and Tullus K. Kidney outcomes for children with lupus nephritis. Pediatric Nephrology 2021; 36:1377-1385.
17. 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.
18. Pons-Estel GJ, Alarcon GS, Scofield L, et al. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arth and Rheum 2010 Feb.; 39:257-268.
19. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol. 117(2):391-397.
20. Tektonidou MG, Lewandowski LN, Hu J, et al. Survival in adults and children with systemic lupus erythematosus: a systematic review and Bayesian meta-analysis of studies from 1950 to 2016. Ann Rheum Dis 2017; 76:2009-2016.
21. Uribe AG, Alarcon GS. Ethnic disparities in patients with systemic lupus erythematosus. Curr Rheumatol. Rep. 2003; 5(5): 364-9.
22. Valenzuela-Almada MO, Hocaoglu M, Dabit JY, Oei-Onomah SA, Basiaga ML, et al. Epidemiology of childhood-onset systemic lupus erythematosus: a population-based study. Arthritis Care and Research 2022; (74)5:728-732.
23. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematous revisited. Kidney Internat 2002; 65: 521-530.

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. Pharmacometrics review

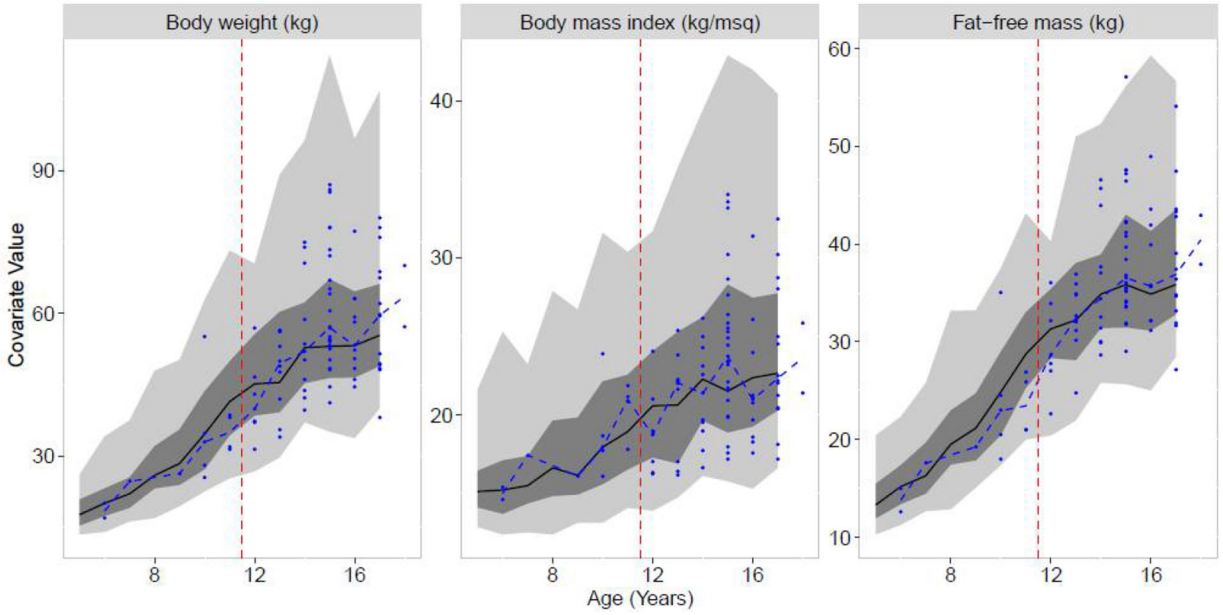
In silico patient population (5 to 17 years old with active LN)

The Applicant conducted a PK simulation for children 5 to 17 years old with active LN. The simulated baseline demographics and disease characteristics are described below:
Body weight and BMI were sampled from the healthy volunteer CDC National Health and Nutrition Examination Survey (NHANES) database, restricted between 5 and 17 years of age and biased 90% towards females as typical seen in SLE and LN. Sampled body weights and BMI values were corrected to represent a paediatric SLE population, and a reduction to 86% (body weight) and to 94% (BMI) of the sampled values was found to minimize the difference in the median values summed over all ages with respect to children with SLE (Figure 8).

