NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Postmarketing Required Pediatric Study
Application Number(s)	sBLA 125370/s-064 and BLA 761043/s-007
Priority or Standard	Priority
Submit Date(s)	October 26, 2018
Received Date(s)	October 26, 2018
PDUFA Goal Date	April 26, 2019
Division/Office	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)/ODE2
Review Completion Date	See Electronic Stamp Date
Established/Proper Name	Belimumab
(Proposed) Trade Name	BENLYSTA
Pharmacologic Class	Monoclonal Anti-BLyS Antibody
Code name	N/A
Applicant	Human Genome Sciences
Dosage form	10 mg/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 aged 5 years and older with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of patients aged 5 years and older with active, autoantibody-positive, systemic lupus erythematosus (SLE) 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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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

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

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

1 Executive Summary

1.1. Product Introduction

Belimumab (Benlysta) is a monoclonal antibody (mAb) that inhibits B-lymphocytes 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 subcutaneous (SC) administered injection formulation available as a ready to use pre-filled syringe and autoinjector was approved in 2017 for the same indication.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This supplement is a 351 (a) biologics license application (sBLA) submitted by Human Genome Sciences, Inc. for belimumab for IV administration in order to fulfil the Pediatric Research Equity Act (PREA) post-marketing required (PMR) study related to the March 9, 2011 approval for BLA 125370 belimumab (Benlysta®) for IV administration. With this supplement, the Applicant proposes to expand the present indication for belimumab for IV administration to include the treatment of children 5 to 17 years of age with active, seropositive SLE who are receiving standard therapy. To support the proposed indication, the Applicant provided the results from a single, adequate and well-controlled pediatric study, BEL114055/C1109, that evaluated the same dose of belimumab IV of 10 mg/kg approved in adults in 93 pediatric subjects with active, antibody-positive SLE on stable immunosuppressive medications. Determination of efficacy in pediatric patients was based on pharmacokinetic (PK) and efficacy results from study BEL114055/C1109, as well as PK exposure and extrapolation of the established efficacy of belimumab plus standard therapy from the phase 3 intravenous studies in adults, studies C1056 and C1057. The adult belimumab IV clinical program employed a novel composite endpoint, the SLE Responder Index (SRI-4), as the primary endpoint at Week 52 in both pivotal IV studies C1056 and C1057, which was also employed in the pediatric belimumab IV study BEL114055/C1109. This supported the relevance of the findings of efficacy from the IV belimumab program to support the benefit:risk assessment on the IV belimumab pediatric program. Due to the statistical uncertainty posed by study BEL114055/C1109's small sample size as a result of the rarity of childhood-onset SLE that precluded formal statistical hypothesis testing, additional support for the efficacy findings of this pediatric study was obtained from a post-hoc Bayesian analysis of study BEL114055/C1109. This Bayesian analysis, which relied on information borrowed from the adult studies C1056 and C1057, supported a statistical conclusion that the treatment effect of belimumab IV in the pediatric population favored belimumab 10 mg/kg as compared to placebo. The drug's safety and pharmacokinetic profiles in pediatric patients were consistent with the overall population in the pivotal adult studies C1056 and C1057, and no new safety signals were identified that warranted discussions of the

data contained in this submission at a public advisory committee meeting or updating the Warning and Precaution section of the current belimumab label.

Based on the totality of data generated from study BEL114055/C1109, together with the efficacy and safety results from the two adequate and well-controlled adult studies C1056 and C1057 conducted with IV belimumab reviewed previously under BLA 125370, the risk/benefit assessment favors approval of the 10mg/kg dosing regimen of belimumab IV as add-on treatment for pediatric patients with active, sero-positive, childhood-onset SLE who are receiving standard therapy. Additionally, the pediatric clinical pharmacology, efficacy and safety data submitted to sBLA 125370/S-064 are adequate to fulfill the PREA postmarketing requirement (2661-5) related to the March 9, 2011 approval for BLA 125370 belimumab (Benlysta®) IV formulation.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary

As mandated by the 2003 Pediatric Equity Research Act (PREA), the FDA required a post-marketing trial of belimumab IV to be conducted in pediatric patients between the ages 5 to 17 years old with childhood-onset systemic lupus erythematosus (cSLE) as part of the marketing approved reached with the applicant. Study 114055/C1109 was an international, multicenter, randomized, double-blind, placebo- controlled, 52-week study that evaluated the efficacy, safety and pharmacokinetics of the marketed 10 mg/kg dose of IV belimumab in 93 pediatric subjects with active, sero-positive SLE despite standard therapy.

Determination of efficacy in pediatric patients was based on pharmacokinetic (PK) and efficacy results from study BEL114055/C1109, as well as PK exposure and extrapolation of the established efficacy of belimumab plus standard therapy from the phase 3 intravenous studies in adults, studies C1056 and C1057. Study 114055/C1109 was an appropriately designed, well conducted study to characterize the pharmacokinetic profile, efficacy and safety of belimumab in a pediatric population with cSLE. This pediatric study employed the same primary endpoint, the Week 52 SRI-4 response rate, used in the pivotal adult belimumab IV studies (C1056 and C1057) to establish the product's effectiveness as a treatment for SLE. A higher proportion of pediatric belimumab IV subjects (52.8%) achieved the SRI-4 endpoint as compared to the pediatric placebo group (43.6%) [odds ratio (95% CI): 1.5 (0.3, 3.5)] which was consistent with the efficacy results observed in the adult belimumab IV studies C1056 and C1057. These results were supported by positive results from major and ancillary secondary endpoints that showed pediatric subjects randomized to the belimumab IV group also had a lower risk of experiencing a severe flare compared to the placebo group as well as a longer duration of time to severe flare (160 days versus 82 days, respectively). Additional support was provided by a post-hoc Bayesian analysis that concluded the treatment effect of belimumab IV in the pediatric population favored belimumab 10 mg/kg as compared to placebo. Results from this study showed that the product's safety and pharmacokinetic profile in pediatric patients was consistent with the overall population in the pivotal adult studies C1056 and C1057 and no new safety signals were identified.

Lower SLE disease activity as well as a decrease in the risk for severe SLE flares may result in less long-term end-organ damage from patients' underlying disease, less treatment with unapproved immunosuppressive agents commonly used to treat childhood-onset SLE with their own inherent toxicities, as well as fewer hospitalizations with less loss of absent school days and ultimately less morbidity and mortality associated with this disease.

Based on the totality of data generated from the adequate and well-controlled pediatric study BEL114055/C1109, together with the efficacy

and safety results from the two well-controlled adult studies C1056 and C1057 conducted with IV belimumab reviewed previously under BLA 125370 and the unmet medical need for safe and efficacious treatments for pediatric patients with SLE, the risk/benefit assessment favors approval of the 10 mg/kg dosing regimen of belimumab IV as add-on treatment for pediatric patients with active, sero-positive, childhood-onset SLE who are receiving standard of care. Belimumab for IV administration will provide a new treatment option and the first approved specifically for childhood onset SLE.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• SLE is a heterogeneous, chronic, autoimmune multisystem disease characterized by autoantibody production with systemic inflammation as a result of immune dysregulation with disease flares alternating with periods of remission. Clinical manifestations of SLE can range from mild to life-threatening, with the mucocutaneous, musculoskeletal, renal and central nervous systems (CNS) being most commonly affected. The most common manifestations of SLE generally are malar rash, photosensitivity, oral ulcers, alopecia, arthritis or arthralgias, fatigue and renal disease. Approximately 10-20% of patients who develop renal disease (lupus nephritis) can progress to end-stage renal failure requiring hemodialysis and organ transplantation. Patients with CNS disease can suffer from a variety of neuropsychiatric manifestations that include headaches, seizures, strokes, cognitive impairment and mood disorders. • This disease primarily affects females between 15 to 40 years of age with estimated prevalence rates in adults ranging from 20 to 70 per 100,000 persons. • Approximately 10-20% of SLE patients have disease onset during childhood. The estimated prevalence rates for childhood-onset SLE (cSLE) ranges from 4.3 to 9.73 per 100,000 persons depending on the country. Although the prevalence of cSLE increases with age, it is rarely diagnosed in children 9 years old and younger.	SLE is a serious disease that can impact virtually any organ system. This disease can cause significant morbidity and mortality as well as impact on patients' function and quality of life especially if it first presents during childhood.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Patients of African-American descent are more likely to have severe disease and renal involvement. • The overall 10-year survival in adult SLE patients is approximately 85-90% • The range of manifestations in cSLE is similar to that seen in adult onset disease except children with cSLE tend to have more aggressive disease with higher rates of renal (30%) and neuropsychiatric (25%) involvement associated with a higher risk of mortality and end-organ damage	
Current Treatment Options	• Aspirin • Corticosteroids • Hydroxycholoroquine and other antimalarials • NSAIDs • Azathioprine • Mycophenolate Mofetil • Cyclophsphamide • Rituximab • Methotrexate Many of the therapies currently used in SLE management are used off-label	The toxicities associated with both the approved drugs for SLE as well as the off-label treatments commonly used to treat it contribute to the long-term morbidity and mortality observed in patients with SLE There is a large unmet medical need for safe and efficacious treatments of children ≤17 years of age with childhood onset SLE as there are currently no treatments specifically approved for this subpopulation.
Benefit	• Study BEL114055/C1109 was a multicenter, international, randomized, double-blind, placebo-controlled study that evaluated the pharmacokinetics, efficacy and safety of 10 mg/kg of belimumab plus standard therapy over 52 weeks in 93 pediatric subjects with active SLE • Determination of efficacy in pediatric patients was based on extrapolation of pharmacokinetic and efficacy results from the adult	Lower SLE disease active as well as a decrease in the risk for severe SLE flares may also result in less long-term end-organ damage from patients underlying disease, less treatment with unapproved immunosuppressive agents commonly used to treat childhood-onset SLE with their own inherent toxicities, as well as fewer hospitalizations with less loss of absent

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	belimumab IV studies C1056 and C1057 reviewed in support of belimumab's original marketing approval[1] • Primary endpoint was the Week 52 SRI-4 response rate comparing the pediatric belimumab IV group versus pediatric placebo group. This was the same novel endpoint used in the pivotal adult belimumab IV studies (C1056 and C1057) to establish the product's effectiveness as a treatment for SLE. The SRI captures clinically meaningful changes in disease activity without significant worsening in overall disease activity[2] • A higher proportion of pediatric belimumab IV subjects (52.8%) achieved the SRI-4 endpoint as compared to the pediatric placebo group (43.6%) [odds ratio (95% CI): 1.5 (0.3, 3.5)] and was consistent with the efficacy results observed in the adult belimumab IV studies C1056 and C1057 • Support for this finding came from analyses of the individual SRI components as well as from other secondary endpoints. • Pediatric subjects randomized to the belimumab IV group also had a numerically lower risk of experiencing a severe flare compared to the placebo group as well as a longer duration of time to severe flare (160 days versus 82 days, respectively) • Additional statistical support that the treatment effect of belimumab IV in the pediatric population favored belimumab 10 mg/kg as compared to placebo came from a post-hoc Bayesian analysis of the pediatric study that relied on efficacy data borrowed from the adult belimumab IV studies (C1056 and C1057)	school days and ultimately less morbidity and mortality associated with this disease.

[1] FDA review of BLA 125370 Belimumab (Benlysta) intravenous formulation dated February 18, 2011
[2] Furie et al., Novel Evidence-Based Systemic Lupus Erythematosus Responder Index. Arthritis and Rheum, 2009;61(9):1143-1151

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Overall, the safety profile of belimumab IV assessed at a dose of 10 mg/kg in the pediatric population that participated in study BEL 114055/C1109 appeared to be similar as compared to placebo and the product's established safety profile in the adult SLE studies (C1056 and C1067). • There were a no deaths or malignancies in the pediatric belimumab IV group. One patient randomized to the placebo plus standard of care group died as a result of uncontrolled SLE. • Many of the serious adverse events and withdrawals from study treatment in the belimumab IV pediatric safety database were related to underlying disease activity or infections. • Opportunistic infections such as pulmonary tuberculosis and herpes zoster including recurrent zoster were observed, consistent with the data seen in adults. • There were no cases of suicide/self-injury which occurred in belimumab IV treated pediatric patients versus three cases in the pediatric placebo group. • Decreases in lymphocytes and serum immunoglobulins were observed in pediatric patients randomized to the belimumab IV treatment group that were not associated with an increased risk for infection. • No new safety signals were identified on review of safety data collected from the open-label portions (Parts B and C) of study BEL 14055/C1109 or the postmarketing safety data for belimumab IV in adult patients with SLE • Limitations associated with the pediatric belimumab IV safety database are the same as those identified for the adult IV belimumab safety database and include the lack of concomitant IV	Identified safety risks associated with the administration of belimumab IV in the adult SLE population include an increased risk for death and serious infections, hypersensitivity spectrum reactions including anaphylaxis, and psychiatric events including depression and suicidality. Potential safety risks with belimumab IV include progressive multifocal leukoencephalopathy (PML), malignancies, immunogenicity, and effects on immunizations including interactions with live vaccines. These risks are reflected in the Warning sand Precautions in the product's current USPI and are adequately conveyed to potential pediatric patients and their caregivers via belimumab IV's current Medication Guide. No new safety concerns were identified on review of the pediatric safety database for belimumab IV that warrants updating the Warnings and Precautions in the product's current USPI. However, the applicant has recently submitted a labeling supplement to update the current Warnings and Precaution statement for depression/psychiatric events associated with the administration of belimumab IV based on data from a long-term safety PMR study in adults. Since SLE typically affects young women of childbearing potential, a pregnancy

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cyclophosphamide or other biologics including those that target B cells (e.g., rituximab), the lack of patients with severe renal lupus and central nervous system disease, and the overall small number of subjects that participated in study BEL114055/C1109 as well as the small number of subjects available for subgroup analyses of gender (males) and age (children between the ages of 5 to 11 years) which precludes determination of the product's safety profile in these subgroups.	registry is currently underway that is collecting prospective information for pregnancies and pregnancy outcomes in subjects with SLE exposed to belimumab. Although no apparent risk for malignancies has been identified with long-term treatment with either formulation of belimumab in adults, it would be prudent to continue monitoring safety data from the ongoing open label extension (Part C) of study C1109 in pediatric patients for the development of potential safety signals such as malignancies to occur with increasing exposure to the product.

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:**			
	x	Clinical outcome assessment (COA) data, such as		Section 8
		x	Patient reported outcome (PRO)	
		x	Observer reported outcome (ObsRO)	
		x	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):		
☐	**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 autoimmune disease with clinical manifestations that 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 10 per 100,000 person-years, with a prevalence in the range of 20 to 70 per 100,000. There is a consistent and striking female predominance, with females comprising approximately 90% of all SLE patients[3]. 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[4]. The estimated prevalence rates for childhood-onset SLE (cSLE) range from 4.3 to 9.73 per 100,000 persons depending on world location[5, 6]. Although the prevalence of cSLE increases with age, it is rarely diagnosed in children 9 years old and younger[7].

In general, the most common SLE manifestations are malar rash, photosensitivity, oral ulcers, arthritis, and renal disease. The incidence and severity of specific SLE manifestations appears to vary by ethnicity and age —compared to SLE patients of European descent, patients of African descent develop renal disease more frequently (~50%, vs. 20 to 30% in patients of European descent) and the disease is more severe. High rates (60 to70%) of renal involvement are also reported in most Asian populations. Other less common but serious manifestations include serositis (16 to 64%, depending on population and report), neurological disorders (9 to 36%), and immune-mediated cytopenias (4 to 43%)[8]. 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 renal (30%) and neuropsychiatric (25%) involvement[9].

For the purposes of clinical trials, the American College of Rheumatology (ACR) has established classification criteria to assist in uniformly identifying patients with SLE (Table 1). Generally adult and pediatric patients are considered to have SLE if they meet at least 4 of the 11

[3] Pons-Estel et al. Understanding the Epidemiology and Progression of Systemic Lupus Erythematosus. Semin Arthritis Rheum 2010 Feb ; 39:257-268
[4] Hiraki LT, Feldman CH, Liu J, et al. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. Arthritis Rheum 2012; 64:2669-76.
[5] Hiraki et al. Arthritis Rheum 2012; 64:2669-76
[6] 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
[7] Hiraki et al. Arthritis Rheum 2012; 64:2669-76.
[8] Borchers et al. The Geoepidemiology of Systemic Lupus Erythematosus. Autoimmunity Reviews 9 (2010): A277-A287
[9] 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.

mentioned criteria. These criteria indicate a minimal requirement, reflecting the heterogeneity of possible clinical manifestations with which an SLE patient may present, and do not ensure a definitive diagnosis of SLE.

Table 1. ACR 1997 Revised Classification Criteria of SLE

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus (SLE)	
Criterion	**Definition**
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid Rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral Ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling or effusion
6. Pleuritis or pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR 2. Pericarditis--documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria >0.5 grams per day or > than 3+ if quantitation not performed, OR 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurological Disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis, or electrolyte imbalance, OR 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia--with reticulocytosis, OR 2. Leukopenia--<4000/mm^3 on at least 2 occasions, OR 3. Lymphopenia--<1500/mm^3 on at least 2 occasions, OR 4. Thrombocytopenia--<100,000/mm^3 in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native NDA in abnormal titer, OR 2. Anti-Sm: presence of antibody to Sm nuclear antigen, OR 3. Positive finding of antiphospholipid antibodies: 1. abnormal serum level of IgG or IgM anticardiolipin antibodies 2. a positive test result for lupus anticoagulant using a standard method, or 3. a false-positive test result for at least 6 months confirmed by treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs.

For the purpose of identifying patients in clinical studies, a person shall be said to have SLE if any 4 or more of these 11 criteria are present, serially or simultaneously, during any interval of observation.

As there is no cure for this chronic disease, therapeutic goals in the chronic management of SLE include controlling active inflammation and preventing or resolving organ damage while improving quality of life and survival. The current overall 10-year survival in adult patients with SLE has improved to 85-90%[10]. However, pediatric patients with cSLE have a higher relative risk of mortality as compared to patients with adult-onset disease (hazard ratio [HR] 3.1, 95% confidence interval [CI] 1.3-7.3)[11]. This disparity in survival has been attributed to the more aggressive disease course seen in cSLE resulting in greater major end-organ damage due to

[10] Ipolito A, Petri M. An update on mortality in systemic lupus erythematosus. Clin Exp Rheumatol 2008;26 Suppl51:S72-9

[11] Hersh AO, Trupin L, Yazdany J, Panopalis P, Julian L, Katz P, et al. Childhood-onset disease as a predictor of mortality in an adult cohort of patients with systemic lupus erythematous. Arthritis Care Res (Hoboken). 2010;62(8):1152-9.

underlying disease activity as well as from the cumulative toxicities and increased risk for infection associated with the immunosuppressive medications used in the management of this disease.

2.2. Analysis of Current Treatment Options

There are currently no approved treatments for pediatric patients with SLE. Table 2 lists the treatments currently that are approved and available for the treatment of adults with SLE.

Table 2. 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 SLE						
Aspirin	Treatment of arthritis and pleurisy of SLE	1948	Initially 3g/d in divided doses; titrate up to plasma salicylate level 150-300mcg/ml for anti-inflammatory effect	Clinical studies	GI bleeding and tinnitus at plasma salicylate levels ≥ 250 mcg/ml	Constitutional and musculo-skeletal manifestations and serositis. No longer used
Prednisone	During an exacerbation or as maintenance therapy in selected cases of SLE	1955	Up to 80 mg/day; use lowest dose to maintain adequate anti-inflammatory response	Clinical studies	↑risk for infections, glucose intolerance, osteoporosis, glaucoma, cataracts, HTN, osteonecrosis, and ↓growth	Low dose: muco-cutaneous and musculo-skeletal manifestations; serositis High Dose: induction therapy for lupus nephritis, CNS disease, and immune cytopenias
Hydroxy-chloroquine	Treatment of discoid and SLE	1955	200 mg BID	Clinical studies	Retinal and corneal deposits, GI complaints, rash, myalgia. Headache and hemolytic anemia in G6PD deficiency	Constitutional, cutaneous and musculoskeletal manifestations
Belimumab	Treatment of active, autoantibody positive SLE despite standard of care	IV: 2011 SC: 2017	10mg/kg via IV infusion at 2-week intervals for the first 3 doses and then at 4-week intervals thereafter	IV: Two phase 3 studies SC: One phase 3 study	↑risk for mortality, serious and fatal infections, hypersensitivity reactions, depression and suicidality	Musculoskeletal, mucocutaneous and immunologic manifestations
Other Treatments (Off-Label)						

NSAIDs	----------	----------	Lowest effective approved dose	Published literature	GI bleeding, CV events, hepatic and renal toxicity, HTN, headache, aseptic meningitis, confusion	Constitutional and musculoskeletal manifestations, headaches and serositis
Azathioprine	----------	----------	2-2.5 mg/kg/d	Published literature	Myelosuppression, hepatotoxicity, malignancies, infections	Steroid sparing and maintenance therapy for lupus nephritis
Methotrexate	----------	----------	7.5-25 mg/week	Published literature	Mucositis, myelo-suppression, hepatotoxicity, cirrhosis, pneumonitis, pulmonary fibrosis, infections	Cutaneous and musculoskeletal manifestations
Cyclophosphamide	----------	---------	IV bolus regimens of 0.5-1g/m body surface area for once monthly for 6 months	Published literature	Myelosuppression, hemorrhagic cystitis, malignancy, lympho-proliferative disorders, infertility and infections	Induction therapy for lupus nephritis, CNS disease, pulmonary hemorrhage, and systemic vasculitis
Mycophenolate Mofetil	----------	----------	500-1500 mg BID	Published literature	Myelosuppression, GI complaints, myalgia, infections	Induction and maintenance therapy for lupus nephritis
[redacted]						(b) (4)

Based on anecdotal reports and non-registrational studies in the published literature, both adult and pediatric SLE patients are usually treated with a combination of immunosuppressive medications that can contribute to the morbidity and mortality associated with this disease due to their associated toxicities. As noted in Table 2 above, there are currently only 4 treatments currently approved for the treatment of SLE in adults, of which belimumab is the only approved therapeutic biologic product. Its currently approved USPI contains a limitations of use for pediatric patients and off-label biologics (e.g., rituximab) and intravenous cyclophosphamide as well as for patients with severe lupus nephritis and severe central nervous system lupus since all of the phase 3 studies conducted in support of the product excluded patients under 18 years of age or who were receiving concurrent treatment with these agents or with these disease manifestations. In view of this, there is a high unmet need for efficacious and safe treatments for pediatric patients with SLE.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Belimumab is an approved therapeutic biologic product that is available and marketed in the U.S. (since 2011) and in over 70 countries worldwide (as of October 2017) 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. An alternative once weekly subcutaneous (SC) administered injection formulation available as a ready to use pre-filled syringe and autoinjector was approved in 2017 for the same indication.

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 not administrating live vaccines to patients receiving this product. The product's USPI has subsequently undergone five major labeling revisions as follows:

- 2012 and 2013: The Warnings and Precautions section for hypersensitivity reactions including anaphylaxis was updated to reflect postmarketing 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 as well as sections 5.2 Serious Infections and 6.1 Clinical Trials Experience 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 as well as new information to the product's Medication Guide regarding the SC formulation

3.2. Summary of Presubmission/Submission Regulatory Activity

As part of the approval action on March 9, 2011 for BLA 125370 Benlysta® (belimumab) intravenous (IV) formulation as a treatment for adult patients with active, seropositive SLE, the Agency required a pediatric postmarketing (PMR 266-1) study of belimumab IV under the Pediatric Research Equity Act (PREA) as follows:

"A phase 2, multicenter study to evaluate the safety, efficacy, and pharmacokinetics of

> belimumab plus background standard therapy in 100 pediatric subjects ages 5 years to 17 years of age with active systemic lupus erythematosus (SLE)"

On September 19, 2014 the Applicant submitted a request for a deferral extension of the timeline for pediatric PMR 266-1 due to study recruitment difficulties. A Deferral Extension Granted letter was issued by the Agency on September 26, 2014 which acknowledged good faith efforts had been made by the Applicant to complete the study and there was sufficient justification for the delay. In view of this, the study completion date was revised, and the final report submission date was extended as follows:

Study Completion: March 2018
Final Report Submission: October 2018

On June 23, 2016, the Applicant requested to revise PMR 266-1 to lower the overall target enrollment from 100 to 70 subjects due to difficulties enrolling pediatric patients between 5 and 17 years of age. Since the Applicant's proposal impacted on the wording of the study's PMR agreement, the proposal was vetted at the October 12, 2016 PeRC meeting who concurred with the proposed changes. The committee also recommended that the review division release the Applicant from the existing PMR 266-1 and reissue a new PMR to reflect the new total number of pediatric SLE subjects (N=70) to be evaluated in the ongoing pediatric study BEL 114055 as well as the related pending milestone dates. On November 14, 2016, a letter was issued by the review division releasing the Applicant from the original PREA PMR that also acknowledged the new PREA PMR 2661-15 and new timeline as follows:

> "A phase 2, multicenter, study to evaluate the safety, efficacy, and pharmacokinetics of belimumab plus background standard therapy in 70 pediatric subjects ages 5 years to 17 years of age with active systemic lupus erythematosus (SLE)"
>
> Study Completion: March 2018
> Final report Submission: October 2018

The Applicant submitted the final study report for the pediatric belimumab IV PMR study BEL114055/C1109 to the Agency on July 17, 2018. Based on the data generated from this study which was conducted in accordance with an agreed pediatric study plan (PsP), they submitted a sBLA for the expansion of belimumab IV's approved indication for the treatment of patients with active, antibody positive systemic lupus erythematosus (SLE) to include children 5 to 17 years of age on October 26, 2018. As there are no currently approved treatments for pediatric patients with SLE and using the rationale that belimumab IV would be a significant improvement over the currently available SLE treatments for children 5 to 17 years of age (e.g., a new subpopulation), the Applicant subsequently requested a priority review request for this sBLA on October 29, 2018 which was granted by the Agency on December 20, 2019.

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

4.1. Office of Scientific Investigations (OSI)

Audits of clinical study sites that participated in the pediatric PMR study BEL114055/C1109 were not requested in support of this application.

4.2. Product Quality

This section is not applicable as there are no new product quality data.

4.3. Clinical Microbiology

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

4.4. Devices and Companion Diagnostic Issues

Not applicable since this formulation of belimumab is administered via intravenous infusion prepared by a pharmacist.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical studies were submitted in support of this supplement for pediatric patients, 5 to 17 years old. Nonclinical studies were reviewed with the original BLA submission for adults ≥18 years old. The non-clinical data supporting the use of belimumab, including in pediatric patients is summarized below.

Cynomolgus monkeys were administered a lyophilized formulation of belimumab by IV administration at doses of 0, 5, 15, 50 mg/kg Q2 week for 26 weeks. The study at initiation consisted of both juvenile and adult animals (age ranges of animals at the start of dosing were as follows: males, 2.5-5.3 years old and females, 2.1-7.4 years old). The study was capable of characterizing toxicity that could be potentially relevant to pediatric patients, 5-17 years old, as well as adult patients. Three monkeys/sex/group were sacrificed at Weeks 13 and 26, respectively. Two monkeys/sex/group were allowed a 32-week recovery period and sacrificed at Week 60. The B-cell (total and mature) populations from the peripheral blood, spleen, and mesenteric lymph nodes (LNs) decreased with statistical significance at Weeks 13 and 26, although findings were not dose-responsive. The finding was attributed to the pharmacological effect of the drug. Recovery of B cell counts was evident by Week 60. There were decreases in lgG, lgM, and lgE levels in the belimumab-treated animals through Week 26 (throughout the treatment period) compared to vehicle-treated animals. Major histopathological observations consisted of lymphoid depletion in the spleen and mesenteric and mandibular LNs, which was attributed to the pharmacological effects of belimumab and considered to be monitorable in the clinical setting. Extramedullary hematopoiesis was also evident in the LNs. The histopathology findings at Week 60 (recovery) showed extramedullary hematopoiesis of the lymph nodes and lymphoid hyperplasia in spleen. These findings were likely the result of a rebound response to B-cell depletion.

The effect of the belimumab on the male or female reproductive organs could not be appropriately evaluated due to sexual immaturity of male monkeys and lack of adequate endpoint assessments in females. Histopathological changes in the ovary consisted of interstitial and germinal cell hyperplasia at Weeks 13 and 26. The incidences of these findings were higher than those of the controls and persisted at all doses through Week 60 suggesting no recovery. No sex hormones were evaluated or menstrual cyclicity in this study. It was possible that observations in the ovary were part of normal physiological changes as the ePPND study, described below, did not suggest any abnormalities.

The findings in juvenile and adult monkeys appeared to be relatively comparable. Safety margins for clinical exposures could be calculated relative to the high dose in the monkey study based upon monitorability of observed findings in the clinical setting. The high dose provides a

5-fold safety margin for the clinical dose of 10 mg/kg on a mg/kg basis (Belimumab has a MW of 147 kDa and safety margins should be calculated on a mg/kg basis).

A combined embryo-fetal and pre- and post-natal development (ePPND) study was conducted with pregnant monkeys that received intravenous administration of belimumab at doses of 0, 5, and 150 mg/kg Q2 weeks. Monkeys in Groups 1 and 2 were administered IV doses of the control vehicle article. Monkeys in Groups 3 and 4 received IV doses of belimumab at 5 mg/kg. Monkeys in Groups 5 and 6 received IV doses of belimumab at 150 mg/kg. IV doses were administered as a slow bolus over 2-5 minutes by the saphenous vein at a dose volume of 7.5 mL/kg. Groups 1, 3, and 5 were dosed within 2 days of confirmed pregnancy (GD20 to GD22), on GD34, and every 14 days until scheduled Caesarian section (C-section) on GD150 or delivery (if prior to GD150, whichever came first). Groups 2, 4, and 6 were dosed within 2 days of confirmed pregnancy (GD20 to GD22), on GD34, and every 14 days until delivery (no later than approximately GD175, whichever came first). The mother and offspring in Groups 2, 4, and 6 were evaluated for approximately 1 year postpartum/postnatal.

All pregnant females had systemic exposure to belimumab and the overall toxicokinetics were linear across the dose range of 5 to 150 mg/kg. Belimumab-related changes in peripheral blood mononuclear cells at GD90 and GD140 consisted of decreases in total and mature B-lymphocytes in pregnant cynomolgus monkeys. For all adult females during gestation, there were no test article-related changes in serum immunoglobulin levels (IgG, IgM, IgA, and IgE).

The mean belimumab concentration in the blood of the umbilical cord was generally 4-fold lower than maternal blood. The mean belimumab concentration in the amniotic fluid was generally 32- to 36-fold lower than maternal blood. The umbilical cord and amniotic fluid data indicated that the test article crossed the placenta, as is expected for an IgG1 antibody.

For the Group 1, 3, and 5 fetuses that underwent teratologic evaluations at GD150, there were test article-related decreases in fetal spleen weight and reductions in B-lymphocyte immunohistochemical staining in inguinal lymph node, mesenteric lymph node, and spleen in fetuses at doses of 5 and 150 mg/kg. Reduction in the density of lymphoid tissue B-lymphocytes was an expected pharmacologic effect and indicated that the drug crossed the placenta during fetal growth and development. There were no apparent test article-elated effects observed for the following: fetal body weight; fetal measurements at Cesarean section (or birth); placental, amniotic fluid, and umbilical cord evaluations; external, visceral (including detailed evaluation of heart) and skeletal examinations; histopathology of selected tissues; and immunohistochemistry evaluations of T-lymphocytes, macrophages, and natural killer cells.

Group 2, 4, and 6 mothers and infants continued study for one year after birth. For all adult females at one year postpartum, there were no test article-related changes in hematologic parameters or serum immunoglobulin levels (IgG, IgM, IgA, and IgE). Changes in peripheral blood mononuclear cells in adult female monkeys postpartum, attributed to the administration of 5 or 150 mg/kg belimumab during gestation, were decreases in total B-lymphocytes counts

and relative increases in monocyte counts. Recovery to baseline levels was apparent in most animals by PPD28 (monocytes) and PPD365 (B-lymphocytes). Decrements in mature B-lymphocyte counts were noted in Phase 1 during gestation. Similar changes in mature B-lymphocyte counts were not clearly evident in adult females through the postpartum interval.

For all infants evaluated up one year after birth, there were no test article-related changes in clinical signs, body weight, physical examinations, neurobehavioral assessment; or hematologic, serum chemistry, coagulation, or urinalysis parameters. The growth and development of the infants were within normal limits for infant cynomolgus monkeys. Alterations in the peripheral blood mononuclear cells of infant cynomolgus monkeys, born to females dosed with belimumab during pregnancy, were limited to dose independent reductions in the mean total B-lymphocyte and mature B-lymphocyte counts at BD7 and BD28. By BD91, the infant peripheral blood mononuclear cells were similar in all groups, including controls. There were no gross, organ weight, organ weight ratio, histologic, or immunohistochemical changes attributable to belimumab administration in these infants that were exposed to belimumab in utero and euthanized approximately one year after birth. The reduction in B-lymphocytes identified by immunohistochemistry in the lymph nodes and spleen of fetuses euthanized on GD150 was reversed by the end of one year after birth. Serum IgG was significantly higher in the 150 mg/kg dose group compared to control infants at BD7 when the data was adjusted for the contribution of belimumab (a fully human IgG1λ monoclonal antibody). There were no significant differences in serum IgG between belimumab -exposed and control infants at other timepoints. Belimumab exposure in utero reduced infant serum IgM from BD7 to BD91 (dose-independent; statistically significant at BD7 and BD91), but values were similar between belimumab-exposed and control infants from BD182 thorough the end of the one-year period following birth.

During the postpartum period, most adult females and infants in the 5 mg/kg belimumab dose group had no measurable serum belimumab levels by PPD91/BD91, while in the 150 mg/kg belimumab dose group, most adult females and infants had no measurable serum belimumab levels by PPD182/BD182. Mean belimumab concentrations for infants in the 5 mg/kg dose group were similar to those for their mothers on BD7 and 2- and 13-fold lower than those for their mothers on BD28 and BD91, respectively. Mean belimumab exposures for infants in the 150 mg/kg dose group were 10-, 9-, 1.4-, and 1.6-fold lower than those for their mothers on BD7, BD28, BD91, and BD182, respectively. Following the last dose administration of belimumab prior to delivery, the mean terminal T½ in adult females was 11 to 12 days, which was consistent with the known terminal half-life from other studies.

There was an increasing level of free BLyS in circulation of mothers and infants postpartum as belimumab serum concentrations declined and prior to repopulation of B cells bearing BLyS receptors.

Monkeys up to 1 year old could potentially model young pediatric subjects. It should be noted that these animals were exposed to belimumab through placental transfer and were not

directly dosed with the drug. Observed effects in these animals were attributed to the pharmacological action of belimumab and were reversible.

6 Clinical Pharmacology

6.1. Summary of Clinical Pharmacology Assessment

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data submitted to sBLA 125370/S-064 to address the PMR requirement. This sBLA is approvable from a clinical pharmacology perspective. In addition, the clinical pharmacology information is acceptable for the fulfillment of the PMR.

6.1.1. Pharmacology and Clinical Pharmacokinetics

The key clinical pharmacology findings for IV belimumab in pediatric patients with SLE in study BEL114055 are summarized below:

1. At steady-state, the observed belimumab concentrations for the younger children (5-11 years) were slightly lower compared to children aged 12-17 years at Week 24 ($C_{max,ss}$: 289 µg/mL vs. 334 µg/mL) and Week 52 ($C_{min,ss}$: 45.0 µg/mL vs. 59.71 µg/mL). Overall, the concentrations in children in both age groups were comparable to those observed in adults in Phase 3 trials (Table 3).

2. Steady-state exposure parameters ($C_{max,ss}$, $C_{min,ss}$, $C_{avg,ss}$, and AUC_{tau}) estimated by the population PK model in pediatric and adults are summarized in Table 4. In general, the exposures in children in both age groups were comparable to the exposures in adults.

Table 3: Summary of Observed Steady-State PK Parameters of Belimumab in SLE Patients Aged 5-11 Years, 12-17 Years (Study BEL114055) and in Adult SLE Patients (Study C1056 and C1057)

Patients	Study	Body weight (kg) Median (Range)	$C_{max,ss}$* (µg/mL) Geo. Mean (CV%)	$C_{min,ss}$** (µg/mL) Geo. Mean (CV%)
Pediatrics (5-11 yrs)	Cohort 2 of Study BEL114055	29.8 (17-55.2) N=10	289 (28.0) N=9	45.0 (61.5) N=9
Pediatrics (12-17 yrs)	Cohort 1&3 of Study BEL114055	53.2 (31.5-85.5) N=43	334 (40.5) N=37	59.7 (57.3) N=33
Adult	Phase 3 Study C1056	73.7 (44.6-165) N=273	311 (36.0) N=204	59.0 (63.3) N=165
Adult	Phase 3 Study C1057	61.5 (36.0-129) N=290	308 (33.3) N=253	48.0 (52.4) N=187

** Steady-state peak samples collected between 0-4 hours after week 24 dosing (day 168)*
*** Steady-state trough samples collected prior to dosing up to week 52*
Source: CSR BEL114055 (Table 71), Clinical Pharmacokinetics Report for C1056 (Table 3-5 of HGS1006-C1056.PK), and Clinical Pharmacokinetics Report for C1057 (Table 3-5 of HGS1006-C1057.PK).

Table 4: Summary of Population Pharmacokinetic Model Derived Steady-State PK Parameters of Belimumab in SLE Patients Aged 5-11 Years, 12-17 Years (Study BEL114055) and in Adult SLE Patients (Study C1056 and C1057)

Patients	Study	N	$C_{max,ss}$ (µg/mL) Geo. Mean (95% CI)	$C_{min,ss}$ (µg/mL) Geo. Mean (95% CI)	$C_{avg,ss}$ (µg/mL) Geo. Mean (95% CI)	AUC_{tau} (day·µg/mL) Geo. Mean (95% CI)
Pediatrics (5-11 yrs)	Cohort 2 of Study BEL114055	10	305 (267-350)	42 (30-60)	92 (71-118)	2569 (1992-3314)
Pediatrics (12-17 yrs)	Cohort 1 &3 of Study BEL114055	43	317 (288-350)	52 (43-63)	112 (99-126)	3126 (2765-3533)
Adult	Phase 3 Study C1056 & C1057	563	311 (306-316)	46 (44-48)	100 (98-103)	2811 (2734-2890)

Source: CSR BEL114055 (Table 74), Clinical Pharmacokinetics Report for C1056 (Table 3-5 of HGS1006-C1056.PK), and Clinical Pharmacokinetics Report for C1057 (Table 3-5 of HGS1006-C1057.PK).

6.1.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosage for adult patients with SLE is as follows:

- 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter

The proposed dosage for pediatric patients with SLE aged 5 to 17 years is the same as adults:

- 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter

Therapeutic Individualization

Not Applicable.

Outstanding Issues

None.

6.2. Comprehensive Clinical Pharmacology Review

6.2.1. 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. The intravenous formulation of belimumab (BLA 125370) was originally approved on March 9, 2010 for the treatment of adult patients with SLE.

Mechanism of action
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.

6.2.2. Clinical Pharmacology Questions

What was the dose justification used for Study BEL114055?
A 10 mg/kg weight normalized dosing was selected for Study BEL114055 based on the safety, efficacy and PK data from the two pivotal phase 3 studies in adults with SLE (Study C1056 and C1057). For subjects 12 years and older, the 10 mg/kg dosing were expected to have similar belimumab exposure compared to adults. For younger subjects aged 5 to 11 years, slightly

lower exposures were expected with 10 mg/kg dosing mainly due to a lower average body mass index (BMI) of younger pediatric subjects.

Even though slightly lower exposures were expected in younger subjects aged 5 to 11 years, it is not likely to compromise efficacy as no clear dose (exposure) response relationship for belimumab was identified in adult patients: the belimumab 10 mg/kg dose achieved statistically significant superiority over placebo in both pivotal Phase 3 trials for the primary efficacy endpoint of the response rate at Week 52, while the 1 mg/kg dose was significantly superior to placebo in Study C1057 and only numerically better than placebo in Study C1056 (P=0.1041).

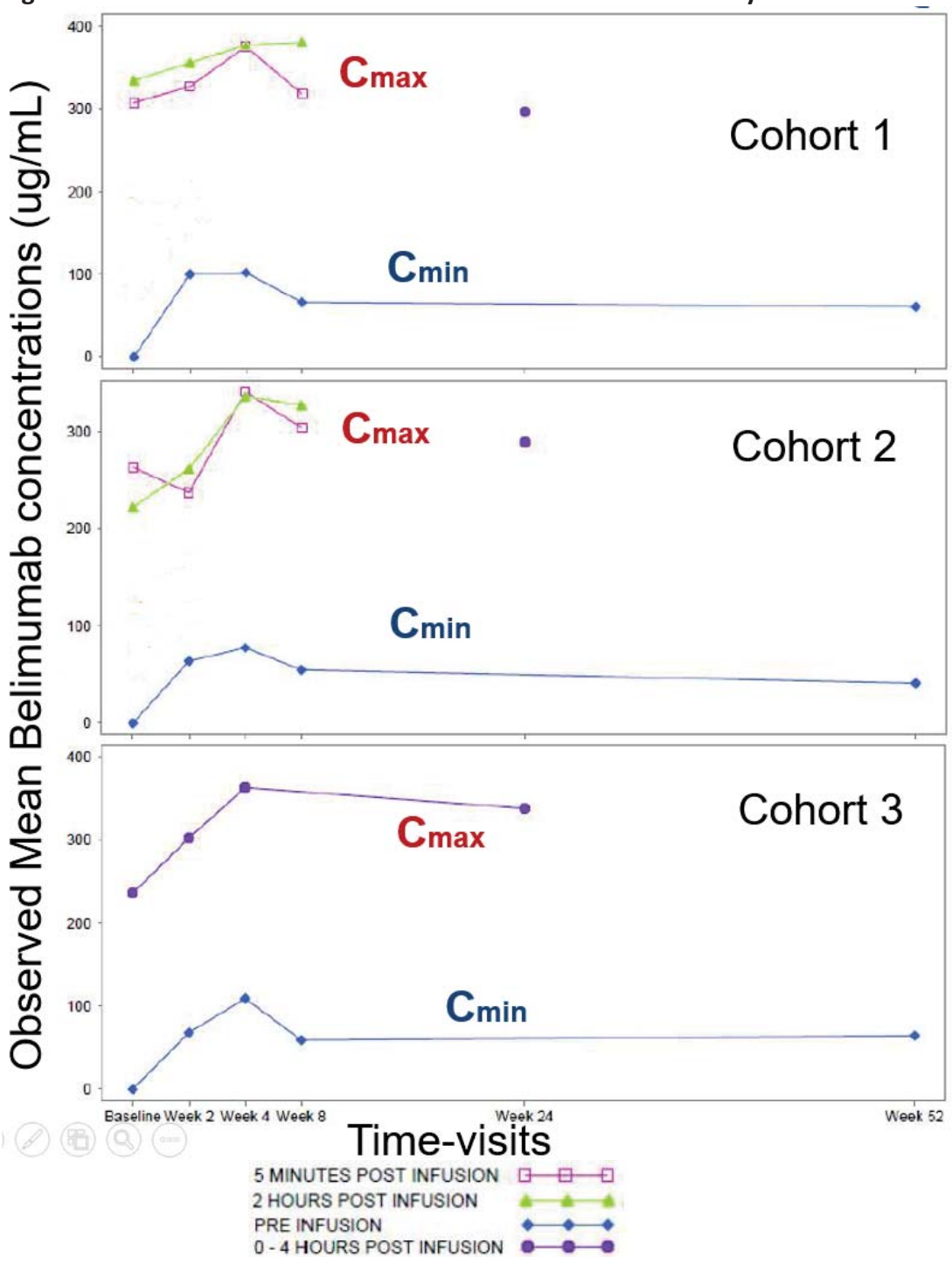
What are the findings from OSIS inspection?

The Office of Study Integrity and Surveillance (OSIS) inspected the bioanalytical portion of study BEL114055 conducted at (b) (4) and recommended that the pharmacokinetic data from the audited site were reliable to support regulatory decision. See memo dated 26 March 2019 in DARRTS (Reference ID 4409728) for further details.

What were the pharmacokinetics of belimumab after intravenous administration to pediatric patients with SLE aged 5 - 17 years?

Observed mean serum belimumab concentration-time profiles for pediatric SLE patients during the 52-week treatment are illustrated in Figure 1 below. Observed pre-dose concentrations reached a stable level around Week 8 for both age groups (cohort 1 & 3: 12-17 years, and cohort 2: 5-11 years).

Figure 1: Observed Mean Belimumab Concentrations from Study BEL114055



Source: CSR BEL114055 (Figure 16)

The observed and population PK model-derived steady-state PK parameters ($C_{min, ss}$ and $C_{max, ss}$) in pediatric SLE patients aged 5-11 years and 12-17 years from Study BEL114055 are shown in Table 5 and Table 6, respectively . The pop PK model predicted the parameters reasonably well.

Table 5: Summary of the Observed and Population PK Model-derived Steady-State PK Parameters for Belimumab in Pediatric SLE Patients Aged 5-11 Years

	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)
Observed[a]	289	45.0
Model-Derived[b]	305	42.0

Geometric mean reported for all PK parameters
[a] n = 9 for all parameters
[b] n = 10 for all parameters
Source: CSR BEL114055 (Table 71 & 74)

Table 6: Summary of the Observed and Population PK Model-derived Steady-State PK Parameters for Belimumab in Pediatric SLE Patients Aged 12-17 Years

	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)
Observed[a]	334	59.7
Model-Derived[b]	317	52.0

Geometric mean reported for all PK parameters
[a] n = 37 for Cmax,ss and n=33 for Cmin,ss
[b] n = 43 for all parameters
Source: CSR BEL114055 (Table 71 & 74)

What were the findings of the Population PK analysis?
The main objectives of the population PK analysis were to:

- Develop a population PK model that characterizes the PK disposition of belimumab following IV administration in pediatric subjects with SLE and evaluate the potential effect of selected covariates on PK parameters.
- Compare belimumab exposure in pediatric SLE patients to exposure in adult SLE Phase 3 patients.

Based on belimumab PK data obtained from 53 pediatric subjects with childhood-onset SLE in Part A of Study BEL114055, a population PK model was developed using the adult belimumab IV population PK model as a starting point. Model development proceeded by evaluating the pediatric PK by fixing the model parameters to the adult estimates, followed by re-estimation of the model parameters fitting to the pediatric data, with refinement of the body-size covariate effects, then finally model reduction using the full covariate model approach. The resulting linear, two-compartment model with first-order clearance from the central compartment characterized the PK in pediatric subjects well. Based on the typical parameter estimates in the overall pediatric population the derived population PK model has a clearance of 158 mL/day, a steady-state volume of distribution of 3.5 L and a terminal half-life of 16.3 days. Based on

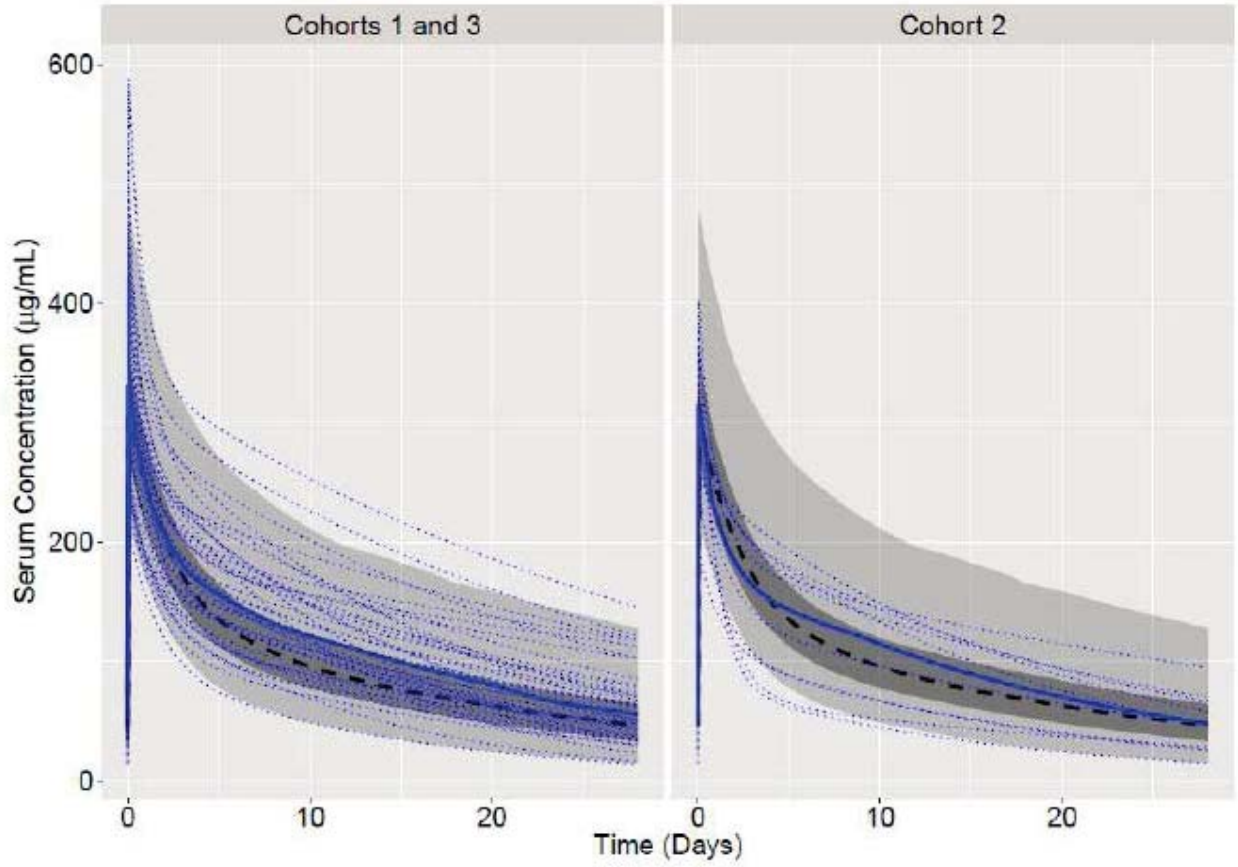
model diagnostics, the final population PK model was able to describe PK data after IV belimumab administration in pediatric patients with SLE.

Individual PK and steady-state exposure parameters provided by the final population PK model are summarized by age group and compared with adult parameters in Table 4. The adult parameters were derived from the 563 subjects who received 10 mg/kg belimumab in the SLE Phase 3 studies. Steady-state exposure parameters $C_{max,ss}$, $C_{min,ss}$, $C_{avg,ss}$, and AUC are similar between the age groups with a trend towards slightly higher exposure in the older compared to the younger age group. Parameters for both pediatric age groups and the overall pediatric population are consistent with the adult exposure parameters with largely overlapping confidence intervals.

Steady-state PK profiles for all pediatric subjects who received belimumab were simulated based on their individual PK parameters, summarized by age group and compared with the prediction intervals for the adult PK profiles (Figure 2). Almost all pediatric profiles are contained in the adult 95% prediction interval; the median pediatric profiles are consistent with the median adult profiles.

Further details are listed in the pharmacometric report in Section 15.

Figure 2: Simulated Steady-State PK Profiles by Age Group Compared to Adult Profiles



Dashed blue lines, individual pediatric profiles; solid blue lines, median pediatric profiles.
Dashed black line, adult population median profile; light grey shaded areas, 2.5th-97.5th percentile (95%) prediction interval for adult profiles; dark grey shade areas, 25th-75th percentile prediction interval for adult profiles.
Source: CSR BEL114055 (Figure 17)

Is the proposed dosing regimen appropriate based on the exposures observed in Study BEL114055?

Both observed and population PK model derived belimumab concentrations for pediatric patients were comparable with the adult concentrations (Table 3 and Table 4). The proposed dosing regimen is appropriate to match the exposure in pediatric patients with that in adults. Additionally, at the proposed dosing regimen, SRI response in pediatric patients at week 52 was found to be greater in belimumab group (52.8%) compared to the placebo group (43.6%) in Study BEL114055 (refer to section 8 for details).

What were the pharmacodynamic biomarkers of belimumab following IV administration to SLE patients aged 5 – 17 years?

A comparison of PD biomarkers between treatment and placebo group are shown in Figure 3-Figure 8, including immunoglobulin G (IgG), anti-dsDNA, CRP, complement (C3 and C4), B cell

subsets (CD19+, CD20+, naïve, memory B cells; as well as activated, plasmacytoid, plasma, short-lived plasma, and SLE subset B cells). The results regarding the pharmacodynamic response were generally consistent with the adult data (Table 7). It should be noted that the relevance of these PD biomarkers to clinical endpoints in SLE have not been established.

Table 7: Median Percent Change from Baseline in Biomarkers at Week 52 in IV Belimumab Phase 2 Pediatric and Pivotal Phase 3 Adult Studies

	BEL114055 (IV)		C1056 (IV)[a]		
Parameter[b]	Placebo	10 mg/kg	Placebo	1 mg/kg	10 mg/kg
Serum Immunoglobulins					
IgG	2.5	-17.7	-0.8	-13.5	-14.4
IgM	6.1	-35.4	-0.47	-28.2	-30.8
IgA	8.4	-18.8	-0.65	-16.1	-17.7
B cells					
CD19+	-18.9	-63.7	-10.4	-48.2	-48.5
CD20+	-18.6	-65.8	-9.2	-46.1	-46.1
Naïve (CD19+/CD20+/CD27-)[c]	-26.7	-77.1	-8.9	-66.7	-69.6
Memory (CD19+/CD20+/CD27+)[c]	0.0	11.7	0	50.0	35.0
Activated (CD19+/CD20+/CD69+)[c]	209.0	-37.9	-15.8	-40.5	-45.1
Plasmacytoid (CD19+/CD20+/CD138+)[c]	150.0	-33.3	-14.4	-50.6	-65.8
SLE subset (CD19+/CD27BRIGHT/ CD38BRIGHT)	92.8	-31.0	6.1	-23.7	-38.5
Plasma (CD19+/CD20-/CD138+)[c]	31.3	-31.8	-0.28	-21.6	-34.9
Short-lived plasma cells (CD19+/CD20-/CD27BRIGHT)[c]	52.5	-30.5	1.2	-11.3	-35.4

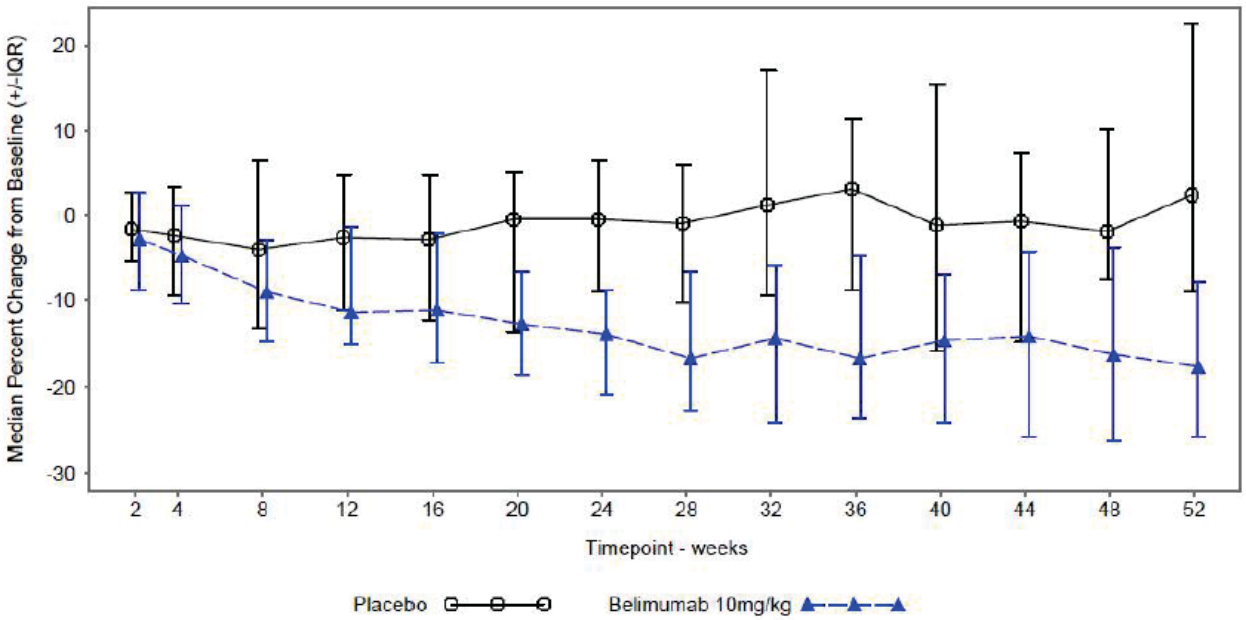
a. Among the two adult IV SLE Phase 3 studies only C1056 measured and reported B cell markers. Immunoglobulin responses in C1057 were very similar to the corresponding responses shown for C1056.
b. Baseline values by dose group are provided in the source tables.
c. Reported in C1056 without "CD19+/"

Source: Module 2.7.2 Summary of Clinical Pharmacology (Table 6)

Immunoglobulin G (IgG)

The median percent change from baseline in IgG is shown in Figure 3. Treatment with BENLYSTA in pediatric patients led to reductions in IgG which were observed as early as Week 8 and sustained through Week 52. At Week 52, there was an adjusted mean increase of 4.3% for the placebo group and an adjusted mean decrease of 15.9% for the belimumab 10 mg/kg group.

Figure 3: IgG Median Percent Change from Baseline (Part A) (ITT Population)

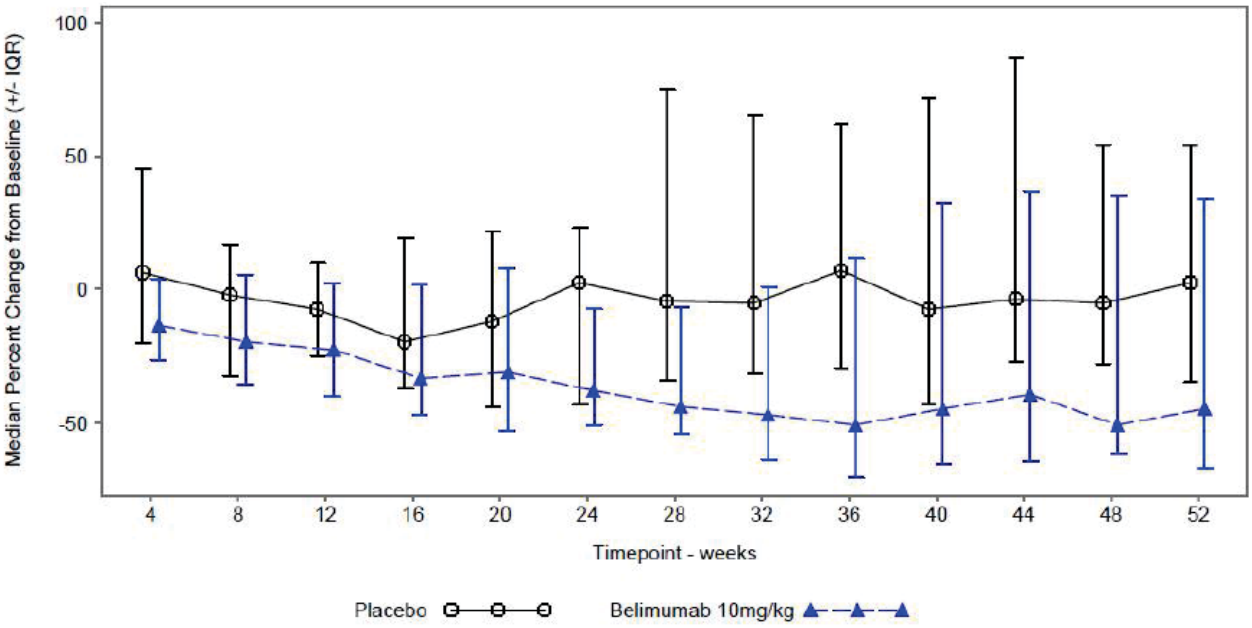


Source: CSR BEL114055 (Figure 23)

Anti-dsDNA

In subjects who were anti-dsDNA positive (≥30 IU/mL) at baseline (27/40 placebo, 38/53 belimumab 10 mg/kg), median percent change in anti-dsDNA antibody levels with time is shown in Figure 4. At Week 4, there was a 13.3% reduction in the belimumab 10 mg/kg group compared with an increase of 6.4% in the placebo group; at Week 52, there was a 44.9% reduction in the belimumab 10 mg/kg group compared with an increase of 2.2% in the placebo group.

Figure 4: Median Percent Change from Baseline in Anti-dsDNA Antibody Levels by Visit among Subjects Positive at Baseline (Part A) (ITT Population)

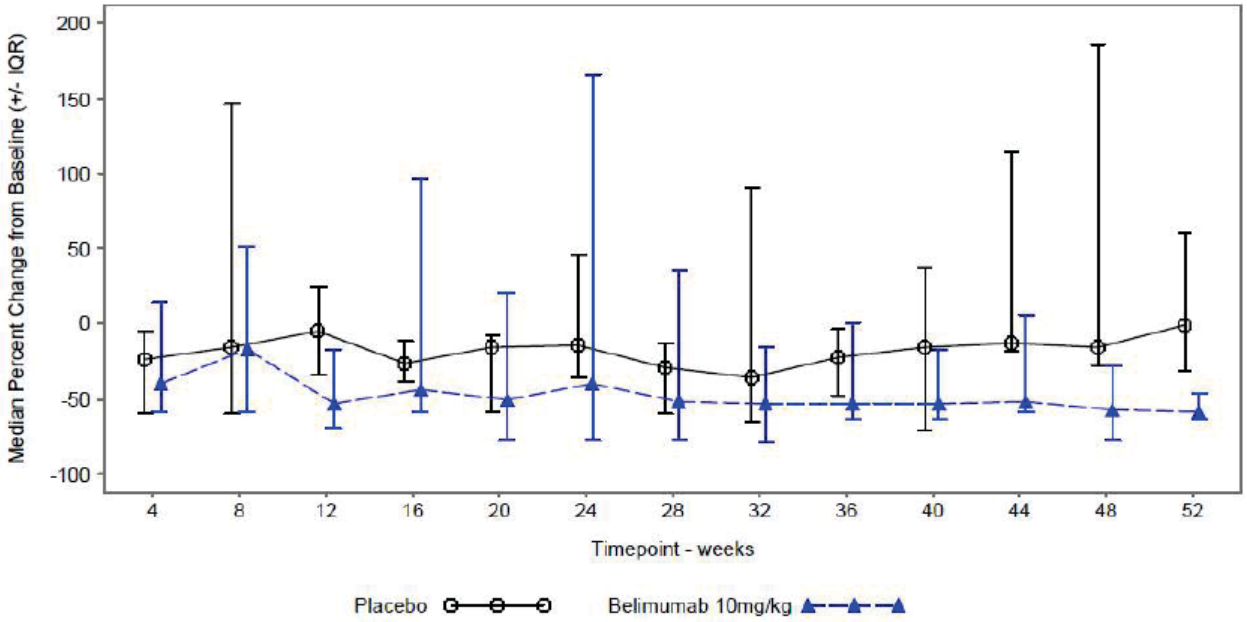


Source: CSR BEL114055 (Figure 24)

CRP

In subjects who were CRP positive (≥4 mg/L) at baseline (12/40 placebo, 10/53 belimumab 10 mg/kg), median percent change in CRP antibody levels is shown over time in Figure 5. At Week 4, the median percent reduction was 39.9% in the belimumab 10 mg/kg group compared with 24.2% in the placebo group; at Week 52, the median percent reduction was 58.8% in the belimumab group and 1.5% in the placebo group.

Figure 5: Median Percent Change from Baseline in CRP Levels by Visit among Subjects Positive at Baseline (Part A) (ITT Population)

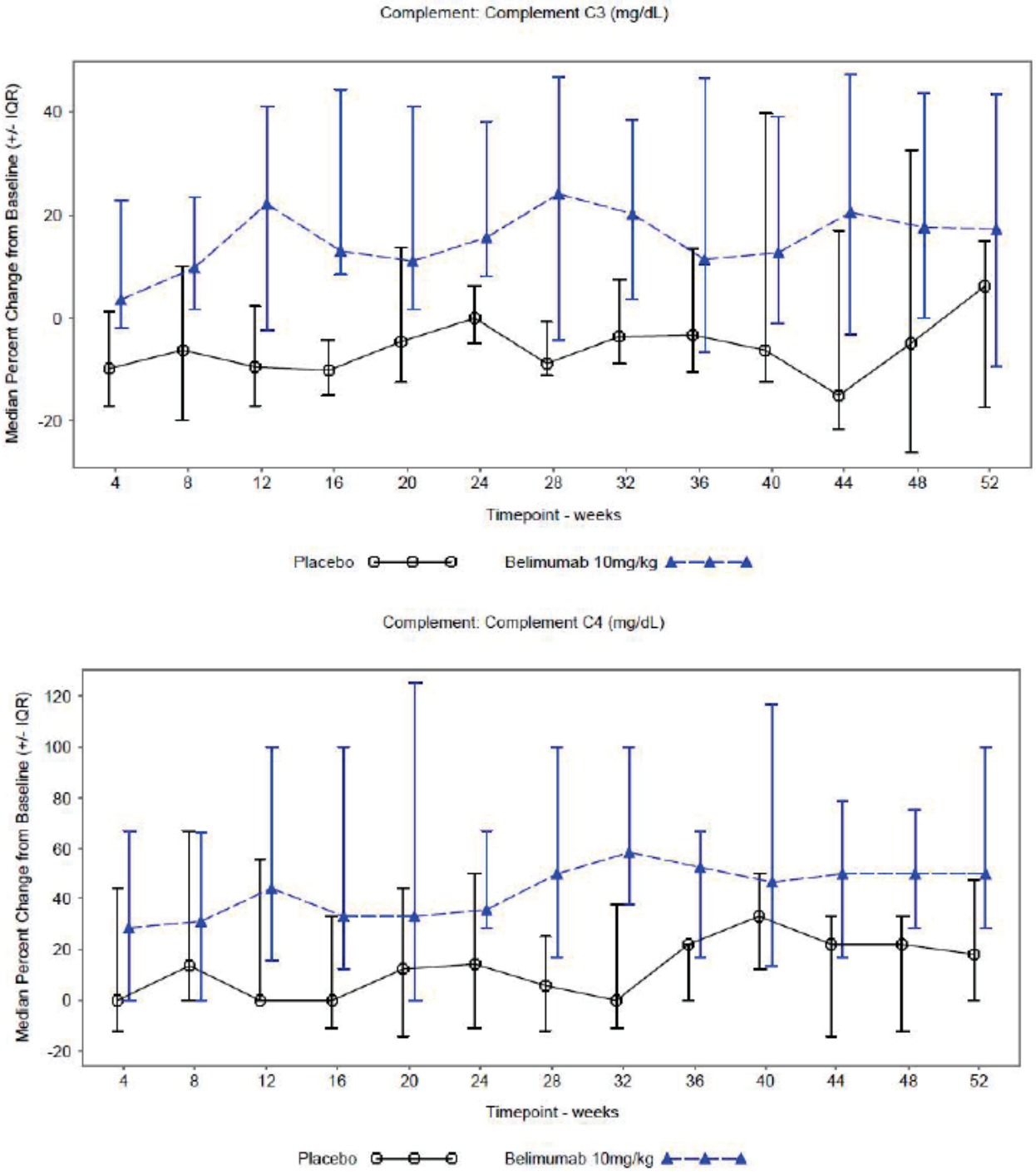


Source: CSR BEL114055 (Figure 25)

Complement (C3 and C4)

Among the subjects who had low complement (i.e., C3 <90 mg/dL and C4 <10 mg/dL) at baseline (C3: 12/40 placebo, 20/53 belimumab 10 mg/kg; C4: 15/40 placebo, 21/53 belimumab), median percent change in C3 and C4 levels from baseline is shown in Figure 6. Beginning at Week 4, there was a 3% increase in C3 and 29% increase in C4 in the belimumab group compared with a reduction of 10% in C3 and 0% in C4 in the placebo group; at Week 52, increases of 17% in C3 and 50% in C4 were observed in the belimumab group vs. increases of 6% for C3 and 18% for C4 for placebo.

Figure 6: Median Percent Change from Baseline in Complement Levels by Visit among Subjects with Low Complement at Baseline (Part A) (ITT Population)



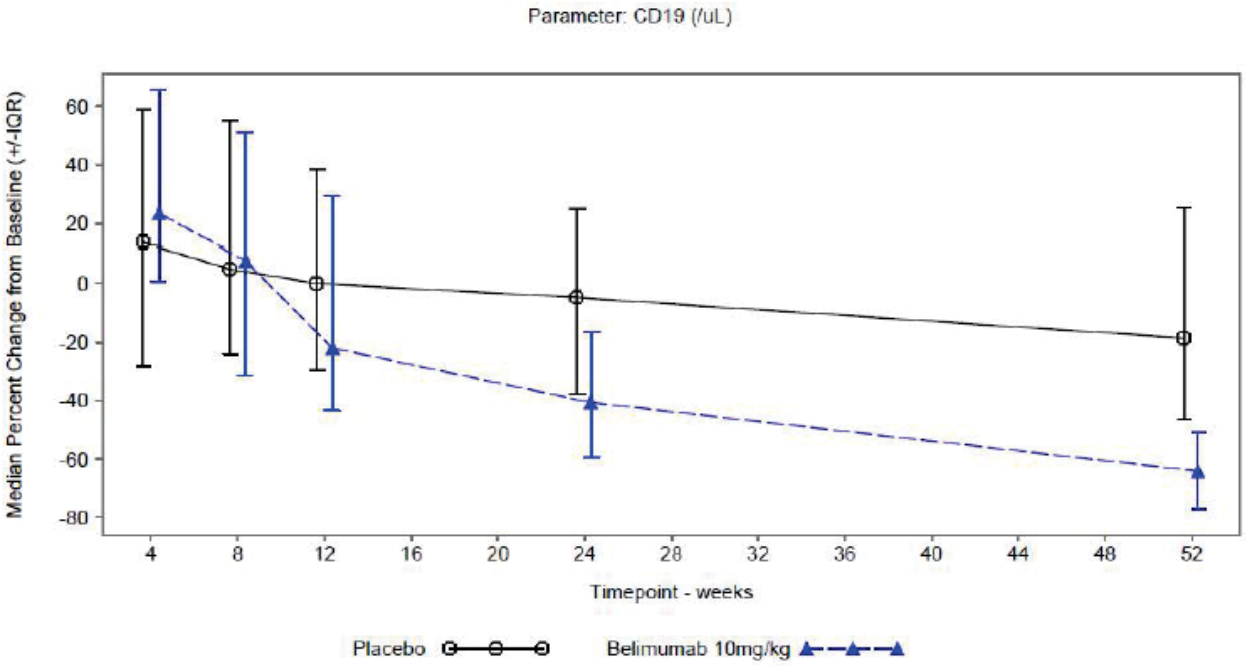
Source: CSR BEL114055 (Figure 26)

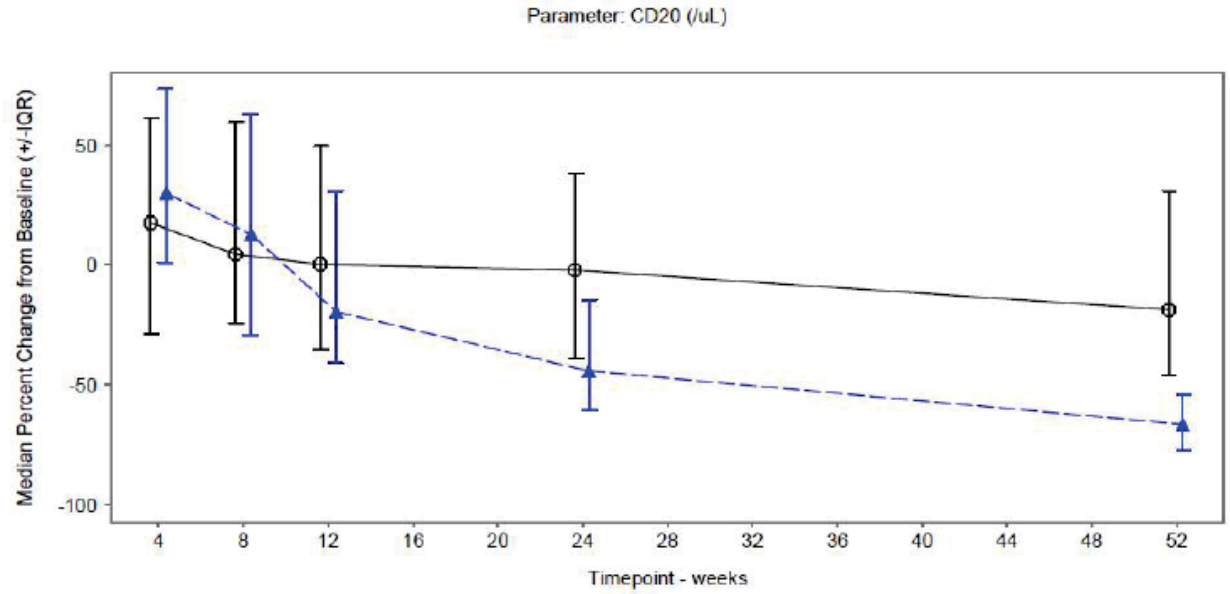
B cell subsets (CD19+, CD20+, naïve, and memory B cells)

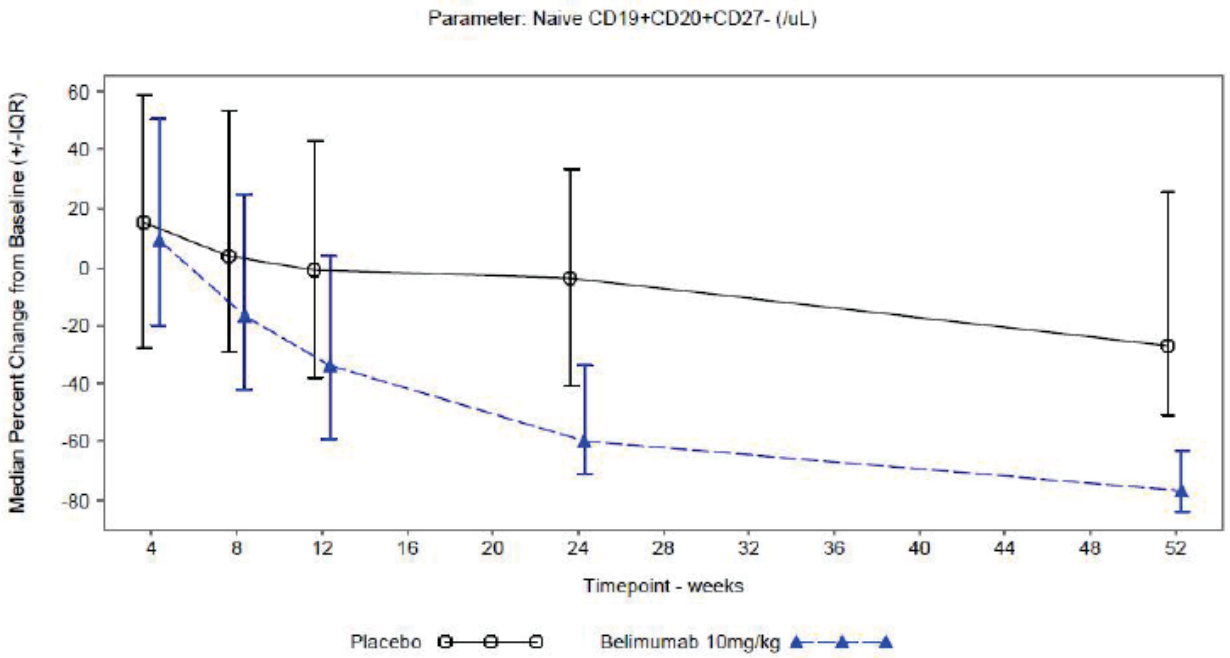
The effect of belimumab 10 mg/kg vs. placebo on CD19+, CD20+, naïve, and memory B cells is shown in Figure 7.

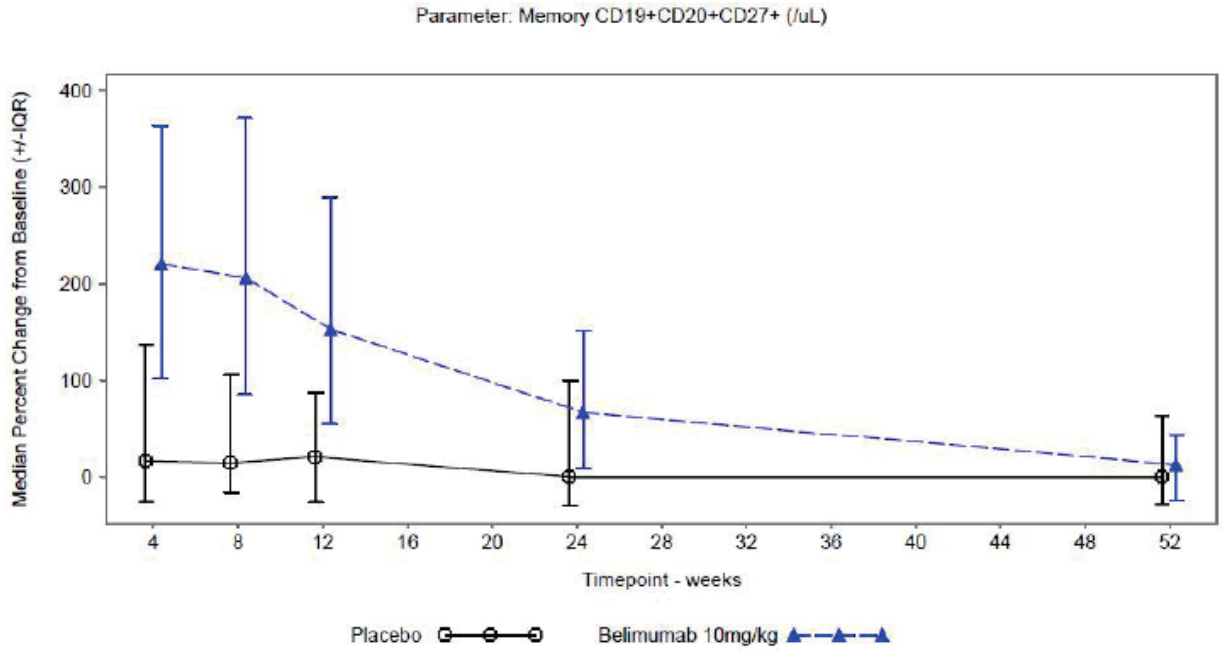
At Week 24, the median percent reduction in CD19+ B cells was 40.9% with belimumab compared with 4.7% with placebo; at Week 52 the median percent reduction with belimumab was 63.7% compared with 18.9% with placebo. Median percent reductions in CD20+ B cells were similar to what was observed for CD19+ in both belimumab and placebo groups.
The median reductions in naïve B cells in subjects treated with belimumab were 17.0% at Week 8 and 77.1% at Week 52; placebo was associated with an increase of 3.6% and a decrease of 26.7% at these time points, respectively. The median percent increase in memory B cells in subjects treated with belimumab was 220.4% at Week 4, 67.1% at Week 24 and 11.7% at Week 52, while placebo was associated with a median percent increase of 16.7% at Week 4 and 0% median percent change at Week 24 and Week 52.

Figure 7: CD19+, CD20+, naïve, and memory B cells Median Percent Change from Baseline (Part A) (ITT Population)









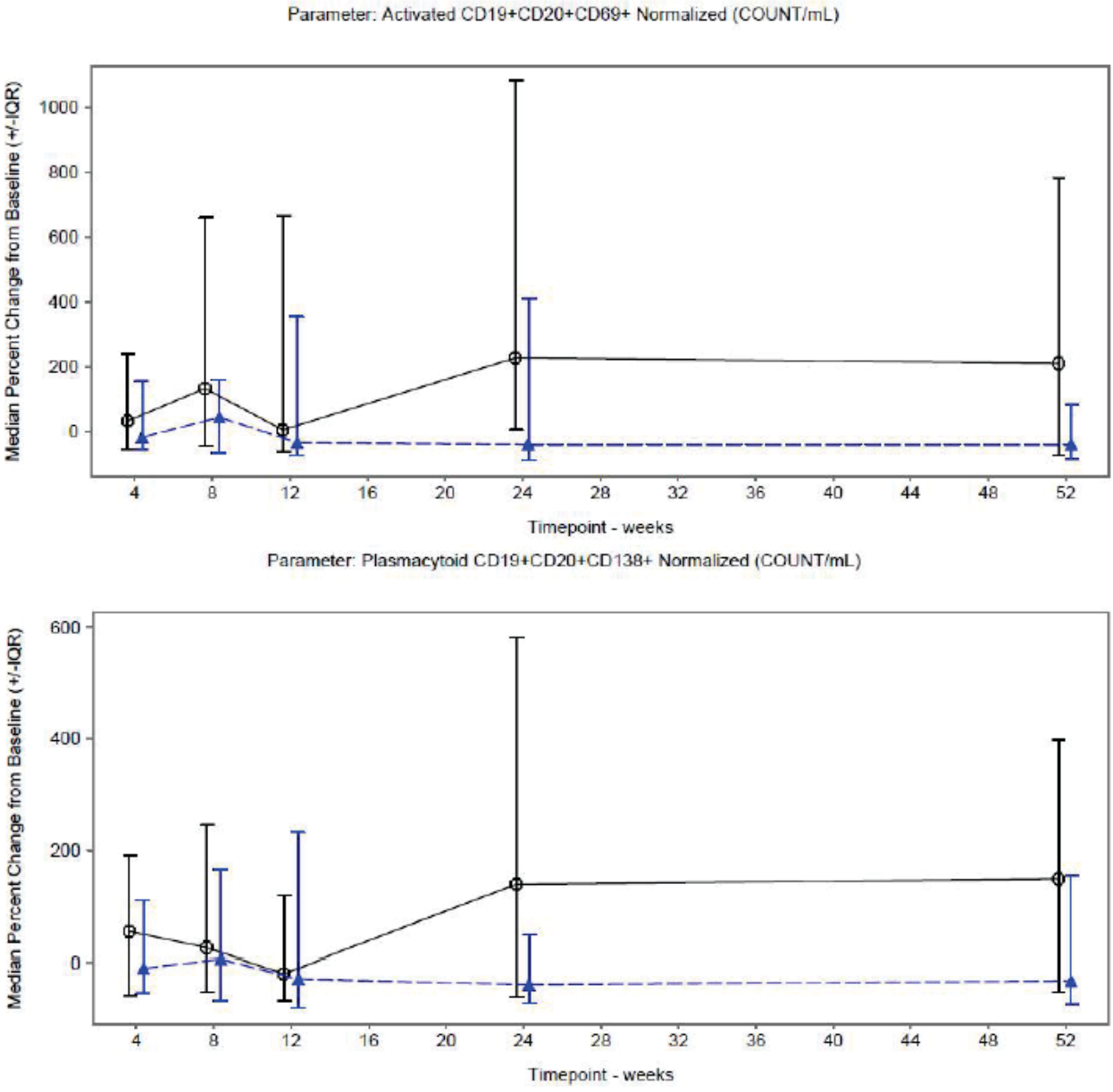
Source: CSR BEL114055 (Figure 27-28)

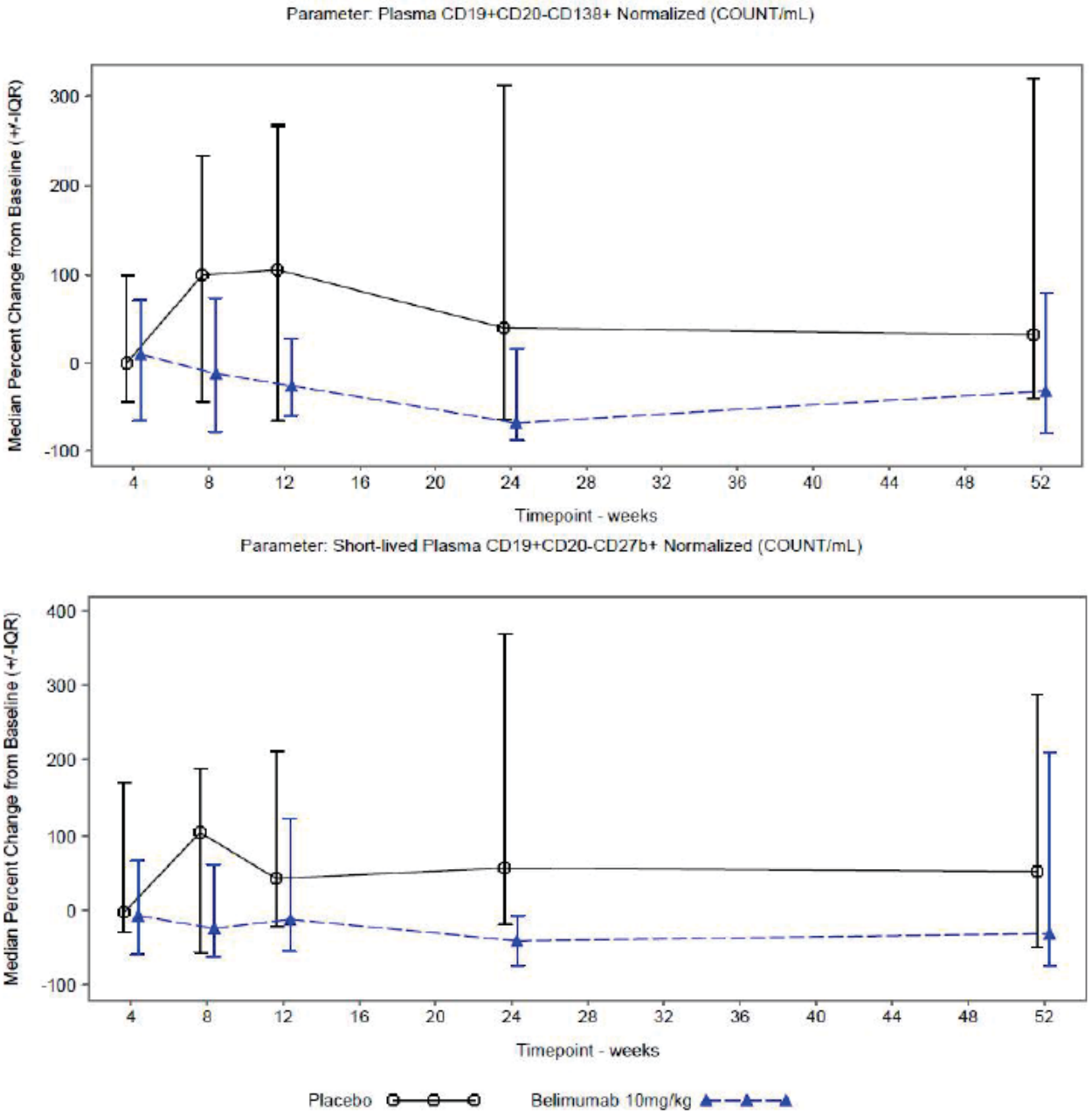
B cell subsets (activated, plasmacytoid, plasma, short-lived plasma, and SLE subset B cells)

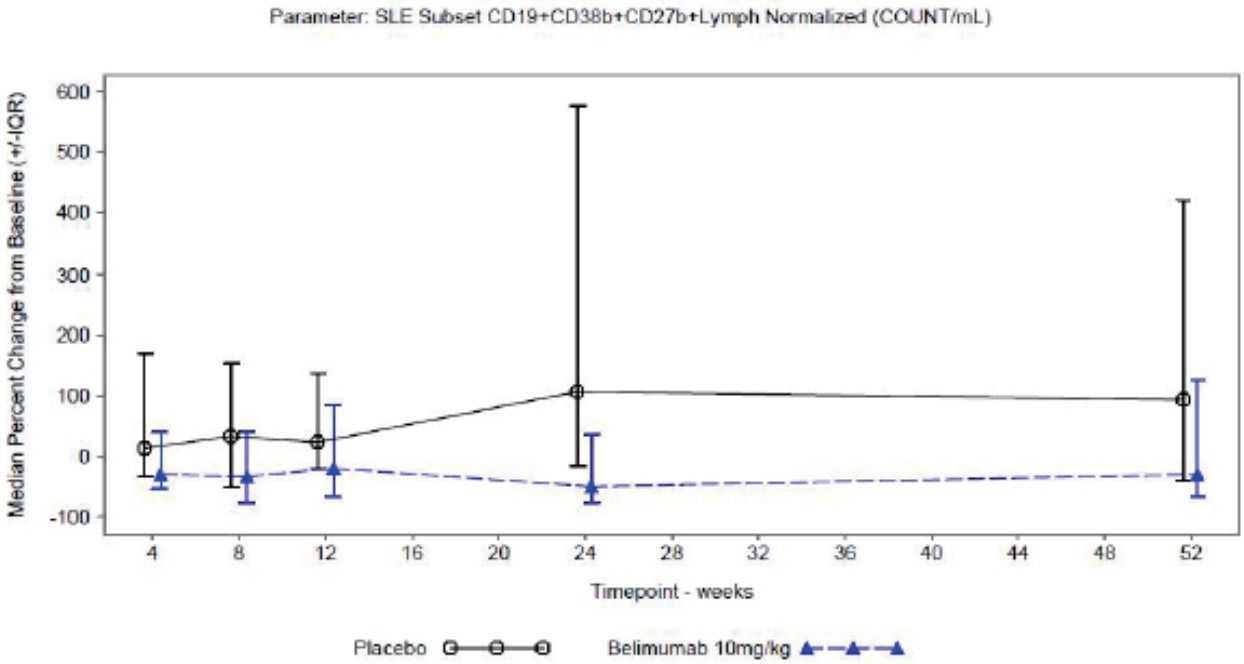
Figure 8 shows the median percent change from baseline for the activated, plasmacytoid, plasma, short-lived plasma, and SLE subset B-cells. At Week 52, for the activated B cells, a 37.9% reduction was observed with belimumab 10 mg/kg and a 209.0% increase with placebo and for plasmacytoid B cells, a 33.3% decrease with belimumab and 150.0% increase with

placebo. Median percent changes in the B cell subset population of plasma and short-lived plasma cells at Week 52 were -31.8% and -30.5%, respectively, with belimumab and 31.3% and 52.5%, respectively, with placebo. Also, a median percent reduction of 31.0% with belimumab compared with an increase of 92.8% with placebo by Week 52 was observed for the CD19+/CD38b+/CD27b+Lymph B cells (i.e., SLE subset). It should be noted that activated, plasmacytoid, plasma, short-lived plasma, and SLE subset B cells represent a smaller proportion of the B cell population and are subject to more inter-subject variability and, therefore, these results should be interpreted with caution.