Fat-free mass (FFM)was then imputed from the corrected body weight and BMI and closely aligned with the FFM estimated in children with SLE from study BEL114055 across the paediatric age range. FFM in children with LN was then imputed from body weight, BMI, and sex. [Janmahasatian, 2005]

$$FFM\ (males) = 9270 \times WT/(6680 + 216 \times BMI)$$
$$FFM\ (females) = 9270 \times WT/(8780 + 244 \times BMI)$$

Figure 8 Body Size Metrics versus Age: Sampled NHANES Population versus Children with SLE



Source: Figure 4 in PopPK children LN simulation report [GSK Document Number 2021N491623_00]
Sample covariates from the NHANES database are shown as 95% prediction interval (light grey region), inter-quartile range (dark grey region) and median (solid black line). The observed values from the Paediatric SLE 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.

The proteinuria and albumin time course profiles were sampled from the belimumab treated arm in the adult LN dataset (study BEL114054) by individual. Based on the Applicant's literature review, proteinuria and albumin changes in response to the standard of care in adult and children with active LN are similar (Table 14 and Table 15). Therefore, the sampling of proteinuria and albumin profiles from the observed adult subjects with active LN is reasonable.

Table 14 Summary of Proteinuria Levels over Time in Adults and Children with LN Receiving Standard Therapy (not Belimumab Treated)

Timepoint	Measure[i]	Adults with LN Belimumab Study BEL114054 (Placebo Arm)[a]	Adults with LN Published Literature[b]	Children with LN Published Literature[b]
Baseline	Mean / median range of uPCR (mg/mg)	3.53 (mean) / 2.47 (median) (Screening: 4.32 / 3.13)	2.41 – 4.27[c]	1.08 – 6.97[f]
	Nephrotic range (%)	41% (Screening: 52%)	39.4% – 49.3%[d]	18% – 66.7%[g]
6 months post-baseline	Mean / median range of uPCR (mg/mg)	1.40 (mean) / 0.73 (median)	NR	0.1 – 1.41[h]
12 months post-baseline	Mean / median range of uPCR (mg/mg)	0.95 (mean) / 0.44 (median)	0.5 – 0.88[e]	0.1 – 1.33[h]

Source: Table 5 in PopPK children LN simulation report [GSK Document Number 2021N491623_00]
a. Baseline data shown are from the overall group (belimumab + placebo) and post-baseline data are from the placebo group.
b. Baseline data shown are from the overall group (treatment + the control/standard of care.) and post-baseline data are from the control/standard of care group.
c. ACCESS Trial Group, 2014; Domingues, 2018, Furie, 2014; Mackay, 2019; Rovin, 2021; Sundel, 2012
d. ACCESS Trial Group, 2014; Furie, 2014; Sundel, 2012
e. Domingues, 2018, Mackay, 2019
f. Aragon, 2010; Hugle, 2015, Lau; 2006; Lau, 2008; Ruggiero, 2013; Sundel, 2012; Wei, 2021; Wu, 2018
g. Hari, 2009; Pereira, 2011; Ruggiero, 2013; Smith, 2018
h. Aragon, 2010; Lau; 2006; Lau, 2008; Wei, 2021
i. Proteinuria measured by the urine protein creatinine ratio (uPCR)
NR, no results available

Table 15 Summary of Serum Albumin Levels (g/dL) over Time in Adults and Children with LN Receiving Standard Therapy (not Belimumab Treated)

Timepoint	Adults with LN Belimumab Study BEL114054[a]	Adults with LN Published Literature[b]	Children with LN Published Literature[b]
Baseline	3.0-3.1 (mean) / 3.1-3.2 (median) (Screening 2.9 / 2.9)	2.6 – 3.35[c]	2.5 – 3.6[e]
6 months post-baseline	3.7 (mean) / 3.8 (median)	NR	3.2 – 3.6[f]
12 months post-baseline	3.9 (mean) / 4.0 (median)	3.99[d]	3.5 –3.7[f]