Figure 8: Activated, Plasmacytoid, Plasma, Short-lived Plasma, and SLE Subset B Cell Median (Range) Percent Change from Baseline (Part A) (ITT Population)




Parameter: Plasma CD19+CD20-CD138+ Normalized (COUNT/mL)
Median Percent Change from Baseline (+/-IQR)
300
200
100
0
-100
4
8
12
16
20
24
28
32
36
40
44
48
52
Timepoint - weeks
Parameter: Short-lived Plasma CD19+CD20-CD27b+ Normalized (COUNT/mL)
Median Percent Change from Baseline (+/-IQR)
400
300
200
100
0
-100
4
8
12
16
20
24
28
32
36
40
44
48
52
Timepoint - weeks
Placebo
Belimumab 10mg/kg



Source: CSR BEL114055 (Figure 29)

What were the Immunogenicity findings?

Immunogenicity was assessed by taking anti-drug antibody (ADA) samples prior to belimumab dosing at: Day 0, Weeks 8, 24, and 52/or Exit, and at the 8-week follow-up visit for subjects who withdraw prior to completion of the 52-week treatment period and for subjects who choose not to enter the continuation protocol.

No subjects in either the belimumab 10 mg/kg or placebo group had a transient or persistent positive anti-belimumab immunogenic response during Part A (double-blind phase). Thus, the effect of immunogenicity on PK, safety and efficacy was not investigated in Study BEL114055.

Does the clinical pharmacology program provide supportive evidence of effectiveness?

See section 6.2.1.

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

Refer to the Clinical Pharmacology Questions in section 6.2.2.

Are the bioanalytical methods properly validated to measure PK and PD in plasma samples?

a. **Belimumab:**

Concentrations of Belimumab (alternative names are HGS-1006, Belimumab, LSB) in human serum were determined using a validated electrochemiluminescence (ECL) immunoassay in support of the pharmacokinetic analysis of Study BEL114055. The method ((b) (4) Method No. ECL-0130) modified an already validated method (b) (4) Method No. ECL-0083) and a partial validation was conducted. Both methods utilize the same electrochemiluminescence (ECL) technology on a Meso Scale Discovery (MSD) platform. The major modification in updating the bioanalytical method was the adjustment to the dynamic range of the method, retaining the lower limit of quantitation at 100 ng/mL but lowering the upper limit of quantitation from 48000 ng/mL to 12800 ng/mL (Table 8). This has been accompanied with adjustments of the concentrations for the calibrants and quality controls (QCs) in the method. The minimum required dilution (MRD) of calibrants, QCs and samples in human serum with assay buffer remains at 1 in 400.

Freeze-thaw stability (up to 7 cycles at – 60 to -80°C), ambient stability (up to 24 hours), refrigerated stability (2 to 8°C for up to 7 days) and long-term frozen stability (up to 3.25 years at -60 to -80°C) were previously established in validation HGS TR-06-10-002 to support both these methods.

A summary of the method modifications and cross-validation results are given in Table 8. Table 9 summarized the performance of the method (b) (4) Method No. ECL-0130) as well as the partial validation results.
Due to the truncation of assay range, an exact side by side comparison could not be performed. The QCs from original method were diluted into the range of the revised method and analyzed. Summary from both methods for same QCs as tested in two validations is given below in Table 10. The mean concentrations for the same QCs using both methods are comparable and the differences are within ±10% (calculated using value difference/value from the original method*100%).

Table 8: Summary of Method Modification(s) and Cross-validation Results

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of an ECL Method for the Quantitation of Benlysta (belimumab) in Human Serum (Addendum 1) GSK Document No. 2017N347244		
Changes in method	Truncation of range with ULOQ reduced from 48000 to 12800 ng/mL with changes to the assay anchor point calibrants. Use of one dilution factor of to 1 in 400 (MRD) in place of 1:400 and 1:8000.		
New validated assay range if any	100 to 12800 ng/mL		
Validation parameters	**Cross validation performance**		**Source location**
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.6 to 2.0%	Table 2 2017N347244
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 5.0%	
QC's performance during accuracy & precision	Cumulative accuracy (% bias) in 162 QCs:	-3.2to 3.1%	Table 3 2017N347244
	Inter-batch %CV	≤ 6.0%	
	Percent total error (TE)	≤ 9.1%	
Cross-validation	6 spiked QCs used in cross validation		Table 8 2017N347244
List other parameters	Results for QCs analysed using original method ECL-0083 and revised method ECL-0130 are given below in Table 3		

Source: Applicant's response to the information request from the agency dated 03/10/2019

Table 9: Summary of Method Performance of the ECL Method ([(b) (4)] Method No. ECL-0130) to Measure Belimumab in Human Serum for Study BEL114055

Bioanalytical method validation report name, amendments, and hyperlinks	[(b) (4)] Method No. ECL-0130: ECL Method for the Detection of Benlysta (belimumab) in Human Serum Validation of an ECL Method for the Quantitation of Benlysta (belimumab) in Human Serum [GSK Document No. 2013N172102]		
Method Description	The electrochemiluminescence immunoassay method is based on a previous validated method ECL-0083. The capture agent is biotinylated BLymphocyte Stimulator (Biotin-BLyS), which is first added to the Streptavidin coated MSD 96-well MULTI-ARRAY™ plate that is pre-blocked for non-specific binding sites. Following the incubation and wash steps, the calibrators, QCs and samples with a MRD of 1:400 are added to the plate, where belimumab is captured by its binding to the Biotin-BlyS coated on the microplate. Following additional incubation and subsequent wash steps, the captured belimumab is detected by the sequential addition of rabbit anti-belimumab antibody, followed by sulfo-tagged goat anti-rabbit antibody (secondary detection antibody). After final wash steps, the read buffer is added. The bound sulfo-tag produces electrochemiluminescence signals that are triggered when voltage is applied by MSD reader. The resulting luminescence signal is measured in ECL units (RLU) and results were analyzed. The concentration of belimumab present in QCs and human serum samples is calculated against a non-linear regression curve for belimumab reference standard.		
Material used for calibration curve and concentration	Belimumab (also known as HGS1006) Lot 71079 (120mg/vial) at a stock concentration of 80 mg/mL		
Validated Assay Range	100 to 12800 ng/mL		
Material used for QC's and concentration	Belimumab (also known as HGS1006) Lot 71079 (120mg/vial) at a stock concentration of 80 mg/mL		
Minimum required dilutions (MRDS)	1 in 400		
Source and lot of reagents (LBA)	Sourced from HGS Biotin BlyS: batch LD-100444 (BlyS lot # 01A05027) Rabbit anti-belimumab antibody: batch JKG6286(p68) Sulfo-tag Goat anti rabbit IgG: batch LD-100445		
Validation Parameters	**Method Validation Summary**		**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Page 8 2013N172102
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.2 to 2.8%	Table 2 2013N172102
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 4.1%	Table 2 2013N172102
QC's performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QC's: 100, 300, 2400, 8000 and 12800	-6.5 to 3.3%	Table 3 2013N172102
	Inter-batch %CV QC's: 100, 300, 2400, 8000 and 12800	≤ 8.0%	Table 3 2013N172102
	Total Error QC's: 100, 300, 2400, 8000 and 12800	≤ 11.1%	Table 3 2013N172102

Selectivity & matrix effect	10 lots tested (spiked at 200 ng/mL) bias ranged 5.7 to 15.9%	Table 5A 2013N172102
Interference & specificity	Interference by Azathioprine (3.75 to 30 µg/mL), Bias -9.1 to 0.9% Interference by Mercaptoprine (0.125 to 2 µg/mL), Bias -29.9 to -0.6% Belimumab spiked at 300 ng/mL Interference by Rituxan (372-381000 ng/mL) Bias -0.1 to 0.8%	Tables 6A & 6B 2013N172102 Table 9 2017N347244
Hemolysis effect	5 lots tested, bias -12.1 to -3.8%	Table 8.5 2014N218109
Lipemic effect	5 lots tested, bias -1.0 to 3.7%	Table 8.5 2014N218109
Dilution linearity & hook effect	Dilution linear up to 1 in 800	Tables 4A & 4B 2013N172102
Bench-top/process stability	Bench to stability for up to 24 hours	Report HGS TR-06-10-002
Freeze-Thaw stability	Freeze-thaw stability: 7cycles from -60 to -80 C to ambient	Report HGS TR-06-10-002
Long-term storage	Long term storage stability at -60 to -80 C for up to 3.25 years	Report HGS TR-06-10-002
Parallelism	NA	
Carry over	Not applicable	
Method performance in Study BEL114055 (sponsor report #2013N178985_00)		
Assay passing rate	47 runs with 5 failed runs (10.6% runs failed)	Tables 8.1 & 8.2 2013N178985
Standard curve performance	Cumulative bias range: -1.4 to 2.2% Cumulative precision: ≤ 4.7%	Tables 8.5 & 8.6 2013N178985
QC performance	Cumulative accuracy (% bias) in 258 QCs: -2.8 to 2.8% Inter batch (%CV): ≤ 12.7% Percent total error (TE): ≤ 15.3%	Tables 8.5 & 8.6 2013N178985
Method reproducibility	ISR was performed on 92% of study samples and 70.7% of samples met the pre-defined criteria	Tables 8.11 & 8.12 2013N178985
Study sample analysis/stability	Calibrants, QCs and samples were stored at -60 to -80° C. All samples were analyzed within the known stability period of 3.25 years	

Source: Applicant's response to the information request from the agency dated 03/10/2019

Table 10: Quality Control Performance for Original and Revised Method

	GSK Document No. 2012N134390 (Method ECL-0083, Original Method)					GSK Document No. 2017N347244 (Method ECL-130, Revised Method)				
QC (ng/mL)	Number Assayed	# Runs	Mean (ng/mL)	Accuracy Bias (%)	Precision (%CV)	Number Assayed	# Runs	Mean (ng/mL)	Accuracy Bias (%)	Precision (%CV)
300	18	6	298.7	-0.4	10.5	12	2	309.211	3.1	6.1
2200	18	6	2318.6	5.4	4.9	12	2	2225.976	1.2	6.0
6000	18	6	6079.9	1.3	7.8	12	2	6523.057	8.7	5.6
36000	18		37070.0	3.0	12.0	12	2	38555.33	7.1	12.2
44000	18	6	45620.5	3.7	4.3	12	2	43487.88	-1.2	3.4
720000	18	6	752288.5	4.5	9.1	12	2	725725.7	0.8	6.1

Source: Applicant's response to the information request from the agency dated 03/10/2019

b. Anti-belimumab antibodies

Anti-belimumab (drug) antibodies were determined in human serum using a validated electrochemiluminescent immunoassay method (GlaxoSmithKline Document Number 2012N148424_05). In brief, pre-diluted (1:2 in sample diluent) serum samples are acidified to dissociate antigen antibody complexes (acid treatment). Acidified serum samples are then neutralized by dilution 1:2 in alkaline tris(hydroxymethyl)aminomethane (TRIS) buffer (0.1 M) containing equimolar levels of biotin-belimumab Fab (capture) and SulfoTag-belimumab Fab (detector) and allowed to re-equilibrate in a 96-well polypropylene plate. Following re-equilibration, the sample (1:8 final dilution)/capture/detector mixture is transferred to a blocked and washed Meso Scale Discovery (MSD) streptavidin-coated assay plate. After incubation, the MSD assay plate is washed, then read buffer is added, and the plate is read for electrochemiluminescence (ECL) counts by a MSD Sector Imager 6000 plate reader. The ratio of the sample ECL signal to negative control (NC) ECL signal is compared to the screening cut point. Samples that give a ratio at or above the screening cut point are considered potentially positive. If a potentially positive sample is identified in the screening assay, it is further tested in the confirmation assay. The confirmatory assay is identical to the screening assay with the exception that the samples are tested in parallel with and without excess unlabeled belimumab (30 µg/mL). The excess unlabeled belimumab is added in the capture/detector solution so that samples are simultaneously exposed to the excess competing drug and labeled capture/detector. Samples that demonstrate a signal reduction at or above a pre-defined threshold (confirmatory cut point) when tested in the presence of added drug in comparison to the signal of the same sample with no added drug are considered confirmed positive.

For details on the bioanalytical methods for the detection of anti-belimumab antibodies included in this application, refer to OBP review for further information.

OCP Conclusions and Recommendations:

The Office of Clinical Pharmacology concludes that similar steady state exposure parameters between pediatric and adult SLE patients supports the efficacy and safety findings in pediatric patients with SLE in Study BEL114055.

The OCP recommends that the clinical pharmacology data submitted to sBLA 125370/S-064 addresses the PMR requirements. This sBLA is approvable from a clinical pharmacology perspective.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

As part of the approval action on March 9, 2011 for BLA 125370 Benlysta (belimumab) intravenous (IV) formulation as a treatment for adult patients with active, seropositive SLE, the Agency required a pediatric postmarketing (PMR 266-1) study of belimumab IV under the Pediatric Research Equity Act (PREA) as follows :

> *"A phase 2, multicenter study to evaluate the safety, efficacy, and pharmacokinetics of belimumab plus background standard therapy in 100 pediatric subjects ages 5 years to 17 years of age with active systemic lupus erythematosus (SLE)"*

Due to study recruitment difficulties the applicant was released from the existing PREA PMR 266-1 in November 2016 and a modified PREA PMR (2661-15) was reissued by the Agency that reflected the new total number of pediatric SLE subjects (N=70) to be evaluated in the applicant's ongoing pediatric study BEL114055/C1109 as follows:

> *"A phase 2, multicenter, study to evaluate the safety, efficacy, and pharmacokinetics of belimumab plus background standard therapy in 70 pediatric subjects ages 5 years to 17 years of age with active systemic lupus erythematosus (SLE)"*

In fulfillment of PMR 2661-15 and in support of expanding the indication for belimumab IV to include the treatment of children 5 to 17 years of age with active, seropositive SLE, the applicant submitted the results from a single pediatric study, BEL114055/C1109, along with cross-referenced efficacy, safety and pharmacokinetic (PK) data from the two pivotal, phase 3 studies, C1056 and C1057, conducted in adult SLE patients reviewed previously in support of the original marketing approval for belimumab IV. The key design features of these studies are summarized in Table 11 below. For purposes of the following statistical and clinical review, this study will be hereafter referred to as study C1109 and the adult phase 3 studies as C1056 and C1057.

Table 11. Key Design Features of Pivotal Pediatric Study BEL 114055/C1109 and Studies HGS1006-C1056 and C1057 Pertinent to Efficacy and Safety

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
Pivotal Controlled Pediatric Study to Support this Supplement								
BEL114055-C1109	01649765	A multicenter, randomized, double-blind, placebo controlled, parallel group pediatric study (Part A) with a long-term open label safety follow-up for subjects who complete Part A (Part B ongoing); and a long-term safety follow-up for subjects who withdrew 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 open label safety extension Part B. Subjects who no longer continued study drug treatment In Part A or B were followed up for long term safety in Part C.	N=93; n=13 subjects 5-11 years old; n=80 subjects 12-17 years old	Pediatric subjects ≥ 5 to 17 years old with SLE as defined by ACR criteria that is active as per SELENA SLEDAI disease activity score ≥ 6 at screening with positive auto-antibodies on stable SLE treatment regimen for ≥ 30 days prior to Day 0. Individuals with severe active lupus nephritis or CNS lupus were prohibited	Total of 29 sites in 10 countries (Argentina, Canada, Japan, Mexico, Peru, Poland, Russian Federation, Spain, United Kingdom, and United States)
Other Studies Pertinent to the Review of Efficacy or Safety (Pivotal Adult Studies reviewed in the original BLA submission)								
HGS1006-C1056		Multicenter, randomized, double-blind, placebo-controlled, 76-week comparative	Belimumab 1 mg/kg, 10 mg/kg or Placebo intravenous infusions on Days 0, 14, 28	SRI Response at Week 52 defined as the proportion of patients with: ≥ 4-point reduction from baseline in SELENA SLEDAI score	Screening and randomization visits with visits on Days 0, 14, 28 and then every 28 days until Week 52.	N=819 BEL1mg/kg= 271 subjects BEL10mg/kg = 273	Adults age ≥ 18 years with SLE as defined by ACR criteria that is clinically active as per SELENA SLEDAI disease activity	65 sites North America, 62 sites Europe and 9 sites Latin America

		parallel group trial	and every 4 weeks thereafter	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		subjects PBO= 275 subjects	score ≥ 6 at screening, with positive with positive autoantibodies on stable SLE treatment regimen for ≥ 30 days prior to Day 0. Individuals with severe active lupus nephritis or CNS lupus were prohibited	
HGS1006-C1057		Multicenter, randomized, double-blind, placebo-controlled, 76-week comparative parallel group trial	Belimumab 1 mg/kg, 10 mg/kg or Placebo intravenous infusions on Days 0, 14, 28 and every 4 weeks thereafter	SRI Response at Week 52 defined as the proportion of patients with: ≥ 4-point reduction from baseline in SELENA SLEDAI score AND no worsening (increase of < 0.30 points from baseline in PGA) AND no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline) AND subject does not drop out before Week 52 AND does not meet treatment failure criteria	Screening and randomization visits with visits on Days 0, 14, 28 and then every 28 days until Week 52.	N=865 BEL1mg/kg= 288 subjects BEL10mg/kg =290 subjects PBO= 287 subjects	Adults age ≥ 18 years with SLE as defined by ACR criteria that is clinically active as per SELENA SLEDAI disease activity score ≥ 6 at screening, with positive with positive autoantibodies on stable SLE treatment regimen for ≥ 30 days prior to Day 0. Individuals with severe active lupus nephritis or CNS lupus were prohibited	41 sites Asian Pacific, 40 sites Latin America and 11 sites Europe

7.2. Review Strategy

This sBLA submission contained one randomized trial, BEL14055/C1109, entitled "A Multicenter, Randomized, Parallel Group, Placebo-Controlled, Double-Blind Trial to Evaluate the Safety, Efficacy and Pharmacokinetics of Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Patients with Systemic Lupus Erythematosus (SLE) – Double Blind Endpoint Analysis (Part A) "which is also known publicly as the "PLUTO" study. The statistical and clinical review of efficacy in the pediatric SLE population focuses primarily on the results of the primary endpoint (the SRI endpoint at Week 52) from the completed double-blind portion of the study (Part A), as well as supportive evidence of efficacy from the three major secondary endpoints (the composite PRINTO/ACR SLE Response Evaluation Criteria, the proportion of subjects with a sustained SRI response, and the proportion of subjects with a sustained ParentGA) at the Week 52 timepoint. Unlike the adult phase 3 studies for IV belimumab (C1056 and 1057), this pediatric study was not sized based on statistical power, thus no formal statistical hypothesis testing was performed for these primary and major secondary endpoints. Instead, results for efficacy endpoints evaluated in study C1109 were summarized using descriptive statistics and calculated odds ratios with 95% confidence intervals comparing the two treatment groups, belimumab versus placebo, and noted where applicable if they were comparable to the results observed in the previously reviewed adult IV belimumab studies C1056 and C1057. The clinical review of overall safety is primarily based on the safety population from study C1109, which is defined as patients who received at least one dose of study drug and includes a review of safety data contained in the submitted clinical study report, line-listings, CRFs and case narratives. The clinical reviewer, who also reviewed the adult phase 3 IV belimumab studies, also provides comments (where applicable) regarding similarities of the product's safety profile in the adult and pediatric SLE populations.

The statistical and clinical review of efficacy and safety included the following:

- Review of the current literature for pediatric SLE
- Review of study C1109, including CSR, protocol, protocol amendments, SAP, and SAP amendments
- Review and assessment of applicant analyses of primary and major secondary endpoints
- Review of datasets submitted as SAS transport files
- Review of patient narratives for deaths ad serious adverse events
- Review of minutes and key meeting discussions and written responses regarding the design of the study protocol
- Review and assessment of the Module 2 summaries including the Summary of Clinical Efficacy, and Summary of Clinical Safety Integrated Summary of Efficacy, Integrated Summary of Safety, and proposed labeling modifications for belimumab IV
- Requests for additional information from the Applicant and review of their responses
- Formulation of the benefit-risk analysis and recommendations
- Review and evaluation of proposed labeling

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

BEL114055/C1109: A Multicenter, Randomized, Parallel Group, Placebo-Controlled, Double-Blind Trial to Evaluate the Safety, Efficacy and Pharmacokinetics of Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Patients with Systemic Lupus Erythematosus (SLE)

Trial Design

Study C1109 was an international, multicenter, efficacy, safety and pharmacokinetic (PK) study in pediatric patients with active, seropositive SLE on stable standard of care (SOC) immunosuppressive medications for their disease. The trial was comprised of the following 3 parts:

- Part A: The 52-week, randomized, double-blind, placebo-controlled treatment period (completed)
- Part B: Long-term, open-label safety follow-up for subjects who completed Part A (ongoing at the time of this review)
- Part C: Long-term safety follow-up for subjects who withdrew at any time from study treatment from Part A or B (ongoing at the time of this review)

Part A consisted of three age cohorts (Cohort 1: ages 12-17 years old; Cohort 2: ages 5-11 years old, and Cohort 3: ages 5-17 years old). Enrollment of eligible candidates into the first two cohorts was to have been staggered to permit PK analysis and dose adjustments and/or changes to study assessments based on safety prior to enrollment of younger subjects in the last cohort (Cohort 3) as follows:

- Cohort 1: The first 12 subjects between the ages 12-17 years were to have been randomized via a 5:1 ratio to belimumab 10 mg/kg plus SOC (n=12) or placebo plus SOC (n=2) for 48 weeks. Safety and PK analyses were to have been conducted after all 12 subjects had received at least 8 weeks of study treatment at which time study enrollment was to have been halted. Administration of study medication to subjects was to have been continued until the safety and PK analysis was completed. Following confirmation of the 10 mg/kg belimumab dose in this older age group, enrollment into Cohort 2 and the older age group (12-17 years) of Cohort 3 was initiated.
- Cohort 2: The first 12 subjects between the ages 5-11 years were to have been randomized via a 5:1 ratio to belimumab 10 mg/kg plus SOC or placebo plus SOC. Safety and PK analyses were to have been conducted after all 12 subjects had received at least 8 weeks of treatment. Subjects in both Cohorts 1 and 2 were to have continued to receive study medications while these analyses were being conducted during which no new subjects ages 5-11 years were to have been enrolled in the study until the 10 mg/kg dose of belimumab was confirmed for the 5-11 years old age group.

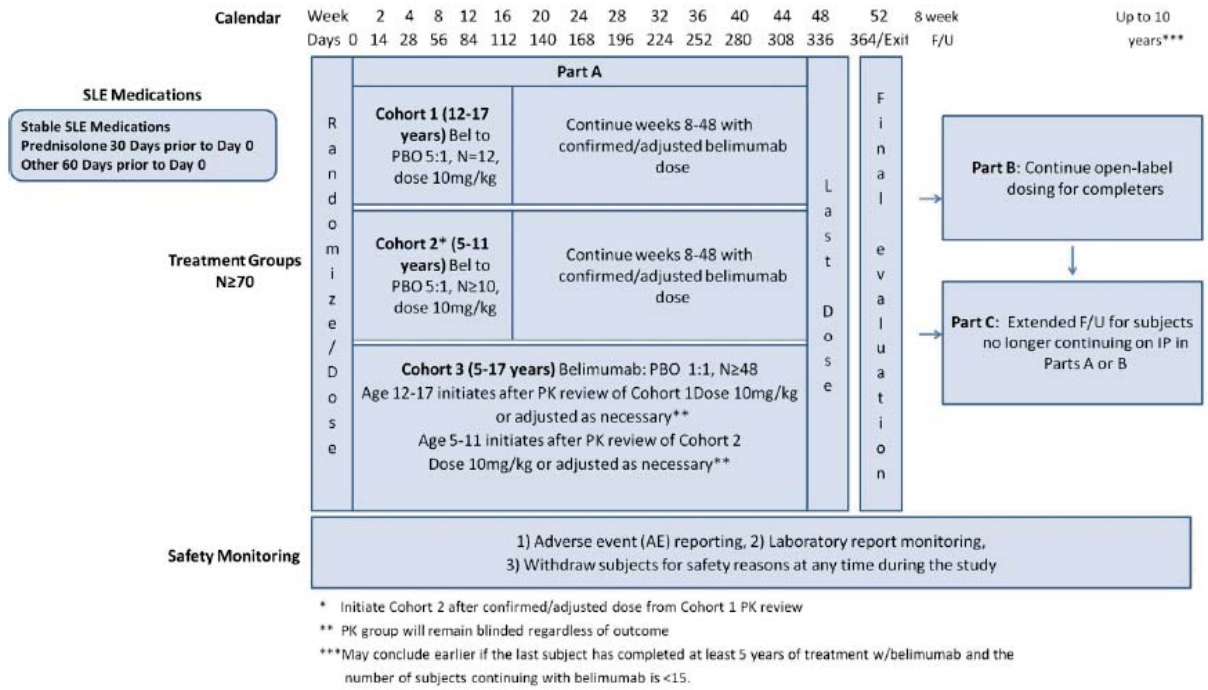
- Cohort 3: This cohort was to have contained the remaining 48 subjects (ages 5 to 17 years) who were to have been randomized in a 1:1 ratio stratified by age group (5-11 years vs 12-17 years) and screening SELENA SLEDAI scores (6-12 vs $\geq$ 13) to belimumab 10 mg/kg plus SOC or placebo plus SOC for 52 weeks. Subjects between the ages of 12 to 17 years were to have been enrolled in this cohort after the enrollment and PK analysis for Cohort 1 had been completed along with confirmation of the 10mg/kg belimumab dose for this age group. Subjects between the ages of 5 to 11 years were to have begun enrollment following the completion of Cohort 2 safety and PK analysis. Enrollment of subjects in the younger age group did not occur because the overall study enrollment target had been achieved by the time the PK analysis had confirmed the dose for the younger age group.

The protocol mandated that any subject who withdrew from Part A of the study was required to return for an exit visit 4 weeks after their last dose of study medication after which they were to have been followed-up for long-term safety (Part C).

Part B is a 10-year open-label continuation phase for subjects who have completed the 48 weeks of treatment and the Week 52 assessment of Part A and is ongoing at the time of this review. Patients who opted to participate in this phase of this study were to have continued to receive belimumab (10 mg/kg confirmed dose) at monthly infusion visits. Subjects who withdrew from Part B were required to return for a safety follow-up visit 8 weeks post last study infusion after which they were to have been followed-up for safety (Part C).

Part C of the study is an ongoing long-term safety follow-up phase for patients who dropped out or withdrew from any portion of the trial. Prior to entering Part C, subjects were required to return for a follow-up visit 8 weeks post last study infusion and then annually for safety evaluations and limited disease activity assessments for 10 years following the first administration of belimumab.

Figure 9. Study Schematic for C1109



Applicant's Fig. 1; p. 24 CSR.

Eligibility

Table 12 summarizes the major inclusion and exclusion criteria for study C1109. These were similar to those used in the adult belimumab IV studies C1056 and C1057.

Table 12. Tabular Summary of Major Inclusion and Exclusion Criteria for Study C1099

Major Inclusion Criteria:

1. Between 5 to 17 years of age
2. Have or have had serially 4 out of 11 American College of Rheumatology (ACR) classification criteria for SLE
3. Active SLE disease defined as a SELENA SLEDAI score ≥ 8 at screening
4. Unequivocally positive anti-nuclear antibody (ANA) test results from 2 independent time points as follows:
    i. Positive test results from 2 independent time points within the study screening period. (A positive ANA test is defined as an ANA titer ≥ 1:80 and/or a positive anti-dsDNA (≥ 30 IU/mL) serum antibody) or
    ii. One positive historical test result and 1 positive test result during the screening period
5. On a stable SLE treatment regimen consisting of any of the following medications (alone or in combination) for a period of at least 30 days prior to Day 0 (i.e., day of first dose of study agent):
    i. Corticosteroids (prednisone or prednisone equivalent, up to 0.5 mg/kg/day):
    ii. Other immunosuppressive or immunomodulatory agents: methotrexate, azathioprine, leflunomide, mycophenolate mofetil, calcineurin inhibitors (e.g., tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine or thalidomide.
    iii. Antimalarials (eg, hydroxychloroquine, chloroquine, quinacrine)
    iv. Non-steroidal anti-inflammatory drugs (NSAIDs)
    NOTE :
    v. Pre-existing SLE medications must be stable for at least 30 days prior to Day 0
    vi. Corticosteroids may be added as new medication, or their doses adjusted only up to 30 days prior to Day 0
    vii. New SLE therapy other than corticosteroids must not be added within 60 days of Day 0
6. Female candidates who are sexually active may participate in the trial if they are not pregnant, nursing or if they are of non-childbearing potential. [Note: For purposes of this study non-childbearing potential is defined as a pre-menarcheal female who has not yet entered puberty as evidence by lack of breast development (palpable glandular breast tissue); or who has undergone a hysterectomy, S/P bilateral oophorectomy or tubal ligation.] Females of childbearing potential must have a negative serum pregnancy test at screening and agree to practice complete abstinence from intercourse or correctly use one of the acceptable methods of birth control listed in the study starting 2 weeks prior to administration of the first dose of study agent until 16 weeks after the last dose of study agent.

Major Exclusion Criteria:

1. Treatment with any B-cell targeted therapy (rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein, TACI-Fc [atacicept], or belimumab) at any time
2. Treatment within 364 days of Day 0 with abatacept or any biological investigational agent other than B-cell targeted therapy
3. Administered 3 or more courses of systemic corticosteroids for concomitant conditions such as asthma or atopic dermatitis within 364 days of Day 0 (topical and inhaled steroids are permitted)
4. Administered intravenous (IV) cyclophosphamide within 90 days of Day 0.
5. Treated with anti-TNF therapy, interleukin-1 receptor antagonist, intravenous immunoglobulin, high dose prednisone (>1.5 mg/kg/d), or plasmapheresis within 90 days of Day 0
6. Treated with a non-biological investigational agent, or any new immunosuppressive/immunomodulatory agent, anti-malarial, NSAID, HMG CoA reductase inhibitor or

angiotensin pathway antihypertensive within 60 Days of Day 0. (Note: New inhaled steroids or topical immunosuppressive agents are permitted. Any NSAID use for <1week is allowed.)
7. Administered a live vaccine or had a change in dose of a corticosteroid, other immunosuppressive/immunomodulatory agent, anti-malarial, or NSAID within 30 days of Day 0.
8. Subjects should be up-to-date with regards to vaccinations as defined by their country-specific guidelines. If subjects are due for administration of live vaccines during the course of the study, the subject may receive them at least 30 days prior to entering the study.
9. Have required hemodialysis within 90 days of Day 0 or are currently on renal replacement therapy
10. Have an estimated glomerular filtration rate of < 30 ml/min as calculated by Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) formulae
11. Have severe lupus nephritis defined as a significant worsening of renal disease manifested by the presence of urinary sediments and other lab abnormalities that may lead to the subject requiring IV cyclophosphamide or high dose IV corticosteroids during the first 6 months of the trial. (Note: Lupus nephritis which can be controlled or managed in the short term with medications allowed in the study will not exclude subjects from participating in the trial nor will any maximum level of proteinuria exclude subjects.)
12. H/O active central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident (CVA), cerebritis or CNS vasculitis) requiring therapeutic intervention within 60 days of Day 0.
13. H/O major organ transplant or hematopoietic stem cell/marrow transplant
14. H/O significant or unstable or uncontrolled acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, hematological, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases) which in the opinion of the principal investigator (PI) could confound the study's results or put the patient at undue risk.
15. H/O any medical disease, lab abnormality, or condition or planning a surgical procedure during the course of the trial that in the opinion of the PI makes the patient unsuitable for the trial
16. H/O malignant neoplasm within the last 5 years
17. H/O acute or chronic infections that required hospitalization for treatment or parental antibiotic or antimicrobial agents within 60 days of Day 0 or the concurrent use of suppressive anti-infective therapy (i.e., antibacterials, antivirals, antifungals, or antiparasitic agents)
18. H/O recent alcohol or drug abuse within 364 days prior to Day 0
19. H/O a positive test for HIV, hepatitis B surface antigen, or hepatitis C antibody. (Note: Patients negative for HbsAg and anti-HBc antibody but positive for anti-HBs antibody are eligible to participate. Patients negative for HBsAg and anti-HBs antibody but positive for anti-HBc antibody will require clarification of their status by testing for HB DNA which if positive will exclude the patient from participation. Patients with documented vaccination against Hepatitis B [primary and secondary immunization and booster] will be considered negative.)
20. H/O IgA deficiency (IgA level <10 mg/dL) or H/O primary immunodeficiency
21. Have a Grade 3 or greater lab abnormality based on the protocol toxicity scale except for the following which are allowed: stable Grade 3 prothrombin time (PT) due to warfarin therapy, stable Grade 3 partial thromboplastin time (PTT) due to lupus anticoagulant and not related to liver disease or anti-coagulant therapy, stable Grade 3 hypoalbuminemia due to lupus nephritis and not related to liver disease or malnutrition, any grade proteinuria, stable grade 3 GGT elevation due to lupus nephritis and not related to alcoholic liver disease, uncontrolled diabetes or viral hepatitis (any abnormalities in AST or ALT must be $\leq$ Grade 2), stable Grade 3 neutropenia, or stable Grade 3 WBC
22. H/O anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.
23. Subjects $\geq$ 12 years of age who have evidence of serious suicide risk including any H/O suicidal behavior in the last 6 months and/or any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) in the last 2 months or who pose a significant suicide risk in the opinion of the investigator.

Treatment
Study infusions were to have been administered over 1 hour on Days 0, 14, 28 and then every 28 days through Week 48 of Part A. All subjects were to have remained under observation for 3 hours after completion of the first 3 infusions during Part A as per current guidelines for the administration of IV infusions.

Study drug was to have been diluted and administered over a minimum of 1 hour in 250 mL of normal saline for subjects weighing >40 kgs and in 100 mL of normal saline for subjects weighing ≤ 40 kgs (the concentration of belimumab in the infusion bag was not exceed 4 mg/mL). Matching placebo infusions of 250 mL or 100 mL normal saline were to have been also administered over a minimum of 1 hour.

Removal of Patients from Treatment or Assessment
Subjects were to have discontinued from this trial if they withdrew consent, received a prohibited concurrent medication or therapy in Part A or Part B, experienced unacceptable toxicity, were deemed a treatment failure in Part A, had an IgG level <250 mg/l (Grade 4) associated with a severe or serious infection, missed 3 or more consecutive infusions, participated in another interventional trial or became pregnant.

Concomitant Medications
The protocol required patients to be on a stable SLE treatment regimen for at least 30 days prior to Day 0 which may have consisted of any of the following medications alone or in combination: steroids (≤ 40 mg/day of prednisone or equivalent), antimalarials, NSAIDs, MTX, azathioprine, leflunomide, mycophenolate mofetil, calcineurin inhibitors, oral cyclophosphamide, 6-mercaptopurine, mizoribine or thalidomide. Changes in background immunosuppressive agents were permitted due to toxicity or shortages as were adjustments in concurrent medications as clinically needed post-administration of the first study infusion during prespecified time periods over the course of the study. However, any changes in the following medications during restricted periods were to have resulted in the subject being considered a treatment failure and withdrawn from the study:

- Antimalarials: Initiation of treatment or changes in dose were permitted between Day 0 and Day 122 visits. After the Day 112 visit, any initiation of new therapy or increase in dose was to be considered a treatment failure
- Steroids: changes in the total dose of systemic steroids were permitted during the first 6 months of the trial (Day 168 visit) but the total systemic dose had to return to within 25% or 5 mg over baseline (Day 0) dose (whichever was higher) by the Day 168 visit, or the subject was to be considered a treatment failure. (Note: The protocol referred study investigators to the 2004 ACR Ad Hoc Working Group on Steroid Sparing Criteria in Lupus for additional guidance regarding this issue.) Intra-articular (IA) steroid injections were permitted between baseline (Day 0) and the Day 308 visit. Patients who receive IA steroids during the 8 weeks prior to the Week 52 visit were to have been considered treatment failures.

- Other Immunosuppressive/Immunomodulatory Agents: doses were permitted to have been increased up to the Day 112 visit. Initiation of any new immunosuppressive/immunomodulatory agent after Day 0 or increase in dose over baseline or Day 112 (whichever was higher) was to be considered a treatment failure
- NSAIDs and Aspirin: Initiation of new treatment used for ≥ 7 days starting after the Day 308 visit was to have been considered a treatment failure

Subjects who initiated therapy with any of the following banned medications or therapies were to have been also considered treatment failures and withdrawn from the study: other investigational agents, anti-TNF therapy, anti-IL6 therapy, other biologics (e.g., rituximab, abatacept, interleukin-1 receptor antagonist), IV immunoglobulin (IVIG), IV cyclophosphamide, plasmapheresis or live vaccines.

Efficacy and Safety Assessments
The following Figure 10, Figure 11, Figure 12, Figure 13 and Figure 14 are tabular flow charts of the scheduled study observations and procedures for Part A:

Figure 10. Schedule of Procedures and Evaluations for Controlled Portion of Study 1109 (Part A)

Procedures	Part A Double-Blind Treatment Period Days 0-364 (Weeks 0-52)																Post Treatment Follow-up		Unscheduled Visit [3]
Study Day	**Screening Period -35 days**	Day 0	Day 14 ± 3 days	Day 28 ± 3 days	Day 56 ± 7 days	Day 84 ± 7 days	Day 112 ± 7 days	Day 140 ± 7 days	Day 168 ± 7 days	Day 196 ± 7 days	Day 224 ± 7 days	Day 252 ± 7 days	Day 280 ± 7 days	Day 308 ± 7 days	Day 336 ± 7 days	Day 364 or Exit (4 wks post dose)[1] ± 7 days	8-Week Follow-up ± 7 days [2]	16 Week Follow-Up ± 7 days[19]	
Study Week		Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52			
Written Informed Consent + Assent	x																		
Subject Demography	x																		
Medical History	x																		
Inclusion/Exclusion Criteria	x																		
Efficacy Assessments																			
Disease Activity Scales																			
SELENA SLEDAI[15]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
SLE Flare Index	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
PRINTO/ACR	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
BILAG[15]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Physician GA	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Parent GA	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		

Source: Applicant's Study Protocol V6; p. 49.

Figure 11. schedule of Procedures and Evaluations for Controlled Portion of Study C1109 (Part A) (cont.)

Procedures	Part A Double-Blind Treatment Period Days 0-364 (Weeks 0-52)																Post Treatment Follow-up		Unscheduled Visit [3]
Study Day	**Screening Period -35 days**	Day 0	Day 14 ± 3 days	Day 28 ± 3 days	Day 56 ± 7 days	Day 84 ± 7 days	Day 112 ± 7 days	Day 140 ± 7 days	Day 168 ± 7 days	Day 196 ± 7 days	Day 224 ± 7 days	Day 252 ± 7 days	Day 280 ± 7 days	Day 308 ± 7 days	Day 336 ± 7 days	Day 364 or Exit (4 wks post dose)[1] ± 7 days	8-Week Follow-up ± 7 days [2]	16 Week Follow-Up ± 7 days[19]	
Pediatric SLICC/ ACR Damage Index		x														x	x		
Quality of Life[18]																			
PedsQL[18]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
PedsQL-Fatigue[18]	x	x		x	x	x		x	x			x				x	x		
Safety Assessments																			
Concomitant Medication	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x		x
Symptom Driven Physical Exam	x	x		x	x	x	x	x	x	X	x	x	x	x	x	x	x		x
Vital Signs [4,5]	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x		x
Weight +Height [5,6]	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x		
12-Lead ECG	x																		
C-SSRS – (≥12 years of age) Baseline/Screeni	x																		

Source: Applicant's Study Protocol V6; p. 50.

Figure 12. Schedule of Procedures and Evaluations for the Controlled Portion of Study C1109 (Part A) (cont.)

Procedures	Part A Double-Blind Treatment Period Days 0-364 (Weeks 0-52)																Post Treatment Follow-up		Unscheduled Visit [3]
Study Day	**Screening Period -35 days**	Day 0	Day 14 ± 3 days	Day 28 ± 3 days	Day 56 ± 7 days	Day 84 ± 7 days	Day 112 ± 7 days	Day 140 ± 7 days	Day 168 ± 7 days	Day 196 ± 7 days	Day 224 ± 7 days	Day 252 ± 7 days	Day 280 ± 7 days	Day 308 ± 7 days	Day 336 ± 7 days	Day 364 or Exit (4 wks post dose)[1] ± 7 days	8-Week Follow-up ± 7 days [2]	16 Week Follow-Up ± 7 days[19]	
ng																			
C-SSRS – Since Last Visit		x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x		
Adverse Events		x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x		x
Serious Adverse Events	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x		x
Laboratory Assessments																			
Hematology [7]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Chemistry (Modified 20 non-fasting) [7]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Urinalysis	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Spot Urine(protein to creatinine ratio)[8]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
PGx Sampling [12]		x																	

Source: Applicant's Study Protocol V6; p. 51.

Figure 13. Schedule of Procedures and Evaluations for the Controlled Portion of Study C1109 (Part A) (cont.)

Procedures	Part A Double-Blind Treatment Period Days 0-364 (Weeks 0-52)																Post Treatment Follow-up		Unscheduled Visit [3]
Study Day	Screening Period -35 days	Day 0	Day 14 ± 3 days	Day 28 ± 3 days	Day 56 ± 7 days	Day 84 ± 7 days	Day 112 ± 7 days	Day 140 ± 7 days	Day 168 ± 7 days	Day 196 ± 7 days	Day 224 ± 7 days	Day 252 ± 7 days	Day 280 ± 7 days	Day 308 ± 7 days	Day 336 ± 7 days	Day 364 or Exit (4 wks post dose)[1] ± 7 days	8-Week Follow-up ± 7 days [2]	16 Week Follow-Up ± 7 days[19]	
Pregnancy Test [5,9,19]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PK Sampling [10,11]		x	x	x	x				x							x	x		x
Immunogenicity		x			x				x							x	x		x
BLys Protein		x																	
C3/C4; CRP	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
B-Cells		x		x	x	x			x							x	x		
anti-dsDNA	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Auto-antibodies [13]	x	x																	
aCL[13]		x																	
IgA, IgG and IgM[14]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Functional Antibodies [18]		x							x							x			

Source: Applicant's Study Protocol V6; p. 52.

Figure 14. Schedule of Procedures and Evaluations for the Controlled Portion of Study C1109 (Part A) (conti.)

Procedures	Part A Double-Blind Treatment Period Days 0-364 (Weeks 0-52)																Post Treatment Follow-up		Unscheduled Visit [3]
Study Day	**Screening Period -35 days**	Day 0	Day 14 ± 3 days	Day 28 ± 3 days	Day 56 ± 7 days	Day 84 ± 7 days	Day 112 ± 7 days	Day 140 ± 7 days	Day 168 ± 7 days	Day 196 ± 7 days	Day 224 ± 7 days	Day 252 ± 7 days	Day 280 ± 7 days	Day 308 ± 7 days	Day 336 ± 7 days	Day 364 or Exit (4 wks post dose)[1] ± 7 days	8-Week Follow-up ± 7 days [2]	16 Week Follow-Up ± 7 days[19]	
Vaccine Antibody Titer [18]																			
PT/PTT	x																		
Study Treatment																			
Administer Study Treatment [17]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	only if going into Part B			
Randomization		x																	
IVRS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x

Time and Events Table – (Continued)

1. The Exit (Day 364) visit will occur approximately 4 weeks after the last dose of study agent. For subjects completing all 48 weeks of treatment and continuing into the safety follow-up with belimumab portion of the protocol (Part B) or safety follow up (Part C), this visit will also serve as their 1st (i.e., Day 0) visit of the open label safety follow up of the study. Only subjects who will continue in Part B will have study drug administered at the Day 364/Week 52 visit after the completion of all Day 364/Week 52 assessments.
2. Subjects stopping treatment in Part A or Part B will return in 4 weeks from last dose for an Exit visit. For subjects withdrawn from Part A or Part B of the study and who are not continuing into Part C, a follow-up visit will occur approximately 8 weeks after last dose of study agent (belimumab in the case of the open label period).
3. Other assessments may be performed as clinically indicated.
4. Vital signs include temperature, sitting blood pressure, and pulse.
5. Complete prior to dosing.
6. The subject's weight at the current visit should be used for calculating the dose to be administered.
7. Refer to Appendix 5 Clinical Laboratory Tests for a listing of laboratory assessments to be completed.
8. A 24-hour urine may be done if clinically indicated (e.g., renal flare).
9. Serum pregnancy test required at screening for all females of childbearing potential. Results of urine pregnancy test at subsequent visits, if required, must be available prior to dose. See Section 6.1 (Screening Procedures) for definition of those exempted from subsequent pregnancy testing.
10. Cohort 1 and Cohort 2: Days 0, 14/Wk2, 28/Wk4, 56/Wk8 - Before the start of infusion, 5 minutes and 2 hours after the end of infusion; Days 2, 7, 16, 21 - Anytime during visit; Day 168/wk24 - 0-4 hours after the end of infusion; Day 364/Wk52 and 8 week follow-up visit - Any time during visit before start of infusion (if applicable). Cohort 3 PK sample schedule: Day 0, 14, 28 – Before the start of infusion and 0-4 hrs after the end of infusion; Day 56 – Before the start of infusion; Day 168/wk24 – 0-4 hrs after the end of infusion; Day 364/wk52 and 8 week follow-up visit – any time during visit before start of infusion (if applicable). [see Table 3 and Table 4 in Section 6.5]
11. Cohort 1 (12-17yrs) subjects (N=12) and Cohort 2 (5-11 yrs) (at least 10 subjects) will be subject to more frequent sampling for PK and intense observation during the study are also detailed in Section 6.5, Table 3 of the protocol.
12. PGx informed consent must be obtained prior to any saliva being taken for PGx research. Refer to Section 9 and Appendix 1 Pharmacogenetic Research. Samples should be drawn prior to dosing but may be taken at anytime during the course of the study.
13. Autoantibodies include: ANA, aCL (IgM, IgG, IgA isotypes), anti-ribosomal P and anti-Sm. Autoantibodies will be measured in all subjects at Day 0 and samples will be collected at the time points specified; however, the assay will be run only on subjects with elevated titers of these autoantibodies at Day 0.
14. Serum immunoglobulin isotypes: IgG, IgM, IgA.
15. Refer to Section 6.2.1.3 for guidelines for scoring proteinuria for SELENA SLEDAI evaluation.
16. Subjects ≥ 8 years of age will complete the PedsQL and PedsQL Fatigue directly. For subjects aged 5-7 years, a parent/guardian will complete the Parent Report version of the PedsQL and PedsQL Fatigue on their child's behalf. Must be completed prior to any study-related discussion with the investigator or study coordinator.
17. Study agent is to be administered to all randomized subjects for 48 weeks in Part A. Subjects completing the double-blind period (Part A) will continue in the open-label, long term continuation portion of the protocol for up to 10 years. The Day 364/Week 52 visit of Part A will serve as the 1st visit of Part B. Only subjects who will continue in Part B will have study drug administered at the Day 364/Week 52 visit after the completion of all Day 364/Week 52 assessments.
18. Blood sample for functional antibodies on all subjects. Vaccine antibody titer test will be completed on subjects who receive a vaccine during the treatment period of this study. A blood sample to measure the pre-vaccination titer will be obtained during a study visit closest to the time prior to the planned vaccination In cases where blood may not be drawn immediately before vaccination, the baseline (Day 0) blood sample will be used as a reference for pre-vaccination titer. A post-vaccine titer will be drawn on the next study visit if it has been at least 21 to 60 days post-immunization.
19. A home pregnancy test will be provided to all female subjects of child bearing potential. These subjects will be contacted by phone approximately 16 weeks after the last dose of belimumab to obtain the results of the test. AEs/SAEs will not be actively solicited, but SAE(s) reported by the subject during this call will be reported to the Drug Safety designee on the SAE worksheet.
20. For subjects enrolled in Japan only, additional PK samples (before the start of infusion and 0-4 hours after the end of infusion) will be taken at the week 12 (3 month) and at the first 6 month visit only in Part B

Source: Applicant's Study Protocol V6; p. 53.

Study Endpoints

Primary efficacy endpoint:
The primary efficacy variable was the SLE Responder Index (SRI) response rate at Week 52 which was 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 the Physician's Global Assessment (PGA) AND
- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Week 52)

To be considered an SRI responder, a patient also could not be considered a treatment failure (based on prespecified criteria) or dropped-out before the Week 52 visit.

Major secondary efficacy variables:

- Proportion of subjects meeting PRINTO/ACR Juvenile SLE Response Evaluation criteria for improvement in juvenile SLE using two different PRINTO/ACR Juvenile SLE Response Evaluation definitions of improvement as follows:
    - At least 50% improvement in any 2 or 5 endpoints below and no more than 30% worsening in more than 1 of the 5 endpoints
    - At least 30% improvement in 3 of 5 endpoints below and no more than 30% worsening in more than 1 of the 5 endpoints
        - Percent change in Parent's Global Assessment (ParentGA) at Week 52
        - Percent change in Physician's Global Assessment (PGA) at Week 52
        - Percent change in SELENA SLEDAI score at Week 52
        - Change in SF-10 for Children Health Survey physical component summary score (PHS) at Week 52
        - Percent change in 24-hour proteinuria at Week 52 (g/24-hour equivalent by spot urine protein to creatinine ratio)
- Proportion of subjects with sustained SRI response (defined as having a response on the primary efficacy endpoint at Weeks 44, 48 and 52)
- Proportion of subjects with a sustained ParentGA response (defined as having a >0.3 improvement in Parent GA at Weeks 44, 48 and 52)

Ancillary secondary endpoints:

- Percentage of subjects with a ≥ 4-point reduction over baseline in SELENA SLEDAI at Week 52 and by visit
- Percentage of subjects with no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at Week 52 and by visit
- Percentage of subjects without PGA worsening (increase of <0.30 points from baseline) at Week 52 and by visit
- Disposition of response including reason for no response
- Sensitivity analyses at Week 52: unadjusted, LOCF and completer
- SRI-S2K at Week 52

- SRI by visit
- SRI6 at Week 52 and by visit

Disease activity:

- Duration of longest response among subjects with at least 1 SRI response
- Absolute change and percent change in SELENA SLEDAI score by visit
- Percentage of subjects with organ improvements by SELENA SLEDAI by visit
- Percentage of subjects with organ worsening by SELENA SLEDAI by visit
- Percentage of subjects with organ improvement by BILAG by visit
- Percentage of subjects with organ worsening by BILAG by visit
- Absolute change and percent change in PGA by visit
- Percentage of subjects with $\geq$ 0.3 point improvement in PGA by visit
- Absolute change and percent change in ParentGA by visit
- Absolute change in pediatric SDI at Week 52/Exit visit
- Worsening (change >0) in pediatric SDI at Week 52/Exit visit

SFI Flare:

- Time to first severe flare over 52 weeks in Part A
- Time to first flare over 52 weeks in Part A

Organ specific:

- Time to first renal flare over 52 weeks in Part A
- Number of subjects with renal flare over 52 weeks among subjects with proteinuria at baseline in Part A
- Absolute change and percent change from baseline in proteinuria by visit
- Shifts in proteinuria by visit
- Absolute change and percent change in proteinuria among subjects with proteinuria at baseline by visit

Steroids (based on average steroid dose between visits):

- Percentage of subjects whose average prednisone dose has been reduced by $\geq$ 25% from baseline during Week 44 to Week 52
- Absolute change from baseline in average daily prednisone equivalent dose (mg/day) by visit
- Percentage of subjects with any decrease in daily prednisone equivalent dose by visit
- Percentage of subjects with any increase in daily prednisone equivalent dose by visit
- Cumulative prednisone dose at Week 52

Statistical Analysis Plan

See Section 8.1.3.1.

Protocol Amendments

Summarized below are the 6 substantial protocol amendments that were made to study C1109:

1. Amendment 1 (implemented on February 21, 2012)
    - Addition of 3-hour post infusion observation period following the first 3 infusions in Part A
    - Additional PK sampling times were included for subjects in Cohort 3
    - Clarifications made to protocol pertaining to Part B and Part C regarding the potential for an earlier end of the study in the event that the number of subjects treated with belimumab for at least 5 years decreased to ≥15 subjects
2. Amendment 2 (implemented on January 31, 2013)
    - Addition of 3-hour post infusion observation period following the first 3 infusions in Part B
    - Removal of exclusion criteria prohibiting enrollment of subjects who had received B cell targeted therapy within 1 year of Day 0 and HCV confirmation by RIBA assay
    - Administration of study medication was modified to permit delivery of study infusion in either 100 mL (for subjects weighing ≤ 40 kgs) or 250 mL (subjects weighing >40 kgs) of saline
3. Amendment 3 (implemented on February 18, 2014)
    - Modification of protocol to include updated safety information regarding PML and delayed hypersensitivity reaction associated with the administration of IV belimumab
    - Entry criterion for high dose steroids was changed from 90 days to 60 days prior to baseline
    - Clarifications regarding treatment failure criteria and study withdrawal criteria were made
    - Addition of a home pregnancy test with a follow-up phone call to subjects at 16 weeks post last dose
4. Amendment 4 (implemented on November 3, 2014)
    - Modification of inclusion criterion lowering the SELENA SLEDAI score from ≥8 to ≥6
    - Entry criterion for IV cyclophosphamide was changed from 90 days to 60 days within Day 0 and allowing subjects with stable Grade 3 lymphopenia to enroll in the study
    - Updating of Applicant's stop dosing criteria for liver chemistry abnormalities
    - Addition of restarting study drug criteria
5. Amendment 5 (implemented on April 22, 2015)
    - Country-specific modification to provide clarification of restarting study treatment after liver event was not applicable to sites in Russia
6. Amendment 6 (implemented on December 12, 2016)
    - Modification reducing the total study target from 100 to 70 subjects with new estimates for sample size re-estimation

- Modification reducing target enrollment for subjects less than 13 years old from 20 to 14 subjects in this age group with a reduction in the target enrollment for Cohort 2 from 10 to 12 subjects
- Additional testing for anti-dsDNA, C3 and C4 to Part B at semi-annual visits
- Removal of immunogenicity testing for subjects who had withdrawn from the study
- Additional PK sampling at the first 12-week and semi-annual visit in Part B for subjects participating in the study at sites in Japan

8.1.1. Study Results

Compliance with Good Clinical Practices

According to statements included in the report for the pivotal trial C1109, the Applicant certified that this study was conducted in compliance with the following: good clinical practice standards as outlined in the Declaration of Helsinki 2008 or the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and applicable country-specific requirements including the constitution of independent ethics committees as per 21 CFR 312.3(b). Written informed consent was obtained from each pediatric subject's parent(s) or legal guardian and from subjects turning 18 years of age to continue participation the trial.

Financial Disclosure

The Applicant completed FDA Form 3454 to document financial conflicts of interest and arrangements with clinical investigators. As per this form, the Applicant certified that no financial arrangement had been entered into with the listed clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2 (a, b, and f).

Patient Disposition

The disposition of patients in the study did not show any major imbalances across the treatment arms (Table 13). There were 53 patients randomized in the belimumab group and 40 in placebo group. Out of 93 total randomized patients, 8 (15.1%) patients in the belimumab group and 9 (22.5%) subjects placebo group had withdrawn from the study before Week 52. Adverse events, investigator discretion, and withdrawal of patient consent were the major reasons for withdrawal from the study. In particular, two more patients withdrew from the study due to adverse event in the placebo group than the belimumab group (5 [12.5%] versus 3 [5.7%]).

Table 13. Subject Disposition for the Controlled Portion of Study C1109 (Part A)

	Belimumab		
	Placebo	10 mg/kg	Total
Randomized	40	53	93
Intent-to-Treat (ITT)[a]	40	53	93
Per Protocol[b]	39	52	91
Completers	31	45	76
Withdrew before week 52	9 (22.5)	8 (15.1)	17 (18.3)
Reason for Withdrawal			
Adverse event	5 (12.5)	3 (5.7)	8 (8.6)
Physician discretion	0	3 (5.7)	3 (3.2)
Lack of efficacy	1 (2.5)	1 (1.9)	2 (2.2)
Protocol deviation	1 (2.5)	0	1 (1.1)
Withdrew consent	2 (5.0)	1 (1.9)	3 (3.2)

Source: Statistical Reviewer's Table

a. Subjects were included in the Intent-to-Treat Population if they have taken at least one dose of study treatment.

b. Subjects were included in the Per Protocol Population if they were in the ITT Population and had no important protocol deviations that could affect the primary endpoint.

Protocol Violations/Deviations

Protocol deviations that were deemed to be "important" as defined by the ICH E3 guidance (e.g., events related to study inclusion or exclusion criteria, adherence to the protocol, conduct of the study, subject management or subject assessment that were likely to affect the interpretation of the results and/or lead to exclusion of any subject data from an analysis) are summarized in Table 14. Overall, the pediatric belimumab IV group (43%) incurred a higher rate of important protocol violations as compared to the pediatric placebo group (33%) during study C1109. Many important protocol deviations that occurred in both treatment groups were related to assessments and/or procedures (e.g., failure to comply with required collection of PK samples, safety and efficacy assessments, informed consent, procedures for handling investigational product, and maintain study blind). However, in the study report, the Applicant noted post-database lock they had identified 6 subjects (3 pediatric placebo subjects and 3 pediatric belimumab IV subjects) who were not recorded as having developed withdrawal criteria in addition to 1 pediatric placebo subject (Subject (b) (6)) who was incorrectly recorded as having developed withdrawal criteria. Therefore, the correct total is 8 subjects in study C1109 who were not promptly withdrawn after receiving prohibited doses of concomitant medications (4 pediatric placebo patients: Subjects (b) (6) and (b) (6); 4 pediatric belimumab patients: (b) (6) and (b) (6). Failure to remove these 8 pediatric subjects from the study should not have impacted on the results of the study's primary outcome (e.g., the SRI-4 endpoint) since these patients were not included in this analysis as they had met the definition of treatment failures for the SRI endpoint because

of having received prohibited doses of concomitant medications.

Table 14. Summary of Protocol Violations for the Controlled Portion of Study C1109 (Part A)

	Placebo (N=40)	Belimumab (N=53)	Total (N=93)
Any Important Protocol Deviation[1]	13 (33%)	23 (43%)	36 (39%)
Assessments and/or Procedures	12 (30%)	21 (40%)	33 (36%)
Developed Withdrawal Criteria but Was Not Withdrawn[2]	2 (5%)	1 (2%)	3 (3%)
Other	1 (3%)	0	1 (1%)
Prohibited Medication or Device	0	0	0
Received Wrong Treatment or Incorrect Dose	0	1 (2%)	1(1%)

Source: Applicant's Table 1.7; p. 224.
[1]Subjects may be included in more than one category.
[2]Post data base lock, 6 subjects (3 placebo, 3 belimumab IV) for whom this deviation should have been but were not recorded and 1 subject (placebo) for whom this deviation was incorrectly recorded. Therefore, a total of 8 subjects (4 [10%) placebo, 4 [8%] belimumab) were not withdrawn after developing withdrawal criteria.

Table of Demographic Characteristics

As summarized in the following tables (Table 15 and Table 16), the treatment groups within study C1109 were generally well balanced with respect to baseline demographics, region, disease characteristics and activity. Overall, the baseline demographic and disease characteristics and activity of this pediatric study were comparable to what was observed in the adult SLE studies C1056 and C1057 reviewed in support of belimumab IV. (Refer to clinical review of BLA 12 5370 dated February 18, 2011.)

The pediatric subjects who participated in this trial were predominantly Caucasian (52%) and female (95%). Five percent (5%) of the pediatric patients were of African American/African in origin and 46% identified their ethnicity as Hispanic or Latino. Most of the pediatric subjects were from South and Central America (41%) followed by Europe (34%), North America (17%), and Asia (7%). The mean age of the pediatric subjects was 14 years and their mean BMI was 22 kg/m^2. No important imbalances in these demographic factors across the treatment groups were noted within Study C1109.

Table 15. Demographic Characteristics of Subjects Enrolled in the Controlled Portion of Study C1109 (Part A)

Demographic Characteristics	Placebo (N=40)	Belimumab (N=53)	Total (N=93)

Gender:			
Female	39 (98%)	49 (93%)	88 (95%)
Male	1 (3%)	4 (8%)	5 (5%)
Race[1]:			
White/Caucasian/European Heritage	21 (53%)	27 (51%)	48 (52%)
Asian	6 (15%)	8 (15%)	14 (15%)
Central/South Asian Heritage	1 (3%)	3 (6%)	4 (4%)
East Asian Heritage	1 (3%)	2 (4%)	3 (3%)
Japanese Heritage	4 (10%)	2 (4%)	6 (7%)
South East Asian Heritage	0	2 (4%)	2 (2%)
African American/African Heritage	2 (5%)	3 (6%)	5 (5%)
American Indian or Alaskan Native	11 (28%)	15 (28%)	26 (28%)
Multiracial	0	0	0
Ethnicity:			
Hispanic or Latino	17 (43%)	26 (49%)	43 (46%)
Not Hispanic or Latino	23 (58%)	27 (51%)	50 (54%)
Age (years):			
Mean (SD)	14.8 (2.17)	13.5 (2.59)	14.0 (2.49)
(Min, Max)	(6, 17)	(6, 17)	(6, 17)
<13 years old	3 (8%)	18 (34%)	21 (23%)
≥13 years old	37 (93%)	35 (66%)	72 (77%)
Height (cm):			
Mean (SD)	155 (11)	152 (14)	153 (13)
(Min, Max)	(117, 173)	(105, 174)	(105, 175)
Weight (kg):			
Mean (SD)	53 (13)	52 (17)	53 (15)
(Min, Max)	(20, 87)	(17, 86)	(17, 87)
BMI (kg/m^2):			
Mean (SD)	22 (4.3)	22 (4.5)	22 (4.4)
(Min, Max)	(15, 34)	(15, 34)	(15, 34)
Country:			
Argentina	5 (13%)	7 (13%)	12 (13%)
Canada	2 (5%)	3 (6%)	5 (5%)
Japan	4 (10%)	2 (4%)	6 (7%)
Mexico	5 (13%)	7 (13%)	12 (13%)
Peru	6 (15%)	8 (15%)	14 (15%)
Poland	2 (5%)	0	2 (2%)
Russian Federation	5 (13%)	6 (11%)	11 (12%)
Spain	5 (13%)	9 (17%)	14 (15%)
United Kingdom	2 (5%)	3 (6%)	5 (5%)
United States	4 (10%)	8 (15%)	12(13%)

Source: Applicant's Tables 1.8 and 1.9; p. 225-226 and p. 227

[1]Subjects who checked more than one race category are counted under individual race category according to the minority rule as well as the multiracial category.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

As shown in Table 16 below, the overall mean duration of SLE disease was 2.4 years for pediatric patients in this trial. Overall, these pediatric subjects had a high baseline level of disease activity as manifested by a SELENA SLEDAI mean score of 10 with 17% of the patients having a baseline SELENA SLEDAI score of $\geq$ 13 points. The two treatment groups were similar in their baseline disease activity with minor differences as assessed by the BILAG organ domain involvement and PGA category, and a major difference in baseline proteinuria >0.5 g/24 hrs (9 [23%] pediatric placebo patients versus 4 [8%] pediatric belimumab IV patients). (Note: Patients with a baseline SELENA SLEDAI score category 0 to 3 were unable to achieve a response of > 4 points necessary for a positive response as assessed by the primary endpoint, the SRI.)

Table 16. Summary of Subject's Baseline Disease Characteristics for the Controlled Portion of Study 1109 (Part A)

Baseline Disease Characteristic	Placebo (N=40)	Belimumab (N=53)	Total (N=93)
SLE Disease Duration (yr.):			
Mean (SD)	2.7 (1.8)	2.7 (2.0)	2.4 (1.9)
BILAG Organ Domain Involvement[1]:			
At least 1A or 2B	29 (73%)	37 (70%)	66 (71%)
At Least 1A	6 (15%)	4 (8%)	10 (11%)
At Least 1A or 1B	36 (90%)	50 (94%)	86 (93%)
No A or B	1 (3%)	3 (6%)	4 (4%)
SELENA SLEDAI Stratification Category			
≤12	33 (85%)	43 (81%)	76 (83%)
≥13	6 (15%)	10 (19%)	16 (17%)
SELENA SLEDAI Category:			
≤7	6 (15%)	7 (13%)	13 (14%)
≥8	33 (85%)	46 (87%)	79 (86%)
SELENA SLEDAI Score:			
Mean (SD)	10.4 (3.6)	10.3 (3.3)	10.3 (3.5)
PGA Category:			
0 to 1	9 (23%)	9 (17%)	18 (19%)
>1 to 2.5	31 (78%)	44 (83%)	75 (81%)
>2.5	0	0	0
PGA Scale:			
Mean (SD)	1.38 (0.42)	1.34 (0.43)	1.36 (0.42)
ParentGA Category			
0-2.5	9 (23%)	15 (28%)	24 (26%)
>2.5-5	15 (38%)	18 (34%)	33 (36%)
>5-7.5	14 (35%)	17 (32%)	31 (33%)
>7.5	2 (5%)	3 (6%)	5 (5%)
ParentGA			
Mean (SD)	4.6 (2.4)	4.3 (2.5)	4.4 (2.5)
Pediatric SDI Category			
0	34 (85%)	46 (87%)	80 (86%)
1	5 (13%)	5 (9%)	10 (11%)
>1	1 (3%)	2 (4%)	3 (3%)
Pediatric SDI Score			
Mean (SD)	0.2 (0.45)	0.2 (0.56)	0.2 (0.51)
Proteinuria Category (g/24 hr):			
≤0.5	31 (78%)	49 (93%)	80 (86%)
>0.5 - ≤1	3 (8%)	3 (6%)	6 (7%)
1 - <2	3 (8%)	1 (2%)	4 (4%)
≥ 2	3 (8%)	0	3 (3%)
Proteinuria Level (g/24 hr)			
Mean (SD)	0.54 (1.1)	0.21 (0.2)	0.35 (0.8)

Source: Applicant's Table 1.17; p. 235-237.
[1]Subjects may be included in more than one category.

Most pediatric subjects who participated in study C1109 had mucocutaneous, immunologic and

musculoskeletal manifestations of SLE disease at baseline as assessed by the SELENA/SLEDAI disease activity index (Table 17). The baseline incidence of musculoskeletal involvement was higher in the pediatric placebo group while higher baseline incidences of mucocutaneous and immunologic involvement occurred in the pediatric belimumab IV group. Remaining baseline disease involvement was generally well balance between the two treatment groups.

Table 17. Summary of Baseline SELENA SLEDAI Organ Involvement for Subjects Who Participated in the Controlled Portion of Study C1109 (Part A)

Organ Item	Placebo (N=40)	Belimumab (N=53)	Total (N=93)
Mucocutaneous	35 (88%)	50 (94%)	85 (91%)
Immunologic	28 (70%)	41 (77%)	69 (74%)
Musculoskeletal	33 (83%)	35 (66%)	68 (73%)
Renal	8 (20%)	10 (19%)	18 (19%)
Cardiovascular and Respiratory	2 (5%)	4 (8%)	6 (7%)
Hematologic	2 (5%)	3 (6%)	5 (5%)
CNS	1 (3%)	2 (4%)	3 (3%)
Vascular	1 (3%)	2 (4%)	3 (3%)

Source: Applicant's Table 1.19; p. 240-1.

A summary of moderate to severe BILAG organ system involvement (A or B score) at baseline is displayed in Table 18 below. The most common organ systems with moderate to severe BILAG involvement in pediatric subjects participating in study C1109 were mucocutaneous (67%), musculoskeletal (67%), and renal (13%). More pediatric subjects had moderate to severe BILAG involvement in study C1109 as compared to the adult SLE subjects who participated in the belimumab IV studies C1056 and 1057. (Refer to clinical review for BLA 125370 dated February 18, 2011.) This is not an unexpected finding since pediatric SLE patients more commonly present with renal or CNS disease involvement than adults with this disease.

Table 18. Baseline BILAG Organ Domain Grade A and B for Subjects Who Participated in the Controlled Portion of Study C1109 (ITT Population)

BILAG Organ Domain[1]/ Grade	Placebo (N=40)	Belimumab (N=53)	Total (N=93)
General			
A	0	0	0
B	3 (8%)	3 (6%)	6 (7%)
Mucocutaneous			
A	3 (8%)	3 (6%)	6 (7%)
B	24 (60%)	40 (76%)	64 (67%)
Neurological			
A	0	0	0
B	0	0	0
Musculoskeletal			
A	2 (5%)	0	2 (2%)
B	29 (73%)	33 (62%)	62 (67%)
Cardiovascular and Respiratory			
A	0	0	0
B	0	1 (2%)	1 (1%)
Vasculitis			
A	0	0	0
B	2 (5%)	8 (15%)	10 (11%)
Renal			
A	1 (3%)	1 (2%)	2 (2%)
B	5 (13%)	7 (13%)	12 (13%)
Hematology			
A	0	0	0
B	9 (23%)	2 (4%)	11 (12%)

Source: Applicant's Table 1.20; p. 242-3.
[1]Organ Domain Categories: A= requires disease modifying treatment; B=mild reversible problems requiring only symptomatic therapy; C=stable mild disease; D=previously affected but currently inactive; and E=system never involved.

The majority (97%) of patients in this trial were overwhelmingly seropositive for ANA and/or anti-dsDNA as shown in Table 19 below. The treatment groups within the trial were also generally well balanced with respect to baseline biomarkers of disease activity with the following exceptions. Slightly higher proportions of patients in the pediatric belimumab IV group were positive for the presence of aCL, had serum IgG levels that were above the upper limits of normal (LLN), or had low levels of C3. This was comparable to what was observed in the adult SLE patients who participated in the belimumab IV studies C1056 and C1057. (Refer to clinical review for BLA 125370 dated February 18, 2011.) Additionally, slightly higher proportions of pediatric patients had serum levels of IgA below LLN and serum IgM levels above the ULN.

Table 19. Summary of Subject's Baseline Serologies, Immunoglobulins, and Complement for for the Controlled Portion of Study C1109 (Part A)

	Placebo (N=40)	Belimumab (N=53)	Total (N=93)
Anti-dsDNA:			
Positive (≥ 30 IU/mL)	27 (68%)	38 (72%)	65 (70%)
Mean (SD)	1461 (3365)	1083 (2735)	1240 (2993)
ANA:			
Positive (≥ 80 Titer)	38 (95%)	49 (94%)	87 (95%)
Mean (SD)	693 (526)	720 (497)	708 (507)
ANA and/or Anti-dsDNA			
Positive:	38 (95%)	52 (98%)	90 (97%)
aCL:			
Positive[1]	8 (20%)	18 (34%)	26 (28%)
IgA:			
Mean (SD)	2.1 (0.9)	2.5 (1.1)	2.3 (1.0)
>ULN (4.63 g/L)	3 (8%)	1 (2%)	4 (4%)
<LLN (0.81 g/L)	4 (10%)	7 (13%)	11 (12%)
IgG:			
Mean (SD)	15 (4.6)	16 (6.1)	15 (5.5)
>ULN (16.18 g/L)	2 (5%)	3 (6%)	5 (5%)
<LLN 6.94 g/L	7 (18%)	15 (28%)	22 (24%)
IgM:			
Mean (SD)	1.3 (1.4)	1.3 (0.7)	1.3 (1.0)
>ULN (2.71 g/L)	3 (8%)	4 (8%)	7 (8%)
<LLN (0.48 g/L)	3 (8%)	1 (2%)	4 (4%)
CRP			
Positive (≥ 4 mg/L)	12 (30%)	10 (19%)	22 (23%)
Mean (SD)	12 (6.2)	21 (23)	16 (16)
C3:			
Mean (SD)	103 (28)	95 (30)	99 (29)
Low (<90 mg/L)	12 (30%)	20 (38%)	32 (34%)
C4:			
Mean (SD)	15 (7.9)	12 (8.0)	13 (8.0)
Low (<10 mg/dL)	15 (38%)	21 (40%)	36 (39%)
BLyS: (µg/L)			
Above LOQ	40 (100%)	50 (100%)	90 (100%)
Mean (SD)	1.26 (0.86)	0.98 (0.89)	1.11 (0.89)

Source: Applicant's Tables 1.23, 1.24 and 1.25; p. 247-250.
[1]aCL was positive if any of the three aCL parameters (IgG, IgA, or IGM) were positive

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All study infusions were administered in clinic by study staff. Overall, treatment compliance was high in study C1109 with 98% of pediatric subjects receiving their scheduled study infusions. Slightly more pediatric subjects randomized to belimumab IV (87%) received between 11-14 infusions over the course of the study as compared to pediatric placebo subjects (80%). This resulted in a mean duration of exposure that was also slightly higher in the pediatric belimumab IV group than in the pediatric placebo group (334 days versus 314 days,

respectively).

Table 20. Study Compliance and Subject Exposure for the Controlled Portion of Study C1109 (Part A)

	Placebo (N=40)	Belimumab (N=53)	Total (N=93)
Percent Compliance[1]:			
Mean (SD)	97 (11)	98 (4.3)	98 (8.0)
Median	100	100	100
(Min, Max)	(33,100)	(80,100)	(33, 100)
Total Number of Infusions:			
1-5	5 (13%)	3 (6%)	8 (9%)
6-10	3 (8%)	4 (8%)	7 (8%)
11-14	32 (80%)	46 (87%)	78 (84%)
Duration of Exposure[2] (days)			
Mean (SD)	314 (107)	334 (79)	326 (92)
Median	364	364	364
(Min, Max)	(28, 374)	(81, 377)	(28, 377)

Source: Applicant's Table 1.33; p. 316.
[1]Percent compliance = 100 (number of infusions prescribed – number of infusions missed)/Number of infusions prescribed
[2]Duration was calculated as last infusion date – first infusion date + 28

The following Table 21 summarizes concomitant SLE medications used by the pediatric subjects who participated in this trial. The usage of concomitant SLE mediations at baseline was generally similar for the two treatment groups in this trial, however, a higher proportion of patients in the pediatric placebo group were taking a slightly higher mean dose of prednisone/equivalent (12.2 mg/day) in addition to other immunosuppressives (68%) and NSAIDs (30%) as compared to the belimumab IV group (9.11 mg/day, 62% and 21%), respectively). A similar pattern of concomitant SLE medication use was observed in the adult SLE belimumab IV studies C1056 and C1057. (Refer to clinical review of BLA 12 5370 dated February 18, 2011.)

Table 21. Summary of Concomitant SLE Medications Used by Subjects at Baseline in the Controlled Portion of Study 1109 (Part A)

	Placebo (N=40)	Belimumab (N=53)	Total (N=93)
Any Steroid Use:	38 (95%)	50 (94%)	88 (95%)
Deflazacort	0	1 (2%)	1 (1%)
Methylprednisone	1 (3%)	0	1 (1%)
Methylprednisolone	2 (5%)	0	2 (2%)
Prednisolone	9 (23%)	9 (17%)	18 (19%)
Prednisone	25 (63%)	40 (76%)	65 (70%)
Prednisone Acetate	1 (3%)	0	1 (1%)
Prednisone or Equivalent Dose at Baseline:			
0 mg/day	2 (5%)	3 (6%)	5 (5%)
>0 - ≤ 7.5 mg/day	16 (40%)	24 (45%)	40 (43%)
>7.5 mg/day	22 (55%)	26 (49%)	48 (52%)
Average Prednisone or Equivalent Dose at Baseline:			
Mean (SD)	12.2 (8.7)	9.11 (5.6)	10.4 (7.2)
Antimalarials:	31 (78%)	44 (83%)	74 (81%)
Any Immunosuppressives:	27 (68%)	33 (62%)	60 (65%)
Azathioprine	5 (13%)	5 (9%)	10 (11%)
Leflunomide	1 (3%)	1 (3%)	2 (2%)
Methotrexate	10 (25%)	13 (25%)	23 (25%)
Mycophenolate	16 (40%)	16 (30%)	32 (34%)
Tacrolimus	4 (10%)	2 (4%)	6 (7%)
Aspirin	4 (10%)	7 (13%)	11 (12%)
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	12 (30%)	11 (21%)	23 (25%)

Source: Applicant's Table 1.28; p. 257-8 and Information request dated 4/2/2019.

Efficacy Results – Primary Endpoint

8.1.1.1. Primary Efficacy Analysis

The primary efficacy endpoint, SRI response at week 52, was analyzed using logistic regression model and the results are given in Table 22. The proportion of subjects who achieved SRI response at week 52 was found to be greater in belimumab IV group (52.8%) compared to the placebo group (43.6%) and the odds ratio was 1.5 with a 95% CI of (0.6, 3.5).

Table 22. Primary Efficacy Analysis of SRI Response Rate at Week 52 from Study C1109 (Part A)

	Placebo N=40	Belimumab 10 mg/kg N=53
Response, n (%)	17 (43.6)	28 (52.8)
Observed difference	-	9.2%
Odds ratio (95% CI)	-	1.5 (0.6, 3.5)

Source: FDA Statistical Reviewer
One subject in placebo did not have a baseline SELENA SLEDAI assessment and, therefore, did not contribute to SRI analyses.
Odds ratio (95% CI) is from a logistic regression model with covariates treatment group, baseline age (5-11 vs. 12-17), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

SRI response at week 52 was the primary efficacy endpoint for IV studies (1056 and 1057) and the endpoint was analyzed using logistic regression model with the following independent variables in the model: treatment group, baseline SELENA SLEDAI score, baseline proteinuria level and race. These studies were analyzed during the original submission and results are given in Table 23 below. The SRI response rates in the pediatric study were consistent with the adult IV studies, particularly for study 1057 with 44% response rate in placebo group and 58% in belimumab 10 mg/kg group.

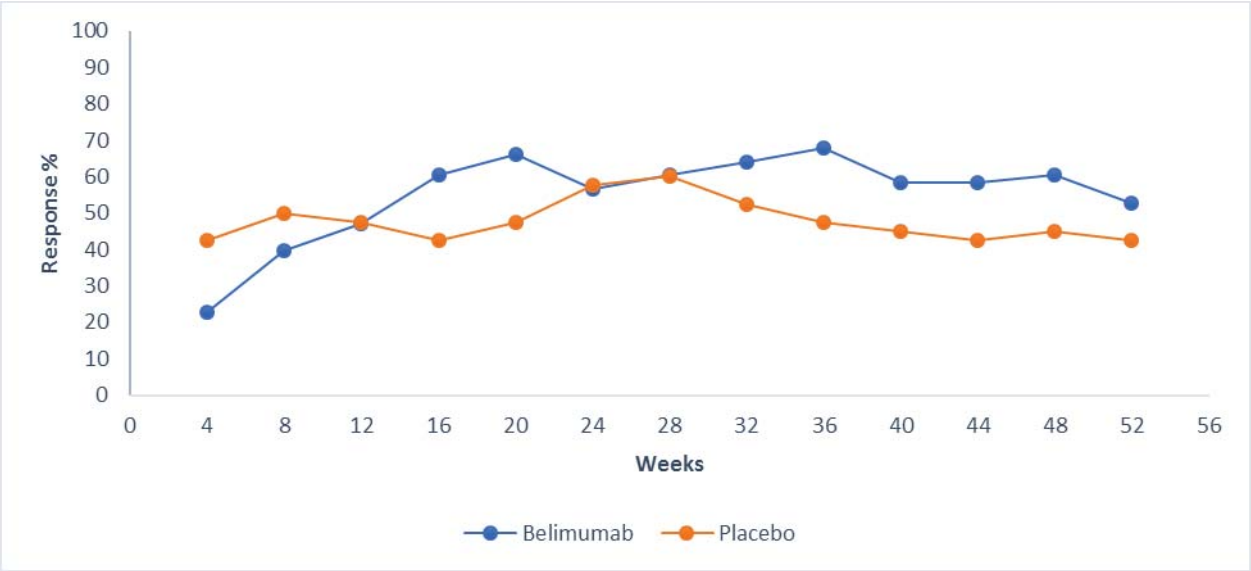
Table 23. Efficacy Analysis of SRI Response Rate from IV Studies 1056 and 1057

	Study 1056			Study 1057		
	Placebo N=275	Belimumab 1 mg/kg N=271	Belimumab 10 mg/kg N=273	Placebo N=287	Belimumab 1 mg/kg N=288	Belimumab 10 mg/kg N=290
Response, n (%)	93 (34)	110 (41)	118 (43)	125 (44)	148 (51)	167 (58)
Observed difference	-	7%	9%	-	8%	14%
Odds ratio (95% CI)	-	1.3 (0.9, 1.9)	1.5 (1.1, 2.1)	-	1.6 (1.1, 2.2)	1.8 (1.3, 2.6)

Source: Review of BLA 125370 Belimumab IV dated February 18, 2011.

The time-response plot (Figure 15) displays the proportion of SRI responders between two groups in the pediatric study over time. The plot shows that the response rates on the belimumab group and the placebo group began to separate at the third month. However, there was an overlap in the response rate at Week 24, and the belimumab IV group showed higher rates from Week 24 onwards with the difference sustained through Week 52.

Figure 15. SRI Response by Visit for the Controlled Portion of Study C1109 (Part A)



Source: FDA Statistical Reviewer

Component analysis of primary endpoint

Each component in the SRI endpoint was analyzed using a logistic regression model with treatment group, baseline age (5-11 vs. 12-17), and baseline SELENA SLEDAI score (≤12 vs. ≥13) as covariates in the ITT population and the results showed a higher percentage of responders in the belimumab IV group compared to the placebo group.

Comparing the SLE Disease Activity Index (SELENA SLEDAI) which captured the subject's condition over the 10 days prior to the visit, the belimumab IV group showed a higher response rate (4-point reduction) than the placebo group (Table 24). The odds ratio was found to be 1.6 with a 95% confidence interval of (0.7, 3.8).

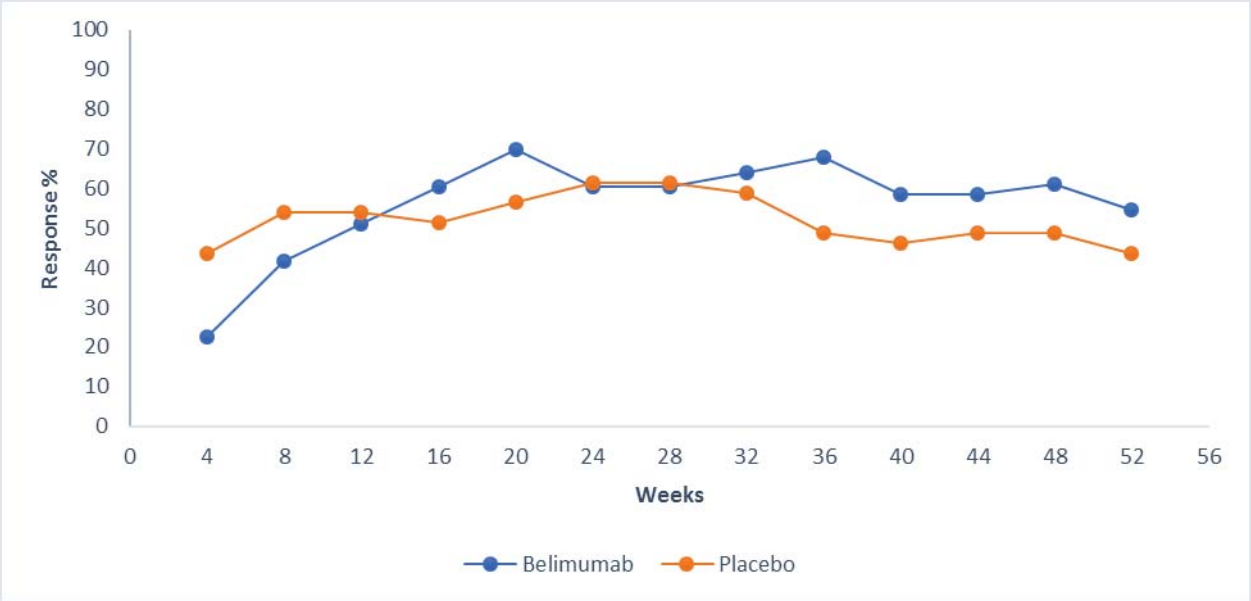
Table 24. Primary Component Analysis - 4 Point reduction in SELENA SLEDAI for Study C1109 (Part A)

	Placebo N=40	Belimumab 10 mg/kg N=53
Response, n (%)	17 (43.6)	29 (54.7)
Observed difference	-	11.1%
Odds ratio (95% CI)	-	1.6 (0.7, 3.8)

Source: FDA Statistical Reviewer
One subject in placebo did not have a baseline SELENA SLEDAI assessment and, therefore, did not contribute to SRI component analyses.
Odds ratio (95% CI) is from a logistic regression model with covariates treatment group, baseline age (5-11 vs. 12-17), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

SELENA SLEDAI percent change from baseline decreased on average over time for both the placebo and belimumab IV groups, with greater decrease in the belimumab IV group (Figure 16). At Week 52, the adjusted mean percent change from baseline was -46.8% in the placebo group and -50.8% in the belimumab IV group with a difference of -4.0% and a 95% CI for difference of (-21.8%, 13.9%).

Figure 16. SELENA SLEDAI ≥ 4 Point Reduction from Baseline by Visit for Study C1109 (Part A)



Source: FDA Statistical Reviewer

The Physician Global Assessment (PGA) score captured the improvement in the disease activity measured in a visual analog scale scored from 0 to 3 (1=mild, 2=moderate, 3=severe). Results from a logistic regression analysis of PGA score in Table 25 showed that the proportion with no

worsening in disease activity was higher in the belimumab IV group (81.23%) compared to placebo (72.76%).

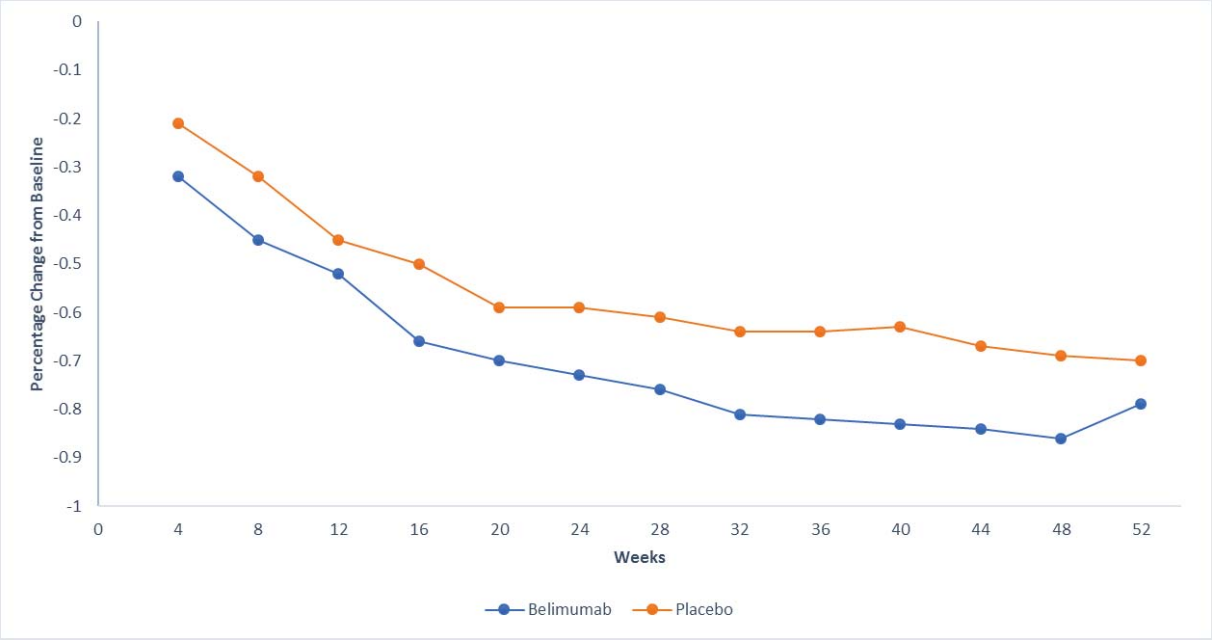
Table 25. Primary Component Analysis - No worsening in PGA for Study C1109 (Part A)

	Placebo N=40	Belimumab 10 mg/kg N=53
Response, n (%)	26 (66.7)	40 (75.5)
Observed difference	-	8.8%
Odds ratio (95% CI)	-	1.7 (0.7, 4.4)

Source: FDA Statistical Reviewer
One subject in placebo did not have a baseline SELENA SLEDAI assessment and, therefore, did not contribute to SRI component analyses.
Odds ratio (95% CI) is from a logistic regression model with covariates treatment group, baseline age (5-11 vs. 12-17), baseline SELENA SLEDAI score (≤12 vs. ≥13) and baseline PGA score.