Source: Table 6 in PopPK children LN simulation report [GSK Document Number 2021N491623_00]
a. Baseline data shown are from the overall group (belimumab + placebo) and post-baseline data are from the placebo group.

b. Mean/median range presented; Baseline data shown are from the overall group (treatment + the control/standard of care.) and post-baseline data are from the control/standard of care.
c. ACCESS Trial Group, 2014; Domingues, 2018; Houssiau, 2002; Rovin, 2012
d. Domingues, 2018
e. Hugle, 2015; Lau; 2006; Lau, 2008; Talat, 2021; Wu, 2018
f. Lau; 2006
NR, no results available

Population Pharmacokinetic Simulation

The Applicant's simulation in children 5 to 17 years old was based on the PopPK model developed previously in adult subjects with active LN. See pharmacometrics review by Dr. Tao Liu for BLA 125370 Supplement 73 in DARRTS on 12/16/2020. The PK of belimumab was described by a two compartment PK model with linear elimination. The final PK parameter estimates are given in Table 16 below.

Table 16 Fixed and Random Effect Parameters of the Adult LN PK Models with Estimated Allometric Exponents

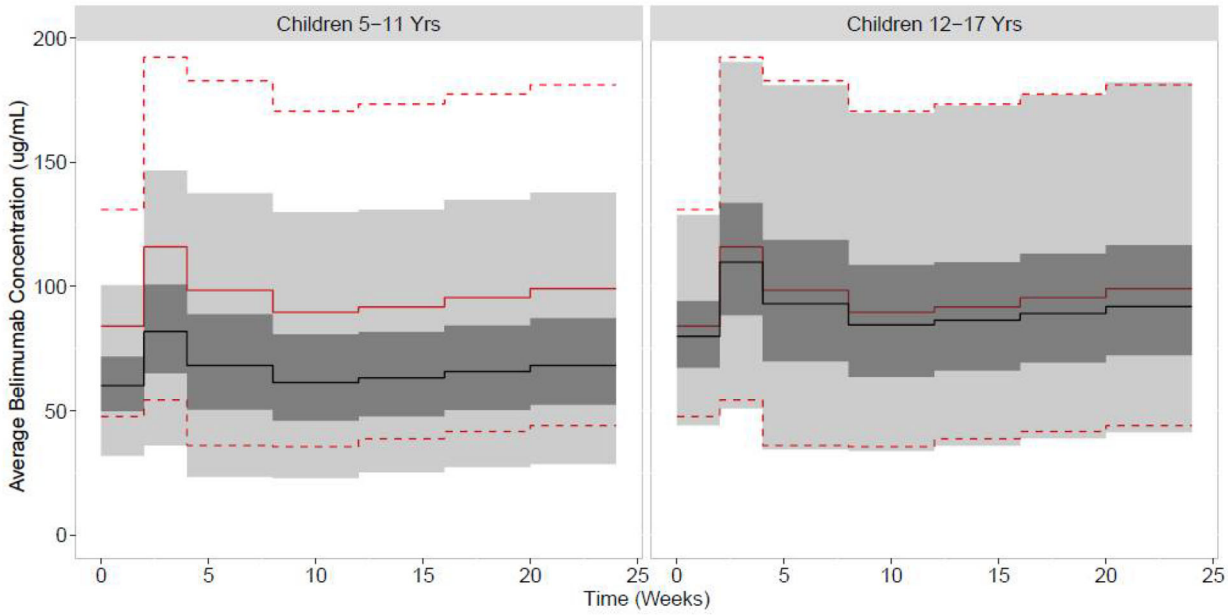
Fixed Effect Parameters		**Model Point Estimate (%RSE, 95% CI)**
CL (mL/day)		175 (2.67%, 165 - 184)
x (FFMBL / 38.4)$^{\theta}$		0.624 (16.5%, 0.422 - 0.825)
x (ALB / 42)$^{\theta 1/(1+\theta 2 \times PROT)}$	θ1	-1.74 (6.13%, -1.95 to -1.53)
	θ2	0.0832 (39.5%, 0.0187 - 0.148)
x (1 + θ×PROT)		0.0663 (24.6%, 0.0344 - 0.0983)
V1 (mL)		2728 (1.82%, 2630 - 2825)
x (FFMBL / 38.4)$^{\theta}$		0.723 (13.5%, 0.531 - 0.914)
Q (mL/day)		487 (6.32%, 427 - 547)
x (FFMBL / 38.4)$^{\theta}$		See FFMBL on CL
V2 (mL)		1992 (4.99%, 1797 - 2187)
x (FFMBL / 38.4)$^{\theta}$		See FFMBL on V1
Residual variability (Normally Distributed)		**Model Point Estimate (%RSE)**
PROP		0.241 (4.47%)
ADD (μg/mL)		0.1 (Fixed)
Inter-individual variability (Log-Normally Distributed)		**Model Point Estimate (%RSE) (%CV)**
ω^2_{CL}		0.0593 (16.7%) (CV=24.7%)
ω^2_{V1}		0.0322 (33.7%) (CV=18.1%)
ω^2_{V2}		0.133 (34.3%) (CV=37.7%)
ω^2_{PROP}		0.346 (14.9%) (CV=64.3%)