Reduction in PGA percent change from baseline was observed in both the treatment arms (Figure 17). However, the reduction was greater in the belimumab IV group compared to the placebo group.

Figure 17. PGA Percent Change from Baseline by Visit for Study C1109 (Part A)



Source: FDA Statistical Reviewer

The BILAG is an organ-based transitional activity instrument which provides disease activity scorings across eight organ systems on an ordinal scale. The difference in percentage of subjects with no new BILAG 1A/2B organ domain scores between two groups were compared using logistic regression model. The odds of not having a new BILAG score was greater for pediatric subjects in the belimumab IV group compared to placebo with an odds ratio of 2.0 and a 95% CI of (0.8, 5.0) (Table 26).

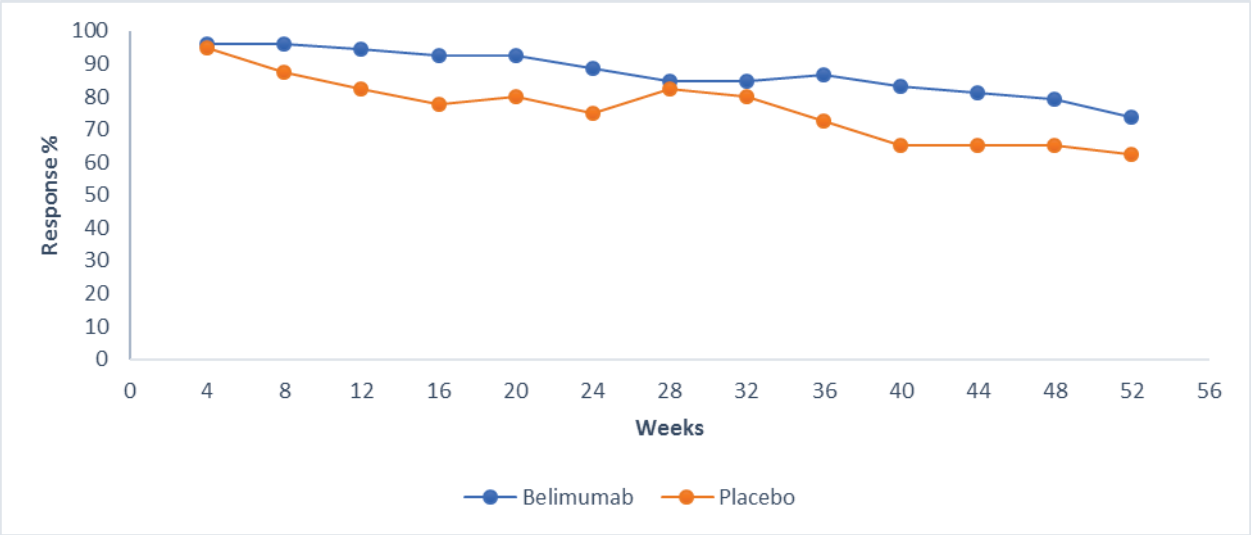
Table 26. Primary Component Analysis – No new 1A/2B BILAG Domain Ccores for Study C1109 (Part A)

	Placebo N=40	Belimumab 10 mg/kg N=53
Response, n (%)	24 (61.5)	39 (73.6)
Observed difference	-	12.1 %
Odds ratio (95% CI)	-	2.0 (0.8, 5.0)

Source: FDA Statistical Reviewer
One subject in placebo did not have a baseline SELENA SLEDAI assessment and, therefore, did not contribute to SRI component analyses.
Odds ratio (95% CI) is from a logistic regression model with covariates treatment group, baseline age (5-11 vs. 12-17), baseline SELENA SLEDAI score (≤12 vs. ≥13) and baseline BILAG domain involvement.

The percentage of subjects in each treatment group who had no new BILAG 1A/2B organ domain scores from baseline is shown in Figure 18. The response rate is declining in both treatment arms over the time and belimumab IV group showed a greater response rate than the placebo group.

Figure 18. BILAG No New 1A/2B Organ Domain Scores by Visit for Study C1109 (Part A)



Source: FDA Statistical Reviewer

Results from the analysis of SRI components in the study C1109 were compared with the previous adult belimumab IV studies (Table 27). The response rates were largely similar to the adult belimumab IV studies, in particular, study 1057.

Table 27. Components of SRI Response at Week 52 for Pediatric and Adult Studies

	Study 1056		Study 1057		Study C1109	
	Placebo N=275	Belimumab 10 mg/kg N=273	Placebo N=287	Belimumab 10 mg/kg N=290	Placebo N=40	Belimumab 10 mg/kg N=53
4- Point Reduction in SELENA SLEDAI, n (%)	98 (36)	128 (47)	132 (46)	169 (58)	17 (43.6)	29(54.7)
OR (95% CI)	-	1.6 (1.1, 2.3)	-	1.7 (1.2, 2.4)	-	1.6 (0.7, 3.8)
No Worsening in PGA, n (%)	173 (63)	189 (69)	199 (69)	231 (80)	26 (66.7)	40 (75.5)
OR (95% CI)	-	1.3 (0.9, 1.9)	-	1.7 (1.2, 2.6)	-	1.7 (0.7, 4.4)
No New 1A/2B BILAG Domain Score, n (%)	179 (65)	189 (69)	210 (73)	236 (81)	24 (61.5)	39 (73.6)
OR (95% CI)	-	1.2 (0.8, 1.7)	-	1.6 (1.1, 2.4)	-	2.0 (0.8, 5.0)

Source: FDA Statistical Reviewer

Sensitivity analyses using different analyses methods provided similar results to the primary analysis (Table 28). However, such analyses largely evaluate results under alternative assumptions such as single imputation using LOCF to those of the primary analysis and

therefore do not comprehensively evaluate the potential effect of violations in missing data assumptions on the reliability of the results.

Table 28. Sensitivity Analysis - SRI Response at Week 52 for Study C1109 (Part A)

	Placebo N=40	Belimumab 10 mg/kg N=53
Unadjusted Response n/N (%)	17/39 (43.6)	28/53 (52.8)
Observed difference	-	9.2
Odds ratio (95% CI)	-	1.5 (0.6, 3.3)
LOCF Response, n/N (%)	18/39 (46.2)	30/53 (56.6)
Observed difference	-	10.5
Odds ratio (95% CI)	-	1.5 (0.7, 3.5)
Completer Response n/N (%)	17/30 (56.7)	27/45 (60.0)
Observed difference	-	3.3
Odds ratio (95% CI)	-	1.2 (0.4, 3.1)

Source: FDA Statistical Reviewer
One subject in placebo did not have a baseline SELENA SLEDAI assessment and, therefore, did not contribute to SRI analyses.
Odds ratio (95% CI) is from a logistic regression model with covariates treatment group, baseline age (5-11 vs. 12-17), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

8.1.1.2. Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The comparative analyses of secondary endpoints showed a higher response in the belimumab IV group compared to the placebo group. Major secondary endpoints in the study included, but not limited to: the proportion of subjects meeting PRINTO/ACR juvenile SLE response criteria for improvement in SLE at Week 52 evaluated using 2 definitions; the 5 components of the PRINTO/ACR juvenile SLE response: percent change in ParentGA, PGA, SELENA SLEDAI score, 24-hour proteinuria and PedsQL GC physical functioning domain score at week 52, the proportion of subjects with a sustained SRI response, and the proportion of subjects with a sustained ParentGA response.

There are two response definitions are considered for this analysis:

- Definition 1: at least 50% improvement in 2 of 5 endpoints with no more than 1 of the remaining endpoints worsening by more than 30% compared to baseline.
- Definition 2: at least 30% improvement in 3 of 5 endpoints with no more than 1 of the remaining endpoints worsening by more than 30% compared to baseline.

PRINTO/ACR Juvenile SLE Response Evaluation: Definition 1

The results from PRINTO/ACR Juvenile SLE Response Evaluation Definition 1 are given in Table 29. The proportion of responders according to definition 1 in the belimumab IV group at week 52 was 60.4% compared with 35.0% in the placebo group (Odds Ratio 2.7; 95% CI: (1.2, 6.5)).

Table 29. Analysis of PRINTO/ACR Juvenile SLE Response at Week 52 (Definition 1) for Study C1109 (Part A)

	Placebo N=40	Belimumab 10 mg/kg N=53
Response, n (%)	14 (35.0)	32 (60.4)
Observed difference	-	25.4%
Odds ratio (95% CI)	-	2.7 (1.2, 6.5)

Source: FDA Statistical Reviewer
Odds ratio (95% CI) is from a logistic regression model with covariates treatment group, baseline age (5-11 vs. 12-17), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

PRINTO/ACR Juvenile SLE Response Evaluation: Definition 2

The proportion of responders according to definition 2 in the belimumab IV group at week 52 was 60.4% compared with 35.0% in the placebo group [Odds Ratio 2.9; 95% CI: (1.2, 7.2)] (Table 30).

Table 30. Analysis of PRINTO/ACR Juvenile SLE Response at Week 52 (Definition 2) for Study C1109 (Part A)

	Placebo N=40	Belimumab 10 mg/kg N=53
Response, n (%)	11 (27.5)	28 (52.8)
Observed difference	-	25.3%
Odds ratio (95% CI)	-	2.9 (1.2, 7.2)

Source: FDA Statistical Reviewer
Odds ratio (95% CI) is from a logistic regression model with covariates treatment group, baseline age (5-11 vs. 12-17), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

The adjusted percent change from baseline in ParentGA at week 52 decreased (i.e., improved) in both the groups (Table 31), with a greater improvement in the belimumab IV group: Estimated difference: 12.8, 95% CI: (-60.7, 35.0)

Table 31. Analysis of ParentGA Percent Change from Baseline at Week 52 for Study C1109 (Part A)

	Placebo N=40	Belimumab 10 mg/kg N=53
Mean (SE)	-1.9 (26.5)	-14.7 (21.5)
Estimated difference	-	12.8
(95% CI)		(-60.7, 35.0)

Source: FDA Statistical Reviewer
Results from ANCOVA model with covariates for treatment group, baseline PGA, baseline age (5-11 vs. 12-17), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

Time to first severe flare over 52 Weeks

The time to first severe flare measurement was analyzed using a Cox proportional hazards model adjusting for baseline age (5-11 vs. 12-17) and baseline SELENA SLEDAI score (≤12 vs. ≥13). The results showed that the subjects in the belimumab group had a 40% lower risk of experiencing a severe flare compared with the placebo group (Table 32). The hazard ratio obtained was 0.4, with a 95% CI of (0.2, 0.8).

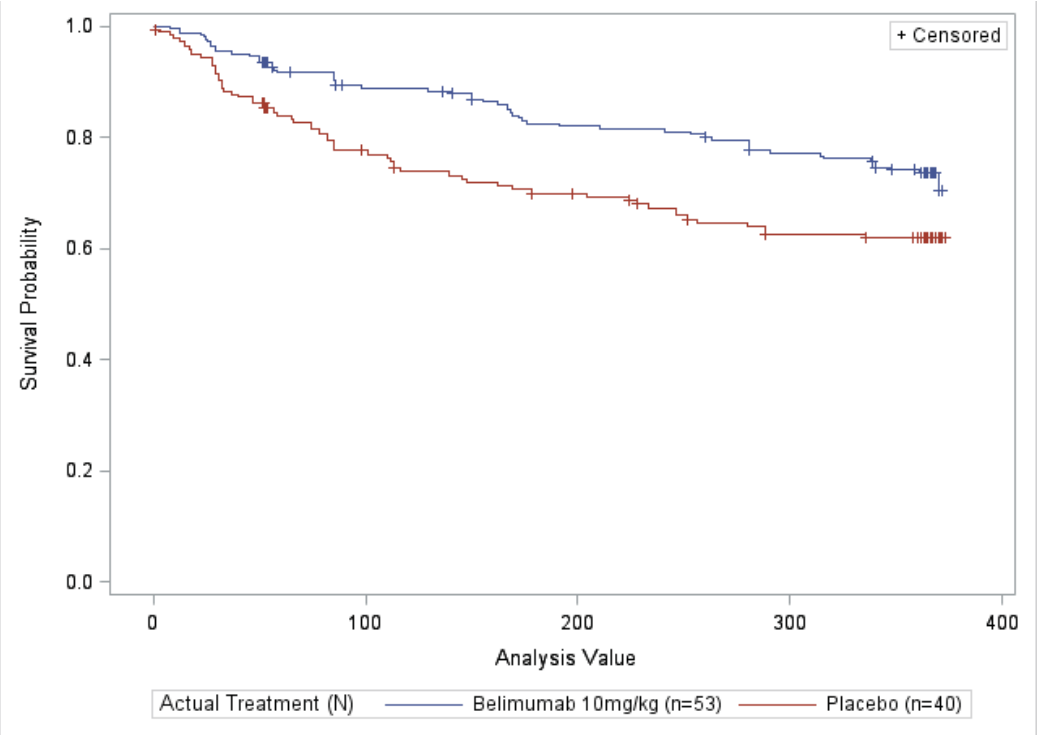
Table 32. Time to first severe flare over 52 Weeks for Study C1109 (Part A)

	BEL114055	
	Placebo N=40	**Belimumab 10 mg/kg N=53**
Severe Flare n (%)	17/40 (42.5)	12/53 (22.6)
Observed difference	-	19.9%
Hazard ratio (95% CI)	-	0.4 (0.2, 0.8)

Source: FDA Statistical Reviewer
Hazard ratio from Cox proportional hazards model adjusting for baseline age (5-11 vs. 12-17) and SELENA SLEDAI score (≤12 vs. ≥13).

The survival plot (Figure 19) compares the probability of not experiencing a severe flare over time and the plot shows that belimumab IV group experienced improvement compared to the placebo group.

Figure 19. Probability of Not Experiencing a Severe Flare over Time for Study C1109 (Part A)



Source: FDA Statistical Reviewer

8.1.1.3. Analysis of Biomarkers

The applicant conducted post-hoc, exploratory exposure-response analysis using biomarkers such as; IgG, anti-dsDNA, complement C3, complement C4, and naïve B cells. At Week 52, the adjusted mean percent change from baseline in IgG was increased by 4.3% for the placebo group and decreased by 15.9% for the belimumab 10 mg/kg group with a treatment difference of 20.2 and 95% CI (-29.1, -11.3). Reductions in IgA and IgM levels were also observed in the belimumab group compared with placebo. For IgA, the adjusted mean percent change increased by 10.9% for the placebo group and a decreased by 15.8% for the belimumab IV group with a treatment difference of -26.65%, and 95% CI: (-35.6%, -17.7%), and for IgM, an increase of 4.6% for the placebo group and a decrease of 39.5% (Treatment difference -44.0%; 95% CI: -54.7%, -33.3%). In subjects who were anti-dsDNA positive, there was a 44.9% reduction in the belimumab 10 mg/kg group at Week 52 compared with an increase of 2.2% in the placebo group. For complement (C3 and C4), there was an increase of 17% in C3 and 50% in C4 observed in the belimumab IV group vs. increases of 6% for C3 and 18% for C4 for placebo (at Week 52). The median reductions in naïve B cells in subjects treated with belimumab IV were 17.0% at Week 8 and 77.1% at Week 52; placebo was associated with an increase of 3.6%

and a decrease of 26.7% at these time points, respectively. Moreover, the biomarker response in pediatric subjects treated with belimumab IV was consistent with that observed in adults.

8.1.1.4. Additional Analyses Conducted on the Individual Trial

8.1.1.4.1. Bayesian Analysis of Efficacy Endpoints

The applicant conducted pediatric study (C1109) to fulfil the post marketing requirement in the US under the Pediatric Research Equity Act (PREA). However, due to the rarity of the disease in children, a fully powered phase 3 pediatric study was not feasible. In order to recruit more pediatric subjects in the study, the applicant amended the protocol to relax eligibility criteria. Despite these efforts to try to increase recruitment, only 93 subjects were enrolled in the study. Thus, C1109 was not adequately powered to make a formal statistical inference on its own due to these enrollment limitations and the rarity of disease in pediatric subjects and so no formal statistical hypothesis testing was planned in the protocol.

The clinical review team believes that the disease and patient response to treatment are likely to be similar between the adults and pediatric subjects. Bayesian methods have been proposed as a means to borrow information between populations where there is the expectation of similar disease and response. Thus, FDA requested that the applicant conduct a Bayesian analysis of the pediatric study (C1109) which borrows information from the previous adult studies (C1056 and C1057). Using these methods will provide more reliable efficacy estimates in the pediatric study, if the assumption that the adult outcomes are similar to the pediatric outcomes is accurate. In order to do this analysis, we need to have information on the same clinically relevant endpoint in both populations.

The pediatric study used the same primary efficacy endpoint as the adult study (SRI response rate at Week 52) and included all of the major secondary endpoints from the adult study (SELENA SLEDAI, BILAG, PGA, SRI, SLE flare index, etc.). We focused this review on the Bayesian analyses of the primary endpoint , SRI response rate.

The inclusion criteria, pharmaceutical form, administration route, and dosing of belimumab (10 mg/kg) in C1109 were largely similar to the two pivotal phase 3 studies in adults with the appropriate modifications for treatment made to pediatric subjects. Pediatric subjects were required to have a clinical diagnosis of SLE in accordance with ACR criteria (same as adults) and an ANA titer ≥1:80 and/or anti-dsDNA ≥30 IU/mL at 2 independent time points within the study screening period (or one positive historical test result and one positive test result). Initially, the pediatric study had a higher SELENA SLEDAI score requirement (≥ 8 at screening). This was subsequently relaxed to same as the adult study (≥6 at screening).

Bayesian Analysis of SRI endpoint

The applicant's primary analysis of the primary efficacy endpoint for the pediatric studies are shown in Table 22 and the results of the phase 3 adult studies are shown in Table 23. The estimated odds ratios are similar, with wider confidence intervals for the pediatric study due to the smaller number of subjects. As discussed above, the clinical division believes that the treatment responses are expected to be similar between the adult and pediatric subjects, therefore, the information from the previous adult studies (C1056 and C1057) could be valuable and relevant to the pediatric population.

An information request (IR) was sent to the Applicant on 14 December 2018, asking the Applicant to conduct additional analyses using a Bayesian mixture prior approach which borrows the information from the adult studies to evaluate the primary endpoint for the pediatric study, SRI response at Week 52. In particular, the statistical review team recommended the Applicant to perform the following analysis:

a. *Conduct a meta-analysis of the adult studies (C1056, C1057) to obtain a single treatment effect estimate and distribution.*
b. *Propose a skeptical prior of the treatment effect for the pediatric population. For example, you may consider a normal prior centered at zero with a standard deviation based on historical studies, i.e., the estimated patient level standard deviation divided by the number of subjects in study C1109.*
c. *Construct the pediatric study prior using a weighted combination of the above components:*
    - *Pediatric Study Prior*$= (1 - a) * f(D) + a * g(D)$
    - *f(D): skeptical prior, g(D): adult treatment effect estimate distribution*
    - *a= relative weight to apply to the adult study data*
d. *Compute the posterior probability of efficacy, by calculating the percentage of posterior samples where the sample of the treatment effect estimate is greater than zero.*
e. *Repeat with different values of a, representing increased weight on the adult data, in the range of 0 to 1 with increments of 0.05.*
f. *Determine the range of weights where the posterior probability of efficacy exceeds specific high thresholds, including 95%, 97.5%, and 99%.*
g. *Produce a plot of the posterior probability of efficacy across the range of potential weights, i.e., where the vertical axis shows the posterior probability of a pediatric treatment effect greater than zero and the horizontal axis shows the value of a.*

The applicant conducted the Bayesian analysis and derived inference on the pediatric treatment effect using the following Bayesian model:

$$y_p \sim N(\delta_p, s_P^2)$$
$$\delta_P \sim (1-a) \times N(0, m * s_P^2) + a \times N(Y_A, s_A^2),$$

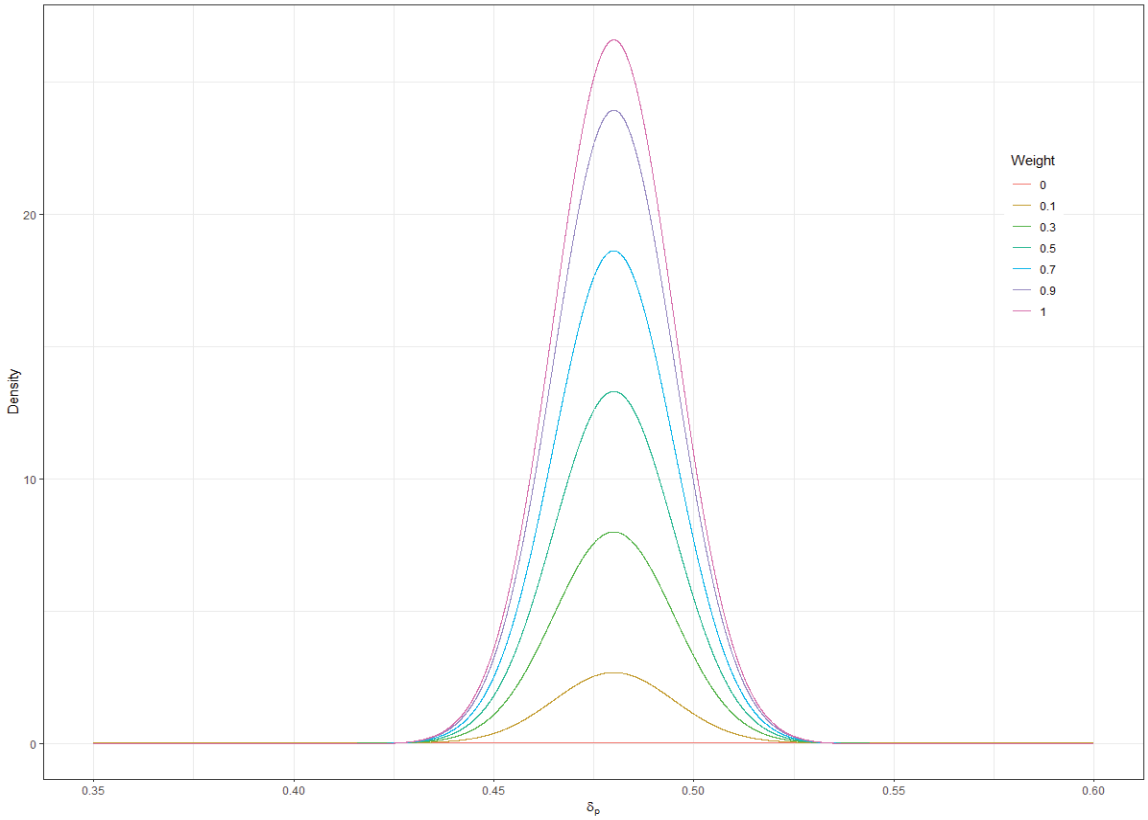
where y_p and y_A are the observed log odds ratios of response from a logistic regression, δ_p is the pediatric treatment effect parameters, s_P^2 and s_A^2 are estimated variances of the log odds ratio, and a is the prior weight assigned to the adult prior component which represents the prior degree of belief in the similarity of the pediatric and adult treatment effects. The mean of the skeptical component was assumed as 0 (i.e. centered at the null hypothesis of no effect) and the variance is assumed to be $m * S_A^2$, where m was chosen such that the effective sample size of this component is worth just one pediatric subject per arm. Thus, the pediatric treatment effect prior can be written as,

$$\delta_p \sim (1-a) \times N(0, 8.27) + a \times N(0.48, 0.015)$$

The modeling was performed on the log odds ratio scale as the outcome is expected to be approximately normal on this scale. With the exception of Figure 21 which uses the odds ratio scale, all the results are presented on the log odds scale.

Figure 20 shows the distribution of pediatric prior across the range of weight values. The higher weights result in a narrow prior distribution centered around the adult mean value and the lower weights generate heavier tailed distributions. In particular, when there is no borrowing from adult population (a=0), the pediatric study prior distribution become flat around mean zero.

Figure 20. Distribution of Pediatric Study Prior across Different Weight Values



Source: FDA Statistical Reviewer

The applicant computed the posterior probability of efficacy (treatment effect greater than zero) by calculating the percentage of posterior samples where the sampled treatment effect estimate was greater than zero. The numerical summaries of the posterior distribution obtained for each prior weight are given in Table 33.

Table 33. Posterior mean, median and 95% credibility interval for the log odds ratio of SRI Response

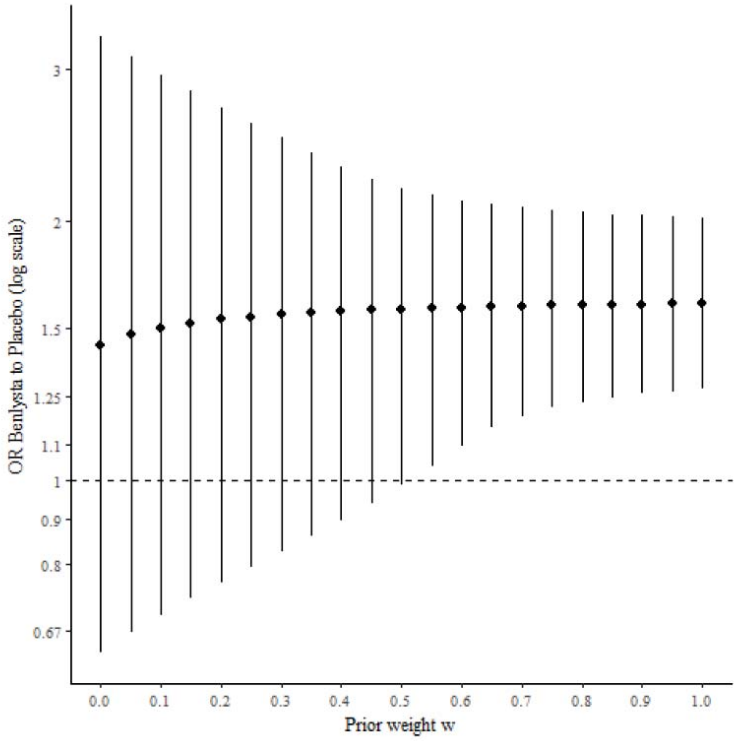
Weight (a)	Mean Log Odds	Median Log Odds	*95% C*redible *I*nterval	Posterior Probability of Efficacy
0.00	0.36	0.36	(-0.46, 1.18)	0.81
0.05	0.39	0.42	(-0.41, 1.13)	0.85
0.10	0.41	0.44	(-0.36, 1.08)	0.89
0.15	0.42	0.45	(-0.32, 1.04)	0.91
0.20	0.43	0.46	(-0.27, 1.00)	0.93

0.25	0.44	0.46	(-0.23, 0.95)	0.94
0.30	0.44	0.46	(-0.19, 0.91)	0.95
0.35	0.45	0.46	(-0.15, 0.87)	0.96
0.40	0.45	0.46	(-0.11, 0.84)	0.96
0.45	0.45	0.47	(-0.06, 0.80)	0.97
0.50	0.46	0.47	(-0.01, 0.78)	0.97
0.55	0.46	0.47	(0.04, 0.76)	0.98
0.60	0.46	0.47	(0.09, 0.75)	0.98
0.65	0.46	0.47	(0.14, 0.74)	0.98
0.70	0.46	0.47	(0.17, 0.73)	0.99
0.75	0.47	0.47	(0.19, 0.72)	0.99
0.80	0.47	0.47	(0.21, 0.72)	0.99
0.85	0.47	0.47	(0.22, 0.71)	0.99
0.90	0.47	0.47	(0.23, 0.71)	1.00
0.95	0.47	0.47	(0.24, 0.70)	1.00
1.00	0.47	0.47	(0.24, 0.70)	1.00

Source: Applicant

The applicant's analysis shows that prior weights of 0.55 or larger lead 95% credible intervals excluding zero and posterior probabilities of efficacy (treatment effect greater than zero) of greater than 97.5%. These two criteria correspond to a rejection of the null hypothesis for a one-sided p-value less than 0.025 in the usual frequentist paradigm. Plots of the posterior mean odds ratio and corresponding 95% credible intervals are shown in Figure 21.

Figure 21. Posterior mean (points) and 95% credibility intervals (lines) of the odds ratio of SRI response



Source: Applicant

The statistical review team re-analyzed these data using a Bayesian logistic regression model, which accounts for the covariates such as treatment, baseline SELENA SLEDAI and age group. The model used is as follows:

$$y_P \sim Bernoulli(\theta)$$
$$\text{with } \theta = logit(\beta_1 + \beta_2 \times trt + \beta_3 \times BaseSledai + \beta_4 \times AgeGroup)$$

with the following prior distributions:

$$\beta_2 \sim (1-a) \times N(0,8.27) + a \times N(0.51,0.016)$$
$$\beta_i \sim N(0,100),\ i=1,3,4$$

The adult treatment effect estimate distribution is based on the Statistical Reviewer's meta-analysis of the adult studies. In the skeptical component of the prior distribution, we retained the same variance assumed by the applicant.

The numerical summaries of the posterior distribution obtained for each prior weight are given in Table 34. A plot of posterior probability of efficacy ($\beta_2 > 0$) with the probability exceeding 97.5% threshold (shown as the red horizontal line) shows that the results are comparable with the applicant's analysis (Figure 22). Again, a prior weight of 0.55 or larger lead to posterior

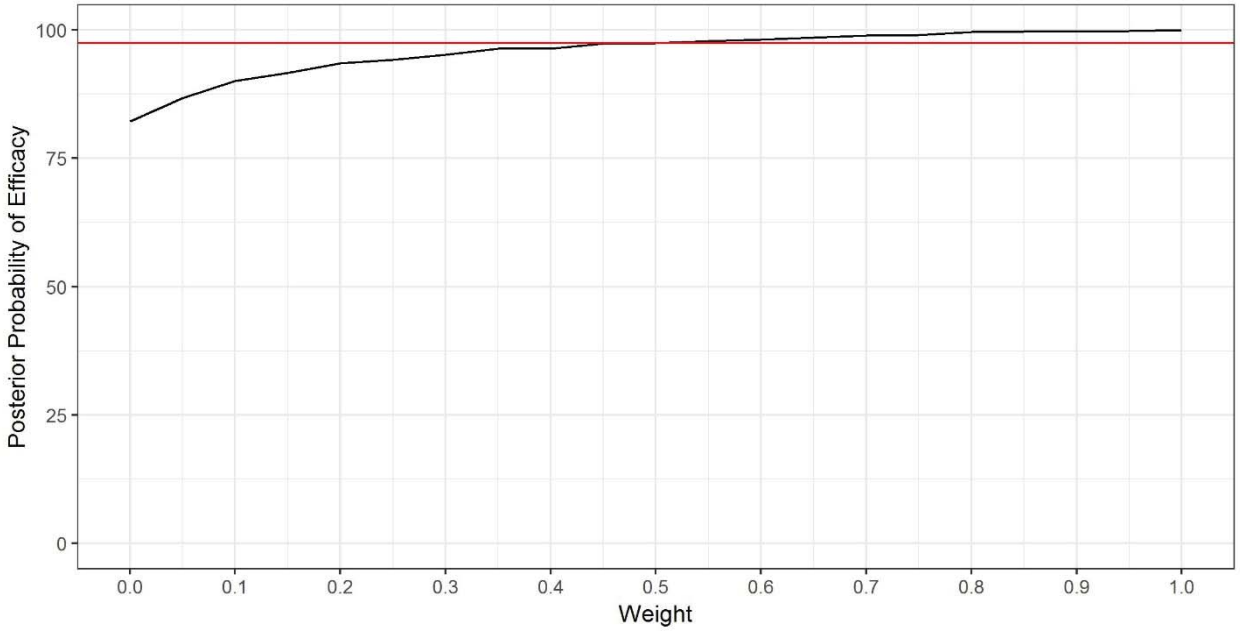
probabilities of efficacy that the 97.5% threshold and 95% credible intervals that exclude zero corresponding a rejection of the null hypothesis with the usual one-sided type I error of 0.025.

Table 34. Posterior mean, median and 95% credibility interval for the log odds ratio of SRI Response

Weight (a)	Mean	Median	95% Credible Intervals	Posterior Probability of Efficacy
0.00	0.40	0.40	(-0.44,1.25)	0.82
0.05	0.43	0.46	(-0.39,1.21)	0.87
0.10	0.45	0.48	(-0.34,1.16)	0.90
0.15	0.45	0.48	(-0.30,1.10)	0.92
0.20	0.47	0.49	(-0.23,1.04)	0.94
0.25	0.47	0.49	(-0.22,1.01)	0.94
0.30	0.47	0.49	(-0.17,0.96)	0.95
0.35	0.48	0.50	(-0.10,0.91)	0.96
0.40	0.48	0.49	(-0.11,0.88)	0.96
0.45	0.48	0.50	(-0.02,0.85)	0.97
0.50	0.49	0.50	(-0.01,0.82)	0.97
0.55	0.49	0.50	(0.05,0.80)	0.98
0.60	0.49	0.50	(0.09,0.78)	0.98
0.65	0.49	0.50	(0.14,0.78)	0.99
0.70	0.50	0.50	(0.19,0.77)	0.99
0.75	0.50	0.50	(0.21,0.76)	0.99
0.80	0.50	0.50	(0.25,0.76)	1.00
0.85	0.50	0.50	(0.25,0.75)	1.00
0.90	0.50	0.50	(0.26,0.75)	1.00
0.95	0.50	0.50	(0.26,0.75)	1.00
1.00	0.50	0.50	(0.26,0.74)	1.00

Source: FDA Statistical Reviewer

Figure 22. Posterior probability of efficacy across different weight values



Source: FDA Statistical Reviewer

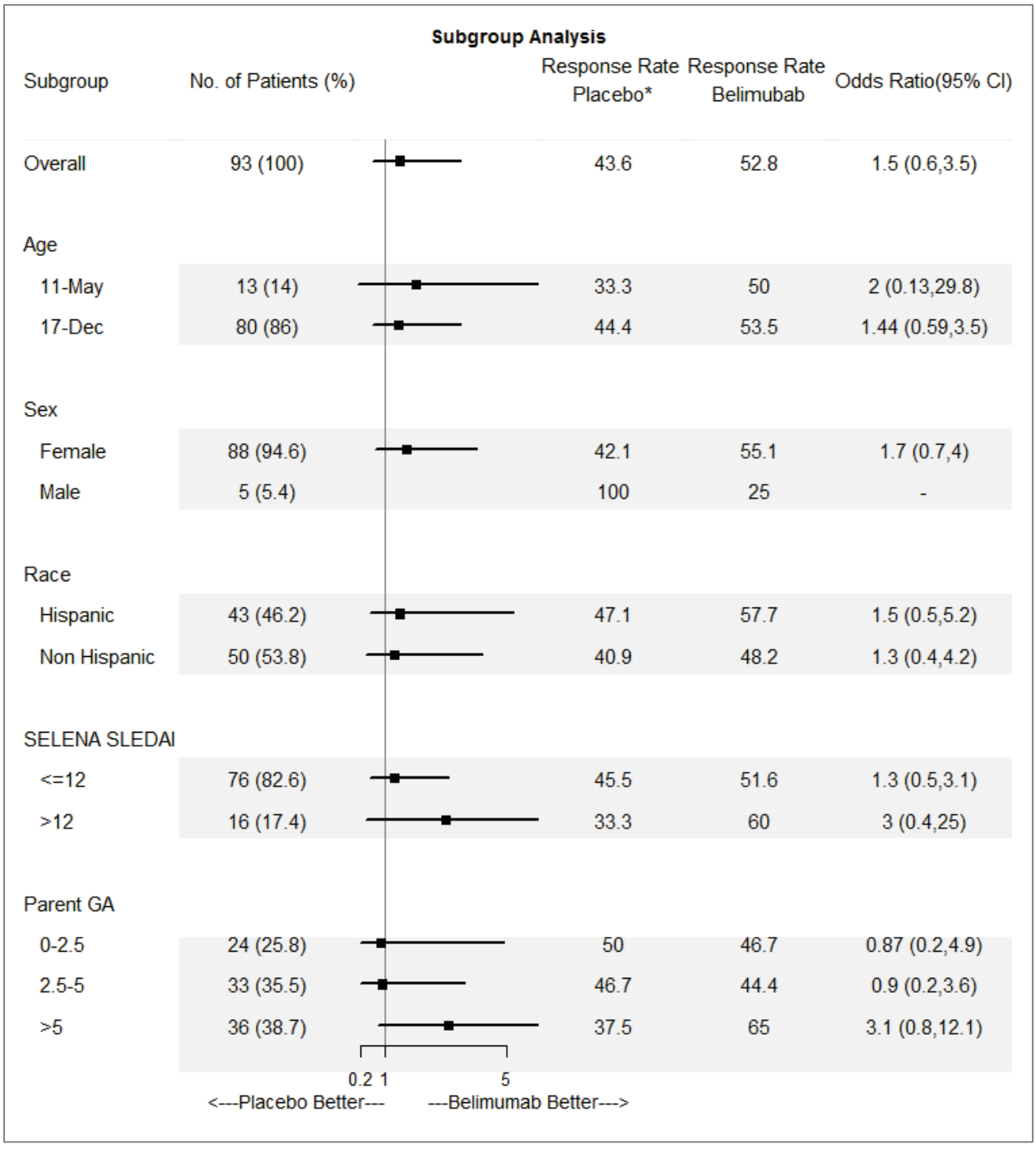
To conclude, borrowing information appears reasonable, as the efficacy results from the pediatric study were largely similar to the results from the previous adult IV studies, with wider confidence intervals for the pediatric study due to the smaller enrollment. As noted above, most of the baseline disease characteristics (Table 15 and Table 16) were similar in the pediatric and adult IV study populations.

Based on discussion and feedback obtained from the clinical team, it appears reasonable to assume at least 55% weight on the relevance of the adult information to the pediatric population and we can therefore conclude that there is at least 97.5% posterior probability that belimumab 10 mg/kg has a positive treatment effect in pediatric subjects.

8.1.1.4.2. Findings in subgroup populations

The subgroup analyses compared efficacy results across treatment arms within different subgroups defined by age, sex, race and SELENA SLEDAI and parentGA values. Figure 23 given below shows that belimumab group has a better SRI response in majority of the subgroups compared to the placebo group.

Figure 23. Subgroup Analysis for Study C1109 (Part A)



Source: FDA Statistical Reviewer

* One subject in placebo did not have a baseline SELENA SLEDAI assessment and, therefore, did not contribute to subgroup analyses.

8.1.1.5. Statistical Issues

The following statistical issues have been identified during the review process.

8.1.1.5.1. Potential Impacts of Missing Data

The 2010 National Research Council (NRC) report *The Prevention and Treatment of Missing Data in Clinical Trials* recommends that "examining sensitivity to the assumptions about the missing data mechanism should be a mandatory component of reporting." As we noted before, up to week 52, 17 (18.3%) subjects had withdrawn from the study: 9 (22.5%) subjects from placebo and 8 (15.1%) subjects from belimumab 10 mg/kg. The patient withdrawal in the pediatric study was consistent with the adult studies (70 (25.5%) subjects from placebo and 64 (23.4%) subjects from belimumab 10 mg/kg in study C1056 and 61 (21.3%) subjects from placebo and 49 (16.9%) subjects from belimumab 10 mg/kg in study C1057). The applicant performed a variety of sensitivity analyses using different analysis methods, such as a logistic regression analyses without adjustment for covariates, an analysis with LOCF for missing data, and analyses restricted to completers and to the per-protocol population. Results from the sensitivity analyses were consistent with the primary analysis.

8.1.1.5.2. Power and Sample size

The study was not powered to conduct formal statistical hypothesis testing. In addition, placebo-controlled phase 3 study in pediatric subjects was not feasible because of the rarity of the disease in children. Furthermore, the sample size calculations were based on enrolment practicality rather than statistical power considerations. Therefore, the data were summarized using descriptive statistics and confidence intervals.

Integrated Review of Effectiveness

8.1.2. Integrated Assessment of Effectiveness

The collective evidence from this comparative clinical study in pediatric SLE subjects supports the conclusion of better efficacy for the belimumab 10 mg/kg IV group compared to the placebo group. Due to enrollment challenges, the pediatric study C1109 was not adequately powered to reach a definitive conclusion by itself. The proportion of subjects who obtained an SRI-4 response at Week 52 was found to be greater in belimumab IV group (52.8%) compared to the placebo group (43.6%) and the odds ratio was 1.5 with a 95% CI of (0.6, 3.5). SRI-4 response at Week 52 of the pediatric study was consistent with the adult IV studies (C1056 and C1057). In particular, the SRI-4 response rate in the pediatric study was found to be largely similar to the Study 1057 (Placebo: 44% and belimumab 10 mg/kg: 58%). Analysis of each individual SRI components also showed higher percentages of responders in the belimumab 10 mg/kg IV group compared to the placebo group. Analysis of major secondary endpoints such as PRINTO/ACR, sustained SRI response, and sustained parentGA response, and other secondary efficacy endpoint results, also showed improvement in belimumab group.

The Agency requested the applicant to conduct a post-hoc Bayesian analysis of the pediatric data using borrowed information from the adult studies C1056 and C1057. The applicant's analysis of the pediatric data indicated that the posterior probability of a positive treatment effect was at least 97.5% when the weight on the prior based on the adult data was 0.55 or more. Independent analysis by the statistical review team showed comparable results. With additional inputs from other review disciplines, assuming a weight of at least 0.55 was found to be reasonable (corresponding to at least a 55% probability that efficacy in pediatrics is similar to that in adults) and concluded that the treatment effect of belimumab in the pediatric population favors belimumab 10 mg/kg IV compared to placebo.

8.1.2.1. Conclusions and Recommendations

In summary, there was evidence of efficacy for belimumab 10 mg/kg IV on pediatric subjects based on the results from the pediatric study C1109. These results of the pediatric study are generally consistent with the results obtained from the two adult IV studies that were reviewed before under the application, BLA 125370. Therefore, the overall package provides evidence of efficacy for the proposed IV administration of belimumab 10 mg/kg for the treatment of SLE in pediatric subjects.

8.2. Review of Safety

8.2.1. Safety Review Approach

This application contained double-blind safety data from pediatric SLE patients collected over 52-weeks of IV belimumab 10mg/kg dosing during Part A of study C1109. Safety data for the 8-week exit-visit for 3 out of the 4 pediatric subjects who withdrew from Part A and did not enter ongoing Parts B or C of study C1109 were included for completeness. For comparative purposes, the application also contained high level analyses of pooled safety data from the completed IV belimumab phase 3, randomized, double-blind, controlled studies conducted in adult SLE patients (LBSL02, C1056, and C1057) with the approved marketed dose (10 mg/kg) as well as crossed-referenced safety data from these studies for all doses (1mg/kg, 4 mg/kg and 10 mg/kg) that were evaluated in the clinical development program for IV belimumab. The focus of the following safety review is on the safety data summarized in the clinical study report for study C1109, the Integrated Summary of Safety and electronic datasets for adverse events (AES), lab data, and vital signs. Interim serious adverse event (SAE) and pregnancy data generated from the ongoing open-label continuation phase (Part B) and the follow-up phase (Part C) of study C1109 were also provided for the reporting period January 25, 2018 through November 20, 2018 in the 120-Day Safety Update submitted on February 8, 2019 and are included in pertinent areas of the following discussion. These data were examined by the clinical reviewer for any additional or new safety signals associated with the administration of IV belimumab in pediatric SLE patients. Since safety data from the three phase 3 studies (LBSL02, C1056 and C1057) has been previously reviewed in support of the marketing approval of IV belimumab for treatment of adults with SLE, it will not be re-presented here but only considered where pertinent in the discussion that follows.

8.2.2. Review of the Safety Database

Overall Exposure

The cumulative duration of pediatric exposure to IV belimumab at the 10 mg/kg dose in study 1109 is shown in Table 20 above with a total mean duration of exposure of 334 days (SD: 79 days).

Adequacy of the safety database:

Since the safety profile of belimumab IV has been previously established based on safety data from 1693 adult subjects with SLE, the size of the safety database for this submission (N=93 pediatric subjects) is adequate to provide sufficient basis for a risk/benefit assessment in the pediatric SLE population.

Issues Regarding Data Integrity and Submission Quality

The data quality submitted was well-organized and adequate to perform a complete review of safety. Several information requests were sent to the applicant during the review of safety for additional analyses which were satisfactory and received in a timely manner.

Categorization of Adverse Events

Verbatim terms of AEs and Disease Related Events (DRE) recorded in the case report forms (CRF) by investigators were coded by the applicant using MedDRA dictionary Preferred Term (PT), High-Level Term (HLT), and System Organ Class (SOC) version 20.1. The MedDRA coding of the information generated from study C1109 conducted by the applicant was generally acceptable. Additionally, the clinical lab and vital sign ranges for clinically significant abnormal results was reviewed and appeared to be appropriate.

Routine Clinical Tests

The following clinical and lab testing were conducted in study C1109 in support of belimumab SC's safety profile:

- Symptom driven physical exam, height and weight
- Vital signs: systolic and diastolic blood pressure, respiratory rate and temperature
- Complete cell count (CBC) with differential and platelet count, hemoglobulin and hematocrit; PT/PTT
- Serum chemistries; albumin, alkaline phosphatase, ALT, AST, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, lactic dehydrogenase, phosphorus, potassium, sodium, direct bilirubin, total bilirubin, and total protein
- Urinalysis: including pH, specific gravity, protein, glucose, ketones, nitrite, occult blood, bilirubin, urobilinogen
- Spot urine for protein to creatinine ratio
- Pregnancy testing

- 12-lead ECG (baseline only)
- Columbia-Suicide Severity Rating Scale (C-SSRS) (in subjects age ≥12 years)
- Serum immunoglobulins (IgG, IgM and IgA), autoantibodies (ANA, anti-dsDNA, and aCl), CRP, and serum complement (C3 and C4)
- BLyS protein and immunogenicity
- FACS of peripheral lymphocytes (B cells: CD19+, CD20+, CD19+/20+/27-naïve, CD19+/20+/27+ memory, CD19+/20+/69+ activated, CD19+/20+/138+ plasmacytoid, CD19+/38b+27b+Lymph SLE subset, CD19+/20-/138+plasma cells and CD19+/20-/27b+ short-lived plasma cells

Overall, the types of clinical lab testing and physical assessments as well as the timing of these assessments were appropriate for the pediatric population studied in this trial and are the same as those employed in the adult belimumab IV studies C1056 and C1057 (refer to review of BLA 125370 dated February 18, 2011 for additional information.)

8.2.3. Safety Results

All safety analyses were performed on the population who received at least one dose of study medication (the Intention-to-Treat [ITT] population) in the pivotal adult and pediatric belimumab IV studies. Table 35 summarizes adverse events (AEs) that were reported in the safety database for the 52-weeks of the controlled portion of study C1109 by pediatric treatment group as well as the previously reviewed pooled safety data from the adult SLE belimumab IV phase 2 and 3 studies LBSL02, C1056 and C1057. The majority of patients experienced at least one AE while participating in these trials. However, unlike the adult belimumab IV studies, the proportions of pediatric patients who experienced a serious adverse event (SAE), an infection, serious infection, or at least 1 AE leading to discontinuation of study treatment were higher in the pediatric placebo group compared to the pediatric belimumab IV group in study C1109. There were also no deaths or malignancies reported in the pediatric belimumab IV group versus 1 death and no malignancies in the pediatric placebo IV group for this study. This is in contrast to the higher proportions of death that occurred in adult patients who received the marketed 10 mg/kg dose of belimumab IV and/or all doses of belimumab IV versus placebo IV as well as the comparable rates of malignancy in all of the adult treatment groups contained in the safety database reviewed in support of belimumab IV's marketing approval, Table 35 (refer to clinical review for BLA 125370 dated February 18, 2011). An in-depth examination of the imbalances between the pediatric treatment groups of study C1109 starting with deaths follows below.

Table 35. Summary of Adverse Events and Deaths in the Controlled Portions of the Pooled IV Adult Studies LBSL02, C1056 and C1057 and Pediatric Study 1109 (Part A) (ITT Population)

	LBSL02/C1056/C1057 Pooled IV Adult Studies			C1099 IV Pediatric	
Number of Subjects with at Least One:	Placebo N=675	BEL 10mg/Kg N=674	BEL (All Doses) N=1458	Placebo N=40	BEL 10mg/kg N=53
Any AE	623 (92%)	625 (93%)	1354 (93%)	33 (83%)	42 (79%)
Any SAE	103 (15%)	113 (17%)	248 (17%)	14 (35%)	9 (17%)
Any Infection	450 (67%)	471 (70%)	1037 (71%)	28 (70%)	30 (57%)
Any Serious Infection	35 (5%)	35 (5%)	88 (6%)	5 (13%)	4 (8%)
Any Malignancy	3 (0.4%)	3 (0.4%)	6 (0.4%)	0	0
Any AE Leading to Discontinuation	48 (7%)	42 (6%)	88 (6%)	5 (13%)	3 (6%)
Deaths	3 (0.4%)	6 (0.9%)	11 (0.8%)	1 (2.5%)	0

Sources: Applicant's Table 3.2; p. 660 and Table 68 from the FDA's Clinical Review for BLA 125370 dated February 18, 2011

Deaths

As of the 120-day safety cut-off November 20, 2018, there was a total of 1 death involving an adolescent patient randomized to the placebo group that occurred over the course of the ongoing pediatric study C1109 (Table 36). An autopsy was not performed and this patient's death while receiving standard of care immunosuppressives and corticosteroids was attributed to worsening of her underlying SLE. In the adult belimumab IV studies, the most common cause of death was due to infectious etiologies, followed by cardiovascular (including stroke) events, suicide, SLE-complications, unknown causes and malignancy. The types of deaths reported in the adult belimumab IV safety database was found to be consistent with the use of concomitant immunosuppressive therapies and with the risks related to underlying and concomitant medical conditions (refer to clinical review of BLA 125370 dated February 18, 2011).

Table 36. Summary of Deaths During the Controlled Portion of Study C1109 (Part A) (ITT Population)

Subject Number	Age/Sex	Cause of Death	Days Since 1st Infusion	Days Since Last Infusion	Pertinent History
Placebo					
(b) (6)	17yo/F	Acute pancreatitis	51	23	Concomitant Meds: Heparin, omeprazole, calcitriol, colecalciferol, mycophenolate mofetil, chloroquine and prednisone. On Day 47 she presented with severe abd. pain with N/V and abd. extension and was hospitalized. Abd. CT showed edema of intestinal wall with mild splenomegaly and mild heterogenous increase of pancreas w/o necrosis. CXR showed bilat. diffuse pulmonary infiltrates. Labs were remarkable for ↑amylase and ↑lipase. She was treated with IV pulse steroids for acute pancreatitis secondary to SLE with initial good initial response but become hypotensive, tachycardic and oliguric with raising lactate levels and refractory metabolic acidosis with recurrent abd. pain, N/V and respiratory failure. She was intubated but died on Day 51 despite aggressive medical treatment. No autopsy performed.

Abd. = abdominal; N/V= nausea and vomiting; w/o= without; CXR=chest x-ray; bilat. = bilateral.

Serious Adverse Events

Table 37 summarizes the serious adverse events (SAEs) observed during the controlled portion of the pediatric study C1109 by MedDRA system organ class (SOC) and preferred term (PT). Overall, a higher proportion of patients experienced treatment-emergent SAEs in the pediatric placebo group than in the pediatric belimumab IV group. Numeric imbalances in SAEs not in favor of the pediatric placebo are noted in most system organ classes with a few exceptions. A higher proportion of SAEs not in favor of the pediatric belimumab IV group occurred in the skin and subcutaneous, cardiac and hepatobiliary disorders system organ classes. Review of the data in Table 37 revealed that most of the SAEs were due to manifestations of pediatric patient's SLE and did not identify any potential patterns or safety signals due to the small numbers of SAEs observed during the controlled portion of pediatric study C1109. Serious infections and infestations and psychiatric disorders will be discussed further with adverse events of special interest (AESIs). Overall, the proportion of SAEs observed in the pediatric belimumab IV treatment group was similar to that observed in the adult belimumab IV pivotal studies reviewed in support of the product's marketing approval (see Table 35 above). However, the types and patterns of SAEs noted in the adult SLE population evaluated in studies LBSL02, C1056 and C1057 were different from those observed in the pediatric population evaluated in study 1109. This finding is most likely due to end-organ damage because of longer duration of underlying SLE disease as well as differences in concomitant medical conditions

(cardiovascular disease and reproductive issues) in the adult population studied (refer to clinical review of BLA 125370 for belimumab IV dated February 18, 2011).

Table 37. Serious Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class (SOC) /Preferred Term (PT) During Controlled Portion of C1109 (Part A) (ITT Population)

MedDRA System Organ Class (SOC)/Preferred Term (PT)[1]	Placebo N=40	Belimumab IV N=53
Number of Subjects with ≥1 Serious Adverse Event (SAE)	**14 (35%)**	**9 (17%)**
Infections and Infestations	**5 (13%)**	**4 (8%)**
Herpes Zoster	1 (3%)	1 (2%)
Abscess Limb	0	1 (2%)
Epiglottitis	1 (3%)	0
Gastroenteritis	0	1 (2%)
Hepatitis A	1 (3%)	0
Influenza	1 (3%)	0
Pneumonia	1 (3%)	0
Vulval Abscess	0	1 (2%)
Renal and Urinary Disorders	**3 (8%)**	**2 (4%)**
Lupus Nephritis	2 (5%)	2 (4%)
Glomerulonephritis	1 (3%)	0
Nervous System Disorders	**2 (5%)**	**2 (4%)**
Headache	2 (5%)	0
Idiopathic Intracranial Hypertension	0	1 (2%)
Post-Herpetic Neuralgia	0	1 (2%)
Gastrointestinal Disorders	**2 (5%)**	**1 (2%)**
Pancreatitis Acute	1 93%)	0
Vasculitis Gastrointestinal	0	1 (2%)
Vomiting	1 (3%)	0
Musculoskeletal and Connective Tissue Disorders	**2 (5%)**	**1 (2%)**
Osteochondrosis	1 (3%)	0
SLE Arthritis	1 (3%)	0
Systemic Lupus Erythematosus	0	1 (2%)
Psychiatric Disorders	**3 (7.5%)**	**0**
Major Depression	1 (3%)	0
Suicidal Ideation	1 (3%)	0
Suicide Attempt	1 (3%)	0
Eye Disorders	**2 (5%)**	**0**
Eye Swelling	1 (3%)	0
Retinal Vasculitis	1 (3%)	0
General Disorders and Administration Site Conditions	**2 (5%)**	**0**
Chest Pain	1 (3%)	0
Pyrexia	1 (3%)	0
Skin and Subcutaneous Tissue Disorders	**0**	**2 (4%)**
Rash	0	1 (2%)
Skin Lesion	0	1 (2%)

Blood and Lymphatic System Disorders	**1 (3%)**	**0**
Anemia	1 (3%)	0
Thrombocytopenia	1 93%)	0
Cardiac Disorders	**0**	**1 (2%)**
Pericardial Effusion	0	1(2%)
Hepatobiliary Disorders	**0**	**1 (2%)**
Hypertransaminasemia	0	1 (2%)
Injury, Poisoning and Procedural Complications	**1 (3%)**	**0**
Ligament Sprain	1 (3%)	0
Metabolism and Nutrition Disorders	**1 (3%)**	**0**
Fluid Overload	1(3%)	0
Respiratory, Thoracic and Mediastinal Disorders	**1 (3%)**	**0**
Pleural Effusion	1 (3%)	0

Source: Applicant's Table 3.7; p. 684.
[1]Subjects are only counted once per SOC/PT.

No safety signals were identified on review of the data collected from the ongoing open-label extension (Part B) or follow-up portion (Part C) of study C1109 contained in the 120-safety follow-up.

Dropouts and/or Discontinuations Due to Adverse Effects

A summary of adverse events by SOC and PT that resulted in patients discontinuing treatment during the controlled portion of study C1109 is shown in Table 38. A higher proportion of pediatric subjects discontinued treatment with placebo as compared to belimumab IV. Examination of the data in this table revealed that Renal and Urinary disorders, Hepatobiliary and Nervous System Disorders were the most common types of AEs resulting in pediatric belimumab IV patients withdrawing prematurely from this trial and no new safety concerns were identified. The higher rate of discontinuations from study treatment seen in the Renal and Urinary Disorders by pediatric placebo patients may be due to the imbalance in renal involvement not in favor of the pediatric placebo group at baseline as a result of the unequal randomization into the two age cohorts. Many of the discontinuations in both treatment groups listed in Table 38 were due to worsening of or new manifestations of underlying SLE disease. Similar patterns of withdrawals due to worsening or new manifestations of underlying SLE disease were observed in the adult patient safety database reviewed in support of belimumab IV's marketing approval (refer to clinical review of BLA 125370 belimumab IV dated February 18, 2011).

Table 38. Discontinuations Due to Adverse Events (AEs) During the Controlled Portion of Study C1109 (Part A) (ITT Population)

MedDRA System Organ Class (SOC)/Preferred Term (PT)[1]	Placebo N=40	Belimumab IV N=53
Number of Subjects with ≥ 1 AE Leading to Discontinuation	**5 (13%)**	**3 (6%)**
Renal and Urinary Disorders	**2 (5%)**	**1 (2%)**
Lupus Nephritis	2 (5%)	1 (2%)
Eye Disorders	**1 (3%)**	**0**
Retinal Vasculitis	1 (3%)	0
Gastrointestinal Disorders	**1 (3%)**	**0**
Pancreatitis Acute	1 (3%)	0
Hepatobiliary Disorders	**0**	**1 (2%)**
Hypertransaminasemia	0	1 (2%)
Infections and Infestations	**1 (3%)**	**0**
Hepatitis A	1 (3%)	0
Nervous System Disorders	**0**	**1 (2%)**
Post Herpetic Neuralgia	0	1 (2%)

Source: Applicant's Table 3.16; p. 706.
[1]Subjects are only counted once per SOC/PT.

Significant Adverse Events

Table 39 is a tabular listing of adverse events observed during the double-blind portion of the pediatric study C1109 by treatment group that were rated as severe in nature by study investigators. A higher proportion of pediatric placebo subjects experienced severe treatment emergent adverse events as compared to the belimumab IV group. The most common severe treatment emergent adverse events in this study were: chest pain, thrombocytopenia and lupus nephritis of which the latter two are manifestations of underlying SLE disease activity. No safety signals were identified on review of the severity data listed in Table 39 which was comparable to that observed in the adult SLE belimumab IV studies (refer to clinical review of BLA 125370 belimumab IV dated February 18, 2011).

Table 39. Severe Treatment Emergent Adverse Events (TEAEs) Reported During Study C1099 (Part A) (ITT Population)

MedDRA System Organ Class (SOC)/Preferred Term (PT)[1]	Placebo N=40	Belimumab IV N=53
Number of Subjects with Any Severe TEAE	**12 (30%)**	**6 (11%)**
Infections and Infestations	**2 (5%)**	**3 (6%)**
Herpes Zoster	0	1 (2%)
Pneumonia	1 (3%)	0
Streptococcal Infection	0	1 (2%)
Epiglottitis	1 (3%)	0
Vulval Abscess	0	1 (2%)
Gastrointestinal Disorders	**1 (3%)**	**1 (2%)**
Abdominal Pain Lower	0	1 (2%)
Pancreatitis Acute	1 (3%)	0
Musculoskeletal and Connective Tissue Disorders	**1 (3%)**	**1 (2%)**
Arthralgia	1 (3%)	0
Osteoporosis	0	1 (2%)
General Disorders and Administration Site Conditions	**2 (5%)**	**0**
Chest Pain	2 (5%)	0
Fatigue	1 (3%)	0
Nervous System Disorders	**2 (5%)**	**0**
Headache	1 (3%)	0
Somnolence	1 (3%)	0
Respiratory, Thoracic, and Mediastinal Disorders	**1 (3%)**	**0**
Pleural Effusion	1 (3%)	0
Lupus Pleurisy	1 (3%)	0
Blood and Lymphatic System Disorders	**3 (8%)**	**0**
Leukopenia	1 (3%)	0
Anemia	1 (3%)	0
Thrombocytopenia	2 (5%)	0
Investigations	**1 (3%)**	**0**
White Blood Cell Count	1 (3%)	0
Neutrophil Count	1 (3%)	0
Renal and Urinary Disorders	**1 (3%)**	**2 (4%)**
Lupus Nephritis	1 (3%)	2 (4%)
Proteinuria	0	1 (2%)
Psychiatric Disorders	**1 (3%)**	**0**
Suicide Attempt	1 (3%)	0
Eye Disorders	**1 (3%)**	**0**
Retinal Vasculitis	1 (3%)	0
Reproductive System and Breast Disorders	**0**	**1 (2%)**
Menorrhea	0	1 (2%)

Source: Applicant's Table 3.26; p. 736-47.
[1]Subjects are only counted once per SOC/PT.

Treatment Emergent Adverse Events

Most pediatric subjects experienced a treatment emergent adverse event (TEAE) during the controlled portion of study C1109. Table 40 lists the frequency of the TEAEs observed in this study by SOC and treatment group. The proportions of pediatric subjects who had a TEAEs were comparable for the two treatment groups. Infections and Infestations, Gastrointestinal Disorders, Musculoskeletal and Connective Tissue Disorders, Nervous System 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 and are similar to what was observed in the safety databases reviewed in support of the IV formulation of belimumab in adult SLE patients (refer to clinical review of BLA 125370 belimumab IV dated February 18, 2011).

Table 40. Common Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class During the Controlled Portion of Study 1109 (Part A) (ITT Population)

MedDRA System Organ Class (SOC)[1]	Placebo N=40	Belimumab IV N=53
Number of Subjects (%) Who Experienced Any TEAE	**33 (83%)**	**42 (79%)**
Infections and Infestations	28 (70%)	30 (57%)
Gastrointestinal Disorders	16 (40%)	18 (34%)
Musculoskeletal and Connective Tissue Disorders	13 (33%)	11 (21%)
Nervous System Disorders	11 (28%)	12 (23%)
Skin and Subcutaneous Tissue Disorders	9 (23%)	10 (19%)
General Disorders and Administration Site Conditions	9 (23%)	9 (17%)
Respiratory, Thoracic, and Mediastinal Disorders	8 (20%)	10 (19%)
Injury, Poisoning and Procedural Complications	7 (18%)	10 (19%)
Blood and Lymphatic System Disorders	7 (18%)	7 (13%)
Investigations	6 (15%)	7 (13%)
Renal and Urinary Disorders	7 (18%)	4 (8%)
Psychiatric Disorders	6 (15%)	3 (6%)
Eye Disorders	2 (5%)	5 (9%)
Immune System Disorders	2 (5%)	4 (8%)
Reproductive System and Breast Disorders	4 (10%)	1 (2%)
Metabolism and Nutrition Disorders	4 (10%)	0
Cardiac Disorders	0	2 (4%)
Vascular Disorders	2 (5%)	0
Endocrine Disorders	1 (3%)	0
Hepatobiliary Disorders	0	1 (2%)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	0	1 (2%)

Source: Applicant's table 3.3; p. 661.
[1]Subjects are only counted once per SOC.

Table 41 lists common adverse events by preferred terms reported by 5% or more pediatric patients in any treatment group during the controlled portion of study C1109. The treatment emergent adverse events most commonly reported by belimumab IV treated pediatric patients were: headache, nasopharyngitis, upper respiratory tract infection, diarrhea, chest pain, herpes zoster, nausea and arthralgia. Overall, the incidence rates for the majority of common TEAEs were either not in favor of the pediatric placebo group or were similar for the two treatment groups with few exceptions. Higher rates of diarrhea, rash, neutropenia and elevated transaminases were reported by the pediatric belimumab IV treatment group than the pediatric placebo patients. No new or unexpected safety issues were identified on review of these data. The data listed in Table 41 is very similar to the data that has been reviewed in support of the safety profiles of the IV and subcutaneous formulations of belimumab (refer to clinical review of BLA 125370 belimumab IV dated February 18, 2011).

Table 41. Common Treatment Emergent Adverse Events by MedDRA Preferred Term Occurring ≥ 5% of Subjects in Either Treatment Group During the Controlled Portion of Study 1109 (Part A) (ITT Population)

MedDRA Preferred Term (PT)[1]	Placebo N=40	Belimumab IV N=53
Headache	11 (28%)	7 (13%)
Nasopharyngitis	8 (20%)	9 (17%)
Upper Respiratory Tract Infection	8 (20%)	6 (11%)
Diarrhea	3 (8%)	7 (13%)
Chest Pain	4 (10%)	4 (8%)
Herpes Zoster	3 (8%)	5 (9%)
Nausea	3 (8%)	5 (9%)
Arthralgia	4 (10%)	3 (6%)
Epistaxis	3 (8%)	4 (8%)
Lupus Nephritis	4 (10%)	3 (6%)
Abdominal Pain	3 (8%)	3 (6%)
Cough	3 (8%)	3 (6%)
Gastroenteritis	3 (8%)	3 (6%)
Pharyngitis	3 (8%)	3 (6%)
Vomiting	4 (10%)	2 (4%)
Back Pain	3 (8%)	2 (4%)
Leukopenia	3 (8%)	2 (4%)
Oropharyngeal Pain	2 (5%)	3 (6%)
Pyrexia	3 (8%)	2 (4%)
Rash	1 (3%)	4 (8%)
Urinary Tract Infection	4 (10%)	1 (2%)
Dyspepsia	3 (8%)	1 (2%)
Neutropenia	1 (3%)	3 (6%)
Pain in Extremity	2 (5%)	2 (4%)
Transaminases Increased	1 (3%)	3 (6%)
Anemia	3 (8%)	0
Blood IgG decreased	2 (5%)	1 (2%)
Bronchitis	2 (5%)	1 (2%)
Influenza	3 (8%)	0
Insomnia	3 (8%)	0
Menorrhagia	2 (5%)	1 (2%)
Pleural Effusion	2 (5%)	0
Suicidal Ideation	3 (8%)	1 (2%)
Conjunctivitis	2 (5%)	0
Dysmenorrhea	2 (5%)	0
Dyspnea	2 (5%)	0
Hypertension	2 (5%)	0
Joint Swelling	2 (5%)	0
Thrombocytopenia	2 95%)	0

Source: Applicant's Table 3.5; 674-682.
[1]Subjects are only counted once per PT.

Laboratory Findings

Laboratory data from the randomized, controlled Phase 3 pediatric trial C1109 were presented as follows: serial changes from baseline at each study visit, serial shifts from baseline to final study visit, and worst grade observed. The Applicant provided normal ranges of values for each lab parameter assessed. These were reviewed and the clinically acceptable range for normal appeared appropriate.

a. Hematology

Since belimumab is a lymphocyte modulating agent and SLE can also affect the hematological system (e.g., hemolytic anemia, leucopenia, lymphopenia, thrombocytopenia, etc.…) the hematological lab data results were examined for possible signs of toxicity. As shown in Table 42, mean hematology parameter values were generally similar across the two treatment groups and no clinically relevant mean changes from baseline were noted in any of the hematological parameters on comparison of the treatment groups.

Table 42. Mean Change Over Baseline in Hematology Parameters During Controlled Portion of Study 1109 (Part A) (ITT Population)

Hematological Parameter	Placebo N=40		Belimumab IV N=53	
	Baseline	Week 52	Baseline	Week 52
Hematocrit (%)				
N	40	31	53	45
Mean (SD)	37.9 (4.34)	36.5 (4.90)	38.5 (4.23)	38.8 (3.68)
(Min, Max)	(27.3, 45.0)	(25.5, 44.2)	(28.2, 46.1)	(30.6, 48.2)
Hemoglobulin (g/L))				
N	40	31	53	45
Mean (SD)	122 (14.0)	118 (17.0	125 (14.0)	125 (13.3)
(Min, Max)	(88,149)	(81, 144)	(93, 153)	(94, 160)
Leukocytes (10^9/L)				
N	40	30	53	45
Mean (SD)	6.09 (2.54)	5.65 (2.10)	6.33 (2.55)	6.04 (2.01)
(Min, Max)	(2.4, 15.9)	(2.5, 10.5)	(2.4, 13.0)	(2.9, 12.7)
Basophils (10^9/L)				
N	40	30	53	44
Mean (SD)	0.016 (0.021)	0.014 (0.13)	0.012 (0.013)	0.023 (0.026)
(Min, Max)	(0.00, 0.10)	(0.00, 0.04)	(0.00, 0.06)	(0.00, 0.14)
Eosinophils (10^9/L)				
N	40	30	53	44
Mean (SD)	0.096 (0.124)	0.081 (0.098)	0.080 (0.111)	0.140 (0.227)
(Min, Max)	(0.00, 0.70)	(0.00, 0.39)	(0.00, 0.52)	(0.00, 1.27)
Lymphocytes (10^9/L)				
N	40	30	53	44
Mean (SD)	1.54 (0.92)	1.52 (0.90)	1.77 (1.16)	1.56 (0.97)
(Min, Max)	(0.17, 3.69)	(0.20, 3.83)	(0.29, 6.40)	(0.27, 5.92)
Monocytes (10^9/L)				
N	40	30	53	44
Mean (SD)	0.282 (0.024)	0.315 (0.196)	0.319 (0.224)	0.366 (0.215)
(Min, Max)	(0.04, 1.07)	(0.00, 0.69)	(0.02, 1.28)	(0.04, 0.83)
Neutrophils (10^9/L)				
N	40	30	53	44
Mean (SD)	4.15 (2.02)	3.72 (1.77)	4.15 (1.92)	3.94 (1.71)
(Min, Max)	(1.67, 11.2)	(1.39, 8.46)	(1.00, 10.3)	(1.17, 7.98)
Platelets (10^9/L)				
N	39	30	53	44
Mean (SD)	287.3 (99.6)	279.4 (99.4)	261 (84.4)	265 (83.8)
(Min, Max)	(69,502)	(16, 527)	(102, 499)	(105, 537)

Source: Modified Applicant's Table 3.46; p. 784-851.

Table 43 lists the hematological parameters that had grade 3 or 4 values reported over the course of study C1109. The incidence of Grade 3 or 4 toxicities for these laboratory parameters were lower in the belimumab IV pediatric treatment group compared to the placebo group.

Table 43. Summary of Hematology Parameters by Worst Toxicity Grade During the Controlled Portion of Study C1109 (Part A) (ITT population)

Hematology Parameter Worst Toxicity Grade	Placebo N=40	Belimumab IV N=53
Hemoglobulin (n)	39	53
Grade 3	2 (5%)	0
Grade 4	0	0
Neutrophils (n)	39	53
Grade 3	2 (5%)	2 (4%)
Grade 4	1 (3%)	0
Platelets (n)	39	53
Grade 3	1 (3%)	0
Grade 4	2 (5%)	0
Leukocytes (n)	39	53
Grade 3	3 (8%)	0
Grade 4	0	0

Source: Modified Applicant's Table 3.54; p. 998-999.
Note: Data are shown as number of subjects (%) meeting the criterion at one or more post-baseline time points. Parameters that do not have a Grade 3 or 4 value are not shown.

For completeness, the Applicant also supplied analyses for reference range shifts from baseline and worsening of toxicities at least 2 Grades from baseline of hematological parameters for study C1109. Review of the data for the reference range shifts from baseline failed to identify any clinically relevant changes or differences in any of the hematological parameters on comparison of the pediatric treatment groups (data not shown). However, higher incidences of worsening of hematological toxicities occurred in the pediatric placebo group as compared to the pediatric belimumab treatment group that may be due to worsening of underlying SLE in the placebo treated pediatric patients (Table 44).

Table 44. Summary of Subjects with Worsening of at Least 2 Grades from Baseline in Hematological Parameters During the Controlled Portion of Study C1109 (Part A) (ITT Population)

Hematological Parameter	Placebo N=40	Belimumab IV N=53
Hemoglobulin (n)	39	53
Any ≥ 2 Grade Shift	4 (10%)	1 (2%)
Grade 0 to 2	4 (10%)	1 (2%)
Leukocytes (n)	39	53
Any ≥ 2 Grade Shift	7 (18%)	5 (9%)
Grade 0 to 2	4 (10%)	5 (9%)
Grade 0 to 3	2 (5%)	0
Grade 1 to 3	1 (3%)	0
Neutrophils (n)	39	53
Any ≥ 2 Grade Shift	8 (21%)	7 (13%)
Grade 0 to 2	5 (13%)	6 (11%)
Grade 0 to 3	1 (3%)	1 (2%)
Grade 0 to 4	1 (3%)	0
Grade 1 to 3	1 (3%)	0
Hemoglobulin (n)	38	53
Any ≥ 2 Grade Shift	2 (5%)	0
Grade 0 to 4	2 (5%)	0

Source: Modified Applicant's Table 3.6; p. 1009-1010.
Note: Data are shown as number of subjects (%) meeting the criterion at one or more post-baseline time points. Parameters that do not have a worsening of at least 2 grades from baseline are not shown.

b. Chemistry

Since SLE can affect the renal system and also cause an autoimmune hepatitis, test results of renal and hepatic function were also examined (Table 45). Mean liver and renal function parameter values were generally similar across the two treatment groups and appeared to remain stable over the course of study treatment. For completeness, mean serum electrolyte values were also reviewed and were also found to be generally similar and without clinically meaningful patterns of change on cross comparison of treatment groups (data not shown).

Table 45. Mean Changes Over Baseline in Liver and Renal Function Parameters During the Controlled Portion of Study 1109 (Part A)

Chemistry Parameter	Placebo N=40		Belimumab IV N=53	
	Baseline	Week 52	Baseline	Week 52
Alk Phos (U/L)				
N	40	29	53	44
Mean (SD)	80.4 (32.8)	73.1 (27.8)	98.3 (54.9)	135 (95.4)
(Min, Max)	(44,160)	(40,168)	(35, 320)	(39, 445)
ALT/SGPT (U/L)				
N	40	29	53	44
Mean (SD)	18.2 (14.2)	18.9 (37.3)	22.4 (25.4)	17.8 (10.1)
(Min, Max)	(7, 86)	(6, 211)	(6, 149)	(6, 55)
AST/SGOT (U/L)				
N	40	29	53	44
Mean (SD)	24.6 (13.7)	24.0 (28.6)	25.7 (14.5)	22.8 (8.82)
(Min, Max)	(14, 91)	(10, 166)	(14, 88)	(11, 61)
GGT (U/L)				
N	40	29	53	44
Mean (SD)	25.8 (49.4)	16.8 (18.2)	22.7 (20.4)	18.9 (9.66)
(Min, Max)	(6, 323)	(6, 106)	(7, 136)	(7, 48)
LDH				
N	40	29	53	44
Mean (SD)	190 (44)	189 (71)	186 (56)	173 (41)
(Min, Max)	(118, 315)	(115, 391)	(121, 412)	(118, 295)
Bilirubin (umol/L)				
N	40	29	53	44
Mean (SD)	6.9 (2.61)	6.2 (2.85)	6.8 (3.55)	7.6 (4.56)
(Min, Max)	(3, 14)	(2, 18)	(3, 20)	(4, 26)
Albumin (g/L)				
N	40	29	53	44
Mean (SD)	40.6 (5.51)	40.4 (7.26)	42.2 (4.49)	42.5 (4.05)
(Min, Max)	(23, 51)	(14, 48)	(29, 52)	(30, 51)
BUN/Creat Ratio				
N	40	29	53	44
Mean (SD)	99.6 (51.5)	94.9 (34.5)	93.6 (28.6)	90.8 (29.3)
(Min, Max)	(45, 296)	(47, 182)	(44, 159)	(47, 170)
BUN (mmol/L)				
N	40	29	53	44
Mean (SD)	4.81 (4.55)	4.96 (2.01)	4.73 (4.50)	4.35 (1.28)
(Min, Max)	(2.0, 9.2)	(2.5, 13.0)	(2.0, 8.5)	(2.6, 8.1)
Creat. (umol/L)				
N	40	29	53	44
Mean (SD)	51.6 (12.7)	55.4 (23.8)	52.3 (12.01)	50.0 (11.9)
(Min, Max)	(27, 83)	(27, 159)	(27, 80)	(27, 80)
Creat. Cl (ml/sec/1.73m^2)				
N	40	22	53	37
Mean (SD)	1.92 (0.45)	1.93 (0.49)	1.83 (0.34)	1.98 (0.36)
(Min, Max)	(1.13, 3.34)	(0.62, 3.1)	(1.24, 2.59)	(1.22, 2.76)
Protein (g/L)				
N	40	29	53	44
Mean (SD)	70.9 (7.46)	70.2 (10.8)	74.2 (5.84)	70.2 (5.34)
(Min, Max)	(46, 87)	(35, 85)	(59, 85)	(60, 81)

Source: Modified Applicant's Tables 3.48 and 3.49; p. 880-943.

The Applicant also supplied analyses for reference range shifts from baseline and toxicity grades for both liver and renal function as well as serum electrolyte parameters for study C1109. Review of the data for the reference range shifts from baseline and toxicity grades failed to identify any clinically relevant changes or differences in any of the liver and renal function parameters or the serum electrolytes on comparison of the pediatric treatment groups (data not shown). Table 46 is a summary of pediatric subjects with worsening of at least 2 grades from baseline in selected liver and renal function and electrolyte parameters. Higher incidences of worsening in ALT, AST and gamma glutamyl transferase occurred in the pediatric belimumab IV group as compared to the pediatric placebo treatment group that may be due to two subjects randomized to the belimumab IV group who met criteria for liver stopping or monitoring criteria over the course of the study. (Refer to Section 8.2.4 below for additional information.) Hypocalcemia, hypokalemia and hypernatremia were the electrolyte parameters with the highest frequency of Grade 2 and 4 abnormalities observed in the pediatric IV belimumab group. Some of these electrolyte abnormalities may be due to the concomitant use of anti-hypertensive medications (e.g., angiotensin-converting enzyme inhibitors) and angiotensin II receptor blockers) that some patients may have been taking due to underlying lupus nephritis.

Table 46. Summary of Subjects with Worsening of at Least 2 Grades from Baseline During the Controlled Portion of Study 1109 (Part A)

Chemistry Parameter Worst Grade Observed	Placebo N=40	Belimumab IV N=53
ALT (SGPT)	39	53
Any ≥2 grade shift	2 (5%)	4 (8%)
Grade 0 to 2	1 (3%)	3 (6%)
Grade 0 to 4	1 (3%)	1 (2%)
AST (SGOT)	39	53
Any ≥2 grade shift	1 (3%)	5 (9%)
Grade 0 to 2	0	3 (6%)
Grade 0 to 4	1 (3%)	2 (4%)
Bilirubin	39	53
Any ≥2 grade shift	1 (3%)	0
Grade 0 to 3	1 (3%)	0
Gamma Glutamyl Transferase	39	53
Any ≥2 grade shift	1 (3%)	3 (6%)
Grade 0 to 2	0	2 (4%)
Grade 0 to 4	1 (3%)	1 (2%)
Hypocalcemia	39	53
Any ≥2 grade shift	0	2 (4%)
Grade 0 to 2	0	2 (4%)
Hypokalemia	39	53
Any ≥2 grade shift	0	1 (2%)
Grade 0 to 2	0	1 (2%)
Hypernatremia	39	53
Any ≥2 grade shift	0	3 (6%)
Grade 0 to 2	0	2 (4%)
Grade 0 to 4	0	1 (2%)
Hyponatremia	39	53
Any ≥2 grade shift	1 (3%)	0
Grade 0 to 4	1 (3%)	0
Albumin	39	53
Any ≥2 grade shift	2 (5%)	0
Grade 0 to 2	1 (3%)	0
Grade 0 to 3	1 (3%)	0
Hyperglycemia	39	53
Any ≥2 grade shift	1 (3%)	1 (2%)
Grade 0 to 2	1 (3%)	1 (2%)
Hypoglycemia	39	53
Any ≥2 grade shift	2 (5%)	0
Grade 0 to 2	1 (3%)	0
Grade 0 to 3	1 (3%)	0
Urate	39	53
Any ≥2 grade shift	1 (3%)	0
Grade 0 to 2	1 (3%)	0

Source: Modified Applicant's Tables 3.61, 3.62, and 3.63; p. 1011-1017.

c. Urinalysis

Although the protocol for study C1109 prohibited the entry of pediatric patients with severe lupus nephritis, some of the participating pediatric patients had disease activity in this organ system. Urinalysis was done via dipstick at each study visit along with collection of spot urines for assessment of protein/creatinine ratio. Table 47 shows no clinically meaningful differences in proteinuria over the course of the study on cross group comparison.

Table 47. Mean Change Over Baseline in Proteinuria for the Controlled Portion of Study C1109 (Part A) (ITT Population)

Urinalysis Parameter	Placebo N=40		Belimumab IV N=53	
	Baseline	Week 52	Baseline	Week 52
Proteinuria (g/L))				
N	40	30	53	45
Mean (SD)	0.54 (1.12)	0.11 (0.44)	0.21 (0.25)	0.08 (0.41)
(Min, Max)	(0.028, 6.126)	(-0.75, 1.90)	(0.04, 1.43)	(-0.26, 2.32)

Source: Modified Applicant's Table 2.38; p. 506-509.

A higher proportion of pediatric subjects in the belimumab IV group (22%) had proteinuria levels shift to high as compared to the placebo group (13%) over the course of study C1109 (Table 48). (b) (4)

Table 48. Proteinuria Shifts Over Baseline During the Controlled Portion of Study C1109 (Part A) (ITT Population)

Urinalysis Parameter	Placebo N=40	Belimuamb IV N=53
Proteinuria:		
Number of Subjects with Normal Proteinuria	30	49
Normal to High	4 (13%)	11 (22%)
Number of Subjects with High Proteinuria	9	4
High to Normal	0	0

Source: Modified Applicant's Table 2.39; p. 510-515.

For completeness, the Applicant also analyzed urinalysis results by toxicity grades. Protein/creatinine ratio was the only urinalysis parameter for which any pediatric subject in either treatment group had either a Grade 3 or Grade 4 toxicities postbaseline (Table 49). Overall, more pediatric subjects randomized to the placebo group had Grade 3 and 4 toxicities for this lab parameter than pediatric subjects in the belimumab IV group and may be due to the imbalance in pediatric patients with underlying lupus nephritis randomized to the placebo group.

Table 49. Urinalysis Parameter Worst Toxicity Grade During the Controlled Portion of Study C1109 (Part A) (ITT Population)

Urinalysis Parameter Worst Toxicity Grade	Placebo N=40	Belimuamb IV N=53
Protein/Creatinine (n)	39	53
Grade 3	1 (3%)	3 (6%)
Grade 4	5 (13%)	0

Source: Modified Applicant's Table 3.58; p. 1007.
Note: Data are shown as number of subjects (%) meeting the criterion at one or more post-baseline time points. Parameters that do not have a Grade 3 or 4 value are not shown.

Review of the analyses for reference range shifts from baseline in urinalysis parameters proteinuria and leukocytes did not identify any clinically relevant differences between the treatment groups (data not shown). Higher incidences of worsening urinalysis toxicities manifested by worsening of at least 2 grades from baseline for urinary erythrocytes and proteinuria occurred in the pediatric placebo group as compared to the pediatric belimumab treatment group that may be due to worsening of underlying lupus nephritis in the placebo treated pediatric patients (Table 50).

Table 50. Summary of Pediatric Subjects with Worsening of at Least 2 Grades from Baseline in Urinalysis Parameters During the Controlled Portion of Study 1109 (Part A) (ITT Population)

Urinalysis Parameter	Placebo N=40	Belimuamb IV N=53
Erythrocytes (n)	39	53
Any ≥ 2 grade shift	14 (36%)	9 (17%)
Grade 0 to 2	14 (36%)	9 (17%)
Protein (dipstick) (n)	39	53
Any ≥ 2 grade shift	6 (15%)	6 (11%)
Grade 0 to 2	6 (15%)	6 (11%)
Protein/Creatinine (n)	39	53
Any ≥ 2 grade shift	3 (8%)	4 (8%)
Grade 0 to 2	1 (3%)	2 (4%)
Grade 0 to 3	0	1 (2%)
Grade 1 to 3	0	1 (2%)
Grade 2 to 4	2 (5%)	0

Source: Modified Applicant's Table 3.64; p. 1018-1019.
Note: Data are shown as number of subjects (%) meeting the criterion at one or more post-baseline time points. Parameters that do not have a worsening of at least 2 grades from baseline are not shown.

d. Immunoglobulins

As shown in Table 51, shifts in IgM levels from normal/high to low were highest in the pediatric belimumab IV groups which is not unexpected since this immunoglobulin has the ability to change most acutely. Review of the analyses for mean absolute values for IgA, IgM, and IgG

were consistent with the results of the shift analysis (data not shown). Similar findings were observed in the adult IV studies.

Table 51. Immunoglobulin Reference Range Shifts from Baseline to Week 52 During the Controlled Portion of Study C1109 (Part A) (ITT Population)

Immunoglobulin Parameter	Placebo N=40	Belimuamb IV N=53
IgA		
Shift from Normal/High to Low	0	0
Shift from Normal/Low to High	0	0
IgG		
Shift from Normal/High to Low	2 (7%)	4 (9%)
Shift from Normal/Low to High	1 (3%)	1 (2%)
IgM		
Shift from Normal/High to Low	1 (3%)	5 (11%)
Shift from Normal/Low to High	0	0

Source: Modified Applicant's Table 4.2; p. 1316-1332.

Since one of the study's individual stopping criteria was a Grade 4 serum IgG level associated with an infection, the applicant included the results for analyses of worst post-baseline toxicity grade and worsening of at least 2 grades from baseline for serum IgG. As shown in Table 52, there was one pediatric subject in each treatment group who had a Grade 3 post-baseline IgG value. Only the pediatric subject (Subject (b) (6)) randomized to placebo who developed a Grade 3 IgG value reportedly had a nonserious infection (nasopharyngitis) within 30-days of this lab finding. Review of the analysis for worsening of at least 2 grades from baseline for IgG resulted in the identified of these same two subjects.

Table 52. Summary of Pediatric Subjects with Worst Toxicity Grade of 3 or 4 for Immunoglobulins During the Controlled Portion of Study C1109 (Part A) (ITT Population)

Immunoglobulin Parameter Worst Toxicity Grade	Placebo N=40	Belimuamb IV N=53
Immunoglobulin G (n)	39	53
Grade 3	1 (3%)	1 (2%)
Grade 4	0	0

Source: Modified Applicant's Table 3.59; p. 1008.
Note: Data are shown as number of subjects (%) meeting the criterion at one or more post-baseline time points. Only IgG was included in this assessment.

Vital Signs

According to the protocol for study C1109, patients underwent measurement of siting blood pressure (BP), pulse and oral temperature at each study visit, but assessment of respiratory rate was not required. Review of the mean changes from baseline by visit for diastolic and systolic

BP, pulse and oral temperature for Study C1109 failed to identify any clinically relevant safety issues associated with belimumab IV in pediatric patients (data not shown).

Electrocardiograms (ECGs)

Serial ECGs were not performed on subjects who participated in the adult and pediatric trials in support of the safety profile of the intravenous formulation of belimumab.

QT

Since belimumab is a therapeutic biological protein that is not expected to interact with cardiac ion channels, the applicant was not required to do a thorough QT study as part of their pre-clinical and clinical development programs for the IV formulation.

Immunogenicity

Immunogenicity assay results for study C1099 are summarized in Table 53. Based on these data, belimumab IV in pediatric subjects does not appear to be immunogenic. In the adult studies, adult IV subjects who received the 10 mg/kg IV dose exhibited lower levels of immunogenicity (0.7%) as compared to adults who received the 1mg/kg IV dose of belimumab (4.8%). This finding in the 10 mg/kg IV group of adults was thought to be due lower assay sensitivity in the presence of high drug concentrations resulting in an underestimation of the actual frequency. (Refer to clinical review of BLA 125370 belimumab IV dated February 18, 2011.)

Table 53. Immunogenicity Results from During the Controlled Portion Study C1109 (Part A) (ITT Population)

Visit	Placebo (N=40)	Belimumab IV (N=53)
Baseline		
n	36	52
Negative	38 (100%)	52 (100%)
Transient Positive	0	0
Persistent Positive	0	0
Week 52		
n	30	44
Negative	30 (100%)	44 (100%)
Transient Positive	0	0
Persistent Positive	0	0

Source: Applicant's table 3.77; p. 1174-75.

The Applicant also provided the results of analyses of functional antibodies that were conducted in pediatric subjects who participated in study C1109 that tested positive at baseline for the presence of antibodies to either tetanus toxin, diphtheria, or pneumococcus. This subgroup of pediatric patients was tested at Weeks 24 and 52 to determine if any changes in

antibody levels had resulted due to prolonged exposure to belimumab IV. As shown in Table 54 below, no clinically meaningful change was noted for anti-tetanus toxin antibodies and anti-diphtheria antibodies in either treatment group. Since serotype 3 antibody was the most commonly positively detected pneumococcal serotype of the 23 serotypes evaluated by the Applicant in pediatric subjects who participated in study C1109, only the results from this evaluation are shown in Table 54. Again, no clinically meaningful difference between the two pediatric treatment groups was noted for serotype 3 nor for any of the other pneumococcal serotype antibodies evaluated (data not shown).