Source: Table 4 in PopPK children LN simulation report [GSK Document Number 2021N491623_00]
Abbreviations: %RSE = relative standard error as percentage of estimate; 95% CI = the 95% confidence interval of the estimate; CL = clearance; V1 = volume of distribution for the central compartment; Q = inter-compartmental flow rate; V2 = volume of distribution for the peripheral

compartment; FFMBL = fat-free mass at baseline (kg); ALB = albumin level (g/L); PROT = proteinuria level (g/g). PROP = proportional residual parameter; ADD = additive
residual parameter; ω^2_{CL} = between-subject log-scale variance on CL; ω^2_{V1} = between-subject log-scale variance on V1; ω^2_{V2} = between-subject log-scale variance on V2; ω^2_{PROP} = between-subject log-scale variance on PROP and CV% = the coefficient of variation calculated as √(exp(ω^2) – 1).

Belimumab concentration-time profiles (N=10,000) were simulated for adults and children with LN for 10 mg/kg IV administered on days 0, 14, 28 then every 4 weeks. Based on the Applicant's PopPK simulation, the primary PK parameters of interest are listed in Table 5, and the simulated concentration time profiles are depicted in Figure 6 in section 6 above. Additional tables and figures summarize the simulation results are given below.

Figure 9 Simulated Average Concentration over Each Dosing Period in Adults and Children with LN Receiving 10 mg/kg IV