Table 54. Functional Antibody Percent Change from Baseline Among Pediatric Subjects Positive at Baseline in Study C1109 (Part A) (ITT Population)

Visit	Placebo (N=40)	Belimumab IV (N=53)
Clostridimum tetani IgG Antibody (IU/mL)		
Baseline		
N	21	27
Mean (SD)	3.03 (4.42)	1.90 (2.15)
(Min, Max)	(0.52, 16.0)	(0.50, 7.82)
Week 52		
N	15	22
Mean (SD)	5.19 (94.4)	-12.3 (59.5)
(Min, Max)	(-88.6, 296)	(-84.6, 216)
Diphtheria IgG Antibody (IU/mL)		
Baseline		
N	40	52
Mean (SD)	0.55 (0.65)	0.70 (0.65)
(Min, Max)	(0.07, 2.01)	(0.04, 2.01)
Week 52		
N	29	52
Mean (SD)	-17.4 (27.5)	0.70 (0.65)
(Min, Max)	(-78.9, 46.7)	(0.04, 2.01)
S. pneumoniae Serotype 3 IgG Antibody (IU/mL)		
Baseline		
N	19	23
Mean (SD)	5.94 (6.03)	6.50 (7.92)
(Min, Max)	(1.3, 22.5)	(1.4, 34.1)
Week 52		
N	15	20
Mean (SD)	-12.3 (21.7)	8.74 (86.9)
(Min, Max)	(-46.0, 50.0)	(-94.5, 305)

Source: Applicant's Table 3.76; p. 1149-1173

8.2.4. Analysis of Submission-Specific Safety Issues

In support of belimumab IV's safety profile in the pediatric population, the Applicant also submitted analyses of adverse events of interest (AEIs) that included deaths, infections including opportunistic infections, hypersensitivity spectrum reactions including anaphylaxis, depression/suicide/self-injury, malignancy and hepatotoxicity. The results for the analyses for death and malignancy are discussed in Sections 8.2.3 and 8.2.8, respectively, of this safety review. The remaining analyses of AEIs are discussed in the following subsections.

8.2.4.1. Infections

Because of its mechanism of action, belimumab would also be anticipated to increase the risk of infections, including serious infections which were prespecified as AEIs. Although serious infections were the most common system organ class adverse event reported, the proportion of serious infections was higher in the placebo pediatric group as compared to the belimumab IV pediatric group in study C1109 (Table 55). The types of serious infections listed in Table 55 are not unusual and are consistent with what one would expect in a pediatric population taking concomitant immunosuppressives. Additionally, the pattern of serious infections is similar to what was observed in the safety database reviewed in support of the IV formulation of belimumab in adult SLE patients (Refer to clinical review of BLA 125370 belimumab IV dated February 18, 2011.)

Table 55. Serious Infections by Preferred Term During the Controlled Portion of Study C1109 (Part A) (ITT Population)

Serious Infections and Infestations/ Preferred Term (PT)[1]	Placebo N=40	Belimumab IV N=53
Infections and Infestations	**5 (13%)**	**4 (8%)**
Herpes Zoster	1 (3%)	1 (2%)
Abscess Limb	0	1 (2%)
Epiglottitis	1 (3%)	0
Gastroenteritis	0	1 (2%)
Hepatitis A	1 (3%)	0
Influenza	1 (3%)	0
Pneumonia	1 (3%)	0
Vulval Abscess	0	1 (2%)

Source: Applicant's Table 3.26; p. 736-47.
[1]Subjects are only counted once per SOC/PT.

Table 56 shows higher incidence rates for all infections of special interest including active tuberculosis and herpes zoster not in favor of the belimumab IV treatment group. No cases of disseminated herpes zoster or sepsis were reported to have occurred in either pediatric treatment group. Of note the safety database submitted in support of belimumab IV in adult SLE patients also contained cases of tuberculosis and disseminated herpes zoster and sepsis.

Table 56. Infections of Special Interest During the Controlled Portion of Study C1109 (Part A) (ITT Population)

Infections of Special Interest[1]	Placebo N=40	Belimumab IV N=53
All Infections of Special Interest	3 (8%)	7 (13%)
All Opportunistic Infections by GSK Adjudication	0	1 (2%)
Opportunistic Infections per GSK Adjudication Excluding Tuberculosis and Herpes Zoster	0	0
All Active Tuberculosis (Pulmonary)	0	1 (2%)
Non-Opportunistic	0	1 (2%)
Opportunistic	0	0
All Herpes Zoster[2]	3 (8%)	5 (9%)
Non-Opportunistic	3 (8%)	5 (9%)
Opportunistic	0	1 (2%)
Recurrent	0	1 (2%)
Disseminated	0	0
Sepsis	0	0
All Candida Infections	0	1 (2%)
Non-Opportunistic	0	1 (2%)
Opportunistic	0	0

Source: Modified Applicant's Tables 3.33 and 3.28; p. 768-769 and p.761-763.
[1]Subjects are only counted once per PT.
[2]Not all Herpes Zoster will be recurrent or disseminated.

8.2.4.2. Hypersensitivity Spectrum Reactions Including Anaphylaxis

Hypersensitivity spectrum reactions including anaphylaxis were also designated as adverse events of interest since the current USPI for belimumab contains Warnings and Precaution statements regarding these types of events. Due to the overlap in symptoms with infusion reactions, hypersensitivity reactions, and anaphylaxis, it is difficult to ensure that these adverse events were adequately captured and classified during the study. Because of this, the Applicant employed various search terms including a MedDRA customized MedDRA query (CMQ) involving broad, narrow and algorithmic searches for "anaphylactic reactions" as well as the Sampson Criteria[12] preferred by the review division. Cases thus identified were also adjudicated by the Applicant. The results of these various analyses are presented in Table 57 below.

[12] Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, et al, J Allergy Clin Immunol, 2006; 117(2):391-397.

Table 57. Post -Infusion Anaphylaxis/Hypersensitivity Adverse Events During the Controlled Portion of Study C1109 (Part A) (ITT Population)

	Placebo N=40	Belimumab IV N=53
Post-Infusion Systemic Reactions:	3 (8%)	4 (8%)
Per Anaphylactic Reaction CMQ Narrow Search	1 (3%)	1 (2%)
Per Anaphylactic Reaction CMQ Broad Search	3 (8%)	4 (8%)
Per Anaphylactic Reaction CMQ Algorithmic Search	1 (3%)	1 (2%)
Serious Anaphylaxis per Sampson Criteria	0	0
Serious Acute Post-Infusion Systemic Reactions/Hypersensitivity per GSK Adjudication	0	0
Serious Acute Post-Injection Systemic Reactions Excluding Hypersensitivity per GSK Adjudication	0	0
Serious Acute Hypersensitivity Reactions per GSK Adjudication	0	0
Serious Delayed Acute Hypersensitivity Reactions per GSK Adjudication	0	0
Serious Delayed Non-Acute Hypersensitivity Reactions per GSK Adjudication	0	0

Source: Modified Applicant's Table 3.28; p. 762-763.

The results from the MedDRA CMQ queries raise concerns regarding their accuracy in capturing and identifying cases of hypersensitivity reactions since the rates of anaphylactic post-infusion system reactions for these various searches are high for both treatment groups. These rates are also higher than the rate of anaphylaxis observed in the pooled adult SLE studies which was low overall (e.g., 0.6% of adult SLE patients who received belimumab IV versus 0.4% placebo patients experienced anaphylaxis). (Refer to clinical review of BLA 125370 belimumab IV dated February 18, 2011.) The results from the MedDRA CMQ queries of the pediatric safety database are also unsupported by the results from the search using the Sampson Criteria or the adjudicated searches conducted by the Applicant for hypersensitivity reactions (Table 57). For completeness, the Applicant also submitted the results of an analysis that looked at post-infusion anaphylactic reactions identified by the MedDRA CMQ broad search during the first six injections of the controlled portion of study C1109 which showed a higher incidence of these types of events occurred following the administration of the second, third and fourth infusions of placebo (Table 58) as compared to the belimumab IV group for which anaphylactic reactions were reported following the first infusion. It does not appear likely that these post-infusion anaphylactic reactions are due to the placebo formulation, and it seems unlikely that placebo patients were unknowingly given active treatment. In both the adult and pediatric belimumab IV studies, subjects inconsistently received prophylaxis for infusion reactions, which included antihistamines and corticosteroids, at the discretion of the investigator. This may have blunted or obscured hypersensitivity responses in these studies.

Table 58. Post-Infusion Systemic Reactions per Anaphylactic Reactions via Customized MedDRA Query (CMQ) Board Search During the First Six Infusions During the Controlled Portion of Study 1109 (Part A) (ITT Population)

	Number (%) of Subjects					
	Infusion Number					
	1	2	3	4	5	6
Placebo, N	40 0	38 1 (3%)	38 1 (3%)	37 1 (3%)	35 0	35 0
Belimumab IV, N	53 2 (3.8%)	53 0	53 0	53 0	50 0	50 0

Source: Applicant's Table 3.37

8.2.4.3. Depression, Suicide and Self-Injury

Since a safety signal for depression and suicidality was noted during the review of the safety database in adults in support of the IV formulation of belimumab which resulted in a Warnings and Precaution statement in the product's USPI, depression and suicidality were also prespecified as AEIs for belimumab IV in the pediatric SLE population. Although the protocol for study C1109 prohibited the 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 ≥ 12 years old, there were pediatric subjects in both treatment groups who experienced depression and as well as pediatric subjects who experienced suicide/self-injury in the placebo group over the course of the trial (Table 59).

Table 59. Depression/Suicide/Self-Injury Adverse Events of Special Interest by Category During the Controlled Portion of Study C1109 (Part A) (ITT Population)

	Placebo N=40	Belimumab IV N=53
Depression/Suicide/Self-Injury	4 (10%)	1 (2%)
Depression	2 (5%)	1 (2%)
Serious	1 (3%)	0
Suicide/Self-Injury	3 (8%)	0
Serious	2 (5%)	0
Serious Suicide/Self-Injury per GSK Adjudication	3 (8%)	0
Suicidal Behavior per GSK Adjudication	2 (5%)	0
Suicidal Ideation per GSK Adjudication	0	0
Self-Injurious Behavior W/O Suicidal Intent per GSK Adjudication	1 (3%) 0	0 0

Source: Applicant's Table 3.28; p. 761-763.
Note: The C-SSRS was only completed for subjects ≥ 12 years of age.

For completeness, the Applicant included an analysis of suicidal ideation or behavior based on the required C-SSRS assessments at each visit which showed three (8%) pediatric subjects in the placebo group and no pediatric subjects in the belimumab IV group had C-SSRS suicidal ideation at any time during the controlled portion of study C1109 (Part A) (Table 60). Additionally, 1 (3%) pediatric subject in the placebo group versus no pediatric subjects in the belimumab IV group had suicidal behavior over the course of Part A of the study (Table 60).

Table 60. Summary of C-SSRS Suicidal Ideation of Behavior During the Controlled Portion of Study C1109 (Part A) (ITT Population)

	Placebo N=40	Belimumab IV N=53
Number of Subjects with ≥ 1 On-Treatment C-SSRS Assessment	**37**	**46**
Suicidal Ideation or Behavior (1-10), Any Event	**3 (8%)**	**0**
Any Suicidal Ideation	3 (8%)	0
1. Wish to be dead	1 (3%)	0
2. Non-specific active suicidal thoughts	1 (3%)	0
3. Active suicidal ideation with any methods (not plan) without intent to act	0	0
4. Active suicidal ideation with some intent to act, w/o specific plan	1 (3%)	0
5. Active suicidal ideation with specific plan and intent	0	0
Any Suicidal Behavior (6-10)	1 (3%)	0
6. Preparatory acts or behavior	0	0
7. Aborted Attempt	0	0
8. Interrupted Attempt	1 (3%)	0
9. Non-fatal actual suicidal attempt	1 (3%)	0
10. Completed suicide	0	0

Source: Applicant's Table 3.28; p. 761-763.
Note: The C-SSRS was only completed for subjects ≥ 12 years of age.
Note: Percentages are based on the number of subjects with at least one on-treatment C-SSRS assessment. For behavior, the numbers of subjects (n) are those with the specified behavior at least once during treatment. For ideation, n refers to the number whose maximum ideation at any on-treatment assessment is the specified ideation. Subjects may have more than one type of ideation and/or behavior.

Five pediatric subjects randomized to placebo and 8 pediatric subjects randomized to belimumab IV in this study had prior histories of suicidal ideation or behavior. Table 61 shows that two (6%) adolescent subjects in the placebo group with histories of C-SSRS pretreatment suicidal ideation or behavior by history reported on-treatment suicidal ideation along with 1 (3%) adolescent placebo patient who reported having suicidal behavior as assessed by this instrument. However, no pediatric or adolescent subjects in the belimumab IV group with a prior history of suicidal ideation or behavior reported on-treatment suicidal ideation or behavior as assessed by the C-SSRS.

Table 61. Summary of Treatment-Emergent[1] C-SSRS Suicidal Ideation or Behavior During the Controlled Portion of Study 1109 (Part A) (ITT Population)

	Placebo N=40	Belimumab IV N=53
Number of Subjects with > 1 On-Treatment C-SSRS Assessment	36	46
Suicidal Ideation or Behavior (1-10)	2/36 (6%)	0/43
Suicidal Ideation (1-5)[2]	2 /36 (6%)	0/43
More Severe Suicidal Ideation (4-5)[2]	1/36 (3%)	0/43
Suicidal Behavior (6-10)	1/36 (3%)	0/43

Source: Applicant's Table 3.44; p. 782.
Note: The C-SSRS was only completed for subjects ≥ 12 years of age.
[1]Treatment emergent for suicidal ideation means that specified event is newly appearing or worsening, relative to the lifetime history, current history and baseline. Treatment emergent for suicidal behavior is relative to the lifetime history. All subjects in this table must have at least one on-treatment C-SSRS assessment and a pre-treatment assessment.
[2]The denominator is the number of subjects with maximum pretreatment C-SSRS ideation score <5.

Table 62 lists the 3 placebo adolescent subjects with either suicide/self-injury and or treatment-emergent C-SSRS suicidal ideation or behavior relative to pre-treatment history during the controlled-portion of study 1109 (Part A).

Table 62. Summary of Subjects with Either Suicide/Self-Injury Adverse Events and/or Treatment-Emergent C-SSRS Suicidal Ideation of Behavior Relative to Pre-Treatment History for the Controlled Portion of Study C1109 (ITT Population)

Subject Number	Age/Sex/ Race	AESI Suicide/Self-Injury Preferred Term	C-SSRS Suicidal Ideation Pretreatment History/ During Treatment	Status
Placebo				
(b) (6)	15yo/F	Suicidal Ideation (Serious) (GSK adjudication and SMQ)	No/No	Completed Study
	15yo/F	Suicidal Ideation (SMQ) Suicidal Ideation (SMQ) Major Depression (Serious) (GSK adjudication)	Ideation: Yes (Item 1)/Yes (Item 1, Item 2, Item 3, Item 4)[a,b] Behavior: No/Yes (Item 8, Item 9, non-suicidal self-injurious behavior)[a,b]	Completed Study
	16yo/F	Suicidal Ideation (SMQ) Suicide Attempt (Serious) (GSK adjudication and SMQ)	Ideation: No/Yes (Item 1 and Item 2)[a]	Completed Study

Source: Review of case narratives for Subjects (b) (6) and Applicant's Table 54; p. 118.
[a]Item1= wish to be dead; item 2=non-specific active suicidal thoughts; item 3= active suicidal ideation with any methods (not plan) without intent to act; Item 4=active suicidal ideation (not plan) with intent; Item 8=interrupted attempt; Item 9=non-fatal actual attempt.
[b]Subject (b) (6) had a "yes" response to C-SSRS suicidal ideation item 1 at screening; a "yes" response to C-SSRS suicidal ideation item 1, item 2, item 3, and item 4 at Week 4 visit; and a "yes" response to C-SSRS suicidal behavior item 8, item 9 and non-suicidal self-injurious behavior at the Week 4 visit. Subject (b) (6) also had a yes response to C-SSRS suicidal ideation item 1, item 2 and item 3 at the Week 8 visit.

8.2.4.3 **Hepatotoxicity**

The protocol for pediatric study C1109 included a listing of conditions based on MedDRA preferred terms that the applicant prespecified as disease-related events (DRE) that could occur in the study population regardless of belimumab exposure. Included on this list was lupus hepatitis. Additionally, the protocol contained criteria for liver stopping or increased monitoring based on liver chemistry results as per FDA premarketing clinical liver safety guidances. Table 63 lists the three pediatric subjects who met criteria for liver stopping or monitoring while participating in the controlled portion of study C1109. The liver function abnormalities in two of these subjects (Subjects (b) (6) were due to either Hepatitis A infection or concomitant treatment with hepatotoxic medications (rifampicin and isoniazid). The etiology of the liver function abnormalities of the third subject (Subject (b) (6)) remains unclear due to the limited amount of information contained in the case report form regarding concomitant medications, alcohol use and lack of a liver biopsy.

Table 63. Pediatric Subjects Who Developed Elevated Liver Functions While Participating in Controlled Portion of Study C1109 (Part A) (ITT Population)

Subject Number	Age/Sex	Days Since 1st Infusion	Days Since Last Infusion	Pertinent History
Liver Stopping Criteria Met				
(b) (6)	15yo/F	Day 89	33 days	Hospitalized on Day 92 complaining of fever, abdominal pain, and Grade 4 ↑in ALT, AST, and GGT. Abdominal ultrasounds were negative as were blood cultures, serologies for viral etiologies and work-up for autoimmune hepatitis. Patient was discharged after AST and ALT spontaneously ↓ to normal but with a persistently ↑GGT (Grade 2). Pt. was subsequently withdrawn from the study. No concomitant meds listed, or liver biopsy performed
Liver Monitoring Criteria Met				
(b) (6)	6yo/F	Day 197	21 days	Placebo patient who was found to have Grade 4 ↑in AST, ALT, and GGT and Grade 3 ↑ total bilirubin because of Hepatitis A infection. She was withdrawn from the study and all her LFTs normalized by Day 226 and remained normal at the 8-week follow-up visit
(b) (6)	13yo/F	Day 195	Same day	Patient found to have Grade 2 ↑ AST and ALT. She had been diagnosed with pulmonary TB on Day 34 and had started on quadruple therapy (rifampicin, isoniazid, ethambutol and pyrazinamide) on Day 45. Quadruple anti-TB therapy was continued thru Day 197 after which she was maintained on dual therapy with rifampicin and isoniazid. Thru Day 305. LFTs normalized by Day 320 and remained normal until study completion.

The 120-day safety update contained two additional serious adverse event reports of drug-induced liver injury (1 case) and acute hepatitis (1 case) that occurred in pediatric patients participating in the open-label continuation phase (Part B). Review of the case report forms for these two cases revealed that the subject with drug-induced liver injury (Subject (b) (6) was taking concomitant medications (NSAIDs, methotrexate and azathioprine) which can cause hepatotoxicity while the other subject with acute hepatitis (Subject (b) (6) an 18-year-old female) had Grade 2 elevations of liver transaminases but without elevation of her serum bilirubin. Work-up for viral etiologies was reportedly negative and this patient's liver test abnormalities returned to normal except for her serum GGT following discontinuation of belimumab treatment. Due to the limited information contained in this case report form (e.g., no information regarding concomitant medications, alcohol use, or liver imaging) the etiology of this subject's liver function abnormalities remains unclear.

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

Not applicable.

8.2.6. Safety Analyses by Demographic Subgroups

Subgroup analyses of adverse events by baseline age (5-11 years [Cohort 2] and 12-17 years [Cohorts 1 and 3]) and Cohort 3 alone were conducted for the double-blind portion of study C1109 (Part A) to determine if there were any drug-demographic interactions. In general, subgroup analysis was limited by the overall small sample sizes of the three study cohorts particularly Cohort 2 which contained the youngest pediatric age group (5-11 years). Since SLE is a disease that primarily affects females, it is not surprising that this study was overwhelmingly comprised of female pediatric patients (88/93; 95%). Due to the paucity of male pediatric patients (5/93; 5%) and the small numbers of Afro-American/African Heritage pediatric subjects (n=5; 5%) as well as pediatric subjects from other racial groups (refer to Table 15 above for breakdown of study subjects by racial group) who participated in this trial, subgroup analyses based on gender and race were not performed since no definitive conclusions regarding the risk for developing adverse events associated with belimumab IV treatment can be made for these demographic groups. (Note: This is consistent with what occurred with the subgroups analyses for the safety database in adult SLE reviewed in support of IV belimumab.)

Table 64 summarizes adverse events (AEs) by baseline age (5-11 years [Cohort 2] and 12-17 years [Cohorts 1 and 3]) and Cohort 3 alone that were reported in the safety database for the controlled portion of study C1109 (Part A). As noted previously, the majority of patients in each cohort experienced an adverse event while participating in this study. Except for any serious infection for Age Group 12-17 years (Cohorts 1and 3), numerical imbalances exist for all these categories not in favor of the placebo subgroups. These imbalances may exist because of the uneven randomization (5:1) utilized by the study's protocol in Cohorts 1 and 2 as well as the study's overall small sample size.

Table 64. Adverse Event Summary by Baseline Age Group and Cohort 3 During the Controlled Portion of Study C1109 (Part A) (ITT Population)

	Age Group: 5-11 yrs. (Cohort 2)		Age Group: 12-17 yrs. (Cohorts 1 and 3)		Age Group: 12-17 yrs. (Cohort 3)	
	PBO (N=3)	BEL IV (N=10)	PBO (N=37)	BEL IV (N=43)	PBO (N=35)	BEL IV (N=33)
Any AE	3 (100%)	10 (100%)	30 (81%)	32 (74%)	29 (83%)	26 (79%)
Any SAE	2 (67%)	1 (10%)	12 (33%)	8 (19%)	12 (34%)	6 (18%)
Any Infection	3 (100%)	8 (80%)	25 (68%)	22 (51%)	24 (69%)	18 (55%)
Any Serious Infection	2 (68%)	1 (10%)	3 (8%)	3 (7%)	3 (9%)	1 (3%)
Any Malignancy	0	0	0	0	0	0
Any AE Leading to Discontinuation	1 (33%)	0	4 (11%)	3 (7%)	4 (11%)	3 (9%)
Deaths	0	0	1 (3%)	0	1 (3%)	0

Source: Modified Applicants tables 103.1 103.2 and 103.3; p. 1254-1277.
Note: Only treatment-emergent AEs are summarized.

For completeness, the Applicant also included subgroup analyses of common and serious adverse events as well as adverse events of special interest by baseline age (5-11 years [Cohort 2] and 12-17 years [Cohorts 1 and 3]) and Cohort 3 alone in support of belimumab IV's safety profile in pediatric SLE patients. Review of these subgroup analyses revealed a consistent pattern of numerical imbalances in favor of belimumab IV but failed to identify any clinically meaningful differences between the two treatment groups. Due to the small sample sizes of the study's cohorts, no definitive conclusions can be drawn based on these subgroup analyses (data not shown).

8.2.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

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. Therefore, the safety database from the controlled portion of study C1109 was examined for cases of malignancy. There were no malignancies reported by pediatric subjects in either treatment group during the double-blind portion (Part A) of study 1109. (Refer to Table 35 and Table 64 above.)

Human Reproduction and Pregnancy

Pregnant females were prohibited from participating in study C1109. Although the study's entry criteria required females of reproductive potential to practice effective forms of contraception

for 1 month prior to receiving study treatment and for 8 weeks after the last dose of belimumab, there was a total of 1 pregnancy reported during the controlled portion of study C1109 involving Subject (b) (6) who was a 17-year-old female subject randomized to the belimumab IV group. This pregnancy ended in a spontaneous abortion at 21 weeks gestation with no apparent congenital anomaly present reportedly in the fetus. Following the spontaneous abortion, this patient was hospitalized for evaluation of abdominal pain and fever that resulted in her being treated for puerperal infection which successfully resolved with the administration of broad-spectrum antibiotics.

As of the 120-day safety cut-off date of 30 November 2018, the applicant reports one additional pregnancy that occurred in Subject (b) (6) while participating in the ongoing open-label continuation phase (Part B) of study C1109. The patient was a 20-year-old female who was hospitalized after presenting with grade 2 pre-eclampsia on Study Day 819 that resolved with treatment with methyldopa, betamethasone, nifedipine, and magnesium sulfate. This patient went on to give birth via cesarean section after 33 weeks of gestation to a live neonate with reportedly no apparent congenital anomaly and without post-delivery complications.

Since SLE typically affects young women of childbearing potential, a pregnancy registry is currently underway that is collecting prospective information for pregnancies and pregnancy outcomes in patients with SLE who received IV belimumab within 4 months prior to conception and/or during pregnancy.

Pediatrics and Assessment of Effects on Growth

Since the majority (95%) of the pediatric subjects in study C1109 were taking concomitant corticosteroids which impacts on growth, no formal assessment of belimumab's effects on growth was conducted due to possible confounding by corticosteroid use. Review of the mean changes from baseline by the Week 52 visit on height and weight are shown in Table 65. Review of these data failed to identify any clinically meaningful changes in height or weight between the two treatment groups.

Table 65. Summary of Changes Over Baseline in Height and Weight for the Controlled Portion of Study C1109 (Part A) (ITT Population)

Visit	Placebo N=40	Belimumab IV N=53
Height (cm)		
Baseline		
N	40	53
Mean (SD)	155 (11.4)	152 (14.4)
(Min, Max)	(117,173)	(105, 175)
Week 52		
N	31	45
Mean (SD)	156 (9.59)	153 (13.0)
(Min, Max)	(125, 173)	(110, 176)
Weight (kg)		
Baseline		
N	40	53
Mean (SD)	53 (13)	52 (17)
(Min, Max)	(20, 87)	(17, 86)
Week 52		
N	31	45
Mean (SD)	55 (11)	53 (17)
(Min, Max)	(31, 78)	(21, 84)

Source: Applicant's Table 3.78; p. 1176-1200.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This application did not contain any overdose information for belimumab. A limited amount of overdose data associated with IV belimumab generated from its clinical development program and spontaneous postmarketing case reports has been previously reviewed in support of both the IV and subcutaneous formulations of belimumab. (Refer to the clinical reviews of BLA 125370 Benlysta IV dated February 18, 2011 and BLA 761043 Benlysta Evo dated June 20, 2017 for additional information.) Doses of up to 20mg/kg of the IV formulation were evaluated in a phase 1 dose escalation study in adults without signs of dose limiting toxicity. Twelve spontaneous postmarketing case reports of adverse events associated with overdoses of IV belimumab in adults as a result in a change in the patients' weight were reviewed in support of the marketing approval of subcutaneous belimumab. The majority of the adverse events reported in these IV belimumab overdose cases were non-serious in nature and included influenza, nausea, dizziness, and vaginal infections. However, there was 1 case report categorized as serious in nature involving a patient who received a single dose of 2400 mg of belimumab IV that resulted in her hospitalization for treatment of an infusion reaction associated with complaints of feeling bad, headache and palpitations.

No evidence of withdrawal effects or increases in disease severity following treatment with belimumab were noted by this clinical reviewer during the review of the follow-up data

collected from patients who participated in the multidose, long term studies post-withdrawal of belimumab IV. (Refer to the clinical review of BLA 125370 Benlysta IV dated February 18, 2011 for additional information.) The applicant is currently conducting study BEL116027 to evaluate the efficacy of a 24-week withdrawal followed by a 28-week reintroduction of belimumab 10 mg/kg IV therapy compared with uninterrupted belimumab 10 mg/kg IV therapy for 52 weeks in subjects with low SLE disease activity receiving belimumab 10 mg/kg plus standard therapy in order to generate data regarding treatment holidays and rebound phenomenon associated with the product.

Safety Concerns Identified Through Postmarket Experience

The IV formulation of belimumab was FDA-approved for marketing in this country on March 9, 2011 and the subcutaneous formulation on July 20, 2017 for the treatment of adult patients with active, autoantibody positive SLE who are receiving standard of care therapy. The applicant estimates the cumulative post-marketing exposure to belimumab to be (b) (4) based on sales data through 31 December 2017. This estimate reportedly reflects exposure to both the IV formulation (b) (4) patient-years) and the subcutaneous formulation (b) (4) patient-years).

According to the Applicant, since both the IV and subcutaneous formulations of belimumab are not approved pediatric use in any country postmarketing exposure for pediatric patients ages 0-17 is not available. However, as of the 120-day safety cut-off date of 30 November 2018, the Applicant reports having collected a total of 11 pediatric reports (3 post-marketing and 8 spontaneous) containing 42 adverse events (AEs) summarized by MedDRA system organ class (SOC) as follows: General Disorders and Administration Site Conditions (12 AEs); Psychiatric Disorders (10 AEs); Injury, Poisoning and Procedural Complications (5 AEs including fetal exposure during pregnancy, product use issues, and off-label use); Infections and Infestations (3 AEs); Investigations (2 AEs); Metabolism and Nutrition Disorders (2 AEs); Nervous System Disorders (2 AEs); Skin and Subcutaneous Tissue Disorders (2 AEs); Congenital, Familial, and Genetic Disorders (1AE); Musculoskeletal and Connective Tissue Disorders (1AE); Renal and Urinary Disorders (1AE); and Vascular Disorders (1AE). Six out of these 42 AEs involving pediatric subjects were classified as serious including 1 case of intentional self-injury involving a 15-month-old male child of a mother who was exposed to belimumab in utero. This child reportedly exhibited behavior issues (including hitting his head when upset) which were not medically confirmed.

Identified safety risks associated with the administration include hypersensitivity spectrum reactions including anaphylaxis, infections and psychiatric events including depression and suicidality. Potential safety risks with belimumab include progressive multifocal leukoencephalopathy (PML), malignancies, immunogenicity, and effects on immunizations including interactions with live vaccines. These are reflected in the Warnings and Precautions in the product's current USPI.

Review of the 120-day safety updated as of the cut-off date 30 November 2018 containing

safety information collected from the ongoing open-label portions (Parts B and C) of study C1109 as well as pediatric postmarketing adverse event reports resulted in no new safety concerns identified.

Expectations on Safety in the Postmarket Setting

The Applicant's postmarketing pediatric safety update suggests that the safety profile of belimumab IV in the pediatric population appears to be consistent with that reviewed in support of its initial marketing approval for adults and no strengthening of the current Warnings and Precautions in the current USPI is indicated.

8.2.9. Integrated Assessment of Safety

Overall, the safety profile of IV belimumab in pediatric patients with cSLE appeared to be similar to placebo consistent with what has been observed in adults. There was one death in the pediatric safety database that occurred in an adolescent subject randomized to placebo as a result of uncontrolled cSLE disease-activity (acute pancreatitis). There were numerically lower rates of serious adverse events and discontinuations of study medication as a result of experiencing an adverse event that occurred in the pediatric belimumab IV group as compared to the pediatric group. The rates for serious adverse events and discontinuations due to adverse events in the IV belimumab group were comparable to those reported in the safety database for the adult population, and were numerically lower than in the placebo group for these types of events. Except for infections, most of the serious adverse events and discontinuations of treatment in the pediatric population were due to manifestations of the patients' underlying, uncontrolled SLE and therefore likley not attributable to toxicities associated with the product. This clinical reviewer would like to believe that the differences in the magnitude for these findings may be due to belimumab IV's efficacy as a treatment for cSLE, however, a definitive conclusion cannot be drawn in view of the small numbers of pediatric patients involved coupled with belimumab's consistent demonstration of marginal efficacy as a treatment for SLE.

Although the overall rate of serious infections was higher in the pediatric placebo group, pediatric patients treated with belimumab IV experienced a higher rate of opportunistic infections such as pulmonary tuberculosis and herpes zoster including recurrent zoster. This is not an unexpected finding since the safety database submitted in support of belimumab IV in adult SLE patients also contained cases of tuberculosis, disseminated herpes zoster, as well as sepsis. There was also no increase in infections or serious infections observed in the belimumab IV treated pediatric patients with treatment-related reductions in immunoglobulins as compared to placebo treated pediatric patients. Based on these findings, no changes to the current Warning and Precaution statement in the product's current USPI for the increased risk for serious infections to occur associated with belimumab IV is warranted.

Since many of the pediatric patients who participated in study C1109 were taking concomitant corticosteroids, and inconsistently received prophylaxis for infusion reactions at the discretion

of study investigators coupled with the lack of an acceptable methodology to classify infusion reactions, hypersensitivity reactions and anaphylactic events contained in the pediatric safety database may have resulted in an underestimation of the risk for anaphylaxis associated with the administration of IV belimumab in this population. However, final review of these type of events did not suggest that prophylactic premedication was warranted for all patients undergoing belimumab therapy and does not support changes to the existing Warning and Precaution statement in the product's USPI regarding hypersensitivity spectrum adverse events.

Although the protocol for study C1109 prohibited the 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 assessment at each study visit with this assessment tool in subjects $\geq$ 12 years of age as a result of psychiatric safety signals noted on review of the adult IV safety database, there were no pediatric subjects in the belimumab IV treatment groups as compared to 3 pediatric placebo subjects who experienced suicidal ideation or suicidal behavior over the course of this trial.

There were no cases malignancy reported in the pediatric safety database. However, the controlled study C1109 was not specifically designed to determine the risk for developing malignancy as a result of treatment with belimumab IV. Although no apparent risk for malignancies has been identified with long-term treatment with either formulation of belimumab in adults, it would be prudent to continue monitoring safety data from the ongoing open label extension (Part C) of study C1109 in pediatric patients for the development of potential safety signals such as malignancies to occur with increasing exposure to the product.

Other than expected decreases in lymphocytes and immunoglobulins, review of the clinical lab test parameters or vital sign data showed no evidence of an adverse effect of belimumab IV on these assessments in the pediatric population.

Although the protocol for study C1109 mandated that subjects of childbearing potential practice effective forms of contraception for the duration of their study participation, a total of 2 pregnancies occurred during this ongoing phase 2 trial. Since SLE typically affects young women of childbearing potential, a pregnancy registry is currently underway that is collecting prospective information for pregnancies and pregnancy outcomes in subjects with SLE exposed to IV belimumab.

Limitations associated with the pediatric belimumab IV safety database are the same as those identified for the adult IV belimumab safety database and include the lack of concomitant IV cyclophosphamide or other biologics including those that target B cells (e.g., rituximab) , the lack of patients with severe renal lupus and central nervous system disease, and the small number of subjects available for subgroup analyses of gender (males) and age (children between the ages of 5 to 11 years) which precludes determination of the product's safety profile in these subgroups.

In view of the consistency of the efficacy and product safety profile as compared to the adult SLE population as well as the lack of new safety signals identified, the risk/benefit assessment supports approval of the 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 in pediatric patients with childhood-onset SLE who are receiving standard therapy.

8.3. Statistical Issues

See Sections 8.1.3.5.1 and 8.1.3.5.2.

8.4. Conclusions and Recommendations

The Applicant evaluated the efficacy, safety and pharmacokinetics of belimumab IV plus standard of care as a treatment for childhood-onset SLE (cSLE) in a phase 2, double-blind, placebo controlled, international trial, C1109. This trial was unique for several reasons. It is the first double-blind, placebo controlled study conducted in pediatric subjects with cSLE. The study's overall design and entry criteria were similar to the common protocol used by the two pivotal phase 3 belimumab IV adult studies C1056 and C1057 and utilized many of the same efficacy parameters including the primary endpoint (the SRI-4 at Week 52) that were assessed in these adult pivotal studies, allowing for comparison and borrowing of data generated in adults. The study also evaluated a new composite pediatric SLE endpoint, the PRINTO/ACR Juvenile SLE Response Evaluation which, while not validated, appeared supportive. The study's overall sample size was small (N=93) as a consequence of the rarity of cSLE so the study was not powered to conduct formal statistical hypothesis testing. Nonetheless, the proportion of pediatric subjects who achieved the primary endpoint, the SRI-4 response at Week 52, was greater in the pediatric belimumab IV group (52.8%) compared to the pediatric placebo group (43.6%) [Odds Ratio (95% CI): 1.5 (0.6, 3.5)]. This efficacy finding was consistent with the modest efficacy results observed in the adult belimumab IV studies C1056 and C1057, in particular with the results from study C1057 (belimumab IV 10mg/kg: 58% versus placebo: 44%). Analyses of the individual SRI components also showed higher proportions of responders in the pediatric belimumab IV group compared to the pediatric placebo group. Additional support was provided by the results from the major secondary endpoint, the PRINTO/ACR, and other secondary analyses such as the sustained SRI response and sustained parentGA. Although a consistent reduction in the risk for SLE disease flares was not observed in the two pivotal adult belimumab IV studies, pediatric subjects randomized to treatment with belimumab IV had a lower risk of experiencing a severe flare compared to the pediatric placebo group as well as a longer duration of time to severe flare (160 days versus 82 days, respectively). These are potentially important clinical findings since a decrease in the risk for severe flares may result in less long-term, end-organ damage for patients' underlying SLE, less treatment with unapproved immunosuppressive agents commonly used to treat cSLE, as well as fewer hospitalizations with less loss of absent school days.

Due to the statistical uncertainty posed by study C1109's small sample size that precluded

formal statistical hypothesis testing coupled with the modest SRI-4 response rate that belimumab is known for, the Applicant conducted a post-hoc Bayesian analysis of study C1109 that relied on borrowed information from the adult belimumab IV studies, C1056 and C1057. The Applicant's analysis of the pediatric data indicated that the posterior probability of a positive treatment effect was at least 97.5% when the prior weight was 0.55 or more. Independent analysis by the statistical review team showed comparable results. With additional inputs from the review disciplines and PeRC discussion, it was determined that it was reasonable to assume a weight of at least 0.55 (corresponding to at least a 55% probability that efficacy in pediatrics is similar to that in adults) to statistically conclude that the treatment effect of belimumab in the pediatric population favored belimumab 10 mg/kg IV as compared to placebo.

Overall, the safety profile of belimumab IV assessed at a dose of 10 mg/kg in the pediatric cSLE population appeared to be similar compared to placebo and the product's established safety profile in the adult SLE population. Many of the serious adverse events and withdrawals from study treatment in the belimumab IV pediatric safety database were related to underlying disease activity or were the result of infections. Opportunistic infections such as pulmonary tuberculosis and herpes zoster including recurrent zoster were the only safety concern raised during the review of the belimumab IV pediatric safety database. This is not an unexpected finding since the safety database submitted in support of belimumab IV in adult SLE patients also contained cases of tuberculosis, disseminated herpes zoster, as well as sepsis (b) (4)

Although the protocol for study C1109 prohibited the 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 a suicidality assessment at each visit for pediatric subjects ≥12 years of age, there were no cases of suicide/self-injury which occurred in belimumab IV treated pediatric patients versus three in the pediatric placebo group. Since many of the pediatric patients who participated in this trial were taking concomitant corticosteroids, this may have resulted in an underestimation of the risk for hypersensitivity spectrum reactions including anaphylaxis to occur with belimumab IV as well as the product's low propensity for immunogenicity observed in this population.

Based on their review of the pharmacokinetic data included in this submission, the clinical pharmacology team concluded that similar steady state exposure parameters between pediatric and adult SLE patients supports the efficacy and safety findings in pediatric patients with cSLE in Study BEL114055/C1109.

Based on the totality of data generated from the adequate and well-controlled pediatric study C1109, together with the efficacy and safety results from the two well-controlled adult studies C1056 and C1057 conducted with IV belimumab reviewed previously under BLA 125370 and the unmet medical need for safe and efficacious treatments for pediatric patients with SLE, the benefit/risk assessment is favorable for the approval of the 10mg/kg dosing regimen of

belimumab IV as add-on treatment for pediatric patients with active, sero-positive, childhood-onset SLE who are receiving standard of care. Additionally, the pediatric clinical pharmacology, efficacy and safety data submitted to sBLA 125370/S-064 are adequate to fulfill the modified PREA PMR 2661-5 related to the March 9, 2011 approval for BLA 125370 belimumab (Benlysta) intravenous (IV) formulation.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not held for this pediatric PMR efficacy supplement since belimumab IV is an approved marketed product with a well-documented safety profile and no new or unexpected safety signals were identified during the review of the safety database comprised of pediatric SLE patients submitted in support of this application.

10 Pediatrics

The Agreed Pediatric Study Plan (iPsP) for IV belimumab was previously submitted to BLA 125370 on June 10, 2010 that included an agreement for a partial waiver of pediatric studies in pediatric SLE patients ≤5 years of age and a deferral in pediatric SLE patients >5 to 17 years of age. The results and review findings for this pediatric PMR supplement were presented and discussed at the March 22, 2019 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, autoantibody-positive, SLE who are receiving standard therapy based on the data reviewed in this application.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

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

1. Changes to Section 1 Indications and Usage, Section 2 Dosage and Administration, Section 6.1 Clinical Trials Experience with Intravenous Administration, Section 6.4 Immunogenicity, Section 8.4 Pediatric Use, Section 12.2 Pharmacodynamics (b) (4) and Section 14 Clinical Studies regarding the appropriate information related to use of belimumab IV in pediatric SLE need to be incorporated
2. A description regarding the lack of corticosteroid reduction associated with belimumab observed in study C1109 needs to be added
3. (b) (4)

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, autoantibody-positive, SLE who are receiving standard therapy since no new safety signals were identified on review of the data contained in this submission.

13 Postmarketing Requirements and Commitment

This submission fulfills the modified PREA PMR 2661-5 related to the March 9, 2011 approval for BLA 125370 belimumab (Benlysta) described as follows:

> "A phase 2, multicenter study to evaluate the safety, efficacy, and pharmacokinetics of belimumab plus background standard therapy in 70 pediatric subjects ages 5 years to 17 years of age with active systemic lupus erythematosus (SLE)."

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

14 Division Signatory (Clinical) Comments

HGS submitted supplement 064 to Biological Licensing Application (BLA) 125370 for intravenous (IV) administration of belimumab (Benlysta) to provide data from a post-marketing required study (PMR 266-1, approval action letter March 9, 2011 for BLA 125370 Benlysta) in support of an expansion of indication to pediatric population, i.e. treatment of patients aged 5 years and older with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The proposed IV dosing regimen is the same as that currently approved for adults, IV belimumab 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

In support of this supplement the Applicant provided data from the pediatric IV belimumab PMR study BEL114055/C1109, titled "A Multicenter, Randomized, Parallel Group, Placebo-Controlled, Double-Blind Trial to Evaluate the Safety, Efficacy and Pharmacokinetics of Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Patients with Systemic Lupus Erythematosus (SLE)". The study was designed to characterize the pharmacokinetic profile, and assess efficacy and safety of IV belimumab in a pediatric population with childhood-onset SLE (cSLE).

Determination of efficacy in pediatric patients was based on pharmacokinetic (PK) and efficacy results from study BEL114055/C1109, as well as PK exposure and extrapolation of the established efficacy of belimumab plus standard therapy from the phase 3 intravenous belimumab studies in adults (C1056 and C1057), reviewed in the original BLA. The primary clinical endpoint for study BEL114055/C1109 was SLE responder index (SRI-4) at Week 52, the same endpoint used in the pivotal adult IV belimumab studies C1056 and C1057. A numerically higher proportion of pediatric subjects (52.8%) treated with IV belimumab achieved the SRI-4 response, as compared to the placebo-treated group (43.6%) [odds ratio (95% CI): 1.5 (0.3, 3.5)] which is consistent with the efficacy results observed in the adult IV belimumab studies C1056 and C1057. Analysis of each individual SRI components also showed higher percentages of responders in the 10 mg/kg IV belimumab group compared to the placebo-treated group. These results were also supported by consistent tends in major and ancillary secondary endpoints favoring the IV belimumab treatment group. For example, pediatric subjects randomized to the IV belimumab group had a numerically lower risk of experiencing a severe flare, as well as a longer duration of time to severe flare compared to the placebo-treated group (160 days versus 82 days, respectively). The team notes that the study was not designed to test a formal statistical hypothesis due to the small sample size. To address the statistical uncertainty posed by study BEL114055/C1109's design, additional support for the efficacy findings of this study was obtained from a post-hoc Bayesian analysis. This Bayesian analysis, which relied on information borrowed from the adult studies C1056 and C1057, further supported a statistical conclusion that the treatment effect of IV belimumab in the pediatric population favored belimumab 10 mg/kg, as compared to placebo. The overall safety of IV belimumab in cSLE population was consistent with the known safety of belimumab in the adult

SLE program. Based on the review of the PK data included in this submission, the clinical pharmacology team concluded, and I agree, that similar steady state exposure parameters between pediatric and adult SLE patients supports the efficacy and safety findings in pediatric patients with cSLE in Study BEL114055/C1109. The review teams concluded, and I agree, that overall package provides evidence of efficacy for the proposed IV administration of belimumab 10 mg/kg for the treatment of SLE in pediatric subjects.