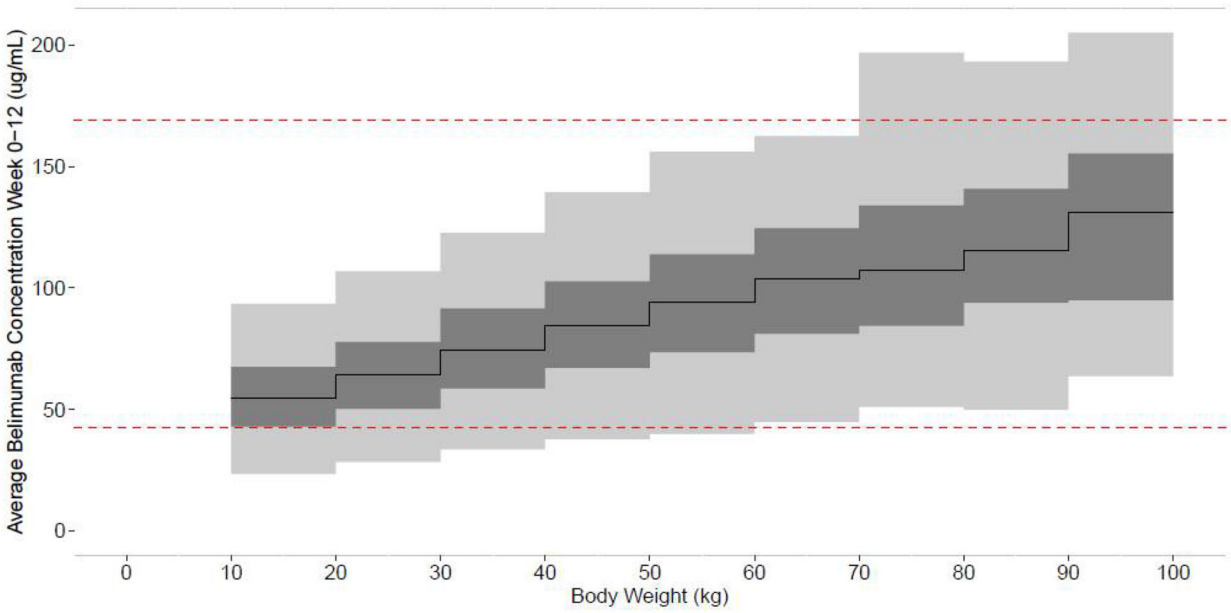
Source: Figure 8 in PopPK children LN simulation report [GSK Document Number 2021N491623_00]
Simulated dosing regimen: 10 mg/kg IV on days 0, 14 and 28 then every 4 weeks. The pediatric median (black solid line), inter-quartile range (dark shaded region) and 95% prediction interval (light shaded region) are shown with the adult median (solid red line) and 95% prediction interval (broken red lines).

Table 17 Belimumab Exposure vs Body Weight in Children with LN Receiving 10 mg/kg IV

	Median (95% Prediction Interval) (µg/mL) [% Below Adult 2.5th Percentile]	
Body Weight	**Cavg(Wk 0-12)**	**Cavg(Wk 0-24)**
10 – 20 kg	55 (23 - 93) [24.1%]	55 (25 - 95) [27.9%]
20 – 30 kg	64 (28 - 107) [13.6%]	64 (29 - 109) [16.1%]
30 - 40 kg	75 (34 - 123) [7.1%]	73 (34 - 124) [7.5%]
40 - 50 kg	84 (38 -139) [5.0%]	83 (39 - 142) [4.6%]
50 - 60 kg	94 (40 - 156) [3.5%]	93 (41 - 157) [3.8%]
60 - 70 kg	104 (45 - 162) [1.6%]	103 (47 - 167) [1.6%]
70 - 80 kg	107 (51 - 197) [1.5%]	106 (52 - 208) [1.2%]
80 - 90 kg	116 (50 - 193) [0.5%]	116 (50 - 198) [1.1%]
90 - 100 kg	131 (64 - 205) [0.0%]	132 (60 - 214) [0.0%]

Source: Table 8 in PopPK children LN simulation report [GSK Document Number 2021N491623_00]

Figure 10 Cavg(Wk 0-12) vs Body Weight in Adults and Children with LN Receiving Belimumab 10 mg/kg IV



Source: Figure 9 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 Paediatric median (black solid line), inter-quartile range (dark shaded region) and 95% prediction interval (light shaded region) are shown with the adult 95% prediction interval (broken red lines).

Reviewer Comment:

The Applicant developed a validated PopPK model in adult patients with active LN and predicted the PK in children 5 years and older with active LN. The model prediction in children 5 years and older assumes the same proteinuria and albumin relationship between adults and children. The proteinuria and albumin relationship in pediatric patients with active LN cannot be estimated due to lack of data, but its relationship appears to be similar between pediatric and adult patients based on literature review. The final PopPK model is acceptable for predicting exposure in children 5 years and older with active LN considering the rarity of the disease. The prediction is based on assumption of same proteinuria and albumin relationship between pediatric and adult patients, and it should be interpreted with caution.

15.5. Additional Clinical Outcome Assessment Analyses

Not applicable.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JIANMENG CHEN
07/26/2022 10:58:18 AM

NIKOLAY P NIKOLOV
07/26/2022 11:02:19 AM