Based on the totality of the data from the belimumab clinical development, including data generated from study BEL114055/C1109, and the efficacy and safety results from the two adequate and well-controlled adult IV belimumab studies C1056 and C1057, the benefit-risk profile of IV belimumab (10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter) is favorable to support the proposed indication for treatment of patients aged 5 years and older with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. Importantly, the Intravenous administration of belimumab will provide the first treatment option in the US specifically approved for pediatric patients with SLE who are receiving standard therapy.

Results from study BEL114055/C1109 are described in the product labeling.

The current submission fulfils the March 9, 2011 PMR 266-1.

The regulatory action for this supplement is Approval. No PMR/PMCs are warranted.

15 Appendices

15.1. References

1. Borchers et al. The Geoepidemiology of Systemic Lupus Erythematosus. Autoimmunity Reviews 9 (2010): A277-A287
2. Furie et al., Novel Evidence-Based Systemic Lupus Erythematosus Responder Index. Arthritis and Rheum, 2009;61(9):1143-1151
3. Hersh AO, Trupin L, Yazdany J, Panopalis P, Julian L, Katz P, et al. Childhood-onset disease as a predictor of mortality in an adult cohort of patients with systemic lupus erythematous. Arthritis Care Res (Hoboken). 2010;62(8):1152-9.
4. Hiraki LT, Feldman CH, Liu J, et al. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. Arthritis Rheum 2012; 64:2669-76.
5. Ipolito A, Petri M. An update on mortality in systemic lupus erythematosus. Clin Exp Rheumatol 2008;26 Suppl51:S72-9
6. 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.
7. 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
8. Pons-Estel et al. Understanding the Epidemiology and Progression of Systemic Lupus Erythematosus. Semin Arthritis Rheum 2010 Feb ; 39:257-268

15.2. Financial Disclosure

See the following completed form.

15.2.1. Covered Clinical Study: BEL114055/C1109: A Multicenter, Randomized, Parallel Group, Placebo-Controlled, Double-Blind Trial to Evaluate the Safety, Efficacy and Pharmacokinetics of Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Patients with Systemic Lupus Erythematosus (SLE)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 111		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Despite due diligence by the Applicant in attempting to obtain financial information from all the participating Principal Investigators and their Sub-Investigators and Coordinating Staff, they were unable to do so from approximately 6 Sub-Investigators and Study Coordinators.

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1 Population PK analysis

15.3.1.1 Introduction

The primary objectives of this analysis were to:

- Develop a population PK model that characterizes the PK disposition of belimumab following IV administration in pediatric subjects with SLE and evaluate the potential effect of selected covariates on PK parameters.
- Compare belimumab exposure in pediatric SLE patients to exposure in adult SLE Phase 3 patients.

15.3.1.2 Model development

15.3.1.2.1 Overall Modeling and Analysis Strategy

The population PK model previously developed for an adult SLE population [Report HGS1006-POPPK], two compartmental with zero-order infusion and first-order elimination, was taken as the starting model used to characterize the PK of the pediatric population (study BEL114055). In the first instance, the adult model without further modification was used to evaluate the pediatric PK, with the population parameters fixed at their adult derived estimates (MAXEVAL=0 argument in NONMEM) (Reference Model, Table 66). The implementation of the covariate effects in the adult model were then updated to be consistent with the pediatric covariate distributions, and the population parameters re-estimated for the pediatric population (Step 1). The full covariate model approach was used to quantify the importance of each covariate effect, and the covariates which had little impact on PK and did not satisfy the selection criterion were removed from the model (Step 2). Additional clinically relevant covariates on the systemic clearance of parent drug (CL) parameter of this reduced model were then tested for significance (Step 3).

Table 66. Model Development Strategy

Model Development Step	Description
Reference Model	Adult population PK model (MAXEVAL=0)
Step 1	Model fitted to pediatric data
Step 2	Model reduction: removal of covariates not relevant for PK
Step 3	Covariate testing

Source: CSR BEL114055 (Table 1 in Attachment 2, page 1521)

15.3.1.2.2 Data

The population PK analysis utilized 560 observations from 53 subjects after excluding the following records:

- All 53 pre-first dose records were excluded from the analysis. All pre-first dose PK samples were below the limit of quantitation (BLQ), except for one sample (0.648 µg/mL).
- one post-first dose BLQ observation was excluded.
- nine post-first dose samples, which were not analyzed (NA) were also excluded.
- Two duplicate dose records were also excluded, originating from an interrupted belimumab infusion for Subject ID=1 and Subject ID=33.

Records excluded from the analysis were retained in the dataset and excluded from the analysis via IGNORE statements. The disposition of included observations and subjects by cohort is provided in Table 67.

Table 67. PK Observations Included in Analysis by Cohort

PK Observations	Cohort 1 N=10	Cohort 2 N=10	Cohort 3 N=33	Total N=53
Observations	153	159	248	560
Observations per subject: Median (Min - Max)	16.5 (10 – 17)	16.5 (14 - 17)	8 (6 - 8)	8 (6 - 17)

Source: CSR BEL114055 (Table 2 in Attachment 2, page 1525)

Table 68 - Table 69 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 68. Baseline Subject Characteristics by Cohort: Continuous Covariates

Subject Characteristic at Baseline	Median (Min – Max)		
	Baseline Age 5-11 Years (Cohort 2) N=10	Baseline Age 12-17 Years (Cohorts 1 and 3) N=43	Overall N=53
Age (Years)	10 (6 - 11)	15 (12 - 18*)	14 (6 - 18)
Weight (kg)	29.8 (17 - 55.2)	53.2 (31.5 - 85.5)	52.3 (17 - 85.5)
Height (cm)	130 (105 - 152)	156 (136 - 174)	154 (105 - 174)
BMI (kg/m^2)	17.8 (15.4 - 23.9)	22.1 (16.2 - 34)	21.4 (15.4 - 34)
Fat-Free Mass (kg)	20.6 (12.6 - 35)	35.6 (22.6 - 57.2)	34.4 (12.6 - 57.2)
eGFR (mL/min/1.73m^2)	124 (94.2 - 141)	103 (74.1 - 155)	105 (74.1 - 155)
IgG (g/L)	16.2 (10.7 - 24.8)	14.0 (4.08 - 31.2)	14.5 (4.08 - 31.2)
Albumin (g/L)	44.5 (35 - 48)	43 (29 - 52)	43 (29 - 52)
Hemoglobin (g/L)	126 (103 - 139)	126 (93 - 153)	126 (93 - 153)
White Blood Cell Count (10^9/L)	6.7 (2.4 - 10.6)	5.8 (2.5 - 13)	5.9 (2.4 - 13)
BLyS (ng/mL)	0.95 (0.48 - 3.84)	0.66 (0.16 - 4.31)	0.695 (0.16 - 4.31)
Proteinuria (mg/mg)	0.143 (0.037 - 0.405)	0.131 (0.047 - 1.43)	0.132 (0.037 - 1.43)
C-Reactive Protein (mg/L)	5.65 (3.9 - 18)	3.9 (3.9 - 83.6)	3.9 (3.9 - 83.6)
Alanine Aminotransferase (IU)	16.5 (8 - 119)	14 (6 - 149)	15 (6 - 149)
Aspartate Aminotransferase (IU)	27 (19 - 88)	21 (14 - 79)	21 (14 - 88)
Total Bilirubin (µmol/L)	5 (4 - 12)	6 (3 - 20)	6 (3 - 20)
SELENA-SLEDAI (score)	11 (4 - 13)	10 (4 - 18)	10 (4 - 18)
Complement C3 (mg/dL)	105 (53 - 179)	94 (40 - 169)	96 (40 - 179)
Complement C4 (mg/dL)	10 (3 - 44)	11 (2 - 29)	11 (2 - 44)
Anti-dsDNA Antibodies (IU/mL)	124 (5 - 660)	120 (5 - 14600)	120 (5 - 14600)
Naïve CD19+CD20+CD27- B Cells (cells/µL)	171 (52 - 585)	134 (20 - 525)	141 (20 - 585)

Abbreviations: BLyS=B-lymphocyte stimulator; BMI=body mass index; eGFR=estimated glomerular filtration rate
* Subject was 17 years of age at screening

Source: CSR BEL114055 (Table 3 in Attachment 2, page 1525)

Table 69. Baseline Subject Characteristics by Cohort: Categorical Covariates

Subject Characteristic at Baseline	Category	Number (%) of Subjects		
		Baseline Age 5-11 Years (Cohort 2) N=10	Baseline Age 12-17 Years (Cohorts 1 and 3) N=43	Overall N=53
Renal impairment	No renal impairment (eGFR≥90 mL/min/1.73m²)	10 (100%)	36 (84%)	46 (87%)
	Mild renal impairment (eGFR=60-89 mL/min/1.73m²)	0 (0%)	7 (16%)	7 (13%)
Proteinuria	< 0.5 mg/mg	10 (100%)	39 (91%)	49 (92%)
	≥ 0.5 mg/mg	0 (0%)	4 (9%)	4 (8%)
Sex	Males	0 (0%)	4 (9%)	4 (8%)
	Females	10 (100%)	39 (91%)	49 (92%)
Race	White	4 (40%)	24 (56%)	28 (53%)
	Asian	1 (10%)	6 (14%)	7 (13%)
	Black	0 (0%)	3 (7%)	3 (6%)
	Other	5 (50%)	10 (23%)	15 (28%)
Ethnicity	Hispanic or Latino	6 (60%)	20 (47%)	26 (49%)
	Non-Hispanic	4 (40%)	23 (53%)	27 (51%)
Immunogenicity	Negative	10 (100%)	43 (100%)	53 (100%)
	Positive	0 (0%)	0 (0%)	0 (0%)
Steroids	Not Administered at Baseline	1 (10%)	2 (5%)	3 (6%)
	Administered at Baseline	9 (90%)	41 (95%)	50 (94%)
ACE Inhibitors	Not Administered at Baseline	9 (90%)	36 (84%)	45 (85%)
	Administered at Baseline	1 (10%)	7 (16%)	8 (15%)
Immunosuppressant	Not Administered at Baseline	4 (40%)	16 (37%)	20 (38%)
	Administered at Baseline	6 (60%)	27 (63%)	33 (62%)
Azathioprine	Not Administered at Baseline	9 (90%)	39 (91%)	48 (91%)
	Administered at Baseline	1 (10%)	4 (9%)	5 (9%)
Methotrexate	Not Administered at Baseline	5 (50%)	35 (81%)	40 (75%)
	Administered at Baseline	5 (50%)	8 (19%)	13 (25%)
Mycophenolate	Not Administered at Baseline	8 (80%)	29 (67%)	37 (70%)
	Administered at Baseline	2 (20%)	14 (33%)	16 (30%)
Anti-Malarial	Not Administered at Baseline	2 (20%)	7 (16%)	9 (17%)
	Administered at Baseline	8 (80%)	36 (84%)	44 (83%)
NSAID	Not Administered at Baseline	10 (100%)	32 (74%)	42 (79%)
	Administered at Baseline	0 (0%)	11 (26%)	11 (21%)
Aspirin	Not Administered at Baseline	9 (90%)	37 (86%)	46 (87%)
	Administered at Baseline	1 (10%)	6 (14%)	7 (13%)

Abbreviations: ACE=angiotensin converting enzyme; NSAID=nonsteroidal anti-inflammatory

Source: CSR BEL114055 (Table 4 in Attachment 2, page 1526)

Model development

Based on belimumab PK data obtained from 53 pediatric subjects with childhood-onset SLE in Part A of Study BEL114055, a population PK model was developed using the adult belimumab IV population PK model as a starting point. Model development proceeded evaluating the pediatric PK fixing the model parameters to the adult estimates, followed by re-estimation of the model parameters fitting to the pediatric data, with refinement of the body-size covariate effects, then finally model reduction using the full covariate model approach. The resulting linear, two-compartment model with first-order clearance from the central compartment characterized the PK in pediatric subjects well. Based on the typical parameter estimates in the overall pediatric population the derived population PK model has a clearance of 158 mL/day, a steady-state volume of distribution of 3.5 L and a terminal half-life of 16.3 days.

15.3.1.3 Results

The parameter estimates for the final model are listed in Table 70. The goodness-of-fit plots for the final model are shown in Figure 24. The Visual Predictive Check (VPC) plot for the final model is shown in Figure 25.

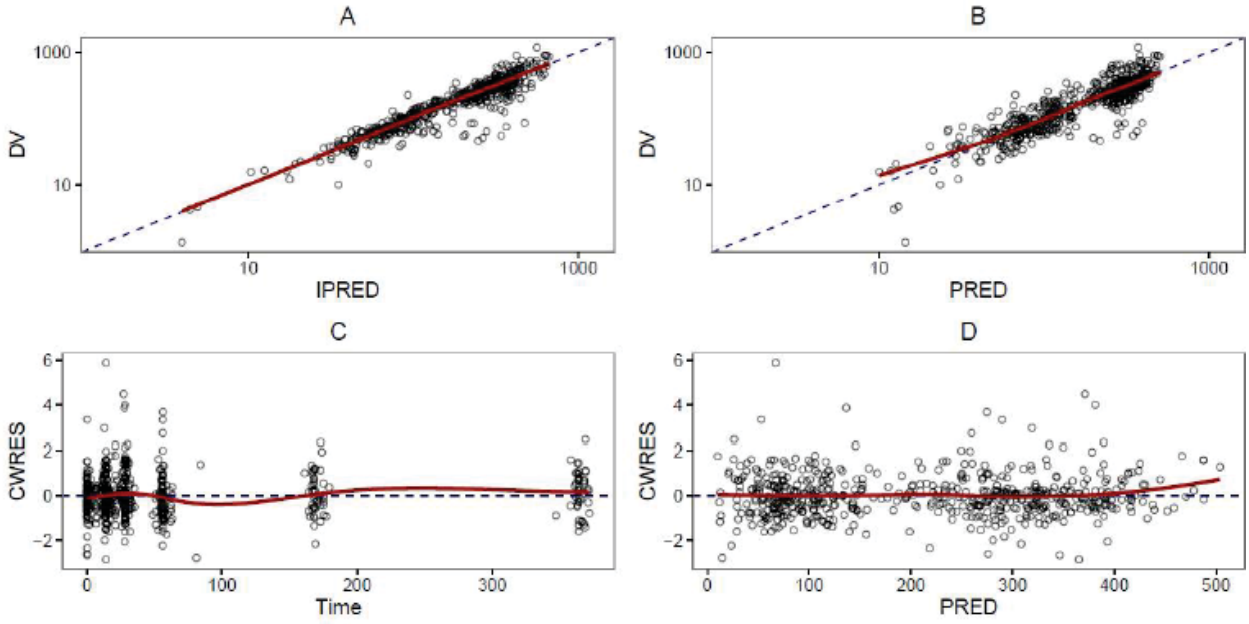
Table 70. Parameter Estimates for the Final Model

Parameters	Model Point estimate (%RSE, 95% CI)	Bootstrap[a] Median (95% CI)
Fixed effects		
CL (mL/day)	158 (3.62%, 147-169)	157 (142-169)
x (BFFM/34.4)$^{\theta}$	0.691 (18.6%, 0.439-0.942)	0.691 (0.418-0.963)
x (BEGFR/105.21)$^{\theta}$	0.561 (34.4%, 0.183-0.939)	0.510 (0.079-0.966)
x (BIGG/14.5)$^{\theta}$	0.396 (24.8%, 0.204-0.588)	0.415 (0.237-0.639)
x (BPROT/0.132)$^{\theta}$	0.184 (26.4%, 0.0888-0.279)	0.176 (0.082-0.289)
V1 (mL)	1927 (3.97%, 1777-2077)	1932 (1782-2090)
x (BFFM/34.4)$^{\theta}$	0.944 (13.5%, 0.694-1.19)	0.941 (0.695-1.220)
x (BWBC/5.9)$^{\theta}$	0.245 (39.9%, 0.0536-0.437)	0.242 (0.020-0.426)
Q (mL/day)	701 (18.6%, 445-957)	700 (150-931)
x (BFFM/34.4)$^{\theta}$	See FFM on CL	
V2 (mL)	1622 (15.2%, 1138-2105)	1635 (1128-2157)
x (BFFM/34.4)$^{\theta}$	See FFM on V1	
Inter-individual variability		
ω^2_{CL}	0.0477 (28.8%, 0.0207-0.0746)	0.0407 (0.0175-0.0674)
ω^2_{V1}	0.0620 (24.7%, 0.0320-0.0920)	0.0572 (0.0306-0.0888)
$\omega^2_{CL/V1}$	0.0366 (34.1%, 0.0122-0.0611)	0.0347 (0.0117-0.0590)
ω^2_{V2}	0.434 (29.1%, 0.187-0.681)	0.418 (0.203-1.413)
Residual variability		
$\sigma^2_{proportional}$	0.0884 (18.3%, 0.0568-0.120)	0.0871 (0.0603-0.120)
$\sigma^2_{additive}$	0.0139 (Fixed)	0.0139 (Fixed)

Source: Parameter_Table.Mod071.pdf, bootstrap_results.Mod071.csv
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 clearance=V2, volume of distribution for the peripheral compartment; BFFM=baseline fat-free mass; BEGFR=baseline calculated estimated glomerular filtration rate; BIGG=baseline IgG levels; BPROT= baseline proteinuria levels; BWBC=baseline white blood cell count
a. Bootstrap parameters based on 1694 successful minimizations (out of 2000 attempts)

Source: CSR BEL114055 (Table 6 in Attachment 2, page 1534)

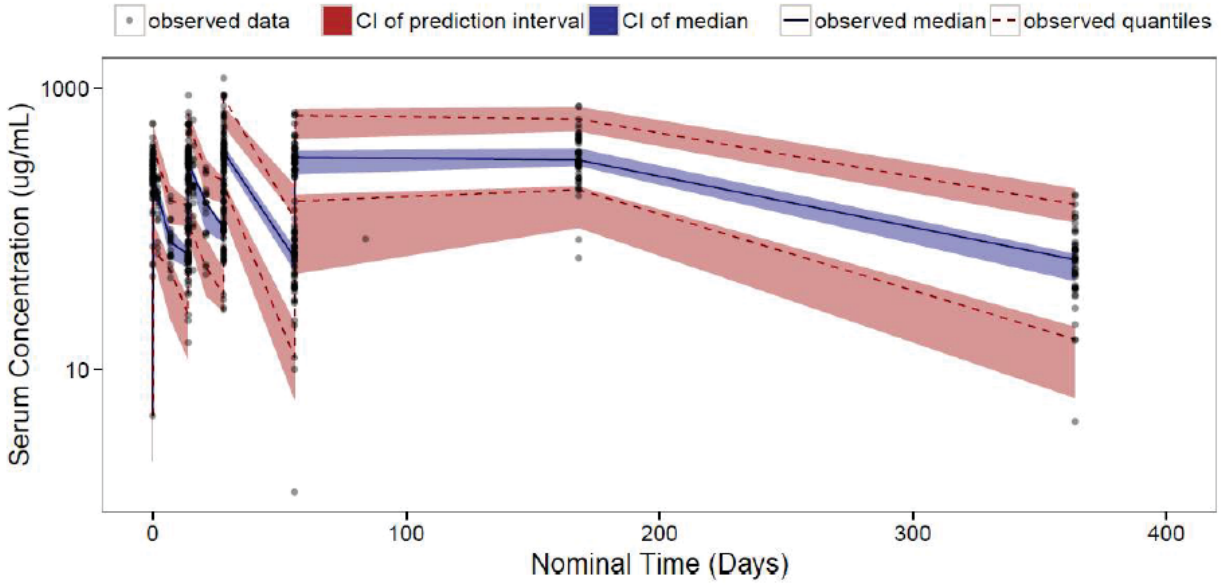
Figure 24. Goodness of fit plots for the final model with respect to the observed data (DV, dependent variable), individual prediction (IPRED), population prediction (PRED) and conditional weighted residuals (CWRES).



Observed data (black points) and the smooth regression line (solid red line) match their theoretical counterparts (dotted black line) for a well specified model.

Source: CSR BEL114055 (Figure 4 in Attachment 2, page 1535)

Figure 25. Visual predictive check of the final model (Mod071) with respect to nominal time



Observed data (black points), observed 2.5th and 97.5th percentiles (dotted red line) with simulated 95% CI (shaded red regions); observed 50th percentile (solid blue line) with simulated 95% CI (shaded blue region).

Source: CSR BEL114055 (Figure 5 in Attachment 2, page 1535)

15.3.1.4 Derived Pharmacokinetic Parameters and Comparison with Adult Belimumab Exposure

Individual PK and steady-state exposure parameters provided by the final population PK model are summarized by age group and compared with adult parameters in Table 71. The adult parameters were derived from the 563 subjects who received 10 mg/kg belimumab in the SLE Phase 3 studies. Steady-state exposure parameters C_{max}, C_{min}, C_{avg}, and AUC are similar between the age groups with a trend towards slightly higher exposure in the older compared to the younger age group. Parameters for both pediatric age groups and the overall pediatric population are consistent with the adult exposure parameters with largely overlapping confidence intervals.

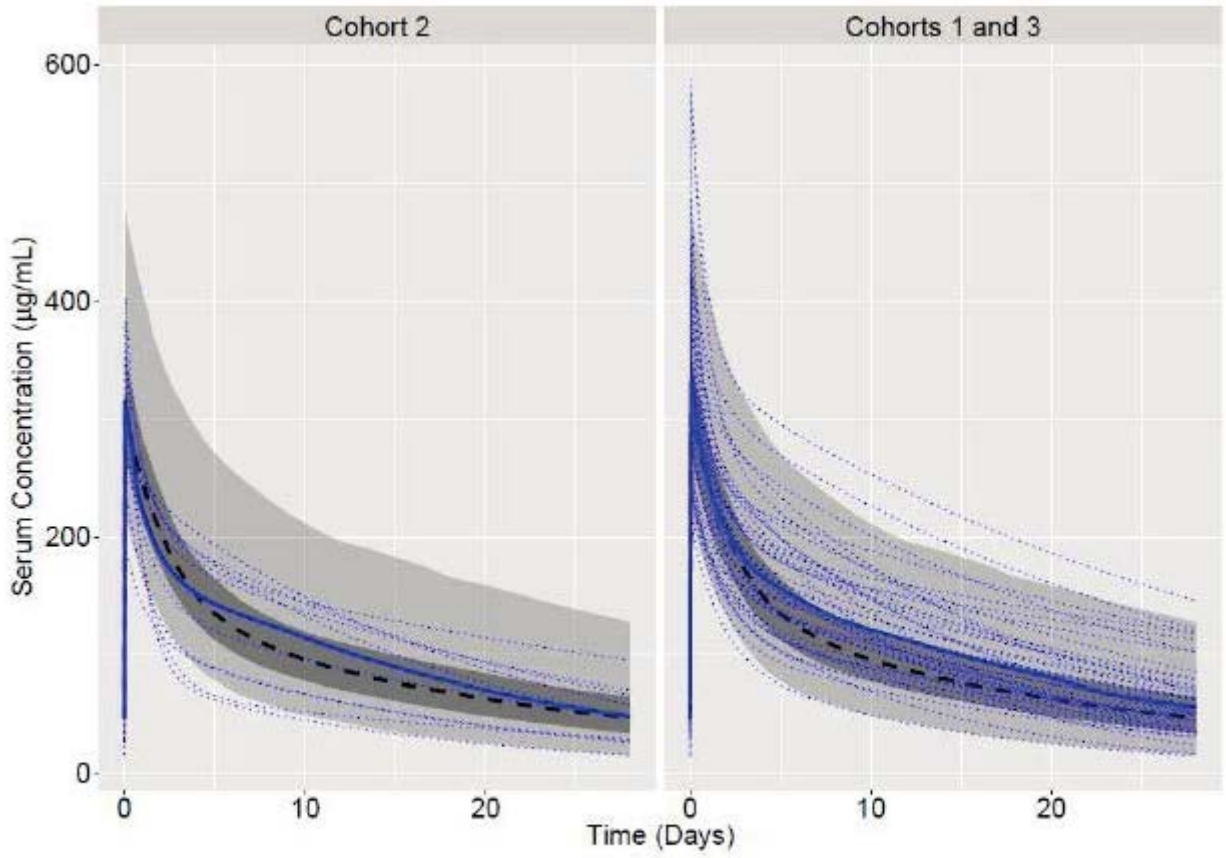
Table 71. Summary of Individual Belimumab Exposure Parameters by Baseline Age Group (Part A)

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)

Steady-state PK profiles for all belimumab-treated pediatric subjects were simulated based on their individual PK parameters, summarized by age group and compared with the prediction intervals for the individual adult PK profiles (563 subjects who received 10 mg/kg belimumab in the SLE Phase 3 studies) in Figure 26. Almost all pediatric profiles are completely contained in the adult 95% prediction interval; the median pediatric profiles are consistent with the median adult profiles.

Figure 26. Simulated Steady-State PK Profiles by Age Group Compared to Adult Profiles



Dashed blue lines, individual pediatric profiles; solid blue lines, median pediatric profiles.
Dashed black line, adult population median profile, light grey shaded areas, 2.5th-97.5th percentile (95%) prediction interval for adult profiles; dark grey shade areas, 25th-75th percentile prediction interval for adult profiles.

Source: CSR BEL114055 (Figure 9 in Attachment 2, page 1542)

Reviewer's comments: *Overall, the population pharmacokinetic model developed using data from Study BEL114055 was able to describe PK data after IV belimumab administration in pediatric patients with SLE. The applicant's analyses were verified by the reviewer, with no significant discordance identified. It's reasonable to use the developed model to support the proposed labeling statement as outlined in* Table 72***.***

Table 72. Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	N.A.	N.A.
	Extrinsic factor	N.A.	N.A.
Derive exposure metrics for specific populations	Cmin, Cmax, Cavg, and AUC at steady state		The applicant's final model is generally acceptable for generating exposure metrics for pediatric patients and support the corresponding labeling statement (**Table 71**).
Predict exposures at alternative dosing regimen	N.A.		N.A.

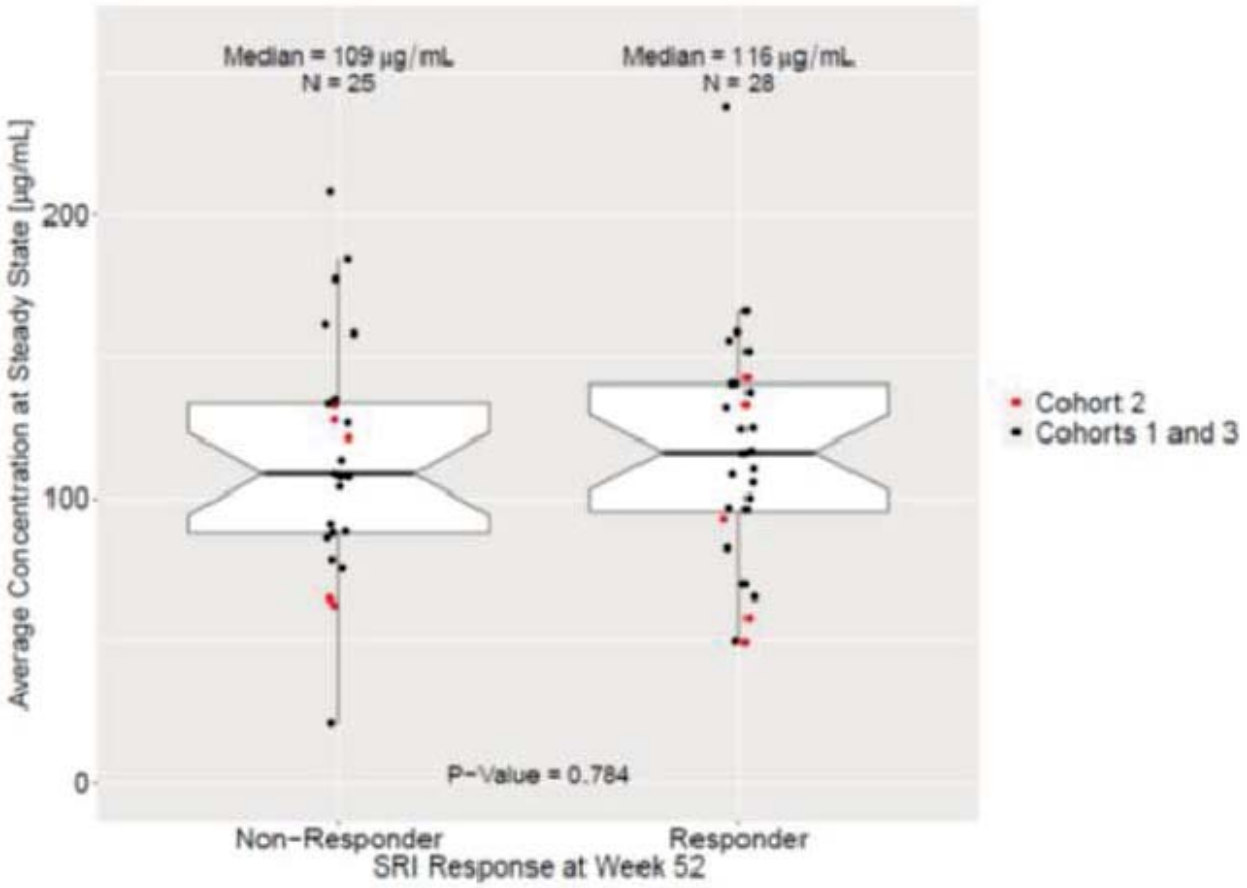
15.3.2. Exposure Response Analysis

15.3.2.1 Applicant' analysis

The Applicant conducted a post-hoc, exploratory exposure-response analysis to assess the impact of between-subject exposure variability on clinical response at Week 52. The response variables assessed were SRI response (Figure 27), the occurrence of an SAE at any time during Part A (Figure 28), changes in biomarkers IgG (Figure 29), the change in SELENA-SLEDAI score (Figure 30), anti-dsDNA (Figure 31), complement C3, complement C4, and naïve B cells. The exploratory exposure-response analysis demonstrated little correlation between efficacy, safety and biomarker response with belimumab exposure, quantified in terms of steady-state Cmax, Cmin, or Cavg.

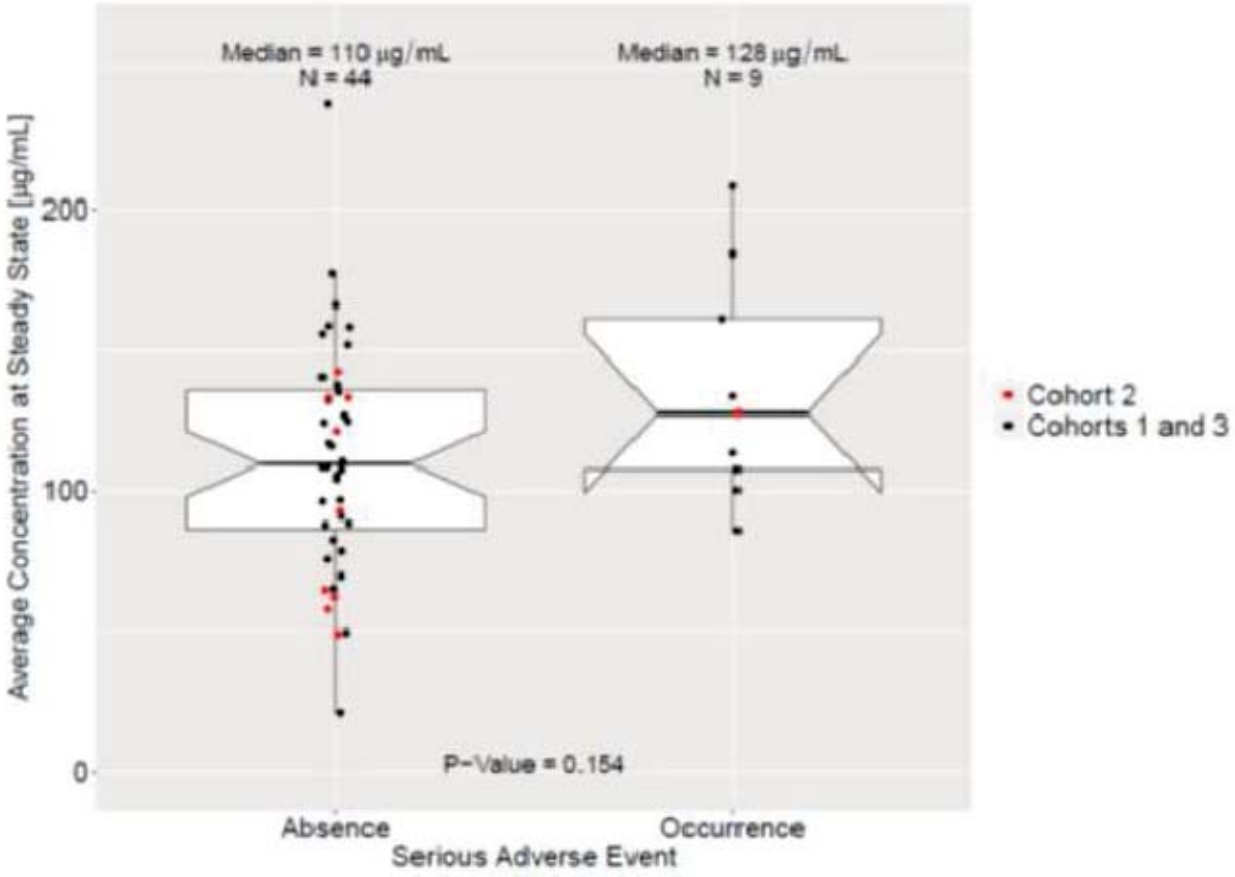
Reviewer's comments:
*No clear trends between efficacy, safety and biomarker response and belimumab exposure were identified. It could possibly be explained by the small sample size (53 pediatric patients) in study BEL1147055. The positive correlation for IgG percent change from baseline (*Figure 29*) was mainly driven by the two outlier observations at +25% and -48% IgG change, after excluding the two outliers, the remaining observations did not reveal an apparent correlation.*

Figure 27. SRI Response at Week 52 versus Belimumab Cavg



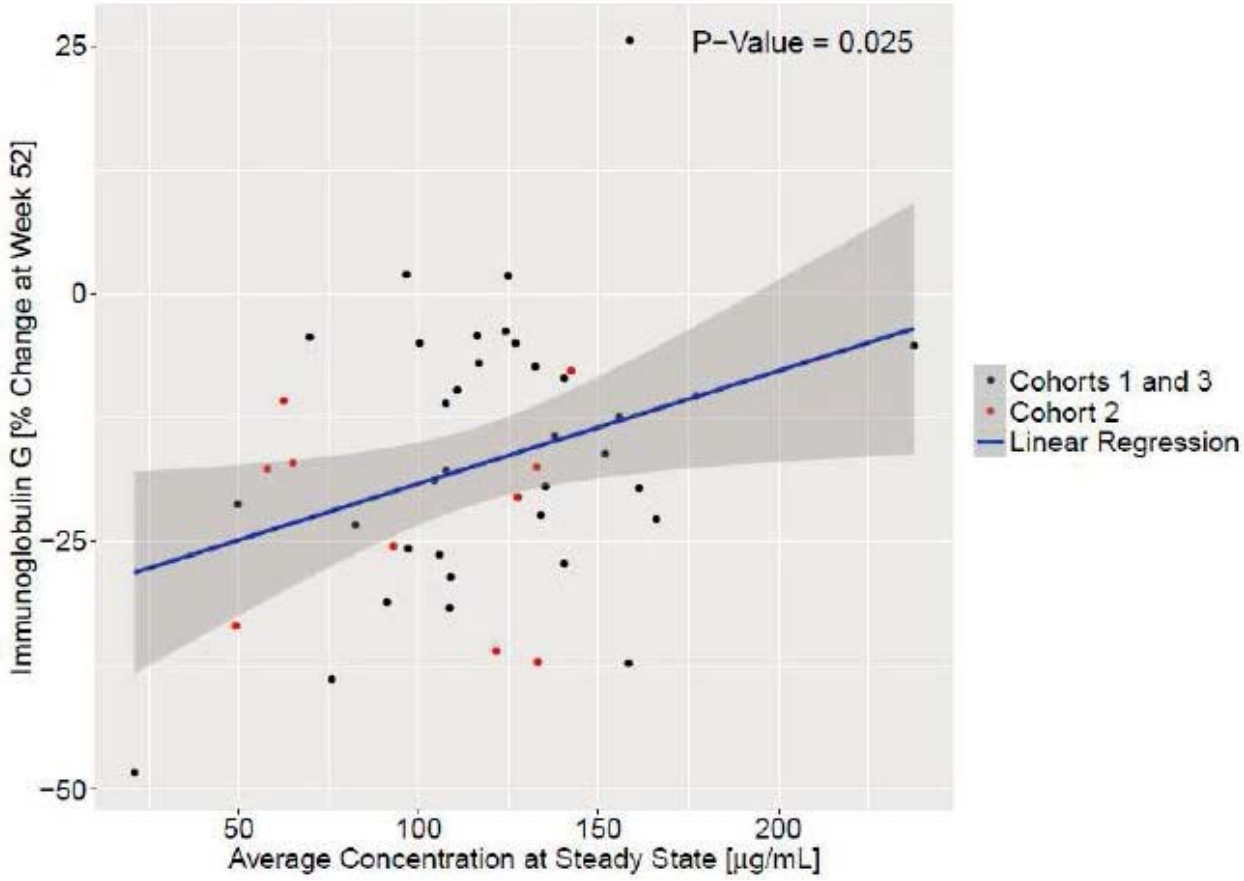
Source: CSR BEL114055 (Figure 18)

Figure 28. Serious Adverse Events versus Belimumab Cavg



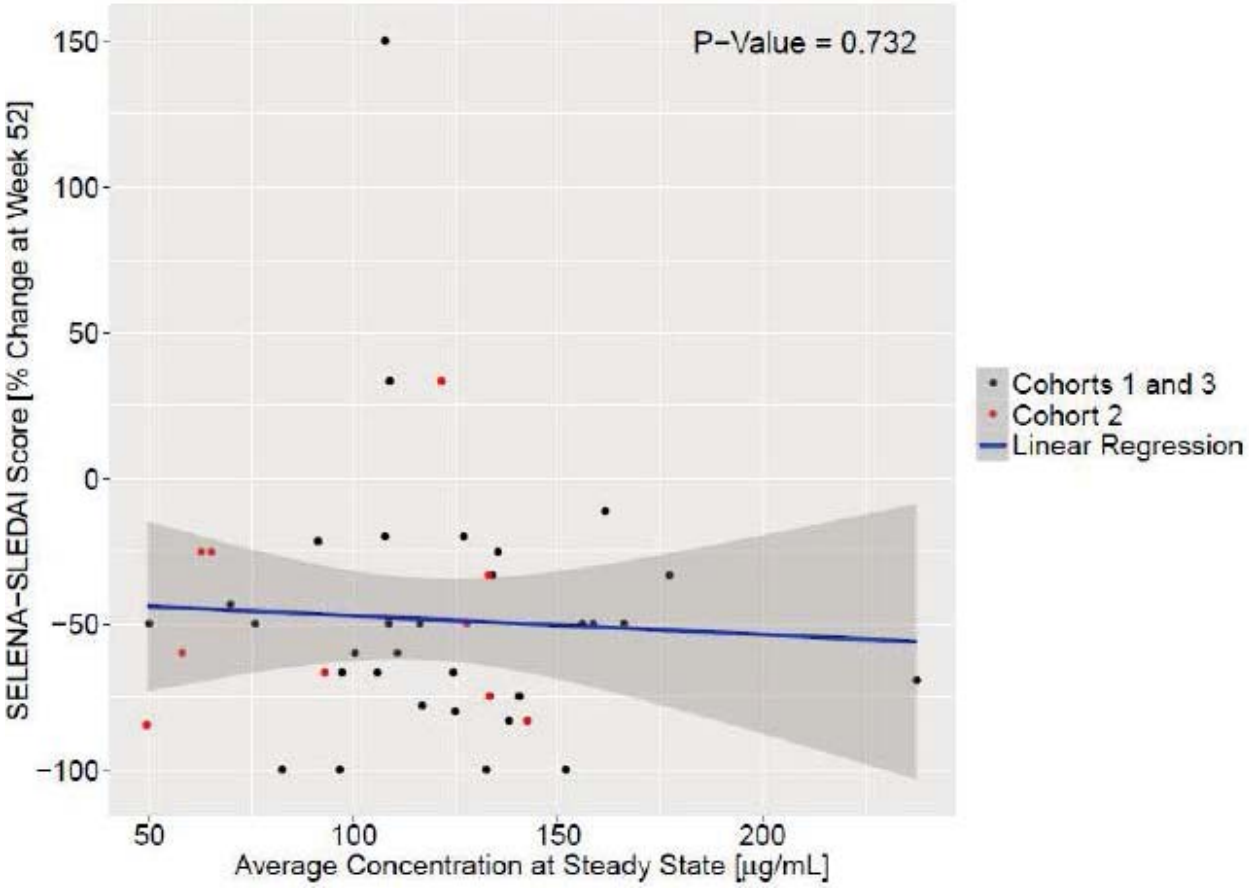
Source: CSR BEL114055 (Figure 19)

Figure 29. IgG Response at Week 52 versus Belimumab Cavg



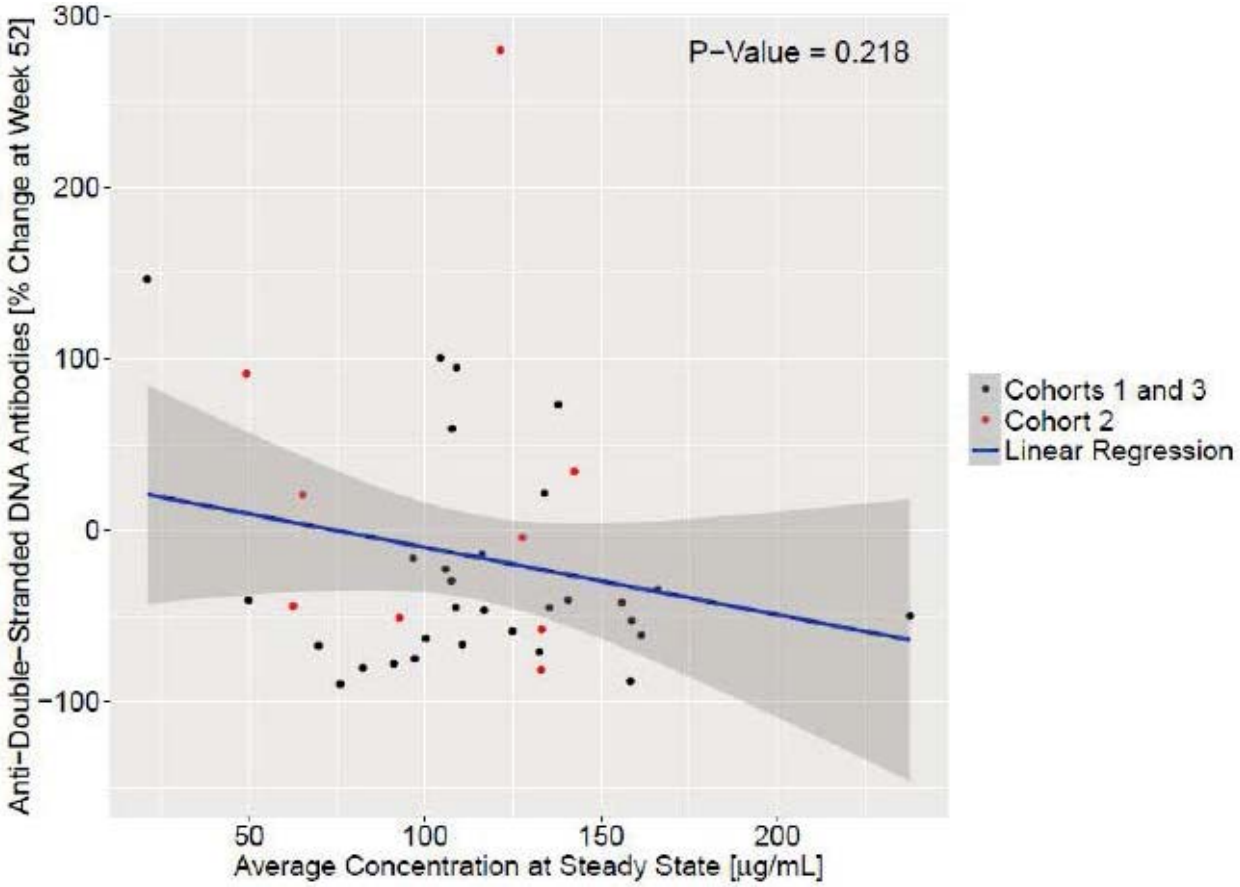
Source: CSR BEL114055 (Figure 20)

Figure 30. SELENA-SLEDAI Response at Week 52 versus Belimumab Cavg



Source: CSR BEL114055 (Figure 21)

Figure 31. Anti-dsDNA Response at Week 52 versus Belimumab Cavg



Source: CSR BEL114055 (Figure 18)

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NIKOLAY P NIKOLOV
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